CLINICAL VIGNETTE

A Rare Case of Acquired Hemophilia Presenting as an "Unusual GI Bleed"

Craig Gluckman, MD and Rimma Shaposhnikov, MD

Patients with acquired hemophilia may present with a spontaneous bleeding diathesis leading to large hematomas, extensive bruising or severe soft tissue bleeding including severe epistaxis, gross hematuria or even gastrointestinal (GI) bleeding. This "unusual cause" for bleeding occurs due to an acquired inhibitory antibody to the coagulation pathway that either decreases the activity or increases the clearance of a specific clotting factor. We describe a rare case of an acquired Factor VIII deficiency initially presenting as a severe upper GI bleed in an elderly patient.

Case Presentation

An 80-year-old male with hypertension and a remote history of prostate cancer was admitted to our community hospital with new onset of symptomatic anemia. His hemoglobin two months prior to admission was 14.0 g/dl, but on admission had dropped to 6.3 g/dl with a normal MCV. The patient reported two days of black and tarry stools, and denied hematemesis or abdominal pain. He was not taking any NSAIDs, aspirin or anti-coagulants. He had been falling frequently at home and was noted to have a bruised and swollen left arm on arrival to the ER. He denied loss of consciousness or any other signs of overt bleeding. On examination, he was hemodynamically stable and his exam was positive only for melena on digital rectal exam and a large, partially circumferential ecchymosis on his left elbow and forearm. He was initially transfused with packed red blood cells and started on a PPI infusion. GI was consulted and an esophagogastroduodenoscopy was scheduled the next day after appropriate resuscitation. Endoscopy revealed multiple gastric antral and post bulbar duodenal ulcers with active oozing and overlying adherent clots. Adequate hemostasis was achieved with epinephrine injection and hemoclip placement. Random gastric biopsies were negative for H. pylori. He showed no evidence of further upper GI bleeding for the remainder of his hospital stay. However, the ecchymosis on his arm had increased in size with new large unprovoked hematomas of both thighs and left flank together with a further drop in hemoglobin. Non-contrast CT abdomen was negative for a retroperitoneal bleed. Given these apparent spontaneous soft tissues bleeds and dropping hemoglobin together with an unexplained elevated activated partial prothrombin time (aPTT), hematology consult was obtained. His platelets and prothrombin time (PT) were normal. Subsequent mixing test was positive suggesting the presence of a clotting factor inhibitor. He was empirically given Kcentra®, an activated prothrombin complex concentrate (aPCC) and recombinant Factor VII (rFVIIa) for his severe soft tissue bleeding. Prior to receiving these, Factor VIII activity was extremely low at 1%, with normal Factor VII (>400%) and normal Factor IX (158%). The quantitative Bethesda assay was positive at 424.0 ($\leq$ 0.5 BU) confirming the presence of a Factor VIII inhibitor. In an attempt to clear the inhibitor, he had been started on prednisone and empiric rituximab was being considered. The patient continued to have spontaneous soft tissue bleeding at multiple sites requiring regular transfusion of blood products and clotting factors. Given the poor response to the current available therapy, he was transferred to a tertiary hospital for a higher level of care but unfortunately demised shortly after arrival following a PEA arrest, felt to be secondary to hemorrhagic shock. The cause for this patient's initial GI bleed and ongoing spontaneous soft tissues hematomas was felt to be due to acquired hemophilia A with severely elevated Factor VIII antibody titer. There was no evidence of a precipitating rheumatologic disease, occult malignancy or offending drug to account for this uncommon condition.

Discussion

Acquired hemophilia due to an acquired inhibitor of the coagulation pathway should be suspected in any patient presenting with severe GI bleeding or with severe, unexplained spontaneous soft tissue or mucosal bleeding. A large hematoma or ecchymosis especially in an older patient without significant trauma or known bleeding disorder should raise the suspicion to the presence of an acquired factor VIII inhibitor. Acquired inhibitors of coagulation are mostly IgG autoantibodies that either inhibit the activity or increase the clearance of an individual clotting factor. In addition, an elevated aPTT with a normal PT should also raise suspicion for acquired inhibitor in a patient not receiving heparin containing products. The most common inhibitory clotting factor antibody is directed against Factor VIII activity, also called acquired hemophilia A. These acquired inhibitory conditions should be differentiated from inherited factor deficiencies (congenital deficiencies of factors VII, IX or XI) and von Willebrand disease (vWD).

