

The hematuria case of a lifetime: Prolonged hematuria in the setting of an isolated prolonged aPTT

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Introduction

An isolated aPTT prolongation in the setting of bleeding represents a rare clinical scenario, albeit one with a limited differential diagnosis. An isolated aPTT entails a normal platelet count, bleeding time, PT and INR. This coagulation profile is highly suspicious for a factor deficiency, severe Von Willebrand disease, or an acquired factor inhibitor. Congenital factor deficiencies include factors VIII, IX, & XI. Acquired inhibitors are antibodies against intrinsic pathway factors. The most common acquired inhibitor is against factor VIII, which is also termed acquired hemophilia A. However other factor inhibitors include lupus anticoagulant, thrombin and factor V (1). There are a variety of mechanisms in which an inhibitor may lead to bleeding, including functional blocking of factors and increased clearance of factors; with the former being the most common mechanism in acquired hemophilia A.

Acquired hemophilia A has an estimated incidence of approximately 1.5 million persons annually (2). This typically is a disorder involving older individuals, with over 80% of cases involving those over the age of 65 (3). The most common clinical presentation for those with acquired factor VIII deficiency and other acquired factor inhibitors is subcutaneous bleeding. Other bleeding manifestations include muscle or retroperitoneal hematomas. When approaching the bleeding patient and an isolated aPTT, a proper medication review should be completed to exclude receipt of heparin or a direct thrombin inhibitor, as these may mimic a similar coagulation profile. A mixing study is the next step in evaluation to elucidate the cause of an isolated prolonged aPTT. A mixing study entails a 50-50 mixture of patient plasma and controlled plasma with a repeat aPTT. The presence of an inhibitor is indicated by the lack of correction following mixing (4).

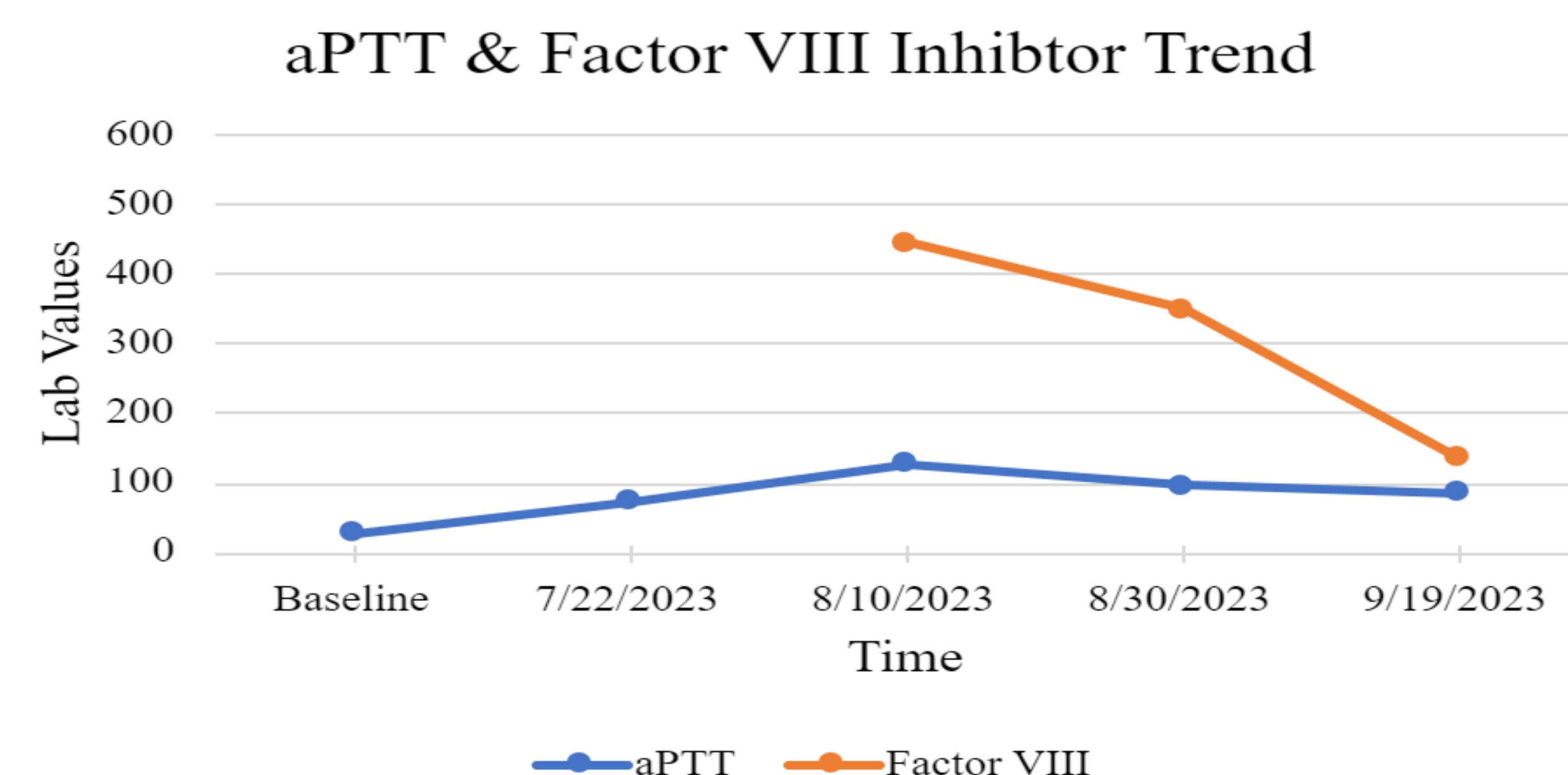
This case highlights the typical presentation for acquired hemophilia A, with the unexpected finding of the additional inhibitor lupus anticoagulant in a patient who demonstrated bleeding without associated thrombosis.

