

World Journal of *Hematology*

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INDEXING/ABSTRACTING

The WJH is now abstracted and indexed in Reference Citation Analysis, China National Knowledge Infrastructure, China Science and Technology Journal Database, and Superstar Journals Database.

RESPONSIBLE EDITORS FOR THIS ISSUE

Production Editor: *Yu-Xi Chen*; Production Department Director: *Xu Guo*; Editorial Office Director: *Yan-Xia Xing*.

NAME OF JOURNAL

World Journal of Hematology

ISSN

ISSN 2218-6204 (online)

LAUNCH DATE

June 2, 2012

FREQUENCY

Continuous Publication

EDITORS-IN-CHIEF

Pier Paolo Piccaluga

EDITORIAL BOARD MEMBERS

<https://www.wjgnet.com/2218-6204/editorialboard.htm>

PUBLICATION DATE

January 5, 2023

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INSTRUCTIONS TO AUTHORS

<https://www.wjgnet.com/bpg/gerinfo/204>

GUIDELINES FOR ETHICS DOCUMENTS

<https://www.wjgnet.com/bpg/GerInfo/287>

GUIDELINES FOR NON-NATIVE SPEAKERS OF ENGLISH

<https://www.wjgnet.com/bpg/gerinfo/240>

PUBLICATION ETHICS

<https://www.wjgnet.com/bpg/GerInfo/288>

PUBLICATION MISCONDUCT

<https://www.wjgnet.com/bpg/gerinfo/208>

ARTICLE PROCESSING CHARGE

<https://www.wjgnet.com/bpg/gerinfo/242>

STEPS FOR SUBMITTING MANUSCRIPTS

<https://www.wjgnet.com/bpg/GerInfo/239>

ONLINE SUBMISSION

<https://www.f6publishing.com>



Venous thromboembolism prophylaxis of a patient with MYH-9 related disease and COVID-19 infection: A case report

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Specialty type: Medicine, general and internal

Provenance and peer review: Unsolicited article; Externally peer reviewed.

Peer-review model: Single blind

Peer-review report's scientific quality classification

Grade A (Excellent): 0
Grade B (Very good): 0
Grade C (Good): C, C
Grade D (Fair): D
Grade E (Poor): 0

P-Reviewer: Chan ASW, China; Luo W, China

Received: July 22, 2022

Peer-review started: July 22, 2022

First decision: September 26, 2022

Revised: October 6, 2022

Accepted: December 6, 2022

Article in press: December 6, 2022

Published online: January 5, 2023



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Abstract

BACKGROUND

The May-Hegglin anomaly is among a group of genetic disorders known as MYH9-related disease. Patients with inherited platelet disorders such as May-Hegglin anomaly are at a variably increased risk for bleeding due to a combination of platelet dysfunction and thrombocytopenia. Patients admitted to the hospital with coronavirus disease 2019 (COVID-19) infection are at an increased risk for a venous thromboembolism event (VTE). The National Institutes of Health COVID-19 treatment guidelines recommend using a prophylactic dose of heparin as VTE prophylaxis for adults who are receiving high-flow oxygen. We describe a patient admitted for COVID-19 infection with pneumonia and a history of May-Hegglin anomaly. The patient presented a challenge to determine prophylactic anticoagulation as there are no clear guidelines for this patient population.

CASE SUMMARY

Herein, we describe the case of a 39-year-old woman admitted with acute hypoxic respiratory failure secondary to COVID-19 pneumonia. She had a history of May-Hegglin anomaly and demonstrated risk for bleeding since childhood, including a life-threatening bleeding event at the age of 9 years requiring blood and platelet transfusions. Her baseline platelet count was $40-50 \times 10^9/L$ throughout her adult life. Her family history was also notable for May-Hegglin disorder in her mother, maternal uncle, maternal grandfather and her son. Computed tomography/pulmonary angiography revealed bilateral consolidative opacities consistent with multifocal pneumonia. Complete blood count was notable for platelet count of $54 \times 10^9/L$. She was admitted for inpatient respiratory support with high-flow oxygen per nasal cannula and was managed with guideline-directed therapy for COVID-19, including baricitinib and dexamethasone. The Hematology/Oncology consultation team was requested to assist with management of VTE prophylaxis

in the setting of active COVID-19 infection and an inherited bleeding disorder. After review of the literature and careful consideration of risks and benefits, it was decided to treat the patient with prophylactic enoxaparin. She was closely monitored in the hospital for bleeding and worsening thrombocytopenia. She had no bleeding or signs of VTE. Her respiratory status improved, and she was discharged home after 5 d of hospitalization with supplemental oxygen by nasal cannula and dexamethasone. At the 6-month follow-up, the patient successfully discontinued her home oxygen use after only a few weeks following discharge.

CONCLUSION

The patient presented a challenge to determine prophylactic anticoagulation as anticoagulation guidelines exist for patients with COVID-19, but there are no clear guidelines for management of patients with COVID-19 and inherited bleeding disorders, particularly those with MYH9-related disease. She was discharged after recovery from the COVID-19 infection without bleeding or thrombosis. As there are no published guidelines for this situation, we present a pragmatic, informed approach to a patient with MYH9-related disease who had an indication for anticoagulation.

Key Words: Venous thromboembolism event; Prophylaxis; MYH9-related disease; Anticoagulation in inherited platelet disorder; Low molecular heparin; COVID-19; Case report

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Core Tip: May-Hegglin anomaly is one of several autosomal dominant disorders described as MYH9 mutation-related diseases (MYH9-RD). A mutation in the *MYH9* gene causes macrothrombocytopenia and a mild to moderate bleeding tendency. Severity of bleeding in patients with MYH9-RD is related to the degree of thrombocytopenia and to physical properties of the large platelets. MYH9-RD is not an absolute contraindication to anticoagulation or antiplatelet agents. If a patient with MYH9-RD presents with an indication for anticoagulation, such as coronavirus disease 2019 infection, one must take a careful history of previous bleeding episodes and weigh bleeding risk against the risk of thrombosis.

Citation: Jiang B, Hartzell M, Yu S, Masab M, Lyckholm L. Venous thromboembolism prophylaxis of a patient with MYH9-related disease and COVID-19 infection: A case report. *World J Hematol* 2023; 10(1): 1-8

URL: <https://www.wjgnet.com/2218-6204/full/v10/i1/1.htm>

DOI: <https://dx.doi.org/10.5315/wjh.v10.i1.1>

INTRODUCTION

May-Hegglin anomaly (MHA) is a rare autosomal dominant platelet disorder characterized by macrothrombocytopenia and leukocyte inclusions. It is one of a group of diseases associated with myosin heavy chain gene defects, now known as MYH9-related disease (MYH9-RD), that present with macrothrombocytopenia, platelet dysfunction and varying clinical features such as sensorineural hearing loss, presenile cataracts and renal failure[1]. Patients with MYH9-RD have a mild to moderate bleeding tendency; thus, these patients are advised to avoid anti-platelet agents and anticoagulants[2]. However, patients with platelet disorders can acquire transient or permanent prothrombotic conditions that necessitate prophylactic or therapeutic anticoagulation.

Conditions such as obesity, hospitalization and immobility increase the risk for venous thromboembolism (VTE), even in patients with thrombocytopenia[3]. Inflammation and excess cytokine production in coronavirus disease 2019 (COVID-19) infection may cause endothelial dysfunction, platelet activation and thrombosis, leading to increased risk of VTE[4-6]. The American Society of Hematology guideline panel suggests using prophylactic-intensity anticoagulation in patients with COVID-19-related critical illness who do not have suspected or confirmed VTE. However, treatment decisions regarding anticoagulation for COVID-19-infected patients with coexisting MYH9-RD are challenging because of a potential increased risk of bleeding[7].

CASE PRESENTATION

Chief complaints

A 39-year-old woman with the past medical history significant for diabetes mellitus, hypothyroidism, obesity, and MYH9-RD (specifically MHA) presented to our medical center for acute hypoxic respiratory failure secondary to COVID-19 pneumonia.

History of present illness

She was admitted for inpatient respiratory support with high-flow oxygen per nasal cannula and was managed with guideline-directed therapy for COVID-19, including baricitinib and dexamethasone.

History of past illness

The patient was diagnosed with MHA in childhood. The patient experienced a life-threatening bleeding event at the age of 9 years during a tonsillectomy requiring blood and platelet transfusions. She was subsequently evaluated by a hematologist and was diagnosed with MHA. She later had another bleeding episode as a child during oral surgery. She had two vaginal deliveries and received a preventive platelet transfusion for one of these, as she had a platelet count of approximately $40 \times 10^9/L$. Her baseline platelet count was $40-50 \times 10^9/L$ throughout her adult life. She denied history of spontaneous bleeding requiring transfusion or hospitalization in the past 9 years but reported mild gum bleeding and menorrhagia not requiring transfusion. She did not receive anticoagulation at any time. She was instructed by her hematologist to avoid nonsteroidal anti-inflammatory drugs or aspirin and used them sparingly.

Personal and family history

Her family history was notable for MHA in her mother, maternal uncle, maternal grandfather and her son.

Physical examination

In the emergency department, the patient's respiratory rate was 26 breaths/min, heart rate 78 beats/min and blood pressure 126/72 mmHg. The patient's SpO₂ was 95% on 5 L of oxygen per nasal cannula. The body mass index was 53.7. She was awake and alert but in moderate respiratory distress, with frequent cough and coarse and diminished breath sounds bilaterally.

Laboratory examinations

Complete blood count was notable for white blood cell count of $4.9 \times 10^3/\mu L$, hemoglobin of 11.4 g/dL, mean corpuscular volume of 72.8 and platelet count of $54 \times 10^9/L$. Peripheral smear revealed hypochromic, microcytic anemia with mild anisopoikilocytosis. Döhle body inclusions were seen in the neutrophils. Frequent macrothrombocytopenia was observed.

Imaging examinations

Computed tomography/pulmonary angiography revealed bilateral consolidative opacities consistent with multifocal pneumonia.

MULTIDISCIPLINARY EXPERT CONSULTATION

The Hematology/Oncology consultation team was requested to assist with management of VTE prophylaxis in the setting of active COVID-19 infection and an inherited bleeding disorder.

FINAL DIAGNOSIS

She was a patient with a platelet disorder who was admitted for severe COVID-19 infection.

TREATMENT

The treatment team felt that the patient's risk for VTE due to active COVID-19 infection, obesity and immobility outweighed her risk of bleeding from anticoagulation in the setting of thrombocytopenia and inherited platelet disorder. She was started on the standard prophylactic dose of enoxaparin 40 mg subcutaneously once daily and monitored carefully for bleeding. On day 3, the dose was escalated to 40 mg subcutaneously twice a day as it is recommended for obese patients. She was closely monitored in the hospital for bleeding and worsening thrombocytopenia.

OUTCOME AND FOLLOW-UP

The patient had no bleeding or signs of VTE. Her respiratory status improved, and she was discharged home after 5 d of hospitalization with supplemental oxygen by nasal cannula and dexamethasone. At the 6-mo follow-up, the patient reported successfully discontinuing her home oxygen use after only a few weeks following discharge. She had no VTE or bleeding episodes. She experienced COVID-19 sequelae, including dyspnea with exertion, palpitations, blurred vision, “brain fog” and diffuse hair loss. She plans to receive a post-COVID assessment at a recovery clinic for her symptoms.

DISCUSSION

Mutations in the *MYH9* gene cause a heterogeneous group of autosomal dominant disorders known as MYH9-RD. The population frequency of pathogenic *MYH9* mutations may be at least 1 in 20000[8]. These include MHA, Epstein syndrome, Fechtner syndrome and Sebastian platelet syndrome. Although these disorders are caused by different *MYH9* mutations, all patients present with macrothrombocytopenia but may later display other pathologies, including loss of hearing, renal failure and presenile cataracts[9].

The *MYH9* gene encodes the heavy chain of non-muscle myosin class II, isoform A, which is the only non-muscle myosin class II isoform expressed in megakaryocytes[10]. *In vitro* studies revealed that platelet aggregation is normal or only slightly defective in MYH9-RD[11,12]. Recent studies revealed that MYH9-RD mutations interrupt megakaryocyte migration toward the vasculature and impair proplatelet release in the bone marrow. This in turn results in macrothrombocytopenia[13].

The bleeding tendency in MYH9-RD is thought to be correlated more with the degree of thrombocytopenia and less with the platelet dysfunction[14-16]. The degree of bleeding tendency is usually mild to moderate and rarely severe. In the majority of patients, thrombocytopenia is the only manifestation of the disease throughout life[17]. Management includes avoiding anticoagulation and medications that hamper the function of platelets. Desmopressin is indicated for mild bleeding and platelet transfusion for severe bleeding[2].

To date, there is no disease-specific treatment for MHA and other MYH9-RD. However, recently a phase II clinical trial showed that a thrombopoietin receptor agonist, eltrombopag, was effective in improving thrombocytopenia and decreasing bleeding tendency in MYH9-RD patients with thrombocytopenia[18].

Due to the concern for bleeding tendency in people with MYH9-related disease, most patients are advised to avoid nonsteroidal anti-inflammatory drugs or anticoagulants. There is limited information about prophylaxis and management of VTE in patients with MYH9-RD and specifically MHA. The large retrospective SPATA-DVT study reported the impact of thromboprophylaxis and thrombotic outcomes in inherited platelet disorders in both elective and major surgeries[19]. Looking specifically at the subgroup of MYH9-RD, approximately 26.7% (8 of 30 surgeries) had excessive postsurgical bleeding, but no cases of VTE were reported in this subgroup. The study did not comment specifically on patients with MYH9-RD having this outcome. However, it concluded that low molecular weight heparin prophylaxis did not significantly influence postsurgical bleeding or need for antihemorrhagic interventions. Although a retrospective study, it inferred that prophylactic anticoagulation for VTE is safe for patients with inherited platelet disorders and should be used for inpatient management of patients at high risk for VTE.

Hospitalized COVID-19 infected patients have a significant risk for VTE, particularly hospitalized patients with severe COVID-19 infection. Severe COVID-19 infection, defined as requiring high-flow oxygen, noninvasive ventilation, mechanical ventilation, vasopressors or inotropes or ICU admission, is associated with high VTE risk despite prophylactic anticoagulation. There are five large clinical trials that compared the outcome and safety of therapeutic anticoagulant dosing with prophylactic anticoagulant dosing for thromboprophylaxis in patients hospitalized for COVID-19 infection (Table 1)[17-21]. HEP-COVID and mrRCT showed superiority of therapeutic heparin in non-critically ill patients. In contrast, the RAPID trial and ACTION study did not observe statistical significance in the primary outcome. The INSPIRATION trial, which specifically studied critically ill patients at time of admission, did not find a benefit from intermediate dose over standard prophylactic dose heparin in the prevention of the composite outcome of VTE, arterial thromboembolism, treatment with extracorporeal membrane oxygenation or mortality within 30 d. Therefore, prophylactic heparin remains the agent of choice for anticoagulation in patients with severe COVID-19 infection. Enoxaparin 40 mg subcutaneously twice daily was commonly used in the clinical trials above for obese patients with adequate renal function.

There is no guidance for starting anticoagulation in COVID-19-infected patients with hereditary platelet disorders such as MYH9-RD, as in our patient. A retrospective review suggested thrombocytopenia was an uncommon finding in all hospitalized COVID-19 patients, with 8% of ICU and 4% of non-ICU patients having initial platelet counts below $100 \times 10^9/L$ [20]. Patients with thrombocytopenia or bleeding risk are not well studied in the above-described clinical trials, as these risk factors were listed as exclusion criteria (Table 2). Guidelines from the Mayo Clinic[21] and the International Society

Table 1 Summary of anticoagulation strategy in major clinical trials on coronavirus disease 2019 thromboprophylaxis

Trial	Anticoagulant	Therapeutic dose arm	Prophylactic dose arm
mpRCT (REMAP-CAP, ACTIV-4a, and ATTAC)[17]	Enoxaparin, dalteparin, tinzaparin, UFH	BMI < 40 and CrCl $\geq$ 30 mL/min: enoxaparin 1 mg/kg SC BID minus 10% or 1.5 mg/kg SC QD minus 10%; Dalteparin 200 units/kg SC QD minus 10% or 100 units/kg SC BID minus 10%; Tinzaparin 175 U/kg SC QD minus 10%; UFH per hospital protocol	BMI < 40 and CrCl $\geq$ 30 mL/min: enoxaparin 40 mg SQ QD; Dalteparin 5000 units SC QD; Tinzaparin 4500 units SC Q24H; UFH 5000 units SC Q8H-12H
		BMI $\geq$ 40 and CrCl $\geq$ 30 mL/min: enoxaparin 0.8 mg/kg SC BID minus 10%	BMI $\geq$ 40 and CrCl $\geq$ 30 mL/min: enoxaparin 40 mg SC BID; Dalteparin 7500 units SC QD; Tinzaparin 8000 units SC QD; UFH 7500 units BID
INSPIRATION[18]	Enoxaparin, UFH	CrCl $\geq$ 30 mL/min: enoxaparin 1 mg/kg SC QD	CrCl $\geq$ 30 mL/min: enoxaparin 40 mg SC QD
		Obesity ¹ and CrCl $\geq$ 30 mL/min: enoxaparin 0.6 mg/kg SC BID	Obesity ¹ and CrCl $\geq$ 30 mL/min: enoxaparin 40 mg SC BID
		15 < CrCl < 30 mL/min: enoxaparin 0.5 mg/kg SC QD	15 < CrCl < 30 mL/min: enoxaparin 40mg SC QD
		CrCl $\leq$ 15 mL/min: UFH 10000 units SC BID	CrCl $\leq$ 15 mL/min: UFH 5000 units SC BID
HEP-COVID[21]	Enoxaparin, UFH	CrCl $\geq$ 30 mL/min: enoxaparin 1 mg/kg SC BID	BMI < 30 and CrCl > 15 mL/min: enoxaparin 40 mg SC QD
		15 < CrCl < 30 mL/min: Enoxaparin 0.5 mg/kg SC BID	BMI > 30 and CrCl $\geq$ 30 mL/min: enoxaparin 40 mg SC BID
			BMI < 30 and CrCl < 15 mL/min: UFH 5000 U SC BID or TID
			BMI > 30 and CrCl < 15 mL/min UFH 7500 SC BID or TID
ACTION[19]	Rivaroxaban, enoxaparin, UFH	Oral route (preferred) CrCl $\geq$ 30 mL/min: rivaroxaban 20 mg PO QD	BMI < 40 and CrCl $\geq$ 30 mL/min: enoxaparin 40 mg SC QD; Fondaparinux 2.5 mg SC QD; UFH 5000U SC Q8H or Q12H
		30 < CrCl < 49 mL/min: rivaroxaban 20 mg PO QD	
		Parenteral route 1: age < 75 enoxaparin 1 mg/kg SC Q12H, age $\geq$ 75 enoxaparin 0.75 mg/kg SC Q12H	BMI $\geq$ 40 and CrCl $\geq$ 30 mL/min: enoxaparin 60 mg SC QD or 40 mg SC Q12H; UFH 7500U SC Q8H or Q12H
		Parenteral route 2 (preferred option in DIC): UFH IV to achieve to achieve a 0.3-0.7 IU/mL anti-Xa concentration	BMI < 40 and CrCl < 30 mL/min: UFH 5000 U SC Q8H or Q12H
RAPID[20]	Enoxaparin, dalteparin, tinzaparin, UFH	BMI < 40 and CrCl $\geq$ 30 mL/min: enoxaparin 1 mg/kg SC Q12H or 1.5 mg/kg SC QD; Dalteparin 200 units/kg SC Q24H or 100 units/kg SC Q12H; Tinzaparin 175 U/kg SC Q24H; UFH ²	BMI < 40 and CrCl $\geq$ 30 mL/min: enoxaparin 40 mg SC Q24H; Dalteparin 5000 units SC Q24H; Tinzaparin 4500 units SC Q24H; Fondaparinux 2.5 mg SC Q24H; UFH 5000 units SC Q8-12H
		BMI $\geq$ 40 and CrCl $\geq$ 30 mL/min: enoxaparin 1mg/kg SC Q12H; Dalteparin 100 units/kg SC Q12H; Tinzaparin 175 units/kg SC Q24H; UFH ²	BMI $\geq$ 40 and CrCl $\geq$ 30 mL/min: enoxaparin 40 mg SC Q12H; Dalteparin 5000 units SC Q12H; Tinzaparin 9000 units SC Q24H; UFH 7500 units SC Q8H
		BMI < 40 and CrCl < 30 mL/min: UFH ² or LMWH per hospital protocol	BMI < 40 and CrCl < 30 mL/min: UFH 5000 units SC Q8-12H or LMWH per hospital protocol
		BMI $\geq$ 40 and CrCl < 30 mL/min: UFH ² or LMWH per hospital protocol	BMI $\geq$ 40 and CrCl < 30 mL/min: UFH 7500 units SC Q8H or LMWH per hospital protocol

¹Weight $\geq$ 120 kg or body mass index $\geq$ 35 kg/m².²Unfractionated heparin intravenous bolus with continuous infusion to titrate to institution specific anti-Xa or activated partial thromboplastin time values. BID: Two times a day; BMI: Body mass index; CrCl: Creatinine clearance; DIC: Disseminated intravascular coagulation; IV: Intravenous; LMWH: Low molecular weight heparin; PO: By mouth; Q12H: Every 12 h; Q24H: Every 24 h; Q8H: Every 8 h; Q8-12H: Every 8-12 h; QD: Daily; SC: Subcutaneous; TID: Three times a day; UFH: Unfractionated heparin.

