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Specificity in the alteration of lesional and non-lesional skin lipids in atopic dogs

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Abstract

The present paper is in the same time an overview of the literature concerning the alterations of lipids in the stratum corneum (SC) of atopic dogs and a review of data based on our publications. Knowing the importance of the SC barrier function for against pathogens in atopic dermatitis, we show for the first time a detailed biochemical analysis of lipids corresponding to the same amount of proteins in the successive layers of canine SC taken using tape stripping and their specificity as compared to humans. Also we show new results concerning the changes in the composition for protein-

bound ceramides, and for the other lipids in involved and non-involved skin areas in atopic dogs. We show how a topical or oral treatment can restore the SC lipid composition and reconstruct the barrier integrity by up-regulating the biosynthesis of protein-bound ceramides.

Key words: Atopic dermatitis; Dogs; Glucosylceramide; Lipids; Ceramide; Stratum corneum

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Core tip: The review concerns the literature on modifications of sphingolipids in the stratum corneum (SC) of atopic dogs. We gave for the first time a detailed biochemical analysis of dog lipids in the successive layers of the SC take by tape stripping, and discussed their specificity by comparison to humans. We showed also the specific composition in protein-bound ceramides and the importance of CerOS in dog skin for barrier integrity. The lipid composition of involved and non-involved skin areas in atopic dogs was described and we showed how a topical or oral treatment can restore the lipid composition of SC and reconstruct the barrier integrity.

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SPECIFICITY OF THE STRATUM CORNEUM ORGANISATION IN DOGS

Stratum corneum (SC) is the outmost layer of the epidermis. It comprises a unique structure made of protein-enriched corneocytes embedded in a lipid-enriched extracellular matrix.

Table 1 Ceramide types of the stratum corneum

Sphingoid base fatty acid	Sphingosine (S)	Phytosphingosine (P)	6-Hydroxy-sphingosine (H)
Normal FA (N)	NS	NP	NH
	Cer 2	Cer 3	Cer 8
Alpha-Hydroxy FA (A)	AS	AP	AH
	Cer 5	Cer 6	Cer 7
Omega-Hydroxy FA (O)	OS	OP	OH
	Cer A		Cer B
Omega Esterified FA (E)	EOS	EOP	EOH
	Cer 1	Cer 9	Cer 4

FA: Fatty acid; NS: Normal fatty acid linked to Sphingosine; NP: Normal fatty acid linked to Phytosphingosine; NH: Normal fatty acid linked to 6-Hydroxysphingosine; AS: Alpha-hydroxy fatty acid linked to Sphingosine; AP: Alpha-hydroxyl fatty acid linked to Phytosphingosine; AH: Alpha-hydroxyl fatty acid linked to 6-Hydroxysphingosine; OS: Omega hydroxyl fatty acid linked to Sphingosine; OP: Omega hydroxyl fatty acid linked to Phytosphingosine; OH: Omega hydroxyl fatty acid linked to 6-Hydroxysphingosine; EOS: Omega esterified fatty acid linked to Sphingosine; EOP: Omega esterified fatty acid linked to Phytosphingosine; EOH: Omega esterified fatty acid linked to 6-Hydroxysphingosine.

SC lipids are composed of polar lipids such as cholesterol-sulphate, neutral lipids such as sterols, fatty acids, triglycerides, wax esters, squalene and extremely hydrophobic species such as ceramides (Table 1). The lipid extracellular matrix containing in few amount the omega-hydroxyceramides (CerOS, CerOP and CerOH), is replacing the plasma membrane of the living cells and it constitutes a scaffold for the intercellular lipid lamellae^[1].

Between the terrestrial mammals, the SC thickness and the organisation are variable.

Regarding the canine skin samples, the intercellular lipid content was less than in other terrestrial species^[2] and humans^[3]. The lipid content also varies among the breeds. The Labrador retriever and Siberian husky are presenting a higher skin lipid content than the poodle^[3].

As shown in a previous paper the results performed on the SC of five healthy dogs showed similar molecular species of ceramides as in Figure 1, but in different quantity concerning free and protein-bound lipids^[4]. For example, in the Labrador breed, 6-hydroxysphingosine was the major long-chain base of ceramides, The other dogs presented mostly sphingosine- based ceramides and low amounts of phytosphingosine and 6-hydroxysphingosine ceramides.

Within the depth in the SC, we observed a variation in free ceramides but not for protein-bound ceramides as well as it was describes in other studies where it was used the cyanoacrylate method^[5,6].

As can be seen from Figure 1, we identified ceramides with omega-hydroxylated long chain fatty acids such as CerOS, CerOP and CerOH, and we showed that CerOS contains omega hydroxy fatty acids species in decreasing order from omega -OH C30:0, omega -OH C29:0, omega -OH C28:0, to omega -OH C32:0.

In conclusion, due to its structure, the Stratum Corneum of healthy dogs show an important role in the skin barrier protection towards environmental factors

and trans-epidermal water loss.

SIMILARITIES OF SC OF HUMAN AND CANINE ATOPIC DERMATITIS

Halliwell^[7] describes for the first time that from the clinical point of view that the canine atopic dermatitis (AD) show many similarities with the human skin^[8]. After 1999, when the American College of Veterinary Dermatology established that any review of AD should be supported by the medically based evidence of atopy, the term “allergic inhalant dermatitis” was replaced by “AD” because of the lack of asthma sign developing in dogs. In this respect, AD is defined as a genetically determined or allergic or inflammatory pathology resulting into a pruritic skin disorder. Environmental allergens^[9] or cutaneous *Malassezia* and *Staphylococcus* infections^[10] are well known to trigger inflammatory changes that are commonly associated with IgE antibodies.

Recently, in a skin model Leiden epidermal model (LEM)^[11], it was used IL-4, IL-13, IL-31, and TNF- α to induce AD-like cytokines disorder in skin (spongiosis and alterations of early stage and terminal stage of expression in differentiation-protein in reconstructed skin). Another effect of TNF- α alone or together with Th2 cytokines consisted in a decrease of the level of long chain free fatty acids (FFAs) and ester linked omega-hydroxy (EO) ceramides, leading to an abnormal lipid organization and a defect in skin barrier integrity. Another cause of exacerbating the pathological changes and the impairment of the synthesis of ultra long-chain ceramides in AD results into a higher amount of the interferon gamma which decreases the very long chain fatty acids and ceramide synthase 3 enzymes necessary for the synthesis of the very long-chain ceramides^[12].

AD in dog species affects up to 10% of dogs and it has an important breed prevalence^[13]. If in humans, mutations in the filaggrin gene accounted for the predisposition to develop AD, in dogs there is no known direct link^[14] and a total absence of correlation has been reported in West Highland White Terriers^[15].

Previously, it was shown that in AD, the genetic defects in proteins structure or enzymes could impair the synthesis of SC lipids by incomplete extrusion of lipid bodies (LBs)^[16,17]. The LBs composition in lipid catabolic enzymes is also changed^[18], resulting in an impairment of lateral packing of the inter-corneocytes lamellar lipids (LL) as observed in humans with AD^[19]. Compared to normal skin, it was observed in the non-lesional skin of atopic dogs, by transmission electron microscopy (TEM), some ultrastructural changes in SC morphology such as larger intercorneocyte spaces, as well as severely disorganised, sporadic and incomplete lamellar lipids (20).

After topical treatment with SLC^[20], or a ceramide-like moisturizer^[21], or other extrinsic lipids^[22] that would be integrated into the nascent lamellar bilayers, it was observed by TEM a new formation of the SC compactum, an increase in the LLs and an improvement of the SC integrity.

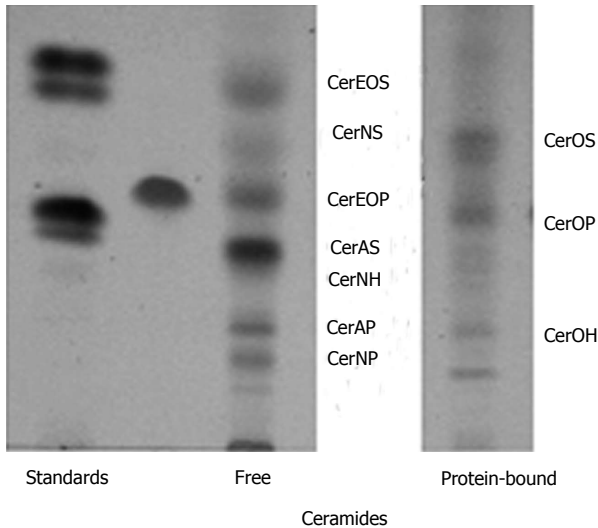


Figure 1 Chromatographic plate with high performance thin-layer of free and protein-bound ceramides from the Stratum corneum of healthy dog skin, Labrador breed. Standards: Left lane; CerNS (ceramide with normal fatty acid and sphingosine): Upper spot; CerAS (ceramide with alpha hydroxy fatty acid and sphingosine): Lower spot; Center lane CerNP (ceramide with normal fatty acid and phytosphingosine); CerEOS: Ceramide with omega esterified fatty acid and sphingosine; CerNS: Ceramide with normal fatty acid and sphingosine; CerAS: Ceramide with alpha-hydroxyl fatty acid and sphingosine; CerNH: Ceramide with normal fatty acid and 6-hydroxysphingosine; CerAP: Ceramide with alpha-hydroxyl fatty acid and phytosphingosine; CerNP: Ceramide with normal fatty acid and phytosphingosine.

EVIDENCE FOR ABNORMAL PRESENCE AND HETEROGENEOUS DISTRIBUTION OF GLUCOSYLCERAMIDE IN THE SC OF ATOPIC DOGS IN NON-LESIONAL AS WELL IN LESIONAL AREAS

An inherent abnormal lamellar structure will cause disorders in cornification as in many ichthyosis, due to a reduced level in protein-bound omega-hydroxyceramides^[4], or alteration in the content of other sphingolipids as in psoriasis^[23] and AD^[5,24-26]. These covalently bound ceramides were first described by Wertz *et al*^[27] in 1989.

Recently, a reduction in the free fatty acid chain length was reported in non-lesional and lesional SC of atopic eczema patients^[28], associated with a reduced ceramide chain length, suggesting a common synthetic pathway.

This finding could be sustained by the results of Haller *et al*^[29] who found that the loss of Abca12 function results in a failure of interaction between glucocerebrosidase and its GlcCer substrate and an accumulation of GlcCer species in SC.

Regarding glucosylceramide, our results^[30] show in atopic dogs a near absence of CerOP, a protein-bound ceramide, with the concomitant presence of glucosylceramide in large amount in the SC.

Moreover, Reiter *et al*^[5] showed that the ratio cholesterol to ceramide in atopic dog SC is higher than in normal SC dogs, in uninvolved as well as in lesional areas. Also, some results from Sugiura *et al*^[31] support the notion that

Table 2 Protein content of strips taken from normal and atopic stratum corneum dogs

Strip number	Healthy dogs ¹	Atopic dogs	
		Non-lesional areas ¹	Lesional areas
1 + 2	96 ± 11	92 ± 12	56 ± 8
3 + 4	105 ± 12	93 ± 12	58 ± 9
5 + 6	96 ± 10	95 ± 10	57 ± 8
7 + 8	97 ± 13	94 ± 11	59 ± 9
9 + 10	103 ± 15	96 ± 12	52 ± 8
11 + 12	105 ± 14	96 ± 13	54 ± 7

¹Reproduced from ref.[30]. Values expressed as µg proteins ± SE (n = 5) per 2 strips (P < 0.05).

AD in non-lesional skin is associated with an impaired homeostasis in a ceramide-generating process.

Concerning our work, we reported in 2011 the lipid patterns in non-involved SC of atopic dogs *vs* normal dogs SC that suggested an impaired biosynthesis of the long chain bases of ceramides^[30,32]. Here we give the complete analysis of free and protein-bound lipids of lesional and non-lesional SC of 5 atopic dogs.

As shown in Table 2, the amount of proteins taken by tape stripping in non-lesional areas of atopic dogs SC was not significantly different from that of normal dogs, but the protein content was reduced by half compared to the non-lesional areas. The lower protein content of lesional areas was likely to be due to the limited sticking of the tapes on inflammatory areas.

The free lipid content of normal and non-lesional and lesional atopic dog SC is given in Table 3. As compared to their respective contents in normal dog SC, cholesterol and fatty acids showed a moderate (10% to 15%) decrease in both non-lesional and lesional SC of atopic dogs. Free ceramides were reduced by 30% to 40%. However, for glucosylceramides which were absent in normal dog SC, large amounts were detected in non-lesional SC of atopic dogs, with a significant concentration also present in lesional areas, showing a deficient activity of the glucocerebrosidase in the atopic dogs skin.

Table 4 shows the protein-bound lipids of the SC. The amount of Cholesterol, fatty acids and omega hydroxy ceramides of the protein-bound lipids show an important decreasing in atopic dog SC, even higher than that of free lipids. The cholesterol amount was reduced by 30%, the fatty acids by 50% and the omega hydroxyceramides, only 20% compare to the amount found in healthy dog SC. Compare to the normal dog SC which does not contain covalently-bound glucosylceramides, we found an important amount in both non-lesional and lesional atopic dog SC.

In a recent study it was shown that a neutral ceramidase isolated from *Pseudomonas aeruginosa* (PaCDase) isolated from a patient with AD could degrade the ceramides in the presence of *Staphylococcus aureus*-derived lipids or neutral detergents in a keratinocyte model^[33].

To illustrate the data shown previously^[34] and the values from Tables 3 and 4, we analysed comparatively in depth by chromatographic plates the free ceramides of

Table 3 Free lipids of stratum corneum of normal and atopic dogs

Lipid class	Normal dogs ¹	Atopic dogs	
		Non-lesional areas ¹	Lesional areas
Cholesterol	96 ± 28	87 ± 31	86 ± 37
Fatty acids	115 ± 32	91 ± 36	89 ± 43
Ceramides	141 ± 37	112 ± 43	105 ± 56
Glucosylceramides	0	31 ± 17	12 ± 10

¹Reproduced from ref.[30]. Values expressed as $\mu\text{g} \pm \text{SE}$ ($n = 5$) per milligram protein.

Table 4 Protein-bound lipids of stratum corneum of normal and atopic dogs

Lipid class	Normal dogs ¹	Atopic dogs	
		Non-lesional areas ¹	Lesional areas
Cholesterol	12 ± 8	9 ± 5	8 ± 6
Fatty acids	23 ± 12	11 ± 9	15 ± 8
Ceramides	36 ± 10	8 ± 7	8 ± 6
Glucosylceramides	0	8 ± 8	7 ± 6

¹Reproduced from ref.[30]. Values expressed as $\mu\text{g} \pm \text{SE}$ ($n = 5$) per milligram protein.

SC from lesional (line 4) and non-lesional (line 3) spots of atopic dog compared to the healthy one (line 1 and 2) (Figure 2).

It is noticeable that in non-lesional areas (4) the proportion of Cer NP and Cer AS dropped as well as in the lesional side, and moreover, Cer EOS (omega-hydroxy ceramide) is totally absent from lesional areas.

We may noticed an heterogenic distribution in SC depth of protein-bound omega hydroxy ceramides, Cer OS and CerOP, in non-lesional (Figure 3A) and lesional (Figure 3B) SC of atopic dog. Compare to non-lesional SC (Figure 3A), in lesional SC (Figure 3B) an important absence of protein-bound céramides, one reason why the SC integrity is markedly altered.

Figure 4 shows comparatively the presence of glucosylceramide in SC of healthy dog, the precursor of ceramides, (Figure 4A) and its presence in non-lesional (Figure 4B) and the lesional (Figure 4C) SC of atopic dog.

Compare to the healthy dog's SC (Figure 4A), in the successive strips of lesional areas of atopic dogs (Figure 4C), the omega hydroxy ceramides are absent in one sample out of two whereas this does not appear so clearly in non-lesional areas (Figure 4B), responding to question why the alteration of the SC integrity occurs.

Table 4 presents the comparison concerning the whole lipids content of protein-bound lipids of Sc of healty dog compare to atopic dog. We may notice that in atopic dog SC, the whole lipids are strongly reduced as compared to normal dogs. The decreasing in CerOS, which accounts for about 75% of the total omega hydroxy ceramides in normal dog SC, is the only species present in atopic dog SC. Table 4 shows also the amount of glucosylceramide in non-lesional and in lesional areas which confirm the heterogenic profile (Figure 4B and C).

This accumulation of glucosylceramide in SC of

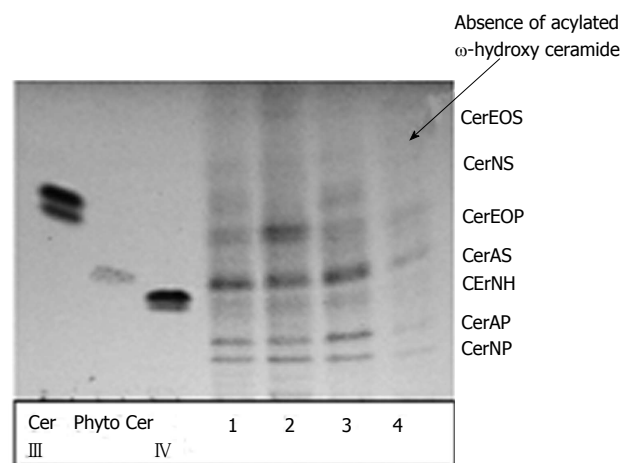


Figure 2 Free ceramides in the stratum corneum of healthy dogs (1, 2) and an atopic dog, non-lesional (3) and lesional areas (4). Standard lipids on the left lanes of the plates: type III and type IV ceramides, phytoceramides.

atopic dogs compared to the normal SC dogs is due to the deficient activity of beta-glucocerebrosidase. This enzyme is known to be essential in acquiring a good SC barrier^[18].

Concerning the free glucosylceramide type of lipids, they are completely absent in the normal dog SC. In a similar way, the free glucosylceramides were present in all layers of non-lesional dog SC in an important quantity. In lesional areas, the concentration of glucosylceramides was much lower and there were some variations in the molecular species visualized in these samples, as glucosylceramides with long-chain fatty acids were prominent in pooled strips 5 + 6.

We found in our studies on dog SC, the cholesterol in the protein-bound fraction, as it was reported in human skin^[35]. Its presence was observed in the successive layers in a striking heterogeneity. In the case of the atopic dogs in non-lesional layers, some layers were more enriched and in lesional layers the content was lowered.

WAYS OF RECOVERY AND TREATMENTS FOR AN EFFICIENT CUTANEOUS BARRIER

One key fact is to restore the barrier function and this requires a decrease to allergen exposure.

Several treatments based on topical application of lipids were designed for patients with allergic contact dermatitis, irritant dermatitis and atopic dermatitis^[22]. For example, the improvement of the skin barrier in children with AD was accelerated after treatment with a pseudoceramides-based moisturizer^[21].

Another study suggested that the application of an emulsion based on an physiological lipid granules would restore the barrier of atopic patients and reduce the clinical symptoms and any side effects^[36].

Concerning the dogs, frequent washing and rinsing of the contact zones may help to decrease allergen exposure. In this respect it was shown previously^[20] that a mixture of lipid complex SLC[®] based mainly on ceramides and cholesterol (Allerderm/Derm-1 Spot-on, Virbac

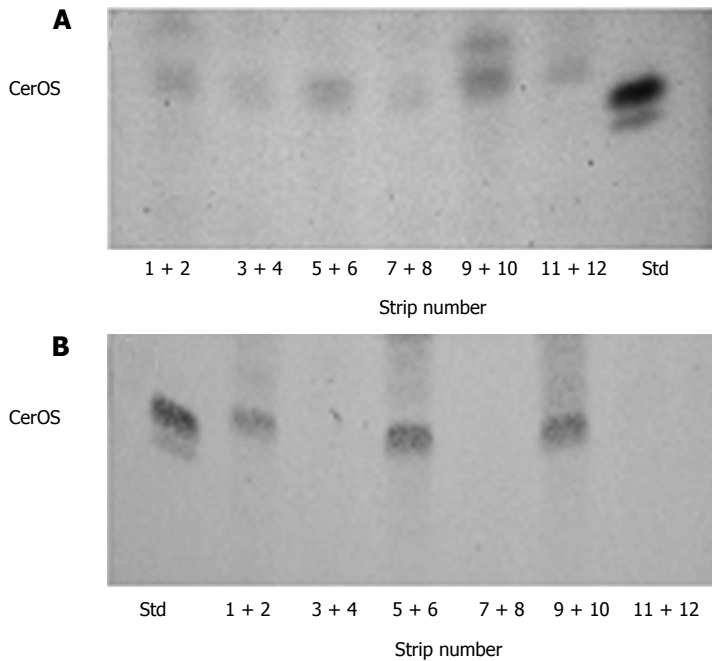


Figure 3 High performance thin-layer chromatography of protein-bound ceramides from non-lesional (A) and lesional (B) stratum corneum of atopic dog (strip tapes taken by two before extraction. Standard ceramide Cer III (CerAS). Figure 3A reproduced from ref.[30] (strips tapes pooled two by two before extraction).

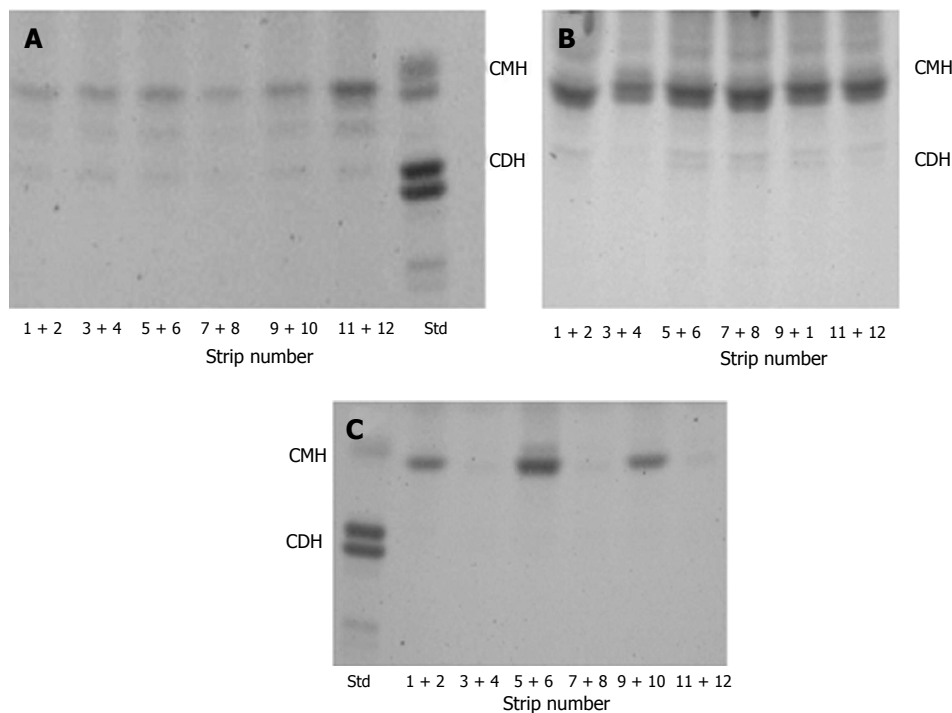


Figure 4 High performance thin-layer chromatography of protein-bound glucosylceramides from non-lesional (B) and lesional (C) stratum corneum of atopic dog compared to healthy dog (A) (strips tapes by two before extraction. Std- mixture of glucosylceramide (CMH) and lactosylceramide (CDH). Figures 4A and 4B reproduced from ref.[30] (strips tapes pooled two by two before extraction).

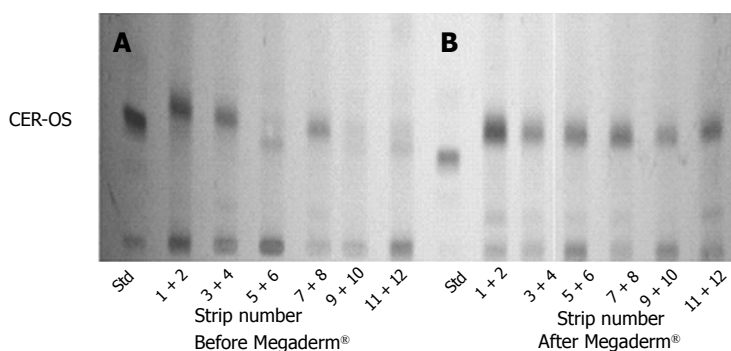


Figure 5 High performance thin-layer chromatography of protein-bound ceramides from SC of non-lesional skin of an atopic dog before (A) and after treatment with Megaderm R (B) (tapes pooled two by two before extraction). Standard-CerOS.

Laboratory) would restructure the SC lipid lamellae. The treatment resulted^[32] into an important increase in lipid biosynthesis of keratinocytes (*i.e.*, protein-bound ceramides CerOS and CerOP, and normal and omega-hydroxy fatty acids) and an efficient barrier formation. Another treatment, Megaderm®, designed by Virbac for atopic dogs was a food supplement based on essential fatty acids and vitamin E^[33].

Figure 5 shows, as most of our previous publications^[30], that the lower lipid content and the marked deficit in protein-like ceramides (Figure 5A) in atopic dogs may be reversed with the feed supplementation with Megaderm® (Figure 5B). This is the most remarkable feature, accounting for the observed accumulation of the intercorneocyte lamellar lipids^[37].

Although it was observed that after feeding for about two months with Megaderm®, the deepest layers of the SC presented several imperfections compared to the SC of healthy dogs, the overall improvement in the lamellar lipid organization and normalization of the protein-bound lipid content did occur, just as with SLC® treatment^[20].

It was recently demonstrated with Fourier-transformed infrared spectroscopy and Raman imaging spectroscopy that the stability of the crystalline structure of free fatty acid, ceramide and cholesterol mixtures strongly depends on the length of the fatty acids built into ceramides^[38]. It can be that the optimal molecular proportions can be best achieved when living epidermal cells are sufficiently supplied with the essential building bricks provided through the treatments.

Of course, besides the dietary supplementation such as Megaderm® or topical treatment such as SLC®, new treatments used in humans suffering from AD may be also applied in dogs.

These are topical ceramide formulations^[39] including targeted CerAP microemulsions^[40], that may contain inhibitors of calcineurin^[41]. They are all aiming at increasing the epidermal lipid content, supplying filaggrin degradation products^[42], regulating the environmental pH^[43,44] and the glucosylceramidase activity^[45,46], and resulting in a decrease of the transepidermal water loss^[47] and inflammation.

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Dermatological conditions of aquatic athletes

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conditions commonly seen in swimmers. This review provides an update on water dermatoses and discusses newly described conditions such as allergic contact dermatitis to chemical ingredients like potassium peroxymonosulfate in pool water. In order to organize water related skin conditions, we have divided the skin conditions into a number of categories. The categories described include infectious and organism-related dermatoses, irritant and allergic dermatoses, and sun-induced dermatoses. The vast majority of skin conditions involving the water athlete result from chemicals and bacteria in the differing aquatic environments. When considering the effects of swimming on the skin, it is also useful to differentiate between exposure to freshwater (lakes, ponds and swimming pools) and exposure to saltwater. The risk of melanoma amongst swimmers is increased, and the use of SPF 30 or greater sunscreen and protective clothing is highly recommended. Swimmers should be reminded to generously apply sunscreen and be instructed on proper sunscreen usage. This review will serve as a guide for dermatologists, athletes, coaches, and other medical professionals in recognition and treatment of these conditions. We also intend for this review to provide dermatologist with a basic framework for the diagnosis and treatment of a few rarely described dermatological conditions in swimmers.

Key words: Aquatics; Dermatitis; Athletes; Practice Gaps; Freshwater dermatitis

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Core tip: Athletes who spend a significant amount of time in the water are subject to a wide array of diseases that include bacterial and fungal infections. These athletes are often exposed to undesirable environments with excessive humidity, heat, cold, wind, and sunlight. These factors may aggravate or cause different skin conditions that require a dermatologist who has specific knowledge of rare aquatic dermatoses.

Abstract

Numerous manuscripts have described dermatologic

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CONDITIONS RELATED TO IMPAIRED SKIN BARRIER AS A RESULT OF CONTACT WITH WATER

Excessive dryness (swimmer's xerosis) is one of the most common conditions seen in water athletes. It is caused by sebum dilution with water, osmotic effect, and stripping off the stratum corneum. Taking long showers with scrubs and soaps after activity also precipitates the problem. Although easy to diagnose, swimmer's xerosis should be differentiated from swimmer's itch and urticaria^[1-5]. Preventative measures include decreasing shower duration and applying ointment based moisturizing preparations before and after pool activities^[4].

Aquagenic acne occurs due to the rebound effect of sebum over-production after continuously washing off the oils from the skin surface. It may present as an acute exacerbation of a preexisting condition or as a new onset disorder. Other mechanisms include the effect of chlorinated compounds in pool water, occlusion of the sebaceous glands by denuded epidermis, and use of comedogenic moisturizing creams and sunscreens. Aquagenic acne typically presents as common acne and should be treated accordingly. Topical or systemic agents can be used depending on level of severity, but it should be noted that some topical agents may cause additional irritation. Specifically, isotretinoin, commonly used for severe acne treatment, may interfere with performance and cause neuromuscular symptoms and myalgias^[6,7].

CONTACT DERMATITIS

Allergic contact dermatitis

Some evidence suggests that swimmers may be more prone to allergic reaction than non-swimmers since swimmers have a higher incidence of positive skin prick tests, asthma, allergic rhinoconjunctivitis, and bronchial hyperactivity^[8-12]. Increased allergy rates may be partly explained by the use of chlorinated or brominated disinfectants in swimming pools that may increase sensitization to other allergens^[13].

Disinfectants may cause allergic contact dermatitis ("pool water dermatitis"). Compounds proven to cause pool water dermatitis include gaseous chlorine, sodium and lithium hypochloride, 1-bromo-3-chloro-5,5-dimethylhydantoin (BCDMH), potassium peroxydisulfate, and aluminum chlorohydrate^[14-17]. Brominated compounds were previously thought to provide an alternative to chlorine, but have shown an increased potential to cause irritant contact dermatitis. BCDMH is a component that slowly releases bromine and chlorine and is believed to be the causative



Figure 1 Allergic contact dermatitis to new swim wear.

agent of an outbreak of swimming pool contact dermatitis in the United Kingdom^[18-20]. Initially, only negative patch tests to BCDMH were seen, and it was believed to be a solely irritant dermatitis. However, positive patch tests for BCDMH were later reported^[16]. It was also proposed that certain individuals may develop an allergic contact dermatitis because of the chlorine, released from BCDMH, but test were negative for BCDMH itself^[21].

Allergic contact dermatitis can also be caused by certain clothing and equipment swimmers use (Figure 1). Early reports described reactions to the components of resins (thioureas, benzothiazole, dithiocarbamate and formaldehyde) in goggles, scuba masks, nose clips, earplugs, fins, fin straps, and swimsuits^[22-29]. Allergic contact dermatitis to dodecyl diaminoethyl glycine, a diving suit disinfectant, has also been described^[30]. Raccoon-like depigmentation was described from use of neoprene goggles in a child, but the etiology (toxic or allergic) was not confirmed^[31].

Irritant contact dermatitis

Irritant contact dermatitis in athletes usually develops as a result of chronic friction (Figure 2). Use of caps and goggles that press tightly against the skin may lead to purpura formation^[4]. A specific irritant dermatitis known as "pool toes" and "pool palms" is caused by friction of the feet and palms against the pool's rough cement bottom^[32-34]. Another form of irritant dermatitis in males is "shoulder dermatitis", which is caused by rubbing an unshaven chin against the shoulder while performing the crawl stroke^[35]. In surfers, nodules may develop in the pretibial area due to continuous friction with the surf board^[35]. These irritant dermatoses usually resolve spontaneously with cessation of the offending activity, but persistent nodules can be treated with topical keratolytics and intralesional corticosteroids.

SKIN INFECTIONS

Athletes who spend a significant amount of time in the water are subject to a wide array of bacterial and fungal infections. Excessive maceration, dryness, and changes in the skin microflora contribute to the development of

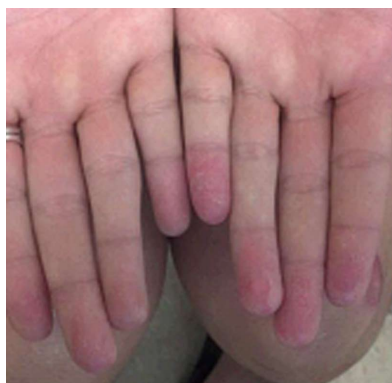


Figure 2 Fingertips that desquamate from the friction of the contact with the sides of the pool.

the skin infections. Additionally, the risk of disease is increasing because of pool overcrowding and common use of showers and towels.

Bacterial infections

Pseudomonas aeruginosa is able to survive in high temperate water and causes several skin conditions including hot tube folliculitis, otitis externa, and hot foot syndrome. Outbreaks of *Pseudomonas* infections may arise from contact with contaminated water^[36-38]. Current studies show that *Pseudomonas* contamination is common in pools and even more so in hot tubs since they are difficult to clean^[39]. To decrease the rate of infection, chloride concentration of the water should be monitored daily. Athletes, especially those who train intensely for a prolonged period of time, are prone to the colonization of the ear canal by *Pseudomonas*^[40].

Hot tub folliculitis presents as a disseminated itchy pustular rash that appears within two days of water exposure. It is prone to localize in the intertriginous areas and may also be seen in a bathing suit distribution. Hot tub folliculitis (Figure 3) is usually a self-limited condition, but systemic symptoms such as low-grade fever, lymphadenopathy, headache and malaise may be rarely seen. It can also be accompanied by other *Pseudomonas* infections including otitis, conjunctivitis, mastitis, and urinary tract infections^[41]. *Pseudomonas* folliculitis may also develop under the suit that has led to the aptly suited description of “diving suit folliculitis”^[42,43].

Pseudomonas is the most frequently implicated pathogen in the development of otitis externa. Swimmers are five times more likely to develop otitis externa than non-swimmers^[44]. Otitis externa presents with pain limited to the external auditory canal, but the ear appears erythematous and swollen with variable discharge (Figure 4). Prophylaxis is generally achieved through proper cleaning and drying of the ear canal in addition to avoidance of excessive moisture in and around the canal. Acidification with a topical solution of 2% acetic acid combined with hydrocortisone for inflammation is effective treatment, although most physicians will also prescribe combination steroid/antibiotic drops. Another dermatoses known as hot foot syndrome has been described as a subcutaneous



Figure 3 Buttock folliculitis.

eruption on the soles of children swimming in the same pool^[38,45]. In both reports *Pseudomonas* was isolated from the swimming pool, but a causative relationship (isolation from the skin lesion) was only performed in one child, leaving debates about the etiology of the condition^[46,47].

Swimmers also show increased rates of skin colonization by *Staphylococcus* and *Streptococcus*^[40]. Bikini bottom is a deep folliculitis of the buttocks that is caused by *Streptococcus* or *Staphylococcus aureus*. It is the result of wearing tight fitting bikinis for prolonged periods of time and presents as firm nodules that manifest along the inferior gluteal crease^[48]. Prevention is aimed at early removal of the swimsuit, while treatment consists of oral antibiotics based on sensitivities.

Recent European and American studies have shown that most swimming pools and showers are contaminated with *Mycobacteria*^[49-52]. Although not necessarily symptomatic, these bacteria can cause granulomatous disease of the lungs and skin^[53]. *Mycobacterium marinum* (*M. marinum*) is ubiquitous in pools, aquariums, freshwater, and saltwater. Since its discovery in Sweden, multiple outbreaks of *M. marinum* outbreaks have been described throughout the world^[54-56]. It also causes so-called “fish tank” or “swimming pool” granuloma which has a predilection for the dorsum of the hands, fingers, and elbows, especially when skin trauma or open wounds are present^[57]. The predilection for the extremities is due to inhibition of growth of *M. marinum* at 37 °C so the organisms tends to infect the cooler parts of the body including the extremities^[57]. The granuloma usually presents as a solitary, erythematous papule or nodule and may be mistaken for sporotrichosis or leishmaniasis^[58,59]. Disseminated infection is rare, although a case of disseminated *Mycobacterium* that presented as erythema nodosum was previously described in a 12-year-old girl^[60]. Histopathology of skin lesions reveal typical tuberculoid granulomas in only 60% of cases, while the other 40% display non-specific inflammation with neutrophils^[61]. Frequently, superficial biopsies fail to show specific changes, but granulomas may be seen in the subcutaneous tissue or synovium. Paucity of microorganisms is the characteristic feature of *M. marinum* infections, and the identification of the microorganism is a challenge. Culture and polymerase chain reactions may also be



Figure 4 *Pseudomonal* infection of external ear canal.

useful for identifying microorganisms^[62,63]. Localized lesions of swimming pool granuloma are self-limited and resolve with scar formation. Patients can be treated with clarithromycin, minocycline and trimethoprim-sulfamethoxazole; multidrug therapy with ethambutol and rifampin is needed if disseminated disease is present^[57]. Although rare in immunocompetent individuals, other mycobacteria, mainly *M. chelonae* and *M. fortuitum* may also cause cutaneous granulomas.

Fungal infections

Several studies have shown that swimming pools are contaminated with dermatophytes, which increases the risk of infection^[64]. Prolonged contact with water causes increased susceptibility to fungal infections, and Kamihama *et al*^[65] found that 63.6% of swimmers are dermatophyte carriers. However, the incidence of tinea pedis among aquatic athletes is not well studied, but early reports have found that it may be up to 10%^[52,66]. *Trichophyton mentagrophytes* accounts for up to 85% of infections and has been isolated from swimming pool decks and locker room floors^[65,66]. Tinea pedis (Figure 5) should be differentiated from pitted keratolysis, caused by *Corynebacteria*, which presents with the small punched-out depressions and an unpleasant smell. Tinea can be prevented by proper foot hygiene and patient education. Initial treatment involves topical antifungals twice daily for one to two months, but systemic antifungal agents may be used if refractory disease is present.

Viral infections

Swimmers and those who use common showers have a greater incidence of plantar warts (Figure 6) and molluscum contagiosum, although the exact incidence in athletes is unknown^[67-69]. Liquid nitrogen, curettage, and salicylic acid are helpful for removal of the lesion. There is not enough evidence to confirm that covering warts helps prevent spread^[70].

HAIR CONDITIONS

Aquatic athletes are prone to develop specific hair conditions. Green hair discoloration, often seen in light-



Figure 5 Tinea pedis on the foot of a swimmer.



Figure 6 Plantar warts on the foot of a swimmer.

haired athletes, is an effect of bleach and copper ion deposition that are used to kill algae^[71]. Seborrheic keratosis may also undergo green color change along with the hair due to copper ion deposition^[72]. Wetting the hair prior to chlorinated water exposure, prompt bathing after exposure, and use of a copper chelating shampoo may mitigate this problem. Hair discoloration coexisting with nail plate damage has also been described in Japanese swimmers and was considered to be a result of cuticle damage due to water friction and hypochlorous acid penetration^[73].

FRESHWATER DERMATITIS

Athletes who swim in marine water may be exposed to conditions transmitted by sea and river microorganisms. Jellyfish, anemones, sponges, corals and rarely Coelenterates (Cnidaria) are known to cause dermatitis and infection if traumatized (Figure 7). Dermatitis can also develop after contact with fish (jellyfish, stingray, weeverfish, stonefish), cones, or sea snakes (Hydrophiidae) due to their venomous toxin (Figure 8). Exposure may result in blistering and skin necrosis along with systemic symptoms, including respiratory muscle paralysis.

Another dermatitis, known as “seabather’s eruption”, is a pruritic eruption that appears under the bathing suit. It is caused by contact with swimming stages of the thimble jellyfish, *Linuche unguiculata*, and it is seen in Florida, the



Figure 7 Coral reef dermatitis that became infected secondary to trauma.



Figure 10 Squamous cell carcinoma on dorsal forearm.



Figure 8 Jellyfish sting on patella.



Figure 11 Squamous cell carcinoma on helix of ear.



Figure 9 Basal cell carcinoma on superior aspect of ear of swimmer.

Caribbean and Brazil. Cercarial dermatitis (swimmers' itch) develops after penetration of *Shistosoma's* larvae through human skin. The exact species of *Shistosomas* that cause the eruption, their animal hosts, and distribution is still under investigation^[74]. The condition is usually self-limited and presents as pruritic papules on exposed body surface areas, usually sparing the bathing suit region.

Onchocerciasis (river blindness) is caused by the filaria *Onchocerca volvulus*. Acquisition of the disease may occur after swimming in the Middle East, Africa or Latin America. Skin changes in onchocerciasis include nodule formation in the area of penetration, a pruritic rash,

lichenification, vitiligo-like changes, and atrophy after microfilaria migration. Early detection and treatment of filaria with ivermectin helps prevent river blindness.

ENVIRONMENT-RELATED CONDITIONS

Outdoor athletes are often exposed to undesirable environmental conditions such as excessive humidity, heat, cold, wind, and sunlight that may aggravate or cause different skin conditions. Sun exposure in athletes may be extreme and can lead to a higher risk of basal cell carcinoma (Figure 9), squamous cell carcinoma (Figures 10 and 11), and melanoma (Figure 12). Moehrle^[75] has found that burns were seen in triathletes despite of use of SPF 25+ sunscreens. However, data regarding the incidence of skin cancers in aquatic athletes is limited to several early studies. In 1992, a screening of surfers demonstrated an increased incidence of basal cell carcinomas in surfers, despite of their young age^[76]. Nelemans *et al*^[77] have shown that the odds of melanoma risk were higher in swimmers, but he contributed it largely to the chlorination of the water in swimming pools.

Use of SPF 30 or greater sunscreen and protective clothing is highly recommended to athletes^[78,79]. When counseling swimmers on sunscreen usage, one should advise use of a sunscreen that contains SPF 30 or greater, is water resistant, and provides broad spectrum UVA



Figure 12 Melanoma on the leg.

and UVB coverage. Swimmers should also be told to generously apply the sunscreen to all bare skin before going outdoors since it can take up to 15 min for skin to absorb sunscreen. Finally, they must be counseled to reapply sunscreen immediately after swimming or every two hours, whichever is sooner.

CONCLUSION

Aquatic athletes present a unique set of challenges for the dermatologist. It is important to educate athletes, parents, and coaches in an attempt to prevent short and long term dermatological sequela.

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From the outside-in: Epidermal targeting as a paradigm for atopic disease therapy

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pathophysiology of AD includes cutaneous inflammation, disrupted epidermal barrier function, xerosis and propensity to secondary infections. AD had previously been thought to arise from the systemic atopic immune response and therapies are therefore directed towards ameliorating Th2-mediated inflammation. However in recent years the focus has shifted towards primary defects in the skin barrier as an initiating event in AD. Links between loss-of-function variants in the gene encoding filaggrin and disrupted activity of epidermal serine proteases and AD have been reported. Based on these observations, a mechanism has been described by which epidermal barrier dysfunction may lead to inflammation and allergic sensitization. Exogenous and endogenous stressors can further exacerbate inherited barrier abnormalities to promote disease activity. Pathways underlying progression of the atopic march remain unclear, but recent findings implicate thymic stromal lymphopoietin as a factor linking AD to subsequent airway inflammation in asthma. This new appreciation of the epidermis in the development of AD should lead to deployment of more specific strategies to restore barrier function in atopic patients and potentially halt the atopic march.

Key words: Atopic dermatitis; Eczema; Filaggrin; Skin barrier; Kallikrein; Thymic stromal lymphopoietin; Allergic sensitization; Atopic march

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Core tip: Atopic diseases [including atopic dermatitis (AD), allergic rhinitis and asthma] are characterised by Th2-type inflammation. Research over the past decade has highlighted a crucial role for primary skin barrier impairment in the pathogenesis of AD and associated atopic phenotypes. Notably, the epidermal protein, filaggrin, epidermal serine proteases, and the pro-Th2 cytokine thymic stromal lymphopoietin, have been implicated in disease development. We review the evidence upholding a role for epidermal defects in the

Abstract

Atopic dermatitis (AD) is a chronic inflammatory skin disorder which can precede asthma and allergic rhinitis in a disease trajectory known as the atopic march. The

initiation of skin inflammation in AD, allergic sensitization and pathogenesis of the “atopic march”, and discuss the clinical implications of these findings.

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INTRODUCTION

Atopic diseases are reaching epidemic proportions^[1-4], affecting up to 20%-30% of children in developed nations^[5-7]. Prominent among these disorders are atopic dermatitis (AD, synonymous with atopic eczema), atopic asthma and allergic rhinitis. Atopic diseases constitute a major source of physical and psychosocial distress^[8-10] and account for a large portion of general paediatric practice^[11]. Atopic diseases demonstrate complex inheritance patterns and extensive phenotypic variation, and as such their aetiology is poorly understood^[12]. However the disorders appear to be underpinned by some common features: they are often associated with elevated levels of total serum IgE and with “atopy” - a personal and/or familial tendency to become sensitized and produce specific IgE against environmental allergens^[13] - but this association is hotly debated^[14,15]. Atopic diseases are thus presumed to arise as a result of interplay between inherited disposition and environmental factors^[16,17].

Longitudinal studies have revealed that approximately half of patients with AD develop asthma later in life and two-thirds go on to exhibit allergic rhinitis^[18]. This phenomenon, dubbed the “atopic march” describes the tendency for AD (usually apparent within the first two years of life) to precede the development of food allergies, asthma and allergic rhinitis in a typical temporal sequence^[17,19,20]. As AD is now a recognised “gateway” to the atopic march, its diagnosis in infants often prompts parental enquiries about disease prognosis as regards the development of subsequent disorders^[17]. AD therefore represents an important focus for interventions which may modify the natural course of atopic disease in high-risk patients.

AD is a chronic, inflammatory skin disease affecting an estimated 10%-20% of children and 1%-3% of adults^[6]. The skin of AD patients shows widespread xerosis (dryness) and a disturbance of epidermal barrier function. AD lesions (Figure 1A and B) are additionally characterised by pruritus and a propensity to secondary infections (Figure 1C). Th2-deviated inflammation is widely accepted in the pathogenesis of atopic disease however inflammation in AD may be biphasic, with an initial Th2 response leading to a Th0/Th1 dominated phase in chronic lesions^[21]. Traditionally it has been presumed that epidermal barrier dysfunction in AD is

a downstream consequence of primary immunologic abnormality (the “inside-outside” hypothesis)^[22]. In recent years this view has been challenged, with new evidence shifting the focus towards an “outside-inside” model in which epidermal abnormality is not the result but rather the stimulus of inflammation^[23]. In light of this concept, this review will evaluate the evidence upholding a pivotal role for the epidermis in atopic disease pathogenesis, and consider the practical implications for therapy.

BARRIER DISRUPTION IN ATOPIC DERMATITIS

The skin forms an essential barrier between the interior of the body and the external environment. Multiple protective roles are fulfilled by the epidermis and many are mediated by its outermost layer (and end product of keratinocyte differentiation), the stratum corneum (SC; Figure 2)^[24,25].

The SC comprises layers of protein-rich anucleate corneocytes interconnected by corneodesmosomes and enclosed within a coat of cross-linked proteins and lipids which together form the cornified envelope (CE)^[26]. The CE replaces the plasma membrane during terminal differentiation of keratinocytes into corneocytes and is in turn surrounded by a matrix of intercellular lamellar sheets enriched by 50% ceramides, 25% cholesterol and 15% free fatty acids (FFAs)^[27]. This amalgam of highly hydrophobic lipids, together with the CE, provides selective permeability to the epidermis.

Intercellular lipids are secreted as precursors from a unique epidermal organelle, the lamellar body (LB), along with the hydrolytic enzymes required for precursor transformation^[24]. At the granular cell-to-corneocyte transition, LBs fuse with the plasma membrane and discharge their contents into the intercellular space by exocytosis. LB extrusion also delivers antimicrobial peptides (AMPs) and the proteases and inhibitors which together orchestrate corneodesmosome cleavage during desquamation. Beneath the SC, the stratum granulosum (SG) provides a second barrier to environmental stressors; keratinocytes in the outer SG layers are intimately connected by tight junctions (TJs) - multi-protein complexes which control paracellular transport.

AD is characterised by widespread skin barrier dysfunction in both lesional and non-lesional skin^[28], as indicated by increases in transepidermal water loss (TEWL)^[29-31] and percutaneous penetration^[32]. This enhanced permeability has been attributed to abnormalities in the composition and architecture of extracellular lipid bilayers, reductions in total lipid and ceramide content^[33] and average ceramide chain length^[34], as well as an altered ceramide profile^[33,35]. The resultant barrier defect renders the skin of AD patients more permissive to the ingress of irritants, allergens and pathogens.

Atopic skin is more susceptible to bacterial and viral infections^[10], reflecting defects in the antimicrobial

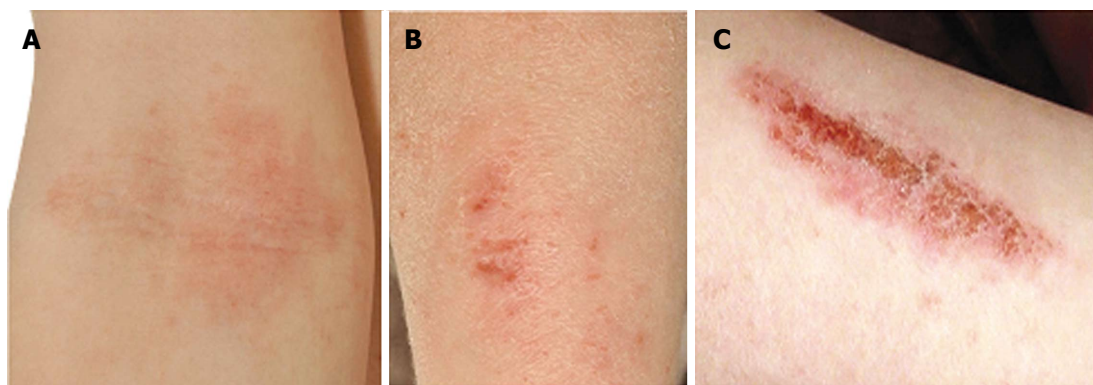


Figure 1 Clinical features of atopic dermatitis. A: Flexural eczema; B: Eczema and ichthyosis; C: Infected excoriation. Clinical photographs (University of Dundee Computing and Media Services, Ninewells Hospital and Medical School) reproduced with patient and/or parental consent.

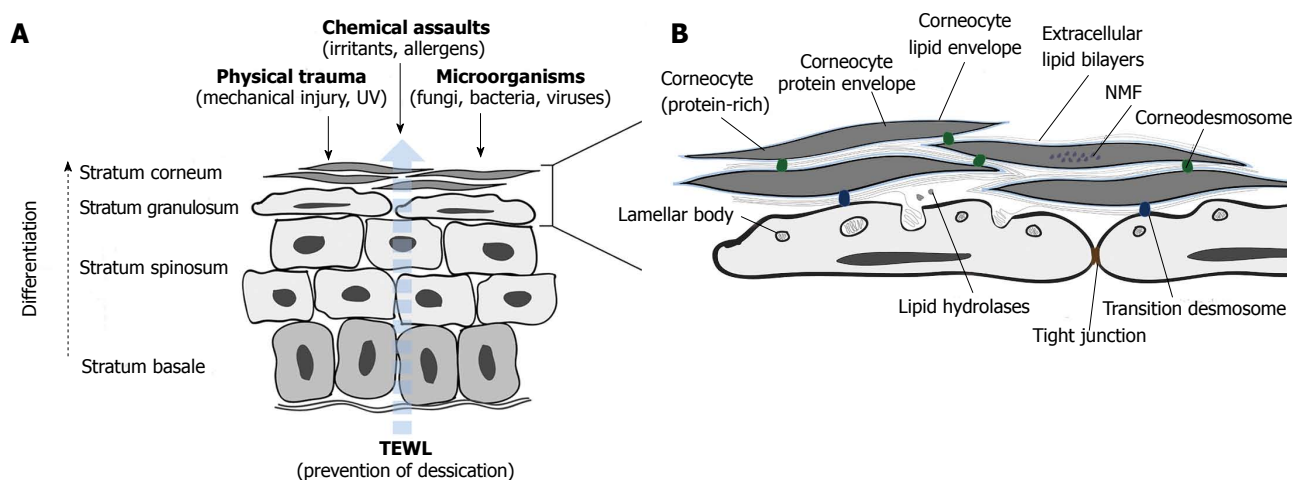


Figure 2 Outside-inside and inside-outside barrier functions of the epidermis. A: The epidermis forms a barrier against multiple external threats and prevents excessive transepidermal water loss (TEWL, indicated by the dashed blue arrow) from the interior of the body; B: Components of the stratum corneum (SC) and stratum granulosum (SG) barriers. During terminal differentiation of SG keratinocytes into corneocytes, lamellar bodies (LBs) fuse with the plasma membrane and their contents is extruded at the SG-SC interface. LB-derived lipids are processed and arranged into continuous bilayers parallel to the corneocyte surface using the covalently bound corneocyte lipid envelope (pale blue) as a scaffold. NMF: Natural moisturising factor.

barrier. 80%-100% of AD patients show colonisation by *Staphylococcus aureus* (*S. aureus*) compared with 5%-30% of non-atopic individuals^[36-38]. Flare-ups of AD are often associated with *S. aureus* infection, but whether infection represents a cause or consequence of inflammation remains unclear.

