World Journal of

Hematology

CASE REPORT

Contents

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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.

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

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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 × 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 × 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

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.

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 $40\text{-}50 \times 10^9/L$ 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 SpO_2 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 100×10^9/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 ≥ 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 ≥ 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 ≥ 40 and CrCl ≥ 30 mL/min: enoxaparin 40 mg SC BID; Dalteparin 7500 units SC QD; Tinzaparin 8000 units SC QD; UFH 7500 units BID
		BMI ≥ 40 and CrCl ≥ 30 mL/min: enoxaparin 0.8 mg/kg SC BID minus 10%	BMI < 40 and CrCl < 30 mL/min: enoxaparin 30 mg SQ QD
INSPIRATION[18]	Enoxaparin, UFH	CrCl ≥ 30 mL/min: enoxaparin 1 mg/kg SC QD	CrCl ≥ 30 mL/min: enoxaparin 40 mg SC QD
		Obesity[1] and CrCl ≥ 30 mL/min: enoxaparin 0.6 mg/kg SC BID	Obesity[1] and CrCl ≥ 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 ≤ 15 mL/min: UFH 10000 units SC BID	CrCl ≤ 15 mL/min: UFH 5000 units SC BID
HEP-COVID[21]	Enoxaparin, UFH	CrCl ≥ 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 ≥ 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 ≥ 30 mL/min: rivaroxaban 20 mg PO QD	BMI < 40 and CrCl ≥ 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 ≥ 75 enoxaparin 0.75 mg/kg SC Q12H	BMI ≥ 40 and CrCl ≥ 30 mL/min: enoxaparin 60 mg SC QD or 40 mg SC Q12H; UFH 7500U SC Q8H or Q12H
			BMI < 40 and CrCl < 30 mL/min: UFH 5000 U 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 7500 U SC BID or TID
RAPID[20]	Enoxaparin, dalteparin, tinzaparin, UFH	BMI < 40 and CrCl ≥ 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 ≥ 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 ≥ 40 and CrCl ≥ 30 mL/min: enoxaparin 1mg/kg SC Q12H; Dalteparin 100 units/kg SC Q12H; Tinzaparin 175 units/kg SC Q24H; UFH[2]	BMI ≥ 40 and CrCl ≥ 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 ≥ 40 and CrCl < 30 mL/min: UFH[2] or LMWH per hospital protocol	BMI ≥ 40 and CrCl < 30 mL/min: UFH 7500 units SC Q8H or LMWH per hospital protocol

[1]Weight ≥ 120 kg or body mass index ≥ 35 kg/m^2.

[2]Unfractionated 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 < 50×10^9/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 < 50×10^9/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 < 25×10^9/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 < 50×10^9/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 < 50×10^9/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 < 25×10^9/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.

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

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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

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.

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: 4.5-11.0×10^9/L), absolute neutrophil count (ANC) of 0.5×10^9/L, and platelets of 15×10^9/L (normal range: 150-400×10^9/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 of g/L, TLC of 2.56 ×
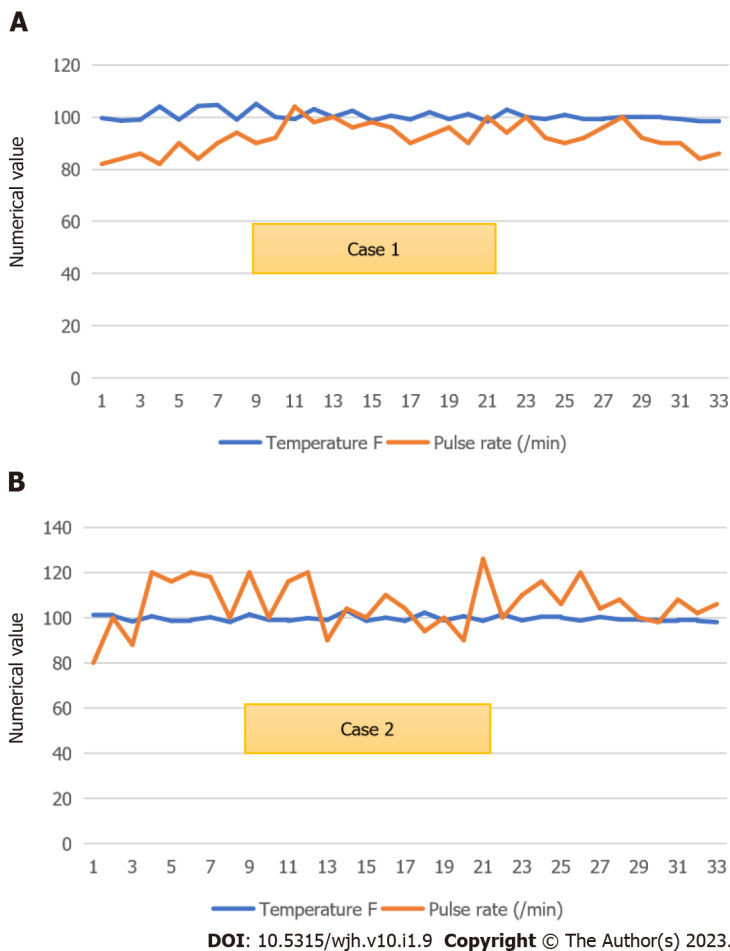
A

B

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 1.6×10^9/L, and platelets of 230×10^9/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. More ever, 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

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