Table 2 Summary of exclusion criteria regarding thrombocytopenia and bleeding risk in major clinical trials on coronavirus disease 2019 thromboprophylaxis

Trial	Anticoagulant	Thrombocytopenia	Bleeding risk
mpRCT (REMAP-CAP, ACTIV-4a, and ATTAC)[17]	Enoxaparin, Dalteparin, Tinzaparin, UFH	Platelet count $< 50 \times 10^9$ /L	ATTAC: DAPT therapy, intracranial surgery or stroke within 3 mo, history of intracerebral AVM, brain aneurysm of CNS mass lesion, intracranial malignancy, history of intracranial bleeding, history of bleeding disorder, GI bleed within 3 mo, thrombolysis within 7 d, current epidural/spinal catheter, major surgery within 14 d, uncontrolled hypertension or other physician perceived contraindications to anticoagulation ACTIV-4a: bleed within last 30 d REMAP-CAP: clinical and/or laboratory bleeding risk to contraindicate anticoagulation
INSPIRATION[18]	Enoxaparin, UFH	Platelet count $< 50 \times 10^9$ /L	Major bleeding within 30 d, major surgery or ischemic stroke within 2 wk, head trauma within 30 d, neurosurgery within 3 mo, intracranial malignancy or AVM
HEP-COVID[21]	Enoxaparin, UFH	Platelet count $< 25 \times 10^9$ /L	Recent bleed within 1 mo, active GI or intracranial malignancy, DAPT therapy, IMPROVE bleed score of ≥ 7
ACTION[19]	Rivaroxaban, enoxaparin, UFH	Platelet count $< 50 \times 10^9$ /L	Use of ASA (> 100 mg) or P2Y12 inhibitor, chronic NSAIDs use, active bleeding, liver failure, blood dyscrasia, prohibitive hemorrhage risk, history of intracranial bleed, DIC, active cancer
RAPID[20]	Enoxaparin, dalteparin, tinzaparin, UFH	Platelet count $< 50 \times 10^9$ /L within 72 h	History of an inherited or active acquired bleeding disorder, bleeding within 30 d requiring hospital presentation, DAPT therapy, Hgb < 80 g/L

ASA: Aspirin; AVM: Arteriovenous malformation; CNS: Central nervous system; DAPT: Dual antiplatelet therapy; DIC: Disseminated intravascular coagulation; GI: Gastrointestinal; Hgb: Hemoglobin; IMPROVE: International Medical Prevention Registry on Venous Thromboembolism; NSAIDs: Nonsteroidal anti-inflammatory drugs; UFH: Unfractionated heparin.

of Thrombosis and Haemostasis[22] advise against anticoagulation in COVID-19 patients with severe thrombocytopenia (platelets $< 25 \times 10^9$ /L) and suggest nonpharmacological prophylaxis with sequential compression devices.

Our patient had several features that put her at an increased risk for thrombosis, including severe COVID-19 infection, obesity and immobility. She also had a history of spontaneous gingival bleeding, menorrhagia and postprocedure bleeding that required transfusion. Based on our assessment of the patient and review of the literature, we felt that the benefit of thromboprophylaxis outweighed the risk of bleeding. With the information above, low molecular weight heparin seemed the best choice for the patient with MYH9-RD, as it has a shorter-half life with reversibility, and was shown to be the optimal choice for patients with severe COVID-19 infection. For these reasons, it was recommended that the patient be given prophylactic anticoagulation with enoxaparin 40 mg once daily, then transition to enoxaparin 40 mg twice daily if there was no evidence of bleeding[23].

CONCLUSION

MYH9-RD is a spectrum of autosomal dominant diseases that present with macrothrombocytopenia, platelet dysfunction and varying clinical features such as sensorineural hearing loss, presenile cataracts, renal failure and mild to moderate bleeding tendency. When these patients are admitted for COVID-19-related critical illness, having a platelet disorder should not exclude them from receiving anticoagulation when it is needed. Low molecular weight heparin seemed to be the best choice for the patient with MYH9-RD, as it has a shorter-half life with reversibility, and was shown to be the optimal choice for patients with severe COVID-19 infection.

FOOTNOTES

Author contributions: All authors contributed equally; all authors conceptualized the manuscript; Jiang B wrote the initial manuscript; Jiang B, Hartzell M, Yu S and Masab M edited and conducted the literature research; Lyckholm L edited and critically corrected and finalized the manuscript; Jiang B, Hartzell M and Lyckholm L were directly involved in the patient management.

Informed consent statement: Informed written consent was obtained from the patient for publication of this report and any accompanying images.

Conflict-of-interest statement: The authors declare that they have no conflicts of interest to disclose.

CARE Checklist (2016) statement: The authors have read the CARE Checklist (2016), and the manuscript was prepared and revised according to the CARE Checklist (2016).

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Country/Territory of origin: United States

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S-Editor: Gong ZM

L-Editor: Filipodia

P-Editor: Gong ZM

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Typhoid with pancytopenia: Revisiting a forgotten foe: Two case reports

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Specialty type: Hematology

Provenance and peer review:

Unsolicited article; Externally peer reviewed.

Peer-review model: Single blind

Peer-review report's scientific quality classification

Grade A (Excellent): 0

Grade B (Very good): B

Grade C (Good): 0

Grade D (Fair): D

Grade E (Poor): 0

P-Reviewer: Chen C, China;
Vyshka G, Albania

Received: August 26, 2022

Peer-review started: August 26, 2022

First decision: September 5, 2022

Revised: September 12, 2022

Accepted: November 29, 2022

Article in press: November 29, 2022

Published online: January 5, 2023



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Abstract

BACKGROUND

Typhoid fever is a public health problem in Asia and Africa. Pancytopenia has been rarely reported during the 20th century. Reports during the last 20 years are scarce.

CASE SUMMARY

Our first patient was a young adult male presenting with febrile neutropenia whose blood and bone marrow cultures grew *Salmonella typhi*. He recovered before discharge from the hospital. The second was a primigravida who had an abortion following a febrile illness and was found to have pancytopenia. The Widal test showed high initial titers, and she was presumptively treated for typhoid. Convalescence showed a doubling of Widal titers.

CONCLUSION

Typhoid fever continued to show up as a fever with cytopenia demanding significant effort and time in working up such patients. In developing countries, the liaison with typhoid continues.

Key Words: Typhoid; Enteric fever; Pancytopenia; Hemophagocytosis; Case report

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Core Tip: Despite the coronavirus disease 2019 pandemic, typhoid fever remains a cause of acute febrile illness and cytopenia. Typhoid fever can rarely cause pregnancy loss, so acute febrile illnesses in pregnancy should not be neglected. Even with significant improvements in sanitation and water supply, contaminated food remains a problematic source of typhoid fever.

Citation: Saha RN, Selvaraj J, Viswanathan S, Pillai V. Typhoid with pancytopenia: Revisiting a forgotten foe: Two case reports. *World J Hematol* 2023; 10(1): 9-14

URL: <https://www.wjgnet.com/2218-6204/full/v10/i1/9.htm>

DOI: <https://dx.doi.org/10.5315/wjh.v10.i1.9>

INTRODUCTION

Typhoid fever is a disease specific to humans and is usually spread by contaminated food and water. It often requires a small infectious dose. It remains a public health nuisance in South Asian countries like India[1]. The most recent incidence among Indian centers was 497 typhoid cases *per* 100000 *per* year[2]. It can present many symptoms, predominantly related to the gastrointestinal system, but can range from encephalopathy to a urinary tract infection[3].

Pancytopenia is a rarely noted complication (6.2%-8.3%)[4]. Isolated thrombocytopenia is a common manifestation and mimics other causes of fever in the tropics such as dengue, scrub typhus, malaria, and leptospirosis[5]. Hemophagocytosis, bone marrow suppression, and disseminated intravascular coagulation are commonly speculated causes of pancytopenia[6]. Reports of pancytopenia in enteric fever during the last 20 years are scarce. Herein, we present 2 cases of pancytopenia in adults associated with typhoid fever: One presented as febrile neutropenia, and the other presented as septic abortion.

CASE PRESENTATION

Chief complaints

Case 1: An 18-year-old boy working in a courier company in Bangalore presented with a history of high-grade intermittent fever for 14 d.

Case 2: A 27-year-old housewife from Cuddalore, Tamil Nadu, primigravida at 12 wk pregnancy, presented with a history of fever of 1 wk, spotting *per vaginum* for 3 d, and cough for 1 d.

History of present illness

Case 1: Five days following the onset of fever, he developed constipation; nausea and anorexia were also present. He was admitted to a nearby hospital for the preceding 5 d before presentation, where his complete blood count (CBC) revealed hemoglobin of 81 g/L (normal range: 14-16 g/L), total leukocyte counts (TLC) of 0.8×10^9 /L (normal range: $4.5-11.0 \times 10^9$ /L), absolute neutrophil count (ANC) of 0.5×10^9 /L, and platelets of 15×10^9 /L (normal range: $150-400 \times 10^9$ /L). Then he was referred to our center. Dengue and Widal tests were negative; the rapid antigen test for coronavirus disease 2019 (COVID-19) was negative. High-resolution computed tomography thorax was normal. He had not been administered any antibiotics before his arrival. He did not give any other history to suggest localization of the fever at admission to our hospital. There were no bleeding manifestations, but he had fatigue upon minimal exertion.

Case 2: She had consulted her obstetrician for spotting; the ultrasonogram showed a single intrauterine gestation without fetal cardiac activity. A CBC in the same hospital showed pancytopenia, with hemoglobin of 90 g/L, TLC of 2.3×10^9 /L, ANC of 1.07×10^9 /L, and platelets of 90×10^9 /L. She was referred for pancytopenia with incomplete abortion.

Personal and family history

Case 1: No significant personal and family history.

Case 2: She was a primigravida.

Physical examination

Case 1: On examination, he had tachycardia of 99 beats/min, fever of 104.6 °F, multiple small (< 1 cm) lymph nodes in both axillary and inguinal regions, and mild splenomegaly (2 cm).

Case 2: At presentation (on day 8 of illness), she looked toxic, with a fever of 103 °F, pulse rate of 140 beats/min, blood pressure of 100/75 mmHg, and a respiratory rate of 22 breaths/min. She was admitted into the obstetrics intensive care unit. On examination, she had a palpable spleen of 2 cm, with an otherwise soft abdomen. There was minimal bleeding through the cervical, and it was open. The uterus was approximately 12 wk, with bilateral fornices free and non-tender on insertion of the tip of the finger, and clots were present in the uterine cavity.

Laboratory examinations

Case 1: Repeat CBC after admission showed hemoglobin of 78 g/L, corrected reticulocyte counts of 0.2%, TLC of 1.67×10^9 /L, ANC of 1.0×10^9 /L, and platelets of 30×10^9 /L. A peripheral smear showed leukopenia and thrombocytopenia without blast cells.

Case 2: The CBC in our hospital revealed hemoglobin of 74 g/L, TLC of 1.16×10^9 /L, ANC of 0.67×10^9 /L, and platelets of 80×10^9 /L. Peripheral smear showed microcytic hypochromic red blood cells and mild anisopoikilocytosis without blasts.

Renal and liver function tests were non-contributory. Lactate dehydrogenase was 670 IU/L. Because of the patient's cough, reverse transcription PCR for COVID-19 was repeated twice and was negative. Chest radiography and high-resolution computed tomography thorax were non-contributory. Serology for toxoplasma, rubella, cytomegalovirus, herpes simplex, and HIV was also negative.

On admission, the procalcitonin value was 0.48 ng/mL (normal range: < 0.05 ng/mL).

FINAL DIAGNOSIS

Case 1: Acute leukemia with febrile neutropenia and an acute febrile illness causing probable hemophagocytic lymphohistiocytosis was considered.

Case 2: The Widal test showed *Salmonella typhi* O agglutinin and H agglutinin titers of 1:320 and 1:320, respectively, suggestive of typhoid fever.

TREATMENT

Case 1: Piperacillin-tazobactam 4.5g Q8h and amikacin 600 mg OD were initiated intravenously. His direct Coombs test was negative. Lactate dehydrogenase of 1441 IU/L (normal range: 140-300 IU/L), ferritin of 6509 ng/mL (25-300 ng/mL), and triglycerides of 151 mg/dL were seen. Bone marrow aspiration and biopsy were performed on day 2; aspiration was reported as a reactive marrow with relative lymphocytosis on day 3. On day 4, peripheral blood culture grew *Salmonella enterica* serovar *typhi* sensitive to ceftriaxone, trimethoprim-sulfamethoxazole, and azithromycin. On reviewing his history, he said he frequented the roadside food stalls near his workplace for the last 2 mo to eat fried rice, noodles, and beef. An abdominal ultrasound showed only mild fatty liver with mild splenomegaly. Thus, antibiotics were switched to ceftriaxone 2 g intravenously OD on day 4. Bone marrow culture also grew the same organism on day 5.

Case 2: Two packed red blood cells and two platelets were transfused. Dilatation and curettage was performed. Pending cultures of blood, urine, and a high vaginal swab, she was empirically initiated on ceftriaxone 2 g intravenously once daily and metronidazole 500 mg IV q8h. A medicine consultation was sought on day 2 of admission for febrile neutropenia. Piperacillin-tazobactam 4.5g IV Q8h and tab azithromycin 500 mg OD were suggested, pending reports of cultures, echocardiography, disseminated intravascular coagulation panel, and febrile panel (dengue, scrub IgM PCR, chikungunya IgM, and Widal). Cultures of blood, urine, and products of conception were sterile; the high transvaginal swab revealed commensal organisms. Echocardiography was normal. D-dimers and fibrinogen were normal.

OUTCOME AND FOLLOW-UP

Case 1: He became afebrile on day 6 (Figure 1A). He was eating well by day 10 of ceftriaxone. His father requested discharge on day 12 due to an impending lockdown to complete antibiotics at a nearby health center. Bone marrow biopsy showed normocellular active marrow with epithelioid cell granuloma.

One week later, when contacted by telephone, he was asymptomatic and was staying at home. He could not come back to the hospital for repeat blood counts.

Case 2: The obstetrician had not initiated piperacillin-tazobactam, and we were asked to transfer the patient to our department on day 6 of admission, considering the pancytopenia, negative cultures, and positive Widal.

We reviewed the patient again on the same day; her cough had subsided, her oral intake had improved, and the toxic appearance was absent. We transferred her to the Medicine ward and continued to treat typhoid fever presumptively. She later said she had been eating dinner in restaurants during Ramadan. By day 7, she had become afebrile (Figure 1B). She was not willing to submit to a bone marrow biopsy since she felt she was improving. Repeat procalcitonin on day 9 of admission was 0.05 ng/mL. After being observed for 2 afebrile days, she was discharged on day 11 to complete 3 d of ceftriaxone at a nearby hospital. At discharge, her CBC showed hemoglobin of 100 g/L, TLC of $2.56 \times$

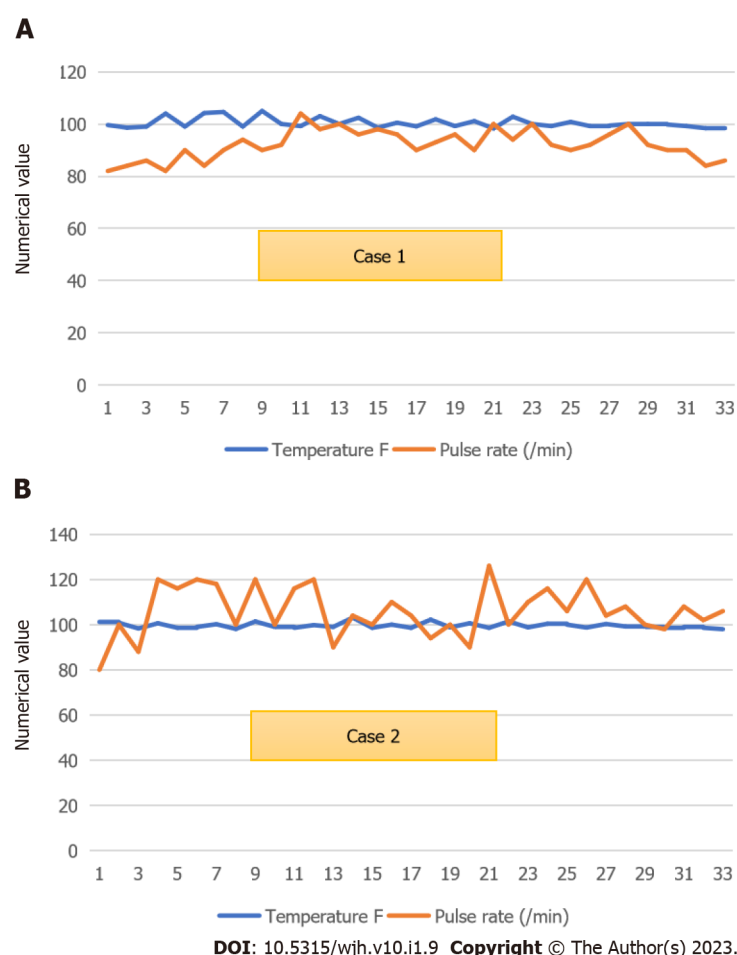


Figure 1 Hospital charts showing vital signs of both patients. A: Temperature and pulse chart of patient 1 showed high-grade fever with relative bradycardia during the hospital course; B: Chart of patient 2 showed high-grade intermittent fever matching the intensity of tachycardia.