In healthy individuals, the desiccating surface, acidic pH and resident microflora of the skin cooperate with AMPs and lipids to provide protection against invading pathogens^[39]. In AD, a number of factors - including the defective epidermal barrier, attenuated innate immune response and increased bacterial adhesion - may promote skin colonisation by *S. aureus*^[40]. Among the human AMPs, levels of the cathelicidin, LL-37, and human beta-defensin-2 (hBD-2) are reduced in AD lesions^[41], and deficiency of sphingosine - a natural ceramide metabolite and potent anti-*S. aureus* agent - is also evident in the SC^[42]. Furthermore, *in vitro* studies have suggested that the Th2 inflammatory response in AD may feed back to the epidermis to promote bacterial colonisation^[41,43]. For

instance, IL-4, which is over-expressed in AD skin, has been reported to increase skin expression of fibronectin and fibrinogen - receptors which may facilitate attachment of *S. aureus* to the SC^[43].

Finally, it should be noted that several other protective functions of the skin barrier are impaired in AD. The skin of AD patients shows disrupted SC integrity (reflected by excess scale^[31]) and widespread xerosis, indicated by reduced SC water content^[30]. Additionally, pruritus - a prominent characteristic of AD^[44] - indirectly aggravates skin barrier impairment *via* the resultant scratching. The itch sensation is believed to result from cross-talk between the SC, keratinocytes, immune cells and nerve fibres^[45]. Excoriations directly disrupt the mechanical barrier of skin, creating additional portals of entry for pathogens. Moreover, it has been reported that a subset of AD patients develop serum IgE which is auto-reactive against a variety of keratinocyte proteins^[46]. Thus damage to the epidermis may itself intensify pruritus, driving the vicious "itch-scratch" cycle of AD^[45].

EPIDERMAL DIFFERENTIATION PROTEINS

Filaggrin-related barrier dysfunction

The outside-inside phenomenon of AD drew sharp attention from the research community when a significant link between loss-of-function variants in the gene encoding filaggrin (*FLG*) and AD was demonstrated in three European case collections^[47]. *FLG* mutations were originally identified as the cause of ichthyosis vulgaris (IV)^[48] and have since been demonstrated to be the strongest known risk factor for AD in European and Asian populations^[49-56]. Cases of AD associated with *FLG* mutations are more likely to be severe, persistent^[57-60], and complicated by secondary infections^[61,62] than non-*FLG*-related cases. Importantly, *FLG* mutations are now established as an independent risk factor at every step of the atopic march including allergic sensitization^[60,63-68], allergic rhinitis^[60,64,66-68], food allergies^[69,70] and the sub-phenotype of asthma associated with AD^[7,60,63,64,66-68].

Profilaggrin is a large precursor molecule (> 400 kDa) containing 10, 11 or 12 tandem repeats of the 37 kDa filaggrin peptide^[71]. Insoluble, heavily phosphorylated profilaggrin is the main constituent of keratohyalin granules in the SG. During terminal differentiation, profilaggrin is dephosphorylated and cleaved in a multistep process to release filaggrin monomers, which bind and aggregate keratin filaments, facilitating the collapse of the cytoskeleton and contributing to the flattening of keratinocytes to produce corneocytes^[72]. Filaggrin, along with several other cytosolic proteins, is cross-linked into the CE by transglutaminases. As corneocytes move outwards through the SC, filaggrin detaches from the CE and undergoes further degradation within the cytosol, ultimately generating a hygroscopic pool of amino acids and derivatives thereof [including pyrrolidone carboxylic acid (PCA) and trans-urocanic acid (UCA)], contributing to natural moisturising factor (NMF)^[73]. NMF appears to play a role in multiple aspects of epidermal homeostasis including SC hydration^[73,74], UV photo-protection^[75], immunosuppression^[76,77] and by acting as a natural acidifier, modulation of enzymatic activity^[78-80] and antimicrobial defence^[81].

Each of the reported null mutations in *FLG* has an equivalent biological effect, producing a truncated profilaggrin molecule^[82]. This precursor cannot be fully processed into filaggrin monomers thus individuals with two *FLG* null alleles (homozygous or compound heterozygous, *FLG*^{-/-}) exhibit an almost complete absence of functional filaggrin^[82]. Inherited filaggrin deficiency results in both intracellular and extracellular changes in keratinocyte architecture and altered epidermal physiology. Histological examination of skin from *FLG*-deficient AD and IV patients reveals increased SC thickness^[83] and a granular cell layer that is either strongly reduced or absent^[84]. At the ultrastructural level, reduction in filaggrin correlates with perinuclear retraction of granular cell keratin filaments, impaired corneocyte integrity and reduced corneodesmosome density, concomitant with reduced SC cohesion^[84]. The molecular mechanisms by which deficiency in filaggrin - an intracellular protein -

impairs the paracellular skin barrier in AD remains unclear. However it is plausible that the cytoskeletal abnormalities associated with filaggrin deficiency impede the granular cell-to-corneocyte transition and thus formation of the SC extracellular environment. Consistent with this hypothesis, impaired cargo loading into LBs, partially compromised LB secretion and disorganised lamellar bilayers are observed in the skin of AD and IV patients^[84,85]. Reduced expression of SG TJ proteins^[84] is also likely to further contribute to barrier impairment.

Alternatively or in addition, it may be the biochemical consequences of filaggrin deficiency that are important in AD pathogenesis. *FLG* null mutations effect a dose-dependent reduction in SC NMF levels^[86-89], which in turn correlate inversely with skin surface pH^[87,89] and TEWL^[89]. Additionally, *FLG* exhibits intragenic copy number variation, and a lower number of repeats correlates significantly with AD risk^[90], SC UCA levels^[90] and the presence of self-perceived “dry skin”^[91]. Thus enhanced TEWL in *FLG*-associated AD can be explained in part by reduced SC hydration; deficiency of hygroscopic NMF components would be expected to result in lower SC water content hence a steeper water gradient across the epidermis. In addition, altered skin pH is likely to perturb the natural balance of enzymatic activities in the SC. The elevated pH of AD patient skin would be predicted to favour the net activity of SC-resident serine proteases (SPs)^[78,80] whilst reducing that of key SC lipid biosynthesis enzymes. SP hyperactivity drives premature degradation of corneodesmosomes and lipid-processing enzymes^[80], likely contributing to defective lamellar bilayer formation. In line with the proposed mechanisms, it has been demonstrated that levels of filaggrin breakdown products correlate with aberrant SC lipid organisation and decreased barrier function in AD patients^[34,86,92]. A recent study using a reconstructed human epidermis model has suggested that filaggrin deficiency may also promote enhanced epidermal sensitivity to UVB^[93], but this connection remains to be demonstrated in patients.

Finally, filaggrin deficiency in AD has implications for the antimicrobial skin barrier. As described, the natural acidity of the SC in healthy individuals provides innate antimicrobial protection - a function which is likely to be diminished in NMF-deficient AD patients. Furthermore, recent data suggest that filaggrin may play a unique role in protection against *S. aureus* infection, by mediating keratinocyte secretion of sphingomyelinase - an enzyme which reduces the number of *S. aureus* α -toxin binding sites on the keratinocyte surface^[94]. These findings indicate a mechanism by which filaggrin-deficient skin may be preferentially targeted by *S. aureus*-induced cytotoxicity. Clinically, the consequences of *FLG* null mutations in AD manifest as a 7-fold increase in the risk of recurrent bacterial infections relative to wild-type *FLG* patients^[62].

Thus our understanding of the mechanisms by which *FLG* genotype translates to disease phenotype remains incomplete. Furthermore, recent findings indicate additional levels of complexity to the *FLG*-AD

relationship which are likely to influence the pathogenic mechanisms discussed above. For instance, preliminary data indicate that epigenetic, as well as genetic variation can influence disease outcome. Indeed, a recent study has shown that methylation of a specific CpG site adjacent to *FLG* can modify the influence of *FLG* null mutations on AD risk^[95]. Whether inherent variation in enzymes involved in profilaggrin biosynthesis and maturation can also affect atopic disease pathogenesis has yet to be ascertained. Future lines of investigation should clarify how individual variations in filaggrin biology at the DNA, RNA and protein levels interact to determine distinct atopic phenotypes.

Epidermal differentiation genes in addition to *FLG*

Whilst inherited variation in *FLG* undoubtedly contributes to skin barrier dysfunction in AD, *FLG* null variants are carried by less than one-third of European patients with AD^[66] and broad defects in epidermal differentiation are characteristic of the disease regardless of *FLG* genetic status^[96]. Taken together, these observations suggest that other factors must modify epidermal homeostasis. Genetic association studies have identified links between AD and gene variants distinct from *FLG* but also located on chromosome 1q21 within the Epidermal Differentiation Complex - a region comprising over sixty genes essential for epidermal structure and function^[97]. Of note, a single nucleotide polymorphism (SNP) 7 kb downstream of the gene encoding hornerin (*HRNR*) and an 8-amino acid insertion in the gene encoding small proline-rich protein 3 (*SPRR3*) have been identified as risk factors for AD^[98,99]. Additionally, a recent study by Margolis *et al.*^[100] using whole-exome sequencing and targeted analysis in an African American cohort has identified mutations in *FLG2* (encoding filaggrin-2) that show a significant association with persistent AD - the first established link between a skin barrier gene and AD in subjects of African descent. However, it should be noted that these risk variants lie within a block of linkage disequilibrium and it remains possible that they are tagging unidentified variants within *FLG*. Hornerin and filaggrin-2 are S100-fused type proteins, and thus share a structural organisation similar to filaggrin. Both proteins mirror the subcellular localisation of filaggrin in the differentiating epidermis are believed ultimately (along with *SPRR3*) to become incorporated into the CE^[97]. The precise contributions of these proteins to skin barrier function remain unknown, but available data indicate that filaggrin, hornerin and filaggrin-2 have overlapping or complementary functions in the epidermis^[97] and the expression of each may be down-regulated in AD skin^[96].

TJs comprise both cytoplasmic and transmembrane proteins, key among which are the claudins, representing the main determinants of barrier selectivity against macromolecules^[101]. Claudin-1 expression is down-regulated in non-lesional AD skin and inversely correlated with Th2 cytokines. Variants within the claudin-1 gene, *CLDN1*, have shown association with AD in two ethnically distinct North American populations^[102]. Interestingly, this

study also demonstrated links between *CLDN1* variants and AD severity, total serum IgE and asthma in subjects of African, but not European ancestry. Given that at present, *FLG* null mutations appear to be considerably less prevalent in African populations relative to European or Asian cohorts^[89], these findings (together with those of Margolis *et al.*^[100] regarding *FLG2*) indicate population specificity in the genetic mechanisms which dominate skin barrier dysfunction in AD.

Finally, protein regulators of lamellar bilayer formation have been implicated in the pathogenesis of AD. Mutations in the gene encoding fatty acid transporter 4 (*FATP4*)^[103] and *MATT* (encoding matrinin, a component of the LB secretory system in flaky tail (*maft*) mice^[104]) are associated with increased risk of AD^[105]. *Maft* mice harbour mutations in both *Flg* and *Matt* genes, and have been used for many years as an experimental model of AD. However, it has recently been shown that *ma/ma* mice, which carry mutations in *Matt* but not in *Flg*, exhibit enhanced TEWL and decreased SC hydration, and develop the spontaneous dermatitis and atopy exhibited by *maft* mice to a greater extent than the filaggrin-null (*Flg*^{-/-}) mice^[104-106]. *Matt* may therefore play a greater role than *Flg* in driving the dermatitis phenotype in *maft* mice, supporting a key role for SC lipid secretion in the development of AD.

Thus skin barrier genes may act alone or in combination with *FLG* to modify AD pathogenesis. Whether or not the same genes are also associated with subsequent steps of the atopic march remains to be elucidated.

Epidermal proteases and protease inhibitors

Maintenance of epidermal physiology is dependent on the coordinated activities of skin-resident proteases and anti-proteases. Perturbation of this balance in favour of protease hyperactivity can result in pathogenic barrier disruption, as exemplified in Netherton syndrome (NS). NS is an autosomal recessive disorder featuring ichthyosis and atopic manifestations, which is caused by loss-of-function mutations in *SPINK5*^[107] - the gene encoding lympho-epithelial Kazal-type-related inhibitor (LEKTI)^[108]. In healthy skin, proteolytic LEKTI fragments specifically co-localise with and regulate the activity of multiple SPs, including members of the kallikrein (KLK) family. KLKs are central to desquamation^[109] and also indirectly promote profilaggrin proteolysis^[110]. In the skin of NS patients, residual LEKTI expression correlates inversely with enhanced KLK activity^[111] resulting in dramatic SC thinning and attenuation of the permeability barrier through unrestricted degradation of corneodesmosomes^[109] and lipid-processing enzymes^[111] respectively. Permeability barrier function may additionally be compromised through activation of protease-activated receptor 2 (PAR-2), which is expressed in nucleated epidermal layers and can be induced by specific SPs to down-regulate LB secretion^[112-114].

A number of association studies have identified SNPs in *SPINK5* which are associated with AD risk in different ethnicities^[115-119]. In particular, one such variant, LEKTI E420K, has also been linked to elevated serum IgE^[118], food allergies^[116], AD severity^[116] and AD-

associated asthma^[120]. *In vitro* analysis has shown protease hyperactivity resulting from the E420K mutation to result in increased corneodesmosomal destabilisation and premature profilaggrin proteolysis^[121], suggesting a functional pathway by which E420K may contribute to filaggrin deficiency and the development of AD. In addition to *SPINK5* polymorphisms, a mutant allele of the *CSTA* gene (which encodes the skin-resident cysteine protease inhibitor, cystatin A) has been reported to associate with AD in a small UK cohort^[122]. Fewer data exist for associations between AD and epidermal protease genes; an association between AD and a putative gain-of-function insertion in the 3' UTR of *KLK7* has been described in a British case-control study^[122] but failed to be confirmed in subsequent investigations^[123,124].

BASIS FOR BARRIER-INITIATED INFLAMMATION

The above pathways together may account for the skin barrier phenotype in AD, but the mechanisms linking epidermal disruption and concomitant allergic inflammation remain unclear. The *maft* and more recently generated *Flg*^{-/-} mouse models^[106,125] serve as useful systems in which to study the aetiology of the immune response in the context of inherited barrier impairment. Although showing differences in disease phenotype, both mice exhibit increased percutaneous allergen penetration and a reduced inflammatory threshold to skin irritants and allergens^[106,126]. Based on these observations, it is widely postulated that inflammation in AD is a secondary reaction to increased entry of allergens and irritants through the compromised skin barrier. Whilst this is yet to be confirmed in human subjects, it is worth noting that AD patients with *FLG* null mutations have a significantly increased risk of allergic sensitization^[60] and irritant contact dermatitis^[127], and display elevated numbers of allergen-specific CD4⁺ T cells compared with wild-type *FLG* patients^[128]. Furthermore, it seems likely that in addition to the inflammatory response to penetrating antigens, barrier impairment itself may intrinsically promote downstream inflammation. For instance, elevated SP activity (induced in AD along the pathways described above) not only promotes epidermal barrier breakdown but leads to increased release of active IL-1 α and IL-1 β ^[129,130] from the corneocyte cytoplasm, thereby initiating inflammation. Furthermore, SP hyperactivity may stimulate inflammation indirectly by accelerating the degradation of transition desmosomes, leading to secretion of IL-1 β , IL-8 and TNF- α from mechanically stressed keratinocytes^[131]. Finally, accumulated data indicate that following activation by SPs, PAR-2^[131], together with pro-inflammatory cytokines, induces NF- κ B-mediated over-expression of the pro-Th2 cytokine, thymic stromal lymphopoietin (TSLP)^[132], and IL-6^[133]. Evidence in support of the latter pathway has been observed in studies of *maft* mice and *FLG* knock-down keratinocytes *in vitro*^[134], suggesting that this immunologic cascade may operate downstream of a primary filaggrin deficiency.

Whilst these data are compelling, the same pathogenic

mechanisms have yet to be demonstrated in human AD. Nonetheless, the strength and number of independent associations between *FLG* and atopic disorders greatly surpass those of any other gene expressed in the skin to date^[123]. As such, filaggrin deficiency is widely regarded as a primary abnormality leading to skin inflammation in AD^[135-138]. Leading on from this, a putative pathogenic pathway has been described in which the reduction in filaggrin acts as a central stimulus for increased SP activity, which in turn triggers the inflammatory response^[139]. AD patients with *FLG* null mutations exhibit increased skin levels of IL-1 cytokines, in a manner inversely correlating with NMF levels^[87]. This observation has been attributed to pH-induced stimulation of SPs, which can promote inflammation by the mechanisms described above^[139]. However, no correlation between SC pH and levels of either IL-1 α or IL-1 β could be demonstrated in the same study, and recent findings have indicated that *FLG* status is not an essential determinant of SC pH^[79,93,106]. Thus whilst these data do not rule out a role for skin pH changes in initiation of inflammation in *FLG*-related AD, it is likely that protease activity and consequently IL-1 levels are modulated by additional factors. For instance, Kezic *et al*^[87] have proposed that increased SC calcium concentration (resulting from reduced SC hydration) may favour the activation of calcium-dependent SPs, but based on our current knowledge, this pathophysiological pathway remains entirely speculative.

INSIDE-OUTSIDE PATHOGENIC MECHANISMS

Despite the undisputed involvement of *FLG* null variants in the atopic march, it is important to note that filaggrin deficiency is observed in AD patients even in the absence of known *FLG* mutations^[96]. Whilst this may be explained in part by other forms of genetic regulation, it is apparent that a number of additional factors can reduce expression of functional filaggrin, resulting in barrier disruption. In particular, accumulating evidence points to components of the acquired immune response as key players in endogenous barrier impairment, prompting the proposition of a self-sustaining “outside-inside-outside” pathogenic loop in AD^[139].

Studies in *maft* mice have shown that following initial sensitization, further defects in barrier function occur, suggesting exacerbation of the primary barrier impairment by the induced inflammatory response^[126]. Consistent with this, the Th2 cytokines, IL-4, IL-13, IL-22 and IL-25, which are over-expressed in AD lesions, have been shown to inhibit expression of filaggrin^[136-138] and profilaggrin-processing enzymes^[140,141] *in vitro*. Inflammation in AD may also compromise skin barrier function by a number of filaggrin-independent mechanisms. The epidermal AMPs, LL-37, hBD-2 and hBD-3, are down-regulated in a Th2-dependent manner^[141,142-144] and roles for Th2 cytokines in disruption of SC lipid synthesis^[145-147], SC protease activity^[148,149] and multiple processes in epidermal

differentiation^[147,149-151] have been reported. Finally, whilst not endogenously perturbing the skin barrier *per se*, the cytokines TSLP and IL-31 induce itch^[152,153], thereby aggravating the itch-scratch cycle.

ENVIRONMENTAL STRESSORS PLAY UPON BARRIER DEFECTS TO EXACERBATE DISEASE ACTIVITY

The avoidance of exogenous irritants is an important part of atopic disease management. Diverse environmental factors are known to exacerbate atopic disorders, but several are now recognised as having detrimental effects on the skin barrier. For instance, prolonged exposure to reduced ambient humidity (as may occur in centrally heated homes) has been shown to accelerate TEWL and promote profilaggrin proteolysis^[73], potentially driving further depletion of cutaneous filaggrin^[139]. External modifiers of skin surface pH may also aggravate disease activity *via* enzyme-mediated pathways; use of neutral-to-alkaline soaps is known to induce SC thinning and precipitate flares of AD^[154]. Protease activity in the epidermis of AD patients may be further intensified by airborne proteins; proteolytic allergens produced by house dust mites and cockroaches have been shown to penetrate the skin and can exacerbate barrier dysfunction^[155,156] both directly, by degrading barrier components^[157,158] and indirectly, through activation of PAR-2^[159-161]. Staphylococcal infection also has a number of implications for skin barrier function. Essential *S. aureus* surface proteins confer resistance to the bactericidal action of human epidermal FFAs and AMPs^[162] and once established on the skin, coagulase-negative staphylococci can secrete peptidases and lipid hydrolases^[163] which may further erode the skin barrier. Indeed it has been shown that elevated levels of the enzyme ceramidase (which catalyses the degradation of ceramide to sphingosine and FFAs) are secreted by the bacterial flora of AD patient skin relative to healthy controls^[164]. Finally, psychological stress (PS) may precipitate atopic diseases^[165] by disturbing the permeability barrier^[166,167], SC integrity^[166] and antimicrobial defences^[168] in the skin of mouse models, *via* a mechanism thought to be mediated by increased production of endogenous glucocorticoids^[167-169].

ALLERGIC SENSITIZATION AND TSLP: THE ATOPIC MARCH

The mechanistic link between AD and subsequent phenotypes in the atopic march remains unclear and has been the subject of intensive research in recent years. Generally, current data favour a model in which the downstream systemic effects of allergen penetration through the impaired skin barrier cause immune cells to mount an exaggerated inflammatory response at any allergen-exposed epithelial surface^[136,154,170]. This theory fits with several observations: (1) AD is usually the first manifestation of atopy^[18]; (2) *FLG* is not expressed in

bronchial airways^[171] nor the oesophageal epithelium beyond the oro-pharyngeal mucosa^[172], suggesting that filaggrin does not directly influence permeability of these epithelia; and (3) allergic sensitization induced by epicutaneous exposure to peanut allergen inhibits subsequent oral tolerance in mice^[173].

Central to the uncertainty over the atopic march is the strength of the connection between early allergic sensitization in AD and the risk of allergic airway disease, with the epidemiological data being somewhat inconsistent^[14]. Functional studies on the atopic march have identified a prominent role for the cytokine TSLP as a promoter of the Th2 response in AD and a trigger linking epicutaneous sensitization to subsequent asthma^[174,175]. TSLP is expressed primarily in lung and skin epithelia^[176] where it is recognised as a “master switch” from epithelial barrier disruption to Th2 inflammation^[177,178]. Accordingly, TSLP expression is up-regulated in the SC of AD patients compared with healthy subjects^[179]. Notably, a recent study using mice in which TSLP is selectively and inducibly ablated in epidermal keratinocytes suggests that skin-derived TSLP is essential for skin allergic inflammation and epicutaneous sensitization, which in turn leads to allergic asthma^[180]. This study, in contrast to previous findings^[181,182], indicated that keratinocyte-derived TSLP acts as an essential “adjuvant” to the Th2 response induced by topical allergen treatment, but that skin expression of TSLP caused by barrier disruption alone (*i.e.*, without allergen) is not sufficient to promote the full inflammatory phenotype. It is also noteworthy that in this model sensitization was achieved through barrier-defective skin (as opposed to intraperitoneal or intradermal injection of allergen^[181,183]), followed by airway challenge, conditions representative of those in human AD. Airway inflammation appears to require an antigen-specific memory CD4⁺ T cell response^[180,183], but occurs independently of TSLP presence in the lung^[175,180,183] and circulating TSLP^[183], suggesting that skin-derived TSLP is both necessary and sufficient for manifestation of asthma symptoms.

The relative importance of TSLP in the human atopic march remains to be clarified. A recent study in an American paediatric AD cohort identified the *TSLP* variant rs1898671 (which produces attenuated TSLP) as protective against the development of persistent AD^[184] however no association with comorbid asthma was identified^[184]. It has further been demonstrated that risk of childhood asthma is influenced by epistasis between *SPINK5* and *TSLP*^[185]. The authors postulate that *TSLP* and *SPINK5* function in a common pathway in which LEKTI deficiency ultimately leads to TSLP production, an exaggerated Th2 response and allergic lung inflammation^[185]. Although the analysed cohort comprised both asthmatic patients with and without concomitant AD, these findings support the view that the systemic consequences of an epidermal pathway are sufficient to induce inflammation at remote epithelia in the human atopic march (Figure 3). Thus it will be interesting to see if evidence for a similar pathway in patients with AD-associated asthma emerges in the

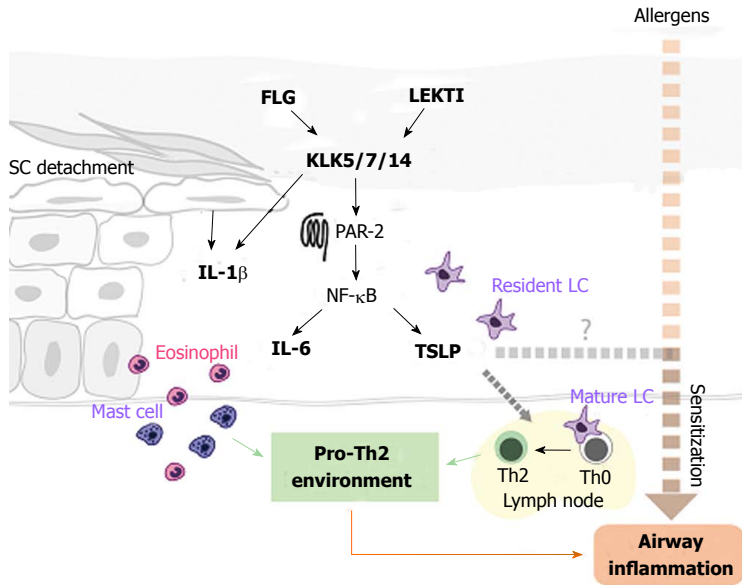


Figure 3 Hypothesised pathways from skin barrier impairment to inflammation and the atopic march. Deficiencies in FLG and LEKTI promote enhanced activity of KLKs, which induce over-expression of TSLP and IL-6 through the PAR-2-NF-κB pathway. KLK hyperactivity also degrades transition desmosomes, inducing the release of pro-inflammatory cytokines from mechanically stressed keratinocytes. The pro-inflammatory environment triggers eosinophil and mast cell recruitment and activation. TSLP activates LCs which promote the differentiation of naïve (Th0) T cells into Th2 cells in lymph nodes. Allergen ingress (dashed red arrow) promotes allergic sensitization and may, with TSLP, stimulate downstream airway inflammation. FLG: Filaggrin; LEKTI: Lympho-epithelial Kazal-type-related inhibitor; KLKs: Kallikrein proteases; TSLP: Thymic stromal lymphopoietin; IL-6: Interleukin-6; IL-1β: Interleukin-1β; LCs: Langerhans cells; SC: Stratum corneum; PAR-2: Protease-activated receptor-2; NF-κB: Nuclear factor kappa-light-chain-enhancer of activated B cells.

coming years. Together, the above findings reinforce the attractive idea that early and aggressive intervention directed towards the skin barrier may impede the progression from AD to subsequent airway inflammation in atopic patients.

CLINICAL IMPLICATIONS: A PARADIGM FOR THERAPY?

The pathogenic mechanisms described above create a strong case for prioritising protection and restoration of the skin barrier in atopic individuals. The current foundations of general AD management include the avoidance of triggering factors and optimal skin care^[165], with efforts to address epidermal barrier defects centred on the regular use of emollients. Emollients help to hydrate the skin and soothe pruritus^[186]; when applied liberally, they can provide a short-term artificial barrier to reduce TEWL and protect against the penetration of allergens and irritants. The benefits of emollient therapy in controlling the cutaneous symptoms of AD are accepted on the basis of clinical experience^[186]. A recent feasibility study of early emollient therapy for AD prevention has shown promising preliminary results^[187], but further trials are warranted before the efficacy of this approach can be confirmed. Thus far, emollient monotherapy has rarely proved sufficient for disease resolution in moderate-to-severe AD, in which the use of anti-inflammatory agents is often necessary for exacerbation management^[165].

However, corticosteroids and topical calcineurin inhibitors are associated with a spectrum of cutaneous and systemic side effects^[165,188] including the impairment of both permeability and antimicrobial barrier functions in AD skin^[189-191]. Interestingly, selected emollients have also been reported to disrupt the skin barrier. The majority of over-the-counter (OTC) moisturisers contain non-physiological ingredients (*e.g.*, petrolatum and lanolin) which function by undefined biological mechanisms and in certain cases have been found to compromise SC

integrity, permeability barrier function^[192] and epidermal differentiation^[193]. The above findings, together with recent advances in our understanding of skin pathophysiology, have shifted interest towards novel “barrier replacement strategies”. Such therapies aim to correct underlying biochemical abnormalities; they are based upon physiological components and may therefore minimise the likelihood of an unfavourable response^[194]. For instance, prescription barrier repair creams (BRCs) are based on SC lipids and differ from their non-physiological counterparts in that they are taken up by keratinocytes, packaged into LBs and ultimately secreted to form lamellar bilayers^[195]. In accordance with the lipid deficits in AD skin, a number of “designer” ceramide-dominant and triple-lipid-based barrier repair formulations have now been tested in AD patients^[196]. Trials of one ceramide-dominant BRC demonstrated significant reductions in disease severity^[197,198] and marked restoration of the epidermal barrier when used as adjunct to topical anti-inflammatories^[197]. Moreover, improvements in severity, pruritus and sleep were comparable to the effects of the TCS fluticasone^[198], suggesting that BRCs hold potential steroid-sparing effects. However small study size, variation in study design, commercial pressures and the possibility of publication bias make such data difficult to interpret. Furthermore, it is worth noting that the direct comparison of OTC emollients with BRCs has demonstrated equal efficacy for the treatment of mild-to-moderate AD^[199], with a notably significant cost disparity between the two treatments. Thus the prescription of BRCs over cheaper and simpler OTC alternatives remains contentious. Large-scale randomized control trials will be necessary to determine whether BRCs are indeed superior for long-term management of AD.

The identification of filaggrin deficiency as a strong predisposing factor for atopic disorders has opened the prospect of filaggrin or NMF restoration as another barrier repair strategy. Topically applied recombinant filaggrin peptide has been shown to penetrate to the SG of reconstructed human epidermis, and is internalised and

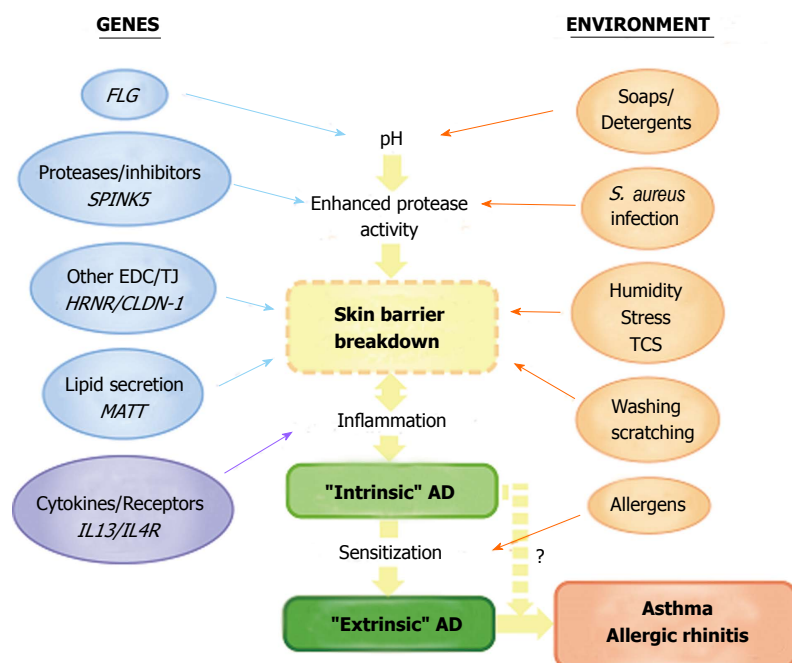


Figure 4 The combination of genetic and environmental factors in the natural history of atopic disease. Note that some allergens (e.g., house dust mite allergens) can also contribute to total protease activity in the skin. Stress: Psychological stress; TCS: topical corticosteroids; *S. aureus*: *Staphylococcus aureus*.

processed to restore epidermal structure in *maft* mice^[200]. Furthermore, a recent study has identified a candidate drug that promotes filaggrin mRNA and protein expression *in vitro*, and suppresses the development of skin inflammation when administered orally in the NC/Nga mouse model of AD^[201]. These findings, whilst preliminary, hold promise for filaggrin restoration as part of future AD therapy. Clarification of the relative importance of the functions of profilaggrin, filaggrin and filaggrin degradation products will be useful in directing research in this area^[202].

Thus the new appreciation of skin barrier pathophysiology should encourage greater clinical emphasis on the optimization of skin care and avoidance of barrier-breaching products in neonates and children. Yet a number of important questions remain. For instance, can restoration of the permeability barrier alone help to normalise epidermal gene expression? Will barrier-based interventions also protect against inflammation and the development of comorbid atopic disorders in patients with AD? Long-term follow-up studies with examination of treatment efficacy at the molecular level will be required. Finally, additional potential treatment avenues (e.g., selective inhibition of SPs and TSLP) have yet to be explored and it is expected that further elucidation of the mechanisms of skin barrier dysfunction in the coming years will identify practicable therapeutic targets.

CONCLUSION

The discovery of loss-of-function mutations in *FLG* has led to a new appreciation of skin barrier dysfunction as primary pathogenic mechanism in atopic disease. Undoubtedly one of the greatest challenges for future research is the dissection of the complex interactions between multiple genetic, environmental and immunologic factors which influence disease pathogenesis (Figure 4). Some interactions with *FLG* have already been identified.

Of note, the combined occurrence of mutations in *FLG*, an epidermal gene, and in the genes encoding IL-10 and IL-13, mediators of acquired immunity, have been shown to have a multiplicative effect on AD risk^[203] and inter-regulation by SC and SG skin barriers at the mRNA and protein levels has been reported^[101,204]. These interactions, whilst yet to be demonstrated in human patients, may present further difficulties in determining the relative importance of individual barrier components in AD pathogenesis. Progress in the molecular genetics of atopic disease has been accelerated by advances in next-generation sequencing techniques, but the additional complexity of multiple gene-gene and gene-environment interactions requires further development of bioinformatics analysis. The integration of genetic, transcriptomic and proteomic analyses is also computationally demanding. However, a recent transcriptomic analysis of AD skin used *FLG* genotype to stratify data and has offered insight into novel pathways and predicted functional networks^[205]. The expanding understanding of epigenetic variation is also predicted to contribute further novel mechanistic insights in the coming years.

Understanding the interplay between atopic genes and environmental factors will be vital to explaining (and perhaps controlling) the rising prevalence of atopic diseases. This will require long-term epidemiological studies in which early genetic profiling of *FLG* and other disease genes is coupled with careful monitoring of patient environment. Such studies may help to explain how specific gene variants act in the context of different external insults to induce a range of related yet distinct atopic phenotypes. Evaluation of *FLG* genetic status is not commonplace in pharmacogenetic studies or current clinical management of AD. However careful clinical examination can identify *FLG* null genotype^[206] and as the multiple influences of filaggrin on atopic disease trajectory are clarified, this will benefit clinical care and

prognostic predictions. More detailed knowledge of genotypes associated with atopic phenotypes could in the future help to direct the prescription of personalised therapeutic regimes, including focused instructions for disease prevention and targeted treatment. Thus early control of skin barrier function in high-risk patients may in future prevent allergic sensitization and what had previously been considered the inevitable path through the atopic march.

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Frontal fibrosing alopecia update

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and treatment modalities of FFA.

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Core tip: Frontal fibrosing alopecia (FFA) is a recently described form of primary cicatricial alopecia, characterized by progressive recession of the frontotemporal hairline and eyebrow loss, occurring predominantly in postmenopausal women. The incidence of FFA has increased significantly during the last decade and we may be facing an epidemic of the disease. Because this condition causes permanent hair loss, prompt diagnosis and treatment are essential for obtaining optimal outcome. This article reviews existing knowledge on epidemiology, etiopathogenesis, clinico-histological features, diagnosis, and treatment modalities of FFA.

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Abstract

Frontal fibrosing alopecia (FFA) is a recently described form of primary cicatricial alopecia, characterized by progressive recession of the frontotemporal hairline and eyebrow loss, occurring predominantly in postmenopausal women. The incidence of FFA has increased significantly during the last decade and we may be facing an epidemic of the disease. Because this condition causes permanent hair loss, prompt diagnosis and treatment are essential for obtaining optimal outcome. This article reviews existing knowledge on epidemiology, etiopathogenesis, clinico-histological features, diagnosis,

INTRODUCTION

Frontal fibrosing alopecia (FFA) is a relatively recently recognized form of primary cicatricial alopecia (PCA), characterized by progressive recession of the frontotemporal hairline and eyebrow loss, occurring predominantly in postmenopausal women. It was described by Kossard^[1] in 1994. The number of patients with this condition has markedly increased over last decade and there are dermatologists who believe that we are facing a possible epidemic of this challenging disease^[2-7]. Due to the clinical and histologic similarities with lichen planopilaris (LPP), many dermatologists consider it to be a clinical variant

of LPP with marginal distribution. Both entities show perifollicular erythema and follicular hyperkeratosis, and lichenoid lymphocytic infiltrate along with perifollicular fibrosis leading to hair follicle destruction^[1,4,5,7-11]. The cause of “marginal march” in FFA is unknown and therefore whether it is an LPP variant or a distinct entity with shared clinical features, remains to be determined^[4,12,13]. The pathogenesis of FFA is poorly understood, although an autoimmune reaction and hormonal androgen-driven factors seem to play a role^[4,9,13]. Several familial cases have been reported that raise the possibility of a genetic inheritance factor^[3,14,15]. Some researchers have also suggested that there may be an environmental trigger for the disease^[16,17]. The natural history of FFA is variable, although slow progression with spontaneous remission is the most frequently reported outcome^[2,8,13,18]. The general uncertainties with this entity begin with an unknown origin and pathogenesis and continue with the difficulty of finding effective treatment. A range of topical as well as systemic treatments has been disappointing. Several researchers have reported stabilization with topical and intralesional corticosteroids, antibiotics, hydroxychloroquine, immunomodulators, and 5-alpha-reductase inhibitors^[2-5,7,11,13,18-21].

EPIDEMIOLOGY

In 1994 Kossard^[1] described 6 postmenopausal women with distinctive progressive scarring alopecia affecting the frontal hairline and frequently extending to the temporal and parietal regions. This contrasted with the usual multifocal appearance of LPP, yet had similar histopathological features. Kossard^[1] named this entity “postmenopausal frontal fibrosing alopecia” and further characterized it clinically and histologically in subsequent studies^[1,8]. Since 1994, numerous case reports and studies on FFA have been published. Several reports have included men and premenopausal women, and it has been proposed that “postmenopausal frontal fibrosing alopecia” is better termed “frontal fibrosing alopecia”. The incidence of FFA is unknown, although most dermatologists agree that there has been an increase in the number of patients with this condition in recent years^[2-7]. A ten-fold increase in the number of cases seen annually over the last decade was described by MacDonald *et al.*^[5]. According to reports published to date, over 85% of the patients reported were white postmenopausal women^[2-5,17,18,20]. However, this condition has also been reported in Black, Asian, and Hispanic male and female patients^[3,4,20]. Several studies showed a high incidence of early menopause, up to 17%, compared with an incidence of 6% in the general population^[2,3]. In addition, several reports described that in a considerable number of women the menopause had been surgically precipitated, post-hysterectomy^[2,3]. The course of the disease does not seem to be affected by the onset of hormone replacement therapy^[4,21]. Age of onset of the disease ranged from 18 to 87 years with the highest incidence in the sixth decade^[2-5,7,20]. One study showed an

earlier age of onset of FFA in black patients, with 74% of those cases starting prior to menopause^[22], yet another study described the age of onset to be similar to that in a white population^[23]. There have been several reports of familial cases of FFA mentioned as well^[3,14,15]. A family history of FFA in 8% of patients was recently described in a multicenter review consisting of 355 patients^[3]. Most researchers found no association between previous medical background and administered medications, except for the increased incidence of autoimmune diseases^[3,5-7,9,13]. One recent study described dyslipidemia, hypothyroidism, hypertension, and osteoporosis as the most frequent comorbidities^[3]. Another study described an association between beta-blockers and nonsteroidal anti-inflammatory drugs, with a possible protective effect of angiotensin-converting enzyme inhibitors^[5]. Concurrent female pattern hair loss or senescent alopecia has been described in 0%-68% of patients^[3-5,7,13]. Thyroid abnormalities are probably the main association described, with an incidence between 9% and 23%^[3,4]. Previous or concurrent lichen planus (LP) was reported in FFA patients, with a frequency ranging from 2% to 17%. Compared to LPP, in which LP is found in 28%-50% of cases, the association between cutaneous and mucosal lichen planus and FFA seems to be less common^[4,5,20]. Other autoimmune diseases reported to be associated with FFA include vitiligo, alopecia areata, atopy, psoriasis, rheumatoid arthritis, lupus erythematosus, and polymyositis^[3-5,20]. FFA has also been described in patients following hair transplantation and face-lift surgery^[24]. One study assessed the socioeconomic and smoking status of patients with FFA and showed an association with the higher affluent group and significant preponderance of nonsmokers within the cohort of Scottish patients comparing with national data^[5]. Another study from Spain showed 87% were nonsmoking patients, but it was found to be similar to the percentage of Spanish women matched by age, so their results did not support the protective effect of tobacco against FFA^[3]. Laboratory work-up that included hormonal profile evaluation was unremarkable in several studies^[3,12,13,19].

ETIOLOGY AND PATHOGENESIS

The etiopathogenesis of FFA remains uncertain. A key element seems to be destruction of the epithelial hair follicle (HF) stem cells located in the bulge region of the HF leading to permanent hair loss.

RELATION TO LPP/LP

Most authors consider FFA as a clinical variant of LPP in a patterned distribution that primarily affects postmenopausal women. In fact, the North American Hair Research classification system currently classifies FFA as a lymphocytic primary cicatricial alopecia within the spectrum of LPP. This hypothesis is based on similar histopathologic features. Both entities show a lichenoid

lymphocytic inflammatory infiltrate involving the upper and midportion of the hair follicle, with perifollicular fibrosis, and hair follicle destruction. Several authors reported coexistent mucosal or cutaneous lesions of LP in patients with FFA and postulated the phenotypical relation of these two conditions^[1,4,5,7,8,10]. Previous or concurrent LP was reported in FFA patients, with a frequency ranging from 2% to 17%, in comparison to LPP, in which LP is found in 28%-50% of cases^[4,5,20]. This indicates that the association between mucosal and cutaneous LP and FFA seems to be less common than in LPP. Poblet *et al*^[12] examined the clinicopathological features of FFA as well as the similarities and differences between FFA and LPP. No clear-cut histological differences between these two entities were reported; however, their study demonstrated that, in general, FFA tends to show more apoptosis and less lichenoid tissue reaction and damage to basal cells, along with spared interfollicular epidermis. In their opinion, whether FFA can be considered a variant of LPP just because they share a common inflammatory pattern, or it is a distinct entity, is still questionable^[12]. Several studies have shown patchy fibrinogen deposition and globular deposits of IgM or IgA along the epidermal or infundibular basement membrane zones (BMZ) in direct immunofluorescence (DIF) in LPP patients, but these findings were not observed in FFA^[6,12,19]. In addition to these histological findings, it appears that there are differences in treatment response, indicating that FFA and LPP should be considered two separate entities. High and moderate potency topical corticosteroid preparations and systemic corticosteroid preparations and hydroxychloroquine were reported as effective in LPP patients, whereas in the cases of FFA the response to these treatments was less impressive if at all. On the other hand, there are several reports of the effectiveness of anti-androgenic drugs such as dutasteride and finasteride in FFA patients^[3-5,7,9-11,13,20,21].

HORMONAL INFLUENCE

Next to an inflammatory process caused by infiltrating lymphocytes, hormonal influence has been also suggested as a potential factor in the pathogenesis of FFA. It is argued that the FFA is a scarring variant of pattern hair loss^[13]. The role of androgens was suggested due to involvement of the androgen-dependent HF at the frontal line and onset of the disease after menopause. It was further supported by reported clinical improvement with anti-androgen therapy, such as 5-alpha-reductase inhibitors (finasteride and dutasteride)^[3,7,13,18]. However, several studies have examined the hormonal profile of patients with FFA and did not show increased levels of androgens or any other hormonal abnormalities^[3,13,19]. According to existing reports, hormone replacement therapy did not cause an improvement in patients with FFA^[7,8,13]. A lack of any correlation to peripheral sex hormone levels or the use of hormone supplementation may suggest that regional factors of the frontotemporal scalp are involved.

In addition, FFA has also been reported in men and premenopausal women^[3-5,7,9,20]. The majority of patients with FFA have experienced progressive hair loss from the frontal hairline that was not preceded by progressive miniaturization of HF. In addition, FFA targets the follicles not linked to the areas of patterned hair loss. For example, involvement of the eyebrows typical of FFA does not occur in cases of androgenetic alopecia. In summary, according to existing data there is not enough evidence to implicate a hormonal basis as the cause of FFA.

GENETIC FACTORS

The occurrence of familial cases of FFA points to a possible genetic contribution^[3,14,15,17]. It is also well documented that inherited genetic traits codetermine susceptibility to autoimmune diseases as well as the influence of different environmental factors. On the other hand, one could argue that the accumulation of a number of cases in the same family simply indicates exposure to a common environmental trigger. The development of FFA in transplanted HF also raises the issue of whether the influence of local factors in the frontal area determines follicular destruction rather than the inherent qualities of the follicles at this site^[24]. Further accumulation of familial cases may allow assessment of the role of genetic factors and identification of gene mutations predisposing to FFA.

AUTOIMMUNITY AND INFLAMMATION

Several studies showed that in FFA the lymphocytic infiltrate and fibrosis selectively affect the HF of the frontal margin and eyebrows. The disease concomitantly involves hair follicles of different types: terminal, intermediate, and vellus hairs, and different stages of the cycling (from anagen to telogen)^[13,25]. Preferential involvement of vellus and intermediate HF is supported by several authors^[13,26]. The reason for this selection is still unknown. A T-cell-mediated autoimmune reaction against follicular keratinocytes appears to play a major role in this process. Important mechanisms implicated in the irreversible follicular destruction include collapse of the HF immune privilege, cytotoxic cell-mediated follicular damage along with increased proinflammatory response, and increased apoptosis^[12,17,27]. The inflammatory cells attack and destroy keratinocytes expressing particular antigens. These target follicular antigens have as yet not been defined. The inflammation is mostly located around the bulge area, where the stem cells are present, thus causing permanent hair loss. The fact that several autoimmune diseases have been associated with FFA also suggests an autoimmune pathogenesis^[3,5-7,9,13].

EPITHELIAL-MESENCHYMAL TRANSITION

Epithelial-mesenchymal transition (EMT) may contribute

to fibrosis in FFA. Previous studies suggested a possible contribution of EMT in renal, liver, and pulmonary fibrosis. Recently, Nakamura *et al.*^[28] demonstrated that an EMT marker, snail 1, was expressed in the fibrotic dermis of FFA patients. This observation suggests a possible role of EMT conversion of HF epithelial cells to fibroblasts regulated by transforming growth factor- β in the pathogenesis of the FFA^[17,28].

PPAR γ DEFICIENCY AND SEBACEOUS GLAND DESTRUCTION

Peroxisome proliferator-activated receptor gamma (PPAR γ) is a member of the nuclear receptor super-gene family that regulates the expression of genes involved in lipid homeostasis and inflammatory responses and has a crucial role in maintaining the pilosebaceous unit. Recent gene expression studies identified a deficiency in PPAR γ -mediated signaling in LPP patients and suggested that the loss of this function may trigger the pathogenesis of LPP. Several authors reported the efficacy of PPAR γ -agonists in treatment of LPP. The deficiency of PPAR γ has yet to be studied in FFA^[16,29].

ENVIRONMENTAL TRIGGERS

The epidemiology of FFA strongly suggests a role of environmental factors in its development. The occurrence of the disease in several members of the same family may indicate exposure to common environmental triggers. A contact sensitizer, environmental toxin, dietary factor, or infectious agent could be responsible for triggering the process in predisposed subjects. For example, photoallergic reaction to pyridoxine hydrochloride found in a wide variety of hair care products, needs to be evaluated as potential trigger for scarring alopecia. Up to date a role of application cosmetic products and hair-care practices in the pathogenesis of FFA were not documented and their role remains unclear. The possible role of microbial antigens or super-antigens in this context remains to be elucidated. Recently the possible link between the aryl hydrocarbon receptor (AHR) and its overexpression in cicatricial alopecia was suggested. Since the ligand for the AHR is activated by dioxin, the possibility that dioxin-like substances can trigger the disease *via* the AHR was discussed recently, but remains unproven^[16,17,29]. Dioxin-like chemicals are environmental pollutants that are ingested mostly with food of animal origin: meat, dairy products, or fish predominate, depending on the country. These toxins persist in the environment and are very slowly eliminated from the human body. Chronic low-dose exposure may lead to the accumulation of dioxins in lipid-rich regions such as sebaceous glands, causing loss of PPAR γ expression and thereby scarring alopecia in susceptible individuals.

In conclusion, future investigation is needed to clarify the pathogenesis of FFA and to define the role of genetic, autoimmune, hormonal, and environmental

factors and lipid metabolism in this challenging condition.

CLINICAL FEATURES

FFA has a distinct clinical presentation characterized by recession of the anterior hairline with loss of follicular orifices in the area of hair loss. The band-like zone of alopecic skin appears pale, shiny, and smooth contrasting to the mottled, photo-aged skin of the forehead. Although the frontal area is most commonly affected, and despite the name “frontal” fibrosing, FFA may appear on other sites, such as the temporo-parietal as well as the retroauricular and occipital areas. Hairline recession usually occurs symmetrically and bilaterally, giving rise to a band of alopecia between 0.5 and 10 cm from its original site (Figure 1A-C). Although the progression is relatively slow, distribution can be widespread, involving the entire hairline and leaving only a band of hair on the top of the scalp, which is described as “clown alopecia”. Increased venous vasculature on the temples is also a common observation (Figure 1B). Perifollicular erythema and papules along the new hairline indistinguishable from that seen in LPP are common findings as well (Figure 1D). Degree of erythema and scaling may be variable, being marked in some, but minimal in others^[1-11,13,18-20]. The striking feature is the unnatural appearance of the hairline caused by loss of both terminal and vellus hair (Figure 1D)^[13,30]. The presence of “lonely hair” described by Tosti *et al.*^[31] is also a useful diagnostic clue (Figure 1E). This sign describes the presence of isolated terminal hairs in the middle of a bald band marking the original hairline prior to hair loss. This is a common but non-specific sign of FFA. While some patients can present with associated itching, pain, and burning sensations, it is not unusual to see patients who are completely asymptomatic without frank inflammation. Most patients with FFA exhibit some degree of eyebrow diminution, recognized as a characteristic feature of this disorder. It can occur either before or after the onset of frontotemporal recession. Hair loss from the lateral third of the eyebrows is typical, but in some cases, there may be diffuse thinning or total loss of eyebrows (Figure 1E). Eyelash involvement was also reported, albeit less frequently (Figure 1E)^[1-11,13,18-20]. Recently, non-inflammatory asymptomatic facial papules, mainly confined to the temporal area of the face, were reported as possible sign of facial vellus hair involvement (Figure 1F)^[32]. Several authors described decrease or absence of facial vellus hair as well as loss of hair from peripheral body sites and generalized hair loss^[2,6,8,13,18]. It should be noted that despite frequent reports of axillary and pubic hair loss, it cannot be clearly attributed to the disease process considering that this is also a common symptom in postmenopausal and older women.

Findings on trichoscopy include the absence of follicular openings, absence of vellus hairs, white dots (corresponding to the follicular fibrosis seen in dark-skinned individuals), and brown halos (expressing the inflammation). Reduced hair density, follicular



Figure 1 Clinical presentation of frontal fibrosing alopecia. A: Fronto-temporal hairline recession in a band-like distribution. The pale, smooth, and atrophic skin of the alopecic area contrasts with the sun-damaged and pigmented skin of the forehead; B: Lateral view: Increased visibility of veins on the forehead; C: Retroauricular area involvement; D: Absence of vellus hairs, perifollicular erythema and hyperkeratosis over the frontal hairline; E: Eyebrow loss and isolated hairs in the middle of the alopecic band ("lonely hair sign"); F: Facial papules over the temporal area indicating vellus hair involvement.

plugging, perifollicular scale (also called peripilar casts), and perifollicular erythema are frequent around the existing hairs at the anterior hairline^[30,33]. Follicular red dots on the forehead corresponding to another sign indicating vellus hair involvement were described recently^[34].

