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Acquired hemophilia A: Presenting as a compartment syndrome

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ABSTRACT

Acquired hemophilia A (AHA) is a condition caused by autoantibodies (mostly immunoglobulin G) against clotting factor VIII in patients with no prior bleeding disorders. It is usually associated with other autoimmune conditions. Subcutaneous bleed, gastrointestinal bleed, deep muscle bleeds, and mucocutaneous bleedings are some of the common manifestations. Understanding the management principles (control the bleeding, eradication of the inhibitors by the immunosuppression) is prudent as late and inaccurate diagnosis can make it fatal. Here, we present a patient with compartment syndrome due to bleeding into the muscles. Laboratory study was remarkable for prolonged active partial thromboplastin time (aPTT) of 62.9 seconds (normal30-40 seconds), factor VIII (FVIII) activity around 2% (normal is 50%-150%), and high inhibitors levels. Due to concern for AHA, she was treated with steroids and NovoSeven (coagulation factor VIIa, recombinant), leading to stabilization of bleeding. Subsequently, the patient was diagnosed with AHA.

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Introduction

Acquired hemophilia A (AHA) is a rare autoimmune and potentially fatal bleeding disorder with an incidence of 1-1.5 cases per 1 million persons per year [1]. It is caused by acquired inhibitors to clotting factor VIII (FVIII); the involvement of any other factor is unknown. More than 50% of cases are idiopathic, and the rest are associated with other autoimmune, dermatological disorders, malignancy, inflammatory bowel disorders, acute hepatitis B and C, and so on [2-4]. There is no known genetic inheritance pattern or ethnic predominance. They are equally seen in males and females [5]. The majority of patients present with hemorrhage into the muscles, skin, or soft tissue [1, 2]. Some of them might present with cerebral hemorrhage, prolonged postpartum bleeding, or excessive bleeding following trauma or surgery. Estimated mortality from AHA is around 7.9% to 22% if not diagnosed promptly [3, 4]. Prognosis depends on the time of diagnosis from the presenting complaints and response to steroids, infusion of recombinant FVIIa and immunosuppressive agents [5, 6]. This case demonstrates the importance of diagnosing AHA earlier on as early treatment initiation has an impact on the patient's overall survival.

Case presentation

A-73-years old female with a past medical history of Grave's disease, no history of prior use of anticoagulation, or bleeding disorder presented to the emergency department with a bruise on the left thigh. This was initially thought to be compartment syndrome/cellulitis. On further testing, compartment syndrome was ruled out. Subsequently, it was found out that active partial thromboplastin time (aPTT) was prolonged at 62.9 seconds (normal 30-40 seconds). Hematology team was consulted. She developed more extensive bruising on the left arms, posterior back, left flank/lumbar, left gluteal, thigh and leg region as well as right chin.

Figure 1

She was found to have a normal factor IX level at 227% but FVIII activity was 2%. There was a concern for acquired hemophilia and she was started on NovoSeven (coagulation factor VIIa, recombinant) for thrombostasis which helped with stabilization of bleeding.

She did not develop further bruising. She was later treated with a maintenance dose of prednisone and cyclophosphamide. A few days later, she developed swelling of the left upper extremity and numbness of the digits of the left upper extremity. She was then diagnosed with compartment syndrome for which she underwent fasciotomy of the left forearm. She was again treated initially with NovoSeven and then switched to Obizur (antihemophilic factor, recombinant). Later, she noticed oozing of bloodfrom the left arm dressing. FVIII activity then was 14%. She was initially given NovoSeven followed by Obizur and then transitioned to Kogenate (antihemophilic factor, recombinant). FVIII activity rose up to 41% before discharge. No further significant bleeding was noted at the site of fasciotomy. She was continued on the maintenance dose of prednisone and cyclophosphamide with no further episodes of bleeding. She continues to follow up with hematology clinic on every 6 months basis.

Variation in FVIII activity (normal 50%-150%) and inhibitor levels during treatment:

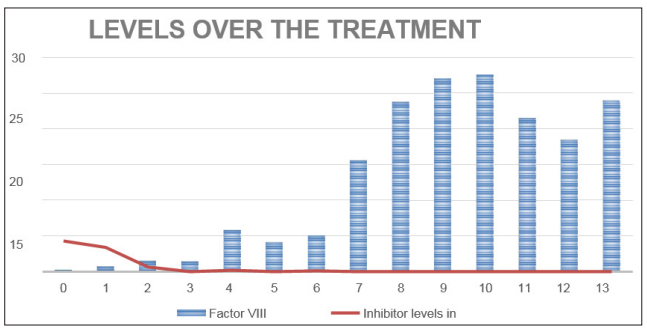

Figure 2

X-axis: months; Y-axis: FVIII activity level Bu– Bethesda Unit

Discussion

AHA is an autoimmune bleeding disorder with biphasic incidence, a small peak incidence in 20- 30 years, and a major one around 60-80 years predominantly involving the elderly population [4, 5].