$10^9/L$, ANC of $1.6 \times 10^9/L$, and platelets of $230 \times 10^9/L$.

One week later, her mother returned to the hospital to show a CBC that had a resolution of pancytopenia. The Widal test repeated 1 wk after discharge (day 17 of admission) showed titers of *Salmonella typhi* O agglutinin 1:640 and *Salmonella typhi* H agglutinin 1:640.

DISCUSSION

The first patient presented in the 3rd wk of illness without other complaints such as diarrhea, abdominal distension, or confusion. The second patient presented during the 2nd week only with fever, cough, and toxemia, which had probably caused an abortion (and also mimicked COVID-19). Good response to antibiotics was observed in both patients and was associated with a significant improvement in cytopenia that reflected the results of previous studies[7]. Both patients had a history of eating food from possibly unhygienic food outlets. The COVID-19-related lockdowns and shutting down of restaurants have led to roadside fast-food stalls remaining as the sole option for getting meals for a section of the population.

Pancytopenia with an acute febrile illness could be due to either viral, bacterial, parasitic, mycobacterial, or fungal infections. Common tropical acute febrile diseases such as dengue, leptospirosis, scrub typhus, and malaria were ruled out in our patients. Viral serologies for HIV, hepatitis B, and hepatitis C were negative. Cultures of blood and fluids were sterile in the second patient, while they gave us the diagnosis for the first. Pancytopenia due to hemophagocytic lymphohistiocytosis was considered in the first patient[8]. Fever, splenomegaly, cytopenia, and elevated ferritin were present, while triglycerides were normal. We could not evaluate natural killer cell cytotoxicity and elevated soluble CD25 since they were unavailable in our hospital. The Widal test was sent for the female patient because she had been buying dinner from food stalls regularly during Ramadan.

Typhoid fever and pancytopenia have been described in some reports from Asia and Africa during the last two decades of the 20th century. In the previous 20 years, there has been only one report each from India[9], Pakistan[8], Nepal[6], Ghana[10], Malawi[11], Spain[12], Turkey[13], and the United

States[14]. Barring Nepal and the African countries, the presentation of all patients was with hemophagocytic lymphohistiocytosis. Pakistan, Nepal, Malawi, Turkey, and Spain described pediatric patients, while the remaining three described young adults. The patient from the United States was also an Indian who had arrived in the country just 2 d before admission, making this report the fourth among adults in the last 20 years. Considering the prevalence of typhoid fever, this is extremely rare.

Bone marrow findings commonly described in typhoid fever include chronic inflammation, hemophagocytosis, or a reactive picture. We continued with bone marrow in the first patient since there was a working diagnosis of acute leukemia. In the second case, bone marrow was not performed since she had already received antibiotics for 6 d and was showing an improving trend. Moreover, she did not consent to the procedure. Bone marrow findings have been classified based on duration from symptom onset into the early phase (showing classically granulocytic hyperplasia with a mild degree of mono histiocytic proliferation until about 10 d from symptom onset), and proliferative phase from 10-25 d, wherein active hemophagocytosis is the characteristic finding. Beyond 25 d, it is categorized as the lysis phase, with well-formed granulomata typical of this phase. Bone marrow changes generally resolve completely following treatment[15]. In the first case, bone marrow showed only mild erythroid hyperplasia with toxic leukocytosis. Therefore, it can be classified as the proliferative phase with an active infection, which is effectively treated by sensitive antibiotics. Peripheral destruction is probably an added component based on increased lactate dehydrogenase and splenomegaly findings.

The Widal test was the only basis for diagnosis in the second patient. Though a single Widal test has often been used controversially to diagnose typhoid fever in developing countries, we presumptively treated her as such. There was no past vaccination for typhoid, and other infections such as malaria, which can cause false-positive results, were ruled out[16]. A doubling of titers 17 d after the first sample was probably suggestive.

Though septic abortion can be linked with typhoid fever, the culture of the products of conception did not reveal anything significant. Typhoid fever has been associated with premature abortions, most of them in the pre-antibiotic era[17]. Typhoid fever can significantly complicate pregnancy leading to abortion, fetal death, and neonatal infection as well as worsen the maternal prognosis.

CONCLUSION

We report 2 cases with typhoid fever and pancytopenia presenting differently, both of whom typhoid was not entertained as the initial diagnosis. One was a confirmed case, while the other had probable typhoid fever. Typhoid fever continues to show up as fever with cytopenia demanding significant effort and time in working up such patients. In developing countries, the liaison with typhoid continues.

FOOTNOTES

Author contributions: Saha RN contributed to drafting the manuscript; Selvaraj J contributed to images and concept; Viswanathan S contributed to literature review and editing; Pillai V contributed to editing and final approval.

Informed consent statement: All study participants or their legal guardian provided informed written consent about personal and medical data collection prior to study enrollment.

Conflict-of-interest statement: All the authors report no relevant conflicts of interest for this article.

CARE Checklist (2016) statement: The authors have read the CARE Checklist (2016), and the manuscript was prepared and revised according to the CARE Checklist (2016).

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S-Editor: Liu GL

L-Editor: Filipodia

P-Editor: Liu GL

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World J Hematol 2023 January 17; 10(2): 15-24



MINIREVIEWS

- 15 Advantageous tactics with certain probiotics for the treatment of graft-versus-host-disease after hematopoietic stem cell transplantation

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INDEXING/ABSTRACTING

The WJH is now abstracted and indexed in Reference Citation Analysis, China National Knowledge Infrastructure, China Science and Technology Journal Database, and Superstar Journals Database.

RESPONSIBLE EDITORS FOR THIS ISSUE

Production Editor: *Yu-Xi Chen*; Production Department Director: *Xu Guo*; Editorial Office Director: *Yan-Xia Xing*.

NAME OF JOURNAL

World Journal of Hematology

ISSN

ISSN 2218-6204 (online)

LAUNCH DATE

June 2, 2012

FREQUENCY

Continuous Publication

EDITORS-IN-CHIEF

Pier Paolo Piccaluga

EDITORIAL BOARD MEMBERS

<https://www.wjgnet.com/2218-6204/editorialboard.htm>

PUBLICATION DATE

January 17, 2023

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INSTRUCTIONS TO AUTHORS

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PUBLICATION ETHICS

<https://www.wjgnet.com/bpg/gerinfo/288>

PUBLICATION MISCONDUCT

<https://www.wjgnet.com/bpg/gerinfo/208>

ARTICLE PROCESSING CHARGE

<https://www.wjgnet.com/bpg/gerinfo/242>

STEPS FOR SUBMITTING MANUSCRIPTS

<https://www.wjgnet.com/bpg/gerinfo/239>

ONLINE SUBMISSION

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Advantageous tactics with certain probiotics for the treatment of graft-versus-host-disease after hematopoietic stem cell transplantation

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Specialty type: Hematology

Provenance and peer review:

Invited article; Externally peer reviewed.

Peer-review model: Single blind

Peer-review report's scientific quality classification

Grade A (Excellent): 0
Grade B (Very good): B
Grade C (Good): C
Grade D (Fair): D
Grade E (Poor): 0

P-Reviewer: Chan WYK, China;
Wang WJ, China; Zhou S, China

Received: August 2, 2022

Peer-review started: August 2, 2022

First decision: October 21, 2022

Revised: November 3, 2022

Accepted: November 23, 2022

Article in press: November 23, 2022

Published online: January 17, 2023



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Abstract

Hematopoietic stem cell transplantation (HSCT) becomes a standard form of cellular therapy for patients with malignant diseases. HSCT is the first-choice of immunotherapy, although HSCT can be associated with many complications such as graft-versus-host disease (GVHD) which is a major cause of morbidity and mortality after allogeneic HSCT. It has been shown that certain gut microbiota could exert protective and/or regenerative immunomodulatory effects by the production of short-chain fatty acids (SCFAs) such as butyrate in the experimental models of GVHD after allogeneic HSCT. Loss of gut commensal bacteria which can produce SCFAs may worsen dysbiosis, increasing the risk of GVHD. Expression of G-protein coupled receptors such as GPR41 seems to be up-regulated in the presence of commensal bacteria, which might be associated with the biology of regulatory T cells (Tregs). Treg cells are a suppressive subset of CD4 positive T lymphocytes implicated in the prevention of GVHD after allogeneic HSCT. Here, we discuss the current findings of the relationship between the modification of gut microbiota and the GVHD-related immunity, which suggested that tactics with certain probiotics for the beneficial symbiosis in gut-immune axis might lead to the elevation of safety in the allogeneic HSCT.

Key Words: Gut microbiota; Hematopoietic stem cell; Reactive oxygen species; Allogeneic hematopoietic stem cell transplantation; Graft vs host disease; Gut-immune axis

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Core Tip: Potential efficacy of probiotics for the treatment of graft vs host disease after hematopoietic stem cell transplantation has been shown here.

Citation: Yoshikawa S, Taniguchi K, Sawamura H, Ikeda Y, Tsuji A, Matsuda S. Advantageous tactics with certain probiotics for the treatment of graft-versus-host-disease after hematopoietic stem cell transplantation. *World J Hematol* 2023; 10(2): 15-24

URL: <https://www.wjgnet.com/2218-6204/full/v10/i2/15.htm>

DOI: <https://dx.doi.org/10.5315/wjh.v10.i2.15>

INTRODUCTION

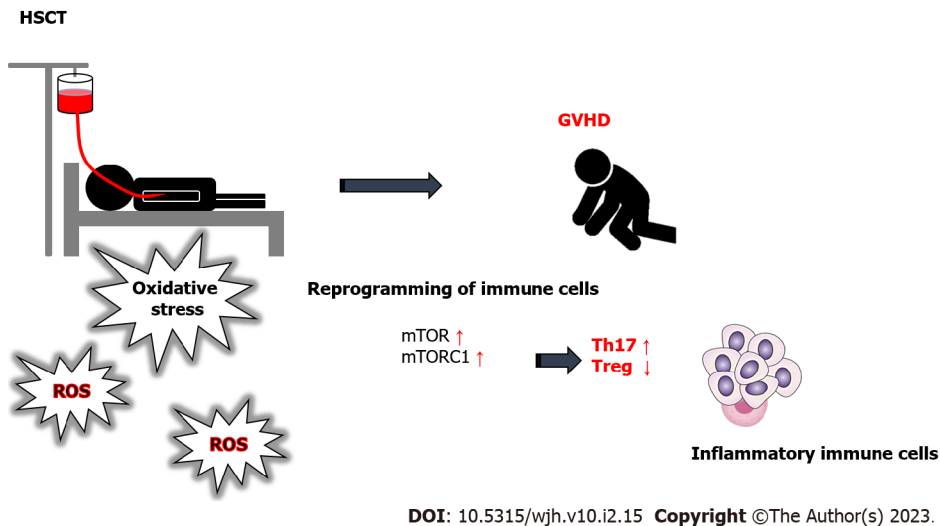
Hematopoietic stem cell transplantation (HSCT) is a broadly accomplished curative therapy for several hematological diseases, which is achieved by circulatory infusion of hematopoietic stem cells to the patients from human leukocyte antigen (HLA)-matched allogeneic donor or from the autologous patient themselves[1] (Figure 1). However, the HSCT techniques are restricted by potentially life-threatening complications, and one of the most serious complications is graft *vs* host disease (GVHD)[2], which is a pathogenic condition that arises when immune cells of the graft might systematically distinguish the host as foreign enemy, and affect the recipient's tissues/organs in the body induced by the influx of donor-derived effector T cells into peripheral tissues[3] (Figure 1). The pathophysiology of GVHD may include donor T cells and/or inflammatory cytokine-mediated injury to patient's tissues as a result of transplant and/or conditioning regimen. Immune reactions underlying the GVHD may also include greater proliferation and/or migration of active immune cells to the target tissue or organ. Several organs could be targeted by the GVHD. Therefore, the patient should be prepared with rigorous chemotherapy and/or radiotherapy to reduce immunological resistance in addition to extinguish residual malignant cells before HSCT.

Remarkably, several risk factors in gut might play important roles in the initiation of GVHD[4]. Gut microbiota has been hypothesized to have a role in GVHD onset[5]. In addition, the path of gut microbiota to the recovery following HSCT might be related to the risk of developing GVHD[6]. It has been suggested that potential modifiable targets of gut microbiota could reduce the risk of GVHD[4,7]. For example, a prolonged gut microbiota-dysbiosis following HSCT has in turn been demonstrated to increase a risk of innate immune system activation and/or systemic infections, causing the development of GVHD[8]. Equally, the prompt recovery of gut microbiota may protect the host against the onset of GVHD by the keen preservation of immune homeostasis[9]. The gut flora can make the difference when it comes to allogeneic HSCT[10]. As prevention and/or treatment of the GVHD are the imperative issue for improving the efficacy of HSCT, it is significant that homeostasis of gut microbiota could possibly reduce the risk of GVHD.

REPROGRAMMING OF IMMUNE CELLS AND GVHD

GVHD is generally characterized by cytokine production, proliferation, and migration of reactive T cells of donor. Therefore, oxidative stress is frequently elevated in the tissues/organs of recipients with allogeneic HSCT, which may further contribute to the progression of the GVHD[11]. Patients with allogeneic HSCT may have various risk factors for developing GVHD such as acute kidney injury[12]. In particular, GVHD is a chief risk factor for the development of renal failure and/or acute kidney injury in HSCT recipients[13]. The other risk factors are sepsis, and nephrotoxic medications including amphotericin B and/or cyclosporine[13]. A reprogramming of immune cells might be a feature of GVHD, which is connected with the differentiation of CD4⁺ cells to the pathogenic type 1 T helper (Th1) and type 17 T helper (Th17) cells as well as the insufficiency of the immune-suppressive regulatory T cells (Tregs)[14] (Figure 1). In addition, the reprogramming of cellular metabolism is also a feature of GVHD, showing that mTOR inhibition may reduce the GVHD and increase the potency of peripheral Tregs as well as induction of Tregs from CD4 positive T cells[14,15]. The immuno-metabolic effects might be aimed at metabolic management of GVHD. In fact, it has been shown that the metabolic reprogramming might represent a promising strategy for the therapeutic target of GVHD[16,17]. Following the HSCT, donor T cells are stimulated by the antigens of mismatched recipient cells to undergo glycolytic metabolic reprogramming and form allogeneic effector T cells[18].

Metabolic cellular regulation is important for immune-regulation, and cytokine production and/or metabolic condition of HSCT recipients have been revealed as a risk of GVHD development[19]. Previous studies have suggested that differences in metabolism of immune cells are significantly associated with the pathology of GVHD[20]. T cells could undergo distinct metabolic reprogramming in response to allogeneic antigens, suggesting that the reactive T cells might depend on glycolysis to meet ATP demands[21]. It is indispensable to evaluate the metabolic reprogramming of T cells in order to appropriately respond to the allogeneic antigens after HSCT[21]. On the other hand, it has been shown that Tregs could suppress the reactive T cells responsible for the GVHD and/or allogeneic graft rejection [22]. Therefore, the immune-suppressive donor Tregs could considerably prevent GVHD and/or graft



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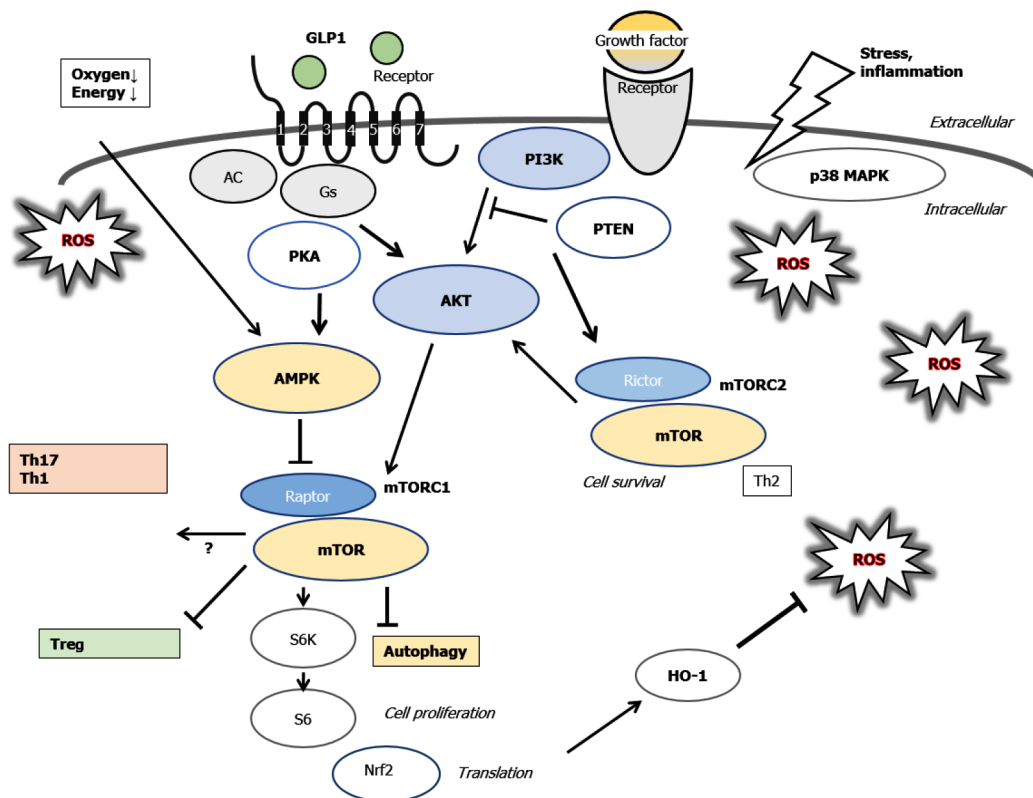
Figure 1 Hematopoietic stem cell transplantation patients likely to suffer from the graft-versus-host disease. Oxidative stress, reactive oxygen species, and/or inflammation may be all involved in the pathogenesis of graft-versus-host disease (GVHD) following the expansion of Th17 cells, which may help increase GVHD severity through the activation of pathogenic inflammatory immune cells. Arrowhead means stimulation and/or augmentation. Hammerhead represents inhibition. Note that some critical intracellular molecular pathways such as those related to mechanistic target of rapamycin (mTOR) or mTORC have been omitted for clarity. ROS: Reactive oxygen species; GVHD: Graft-versus-host disease; HSCT: Hematopoietic cell transplantation.

rejection[23]. In fact, adoptive transfer of human Tregs has demonstrated significant efficacy in preventing GVHD after allogeneic HSCT[24].

Blockade of the nutrient sensor mechanistic target of rapamycin (mTOR) using its antagonist, such as rapamycin, is an additional key aspect of metabolic reprogramming in GVHD[25]. Mechanistic target of rapamycin complex 1 (mTORC1) is sensitive to rapamycin inhibition, while mTORC2 is not[25]. Hyperactivation of mTORC1-signaling might be necessary for the pathogenesis of inflammatory bowel disease which is multi-factorial chronic intestinal inflammation driven by pathogenic T cells[26]. Tregs are tightly controlled by the activation of nutrient-fueled mTORC1[27]. Inhibition of mTORC1 may protect the bioactivity and/or homeostasis of human Tregs from apoptosis[28]. Cytokine situation towards Th17 over Treg immunity could be found through impaired autophagy by decreasing mTORC1[29]. It has been shown that the mTORC1 could drive the proinflammatory expansion of Th1, Th17, and double-negative T cells, and might inhibit the development of Tregs[30] (Figure 2).

