CLINICAL VIGNETTE

Acquired Hemophilia

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Case Review

A 60-year-old woman was referred for evaluation of significant bruises following minor trauma on her limbs for one year. The bruises were raised and painful and gradually faded. There was no gingival bleeding, epistaxis, petechial rash, hemarthrosis, GI bleeding, or hemoptysis. She is post-menopausal and had no history of significant menorrhagia. She had no history of invasive procedures or surgery except for a dental procedure more than two decades ago. She has osteopenia and hyperlipidemia but no other significant chronic problems and takes no prescription medications, only multivitamins, calcium, and Vitamin D. Recently, while travelling in New York, she developed painful swelling of the right hamstring and was evaluated by an orthopedist. Labs were remarkable for a prolonged PTT, confirmed on repeated testing. She was also evaluated by a rheumatologist for mild proximal interphalangeal joints swelling. She has taken Ibuprofen and acetaminophen in the past but none recently. There was no family history of abnormal bleeding.

Physical examination revealed bruises at various stages of resolution, some of which were raised. They were predominantly on her limbs with small areas of bruising on the trunk. The rest of the physical examination was normal.

Labs included a normal CBC: Hgb 13.2, platelets of 279K, WBC 8.6 with normal differential. Her comprehensive metabolic panel was normal, as were Creatinine kinase, uric acid, CRP, TSH and Vitamin B12. Her PTT was prolonged at 58 seconds [normal 23.6-35.5]

Additional coagulation studies were obtained and are listed in Table 1.

Table 1: Additional Coagulation Studies

PT 10.9 [normal 9.4-12.3 second] INR 1.04
PTT 46 [normal 21-34 sec] Control–Immediate 30 [normal 23-33 sec]
1:1 mix Immediate 36 [normal 23-33 sec] Control –Incubated 36 [normal 23-33 sec]
1:1 Incubation 43 [normal 23-33 sec] Thrombin time 16.2 [<20.0]
Fibronogen 329 [normal 200-500 mg / dL]
D Dimer Quantitative 0.23 [<0.50 mg/L LFEG] VWF activity 214 [50-150%]
VWAg 179 [50-150%]

VW multimer assay - normal pattern Platelet Function Assay Collagen / EPI 81 [normal 82-150 second] Collagen / ADP not performed

Repeat APTT 52.1 second [23.4-35.4] APTT 1:1 Normal pool mix 37.6 second [23.4-36.4] APTT 1:1 saline mix 67.5 second [23.4-150] APTT 1:1 Normal pool mix, at 60 minute Incubation at 37 Deg. C 49.2 sec PTT-LA 71.9 [0 - 50 second] PTT-LA Mix 58.2 [0 – 50 second] Hexa Phospholipid 8.3 [0 – 8 second] DRVVT 37.9

Repeat DRVVT screen was normal at 33.6 sec [normal <55.1] Anticardiolipin Antibodies were negative Factor VIII Activity 1% [repeat 29] [50-150] Factor VIII Chromogenic 4% [50-170] Factor VIII Quantification (nonfunctional) 56% [64-189] Factor VIII Inhibitor Assay human Bethesda Titer 70 [normal <0.6]

Other baseline blood work included negative Rheumatoid factor 4 IU/ml; cyclic citrullant Antibody < 15.6 units [normal 0-199], HLA B27negative, ANA negative, Hepatitis B and C serologies negative, Vasculitis panel including ANCA negative, Anti-phospholipid Antibody panel including Anti B2 glycoprotein Ab were negative. Lupus Anti Coagulant was 0.7 [normal <1.2].

Discussion

Although acquired Hemophilia A (AHA) is a rare autoimmune hemorrhagic disorder, it is the most frequent cause of acquired coagulation factor deficiency. In AHA, autoantibodies to factor VIII are the inhibitors and cause of factor VIII deficiency, unlike in congenital Hemophilia A with development of inhibitors which are alloantibodies.[1-4]
Patients without family or past personal history of bleeding may present with bleeding, which may be life threatening. Most bleed into subcutaneous tissues and muscle. Mucosal bleeding can be present but unlike congenital hemophilia, joint hemorrhages are rare. Post-partum hemorrhage and retroperitoneal hemorrhages can be life threatening.[1,2,5] There are two peaks of age distribution, the smaller peak between the ages of 20 and 30, usually female and usually related to pregnancy and postpartum.[6,7] The second peak is in patients

older than 60. In almost 50% patients no cause is identified; in the remaining patients, in addition to pregnancy and the post-partum period, autoimmune disorders are most commonly associated.[8] Other associations include malignancies, both carcinomas and hematological malignancies, most often CLL.[9-12] Acquired Hemophilia A has also been associated with medications including Penicillins, sulfonamides, phenytoin, and clopidogrel. Association with Bacillus Calmette Guerin vaccination has also been reported as well as immunotherapies such as Interferon, Ipiluminab and Fludarabine, however, causation is not settled.[13,14] There appears to be increased risk in the presence of certain gene polymorphisms (e.g. HLA, CTLA4) and auto reactive CD4+T lymphocyte and elevated BAFF levels (B cell activating factor belonging to the tumor necrosis factor family) have been reported. [15,16]