HISTOPATHOLOGY

A 4-mm punch biopsy from an active inflammatory lesion within the hair-bearing margin of the alopecic patch is preferred for pathological study. Horizontal sections seem more informative than vertical orientation. Typical histopathological findings in FFA show lymphocytic infiltrate mainly localized to the isthmus and infundibular regions with the lower portion of HF being spared. The inflammatory infiltrate shows lichenoid characteristics of variable severity, with a follicular interface dermatitis pattern, whereas the overlying interfollicular epidermis

is spared. The number of HFs is reduced, perifollicular lamellar fibrosis is evident, and HFs are often replaced by fibrous tracts. The sebaceous glands are absent or only focally present, and the external root sheaths may show vacuolar degeneration of the basal layer and apoptosis of follicular keratinocytes. Perivascular and periadnexal inflammation is absent. Histopathologic findings are variable according to disease progression. In its active stage the inflammation is much more prominent, while in the "burned-out" stage the specimen may show only a follicular scar. Most authors consider FFA as a clinically distinct variant of LPP with patterned distribution, based on their similar histopathological findings^[1,6,8]. However, recently a number of subtle histopathological differences between these two entities were described^[12]. In general, the lichenoid tissue reaction was shown to be milder in FFA than in LPP. While LPP cases may show intense damage of the basal cell layer, this feature is not observed

in FFA. The involvement of interfollicular epidermis was not found in FFA, but it is common in LPP. FFA cases tend to show much more apoptosis than LPP. The foreign body reaction to the follicular destruction of the external root sheath and the hair shafts trapped in the dermis were found to be more frequent and more prominent in FFA^[12]. In addition, immunofluorescence tests are negative in FFA, while they can show patchy fibrinogen deposition and globular deposits of IgM or IgA along the epidermal or infundibular basement membrane zones in LPP^[6,12,19]. It was also reported that there may be a predilection for the involvement of intermediate and vellus follicles in FFA^[13]. Recently, the sign of “follicular triad” was suggested as a possible diagnostic clue to the diagnosis of FFA^[26]. This sign describes the simultaneous involvement of HF of different types: terminal, intermediate (0.03–0.06 mm), and vellus (< 0.03 mm) and in different stages of cycling (anage, catagen, and telogen) with inflammatory infiltrate and perifollicular fibrosis. Although clinically noninflammatory, several studies have shown that histologically eyebrow, facial, and peripheral hair loss demonstrate inflammation and fibrosis, suggesting that the process of permanent hair loss is generalized rather than localized only to the frontal scalp^[2,6,13].

DIAGNOSIS

In most cases the diagnosis of FFA can be made on clinical grounds and supported by trichoscopy. When the clinical diagnosis is not conclusive, for example, in the early stages when the follicular density is almost normal, in partially treated cases, or in advanced cases when clinical signs of inflammation are subtle, a dermoscopy-guided biopsy from a site of disease activity is indicated to provide for histopathological confirmation^[2,5,10,13].

Key features of FFA that help to make clinical diagnosis are as follows: (1) largely affects postmenopausal women; (2) symmetric and progressive band-like recession of the fronto-temporal region with loss of follicular ostia; (3) pale and atrophic skin devoid of follicular orifices in the zone of alopecia, contrasted with the hyperpigmented sun-damaged skin of the forehead; (4) perifollicular erythema and follicular hyperkeratosis around the existing hairs at the margin of alopecia; (5) presence of isolated terminal hairs in the bald band on the forehead (“lonely hair” sign); and (6) marked decrease or complete loss of the eyebrows.

On trichoscopy: (1) absence of follicular openings; (2) reduced hair density, absence of vellus hair at hairline margins; (3) follicular plugging, perifollicular scale, and erythema around the existing hairs at the margin of alopecia; and (4) peripilar white dots and brown halos (incontinentia pigmenti).

Histopathological features include: (1) lichenoid lymphocytic infiltrate mainly localized to the isthmus and infundibulum; (2) follicular interface dermatitis pattern, with sparing of interfollicular epidermis; (3) reduced number of HFs, perifollicular lamellar fibrosis,

replacement of HFs by fibrous tracts; (4) the sebaceous glands are absent or only focally present; (5) vacuolar degeneration of the basal layer and apoptosis of follicular keratinocytes in the external root sheaths; (6) absence of perivascular and periadnexal inflammation; and (7) follicular triad sign: simultaneous involvement of different types of hairs (terminal, intermediate, and vellus) and in different stages of cycling (anage, catagen, and telogen).

DIFFERENTIAL DIAGNOSIS

FFA should be differentiated from several conditions that cause marginal scalp hair loss. In some cases it is difficult to distinguish between FFA and alopecia areata involving hairline, for example in sisaipho or ophiatic pattern alopecia areata. Presence of follicular orifices, exclamation mark hairs, yellow dots, black dots, and dystrophic hairs on dermoscopy can help establish the diagnosis of alopecia areata. On the other hand, lack of follicular ostia, perifollicular inflammation, and symmetric eyebrow involvement appear in FFA. When it is difficult to differentiate between the diseases clinically, skin biopsy is recommended.

Frontotemporal form of female pattern hair loss (FPHL) is another condition that may be confused with FFA. Unlike FFA, female pattern hair loss is not a cicatricial process. In FPHL, the vellus hair is present, and there is no perifollicular inflammation or scale.

Another condition that can cause hair loss in the periphery of the scalp is traction alopecia. Differentiation from traction alopecia can usually be made from the history of traction or chemical straightening, and supported by the finding of broken hairs of various lengths in the affected area. There is no eyebrow and peripheral hair loss or perifollicular inflammation, and vellus hair is preserved. The lichenoid follicular inflammation and fibrosis are absent and sebaceous glands are preserved in histologic sections.

Cicatricial marginal alopecia was recently described by Goldberg^[35] in women who presented with hair loss limited to the periphery of the scalp. There was no history of traction. The clinical picture revealed hair thinning or almost complete alopecia of the scalp margin and eyebrows were not involved. Dermoscopic features were characterized by low hair density with loss of follicular ostia, reduced diameter of remaining hairs, and absence of perifollicular erythema or hyperkeratosis. Histological sections revealed a decrease in HF density with normal sebaceous glands and no signs of inflammation.

There are cases where the possibility of genetic family high hairline should be considered. In this condition, the front line of hair can be located relatively high, but it has a natural appearance, and contains all types of hair (terminal, intermediate, and vellus). There are no clinical signs of inflammation or eyebrow involvement.

The differential diagnosis with other diseases from the PCA group can be challenging. The distribution

pattern of alopecia (single plaque, multifocal, hairline recession), the involvement of other hairy sites (eyebrows, axillae, body hair), and the presence of other associated cutaneous manifestations may allow clinical distinction in a large number of cases.

While FFA patients are mostly asymptomatic and only rarely have mild itching, intense pruritus, pain, burning, and scalp tenderness are common in LPP patients. The distribution of the hair loss also differs. There is a multifocal disease with a predilection to central scalp in LPP. The involvement of hair in the peripheral portion of the scalp typical for FFA is uncommon. Histologic sections of LPP show less apoptosis and more inflammation. DIF is not uncommonly negative, with some cases showing patchy deposition of fibrinogen and IgM, or less commonly IgA and C3, along the follicular BMZ. Elastin staining reveals a superficial, wedged-shaped scar associated with loss of the upper follicular elastic sheath.

Piccardi-Lasseueur-Graham-Little Syndrome is classically considered a type of LPP; however, several researchers suggest that it is a distinct entity. It is characterized by a triad of scarring patchy scalp alopecia, nonscarring alopecia of the axillae and the pubic area, and grouped or disseminated follicular papules with spinous scale on the trunk and extremities. Face and eyebrows can be also affected. Pathology shows features of both LPP and keratosis pilaris atrophicans.

Fibrosing alopecia in a pattern distribution was described by Zinkernagel *et al.*^[36]. This entity shares clinical and histologic features similar to LPP, but is limited to an area of androgenic hair loss. The centrovertical scalp is usually diffusely affected, but some patients also have frontotemporal loss similar to that seen in FFA. Biopsy specimens demonstrate the HF miniaturization and a lichenoid inflammatory infiltrate targeting the upper follicle region.

Discoid lupus erythematosus (DLE) is usually multifocal and does not have a predilection for the marginal scalp. In contrast to FFA, the center of lesion, rather than the hair-bearing periphery, is affected in the active disease stage. A search for DLE elsewhere on the body or for coexisting signs of systemic lupus erythematosus is essential. The histologic presentation of DLE is also different. Superficial and deep perivascular and perieccrine inflammation and dermal mucin deposition are typical features of DLE and are not found in FFA. In addition, the interface change is vacuolar and not lichenoid, often with a thickened basement membrane. The interfollicular epidermis is generally not spared. The dermal sclerosis is usually less severe than in FFA and telangiectases are present. The DIF of DLE is usually specific with deposition of immunoglobulin (Ig) G or IgM and C3 in a granular or homogenous band-like pattern at the dermal interface with the follicular epithelium and epidermis. Elastin staining reveals a diffuse dermal uptake that spares the fibrous tracts of extinct follicles.

Pseudopelade of Brocq is another type of PCA that predominantly affects the vertex and parietal areas of

scalp with irregular multifocal areas of scarring alopecia. The lesions are asymptomatic, limited to the scalp, with no visible perifollicular inflammation or follicular hyperkeratosis. Multifocal coin-sized plaques and larger polycyclic or irregular plaques of alopecia coalesce and create a “footprints in the snow” pattern. There are no pathognomonic features on histology. In early lesions, massive lymphocyte-mediated apoptosis of the follicular sheath has been observed. Lymphocytic perifollicular infiltrate around the infundibulum without interface changes, and prominent concentric lamellar fibroplasia are described as established disease features. Findings on DIF are usually negative, but scanty IgM deposition along the follicular infundibular basal membrane zone can be seen. Elastin stains reveal hyalinized dermis with markedly thickened elastic fibers throughout and broad follicular fibrous tracts with intact elastic sheaths, unlike the pattern seen in LPP and DLE.

Central centrifugal scarring alopecia predominantly occurs in adult black women and presents with asymptomatic, noninflammatory alopecia that begins in the midline central scalp, with gradual centrifugal spread over the years. The histologic features are not specific in this type of PCA and resemble Pseudopelade of Brocq.

Alopecia mucinosa has a polymorphous presentation and can be nonscarring or scarring. Histology is diagnostic showing mucinous degeneration of the follicular and sebaceous epithelium associated with perifollicular and perivascular lymphocytic infiltrate.

Keratosis Follicularis Spinulosa Decalvans (KFSD) may also share features similar to FFA. Unlike FFA, it usually begins in infancy and may improve during puberty. There are sporadic and familial cases. Men are more likely to present with a more severe disease. Triad of KFSD includes widespread keratotic papules succeeded by atrophy, cicatricial alopecia, and photophobia. Alopetic plaques have multifocal distribution with patchy involvement of the scalp, eyebrows, and eyelashes, with perifollicular hyperkeratosis and erythema at the edges. It can be associated with focal palmoplantar keratoderma. In some cases, follicular pustules appear at the hair-bearing margins, resembling folliculitis decalvans. The histopathology shows a mixed inflammatory infiltrate with follicular plugging, hypergranulosis, and neutrophilic spongiosis of the infundibulum and adjacent epidermis in acute disease and perifollicular lymphocytic infiltrate thereafter.

Neutrophilic type cicatricial alopecia can also simulate FFA, especially in advanced stages of the disease, when pustules and crusts are absent, and neutrophilic infiltrate of folliculitis decalvans disappears. Multifocal distribution without predilection to marginal scalp and presence of tufted HFs are characteristic of folliculitis decalvans.

TREATMENT AND PROGNOSIS

Because the disease has been described relatively recently, little is known about the natural history of FFA. The

rate and extent of frontal recession is highly variable. According to several studies an average rate of recession is 0.9-1.05 mm per month^[2,3,5]. It has been described that FFA may advance slowly and stabilize over time regardless of treatment continuation, whereas in some patients the recession progresses despite therapeutic intervention and eventually involves the entire scalp^[2,8,13,18]. One recent study demonstrated that eyelash loss, presence of facial papules, and body hair involvement may be associated with poor prognosis, while eyebrow loss as the initial clinical presentation was associated with mild forms of FFA^[3]. It has also been described that visible erythema does not always correlate with alopecia progression^[5]. Because the alopecia is cicatricial, hair regrowth is not possible, except when therapy has been started at the very beginning of the disease; therefore, early diagnosis is crucial. The treatment goals are to abort the disease progression, prevent further alopecia, and reduce symptoms. The fact that FFA progression is slow, with spontaneous cessation of the disease years after onset, makes both treating the disease and assessing the effectiveness of the administered treatment difficult. Given the tendency of FFA for spontaneous stabilization, some apparent responses may simply have been part of the natural course of the disease. The available evidence on the treatment of FFA comes from retrospective observation studies. There are no controlled clinical trials to evaluate the available modalities. It should be noted also that there is currently no standardized outcome measure for the evaluation of treatment efficacy in FFA. Several researchers have used LPP activity index in order to assess treatment efficacy in FFA patients^[20,37]. In view of the differences that exist between FFA and LPP, such as a lower weight of subjective symptoms and clinical signs of inflammation in FFA, the relevance of this index in FFA patients is questionable. Recently, a clinical severity scale of FFA was suggested, basing on measuring the area of hairline recession. It includes 5 grades of severity: I (< 1 cm), II (1-2.99 cm), III (3-4.99 cm), IV (5-6.99 cm), and V ($\geq$ 7 cm, also called clown alopecia), which are grouped as mild FFA (grades I and II) and severe FFA (grades III, IV, and V)^[5]. We believe that the main measure to be considered in evaluating the treatment efficacy in FFA is progression of hairline recession. Changes in erythema or subjective symptoms should be evaluated separately. Treatment of FFA has been disappointing. It is unclear whether treatments alter the natural history of the disease. Several topical and systemic therapeutic options have been reported to have some efficacy in halting the disease progression in retrospective studies.

TOPICAL CORTICOSTEROIDS

According to previous reports, almost all patients had been treated with moderate to high potency topical corticosteroids. Although in some cases this treatment resulted in reduced inflammation, it did not halt progression of alopecia in most cases^[7,11,21].

INTRALESIONAL CORTICOSTEROIDS

Intralesional corticosteroid injections have been considered as first-line treatment by most researchers. Triamcinolone acetonide at a concentration of 5-10 mg/mL (to a maximum of 2 mL) for the scalp and 2 mg/mL for the eyebrows (location is more susceptible to atrophy) every 4-8 wk produced a response rate of up to 60%^[21]. Higher concentrations of triamcinolone acetonide were reported as well, and in these cases the time intervals between injections were longer. For example, triamcinolone acetonide injections at a concentration of 20 mg/mL were made every 3 mo^[13,18]. However, most researchers prefer to employ a lower concentration in order to reduce the risk of cutaneous atrophy. Intralesional corticosteroids are more effective in the early stages of the disease, especially in patients with prominent clinical and histologic inflammation. Once alopecia has advanced to the fibrotic phase, it provides no benefit and may even worsen the fibrosis and atrophy that characterize the advanced stages of FFA^[18,19]. It should be noted that in most reported cases this treatment was given in combination with other treatment modalities, which makes it difficult to judge its own efficacy. Several researchers have emphasized that the results of this treatment are less impressive compared with those in the cases of LPP^[2-5,29].

SYSTEMIC CORTICOSTEROIDS

Administration of oral prednisone may be useful in rapidly progressive diseases, especially when the signs of inflammation are prominent. However, after the discontinuation of treatment a relapse is common. There are different protocols in the literature. Usually oral prednisone is administered in the dose of 0.5-1 mg/kg per day for a period of 1 to 18 mo and tapered to discontinuation over 2-4 mo^[1,8,32,38]. There are researchers who preferred intramuscular triamcinolone pulses of 0.5-1 mg/kg every 3-4 wk for 3-4 mo^[13,29]. The combined treatment of systemic corticosteroids with other topical or systemic treatments was also described. Existing literature indicates that, like with other anti-inflammatory treatments, corticosteroids in FFA are less effective than in LPP.

ANTIMALARIALS

Because there is an opinion that FFA is a clinical variant of LPP, antimalarial medications known to be effective in LPP were one of the frequently used systemic medications in FFA patients. According to existing reports, results are inconclusive. There are studies that show the disease stabilization in more than 50% of cases^[3,7,20,29,37]. Other studies have noted less impressive results or simply a lack of efficacy^[2,6,11,39]. Protocols described include administration of hydroxychloroquine in a dose of 200-400 mg per day, or chloroquine diphosphate 250 mg per day, for at least 6 mo^[3,7,32].

TETRACYCLINE ANTIBIOTICS

Several reports describe treatment with tetracycline 500 mg twice daily or minocycline 100 mg twice daily in FFA patients. Like other anti-inflammatory treatments, tetracyclines caused a decrease in inflammation in some cases, but their efficacy in controlling the alopecia was uncertain^[4,20].

TOPICAL CALCINEURIN INHIBITORS

Topical tacrolimus and pimecrolimus were used with disappointing results in most patients^[2,5,7,11].

5-ALPHA-REDUCTASE INHIBITORS

Although the hormonal basis of FFA has not been proven, several retrospective studies have shown efficacy of anti-androgen therapy with 5-alpha-reductase inhibitors, finasteride and dutasteride. A number of studies comparing the efficacy of various treatments in patients with FFA suggest that this treatment is more effective than others in halting the disease progression. Due to its teratogenic potential (pregnancy category X) this treatment needs to be combined with oral contraceptive therapy in premenopausal women. Several open label studies demonstrated the efficacy of finasteride at a dose of 2.5 mg daily given for at least 6 mo^[3,4,7,13,18]. Treatment with dutasteride was also reported to be effective, producing even more impressive results than with finasteride, probably due to its ability to achieve greater suppression of dihydrotestosterone^[7,25]. Therapeutic protocols of treatment with dutasteride reported in the literature include treatment at a dose of 0.5 mg per day for at least six months^[40] or loading dose of 0.5 mg per day for 2 wk and reducing to maintenance dose of 0.5 mg per week thereafter^[2-4,7,25]. Some authors question the effectiveness of 5-alpha-reductase inhibitors in treatment of FFA. They argue that in all cases reported, the treatment with 5-alpha-reductase inhibitors was combined with other medications, such as topical or intralesional corticosteroids^[40], calcineurin inhibitors^[40], or minoxidil^[13,18,40], thus making it difficult to judge which of medications given can be associated with the outcome. Some authors also suggest that the improvement obtained may be related to a positive effect of medications on accompanying female pattern hair loss by preventing miniaturization and stimulating of remaining hairs^[5,11]. Therefore, although several preliminary reports are promising, further evaluation of the therapeutic role of dutasteride with randomized controlled trials is warranted.

TOPICAL MINOXIDIL

Limited reports on the use of topical minoxidil solution did not slow the progression of FFA in most patients^[3,9,19,21]. It should be noted that in several reports the treatment with minoxidil was combined with topical steroids and 5-alpha-reductase inhibitors. These studies showed positive results. It is unclear whether the results are related to the effect of

minoxidil or to the additional medication that had been taken, and if the improvement is due to the influence on FFA or on an accompanying female pattern hair loss.

OTHER

Limited reports on the use of PPAR- γ agonists, methotrexate, cyclosporin^[29], mycophenolate mofetil^[20], griseofulvin^[9], isotretinoin, acitretin, and UVB^[3,21] on FFA preclude any conclusion regarding efficacy.

HAIR TRANSPLANTATION

There is some concern about hair transplantation in FFA patients because of reported cases of FFA that began after hair transplantation in patients with androgenetic alopecia^[24,37]. There is also a description of the development of FFA following face-lift surgery^[37,41]. However, several reports have shown promising results^[21,42]. It was suggested that hair transplants might be proposed when there is no progression of the disease for at least 1 year.

COSMETIC CAMOUFLAGE

Different methods of camouflage including wigs, hairpieces, scalp micropigmentation, and eyebrow tattooing may be recommended to cover hair loss in severe refractory and end-stage cases of FFA^[2,5].

CONCLUSION

FFA is form of PCA, characterized by progressive recession of the frontotemporal hairline and eyebrow loss, occurring predominantly in postmenopausal women. The pathogenesis of FFA is poorly understood, although an autoimmune reaction and hormonal androgen-driven factors seem to play a role. Typical histopathological findings of FFA show lichenoid lymphocytic inflammatory infiltrate localized to the upper portion of hair follicle, perifollicular fibrosis, and HF destruction. Therapeutic options are limited. Long-term prospective cohort studies are needed to further elucidate the etiopathogenesis, to evaluate the effectiveness of existing treatments, and to find new treatment options. Until then, management of this fascinating disorder remains unsatisfactory.

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Knowledge explosion for monogenic skin diseases

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variations that are responsible for monogenic skin diseases. These advances provided a solid basis for subsequent studies elucidating mechanisms of monogenic skin diseases and improving our understanding of common skin diseases. Furthermore, these discoveries also contributed to the development of novel therapeutic modalities for monogenic skin diseases. In this review, we have used the disease spectrum caused by mutations in the *CYLD* gene - Brooke-Spiegler syndrome, familial cylindromatosis and multiple familial trichoepithelioma type 1 - as a model for demonstrating the knowledge explosion for this group of diseases.

Key words: Familial trichoepitheliomatosis; Familial cylindromatosis; Brooke-Spiegler syndrome; Monogenic skin diseases

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Core tip: Although dermatology is a morphology-orientated specialty, genetic investigation can help understand the events taking place in the skin of the affected patients. Genetic investigation of Brooke-Spiegler syndrome, familial cylindromatosis and multiple familial trichoepithelioma type 1 further supported the clinical hypothesis that these monogenic skin diseases are not different entities, but rather clinical variants of a disease spectrum caused by mutations in the cylindromatosis (*CYLD*) gene. In addition to understanding the underlying mechanisms of these allelic variants, genetic investigation can also accelerate the development of novel therapeutic modalities, such as therapy using tropomyosin-receptor-kinase specific lestaurtinib for patients with germline *CYLD* mutations.

Abstract

During the past few decades, the investigative technologies of molecular biology - especially sequencing - underwent huge advances, leading to the sequencing of the entire human genome, as well as the identification of several candidate genes and the causative genetic

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INTRODUCTION

From ancient times to the present, the basic approach for diagnosing skin diseases has been to classify the diseases according to their visible signs and symptoms. This approach highlights that dermatology is still a highly morphology-orientated specialty. The end of the 18th century saw great breakthroughs in dermatology: the first comprehensive textbook of modern dermatology was published in 1799 by Francesco Bianchi^[1] and the first great school of dermatology was established in Paris in 1801^[2]. Since that time, the desire to understand the nature of observed skin lesions constantly drives the development of dermatology and the incorporation of novel investigative methods into its everyday practice.

Among these methods, dermatohistopathology has had the highest impact on the diagnosis of skin diseases. Although the microscope was invented by Anton van Leeuwenhoek as early as 1673, the first standardized and classified nomenclature of dyes and stains was prepared only in 1924^[3,4]. Since that time, enzyme histochemistry, electron microscopy, polarizing microscopy, immunohistochemistry and *in vivo* confocal microscopy have all become diagnostic tools in dermatohistopathology and have been integrated into everyday dermatology practices^[3,4]. In recent decades, developments in the investigative fields of clinical genetics and genomics have further accelerated our knowledge about skin diseases.

Breeding agricultural plants and animals characterized the pre-Mendel era of genetics^[5,6]. After Gregor Mendel established the basic rules of heredity in the nineteenth century^[7], several major discoveries, such as the identification of DNA as the material encoding inheritable information, of the genetic code and of the mechanisms of gene expression, have initiated the era of molecular genetics^[8,9]. Very recently, the enormous technical development of sequencing methods and platforms has resulted in large-scale genomic projects, which produce amounts of data that were unimaginable a few decades ago^[10,11].

These discoveries and techniques have been used to identify several normal genetic variations, as well as candidate genes and their disease-causing mutations, accelerating the elucidation of the genetic background of several monogenic skin diseases. In this review, we present the knowledge explosion for monogenic skin diseases, using as an example the disease spectrum caused by mutations in the *CYLD* gene, which involves Brooke-Spiegler syndrome (BSS) (OMIM 605041), familial cylindromatosis (FC) (OMIM 132700) and multiple familial trichoepithelioma type 1 (MFT1) (OMIM 601606) (Table 1).

DISCUSSION

BSS is a rare monogenic skin disease characterized by the development of a wide variety of benign skin appendageal tumors, such as cylindromas, trichoepitheliomas and/or spiradenomas^[12,13]. BSS was named after the two physicians who first reported these neoplasms in 1892 and 1899: Henry G Brooke and Eduard Spiegler, respectively^[14,15].

FC, which was originally considered a separate rare disease, is characterized by the development of cylindromas^[16]. FC was first reported in 1842 and 1899 by Henry Ancell and Eduard Spiegler, respectively^[15,17]. MFT1, which was also reported as another rare entity, is characterized by the development of trichoepitheliomas^[16] and was first reported in 1892 by Brooke^[14] and Fordyce^[18].

Comparing the clinical features of these tumors, cylindromas are benign, skin-colored tumors usually present as multiple turban-like protrusions on the scalp, trichoepitheliomas are small, benign, skin-colored tumors, typically located at the center of the face, and spiradenomas are purple, benign, nodular tumors, usually located on the trunk or limbs^[19]. The histological characteristics of cylindromas are dermal nodules of epithelial cells lined by membrane-like basement material and arranged in a “jigsaw puzzle” pattern, of trichoepitheliomas are dermal nodules of basaloid cells with peripheral palisades arranged in nests or cribriform patterns and of spiradenomas are dermal nodules comprised of large light-colored epithelial cells with abundant cytoplasm at the center and small darker epithelial cells at the periphery^[20-22]. Hybrid tumors can also occur, such as spiradenocylindromas, which exhibit the characteristics of both cylindromas and spiradenomas^[23].

The candidate gene for BSS was first mapped to chromosome 16q12-q13 in 2000^[24], and the causative *CYLD* gene and its first pathogenic mutation was identified in an affected German pedigree in 2002^[25]. The candidate gene for FC was first mapped to chromosome 16q12-q13 in 1995^[26], however, the causative *CYLD* gene and the first 21 pathogenic mutations were identified as late as 2000^[27]. It was first suggested in 1995 that MFT1 and FC may be caused by the dysfunction of the same gene, since both type of tumors can occur in the same patient or in different patients within a single family^[28]. The causative gene for MFT1 was identified as *CYLD*, and the first pathogenic mutation was detected in an affected Turkish family in 2003^[29].

These clinical variants - BSS, FC and MFT1 - were originally described as distinct clinical entities. However, due to their overlapping clinical symptoms and their manifestation within the same family, they are currently considered as part of a phenotypic spectrum of the same entity^[30-32]. This hypothesis is supported by genetic evidence: several mutations - the c.1112C/A p.S371X, the c.2272C/T p.R758X and the c.2806C/T p.R936X nonsense mutations - lead to the development of all three clinical variants (Table 2)^[33-42].

Presumably, this is due to the fact that the nonsense mutations of the *CYLD* gene are in general recurrent ones and develop due to *de novo* events indicating mutational hotspots on the gene^[33]. Patients carrying the same nonsense mutation from different mutational events often exhibit extreme phenotypic differences, which might be the consequences of yet unknown genetic factors that modify the development of the phenotype.

To date, a total of 99 disease-causing *CYLD* mutations have been reported worldwide (Figure 1)^[43-46]. The majority (82%) of *CYLD* mutations identified to date

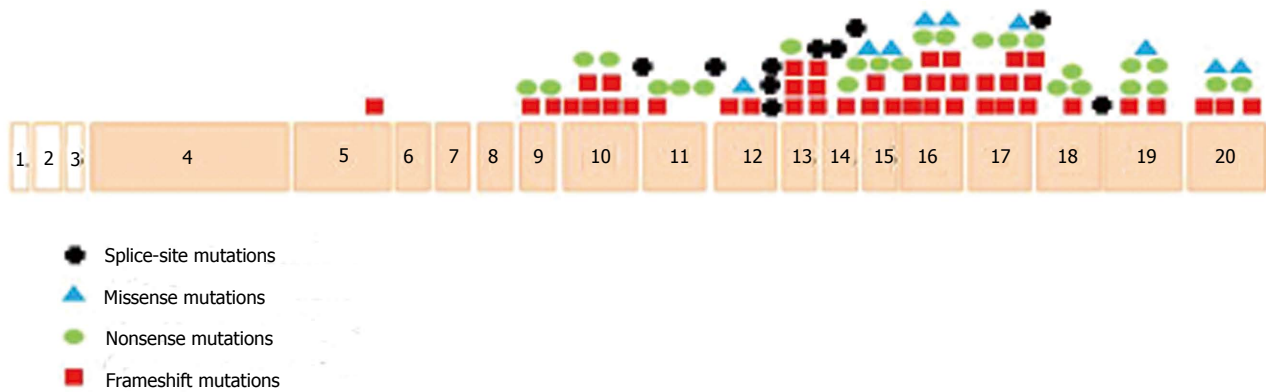


Figure 1 *CYLD* gene mutations identified to date.

Table 1 Classification of the clinical variants within the disease spectrum caused by <i>CYLD</i> mutation			
Name of clinical variant	Familial cylindromatosis	Brooke-Spiegler syndrome	Multiple familial trichoepithelioma type 1
Clinical symptoms	Cylindromas	Cylindromas Trichoepitheliomas Spiradenomas	Trichoepitheliomas
Genetic background	Any type of mutation	Any type of mutation	Any type, but mainly missense mutations

Table 2 Reported clinical variants and geographic distributions of the most common recurrent mutations of the <i>CYLD</i> gene				
<i>CYLD</i> cDNA	<i>CYLD</i> protein	Detected in patients with	Nationality	Ref.
c.1112C > A	p.S371X	BSS, FC, MFT1	American, African American, Irish, Dutch, Austrian, Czech, Slovak, Chinese	Bignell <i>et al</i> ^[27] , 2000; Bowen <i>et al</i> ^[30] , 2005; Saggar <i>et al</i> ^[32] , 2008; Linos <i>et al</i> ^[40] , 2011; Kazakov <i>et al</i> ^[39] , 2011; Grossmann <i>et al</i> ^[33] , 2013; Kacerovska <i>et al</i> ^[51] , 2013; Lv <i>et al</i> ^[41] , 2013; Van den Ouweland <i>et al</i> ^[36] , 2011
c.2272C > T	p.R758X	BSS, FC, MFT1	American, South African, Austrian, Czech, Dutch, Chinese, Japanese	Bignell <i>et al</i> ^[27] , 2000; Kazakov <i>et al</i> ^[38] , 2009; Kazakov <i>et al</i> ^[39] , 2011; Grossmann <i>et al</i> ^[33] , 2013; Oiso <i>et al</i> ^[42] , 2004; Zhang <i>et al</i> ^[37] , 2006; van den Ouweland <i>et al</i> ^[36] , 2011
c.2806C > T	p.R936X	BSS, FC, MFT1	American, Canadian, Anglo-Saxon, Czech, Hungarian, Chinese	Bignell <i>et al</i> ^[27] , 2000; Bowen <i>et al</i> ^[30] , 2005; Saggar <i>et al</i> ^[32] , 2008; Kazakov <i>et al</i> ^[38] , 2009; Grossmann <i>et al</i> ^[33] , 2013; Young <i>et al</i> ^[31] , 2006; Nagy <i>et al</i> ^[35] , 2013

BSS: Brooke-Spiegler syndrome; FC: Familial cylindromatosis; MFT1: Multiple familial trichoepithelioma type 1.

are located between exon 12 and 20. This finding has a significant diagnostic relevance, as mutation screening of the affected individuals should begin with examination of the exon 12-20 region. Within this region, exons 16 and 17 contain the highest number of mutations (16%). Now that, because the causative mutation can be identified prenatally as well as preimplantation, diagnosis can be offered to affected families. This information can have a huge impact on family planning, since the symptoms of all clinical variants can be very stigmatizing^[35].

Several functional studies have been performed to elucidate the underlying mechanism of the *CYLD*-mutation disease spectrum. The *CYLD* gene encodes an enzyme with deubiquitinase activity, which is involved in the post-translational modification of its target proteins by removing Lys63-linked ubiquitin chains^[47]. *CYLD* interacts with several members of the NF-κB signaling pathway, including the TRAF2, TRAF6, NEMO and BCL3 proteins, acting as a negative regulator^[48]. Mutations of the *CYLD* gene, in general, result in decreased activity of the *CYLD* enzyme. The reduced activity leads to the hyperubiquitination of interaction partners and influences several signaling pathways, such as the NF-κB pathway, as well as affects several biological processes, such as the development of the skin appendages and tumor formation^[34].

It is interesting to note that, although the *CYLD* protein is expressed in a wide range of human tissues, the reason why dysfunction manifests only in skin symptoms is still unclear^[49-51]. Moreover, patients carrying the same mutation from different mutational events often exhibit extreme differences in their clinical and histological manifestations^[35]. These differences might be the consequences of yet unknown genetic, environmental and/or lifestyle factors that modify the development of the phenotype. Further

studies are needed to elucidate the putative factors that are responsible for the observed late onset of the symptoms, for the development of only skin manifestations and for the great variation in phenotypes and histological findings.

To date, no causative therapy is available for BSS. However, recent gene expression studies demonstrated that tumors with somatic *CYLD* mutation have impaired *TRK* signaling and treatment with a small *TRK*-inhibiting molecule, lestaurtinib, can reduce colony formation and proliferation of tumor cells with somatic *CYLD* mutation^[52]. These data may have huge clinical significance, since lestaurtinib treatment might be a novel therapeutic modality for patients suffering from symptoms caused by germline *CYLD* mutations.

CONCLUSION

Although dermatology and genetics are considered separate disciplines, the combination of these two fields has already resulted in enormous improvement in the understanding of monogenic skin diseases, such as the skin-disease spectrum caused by mutations in the *CYLD* gene. Genetic studies have proved that BSS, FC and MFT1, which were originally considered different entities, result from mutations of the same gene. Moreover, mutations of the *CYLD* gene have been reported in patients presenting all clinical variants. Genetic screening and the identification of the disease-causing mutation have already been of great significance for family planning in prenatal and preimplantation diagnosis. Furthermore, molecular biological investigation demonstrated that all known *CYLD* mutations lead to decreased activity of the encoded *CYLD* deubiquitinase enzyme and, thus, influence several signal transduction pathways. Currently, only symptomatic surgical treatment is available for patients with BSS, FC or MFT1. Gene expression studies of solid tumors carrying the *CYLD* mutation identified modifications in the *TRK* signaling pathway and raised the possibility that treatment with lestaurtinib could potentially be a novel therapeutic modality for patients with germline *CYLD* mutation. Future genetic studies could also provide a solid basis for the development of novel causative therapies that will be more specific and effective than the symptomatic treatments currently available for patients with the FC, BSS and MFT1 variants.

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Primary cutaneous B cell lymphoma: Clinical features, diagnosis and treatment

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lymphoma are indolent forms and often confined to skin at presentation and during the course of the disease. But primary cutaneous diffuse large B cell lymphoma, leg type and intravascular large B cell lymphoma are more aggressive forms that may disseminate to extra-cutaneous tissues. There is not a treatment consensus since they are rare entities. Local therapies like radiotherapy, surgery or intralesional steroids are options for localized disease in indolent forms. More disseminated disease may be treated with a systemic therapy like single agent rituximab. However combination chemotherapies which are used in systemic lymphomas are also required for aggressive PCBCL. Although indolent forms have relatively better prognosis, early relapses and disseminated diseases are mostly observed in aggressive form with a consequent poor prognosis.

Key words: Primary cutaneous lymphomas; Diagnosis; Treatment; Bcell lymphoma

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Abstract

Primary cutaneous B cell lymphoma (PCBCL) is defined as B cell lymphomas that presents in the skin without any evidence of extra-cutaneous involvement at diagnosis. They are the second most common type of primary cutaneous lymphomas accounting for 25%-30%. Since the prognosis and treatment differ from systemic lymphomas involving the skin, differential diagnosis is very important. PCBCL is a heterogeneous group of disease comprising different B cell lymphomas with distinct treatment and prognosis. PCBCL is divided into 5 subclasses according to World Health Organization and European Organization of Research and Treatment of Cancer classification. Primary cutaneous marginal zone lymphoma and primary cutaneous follicle center

Core tip: Primary cutaneous B cell lymphoma is a type of lymphoma that presents in the skin without evidence of extra-cutaneous involvement. Prognosis and treatment being different from systemic lymphomas involving the skin makes differential diagnosis very important. It is a heterogeneous group of diseases that consists of indolent (primary cutaneous marginal zone lymphoma, primary cutaneous follicle centre lymphoma) and aggressive forms (primary cutaneous diffuse large B cell lymphoma, leg type and intravascular large B cell lymphoma). The indolent forms are mostly confined to the skin and have good prognosis whereas aggressive forms present with disseminated disease and are treated mostly with systemic combination chemotherapies.

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INTRODUCTION

Primary cutaneous lymphomas (PCL) are neoplastic proliferation of lymphocytes in the skin. They are the second most common extranodal non-Hodgkin lymphomas. PCL can be divided into two main groups; primary cutaneous T cell lymphoma and primary cutaneous B cell lymphoma (PCBCL).

PCBCL is defined as B cell lymphomas that present in the skin without any evidence of extra-cutaneous involvement at diagnosis. They are the second most common type of PCL, accounting for 25%-30%^[1-5]. Since the prognosis and treatment differ from systemic lymphomas involving the skin, differential diagnosis becomes crucial.

PCBCL is a heterogeneous group of diseases consisting different B cell lymphomas with distinct treatment and prognosis. Their clinical presentation is relatively uniform, mostly manifested by nodules (Figure 1). The indolent forms, primary cutaneous marginal zone lymphoma (PCMZL) and primary cutaneous follicle center lymphoma (PCFCL) are often confined to the skin during the course of the disease. Although all body parts can be affected, specific distribution of the subtypes may provide information for differential diagnosis^[6].

CLASSIFICATION

PCBCL are divided into 5 subclasses according to World Health Organization and European Organization of Research and Treatment of Cancer (WHO-EORTC) classification^[2] (Table 1).

In WHO classification of tumours of hematopoietic and lymphoid tissues, primary cutaneous diffuse large B cell lymphoma, leg type (PCLBCL-LT) is classified under the heading of diffuse large B cell lymphoma not otherwise specified, NOS. PCFCL and intravascular large B cell lymphoma (IVL) are considered specific entities. PCMZL can be classified under the heading of extranodal marginal zone lymphoma of mucosa-associated lymphoid tissue (MALT lymphoma)^[7].

DIAGNOSIS AND INITIAL EVALUATION

Thorough physical examination including the inspection of all the parts of the skin and detailed history giving special attention to B symptoms (weight loss, fever, night sweats), laboratory tests including serum antibodies or polymerase chain reaction based analysis for bacterial aetiologies should be performed. An adequate biopsy of the lesion, preferably excisional biopsy or a punch biopsy of at least 4 mm for routine histology and immunohistology is crucial for the diagnosis of PCL (Figures 2 and 3). Pathological lymph nodes should be biopsied for possible involvement. Bone marrow aspiration and biopsy is optional

Table 1 World Health Organization and European Organization of Research and Treatment of Cancer classification of primary cutaneous B cell lymphoma (2005)

Primary cutaneous B cell Lymphoma
Primary cutaneous marginal zone B cell lymphoma
Primary cutaneous follicle center lymphoma
Primary cutaneous diffuse large B cell lymphoma, leg type
Primary cutaneous diffuse large B cell lymphoma, other
Intravascular large B cell lymphoma

for most of the PCBCL with indolent course but is required in more aggressive CL like PCLBCL-LT and IVL^[6,8-10]. However, differentiating early stage and rare variants of PCL from benign lymphoproliferative diseases can sometimes be complicated. Molecular analysis by demonstrating the clonality of B cells is an option^[11]. Demonstration of monoclonal rearrangement of immunoglobulin by polymerase chain reaction (PCR) is a useful diagnostic tool when used in conjunction with data from the clinician and pathologist. Flow cytometric immunophenotyping is also a feasible and reliable method for detecting clonality in PCBCLs and can provide additional prognostic and therapeutic information^[12]. Radiologic examinations [chest X-ray, ultrasonography, computed tomography (CT), and positron emission tomography combined with CT (PET/CT)] are contributory tools to exclude skin involvement of a systemic lymphoma^[6].

STAGING

TNM classification for cutaneous lymphomas other than mycosis fungoides and Sezary syndrome was established by International Society for Cutaneous Lymphomas (ISCL) and Cutaneous Lymphoma Task Force of the European Organization of Research and Treatment of Cancer (EORTC) in 2007 (Table 2). However this classification does not give much information about the prognosis and survival^[8,13].

PRIMARY CUTANEOUS MARGINAL ZONE LYMPHOMA

PCMZL is an indolent B cell lymphoma characterized by infiltration by a combination of small B cells, marginal zone cells, lymphoplasmacytoid cells, and plasma cells^[2]. According to WHO classification it is listed under the heading of extranodal marginal zone lymphoma of MALT lymphoma^[7]. Cases formerly known as “immunocytoma” as well as “non-myelomatous plasmacytomas” of skin are now included in this category. It makes up approximately 7% of all PCL^[13,14]. It is mostly presented as red to violaceous nodules sometimes surrounded by an erythematous halo, mainly on the trunk and extremities although papules and plaques have also been reported^[2,6]. Lesions may be solitary (51%), localized (26%), or multifocal (23%)^[14]. It usually presents in the fifth or sixth decade and more common in men than women^[14]. Extra-cutaneous involvement at the time of diagnosis and dissemination to extra-cutaneous sites

Table 2 International Society for Cutaneous Lymphomas and European organization of Research and treatment of cancer TNM classification staging for cutaneous lymphomas other than mycosis fungoides and Sezary syndrome

T
T1: Solitary skin involvement
T1a: A solitary lesion less than 5 cm diameter
T1b: A solitary lesion greater than 5 cm diameter
T2: Regional skin involvement
T2a: All disease in a 15-cm-diameter circular area
T2b: All disease in a 15 and 30 cm diameter circular area
T2c: All disease in a 30-cm-diameter circular area
T3: Generalized skin involvement
T3a: Multiple lesions involving 2 noncontiguous body regions
T3b: Multiple lesions involving 3 or more body regions
N
N1: Involvement of 1 peripheral lymph node region that drains an area of current or prior skin involvement
N2: Involvement of 2 or more peripheral lymph node regions or involvement of any lymph node region that does not drain an area of current or prior skin involvement
N3: Involvement of central lymph nodes
M
M0: No evidence of extra-cutaneous disease (other than lymph node)
M1: Extracutaneous disease is present (other than lymph node)

T: Tumor; N: Lymph node; M: Metastasis.

are uncommon but recurrence in the skin is frequent^[14]. Elevated lactate dehydrogenase, beta-2-microglobulin levels, abnormal complete blood count values and B symptoms are uncommon and considered as clues for a systemic disease^[14].

Although there is no clearly identified risk factor or hereditary tendency, associations with infectious agents, especially *Borrelia burgdorferi*, and autoimmune diseases have been reported. A link between the PCBCL and *Borrelia burgdorferi* has been documented in some studies in Europe and healing of the lesion with antibiotic treatment has been reported by some researchers. However, this could not be confirmed by other studies carried out especially in the United States and Asia^[15-21].

The diagnosis of the disease can be established by histopathologic examination of the skin biopsy and exclusion of a systemic disease. Excisional biopsy is preferred but if an excisional biopsy is not appropriate, it can be substituted by a punch biopsy of an adequate length^[9]. Morphologically, skin biopsy specimens depict nodular to diffuse infiltrates with sparing of the epidermis^[2,21].

The differentiation of PCMZL from reactive skin changes and other cutaneous lymphomas is important. Morphologic and immunophenotypic features and demonstration of clonality will aid in the differential diagnosis.

Treatment

Treatment depends on the symptoms of the patient, stage of the disease and the number of the lesions. The treatment options include antibiotics, rituximab, chemotherapy, intralesional interferon alfa, radiotherapy and excision.

Radiotherapy is a rational option especially for patients with solitary lesion or a few lesions that can be treated in one radiotherapy field^[6,22-25]. The margins of the radiation

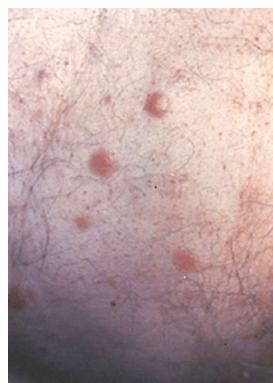


Figure 1 Primary cutaneous B-cell lymphoma. Red-brown nodules scattered on the trunk.

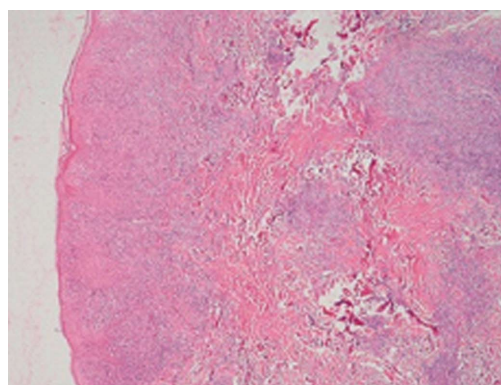


Figure 2 Widespread lymphoid infiltration with clusters of mononuclear cells involving the dermis (HE, x 10).

field should be clinically free of the disease^[6]. With local radiotherapy, complete remission (CR) and 5 year disease specific survival (DSS) rates are over 95%^[6,22,24]. Even though approximately half of the patients experience cutaneous relapses, extra-cutaneous relapses are very rare.

Surgery is used frequently in patients with local lesion. CR rate is nearly 100% but skin relapses are not so uncommon^[6]. In an Italian study, CR and relapse rates were reported as 97.4% and 31.6%, respectively. In the same study, 97.6% of the PCMZL patients achieved CR and 46.9% of them had relapse after radiotherapy^[24].

Topical steroids, triamcinolone, nitrogen mustard and cryotherapy are other local therapies with good responses^[13,25,26]. Intralesional interferon treatment is another alternative strategy. In small case series of 8 patients, CR was 100% but two of them relapsed and second CR was achieved with another cycle of IFN- α ^[25,27]. There is very limited data on intralesional^[28] or systemic rituximab^[29] treatment. Three of 5 patients achieved complete (1 patient) and partial (2 patients) responses^[29]. Although the experience with rituximab is very limited it can be an alternative treatment option. Treatments with chemotherapy with a single agent such as chlorambucil or combination of medications have also been reported in the literature, especially in multifocal diseases. The response rates are relatively good in patients with disseminated disease^[6,25]. In asymptomatic patients with disseminated disease a close

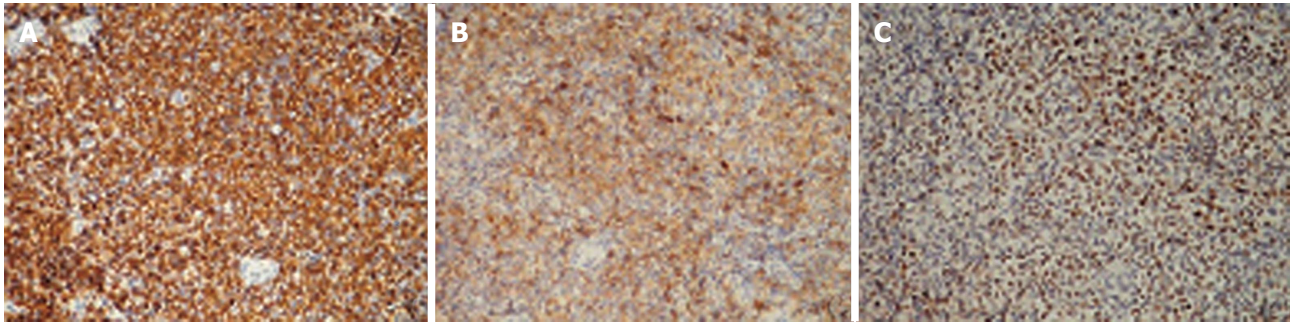


Figure 3 Immunophenotype of lymphoid cells: Immunohistochemical staining shows expression of CD20 (A), CD10 (B), and Bcl-6 (C) (Original magnifications $\times 20$).

follow up/wait-and-see strategy and treatment of only symptomatic lesions can also be performed.

A trial with an antibiotic treatment may be a rational option for *Borrelia burgdorferi* positive patients before more aggressive therapies^[6,25].

PRIMARY CUTANEOUS FOLLICLE CENTER LYMPHOMA

It is a tumour of neoplastic follicle centre cells, centrocytes and centroblasts. It is the most common type of PCBCL, accounting about two thirds of all cases^[30]. It typically presents with solitary or multiple firm, erythematous, painless, papules, plaques, or tumours in middle ages with a slight predominance in males. It has a predilection for the head, neck, and trunk. Multifocal presentation is a rare entity^[2,24,31]. It is an indolent lymphoma with a very slow progression rate and long latent period^[32]. Extra-cutaneous dissemination is a rare, just like PCMZL cases.

The diagnosis is based on the histological and immunohistochemical examination of biopsy material and ruling out the systemic disease. PCFCL shows nodular or diffuse infiltration of the dermis and subcutaneous tissue; sparing of the epidermis is almost a rule. Microscopically, typically large, often multilobulated centrocytes and large centroblasts with prominent nucleoli in variable numbers are present^[6]. Tumours show 3 different growth patterns; follicular, follicular and diffuse (mixed) and diffuse.

Differential diagnosis from systemic lymphomas and reactive follicular hyperplasia is critical since the treatment and prognosis are completely different. Strong expression of Bcl-2, Bcl-6, and CD10 and t(14,18) should raise the suspicion of systemic follicular lymphoma with skin involvement^[33]. Unlike the follicles seen in cutaneous follicular hyperplasia, the follicles in PCFCL are ill-defined, have a decreased mantle zone and lack tingible body macrophages.

According to ISCL/EORTC guidelines, bone marrow evaluation is optional for staging in PCFCL^[13]. However, bone marrow involvement is demonstrated in 11% of the patients with PCFCL presenting in the skin. Among them, bone marrow was the only extracutaneous involvement in 9 patients. Their prognosis is worse in comparison to patients presenting only with skin

involvement^[34]. Although there is not a consensus, these results indicate that BMB/A should be included in the staging system in PCFCL patients presenting with skin lesions^[6,34].

TREATMENT

Surgery and radiotherapy are the first line treatment options for single or localized lesions. Multifocal lesions can be treated with many different modalities including radiotherapy, intralesional or local therapies. Close follow up and observation may also be an option in asymptomatic patients since it is a very slowly progressive disease.

In patients presenting with solitary or localized skin lesions, radiation therapy covering also the clinically normal margins around the lesion is the preferred mode of treatment^[9]. Although radiotherapy is mostly preferred in patients with solitary or localized disease, multifocal disease can also be treated with radiotherapy^[35]. PCFCL is highly sensitive to radiotherapy with a 99% CR rate and 100% 5 year over-all survival^[9,36]. Solitary lesions that are small and well-demarcated can be treated with surgical excision but relapse rate is as high as 40% after excision^[9]. Other local treatment options with good results are topical or intralesional steroids, cryotherapy, intralesional interferon alpha^[9,27,37].

In patients with very extensive skin lesions, systemic rituximab is the first choice of treatment. Rituximab, systemic or intralesional, have been used in limited number of patients with PCFCL in the literature. CR has been achieved in 10/11 PCFCL patients treated with systemic rituximab while 3 patients had relapse after achieving CR^[38]. Intralesional rituximab also have similar effectiveness that is confirmed only in small number of cases^[9,39].

Combination chemotherapy should be considered only in patients with progressive and disseminated disease or patients with large tumour burden who do not respond to other treatment modalities^[9,23,25]. Almost one third of the patients had relapse after an initial treatment and most of the relapses occurred in the skin and can be treated with the initial treatment strategy. Dissemination to extra-cutaneous sites is uncommon^[9]. Even though it is an indolent lymphoma, lesions presenting in the leg

has poorer prognosis and these lesions should be treated more aggressively^[9].

PRIMARY CUTANEOUS LARGE B CELL LYMPHOMA, LEG TYPE

Primary cutaneous large B cell lymphoma, leg type (PCLBCL-LT) is a PCBCL with predilection to legs that is histologically characterized by infiltration by centroblasts and immunoblasts. It is classically a disease of patients in their seventies with a female predominance^[7]. It mostly occurs on legs unilaterally or bilaterally but, less than one third of the patients may present with lesions in an area other than the leg^[2,6,40,41]. The prognosis is worse compared to other PCBCLs with higher relapse rates of extra-cutaneous dissemination. Rapidly growing red or red to bluish skin lesion especially on the lower leg is typical^[2,30,40].

The differential diagnosis especially from PCFCL is important; PCFCL typically comprises centrocytes which don't express bcl2 or MUM1 in contrast to PCLBCL - LT. The site of presentation is also different since PCFCL has a predilection to trunk and head.

In contrast to indolent cutaneous lymphomas, BMB/A should be examined before initiating the therapy to exclude a systemic involvement.

Nearly all of the PCBCL-LT cases have at least one genetic alteration and half of them have combined several alterations. These mutations support lymphomagenesis with NF- κ B activation and guide for targeted therapies^[42].

