CASE REPORT

ACQUIRED HAEMOPHILIA A

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Acquired haemophilia A (AHA) is a rare disease believed to be caused by spontaneous inhibition of clotting Factor VIII by autoantibodies. This is in contrast to the more common congenital haemophilias which are largely due to an absolute deficiency in coagulation factors. It has a prevalence of approximately one per million per year. However, this figure may be underestimated because there are many undocumented cases due to a lack of recognition. Patients who develop this disease may present with catastrophic bleeding despite having no previous bleeding history. In this study, we report a case of acquired Haemophilia A presenting with spontaneous unprovoked bruising and discuss the approach to diagnosis and how to alert the clinician to suspect this potentially rare but devastating disease.

Keywords: Acquired haemophilia, mixing test, inhibitors, bleeding, elderly

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CASE REPORT

A 62-year-old gentleman presented with unprovoked spontaneous bruising over the bilateral ankles a day before seeking medical attention (Figure 1). He was not known to have any previous bleeding tendencies before this episode. In addition, he denied being on any blood thinning agents and traditional supplements. There was also no history of preceding trauma to the bilateral ankles. His family history was insignificant for any bleeding disorders nor was there any history of consanguineous marriage. He had also denied any constitutional symptoms.

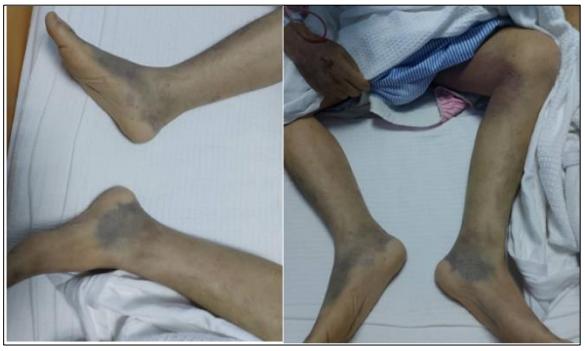

Figure-1: Photographs on admission showing bruising over the medial aspect of bilateral ankles and the left inner thigh.

Physical examination on assessment revealed a gentleman who was alert and haemodynamically stable under ambient air. Closer inspection revealed bruising and purpuric rashes over the medial aspect of the bilateral ankles and the left thigh. There was no associated haemarthroses. The lesions were non-tender. There were no palpable lymph nodes, nor were there any evidence of hepatosplenomegaly. He had also no physical signs to suggest an underlying connective tissue disease. His routine blood work including platelet count was unremarkable, except for an isolated prolonged activated partial thrombin tine (aPTT) which was corrected immediately on the mixing test. However, an incubation mixing test two hours later did not correct the apTT.

These results suggested the presence of an acquired inhibitor of coagulation. The lupus anticoagulant sent was negative. Further testing the presence of a Factor VIII inhibitor with a titre of 22 Bethesda Units. Factor VIII activity was recorded at only 1%. He was diagnosed with acquired haemophilia A (AHA). Workup for connective tissue disease and a malignancy screen was otherwise negative.

He was started on intravenous hydrocortisone and activated Factor VII as well as anti-inhibitor coagulant complex on confirmation of the diagnosis. His ward stay was complicated by bleeding into the left biceps muscle, trunk and left flank (Figure 2) and an unprovoked scalp haematoma which later extended into the facial and muscles of mastication. This was confirmed with a computed tomography of the face. He required many cycles of activated Factor VII and anti-inhibitor coagulant complex to achieve haemostasis. Due to the bleeding episodes, he even required multiple episodes of blood transfusion to maintain adequate haemoglobin.

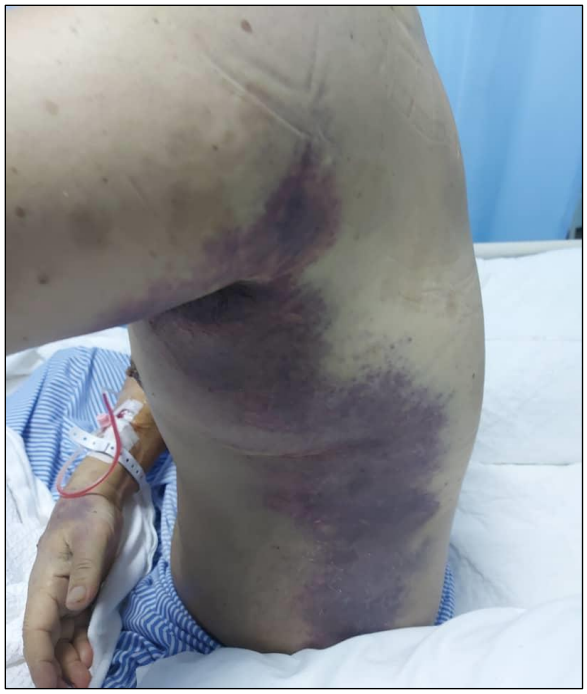

Figure-2: Photograph approximately one week into admission showing extensive bruising extending to the left lateral trunk and flank

The patient began to show signs of improvement after approximately one month of hospital stay with continuous immunosuppression and no new episodes of unprovoked bleeding. A repeated Factor VIII inhibitor level showed a significant reduction to only 2.1 Bethesda Units. He was discharged with high-dose oral Prednisolone and is currently under follow-up under Haematology. He remains well with no recurrence of unprovoked bleeding to date.