Inhibitors in both congenital and acquired Hemophilia are usually polyclonal and directed to either the C2 domain (interfering with binding of phospholipids and VWF to factor VIII) or directed to the A2 and A3 domains (binding site for IXa and X and therefore interfering with Xase complex formation).[17,18]

When inhibitors develop in congenital hemophilia A, they are Type 1 inhibitor alloantibodies which follow linear kinetics, while autoantibodies responsible for Acquired Hemophilia A are type 2 inhibitors and do not follow linear kinetics. Therefore at high titers of inhibitor in AHA, it is difficult to effectively treat with factor VIII concentrate replacement.[19,20] Although inhibitor in AHA is measured by the Bethesda method, the titer does not correlate with severity or frequency of bleeding.[21,22] Although spontaneous regression has been reported, treatment is usually indicated when inhibitor is identified because of risk of severe or fatal bleeding.

The diagnosis should be suspected in a bleeding patient with prolonged activated Partial Thromboplastin Time, which does not correct, especially on prolonged incubation in the mixing study. APTT is performed by recalcified citrated plasma in the presence of thromboplastic material that does not have tissue factor activity (hence term Partial) and negatively charged particles (kaolin, silica, or celite), which results in contact factor activation and thereby initiating coagulation via the intrinsic system.[23] The PTT is prolonged with deficiency or inhibitor to clotting factors except for factor VII. Lupus anticoagulants and other antiphospholipid antibodies are antibodies directed against plasma protein bound to anionic phospholipid causing a prolonged aPTT by interfering with in vitro assembly of prothrombin complex.[24] Also in vWD, factor VIII may be low and may have prolongation of PTT.

In this patient, PTT results were reported from different labs, with times varying from 32 to >68 seconds. This variability was likely related to reagents and other conditions of testing and similarly had different DRVVT. The DRVVT mixing study is performed with pooled plasma along with a limited quantity of thromboplastic material and is therefore sensitive to amount of phospholipid available for assembly of prothrombin complex and thus presence of aPLS. If the aPTT remains prolonged after mixing with normal plasma, an inhibitor is the cause of prolonged PTT. There is, however, no standardized source of reagent, instrument and various aspects of the test, hence the unreliability of a single positive or negative test for Lupus Anticoagulant. Some inhibitors can take longer to inhibit clotting factors in pooled plasma in a mixing study and aPTT may appear to be corrected initially in a mixing study and prolonged again later after incubation from 30 to 120 minutes. Delayed reactivity is often seen with factor VIII inhibitor.[23,24]

If a patient with acquired Hemophilia A is actively bleeding, options to help stop bleeding include use of bypassing agents, either activated prothrombin complex or activated recombinant factor VII.[25,26] Overcoming inhibitors at increasing doses of concentrates or recombinant factor VIII usually does not work in AHA with high inhibitor titers but may be used as adjunctive treatment. At low titers of inhibitors (ie <5) and non-life threatening bleeding, DDAVP may be useful.[26,27] Elimination of the inhibitor is mainstay of treatment of AHA. Immunoabsorption or selective plasmaphresis has been helpful as adjunctive treatment in acute bleeding.[28] Immunosuppression to decrease and ultimately eliminate the formation of factor VIII inhibitors is the most important part of the treatment. Steroids and chemotherapies like cyclophosphamide alone or in combined regimen have been most successful. Other agents include cyclosporine, azathioprine, mercaptopurine, and vincristine.[29,30] Intravenous immunoglobin therapy has been tried but is less effective and less durable than cytotoxic chemotherapy.[31] Chimeric monoclonal antibodies directed against CD20, such as Rituximab, have been shown to be quite effective even in patients who did not respond to prednisone or cyclophosphamide. Although Rituximab treatment may take longer to produce a response, remissions have been reported.[32-34] Combination therapy may need to be employed in patients. Although some patients with lower titers, especially in postpartum related and drug induced inhibitors, may have spontaneous remission, treatment of the underlying cause may also lead to elimination of the inhibitor, and treatment is warranted because of high mortality rate from bleeding.

There is high infection related mortality from immunosuppression and underlying conditions, so vigilance for infection should be high and should be aggressively managed in patients on treatment.[25,35]

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