CASE REPORT

A case report of acquired Haemophilia A: A rare medical emergency

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SUMMARY

Acquired Haemophilia A (AHA) is a rare potentially life-threatening bleeding disorder caused by the presence of autoantibodies against coagulation factors. It is usually characterised by severe spontaneous haemorrhage, which can lead to high morbidity and mortality. The diagnosis is often challenging. Treatment requires vigilant and accurate laboratory investigations, control of bleeding episodes, and eradication of inhibitors using bypassing agents and/or immunosuppressive agents. Hereby, we present a case report of unusual bleeding episodes with isolated raised activated partial thromboplastin time (APTT).

INTRODUCTION

Acquired haemophilia A (AHA) is a rare but serious autoimmune bleeding disorder caused by the spontaneous formation of autoantibodies directed against plasma coagulation factors, i.e. factor VIII (FVIII). The condition is usually idiopathic but is commonly associated with autoimmune diseases, pregnancy, malignancy, infections, and dermatological conditions.[1] Genetic and environmental factors, along with the immune response in elderly individuals, are thought to lead to breakdown in immune tolerance, causing development of autoantibodies against FVIII.[2]

AHA has reported an incidence of 1.5 cases per million persons per year, which increases with increasing age and is primarily seen in patients aged 60 to 80 years. There is neither any hereditary pattern nor gender preponderance. Mortality rate is 8–22%.[3] Majority of the cases affect the adult population unlike congenital haemophilia. Median age at presentation is 60–67 years. Two peaks in AHA incidence are typically observed: one associated with pregnancy and another with older age (>60 years).[4]

Patients typically present with spontaneous bleeding or even asymptomatic with an isolated prolonged activated partial thromboplastin time (APTT) due to acquired FVIII deficiency. The bleeding phenotype of AHA is variable, ranging from life-threatening bleeds to mild or no bleeding. Subcutaneous hematomas are characteristic of AHA and can be the first sign of the disease. An isolated prolonged APTT is almost pathognomonic to AHA. Neutralising antibodies (inhibitors) are detected using the Nijmegen-modified Bethesda assay. A prolonged APTT should never be ignored prior to invasive procedures.[4]

The main goal of therapy is to control acute bleeding and prevent injury, whereas the mainstay of treatment is bypassing agents, including recombinant activated factor VII (rFVIIa), activated prothrombin complex concentrate (APCC), or recombinant porcine FVIII (rpFVIII) in bleeding patients.

AHA represents a clinical challenge, as lack of familiarity of AHA can result in delayed diagnosis and/or inadequate treatment, contributing to high mortality and morbidity rates. Hence, we report a case report of an elderly with AHA with an underlying skin condition.

CASE REPORT

This is a 75-year-old gentleman with underlying hypertension, chronic kidney disease stage 4 (stable), bilateral knee osteoarthritis, gouty arthritis, and plaque psoriasis (in remission), presented to outpatient clinic with progressive and spontaneous bruises with mild swelling over the medial aspect of bilateral forearm for the past 2 weeks. Prior to the presentation, he experienced dactylitis and tenderness of the small joints of the fingers for the past 1 month. He also had recent flare up of the skin psoriasis in the past 2 month, which resolved after topical application of steroid cream and emollients. Otherwise, there is no evidence of septic arthritis nor clinical features of tophaceous gout.

He visited family physician and was given intramuscular Diclofenac for pain relief; however, the pain was partially relieved and progressive worsening bruises spread to medial aspect of thigh, left flank, and medial aspect of bilateral forearm. Clinically, it showed haematoma and ecchymosis over the flank (Figure 1), medial thigh, right forearm, and left medial arm.

His previous medications included T. Furosemide 40 mg daily, T. Amlodipine 10 mg daily, T. Calcium Carbonate 500 mg twice daily, T. Rocaltriol 0.25 µg every other day, and T. Allopurinol 150 mg daily. He had no history of spontaneous bleeding, malignancy or blood disorder, and blood transfusion. He denied taking over the counter medications, steroids, non-steroidal anti-inflammatory drugs (NSAID), or traditional herbs.

The initial blood investigations are as follows: Haemoglobin (Hb) 11.0 g/dL, WBC 6.6 x 10^9/L, Plt 178 x 10^9 /L, HCT 34.5%, INR 0.97, Prothrombin time (PT) 13.0 s, Partial

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Table I: Blood investigations

