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

Jiang B *et al*. VTE prophylaxis in MYH-9-RD patient

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Abstract

BACKGROUND

The May-Hegglin anomaly is among a group of genetic disorders known as MYH9-related disease (MYH9-RD). Patients with inherited platelet disorders such as May-Hegglin anomaly are at variably increased risk for bleeding, due to a combination of platelet dysfunction and thrombocytopenia. Patients admitted to hospital with coronavirus disease 2019 (COVID-19) infection are at increased risk for venous thromboembolism event (VTE). National institute of health COVID-19 treatment guideline recommends using prophylactic dose of heparin as VTE prophylaxis for adults who 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. CBC 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 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 while anticoagulation guidelines exist for patients with COVID-19, there are no clear guidelines for management of patients with COVID-19 and inherited bleeding disorders, particularly those with MYH9-RD. 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 has an indication for anticoagulation.

Key Words: Venous thromboembolism event; Prophylaxis; MYH9-related disease; Anticoagulation in inherit platelet disorder; Low molecular heparin; Coronavirus disease 2019; 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). The *MYH9* gene encodes the heavy chain of non-muscle myosin. A mutation in the *MYH9* gene leads to interruption of megakaryocyte migration toward the vasculature and impairs proplatelet release in the marrow, therefore causing macrothrombocytopenia and mild to moderate bleeding tendency. It may be misdiagnosed as treatment-resistant immune thrombocytopenia. 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 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 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 potential increased risk of bleeding[7].

CASE PRESENTATION

Chief complaints

A 39-year old woman with past medical history significant for diabetes mellitus, hypothyroidism, obesity, and MYH9-RD (specifically May-Hegglin anomaly) 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 May-Hegglin anomaly 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 May-Hegglin anomaly. She later

had another bleeding episode as a child during an 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 × 10^9/L. Her baseline platelet count was (40-50) × 10^9/L throughout her adult life. She denied history of spontaneous bleeding requiring transfusion or hospitalization in the past nine 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 non-steroidal anti-inflammatory drugs (NSAIDs) or aspirin and used them sparingly.

Personal and family history

Her family history was notable for May-Hegglin disorder 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 Liters of oxygen per nasal cannula. The BMI 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

CBC was notable for WBC count 4.9 × 10^3/μL, hemoglobin 11.4 g/dL, MCV 72.8 and platelet count 54 × 10^9/L. Peripheral smear revealed hypochromic, microcytic anemia with mild anisopoikilocytosis. Dohle 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 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 40mg subcutaneously once daily, and monitored carefully for bleeding. On day 3, the dose was escalated to 40mg 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 6-mo follow up, the patient successfully discontinued 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 is establishing with a post-COVID assessment and 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 20 000[8]. These include May-Hegglin anomaly (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 (NM IIA), which is the only non-muscle myosin class II isoform expressed in megakaryocytes (MKs)[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 MK migration toward the vasculature and impair pro-platelet 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 degree of thrombocytopenia and less with 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 May-Hegglin 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 NSAIDs 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 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 post-surgical 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 (LMWH) prophylaxis did not significantly influence post-surgical bleeding or need for anti-hemorrhagic 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, pressers 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 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 40mg 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 of Thrombosis and Haemostasis[22] advise against anticoagulation in COVID-19 patients with severe thrombocytopenia (platelets < 25 × 10^9/L) and suggest non-pharmacological 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 post-procedure 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, LMWH 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 would be given prophylactic anticoagulation with enoxaparin 40 mg once daily, to then transition to enoxaparin 40 mg twice daily if there was no evidence of bleeding[23].

CONCLUSION

MYH9-RD is a spectral of autosomal dominant diseases that present with macrothrombocytopenia, platelet dysfunction and varying clinical features such as sensorineural hearing loss, presenile cataracts, and renal failure, they have mild to moderate bleeding tendency. When these patient are admitted for COVID-19 related critical illness, having platelet disorder should not exclude them from getting anticoagulation when it is needed. LMWH 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.

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