Case Report **IJCR (2020) 4:115**

International Journal of Case Reports
(ISSN:2572-8776)

Idiopathic Acquired Factor VIII deficiency presenting with compartment syndrome: A case report and Literature Review

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ABSTRACT

Haemophilia is a disorder that affects the ability of the blood to form clots. The congenital form of the disease is the most prevalent, is inherited as X-linked recessive and it causes deficiency of clotting Factor VIII or IX. clinically it presents with joint bleeding. Its counterpart, acquired haemophilia is a rare condition that usually presents with cutaneous, soft tissue or internal bleeding.

The pathophysiology of the disease is centred on the formation of auto antibodies which inactivate factor VIII. Haematologically this is reflected as a prolonged aPTT with normal PT and failure of mixing studies to correct aPTT to more than 50%. To confirm the diagnosis Bethesda assay has to be performed to detect the presence of factor inhibitors. In half of the cases it is associated with an underlying condition such as autoimmune diseases, malignancy, pregnancy or infections.

The mainstay treatment is to control the bleeding with bypassing agents such as recombinant factor VIIa or Factor VIII inhibitor bypassing agent as well as eradicating the inhibitor with immunosuppressive and/or cytotoxic agents. Here we report a patient with idiopathic acquired haemophilia who presented with a thigh compartment syndrome. He was successfully treated with fasciotomy, bypassing agents and immunosuppressive therapy.

Keywords: Acquired, Haemophilia, Factor VIII, compartment syndrome

Abbreviations: PT=Prothrombin time; aPTT=activated partial thromboplastin time; INR=international normalized ratio

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How to cite this article:
Khalid E. Ahmed, Amna Gameil, Marcus D. Lance, Arshad H. Chanda, Lubna Riaz, Anas Hamad, Ahmed A. Shible, Shehab F. Mohamed. Idiopathic Acquired Factor VIII deficiency presenting with compartment syndrome: A case report and Literature Review . International Journal of Case Reports, 2020 4:115

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Introduction:

Haemophilia is a rare disorder that presents with bleeding tendency. The congenital form of the disease is the most prevalent. It is inherited as X-linked recessive and causes deficiency of clotting Factor VIII or IX. It usually presents with joint bleeding. On the other hand, acquired haemophilia A (acquired factor VIII deficiency) is a condition that usually presents with cutaneous, soft tissue or internal bleeding. The main cause is formation of antibodies directed against factor VIII[1]. The Prevalence of this disorder is estimated to be 1 to 1.5 per million annually[2]. Etiologically 50% of the cases are associated with underlying conditions such as malignancy, infections, autoimmune diseases, pregnancy while the rest of the cases are idiopathic[3]. Frequently The clinical presentation is spontaneous or trauma related mucosal or soft tissue bleeding.

Patients presenting with unusual bleeding without family history of bleeding disorder and a prolonged aPTT without anticoagulant use suggest an acquired haemophilia. However, before the diagnosis is made other causes of prolonged a PTT should be ruled out including anti phospholipid antibodies and factor XII deficiency which both are associated with thrombophilia. Mixing studies are used to demonstrate if an inhibitor is present and if so, Bethesda method is used to quantify the inhibitor.

Case presentation:

We report a case of 34 years old previously healthy gentleman without family history of bleeding who presented to the emergency room in July 2019 with 2 days history of spontaneous right thigh pain and progressive swelling resulting in difficult walking. There was no history of recent trauma to the thigh or bruising over the skin. He had no past history of easy bruising, joint swelling, epistaxis, gum bleeding, upper or lower GI bleeding. He did not report any intoxication like smoking, alcohol consumption or use of illicit drugs. He did not use any anti platelet, anti-coagulant medication or NSAIDS recently.

On Examination he looked well, was conscious, alert and oriented to time, place and person. There was no pallor, jaundice or cyanosis. Local examination of the right thigh showed diffuse swelling from the inguinal region to the anterior aspect of the knee with tenderness on palpation. Hip and knee movements were restricted due to pain. Distal neurovascular bundle examination was intact with normal pulses.

Examination of oral cavity did not reveal any mucosal bleeding. General survey did not show any bruises or petechiae. No lymph-adenopathy or hepatosplenomegaly was identified. Careful dermatological examination did not show any sign of skin disorder or auto immune diseases such as SLE or dermatomyositis. Cardiovascular, respiratory and nervous system examination were un remarkable.

Radiological investigations done in the ED included US-doppler scan which ruled out deep vein thrombosis of the right lower limb. CT scan with contrast and MRI showed swelling of the muscles in the anterior and lateral compartment of the right thigh with possible haemorrhagic component (see figure 1). the patient was referred to the Orthopedic department with the suspicion of Right thigh compartment syndrome without vascular compromise. in the same evening the patient went for decompressive fasciotomy. Intra operatively the anterior compartment muscles were found to be hemorrhagic. During the operation the patient needed massive transfusion, He received 22 units of packed RBCs, 18 units of fresh frozen plasma, 6 units of prothrombin concentrate and 16 units of cryoprecipitate to control the bleeding.