Subcutaneous bleed, gastrointestinal bleed, deep muscle bleeds, mucocutaneous bleedings, excessive bleeding precipitated by events like trauma/surgery, or prolonged postpartum bleeding, are some of the common manifestations [2-4]. Subcutaneous bleed is much more common accounting for around 80% of the cases [7]. Rarely patients present with intraarticular bleeding unlike congenital hemophilia (CHA). AHA is more severe and potentially fatal compared to CHA due to extensive hemorrhage on presentation, delay in diagnosis and treatment [4,5].

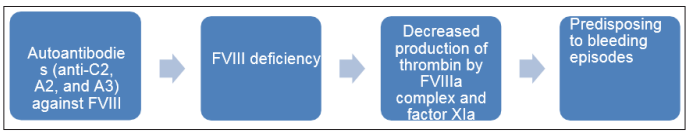

Figure 3

Most cases (50%) are idiopathic but AHA is also associated with autoimmune disorders (most commonly RA), IBD, dermatological disorders (e.g. pemphigus or psoriasis), infections (e.g. acute hepatitis B and C), malignancies (e.g. breast, melanoma, pancreas, lung, prostate), diabetesmellitus [3-5]. This patient had a remote history of Grave's disease [8].

Diagnosis is based on clinical presentation and laboratory studies. Laboratory workup shows normal bleeding time, prothrombin time, platelet count, negative lupus anticoagulant, but prolonged aPTT [5, 6, 9]. aPTT is not reversed on a mixing study which determines the presence of inhibitors. Evidence of reduced FVIII activity level and presence of FVIII inhibitor plays a vital role in diagnosis [6, 9, 10]. The severity of bleeding is determined by inhibitor titers level which is measured in Bethesda units

(BU) [10]. The activity level of factor VII and IX is important to establish inhibitor specificity.

Management is to control the bleeding, treat the underlying condition if any, and eradicate the inhibitor [11]. In acute settings, treating the presenting complaints and infusion of recombinant FVIIa (NovoSeven, Obizur, Kogenate) early on the disease is critical to improve the overall survival and facilitate hemostasis [12-15]. Recombinant factor VIIa (rFVIIa), FVIII inhibitor bypassing activity (FEIBA), or an activated prothrombin complex concentrate (APCC) should be considered in the patient with severe bleeding and inhibitor titers of 5 BU or higher [12-15]. The next step is to eradicate the inhibitor by treating the underlying cause if known and use of immunosuppressive agents.

Some studies have shown benefit from treatment with desmopressin with very low inhibitor titers (<3 BU) [16]. Immunosuppressive agents used are prednisone 1 mg/kg/day in addition to cyclophosphamide to increase the response rate [6,7, 17]. In case of intolerance or resistance to standard therapy, rituximab can be considered. Administration of IVIG in addition to immunosuppressive therapy has shown no benefit [17]. Cyclosporine is considered in a patient who has underlying systemic lupus erythematous [18]. There is limited evidence for the use of calcineurin inhibitors and mycophenolate mofetil [18, 19].

Conclusion

Acquired hemophilia A is a potentially fatal autoimmune disorder which most often is underdiagnosed or misdiagnosed due to its rarity. Most of the time it is idiopathic and in some cases, it is associated with other autoimmune disorders. The usual presentation is with mucocutaneous bleeding and bleeding into muscles, skin and soft tissue, and rarely joints.

Diagnosis is made by prolonged aPTT followed by no reversal on mixing studies, decreased level of FVIII activity, and presence of FVIII inhibitor. Management is to treat the underlying cause and to eradicate the inhibitor. Patients are usually administered with an infusion of rFVIIa, APCC, or FEIBA. The inhibitor is eliminated by treating the underlying etiology and with immunosuppressive agent (prednisone, cyclophosphamide, rituximab, or cyclosporine). IVIG has no role or limited efficacy in the treatment. Long- term immunotherapy is not recommended due to its associated side effects. There is no standard guidelines for using combination of various immunosuppressive agent. In this case, combination of prednisone and cyclophosphamide worked well for the patient even though she had one episode of bleeding after being on this regimen with no further episodes anymore. Early diagnosis and initiating the treatment is crucial in the overall prognosis as demonstrated in this case report.

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