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Acquired Hemophilia of Unknown Etiology in an Elderly Man: Case Report

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Data Collection B
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Data Interpretation D
Manuscript Preparation E
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Patient: Male, 90
Final Diagnosis: Acquired heamophilia
Symptoms: Bruising
Medication: —
Clinical Procedure: —
Specialty: Hematology

Objective: Unknown ethiology

Background: Acquired hemophilia is a rare but potentially dangerous bleeding disorder caused by autoantibodies against coagulation factors. It affects 1 to 1.5 per 1 million people each year. While 50% of cases could be idiopathic, other causes include malignancies, diabetes, pregnancy, infection, and autoimmune disorders.

Case Report: We report a case of a 90-year-old male who developed a spontaneous hematoma on the dorsum of his right hand, with no prior history of trauma or any other mucosal bleeding. His activated partial thromboplastin time (aPTT) was found to be prolonged (>180 seconds) with a very low level of factor VIII (0.1%).

Conclusions: As workups did not identify the source, including malignancy and autoimmune diseases, of his acquired hemophilia, it is believed to be idiopathic. He was started on intravenous recombinant factor VIIa (NovoSeven) to control the bleeding in combination with an immunosuppressive therapy of cyclophosphamide and prednisolone. In approximately 10% of patients with acquired hemophilia, underlying malignancy, such as squamous cell cancer, chronic lymphocytic leukemia, non-Hodgkin lymphoma, and multiple myeloma can present and commonly develop in elderly patients. Therefore, patients diagnosed with idiopathic acquired hemophilia should be given long-term follow up.

MeSH Keywords: Autoantibodies • Factor VIII • Hemophilia A

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Background

Acquired hemophilia (AH) is a rare but potentially dangerous bleeding disorder which is caused by the spontaneous formation of autoantibodies against coagulation factors, most commonly factor VIII [1]. This condition is characterized by spontaneous and post-traumatic subcutaneous bleeding and mucosal hemorrhage. It affects 1 to 1.5 per 1 million people each year and affects both men and women [2,3]. Up to 50% of acquired hemophilia cases could be idiopathic and is also associated with conditions such as malignancies, diabetes, pregnancy, infections and autoimmune disorders [3].

Case Report

We report a case of a previously healthy 90-year-old male who was independent in his activities of daily living (ADL), who developed a spontaneous hematoma on the dorsum of his right hand in February 2017. The hematoma first started out as a coin shaped bruise without any preceding trauma, and gradually progressed to the size of 6 cm x 6 cm at the time of presentation (Figures 1, 2).

A year prior to the development of the hematoma, he started noticing easy bruising with minor trauma. He reported an episode of excessive bruising on his back, upper limbs, and torso after a fall in the bathroom. In addition to that, he also reported having lethargy and palpitations. However, as the symptoms did not get in the way with his daily living, he did not seek medical treatment until the development of his current hematoma. All other hematological symptoms were nil of significance and he had no co-morbidities. He has no current or past history of smoking, drinking alcohol, illicit drug use or used any form of traditional medication.

Generally, he appeared to be alert and conscious. On examination of his hand, the hematoma was noted to be 6×6 cm in size and was warm and tender to touch. Apart from noticeable palmar pallor, there were no other positive hematological signs. A careful dermatological examination was also performed and no evidence of dermatological diseases, such as psoriasis and pemphigus were found. Cardiovascular, respiratory and gastrointestinal examinations were also nil of significance. Investigations done are summarized in Table 1.

Chest x-ray was also done, which returned normal. The gastroenterologist was reluctant to perform endoscopy or colonoscopy due to his coagulopathy and lack of gastrointestinal symptoms like PR bleeding.

Prior to his current admission, he had undergone 6 aspirations of the hematoma, all of which helped reduce the size of the hematoma but did not stop it from recurring. During the last aspiration, his hemoglobin was noted to be 4.1 g/dL and hence, he was immediately transfused with 2 units of blood. He was then started on intravenous (IV) hydrocortisone 100 mg (3 times daily) and IV tranexemic acid 500 mg (3 times daily).