Pre- operative hematological investigations showed a prolonged aPTT of 71.2 sec (24.6-31.6) with a normal PT-INR. Mixing studies failed to correct the aPTT by more than 50%, thus the sample was sent for Bethesda assay which confirmed the presence of 70.4 units/ml of factor VIII inhibitor. The level of other clotting factors

including factor XII were normal. Complete blood count (CBC) and peripheral smear showed only normochromic, normocytic anemia while other investigations including anti-nuclear antibodies, anti-neutrophil cytoplasmic antibodies, Rheumatoid factor, anti-Cyclic citrullinated peptides antibodies, Lupus screen, complement level, hepatitis B, C and HIV were all unremarkable.

In an attempt to rule out an underlying occult malignancy CT chest, abdomen and pelvis with contrast was done and the only significant finding was mural thickening and surrounding fat stranding of a short segment in the sigmoid colon probably representing sigmoid diverticulitis. Subsequent Colonoscopy performed by the gastroenterology team did not reveal any masses or suspicious lesions.

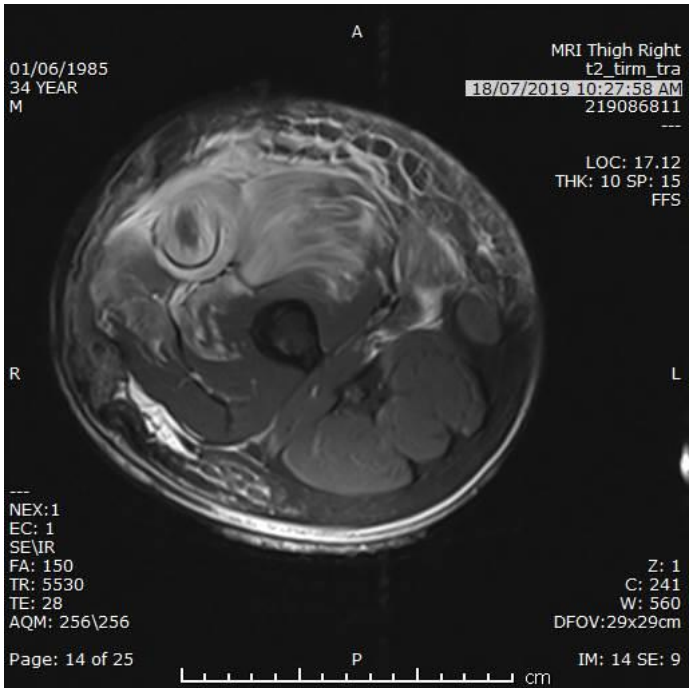

Figure 1: MRI of the right thigh: swelling and hemorrhage of the muscles in the anterior compartment

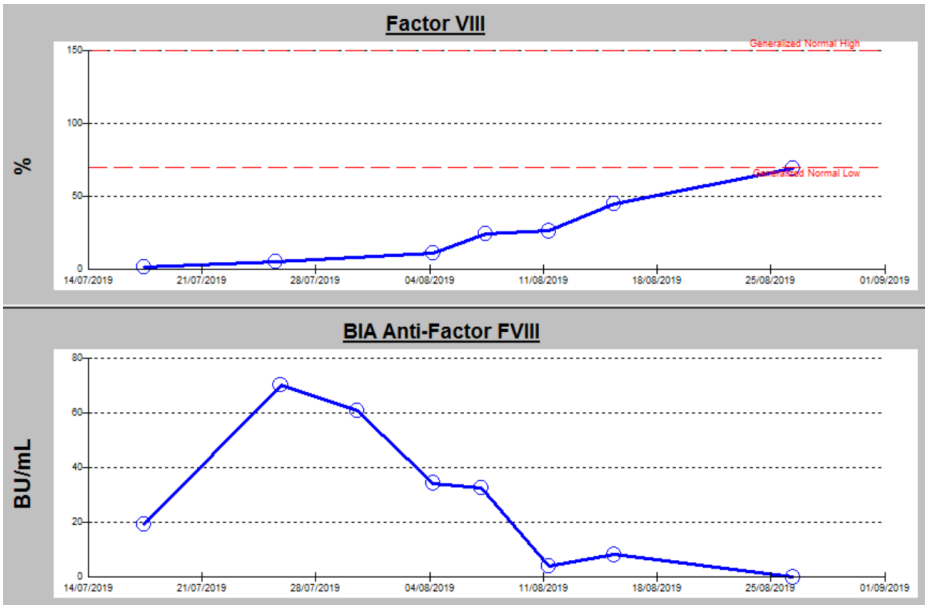

Figure 2: serial measures of Factor VIII and factor VIII inhibitor level while on Immunosuppressive therapy

During this admission the patient was treated with recombinant Factor VIIa (Novo 7) intravenously and later on substituted with FEIBA (Factor eight inhibitor bypassing agent) due to shortage of Novo 7. He was commenced on steroids (1 mg/kg/day of prednisolone with a weekly tapering plan), later during his hospital stay he was started on rituximab (weekly dose for a total of 4 doses), then cyclophosphamide (1 mg/kg/day) was also added to his regimen. He led a good recovery from the fasciotomy wound with no major bleeding and gradually regained his ability to walk independently. The trend of Factor VIII and Factor VIII inhibitor depicted in figure 2 shows a good response to immunosuppressive and cytotoxic treatment. We concluded that the diagnosis would be Idiopathic acquired factor VIII deficiency as no underlying condition was identified.