PROMISING ROLES OF GUT-MICROBIOTA IN THE TREATMENT OF GVHD

Gut microbiota might be associated with the development of GVHD, in which loss of diversity in the microbiota could be a risk factor for the GVHD[31,32]. Gut microbiota might be perturbed due to basic HSCT condition, various infections, and/or use of antibiotics, resulting in increased inflammatory factors influencing the Treg/Th17 balance, thus promoting the development of GVHD. It is noteworthy that these inflammatory factors are associated with the Treg/Th17 balance. Therefore, gut microbiota with inflammatory diseases could affect GVHD and/or the balance of Treg/Th17[33,34]. In general, diet has an influence on the construction of gut microbiota. In particular, the activities of gut microbiota may rely on a well-adjusted production of short-chain fatty acids (SCFAs) such as acetate, propionate and/or butyrate, which are mainly the products of gut fermentation of non-digestible polysaccharides such as cellulose and/or resistant starch in vegetables[35]. SCFAs have been recognized as mediators of immune responses, including pathways of cytokine production, which is important to minimize the risk of GVHD[36]. It has been shown that SCFAs are effective antimicrobial and/or anti-inflammatory compounds supporting the epithelial barrier for metabolic homeostasis in the host[37]. Therefore, some microbial metabolites including the SCFAs might protect against the GVHD by adjusting immune-reactions[38]. Remarkably, increased production of microbiota-derived SCFAs could improve the Treg/Th17 balance[39]. In addition, elevated production of SCFAs may lead to the enhanced Treg generation and the suppressed Th17 development[40]. Moreover, SCFAs may up-regulate the production of anti-inflammatory cytokines resulting in the induction of Tregs[41]. Therefore, loss of beneficial gut commensals that can produce SCFAs might affect the severity of GVHD. Clinical-scale production of human Tregs might be complex and difficult in another way. It has been shown that certain microbiota strains with the high production of butyrate could decrease GVHD[36,42]. Interestingly, the butyrate, isovaleric acid, and/or branched-chain fatty acids could activate mTORC1 in hepatocytes, suggesting that a diet could potentiate the mTORC1 *via* the alterations in gut microbiota



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Figure 2 Several modulator molecules linked to the mechanistic target of rapamycin (mTOR)/mTORC1 signaling pathway for the alteration of Th17, Th1, and/or Treg cells are demonstrated. Example molecules known to act on the adenosine monophosphate-activated protein kinase/mTOR and/or PI3K/AKT signaling pathway are also shown. Note that some critical events such as immune activation and/or cytokine-induction in cases of inflammation and/or oxidative stress have been omitted for clarity. Arrowhead means stimulation whereas hammerhead represents inhibition. GLP1: Glucagon-like peptide-1; PKA: Protein kinase A; AMPK: Adenosine monophosphate-activated protein kinase; mTOR: Mammalian/mechanistic target of rapamycin; PI3K: Phosphoinositide-3 kinase; PTEN: Phosphatase and tensin homologue deleted on chromosome 10.

[43]. In addition, it has been indicated that GPR41, a G protein-coupled receptor for SCFAs including butyrate, could evoke the mTORC1 phosphorylation[44]. On the contrary, the specific modification of microbial metabolites could have another effect on the condition of GVHD, suggesting that an unrecognized role of microbial metabolites has beneficial effects on GVHD[36].

Gut microbiota possess the great capability to produce D-amino acids which are applied as nutrients to keep bacterial growth and to control spore sprouting[45]. In general, various bacterial species could produce racemases that convert L-amino acids to D-amino acids[46]. Accordingly, higher D-amino acids levels have been linked to the mass of gut microbiota[47]. Interestingly, D-serine suppressed the proliferation of activated CD4 positive T cells and limited their ability to differentiate to Th1 and/or Th17 cells[48]. Consequently, D-amino acids could be effective in preventing GVHD[49]. Similarly, it is well known that disruption of gut microbiota-diversity could exacerbate GVHD[50]. Probiotics and/or prebiotics could also activate the growth of several microorganisms in the gut for health profits of the host[51]. Remarkably, a low diversity of microorganisms might diminish the favorable effect of prebiotics[52]. Therefore, elucidation of the structures, functions, and/or activities of gut microbiota in the host might contribute to the safety of various treatment in HSCT. Undoubtedly, intervention tactics including prebiotics, probiotics, and/or fecal microbiota transplantation (FMT), directing the gut microbiota could become potential new treatment options for the GVHD (Figure 3).

PROBIOTICS AS A NUTRITIONAL SUPPORT FOR BENEFICIAL GUT-IMMUNE AXIS

Gut microbiota consists of a numerous multispecies community that may establish symbiosis with the host, which are defined as constructively functional microorganisms with a health benefit on the host [53]. The gut microbiota are influenced by many factors such as diet, use of antibiotics, and/or geographic environment[54]. Changes in the microbiota are known to be affected by those dietary and/or environmental factors, which have been revealed to initiate redox signaling within the gut mucosa cells[55]. Mechanisms of redox signaling might lead to an inflammatory incident. Thus, the gut microbiota may be also arrested in a sophisticated balance at this viewpoint. Consequently, gut

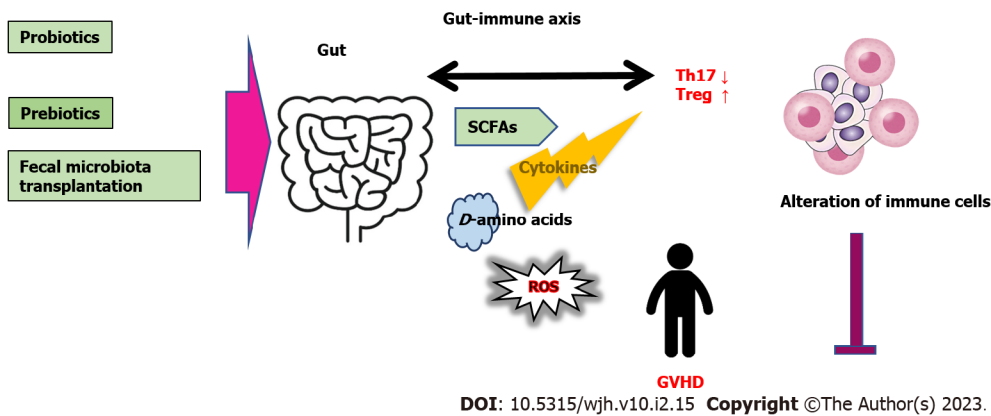


Figure 3 The gut microbiota could support to take a favorable action against the disease-progression of graft-versus-host disease by affecting the gut-immune axis, which may contain the inhibition or production of cytokines, reactive oxygen species, short-chain fatty acids, and certain D-amino acids. Probiotics, prebiotics, and fecal microbiota transplantation might be potential therapy for the alteration of gut microbiota. Arrowhead indicates stimulation whereas hammerhead shows inhibition. Note that several important activities such as cytokine-induction or anti-inflammatory reaction have been omitted for clarity. FMT: Fecal microbiota transplantation; ROS: Reactive oxygen species; GVHD: Graft-versus-host disease; SOD: Superoxide dismutase; SCFAs: Short chain fatty acids; Th17: Type 17 T helper cell; Treg: Regulatory T cell; GVHD: Graft-versus-host disease.

microbiota, reactive oxygen species (ROS), oxidative stress, inflammation, and several inflammatory diseases might be closely associated with each other. In fact, perturbations in the microbial balance may be associated with the initiation of inflammatory bowel diseases[56]. The ROS are defined as oxygen hugging energetic molecules capable of reacting with various organic molecules in a cell, which are also derived from inflammatory reactions[57]. Generally, living cells reluctantly release ROS for essential ATP synthesis, which may cause DNA damage in cells[58,59]. Some important physiological roles of ROS include the regulation of enzymes involved in autophagy, DNA synthesis, and/or DNA repair [60]. Certain degrees of ROS could change the signaling pathways to control mRNA and/or protein expression, which governs the cell destiny either survival or death[58,61]. Therefore, gut microbiota might also govern the cell destiny in some cases[62]. Understanding redox regulation of physiological processes seems to be important for developing therapeutic approach with gut microbiota. In addition, patients who undergo HSCT are often suffering from nutritional deficiencies with weight loss possibly due to treatment side effects[63]. Accordingly, nutritional support after the HSCT for the beneficial gut microbiota has become a strategic aspect to be considered.

Probiotics, a procedure for the manipulation of gut microbiota, are active microorganisms that have been deliberated to nutritionally contribute to the host health with adequate amounts of administration. Most probiotics are firstly isolated from healthy human individuals and estimated to be safe. It has been revealed that probiotics could reduce inflammation and/or oxidative stress[64]. For example, probiotics with certain bacteria such as *Akkermansia* and *Lactobacillus* could alleviate systemic metabolism in inflammatory diseases[65]. Therefore, probiotics with administration of *Lactobacillus plantarum* is reasonable to minimize the risk of developing a GVHD in patients undergoing HSCT[66]. Probiotics could inspire the gut immune system. For example, the immune-stimulatory effects of several *Lactobacillus* species have been discovered. In addition, *Lactobacillus gasseri* and *Lactobacillus johnsonii* could alter the enteric cytokine production by activating dendritic cells[67]. Probiotics could be utilized in treating various diseases. Gut microbiota could induce the maturation of dendritic cells and/or the differentiation of naive T cells into several lymphocyte subsets including Th17 and/or Treg cells[68]. Th17 cells are particularly affected by the abundance of specific commensal bacteria[69]. In the homeostasis of gut microbiota, non-pathogenic bacteria may play a significant role in the stability of adaptive immunity by the regulation of Treg cells[70]. Diet-induced shifts in microbiota composition might have insightful effects on the host immunity especially on T cells[71]. Curiously, high salt intake with diet could drive autoimmunity by inducing Th17 cells[72]. As mentioned above, production of D-amino acids might be correlated with a relative profusion of bacterial species with specific racemases in the gut microbiota [73]. Higher levels of D-amino acids with the higher mass of gut microbiota may suggest that increased abundance of such bacteria is associated with a stressed gut environment for the recovery[47,74]. In addition, different bacterial species may produce distinct profiles of D-amino acids[75]. Successful alteration in the composition of gut microbiota might be considered as an innovative therapeutic tactics [76]. D-amino acids and ROS-biosynthesis in the gut could be relevant to the improvement and pathogenesis of the GVHD, respectively[77].

There might be intricate innate or adaptive immune mechanisms in the mucosa of gastrointestinal tract. Both innate and adaptive immune mechanisms are integrated with the active phase of gut pathologies[78]. In addition, the immune system might link the gut microbiota even to the progress of neuropsychiatric disorders such as depressive behaviors[79]. Specific gut microbiota metabolites could

alter the Treg/Th17 ratio[80]. In addition, the imbalance of the Treg/Th17 ratio has been implicated in the development of chronic stresses[81]. There might be a probable crosstalk between adaptive immune system and the gut microbiota raising a gut-immune axis (Figure 3).

FUTURE PERSPECTIVES

FMT is known for its outstanding efficacy in recurrent *Clostridioides difficile* infection with more than 90% rate of cure[82], which may aim to restore gut homeostasis by transferring gut bacteria and microbes from healthy individuals' stool[83]. FMT in patients with GVHD has also been associated with favorable clinical outcomes[84]. The treatment seems to be generally safe, but serious adverse events such as pneumonia and/or sudden death have been reported[85]. At present, the long-term safety remains unclear[86,87]. As a matter of fact, the detailed effect of modifications in gut microbiota on the disease processes of GVHD in HSCT has not been well understood. However, it has been revealed that protecting the intestinal microenvironment could be a novel strategy to manage GVHD[88]. Even if it remains unclear whether the effect of modifications of microbiota are indirect to the severity of GVHD or not, they may be advantageous for the prevention and/or treatment of GVHD in HSCT recipients. Immunologically, it has been shown that a disturbed association between intestine-epithelial cells and the gut microbiota could cause pathogenic responses to the host[89]. For example, a high-calorie diet can potentially rearrange the gut microbiota, which could disturb the balance of Th17/Treg cells, interrupt the immunological homeostasis, then exacerbate an inflammatory damages[90]. Several human studies have revealed that loss of diversity of gut microbiota following the allogeneic HSCT may be linked to the considerable gut injury[91]. In addition, prolonged antibiotic use may also decrease the diversity, which might increase the risk of GVHD[92]. These findings may indicate potential changeable targets to decrease the risk of GVHD and/or to increase the safety survival rate after allogeneic HSCT. The allogeneic HSCT is a solid potential therapeutic option for patients with a diversity of malignancies. Therefore, further in-depth studies will be mandatory to define the immune responses controlled by gut microbiota involved in the development of inflammatory severe responses after allogeneic HSCT. A deeper investigation into internal molecular mechanisms and/or immune-neurological pathways should be carried out in the future.

CONCLUSION

Probiotics and/or fecal microbiota transplantation might have a potential efficacy for the treatment of GVHD after hematopoietic stem cell transplantation.

FOOTNOTES

Author contributions: Yoshikawa S and Matsuda S contributed conception of the study; Yoshikawa S, Taniguchi K, Sawamura H, Ikeda Y, Tsuji A, and Matsuda S wrote sections of the manuscript; all authors contributed to manuscript revision, and have read and given final approval of the version to be submitted.

Conflict-of-interest statement: All the authors declare that they have no competing financial interest.

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S-Editor: Liu JH

L-Editor: Ma JY - MedE

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World Journal of *Hematology*

World J Hematol 2023 March 24; 10(3): 25-41



REVIEW

- 25 Role of hematological parameters in pathogenesis of diabetes mellitus: A review of the literature
Rafaqat S, Rafaqat S

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INDEXING/ABSTRACTING

The WJH is now abstracted and indexed in Reference Citation Analysis, China National Knowledge Infrastructure, China Science and Technology Journal Database, and Superstar Journals Database.

RESPONSIBLE EDITORS FOR THIS ISSUE

Production Editor: *Yu-Xi Chen*; Production Department Director: *Xu Guo*; Editorial Office Director: *Yan-Xia Xing*.

NAME OF JOURNAL

World Journal of Hematology

ISSN

ISSN 2218-6204 (online)

LAUNCH DATE

June 2, 2012

FREQUENCY

Continuous Publication

EDITORS-IN-CHIEF

Pier Paolo Piccaluga

EDITORIAL BOARD MEMBERS

<https://www.wjgnet.com/2218-6204/editorialboard.htm>

PUBLICATION DATE

March 24, 2023

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ARTICLE PROCESSING CHARGE

<https://www.wjgnet.com/bpg/gerinfo/242>

STEPS FOR SUBMITTING MANUSCRIPTS

<https://www.wjgnet.com/bpg/gerinfo/239>

ONLINE SUBMISSION

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Role of hematological parameters in pathogenesis of diabetes mellitus: A review of the literature

Sana Rafaqat, Saira Rafaqat

Specialty type: Biochemical research methods

Provenance and peer review: Unsolicited article; Externally peer reviewed.

Peer-review model: Single blind

Peer-review report's scientific quality classification

Grade A (Excellent): 0
Grade B (Very good): B
Grade C (Good): C
Grade D (Fair): 0
Grade E (Poor): 0

P-Reviewer: Emran TB, Bangladesh; Zheng L, China

Received: December 7, 2022

Peer-review started: December 7, 2022

First decision: December 20, 2022

Revised: January 3, 2023

Accepted: March 9, 2023

Article in press: March 9, 2023

Published online: March 24, 2023



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Abstract

Diabetes mellitus (DM) is characterized by hyperglycemia and abnormalities in insulin secretion and activity. There are numerous hematological parameters; however, this review article only focuses on red blood cells, hemoglobin, hematocrit, red blood cell indices, platelet count, white blood cells, lymphocytes, neutrophils, monocytes, eosinophils, neutrophil-to-lymphocyte ratio, platelet-to-lymphocyte ratio, and monocyte-to-lymphocyte ratio, which play an essential role in the pathogenesis of DM. Also, this review article aims to report the relationship between these hematological parameters and the development of DM. In conclusion, this article shows that increased levels of platelets, red blood cells, hematocrit, lymphocytes, eosinophils, neutrophils, neutrophil-to-lymphocyte ratio, platelet-to-lymphocyte ratio, and monocyte-to-lymphocyte ratio and decreased levels of hemoglobin are involved in the pathogenesis of DM. However, the role of basophils in DM is unknown yet.

Key Words: Hematological parameters; Diabetes mellitus; Pathogenesis; Type 2 diabetes mellitus

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Core Tip: This review paper aims to determine the association between hematological parameters and diabetes with recent major advances, discoveries, significant gaps in the literature, current debates, and potential directions for future research. There are numerous hematological parameters, but this review article only focuses on red blood cells, hemoglobin, hematocrit, red blood cells indices such as mean cellular/corpuscular volume, mean cellular/corpuscular hemoglobin, mean cellular/corpuscular hemoglobin concentration, and red cell distribution width, platelet count, white blood cells, lymphocytes, neutrophils, monocytes, eosinophils, neutrophil-to-lymphocyte ratio, platelet-to-lymphocyte ratio, and monocyte-to-lymphocyte ratio, which play a pathophysiological role in different types of diabetes mellitus.

Citation: Rafaqat S, Rafaqat S. Role of hematological parameters in pathogenesis of diabetes mellitus: A review of the literature. *World J Hematol* 2023; 10(3): 25-41

URL: <https://www.wjgnet.com/2218-6204/full/v10/i3/25.htm>

DOI: <https://dx.doi.org/10.5315/wjh.v10.i3.25>

INTRODUCTION

Diabetes mellitus (DM) is a series of metabolic diseases that is characterized by hyperglycemia and abnormalities in insulin secretion and activity. Diabetes has been classified into several forms such as type 1 DM (T1DM), type 2 DM (T2DM), gestational diabetes, and other diabetes subtypes are maturity-onset of diabetes in young people and latent autoimmune diabetes in adults. The risk factors for diabetes include heredity, obesity, physical inactivity, poor diet, stress, urbanization, impaired glucose tolerance, and hypertension. Patients with diabetes who have chronic hyperglycemia have a higher risk of long-term damage to and dysfunction of many organs, especially the eyes (retinopathy), kidneys (nephropathy), nerves (neuropathy), heart (cardiovascular pathology), and blood vessels (vasculopathy), which ultimately lead to a variety of diabetic complications[1]. These complicated problems of diabetes affect patients' quality of life while also raising the risk of morbidity and mortality[2]. The global prevalence of diabetes in individuals over 18 years of age has climbed from 4.7% in 1980 to 9.3% (463 million) in 2019, and it is predicted to rise to 10.2% (578 million) by 2030 and 10.9% (700 million) by 2045, according to an epidemiological survey, which found that DM is widespread around the world[2, 3]. Diabetes continues to be a metabolic disease that endures throughout life and is challenging to cure, despite advancements in medical technology and substantial research into the condition. As a result, the focus of diabetes diagnosis and treatment has shifted to minimizing the occurrence of complications, regulating the development of complications, and enhancing the quality of life[4]. In clinical practice, reference ranges for hematological and immunological parameters are frequently used to evaluate health and disease conditions. The reference ranges may also serve as crucial biomarkers for evaluating the course of a disease or a treatment's effectiveness. Depending on factors including age, gender, race, environment, and genetic background, these parameters may change[5]. The purpose of this review paper is to determine the association between hematological parameters and diabetes with regard to recent major advances and discoveries, significant gaps in the literature, current debates, and potential directions for future research. There are numerous hematological parameters, but this review article only focuses on red blood cells, hemoglobin, hematocrit, red blood cell indices, platelet count, white blood cells, lymphocytes, neutrophils, monocytes, eosinophils, neutrophil-to-lymphocyte ratio, platelet-to-lymphocyte ratio, and monocyte-to-lymphocyte ratio, which play a pathophysiological role in DM, as explained in Figure 1. Several databases, including Google Scholar, PubMed, and Science Direct, were searched to identify the relevant literature. The investigation was completed on November 15, 2022. A few specific terms were used to search the published literature: Pathophysiology, diabetes, and hematological parameters. Comparable articles were discovered by searching through the references of the relevant articles. Clinical investigations were conducted in English. Although favoring more recent studies, we did not impose a time restriction.

