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CLINICAL VIGNETTE

Extreme Thrombocytosis

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Case Report

A 32-year-old Hispanic man with no significant past medical history presented with severe left-sided sharp chest pain after an episode of mechanical fall. CT scan of the chest revealed a large left-sided high-density fluid collection suspicious for hemothorax. A chest tube was inserted and drained 1,750 ml of blood. His CBC showed a hemoglobin of 13.9 g/dL and platelet count of $339 \times 10^3/\mu\text{L}$. The chest tube was removed five days later, but a repeat CT chest showed rapid reaccumulation of fluid in the left lung despite initial improvement. He was evaluated by a thoracic surgeon and then underwent left thoracoscopy and left lower lobe decortication. Another 1,300 ml of old blood was evacuated during the surgery, and the chest tube was reinserted. The chest tube subsequently drained another 450 ml of blood until the bleeding finally stopped. His CBC at this time showed a hemoglobin level of 6.9 g/dL and platelet count of $489 \times 10^3/\mu\text{L}$. He was transfused with packed red blood cells, and his hemoglobin level responded appropriately. However, his platelet count rapidly increased after surgery and reached $1,223 \times 10^3/\mu\text{L}$ on post-operation day 8. His surgeon consulted hematology for workup and management of the extreme thrombocytosis.

Discussion

Thrombocytosis is a common abnormal CBC finding in routine clinical practice. Etiology of the thrombocytosis is divided into two groups: reactive thrombocytosis and autonomous thrombocytosis. Autonomous thrombocytosis refers to thrombocytosis in the setting of a primary bone marrow disorder such as a chronic myeloproliferative disorder or myelodysplastic disorder. Some examples of these disorders include essential thrombocytosis, polycythemia vera, primary myelofibrosis, chronic myeloid leukemia and myelodysplastic syndrome. Reactive thrombocytosis refers to thrombocytosis secondary to another medical or surgical condition in the absence of myeloproliferative/myelodysplastic syndrome. Frequently these are conditions involving acute or chronic inflammation and tissue injuries such as infection, postsurgical state, post-splenectomy state, malignancy or acute blood loss/iron deficiency.¹ In clinical practice, most patients with thrombocytosis have reactive thrombocytosis.^{1,2} A thorough history and physical examination is usually sufficient in helping the physician make the correct diagnosis of reactive thrombocytosis.

Extreme thrombocytosis, defined as a platelet count $>$ or $=$ $1,000 \times 10^3/\mu\text{L}$, is an uncommon finding that frequently makes

the treating physician nervous. Reactive thrombocytosis is still the most common cause of the extreme thrombocytosis. In a study of 280 patients with extreme thrombocytosis, 82% had reactive thrombocytosis, and 14% had a myeloproliferative disorder. Four percent of the patients had cases of uncertain etiology.³ When it occurs, patients are at risk for vasomotor symptoms, venous thrombosis, arterial thrombosis, and bleeding. Generally, these events are less likely to occur in association with reactive thrombocytosis than autonomous thrombocytosis.^{4,5,6,7}

Thrombosis is one of the feared complications of extreme thrombocytosis. However, it is not frequently seen in patients with reactive thrombocytosis.^{3,6,7} In the previously mentioned study of 280 patients with extreme thrombocytosis, the rate of vaso-occlusive events with autonomous thrombocytosis was 24%, while it was only 1% for patients with reactive thrombocytosis.³ If thrombosis occurs with extreme thrombocytosis, it is recommended to proceed with platelet apheresis along with standard anticoagulation therapy for at least three months. Platelet apheresis is a category II recommendation in a patient with symptomatic thrombocytosis per American Society of Apheresis guideline.⁸ A platelet lowering agent should also be considered to keep the platelet count below $400 \times 10^3/\mu\text{L}$, especially in patients with autonomous thrombocytosis.^{5,9}

Bleeding is an unexpected, also feared, complication of extreme thrombocytosis. The thrombotic condition changes into a bleeding tendency when platelet count increases to above $1,000$ - $1,500 \times 10^3/\mu\text{L}$ as a result of a functional von Willebrand factor (vWF) deficiency. This is due to the increased number of platelet binding to large vWF multimers resulting in clearance of these multimers from the plasma.^{10,11,12} The increased removal of large vWF multimers then lead to decreased in ristocetin cofactor/von Willebrand factor antigen and the collagen binding activity/von Willebrand factor antigen ratios.¹¹ Because many patients with thrombocytosis are also on aspirin, which can further increase bleeding risk, physicians need to be aware of this unusual and unexpected clinical manifestation. If bleeding occurs, patients need to stop taking all antiplatelet agents and anticoagulants. When acquired von Willebrand disease is suspected, decreasing the platelet count by apheresis or cytoreductive agents usually reverses both the clinical and laboratory findings of the acquired von Willebrand disease.

Vasomotor symptoms such as headaches, vision changes, lightheadedness, chest pain, erythema, and burning pain in the

hands and feet are seen in both reactive and autonomous extreme thrombocytosis. These symptoms are likely due to platelet-mediated endothelial injury in small vessels.¹³ Low-dose aspirin is effective in controlling the symptoms. It is reasonable to rule out secondary von Willebrand disease in extreme thrombocytosis with ristocetin cofactor activity level before starting patients on aspirin.

Not every patient with extreme thrombocytosis needs platelet apheresis or cytoreductive therapy.¹⁴ If a patient presents with bleeding or thrombosis, immediate appropriate treatment and platelet reduction would be needed. However, if the patient is asymptomatic, a comprehensive history and physical examination should be performed to look for many of the common causes of reactive thrombocytosis. Treatment for the underlying cause of the reactive thrombocytosis is usually sufficient to improve the thrombocytosis. However, if there are no obvious reactive causes found, work up for autonomous thrombocytosis should begin. If the patient is diagnosed with essential thrombocytosis, a type of myeloproliferative disorder, the need for cytoreductive therapy would then be based on patient's baseline thrombo-hemorrhagic risk. Hydroxyurea or anagrelide are typically used to maintain platelet count in the range of 100 to 400 x 10³/uL if cytoreductive therapy is indicated.^{9,15}

Clinical Case Follow-up

At the time of hematology consultation, the patient did not have any headaches, visual symptoms, lightheadedness, chest pain, or erythromelalgia. He also did not have any further bleeding. The iron panel revealed iron level of 17 mcg/dL, iron saturation of 5.9%, TIBC of 290 mcg/dL and ferritin of 404 ng/mL. C-reactive protein was elevated at 7.03 mg/dL. Ristocetin cofactor level was normal at 121% which ruled out acquired von Willebrand disease. Based on the history and available laboratory evaluation, he was diagnosed with reactive extreme thrombocytosis due to recent trauma, blood loss, and surgery. He was started on low-dose aspirin and given intravenous iron replacement therapy. Approximately one month later, his hemoglobin level improved to 13.5 g/dL and platelet count decreased to 294 x 10³/uL. Currently, he has recovered from his hemothorax and is doing well.

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