Discussion:

Acquired haemophilia is a condition caused by autoantibodies that act to inactivate Factor VIII. In contrast to the classical congenital haemophilia (X linked recessive condition) acquired haemophilia affects both males and females equally. The incidence of this rare disease increases with age from 0.3 in those aged 16-64 years to 9 per million in those aged 65-84 years and 15 per million in those older than 85 years[4].

In approximately 50% of the cases an underlying condition can be identified. These include auto immune conditions (e.g. rheumatoid arthritis, systemic lupus erythematosus), lymphoproliferative neoplasms, pregnancy and solid organ malignancies. Secondary causes are more likely to be identified in elderly patients with co morbid conditions[5]. In our patient however, history, examination and extensive radiological and laboratory investigations failed to reveal any underlying condition.

While congenital Haemophilia usually presents with joint bleeding due to the fact that there is the lowest amount of tissue factor, acquired haemophilia is frequently reported to present with cutaneous, soft tissue and internal haemorrhage. The severity of bleeding in acquired Haemophilia does not seem to correlate with level of factor VIII or the inhibitor, this is supported by the results of a review done by the European acquired Haemophilia registry that included about 500 patients. This review showed that while 89% of the patients were diagnosed following a bleeding event that led to further investigations, 48 patients were diagnosed only on the basis of a prolonged aPTT, of these, 33 patients reported no bleeding event and 15 patient developed bleeding after they were diagnosed[6].

The diagnosis of acquired Haemophilia requires a careful interpretation of coagulation screening and a high degree of suspicion because other causes like contamination with anticoagulants and other factor deficiencies are much more common. A prolonged aPTT with a normal PT indicates a problem in the intrinsic pathway (Factor VIII, IX, XI or XII). If the primary pathology is a factor deficiency then mixing the patient's plasma with normal human plasma in 1:1 ratio should result in correction of the aPTT by more than 50%. Failure of mixing studies to correct the aPTT is evidence that an inhibitor is present and the sample should be sent for investigation by Bethesda assay for the sake of identifying the inhibitor [4]. In our case Bethesda assay was done because mixing study failed to correct his aPTT by more than 50%. The essay confirmed the presence of 70.4 Bethesda units/ml of factor VIII inhibitor. Although clinically unlikely because our patient suffered from a bleeding, we excluded the presence of lupus anticoagulant and deficiency of coagulation factors affecting the intrinsic pathway. In both situations a prolonged aPTT with a normal PT might be found too.

The goal of treatment in acquired haemophilia is to control the bleeding, to initiate immunosuppressive therapy to eradicate the inhibitor and treat an underlying cause if identified. Bypassing agents such as recombinant Factor VIIa (rFVIIa or NovoSeven) and FEIBA (Factor VIII inhibitor bypassing

agent) are the first line for controlling the bleeding[7], both of which were used in our patient. They act to activate factor X directly without the need for Factor VIII or IX. Desmopressin and factor VIII concentrates are also alternative agents that have been used to control the bleeding but according the European registry of acquired haemophilia they were not as successful as the bypassing agents particularly not in situations with heavy bleeding.

In a survey of 215 patient with acquired haemophilia, the overall mortality without immunosuppressive therapy was 41%. This percentage dropped to 20% with immunosuppressive treatment[7]. The European Haematology Association recommends that patients with acquired haemophilia should immediately receive inhibitor eradication treatment. The regimens applied include corticosteroids either alone or in combination with other agents such as cyclophosphamide, cyclosporin, azathioprine or rituximab. The most common regimen achieves complete remission in 70-80% of the cases. It is composed of prednisolone 1-2 mg/kg/day either alone or in combination with cyclophosphamide 1-2 mg/kg/day for 5 weeks duration[8].

Outpatient clinic follow up for patients with acquired haemophilia is recommended because in 10% of these patients acquired haemophilia preceded the diagnosis of malignancy[9].

Conclusion:

A patient presenting with spontaneous bleeding in unusual sites without family history of bleeding and an isolated prolonged aPTT should always lift the attention of the physician to look for acquired and rare causes such as acquired haemophilia. Due to the rarity of such conditions a high index of suspicion is needed. In further work up thorough investigations are needed to rule out any underlying malignancy or autoimmune conditions that may be associated with acquired haemophilia. The main treatment strategy for acquired haemophilia is to give bypassing agents to control the bleeding as well immunosuppressive therapy to eradicate the inhibitor.

Conflict of interest: The authors declare that there is no conflict of interest regarding the publication of this article

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