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Case Report

Deep venous thrombosis in a patient with acquired factor VIII deficiency: a case report

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Abstract

Acquired factor VIII deficiency is a rare disorder with a high rate of morbidity and mortality, commonly presents with bruises or bleeding in patients without previous bleeding diathesis. Presentation with thrombosis is extremely rare but if it presents with thrombosis then diagnosis and management become challenging. Balance in anticoagulation and monitoring for bleeding remains the cornerstone of treatment. We are presenting a case of 60 years old female who presented with left leg swelling and diagnosed as deep venous thrombosis and started on anticoagulation. She developed hematoma on the right arm and on further workup she was diagnosed with acquired factor VIII deficiency, treated with steroid and cyclophosphamide which resulted in a good response.

Keywords: deep venous thrombosis, factor VIII deficiency, hemophilia

Introduction

Acquired factor VIII deficiency is a rare disorder with an annual incidence of 1-4 patients per million/year [1]. Although it is uncommon, this condition is associated with a high rate of morbidity and mortality. It presents with bleeding in up to 90% of affected patients and the mortality ranges from 8% to 22% [2-5]. Age distribution of acquired hemophilia is typically biphasic, there is a small peak in incidence among women aged 20-30 years and a major peak among 60-80 years old males [6]. Acquired factor VIII deficiency is associated with multiple other diseases including autoimmune disorders, inflammatory bowel disease, ulcerative colitis, dermatologic disorders (e.g., psoriasis, pemphigus), respiratory diseases (e.g., asthma, chronic obstructive pulmonary disease), allergic drug reactions, diabetes, acute hepatitis B and C infections, malignancies (e.g., prostate, lung, colon, pancreas, stomach, bile duct, head and neck, cervix, breast, kidney melanoma) [6]. In this paper, we present a case of 60 years old female who was diagnosed with acquired factor VIII deficiency and treated with steroid and cyclophosphamide.

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Case

A 60-year-old lady with known case of interstitial lung disease presented with complaint of left leg swelling and pain for the last three days and shortness of breath for one day. She didn't have any trauma, insect bite, cough or fever. On examination, her left leg was swollen and there was bruising on the medial side of the leg. Her initial laboratory test showed hemoglobin (Hb) of 11.4 g/dL (11-14.5 g/dL), total leukocyte count $9.3x10^9$/L ($4.6-10.8x10^9$/L), neutrophils 61.5% (34.9-76.2%), lymphocytes 26.1% (17.5-45%), a raised activated partial thromboplastin time (APTT) of 105 seconds (2.9-34.5) with international normalized ratio (INR) of 0.9 (0.9-1.3) and prothrombin time (PT) of 10.0 seconds (9.1-13.1). Her APTT was repeated which came out to be 110 seconds.

Doppler ultrasound showed deep venous thrombosis (DVT) in the left common femoral, deep femoral and peroneal veins. Owing to her raised APTT, it was assumed that she might be having lupus so work up was sent and she was started on anticoagulation. After receiving a single dose of rivaroxaban, she started developing bruises and swelling of her right upper limb. Her Hb dropped from 10.2 to 8.8 g/dL. Doppler ultrasound of her right upper limb was negative for upper limb DVT but it showed hematoma formation. Hence, anticoagulation was stopped. Meanwhile, ANA profile (anti-neutrophilic antibodies), Lupus anticoagulant and anticardiolipin which were sent earlier came out to be negative. The mixing study was performed for prolong APTT, which did not show improvement with normal plasma and suggestive of the presence of an inhibitor. Coagulation factors were sent which showed factor VIII activity less than 1% (Normal range: 50-149), factor IX levels were 150% (50-163) and VWAF (von-Willebrand factor) levels were 308% (50-160). She was diagnosed to have acquired factor VIII deficiency. At the age of 60, it is usually associated with malignancy, so chest, abdomen and pelvis computed tomography (CT) was performed to check for malignancy but it was negative. Therefore, she was labeled as having idiopathic acquired hemophilia and started on treatment.