ROLE OF HEMATOLOGICAL PARAMETERS IN DIABETES MELLITUS

The following hematological parameters are considered in this paper: Red blood cells, hemoglobin, hematocrit, red blood cell indices, platelet count, white blood cells, lymphocytes, neutrophils, monocytes, eosinophils, neutrophil-to-lymphocyte ratio, platelet-to-lymphocyte ratio, and monocyte-to-lymphocyte ratio (Table 1).

Table 1 Summary of role of hematological parameters in diabetes mellitus

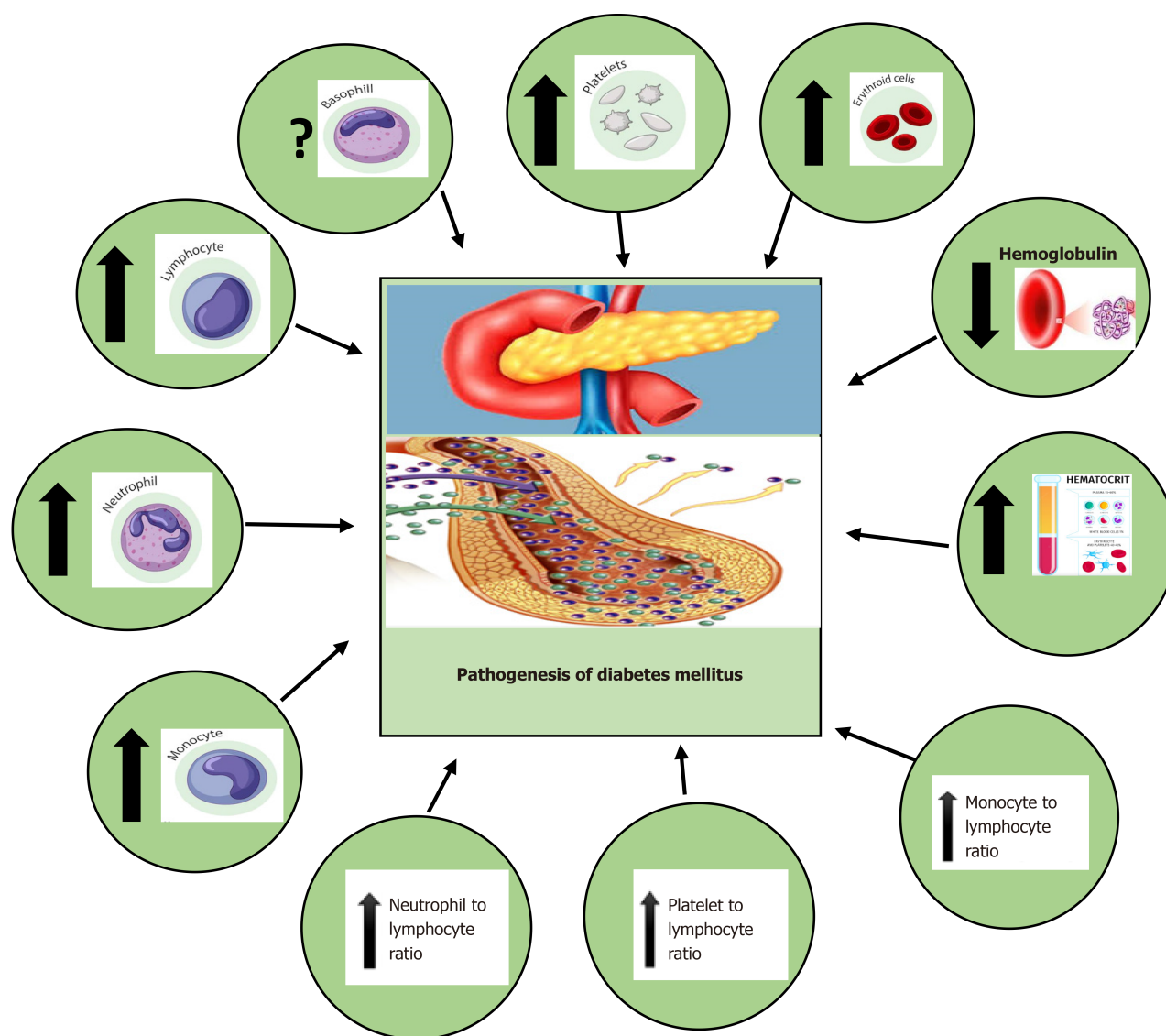
Ref.	Hematological parameter	Main finding of hematological parameters in diabetes
Alamri <i>et al</i> [8], 2019	RBC count	Hyperglycemia had a significant impact on RBC count and physiological function, which could be efficiently restored with adequate glycemic control
Rashed <i>et al</i> [9], 2020	RBC count	RBC characteristic was an appropriate tool for assessing diabetes patients
Vilahur <i>et al</i> [10], 2018	RBC count	RBCs in T2DM patients need to be monitored
Wang <i>et al</i> [11], 2021	RBC count	Erythrocyte-related indicators could offer more clinical data and could be used to track the development of diabetes and associated complications
Sonmez <i>et al</i> [14], 2010	Hemoglobin	Hemoglobin may restrict the endothelium-mediated vaso-regulation in diabetes
Lee <i>et al</i> [15], 2018	Hemoglobin	High hemoglobin levels were strongly associated with a lower risk of developing diabetic retinopathy
Rossing <i>et al</i> [16], 2004	Hemoglobin	Diabetes increases a person's vulnerability to low hemoglobin levels through diabetic nephropathy and diabetic retinopathy
Ranil <i>et al</i> [17], 2010	Hemoglobin	Diabetes increases a person's vulnerability to low hemoglobin levels through diabetic nephropathy and diabetic retinopathy
Yang <i>et al</i> [18], 2017	Hemoglobin	Lower hemoglobin levels were linked to higher vibratory sensory thresholds and an increase in the prevalence of diabetic peripheral neuropathy
Kwon <i>et al</i> [19], 2012	Hemoglobin	Correlation between low hemoglobin concentration and diabetes profiles
Chen <i>et al</i> [20], 2018	Hemoglobin	Glucose effectiveness, first- and second-phase insulin secretion, and insulin resistance were linked to hemoglobin
Tamariz <i>et al</i> [22], 2008	Hematocrit	Increased blood viscosity and hematocrit as new risk factors for insulin resistance and T2DM
Capoglu <i>et al</i> [23], 2002	Hematocrit	Impaired glucose tolerance and T2DM may both be independent risk factors for high hematocrit levels
Dillon <i>et al</i> [24], 1965	Hematocrit	Individuals with chronic diseases and anemia need to be understood in the context of declining hematocrit
Feng <i>et al</i> [25], 2020	Hematocrit	The hematocrit index had a strong correlation with insulin resistance and inflammation under impaired fasting blood glucose
Natali <i>et al</i> [26], 2005	Hematocrit	Direct adverse influence on nitric oxide availability might also contribute to the association between high hematocrit and cardiovascular disease in addition to blood rheology
Teodorczyk <i>et al</i> [29], 2012	Hematocrit	The blood glucose monitoring system offered precise blood glucose values that were insensitive to hematocrit values between 20% and 60%
Tripathy <i>et al</i> [27], 2022	Hematocrit	HbA1c and hematocrit markers during the first trimester of pregnancy were found to be a more sensitive and specific early screening method for gestational diabetes mellitus
Wu <i>et al</i> [28], 2018	Hematocrit	HbA1c and hematocrit combined for gestational diabetes mellitus screening might be a valuable method to predict gestational diabetes mellitus
Aberle <i>et al</i> [30], 2020	Hematocrit	SGLT2 inhibition with dapagliflozin causes a continued increase in hematocrit concentration
Evan <i>et al</i> [31], 1983	MCV	Elevated MCV and its underlying relationship with clearly elevated plasma osmolarity in patients with diabetic ketoacidosis
Davidson <i>et al</i> [34], 1981	MCV	No correlation exists between the MCV level and the type of diabetes, treatment, or management
Muntoni <i>et al</i> [32], 1986	MCV	The connection between fasting plasma glucose and MCV
Kwenda <i>et al</i> [33], 2019	MCV	MCV was a suitable marker for the diagnosis of diabetic nephropathy in patients with T2DM
Xiong <i>et al</i> [35], 2017	RDW	Higher risk and a less favorable prognosis for diabetic nephropathy were indicated by high levels of RDW in T2DM patients
Renuka <i>et al</i> [40], 2020	MCV, MCH, MCHC, RDW	HbA1c showed a negative connection with MCV, MCH, and MCHC, and a favorable link with RDW
Alamri <i>et al</i> [8], 2019	MCV, MCH, MCHC, RDW	Higher blood sugar levels elevated the number of red blood cells, MCV, MCH, and MCHC. Poor glycemic management had a negative correlation with red blood cell distribution width
Kannan <i>et al</i> [41], 2019	MCV, MCH, MCHC, RDW	Red-cell turnover indices had a major impact on an HbA1c below 7%, and clinicians must conduct additional testing utilizing plasma glucose levels to determine whether a patient had diabetes or pre-diabetes
Jaman <i>et al</i> [39], 2018	MCHC, RDW	RDW and MCHC can be used as supplemental indications of declining glucose control in

		patients with T2DM
Arkew <i>et al</i> [44], 2022	MCV, MCH, MCHC, RDW	A significant inverse relationship between RBC parameters and glycemic control was found in T2DM
Nada <i>et al</i> [45], 2015	RDW	RDW measurements in diabetic hypertensive individuals following indapamide antihypertensive medication or thiazide and angiotensin receptor blocker therapy were equivalent
Wang <i>et al</i> [36], 2020	RDW	High RDW was linked to a high likelihood of developing diabetes in Chinese individuals
Zhao <i>et al</i> [42], 2022	RDW	The ratio of RDW to albumin was a risk factor for diabetic retinopathy patients
Yin <i>et al</i> [37], 2018	RDW	A lower likelihood of having poor glycemic control was observed in T2DM individuals whose RDW was larger
Bhutto <i>et al</i> [38], 2019	RDW	RDW, a cheap and easily accessible test that could be employed as a measure of glycemic level, had a strong connection with HbA1c
Atalay <i>et al</i> [43], 2018	RDW	RDW and RDW/MCV ratio were discovered to help predict diabetic ketoacidosis and to be linked with diabetic ketoacidosis
Akinsegun <i>et al</i> [46], 2014	Platelet count	Mean platelet volume was lower in cases than in controls while the mean platelet count was higher for diabetes therapy-receiving patients compared to non-diabetic controls
Rodriguez <i>et al</i> [47], 2020	Platelet count	MPV is strongly and consistently associated with diabetes
Sterner <i>et al</i> [48], 1998	Platelet count	Elevated platelet levels were linked to both female gender and early indications of diabetic nephropathy
Jindal <i>et al</i> [49], 2011	Platelet count	Platelet indices in diabetic and non-diabetic patients were significantly different
Lee <i>et al</i> [50], 2017	Platelet count	High blood glucose levels cause neutrophils to release S100 calcium-binding protein A8/ A9, which then binds to the Kupffer cells' receptor for advanced glycation end products and increases the liver's synthesis of thrombopoietin
Kheradmand <i>et al</i> [51], 2021	WBC count	Substantial relationship between diabetes and WBC count
Twig <i>et al</i> [52], 2013	WBC count	WBC count among young healthy persons was a separate risk factor for diabetes occurrence
Vojarova <i>et al</i> [53], 2002	WBC count	High WBC indicated a deterioration of insulin action and the onset of type 2 diabetes in Pima Indians
Kuo <i>et al</i> [54], 2020	WBC count	Elevated WBC count was substantially linked with all four diabetes factors (glucose effectiveness, insulin resistance, and first- and second-phase insulin secretion) in Chinese young men
Veronelli <i>et al</i> [55], 2004	WBC count	Significance of weight loss in lowering WBC counts in patients with morbid obesity, impaired glucose tolerance, or T2DM
Park <i>et al</i> [56], 2021	WBC count	WBC count might help to identify non-obese people who were likely to develop T2DM
Andreone <i>et al</i> [57], 2018	Lymphocytes	The function of T-effector lymphocytes in adipose and hepatic tissues throughout diabetes mutually increases pancreatic-cell stress and exacerbates the condition
Giese <i>et al</i> [59], 2021	Lymphocytes	Significant increases in mitochondrial oxygen consumption rate (OCR) and increased basal glycolytic activity, indicate an altered metabolic immune cell profile in peripheral blood mononuclear cells from diabetic INSC94Y transgenic pigs
Wu <i>et al</i> [58], 2020	Lymphocytes	The diabetic group with COVID-19 had a lower lymphocyte count
Otton <i>et al</i> [60], 2002	Lymphocytes	The metabolism of lymphocytes taken from mesenteric lymph nodes of alloxan-induced diabetic rats changed since glucose and glutamine were crucial for lymphocyte function
Huang <i>et al</i> [65], 2016	Neutrophils	Antineutrophil therapy can inhibit or slow the progression of autoimmune diabetes and insulinitis
Insuela <i>et al</i> [61], 2019	Neutrophils	Molecular pathways behind the degradation of neutrophil activities in diabetes and their connection to a high vulnerability to bacterial infections
Dowey <i>et al</i> [64], 2021	Neutrophils	Neutrophil targeting as a therapeutic approach reduces inflammation and boosts host immunity in diabetes patients to enhance infection clearance
Yu <i>et al</i> [62], 2020	Neutrophils	Neutrophil-mediated inflammation played a role in the development of diabetic kidney disease
Woo <i>et al</i> [63], 2011	Neutrophils	Neutrophil-mediated inflammation may be a key player in the etiology of DR
Valtierra <i>et al</i> [66], 2020	Monocytes	Effects of monocyte and macrophages on glycemic/metabolic control factors, non-obese participants, or T2DM
Min <i>et al</i> [67], 2012	Monocytes	Monocytes as a marker were affected by diabetes
Mokgalabon <i>et al</i> [68], 2020	Monocytes	Patients with T2DM had higher levels of monocyte activation
Kitahara <i>et al</i> [69], 1980	Monocytes	Increasing blood sugar levels in diabetic patients were linked to the metabolic activation of

		monocytes
Wan <i>et al</i> [70], 2020	Monocytes	Decreased peripheral blood monocyte levels in diabetes patients were linked to higher risks of diabetic retinopathy
Giulietti <i>et al</i> [71], 2007	Monocytes	Monocyte mediated inflammation was able to be controlled by 1,25-dihydroxyvitamin D in T2DM patients
Neuwirth <i>et al</i> [72], 2012	Eosinophils	Eosinophils may be a component of a complex innate immune cells network that is involved in the onset of diabetes
Ngamal <i>et al</i> [73], 2021	Eosinophils	Higher serum HbA1c levels were associated with a higher risk of developing complications from diabetes
Zhu <i>et al</i> [74], 2013	Eosinophils	Increased percentage of peripheral eosinophils was linked to a lower incidence of T2DM
Fukui <i>et al</i> [75], 2009	Eosinophils	Microalbuminuria (degree of albumin excretion rate) in men with T2DM may be related to allergic diseases
Babazadeh <i>et al</i> [76], 2021	Eosinophils	Relationship between eosinophil counts and HbA1c in patients with diabetes and coronary artery disease
Hussain <i>et al</i> [77], 2017	NLR	NLR can be employed as a disease monitoring technique when diabetes patients were being followed up
Rahar <i>et al</i> [78], 2021	NLR	NLR is a novel, basic, and relatively inexpensive marker that was useful for assessing systemic inflammation in diabetes and had a correlation with the severity of T2DM
Mertoglu <i>et al</i> [79], 2017	NLR	Patients with prediabetes and diabetes exhibited a marked increase in the inflammation marker NLR
Wang <i>et al</i> [81], 2020	NLR	As indicators of the systemic inflammatory response in patients without a linked family history, NLR and PLR were related to the presence of diabetic retinopathy
Li <i>et al</i> [82], 2020	NLR	Greater NLR values were a valid biomarker for the development of diabetic retinopathy
Jaaban <i>et al</i> [83], 2021	NLR	Elevated NLR and PLR were substantially related with diabetic nephropathy
Rahar <i>et al</i> [78], 2021	NLR	NLR was useful for assessing systemic inflammation in diabetes and correlated with the severity of diabetic nephropathy
Sefil <i>et al</i> [80], 2014	NLR	Elevated HbA1c combined with increased NLR observed in T2DM patients suggested that regulation of HbA1c and NLR might be significantly related
He <i>et al</i> [85], 2022	NLR	The presence of T2DM with higher NLR was linked to worse clinical outcomes
Umarani <i>et al</i> [87], 2020	NLR	NLR as an early and predictive marker for microvascular problems in individuals with diabetes mellitus
Wan <i>et al</i> [86], 2020	NLR	Greater NLR level was linked to a higher prevalence of cardiovascular disease and diabetic kidney disease in diabetic adults
Wang <i>et al</i> [88], 2020	NLR	Increased likelihood of clinically significant depression symptoms is independently linked to elevated levels of NLR in diabetics
Liu <i>et al</i> [89], 2020	NLR	NLR was an easier, quicker, and more effective diagnostic for prognosis prediction in T2DM patients with COVID-19
Du <i>et al</i> [90], 2021	PLR	PLR may facilitate the early detection of high-risk patients and offer recommendations for additional measures to prevent cognitive deterioration in T2DM patients
Atak <i>et al</i> [91], 2019	PLR	PLR may help predict the onset and control levels of T2DM
Elsayed <i>et al</i> [92], 2021	PLR	Greater NLR and PLR were linked to diabetes problems
Zeng <i>et al</i> [93], 2022	PLR	PLR might be an independent risk factor for assessing DR in people with T2DM
Jaaban <i>et al</i> [83], 2021	PLR	Increased NLR and PLR could be used as risk indicators for diabetic nephropathy prediction and prognosis
Zhang <i>et al</i> [94], 2021	PLR	PLR may serve as a useful marker for the early detection and evaluation of the severity of diabetic foot ulcer
Alfhili <i>et al</i> [95], 2022	MLR	Elevated MLRs were more likely to occur and associated with impaired fasting glycemia and hyperglycemia
Yue <i>et al</i> [96], 2015	MLR	MLR may be clinically and pathophysiological significant in DR; however, its prediction power was only moderate
Wang <i>et al</i> [97], 2022	MLR	MLR was significantly related to proliferative diabetic retinopathy in patients with T2DM
Wang <i>et al</i> [88], 2020	MLR	Elevated MLR and NLR may be poor predictors of clinical outcomes in patients with gestational diabetes mellitus

Kocak <i>et al</i> [98], 2020	MLR	MLR could act as a predictive and efficient marker for diabetic kidney injury in diabetic people
Alsayyad <i>et al</i> [99], 2019	MLR	In the early and intermediate phases of diabetic nephropathy, MLR may be used as a candidate for an inflammatory marker
Huang <i>et al</i> [100], 2020	MLR	MLR is a potent independent predictor of diabetic nephropathy

RBC: Red blood cell; T2DM: Type 2 diabetes mellitus; RDW: Red blood cell distribution width; MCV: Mean cellular/corpuscular volume; MCH: Mean cellular/corpuscular hemoglobin; MCHC: Mean corpuscular hemoglobin concentration; WBC: White blood cell; NLR: Neutrophil-to-lymphocyte ratio; PLR: Platelet-to-lymphocyte ratio; MLR: Monocyte-to-lymphocyte ratio.