During this admission, he was started on cyclophosphamide (tablet, 50 mg), prednisolone (tablet, 30 mg), ferrous femorate (tablet, 40 mg) and folic acid (tablet, 5 mg). Besides

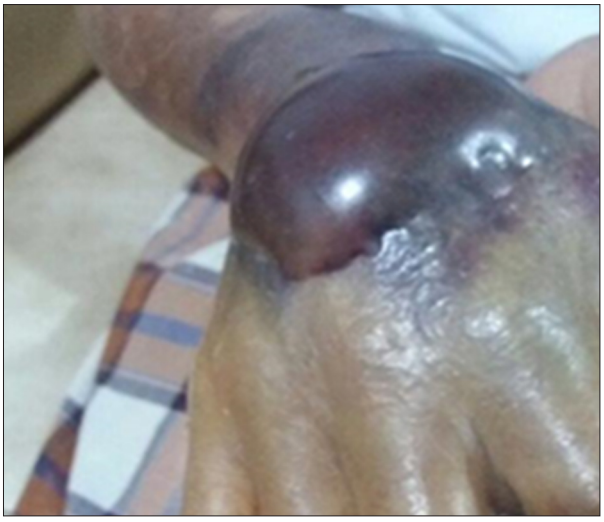

Figure 1. Initial coin shaped lesion. Initial hematoma on the dorsum of the patient's right hand. The hematoma, notably filled with blood, initially presented as a coin shaped lesion with the surrounding skin being edematous and erythematous.

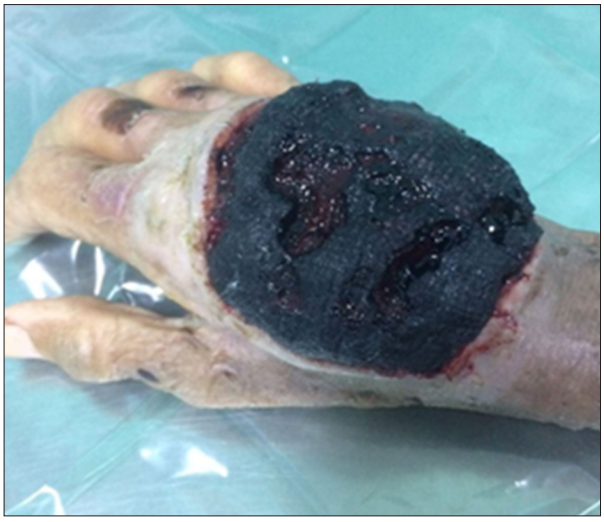

Figure 2. 6×6 cm hematoma. The lesion progressively enlarged to 6×6 cm hematoma, with a depth of 1 cm on the dorsum of the patient's right hand on admission. The color of the hematoma became progressively darker with the surrounding skin and digits looking paler in comparison.

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Table 1. Investigations.