Treatment

PCLBCL-LT is a more aggressive disease with extra-cutaneous progression, lower remission and higher relapse rates^[24,41]. Multiple skin lesions, bcl-2 expression, are independent prognostic factors in these patients^[43]. Patients who presents with multiple lesions on the leg has worse prognosis than lesions on other sites or single lesions^[43]. Another factor with a high prevalence associated with poor prognosis in PCLBCL-LT patients is MYD88L265P mutation^[44]. This mutation activates the nuclear factor- κ B pathway and is associated with shorter survival rates. Patients harboring this mutation will be candidates for new targeted therapies in the future^[44].

Local disease control methods like radiotherapy or topical treatment are not effective in PCLBCL -LT patients. Five year overall survival and disease free survival have been calculated as 67% and 33%, respectively, when treated with radiotherapy^[36]. More than half of the patients relapse after RT^[9]. Radiotherapy is an option as a palliative regimen especially in elderly patients who cannot be treated with systemic therapies^[6,25].

Single agent rituximab is a reasonable therapy for elderly who can't tolerate combination chemotherapies. In a retrospective analysis of 60 PCLBCL-LT patients, all but one patient achieved CR (91.6%), with a 2 year survival of 81% when treated with combination chemotherapies plus rituximab. Two year survival rate

was 59% in the group of patients who were treated with other therapies and CR rate was 62%^[41].

Similar to systemic diffuse large B cell lymphomas, PCLBCL-LT should be treated with anthracyclin based combination chemotherapies with or without rituximab. RT can supplement systemic chemotherapies. RCHOP $\pm$ rituximab should be considered as first line chemotherapy^[2,9,41]. Since large randomized clinical trials are lacking, the efficacy of the treatment options are not well documented.

Primary cutaneous DLBCL others, are lymphomas rather than DLBCL-LT^[2]. It is a rare entity including morphologic variants of diffuse large B-cell lymphoma, such as anaplastic or plasmoblastic subtypes or T-cell/histiocyte rich large B-cell lymphomas and^[2] intravascular large B cell lymphoma cutaneous variant.

INTRAVASCULAR LARGE B CELL LYMPHOMA

Intravascular large cell lymphoma (ILCL) is a rare subtype of large cell lymphoma that is characterized by the proliferation of lymphoma cells within the lumina of small blood vessels. They are more common in elderly patients, with a predilection to central nervous system and skin^[2,45-47]. It has poor prognosis. The diagnosis is difficult because of divergent clinical presentation and absence of lymphadenopathy. Random skin biopsy is beneficial for early diagnosis in ILCL^[48].

Cutaneous variant of the disease presents with nodules, plaques, or macules in younger female patients^[47]. The clinical presentation is diverse with painful, indurate, erythematous eruption, poorly circumscribed plaques, large solitary plaques, painful blue-red palpable nodules, tumours, ulcerated nodules, small red palpable spots, and erythematous and desquamated plaques. Lesions may be single or multiple, mostly on the leg, thigh and trunk^[47]. Pain and oedema usually accompany the lesions. The differential diagnosis from inflammatory diseases and erythema nodosum is critical.

Patients mostly present with a disseminated disease even though there are also cases with lesions confined to the skin only. Blood vessels are filled with neoplastic B cells that cause occlusion of the venules, capillaries and arterioles. Immunophenotypically, the neoplastic cells are mature B cells but rarely T cell phenotype can be seen^[47]. B symptoms and bone marrow involvement are less common in cutaneous variant. Cutaneous variant has a better prognosis with a 3 year survival of 56% and better performance status^[47]. Multiagent chemotherapies are the preferred therapies in these patients^[9].

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Salivary gland disease in human immunodeficiency virus/ acquired immunodeficiency syndrome: A review

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oral manifestation and causes substantial morbidity. Parotid gland swelling due to sicca syndrome, parotid lipomatosis, sialadenitis, diffuse infiltrative lymphocytosis syndrome, benign lymphoepithelial lesions, neoplasms (benign or malignant) of salivary gland, parotid gland inflammation, diminished flow rates of saliva and xerostomia have been documented that also affects the health- associated characteristics of life in subjects infected with HIV. There is a necessity for health care researchers to diagnose it, particularly as it might worsen if left undiagnosed. The precise characteristic of alterations in dynamics of salivary gland structure and functionality with long-standing usage of highly active anti-retroviral therapy still remains unknown. HIV positive children also present with bilateral parotid enlargement and the syndrome state with classical clinical and cytological features of predominated lymphoid hyperplasia. Though various case reports and studies have been extensively published on different aspects of HIV-SGD, it has not been described solely, thus leading to occasional confusion of nomenclature and clinical presentation of HIV-SGD. This article reviews the pathogenesis of HIV-related SGD and its components and various other miscellaneous disorders affecting the salivary glands in HIV/AIDS.

Key words: Human immunodeficiency virus; Acquired immunodeficiency syndrome; Salivary gland diseases; Antiretroviral therapy; Highly active; Xerostomia

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Abstract

The effect of human immunodeficiency virus (HIV) infection on salivary glands has diagnostic and prognostic significance. HIV-salivary gland disease (HIV-SGD) is comprehensively ascertained amongst the major critical acquired immunodeficiency syndrome (AIDS)-related

Core tip: Since the discovery of human immunodeficiency virus (HIV), the world has kept acquired immunodeficiency syndrome high on the agenda, rallying around global and regional commitments to turn the tide on HIV infection. There is limited data on the documentation of HIV salivary gland disease and the influence of highly active anti-retroviral therapy occurring on various components of salivary gland disorders in HIV. The purpose of

writing this article is to review the clinical manifestations and the pathogenesis of salivary gland disorders in HIV in era of antiretroviral therapy and provide an update on latest treatment modalities in the management of various salivary gland disorders.

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INTRODUCTION

Since the discovery of human immunodeficiency virus (HIV), the world has kept acquired immunodeficiency syndrome (AIDS) high on the agenda, rallying around global and regional commitments and goals to address and turn the tide on HIV infection. HIV affects almost all the structures in the body. Patients with HIV infection are prone to salivary gland disease. The initiation of highly active antiretroviral therapy (HAART) has coincided with reduced prevalence of oral manifestations in HIV/AIDS infected patients in the developed and developing countries. These oral manifestations can act as markers of immune reconstitution or as a marker of HAART failure. However, there is limited data on the documentation of HIV salivary gland disease (HIV-SGD) and the effect of HAART on various components of salivary gland disorders in HIV. In resource constrained nations, the relatively easier diagnosis of HIV-SGD can help in the early diagnosis of HAART failure, thus helping in an early initiation of other drugs in HAART. The purpose of writing this article is to review the clinical manifestations and the pathogenesis of salivary gland disorders in HIV in era of antiretroviral therapy and provide an update on the latest treatment modalities in the management of various salivary gland disorders.

HIV-SGD

The latest criteria given by the Oral HIV/AIDS Research Alliance (OHARA) gives description of SGD as asymptomatic long standing enlargement of parotid glands, usually bilaterally^[1]. The clinical presentation of HIV-SGD simulates Sjögren's syndrome. There are however noticeable serologic and histopathological distinctions concerning both the diseases^[2]. There is absence of anti-Ro (SS-A) and anti-La (SS-B) antibodies in subjects with HIV-SGD. HIV-SGD is typically seen in young males as compared to Sjögren's syndrome that occurs predominantly in middle aged females^[2]. In HIVSGD, minor salivary gland histopathology constitutes predominantly peri-acinar, perivascular, and periductal lymphocytic infiltrates with most of the penetrating cells being CD8 cells^[2]. With the advent of HAART, the prevalence of HIV-SGD has increased in developed countries. The prevalence has

been reported to be 5% (Patton *et al*^[3]) - 10% (Mandel *et al*^[4]). Navazesh *et al*^[5] had found an increased prevalence of HIV-SGD in a study of HIV infected women where HAART primarily comprised of Protease inhibitors. In contrast, in developing countries there have been few cases of HIV-SGD following HAART^[6-8]. The probable association between HIVSGD pathogenesis and BK polyomavirus (BKPyV) has been validated with demonstration of HIVSGD-derived BKPyV oral tropism and proficient viral copying in salivary gland cells^[9]. The presence of lymphoid tissue within a salivary gland capsule has been observed only in parotid gland while the submandibular lymph nodes lie adjacent to, but outside the glandular capsule^[9]. An awareness of HIV-SGD may prevent unnecessary surgeries in these patients, a biopsy being necessary only in those cases suspected of harboring a malignancy^[10]. The homeostasis of the oral cavity is altered in subjects with HIV-SGD due to quantitative variations ensuing in the saliva such as reduced secretory levels of lysozyme, sodium, calcium chloride, total anti-oxidant capacity and cystatin^[11].

XEROSTOMIA AND HAART

HIV infected patients have been reported to be having a considerably greater possibility of salivary gland hypofunction and xerostomia as compared to patients who are not infected^[12]. Xerostomia has been documented in HIV subjects with varying prevalence ranging from 10% in American homosexual males, 9% in 74 Dutch patients, 35.5% of 200 Indian patients, and 80% patients from Peru^[13-16]. The reduced absolute CD4 cell counts were substantially correlated with a greater frequency of zero unstimulated salivary flow rates in HIV patients^[17]. Lin *et al*^[18] had reported that there is reduction in unstimulated salivary flow rates and stimulated salivary flow rates even in early stages of HIV infection. Reduced salivary flow rates have also been attributed to HIV infection, side effect of HAART, or in correlation to considerable salivary gland disease^[19,20]. It is difficult to determine whether the subjective alterations related to salivary flow (hyposalivation, xerostomia, and dysgeusia) can be attributed to HIV disease or HAART^[21]. Among HAART, protease inhibitors (PI) and nucleoside reverse transcriptase inhibitors (NRTIs) have been especially been known to induce xerostomia probably by exertion of an anti-secretory effect on acinar cells^[12]. Other researchers had suggested that the PIs changes adipose tissue deposition within the salivary gland^[22]. However López-Verdín *et al*^[21] and Nittayananta *et al*^[6] found no significant difference in salivary flow rates when they compared HAART with PIs and HAART without PIs.

HIV p24 antigen in the salivary gland and a viral load of greater than 10000 copies were also found to correlate with a higher prevalence of xerostomia^[23]. There was a reduction of stimulated and unstimulated salivary flow rates in HIV patients on HAART^[6,12]. A considerable diminution of saliva in response to proportion of the increased number of years of usage of antiretroviral therapy has

also been reported^[21]. However documentation in all the epidemiologic studies has relied on the presumptive criteria of EC-Clearinghouse classification which will not give the true prevalence of xerostomia. Most studies have been done on limited sample size, have been cross sectional and the terminologies of salivary gland hypofunction and xerostomia have been interchanged frequently for subjective signs and objective clinical observations^[12]. The subjective (finding negligible saliva) and objective (*i.e.*, clinical presentation of major salivary glands, stimulated and unstimulated salivary flow rates) processes have been comprehensively documented in very few studies^[6,12,17]. However, studies have taken different parameters like unstimulated and chewing gum stimulated whole saliva and parotid gland saliva. Wang *et al*^[24] had found unstimulated whole salivary flow rates to be more sensitive to dry mouth complaints rather than stimulated whole salivary flow rate. Therefore research should be conducted on unstimulated whole saliva in a preferably longitudinal study to understand the exact effects of HAART and HIV on salivary gland hypofunction.

The sequelae of reduced salivary flow are increased caries prevalence, increased oral candidiasis, dysgeusia and periodontal diseases^[17,21]. The Usage of crystal methamphetamine is frequented with greater HIV acquisition, and it is correlated to sudden generalized dental caries recognized as “meth mouth” in HIV positive patients^[25]. Lithium, muriatic and sulfuric acids and lye, the constituents of crystal methamphetamine, have been considered as causative factors. In a study conducted in 2009, high concentrations of the HIV p24 antigen in the salivary gland and a viral load of greater than 10000 copies were found to correlate with a higher prevalence of xerostomia^[5].

PAROTID LIPOMATOSIS

Abnormal fat deposition in HIV patients on HAART (PI) has been documented in abdomen, dorsal cervical areas and Parotid gland^[26]. Olivé *et al*^[27] were first to document parotid lipomatosis in two patients on Protease Inhibitors. The protease inhibitors stimulate peripheral lipodystrophy that is triggered by inhibition of proteins which control metabolism of lipids^[26]. The above process ensues in decreased differentiation and a rise in peripheral adipocytes's apoptosis with impaired fat storage^[27].

LYMPHOEPITHELIAL CYSTS

A rare condition of Lymphoepithelial lesions observed in the parotid gland is correlated with a greater frequency in HIV patients^[28]. The persistent generalized lymphadenopathy (PGL) is a characteristic feature of HIV patients. Lymphoepithelial lesions represent a probable confined or limited expression of PGL^[28]. However, the etiopathogenesis of lymphoepithelial lesions is still unknown. The lymphoepithelial lesions may originate from inclusions of the major salivary gland located in lymph nodes (mainly intra-parotid lymph nodes). Another

possibility of lymphoepithelial lesion developing from the parenchymal component of the salivary glands has also been postulated^[28-30]. Parotid lympho epithelial cysts are easily diagnosed by ultrasonography. These lesions often become large leading to societal stigmata^[28]. The lymphoepithelial lesions are typically benign. However there is always a distinct possibility of their conversion to lymphomas. Thus, continuous and periodic follow-up should be conducted for these lesions and should not be disregarded^[31]. There are also bilateral parotid swellings observed in diffuse infiltrative lymphocytosis syndrome (DILS), a condition typified by a penetration of constant CD8 cells lymphocytosis that results in swelling of the gland^[4,28].

DiGiuseppe *et al*^[32] postulated persistent generalized lymphadenopathy to be a cause of benign lymphoepithelial lesions in parotid gland. An increased viral load is also known to be associated with salivary gland enlargement by altering the expression of strategic cellular genes^[33]. Ihrler *et al*^[30] had demonstrated a secondarily lymphoid penetration of parenchymal component of the salivary gland that induces a lymphoepithelial reaction of striated salivary gland ducts. Owotade *et al*^[34] had reported 5 cases of parotid gland enlargement and had managed them with different modalities like Fine needle Aspiration, Anti-retroviral therapy and parotidectomy.

The conditions that can simulate lymphoepithelial cysts are salivary gland duct retention cyst (mucocele), mucosa associated lymphoid tissue lymphoma that may possess cystic constituent and polycystic parotid disease^[35]. The possibility of papillary cystadenoma lymphomatosum should also be excluded in these patients^[36].

RANULA

The involvement of ranula as an oral manifestation in HIV patients has been suggested which still has not been established. However, Syebele *et al*^[37] had demonstrated a mixed and delayed response (3-6 mo) of ranulas for regression to HAART. The precise etiopathogenesis of the association amongst these dual dissimilar pathological conditions is ambiguous. Chidzonga *et al*^[38] had documented a high prevalence rate (88.5%) of HIV subjects within a cohort of 38 patients with sublingual ranula. A case report documented that without any surgical intervention, sublingual mucocele had entirely lapsed after initiation of HAART^[39]. Syebele *et al*^[39] had also proposed research on association between ranulas and HIV infection to establish the likely result of HAART on ranula. Case control studies are required to evaluate the degree of periductal lymphocytosis, isolation of viral particles and chemical analysis of the mucus present in ranula^[40].

SALIVARY GLAND NEOPLASMS

Patients with HIV/AIDS demonstrate augmented possibility of malignancy, predominantly viruses triggered cancers^[41]. The greatest risk for salivary gland carcinoma was found to be lymphoepithelial carcinoma, which is

an undifferentiated carcinoma associated with Epstein Barr virus and also having a prominent non-neoplastic lymphoplasmacytic infiltrate^[41]. The most common site of involvement is parotid gland. The common histological subtypes of salivary gland malignancy like mucoepidermoid carcinoma and adenoid cystic carcinoma seen in general population are not commonly seen in HIV patients^[41]. High grade Non-Hodgkin's lymphoma and Kaposi's sarcoma are the other frequent malignancies associated with salivary glands in HIV patients^[42]. The greater probability of squamous cell carcinomas of both nasopharynx and salivary glands could be ascribed to tobacco or alcohol usage, which are frequent in HIV subjects and related to other malignancies in the head and neck region^[43]. Rare case reports of primary squamous cell carcinoma affecting Stensen's duct and developing from Cheilitis glandularis were documented in subjects infected with HIV^[44,45].

HIV-ASSOCIATED SIALADENITIS AND SICCA COMPLEX

In a study conducted in 2009 in 105 AIDS patients the researchers found the most common infectious conditions affecting the sublingual and submandibular glands were mycobacteriosis followed by cytomegalovirus (CMV) and cryptococcosis^[46]. HIV p24 was observed in lymphocytes and macrophages correspondingly^[46]. The highest prevalence of cells seen in chronic nonspecific sialadenitis were CD8 lymphocytes, while CD68 macrophages were predominant in the mycobacteriosis-associated granulomatous and nonspecific diffuse macrophagic sialadenitis^[46]. Parotid gland histopathological changes were observed in more than half of the HIV infected patients in a research conducted by Vargas *et al*^[47]. Chronic sialadenitis of non-specific origin (29 cases) was the frequent change observed followed by various conditions of infectious origin (22 cases). Amongst the infectious conditions, 10 patients had Mycobacteriosis, followed by nine patients with cytomegalovirus infection, cryptococcosis in three patients and lastly histoplasmosis in two patients^[47]. Wax *et al*^[48] had reported three patients of CMV sialadenitis who clinically had nodules in parotid gland in HIV/AIDS patients. A possible complication of sialolithiasis in HIV positive patient with the usage of HAART drug atazanavir was suggested^[49].

SALIVARY GLAND DISEASE IN CHILDREN

HIV positive children often present with bilateral parotid enlargement and the syndrome state with classical clinical and cytological features of lymphoid hyperplasia predominated^[50]. Parotid gland enlargement is a common condition found in pediatric patients with HIV infection. In the pediatric HIV population, its prevalence is 1% to 10%^[51]. DILS or Sjogren syndrome- resembling condition, first seen in pediatric HIV infection, is a CD8 lymphocyte facilitated syndrome that might involve the submandibular

as well as parotid salivary glands^[52]. HLA-DR11 and HLADR5 have been associated with salivary gland enlargement in HIV infected children signifying a possible genetic predilection^[53].

RECENT ADVANCES IN RESEARCH AND MANAGEMENT OF SALIVARY GLAND DISEASE

More studies need to be done for exact association between HAART and hypo salivation. Longitudinal studies documenting xerostomia need to be done measuring the salivary flow subjectively prior to HAART and after HAART. There should be more research on the role of Ranula as an oral mucosal finding in HIV patients. Artificial salivary glands are also being formulated^[54]. HAART's success has resulted in patients with xerostomia, a risk factor for caries and its potential sequelae, thus affecting the patient's quality of life.

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Trichoscopy: Essentials for the dermatologist

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up of hair and scalp disorders. Structures which may be visualized by trichoscopy include hair shafts of different types, the number of hairs in one pilosebaceous unit, hair follicle openings (dots), the peri and interfollicular areas and the vasculature. This review summarizes the current knowledge about trichoscopic findings which may aid in the diagnosis of alopecia. Besides diagnosing alopecia, it has the potential for obviating unnecessary biopsies and when a biopsy is still needed it is helpful in choosing an ideal biopsy site. Moreover, trichoscopy can be a valuable tool for evaluating the treatment response photographically at each follow-up. Finally, we have discussed the utility of dermoscopy in inflammatory scalp disorders and infections.

Key words: Alopecia; Dermatitis; Scalp; Dermoscopy; Dermatoscopy; Epiluminiscence microscopy; Diagnosis

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Core tip: Trichoscopy refers to the dermoscopy of the hair and scalp disorders. This is a noninvasive, in office technique that can be performed with a hand-held dermatoscope or a digital videodermoscopy system. Trichoscopy is useful for the diagnosis and follow-up of hair and scalp disorders. In this article, we have briefly described the most important trichoscopic patterns and structures.

Abstract

Noninvasive *in vivo* imaging techniques have become an important diagnostic aid for dermatology. Dermoscopy, also known as dermatoscopy, has been shown to increase the clinician's diagnostic accuracy when evaluating cutaneous neoplasms. Dermoscope, both hand-held and videodermoscope, are nowadays a basic instrument for almost all the dermatologists around the world. Trichoscopy is the term coined for dermoscopic imaging of the scalp and hair. Routinely using dermoscopy and recognizing the structures and patterns of the different types of alopecia will likely improve the observer's sensitivity for diagnosis and follow

Moreno Romero JA, Grimalt R. Trichoscopy: Essentials for the dermatologist. *World J Dermatol* 2015; 4(2): 63-68 Available from: URL: <http://www.wjgnet.com/2218-6190/full/v4/i2/63.htm>
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INTRODUCTION

Non-invasive *in vivo* imaging techniques have become an important diagnostic aid for evaluating hair and scalp disorders. Trichoscopy is the term coined for

Table 1 Hair shafts

> 20% of vellus hairs	AGA, long lasting AA
Exclamation mark hairs	AA, trichotillomania, chemotherapy-induced alopecia
Pohl-Pinkus constrictions	AA, chemotherapy-induced alopecia, blood loss, malnutrition, chronic intoxication
Comma hairs	Tinea capitis
Corkscrew hairs	Tinea capitis
Coiled hairs	Trichotillomania
Flame hairs	Trichotillomania
Tulip hairs	Trichotillomania, AA
Regrowing pigtail hairs	AA, cicatricial alopecia
Zig-zag-shaped hairs	Tinea capitis

AGA: Androgenetic alopecia; AA: Alopecia areata.

dermoscopic imaging of the scalp and hair.

Trichoscopy is a simple and non-invasive technique that can be performed with both handheld dermatoscope and digital videodermatoscopy system^[1]. The usual working magnifications with videodermatoscope are 20-fold to 70-fold. While the hand-held dermatoscope with 10-fold magnification may give easy and quick evaluation of hair, it does not precisely measure or document the observed findings^[2].

The method allows quick identification of hair and shaft abnormalities without the need of hair sampling for *ex vivo* evaluation, *i.e.*, optical or scanning electron microscopy. It is also a helpful tool in differential diagnosis of common acquired hair diseases, such as androgenic alopecia or diffuse alopecia areata^[2].

TRICHOSCOPY STRUCTURES AND PATTERNS

Structures which may be visualized by trichoscopy include hair shafts, hair follicle openings, the perifollicular epidermis and the cutaneous microvessels.

Hair shafts

Trichoscopy allows analysing acquired and congenital hair shaft abnormalities.

Dermoscopy of the normal scalp shows regularly distributed follicular units, containing 1-4 hair shafts^[1]. A normal terminal hair is uniform in thickness and color throughout its length. However, up to 10% of normal scalp hairs are vellus hairs that are lightly pigmented and measure < 3 mm in length and < 30 µm in thickness^[1,3].

Trichoscopy also allows diagnosing most genetic hair shaft dystrophies such as monilethrix, trichorrhexis nodosa, trichorrhexis invaginata, pili torti or pili annulati^[4] (Table 1).

Hair follicle openings: Dots

The term "dots" refers to the small, round hair follicle openings seen on trichoscopy. Trichoscopy may distinguish

Table 2 Dots

Black dots	Active AA, dissecting cellulitis, tinea capitis, chemotherapy-induced alopecia, trichotillomania, after laser depilation, after trichogram, incidental finding in other diseases
Yellow dots	AA: Marker of disease severity Discoid lupus erythematosus: Large, dark yellow to brownish-yellow dots Androgenic alopecia: "Oily" appearance and predominance in frontal area Dissecting cellulitis, trichotillomania: Imposed over dark dystrophic hairs
White dots	Primary folliculocentric alopecias, lichen planopilaris: Fibrotic white dots Dark skin, sun exposed areas: Pinpoint white dots
Red dots	Discoid lupus erythematosus, vitiligo
Pink-grey/grey dots	Frontal fibrosing alopecia (eyebrows)

AA: Alopecia areata.

whether hair follicle openings are normal, empty, fibrotic or containing biological material, such as hyperkeratotic plugs or hair residues.

Black dots (cadaverized hairs) represent pigmented hairs broken or destroyed at scalp level.

Yellow dots are follicular infundibula with keratotic material and/or sebum. They vary in color, shape and size^[4].

White dots may appear as fibrotic white dots or pinpoint white dots. The classic, big, irregular white dots represent areas of perifollicular fibrosis, observed in primary, folliculocentric cicatricial alopecias, and most commonly in lichen planopilaris^[3]. The pinpoint white dots are small and regular, with occasional peripheral hyperpigmentation. They correspond to empty hair follicles or to the eccrine sweat ducts openings. They are observed in sun exposed areas and in dark skin phototypes.

Red dots have been described in discoid lupus erythematosus and in patients with vitiligo.

Pink-grey and grey dots have been observed in the eyebrow area of patients with frontal fibrosing alopecia^[3]. This finding is believed to be a favourable prognostic factor for eyebrow regrowth (Table 2).

Peri and interfollicular areas

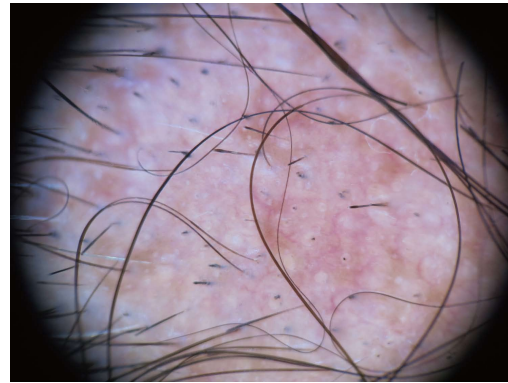
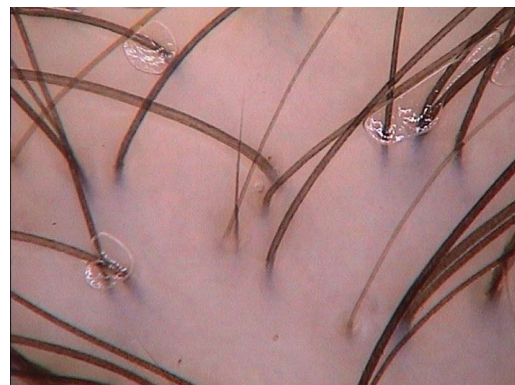
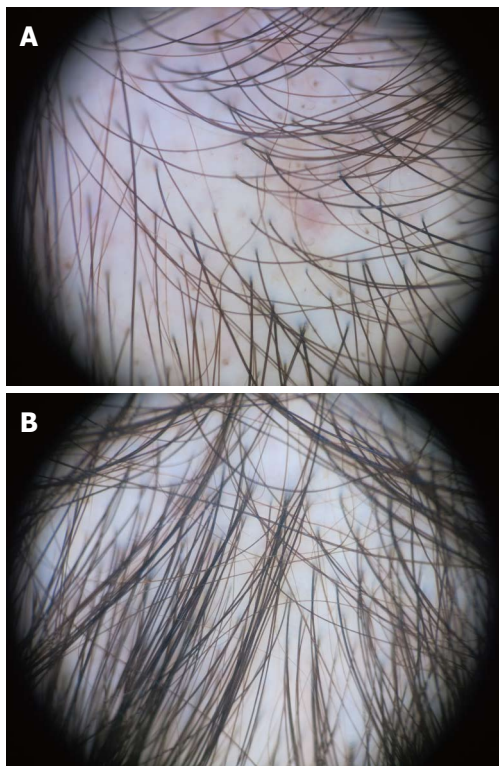
The classification of peri- and interfollicular skin surface abnormalities in trichoscopy is based on features related to scaling, color, discharge and surface structure^[3] (Table 3).

Blood vessels

Appearance of cutaneous microvessels in trichoscopy may vary in type and number depending on disease and activity of the process. Several inflammatory scalp disorders are characterized by a specific pattern of blood vessel arrangement on trichoscopy^[3,4].

Table 3 Peri- and interfollicular areas

Epidermal scaling	Diffuse scaling: Healthy individuals, psoriasis, seborrheic dermatitis Perifollicular scaling and tubular scaling structures: Lichen planopilaris, frontal fibrosing alopecia, folliculitis decalvans
Hyperpigmentation	Honeycomb: Sun exposed areas, dark skin phototypes Perifollicular: Androgenetic alopecia Scattered interfollicular: Discoid lupus erythematosus
Yellow or yellow-red discharge	Folliculitis decalvans, bacterial infections, dissecting cellulitis, tinea capitis
Structural changes in the skin surface	Starburst pattern hyperplasia in folliculitis decalvans


Figure 1 Male androgenetic alopecia. Hair shaft thickness heterogeneity and predominance of follicular units with only one hair (Dermlite photo®).

Figure 3 Alopecia areata. Exclamation mark signs and black dots (Dermlite photo®).

Figure 4 Telogen effluvium. Short regrowing hair (videodermoscopy, 70 x magnification). Photo courtesy of Prof. Lidia Rudnicka.

Figure 2 Female androgenetic alopecia. Significant (> 20%) diversity of hair shaft diameter. Note also yellow dots. Higher hair density and less variability in the occipital area (B) compared to the frontal area (A) (Dermlite photo®).

ALOPECIA

The interest for trichoscopy had greatly increased in the last years. There is an extensive literature on the different types of alopecia. Nowadays it has become an indispensable technique in the evaluation of the hair loss patient.

We have summarized the main trichoscopic findings in the most common types of non cicatricial (Table 4) (Figures 1-5) and cicatricial alopecia (Table 5, Figures 6-8). In addition, there are some diagnostic algorithms in use for alopecia using trichoscopy (Figure 9).

ADVANTAGES AND LIMITATIONS OF TRICHOSCOPY

Standard methods used to diagnose hair disorders are clinical inspection, pattern of hair loss, pull test, trichogram, biopsy, chronology of preceding events, and screening blood test. They vary in sensitivity, reproducibility, and invasiveness. There is accumulated evidence that the use of trichoscopy in the clinical evaluation of hair disorders improves diagnostic capability beyond simple clinical inspection^[5-7]. Trichoscopy have the advantages of being a quick and non-invasive, semiquantitative method. Trichoscopy allows to evaluate larger areas than other invasive techniques like biopsy or

Table 4 Trichoscopic findings in common types of non cicatricial alopecia

AGA	AA	Telogen effluvium	Trichotillomania
Hair shaft thickness heterogeneity	Exclamation mark hairs	Empty follicles	Simultaneous, chaotic coexistence of multiple hair shaft abnormalities
Increased proportion of vellus hairs	Broken hairs	Increased proportion of single-hair follicular units	Hairs broken at different lengths
> 10% thin hairs in the frontal area	Clustered short vellus hairs	Short regrowing hairs	Short hairs with trichoptilosis (split ends)
Increased proportion of single-hair follicular units	Pigtail hairs	< 20% hair diameter diversity	Coiled hairs
Yellow dots	Black dots	Brown perifollicular discoloration	Exclamation mark hairs
Perifollicular discoloration (peripilar sign)	Numerous yellow dots	No significant difference between frontal and occipital areas	Black dots
All the trichoscopic features appear most prominently in the frontal scalp area compared to the occipital area			Others: flame hairs, V-sign, hook hairs, hair powder and tulip hairs

AGA: Androgenetic alopecia; AA: Alopecia areata.

Table 5 Trichoscopic findings in common types of cicatricial alopecia

LPP	FFA	DLE
Intense perifollicular scaling, tubular structures	Minor perifollicular scaling	Large yellow dots (follicular keratotic plugs)
Violaceous inter or perifollicular areas	Perifollicular erythema	Mottled dyschromia
Fibrotic white dots	Strong predominance of single-hair follicular units at the hair-bearing margin	Thin and radial arborizing vessels that emerge from yellow dots ("red spider in yellow dot")
Blue grey dots	Absence of vellus hairs	Thick arborizing vessels at the periphery of the lesion
Small hair tufts	Pink-grey and grey dots in the lateral eyebrow area	Follicular red dots

LPP: Lichen planopilaris; FFA: Frontal fibrosing alopecia; DLE: Discoid lupus erythematosus.

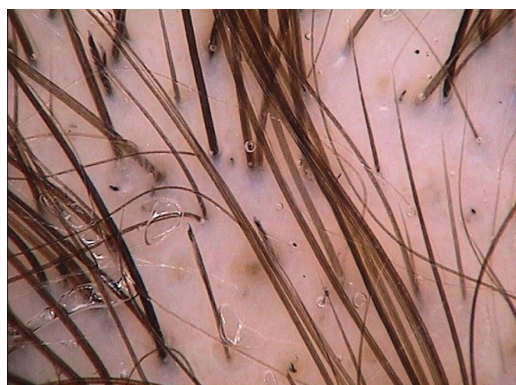


Figure 5 Trichotillomania. Hairs broken at different lengths, with trichoptilosis (split end) and black dots (videodermoscopy, 70 × magnification). Photo courtesy of Prof. Lidia Rudnicka.

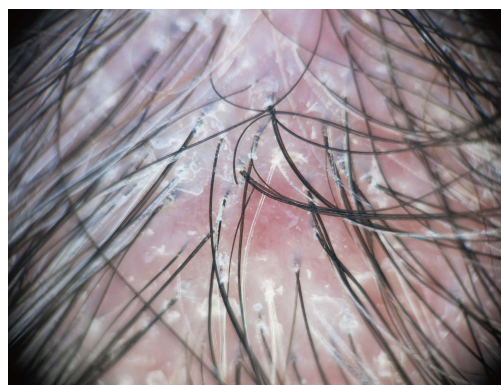


Figure 6 Lichen planopilaris. Intense perifollicular scaling and tubular structures (Dermlite Photo®).

trichogram.

A recent study have demonstrated superiority of trichoscopy as compared to the trichogram, in the diagnosis of female androgenetic alopecia, especially in early cases^[8].

An additional advantage of trichoscopy is that it allows digital surveillance and monitoring of the patients. Photographic evaluation at each visit is very appreciated by patients^[9].

By the other hand, the use of trichoscopy can result in lower diagnostic accuracy if the physician does not

recognize or correctly interpret the significance of structures. Moreover, trichoscopy can lead to lower diagnostic accuracy when patients are diagnosed using dermoscopy alone, without clinical context.

OTHER USES OF TRICHOSCOPY

Dermatoscopy in inflammatory scalp disorders and infections

Psoriasis and seborrheic dermatitis: Dermatoscopy of both cases shows diffuse or localized scales, which tend to be more yellowish in seborrheic dermatitis and



Figure 7 Frontal fibrosing alopecia. Absence of follicular openings, predominance of follicular units with only 1 hair, mild perifollicular scaling and perifollicular erythema (Dermlite photo®).

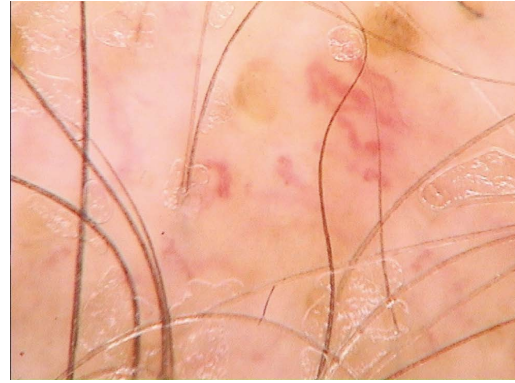


Figure 8 Discoid lupus erythematosus. Characteristic large yellow dots and arborizing vessels (videodermoscopy, 70 x magnification). Photo courtesy of Prof. Lidia Rudnicka.

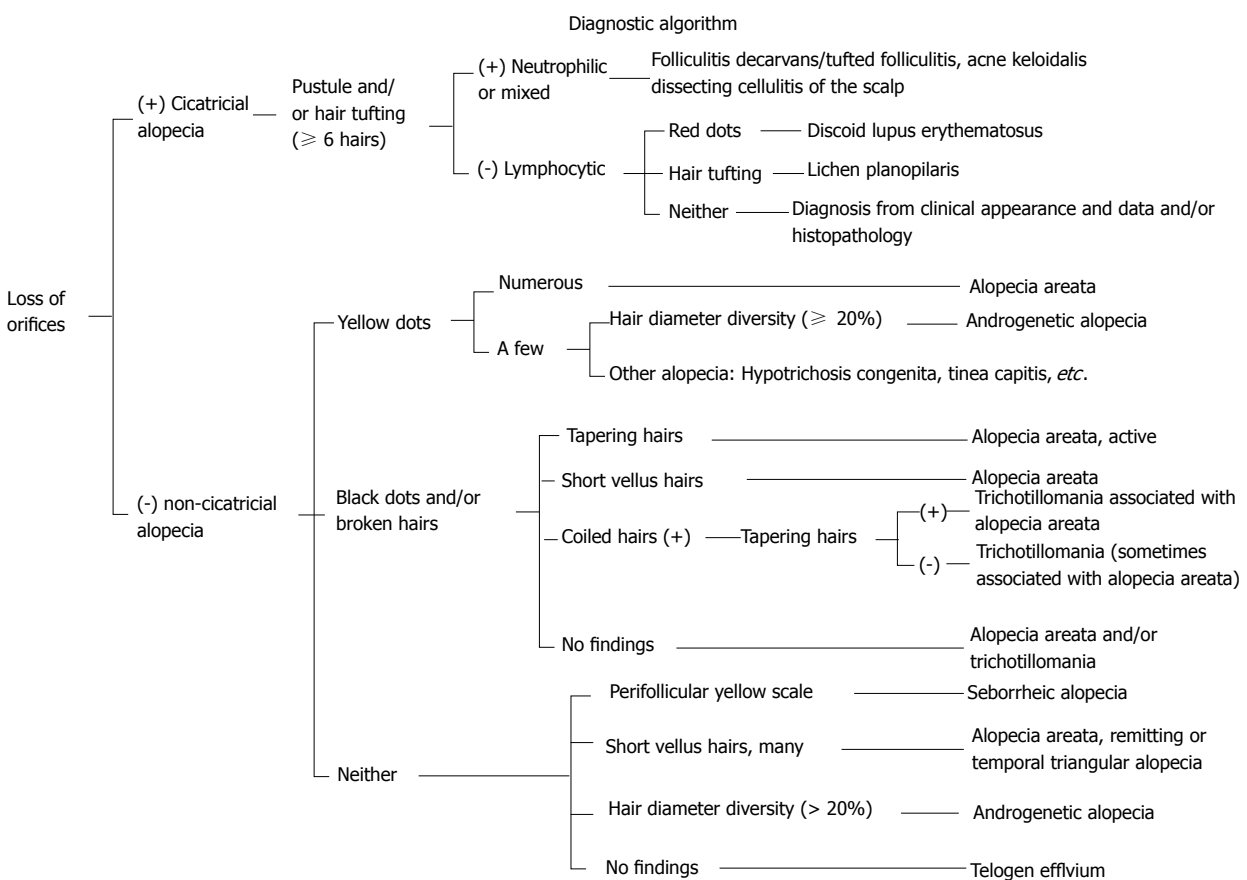


Figure 9 Diagnostic algorithm for trichoscopic findings of hair loss diseases. From Inui S. Expert Rev Dermatol 2012: 7.

more withish in psoriasis.

The major difference in this cases is the vascular pattern. Psoriasis shows red dots, globules and glomerular vessels. In seborrheic dermatitis the most common findings are arborizing and atypical red vessels and the absence of red dots and globules^[1].

Pediculosis capitis: Trichoscopy is useful to observe the adult parasites ant to evaluate if the nits are empty or not.

Piedra and tinea capitis: Many features have been

described in mycotic infections and dermatoscopy is very useful in these cases.

Trichoscopy guided biopsy

Trichoscopy may be used to select the best area from which to obtain a biopsy specimen^[3].

Trichoscopy in general medicine

This includes possible application of trichoscopy in identifying follicular spicules in multiple myeloma, follicular mucinosis in lymphoproliferative disorders, scalp lesions in Langerhans histiocytosis or altered

interfollicular microvessels in dermatomyositis and scleroderma^[4].

Ex vivo dermatoscopy of scalp biopsies

Ex vivo assessment of scalp biopsies by dermatoscopy can identify the correct plane of transversal bisection and it is useful to control the tissue processing^[10].

Trichogram using dermatoscopy

It has been proposed the use of dermatoscopy when performing a trichogram, instead of using the optical microscope, as most of dermatologist nowadays have a dermoscope^[1].

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Mycosis fungoides and Sézary syndrome: Role of chemokines and chemokine receptors

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syndrome is an aggressive leukemic form of CTCL characterized by a clonal population of malignant T cells in the peripheral blood. Various forms of skin-directed and systemic treatments are available for mycosis fungoides and Sézary syndrome. However, current treatments are generally not curative, and can only control the disease. Currently, the etiology and pathogenesis of mycosis fungoides and Sézary syndrome are not well defined. Proposed mechanisms include chronic antigenic stimulation by infectious agents, expression of specific adhesion molecules, altered cytokine production, mutations of oncogenes and tumor suppressor genes, and avoidance of apoptosis. In recent years, a number of chemokine receptors and their corresponding chemokine ligands have been found to contribute to the migration and survival of lymphoma cells in mycosis fungoides and Sézary syndrome, including CC chemokine receptor 4 (CCR4), CCR10, C-X-C chemokine receptor type 4 (CXCR4), CCR7, CCR3 and CXCR3. Since chemokines and chemokine receptors have been found to play important roles in the pathophysiology of mycosis fungoides and Sézary syndrome, they may be potentially useful targets for the development of new treatments for these diseases in the future.

Key words: Mycosis fungoides; Sézary syndrome; Skin-homing; Chemokines; Chemokine receptors

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Abstract

Mycosis fungoides is the most common form of cutaneous T-cell lymphoma (CTCL), and is characterized by a clonal expansion of malignant CD4⁺ T lymphocytes with skin-homing properties. Clinically and pathologically, mycosis fungoides can be categorized into patch, plaque and tumor stages. The clinical course of mycosis fungoides is usually chronic and indolent, but a proportion of patients may develop progressive disease with peripheral blood, lymph node and visceral organ involvement. Sézary

Core tip: Mycosis fungoides and Sézary syndrome are characterized by a clonal expansion of malignant CD4⁺ T lymphocytes with skin-homing properties. Currently, treatment options for mycosis fungoides and Sézary syndrome are limited. The lack of effective targeted therapy results in part from the poor understanding regarding the pathophysiology of these diseases. Recently, a number of chemokines and chemokine receptors have been found to contribute to the pathogenesis of mycosis fungoides and Sézary syndrome, including the

CC chemokine receptor 4 (CCR4)/chemokine (C-C motif) ligand 17 (CCL17), CCR10/CCL27, C-X-C chemokine receptor type 4/chemokine (C-X-C Motif) ligand 12 and CCR7/CCL21 axes. Therefore, these chemokines and chemokine receptors may be potentially useful targets for the treatment of these lymphomas in the future.

Hu SC. Mycosis fungoides and Sézary syndrome: Role of chemokines and chemokine receptors. *World J Dermatol* 2015; 4(2): 69-79 Available from: URL: <http://www.wjgnet.com/2218-6190/full/v4/i2/69.htm> DOI: <http://dx.doi.org/10.5314/wjd.v4.i2.69>

INTRODUCTION

Cutaneous T-cell lymphoma (CTCL) is a group of diseases characterized by malignant T lymphocytes infiltrating the skin, and includes mycosis fungoides, Sézary syndrome, lymphomatoid papulosis, anaplastic large cell lymphoma, subcutaneous panniculitis-like T-cell lymphoma, cutaneous natural killer/T-cell lymphoma, and primary cutaneous peripheral T-cell lymphoma^[1]. This Editorial focuses on mycosis fungoides and Sézary syndrome.

Mycosis fungoides is the most common form of CTCL, and is characterized by a clonal expansion of malignant CD4⁺ T lymphocytes with skin-homing properties^[2]. It is more common in the middle-aged and elderly, and is about twice more common in males than females^[3]. However, mycosis fungoides can also occur in children and young adults^[4]. Clinically and pathologically, mycosis fungoides can be categorized into patch, plaque and tumor stages. The clinical course of mycosis fungoides is usually chronic and indolent, but a subset of patients may develop progressive disease with peripheral blood, lymph node and visceral organ involvement^[5]. Patients with mycosis fungoides also have a higher risk of developing a second malignancy, especially other types of lymphomas^[6,7].

Sézary syndrome is an aggressive leukemic form of CTCL showing a clonal population of malignant T cells in the peripheral blood. Traditionally, mycosis fungoides and Sézary syndrome have been regarded as a spectrum of diseases with a common pathogenesis. More recently, investigations have indicated that mycosis fungoides and Sézary syndrome are two different diseases which originate from distinct T-cell subsets^[8]. Mycosis fungoides is believed to be a lymphoma arising from skin resident "effector" memory T cells, in which atypical lymphocytes remain confined to the skin. On the other hand, Sézary syndrome is regarded as a lymphoma of "central" memory T cells, in which atypical lymphocytes circulate between the blood, skin and lymph nodes. This may partially account for the differences in biologic behaviors and prognosis between these two diseases.

CLINICAL FEATURES

Classically, mycosis fungoides presents as erythematous patches and plaques, often associated with scaling (Figure 1). The skin lesions are usually located on non-sun exposed areas, such as the chest, abdomen, back, buttocks, groin and thigh. However, any region of the body can be affected. Pruritus is a common symptom. The skin lesions have usually been present for months to years, and they may gradually become thicker and develop into tumors. The three different types of skin lesions (patches, plaques, tumors) can sometimes be seen in a single patient concurrently. In certain patients, mycosis fungoides may progress into an erythrodermic form with generalized erythema and scaling of the skin^[5].

Sézary syndrome is an aggressive leukemic form of CTCL. It is characterized by erythroderma (generalized erythema and scaling of the skin involving more than 80% of the body surface area), and a clonal population of malignant T lymphocytes in the peripheral blood^[9,10]. Lymphadenopathy may or may not be present. This disease usually develops de novo without preceding mycosis fungoides.

HISTOPATHOLOGY AND IMMUNOPHENOTYPE

On histopathological examination, skin lesions of mycosis fungoides are characterized by atypical lymphocytes infiltrating mainly the dermis (Figure 2). The atypical lymphocytes are usually hyperchromatic, may have a haloed appearance, and show irregular, convoluted, or cerebriform nuclei^[11]. They often accumulate in a band-like distribution at the dermoepidermal junction. They show a tendency for epidermotropism (migration into the epidermis without epidermal spongiosis), and may form aggregates with Langerhans cells in the epidermis (Pautrier's microabscess)^[12]. There may be an accompanying infiltrate of reactive inflammatory cells.

On immunohistochemical staining, the atypical lymphocytes in mycosis fungoides are usually CD4⁺, and there is an elevated CD4:CD8 ratio^[11,13]. However, in a minority of cases the atypical lymphocytes are CD8⁺^[14]. The atypical cells are also CD45RO⁺, which is a marker of memory T cells^[15]. In addition, there is a loss of T cell antigens (including CD2, CD5, CD7 and CD26)^[15]. In Sézary syndrome and certain cases of mycosis fungoides, Sézary cells can be detected in the peripheral blood by flow cytometry, and are identified as CD4⁺CD7⁻ and/or CD4⁺CD26⁻ cells^[16,17].

The skin lesions of mycosis fungoides may show a dominant T cell clone. This is demonstrated by the presence of clonal T cell receptor gene rearrangement on polymerase chain reaction (PCR) analysis of the skin^[18,19]. In Sézary syndrome patients, a large clonal population of atypical T lymphocytes may be found in the peripheral blood, determined by molecular methods (T cell receptor gene rearrangements by PCR) and flow

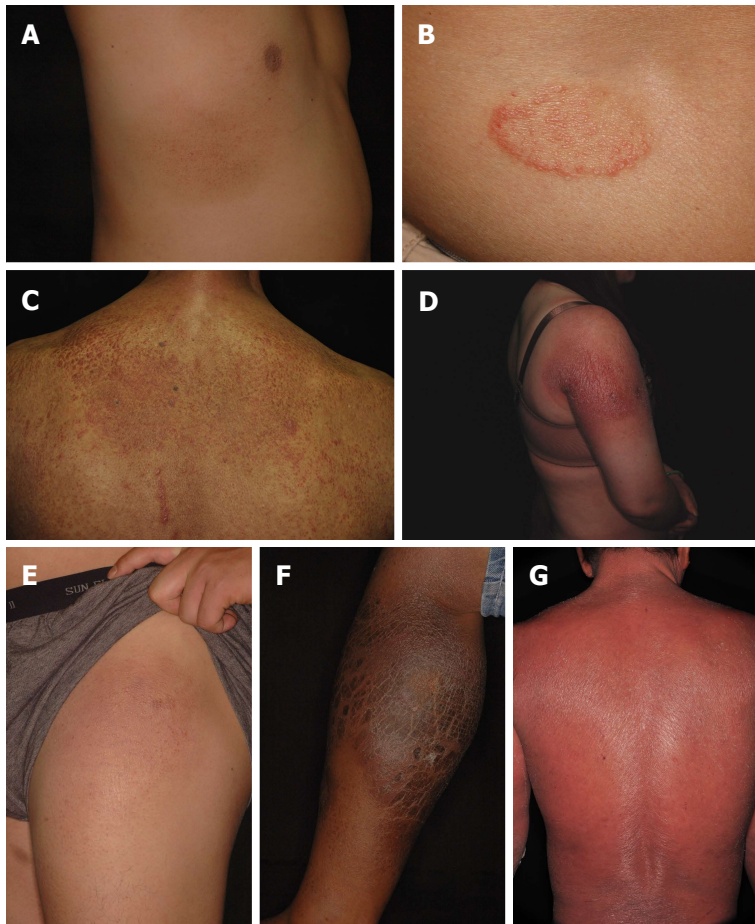


Figure 1 Clinical images showing patch stage (A), plaque stage (B-E), tumor stage (F), and erythrodermic (G) mycosis fungoides.

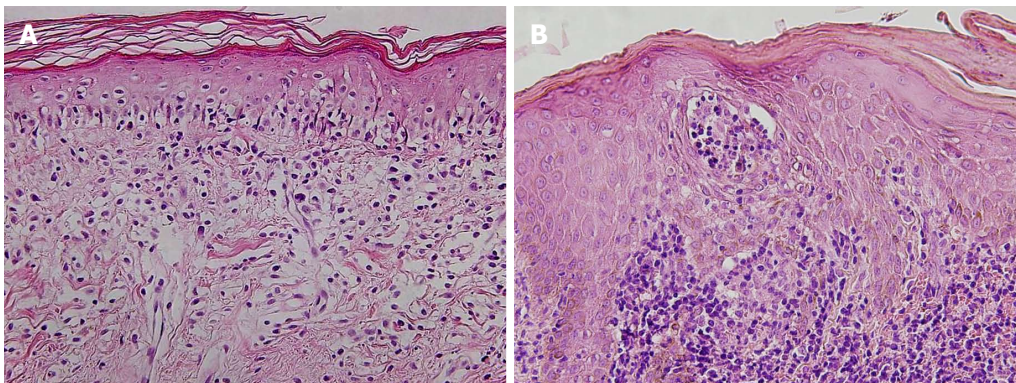


Figure 2 Pathological examination of mycosis fungoides lesions reveals atypical lymphocytes with epidermotropism (A) and formation of Pautrier's microabscess (B).

cytometry (expression of specific T cell receptor V β epitopes)^[10,20].

EVALUATION OF PATIENTS

Patients should undergo a detailed physical examination to determine the total body surface area involved by lymphoma, as well as the surface area involved by patch, plaque and tumor stages^[10]. This provides a measure of the skin tumor burden.

Laboratory tests that should be performed in

patients with mycosis fungoides and Sézary syndrome include a complete blood count with differential counts, electrolytes and lactate dehydrogenase. A skin biopsy should be undertaken for histopathological examination, immunohistochemistry and T cell receptor gene rearrangement studies. Peripheral blood should be examined for Sézary cell count and clonality of circulating T cells. Computed tomography scans with positron emission tomography are useful for determining internal organ involvement^[21]. Lymph node biopsy should also be performed in cases with lymphadenopathy.

STAGING AND PROGNOSIS

The staging of mycosis fungoides is based on the International Society for Cutaneous Lymphomas/European Organization for Research and Treatment of Cancer system, and takes into account the extent of skin involvement (T), lymph node disease (N), visceral involvement (M), and the presence of Sézary cells in the peripheral blood (B). The TNMB classification is converted into a clinical stage^[10,22].

The prognosis in patients with early stage mycosis fungoides (stage I A) is good, and these patients have a similar life expectancy as the general population^[23]. Poor prognostic factors for mycosis fungoides include advanced stage, older age, elevated lactate dehydrogenase levels, presence of erythroderma, large cell transformation, presence of a clonal population of atypical lymphocytes in the peripheral blood, and high Sézary cell count^[24-28]. The presence of CD8⁺ T cells in the skin of mycosis fungoides patients is associated with better prognosis, since this may lead to a host anti-lymphoma response^[29].

