Acquired factor VIII inhibitor and lupus anticoagulant presenting with prolonged aPTT: a case report

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Abstract

Acquired factor VIII inhibitor is a rare occurrence and may cause severe bleeding by interfering with the coagulation cascade. We report an interesting case of a 59-year-old white man with an acquired factor VIII inhibitor and lupus anticoagulant. Clinical findings included large hemorrhagic areas of the extremities, a prolonged activated partial thrombin time (aPTT) that did not correct with mixing studies and an elevated Bethesda assay. Treatment consisted of high-dose steroids with a tapering dosage. An acquired factor inhibitor should be considered in patients presenting with a prolonged aPTT that does not correct with mixing studies.

Keywords

Factor VIII inhibitor; lupus anticoagulant.

Introduction

Acquired factor VIII inhibitor is a rare occurrence among bleeding disorders. Factor VIII is an X-linked gene product that combines with factor IXa in the presence of phospholipids and calcium, which then activates factor X. Factor VIII functions as a catalyst for the coagulation pathway. Low levels of factor VIII can be an inherited condition referred to as classic hemophilia A; however this case study focuses on the acquired autoantibody inhibitors to factor VIII. The likely clinical findings in a deficiency or inhibition of factor VIII are easy bruising and deep muscle-joint and posttraumatic bleeding. A mild case may not be apparent until there is a traumatic or surgical challenge in the second or third decade of life. A severe case is diagnosed routinely within the first year of life, likely from post circumcision bleeding or unexplained intracranial hemorrhage.

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Case report

A 59-year-old white man with a history of hypertension, asthma, and chronic steroid and narcotic use for degenerative spine disease was admitted to our hospital for pain management. On admission the patient was found to have a slightly increased activated partial thrombin time (aPTT) of 35.1 s (normal 26.1–33.5 s) and a normal prothrombin time (PT) of 12.1 s (10.0–12.4 s). On the fifth day of hospitalization the patient developed a sudden non-traumatic bleed on his left forearm and on his right inner thigh.

This patient denied previous non-traumatic bruising or unexplained bleeding. He had undergone multiple uncomplicated back surgeries and a hip replacement within the previous 10 years. He denied using aspirin, non-steroidal anti-inflammatory drugs, warfarin or other herbs and vitamins in the past month. He had a history of high-dose narcotic needs for pain relief (i.e. dilaudid 100–200 mg/day). No family history of bleeding disorders was noted in his parents, grandparents or his brother. Chronic medications included atorvastatin, furosemide, spironolactone, prednisone, diazepam, alfuzosin, dutasteride, valacyclovir, ducosate, hydromorphone and oxycodone.

Physical examination was significant for a hematoma measuring approximately 14 cm×10 cm on the right thigh and a 5 cm×4 cm hemorrhage on the right forearm and wrist. No obvious trauma was noted including venapunctures. No hepatosplenomegaly was appreciated and no petechiae were seen.

Laboratory results on the day of the bleeds included a white blood cell count of 9000/µl (normal 3800–10,800/µl) with normal differential, hemoglobin 10 g/dl (normal 14–18 g/dl) (down from 12.5 g/dl on admission) and platelet count of 394,000/µl (normal 150,000–450,000/µl). The aPTT had risen to 51.6 s. PT/internationalized normalized ratio remained normal, and complete metabolic panel was within normal limits. Repeat aPTT was performed 2 additional times that day to confirm the change and to ensure appropriate tubes were utilized.

A mixing study was ordered to confirm the presence of an inhibitor. Lupus anticoagulant was noted and confirmed with a dilute Russell’s viper venom time assay. These findings did not explain spontaneous bleeding; so further coagulation testing was pursued. Thrombin time was 16.6 s (11.5–17.9 s). Fibrinogen level was 502 mg/dl (normal 200–400 mg/dl), D-dimer at 8.76 mg/l (normal 0.00–1.94 mg/l) and haptoglobin 256 mg/dl (normal 30–200 mg/dl). The von Willebrand factor, cadiolipin antibody, factor IX, factor XI and factor XII assays were normal.

Systemic lupus erythematosus work-up showed a negative anti-neutrophil cytoplasmic antibody screen, negative Sjogren antibody SS-B and SS-A, and a normal total complement count. DNA double-stranded antibody and Smith antibody were both negative. β2-Glycoprotein antibodies for IgA, IgG and IgM were negative. The patient was found to have normal immunoglobulin levels.

Factor VIII activity was <1% (normal 50–180%). In light of the mixing study and his clinical history, a factor VIII inhibitor was suspected. Thus a Bethesda assay was obtained and was 70.4 Bethesda units (normal <0.4).