Test	Results	Comments
Full blood count	Hemoglobin: 7.3 g/dL (13.0–17.0 g/dL) MCV: 74 fL (83–101 fL) WCC: 14.810^3 µL (4.0–10.0 µL) Platelet: 675 10^3/µL (150–400/L)	Showed a picture of microcytic anemia with a raised white cell and platelet count.
Coagulation profile	PT: 10.9 seconds (8.8–11 secs) INR 1.04 (0.8–1.2) aPTT: > 180 seconds (27.5–38.5 secs) Factor VIII: 0.1% (50–150%) Factor IX: 14.1% (50–150%)	Showed prolonged aPTT with a normal PT There was a depletion of factor VIII and factor IX*
Peripheral blood film	Red blood cell: Showed moderate anemia, with hypochromic microcytic red cells. Pencil cells and target cells were also noted. White blood cell: The counts were raised with predominantly neutrophils. No blasts or abnormal lymphoid cells were seen. Platelets: Adequate counts	Hypochromic microcytic anemia Features to rule out ongoing infections/ inflammation
Mixing test	Showed prolonged mixing aPTT with the following values: aPTT mixing: >180 seconds aPTT control: 34.1 seconds aPTT mixing (incubation): >180 seconds	This shows that the mixing test is not correctable, thus suggesting the presence of inhibitors rather than factor deficiency
Bethesda assay	Factor VIII inhibitor levels: >200 Bethesda units/mL	Bethesda units of at least 5 units (BU/mL) show high titer-inhibitor while titers of 5 BU/mL show a low titer-inhibitor [4]
Antinuclear antibody test	No antibodies detected	
Rheumatoid factor	<10 IU/mL (<15 IU/mL)	Values were normal
Tumor markers	AFP: 1.96 ng/mL (0–8 ng/mL) CEA: 1.2 ng/L (0–2.5 ng/mL) PSA: 0.341 ng/L (0–4 ng/mL)	Tumor markers were within normal limits

* A complete coagulation profile inclusive of all clotting factors is unavailable at our clinical setting and therefore was not performed.

that, IV recombinant factor VIIa (5 mg) was also added to his medication regime on day 5 of admission, half an hour prior to the scheduled surgery for the removal of the hematoma. Operatively, the hematoma was successfully removed with minimal bleeding. Post-surgery, the recombinant factor VIIa was ceased while cyclophosphamide and prednisolone were continued. His wound post-surgery was clean, with serous discharge and minimal slough (Figure 3).

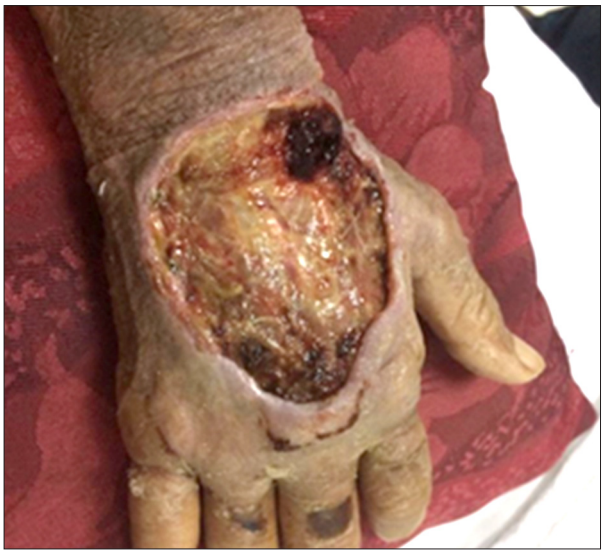

Figure 3. Post-Surgical wound. Dorsum of patient's right hand post-surgical removal of the hematoma. The wound is clean with minimal slough and minimal serous discharge. There is also no pus discharge and healthy granulation tissue is seen. Minimal scab at the peripheries of the wound is noted.

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This case was unique as we found that this disease has only been reported twice so far in Malaysia [4]. The purpose of this case report was to create awareness and treatment options for acquired hemophilia among primary care physicians as it is often unrecognized or misdiagnosed.

Discussion

Acquired hemophilia (AH) is a rare disorder that is caused by the production of autoantibodies which act to inactivate factor VIII. Based on a case series *Acquired Hemophilia in a Malaysian Hospital* published by the Oxford Medical Case Reports, AH is a rare disorder with a prevalence of 1 per million per year, affecting both genders equally. The prevalence rate of AH in Malaysia is, however, unknown [5].

In up to 50% of patients with AH, an underlying medical condition can be identified, including autoimmune diseases (rheumatoid arthritis, systemic lupus erythematosus inflammatory bowel disease, etc.), solid tumors, lymphoproliferative malignancies, and pregnancy. These patients are often elderly and have co-morbidities and co-medications, such as heparin, that may influence the clinical picture [6]. However, our patient had no underlying medical conditions, nor did he have any co-morbidities or co-medications, adding to the uniqueness of this case. Investigations and physical examinations carried out also did not detect a cause for his acquired hemophilia.