ETIOLOGY AND PATHOGENESIS

The etiology and pathogenesis of mycosis fungoides and Sézary syndrome is currently not well defined. It has been proposed that mycosis fungoides is caused by chronic antigenic stimulation, which results in lymphocyte proliferation and eventually a clonal expansion of CD4⁺ T helper cells in the skin. Certain infections, such as *Staphylococcus aureus* and *Chlamydia* species, have been implicated in the etiology of mycosis fungoides^[30-32].

Atypical lymphocytes in patients with mycosis fungoides and Sézary syndrome have been found to express the adhesion molecule cutaneous lymphocyte antigen, which may mediate the migration of lymphoma cells to the skin^[33].

The cytokine profile in mycosis fungoides also changes according to the stage of the disease. In early stages of mycosis fungoides, Th1 cytokines [(interferon- γ , interleukin-12 (IL-12), IL-2] predominate^[15,34]. In later stages of mycosis fungoides and Sézary syndrome, a shift from Th1 to Th2 cytokine profile is found, including IL-4, IL-5, IL-10, and IL-13^[35-37].

T cell proliferation and cell cycle control may be dysregulated in patients with mycosis fungoides. Amplification and overexpression of the oncogene JUNB were found in a subset of patients with mycosis fungoides and Sézary syndrome^[38]. Increased expression of the oncoproteins ras and myc has been implicated in the pathogenesis of mycosis fungoides^[39].

Atypical lymphocytes in mycosis fungoides and Sézary syndrome have also been shown to be resistant to apoptosis. Fas is a death receptor which can mediate apoptosis, and studies have shown that low Fas expression and impaired Fas-mediated apoptosis may play a role in the pathogenesis of mycosis fungoides^[40-42].

CHEMOKINES AND CHEMOKINE RECEPTORS IN MYCOSIS FUNGOIDES AND SÉZARY SYNDROME

Chemokines and chemokine receptors were initially found to play important roles in mediating the chemotaxis (directional migration) of leukocytes^[43]. Chemokines are a family of small polypeptides, and are categorized based on the location of cysteine residues near their amino termini into four families (C, CC, CXC, and CX3C). Chemokines bind to chemokine receptors, which are seven-membrane spanning, G-protein-coupled receptors. There are more than 50 different chemokines and at least 18 different chemokine receptors identified to date^[44]. There are redundancies in the binding between chemokines and chemokine receptors, as some chemokines bind to multiple chemokine receptors, and vice versa. The activation of chemokine receptors by chemokines may activate various downstream signaling pathways, including the mitogen-activated protein kinase, phosphoinositide-3 kinase, and mammalian target of rapamycin (mTOR) pathways.

In recent years, various types of cancer cells have been found to express chemokine receptors, which have been shown to play important roles in cancer growth, progression and metastasis^[45]. Apart from mediating cancer cell migration, chemokine receptors have also been demonstrated to mediate cancer cell proliferation, survival/apoptosis, and angiogenesis^[46,47]. A number of chemokines and chemokine receptors have been found to contribute to the migration and survival of lymphoma cells in mycosis fungoides and Sézary syndrome (Table 1)^[48-50].

CHEMOKINE RECEPTOR CC CHEMOKINE RECEPTOR 4

The chemokine receptor CC chemokine receptor 4 (CCR4) has been found to be important in mediating the migration of normal lymphocytes to inflamed skin^[51,52]. There are increased percentages of T lymphocytes expressing CCR4 in the blood and skin lesions of patients with CTCL (including mycosis fungoides and Sézary syndrome)^[8,53-55]. CCR4 expression is also seen in mycosis fungoides tumors with large cell transformation^[56]. Furthermore, CCR4 was found to be expressed by mycosis fungoides cell lines, and activation of the CCR4 receptor promoted migration of lymphoma cells^[57]. The CCR4 ligand chemokine (C-C motif) ligand 17 (CCL17) (thymus and activation regulated chemokine) is produced by activated epidermal keratinocytes, dendritic cells and endothelial cells, and its expression is upregulated in the skin lesions and serum of mycosis fungoides patients^[58,59]. In addition, serum CCL17 levels were found to correlate with disease activity in patients with mycosis fungoides^[59].

Table 1 Role of chemokines and chemokines receptors in the pathogenesis of mycosis fungoides and Sézary syndrome^[8,16,51-85]

Chemokine receptor	Chemokine	Role in pathogenesis of mycosis fungoides and Sézary syndrome
CCR4	CCL17 (TARC) CCL22	Increased percentages of T lymphocytes expressing CCR4 in the blood and skin lesions of CTCL patients Activation of CCR4 promoted migration of mycosis fungoides cell lines CCL17 expression is upregulated in the skin lesions and serum of mycosis fungoides patients
CCR10	CCL27 (CTACK)	CCR10 is expressed by malignant lymphocytes in skin lesions and peripheral blood of patients with mycosis fungoides and Sézary syndrome The level of CCL27 is increased in the serum and skin of patients with mycosis fungoides
CXCR4	CXCL12 (SDF)	CXCR4 is expressed by Sézary cells, and acts as a chemotactic factor for Sézary cells Loss of the cell-surface antigen CD26 (which cleaves and deactivates the CXCL12) is a characteristic feature in Sézary syndrome
CCR7	CCL19 (MIP-3b) CCL21 (SLC)	CCR7 is expressed on atypical lymphocytes of Sézary syndrome CCR7 promotes migration of Sézary cells CCR7 was expressed in mycosis fungoides skin lesions, and its expression correlated with subcutaneous extension of lymphoma cells Activation of CCR7 by its ligand CCL21 promotes MyLa (mycosis fungoides cell line) cell migration through the mTOR pathway
CCR3	Eotaxin-3 Eotaxin-1	Skin lesions of CTCL show higher expression of CCR3 and eotaxin-3 CTCL patients show higher serum levels of eotaxin-3 and eotaxin-1
CXCR3	CXCL9 CXCL10 CXCL11	CXCR3 is expressed in low-grade mycosis fungoides

CCR: CC chemokine receptor; CCL: Chemokine (C-C motif) ligand; TARC: Thymus and activation regulated chemokine; CTCL: Cutaneous T-cell lymphoma; CTACK: Cutaneous T-cell attracting chemokine; CXCR4: C-X-C chemokine receptor type 4; CXCL12: Chemokine (C-X-C Motif) ligand 12; SDF: Stromal cell-derived factor; MIP: Macrophage inflammatory protein; SLC: Secondary lymphoid-tissue chemokine.

Therefore, the interaction between CCR4 and CCL17 may play a role in the homing of mycosis fungoides cells to the skin or promote the survival of lymphoma cells.

CHEMOKINE RECEPTOR CCR10

The chemokine receptor CCR10 has been found to be expressed by normal lymphocytes which home to the skin^[60,61]. CCR10 has been demonstrated to be expressed by malignant lymphocytes in skin lesions of mycosis fungoides and Sézary syndrome, and mediated migration of Sézary cell line^[62,63]. In patients with mycosis fungoides and Sézary syndrome, increased numbers of lymphocytes expressing CCR10 was also found in the peripheral blood^[63-65]. The CCR10 ligand CCL27 (cutaneous T-cell attracting chemokine), a skin-specific chemokine, is synthesized by epidermal keratinocytes^[66,67]. The level of CCL27 was increased in the serum and skin of patients with mycosis fungoides^[63,68], and may act as a therapeutic marker following interferon- α and psoralen and ultraviolet-A (PUVA) treatment^[69].

CHEMOKINE RECEPTOR C-X-C CHEMOKINE RECEPTOR TYPE 4

The chemokine receptor C-X-C chemokine receptor type 4 (CXCR4) may also be involved in homing of mycosis fungoides and Sézary cells to skin. CXCR4 has been demonstrated to be expressed by Sézary cells, and acts as a chemotactic factor for Sézary cells^[55]. CXCR4 has also been shown to be expressed in mycosis

fungoides skin lesions^[70]. The ligand for CXCR4 is the chemokine chemokine (C-X-C Motif) ligand 12 (CXCL12) (also known as stromal cell-derived factor 1), which is expressed by skin dermal fibroblasts and endothelial cells^[71,72]. In Sézary syndrome, loss of the cell-surface antigen CD26 is a characteristic feature^[16,73]. CD26 is a dipeptidyl peptidase which cleaves and deactivates CXCL12, preventing it from activating CXCR4. The downregulation of CD26 and subsequent increased levels of CXCL12 may promote CXCL12-induced chemotaxis of Sézary cells^[55].

CHEMOKINE RECEPTOR CCR7

CCR7 is a chemokine receptor which has been discovered to mediate the migration of T lymphocytes and dendritic cells to lymphatic vessels and lymph nodes^[74-76]. The ligands for CCR7 are CCL19 (also known as macrophage inflammatory protein-3b, MIP-3b) and CCL21 (also known as secondary lymphoid-tissue chemokine). CCR7 has been found to be involved in the lymph node metastasis of certain cancer cells^[77-79]. In addition, CCR7 plays a role in cancer cell proliferation, migration and invasion.

Previous studies have indicated that CCR7 is expressed on atypical lymphocytes of Sézary syndrome^[8,64,65], and may promote migration of Sézary cells^[80]. CCR7 is also expressed in tumor-stage mycosis fungoides^[70]. Recently, our research group found that CCR7 was expressed in 62% (13 out of 21) of mycosis fungoides skin tissue specimens, and its expression correlated with subcutaneous extension of lymphoma cells (an indication of lesion thickness). In addition, we showed that CCR7

Table 2 Current treatment strategies for mycosis fungoides and Sézary syndrome

Skin-directed therapies	Systemic therapies
Topical corticosteroids	Oral retinoid (bexarotene)
Topical nitrogen mustard	IL-12
Topical retinoid (bexarotene)	Interferon- α
Ultraviolet light phototherapy (PUVA, narrowband UVB)	Histone deacetylase inhibitors
	Extracorporeal photopheresis
Radiation therapy	Methotrexate
	Chemotherapy
	Hematopoietic stem cell transplantation

PUVA: Psoralen and ultraviolet-A; IL-12: Interleukin 12.

expression was increased on the surface of MyLa cells (a human mycosis fungoides cell line) compared to peripheral blood mononuclear cells. Activation of CCR7 by its ligand CCL21 promoted MyLa cell migration but not proliferation. We also demonstrated that the CCL21-induced MyLa cell migration was mediated through the mTOR pathway^[81].

OTHER CHEMOKINE RECEPTORS

It has been demonstrated that in skin lesions of CTCL (mycosis fungoides), keratinocytes, endothelial cells and dermal fibroblasts showed higher expression of eotaxin-3 compared to normal skin. In some advanced cases of CTCL, atypical lymphocytes in skin lesions were found to express CCR3, the chemokine receptor for eotaxins. These patients also show higher serum levels of eotaxin-3 and eotaxin-1. Therefore, the interaction between eotaxins and CCR3 may play a role in the pathogenesis of mycosis fungoides^[82].

In addition, the chemokine receptor CXCR3 has been found to be expressed in low-grade (patch and plaque stage) mycosis fungoides, especially in the epidermotropic lymphoma cells^[83-85].

MANAGEMENT: SKIN-DIRECTED THERAPIES

There are a variety of different treatment strategies available for mycosis fungoides and Sézary syndrome (Table 2), depending on the severity of the disease and patient factors^[86-89]. Since mycosis fungoides and Sézary syndrome are generally not curable, chronic management is required in order to control the disease. In early stage mycosis fungoides, (stages I A-II A), lymphoma cells are mainly confined to the skin, and skin-directed therapies are usually used. In advanced stage mycosis fungoides (stages II B-IV B) and Sézary syndrome, systemic therapies may be selected, including immunotherapy, targeted therapies and chemotherapy^[90]. Each of the different treatment strategies are associated with various adverse effects, the discussion of which is beyond the scope of this Editorial.

In early stage mycosis fungoides, topical corticosteroids is the most commonly used form of treatment^[91]. It can also be used in combination with other therapies in advanced stages of disease. Topical nitrogen mustard (a DNA alkylating agent) or topical retinoids (bexarotene, tazarotene) may also be used in early stage mycosis fungoides^[92,93].

Phototherapy with ultraviolet light may be effective for patients with early stage (stages I A-II A) mycosis fungoides. Forms of phototherapy include PUVA with oral 8-methoxypsoralen, and narrowband ultraviolet B (311 nm)^[94-96].

Ionizing radiation therapy has deeper penetration compared to ultraviolet phototherapy^[97]. Total skin electron beam therapy may be used for patients with rapidly progressive or refractory disease, and plaque or tumor lesions involving large body surface area^[98,99]. Localized radiotherapy may be suitable for patients with localized tumor lesions^[100].

MANAGEMENT: SYSTEMIC THERAPIES

The oral retinoid bexarotene is used for the treatment of refractory mycosis fungoides and Sézary syndrome in all stages^[101,102]. Bexarotene acts by modulating cell differentiation and apoptosis, and also decreases the expression of CCR4 on malignant lymphocytes, which may inhibit their ability to migrate to the skin^[103,104].

In mycosis fungoides and Sézary syndrome, there is an increased expression of Th2 cytokines (including IL-4, IL-5, and IL-10). IL-12 is a Th1-promoting cytokine, and has been shown to be efficacious in some patients^[105]. Interferon- α may also be effective for different stages of mycosis fungoides, and act by inducing Th1-mediated immune responses to atypical lymphocytes^[106].

In extracorporeal photopheresis, the circulating lymphocytes are separated from the patients' peripheral blood, 8-methoxypsoralen is added, and the cells are treated with ultraviolet-A light. This treatment is indicated for erythrodermic mycosis fungoides and Sézary syndrome^[107,108].

Chemotherapy drugs may be used for refractory or progressive mycosis fungoides and Sézary syndrome. Methotrexate is an antifolate agent which acts by

inhibiting dihydrofolate reductase and thereby inhibits proliferation of lymphocytes^[109]. Hematopoietic stem cell transplantation may be used in advanced stage mycosis fungoides and Sézary syndrome, and have the potential for curing the disease^[110].

CONCLUSION

Mycosis fungoides and Sézary syndrome are characterized by a clonal expansion of malignant CD4⁺ T lymphocytes with skin-homing properties, and have potential for lymph node, blood and visceral organ dissemination. Currently, treatment strategies for mycosis fungoides and Sézary syndrome are limited. The lack of effective targeted therapy results in part from the current poor understanding regarding the pathophysiology of these diseases. Since chemokines and chemokine receptors have been found to play important roles in the pathogenesis of mycosis fungoides and Sézary syndrome, they may be useful targets for the development of new treatments for these diseases^[111]. Previously, antibodies against CCR4 which induce antibody-dependent cellular cytotoxicity have been used in the treatment of mycosis fungoides and Sézary syndrome^[112]. In addition, chemokine-toxin fusion proteins (for example CCL17 ligated to the Pseudomonas exotoxin 38) have been demonstrated to selectively target and kill lymphoma cells which express CCR4^[113]. Therefore, further investigations are warranted to determine whether modulation of chemokines and chemokine receptors may be potentially useful for the treatment of mycosis fungoides and Sézary syndrome in the future.

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Review of the cutaneous manifestations of autoimmune connective tissue diseases in pediatric patients

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features that are unique to pediatric presentations of lupus erythematosus, juvenile idiopathic arthritis, juvenile dermatomyositis, juvenile onset systemic sclerosis and morphea. Each of these disorders has a distinct appearance corresponding to a particular cutaneous and systemic clinical course and prognosis. Awareness of the associated potential systemic complications can also alert the clinician to make astute management decisions when confronted with a probable rheumatologic case. Cutaneous symptoms may predate onset of systemic symptoms and by keeping the rheumatologic differential diagnoses in mind, the dermatologist can play a key role in potentially offsetting autoimmune disease burden in children.

Key words: Lupus erythematosus; Juvenile idiopathic arthritis; Juvenile dermatomyositis; Systemic sclerosis; Morphea

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Core tip: Early recognition of cutaneous manifestations of connective tissue disease can positively impact disease course. This review summarizes key cutaneous findings of some of the more common pediatric autoimmune connective tissue disorders, including lupus erythematosus, neonatal lupus, juvenile idiopathic arthritis, juvenile dermatomyositis, systemic sclerosis, and morphea.

Abstract

Autoimmune connective tissue diseases are chronic inflammatory disorders associated with complex genetic and environmental interplay resulting in a variety of cutaneous and systemic manifestations. Pediatric onset of these disorders carries a unique diagnostic pressure for the clinician due to the potential years of disease burden and complications. Mortality and morbidity from these disorders has fallen dramatically over the past fifty years due to increasing awareness of these disease sequelae and utilization of systemic treatment modalities when necessary. This review highlights the clinical

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INTRODUCTION

Autoimmune connective tissue diseases are complex

multisystem disorders. These disorders are associated with genetic and environmental factors, triggering intricate interactions between inflammatory cell responses and mediators, ultimately resulting in clinical manifestations. Dermatologists have the unique opportunity to diagnose some of these autoimmune disorders based on cutaneous findings which may predate systemic symptoms. The patient then benefits from close surveillance for complications and related conditions. Early recognition is of particular importance in the pediatric population as prompt intervention can often positively impact disease course.

The purpose of this review is to highlight the cutaneous manifestations of several of the more common pediatric autoimmune connective tissue diseases, including lupus erythematosus, juvenile idiopathic arthritis (JIA), juvenile dermatomyositis, systemic sclerosis, and morphea. We describe the disease course, highlighting the unique aspects of the pediatric presentation, potential complications seen in these disorders, key dermatologic and serologic findings, and offer a brief review of management options.

LUPUS ERYTHEMATOSUS

Lupus erythematosus (LE) was initially described as a disorder limited to the skin by Cazenave in 1851^[1]. Subsequently, Kaposi clarified the skin findings as one component of a disease that can potentially affect multiple organs, hence coining the term systemic lupus erythematosus (SLE)^[2]. Today, cutaneous lupus erythematosus (CLE) is considered a subset of SLE and is further sub-characterized based on the various cutaneous morphologies that are observed. Cutaneous LE is 2-4 times more common than SLE in the pediatric and adult populations^[3,4]. Recognition of CLE is essential as a subset of patients, particularly pediatric patients, may have or develop systemic involvement.

SLE is a chronic autoimmune disorder that can affect multiple systems including the skin, joints, kidneys, heart and central nervous system and therefore can incur significant morbidity. More recently, it has been reported that patients are also at increased risk for atherosclerosis^[5]. The pathogenesis is complex, involving genetic predisposition as well as environmental triggers, particularly medications and ultraviolet (UV) radiation exposure. Furthermore, UV radiation has been implicated in triggering and exacerbating cutaneous LE^[6,7]. About 80% of patients with SLE will display cutaneous involvement at some time during the disease course, with up to 60% for whom it is the presenting symptom^[8,9]. Although the majority of patients are adult women within their childbearing years, approximately 20% of patients are diagnosed prior to the age of 16 years of age^[10]. Pediatric onset SLE is a special subset of this disease and portends a more severe and aggressive disease course, particularly among non-Caucasian patients^[11-13]. Approximately 50 years ago, pediatric

onset SLE was associated with a 100% mortality rate. However, with the utilization of more aggressive therapy, pediatric patients currently have been able to achieve survival rates > 90% with systemic anti-inflammatory medications to restrain and manage immune dysregulation^[14]. Underscoring the severity seen in the pediatric population, systemic medications are used almost 4 times more frequently than in the adult populations^[9,15,16].

Diagnosis of SLE was recently updated in 2012 by the Systemic Lupus International Collaborating clinics^[17]. Eleven clinical and 6 immunologic criteria were identified and currently the diagnosis of SLE requires fulfillment of at least 4 criteria, with at least 1 from either category (Table 1). These criteria would allow for a diagnosis of SLE based on skin findings alone (acute cutaneous lupus, chronic cutaneous lupus, oral or nasal ulcers and non-scarring alopecia) in the setting of positive serologic markers. Early diagnosis is imperative to minimize potential end organ damage^[18]. This is particularly critical for pediatric patients as this group is more likely to have associated renal and neurologic disease^[9]. Serology can be helpful in predicting disease course. In pediatric patients, anti-dsDNA, anti-ribosomal P and anti-histone antibodies are more frequently seen. Anti-dsDNA autoantibodies are associated with significant renal disease while the presence of anti-ribosomal P autoantibodies appears to be inversely correlated with kidney involvement^[19]. The presence of antiphospholipid antibodies is generally associated with a poorer prognosis^[20].

Cutaneous lupus erythematosus can be categorized into three major forms which are described as acute, subacute CLE (SCLE) and chronic cutaneous lupus^[21]. Within the chronic category, several subtypes are included: discoid lupus erythematosus (DLE), lupus erythematosus tumidus (tumid lupus), lupus panniculitis, and chilblain lupus erythematosus. Importantly, the three major types of cutaneous lupus are not mutually exclusive and more than one subtype of cutaneous disease may occur in the same person^[22].

Acute cutaneous lupus is commonly associated with active SLE and can be further categorized into localized and generalized forms^[3]. The classic localized form manifests as what is known as the "malar rash" extending over the nasal bridge with sparing of the nasolabial folds. This finding can be as subtle as mild erythema, or more pronounced with features of intense edema and scaling (Figure 1). This finding may last from a few hours to several weeks. A malar rash is associated with the onset of SLE in 61% of pediatric cases^[8]. The malar rash may be misdiagnosed as seborrheic dermatitis, rosacea, parvovirus B19 infection, sunburn or other facial dermatoses^[23]. The generalized form of acute cutaneous lupus is rare and appears as widespread symmetric erythematous macules and papules on the torso and extremities, sometimes associated with pruritus^[3] (Figure 2). Involvement of the dorsal hands can provide diagnostic clues.

Table 1 Cutaneous findings, diagnostic criteria, and treatments for juvenile systemic connective tissue disease

Disease	Cutaneous findings	Diagnostic criteria	Treatment
Lupus erythematosus	Acute cutaneous lupus Malar rash Generalized erythematous macules and papules, sparing the knuckles on dorsal hands Mucosal ulcerations Bullous lupus Subacute cutaneous lupus Photodistributed annular eczematous or psoriasiform plaques Chronic cutaneous lupus Discoid lupus Lupus panniculitis Chilblain lupus Tumid lupus	Systemic lupus erythematosus requires fulfillment of ≥ 4 criteria with at least 1 criterion from either category: Clinical criteria Immunologic criteria Acute cutaneous lupus ANA Chronic cutaneous lupus Anti-dsDNA Oral ulcers Anti-Smith Nonscarring alopecia Anti-phospholipid antibody Synovitis Low complement Serositis Direct Coombs' test Renal disease Neurologic disease Hemolytic anemia Leukopenia Thrombocytopenia	Mild skin-limited disease Photoprotection Topical corticosteroids Calcineurin inhibitors Hydroxychloroquine Refractory skin disease and systemic disease Hydroxychloroquine Systemic corticosteroids Methotrexate Dapsone (bullous lupus) Other steroid sparing immune modulators
Systemic juvenile idiopathic arthritis	Transient salmon-pink macules and edematous papules Flagellate erythema	Onset before 16 yr of age, ≥ 6 wk of arthritis, ≥ 2 wk of fever At least one of the following: Evanescent eruption Generalized lymphadenopathy Splenomegaly Serositis	Systemic corticosteroids Methotrexate Biologic agents Supportive symptomatic measures for skin manifestations
Juvenile dermatomyositis	Gottron's papules-lichenoid papules overlying phalangeal joints, elbows, knees Heliotrope rash of eyelids Poikiloderma of upper back and chest Hyperkeratosis and fissuring of fingertips Mucosal ulcers Gingival telangiectasia Calcinosis cutis	Fulfillment of all five criteria: Symmetric proximal muscle weakness Elevated skeletal muscle enzymes Electromyography changes ¹ Muscle biopsy abnormalities ¹ Characteristic skin findings	Photoprotection Hydroxychloroquine Systemic corticosteroids Methotrexate IVIG Other steroid sparing immune modulators
Juvenile onset systemic sclerosis	Limited Sclerosis limited to distal extremities and face CREST (calcinosis, Raynaud's phenomenon, esophageal dysmotility, sclerodactyly and telangiectasias) Diffuse Diffuse sclerosis	Skin sclerosis and ≥ 2 of the following: Sclerodactyly Raynaud's phenomenon Nailfold capillary abnormalities Digital tip ulcers Dysphagia Gastroesophageal reflux Neuropathy Carpal tunnel syndrome Tendon friction rubs Arthritis Myositis	Avoidance of vasospasm triggers Arrhythmias Heart failure Renal crisis New-onset arterial hypertension Pulmonary fibrosis Decreased DLCO Pulmonary arterial hypertension Antinuclear antibodies SSc-selective autoantibodies
Morphea	Linear Linear erythematous indurated plaques En coup de sabre-indurates plaques affecting forehead and scalp Parry Romberg-indurated plaques of the face with ipsilateral facial atrophy Circumscribed Isolated indurated plaques Generalized 4 or more circumscribed type plaques that are larger than 3 cm in diameter Involving at least 2/7 anatomic sites: head-neck, right upper extremity, left upper extremity, right lower extremity, left lower extremity, anterior trunk or posterior trunk Pansclerotic Diffuse involvement of the limbs, trunk, face and scalp with fixation of underlying structures Mixed 2 or more different types of morphea present	No sclerosis of internal organs, except for rare involvement of underlying fascia, muscle and bone	Topical corticosteroids Calcipotriene UVA1 phototherapy Severe or critical location of lesions Systemic corticosteroids Methotrexate

¹These tests are typically not done in children and have been clinically replaced with MRI evidence of muscle inflammation and autoantibodies compatible with juvenile dermatomyositis.



Figure 1 Acute cutaneous lupus erythematosus. The facial erythema on the malar cheeks appears as erythematous plaques with scale. There is distinct sparing of the nasolabial folds.



Figure 2 Acute cutaneous lupus erythematosus. Pink edematous papules on the extremities.

Erythematous plaques characteristically involve the skin between the joints more than the skin overlying the knuckles. Cuticle overgrowth and dilated cutaneous blood vessels may be seen underlying the proximal nail fold (Figure 3). Mucosal involvement in acute cutaneous lupus manifests as mucosal ulcerations, gingivitis, or silvery white changes on the vermillion border, gingiva, buccal and nasal mucosa. These findings may be seen in 3% of patients with cutaneous LE and up to 30% of pediatric patients with SLE^[24]. Mucosal findings may be severe in acute SLE flares and have even been mistaken for drug-induced toxic epidermal necrolysis^[25]. A rare, but distinctive, variant of acute CLE is bullous lupus erythematosus. This condition is characterized by localized or generalized tense subepidermal vesicles and bullae arising on normal or erythematous skin. The bullae herald the presence of circulating auto-antibodies to collagen VII^[26]. Sun-exposed sites of the trunk, limbs and face are particularly affected; small blisters along the vermillion border of the lips can be seen in up to 30% of cases^[27,28].

SCLE is typically limited to sun-exposed skin. This form of cutaneous lupus is the least common type presenting in the pediatric population, however when present, is more frequently associated with systemic disease as compared to the adult population^[22,29].



Figure 3 Acute cutaneous lupus erythematosus on the dorsal hands. Note the erythematous edematous papules coalescing into plaques on the dorsal fingers with sparing of the phalangeal joints. Note the dilated cutaneous vessels under the proximal nail fold particularly of the index finger.

The lesions of SCLE tend to demonstrate an annular configuration, often with raised red borders, and manifesting eczematous to psoriasiform epidermal features. Due to the superficial location of the inflammation, these lesions rarely result in scarring. Interestingly, the midface skin is usually spared, with more frequent involvement of the sides of the face, upper trunk and extensor aspects of the arms; lip involvement has also been described^[25]. The differential diagnosis of SCLE in children includes urticaria, eczematous dermatitis and erythema multiforme. Anti-Ro and La autoantibodies are often associated with SCLE, and subsequently patients may also have dry eye and dry mouth symptoms and organ involvement consistent with Sjogren's syndrome^[22].

Chronic cutaneous lupus is the most common subtype of cutaneous LE among pediatric patients, specifically the morphology known as discoid DLE. Children with DLE have an increased risk of developing SLE as compared to adults, with approximately 23%-26% developing SLE, vs 5%-20% of adults^[30,31]. Discoid LE is most often localized to the face, scalp and ears as it preferentially appears on sun-exposed areas and is found to be exacerbated by UV radiation^[4,24]. A generalized form of DLE has been described where there is widespread distribution including mucosal surfaces. The latter presentation is associated with a higher rate of progression to SLE^[4,6]. The lesions are typically round to annular, slightly indurated, erythematous to violaceous plaques with adherent scale, often with follicular plugging which is described as "carpet tack-like." Older lesions will demonstrate atrophy, dyspigmentation resulting in scarring, and alopecia in hair bearing areas (Figure 4). Lip involvement can be present with lesions blurring the sharp vermillion border^[25]. Linear presentations following the lines of Blaschko have also been described in children^[32,33]. Squamous cell carcinoma has been reported in longstanding lesions of DLE^[34].

Other subtypes of chronic cutaneous lupus include lupus panniculitis, chilblain lupus erythematosus and



Figure 4 Discoid lupus erythematosus. These lesions will typically favor the head and neck. A: Earlier lesions can present as erythematous papules and annular plaques with scaling; B: This patient had more chronic lesions involving her cheek, nose, chin and conchal bowl with significant dyspigmentation; C: Widespread symmetric involvement can be seen in generalized discoid lupus.

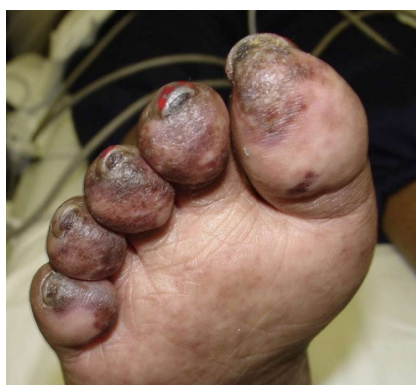


Figure 5 Chilblain lupus erythematosus. Violaceous plaques with overlying scale on the distal toes.

tumid lupus, all of which are rare in children. Lupus panniculitis results in firm subcutaneous nodules and can present in association with DLE. Lesions tend to involve areas of increased fat deposition such as the chest, upper arms and thighs and sometimes in areas where patients report a history of trauma^[3,28]. Lupus panniculitis can last for many years, and due to the deep nature of the inflammation, the lesions can leave disfiguring atrophic scars. Chilblain lupus appears as painful, itchy, violaceous papules, plaques, or erosions on cold-exposed surfaces such as the tips of the digits (Figure 5). This finding represents cold-induced vasospasm of the hands and feet and may even resemble frostbite. Twenty percent of adult patients with chilblain lupus are reported to evolve into SLE^[35]. A dominantly inherited familial form of chilblain lupus erythematosus has been described due to a mutation in *TREX1*^[36]. Tumid lupus presents as red to purple edematous plaques without epidermal change that remain fixed in shape, often in a polycyclic pattern, on sun exposed sites. These lesions tend to heal without scarring.

The major histologic findings associated with most forms of cutaneous lupus erythematosus include basement membrane thickening in the setting of an interface lymphohistiocytic infiltrate and increased dermal mucin deposition^[37]. In acute cutaneous lupus

the dermal infiltrate can be subtle, while in SCLE there can be significantly more superficial dermal involvement. In DLE lesions, liquefactive degeneration of the basal layer with lymphohistiocytic involvement of periadnexal structures, follicular plugging and fibrosis is notable. Lupus panniculitis exhibits lobular infiltrates within the subcutaneous fat. In contrast, lupus tumidus will not exhibit the epidermal changes, but demonstrates notably increased dermal mucin deposition. Direct immunofluorescence of lesional and nonlesional skin in the setting of LE will typically exhibit a granular deposition of IgG and/or IgM along the dermal epidermal junction and around hair follicles^[37].

Special mention needs to be made of non-specific skin findings observed in LE patients. These findings may be suggestive of SLE and when they coincide with systemic symptoms suggestive of SLE, such as joint pain, the physician must be alert for additional signs of lupus (Table 2). The most common non-specific findings are those representing cutaneous vascular disease such as Raynaud phenomenon, livedo reticularis, and cutaneous vasculitis. Other nonspecific findings which may be associated with SLE include urticaria, erythema multiforme, and nonscarring alopecia.

The management of pediatric cutaneous LE is dependent on extent of disease. In general, patients should be advised to avoid the sun as much as possible and to employ UV protection at all times. If the disease is localized, treatment with topical corticosteroids or calcineurin inhibitors may be adequate; however, the routine use of hydroxychloroquine in all LE patients, including those with skin-limited disease, is becoming more strongly favored. Hydroxychloroquine has been shown to increase survival and lengthen remission in adults and to specifically reduce the prevalence of renal disease^[3,38,39]. Refractory cutaneous disease may require additional antimalarial agents, systemic corticosteroids, and steroid sparing agents such as methotrexate and mycophenolate mofetil^[3].

NEONATAL LUPUS

Neonatal lupus is a passively acquired autoimmune

Table 2 Nonspecific cutaneous findings suggestive of systemic lupus erythematosus (modified from Bologna)^[1]

Diffuse non-scarring alopecia
Raynaud's phenomenon
Nailfold telangiectasia and erythema
Vasculitis
Urticarial vasculitis
Small vessel vasculitis (<i>e.g.</i> , palpable purpura)
Polyarteritis nodosa-like lesions
Ulcerations
Cutaneous signs of antiphospholipid syndrome
Livedo reticularis
Ulcerations
Acrocyanosis
Atrophie blanche-like lesions
Degos'-like lesions
Livedoid vasculopathy
Palmar erythema
Papular and nodular mucinosis

disorder of neonates born to mothers with circulating connective tissue autoantibodies Ro, La, and less commonly, U1-ribonucleoprotein^[40]. Approximately 50% of mothers are asymptomatic at the time of the infant's diagnosis, therefore diagnosis in the child can alert the clinician to recommend connective tissue disease evaluation for the mother^[40]. The data suggests that approximately 50% of mothers who are asymptomatic at the time of their child's diagnosis will develop symptoms of connective tissue disease within 3 years^[41,42]. Only 10% of these women will meet full criteria for SLE within 6 years of follow up^[42]. Cutaneous lesions of neonatal LE are transient. Cutaneous manifestations typically resolve within 6-8 mo after birth, as maternal autoantibodies disappear from the infant's circulation^[42,43]. The gravest complication of neonatal lupus is cardiac conduction abnormalities which are typically permanent. Conduction abnormalities occur in 15%-30% of cases^[42]. The developing fetal heart undergoes a complex pattern of growth, programmed apoptosis and folding, during which Ro and La antigens are expressed on fetal myocytes. These myocytes are targeted by the maternal autoantibodies causing scarring within the fetal conduction pathway and resulting in dysrhythmias and/or complete heart blocks without structural anomalies. Almost all patients with this complication will require a pacemaker at some point in their life^[42]. Other potential complications of neonatal lupus include liver involvement with conjugated hyperbilirubinemia, splenomegaly, hematologic abnormalities, hydrocephalus, hemorrhagic strokes and seizures^[42,44,45].

Cutaneous features of neonatal lupus typically appear at a mean of 6 wk after birth, though it can be present at the time of delivery in some cases^[46,47]. The classic facial lesions are erythematous annular and polycyclic plaques with or without scale located on the scalp and periocular region of the face. Confluent erythematous papules or even pustules are also seen^[44]. The pattern noted on the face is often referred to as "owl

**Figure 6** Neonatal lupus. Annular lesions with central atrophy particularly concentrated around the eyes.

like" or "raccoon like" (Figure 6). Annular plaques may also be found on the trunk and extremities and in the groin region, thus involving non-sun-exposed sites^[47,48]. Many lesions resolve without sequelae over a mean duration of 17 wk, however approximately 25% can leave residual dyspigmentation, persistent telangiectasia and atrophic scarring of the affected areas. It is unclear if treatment with topical steroids prevents lingering skin findings. Strict UV protection is recommended as it is in all forms of CLE^[47]. All patients with neonatal lupus should be followed regularly as long term follow up studies have reported cases of autoimmune thyroiditis, type 1 diabetes mellitus and JIA. To date, there have been no reports of cases of SLE, dermatomyositis (DMS), or systemic sclerosis in patients with a history of neonatal lupus^[47,49].

SYSTEMIC JIA

JIA is a term that refers to a group of six chronic arthritides in children less than 16 years of age. Of these six subtypes, only two are associated with cutaneous findings, systemic onset arthritis and psoriatic arthritis. Due to the connective tissue disease focus of this review, skin manifestations of psoriatic arthritis will not be discussed here. Systemic JIA is considered a subset of JIA and is a diagnosis of exclusion defined as arthritis with, or preceded by, daily fevers of at least 2 wk duration in the setting of specific systemic signs of inflammation (Table 1). Cutaneous findings are found in 25%-50% of patients and may precede fevers, arthritis or organ involvement by several years^[24]. Pathophysiology of this disease remains obscure, and current theories point to an autoinflammatory etiology. A genetic component has been identified as subgroups of patients have been identified to have mutations in MEFV and LACC1^[50,51].

Joint involvement will result in severe, recalcitrant and destructive progressive polyarticular disease in 50% of patients. Other complications of systemic JIA include serositis, uveitis, hepatosplenomegaly, pleuritis, and pericarditis. A particularly severe complication is macrophage activation syndrome which can be life



Figure 7 Juvenile idiopathic arthritis. Erythematous papules coalescing into plaques with surrounding pallor, typically evanescent in nature.

threatening.

The classic evanescent cutaneous eruption associated with systemic JIA is described as 2-5 mm salmon-pink macules and edematous papules that arise with fevers and typically resolve within hours of defervescence. This eruption is not usually pruritic and can involve the chest, proximal extremities and pressure points^[52] (Figure 7). These cutaneous findings will coincide with an elevation in acute phase reactants such as erythrocyte sedimentation rate, C-reactive protein, ferritin and platelets. Biopsy findings are variable and non-specific^[37]. Adult-onset Still's disease is typically considered the adult version of systemic onset JIA. An eruption of persistent pruritic papules and plaques variably associated with a flagellate erythema has been described in adult-onset Still's disease. The histologic findings in these cases are notable for a characteristic pattern of dyskeratotic keratinocytes in the upper layer of the epidermis and extending into the stratum corneum^[53-58]. A similar eruption with consistent histologic findings has been observed in a child with systemic onset JIA (authors' experience) (Figure 8).

Management of the cutaneous features of systemic onset JIA is contingent on treatment of the systemic disease. First line treatment includes non-steroidal anti-inflammatory medications in association with physical therapy. For severe cases, systemic corticosteroids, methotrexate, other steroid-sparing medications or biologic agents may be necessary. Recently, genetic variations in patients with systemic onset JIA has helped to elucidate treatment response patterns^[59,60]. Earlier aggressive therapy is associated with longer remission^[61,62].

JUVENILE DMS

DMS is an immune-mediated process triggered by exposure to various exogenous factors in genetically predisposed individuals. The skin, striated muscles and internal organs may be affected. It is the most common inflammatory cause of myopathy in children^[63]. Traditional diagnostic criteria for juvenile DMS include cutaneous findings in conjunction with serologic findings



Figure 8 Juvenile idiopathic arthritis presenting as flagellate erythema. Erythematous and hyperpigmented persistent plaques in a flagellate pattern.

and signs and markers of myopathic disease, including muscle electromyographic changes and histopathologic features (Table 1). Radiographic studies to document muscle involvement are often substituted for the more invasive diagnostic procedures^[64,65]. A subtype known as amyopathic DMS is diagnosed when cutaneous findings are present in the absence of muscle symptoms for at least 6 mo. Amyopathic disease is thought to represent an estimated 20% of all dermatomyositis cases^[66]. In children, it has been suggested that a quarter of patients with amyopathic DMS will progress to classic DMS in a mean follow up period of 4 years^[67]. Dermatomyositis is rarely associated with malignancy in children, whereas in adults associated malignancy is present in 14%-30% of cases^[66-68]. Females are at higher risk for DMS overall. A bimodal pattern of onset is seen in childhood with peak ages of onset between 2-5 years of age and 12-13 years of age^[63]. Recent literature suggests that patients who present at the younger age peak may have a milder disease course^[69].

Onset of DMS can be insidious in up to 43% of the cases and by the time the diagnosis is made, the patients may have experienced subtle weakness, anorexia, malaise, and abdominal pain in addition to cutaneous findings for over 2-6 mo^[63,67,70]. Male gender and proximal muscle weakness evidenced by a positive Gower's sign is associated with poor prognosis for complete clinical remission^[71]. Complications of DMS include hypertriglyceridemia with insulin resistance, calcinosis cutis, muscle weakness and atrophy, lipodystrophy, and infections, particularly from gram negative organisms. Lipodystrophy and small vessel vasculitis affects an estimated 10% of the pediatric disease population and these patients demonstrate an increased incidence of concomitant insulin resistance and hyperlipidemia^[72].

Most patients will present with proximal muscle weakness and the hallmark dermatologic findings of Gottron's papules and heliotrope rash around the eyes. Gottron's papules are small purple or pink lichenoid papules on the dorsum of the hands, overlying the metacarpophalangeal, proximal interphalangeal and distal interphalangeal joints (Figure 9). These

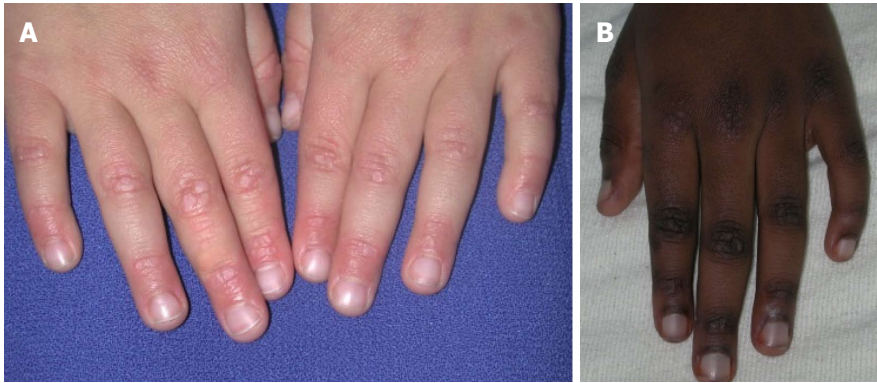


Figure 9 Dermatomyositis. Gottron's papules with (A) pink to (B) violaceous flat-topped papules overlying the dorsal joints of the fingers with sparing of the skin in between the joints, a finding occasionally mistaken for flat warts. Also note the erythema noted around the proximal nail folds.



Figure 10 Dermatomyositis. Lichenoid papules and plaques over bony prominences of the knees and elbows.



Figure 11 Dermatomyositis. Heliotrope sign with prominent capillary vasculature around the eyelids and characteristic pink-purple patches involving the cheeks, chin and temples.

papules may resolve with atrophy, telangiectasia and dyspigmentation. Similar small pink to purple papules, almost psoriasiform in nature, can be found on bony prominences over the knees, elbows and ankles (Figure 10). The heliotrope rash is a purplish red discoloration that involves the eyelids most commonly. The notable purple red patches are sometimes accompanied by edema. Temples, forehead, cheeks and ears can be similarly affected^[24] (Figure 11). Erythema with scaling may involve the scalp and can be mistaken for seborrheic dermatitis, psoriasis or even CLE^[73]. The histologic findings that correlate with most of these clinical features demonstrate vacuolar changes of basal keratinocytes, dermal mucin accumulation and a mild to moderate dermal lymphocytic infiltrate, sometimes with features of dermal sclerosis^[37].

In the setting of chronic DMS, poikiloderma (dyspigmentation, telangiectasia and epidermal atrophy overlapping in the same region) is often present. Poikilodermatous change involving the upper back and anterior chest in a photodistributed manner is classically referred to as the "shawl sign". Ragged cuticles and nail fold telangiectasia can be appreciated in up to 68% of patients. "Mechanic's hand" is a phrase that describes hyperkeratosis and fissuring at the fingertips with associated palmar erythema. Mucosal findings include mouth ulcers, gingival telangiectasia and gingival bleeding.

Calcinosis cutis is a complication associated with significant morbidity and is more prevalent in juvenile DMS as compared to adult counterparts, affecting 18%-25% of pediatric patients. This finding correlates with disease chronicity. Fortunately, with newer management regimens focusing on early aggressive therapy, the incidence is steadily decreasing^[63,70,72]. Lesions of calcinosis cutis are hard nodules in areas that are prone to trauma such as the buttocks, elbows, knees, fingers and shoulders. The nodules are occasionally deeply seated into the fascia and intramuscular connective tissue. These lesions may connect to the skin surface and result in chalky drainage. Complications such as cellulitis and ulceration may ensue^[24].

Prior to the use of corticosteroids in the treatment of juvenile DMS, the disease had a mortality rate of 30%. Standardized treatment protocols have resulted in lowered mortality rates of 0.7%-3.1%. The mainstay of treatment is systemic corticosteroids, methotrexate and IVIG. Other treatments include hydroxychloroquine and cyclosporine^[64]. Studies using biologic therapies including etanercept and rituximab have demonstrated mixed results^[64,74,75]. Patients with amyopathic DMS can be treated with hydroxychloroquine, topical corticosteroids and photoprotection^[76]. Treatment of calcinosis cutis can be unsatisfying. The most promising treatments in children include bisphosphonates, calcium channel

blockers and surgical excision of larger lesions^[77].

JUVENILE ONSET SYSTEMIC SCLEROSIS

Juvenile onset systemic sclerosis (jSSc) is a rare disorder of unclear etiology that causes vascular dysfunction, immune dysregulation and finally tissue fibrosis due to deposition of collagen and other extracellular matrix proteins. The organs prominently affected are skin, blood vessels and internal organs. Of the organs, the lungs are of particular concern as almost all patients will exhibit pulmonary function test abnormalities resulting in significant morbidity and mortality^[78]. The onset of this disease is insidious and it can take 1-4 years on average until the diagnosis is made, highlighting the importance of disease awareness. Ten percent of all patients with this disease will present in childhood^[79]. Diagnostic criteria set forth by the Pediatric Rheumatology European Society and American College of Rheumatology require the presence of cutaneous sclerosis proximal to the metacarpophalangeal joints in addition to 2 minor criteria involving extracutaneous organs^[80,81] (Table 1). There are two known types of jSSc, limited and diffuse. The limited type is characterized by distal extremity disease and facial involvement. These patients may also fulfill criteria for CREST syndrome (calcinosis, Raynaud's phenomenon, esophageal dysmotility, sclerodactyly and telangiectasia). The diffuse type involves both the distal and proximal portions of the extremities including the hands and face. The limited subtype appears to have a more benign course. In both subtypes, the diseases will often affect the fingers and hands first, with subsequent spread to the proximal extremities and trunk in symmetric fashion. Compared to adults, juvenile onset systemic sclerosis has a higher survival rate (98% vs 75%), is more likely to be involved in rheumatologic overlap syndromes, and is less likely to be complicated by pulmonary artery hypertension and renal crisis^[82].

The cutaneous manifestations of jSSc underscore the vascular dysfunction central to this entity. The most common initial presentation of jSSc is Raynaud's phenomenon, present in approximately 75% of cases, followed by proximal skin induration (66%), sclerodactyly (55%), and digital tip ulcers (35%)^[79]. Raynaud's phenomenon is characterized by vasospasms causing pallor, cyanosis, pain, numbness, tingling, swelling, and hyperhidrosis of acral surfaces, most typically affecting the hands and feet and occasionally the nose, lips, cheeks and ears^[24]. Episodes can be precipitated by cold and emotional stress. Sclerodactyly in children tends to appear edematous at first, with progression to shiny skin overlying tapered fingertips associated with decreased range of movement. In addition to the sclerotic changes, calcifications, ulcerations, and matted telangiectasias will develop^[79,83]. Dyspigmentation of the overlying skin has been described to have a "salt and pepper" appearance due to retained pigment in a perifollicular pattern within areas of hypopigmentation^[24]. Ichthyotic

skin changes of the proximal extremities have been reported as a prodromal presentation of jSSc^[84]. Histologically, skin biopsy reveals compact or hyalinized collagen in the dermis with atrophic adnexal structures and thinning of the overlying epidermis. The different subtypes of systemic sclerosis cannot be differentiated on microscopic exam^[1].

Lifestyle recommendations are critical to the management of the cutaneous symptoms in this disorder. Patients must be advised to avoid vasospasm triggers such as stress, cold and smoking. Currently most treatment modalities are based on adult studies. In adults, there have been randomized controlled trials that support methotrexate in managing and treating the early stages of disease^[85,86]. For patients with recalcitrant disease, human autologous stem cell transplants have been reported to improve symptoms in a limited number of cases^[87]. Due to the risk of contractures with jSSc, physiotherapy is critical.

MORPHEA

Morphea is a distinct inflammatory disease affecting the skin and underlying tissues leading to localized sclerosis. For this reason, another term for morphea is "localized scleroderma." However, morphea displays a clinical course distinct from that of systemic sclerosis and thus "morphea" is the preferred term to prevent confusion. The Childhood Arthritis and Rheumatology Research Alliance (CARRA) recently reported baseline data of 259 patients within their registry. The majority of patients were female (71%) and were more likely to be Caucasian (81%). Here they reported that the mean age of onset was 9.5 years, however almost 40% had at least a 5 year delay in diagnosis^[88]. Approximately half of all cases of morphea present in childhood. In children, disability due to the disease and associated extracutaneous complications is more severe than it is in adult patients^[89].

When a patient presents with morphea, the differential diagnosis of systemic sclerosis may be entertained. The distinction between morphea and systemic sclerosis is a clinical one with the latter characteristically exhibiting Raynaud's phenomenon and sclerodactyly as mentioned in the previous section (Table 1). Morphea is non-life-threatening, but can be significantly debilitating and disfiguring. Limb involvement, particularly when overlying a joint, can cause permanent limb asymmetry, contractures, ulcerations and joint immobility. Ocular and central nervous system manifestations have been reported in cases where there is underlying disease focused on the face or scalp. Esophageal involvement is not uncommon in children^[90]. Restrictive lung disease can result from generalized morphea subtypes^[91,92]. Other potential complications include calcinosis cutis and rarely squamous cell carcinoma in lesions of morphea, particularly of the pansclerotic type^[93,94].

Morphea is classified into 5 groups: Linear, circumscribed, generalized, pansclerotic and mixed. Mixed

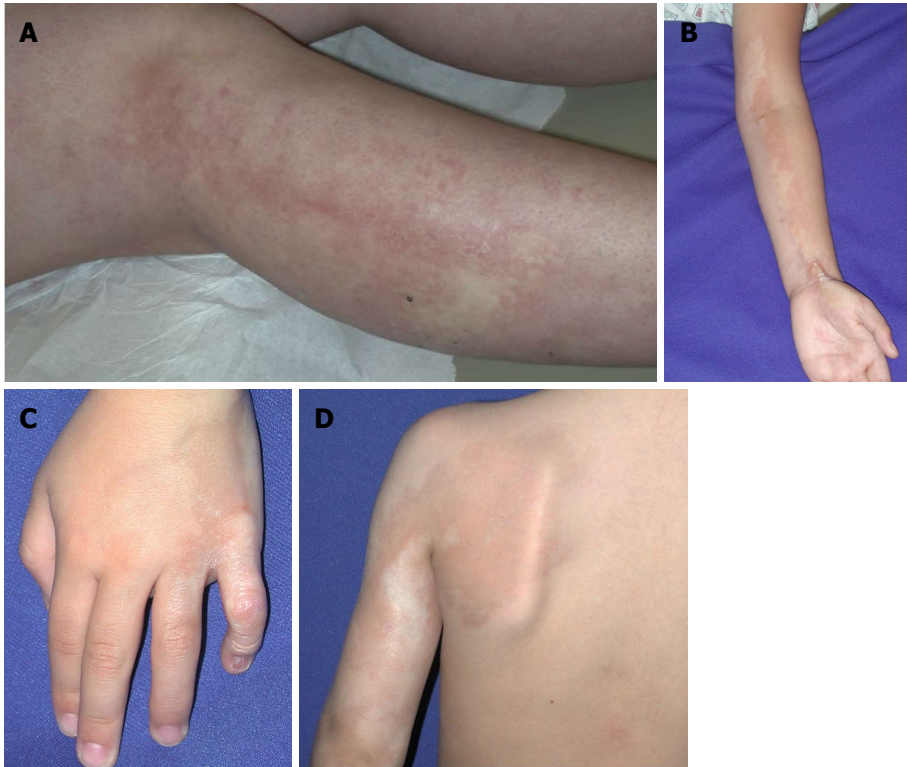


Figure 12 Linear morphea overlying joints. Early indurated plaques with lilac-colored border (A); (B) Advanced sclerotic and hypopigmented plaques on the left arm (C) with flexion contraction of the left fifth finger; (D) residual hyperpigmentation on the left shoulder.

type refers to presentations where 2 or more different types of morphea present on the same patient^[92]. In children, linear morphea is most common; in adults the circumscribed type is more common. Approximately 51%-65% of pediatric cases are of the linear subtype, followed by circumscribed morphea (26%), generalized morphea (7%) and pansclerotic morphea (2%). Histologically, the hallmark of well-developed lesions of morphea is thickened dense bundles of collagen in the dermis. Additionally, vascular changes of endothelial swelling and edema with a perivascular lymphocytic infiltrate and plasma cells may be appreciated^[1,37]. Slightly over 10% of pediatric patients will report an inciting event that is attributed to the onset of the morphea, such as trauma, infection, vaccination or insect bite^[91,92].

