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CASE STUDY

Acquired Haemophilia A – A Clinician's Nightmare: Case Report

Pratibha Singh, Karthik Kumar, Prakas Mandal, Uttam Nath, Tuphan Dolai

Background: Acquired haemophilia A (AHA) is a rare autoimmune bleeding disorder characterized by the formation of inhibitory antibodies against endogenous Factor VIII (FVIII), interfering with its function. Though a rare disorder, with around 1.5 cases per million, it is more prevalent among the elderly. There is a wide phenotype of bleed presentation, and nearly half of patients will have an underlying malignancy or autoimmune disorder. Mortality is estimated to be more than 20% in patients aged over 65 years.
Case: We report the case of an 82-year-old woman who presented with a sudden onset of spontaneous ecchymosis, and haematoma over the right scapular region, extending to the right breast, flank, and abdomen. She was planned for exploration in view of impending compartment syndrome when a diagnosis of AHA was confirmed. Investigations revealed isolated prolonged activated partial thromboplastin time (aPTT) and FVIII activity estimated at 2.8%. During the first week of treatment, she received haemostatic management with bypassing agent NovoSeven (recombinant Factor VIIa (rFVIIa)), starting at a dose of 90 mcg/kg, every 4 hours, along with tranexamic acid. Combination immunosuppressive therapy (IST) was initiated with methylprednisolone @1mg/kg and cyclophosphamide (50-100mg/day). Bypassing agents were continued for 2 days; the patient had a transient response, and no expansion of haematoma was observed. As the serial inhibitor titre was persistently > 20 BU, the patient received 1 dose of rituximab @ 375mg/m^2 in combination with corticosteroids. During the second week of treatment, the patient developed respiratory distress and was managed in intensive care for possible complications of IST. She later developed pneumonia and died due to its complications. The patient's age at presentation, the presence of a high inhibitor titre, and dual IST were possible risks and prognostic factors in this case.
Conclusion: Early diagnosis and careful, effective management of AHA is essential for achieving remission. Its prevalence among the elderly population increases the likelihood of comorbidities and raises the need for a multi-departmental approach. Appropriate use of bypassing agents for haemostatic control is key, alongside careful stratification and consideration of the risks of IST. IST-related mortality and complications mandate an individualized approach to treatment.

Keywords: *Coagulation, Bleeding disorders, Acquired haemophilia A, Bethesda assay, Case study*

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Acquired haemophilia A (AHA) is a rare bleeding disorder with an incidence of up to 1.5 cases per million persons per year occurring equally in both genders, particularly in the elderly [1]. It is caused by the spontaneous production of neutralizing immunoglobulin G (IgG) autoantibodies (inhibitors) targeting the activity of endogenous Factor VIII (FVIII) [2]. Recent research suggests that the breakdown of immune tolerance is caused by a combination of genetic and environmental factors [3]. AHA is associated with a higher mortality risk than hereditary FVIII deficiency (haemophilia A) due to its atypical presentation and under suspicion. Approximately 30% of the patients do not require haemostatic treatment, but bleeding severity varies and can be life-threatening [4]. It commonly presents as skin and subcutaneous bleeds (>30%) rather than deep-seated bleed/joint bleeds, followed by gastrointestinal bleeding, retroperitoneal, and other sites of bleeding. Nearly half of patients will have an underlying malignancy or autoimmune disorder, but it may also be idiopathic or present with isolated prolonged activated partial thromboplastin time (aPTT) without bleeding. Mortality in AHA is estimated to be more than 20% in patients over 65 years old. [5]

Treatment of AHA involves a two-tiered approach. Haemostasis is optimized using haemostatic agents such as recombinant activated factor VII or activated prothrombin complex concentrate (aPCC), and eradicating inhibitors using immunosuppressive agents such as glucocorticoids, rituximab or cyclophosphamide [6]. Early FVIII recovery is a good predictor of survival. AHA has a high rate of recurrence despite immunosuppressive therapy; hence, close monitoring of factor VIII activity is required for follow-up.