Clinically, AH lacks the genetic inheritance pattern seen in its congenital counterpart and thus affects both males and females equally. Most cases that have been reported occurred in adults, with the median age of between 60 and 67 years at presentation. However, there is a wide range of reported cases, ranging from 2 years of age to 89 years of age [7]. The incidence per million per year increases with age, from 0.3 in those 16 to 64 years of age to 9 per million in those 65 to 84 years of age, and 15 per million in those aged 85 and older [8].

In contrast to the typical manifestation of congenital hemophilia in which bleeding occurs into joints, the prominent feature in acquired hemophilia is extensive cutaneous purpura and internal hemorrhage. While the reason for the difference in manifestation is unknown, the majority of cases of acquired hemophilia that have been reported presented with soft tissue hemorrhage and purpura, which was seen in our patient, both of which can progressively worsen into compartment syndrome. Other less common manifestations of AH are hematuria, gastrointestinal bleeding, and prolonged postpartum bleeding [9].

The severity of bleeding in AH while spontaneous does not have any relationship with the factor VIII level nor does it correspond to the strength of the inhibitor. There is also no correlation between the aPTT and the bleeding severity in AH. Based on review of 501 patients by the European Acquired Hemophilia Registry (EACH2), in most cases (89.0%), the diagnosis of AHA was precipitated by a bleeding event that led to further hemostatic investigation and confirmation of the disorder. Forty-eight patients were diagnosed with AH on the basis of a prolonged aPTT. However, in 33 of these cases, no bleeding event was reported, and in 15 patients a bleeding event occurred only after diagnosis [10]. This is different from factor deficiency whereby the lower the levels of factors, the higher the propensity and severity of bleeds [8]. Following invasive procedures, severe bleeding can occur, with fatal hemorrhage seen in 9% to 22% of cases. In contrast, only 30% of mild bleeding cases have been reported, which require no hemostatic treatment. However, these patients are at risk of fatal bleeding until the inhibitor has been eradicated [8].

AH is diagnosed based on features of clinical manifestations and is confirmed based on laboratory investigations, with the first-line tests being a prolonged activated partial thromboplastin time (aPTT) with a normal PT. Our patient had a prolonged aPTT of more than 180 seconds, and thus, a mixing test was performed. Mixing tests mix the patient's plasma with that of a pooled normal plasma in a ratio of 1: 1. A patient who has an inhibitor to factor VIII will cause the factor VIII in the normal plasma to be inhibited as well, and hence the aPTT measured will not be corrected. Failure of normal plasma to correct the aPTT by more than 50% is usually taken as evidence that an inhibitor is present and should be sent for further investigation by Bethesda assay [8].

In our patient, a Bethesda assay was performed as his aPTT was not corrected by more than 50%. The assay detected >200 units/mL of factor VIII inhibitor, showing a high titer of factor VIII inhibitors. It is also important to note that, although low factor IX levels of 14.1% were detected in our patient, it was likely due to it being artifactually reduced by interference from the FVIII inhibitor. Besides the presence of an inhibitor, a prolonged aPTT with a normal PT could also be caused by a deficiency of one of the intrinsic coagulation factors (FVIII, IX, XI, or XII) or be caused by the presence of a lupus anticoagulant [8]. A Lupus test was not performed as Lupus typically presents with thrombosis, and not bruising, and was not in line with the clinical picture of our patient [11]. Contact deficiency was also not considered as it is most likely to be asymptomatic, as opposed to our patient, who had recurrent symptoms [12].