Linear morphea is the most common subtype in children and is divided into 2 subtypes by area of involvement: trunk/limbs and head^[95]. Linear morphea presents as a linear, erythematous strip that extends longitudinally in a series of indurated plaques, ultimately joining into a scar-like band. When linear morphea involves skin overlying a joint, there is risk of involvement of the underlying fascia, muscle and tendons (Figure 12). The inherent stiffness of the skin, as well as any deeper manifestations, can ultimately impact the joint mobility. Linear lesions can also extend circumferentially and produce significant limb size discrepancies^[24]. When linear morphea affects the head, various presentations, including en coup de sabre and

Parry-Romberg syndrome, are described. En coup de sabre is a term used for linear morphea affecting the forehead and scalp (Figure 13). Underlying findings on brain MRI/CT scans, including T2 hyperintensities, calcifications and ipsilateral cerebral atrophy, can be found in up to 73% of patients and can be associated with neurologic symptoms including seizures^[96]. Parry-Romberg syndrome (progressive hemifacial atrophy) describes a subset of facial morphea cases involving the lower half the face with associated ipsilateral atrophy (Figure 14). In this particular presentation, the entire distribution of the trigeminal nerve, including the eye and tongue, may be affected. Associated symptoms can include alopecia, seizures and headaches^[24,95].

Circumscribed morphea is characterized by slightly elevated, flesh colored or erythematous edematous plaques with an advancing border. The active border classically appears "lilac", or violaceous, in color leaving a trail of central sclerotic, scar-like tissue (Figure 15). There can be associated hair and sweat gland loss. The lesions can be asymptomatic or slightly pruritic and are often initially not noticed by the patient. The trunk is the most common location, affected by one or multiple asymmetric lesions. Clinical activity correlates with the presence of the lilac border. The active period of disease is felt to be on average 3-5 years. Once the lilac hue at the border disappears, the progression also seems to arrest^[1]. Residual atrophy and dyspigmentation are commonly observed. The term generalized morphea is used when there are 4



Figure 13 En coup de sabre morphea. Early presentation with an erythematous patch in paramedian forehead location extending into the scalp with hair loss.



Figure 14 Parry-Romberg syndrome. Note the resulting asymmetry of the right lower face due to loss of subcutaneous fat.

or more circumscribed plaques of morphea that are larger than 3 cm in diameter and involve at least 2 out of 7 anatomic sites: head-neck, right upper extremity, left upper extremity, right lower extremity, left lower extremity, anterior trunk, and posterior trunk^[95].

Pansclerotic morphea is a rare disabling variant more commonly seen in children than in adults. Diffuse involvement of the limbs, trunk, face and scalp occurs. In contrast to systemic sclerosis, pansclerotic morphea notably spares the fingertips and toes (Figure 16). Superficial and deep involvement by the sclerotic process leads to fixation of underlying structures. Internal organ involvement is notably absent, differentiating this entity from systemic sclerosis. Onset is usually before 14 years of age. Severe disability may result due to persistent atrophy of the underlying musculature^[24,95].

Treatment of morphea depends on the site of involvement, extent of disease and level of disease activity. Aggressive treatment is indicated for linear morphea overlying joints or near joints, facial disease, generalized and pansclerotic morphea. The standard treatment protocols involve use of systemic corticosteroids initially while bridging to longer term management with methotrexate. Randomized controlled studies have demonstrated response rates to be as high as 75% with this protocol^[97]. Increased relapse rates



Figure 15 Circumscribed morphea. Inflamed lilac border around indurated sclerotic plaques.

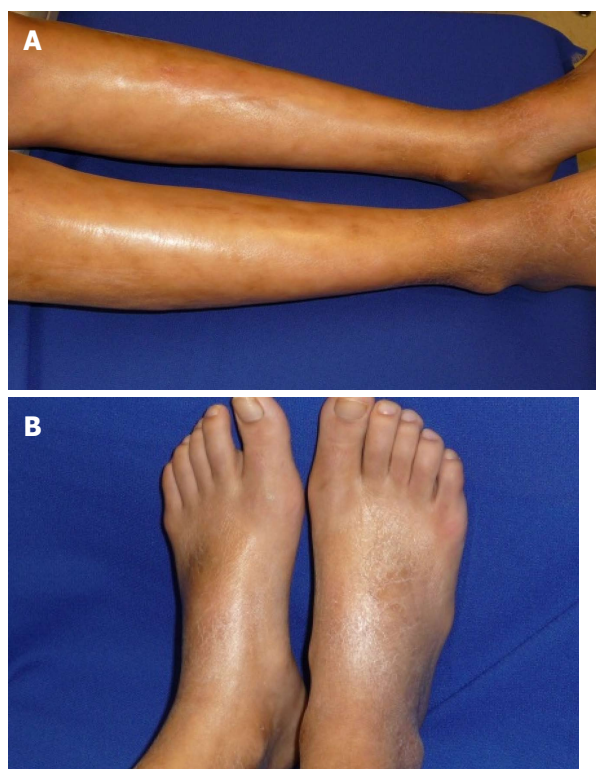


Figure 16 Pansclerotic morphea. A: Sclerosis of the skin bound down to underlying skin making the skin appear wooden with an uneven, taut shiny texture to the skin; B: Note the sparing of the toes which differentiates pansclerotic morphea from systemic sclerosis.

have been associated with shorter methotrexate courses (< 2 years) and shorter tapering regimens^[98]. Milder presentations of morphea may be managed with topical regimens including calcipotriene and corticosteroids. UVA1 phototherapy has recently been shown to have efficacy in morphea^[99,100]. Any consideration of surgical reconstructive procedures must be delayed until evidence of active disease has been thoroughly ruled out^[101].

CONCLUSION

In summary, there is a wide array of cutaneous findings

observed in the setting of autoimmune connective tissue diseases affecting pediatric patients. Timely diagnosis of these entities can be challenging as many symptoms are of gradual onset. Dermatologists have the opportunity to provide critical assistance by early recognition of suggestive findings, allowing for prompt treatment of disease and improved clinical outcome.

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Review of allergic contact dermatitis: Scratching the surface

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Abstract

Contact dermatitis-including allergic contact dermatitis (ACD)-n and results in over four million lost work days per year in the United States alone. ACD is a classic example of a type IV delayed hypersensitivity reaction, and represents a significant burden on the health system, economy, and patient quality of life. Thorough history taking, clinical examination, histologic evaluation, and patch testing are keys to diagnosing contact dermatitis. Patch testing, especially with comprehensive and customized panels based on the patient's exposure history, is particularly useful in identifying potential allergens in

the case of allergic contact dermatitis. ACD management requires a combination of direct medical intervention, patient education, and appropriate environmental modification to prevent exposure to offending allergens in the home or workplace. Continuing advances in the study of ACD has led to an increased understanding of the disease processes, new methods for diagnosis, and improved management. This article reviews ACD-aiming to connect recent investigational data with the current clinical understanding of disease pathophysiology, diagnostic techniques, and management strategies.

Key words: Allergic contact dermatitis; Occupational dermatitis; Skin sensitization; Contact allergens; Patch testing

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Core tip: Allergic contact dermatitis (ACD) affects approximately 20% of the adult population and results in over four million lost work days per year in the United States. Continuing advances in the study of ACD have led to an increased understanding of the disease processes, new methods for diagnosis, and improved approaches for treatment. This article discusses ACD holistically, aiming to connect recent investigational data with current clinical understanding to review disease pathophysiology, diagnostic techniques, as well as management strategies.

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INTRODUCTION

Contact dermatitis (CD) is a common inflammatory skin

reaction that follows direct contact of substances with the skin^[1,2]. Contact dermatitis affects approximately 20%^[3,4] of the adult population and is responsible for over eight million outpatient visits to dermatologists per year in the United States alone^[5]. Occupational related CD represents 90% of all occupation related skin disorders and results in over four million lost work days per year^[6,7]. CD represents a significant burden on the health system, economy, and patient quality of life^[4,7,8].

Contact dermatitis is divided into two distinct disease processes: irritant contact dermatitis (ICD) and allergic contact dermatitis (ACD). ICD is characterized by solitary or cumulative exposure to irritants (both chemical and physical) that induce direct keratinocyte damage and local inflammation, regardless of prior exposure^[2,4]. In contrast, ACD is an example of type IV delayed-type hypersensitivity, which is divided into distinct phases: sensitization, elicitation, and inflammatory regulation^[2,4,9,10]. Sensitization is the immunologic priming response following the initial topical exposure of a chemical allergen. Subsequent exposures at the same or distant sites on the skin result in a more vigorous secondary immune response at the point of contact, referred to as elicitation^[1,4]. The extent and severity of these hypersensitivity responses are controlled by underlying inflammatory regulation pathways. The clinical presentation of these phases is referred to as ACD^[4]. Continuing advances in the study of ACD have led to an increased understanding of the disease processes, methods for diagnosis, and approaches for treatment. This ACD review article will aim to connect investigational data with current clinical understanding to review disease pathophysiology, diagnostic techniques, as well as management strategies.

MECHANISM OF ACD

ACD is a multifactorial disease, resulting both from genetic and environmental factors^[2,5]. ACD is characterized as a type IV delayed hypersensitivity reaction^[10]. Once one or more potential allergens come in contact with the skin, a series of phases—sensitization, elicitation, and inflammatory regulation—occur that lead to an inflammatory response to the allergen(s)^[1,2,5,9]. The precise roles these phases play in ACD are still under investigation. ACD in humans typically develops in response to repeated subthreshold exposures to contact allergens with clinical signs and symptoms of dermatitis developing gradually overtime^[5,9]. Interestingly, our current understanding of ACD pathophysiology is primarily based on animal studies using the contact hypersensitivity (CHS) model^[5,10]. In CHS studies, potent lipophilic compounds are applied directly to a rodent's skin. This serves as the sensitization phase. Five to seven days later the same compound is applied to a different location, resulting in the elicitation response. Given the short time course and potency of compounds used for

priming an immunologic response, the CHS model depends on innate inflammatory mechanisms more than ACD. Regardless, it requires T cell antigen specific response, and is recognized as an analogous delayed-type IV hypersensitivity reaction^[5].

For a cutaneous immune response to be induced, contact allergens must be able to penetrate the stratum corneum, the water impermeable outer layer of the skin, in order to gain access to the deeper living layers of the epidermis^[1,4,11]. Filaggrin proteins are critical for maintaining epidermal homeostasis, aiding in the alignment of keratin filaments in the corneocytes and hydration of the stratum corneum^[10]. Without these proteins, there is impaired skin barrier function, allowing for easier penetration of chemical irritants and allergens. Patients with a history of atopic dermatitis and filaggrin mutations have an increased risk, four to seven fold, of developing contact dermatitis^[12].

Contact allergen characteristics also play a critical role in developing ACD. Most contact allergens are small organic chemicals or metal ions with molecular weights of < 500 daltons and lipophilic residues. These compounds are small enough to reach the horny layer of the epidermis, but too small to be immunogenic on their own^[1,4,10]. Allergen sensitization potential depends on forming stable reactions with proteins and creating hapten-protein conjugates^[4]. Sensitizing metals (*e.g.*, nickel, chrome, cobalt, *etc.*) react readily to form stable non-covalent protein-metal complexes. However, a majority of contact allergens cannot bind directly to host proteins and require either environmental or direct enzymatic changes in order to transform into reactive metabolites capable for forming covalent bonds^[2,9,10,13]. Allergens that undergo activation from the external environment such as photosensitizers with ultraviolet radiation or auto-oxidizing agents such as the fragrances D-limonene or linalool are referred to as pre-haptens. Alternatively, allergens that are modified through the natural detoxification processes of keratinocytes (*e.g.*, cytochrome P450 isoenzymes, UDP glucuronosyltransferase, glutathione S-transferase, *etc.*) into highly reactive intermediates are termed pro-haptens^[14]. Some familiar pro-haptens include natural products (urushiol), dyes (paraphenylene diamine, disperse blue), fragrances (eugenol), drugs (sulfamethoxazole), and industrial chemicals (styrene, ethylenediamine)^[1,13]. Once haptenated proteins are formed, they activate an inflammatory cascade attracting dendritic cells (DCs) to the contact site^[2]. Haptens are phagocytosed by DCs triggering the first phase of ACD, sensitization^[1].

As part of the sensitization process, the protein-allergen complexes are broken down and expressed as peptide epitopes on the grooves of MHC class I and II molecules. These antigen bearing DCs migrate from the initial contact site to regional lymph nodes where CD8⁺ and CD4⁺ T-lymphocytes in the paracortex are primed. Here T-cells undergo differentiation into effector T-helper (Th) cells, cytotoxic T-cells, and

Table 1 Key points in allergic contact dermatitis history taking^[18-20]

Topic	Details
Demographics	Age, sex, race, ethnicity
Past medical history	Personal history of atopic dermatitis, asthma, allergic rhinitis or other allergic diseases, co-morbidities, current medications, and medical device implantation (including dental implants such as braces, crowns, or fillings)
Family history	Atopic dermatitis, allergic rhinitis, or asthma
Occupational history	Current job description, materials handled at work, type and regularity of chemical exposures, previous employment history, and symptoms at work
Dermatitis specific history	Initial rash: date/duration, area(s) affected, symptoms, pattern/progression of eruption, frequency of recurrence, and treatments attempted Current rash: areas affected, severity, and changes during work week vs weekend
Home environment	Location (urban, suburban, or rural), pets (Dogs, cats, birds, rodents, livestock, <i>etc.</i>), house cleaning activities, and detergents used
Personal care	Hand washing frequency, deodorant, lotion, cream, perfume/cologne, hair styling aides, nail polish remover, makeup use, <i>etc.</i>
Sports/hobbies	Type of equipment used, indoor vs outdoor, and symptoms with activity
Jewelry/piercing/tattoos	Type, location and frequency of jewelry use, type and location of piercings, history of temporary or henna based tattoos

T-regulatory (Treg) cells, which over the course of weeks to months begin to circulate into the peripheral blood^[2,5,10].

Future re-exposure to sensitized contact allergens are recognized by DCs and result in a vigorous immune response (elicitation) and a classic inflammatory rash typically within 12 to 72 h^[4,9]. Resolution and regulation of the inflammatory response involves clearance of haptens and activation of CD4⁺ regulatory T cells^[2,5,10]. Studies have found haptens may remain in the for skin weeks to months following the initial exposure, suggesting the importance of anti-inflammatory cytokine production from local skin cells in addition to regulatory cells^[15]. While their precise action remains unknown, increasing evidence suggests CD4⁺ Treg cells control the priming and expansion of hapten specific CD8⁺ cells in the skin^[16]. Other mechanisms, including MicroRNA have been found to have a regulatory component^[17]. MicroRNA segments bind to sections of inflammatory sequences of mRNA, blocking and thereby inhibiting their effective translation. The accelerated turnover and breakdown of the transcripts alters gene expression and likely contributes to the dysregulation of inflammation in allergic contact dermatitis^[17].

DIAGNOSIS

Timeliness of diagnosis for ACD is essential for improved outcomes in the management of this disease. Making a diagnosis of ACD entails the following steps: (1) detailed history; (2) suggestive physical exam findings; (3) supportive histological evidence, and (4) patch testing^[3].

Clinical history and physical

Recognizing the clinical symptoms, exposure history, morphology, and distribution of lesions are important in the diagnosis of ACD. The first step in diagnosis is a obtaining a detailed history in order to determine the clinical relevance of various patch test allergens.

This may require extensive questioning. Standardized screening questionnaires are helpful to ensure comprehensive data collection regarding demographics, past medical history, family history, occupational history, home environment, hobbies, jewelry, tattoo use, use of personal care products, disease course and response to previous treatments (see Table 1 for key topics and relevant details to discuss when screening patients for ACD)^[18-20].

Many ACD cases can be traced to occupation^[20]. Certain professions-e.g., health professionals, construction/factory workers, machinists, cooks, janitors, farmers, hair dressers, among others-have an increased risk of developing occupational ACD^[21]. However, exposure to common industrial allergens, including cements, glues, plasters, and solvents, may also occur at home^[20]. Gathering a history should include information about temporality (*i.e.*, when do symptoms worsen or improve) and location (*i.e.*, where is the patient when symptoms worsen or improve)^[22]. For example, if symptoms improve on weekends or vacations, it suggests occupational relation. In contrast, symptoms that worsen during holidays or weekends may indicate recreational exposure to allergens.

Physical exam also provides important diagnostic clues. While dermatitis can have various morphologies, lesions typically present acutely as erythematous, edematous, or urticarial appearing papules, plaques, vesicles and bullae that become increasingly eczematous and weeping^[18,23]. In areas with thinner skin (*e.g.*, eyelid, penis, and scrotum), lesions are more edematous, with fewer superimposed vesicles^[18,23]. Intense pruritus leads to secondary changes of excoriation; subsequent impetiginization may also be observed. With persistent or repeated exposure, sub-acute or chronic ACD may develop. In sub-acute ACD, the skin remains erythematous and edematous as vesicles are replaced by erosions, oozing, crusting, and desquamation. With chronic exposure, the skin becomes dry, thick, and scaly with dermal infiltration, lichenification, and fissuring^[23].

Table 2 Allergic contact dermatitis distribution and commonly associated sources of exposure^[18,23]

Location	Type of exposure
Face/eyelids	Cosmetics, topical medications, or airborne allergens (volatile chemicals, sprays, dust, <i>etc.</i>)
Scalp/neck/posterior auricular folds	Hair dyes or shampoos
Sun exposed (face, upper chest, neck, arms)	Phototoxic or photoallergic reaction
Neck/upper chest	Fragrance in perfume or lotions
Hands	Occupational dermatitis (wet work or chemicals)
Trunk and axillary folds	Cloth dyes or textile exposure
Waist band	Rubber component of elastic waistband, nickel from belt buckle or buttons
Dorsal feet	Shoe chemicals (<i>e.g.</i> , rubber accelerators, potassium dichromate)

The inflammatory response is typically localized to areas directly in contact with the allergen. However, depending on the allergen sensitivity, the inflammatory response in ACD is well known for its ability to extend beyond areas of direct contact—a feature which distinguishes it from ICD^[23]. Additionally, allergens have the potential for secondary transfer, leading to inflammatory presentation beyond the area of initial contact. This is typically seen as “kissing lesions” in flexor regions or areas touched by contaminated hands^[23]. While the hands are the most common site for ACD, other common areas include the face, eyelids, lips, upper chest, arms, trunk and axilla, and dorsal feet. Recognizing distribution patterns can be a helpful in understanding ACD exposure (see Table 2 for examples of ACD location and distribution, as well as commonly associated sources of exposure)^[18,23].

Histology

Cutaneous changes in ACD can also be observed histologically via light microscopy. Histologic evaluation is important to rule out other conditions that may otherwise clinically resemble contact dermatitis on physical exam. Characteristic findings depend on the severity of response to offending allergens and the time of biopsy after contact with allergen^[18,24].

In acute ACD, the epidermis is normal in thickness, and significant inflammatory infiltrates can be observed perivascularly in the dermis^[24,25]. Additionally, eosinophilic spongiosis is also a prominent feature - characterized by intercellular edema leading to disruption of intercellular bridging between keratinocytes^[24,25]. Fluid accumulation progresses into intra-epidermal vesicles, while dermal perivascular lymphocytic infiltrate and blood capillary dilation result in dermal edema^[25,26]. Other common histologic features include, hyperkeratosis, spindled and stellate dermal dendritic fibrohistiocytic cells scattered in the interstitium, and occasional Langerhans cell microgranulomas^[24-26].

In sub-acute and chronic cases of ACD, histology is difficult to distinguish from nummular dermatitis or lichen simplex chronicus. Furthermore, while the histologic criteria of ACD occur reliably, they are relatively non-specific and are not readily distinguishable from ICD^[18,24]. Sub-acute ACD is characterized by acanthosis and parakeratosis in the superficial cornified layer. Untreated or chronic cases are notable for epithelial

ridges that become elongated and broadened. Biopsy is used most commonly for scientific research and is only clinically indicated in patients presenting with atypical symptoms in order to rule out alternative diagnoses (*e.g.*, cutaneous T Cell lymphoma). While histology can aid in diagnosis, current methods do not allow pathologists to readily differentiate ACD from other types of spongiotic dermatitis^[27]. Ultimately, diagnosis relies on a combination of history, clinical findings, histology, and positive epicutaneous patch test results^[23].

Patch test

Epicutaneous patch testing is the gold standard method for identifying contact allergies^[14,28]. Initially a very time consuming process, a majority of patch testing now relies on emulsified gel systems with pre-loaded allergens coated on water impermeable polyester backings. Once applied, allergens are released onto the skin as the dehydrated gel becomes moisturized by transepidermal water. Exposure reactions are then examined at 48 h and re-examined at 72-96 h, directly linking particular contact allergens with hypersensitivity reactions.

Established in 1995, the thin layer rapid use epicutaneous (TRUE) test pioneered this new generation of standardized patch testing. Currently, it remains the only patch test system approved by the Food and Drug Administration. The TRUE test contains a negative control and 35 antigens which includes allergens responsible for up to 80% of clinical allergic contact dermatitis cases^[29,30]. The convenience of the TRUE test has allowed for widespread use of diagnostic patch testing in academic centers and private practice dermatology offices. However, with over 4000 known contact allergens, relying on such a limited number of antigens will predictably result in missed diagnoses of ACD^[14,29]. Many studies have highlighted this concern, such as Saripalli *et al.*^[31] who showed that only one quarter of patients would have all clinically relevant allergens identified with the TRUE test, while another quarter would have none identified at all. Similarly, a 2009 study by Warshaw *et al.*^[32] found that the 36 chamber TRUE test missed 26.7% of contact antigens, particularly common rubber and perfume allergens typically included in an extended 70 antigen panel. Given the TRUE test's restricted diagnostic power,

there is a growing emphasis on more comprehensive screening^[19,29,30].

The North American Contact Dermatitis Group (NACDG) was among the first groups to pool ACD data in order to generalize the prevalence of reactivity to allergens in patch tests^[7,30]. Based on these results, the most common allergens are selected biennially by consensus for the North American series panel—a larger 70 antigen patch test series^[7]. An example of a popular addition to this larger series is fragrance mix II (a combination of 6 perfume allergens), which in combination with fragrance mix I has been shown to increase fragrance allergy detection by 30% more than fragrance mix I alone^[33]. Other efforts to raise awareness for contact allergens includes the dubious recognition of “Allergen of the Year,” awarded annually by the North American Contact Dermatitis Society to draw attention to common, but under recognized contact allergens. Various dermatology organizations offer alternative patch test series, for example the International Contact Dermatitis Research Group utilizes the widely accepted European Standard patch test series^[7]. Other series include the Minimum International Standard, British Baseline, and Japanese Standard.

Logistics and expense prevents including many allergens in a baseline panel. However, supplemental panels should be selected in order to include contact allergens with a higher pre-test probability of being positive according to a given patient’s exposure risk (e.g., bakery, dental technicians, hair dressing, metal implants, photochemicals, or metal working, etc). Hence, a detailed history is essential for identifying potential allergens. For example, if an allergen in the workplace is suspected, the occupational history needs to include details about the worker’s job, their exposures at work, their use of personal protective equipment, work and skin care practices, the relationship of the symptoms to work, and whether other workers are also affected^[22]. Examples of specialized series focused on particular industries or jobs include: bakery, dentistry, hairdressing, metal working, and photochemical panels. Examples of specialized series focused on particular chemicals include: acrylates, epoxy, isocyanates, metals, oils and coolants, plastics and glues, and rubber. Specialized trays have been found to have a clear added value, with studies finding 5% of plastics and glue allergies as well as 11% of rubber allergies going undetected by standard screening trays^[34,35].

Despite the availability of patch testing and the relative technical ease of administering the test, there are limitations^[14,29]. Reading patch test results in particular is dependent on practitioner skill and experience. The NACDG estimates the sensitivity and specificity of patch testing to be both below 85%, with a false positive range of 15%-18%^[36]. This confusion often arises during evaluation of weak positive results. Cases of extensive erythema and induration make differentiation between ICD and ACD difficult,

particularly in the face of unclear clinical relevance^[14]. While ICD tends to decrease by reading at 72 compared to ACD, many cases will not change in appearance, stretching the limits of morphologic interpretation. According to guidelines for interpretation, ICD cannot be definitively ruled out, and ACD cannot be definitively ruled in^[14]. In cases with unclear positivity or unclear clinical relevance, alternative tests such as repeated open application test (ROAT) and usage testing should be considered.

The ROAT utilizes one test allergen at a time without occlusion, minimizing rates of ICD and false positive reactions^[3,14,37]. It requires the application of 0.1 mL of the test allergen to a pre-specified area (usually the antecubital fossa) twice daily for up to 28 d, or until an eczematous reaction pattern develops^[37]. The ROAT allows practitioners to test the clinical relevance of previous patch test results. It is important to note that although a patient might display negative results when the allergen is applied on normal skin, ACD may still manifest during episodes of skin disease or damage^[37].

Another alternative for negative or unclear patch test results is usage testing. This involves having the patient use a product with specific ingredients, in order to test sensitivity under real world conditions. This method allows for all factors that may predispose a patient for ACD (friction, damaged or pre-sensitized skin) to be tested^[38]. However, this method of testing is limited because it is unable to distinguish an ICD vs ACD response. A discussion of proper methodology for patch testing with non-standardized allergens has been reviewed thoroughly by De Groot (2009)^[39]. Despite these limitations, patch testing remains the most reliable method of diagnosing ACD.

Confocal microscopy

A proposed alternative to patch testing is reflectance confocal microscopy (RCM)^[40,41]. RCM is a relatively new non-invasive *in vivo* imaging technique that allows for real-time imaging of the epidermis and superficial dermis^[11,40,41]. ACD and ICD are histologically very similar, and are not easily differentiated with traditional histologic methods. However, subtle differences do exist—with deeper, more prominent infiltrate and follicular spongiosis in ACD compared to ICD^[11]. These distinctions are deemed less reliable and not histologically definitive given the risk of specimen damage during biopsy collection and the introduction of handling artifacts during fixing and staining^[25,26]. In contrast, RCM allows evaluation of cellular and subcellular changes over time with serial observations of affected areas. Astner *et al.*^[40,41] demonstrated the ability to distinguish ACD from ICD, offering RCM as a promising alternative method of diagnosing ACD.

Once patch testing and clinical history both confirm ACD, measures should be taken to treat symptoms and prevent further exposure.

MANAGEMENT

Successful management of ACD necessitates both prevention and therapy, initially managing symptoms with corticosteroids, while allergen identification and avoidance education are completed^[19].

Prevention

ACD prevention relies on allergen avoidance^[19]. This requires eliminating exposure to substances clinically suspected and diagnostically confirmed to be causative from the home and work environment. Avoidance of the offending allergen(s) can drastically reduce incidence and severity of ACD^[20]. However, even with avoidance, ACD can persist-this is particularly notable in patients with ACD caused by chromate in which less than 20% of cases clear after 10 years^[42]. Protective equipment at work should be considered if symptoms or risk of allergen exposure persist. Barrier protection, such as gloves, safety goggles, and respirators, are effective for some workers^[20,22]. If occlusive gloves are used regularly they may cause skin irritation. Cotton liners should be recommended to prevent the development of impaired skin barrier function^[32].

In addition to barrier equipment, protective creams may also improve skin barrier function. Topical skin protectant (an emulsion with perfluoroalkylpolyether) and quaternium 18-bentonite lotion can prevent urushiol-induced dermatitis, while creams containing the chelator diethylenetriaminepentaacetic acid can prevent nickel, chrome, and copper dermatitis^[43]. However, in general there is mixed evidence for the effectiveness of pre-work barrier creams^[44]. They may be more effective if used in combination with cleansing and after-work creams or emollients. Pre-work barrier creams should not be used by workers who wear latex gloves, because they may increase allergen uptake from gloves^[19,43].

Education is an essential part of prevention. Holness *et al.*^[45] found that workers seldom receive health and safety training related to skin protection. Thus, it is important for practitioners to set aside ample time to counsel patients on allergen avoidance and barrier protection methods. Encouraging patients to read product labels in order to screen for ingredients is an important part of behavior modification. However, practitioners should recognize that ingredient names are complex and may make compliance difficult^[19,46,47]. Physicians should consider using free web-based resources (e.g., www.contactderm.org, www.allergyfreeskin.com, or www.mypatchlink.com) that provide patient-friendly education, including detailed lists of products free of patients' particular allergens in order to help improve allergen avoidance and quality of life^[19,43,46]. While the efficacy of various forms of education remains unknown, failure to educate patients on how to avoid, or protect against, contact allergens may result in therapy regimens that are ineffective at controlling chronic ACD and episodes of

relapse.

Therapy

Topical steroids are the mainstay of ACD symptomatic therapy. The spectrum of potency and ingredients allows the titration of treatment to match the severity and location of the dermatitis. The combination of barrier creams with moderate to high potency steroids have repeatedly been shown to successfully control ACD symptoms^[43]. However, long term topical steroid use is often discouraged. In widespread or poorly controlled cases, short term pulse therapy paired with systemic corticosteroids may be considered to bring dermatitis under control rapidly. Additionally, in cases of secondary impetiginization, topical antibiotics (e.g., mupirocin) or oral antibiotics, such as cephalosporin or penicillinase resistant penicillin, are appropriate^[43].

Less well studied alternatives treatments include topical calcineurin inhibitors, ultraviolet light therapies (PUVA or UVB), or systemic immune modulating therapies (azathioprine, cyclosporine, methotrexate). Interestingly, since histamine is not a primary inflammatory mediator responsible for pruritus in ACD, anti-histamine treatments are less effective, and are often only prescribed for their sedating side-effects^[14].

CONCLUSION

ACD is one of the leading causes of occupational skin diseases and significantly impacts quality of life. The best prognostic indicator for treatment of ACD is early recognition and intervention. Accurate identification of an offending allergen requires a detailed history of potential exposures and a physical examination to confirm the signs of ACD. Patch testing remains the gold standard for diagnosis, but is ultimately limited by the expertise of the clinician and the availability of relevant contact allergens. Management of ACD is multifactorial, relying on both prevention (eliminating allergen exposure, using protective equipment, and educating the patient) and medical therapy (typically topical corticosteroids).

While there continue to be significant improvements in our understanding of ACD, there is still much to be learned, particularly in the arenas of prevention and treatment. Patient education is critical for compliance with ACD prevention strategies. Future ACD management research should focus on the efficacy of various forms of patient education (handouts vs online resources vs healthcare led seminars, etc.). Additionally, ACD treatment is relatively limited to traditional corticosteroid regimens. The field would benefit from large, prospective longitudinal studies of alternative treatment techniques. Regardless of the research focus, studies that evaluate functional outcomes measures, such as time to return to work, would go far to enhance our understanding of the practical effectiveness of current management and treatment methods.

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Nicolau syndrome: A literature review

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and histopathology are reported and are associated with disease status. Three phase treatment is recommended for the patients with NS. Initially pain control and rule out differential diagnosis and in acute phase steroid therapy, heparin and pentoxifylline are useful. In necrotic phase, surgical treatment is needed depending on size of the affected site. NS is not well understood so far, however three phase treatment could lead to good result on basis of literature review.

Key words: Nicolau syndrome; Livedoid dermatitis; Embolia Cutis Medicamentosa; Drug hypersensitivity; Dermatitis; Diclofenac

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Core tip: To our knowledge, there is no literature review of nicolau syndrome (NS) and we report this review article for understanding NS.

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Abstract

Nicolau syndrome (NS) is a rare cutaneous adverse reaction after intra-muscular or intra-articular injection. Clinical features of NS are presented by three typical phases (initial, acute and necrotic phases). The cause of NS is acute vasospasm, inflammation of arteries and thromboembolic occlusion of arteriole related various drugs. Many results of laboratory test, imaging studies

INTRODUCTION

Nicolau syndrome (NS) (Embolia Cutis Medicamentosa or Livedoid dermatitis) is an uncommon cutaneous adverse reaction after intra-muscular or intra-articular injection of various drugs. NS was first reported in 1925 after the muscular injection of bismuth for the syphilis in the gluteal area^[1,2]. The usual characteristics of the injected lesion are pain immediately after injection, subsequently erythematous lesion, livedoid and hemorrhagic patch, and NS leads to necrosis of skin, adipose and muscle layers. The syndrome has been related to the injection of various drugs, including non-steroidal anti-inflammatory drugs

Table 1 Clinical features and three phase treatment of nicolau syndrome

Phase	Clinical features	Treatment
Initial	Intense pain	Analgesics
	Erythema	Systemic antibiotics ¹
	Radiating pain	No ice pack
	Faintness, syncope	
Acute	Livedoid plaque	Systemic steroid
	Violaceous patch	Anticoagulant agent
	Non-necrotic	
Necrotic	Necrotic indurated plaque	Surgical debridement
	Ulceration with necrosis	Plastic surgery

¹Systemic antibiotics: Until rule out cellulitis.

(NSAIDs), etanercept, pethidine, antibacterial agents, chlorpheniramine maleate, corticosteroids, vitamin, sulphonamide, lidocaine, phenobarbital, chlorpromazine, thiocolchicoside and vaccines. To our knowledge, there were no literature review of NS and we report this review article for understanding NS.

RESEARCH

Literature search and selection criteria

The expansion of the search for this review was conducting during the last week of August 2014 using the MEDLINE (December 1966 to August 2014). The following medical terms were searched: "Nicolau syndrome", "Embolia Cutis Medicamentosa", "Embolus Cutis Medicamentosa", and "Livedoid dermatitis". Results were limited to human subjects, written in English (except one which is first described report by France), and published in peer-reviewed journals. There is one review article that is limited to children cases^[3]. And 80 cases less than 12 years old was reported in Italian^[4].

Clinical features

Clinical features of various patients suffering from NS are divided to three steps; initial, acute and necrotic phases (Table 1).

Initial phase of NS is presented by intense pain immediately or soon after the injection with a bluish discoloration^[5]. Some patient complaints radiating pain to affected extremity or neurologic symptom such as peroneal neuropathy^[6-9]. Faintness or syncope may occur^[10]. Pain at the injection site is first sign subsequently erythema or hemorrhagic lesion and cutaneous necrosis or soft tissue and of the muscle develop eventually.

Acute phase occurs 24 h to 3 d later. In this phase, erythematous lesion develop at the injection site^[11] or indurated painful livedoid plaque with the border of the violaceous and reticular plaque^[12] develop. That is non-necrotic plaque or patch.

Necrotic phase as a final stage reveals that the injection site progress to violaceous, necrotic, crusted, indurated plaque. The lesion is progressing to erythema,



Figure 1 Photography of right gluteal lesion three weeks post injection illustrating the nature and extent of the eschar.

swelling and tender induration with central necrosis. Finally necrotic phase comes 5 d to 2 wk. A painful indurated erythematous plaque with black necrosis^[11,13] or a large necrotic skin patch with ulceration over the injection site is observed^[6] (Figure 1).

The most common sites are the buttocks however NS also has been reported on the shoulder^[10], thigh^[14-19], knee, ankle, breast^[20] and abdomen^[21,22]. In some complicated cases, critical complications such as extensive skin necrosis, transient or persisting ischemic changes of the ipsilateral limb and several neurological deficit may occur.

Pathogenesis and etiology

Pathogenesis of NS is not clear but a vascular origin is the most reasonable hypothesis. Acute vasospasm, inflammation of arteries and thromboembolic occlusion of arteriole are the key mechanisms^[12]. The leakage of around artery and neural space has been suggested as cause of intense pain. Moreover, sympathetic nerve stimulation and vasospasm lead to ischemic change and skin necrosis. Unintended intravascular injection of drugs also has been proposed as causing inflammation or thromboembolic occlusion of the arterioles. These may cause arterial intimal necrosis, destructure the arterial membrane and induced subsequently cutaneous necrosis^[12,23]. Few patients with NS after intramuscular injection of diclofenac have been reported even though which is a commonly used NSAIDs. Diclofenac as a cyclo-oxygenase inhibitor inhibits prostaglandin synthesis and causes vasoconstriction. Therefore, a vasospastic effect of diclofenac is the suggested pathogenetic mechanism of NS^[24].

Many drugs (Table 2) related to NS have been reported such as cyanocobalamin (vitamin B₁₂)^[12], lidocaine^[20], vitamin K^[17,18], etanercept^[21], naltrexone^[25], ketorolac^[26], ketoprofen^[27,28], meperidine^[27], gentamycin^[29], chlorpheniramine maleate^[30], Trabit (phenylbutazone, salicylamide, dexamethasone and lidocaine)^[31], triamcinolone^[31], benzathine penicillin^[23,31,32], salicylate bismuth^[2], ibuprofen^[2], Interferon β ^[5], penicillin G^[12], thiocolchicoside^[7], glatiramer acetate^[22,33], piroxicam^[8], DPT(diphtheria-tetanus-pertussis)^[15], DTP-polio-Hib^[14],

Table 2 Drug list related to nicolau syndrome

Drug	Target disease or symptom of using drug	Ref.	Duration of necrosis	Affected site
Naltrexone	Alcohol dependency	Perli <i>et al</i> ^[25]	Over 7 d	Buttock
Etanercept	Psoriatic arthritis	Guarneri <i>et al</i> ^[21]	10 d	Abdomen
Ketorolac	NS	Marangi <i>et al</i> ^[26]	2 wk	Buttock
Ketoprofen	Knee pain	Kim <i>et al</i> ^[27]	NS	Buttock
	COM	Lee <i>et al</i> ^[28]		
Meperidine	Operation site pain	Kim <i>et al</i> ^[27]		Buttock
Gentamycin	Elbow sprain	Kim <i>et al</i> ^[29]		Buttock
Chlorpheniramine maleate	Pruritus	Nischal <i>et al</i> ^[30]	7 d	Arm
Trabit	Back pain	Ruffieux <i>et al</i> ^[31]		Buttock
Triamcinolone acetonide	Lichen planus of scalp	Ruffieux <i>et al</i> ^[31]		Buttock
Salicylate bismuth	Syphilis	Corazza <i>et al</i> ^[2]	A few days	Buttock, thigh
Ibuprofen	Coxarthrosis	Corazza <i>et al</i> ^[2]		Buttock
Interferon β		Ozcan <i>et al</i> ^[5]	3 d	Arm
Benzathine penicillin	Cellulitis	Ruffieux <i>et al</i> ^[31]		Buttock,
	NS	De Sousa <i>et al</i> ^[32]	1 d	L/Ext.
		Ocak <i>et al</i> ^[23]		
Penicillin G	Fever and cough	Luton <i>et al</i> ^[12]	2 d	Buttock,
				L/Ext.
Cyanocobalamin		Luton <i>et al</i> ^[12]		Buttock
Thiocolchicoside	Back pain	Guarneri <i>et al</i> ^[7]	2	Buttock
Glatiramer acetate	Multiple sclerosis	Harde <i>et al</i> ^[22]	2 d	Lower
		Koller <i>et al</i> ^[33]		abdomen
Piroxicam	Ankle sprain	Lee <i>et al</i> ^[8]		Ankle
DPT	Vaccination	Erkek <i>et al</i> ^[15]	2 wk	Thigh
DTP-polio-Hib	Vaccination	Bégin <i>et al</i> ^[14]	2 wk	Thigh
Hydroxyzine	Itching	Gayken <i>et al</i> ^[16]		Thigh
Calcium hydroxide	Bleeding in the distal root canal	Willbrand <i>et al</i> ^[34]		Cheek
Lidocaine	Core needle biopsy on breast	García-Vilanova-Comas <i>et al</i> ^[20]		Breast
Vitamin K	Prematurity	Puvabanditsin <i>et al</i> ^[18]	2 wk	Thigh
Mesotherapy injections	Tendinopathy	Zaragoza <i>et al</i> ^[35]	3 wk	Knee

NS: Non-specific; COM: Chronic otitis media; Trabit: Phenylbutazone, salicylamide, dexamethasone and lidocaine; L/Ext: Lower extremity; DPT: Diphtheria-tetanus-pertussis.

hydroxyzine^[16], calcium hydroxide^[34] and mesotherapy injections^[35]. However, diclofenac sodium is the major drug of NS.

Laboratory test

Blood result is unremarkable^[6]. Initially there was no evidence of cellulitis. Some studies reported that The biologic markers suggesting muscle damage such as creatine kinase, myoglobin, aspartate transaminase, alanine transaminase and lactate dehydrogenase are elevated although white cell count, inflammatory markers and renal function were unremarkable^[36]. Otherwise leukocytosis, increased serum glutamic oxalacetic transaminase, lactic dehydrogenase and myoglobinuria were found^[12].

Imaging studies

Ultrasonography do not identify any definite abscess or sign of fluid collection^[19,25] but shows an evidence of an area of diffuse edema within the muscles^[2]. Necrotic

lesion reveals a diffuse hyperechogenic area with inflammation involving the subcutaneous area and the muscles^[11].

Computed tomography reveals a well-defined lesion of the diffuse adipose inflammation with central gas collection^[25,37]. However the muscle tissue is uninvolved and there is no liquid collection^[24]. Extension of involved lesion is usually limited out of the muscular fascia^[13,37].

Magnetic resonance imaging reveals a subcutaneous liquid collection up to the fascia and muscle tissue appears uninvolved^[11] or only diffuse change of signal intensity in the adipose layer at the injection site showing extensive edema in the subcutaneous fat^[36] in acute phase. Progressing to necrotic phase, MRI reveals focal muscle necrosis and the residual muscle edema^[36] however the muscle is spared and there is no liquid collected under the eschar tissue in some case^[38].

Histopathology

Histopathologic findings are mainly reported in necrotic

phase because surgical debridement is performed in this phase. Histopathology revealed fibrosis of adipose tissue, fat necrosis and predominantly eosinophilic infiltration^[25] and inflammation infiltrating subcutaneous adipose tissue without any vasculitis or granuloma^[5]. There is no evidence of malignancy or vasculitis^[6].

Cultures

Bacterial, fungal and mycobacterial cultures were negative^[8,25,38] or resident flora^[7,39]. *Pseudomonas aeruginosa* and *Staphylococcus aureus*^[5,6,16,19,27,30]. *Pseudomonas aeruginosa* leads to use piperacillin intravenously^[6].

Differential diagnosis

Initial differential diagnosis includes a local toxic reaction to drugs, acute bleeding and acute compartment syndrome^[16,36]. Especially shoulder region is differentiated from cardiac problem checking an ECG, cardiac enzyme levels, and a chest radiograph^[10]. Also the differential diagnosis includes vasculitis, fat embolism, left atrial myxomas and Hoigne syndrome^[12]. Patients would be admitted for presumed cellulitis^[12,16,25]. Misdiagnosis of cellulitis lead to use antibiotics and it can be failure of treatment for NS^[12]. Suspicious malignancy has to be checked by surgical extirpation of the plaque of the lesion and biopsy for macroscopic examination^[20].

Treatment

There is no consensus of treatment of NS so far. However we suggest the treatment of NS step by step as the three phases (Table 1). Phasic treatments depend on the extent of the necrotic lesion and ranges from medication to surgical debridement.

Initial phase: Because of severe pain, conservative pain control with analgesics and dressings is usually recommended. And differential diagnosis is most important in the initial phase. Ice pack application increases the acute focal vasospasm and can aggravate the disaster^[10,40]. Until cellulitis of affected site is ruled out, systemic antibiotics are suggested. After any signs of cellulitis ruled out such as fever, elevated white blood cell count, C-reactive protein and erythrocyte sedimentation rate, prophylactic antibiotics might be useful.

Acute phase: Hypothesis of vascular origin and inflammatory sequelae is most reasonable. For this reason systemic steroid and anticoagulant agent are usually used^[12,36]. Hyperbaric oxygen treatment was given to patient with the assumption of microarterial thrombi as well as heparin and pentoxifylline^[23]. Subcutaneous injection of heparin 5000 to 10000 U b.i.d.^[12] and intravenous infusion of betamethasone diphosphate 24 mg/d induce improving symptom within 2 d^[12]. Patient responses rapidly to methylprednisolone 1g IV q.d. or dexamethasone 32 mg intravenous

injection for three days and pentoxifylline 400 mg PO t.i.d.^[12]. Warm intermittent compression^[12] is also recommended.

Necrotic phase: The patients with NS undergo surgical debridement of the affected skin, subcutaneous tissue and muscle in case of clinical and radiographic evidence of tissue necrosis^[2,6,13,16]. And after the ulcerative necrotic lesion was filled with healthy granulation, split-thickness skin graft or reconstructive surgery were performed. Finally the wound healed well and uneventfully with atrophic skin scar or wound contraction^[30].

Special condition

If the patient is necessary to maintain following drugs, continuation of treatment with glatiramer acetate at other injection sites is recommended^[22,33]. Also further injection of etanercept at other site is tolerated without complication^[21].

Prevention

Confirmation to extra-vascular leakage of the drugs is necessary to perform injection after having aspirated with the syringe^[2]. And upper outer quadrant of the buttock area is the recommendable site for the intramuscular injection, which has fewer vessels^[41].

CONCLUSION

Clinical differentiation alone is difficult to make a diagnosis of NS and the imaging and laboratory tests assist in the clinical decision^[36]. By this literature review, three phase treatment is recommended for NS.

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New innovation of moisturizers containing non-steroidal anti-inflammatory agents for atopic dermatitis

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Abstract

Atopic dermatitis is a chronic, relapsing and extremely pruritic eczematous disease which commonly affects children. The standard management consists of a combination of anti-inflammatory drugs in adjunctive with skin care management particular moisturizer application. A concern for the side effects associated with long term use of corticosteroids has also been considered. There has been an emerging interest in moisturizer containing non-steroidal anti-inflammatory agents such as herbal extracts, vitamins, mineral and lipids. The *in vitro* and the *in vivo* studies of each agent were reviewed. The clinical study on the efficacy of moisturizers containing these agents were also demonstrated including the author's studies and clinical

experience. These moisturizers might be considered as an alternative treatment in acute flare of mild to moderate atopic dermatitis.

Key words: Non-steroidal anti-inflammatory agents; Moisturizer; Atopic dermatitis

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Core tip: The skin care management particular moisturizers play an important role in atopic dermatitis. The side effects of corticosteroids are limited in their use in this disease. Take together, a new moisturizer containing various anti-inflammatory substances have been developed to be used as an alternative treatment to avoid the side effects of corticosteroids. These agents are divided into herbal extracts, vitamins, minerals and lipids. The clinical trials on the effectiveness of these moisturizers were reviewed. The author's clinical experience also discussed.

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INTRODUCTION

Atopic dermatitis (AD) is a chronic, relapsing and extremely pruritic eczematous disease which commonly affects children and influences the quality of life.

The etiology of AD seems to result from a combination of barrier dysfunction, immunodys function, genetics, autoimmunity, *Staphylococcus aureus* and environmental factors^[1].

The standard management of AD consists of a combination of anti-inflammatory drugs in adjunction

Table 1 Type of anti-inflammatory agents

Herbal extracts
Licorice
<i>Glycyrrhiza inflata</i> (Licochalcone A)
<i>Glycyrrhiza glabra</i> (Glycyrrhetic acid)
Chamomile
<i>Matricaria recutita</i> (Bisabolol, chamazulene, apigenin)
Vitamins and minerals
Provitamin B5 (Dexpantenol)
Vitamin B3 (Niacinamide)
Zinc
Lipids
Natural sources of lipids
N-palmitoylethanolamide extracted from palm oil
Linoleic acid extracted from:
Shea butter (<i>Butyrospermum parkii</i>)
Canola oil
Argar oil
Kernel oil
Spent grain wax
<i>Portulaca oleracea</i> Linn
Phytosterol extracted from shea butter
Synthetic lipids
Ceramides
Pseudoceramides

with skin moisturization and avoidance of triggering factors. A concern for the side effects associated with long term use of corticosteroids has also been considered.

For the past five years, there has been an emerging interest in moisturizer containing non-steroidal anti-inflammatory agents such as herbal extracts, vitamins, minerals and lipids. The anti-inflammatory property of these agents are demonstrated in *in vitro*, *in vivo* studies, as well as the clinical trials on the patients with AD, psoriasis and seborrheic dermatitis.

From the literature reviews of clinical researches on these moisturizers, they are divided into 3 groups according to the active ingredients of anti-inflammatory agents as follows: herbal extracts, vitamins, minerals and lipids (Table 1). The evidence of the clinical studies on the effectiveness of moisturizers containing anti-inflammatory agents are summarized in Table 2.

HERBAL EXTRACTS

There are two active ingredients extracted from two species of Licorice: (1) Licochalcone A (LA), extracted from *Glycyrrhiza inflata*; and (2) Glycyrrhetic acid, extracted from *Glycyrrhiza glabra*.

There is an *in vitro* study that demonstrates that LA, a major phenolic component of *Glycyrrhiza inflata*, has anti-inflammatory as well as antimicrobial effects^[2,3]. It could inhibit cytokines production from T cells and monocytes as well^[2-4]. The study shows that LA could reduce shave-and ultraviolet (UV)-induced redness^[4]. Moreover, the improvement of the rosacea patients is also reported in a clinical study in which skin care product containing LA was applied for 8 wk^[5].

In 2010, Udompataikul *et al*^[6], conducted a comparative trial of moisturizer containing LA and linoleic acid vs 1% hydrocortisone (HC) for the treatment of childhood AD. It was a randomized controlled-investigator blind study. LA lotion were applied on one side of the patients' body and HC lotion on the opposite side, twice daily for 6 wk. The clinical outcome was assessed using the scoring of AD (SCORAD) score. The relapse rate was recorded and analysed using survival analysis. Thirty patients were enrolled, 26 patients completed the protocol. The mean age was 5.8 years old. The average baseline SCORAD score was 28 on both sides (moderate severity). The response rate of both agents was 73.33%. There was no statistical significant group difference in the reduction of SCORAD score. Though the edema and erythema score in HC treated area had more rapid improvement than that of LA treated side, there was no significant difference. The relapse rate of HC-treated side was higher than that of LA-treated side. However, there was no significant difference. No side effect was observed from both agents. It was concluded that the effectiveness of moisturizer containing LA was equal to that of HC lotion. It could be used as an alternative treatment for both acute flare and in maintenance phase of mild to moderate childhood AD.

There was also a multicenter, randomized, split-side double blind study in 55 children between the age of 3 mo to 14 years with mild to moderate AD. It was shown that LA had a similar result in terms of improved SCORAD and reduces transepidermal water loss (TEWL) compared with 1% HC^[7].

In 2014, Angelova-Fischer *et al*^[8], designed a comparative study of moisturizer consisted of LA, linoleic acid, decanediol and menthoxypropanediol (LALDM) vs 1% HC for mild to moderate AD treatment. Twenty patients were included. The mean age was 26.2 years old (16-65 years old). It was discovered that LALDM and 1% HC can reduce SCORAD scores, pruritus, erythema, TEWL and increase in skin conductance without statistically significant difference between two groups. Moreover, LALDM can reduce *Staphylococcus aureus* colonization with statistically significant difference from 1% HC. Decanediol has antibacterial activity. Menthoxypropanediol, a synthetic derivative of menthol can improve the pruritic symptom by triggering cold-sensitive receptors in the skin which is responsible for cooling sensation.