The patient was started on prednisone 80 mg daily. The aPPT began normalizing over a 5-day period back to 42.3 s. The patient had no further significant bleeding during his hospitalization.

His pain had stabilized and he was subsequently transferred to a rehab facility on a tapering dose of prednisone with plans to carefully monitor his symptoms and hematologic findings.

Discussion

Acquired factor VIII inhibitor is a rare disorder often leading to severe hemorrhage. The most common presenting sign is unexplained excessive bruising and bleeding in patients typically older than 60 years[1]. The mixing study should not correct and a factor VIII level should be nearly undetectable. A coagulation panel (PT, aPTT, thrombin clot time, fibrinogen, platelet count, platelet function assay and/or bleeding time) is recommended in the initial work-up of a patient who presents with prolonged bleeding or hemaearthrosis. The solitary finding of a prolonged aPTT should prompt the ruling out of common causes such as heparin or other anticoagulant medications and inappropriate blood draw through a peripheral venous line.

Subsequent evaluation for a prolonged aPTT should include both inherited disorders and acquired disorders of clotting factors (hemophilia); specific inhibitors, non-specific inhibitors and von Willebrand disease (vWD). vWD is the most common hereditary coagulation abnormality with about 0.01% prevalence in the general population. vWD usually presents early in life with a prolonged bleeding time and prolonged aPTT as well as a family history of bleeding[2].
A deficiency of a specific factor corrects with a mixing study and also presents early in life, usually with a known family history of bleeding disorders. A non-specific inhibitor such as lupus anticoagulant (LA) typically prolongs aPTT however it is associated predominantly with thrombotic events[3].

The effects of an LA can be confounding when investigating a prolonged aPTT so different aPTT reagents may be used to help minimize these effects. Studies have concluded that different aPTT reagents vary in sensitivity most likely because of the heterogeneity of LAs; therefore more than one aPTT reagent should be used in the detection of LA[4]. A more recent study that evaluated clotting times in the detection of LA concluded that both low and high concentrations of phospholipids should be used in the screening and confirmatory procedure; and then compared to a reference of normal plasma, which will help increase the sensitivity[5]. Furthermore, a mixing study may be performed immediately or after incubation. Fast reacting inhibitors will not correct the immediate mix, whereas slow acting or time-dependent inhibitors allow the immediate mix to correct which makes for a false result. It is therefore essential to follow up a corrected immediate mix study with an incubated mix study to diagnose a time-dependent inhibitor[6,7]. When a mixing study does not correct and factor VIII levels are undetected, the investigation should focus on an inhibitor. The confirmatory gold standard for the factor VIII inhibitor is the Bethesda assay.

The Bethesda assay is a measurement of the amount of factor VIII inactivated by the patient’s plasma incubated with normal plasma under specific conditions. One Bethesda unit (BU) is equal to the amount of antibody that will neutralize 50% of factor VIII in a 1:1 mixture of the patient’s plasma and normal plasma. An inhibitor should be used in the detection of LA[8]. A more recent study that evaluated clotting times in the detection of LA concluded that both low and high concentrations of phospholipids should be used in the screening and confirmatory procedure; and then compared to a reference of normal plasma, which will help increase the sensitivity[5]. Furthermore, a mixing study may be performed immediately or after incubation. Fast reacting inhibitors will not correct the immediate mix, whereas slow acting or time-dependent inhibitors allow the immediate mix to correct which makes for a false result. It is therefore essential to follow up a corrected immediate mix study with an incubated mix study to diagnose a time-dependent inhibitor[6,7]. When a mixing study does not correct and factor VIII levels are undetected, the investigation should focus on an inhibitor. The confirmatory gold standard for the factor VIII inhibitor is the Bethesda assay.

The Bethesda assay is a measurement of the amount of factor VIII inactivated by the patient’s plasma incubated with normal plasma under specific conditions. One Bethesda unit (BU) is equal to the amount of antibody that will neutralize 50% of factor VIII in a 1:1 mixture of the patient’s plasma and normal plasma. Because high residual factor VIII levels in non-hemophilic patients with acquired inhibitors, it is difficult to determine the inhibitor level with the Bethesda assay. The results of the assay underestimate the actual in vivo level of human factor VIII autoantibodies and are considered less valuable in guiding therapy for non-hemophiliacs. This frequently causes more factor VIII to be administered to maintain hemostatic levels in patients with autoantibodies to factor VIII[9].