The main aim in treatment of patients with AH is to control bleeding, avoid procedures that can induce bleeds, initiate immunosuppression to eradicate inhibitors, and treat underlying co-morbidities [9]. The first-line treatment to control bleeding in AH is the use of a bypassing agent, either recombinant factor VIIa (rFVIIa, NovoSeven), which was used in our patient, or

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the activated prothrombin complex concentrate (aPCC) (FEIBA; factor VIII inhibitor bypassing activity) [9]. Patients with inhibitors of more than 5 BU/mL are generally refractory to FVIII replacement therapy and immune tolerance therapy is usually started to eradicate the inhibitors. Alternatively, FVIII bypass agents or recombinant activated factor VII can also be used as bleeding prophylaxis [4,13]. However, immune tolerance regimens are considered to be of limited efficacy in patients with titers of more than 200 BU/mL, as seen in our patient [4]. Prior to surgical removal of our patient's hematoma, he was started on NovoSeven, a recombinant factor VIIa which activates factor X directly without the need for factor VIII or IX to control the bleeding during the procedure [7].

Alternative treatments that have been used as a hemostatic agent include FVIII concentrates and desmopressin, aimed at increasing the levels of circulating factor VIII. However, based on the United Kingdom and the EACH2 registry, patients treated with bypassing agents had a significantly higher rate of bleeding control as compared to patients receiving factor VIII concentrates or desmopressin. In addition to that, the American Food and Drug Administration (FDA) and the European Medicines Agency (EMA) have recently approved the marketing of a porcine origin factor VIII (susoctocog alfa, Obizur, Baxalta, Bannockburn, IL, USA) for use in patients with AH. This new recombinant product eliminates the risk of allergic reaction, as opposed to other plasma-derived porcine factor VIII concentrates that have been used in the past. Starting at a dose of 200 U/kg, and further adjusting the dose to maintain target levels of factor VIII, this recombinant has been proven to be effective in controlling bleeding episodes in 86% of cases without resulting in any adverse reactions [14].

Besides that, based on the Journal of European Hematology Association, it is recommended that patients with AH should undergo immediate inhibitor eradication with immunosuppressive therapy. In a survey of 215 patients, 64% of patients who were not treated with immunosuppressive therapy died due to complications from inhibitors. The overall mortality without treatment reported was 41%. However, with immunosuppressive therapy, mortality was reduced to 20%, with 11% of it contributed by inhibitor factors [9]. The immunosuppressive regimens applied most successfully to suppress autoantibody production have included corticosteroid therapy alone or in combination with cytotoxic agents (cyclophosphamide, azathioprine, 6-mercaptopurine, and vincristine), rituximab, cyclosporin A, and FVIII immune tolerance. The most commonly used therapeutic strategy, which achieves complete remission in approximately 70–80% of patients, utilizes steroids alone (prednisone 1–2 mg/kg/day for 4–6 weeks) or in combination with cyclophosphamide (1–2 mg/kg per day for a maximum of 5 weeks) [14].

Conclusions

In this case report, we reported a case of a 90-year-old male who developed acquired hemophilia based on his isolated prolonged aPTT of >180 seconds and a deficiency of factor VIII, in which only 0.1% was detected. While his age of presentation lies outside the median ages reported, his clinical manifestation of soft tissue hemorrhage fits into the description of AH perfectly. He was treated with recombinant factor VIIa to control his bleeding and was also started on combination immunosuppressive therapy, i.e., prednisolone and cyclophosphamide. However, during his 6-month follow-up at the outpatient clinic, it was found that his aPTT was still prolonged to more >180 seconds. *The International Recommendations on the Diagnosis and Treatment of Patients with Acquired Hemophilia A,* recommends the commencement of second-line therapy using rituximab, a cytotoxic agent if first-line immunosuppression therapy fails, as seen in our patient [6]. The cause of his AH is believed to be idiopathic in nature, as efforts made did not identify any source of his AH. It has been reported that 10% of patients with acquired hemophilia are related with underlying malignancy, such as squamous cell cancer, chronic lymphocytic leukemia, non-Hodgkin lymphoma and multiple myeloma [15]. Hence, he should be given long-term follow-up as there have been reported cases in which AH was detected before the diagnosis of neoplasm [15].

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Conflict of interests

None.

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