CASE PRESENTATION

An 82-year-old hypertensive female presented in the emergency department with complaints of spontaneous reddish-purple patches over her right shoulder, extending to some parts of the back and chest, right flank, and abdomen over the previous three days (Figures 1 and 2). The patient was previously healthy with no history of any antecedent insult in the form of trauma, infection, anticoagulants or antiplatelet drugs.

On general examination, she had pallor, along with swelling over the right shoulder with discoloration and extension as mentioned. The swelling had minimal fluctuation and was painful, with superficial discoloration in the form of ecchymosis. High-resolution computed tomography (HRCT) of the thorax was suggestive of a large haematoma in the right lateral chest wall. The patient was initially reviewed by the Department of General Surgery and was planned for exploration in view of the large haematoma and the possibility of impending compartment syndrome.

A complete blood count showed a haemoglobin level of 5g/dL, a total leukocyte count of 5,680 with a normal differential, and a platelet count of 155 x 103/µL. Coagulation screening showed a significant prolongation of aPTT at 55s (26-29s), and a normal prothrombin time (PT) of 10s (10-13s). Fibrinogen was 208 mg/dL, and thrombin time was 18s. Keeping in mind acute bleeding with a prolonged aPTT in an elderly patient, AHA was suspected, and an aPTT based mixing study was advised, while simultaneously other causes of prolonged aPTT (e.g., lupus anticoagulant) were ruled out. The immediate mixing and incubated mixing revealed the presence of a time- and temperature-dependent inhibitor. Consequently, FVIII activity showed 2.8% and factor IX (FIX) 71.8%. Inhibitor titre by the Bethesda assay was 32 BU, which is classified as a high titre inhibitor. The patient was diagnosed to be a case of AHA.

Treatment with a bypassing haemostatic agent, NovoSeven (recombinant Factor VIIa (rFVIIa)), was started at a dose of 90 mcg/kg, every 4 hours, along with tranexamic acid. Due to this being a case of high titre inhibitor with moderate FVIII deficiency, combination immunosuppressive therapy (IST) was considered, and the patient was initiated on a combination of methylprednisolone at a dose of 1mg/kg along with cyclophosphamide (50-100mg/day). The bypassing agents were continued for 2 days, after which they were discontinued due to financial constraints. The patient had a transient response to this therapy as no expansion of haematoma was observed on subsequent monitoring. As the serial inhibitor titre was persistently > 20 BU, therapy with monoclonal antibody CD20 rituximab (RTX) was considered; the patient received 1 dose of rituximab @ 375mg/m2 in combination with corticosteroids.

During the second week of therapy, the patient began to develop some respiratory distress. She was managed in the intensive care unit for the possible complications of immunosuppressive therapy (IST). She later developed pneumonia and died due to its complications. The patient's age at presentation, the presence of a high inhibitor titre, and dual IST were possible risks and prognostic factors in this case.

Figure 1. Haematoma extending over anterior chest wall, right flank

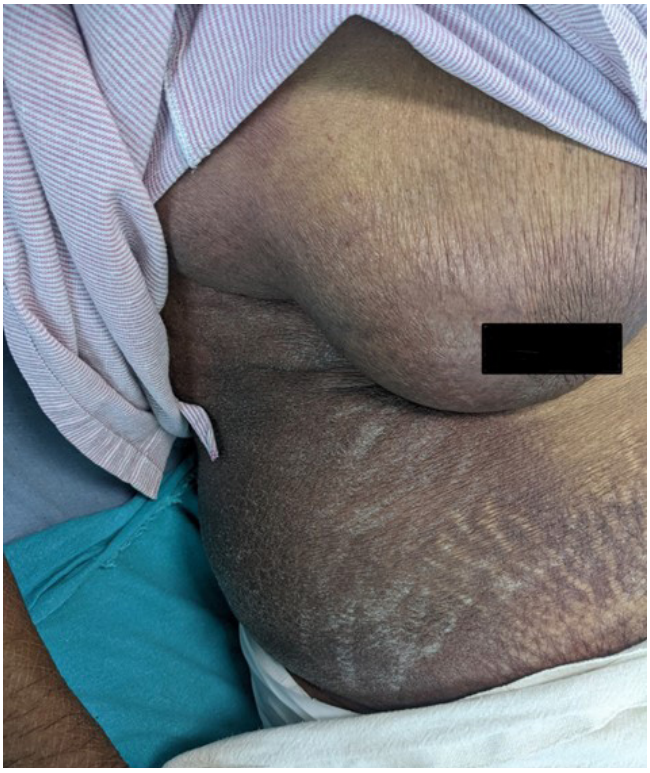
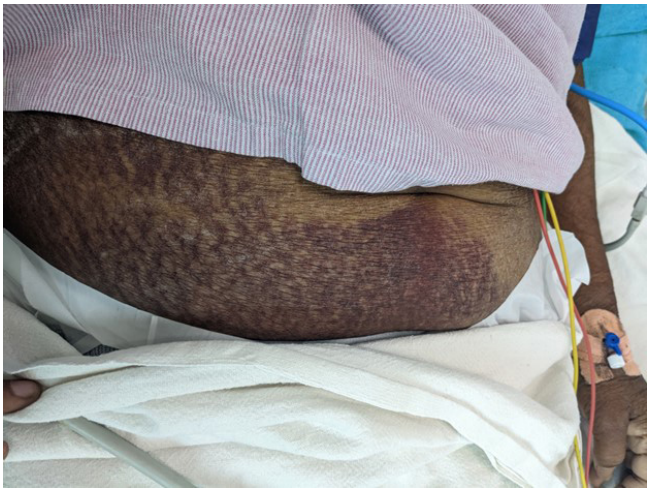