DOI: 10.5315/wjh.v10.i3.25 Copyright ©The Author(s) 2023.

Figure 1 Overview of hematological parameters involved in the pathogenesis of diabetes mellitus. The upward arrows indicate the increased levels of platelets, red blood cells, hematocrit, lymphocytes, eosinophils, neutrophils, neutrophil-to-lymphocyte ratio, platelet-to-lymphocyte ratio, and monocyte-to-lymphocyte ratio. The downward arrow indicates the decreased levels of hemoglobin. The (?) sign shows the unknown role of basophils in diabetes mellitus yet.

Red blood cells

Red blood cells, also known as erythrocytes, are the cells that consume the most glucose. The morphology, metabolism, and function of erythrocytes are invariably subject to several alterations when there is persistent hyperglycemia, which further influences hemorheology and microcirculation[6,7]. As they mature, erythrocytes shed all of their organelles, making them fairly unusual cells. They decrease the amount of energy consumed for the major functions that they must carry out and only conserve a small number of metabolic pathways for getting energy. Because of this, erythrocytes are extremely sensitive to any disease. In diabetic patients, glucose metabolism disorders have a significant impact on the morphological structure and physiological processes of erythrocytes. These disorders also cause

inadequate microcirculation perfusion, hypoxia, and oxidative stress which promote the development of diabetic complications and lower the quality of life for diabetic patients. Because erythrocytes play a significant role in the pathological development of diabetic complications, the relevant erythrocyte markers also correlate with the onset and advancement of these conditions. All body tissues are affected by hyperglycemia, and the bone marrow is one of them. This result is connected to red blood cell physiology, chemical changes, and protein glycation. Alamri *et al*[8] evaluated the changes in both the pathology and regular physiology associated with chronic diabetes complications, as well as the impact of hyperglycemia on various RBC parameters. It was found that hyperglycemia had a significant impact on red blood cell count and physiological function, which could be efficiently restored with adequate glycemic control. Furthermore, Rashed *et al*[9] described that diabetic patients had significantly increased mean red blood cell count, hemoglobin concentration, and hematocrit values. Red blood cell lifespan was shortened by the low level of HbA1c, which was influenced by red blood cell characteristics and decreased in patients with hyperglycemia. As a result, red blood cell characteristics are an appropriate tool for assessing diabetes patients. Moreover, endothelial dysfunction is a novel risk factor for type 2 DM (T2DM), but it is unknown how much erythrocytes affect the availability of nitric oxide. In the same context, Vilahur *et al*[10] suggested that red blood cells in T2DM patients need to be monitored. Although there have been many advances in the study of diabetes, the prevention and management of its consequences continue to be significant public health issues. Wang *et al*[11] concluded that erythrocyte-related indicators could offer more clinical data and could be used to track the development of diabetes and associated complications as red blood cells could sense blood glucose changes early and continually.

Hemoglobin

Hemoglobin is a metalloprotein that carries oxygen and is primarily found in red blood cells. Hemoglobin level is expressed as the amount of hemoglobin in grams per deciliter of whole blood. The levels of hemoglobin should be between 14 to 18 g/dL in adult men, and between 12 and 16 g/dL in adult women[12]. In addition to its role as an oxygen carrier, hemoglobin serves as an antioxidant and an iron metabolism regulator in tissues[13]. The dysfunction of hemoglobin leads to a pathological condition. Anemia symptoms are caused by a decrease in hemoglobin, whether or not there is an absolute reduction in red blood cells. Whereas, in the case of hemolysis, the hemoglobin metabolite bilirubin contributes to related jaundice, and circulating hemoglobin might result in renal failure. Nitric oxide is primarily transported by and buffered by hemoglobin. The inverse relationship between hemoglobin levels and endothelial function in human diseases has been determined. Because anemia in these patients begins earlier than in other renal diseases, it is crucial to determine whether this link also exists in diabetic patients with stage 1 to 2 chronic kidney disease. Sonmez *et al* described that endothelial function was inversely correlated with hemoglobin levels, and proteinuria was an effect modifier of this correlation in diabetic patients with stage 1 to 2 chronic kidney disease. The main finding was that proteinuria revealed a circumstance in which hemoglobin may restrict the endothelium-mediated vaso-regulation in diabetes[14].

Patients with T2DM are at an increased risk of developing diabetic retinopathy due to anemia. Diabetes-related retinopathy may also be correlated with hemoglobin levels. According to Lee *et al*[15], high hemoglobin levels were strongly associated with a lower risk of developing diabetic retinopathy in Korean patients with T2DM. In contrast, both Rossing *et al* and Ranil *et al* demonstrated that low hemoglobin concentration in patients with DM was linked to a decrease in glomerular filtration rate. Diabetes increases a person's vulnerability to low hemoglobin levels through diabetic nephropathy and diabetic retinopathy[16,17]. In the same way, Yang *et al*[18] found that lower hemoglobin levels were linked to higher vibratory sensory thresholds and an increase in the prevalence of diabetic peripheral neuropathy. In contrast, Kwon *et al*[19] explained that there were no clear mechanisms that showed the correlation between low hemoglobin concentration and diabetes profiles. As a result, doctors need to be aware of how anemia may affect people with diabetes. Increased insulin resistance and reduced insulin output are characteristics of diabetes. The functions of glucose effectiveness and first and second phase insulin secretion have been ignored. These elements are referred to as diabetic factors. It has been demonstrated that hemoglobin is associated with insulin resistance and first-phase insulin secretion but not with second-phase insulin secretion and glucose effectiveness. Chen *et al*[20] examined the relationship between hemoglobin and functions of glucose effectiveness and first and second-phase insulin secretion, determined which one had the closest correlation to hemoglobin, and demonstrated how practically all diabetic factors for diabetes were linked to hemoglobin. The relationship between insulin resistance and hemoglobin was the closely associated in Chinese patients with diabetes.

Hematocrit

Hematocrit is the ratio that is calculated by the volume of red blood cells and plasma. The normal ranges of hematocrit for men are 40% to 54%, whereas for women, they are 36% to 48%. Since hematocrit is calculated using whole blood, plasma volume is necessary. Hematocrit will be higher in a patient with severe dehydration than in a patient with normovolemia. Patients will have lower hematocrit if they are fluid-overloaded[21]. Increased blood viscosity may increase the risk of insulin resistance and T2DM by reducing the amount of glucose, insulin, and oxygen that can reach metabol-

ically active tissues. A validated formula based on baseline total plasma proteins and hematocrit was used to assess the viscosity of whole blood. Tamariz *et al*[22] depicted that increased blood viscosity and hematocrit should have been considered as a new risk factor for insulin resistance and T2DM. Capoglu *et al*[23] reported that impaired glucose tolerance and T2DM might be independent risk factors for high hematocrit levels. In addition, Dillon reported that less sugar was present in erythrocytes than in plasma. Changes in hematocrit would have an inverse effect on the concentration of whole blood sugar, which was midway between erythrocyte and plasma levels. The author provided information on glucose tolerance in individuals with chronic diseases and anemia that needs to be understood in the context of a declining hematocrit level that artificially raises blood sugar levels[24]. Feng *et al*[25] explained that the red blood cell count times hematocrit index had a strong correlation with whether or not the body exhibits insulin resistance and inflammation under impaired fasting blood glucose, making it a possible biomarker for determining prediabetes risk. However, Natali *et al*[26] demonstrated that hematocrit was inversely correlated with small vessel endothelium-dependent dilatation in both diabetics and non-diabetics. Thus, a direct adverse influence on nitric oxide availability might also contribute to the association between high hematocrit and cardiovascular disease in addition to blood rheology. Tripathy *et al*[27] found that the combined computation of HbA1c and hematocrit during the first trimester of pregnancy was a more sensitive and specific early screening method for gestational DM. Wu *et al*[28] revealed that HbA1c and hematocrit combined might be a valuable screening method to predict gestational DM. Teodorczyk *et al*[29] evaluated that the blood glucose monitoring technology offered precise blood glucose values that were insensitive to hematocrit values between 20% and 60%. Recent therapeutic research demonstrated that sodium-glucose cotransporter 2 inhibitors improved cardiovascular outcomes in high-risk T2DM patients. Aberle *et al*[30] found that sodium-glucose cotransporter 2 inhibition with dapagliflozin causes a continued increase in hematocrit concentration in T2DM individuals taking long-term insulin therapy.

Red blood cell indices

Red blood cells have been classified into four indices including mean cellular/corpuscular volume, mean cellular/corpuscular hemoglobin, mean cellular/corpuscular hemoglobin concentration, and red cell distribution width. The mean cellular/corpuscular volume is the volume fraction of a red blood cell, which is the mean volume of all the red blood cells in a sample, calculated by dividing hematocrit by the RBC count, expressed in the unit of femtolitres (fL). The average range of mean corpuscular volume is 80 to 94 fL. Mean cellular/corpuscular hemoglobin is the average mass of hemoglobin in a single red blood cell measured in picograms (pg), computed by dividing the number of red blood cells by the total amount of hemoglobin. The average range of mean cellular/corpuscular hemoglobin is 27 to 31 pg. The average amount of hemoglobin in one liter of red blood cells is known as the mean corpuscular hemoglobin concentration, which is the average amount of hemoglobin in each red blood cell. It is calculated by dividing hemoglobin by hematocrit. The range is 31.5 to 35 g/dL normally. Red cell distribution width is a metric that assesses variance in red blood cell volume or size. Red cell distribution width for adults has reference values of 11.6%–14.6%[13]. Mean red cell volume was discovered to be considerably higher in diabetic patients. Evan *et al*[31] provided evidence that elevated mean corpuscular volume in diabetic ketoacidosis and its underlying association with elevated plasma osmolality, represented osmotic imbalance that might lead to cerebral oedema pathogenesis during the treatment of these patients. In order to overcome this state, clinicians should have replaced fluid and insulin therapy. In addition, Muntoni *et al*[32] observed the connection between fasting plasma glucose and mean red cell volume suggesting that the increase in the mean cell volume in insulin-dependent diabetic patients might be due to an increase in the intraerythrocytic osmolality. In the same way, Kwenda *et al*[33] detected that mean corpuscular volume was a suitable marker for the diagnosis of diabetic nephropathy in patients with T2DM and demonstrated that increased mean cell volume in diabetic nephropathy due to hemodynamic changes occurred, initiated by the leakage of albumin from glomerular capillaries, excessive release of mesangial cell matrix, glomerular basement membrane thickening, and injury to podocytes. However, Davidson *et al*[34] examined that there was no correlation between the mean red cell volume and the type of diabetes, treatment, or management by measuring the levels of random blood glucose and glycosylated hemoglobin. Red cell distribution width is significantly higher in diabetic patients than in healthy subjects, and it is especially higher in uncontrolled glycemia. Red cell distribution width is commonly considered an inflammatory marker and a measure with considerable prognostic value for mortality in diseased and healthy populations. Xiong *et al*[35] found that higher risk and poor prognosis for diabetic nephropathy were indicated by high levels of red cell distribution width in T2D patients. Likewise, Wang *et al*[36] showed that high red cell distribution width was linked to a high likelihood of developing diabetes in Chinese individuals. Red cell distribution width, an accessible, noninvasive, and practical indicator, could be considered for inclusion in the risk assessment of high-risk groups for diabetes. In another study, Yin *et al*[37] explained that higher red cell distribution width in T2D patients was associated with a considerably lower likelihood of experiencing poor glycemic control. Red cell distribution width might be used for assessment of T2D patients that carry the risk of having poor glycemic control.

In diabetes patients, red cell distribution width could be employed as a measure of glycemic level, and had a strong connection with HbA1c[38]. Also, Jaman *et al*[39] demonstrated that the glycemic marker HbA1c was correlated with red cell volume, mean corpuscular volume, mean corpuscular hemoglobin concentration, and red cell distribution width. The findings of this study were that red cell distribution width and mean corpuscular hemoglobin concentration could be used as supplemental indicators of decreasing glucose regulation in T2DM patients. However, Renuka *et al*[40] indicated that HbA1c showed a negative connection with red cell volume, mean corpuscular volume, and mean corpuscular hemoglobin concentration, and a favorable link with red cell distribution width. The authors found that interpretation of HbA1c readings using hematological markers including red cell volume, mean corpuscular volume, and mean corpuscular hemoglobin concentration was important to diagnose and treat pre-diabetes and diabetes. In addition, Kannan *et al*[41] found that red cell turnover indices had a major impact on an HbA1c level below 7%, and clinicians must conduct additional testing utilizing plasma glucose levels to determine whether a patient had diabetes or pre-diabetes. When determining whether a patient had diabetes or pre-diabetes, 75 gm oral glucose tolerance test should be used instead of HbA1c in patients whose red blood cell distribution width is greater than 17.

The ratio of red blood cell distribution width to albumin is a risk factor for diabetic retinopathy. The effect of red blood cell distribution width-to-albumin ratio in diabetic retinopathy in diabetic patients should be confirmed by further studies[42]. In the same way, Atalay *et al*[43] have shown that the red cell distribution width and red cell distribution width-to-mean cell volume ratio could predict and be linked with diabetic ketoacidosis. These variables, however, did not help in the prediction of hyperosmolar non-ketotic acidosis. Arkew *et al*[44] found that red blood cell parameters of T2DM patients differed statistically significantly from those of the control group. A significant inverse relationship was found between RBC parameters including red blood cells, mean corpuscular volume, mean corpuscular hemoglobin, mean corpuscular hemoglobin concentration, and glycemic control. Therefore, red blood cell parameter evaluation was essential for improved management of patients with T2DM. However, Alamri *et al*[8] suggested that the presence of higher blood sugar levels elevated the number of red blood cells, mean corpuscular volume, mean corpuscular hemoglobin, and mean corpuscular hemoglobin concentration. Poor glycemic management had a negative correlation with red blood cell distribution width, suggesting that the longevity of red blood cells was simultaneously shortened by hyperglycemia and the development of macro- and micro-angiopathies. Nada *et al*[45] showed that red cell distribution width measurements in diabetic hypertensive individuals following indapamide antihypertensive medication or thiazide and angiotensin receptor blocker therapy were equivalent to those of the general population.

Platelet count

Platelet count and mean platelet volume are indicators of thrombotic potentials and risk factors for microvascular problems in diabetics. Akinsegun *et al*[46] found that mean platelet volume was lower in diabetes cases than in controls while the mean platelet count was higher in diabetes-receiving therapy patients compared to non-diabetic controls. Both indicators were within the normal reference range in diabetes treatment-receiving patients and healthy people. T2DM is a significant risk factor for cardiovascular disease. Given that platelets contribute to atherothrombosis, which is a primary cause of cardiac events, platelet function is important to understand diabetes management. Rodriguez *et al*[47] demonstrated that platelet function measured by the aggregation to adenosine diphosphate, collagen, or epinephrine was not consistently associated with diabetes but mean platelet volume was strongly associated, indicating that future research might be focused on how mean platelet volume segments pre-diabetes and diabetes for risk prediction. According to the findings of Sterner *et al*[48], elevated platelet levels were linked to both female gender and early indications of diabetic nephropathy provided that patients with DM had elevated platelet levels that exacerbated the diabetic nephropathy prevalence. DM is a prothrombotic condition with increased platelet reactivity. Mean platelet volume measured in DM correlated with retinopathy. Jindal *et al*[49] investigated platelet indices in diabetic *vs* non-diabetic patients and compared them to determine their usefulness as predictors of complications in patients with DM. Platelet indices such as platelet distribution width differed between diabetes and controls, also in the group of diabetic patients with and without microvascular problems. The majority of individuals with diabetes complications could be classified by discriminant analysis using platelet distribution width and mean platelet volume. DM is linked to a higher risk of cardiovascular disease. Lee *et al*[50] showed that high blood glucose levels cause neutrophils to release S100 calcium-binding protein A8/A9, which then binds to the Kupffer cells' receptor for advanced glycation end products, and increases the synthesis of thrombopoietin in the liver. Megakaryocyte proliferation and enhanced platelet production are transported by thrombopoietin. These research findings validated the significance of glycemic control and discovers potential therapeutic targets for restoring platelet numbers and function in patients with diabetes.

White blood cells

White blood cells are a useful indicator of the risk of DM. Kheradmand *et al*[51] examined the relationship between white blood cell count and T2DM, and found a significant relationship between them in a large-scale population-based Tabari cohort study. Additionally, Twig *et al*[52] observed that

white blood cell count was an independent risk factor for diabetes prevalence among young healthy persons. White blood cell count was a significant independent risk factor for diabetes in young men. In the same way, Vozarova *et al*[53] showed that high white blood cells indicated a deterioration of insulin action and the onset of T2DM in Pima Indians. It has been suggested that chronic immune system activation leads to T2DM development. In addition, diabetes factors including insulin resistance, decreased first and second-phase insulin secretion, and glucose effectiveness, are essential for the development of T2DM observed to be more common in younger persons. Kuo *et al*[54] found that the relative order of the tightness from the highest to lowest was glucose effectiveness, insulin resistance, and first and second-phase insulin secretion, and elevated white blood cell count was significantly correlated with all four diabetes factors in Chinese young men. Obesity increases the white blood cell count, which leads to an enhanced risk of atherosclerosis. Impaired glucose tolerance is characterized by a raised white blood cell count, and T2DM macroangiopathic and microangiopathic consequences are also linked to elevated white blood cell counts. Veronelli *et al*[55] highlighted the significance of weight loss in lowering white blood cell counts in patients with morbid obesity, regardless of whether the condition was simple or exacerbated by impaired glucose tolerance or T2DM. Furthermore, Park *et al* showed that a higher white blood cell count indicated a future event of T2DM risk in community-dwelling non-obese Korean people. White blood cell count might help to identify non-obese people who were likely to develop T2DM[56].

