Acquired Factor VIII Inhibitor: A Rare Etiology for Bruisability and Anemia

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Abstract Acquired factor VIII inhibitor is a very rare cause of easy bruisability, muscular hematomas, and subsequent anemia in the elderly patient population. The incidence of acquired factor VIII inhibitor is one in one million. Here we report an elderly patient who presented to the hospital for bruising easily fatigue and was found to have acquired factor VIII inhibitor on further investigation. He responded to the treatment appropriately, and hemostasis was achieved successfully with recombinant VII concentrates and eradication of the inhibitor with Imuran and steroid combination.

Keywords Acquired factor VIII inhibitor · Hemostasis · Bruisability · Hematomas · Anemia

Case Report

An 86-year-old male with hypertension and an unobstructed inguinal hernia presented to our institution with 2 weeks history of generalized weakness, fatigue, and easy bruisability. He also complained of melena, but denied hematemesis or hematochezia. He also denied any loss of appetite but complained of 30 pounds weight loss in 2 months. Family history indicated no hematological or oncological problems. He denies any history of smoking or alcohol or drug abuse. He is using Lisinopril for hypertension and denied any usage of herbal or over the counter medication. The patient underwent a lab work up, revealed

hemoglobin of 7.3 g/dl and hematocrit of 23.3 %. Liver function test showed high total and indirect bilirubin levels.

His basic metabolic profile was within normal limits. A coagulation profile, lactic dehydrogenase (LDH), and serum haptoglobin were ordered. Lab work up revealed platelet count of 327,000/ml, activated partial thromboplastin time (aPTT) of 69.4 s, with a normal prothrombin time (PT) (14.4 s), international normalized ratio (INR) (1.1), and low serum haptoglobin (14) and elevated LDH. Mixing studies were performed, after mixing 1:1 of the patients' plasma with the plasma that contains 100 % of clotting factors; PTT did not correct suggesting the presence of an inhibitor. Despite multiple blood transfusions his hemoglobin/hematocrit remained low. A thoracic/abdominal/pelvic CT scan revealed multiple hematomas suggesting a bleeding diathesis. An acquired factor inhibitor was suspected as had neither the history nor family history of the hemophilia. A hematological consult was sought for evaluation of probable hemolytic anemia and acquired factor inhibitors. A recommendation for prednisone 1 mg/kg/day and recombinant factor VII concentrates (rVIIa) was made in order to achieve hemostasis. We had achieved hemostasis successfully with factor rVIIa. Later, coagulation studies revealed a factor VIII inhibitor at a concentration of 5.7 Bethesda units. A secondary etiology for anemia was ruled out after an esophagogastroduodenoscopy (EGD) and colonoscopy were performed. EGD and colonoscopy failed to reveal any significant pathology. His hospital course was complicated by multiple hematomas on the abdomen and shoulder blades, multiple episodes of drop in hemoglobin. Factor rVIIa infusions were successful in achieving hemostasis all of the times. Age appropriate cancer screening with PSA levels, colonoscopy were performed. Serum plasma electrophoresis (SPEP), urine electrophoresis (UPEP), antinuclear

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antibody (ANA), rheumatoid arthritis, systemic lupus erythematosus (SLE) screenings were also performed. We excluded usage of any herbal/over the counter drugs, skin disorders, solid tumors, and lymphoproliferative disorders by careful history, physical examination, and CT scans of the thorax, abdomen pelvis, bone marrow biopsy, peripheral blood flow cytometry, respectively.

We opted to use Imuran 200 mg daily and a steroid taper. The patient's easy bruisability started decreasing after 2 weeks of steroid and 1 week of Imuran. He was discharged home subsequently with Imuran, steroid, and hematology follow up. His post discharge course was complicated by a large retroperitoneal and extraperitoneal abscess. Surgery was performed to drain the abscess, Imuran to 50 mg/day and the steroid was continued during the surgical period to treat probable adrenal insufficiency secondary to the high dose steroid and chronic low dose steroid usage with in last 2 months. We achieved hemostasis during the perioperative period with recombinant factor VII concentrates (rVIIa). The patient was discharged home after stabilization.

Discussion

Acquired hemophilia A or acquired factor VIII inhibitor is a rare disorder with an incidence of approximately 1–4 cases/million/year [1, 2]. Although it was reported in all age groups, the most common age of presentation is between 60- and 70-years-old. The second peak age of incidence is between 20 and 30 years, that's in post-partum female patients. The most common clinical presentations are muscular bleeding, hematuria, epistaxis, gastro intestinal bleeding, intracranial hemorrhage, and post-partum bleeding. Clinical presentation of acquired hemophilia doesn't include hemarthrosis like the inherited hemophilia A [1–3]. Patients will have non-complement fixing, IgG antibodies. Precipitation of factor VIII by these antibodies will depend both on temperature and time. The patient's serum may need to be incubated for up to 2 h if the antibody concentration is low [3]. Once acquired factor VIII inhibitor is suspected, factor VIII activity should be evaluated, as well as the inhibitor titers as they will guide the management plan.