Treatment, follow-up and outcome

She was initially given eight units of cryoprecipitate two times a day in order to prevent bleeding, however, her Hb kept on decreasing and factor VIII levels were undetectable. She was then started on prednisolone 1 mg/kg for three days and then tapered to 15 mg twice a day and cyclophosphamide 1 mg/kg. Her clinical condition improved, Hb became stable and she was discharged home with clinic follow-up.

On follow-up four weeks after discharge, she remained stable and her condition improved. Factor VIII increased to 83% (50-149%) from less than 1%, APPT reduced to 24 seconds from 74 seconds.

Discussion

Acquired hemophilia is a rare hematological disorder characterized by the development of antibodies against clotting factors that either inhibit the activity or increase the clearance of them, most commonly against factor VIII in patients with previously normal hemostasis [4]. It has a mode of presentation different from that of hereditary hemophilia as it presents with bleeding into the skin, muscles and mucous membranes (e.g., epistaxis, gastrointestinal and urologic bleeds, retroperitoneal hematomas, postpartum bleeding), whereas hemarthroses, a typical feature of congenital factor VIII deficiency, are uncommon [3,7]. For example, in the above-mentioned case, it presented with bruises.

The diagnosis of acquired hemophilia is suspected in cases when there is a sudden onset of large bruises or ecchymosis in an elderly patient who has no known bleeding disorder and is not on any anticoagulant. There is a single case report of DVT and pulmonary embolism complicating acquired hemophilia so far which was successfully treated with balanced anticoagulation and hemostasis [8]. The diagnosis is also suspected when APTT is raised with normal PT and INR. In our case, APTT was 105 seconds, PT was 10.0 and INR was 0.9. This is followed by confirming the raised APTT by simply redrawing the sample or doing a reptilase and thrombin time. In case if heparin is present, thrombin time is prolonged and the reptilase time is normal (9). Then the mixing study is performed in this assay varying amount of patient's plasma and pooled plasma is mixed and APTT is measured. Correction of the prolonged APTT indicates vWD (von-Willebrand disease) or clotting factor deficiency while persistent elevation indicates the presence of inhibitor. The mixing study establishes the presence of the antibody without identifying its specificity. The Bethesda assay both establishes the diagnosis of a factor VIII inhibitor and quantifies the antibody titer [10].

Treatment of acquired factor VIII deficiency includes two different steps, i.e. control of bleeding and elimination of inhibitor. Control of bleeding includes administration of desmopressin acetate, factor VIII concentrate or activated prothrombin complex concentrate depending upon the severity of bleeding [11,12]. Elimination of inhibitor includes administration of steroids with or without immunosuppressant. The use of prednisolone initially followed by addition of cyclophosphamide to steroid-resistant cases has been proven effective in a prospective randomized trial with the conclusion that all patients with acquired antibodies should be treated initially with prednisolone, cyclophosphamide to be added as second-line therapy in steroid-resistant cases [13]. In a case series published by Shaffer and Phillips, the association of oral cyclophosphamide and prednisone was successful in achieving complete remission in all of

the nine consecutive acquired hemophilia patients enrolled [14]. Other combinations, such as prednisone with azathioprine or prednisone with cyclophosphamide and vincristine, were also proven effective [15,16]. Cyclosporine alone or in combination with steroids has been used successfully as salvage therapy [17,18]. Intravenous immune globulin (IVIG) has been proved to be beneficial in lowering the titer of antibody [19,20].

Conclusion

Acquired hemophilia is a life-threatening condition. It is a rare disorder so needs a high index of suspicion to diagnose. Co-existence of DVT with acquired hemophilia is extremely rare and it makes the scenario more complex and difficult to treat. Balance in anticoagulation and monitoring for bleeding remains the cornerstone of treatment. The combination of prednisolone and cyclophosphamide has proven to be beneficial in the management of such patients.

Conflict of interest

The authors declare that they have no conflict of interest.

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