Lymphocytes

T lymphocytes play an important role in the adaptive immune system linked to the regulation of metabolism of various tissues in both healthy and disease conditions. Several studies suggested that the adaptive immune system has a significant role in the pathogenesis of diabetes, including the impact of various hormones and neurotransmitters on the maturation of central and peripheral T lymphocytes, especially in the context of the metabolic burden due to diabetes. Furthermore, the function of T-effector lymphocytes in adipose and hepatic tissues throughout diabetes mutually increases pancreatic cell stress and exacerbates the condition[57]. In a study, Wu *et al*[58] showed that the diabetic group with coronavirus disease 2019 (COVID-19) had a lower lymphocyte count, reached the minimal count more quickly, and spent more time in the hospital. The minimal lymphocyte count was adversely linked with the days spent in the hospital and the days with positive severe acute respiratory syndrome coronavirus 2 nucleic acid. Giese *et al*[59] discovered a significant increase in mitochondrial oxygen consumption rate and increased basal glycolytic activity in peripheral blood mononuclear cells from diabetic INSC94Y transgenic pigs, indicating an altered metabolic immune cell profile. This research offered additional perspectives on the molecular pathways behind dysregulation of immune cells as a result of chronic hyperglycemia. Diabetic states with poor glucose management result in increased susceptibility to infections. Otton *et al*[60] observed that the metabolism of lymphocytes taken from mesenteric lymph nodes of alloxan-induced diabetic rats changed since glucose and glutamine were crucial for lymphocyte function. In short, the alterations observed in newly acquired cells were restored by insulin injection *in vivo* or in the culture medium. Alloxan-induced diabetes did alter lymphocyte metabolism, and this may be a key contributing factor to lymphocyte function deterioration.

Neutrophils

Neutrophils, the most prevalent immune cell type and the first immune cells to respond to inflammation, have a unique role in the etiology of diabetes. Neutrophils may play a crucial role in the development and maintenance of T1DM. Islet cells may be destroyed by cytotoxic substances such as degranulation products, cytokines, reactive oxygen species, and extracellular traps that are generated during the maturation or activation of neutrophils. Through cell-cell interactions with other immune and non-immune cells, these cells can trigger a diabetogenic T-cell response and accelerate the onset of T1DM. The main metabolic defect in T1DM and T2DM, persistent hyperglycemia, mediates the dysregulation of neutrophil responses to infection. Both T1DM and T2DM patients frequently experience chronic and recurring infections, which increases morbidity and mortality. The high frequency of bacterial infections in diabetes is linked to a failure of neutrophil activities, including migration, ROS production, phagocytosis, and bacterial death. In diabetes, molecular pathways have impaired neutrophil function, and their connection increases the risk of bacterial infections in diabetic patients [61]. Neutrophils have a significant role in the onset of diabetic kidney damage. Yu *et al*[62] evaluated the relationship between diabetic kidney damage in autoimmune diabetes and circulating neutrophils. The strong relationship between neutrophil counts and diabetic kidney damage in autoimmune diabetes patients suggests the prospect that neutrophil-mediated inflammation plays a role in the development of diabetic kidney damage. Moreover, Woo *et al*[63] showed that systemic factors, such as inflammatory indicators, were associated with diabetic retinopathy. Both diabetes and diabetic retinopathy had elevated systemic neutrophil counts that were related to both their existence and severity. The findings suggested a link between diabetic retinopathy and systemic subclinical inflammation, and that neutrophil-mediated inflammation might be a key player in the etiology of diabetic retinopathy. A study by Dowe *et al*[65] suggested that neutrophil targeting was a therapeutic approach that reduces inflammation and boosts host immunity in diabetes patients to enhance infection clearance. Future research must be advanced to investigate innovative therapeutics for the reduction of morbidity and

mortality of diabetes[64]. Furthermore, appropriate antineutrophil therapy can inhibit or slow the progression of autoimmune diabetes and insulinitis.

Monocytes

Monocytes express cell surface indicators of inflammation and activation status. In a study by Valtierra *et al*[66], the effects of monocyte and macrophages on glycemic/metabolic control factors, non-obese participants, or T2D were observed. T2DM-related glycemic/metabolic control affects monocyte and monocyte-derived macrophage morphologies, providing insight toward an immune-suppressive and anti-inflammatory phenotype. The research findings of Min *et al*[67] implied that the presence of diabetes complications affected the circulating monocyte phenotype. These monocyte alterations might indicate enhanced risk of diabetes complications and may be biologically linked to diabetes. Mokgalabon *et al*[68] performed a meta-analysis and higher levels of monocyte activation were found in patients with T2DM. In a study by Kitahara *et al*[69], the metabolic activity of monocytes among diabetic patients and controls was investigated, and it was found that increasing blood sugar levels in diabetic patients were linked to the metabolic activation of monocytes. Such activation can potentially harm the diabetic host by causing cell deterioration by releasing harmful oxygen products. However, Wan *et al* [70] demonstrated that diabetic patients with decreased peripheral blood monocyte levels were linked to higher risks of diabetic retinopathy, suggesting that the recruitment and inflow of monocytes into the retina contributes to diabetic retinopathy progression. In addition, Giulietti *et al*[71] suggested that the pathophysiology of T2DM and the development of common diabetic comorbidities, primarily atherosclerosis, may be related to inflammation and the activation of the innate immune system, indicating that pro-inflammatory characteristics of monocytes are controlled by 1,25-dihydroxyvitamin D3 in T2DM patients.

Eosinophils

T1DM is an autoimmune condition appearing from the death of pancreatic beta cells by T lymphocytes. A few inflammatory and autoimmune illnesses have recently been linked to the pathophysiology of cationic alpha-defensin molecules. Neuwirth *et al*[72] found transcriptional active eosinophils in diabetic patients, indicating that eosinophils may be a component of a complex innate immune cell network that is involved in diabetes pathogenesis. Eosinophils, a component of leukocytes, are crucial to maintain metabolic homeostasis, particularly in T2DM patients. Ngamal *et al*[73] measured the eosinophil count and HbA1c in T2DM patients, suggesting that higher serum HbA1c levels were associated with a higher risk of developing complications from diabetes. The authors recommended that additional research was needed to determine the relationship between eosinophil-to-lymphocyte ratio and other fasting blood glucose measurements or inflammatory markers. However, Zhu *et al*[74] concluded that an increased percentage of peripheral eosinophils was linked to a lower incidence of T2DM. The inverse relationship of eosinophil with insulin resistance was found in Chinese diabetic participants. Individuals with allergic rhinitis or asthma have a higher chance of developing atherosclerosis. In a study by Fukui *et al* [75], peripheral eosinophil count was compared to assess their associations with cardiovascular mortality and diabetic nephropathy in type 2 diabetes patients, and they concluded that microalbuminuria (degree of albumin excretion rate) in men with T2DM may be related to allergic diseases. Multiple immunological diseases have been linked to increased serum eosinophil levels. Eosinophilia has been demonstrated to be a biomarker for coronary artery disease. Babazadeh *et al*[76] studied the relationship of eosinophil counts with HbA1c in patients with diabetes and coronary artery disease. However, anticholinergic effect on cognition (AEC) was not significantly correlated with HbA1c. The authors suggested that future research should be needed to examine the relationship between AEC as a precursor to coronary artery disease and other indicators of diabetes state or glycemic management.

Neutrophil-to-lymphocyte ratio

Increased neutrophil-to-lymphocyte ratio is a predictor of several cardiac and non-cardiac disorders, as well as an inflammatory biomarker. Hussain *et al*[77] evaluated the relationship between neutrophil-to-lymphocyte ratio and various levels of glycemic control in T2DM patients. The authors found increased neutrophil-to-lymphocyte ratio levels with elevated HbA1c and poor glycemic control. Higher values of neutrophil-to-lymphocyte ratio indicate worst glycemic control, and it could be employed as a disease monitoring technique when diabetes patients were being followed up. Rahar *et al*[78] found that neutrophil-to-lymphocyte ratio, a novel, basic, and relatively inexpensive marker, was a useful indicator for assessing systemic inflammation in diabetes and had a correlation with the severity of T2DM. In addition, Mertoglu *et al*[79] examined neutrophil-to-lymphocyte ratio as an accurate diagnostic marker by examining its relationships to prediabetes and T2DM. Patients with prediabetes and diabetes exhibited a marked increased level of the neutrophil-to-lymphocyte ratio. This ratio considerably declined but increased in the later stages of prediabetes and the early stages of diabetes. Values for neutrophil-to-lymphocyte ratio may be accurate predictors of prediabetes and DM. Sefil *et al*[80] examined the relationship between neutrophil-to-lymphocyte ratio and HbA1c regulation. The authors discovered elevated HbA1c with increased neutrophil-to-lymphocyte ratio in T2DM patients, suggesting that regulation of HbA1c might be significantly related to neutrophil-to-lymphocyte ratio.

Diabetic retinopathy is a specific neurovascular consequence of DM. Family history is a risk factor for diabetic retinopathy that can contribute to prediction and diagnosis. Hence, Wang *et al*[81] investigated the risk factors such as inflammatory response indexes and neutrophil-to-lymphocyte ratio in diabetic retinopathy patients with or without a family history of diabetes. The authors determined indicators of the systemic inflammatory response in patients without a linked family history, indicated that neutrophil-to-lymphocyte ratio was related to the presence of diabetic retinopathy, and supported the reclassification of diabetic retinopathy in addition to Hb. In the same way, Li *et al*[82] findings showed that greater neutrophil-to-lymphocyte ratio values were a valid biomarker for the development of diabetic retinopathy. Similarly, Jaaban *et al*[83] found that elevated neutrophil-to-lymphocyte ratio was significantly related to diabetic nephropathy, suggesting that neutrophil-to-lymphocyte ratio could be used as a risk indicator for the prediction and prognosis of diabetic nephropathy. Moreover, Rahar *et al* [78] found that neutrophil-to-lymphocyte ratio was a useful marker for assessing systemic inflammation in diabetes and had a correlation with the severity of diabetic nephropathy. Also, Klisic *et al*[84] found independent correlations between HbA1c and neutrophil-to-lymphocyte ratio indexes such as derived neutrophil-to-lymphocyte ratio and monocyte/granulocyte-to-lymphocyte ratio, and platelet-to-neutrophil ratio exceeded platelets in respect of HbA1c. The prompt detection of abnormalities in glucose homeostasis in individuals with prediabetes and overt diabetes may be largely facilitated by these novel markers. Inflammation greatly influences the origin and progression of coronary artery disease. The neutrophil-to-lymphocyte ratio, a novel inflammatory biomarker, has not been linked to clinical outcomes in coronary artery disease patients with various glycemic metabolisms after percutaneous coronary intervention. He *et al*[85] discovered how neutrophil-to-lymphocyte ratio affected individuals undergoing percutaneous coronary intervention, regardless of whether they had T2DM or not. The presence of T2DM with a higher neutrophil-to-lymphocyte ratio was linked to worse clinical outcomes in coronary artery disease patients. The risk classification of coronary artery disease patients may benefit from identifying patients with increased neutrophil-to-lymphocyte ratio and T2DM. Furthermore, Wan *et al*[86] found that the neutrophil-to-lymphocyte ratio was a cheap and simple laboratory marker that can detect systemic inflammation. Apart from diabetic retinopathy, a greater neutrophil-to-lymphocyte ratio level was linked to a higher prevalence of cardiovascular disease and diabetic kidney disease in diabetic adults. In addition, Umarani *et al*[87] found that neutrophil-to-lymphocyte ratio might be an early and predictive marker for microvascular problems in individuals with DM. Consistently, Wang *et al*[88] found that an increased likelihood of clinically significant depression symptoms was independently linked to elevated levels of neutrophil-to-lymphocyte ratio in diabetics. To better understand the involvement of neutrophil-to-lymphocyte ratio in depression in diabetes individuals, prospective research is required. Additionally, Liu *et al*[89] found that neutrophil-to-lymphocyte ratio was an easier, quicker, and more effective diagnostic for prognosis prediction in T2DM patients with COVID-19.

Platelet-to-lymphocyte ratio

According to emerging research, the platelet-to-lymphocyte ratio may be a new potential indicator of the inflammatory response. A higher platelet-to-lymphocyte ratio was related to cognitive decline in T2DM patients. The platelet-to-lymphocyte ratio may facilitate the early detection of high-risk patients and offer recommendations for additional measures to prevent cognitive deterioration in T2DM patients [90]. Atak *et al*[91] found that platelet to-lymphocyte ratio, which is a low-cost and simple-to-use indicator, may help predict the onset and control levels of T2DM. Additional prospective studies are required to confirm the association between platelet-to-lymphocyte ratio and HbA1c. Elsayed *et al*[92] found that patients with T2DM might have an independent relationship between platelet-to-lymphocyte ratio and poor blood glucose control. Consequently, greater platelet-to-lymphocyte ratios were linked to diabetes complications. Diabetic retinopathy, a serious and specific neurovascular consequence of T2DM, continues to be the largest contributor to vision loss and accidental blindness in individuals aged 20 to 74 years. Studies suggested that chronic inflammation plays a significant role in the pathophysiology of diabetic retinopathy. Zeng *et al*[93] explored the relationships between the platelet-to-lymphocyte ratio and diabetic retinopathy. It had been found that platelet-to-lymphocyte ratio might be an independent risk factor for assessing diabetic retinopathy in patients with T2DM. Similarly, Jaaban *et al*[83] showed that increased platelet-to-lymphocyte ratio was significantly correlated with diabetic nephropathy, suggesting that it could be used as a risk indicator for diabetic nephropathy prediction and prognosis. In addition, Zhang *et al*[94] found that platelet-to-lymphocyte ratio is markedly increased in diabetic foot ulcer patients and positively connected with the Wagner grade of diabetic foot ulcer, suggesting that it might serve as a useful marker for the early detection and evaluation of the severity of diabetic foot ulcer.

Monocyte-to-lymphocyte ratio

Inflammation plays a role in disturbed metabolic control that leads to hypoglycemia, impaired fasting glycemia, or hyperglycemia. Alfihili *et al*[95] found that elevated monocyte-to-lymphocyte ratio was correlated and associated with the risk of impaired fasting glycemia and hyperglycemia. However, comprehensive prospective cohort studies are required to determine disease onset, to explore the linkage between monocyte-to-lymphocyte ratio and fasting blood glucose, and to assess the prognostic

significance of this novel marker. Diabetic retinopathy is the most prevalent consequence of T2DM and the main cause of adult blindness. Although the pathophysiology of diabetic retinopathy is not completely understood, inflammation is thought to have a key factor. The platelet-to-lymphocyte ratio, monocyte-to-lymphocyte ratio, and neutrophil-to-lymphocyte ratio may be new potential indicators of inflammatory conditions. According to the research by Yue *et al*[96], platelet-to-lymphocyte ratio and neutrophil-to-lymphocyte ratio were greatly elevated in diabetic retinopathy patients. The authors found that the monocyte-to-lymphocyte ratio was a risk factor for diabetic retinopathy after potential contributing factors were considered. The monocyte-to-lymphocyte ratio may be clinically and pathophysiologically significant in diabetic retinopathy; however, its prediction ability is limited. In addition, Wang *et al*[97] demonstrated that the monocyte-to-lymphocyte ratio was significantly related to proliferative diabetic retinopathy in patients with T2DM. Monitoring T2DM patients may be a great opportunity to assess their monocyte-to-lymphocyte ratio. Inflammation is a key pathogenetic mechanism in diabetic kidney injury. The identification of microalbuminuria is crucial to preventing diabetic patients from developing end-stage renal failure. Inflammation is identified by a combination of high monocyte and low lymphocyte numbers. The monocyte-to-lymphocyte ratio is used as a marker in inflammatory disorders. Kocak *et al*[98] indicated that the monocyte-to-lymphocyte ratio had a strong relationship with microalbuminuria, and could act as a predictive and efficient marker for diabetic kidney injury in diabetic patients. In addition, Wang *et al*[88] discovered that elevated monocyte-to-lymphocyte ratios were considered to be indicators of systemic immunological inflammation but were found to be an unfavorable indicator of clinical outcomes in patients with gestational DM. The neutrophil-to-lymphocyte ratio, platelet-to-lymphocyte ratio, and lymphocyte-to-monocyte ratio may be routinely measured, and are considered to be indicators of patient survival in renal diseases and cancer. Alsayyad *et al*[99] found that lymphocyte-to-monocyte ratio might be used as an inflammatory marker in the early and intermediate phases of diabetic nephropathy, but it was no more effective than neutrophil-to-lymphocyte ratio as a screening tool for diabetic nephropathy diagnosis. In addition, Huang *et al*[100] evaluated the monocyte-to-lymphocyte ratio as a potent independent predictor of diabetic nephropathy.

CONCLUSION

Hematological parameters play a significant role in the progression and pathogenesis of DM. Also, major hematological parameters such as red blood cells, hemoglobin, hematocrit, red blood cell indices, platelet count, white blood cells, lymphocytes, neutrophils, monocytes, eosinophils, neutrophil-to-lymphocyte ratio, platelet-to-lymphocyte ratio, and monocyte-to-lymphocyte ratio, play pathophysiological roles in DM. The role of basophils in diabetes has not been studied yet. Therefore, further studies are required to find the association between basophils and DM.

ACKNOWLEDGEMENTS

The corresponding author is grateful to her mother, Mrs. Tahira Rafaqat, and her father, Mr. Rafaqat Masih.

FOOTNOTES

Author contributions: All authors contributed equally to this work.

Conflict-of-interest statement: All the authors report no relevant conflicts of interest for this article.

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World Journal of *Hematology*

World J Hematol 2023 December 29; 10(4): 42-47



CASE REPORT

- 42 Unusual presentation of extramedullary blast crisis in chronic myeloid leukemia: A case report

Mishra R, Garg S, Bharti P, Malla DR, Rohatgi I, Gautam S

ABOUT COVER

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INDEXING/ABSTRACTING

The WJH is now abstracted and indexed in Reference Citation Analysis, China Science and Technology Journal Database, and Superstar Journals Database.

RESPONSIBLE EDITORS FOR THIS ISSUE

Production Editor: *Yu-Xi Chen*; Production Department Director: *Xu Guo*; Editorial Office Director: *Ji-Hong Lin*.

NAME OF JOURNAL

World Journal of Hematology

ISSN

ISSN 2218-6204 (online)

LAUNCH DATE

June 2, 2012

FREQUENCY

Continuous Publication

EDITORS-IN-CHIEF

Pier Paolo Piccaluga

EDITORIAL BOARD MEMBERS

<https://www.wjgnet.com/2218-6204/editorialboard.htm>

PUBLICATION DATE

December 29, 2023

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PUBLICATION ETHICS

<https://www.wjgnet.com/bpg/GerInfo/288>

PUBLICATION MISCONDUCT

<https://www.wjgnet.com/bpg/gerinfo/208>

ARTICLE PROCESSING CHARGE

<https://www.wjgnet.com/bpg/gerinfo/242>

STEPS FOR SUBMITTING MANUSCRIPTS

<https://www.wjgnet.com/bpg/GerInfo/239>

ONLINE SUBMISSION

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Unusual presentation of extramedullary blast crisis in chronic myeloid leukemia: A case report

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Specialty type: Hematology

Provenance and peer review:

Unsolicited article; Externally peer reviewed.

Peer-review model: Single blind

Peer-review report's scientific quality classification

Grade A (Excellent): 0
Grade B (Very good): 0
Grade C (Good): 0
Grade D (Fair): 0
Grade E (Poor): 0

P-Reviewer: Liu C, China

Received: October 3, 2023

Peer-review started: October 3, 2023

First decision: November 2, 2023

Revised: November 15, 2023

Accepted: December 19, 2023

Article in press: December 19, 2023

Published online: December 29, 2023



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Abstract

BACKGROUND

Extramedullary blast crisis in chronic myeloid leukemia (CML) is an uncommon occurrence of leukemic blast infiltration in regions other than the bone marrow. Malignant infiltration of the serosal membranes should be considered in cases where CML presents with ascites or pleural effusion.