We need to exclude the secondary etiology for the acquired hemophilia. The well described associations are autoimmune disorders like systemic lupus erythematosus, dermatomyositis, rheumatoid arthritis, sjogrens syndrome; solid, and lymphoproliferative malignancies; skin disorders like pemphigus, epidermolysis; medication like penicillin, and interferon.

Management of acquired factor VIII inhibitor has two phases; first is achieving hemostasis and second is inhibitor eradication.

Hemostasis Achievement

The clinical condition of the patient and titers of factor VIII inhibitor will help to determine the need to bypass factor VIII in the indirect coagulation cascade.

It is recommended to use factor VIII bypassing agents in patients with severe bleeding irrespective of the inhibitor levels. It's also prudent to use these by passing agents when the inhibitor levels are high (greater than 5 BU) and to the patients who are not responding to of human factor VIII concentrates infusion. Retroperitoneal or retropharyngeal hematomas, muscular hematomas, intra cranial, gastro intestinal bleeding are some of the critical bleeding disorders. Most of the times we need to use clinical judgment along with hemoglobin (Hb) monitoring while treating these patients [2].

The treatment options in above circumstances are either activated prothrombin complex concentrate (aPCC or FE-IBA) or recombinant factor VIIa (rVIIa). Response to the treatment is solely monitored by the clinical response, and Hb monitoring. If we failed to achieve hemostasis with above mentioned regimens we can use second line of agents like human factor VIII concentrates, desmopressin (DDAVP), immune adsorption and or plasmapheresis. Some physicians use factor VIII concentrates in addition to plasmapheresis to achieve quick hemostasis [2].

If the inhibitor titers are low (less than 5 BU) and non-life threatening bleeding, we could opt to treat with high doses of human factor VIII concentrates in order to rise the factor VIII levels. The common dose recommended is 20 IU/kg for each BU of the inhibitor and 40 IU/Kg of body weight as a bolus, and if possible, monitor the factor VIII activity levels 10 min after the bolus administration. Repeat boluses if the response is inadequate. The down side of the regimen is unpredictable response. During minor bleeding episodes (mucosal bleeding, hemarthrosis, and hematomas) and low titers of the inhibitors, desmopressin (DDAVP) has shown to be beneficial even though the experience is limited. The desmopressin dosage used here was 0.3 µg/Kg/day for 3–5 days. Desmopressin should not be used alone in patients with major bleeding episodes or with high levels of the inhibitor [1, 4].

It is highly recommended to use the bypassing agents as a prophylactic treatment even for minor invasive procedures [2].

Eradication of the Inhibitor

It is complex and is recommended to use immunosuppressive therapy for all the patients with acquired factor VIII inhibitor soon after diagnosis confirmation. Most of the medications are used in an off-label manner. Prednisone 1 mg/kg/day alone will result in remission in nearly

30 % of the patients. Adding cyclophosphamide to prednisone will increase the remission rate [1, 5]. Even though, there is a significant improvement in inhibitor eradication rate; there is no significant survival benefit. That could be secondary to cyclophosphamide side effects [5]. Other regimes which have been utilized are azathioprine, vincristine, mycophenolate mofetil which also showed similar efficacy [1, 2, 4, 5]. In most cases, response takes at least 3–6 weeks to several months. Relapses are not unusual, and patients will respond to re-initiation of the immunosuppressive therapy.

Some physicians consider rituximab as a first line therapy even though it is recommended only for refractory cases or first line therapy failure [6]. Even with advancements in treatment within the last few years, mortality of acquired hemophilia A is still high.

We followed this patient at 3 weeks intervals with PTT, and factor VIII inhibitor levels. We were able to achieve the inhibitor eradication at 6 weeks. We tapered the steroids slowly and discontinued the Imuran after 3 months. Patient was relapsed in 4 months after the discontinuation of Imuran and was able to achieve a second remission with Imuran. Relapses are not uncommon after the discontinuation of the immunosuppressive therapy. The median time for the relapse is 7–9 months. For relapses we might need to opt for life long immunosuppressive therapy, and generally they will respond appropriately to previous regimen. In high risk patients we could opt for the lifelong

immunosuppressive after assessing the benefits and risks. The risks of immunosuppressive therapy are bone marrow suppression, infections, toxic hepatitis, and secondary malignancies. We are planning to follow him with the PTT and factor VIII inhibitor levels every month for the first 6 months, and at 2 months intervals for 6–12 months with the PTT and factor VIII inhibitor levels, and after that every 6 months [1–6].

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