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CLINICAL VIGNETTE

Elevated aPTT in a Hospitalized Patient – Case Report of Factor VIII Inhibitor in a Cancer Patient

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Case

An 88-year-old female was brought to the emergency department from her nursing home due to weakness and ecchymosis. She reported new onset of severe, generalized weakness to the point she could no longer accomplish her ADL's. On physical exam, she appeared chronically ill, pale, and was essentially bed bound. Her left elbow and upper arm has a large area of ecchymosis as did her left buttock region. Her past medical history included a distant history of bypass surgery for coronary artery disease, possible transient ischemic attacks (TIA), along with hypercholesterolemia and hypertension. No previous history of bleeding or excessive bruising. She was on a statin, an ACE inhibitor, a beta blocker, and an aspirin 81mg. Initial labs in the ER showed a hemoglobin of 7, along with an elevated white blood cell count of 12K with normal platelet count of 220. Her PT was normal, at 11 seconds, but her aPTT was prolonged at 80 seconds. Chest X-ray showed a large right upper lobe mass. On CT, she had a 4 cm RUL mass, along with bilateral hilar and mediastinal lymphadenopathy, suspicious for lung cancer.

We requested a mixing study to determine the cause of her significantly elevated aPTT. We found that she did not correct her aPTT with addition of normal plasma, and she exhibited further prolongation with incubation. This was suggestive of the presence of a specific factor VIII inhibitor. On further testing, we found a Factor VIII activity of <1% and a Factor VIII inhibitor level of 21 Bethesda units. Therefore, our diagnosis was acquired Factor VIII inhibitor, also known as acquired hemophilia A. Screening for underlying auto-immune disorders such as lupus or rheumatoid arthritis was negative. Therefore, the etiology of her acquired Factor VIII inhibitor was due to underlying malignancy, likely lung cancer.

In terms of management, we recommended using activated prothrombin complex concentrate (aPCC), along with a short course of high dose prednisone. However, due to her history of TIA's in the past, she was afraid of developing another thrombotic or ischemic event; therefore, she refused treatment with aPCC. In addition, she also refused further work up for her possible lung cancer, specifically due to risk of bleeding. We started her on high-dose prednisone and supported her with transfusions of packed red blood cells as necessary. Given her progressive decline in performance status and the risks of therapy, she and her family, chose to pursue comfort measures only, and ultimately, she was discharged to home hospice.

Discussion

It is not uncommon to see patients, both in the inpatient and outpatient setting, with ecchymosis. However, in cases of unprovoked, severe ecchymosis, possibly even spontaneous hematomas, we should be alerted to the possibility of a serious underlying bleeding diathesis. Evaluation for such patients begins with a detailed history as it will direct laboratory testing and ultimately management. For instance, mucocutaneous bleeding and petechiae generally are more common in platelet disorders, whereas large, subcutaneous ecchymosis, hemarthroses, and muscle hematomas are more consistent with clotting deficiencies. Our patient had a large palpable area of ecchymosis, along with deep soft tissue hematoma. These findings, in an elderly patient without history of bleeding disorder or trauma, should raise the clinical suspicion of acquired Factor VIII inhibitor, which could be considered a medical emergency.

Initial laboratory evaluation begins with a CBC, PT, and aPTT with examination of the blood smear. An abnormal CBC and/or smear usually will help in the diagnoses of a platelet related problem. A prolonged PT would be indicative of an abnormality in the extrinsic pathway, such as warfarin therapy, liver disease, vitamin K deficiency, or early DIC. In our patient the CBC, smear, and PT were all normal. The issue was a significantly prolonged aPTT, pointing to an intrinsic pathway issue. In these cases, it is either a factor deficiency (hemophilia A, hemophilia B, Factor XI deficiency) or an acquired inhibitor, such as antiphospholipid antibodies, or acquired antibodies to Factor VIII, IX, or XI. To differentiate between the two, a mixing study is necessary. If the mixing study corrects with the addition of normal plasma, it is most likely a deficiency. However, if the abnormal aPTT does not correct or only partially corrects, it is more likely to be an inhibitor. In cases of Factor VIII inhibitors, the aPTT may initially correct after addition of normal plasma, then become prolonged after 60 to 120 minutes of incubation. The suspicion of a Factor VIII inhibitor could then be confirmed with a Factor VIII activity level, and a Bethesda assay to quantify the inhibitor level, which was done with our patient.

The most common auto-antibodies that affect clotting and lead to clinically significant bleeding are those that interfere with the activity of Factor VIII.[1] Given the rarity of this condition, information on epidemiology and etiology is sparse. Based on a patient survey study, most patients are over the age of 50, and identifiable causes included pregnancy/postpartum, rheumatoid

arthritis, systemic lupus erythematosus, drug reactions, and malignancy.[2]

In a small review of 27 cases of malignancy and acquired Factor VIII antibodies, the authors found that there was a close temporal relationship between the diagnosis of cancer and the detection of Factor VIII antibodies.[3] Furthermore, there was no specific relationship with specific tumor types (though prostate and lung were more common). The authors hypothesized that this condition is an "auto-immune reaction to the tumor." They compared it to other autoimmune phenomena we see in cancer patients, such as immune thrombocytopenia, auto-immune hemolytic anemia, and auto-immune skin disorders. This theory is further supported by the fact that in their review cancer patient treated with immunosuppressive therapies had better outcomes.

The recommended initial treatment of Factor VIII inhibitors is two pronged.[4] First, control the bleeding; then, eliminate the source of the inhibitor. Treatment options to control the active bleeding may include aPCC, dDAVP, or even Factor VIII concentrates. The decision on which agent or combination of agents to use will depend on the severity of the bleeding and the titer level of the inhibitor. Elimination of the inhibitor generally requires the use of immunosuppressive therapies, such as glucocorticoids, cyclophosphamide, rituximab, or even immune globulin.

Although acquired Factor VIII inhibitor is a rare phenomenon in cancer patients, it is a potentially catastrophic complication, which, if identified early enough, may be reversed and treated effectively.

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