Glycyrrhetic acid also possesses anti-inflammatory property^[9]. Abramovits *et al*^[10], conducted a randomized, vehicle-controlled clinical trial to examine the effectiveness of MASO63DP cream, which composed of shea butter and Glycyrrhetic acid, in the management of mild to moderate AD. 218 patients, age between 18-84 years old, were included in this 50-d study. The clinical outcomes were assessed using Eczema Area and Severity Index score and Investigator's Global Assessment. It was found that the incidence of rash

Table 2 Evidence of the clinical studies on the effectiveness of moisturizers containing anti-inflammatory agents

Ref.	Active ingredients	Design + Population + Age	Outcome measurement	Results
Udompataikul <i>et al</i> ^[6]	Licochalcone A, LA	Randomized controlled-investigator blind; <i>n</i> = 28, mean age = 5.8 yr old (2-15 yr old)	SCORAD score	Response rate 73.33% The effectiveness of LA was equal to 1% HC
Wanankul <i>et al</i> ^[7]	Licochalcone A, LA	Randomized, double-blind, split-side, study <i>n</i> = 55, age 3 mo-14 yr old	SCORAD score, TEWL	The effectiveness of LA was equal to 1% HC
Angelova Fischer <i>et al</i> ^[8]	LALDM	Randomized controlled-investigator blind, study; <i>n</i> = 20 mean age = 26.2 yr old	SCORAD score, TEWL, skin -conductance, <i>Staphylococcus aureus</i> colonization	LALDM was equal to 1% HC, and LALDM can reduce <i>Staphylococcus aureus</i> colonization
Abramovits <i>et al</i> ^[10]	Glycyrrhetic acid, shea butter (MASO63DP)	Randomized, vehicle-controlled study; <i>n</i> = 218, age 18-84 years old	EASI score, IGA	The effectiveness of MASO63DP was more effective than vehicle
Boguniewicz <i>et al</i> ^[11]	Glycyrrhetic acid, shea butter (MASO63DP)	Randomized, vehicle-controlled study; <i>n</i> = 142, age 18-84 yr old	EASI score, IGA	The effectiveness of MASO63DP was more effective than vehicle
Udompataikul <i>et al</i> ^[20]	Dexpanthenol, petrolatum	Open label; <i>n</i> = 30 mean age 7.19 yr old	SCORAD score	The effectiveness of dexpanthenol ointment was equal to 1% HC
Eberlein <i>et al</i> ^[30]	PEA, phytosterol ceramide in dermal membrane structure	Multicenter study (moisturizers as adjuvant treatment) <i>n</i> = 2456 (adult 1533, children 923)	Clinical and pruritic VAS	Pruritus reduction (VAS), Improvement of sleep quality, Reduction of previous use of topical corticosteroid were significant difference
Udompataikul <i>et al</i> ^[20]	Linoleic acids from Spent grain wax, shea butter, argan oil; phytosterols (LP)	Randomized investigator blind; <i>n</i> = 31, age = 4.24 yr old	SCORAD score	The effectiveness of LP was equal to 1% HC
Lee <i>et al</i> ^[40]	Multilamellar emulsion - pseudoceramide, type III synthetic ceramide (PC)	An open crossover study	Clinical	PC cream was more effective than urea cream

LA: Linoleic acid; SCORAD: Score of Atopic Dermatitis; EASI: Eczema Area and Severity Index; IGA: Investigator's Global Assessment; TEWL: Transepidermal Water Loss; VAS: Visual Analogue Scale; LALDM: Licochalcone A, linoleic acid, decanediol menthoxypropanediol; PEA: N-palmitoyl ethanolamine.

was 2.1% in MASO63DP group vs 5.5% in the vehicle group. MASO63DP was statistically more effective than vehicle. Two patients discontinued using MASO63DP because of an adverse effect^[10]. Boguniewicz *et al*^[11], also conducted the same clinical study in 142 childhood AD patients. It was concluded that MASO63DP is an effective monotherapy for mild to moderate AD in infant and children^[11].

Chamazulene (terpenoids) is a major active ingredients extracted from chamomile (*Matricaria recutita*). It possesses anti-inflammatory property by inhibiting histamine release from mast cells and leukotriene B₄ from white blood cells^[12,13]. In addition, Apigenin, flavonoids agents found in chamomile also has anti-inflammatory and antioxidant effect^[14]. It was discovered that these active agents decrease UV induced erythema^[15]. Chamomile is commonly used as an active ingredient in combination with Zinc or dexpanthenol (DT) in protective cream for irritant contact diaper dermatitis.

VITAMINS AND MINERALS

DT, an alcoholic analog of pantothenic acid, as water-in-oil emulsion, is rapidly penetrated through the skin^[16].

Pantothenic acid is essential for normal epithelial function and is a component of coenzyme A, a cofactor for catalytic enzyme in carbohydrate, fatty acid, protein, sterol and porphyria metabolism^[17], 2%-5% of DT acts like a humectant moisturizer^[17-19]. It was shown that DT has anti-inflammatory action on UV-induced erythema and irritation model^[17]. Furthermore, DT plays an important role in wound healing by activation of fibroblast proliferative and acceleration of re-epithelization. The ointment consisted of 2%-5% DT is effective for the treatment of burns, anal fissures, leg ulcers, diaper dermatitis, and sodium lauryl sulfate induced irritant contact hand dermatitis in AD patients^[17]. The comparative study of 5% DT in w/o emulsion vs 1% HC ointment in the treatment of mild to moderate childhood AD was also investigated^[20]. Thirty patients with mean age of 7.19 years old enrolled.

Twenty-six patients completed the study. The results exhibited that the efficacy of DT and HC to reduce SCORAD scores were not significantly different at the end of the study (week 8). However, HC could relieve edema faster than DT with a significant difference (within week 1 vs week 2 respectively). Hence, this study also demonstrates that DT has a beneficial role as an alternative treatment in mild to

moderate severity of childhood AD.

Niacinamide (vitamin B3) demonstrates anti-inflammatory action by inhibiting the histamine release from mast cells^[21]. It also increases ceramides biosynthesis and other stratum corneum lipids to improve the epidermal barrier function^[22]. Zinc exhibits the anti-inflammatory response by blocking cytokine release from monocytes^[23]. It is commonly used in the barrier cream for the treatment and prevention of irritant contact diaper dermatitis.

LIPIDS

Lipids with the occlusive effect, help prevent TEWL from the skin. As a result, it keeps the skin moist. The types of lipids which possess anti-inflammatory properties are as follows.

Natural sources of lipids

N-palmitoylethanolamine: N-palmitoylethanolamine (PEA), a fatty acid derivative that belongs to the family of N-acylethanolamines. PEA used in commercial moisturizers, is extracted from palm oil. It is physiologically produced by keratinocyte and is found in the stratum granulosum of human skin. The major roles of PEA are to be used as an anti-inflammatory, antioxidant and analgesic compound. The mechanism of action is *via* cannabinomimetic action on cannabinoid receptors (CBR) located on mast cells and cutaneous nerve fibers^[24,25]. CBR agonists significantly decrease histamine induced pruritus and vasodilatation after they are topically applied on the skin^[26]. An anti-inflammatory action of PEA was clinically demonstrated. PEA was incorporated into a lamellar matrix cream which was used in these studies. It was shown that this cream could alleviate the irritative facial skin lesions^[27] and uremic pruritus^[28]. Moreover, HC cream and this cream were equally effective in 18 patients with mild to moderate AD^[29]. A recent 6-wk multicenter trial study illustrated that intensities of erythema, pruritus, excoriation, scaling, lichenification and dryness were significantly reduced with a combined score of 58.6% among the whole group of patients according to the doctors' reports. A pruritus reduction on visual analogue scales from 6 d through 6 wk of treatment with significant difference from baseline was reported, and the patients' sleep quality was significantly improved as well. Previous use of topical corticosteroids were significantly reduced by 56% while the average weekly application rate decreased by 62%. Therefore, this cream demonstrates a benefit in the AD management^[30].

ESSENTIAL FATTY ACIDS AND STEROLS

Essential fatty acids like Omega 3, Omega 6 and sterols as phytosterols possess an anti-inflammatory property. They help reduce the production of prostaglandins.

They are found in the seeds of many plants, including shea butter, spent grain wax, argan oil, kernel oil, canola oil^[31], as well as in the roots, leaves and stems of purslane (*Portulaca oleracea* Linn)^[32,33].

Recently, the study of moisturizing cream consisted of linoleic acids from spent grain wax, shea butter, argan oil and phytosterols from shea butter has been conducted in 31 patients with mild to moderate AD. The mean age was 4.24 years old. It was also shown that this cream is equally effective to HC. Thus, it is considered as an alternative monotherapy for childhood AD with mild to moderate severity^[34].

Synthetic lipids

Natural stratum corneum ceramides structurally consist of a polar amide group and non-polar alkyl chains. They are capable of assembling to form the lamellae^[35]. However, since the natural ceramides are extremely expensive and difficult to formulate, the new pseudoceramides, for example 1,3-bis-(N-(2-hydroxyethyl)-palmitoylamino)-2-hydroxypropane, have been developed^[35]. Pseudoceramides have similar molecular properties to ceramides. The synthetic ceramides have been developed as well.

Park *et al*^[36], discovers that the molecular organization of multilamellar emulsion-pseudoceramide and type III synthetic ceramide as characterized as the lateral hexagonal phase are similar to the human stratum corneum intercellular lipid. Moreover, synthetic ceramides show anti-inflammatory effect both in *in vitro* and *in vivo*, and prove to be beneficial in an animal model of AD^[37-39].

There was a clinical comparative study on anti-inflammatory property of multilamellar emulsion containing pseudoceramide and synthetic ceramide (ME) vs urea cream. It concluded that ME cream was more effective than that of urea in mild to moderate childhood AD^[40].

AUTHOR'S CLINICAL EXPERIENCE AND COMMENTS

From author's clinical practice experience, corticosteroids, calcineurin inhibitors and moisturizer skin care are standard treatment for AD patients. Nevertheless the moisturizers containing anti-inflammatory agents can be used as an alternative treatment instead of corticosteroids or calcineurin inhibitors in mild to moderate severity of AD patients, and in the maintenance phase as well. They are particularly suitable for some selected cases whose parents are corticosteroid phobia. However, the anti-inflammatory responses especially, the edema and erythema parameter might be slower than corticosteroids. This information should be informed to the patients. In these particular cases, when these moisturizer that contained anti-inflammatory agents were used to treat as an alternative first line of treatment for a couple of weeks with slow response rate, the

corticosteroids should be added on. It was found that these moisturizers could reduce the frequency of corticosteroids use in the treatment.

CONCLUSION

Because particular skin care moisturizers play an important role in AD management, the side effects of an anti-inflammatory agents like corticosteroids are limited in their use in AD. Taken together, new moisturizers containing various substances have been developed to be used as monotherapy in mild to moderate AD. These agents are herbal extracts, vitamins and minerals and lipids. They can be used as an alternative treatment and in the maintenance phase of AD. The further researches for new anti-inflammatory substance should be conducted.

However, the long term side effect of the treatment with these moisturizers should be warranted, and the pricing of these moisturizers should also take into consideration.

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Identifying and managing naevus dysmorphia in clinical practice

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the appearance of a clinically small melanocytic naevus. The naevus is perceived by the patient to be disfiguring. Such perception leads to maladaptive behaviours and is often associated with low mood, as well as high levels of anxiety and social avoidance. Affected individuals form a diverse group. However, what they have in common is that the distress experienced is disproportionate to the objective visual appearance of the mole. There is a range of severity of the impact on the individual's well being. Naevus dysmorphia may or may not be a cutaneous manifestation of body dysmorphic disorder (BDD). It is essential that patients with naevus dysmorphia are identified and distinguished from patients requesting removal of a mole for other uncomplicated cosmetic reason. Patients with naevus dysmorphia can be challenging to treat and communicate with. Surgical excision of the naevus will not address the underlying psychopathology and so it may not result in long-term positive outcome. Ideally, a detailed psychological assessment and formulation can be made potentially followed by psychological therapy tailored to the needs of the individual. A therapeutic trial of appropriate psychopharmacological course may be indicated in certain cases, *e.g.*, when symptoms of a depressive disorder, anxiety disorder or BDD are present. A case series of 10 patients with naevus dysmorphia is presented, in order to highlight the above issues.

Key words: Naevus dysmorphia; Body dysmorphic disorder; Body image dissatisfaction; Psychological distress

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Core tip: Naevus dysmorphia is a form of body image dissatisfaction. A preoccupation with a simple melanocytic naevus that causes significant distress to the individual and impacts on their wellbeing are central features. Symptoms are often consistent with body dysmorphic disorder but the impact can be less severe. Patients tend to present to dermatology or

Abstract

Naevus dysmorphia is a form of appearance concern/body image dissatisfaction, which describes a preoccupation with

cosmetic surgery requesting removal of a mole. An extended history is needed to fully assess the perceived "problem". Excision alone will not necessarily address the underlying psychological issues. Liaison with clinical/health psychology and/or psychiatry can be desirable in individual cases.

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INTRODUCTION

Naevus dysmorphia is a specific form of body image concern/appearance concern, which describes a morbid preoccupation with the appearance of a clinically small melanocytic naevus, which the individual is convinced is unsightly resulting in distress, behavioural adaptations and negative impact on their wellbeing. An extended history is desirable including assessment for associated psychiatric disorders including body dysmorphic disorder (BDD), depressive disorder and suicidal ideation. Patients often present to general or cosmetic dermatology or cosmetic surgery clinics requesting surgical removal of the "offending" mole. Simple excision does not necessarily address the underlying reasons for the person's overvalued perceptions of their appearance and preoccupation with the feature. A detailed psychological assessment and appropriate psychological therapy is recommended.

We are not aware of any previous detailed descriptions or case series of naevus dysmorphia *per se*.

CASE REPORT

Patient 1

A 16-year-old girl presented with 2 moles on her right arm and 2 moles on right lower leg which she had found "disgusting". The appearance of the moles had distressed her to such an extent that she bought Dermatend[®][1] on the internet and treated the areas in an attempt to remove them. Dermatend[®] contains the escharotic agent *Sanguinaria canadensis* which has been marketed as a skin tag and mole remover. On attendance at clinic it became apparent that she was generally distressed by the appearance her skin (cutaneous dysmorphia) stating that "she hated her pale skin and all her moles" and wished to have 3 further moles removed from her face.

Excision of the pink plaques at the site of the Dermatend[®] application was performed in order to obtain a histological diagnosis. A discussion around body image disorders appeared to be productive and a referral to health psychology was made. However, the patient did not attend for psychological therapy and

was lost to follow-up.

Patient 2

A 36-year-old man presented with a small intradermal naevus above his left eyebrow. He had previously undergone multiple minor surgical procedures to correct perceived defects including 2 rhinoplasties and removal of a chickenpox scar. The index mole was small and inconspicuous, but was causing him such a high level of anxiety and distress that he stated he would "remove it himself with a kitchen knife", if he was not offered excision. Significantly, he had been recently removed from his GP register for aggressive behaviour.

He had had a shave excision of the naevus due to the favourable risk:benefit ratio. He was also referred to health psychology, but he failed to attend.

Patient 3

A 29-year-old woman presented with multiple small melanocytic naevi on her left cheek, neck and left lower lip. She appeared very self-conscious of the appearance of the moles and described them as "ugly". She had adopted safety behaviours, such as covering her face with her hands regularly to hide the moles and constantly checking her appearance in the mirror. Her husband reassured her constantly that she "looked fine" and that he did not notice the moles.

Interestingly, she had a skin graft on her left neck following a burn in childhood adjacent to one of the problematic moles. However, the appearance of the graft did not seem to concern her, despite it being more obvious to the onlooker than the mole (Figure 1). She retained good insight of the fact that other people did not view the moles in the same way as she did. She had a shave biopsy of one mole and engaged in a course of cognitive behavioural therapy with good outcome.

Patient 4

An 18-year-old girl presented with a 1 cm congenital melanocytic naevus on her left thigh which she found "repulsive".

She had become more concerned with the appearance over the past 4 years and had started to adopt avoidance behaviours, such as wearing tights and avoiding swimming, in order to conceal the appearance of the mole. She reported doing gymnastics as a child and being ashamed to wear a leotard out of fear that the mole would be exposed. She recalled that her mother had advised her to "cover it with a plaster". She was reassured of the benign nature of the mole and warned of the risks of excision including unpredictable scarring, bleeding and surgical site infection. Nevertheless, she remained adamant that she "must have the mole removed". She did not wish to undergo a psychological assessment. A separate referral was made by the GP to plastic surgery, who excised the mole.

Patient 5

A 16-year-old hairdresser presented with a mole on



Figure 1 The skin graft following childhood burn is more obvious to the onlooker than the neighbouring naevus that this 29-year-old woman perceives as “ugly”.



Figure 2 Multiple small, banal naevi on trunk and 2 large, conspicuous tattoos on right and left chest.

her left cheek. Over the past year she had become more aware of the mole. She described it as “dirty and horrible.” She stated that the mole was “all she could see when she looked in the mirror” and that she would be keen to remove it herself, if this was possible. She always wore heavy make-up and smiled as much as possible to try to hide the mole in the left nasolabial fold. She was advised of the risks of unpredictable scarring on a prominent part of the face and surgical intervention was not performed. She was offered referral to health psychology for further assessment and psychological therapy, but she declined.

Patient 6

A 16-year-old school girl presented with concern about the appearance of a small mole on her left infraclavicular skin which she had “hated” for 6 years. When she said or heard the word “mole” she felt nauseous. She refused to expose the mole in public. She missed physical education classes and avoided wearing low-cut tops. On further enquiry, she also had significant concerns about several other aspects of her appearance, including “a big nose”, “large forehead, and “oily skin”, despite minimal objective findings. Depressive symptomatology with suicidal ideation were present. She did engage with clinical psychology and psychiatry and her psychological symptoms improved using a multidisciplinary approach (excision of the naevus, Cognitive Behavioural Therapy, and oral fluoxetine).

Patient 7

A 48-year-old woman presented with distress about the appearance of a mole on her cheek which had several terminal hairs growing within it. She thought about this mole every day and became anxious with social avoidance behaviours and ideas of reference, *i.e.*, that people were noticing it and thinking it was “horrible”. She lived with a daily fear of negative evaluation of this mole. She had a past history of depressive disorder and panic attacks. A simple

excision biopsy was performed. A discussion and psycho-education about body image and appearance distress was provided. The patient reported increased wellbeing 2 mo post-treatment at review.

Patient 8

A 28-year-old single woman demanded removal of multiple small moles from her body. She described these as “disgusting”. She claimed they had caused her to become depressed and unable to take appropriately care of her 3-year-old daughter on holiday. She said she had always “hated” her moles since her early teens. She avoided socialising and attributed this to her moles, which she considered “very ugly” and “making her look like a Dalmatian”. She blamed her moles for the fact that she can’t look after her child properly. She had a history of depressive disorder, self-harm and recreational drug misuse. She felt that removing all her moles would “fix” many of her problems in life. She threatened with suicide if she was refused excision. It was felt that her expectations were not realistic and a referral to health psychology was suggested in the first instance. However, she declined psychology referral and was lost to follow-up.

Patient 9

A 24-year-old single man, had asked his GP if he could have all his moles removed as he “hated” them so much. He said he’d “rather have lots of scars than lots of moles”. He was very anxious about going on holidays abroad, because he felt unable to take his top off at the beach or swimming pool. He attributed this to the shame he felt about his appearance. He avoided communal changing rooms or showers. He had a significant history of childhood psychological trauma.

On skin examination of his torso, several large tattoos were noticed (Figure 2). On further discussion he disclosed that he used tattoos to distract attention from the moles. In specific, he said that he “got tattooed to try and take people’s eye off the moles”, so they “noticed the tattoos more than the moles”. An excision biopsy of a naevus on the right flank was



Figure 3 Muscular body habitus, several small melanocytic naevi and 4 tattoos.

performed. This mole was particularly troubling him aesthetically. Efforts were also made to engage him in psycho-education about body image concerns. Referral to a Clinical/Health Psychologist was also suggested. However, the patient was lost to follow up.

Patient 10

An 18-year-old man presented as extremely self-conscious about moles on his trunk, especially on his back, since the age of 13 years old. He said he had avoided swimming ever since. He exhibited several avoidance behaviours, *e.g.*, persistently avoiding mirrors and refraining from using communal changing rooms. He was a body builder and had developed striae distensae around anterior axillary folds. On enquiry, he presented with considerable insight into his unhelpful perception about his skin and felt that his concerns may appear “stupid” to others. However, he was unable to change his beliefs and behaviours. He had a large circumferential tattoo on his left arm and another group of tattoos across his shoulders and right wrist (Figure 3). He said the reason for his tattoos was to distract his and others’ attention from the moles. However, despite this, he still thought about his moles every day, including the ones in the tattooed areas. Two naevi were excised from his back. Discussions around his body image were productive and advice on coping mechanisms was provided, whereas web-based cognitive behavioural therapy was suggested mainly to improve self-confidence and help reframing his negative thoughts about appearance.

DISCUSSION

This case series illustrates a range of manifestations of naevus dysmorphia. The discrepancy between objective/clinical (visibility of the naevus) and perceived “severity” is common to all cases, as are obsessive thoughts, preoccupation, and social anxiety/avoidance. The use of emotionally charged language, such as “horrible” or “disgusting”, to describe the appearance of the naevi is another common feature. Non-attendance at clinic

follow-up was common, which may be due to avoidance or denial of underlying emotional issues perhaps. In some cases there was a history of negative life events. In some cases there was associated low mood, self-harm and suicidal ideation, as well as anger/frustration. In our clinical experience, in most cases, the issues around the egosyntonic nature of naevus dysmorphia were striking, *i.e.*, the statements and experiences about the naevi and the skin are actually reflective of basic cognitions and emotions about the self. This is further demonstrated by the use of emotionally charged language these patients use to describe their naevi, *i.e.*, “hate, ugly, horrible, disgusting, repulsive”, *etc.*, which are indicative of their low self-worth and point towards deeply seated feelings of shame about the self. When such feelings are verbalised during appropriate treatment positive outcomes can occur with great relief^[2].

As depressive symptomatology, anxiety, shame and guilt can be indicative of psychological trauma, one could suggest that the above presentations might be manifestations of previous or ongoing complex and relational psychological trauma presentations. Psychological trauma in skin disorders and dermatology in general is largely under-researched. Some of the authors are currently undertaking a pilot study to establish the prevalence of psychological trauma in dermatology (AF and ZC). The findings of this investigation will be presented elsewhere.

In put clinical experience, the self-concept of the individual underlies their presentation and may explain the range of reactions and prognosis. The self-concept, *i.e.*, how we see ourselves and how we think others see us, is very complex and evolves across the lifespan, with many factors both genetic and acquired contributing. The self-concept may be especially brittle in adolescence when a degree of appearance concern is common^[3].

Modern society’s rigid “Barbie doll” stereotypes of health and beauty likely contribute to unrealistic expectations regarding appearance, which contribute to appearance-related concerns^[4]. Children and adolescents are exposed to images of certain body sizes and shapes portrayed by the media, where some features are depicted as more beautiful and desirable than others, *e.g.*, being very slim, having “flawless skin”, no body or facial hair and looking eternally youthful^[3]. Other influences on body dissatisfaction include parents’ beliefs and behaviours and peers/social interaction. Genetic and neurochemical factors may have a role to play. Previous psychological trauma, which may not have been previously disclosed, may also contribute to body image anxiety and associated low self-esteem. Psychological trauma could also account for persistent and treatment resistant symptoms of depression and anxiety. By adolescence, some individuals are so anxious about their appearance that they seek to alter it by seeking cosmetic surgery, dieting to lose

weight, taking supplements or even anabolic steroids to increase muscle mass or performing excessive exercise regimens to try and achieve “the perfect figure”. These behaviours are thought to be a response to an internalised sociocultural appearance ideal^[5].

“Clear” skin is considered beautiful and desirable by many adolescents especially girls. Any minor blemish, such as a mole, may be considered undesirable. In certain individuals, their beliefs, feelings and behaviours around the mole start to impact considerably on daily life.

When meeting a patient with disproportionate concern about the appearance of a small naevus, the dermatologist is called to be psychologically-minded and take a detailed history. Relational skills are vital with good communication being crucial in developing a therapeutic relationship based on person centred care, *i.e.*, developing trust, empathy and acceptance of the patient's individual circumstances and needs.

A discussion around the topic of “body image concern” is useful in patient engagement. Appearance value and valence are important topics. In specific, a person may think he/she is not good looking, but, if appearance does not matter that much to them, then they will not be as distressed as someone else for whom appearance is a key aspect they use to define their self-worth. When “red flags” are found that suggest severe appearance distress and BDD^[6], *e.g.*, significant preoccupation, marked distress, lack of insight into the unrealistic nature of the cognitions about the naevus, extreme behaviours or avoidance related to the mole, regular checking behaviours, and large negative impact on daily life, then referral to psychiatry is desirable. However, in practice, the threshold for diagnosing BDD remains subjective and differentiation from “normal”-albeit excessive-appearance concern can be difficult.

The three diagnostic criteria for the diagnosis of BDD are^[7]; (1) Preoccupation with some imagined defect in appearance or markedly excessive concern about a slight physical anomaly; (2) The preoccupation causes clinically significant distress or impairment in social, occupational or other important areas of functioning; and (3) The preoccupation is not better accounted for by another psychiatric disorder.

The presence of disabling anxiety or depressive symptomatology, excessive concern about other aspects of body image, history of psychological trauma, history of mental illness, history of extreme dieting or self-induced vomiting/use of laxatives and/or diuretics for weight control, suicidal ideation^[8]/self harm or suicidal attempts should prompt further assessment by clinical psychology or psychiatry. An empathic non judgemental approach is needed to facilitate engagement. A discussion around and psycho-education about the pros and cons of surgically excision of the mole is necessary. In individual cases when the risk: benefit ratio is favourable then excision might be a reasonable and even beneficial course of action.

It is desirable for Dermatologists to have a good up-to-date understanding of the psychology of appearance and appearance concerns, over and above BDD alone. A proportion of 65% of patients with BDD will present with a perceived defect on their skin and will attend Dermatology outpatient clinics^[9].

A study by Phillips had shown that 11.9% of 268 patients attending dermatology outpatients screened positive for body dysmorphic disorder which is significantly higher than the general population level of 1%-2%^[10].

BDD is undoubtedly a serious concern in dermatology. However, an understanding of the wider range of appearance distress and body image dissatisfaction is also very important, if we are to make effective, safe and person centred clinical decisions. Management of patients with naevus dysmorphia is challenging. On one hand, simply reassuring the patient and discharging will often result in “doctor-shopping” for another opinion, in seeking private treatment or in often risky attempts of “home treatment”. On the other hand, simply excising the lesion will not cure the problem as it does not address the underlying body image concern and the vicious circle of anxiety, low mood and anxiety, which can eventually lead to “revolving door” effects or disengagement with health services. The situation needs to be handled gently and empathetically. It is essential that the patient feels that you are on their side and want to help, rather than against them. Therefore, engaging the patient is the first step, whereas normalization, *i.e.*, explaining that other people have similar problems and have managed to manage effectively, as well as psycho-education about appearance distress and how best to cope with it are essential. Psychology referral might also be required for some patients. There are several treatment options which need to be tailored to the individual and the level of insight that they retain. These include surgical removal of the lesion, psychological therapies, and use selective serotonin uptake inhibitors. Several of these options can be used alone or in combination and a pragmatic approach is often required.

Physical removal of a mole BDD is controversial. A study carried out by Philips examined medical or physical treatment, *e.g.*, removal of a lesion in patients with BDD. Twelve out of 16 patients in the study had a lesion excised and 75% of these did not report a change in symptoms of BDD. However, a second study by Mühlbauer *et al.*^[11] showed that there was a subset of patients that would benefit from removal a lesion and derived criteria for excision of lesions in BDD patients. They found patients with mild BDD, and a minor lesion, with realistic expectations of a simple procedure for a real, albeit minor defect would benefit from surgical excision^[11].

COMMENTS

Case characteristics

Ten patients with obsessive thoughts, social anxiety and behavioural changes

related to a disproportionate distress about the appearance of a clinically small mole.

Clinical diagnosis

Patients with naevus dysmorphia clinically have a small benign naevus or a number of naevi.

Differential diagnosis

The differential diagnosis is severe and often complex appearance concern or body dysmorphic disorder.

Treatment

Removal of the naevus may be considered, but is cautioned when patient expectation is unrealistic and psychological "red flags" are present.

Related reports

Readers can get further information from texts on body dysmorphic disorder and the psychology of appearance.

Term explanation

Dysmorphia—a disproportionate concern regarding an aspect of appearance [as been used in conjunction with muscle, acne and skin (cutaneous) previously in the literature].

Experiences and lessons

The paper highlighted main challenges in patient engagement, the blurred boundary between expected and pathological appearance concern and the lack of evidence to know when excision of the mole is safe, reasonable and justified, and when it is cautioned or contraindicated. Dermatologists need to be aware of the discrepancy between perceived and clinical severity and how this is manifested in patients with suspected naevi dysmorphia and other similar types of appearance disturbances. Being able to assess psychological "red flags" within the context of a non-judgmental and trusting therapeutic relationship are key for safe, effective and person centred clinical management of patient with such difficulties.

Peer-review

This is an interesting case series report concerning one naevus dysmorphia which is a traumatic problem of many people in "postindustrial society". The considerable value of this work is presentation of psychological and sociological aspects of this body dysmorphic disorders, because these questions are often passed over in publications concerning somatic diseases.

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Helicobacter pylori and inflammatory skin diseases

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Abstract

Throughout the history of mankind, infections have been the major cause of diseases. Over the last decades, not only the incidence of emerging infectious diseases have increased, but also tremendous strides have been made in understanding the biology of several pathogenic microorganisms. *Helicobacter pylori*

(*H. pylori*) is a spiral-shaped, gram-negative bacterium, which infects over the half of the world's population. *H. pylori* has been implicated in the pathogenesis of a number of gastrointestinal disorders. However, new researches have demonstrated that *H. pylori* is also involved in the pathogenesis of various extragastric diseases. The difference in the clinical outcome of *H. pylori* infection may be explained, at least in part, by host response to the infection and *H. pylori* virulence factors. It is obvious that as developments in the research on *H. pylori* spring up, an understanding of the pathophysiology of *H. pylori* infection will continue to be identified. Here in this review, we summarize the current knowledge about *H. pylori* and its association with inflammatory skin diseases.

Key words: *Helicobacter pylori*; Etiopathogenesis; Skin diseases; Inflammatory

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Core tip: *Helicobacter pylori* (*H. pylori*) is a worldwide bacterium found almost entirely in humans. Although the majority of infected individuals remain asymptomatic, *H. pylori* has been implicated in the etiology of several gastric and extragastric disorders. *H. pylori* is generally acquired during childhood and persists lifelong due to the failure of the immune response to eradicate the bacterium. *H. pylori* has mechanisms to evade the immune response and to establish local and low-grade systemic inflammation. A number of studies have revealed that *Helicobacter pylori*-induced chronic low-grade inflammation may contribute to the pathogenesis of several disorders, including inflammatory skin diseases.

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HELICOBACTER PYLORI

Helicobacter pylori (*H. pylori*) is a gram-negative, spiral-shaped bacterium, which is thought to infect about half of the world's population. Barry Marshall and Robin Warren were the first researchers to isolate and culture this motile, S-shaped rod from human stomach, which was followed by demonstration of development of several upper gastrointestinal disorders, including chronic gastritis, peptic ulcer disease, gastric mucosa-associated lymphoid tissue (MALT) lymphoma and gastric cancer in the presence of *Helicobacter pylori*-induced gastric mucosal inflammation^[1-4]. The prevalence of *H. pylori* varies significantly according to geographic region and country, those from developing countries are more prone to acquire *H. pylori* than subjects from highly developed industrialized countries^[2]. One of the most successful human pathogen, *H. pylori*, exhibits a strict tropism for gastric epithelial lining, adhering specially to gastric epithelium, colonizing in the gastric mucosa, subsequently triggering the responsible inflammation for the resultant gastrointestinal diseases. Although there are a number of hypotheses to explain the precise underlying pathogenetic mechanism, one of the most appreciated one is that host immune response and *H. pylori* virulence factors interplay between each other in the development of these diseases^[1,3-6].

Despite the worldwide high prevalence rate and the fact that *H. pylori* is most commonly acquired early in the childhood and if untreated, infection is lifelong, the majority of the individuals infected with *H. pylori* are asymptomatic^[1,3-6]. Both the genetic characteristics of the host and genetic differences between strains of *H. pylori* determine the clinical outcome of the colonization^[5,7]. *H. pylori* produces a number of virulence factors, including flagellins, which provide motility essential for evading from gastric peristalsis and immune challenge of the host, adhesins, conjugated proteins involved in the attachment of the organism to host cell surface. It has been long appreciated that key pathogenic pathways involved in *H. pylori* infection include chronic gastric inflammation and alternation of gastric physiology, including breakdown of protective gastric mucosal barrier. *H. pylori* produces different kinds of enzymes that are important in these pathogenetic effects^[1,3-6]. The expressions of virulence-associated genes, cytotoxin-associated gene A (*cagA*) and vacuolating cytotoxin gene A (*vacA*), have been shown to be closely related with the diversity of clinical outcome of *H. pylori* infection. CagA protein, which is encoded by *cagA* gene, is associated with increased risk of developing atrophic gastritis, peptic ulcer and gastric cancer. The cytotoxin, vacA, causing severe vacuolation, has multiple effects on gastric epithelial cells: forms channels in membranes, alternates endosome/lysosome functions, increases transcellular permeability, induces apoptosis and promotes immune tolerance against *H. pylori*^[3,4,6,8].

An host-adapted pathogen, *H. pylori* has ability to mount an effective anti-immune response within the

infected host, which results in a chronic lifelong infection. Although *H. pylori* employs elaborate strategies to evade the host's immune system, complete avoidance from immune activation is not possible. When some of *H. pylori* proteins cross the gastric mucosal barrier, both innate and acquired defence mechanisms are activated^[8,9]. There has been considerable evidence suggesting that systemic immune response evoked by *H. pylori* participates in the development of diseases other than gastrointestinal in origin. Although there are many more questions to be answered, *H. pylori* has been implicated as the causal agent of several extragastric diseases, including neurodegenerative, cardiovascular, pulmonary, endocrinological, ocular, autoimmune and dermatological ones^[9-12]. In this review, we aimed to present a summary concerning association of *H. pylori* with inflammatory skin diseases. We briefly have reported on the present state of basic knowledge and a concise analysis of clinical studies conducted to evaluate the relation of *H. pylori* with inflammatory skin diseases.

PSORIASIS

Psoriasis is a common chronic inflammatory dermatosis characterized by erythematous, sharply demarcated papules and plaques covered by silvery white scales most commonly affecting scalp, lumbosacral region and extensor surfaces of elbows and knees in a symmetrical pattern. Psoriasis appears worldwide affecting both genders equally^[13]. Psoriasis is an immune-mediated disorder. Although the immunopathogenesis of psoriasis has not been fully elucidated yet, it has been revealed that the main role in the immunological cascade of psoriasis is played by T cells. Interaction between inflammatory cytokines, dendritic cells, macrophages, and T-helper type 1 (Th1), Th17, regulatory T cell, Th22 cells contribute to the disease pathogenesis^[14].

Genetic and environmental factors are involved in the etiology of psoriasis^[15]. Environmental factors that have been claimed to contribute psoriasis include streptococcal tonsillitis^[16], smoking^[17], alcohol consumption^[18], medications, stress, human immunodeficiency virus infection and trauma^[15]. There is a growing body of evidence showing that superantigen-mediated T cell activation plays a critical role in the psoriasis pathogenesis. Superantigens are toxins produced by pathogenic bacteria and viruses. It has been suggested that *H. pylori* toxins, including the aforementioned ones can act as super-antigens, which mount inflammatory response dominated by activated T cells and monocytes. Indeed, superantigens have been presumed to directly trigger the inflammatory cascade, which is mediated by antigen-presenting cells, such as macrophages, dendritic cells and keratinocytes, thus contributing to development of psoriasis^[19].

Several studies have been conducted to evaluate the role of *H. pylori* in the pathogenesis of psoriasis^[20-26]. In one of the earlier studies about the possible relationship between *H. pylori* and psoriasis, Halasz^[21] investigated

serum immunoglobulin G (IgG) antibody titers against *H. pylori* in 33 psoriatic patients and established a causative link of this pathogen with psoriasis. In 2003, Qayoom *et al.*^[22] also investigated *H. pylori* seropositivity in a group of psoriasis patients and compared it to a group of healthy subjects. Although the seropositivity of *H. pylori* among the patients and controls were lower than the expected prevalence range, meaning that lower than the general population's, since there was a statistically significant difference between the patient and control group and subjects with known upper gastrointestinal complaints were excluded from the study, they interpreted their study results as supporting a causal role of *H. pylori* in the pathogenesis of psoriasis^[22].

Onsun *et al.*^[20] conducted a large-scale study to investigate the prevalence of *H. pylori* seropositivity in patients with psoriasis. Their study also aimed to figure out the relationship between disease severity and *H. pylori* infection, and to evaluate the impact of *H. pylori* infection on the response to psoriasis treatment. By means of assessing the *H. pylori* stool antigen in a total of 300 patients with psoriasis and 150 non-psoriatic healthy controls, it was found out that 184 psoriatic patients were infected with *H. pylori*. Fifty patients, which were selected from these *H. pylori* infected patients, randomized into two groups to receive acitretin with *H. pylori* eradication treatment or acitretin alone. In addition, they segregated 25 patients from the *H. pylori* infected patients, who received only *H. pylori* eradication treatment, not any systemic treatment for psoriasis. It was observed that disease severity index, Psoriasis Area Severity Index scores, were significantly higher in patients with *H. pylori* infection and *H. pylori* eradication treatment improved both the effectiveness of acitretin therapy and also the clinical outcome of the patients who did not receive acitretin^[20].

In the literature, although there are also case reports describing the benefits of *H. pylori* eradication therapy in chronic psoriasis^[27] and palmoplantar psoriasis^[28,29], it is inevitable to detect studies showing that *H. pylori* infection is not associated with psoriasis^[23,24,26]. In 2001, Fabrizi *et al.*^[23] performed [¹³C] urea breath test (¹³C-UBT) on 20 patients with psoriasis and a control group of 29 patients without any skin disorders, who were aged between 5 and 19 years, in order to investigate the presumed relationship between *H. pylori* and psoriasis. Results uncovered that the prevalence of *H. pylori* in children and teenagers with psoriasis was low and did not differ between the patient and control groups^[23]. In a case-control study including 61 patients with psoriasis and 61 healthy individuals, Azizzadeh *et al.*^[26] investigated seropositivity of *H. pylori* by measuring serum IgG antibody titers of *H. pylori* with enzyme-linked immunosorbent assay method. Accordingly, their study results revealed that there was no clear evidence to prove a causal relationship between psoriasis and *H. pylori* infection^[26].

There have been several studies about the pathogenesis of psoriasis, which is regarded to be one of the

most common and exceptional disease in dermatology practice. A lot of interest has been focused on the immune/inflammatory pathway in the pathogenesis of psoriasis.

Although the exact pathogenetic role of infectious agents remains to be determined and questions of paramount importance await to be answered, the superantigen theory has drawn growing interest in the immunopathogenesis of psoriasis^[19]. It is obvious that there is a contradiction between the study results, which are about the causative role of *H. pylori* in the development of psoriasis^[20-26] and further studies are needed to elucidate this possible role.

LICHEN PLANUS

Lichen planus is a chronic, inflammatory, papulosquamous dermatosis that affects skin, scalp, nails and mucous membranes. Lichen planus is a distinctive disease, which is designated by well-known six "Ps" mnemonic, that stands for: pruritic, polygonal, planar, purple, papules and plaques. Although the etiology of lichen planus is still under discussion, it is believed that lichen planus is a T-cell mediated autoimmune disease, of which pathogenesis is centralized on abnormal immune response^[30,31]. Up to date, several studies have been conducted to evaluate the relationship of *H. pylori* with lichen planus^[24,32-37]. In one of the earlier studies, it was revealed that the prevalence of peptic ulcer was three-fold higher in patients with chronic/repeating lichen planus when compared with controls^[32].

In a hospital based cross-sectional descriptive study, *H. pylori* stool antigen was assessed in 105 lichen planus patients and it was found out that stool antigen was positive in 77% of the patients^[33]. Likewise, Moravvej *et al.*^[34] demonstrated higher ¹³C-UBT rates in patients with lichen planus when compared with the control group. These studies suggest that *H. pylori* has a role in the etiology of lichen planus. A possible mechanism of pathogenesis relies on in the induction of autoimmunity by infectious agents. Lichen planus is a multifactorial disease, in which certain infectious diseases have been proposed to be associated with autoimmune processes in susceptible individuals^[32].

On the other hand, in the literature there are studies which do not establish any clear evidence of causality relationship between *H. pylori* and lichen planus. In one of them, ¹³C-UBT performed in 30 patients with cutaneous lichen planus, in 30 patients with oral lichen planus, and in 30 healthy individuals. Accordingly, no significant association was found between lichen planus and *H. pylori* infection^[35]. Daudén *et al.*^[24] also investigated the prevalence of *H. pylori* infection in patients with psoriasis and lichen planus by performing ¹³C-UBT and their study did not prove any pathogenetic role of *H. pylori* in the development of psoriasis and lichen planus^[24]. Moreover, there are studies particularly focusing on the relationship of *H. pylori* with oral lichen planus, which also do not support the pathogenetic

role^[36,37]. As in psoriasis, the association of *H. pylori* with lichen planus seems to be mainly explained by induction of autoimmunity by infectious agents^[32]. However, there are studies with conflicting results^[24,32-37]. We suppose that further studies will demonstrate the presumed role of *H. pylori* in the pathogenesis of lichen planus.

PRURITUS AND PRURIGO NODULARIS

Pruritus, which is a common manifestation of several dermatologic diseases is defined as an unpleasant sensation that causes an intense desire to scratch. Pruritus is not only a symptom of a dermatosis, but also appears to be related with several systemic, neurologic and psychologic diseases^[38]. Prurigo nodularis is a chronic dermatosis characterized by multiple lichenified papulonodular lesions located especially on extensor surfaces of the limbs. Prurigo nodularis is an intensely pruritic condition, which is almost entirely resistant to treatment. Although the etiology of prurigo nodularis has not been fully elucidated yet, a wide variety of systemic diseases have been implicated in the pathogenesis of prurigo nodularis^[39,40].

H. pylori is one of the infections which has been reported to be associated with chronic pruritus and prurigo nodularis^[19,41-44]. In 1999, Neri *et al*^[42] screened 42 prurigo nodularis patients for *H. pylori* infection and found out that 40 patients were colonized with *H. pylori* and after *H. pylori* eradication treatment chronic itching was greatly reduced in 39 of these 40 patients^[42]. Two Japanese studies have shown causal role for *H. pylori* in pruritic skin diseases^[43,44]. Sakurane *et al*^[44] examined serum levels of IgG antibody against *H. pylori* in 198 skin-diseased patients, 32 of which were diagnosed with pruritus cutaneous and 17 of which were diagnosed with prurigo chronica multiformis. One hundred and two of them were detected to be infected with *H. pylori* and after *H. pylori* eradication treatment, in 58% of patients with pruritus cutaneous and in 50% of patients with prurigo chronica multiformis intractable pruritus was subsided^[44].

Likewise, Shiotani *et al*^[43] investigated the prevalence of *H. pylori* infection and also the incidence of gastric cancer in patients with pruritic skin diseases. It was found out that 73.5% of patients with pruritus cutaneous and 76.2% of patients with prurigo chronica multiforme were *H. pylori* positive and early stage gastric cancer was detected in 5.6% of patients with cutaneous pruritus and 18.8% of patients with prurigo chronica multiforme. However, in the improvement of pruritus, *H. pylori* eradication treatment was effective only in one patient, who was diagnosed as prurigo chronica multiforme^[43]. The association of *H. pylori* with refractory pruritus and the beneficial effect of eradication therapy in this indication have been also shown in other studies^[41].

SWEET'S SYNDROME

Sweet's syndrome, also designated as acute febrile

neutrophilic dermatosis, is a neutrophilic dermatosis characterized by acute onset fever, neutrophilia, erythematous to violaceous tender plaques and nodules on face, neck, upper extremities and a typical histopathological finding of a dense upper dermal neutrophilic infiltrate^[45-49]. Sweet's syndrome is classified according to etiological and pathogenetic aspects of the disorder^[46,47]. Classical Sweet's syndrome, which generally occurs in women in their third to fifth decade of life is often associated with upper respiratory or gastrointestinal track infections, inflammatory bowel diseases and pregnancy. On the other hand, several other underlying diseases have been suggested as a predisposing factor for classical type of Sweet's syndrome^[46,47].

In 1997, Kürkçüoğlu *et al*^[50] reported a 42-year-old woman who presented with a six-month history of recurrent episodes of fever, arthralgia, colicky abdominal pain and well-defined, infiltrated, erythematous plaques measuring up to 2 cm on face, neck and extremities. Her laboratory investigations showed elevated sedimentation rate and leukocytosis with neutrophilia. Gastrointestinal endoscopy revealed gastritis and *H. pylori* was identified in the gastric mucosal biopsy. Kürkçüoğlu *et al*^[50] asserted that after *H. pylori* eradication treatment, patient's skin lesions dramatically improved^[50]. Although this is the only case of *H. pylori* associated-Sweet's syndrome so far, since Sweet's syndrome is considered as an abnormal immunological reaction to a variety of microbial insults^[46], this case can prove the relation of *H. pylori* with Sweet's syndrome.

ROSACEA

Rosacea is a common chronic inflammatory disorder, characterized by multiple clinical features including flushing, facial erythema, inflammatory papules, pustules and telangiectasias^[51]. Several factors have been implicated in the pathogenesis of rosacea, which include genetic, environmental, vascular, inflammatory factors and microorganisms^[52]. It is known that there is an association between rosacea and some gastrointestinal disorders. In addition, since a similar seasonal variation has been observed between peptic ulcer and rosacea, also both rosacea and peptic ulcer respond well to metronidazole, it has been proposed that *H. pylori* infection might play a triggering role in the pathogenesis of rosacea^[52,53].

H. pylori produces cytokines that contribute to inflammation in gastric mucosa and host response emerges which leads to infiltration of inflammatory cells^[54]. *H. pylori* is proposed to induce rosacea by cytotoxin mediated chronic inflammation and gastrin induced flushing^[55]. Increased activity of reactive oxygen species have been reported in patients infected with *H. pylori* and rosacea is associated with generation of reactive oxygen species that are released by inflammatory cells^[56,57]. Since the first report of an association between rosacea and *H. pylori* by Rebora *et al*^[58] in 1994, there have been numerous studies investigating the prevalence of *H. pylori* infection in

rosacea patients^[58-61]. The results of those studies are conflicting, as some suggest that the prevalence of *H. pylori* infection is significantly increased in rosacea patients^[59-61] and others suggest no association between *H. pylori* infection and rosacea^[51,61-64]. This discrepancy might be due to different methods of evaluation of *H. pylori* infection between these studies. The effect of *H. pylori* eradication treatment in rosacea patients have been also studied. Several authors reported significant decrease in the severity of rosacea with *H. pylori* eradication therapy, especially in cases with papulopustular type^[52,62,64,65]. But it was also suggested that the improvement of rosacea symptoms after the treatment of *H. pylori* might be due to the antioxidant effects of the drugs used rather than *H. pylori* eradication^[66].

El-Khalawany *et al.*^[52] studied 68 patients with rosacea concomitant with dyspeptic symptoms and 54 controls only with dyspeptic symptoms to assess the role of *H. pylori* in rosacea patients who had dyspeptic symptoms. Screening for *H. pylori* was performed with *H. pylori* serum IgG and stool antigen test and gastric endoscopy was performed in *H. pylori* positive cases. *H. pylori* vacA alleles, cagA and epithelium factor antigen (iceA) genotypes were assessed by polymerase chain reaction. Significantly higher number of patients than controls were infected with *H. pylori* and 63.3% of the infected patients had papulopustular rosacea (PPR). Gastric ulceration and inflammation was also higher in PPR cases than erythematotelangiectatic (ETR) cases and controls. Analysis of *H. pylori* genotypes revealed that vacA s1m1 was more detected in PPR cases and there was a significant elevation of cagA/vacA s1m1 positivity in ETR cases. After the eradication regimen of *H. pylori*, a significant improvement was observed in PPR cases compared with ETR patients. The authors concluded that *H. pylori* had a significant etiological role in rosacea patients who had dyspeptic symptoms and the PPR type was more influenced by *H. pylori* infection. The authors suggested that the role of *H. pylori* in PPR is different from that in ETR and this is regarded to be caused by certain virulent strains that increases the inflammatory response in gastric mucosa and cutaneous lesions^[52]. In addition, Boixeda de Miquel *et al.*^[65] observed higher improvement rates in PPR lesions compared with ETR after eradication of *H. pylori* suggesting an association between inflammatory rosacea and *H. pylori* infection^[65].

Szlachcic *et al.*^[61] examined the prevalence of *H. pylori* by 13C-UBT, Campylobacter-like organism test (CLO-test), *H. pylori* culture and serology in rosacea patients and controls with dyspeptic symptoms. They also investigated the presence of *H. pylori* in oral cavity by CLO-test, *H. pylori* culture and saliva anti-*H. pylori* antibodies. They performed gastroduodenoscopy and fundic biopsy samples were taken for histological evaluation. *H. pylori* infection was significantly higher in the rosacea group and a noticeable number of rosacea patients showed chronic active gastritis predominantly in the antrum and corpus while those in the control

group showed mild gastritis confined to antrum only. Among rosacea patients, 67% were CagA positive, while in the control group only 32% were CagA positive. With anti-*H. pylori* therapy the symptoms of rosacea disappeared or decreased in most of the subjects. As the eradication rate of *H. pylori* was lower in the oral cavity than gastric mucosa the authors suggested that the lack of improvement of cutaneous symptoms in rosacea after eradication of *H. pylori* from the gastric mucosa may depend on the bacteria in the oral cavity^[61]. As a conclusion, especially papulopustular rosacea can be considered as one of the extragastric symptoms of *H. pylori* infection and the eradication of *H. pylori* may lead to improvement of rosacea and associated gastrointestinal symptoms.

BEHÇET'S DISEASE

Behçet's disease (BD) is a systemic vasculitic syndrome, characterized by recurrent aphthous stomatitis, genital ulcers, skin lesions and relapsing uveitis. Also articular, vascular, gastrointestinal, cardiopulmonary and neurological involvements may be observed in these patients^[67,68]. Though the exact etiology of the disease has not been fully elucidated yet, environmental factors including viral and bacterial agents and genetic factors are implicated in the pathogenesis of BD^[67]. As *H. pylori* infection is more prevalent in areas where BD is common and both BD and *H. pylori* may cause ulcers in the gastrointestinal tract, it has been suggested that *H. pylori* may play a role in the pathogenesis BD. The possible mechanism of action of *H. pylori* and other bacterial infections in the pathogenesis of BD might be related with molecular homology of bacterial antigens and human heat shock protein, which is proposed as a possible antigen in BD^[69].

Lankarani *et al.*^[69] investigated *H. pylori* infection in 48 patients with BD using serology and ¹³C-UBT. They demonstrated higher ¹³C-UBT positivity rates in patients with BD but the results of serology was not significantly different between two groups. They suggested that the reason for these conflicting findings may be related with the fact that serology can not differentiate between ongoing infection and previous exposure^[69]. Cakmak *et al.*^[68] investigated 40 patients with BD with fiberoptic esophagogastroduodenoscopy and ¹³C-UBT and no significant difference was found in *H. pylori* positivity rates between the patient and control groups^[68]. Ersoy *et al.*^[70] reported that there was no difference between BD patients and the control group in respect to *H. pylori* prevalence rates when biopsy specimens taken during upper gastrointestinal endoscopy were compared^[70].

Apan *et al.*^[67] investigated *H. pylori* seropositivity and cagA status in patients with BD. While the seropositivity of *H. pylori* was not significantly different between the patient and control groups, the prevalence of cagA positivity was significantly higher in BD compared to controls and *H. pylori* eradication therapy had significantly decreased the clinical symptoms of the BD

Table 1 Summary of some of the studies concerned with the association of *Helicobacter pylori* in the pathogenesis of inflammatory skin diseases, shown in order of publication date

Ref.	Study design	Result
Halasz ^[21]	Investigation of serum <i>H. pylori</i> IgG antibody titers in 33 psoriatic patients	Suggesting a potential link of <i>H. pylori</i> with psoriasis
Daudén <i>et al</i> ^[24]	Performing ¹³ C-UBT on 84 patients with psoriasis and 61 patients with lichen planus	Suggesting no evidence of a link between <i>H. pylori</i> and psoriasis and <i>H. pylori</i> and lichen planus
Fabrizi <i>et al</i> ^[23]	Performing ¹³ C-UBT on 20 psoriatic patients and 29 healthy controls	Suggesting no evidence of a link between <i>H. pylori</i> and psoriasis
Szlachcic ^[61]	Performing ¹³ C-UBT, CLO-test, oral cavity CLO-test, bacterial culture and fundic biopsy, investigation of serum and saliva <i>H. pylori</i> IgG and IgA antibody titers	Suggesting a potential link of <i>H. pylori</i> with rosacea and improvement of symptoms of rosacea with <i>H. pylori</i> eradication treatment
Qayoom <i>et al</i> ^[22]	Investigation of serum <i>H. pylori</i> seropositivity in 50 psoriatic patients and healthy controls	Suggesting a potential link of <i>H. pylori</i> with psoriasis
Novák <i>et al</i> ^[73]	Investigation of serum <i>H. pylori</i> seropositivity in 11 adult HSP and 20 healthy adult patients	Suggesting a potential link of <i>H. pylori</i> with HSP
Shiotani <i>et al</i> ^[43]	Investigation of serum <i>H. pylori</i> IgG antibody titers in 134 patients with pruritic skin diseases	Suggesting a potential link of <i>H. pylori</i> with pruritic skin diseases and <i>H. pylori</i> positivity in pruritic skin diseased patients with gastric cancer
Moravvej <i>et al</i> ^[34]	Performing ¹³ C-UBT on 80 patients with lichen planus and 80 patients with other skin diseases	Suggesting a potential link of <i>H. pylori</i> with lichen planus
Ersoy <i>et al</i> ^[70]	Performing endoscopy, histopathological examination and RUT in 45 patients with BD and 40 healthy controls	Suggesting no evidence of a link between <i>H. pylori</i> and BD
Cakmak <i>et al</i> ^[68]	Performing ¹³ C-UBT in 40 patients with BD and 40 healthy controls	Suggesting no evidence of a link between <i>H. pylori</i> and BD
El-Khalawany <i>et al</i> ^[52]	Investigation of serum <i>H. pylori</i> IgG antibody titers and <i>H. pylori</i> stool antigen in 68 patients with rosacea and 54 healthy controls and performing <i>H. pylori</i> genotyping	Suggesting a potential link of <i>H. pylori</i> with rosacea and certain virulent strains with rosacea subtypes
Onsun <i>et al</i> ^[20]	Investigation of <i>H. pylori</i> stool antigen in 300 psoriatic patients and 150 healthy controls; investigation of <i>H. pylori</i> stool antigen in 25 patients before and after acitretin treatment	Suggesting a potential link of <i>H. pylori</i> with the etiology and the severity of psoriasis
Lankarani <i>et al</i> ^[69]	Performing ¹³ C-UBT and investigation of <i>H. pylori</i> seropositivity in 48 patients with BD and 48 healthy controls	Suggesting a potential link of <i>H. pylori</i> with BD

H. pylori: *Helicobacter pylori*; Ig: Immunoglobulin; ¹³C-UBT: ¹³C urea breath test; CLO-test: Campylobacter-like organism test; HSP: Henoch-Schonlein purpura; RUT: Rapid urease test; BD: Behçet's disease.

patients^[67]. Avci *et al*^[71] reported that although *H. pylori* seroprevalence between BD patients and controls did not show significant difference, in patients with BD who had *H. pylori* infection various clinical manifestations regressed after the eradication of *H. pylori*^[71]. These findings suggest that although the prevalence of *H. pylori* is not increased in BD patients, eradication therapy of *H. pylori* may improve the clinical outcome of BD in *H. pylori* infected patients.