Figure 2. Ecchymotic patch extending over lower abdomen



DISCUSSION

AHA is a rare, often unrecognized, and potentially life-threatening bleeding disorder due to the formation of inhibitory antibodies against endogenous FVIII. It affects 1-1.5 per million cases annually, predominantly in the elderly (median age 64-78 years), and occurs equally in males and females [6]. Though the majority of cases are idiopathic (51.9%), there have been instances where a more frequent association has been found with pregnancy (1-5%) or within 1 year following childbirth, in autoimmune disorders such as rheumatoid arthritis, multiple sclerosis, systemic lupus erythematosus, polymyalgia rheumatica (11.6%), and in infections like acute hepatitis A and B, Covid19 or malignancies (11.8.%), making a multidisciplinary approach to treatment essential for each patient (see Table 1) [7]. A diagnosis of AHA should be suspected if a previously healthy patient presents with a new onset of bleeding with a prolonged aPTT in the absence of any similar past or family history, alongside negative results for screening for any trauma, autoimmune processes, infections, and neoplasms. Bleeding manifestations are variable and may range from life-threatening bleeds to mild or no bleeds. Bleeding in joints and closed cavities is less common [8]. Our case presented with extensive subcutaneous bleeding followed by muscle bleeds, with impending compartment syndrome. A similar presentation and demographic was described in a case reported by Perotti Abad et al., where an elderly female presented with cutaneous and mucosal bleeding in the oral cavity, idiopathic in nature in the absence of any family or significant past history [9].

The pathophysiology of AHA is less understood but primarily revolves around immune breakdown and antibody formation. The immune system erroneously recognizes endogenous FVIII as foreign due to a combination of environmental and genetic factors, resulting in polyclonal IgG1 and IgG4 autoantibodies to its A2 and C2 domains, resulting in a functional deficiency [10]. The interaction between FVIII and the interacting antibody is different from congenital haemophilia A (type I kinetics), where FVIII activity declines in direct proportion to the concentration of the inhibitor. In AHA, autoantibodies exhibit complex second-order inhibition, resulting in rapid initial FVIII inactivation, followed by a plateau phase where a measurable amount of FVIII activity persists, regardless of further increases in inhibitor concentration [11]. This residual factor level does not confer any protective effect against bleeding, making both treatment and assessing an accurate inhibitor titre difficult.