DISCUSSION

Acquired haemophilia A is the most common cause in the family of the acquired inhibitors of coagulation. Specifically, there are inhibitors to Factor VIII, thus reducing its activity. Antibodies to other clotting factors (factor V and IX) are exceedingly rare. The bleeding in acquired haemophilia A is usually acute may be mild, but when severe, carries a high risk of death.

Multiple case series and reports have documented some possible associated diseases in about 50% of cases, with the remaining being labelled as idiopathic. The most commonly reported associations are autoimmune diseases, solid organ and lymphoproliferative malignancies, skin disorders, drugs and pregnancy.[2]

Mortality ranges between 9% and 33% in the first two months after diagnosis if untreated.[3] The average age of onset is 65 years old, but it has a biphasic distribution. The first peak comprises young women starting in the postpartum period or the presence of autoimmune systemic diseases while the second peak affects patients over 60 years of age with no clear gender differences.[4]

Patients usually present with subcutaneous and mucocutaneous bleeding, followed by muscle, gastrointestinal, genitourinary and retroperitoneal bleeds[5]. This is in contrast to the congenital haemophilias where haemarthroses are the most common presentation. Our patient above presented with both subcutaneous bleeding and had also developed intramuscular haematoma which is consistent with the reported clinical presentations.

AHA requires a high level of suspicion and needs to be treated emergently due to the high mortality rate. However, this disease often goes unrecognized due to various confounding factors. Based on a large international study, the time from initial bleeding presentation to diagnosis was two to seven days in 121 patients (25.5%), and the time to diagnosis was greater than seven days in 161 patients (35.3).[4]

Potential barriers to early diagnosis include laboratory testing delays and also a lack of recognition of abnormal test results. Alternative explanations such as senile purpura and pre-existing antiplatelet for another primary indication, were also noted to contribute to the reported diagnostic delays.[6]

The first suspicion of this disease usually stems from a coagulation profile demonstrating an isolated prolonged apTT ratio in a patient with unexplained bleeding. The platelet count is usually normal. An isolated prolonged apTT raises two possibilities; either an absolute deficiency of the clotting factors in the intrinsic pathway or the presence of antibodies or inhibitors towards these factors.[7]

The next step is the mixing test in which equal amounts of the patient's plasma and control plasma are mixed in a 1:1 ratio. Normalization of the apTT indicates a deficiency of coagulation factors in the patient, however, an apTT that fails to correct with the mixing test implies the presence of an inhibitor[7]. It is important to note however that in acquired haemophilia A, the inhibitor is time and temperature dependent and therefore the initial mixing test may be normal.[8] Our patient's case illustrates this perfectly, in that the initial mixing test was normal. It was only when the incubation mixing test was repeated two hours later that it was revealed that the apTT had failed to correct. This implies that the inhibitor takes time to bind and inhibit factor activity.[8] Lastly, the Bethesda assay is performed to quantify the inhibitor titre and confirm the diagnosis. This is reported in Bethesda Units (BU). The stronger the inhibitor, the higher the BU[9]. Generally, a titre greater than 5 BU is indicative

of a high titre inhibitor. Our patient had a reported inhibitor titre of 22 BU, which reflected the difficulty in controlling his bleeding symptoms.

The principle of treatment is a two-pronged approach. First and foremost, control of haemostasis needs to be prioritized. This is generally managed by Factor VIII bypassing agents.[10] The two most common agents are recombinant FVII and also activated prothrombin complex concentrates (apCC). As the name suggests, these agents bypass the need to rely on Factor VIII for coagulation. Secondly, there is a need to suppress the primary pathology, which is the elimination of the inhibitor. This is achieved by immunosuppression with corticosteroids or steroid-sparing agents.[10]

The response towards immunosuppressive therapy, in particular the time to achieve remission, varies largely among patients. The median time to remission is 5 weeks. FVIII activity at presentation, inhibitor titer and autoantibody isotype are prognostic markers for remission and survival. Definitions of remission vary across studies and registries. A best-accepted definition from a UK surveillance study defined complete remission as: FVIII normal, inhibitor undetectable, and immunosuppression stopped or reduced to doses used before AHA developed without relapse.[10]

Our paper adds to the body of existing literature and demonstrates the possibilities of the differing clinical presentation of AHA. Our patient initially presented with spontaneous bruising and later developed a haematoma of the left biceps and also an unprovoked extracranial haematoma with extension into the left facial and masseteric muscles at different time intervals. Due to the high inhibitor titre at 22BU, he proved difficult to treat and had an inpatient stay of approximately one month.

In conclusion, AHA needs to be promptly recognized and treated as delays in diagnosis may have devastating outcomes. Our patient was fortunate in that the suspicion of AHA was raised immediately on admission prompting immediate immunosuppression and haemostatic control with a favourable outcome.

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Conflicts of Interest

The authors declare no conflicts of interest.

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