HENOC-SCHONLEIN PURPURA

Henoch-Schonlein purpura (HSP) is a type of leukocytoclastic vasculitis of small vessels, characterized by IgA containing deposits in the skin, joints, gastrointestinal mucosa and glomeruli^[72,73]. It is commonly observed in children and characterized with palpable purpura, abdominal pain, gastrointestinal hemorrhage, arthralgia and renal involvement^[72,74]. Though the pathogenesis of HSP is not clear, it is thought that an antigenic particle, which may be related with exogenous sources like bacterial and viral infections, vaccinations and drugs, elicits an antigenic stimulus, causes elevation of circulating IgA and complement activation, eventually leading to vasculitis^[72,75].

Few case reports have described an association

between *H. pylori* infection and HSP in children and adults^[76,77]. In addition, resolution of gastrointestinal symptoms and purpuric rashes have been described in HSP patients with *H. pylori* eradication treatment^[72,75,78]. These reports suggest a causative role of *H. pylori* in the pathogenesis of HSP. Xiong *et al*^[79] performed a meta-analysis about the association of *H. pylori* infection with HSP development in Chinese children. They reported that 49.27% (369/749) of children with HSP had the evidence of *H. pylori* infection compared with 23.39% (131/560) of children in the control group and *H. pylori* eradication therapy was capable of reducing the recurrences of HSP. They suggested it is advisable to screen *H. pylori* infection in children with HSP, particularly in those with gastrointestinal manifestations^[79].

Cai *et al*^[80] investigated the effect of *H. pylori* eradication therapy on prognosis in children with HSP. 153 children with HSP were divided into three groups: group 1 included patients with *H. pylori* infection who received *H. pylori* eradication therapy in addition to conventional therapy, group 2 included control group, in which patients were *H. pylori* positive but only received conventional therapy for HSP, group 3 included *H. pylori* infection-negative group, who also received conventional therapy for HSP. The response

and recurrence rates of HSP were not significantly different between three groups but the incidence of HSP nephritis was significantly lower in the *H. pylori* infection treatment group. The authors concluded that *H. pylori* eradication therapy may be useful in reducing the incidence of HSP in children infected with *H. pylori*^[80].

Novák *et al.*^[73] investigated *H. pylori* antibodies in 11 adult patients with HSP and the serological investigations revealed *H. pylori* infection in 10 patients. Patients in the acute phase had significantly higher levels of anti *H. pylori* IgG levels compared to patients in remission phase. In addition, anti *H. pylori* IgA levels were elevated with significant difference in patients in the remission phase^[73]. We suggest that it would be useful to investigate *H. pylori* infection in patients with HSP, especially if they have gastrointestinal manifestations of HSP. Summary of some of the studies concerned with the association of *H. pylori* in the pathogenesis of inflammatory skin diseases is shown in Table 1.

CONCLUSION

H. pylori is a world-wide spread bacterium, which is estimated to infect more than half of the world's population. *H. pylori* has been implicated in the pathogenesis of a number of gastrointestinal system disorders, also classified as a gastric carcinogen since it has been proven that *H. pylori*-induced chronic gastric inflammation triggers the events that can promote gastric carcinogenesis. Recent studies have suggested that *H. pylori* induces not only local inflammation, but also systemic inflammation. There is a growing body of evidence concerning the causative role of *Helicobacter pylori*-induced systemic inflammation in the pathogenesis of several extragastric diseases, including endocrinological, autoimmune and dermatological ones. However, conflicting results were noted among the individual studies, which evaluate the pathogenetic role of *H. pylori* in the development of these diseases. In this review, we have concentrated on the pathogenetic role of *H. pylori* in the pathogenesis of inflammatory skin diseases. On the other hand, we think that there is a need for further studies to better define the role of *H. pylori* in inflammatory skin diseases.

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X linked recessive ichthyosis: Current concepts

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aspects of the X-linked ichthyosis (XLI) and make a compilation of the some historic details of the disease. The aim of the present study is an update of the XLI. Historical, clinical, epidemiological, and molecular aspects are described through the text. Recessive XLI is a relatively common genodermatosis affecting different ethnic groups. With a high spectrum of the clinical manifestations due to environmental factors, the disease has a genetic heterogeneity that goes from a point mutation to a large deletion involving several genes to produce a contiguous gene syndrome. Most XLI patients harbor complete *STS* gene deletion and flanked sequences; seven intragenic deletions and 14 point mutations with a complete loss of the steroid sulfatase activity have been reported worldwide. In this study, we review current knowledge about the disease.

Key words: *STS* gene; X-linked ichthyosis; Steroid sulfatase; Gene deletion; Contiguous gene syndrome; Genodermatosis

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Core tip: In the present study we describe the current knowledge of historical, clinical, epidemiological, physiopathological and molecular data in the X-linked ichthyosis (XLI). We consider that this review is important due to XLI is one of the most frequent genodermatosis that affects similarly to different ethnic groups worldwide.

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Abstract

In the present review, we describe the most important

HISTORY

The term ichthyosis has been used for over 2000 years

and comes from the Greek root "ichthys" meaning fish. In the nineteenth century, the Indians and Chinese referred to the disease as "a condition of snakeskin or fish scales" and at the time of the Arab physician Avicenna as "nigra albarras". The first description of ichthyosis documented in the medical literature was in the work "On cutaneous diseases" by Wilan^[1] in 1908. Cockayne^[2] in 1933, was the first to describe cases of ichthyosis in males and used the genetic classification. In 1965, Wells *et al*^[3] could distinguish the X-linked ichthyosis (XLI) from the dominant ichthyosis vulgaris. They suggested that the onset of dominant form was present after three months with a less body affection. In 1978, Koppe *et al*^[4] and Webster *et al*^[5] identified the absence of the steroid sulfatase (STS) enzyme in fibroblasts of patients with XLI.

EPIDEMIOLOGY AND ETIOLOGY

XLI (OMIM 308100) is a genodermatosis caused for STS deficiency^[4,5]; it is characterized by abnormal desquamation and hiperqueratosis in the skin^[6], and is due excessive amounts of cholesterol sulfate in the epidermis^[7]. XLI has a frequency of one to two in 6000 men^[8]. With respect to the genetics of X-linked recessive disorders, these diseases are generally restricted to males, these ones transmit the affected gene only to females (obligated carriers). Carriers of the X-linked gene defect have a risk of 50% to have affected males or carriers females.

The STS protein has 583 amino acids with a molecular weight of 62 kDa. The first 22 amino acids correspond to the leader peptide, which is cleaved post-translationally to give rise to the mature enzyme^[9]. STS protein has 4 glycosylation sites^[10]. The STS enzyme is attached to the rough endoplasmic reticulum and hydrolyzes the sulfate groups of the sulfated 3 β -hydroxysteroids such as dehydroepiandrosterone sulfate (DHEAS), cholesterol sulfate, pregnenolone sulfate and androstenediol 3 sulfate^[11-13], metabolites that serve as precursors for estrogens, androgens, and cholesterol. STS is expressed on placenta, breast, immune system, brain, liver, reproductive tract and blood cells^[10]. In placenta, STS deconjugates DHEAS, a previous step for the oestrogen synthesis during pregnancy. STS enzyme is upregulated by tumor necrosis factor α and interleukin (IL)-6, while IL-1 β and interferon- γ downregulate it by inhibiting nuclear factor-kappa-B and activating glucocorticoid receptor. Retinoids and 1,25(HO)₂-vitamin D3 induce its activity and expression^[14,15].

The STS gene is located in the Xp22.3 region^[16,17], and has 10 exons, 2 untranslated regions (at the 5' of 206 bp and at the 3' of 668 bp), and one open reading frame of 1752 bp^[18-20]. The Xp22.3 region escapes to X-inactivation^[16,21]. More than 90% of XLI patients present a complete STS gene deletion and flanked sequences, the remainders have showed 7 intragenic deletions^[22-28] whereas 14 point mutations

with a complete loss of the STS activity^[29-38] have been reported. Contiguous gene deletions around the STS leading to a more complex phenotype associated with short stature, chondrodysplasia punctata, Kallman syndrome and ocular albinism^[39].

One explanation for the deletion of the STS gene and flanking sequences on the short arm of the X chromosome is the presence of families of repeated sequences in low copy number (G1.3 and CRI-S232) on both sides of the STS gene^[40-43]. In women, the presence of these sequences could produce an unequal homologous recombination; however, another proposed mechanism is a mismatch by sliding DNA chains as shown the paternal origin of the affected X chromosome^[22,44-46].

CLINICAL FEATURES

Mothers of affected fetus con XLI may present delayed or prolonged labor due the absence of STS enzyme in the placenta^[47]. Onset of symptoms of the XLI is in the first months of life by the presence of polygonal, loosely adherent translucent scales with a generalized distribution^[48]. The scales predominantly are in anterior abdomen, preauricular area, neck, axillae and extension zones of the limbs^[3,49-52]. The scalp is affected in childhood and this affection disappears in the adulthood. Generally, scales spare palms, soles, popliteal and antecubital fossae and the mid-face^[52-54]. Clinical manifestations are worse in cold/dry weather. XLI patients have low sweat production due to a decrease numbers of sweat gland^[55]. Filaggrin mutations may be associated with ichthyosis vulgar, xerosis and atopic dermatitis exacerbating the XLI phenotype^[56,57]. Extracutaneous manifestations, such as ocular defects, have been observed in 10%-15% of patients and up to 25% of carrier mothers^[58]. Diffuse deposits in the corneal stromal and descemet membrane^[59], may appear at any time of life, they predominate in the 2nd and 3rd decade without affect visual acuity^[60,61]. Back embryotoxon, deuteranopia, corneal erosion^[62,63] has also been observed. Cryptorchidism is observed in 20% of cases^[64], with a cancer high risk of testicular germ cells^[65]. Neurological alterations have been observed in patients with XLI, such as epilepsy, electroencephalogram abnormalities, mental retardation, hyposmia^[66], attention deficit hiperactivity disorder, autism and speech deficit; these manifestations have been attributed to altered sterol metabolism in the central nervous system^[67,68] frequently associated with contiguous gene deletion. Others anomalies less frequent are seizures, psychological disorders^[69,70], pyloric hypertrophy^[71,72], abdominal wall defects, leukemia, nodular heterotopia periventricular^[73,74] and steroid-resistant nephrotic syndrome^[75].

PHYSIOPATHOLOGY

Cholesterol sulfotransferase (SULT2B1b) generates cholesterol sulfate (CS) in lower nucleated cell layers

(stratum basal) of the epidermis, increasing the concentration of CS from 1% to 5% on the stratum granulosum^[52]. STS enzyme decreases CS to 1% in the stratum corneum (outer epidermis)^[52,76,77]. The increase of CS induces the expression of the skin barrier protein filaggrin and plays a role in the differentiation of normal keratinocyte^[78,79]. Rupture of CS cycle by STS defect produces an increase of CS from 1% to 10%-12% in the stratum corneum of the epidermis^[7]; this results in: (1) a decrease barrier function with a failure of the normal liquid-crystalline transition phase of intercellular lipids; and (2) an abnormal corneocyte retention stimulating the hyperplasia epidermal-inflammation and a thickened stratum corneum. The increase of CS is in relation with the decrease of the activity serine protease and the increase of Ca^{2+} , producing corneodesmosomal retention^[6,52,80]. Besides, the dark color of the scales could be explained by the presence of large amounts of melanosomes in the corneal cells^[81].

LABORATORY DIAGNOSIS

Prenatal diagnosis can be carried out through the study of triple marker in second trimester of pregnancy which detects low or absent serum levels of estriol. The suspect of a fetus with XLI is associated with a decrease level of estrogen and the presence of unhydrolyzed steroid sulfates in maternal urine^[82-84]; a history of prolonged labor and delivery increases this possibility. The analysis of the *STS* gene through southern blot, *in situ* hybridization, polymerase chain reaction can be made on chorionic villi or amniotic liquid when the familial genetic defect is known^[85]. Determination of steroid sulfatase activity and polymerase chain reaction, fluorescence *in situ* hibridation and DNA of the *STS* gene analyses allow to discard XLI^[31,32,34,41,86]. New techniques as MLPA, DNA microarrays, total exome sequencing is helping to prove the complete deletion, partial deletions or point mutations in the *STS* gene. Histopatological study is not useful for the diagnosis of XLI, however it may be useful in the differential diagnosis of XLI with other specific histopathology entities^[6].

DIFFERENTIAL DIAGNOSIS

XLI differential diagnosis mainly is with ichthyosis vulgaris and others ichthyosis like lamellar ichthyosis^[50,54,87]. Ichthyosis vulgaris (IV) is characterized by symmetric light gray scaling, generally after 3 mo of age; flexion zones are affected and inheritance pattern is dominant autosomal, nevertheless in some cases it can be acquired. Biopsy studies of skin appear similar in both cases. In sporadic cases is most difficult to establish the correct diagnosis, because it is not present a specific inheritance pattern. In familiar cases, genealogy is an important tool to correctly identify XLI from IV. The determination of STS activity is the golden standard in the differential diagnosis of both diseases but molecular studies of *STS* or *FLG* genes are also useful to perform

the correct diagnosis.

MANAGEMENT

XLI has not definitive treatment, but fortunately, except for the aesthetic appearance, rarely affects normal life function. XLI mainly affects the skin that is exacerbated in winter, but improves in summer. Lubricants, humectants and keratolytic agents are indicated when there is excessive large scale or keratinization^[88]. There are few studies on the treatment of XLI, one study used tazarotene 0.05% and glycolic acid 70% in a patient with a large deletion of the *STS* gene, with good response, but with a remission to the 8 and 2 mo, respectively^[89], another study used calcipotriol in 8 cases with XLI and 11 patients with congenital ichthyosis and showed reduction of scaling and roughness^[90]. On a heterogeneous study^[91], liarozone vs oral acitretin were compared with no significant differences^[92]. Generally, XLI treatment is based upon studies in other groups of congenital or heterogeneous ichthyoses^[93-95]. In neonates and infants, keratolytics should be handled with caution because they are absorbed due to the immature skin barrier causing toxicity. Any treatment regimen works for everyone, and the best therapy for each patient may be the result of months or years of painstaking effort on both the physician's and the patient's behalf. It is important to keep in mind the cost of the topical treatments^[88]. Multidisciplinary management with various specialists such as dermatologists, geneticists, ophthalmologists, psychologists, gynecologists should be considered.

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Mycosis fungoides: A mimicker of benign dermatoses

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Abstract

Mycosis fungoides, the most common primary cutaneous lymphoma, may present with a broad spectrum of clinical features. As both clinical and dermatopathological findings in mycosis fungoides occasionally closely imitate

other dermatoses, correct diagnosis may be a challenge both for clinicians as well as dermatopathologists. As a consequence, diagnosis of cutaneous lymphoma may be initially missed and, therefore, prompt and adequate therapeutic measures delayed. Hence, the purpose of our article was to give an overview of hitherto published "mimickers" of mycosis fungoides with a review of its diverse clinical features to alert the clinicians about the wide spectrum of this dissimulating disease. By integrating our own encountered atypical cases of mycosis fungoides we provide a comprehensive illustrated histological and molecular genetic workup thereof and thereby critically revise the different available diagnostic tools of daily routine. Finally, we derive a practical algorithm to obtain the correct diagnosis even in such ambiguous cases of mycosis fungoides.

Key words: Mycosis fungoides; Cutaneous lymphoma; Mimicker; Imitator; Inflammatory dermatosis

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Core tip: Mycosis fungoides, the most common cutaneous lymphoma, may imitate diverse diagnoses both on clinical and on histological grounds. Hence, the former "great masquerader" syphilis may be regarded as being outpaced. As diagnosis of such ambiguous, atypical cases of mycosis fungoides may be a challenge for the dermatologist and pathologist and consecutively adequate therapeutic measures may be delayed we herein give a comprehensive overview on previously published cases accomplished by our own data. We conclude that a multi-step diagnostic algorithm including meticulous clinicopathological correlation together with molecular genetic analysis should be applied in such protean cases to obtain the correct diagnosis.

Wobser M, Geissinger E, Rosenwald A, Goebeler M. Mycosis fungoides: A mimicker of benign dermatoses. *World J Dermatol* 2015; 4(4): 135-144 Available from: URL: <http://www.wjgnet.com/2218-6190/full/v4/i4/135.htm> DOI: <http://dx.doi.org/10.5314/wjd.v4.i4.135>

INTRODUCTION

Traditionally, syphilis has been designated as the “great imitator” within different medical disciplines^[1,2]. As the rash of secondary syphilis is highly variable in appearance, cutaneous signs of treponemal infection may be easily mistaken for a wide range of other common dermatological conditions such as psoriasis, tinea corporis, pityriasis rosea, vitiligo and viral exanthems. Of interest, an increasing plethora of case reports and a few recent systematic reviews thereof^[1] denote, that a “novel” dermatological mimicker, namely mycosis fungoides, has evolved within this field of clinical masqueraders.

Mycosis fungoides (MF), the most common primary cutaneous lymphoma, is a low-grade lymphoproliferative disorder of skin-homing mature CD45RO+ T-cells^[2]. Classically, mycosis fungoides is limited to the skin presenting with erythematous patches or slightly scaling infiltrated plaques. On histology, a band-like, epidermotropic infiltrate of small to medium-sized lymphocytes, some with atypia (“haloed” intraepidermal lymphocytes with hyperchromatic, indented or cerebriform nuclei) is characteristic^[3]. In most cases the lymphocytes belong to the CD4⁺ subtype, and may exhibit variable loss of T-cell antigens such as CD2, CD5 or CD7 and a monoclonal T-cell receptor (TCR) gene rearrangement. During the further clinical course, tumors may develop in a minority of patients, mostly in longstanding, therapy-refractory lesions. Whereas prognosis of early stages is excellent, tumor stage or the rare occurrence of nodal, blood or visceral dissemination is associated with a worse prognosis with 5-year survival rates of less than 30%^[4,5].

Especially in early lesions of mycosis fungoides, *i.e.*, patch-stage disease, diagnosis may be difficult due to often non-specific clinical and histological findings and further clinicopathological follow-up is crucial^[6]. Beside the rather classical presentation of mycosis fungoides, *i.e.*, patches evolving to plaques and rarely tumors, peculiar variants have been described due to unique clinical signs and/or divergent histopathological findings, thus making diagnosis even more challenging. Two particular variants of mycosis fungoides have already been adopted as separated subtypes in the current WHO-/EORTC-classification of cutaneous lymphoma, namely “granulomatous mycosis fungoides/granulomatous slack skin” and “folliculotropic mycosis fungoides”^[7]. To distinguish these subtypes from otherwise conventional mycosis fungoides is of eminent importance as a worse prognosis has been attributed to these variants^[8,9] and, therefore, more aggressive therapeutic measures or at the least closer follow-up examinations are warranted.

In addition to these two variants, recent observations have emphasized that cutaneous manifestations of mycosis fungoides can rarely present with clinical features

closely imitating various other benign or rarely malignant dermatoses. Its dissimulating capacity often poses a diagnostic dilemma for the clinician, leading to delayed diagnosis and often inappropriate therapeutic measures.

Therefore, the purpose of this article is to provide a comprehensive overview on published cases of mycosis fungoides imitating different diseases primarily on clinical grounds. In addition, we integrate our own atypical cases of mycosis fungoides to exemplarily delineate the diagnostic workup of such ambiguous cases.

REVIEW OF PUBLISHED “MIMICKING” CASES OF MYCOSIS FUNGOIDES

As modern immunohistological and molecular genetic capabilities have significantly improved the diagnosis of cutaneous lymphoma, a vast plethora of clinically atypical variants of cutaneous lymphomas could be unveiled with the aid of these technical facilities. Especially the skin lesions of the most common cutaneous lymphoma subtype, mycosis fungoides, can imitate a wide variety of otherwise benign dermatoses (Table 1), and thus pose major diagnostic obstacles both to the dermatologist as well as the dermatopathologist^[10]. Taking together, more than 40 different benign dermatoses - mainly inflammatory dermatoses such as psoriasis or granulomatous diseases - have been described as being clinically imitated by mycosis fungoides. These can be attributed to more than 10 leading clinical signs, mostly with psoriasiform or eczematous characteristics. In such cases, associated dermatopathological findings may also closely imitate its benign counterpart, *i.e.*, psoriasiform epidermal hyperplasia in psoriasis vulgaris-like variants of mycosis fungoides, subepidermal blisters in bullous pemphigoid-like presentations, interstitial histiocytes and giant cells in granuloma annulare-like mycosis fungoides or interface dermatitis in mycosis fungoides with lichen planus-like skin lesions. In some cases, the reactive infiltrate may even overwhelm the malignant lymphoma cells, as it is often the case in granulomatous mycosis fungoides or slack skin syndrome. Especially in these instances, a thorough cytological assessment, extensive immunophenotyping of the infiltrate and, finally, molecular genetic techniques will be crucial diagnostic adjuncts in arriving at the correct diagnosis.

Review of own “mimicking” cases of mycosis fungoides and diagnostic workup

To delineate this diagnostic workup of atypical cases of mycosis fungoides - which in many cases will require an individualized strategy - we herein provide an exemplifying set of own encountered cases on that topic (Table 2). Similar cases of most of these “mimickers” have already been reported in literature. Therefore, most of our cases fit well into one of the categories summarized in Table 1. Selected illustrated cases (case 1, 2, 5) and the clinicopathological workup are shortly

Table 1 Review of hitherto published cases of clinical masqueraders of mycosis fungoides

Leading clinical sign	Differential diagnosis	Ref.
Eczematous	Seborrheic eczema	Nashan <i>et al</i> ^[1] , Van Doorn <i>et al</i> ^[31]
	Rosacea	Sherertz <i>et al</i> ^[32]
	Atopic eczema	Kazakov <i>et al</i> ^[33]
	Palmoplantar eczema	Spieth <i>et al</i> ^[34] , Goldberg <i>et al</i> ^[35]
	Perioral dermatitis	Spieth <i>et al</i> ^[34]
Psoriasiform	Other	Spieth <i>et al</i> ^[34]
	Psoriasis palmoplantaris	Spieth <i>et al</i> ^[34] , Nashan <i>et al</i> ^[1]
	Psoriasis vulgaris	Zackheim <i>et al</i> ^[36]
	Tinea corporis	Chave <i>et al</i> ^[37]
	Chronic discoid lupus erythematoses	Veysey <i>et al</i> ^[38]
Erythematous	Tinea pedum	Hubert <i>et al</i> ^[39]
	Erysipelas	Brill <i>et al</i> ^[40]
	Annular erythema	Lim <i>et al</i> ^[41] , Cogrel <i>et al</i> ^[42] , Bernardini <i>et al</i> ^[43]
	Erythema multiforme	Kazakov <i>et al</i> ^[33]
	Alopecia areata	Burg <i>et al</i> ^[44]
Alopecia		Kazakov <i>et al</i> ^[33]
Hypopigmented	Pityriasis versicolor	Whitmore <i>et al</i> ^[45]
	Pityriasis alba	Ardigó <i>et al</i> ^[46]
	Vitiligo	Kazakov <i>et al</i> ^[33]
	Leprosy	Kazakov <i>et al</i> ^[33]
	Postinflammatory hypopigmentation	Willemze <i>et al</i> ^[47] , Barnhill <i>et al</i> ^[48]
Hyperpigmented	Acanthosis nigricans	Kazakov <i>et al</i> ^[33]
	Ashy dermatosis	Fink-Puches <i>et al</i> ^[19]
	Lichen aureus	Barnhill <i>et al</i> ^[48]
	Purpura pigmentosa	Kneitz <i>et al</i> ^[49]
	Bullous pemphigoid	Roeningk <i>et al</i> ^[50]
Bullous	Pemphigus vulgaris	Wain <i>et al</i> ^[51]
	Mucositis	Goldberg <i>et al</i> ^[35] , Wobser <i>et al</i> ^[52]
	Verruca vulgaris	Bahadoran <i>et al</i> ^[53]
	Keratosis lichenoides chronica	Eisman <i>et al</i> ^[54] , Kütting <i>et al</i> ^[55] , Badawy <i>et al</i> ^[56]
	Ichthyosis	Klemke <i>et al</i> ^[57]
Hyperkeratotic	Follicular hyperkeratosis	Breneman <i>et al</i> ^[58]
	Porokeratosis Mibelli	Bazza <i>et al</i> ^[59]
	Seborrheic keratosis	Yoo <i>et al</i> ^[60]
	Bowen's disease	Marzano <i>et al</i> ^[61]
	Pseudolymphoma	Hur <i>et al</i> ^[12] , Pereiro <i>et al</i> ^[62] , Nashan <i>et al</i> ^[1]
Papular	Papuloerythroderma Ofuji	Peris <i>et al</i> ^[63] , Lacour <i>et al</i> ^[64] , Oliwiecki <i>et al</i> ^[65] , Vollmer <i>et al</i> ^[66]
Pustular	Comedones, cysts	Moreno <i>et al</i> ^[67]
	Palmoplantar pustulosis	Camisa <i>et al</i> ^[68]
	Generalized pustulosis	Ho <i>et al</i> ^[69] , Carbia <i>et al</i> ^[70]
	Pyoderma gangraenosum	Jouary <i>et al</i> ^[25] , Goerdts <i>et al</i> ^[71] , Topar <i>et al</i> ^[72] , Kempf <i>et al</i> ^[7] , van Haselen <i>et al</i> ^[73]
	Granuloma annulare	Spieth <i>et al</i> ^[34]
Granulomatous	Rosacea	Bessis <i>et al</i> ^[74]
	Sarcoidosis	Woollons <i>et al</i> ^[75]
	Necrobiosis	Goldstein <i>et al</i> ^[76]
	Gangrene	Machler <i>et al</i> ^[77] , Morcos <i>et al</i> ^[78]
	other tumors	Bessis <i>et al</i> ^[74]
Others	cutis laxa	
All	12 major clinical signs 47 differential diagnoses	

reviewed below to better and more vividly illustrate the core message of this review and the complexity of the topic.

Case 1

A 75-year-old patient presented with extensive patches and plaques, some of them with unusual configuration being clinically undistinguishable from tinea corporis, granuloma annulare or erythema exsudativum multiforme (Figure 1). Repetitive mycological examinations (KOH, fungal cultures) were negative. Corresponding to the simultaneous presence of more classical patches and plaques on whole-body examination, biopsies of different

lesions revealed classical histological features consistent with CD4⁺ mycosis fungoides. Vacuolar interface reaction or granulomatous features - as would be suggestive of erythema exsudativum multiforme or granuloma annulare - were absent. Due to this histopathologically clear-cut diagnosis of mycosis fungoides, we refrained from further molecular genetic testing of the biopsy specimens. The patient responded to oral PUVA therapy in combination with bexarotene. This case shall provide an example that thorough clinical examination (revealing classical patches or plaques of mycosis fungoides) may provide the major contribution to the diagnostic workup of atypical cases in certain instances.

Table 2 Clinical, histological and molecular genetic features of our own encountered cases of dermatological mimickers of mycosis fungoides

Patient	Leading clinical sign	Differential diagnosis	Otherwise atypical lesions	Otherwise classical MF lesions		Histological findings	Molecular genetic findings
				At time of presentation	During clinical course		
1	Erythematous	Erythema exsudativum multiforme	Yes	Yes	Yes	Classical MF	Not done
2	Psoriasiform	Tinea corporis	No	No	No	Classical MF	Monoclonal
	Granulomatous	Granuloma annulare				Classical MF	
3	Papular	Papuloerythroderma Ofuji	No	No	No	MF/SS with folliculotropism, only slight epidermotropism	Monoclonal
4	Psoriasiform	Psoriasis	No	Yes	Yes	Classical MF	Monoclonal
5	Granulomatous	Granuloma annulare	No	Yes	Yes	Transformed MF with folliculotropism and giant cells	Biclonal
6	Hyperpigmented	Urticaria pigmentosa	No	No	Yes	Purpuric CD8 ⁺ MF	Monoclonal
7	Hypopigmented	Vitiligo	No	Yes	Yes	Purpuric CD8 ⁺ MF	Monoclonal
8	Hyperkeratotic	Plantar eczema	No	No	No	Classical MF	Monoclonal
9	Ulcerative	venous ulcer	No	Yes	Yes	Tumor stage MF	Not done
10	Eczematous	Rosacea	Yes	No	No	Folliculotropic MF	Polyclonal
10	Granulomatous	Anetoderma	No	Yes	Yes	MF with elastolysis	Monoclonal
	Bullous	Bullous pemphigoid				CD8 ⁺ and CD30 ⁺ MF, subepidermal blistering	

MF: Mycosis fungoides; SS: Sézary syndrome.



Figure 1 Mycosis fungoides presenting with annular lesions. Clinical photographs of an 80-year-old male patient (case 1) with slowly progressive annular, cockadiform and arcuate lesions resembling tinea corporis (A), erythema exsudativum multiforme (B), and granuloma annulare (C), respectively.

Case 2

This patient was a 71-year-old patient presenting with slightly itchy skin lesions showing slow progression under topical steroids and UV-light therapy during several years. To note, a characteristic sparing of skin folds resembling Ofuji’s papuloerythroderma was noted (Figure 2C and D). After 3 years of an otherwise

eventless course, follow-up examinations revealed an elevated leukocyte count with pathological CD4⁺ CD7⁻ T-cell population in the peripheral blood corresponding to circulating Sézary-cells. Clonally identical neoplastic T-cells could also be detected in enlarged lymph nodes and bone marrow, so that stage 4 mycosis fungoides was diagnosed. The patient is currently scheduled



Figure 2 Mycosis fungoides resembling rosacea and Sézary-syndrome mimicking Ofuji's papuloerythroderma. A: Clinical images of a 46-year-old patient with granulomatous mycosis fungoides imitating rosacea and at the same time exhibiting clinical features of dermal elastolysis due to granulomatous slack skin syndrome (B) (case 9); C and D: Clinical images of a 71-year old patient with mycosis fungoides/Sézary-syndrome masquerading as Ofuji's papuloerythroderma (case 2).

under bexarotene in combination with extracorporeal photophoresis. Under this regimen, stabilization of all lymphoma manifestations could be achieved. This case highlights that the matter of "mimikry" is even more complex. On the one hand, primarily benign dermatoses such as papuloerythroderma Ofuji may antedate overt lymphoma, thus being designated as putative precursor dermatoses^[11]. On the other hand, however, mycosis fungoides and its leukemic counterpart may disguise as Ofuji's papuloerythroderma and thus may delay the correct diagnosis of malignant disease^[12].

Case 5

A 46-year-old patient presented with slowly progressive hyperpigmented brown to red papules and disseminated small macules on trunk and extremities highly resembling cutaneous mastocytosis/urticaria pigmentosa (Figure 3A). However, Darier's sign was negative and histological examination of two representative lesions revealed an atypical CD8⁺ epidermotropic infiltrate with extensive purpura, interface dermatitis, melanophages and haemosiderophages without increased mast cell count (Figure 4C, inset). At both biopsy sites the same T-cell clone was identified. Hence, purpuric/hyperpigmented CD8⁺ mycosis fungoides with atypical clinical manifestation was diagnosed. During further follow-up over the subsequent months blood involvement by clonally identical CD8⁺ T-cells was unrevealed and enlarged, suspicious lymph nodes were histologically proven to be involved by lymphoma. This peculiar imitator of case 5, mimicking urticaria pigmentosa/cutaneous mastocytosis, respectively, has not been previously described in literature. However, cases of mycosis fun-

goides with clinical features of pigmented purpuric eruptions including lichen aureus are well known^[13-20]. Hyperpigmented or purpuric lesions of mycosis fungoides often show an otherwise uncommon CD8⁺ and cytotoxic phenotype of the neoplastic lymphocytes. Their cytotoxic effects on keratinocytes may result in prominent interface changes with resulting pigment incontinence. Moreover, capillary damage conveyed by perivascular lymphocytes releasing cytotoxic granules may lead to the observed purpuric changes. TCR γ ⁺ and CD8⁺ cytotoxic cases of cutaneous lymphomas are usually associated with a poor therapeutic response even to multimodal aggressive treatment and therefore a dismal prognosis with 5-year survival rates below 30%^[21-23]. Our patient initially exhibited rather rapid progression with peripheral blood and lymph node involvement of CD8⁺ lymphoma, however, achieved stabilization of lymphoma at time of submission of the manuscript under monochemotherapy with liposomal doxorubicin during a follow-up of 3 mo.

CONCLUSION

These exemplifying cases together with the prior integrating review of literature clearly delineates that, first, thorough clinical examination remains the mainstay in diagnosing ambiguous cases of mycosis fungoides. Thus, most of our patients showed one or more further classical lesions of mycosis fungoides, either at time of initial presentation (6 out of 10) or later on during clinical follow-up (7 out of 10), so that diagnosis could be readily suspected based on thorough clinical whole-body examination and close follow-up examinations. Of note, some of our cases showed more than one



Figure 3 Mycosis fungoides as imitator of benign inflammatory dermatoses. Clinical photomicrographs of skin lesions of mycosis fungoides mimicking urticaria pigmentosa (A) (case 5), plantar eczema (B) (case 7) and vitiligo/pityriasis alba (C) (case 6).

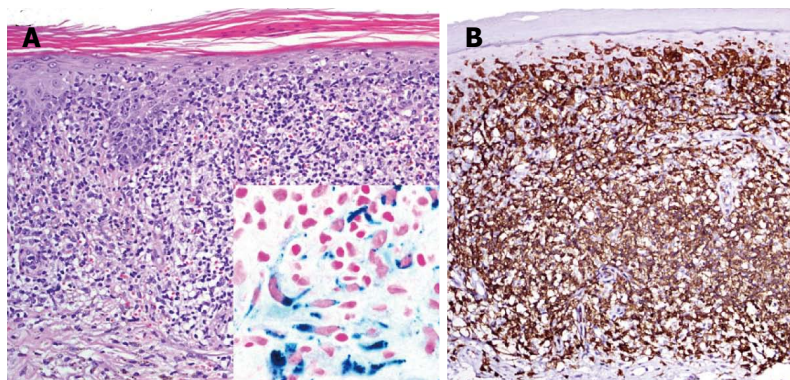


Figure 4 Histological findings. A: Case 5 exhibits extensive purpuric changes, pigment incontinence, interface dermatitis (HE staining, magnification 400 $\times$. Inset iron staining); B: CD8⁺ cytotoxic epidermotropic infiltrate is depicted (CD8 immunohistochemical staining).

atypical, imitating feature (case 1 and 9).

In a next step, we further correlated the corresponding histological findings as well as the results of the PCR-analysis of the TCR gene rearrangement in such clinically ambiguous cases.

All of those patients, who did not show any leading clinical signs suggestive of cutaneous lymphoma (4 out of 10) additionally demonstrated peculiar histological findings, such as uncommon immunophenotype (*e.g.*, positive staining for CD8 or cytotoxic molecules), interface dermatitis, nearly absent epidermotropism, extensive folliculotropism or granulomatous changes. Especially CD8⁺ variants of mycosis fungoides tend to show distinct histological features. These include a subtle to prominent interface dermatitis with vacuolar degeneration of keratinocytes, subepidermal blistering/papillary edema in the absence of antiepidermal antibodies, or purpuric changes. As mentioned above, some of these characteristics may be due to the coexpression of cytotoxic molecules (perforin, granzyme B) by the

lymphoma cells with putative consecutive proapoptotic properties on nearby stroma cells. Distinction from otherwise aggressive cutaneous lymphoma subtypes such as the provisional category of CD8⁺ primary cutaneous aggressive epidermotropic T-cell is of outstanding importance in patient management. Clinical signs (rapid onset of multiple disseminated ulcerated plaques, papules and tumors without prior patches and plaques, mucosal involvement) and symptoms (reduced performance state, fever, weight loss) and histological features (striking pagetoid epidermotropism of highly proliferating, atypical CD8⁺ lymphoma cells, epidermal necrosis and extensive ulceration) hint to this aggressive subtype^[24]. Prompt and adequate, mostly more aggressive therapeutic measures are warranted for this fatal lymphoma subtype with an often dismal prognosis. Granulomatous features of mycosis fungoides may mimic palisading or necrobiotic granuloma reminiscent of granuloma annulare^[25] or a more interstitial pattern is present reminiscent of palisading and granulomatous

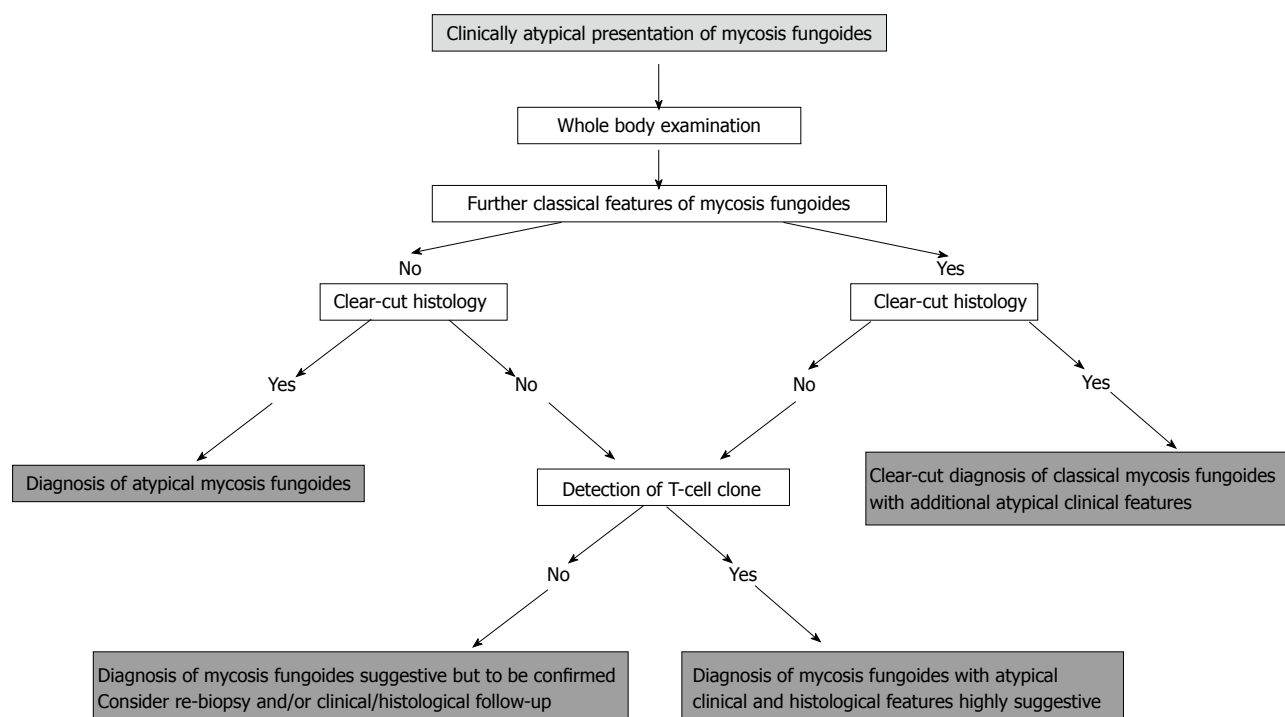


Figure 5 Schematic diagnostic algorithms for the clinical and histopathological work-up of “mimicking” cases of mycosis fungoides.

disease. Elastolysis and elastophagocytosis observed in the distinct and rare lymphoma subtype granulomatous slack skin syndrome^[26] may dissimulate elastolytic giant cell granuloma on histological grounds. Stains for microorganism or culture are to be included within the diagnostic workup if infectious processes (e.g., mycobacterial or deep fungal infections) are suspected.

Usually, such lymphoid infiltrates with an ambiguous clinical picture as well as a challenging, arbitrary histology at time of initial presentation reveal a dominant T-cell clone on molecular genetic testing, thus providing the final decisive and pivotal step for correct diagnosis. This was also the case in our patient cohort. In this context, it has recently been shown that molecular genetic analysis is especially important in granulomatous lymphoma variants, a special subtype in which clinical manifestations may be atypical and on histology only the minority of the cellular infiltrate may actually be built up by the lymphoma cells itself^[7,27,28]. Recently, it was shown that the proof of a dominant T-cell clone represents an important diagnostic tool to distinguish ambiguous cases of granulomatous lymphoma from reactive granulomatous disorders such as sarcoidosis, granuloma annulare or necrobiosis lipoidica, all presenting with overlapping clinical and histological features. Whereas in granulomatous lymphoma a TCR rearrangement was present in > 90% of cases, a monoclonal T-cell population was present in only 13% of the cases of granuloma annulare and could not be detected in sarcoidosis^[27]. A persistent T cell clone is present in most cutaneous T-cell lymphomas, especially in advanced stages, most likely representing the disease causing tumour clone. Repetitive biopsies with tracking and

comparative analysis of the lesional T-cell clones over the time course clearly improve diagnostic accuracy (“dual clonality”)^[29]. This is also true for the differentiation from benign granulomatous diseases^[28]. In addition, recent data have delineated that further, transiently appearing T cell clones frequently occur during the course of disease. The biological relevance of these additional clones is still unclear and has to be determined. Nevertheless, it may of interest to track additional T cell clones for diagnostic analyses^[28]. On the contrary, however, molecular genetic analysis may also come to its limits as clone detection may be susceptible to faults such as it depends upon the applied technique, the density of the lymphoma infiltrate within the histological specimen and the quality of the investigated tissue. The detection rate may be enhanced by laser capture microdissection in sparse infiltrate, which, however, is not practical in every-day routine^[30]. Hence, the application of molecular genetic techniques with analysis of the TCR rearrangement may in certain circumstances turn out to be the ultimate, pivotal diagnostic step in ambiguous cases. This point not for the first time again to its substantial, indispensable value in the diagnostic algorithm of cutaneous lymphoma (Figure 5).

To summarize, the comprehensive review of previously published data accomplished by our own cases underline that in ambiguous cases of mycosis fungoides a meticulous clinicopathological correlation including follow-up examination together with molecular genetic analysis provide decisive diagnostic adjuncts in finally obtaining the correct diagnosis. The intention of our article was to provide a comprehensive, illustrated overview of the fascinating and versatile nature of cutaneous

lymphoma. By this, we intended to alert the clinician and dermatopathologist of rare and protean variants of mycosis fungoides, hence, not to miss the correct diagnosis and unnecessarily delay appropriate therapeutic measures.

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Zosteriform cutaneous leiomyoma-Type II : An uncommon presentation

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Abstract

Cutaneous leiomyomas are rare, benign smooth muscle

tumors, characterized by painful nodules in most of the cases. They can occur in multiple disseminated, segmental or zosteriform and solitary forms. Segmental or zosteriform leiomyoma can occur either alone (Type I), or with scattered nonsegmental lesions elsewhere (Type II); the latter variety occurring rarely. Here we present a case of Type II zosteriform leiomyoma in a middle aged individual.

Key words: Cutaneous; Leiomyoma; Zosteriform

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Core tip: The most interesting feature of this case is the rarity of the presentation of the entity. Leiomyoma is not uncommon but zosteriform presentation is a relatively rare condition. Besides, discrete lesions apart from the zosteriform pattern, gives it the nomenclature of Type II zosteriform leiomyoma which is worth reporting.

Das A, Podder I, Ghosh A. Zosteriform cutaneous leiomyoma-Type II : An uncommon presentation. *World J Dermatol* 2015; 4(4): 145-147 Available from: URL: <http://www.wjgnet.com/2218-6190/full/v4/i4/145.htm> DOI: <http://dx.doi.org/10.5314/wjd.v4.i4.145>

INTRODUCTION

Cutaneous leiomyomas are rare, benign painful tumors arising from smooth muscle cells. According to their site of origin, they are of three types; piloleiomyoma (most common variant), angioleiomyoma and genital leiomyoma^[1]. These tumors can occur either singly or multiply. When multiple they can be arranged in diffuse (disseminated), blaschkoid or segmental (zosteriform) patterns^[2]. Zosteriform leiomyomas commonly occur only along single dermatomes unilaterally (Type I); or in rare



Figure 1 Multiple papulo-nodules on the back and shoulders. Note the grouped as well as discrete arrangement of the lesions.



Figure 2 Close-up view of the zosteriform pattern of distribution of the papulo-nodules on the left side of the back.

cases they may be associated with scattered, isolated, nonsegmental lesions elsewhere (Type II)^[1]. Multiple leiomyomas may be associated with uterine leiomyomas and/or aggressive renal cell carcinomas. Here we present a case of Type II zosteriform leiomyoma; as this variety is extremely rare in occurrence.

CASE REPORT

A 33-year-old male patient presented to us with multiple painful swellings, mainly on his back for the last 12 years. There were a few isolated lesions on the upper portion of his back, while several lesions were grouped together, near the middle portion, only on the left side (Figure 1). The isolated, scattered lesions developed earlier; all the lesions progressively increased in size over time. The patient also gave history of associated paroxysmal burning pain, which exacerbated on exposure to cold, touch or physical stress. Worsening of pain with cold was elicited. There was no history of any urinary disturbance. Family history was unremarkable. Cutaneous examination, revealed the lesions to be skin colored to erythematous, firm, tender papules and nodules, varying in size from 0.5 to 2 cm. The grouped lesions were present along the T9 and T10 dermatomes, in a segmental or zosteriform distribution, on the posterior aspect, unilaterally only over the left side (Figure 2).

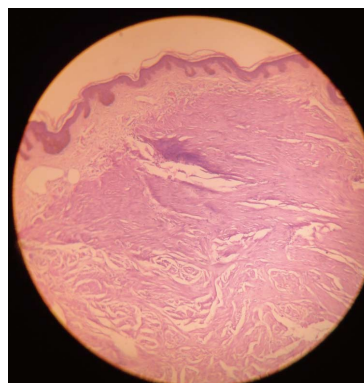


Figure 3 Bundles of spindle-shaped cells arranged in an interlacing and whorled pattern (H and E, 40 x).

Few scattered isolated lesions were present on the upper part of back, shoulder distributed bilaterally. Hair, nails and mucosae were normal. Systemic examination was non contributory. Routine blood biochemical investigations did not reveal any abnormality. Ultrasound examination of the lower abdomen showing the kidney, ureter, bladder region was within normal limits. Human immunodeficiency virus serology was non reactive. Two nodules (zosteriform distribution and isolated) were subjected to excisional biopsy and histopathological examination (HPE) which showed bundles of spindle-shaped cells arranged in an interlacing and whorled pattern with elongated nuclei having rounded ends confirming the diagnosis of piloleiomyoma (Figure 3). The patient was started on nifedipine 10 mg thrice-daily, and advised periodic follow-up. The pain has decreased to a significant extent.

DISCUSSION

Cutaneous leiomyomas are benign smooth muscle tumors, which may occur singly or multiply. According to their site of origin they can be classified into three types^[1,2]: (1) Piloleiomyoma - derived from the arrector pili muscles of hair follicles; (2) Angioleiomyoma (vascular leiomyoma) - arising from the tunica media of veins; and (3) Genital leiomyoma - mainly arising from the dartos muscle of scrotum; rarely they may be present over the labia majora and nipples^[1]. Piloleiomyoma is the most common type, frequently occurring multiply.

Multiple cutaneous leiomyoma is the most common clinical variety, most commonly situated over the trunk and extremities. However, rarely they may occur on the tongue or any other part of mouth^[1]. These lesions can be arranged in diffuse (disseminated), blaschkoid, linear or segmental (zosteriform) patterns^[3]. Segmental or zosteriform leiomyoma can be classified into two types based on pathogenesis as proposed by Happle^[4]; in Type I segmental leiomyoma there is a novel post zygotic segmental mutation; clinically characterized by the presence of dermatomal distribution only, while in Type II segmental leiomyoma there is post zygotic mutation in a heterogeneous embryo with subsequent loss of

heterozygosity, resulting in segmental lesions along scattered, isolated, nonsegmental lesions. The index case had both discrete lesions as well as in a segmental or zosteriform pattern, unilaterally over the left side; thus a diagnosis of Type II segmental pilar leiomyoma was attained. Type II segmental leiomyoma has been rarely reported in the literature, which is commonly unilateral along a single dermatome^[4,5]. However, bilateral involvement^[6] and unilateral multisegmental distribution^[2] have recently being reported. A loss of function mutation in the gene encoding fumarate hydratase on chromosome 1q has been found to predispose individuals to Type II segmental leiomyoma^[7].

The lesions of leiomyoma are frequently painful, which may occur due to local pressure exerted by the tumor on cutaneous nerves or due to degranulation of infiltrating mast cells, or due to muscle contraction; the exact cause is yet to be elucidated. Multiple piloleiomyomas may be associated with several conditions *viz.* Reed's syndrome (multiple cutaneous and uterine leiomyomas, hereditary leiomyomatosis and renal cell carcinoma)^[1], erythrocytosis/polycythemia, and visceral involvement (gastrointestinal tract and retroperitoneal area)^[4], *etc.*. Our patient has been advised regular follow up to detect any sign of RCC at the earliest. As leiomyoma is a painful tumor, all other painful cutaneous tumours may be considered as differential diagnoses; as summed up by the mnemonic: "blend an egg" representing: Blue rubber bleb naevus, leiomyoma, eccrine spiradenoma, neuroma, dermatofibroma, angiolipoma, neurilemmoma, endometrioma, glomus tumor and granular cell tumor^[8]. Apart from the characteristic clinical features, HPE also clinched our diagnosis in favour of leiomyoma.

Treatment of the leiomyomas is not satisfactory. For solitary lesions curative surgery is the treatment of choice, preferably with preoperative embolization to minimize perioperative blood loss; whereas in case of extensive lesions various agents have been used to alleviate the associated pain like nifedipine, doxazosin, gabapentine, topical 9% hyoscine hydrobromide^[2], phenoxybenzamine and botulinum toxin^[9]. Liquid-nitrogen cryotherapy and CO₂ laser ablation have been used with varying success^[4]. Besides, there are reports of cases successfully treated with oral doxazosin^[10]. Our patient was started on oral nifedipine, and advised regular follow-up.

COMMENTS

Case characteristics

Multiple painful swellings on the back for the preceding 12 years.

Clinical diagnosis

Leiomyoma.

Differential diagnosis

Leiomyoma, neurofibroma, and eccrine spiradenoma.

Laboratory diagnosis

Routine blood biochemical investigations did not reveal any abnormality. Human immunodeficiency virus serology was non-reactive.

Imaging diagnosis

Ultrasound examination of the lower abdomen showing the kidney, ureter, bladder region was within normal limits.

Pathological diagnosis

Histopathological examination which showed bundles of spindle-shaped cells arranged in an interlacing and whorled pattern with elongated nuclei having rounded ends confirming the diagnosis of piloleiomyoma.

Treatment

Patient was prescribed oral nifedipine, and advised regular follow-up.

Related reports

Sahoo B reported a case of Zosteriform pilar leiomyoma. A case of unilateral segmental Type II leiomyomatosis Vasani RJ.

Experiences and lessons

A clinical differential diagnosis of leiomyoma should be considered in a patient presenting with zosteriform distribution of painful papules and nodules.

Peer-review

It is an interesting case presented, as long as there are only a few reported with zosteriform distribution.

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