Laboratory investigations generally show a normal blood picture with a normal platelet count, although in some cases decreased haemoglobin can be seen due to the extent of bleeding. There is also an abnormal coagulation profile in the form of prolonged aPTT. Further confirmation of AHA diagnosis involves performing mixing studies, testing FVIII activity (FVIII:C), and quantifying inhibitor concentration using the Bethesda assay. As per the literature,

Table 1. Conditions associated with acquired haemophilia A

Malignancies [12]	• Chronic lymphocytic leukaemia • Cancer of the prostate • Cancer of the lung • Cancer of the colon • Multiple myeloma • Waldenstrom macroglobulinemia
Autoimmune disorders [13]	• Rheumatoid arthritis • Systemic lupus erythematosus (SLE) • Multiple sclerosis • Myasthenia gravis • Autoimmune haemolytic anaemia (AIHA)
Infections and others [7]	• Acute hepatitis B infection • Acute hepatitis C infection • Chronic graft versus host disease (GvHD) • Inflammatory bowel disease

FVIII activity (FVIII:C) is <1% in 50% of cases, <5% in 75% cases, and <40% in 100% of cases [8].

Principles of management are guided by a two-tiered approach which involves management of acute bleeding with haemostatic measures and eradication of inhibitors using immunosuppressive measures. In some cases, where residual FVIII activity is more than 5% and the inhibitor titre is less than 2 BU, desmopressin (0.3-0.4mg/kg) has been reported to be useful [10]. The autoantibody titre does not directly correlate with the severity of bleeding, hence treatment recommendations rely heavily on clinical judgement. Major bleeding, such as that seen in our case, with a high inhibitor titre are treated with bypassing agents, namely aPCC or rFVIIa. Though studies have described the superiority of rFVIIa over aPCC, cost is a limiting factor in its widespread use [15].

The second step of management is to suppress inhibitor formation through immunosuppression (IST). IST is reported to result in remission of AHA in 60%-90% of cases [14]. Prospective data has demonstrated that remission is unlikely within 21 days of IST in patients with FVIII:C below 1% or with a high inhibitor titre of more than 20 BU [14], therefore a combination of corticosteroids (prednisolone 1mg/kg/day) and cyclophosphamide (50-100mg/day) is usually recommended, as per recent guidelines [16]. This course of treatment was initiated in our case. Other options for immunosuppression include azathioprine, vincristine, rituximab, cyclosporin, and FVIII immune tolerance. In our case, rituximab was further added as there was no adequate response after 3 weeks. Literature review suggested that 42 patients treated with rituximab had similar outcomes to 44 control patients treated with cyclophosphamide and steroids [17]. However, data from the European Acquired Haemophilia Registry (EACH2) does not support these findings; 30/51 (59%) patients treated with a rituximab based regimen achieved a stable remission, but this was less than for patients treated with corticosteroids and cyclophosphamide [7].

A fundamental paradigm shift has occurred in AHA mortality patterns over recent decades. Contemporary registry data show bleeding mortality has decreased to 3-9% with modern haemostatic management, but with a concerning increase in immunosuppressive therapy (IST)-related mortality, particularly from infectious complications. The GTHAH 01/2010 study followed a strictly prospective design and documented high rates of IST-related adverse events and mortality, the most common cause being infections, followed by cardiovascular disorders, underlying disease and, lastly, bleeding [14]. Certain prognostic factors have been established based around balancing the length of and risks associated with IST, bleeding risk, and achieving complete remission. It has been observed that a high inhibitor titre, severe bleeding and corticosteroid monotherapy are less likely to result in complete remission [18]. Bleeding tends not to be a frequent cause of mortality; rather, predictors for mortality include advanced age (>75 years), malignancy, infection, ICU admission, and low FVIII activity at baseline [14,18]. These predictors were all present in the patient reported in our case.

CONCLUSION

The treatment of AHA continues to be a challenge. Early diagnosis and careful, effective management is essential to achieving remission. Its prevalence among the elderly population raises the likelihood of comorbidities and an increased need for multi-departmental approach to patient treatment and care. Appropriate use of bypassing agents for haemostatic control is key, alongside careful stratification and consideration of the risks of IST, particularly in elderly patients. Bypassing agents provide bleeding control with high efficacy. IST-related mortality and complications mandate an individualized approach to treatment. Adequate prophylaxis and monitoring should be prioritized while using these agents, and continued monitoring of inhibitor titre and FVIII:C is essential.

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Conflict of interest

The authors have advised no interests that might be perceived as posing a conflict or bias.

Consent

Informed consent was obtained from the individual reported in this case study. There are no personal details or images violating patient's identity.

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