CASE SUMMARY

A 23-year-old female with CML presented with progressively worsening ascites and pleural effusion despite first-line tyrosine kinase inhibitor treatment. Her blood work indicated leukocytosis with myelocyte bulge and 2% blasts. Analysis of the patient's bone marrow confirmed the chronic phase of CML. Abdominal ultrasound revealed hepatosplenomegaly with ascites. The fluid investigation of both ascites and pleural effusion revealed a predominance of neutrophils with exudate. However, no acid-fast bacilli or growth was observed after culturing. Although hydroxyurea reduced cell counts, there was no observed effect on ascites or pleural effusion. Repeat investigation of the ascitic and pleural fluid revealed a polymorphous myeloid cell population consisting of myelocytes, metamyelocytes, band forms, neutrophils and a few myeloblasts. Extramedullary blast crisis was suspected, and mutation analysis was performed. We switched the patient to dasatinib. The patient's symptoms were relieved, and ascites and pleural effusion diminished.

CONCLUSION

Serosal membrane involvement in CML is extremely rare. In this case, the patient responded well to dasatinib treatment.

Key Words: Chronic myeloid leukemia; Extramedullary blast crisis; Serosal infiltration;

Ascites; Pleural effusion; Case report

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Core Tip: Extramedullary blast crises exhibit diverse presentations, underscoring the importance of awareness of possible sites of occurrence. In cases of chronic myeloid leukemia with ascites or pleural effusion, it is essential to consider the possibility of malignant infiltration of serosal membranes as a potential diagnosis. Recognizing these signs early can lead to timely intervention and management.

Citation: Mishra R, Garg S, Bharti P, Malla DR, Rohatgi I, Gautam S. Unusual presentation of extramedullary blast crisis in chronic myeloid leukemia: A case report. *World J Hematol* 2023; 10(4): 42-47

URL: <https://www.wjgnet.com/2218-6204/full/v10/i4/42.htm>

DOI: <https://dx.doi.org/10.5315/wjh.v10.i4.42>

INTRODUCTION

Extramedullary blast crisis (EBC) in chronic myeloid leukemia (CML) is an uncommon occurrence of leukemic blast infiltration in regions other than the bone marrow. The most prevalent site of involvement in EBC is the lymph nodes, followed by the bone and skin[1]. Serosal membrane involvement is exceedingly uncommon in CML. Currently, there are only a few case reports describing pleural effusion and ascites in CML. Herein, we described a patient with CML treated with tyrosine kinase inhibitor therapy who developed EBC with concomitant ascites and pleural effusion.

CASE PRESENTATION

Chief complaints

A 23-year-old female presented to our hospital with the chief complaint of progressive distension of the abdomen. The patient also experienced swelling of the legs for 2 mo prior to presentation and right-sided chest pain that increased during inspiration.

History of present illness

The patient experienced nonspecific malaise, growing weariness, and anorexia for 2 wk prior to presentation.

History of past illness

The patient had been diagnosed with CML 3 years prior to presentation and was under imatinib therapy (600 mg once a day). The patient had been regular with her treatment regimen and was symptomatically better until the time she started having these symptoms.

Personal and family history

There was no history of similar illnesses in the patient's family.

Physical examination

The patient was afebrile with normal vitals. She had pallor and bilateral pitting pedal edema that extended above her ankles. An evaluation of the respiratory system indicated a dull note with reduced breath sounds at the right infraaxillary and infrascapular areas. Abdominal examination revealed tense ascites and splenomegaly extending up to the umbilicus.

Laboratory examinations

Initial laboratory investigations revealed that the patient was anemic with hemoglobin of 8.9 g/dL (normal range: 12-15 g/dL). It also revealed leukocytosis with white blood cell counts of 68000 (P68/L24/B4/E2) and thrombocytosis with platelets of 600000. Hyperkalemia (5.7 mmol/L; normal range: 3.5-5.5 mmol/L), hyperphosphatemia (6.9 mg/dL; normal range: 2.5-4.5 mg/dL) and elevated lactate dehydrogenase levels (572 IU/L; normal range: 105-270) were also observed. Findings for liver and renal function tests, coagulation profile and serum procalcitonin level were all normal.

Thoracentesis was performed under ultrasound guidance, and the aspirated fluid was exudative (protein 5.3 g/dL; normal range: 1.5 g/dL) along with 600 cells/mm³ with polymorphic preponderance (normal range: < 5 cells/mm³). The serum ascites albumin gradient level in the ascitic fluid was 0.9, and the cytobiochemical profile was comparable (300 cells/mm³; normal range: < 5 cells/mm³; protein 5.1 g/dL; normal range: 1.5 g/dL). In pleural and ascitic fluid, the adenosine deaminase levels were 4.3 U/L and 8.1 U/L, respectively (normal range: < 40 U/L). There were no pathogenic organisms or acid-fast bacilli found in pleural and ascitic fluid cultures.

The peripheral smear showed leukocytosis with myeloid bulge and bimodal myeloid population. Both mature and immature myeloid proliferation with 2% blasts (normal range: < 5% blasts) were observed. Myelocytes made up 13% of the myelogram. Metamyelocytes and band formations were 16% and 5%, respectively. An impression of CML in the chronic phase was reported. The neutrophil alkaline phosphatase score was 24 (normal range: 20-150). The Mantoux, viral markers, thyroid function test and autoimmune profile findings were unremarkable, while blood and urine cultures showed no growth. The levels of tumor markers carbohydrate antigen 125, carcinoembryonic antigen, and carbohydrate antigen 19-9 were within normal limits. A myelogram comparable to the peripheral smear was seen in the bone marrow aspirate, with 2% blasts. The biopsy revealed CML in the chronic phase with fibrosis (World Health Organization grade 2) and limited collection of blasts.

Imaging examinations

The chest X-ray (Figure 1A) confirmed pleural effusion (right > left), while the ultrasound revealed hepatosplenomegaly with ascites. Contrast-enhanced computed tomography (Figure 2) confirmed the sonographic findings, revealing smooth enhancing peritoneum with omental caking. Computed tomography ruled out any mass or space-occupying lesions. Two-dimensional echocardiography was suggestive of mild pericardial effusion with normal ejection fraction.

FINAL DIAGNOSIS

Ascitic fluid was sent for smear testing, which revealed the presence of malignant cells. It possessed a polymorphous myeloid cell population that included myelocytes, metamyelocytes, band forms, neutrophils, and a few myeloblasts. Analysis of the pleural effusion identified several kinds of myeloid cells (Figures 3 and 4). We diagnosed the patient with EBC in the form of ascites and pleural effusion.

TREATMENT

We initially treated the patient with hydroxyurea. This treatment reduced cell counts, but the patient's symptoms were not relieved. Since the patient was receiving imatinib treatment, mutation analysis was performed. We identified a G250E mutation in the BCR-ABL protein. We recommended dasatinib (100 mg once a day) and a stem cell transplantation. The patient consented to dasatinib treatment but declined the stem cell transplantation treatment.

OUTCOME AND FOLLOW-UP

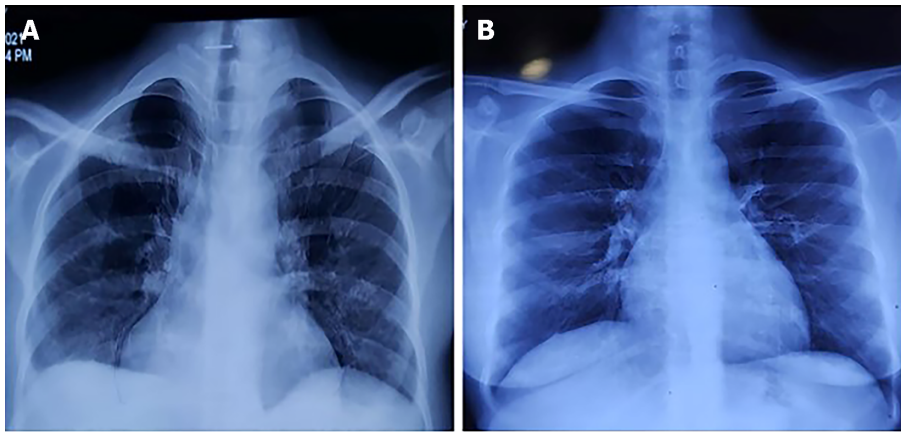
The peripheral smear was repeated 1 mo after switching to dasatinib treatment. No immature myeloid cells were observed. Chest X-ray (Figure 1B) and abdominal ultrasound 3 mo after beginning the dasatinib treatment revealed that the pleural effusion and ascites had disappeared. We also observed that the spleen shrank to 12 cm. The patient's symptoms were also relieved, and her overall health had improved. She continued dasatinib treatment without any significant side effects.

DISCUSSION

Blast crisis in CML is classified according to the place of origin (medullary or extramedullary) and cell type (myeloid, lymphoid, or mixed). At least one of the following[2] characterises the CML blast crisis: (1) 20% myeloblasts or lymphoblasts in blood or bone marrow; (2) Large clusters of blast cells in bone marrow biopsies; or (3) The emergence of chloroma.

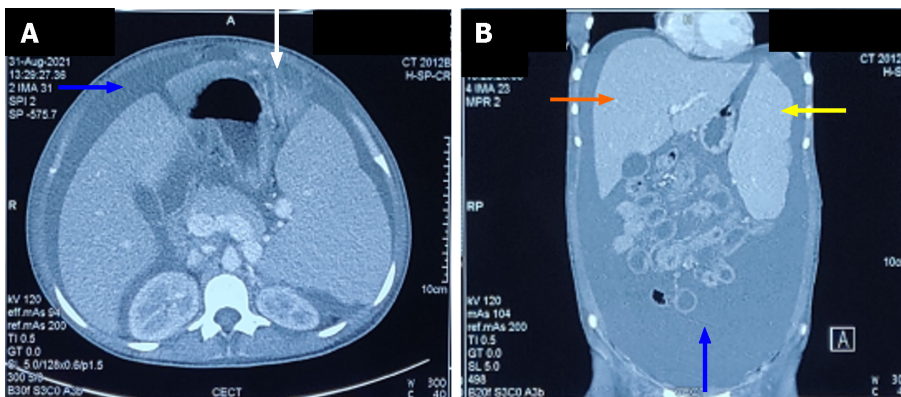
EBC is widely recognized in CML and is present in 8%-15% of patients over the course of the illness[3,4]. EBC often manifests as a tumorous mass known as a chloroma. However, it can also manifest as a diffuse infiltrate. Lymph nodes (40%-61% of cases) are the most common location of extramedullary disease, followed by bone (22%-37% of cases) and skin or soft tissues (20%)[5]. Hepatosplenomegaly is not considered EBC in CML patients. EBC is particularly common during the accelerated phase of CML or during the blast crisis. Extramedullary disease in CML is an indicator of poor prognosis and indicate a change in therapy usually reserved for blast crisis treatment[6].

Serosal membrane involvement in CML is extremely rare. Aleem and Siddiqui[4] described a patient in the chronic phase of CML who presented with massive ascites. They postulated that the cause was mesenteric/peritoneal infiltration. The response to imatinib was outstanding, with a full cytogenetic response and complete elimination of ascites. Likewise, Deshpande *et al*[7] reported a case of CML with extramedullary illness manifesting as tense ascites. Both the ascitic fluid and a peripheral blood smear included all phases of granulocytes and a few blast cells. A favorable response was reported after imatinib therapy. Ridha *et al*[8] described a CML patient who developed pleural effusion during imatinib therapy. A diagnosis of EBC in the form of pleural effusion was established based on cytological investigation of the pleural fluid, which revealed cells with the morphological hallmarks of myeloblasts. The patient continued to receive imatinib but died after 1 mo. Nuwal *et al*[6] described a case of a 26-year-old male with CML who presented with pleural



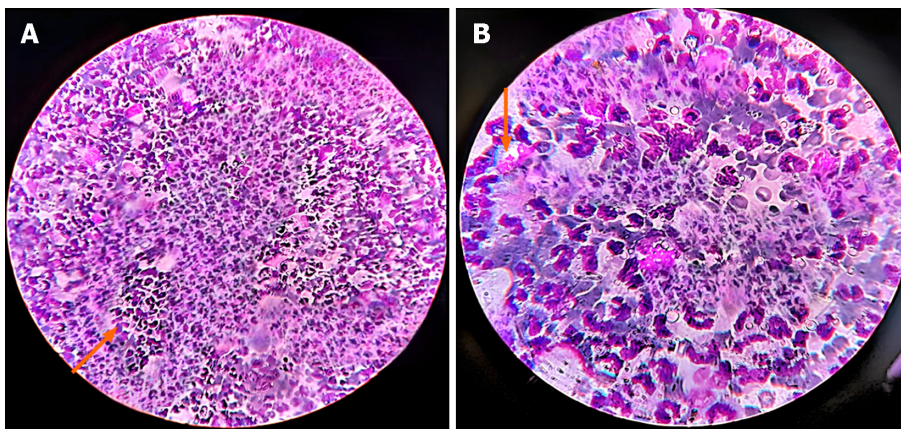
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Figure 1 Chest X-ray. A: Chest X-ray performed at presentation; B: Chest X-ray performed 3 mo after receiving dasatinib therapy.



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Figure 2 Contrast enhanced computed tomography of abdomen showing ascites (blue arrow), omental caking (white arrow), hepatomegaly (orange arrow), and splenomegaly (yellow arrow). A: Axial section; B: Coronal section.

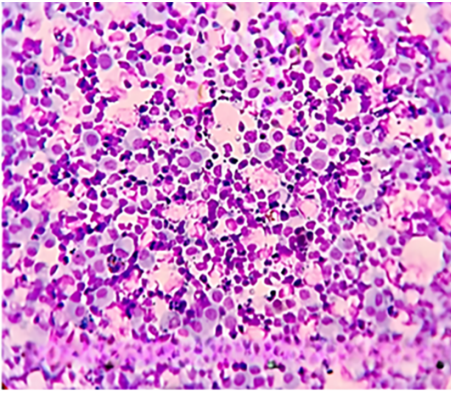


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Figure 3 Ascentic fluid cytospin smear preparation showing cells of myeloid series. A: 30 × magnification; B: 100 × magnification.

effusion as the initial clinical symptom.

The mechanism of pleural effusion in CML patients is unknown. However, several hypotheses exist. The first includes leukemic infiltration into the pleura that frequently occurs during or soon before bone marrow progression to the blast crisis phase. The lymph nodes, bone, and nervous system are the most affected locations, with infiltration of the brain, testis, skin, breast, soft tissue, synovial, gastrointestinal tract, ovaries, kidneys, and pleura occurring less frequently.



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Figure 4 Pleural fluid cytospin smear preparation showing cells of myeloid series.

Pleural involvement has been infrequent, and isolated pleural blast crises in the absence of medullary change are extremely unusual.

Extramedullary hematopoiesis is another probable source of pleural effusion in CML, albeit the pleura is an uncommon location for this process. Extramedullary hematopoiesis, as opposed to pleural leukemic infiltration, contains hematopoietic cells of the erythroid, myeloid and megakaryocytic types.

Pleural effusions in CML can also be caused by blockage of pleural capillaries or penetration of interstitial tissue by leukemic cells during uncontrolled leukocytosis and enhanced capillary permeability owing to cytokine release. Predisposing variables including leukostasis and platelet dysfunction may play a role in CML hemorrhagic effusion.

Non-malignant causes of effusion have also been proposed. This would include infection and hypoproteinemia. As a result, this cause must be confirmed by blood investigations using a specific stain to identify bacteria and/or the presence of necrotic material.

Drug-induced pleural effusion is another probable cause of pleural effusion in CML. Dasatinib and imatinib are tyrosine kinase inhibitors that are efficacious in treating CML patients. The pathogenesis remains unclear. However, off-target tyrosine kinase inhibitors may influence the immune system.

The mechanism of ascites in CML may be similar to the presence of pleural effusion in CML but has not been investigated due to the rarity of this type of occurrence. Despite our extensive literature search, we did not find another published case in which the patient presented with concomitant ascites and pleural effusion as EBC in a case of CML. Moreover, our patient was already receiving tyrosine kinase inhibitor therapy.

The basic objective of CML blast crisis treatment is to return to the chronic phase. Once the patient is in the chronic phase, it is recommended that the patient should proceed with an allogeneic hematopoietic cell transplantation. Treatment varies according to the blast lineage [*i.e.* myeloid (70%) *vs* lymphoid (30%)] [10,11].

Administration of a tyrosine kinase inhibitor (with or without chemotherapy) followed by an allogeneic hematopoietic cell transplantation is the chosen treatment in myeloid crisis. According to studies, treating *de novo* myeloid blast crisis with a tyrosine kinase inhibitor alone and then assessing the response is recommended. In cases where the myeloid blast crisis occurs during tyrosine kinase inhibitor treatment, the recommended treatment is acute myeloid leukemia-type induction chemotherapy in combination with a more potent tyrosine kinase inhibitor [10,11].

In the case of our patient, we switched to a second-generation tyrosine kinase inhibitor based on mutation analysis. The patient had a favorable response. Patients who are receiving tyrosine kinase inhibitor treatment are more likely to experience lymphoid blast crisis [11]. Transition to a second-generation or third-generation tyrosine kinase inhibitor is required for these individuals. Tyrosine kinase inhibitors can be used alone or in conjunction with lower-intensity chemotherapy.

There is a lack of data on which TKI should be utilized as the first-line treatment for patients experiencing a blast crisis. It is also unknown whether the treatment should be different if the patient is a candidate for a hematopoietic cell transplant. In general, treatment with a second-generation tyrosine kinase inhibitor (*e.g.*, dasatinib, nilotinib) is recommended. If the disease progression/blast crisis occurs while the patient is receiving imatinib for early stage CML, second generation tyrosine kinase inhibitors should be administered. Ponatinib can also be recommended if the progression occurred while the patient was on dasatinib, nilotinib or bosutinib.

The limitations of our case included a lack of adequate clinical investigations (no genetic tests were performed) at the time of the first diagnosis as well as the failure to obtain evidence of chloroma on the ultrasound-guided fine needle aspiration cytology of the omentum.

CONCLUSION

EBC can manifest in a number of ways in a variety of locations. It is critical for clinicians to be aware of potential sites of presentation. Serosal involvement in CML is rare, and concurrent involvement of the peritoneum and pleura has not been

described previously. Investigation for malignant cells in the fluid should be performed in CML patients.

FOOTNOTES

Author contributions: Mishra R, Garg S and Bharti P contributed to the evaluation, diagnosis and management of the patient; Malla DR and Gautam S carried out the necessary procedures for the diagnosis; Rohatgi I analyzed the data, compiled the necessary reviews and wrote the manuscript; all authors read and approved the final manuscript.

Informed consent statement: All study participants, or their legal guardian, provided informed written consent prior to study enrollment.

Conflict-of-interest statement: All the Authors have no conflict of interest related to the manuscript.

CARE Checklist (2016) statement: The authors have read the CARE Checklist (2016), and the manuscript was prepared and revised according to the CARE Checklist (2016).

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S-Editor: Lin C

L-Editor: A

P-Editor: Chen YX

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