Factor VIII inhibitors are mainly of the IgG subclass type. The cause of the autoantibody is often unclear in non-hemophiliacs, although autoimmune diseases such as systemic lupus erythematosus, Sjogren syndrome and rheumatoid arthritis are found to be in association. There have been reports that the inhibitor has been associated with chronic renal failure, hepatic cirrhosis and medications such as penicillin and interferon. Cancer, particularly lymphoproliferative disorders have also been noted to have an association with factor VIII inhibitors[10–13]. There have been connections made between acquired factor VIII inhibitor and pregnancy which mainly presented as post partum hemorrhage that did not initially resolve with standard management[9]. Hemophilia A (factor VIII deficiency) patients who are exposed to replacement are estimated to have a 20% lifetime risk of developing a factor VIII inhibitor[14,15].

The management of factor VIII inhibitor focuses on the acute situation of hemorrhage and also on the long-term eradication of the inhibitor. The acute treatment makes use of bypassing agents and strategies for raising factor VIII levels. Currently the first-line treatment for acute hemorrhage is with bypassing agents such as recombinant activated factor VII (rFVIIa) and the activated prothrombin complex concentrate (aPCC) factor 8 inhibitor bypassing activity (FEIBA)[16–18]. These bypassing agents have produced promising results in both moderate bleeding and severe bleeding[19–21]. However, rFVIIa is preferred because of its excellent efficacy and safety profile[22]. With regard to the therapeutic strategies of raising factor VIII levels, desmopressin used alone or in combination with human factor VIII may be effective in those with a low titer of inhibitor and experiencing non-life threatening hemorrhage, minor bleeding or for hemostatic coverage of invasive procedures[23–25].

Long-term treatment with the intent to eradicate the inhibitor focuses on the use of the following options, which have been variably combined: immunosuppressive agents, high-dose intravenous immunoglobulin, immunoadsorption and immune tolerance.

Immunosuppressive agents such as prednisone with azathioprine or prednisone with cyclophosphamide and vincristine, have shown promising results[26,27]. However, these agents must be used with caution due to the adverse effects such as infection from the immunosuppressive therapy or infertility from cytotoxic agents[28,29]. Intravenous immunoglobulins are not considered a first choice for the suppression of factor VIII inhibitor according to the current clinical trials but may be used in combination with other types of eradicators because they are well tolerated and have few toxic effects[30]. Immunoadsorption is very costly and technically demanding so it is limited to specialized centers but it allows for the temporary, rapid, extracorporeal removal of inhibitor, which makes it ideal for severe bleeding with high-titer...
inhibitors. It has been proposed that immune tolerance protocols may be effective in the eradication of factor VIII inhibitor based upon the idea that the exogenous infusion of factor VIII stimulates the immune system and increases the susceptibility of the inhibitor-producing B-cell clones to the effect of cytotoxic agents. Unfortunately it is not considered first-line therapy because these positive results are only preliminary and have not yet been validated by further large controlled studies.

An interesting development is the treatment of factor VIII inhibitor with rituximab, a monoclonal antibody originally used for B-cell non-Hodgkin lymphoma. Various studies have shown positive clinical response with the use of rituximab alone or in combination with immunosuppressive agents. However, the promising response illustrated by the data should not be over interpreted because it mainly stems from case reports and small studies. In addition, the majority of patients were given concomitant immunosuppressive therapy, which makes it difficult to evaluate the actual effectiveness of rituximab. Thus it is recommended that rituximab is used as a second-line treatment in combination with immunosuppressive therapy because of the lack of large prospective studies.

Since our patient did not have an active bleed and was originally on low-dose prednisone for his severe pain, the decision was made to increase this dose to 80 mg daily and slowly taper the dose while monitoring for a response. Over the course of 7 days, the aPTT had dropped from 75.8 s to 43.4 s. He had no further spontaneous bleeding during his hospitalization and was transferred to a rehab facility secondary to his lumbar disk disease. The plan was to repeat his coagulation screen every week as we tapered his steroids, giving consideration to cytoxan or rituximab if he failed steroids.

Conclusion

The presented case was particularly interesting since our patient was found to have both a lupus anticoagulant and factor VIII inhibitor without a prior history of thrombosis or bleeding. Our patient did present with significant spontaneous hemorrhages. A mixing study indicated the presence of an inhibitor and further testing confirmed a lupus anticoagulant but this did not explain the clinical case. The hemorrhaging could have been explained by an undetectable factor VIII level but the patient’s age and lack of historical bleeding suggested a factor deficiency to be very unlikely.

Teaching points

The Bethesda assay was critical in diagnosing our patient. Once we confirmed a factor VIII inhibitor, based on the literature, we opted for a pulse of steroids for our patient. He received 80 mg of prednisone daily and within 1 week his aPTT had dropped from 75.8 s to 43.4 s. He had no further spontaneous bleeding during his hospitalization and was transferred to a rehab facility secondary to his lumbar disk disease. The plan was to repeat his coagulation screen every week as we tapered his steroids, giving consideration to cytoxan or rituximab if he failed steroids.

References