Case

A 66-year-old female presented for evaluation of new onset hematuria. She denied preceding urologic procedures, UTI, heparin or direct thrombin inhibitor use, or other risk factors. Her baseline history is significant for recent bleeding from severe PUD one month prior and long-standing anemia of chronic disease from rheumatoid arthritis. However, she denied other overt bleeding on admission.

On hospital arrival the patient was hemodynamically stable. Her pertinent labs include a hemoglobin of 6.8 (baseline 8-9) and a platelet count within normal limits. Her aPTT was 128 (baseline 75 1 month ago and 28 6 months prior), PT 12.8, and an INR of 1.8. A follow up mixing study showed no correction of aPTT on immediate and prolonged incubation. Her Factor VIII activity was reduced < 1. Lupus anticoagulant panel was positive. Her Factor VIII inhibitor factor resulted at 446.6 Bethesda units

The patient was started on continuous bladder irrigation and supportive cares including one packed red blood cell unit with correction of hemoglobin to her baseline. For medical treatment to control her bleeding, she was initiated on recombinant Factor VIIa concentrate to bypass the inhibitor. She also received antifibrinolytic Amicar therapy. To eliminate the presumed inhibitor, she was initiated on high-dose steroids. With these measures she showed an interval improvement in her aPTT and her gross bleeding improved. On confirmation of her diagnosis, she was started on cyclophosphamide and rituximab. Her factor VIII inhibitor decreased to 350.6 BU after the first dose of cyclophosphamide and rituximab.



Discussion & Conclusions

- The most common inhibitors include acquired factor VIII and lupus anticoagulant. Both will present with lack of correction with a mixing study. In our case, the patient demonstrated positivity for both factor VIII inhibitor and lupus anticoagulant. Although the presence of lupus anticoagulant was detected, this was likely an incidental finding and was likely not clinically significant. The presence of lupus anticoagulant should be associated with thrombosis as opposed to bleeding.
- When aPTT does not correct on mixing, follow-up studies includes use of the Bethesda assay, which helps to diagnose the factor inhibitor and quantify the antibodies. Once confirmed, the mainstay of treatment includes bleeding control and elimination of the inhibitor. Bleeding control may be achieved with use of a factor eight inhibitor bypassing activity (FEIBA) or recombinant activated factor VII. Medical therapy to eliminate the inhibitor may be based on high or low inhibitor titers, and may include regimens of prednisone, cyclophosphamide and/or rituximab (5).

References

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