In a population based European cohort study, the incidence of acquired factor VIII inhibitor was 1.3 to 1.5 cases per million population per year.[1] The most common associated precipitating conditions were malignancy, post-partum or an autoimmune conditions. In post-partum females the condition is usually diagnosed within two to three months post-partum and mostly associated with the first pregnancy.[2] The outcome in

these primigravidas is usually excellent. Inhibitory antibodies to factor VIII is a rare complication of solid organ tumors. There is also an association with some medications including certain anti-biotics and immunomodulatory agents. These antibodies however often resolve with withdrawal of the offending drug.

As in the above case, symptomatic patients often present with spontaneous soft tissue or mucosal bleeding. Unprovoked hemarthroses, commonly seen in congenital factor VIII deficiency, are unusual in patients with the acquired form of the disease. In a patient with a prolonged aPTT but a normal PT, who has not received heparin, deficiencies of factors VIII, IX or XI can either be hereditary (congenital) or acquired. It is reasonable to repeat a blood sample from an uncontaminated vein if heparin was thought to be the culprit. Once this has been done, to differentiate a hereditary from an acquired cause, a mixing test (inhibitor screen) can be done. A correction of the prolonged aPTT suggests a factor deficiency or vWD, but if the aPTT continues to remain prolonged after mixing and incubation, this indicates the presence of a coagulation factor inhibitor. Finally, a Bethesda assay is used to quantitatively define the factor VIII inhibitor activity and antibody titer.

Once diagnosed, an attempt should be made to identify the precipitating cause, while controlling the bleeding with replacement products and eliminating the inhibitor. For patients like ours with severe bleeding and high titers of inhibitory antibodies, it is recommended to use activated PCC (such as factor VIII inhibitor bypassing activity- FEIBA) or rFVIIa while further evaluation is underway. FEIBA is the only aPCC available in the US.[3] There are no comparative trials to determine whether an aPCC or rFVIIa is more effective in the setting of a high titer inhibitor and active bleeding. Results from an uncontrolled European registry in 501 patients with acquired factor VIII deficiency suggest that the two agents have similar efficacy.[4] Thus, the choice between aPCC and rFVIIa should likely be guided by local experience, availability and cost considerations.

In order to eliminate the Factor VIII inhibitor, immunosuppressive medications are used. There is no good data to suggest a preferred regimen nor whether the decision should be based on inhibitor titer or factor VIII level. The European Acquired Hemophilia Registry notes the most employed initial therapy was glucocorticoids alone, glucocorticoids plus cyclophosphamide or glucocorticoids plus rituximab.[5] This group reported complete remission was highest in the glucocorticoids plus cyclophosphamide treated patients. They found that second-line therapy was successful in approximately 60 percent of cases that failed first-line therapy and outcome was not affected by the choice of first-line therapy.

The response to treatment is monitored by observing a decrease in bleeding and a reduction in the titer of the inhibitor. The inhibitor titer drops very slowly during treatment so aPTT level and inhibitor titer should only be tested every 2-4 weeks once treatment has been started. The relapse rate after a first complete remission has been estimated at about 20%, with most of such relapsing patients achieving a second complete remission.[6]

Conclusion

Acquired hemophilia is a rare cause of otherwise unexplained or “unusual GI bleeding”. It should be suspected when bleeding occurs in the setting of an elevated aPTT with a normal PT, in a patient not receiving heparin products. Prompt diagnosis together with infusion of replacement blood products and elimination of the inhibitory clotting factor, remain key to decreasing the morbidity and potential mortality associated with this often unexpected condition.

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