Haemoglobin	11.0	6.7	Reticulocytes	2.8%
White blood cells	6.6	16.8	LDL	238
Platelet	178	228	D-Dimers	0.2
Haematocrit	34.5%	20.3	ANA	Negative
Prothrombin time	13.0s	12.5	CEA	3.9
Partial Thromboplastin Time	70.7s (high)	48.0 (high)	CA 19-9	9.5
INR	0.97	0.92	AFP	<1.7
Urea	8.5	18.7		
Creatinine	149.4	250	Lupus anticoagulant	Negative
Sodium	140	138	Anti-cardiolipin	Negative
Potassium	3.8	4.2	Anti-beta-2 glycoprotein 1 antibodies	Negative
Chloride	101	101		
PTT mixing study		**Full blood pictures**		
APTT mixing	42s	Reactive leucocytosis. No evidence of haemolysis.		
Rosner index	12.3%			
APTT mixing (2 hour) 53.5s (high)				
Rosner index(2 hour) 29.5% (high)				
Factor VIII	3% (low)			
Factor IX	104%(normal)			
Factor VIII inhibitor	5.8 BU			

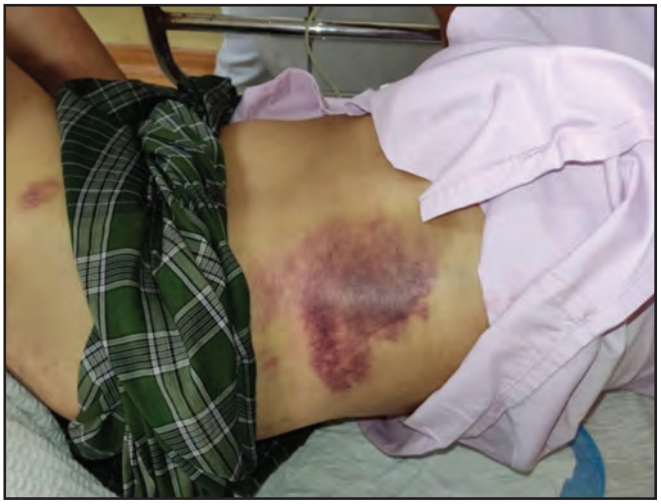


Fig. 1: Haematoma and ecchymosis over left flank.

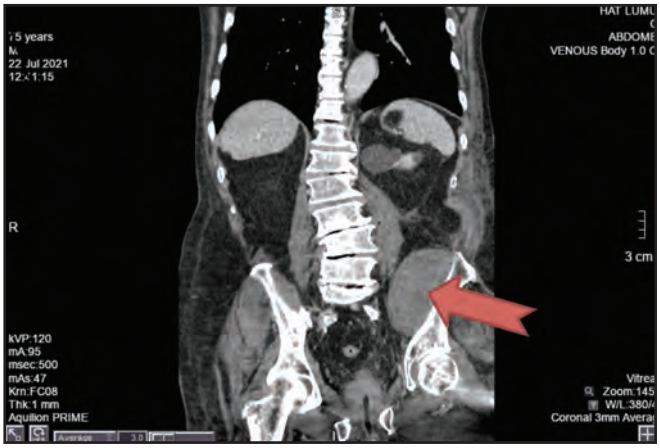


Fig. 2: Haematoma of the left Iliac muscle.

Thromboplastin Time (PTT) 70.7 s, Urea 8.5 mmol/L, Creatinine 149.4 µmol/L, Na 140 mmol/L, Potassium K 3.8 mmol/L, Chloride 101 mmol/L.

We repeated laboratory workup and noticed that Hb dropped abruptly from baseline 11.0 g/dL to 6.7, HCT 34.5% to 20.3%, leucocytosis WBC raised to 16.8 x 10^9, and Urea raised from 8.5 to 18.7 mmol/L. Notably, isolated raised PTT 48.0 s, PT 12.5 s, INR 0.92.

A PTT mixing study was immediately performed, which showed isolated raised APTT was not corrected. Rosner index was more than 15%. Low factor VIII was 3%. Bethesda assay revealed factor VIII inhibitor of 5.8 Bethesda Unit (BU). Features are consistent with Acquired Haemophilia A (AHA) (Table I).

Other relevant investigations include Full Blood Pictures showing no evidence of haemolysis, Reticulocytes 2.8%, LDH 238, D-dimers 0.2 (negative). TFT was normal. Infective screening was non-reactive. ANA was negative. Tumour markers CEA 3.9 IU/ml, CA 19-9 9.5 IU/ml, AFP <1.7 IU/ml. Thrombophilia screening showed that Lupus Anticoagulant (LA) antibodies, anti-cardiolipin antibodies, and anti-beta-2-glycoprotein 1 antibodies were all negative.

Urgent CT abdomen and pelvis with contrast showed enlarged left iliacus muscle due to acute intramuscular haematoma measuring 4.5 (AP) x 5.6(W) x 10.4(H) cm at its anterior aspect (Figure 2); enlarged left quadratus lumborum muscle due to subacute intramuscular haematoma measuring 1.6 (AP) x 2.6 (W) x 2.5 (H) cm at its anterior aspect; and enlarged left external oblique muscle due to

subacute intramuscular haematoma measuring 1.1 (AP) x 6.0(W) x 3.8 (H) cm over the left 10th intercostal space laterally. No free fluid was found. Abdominal aorta and its main branches are patent with no thrombosis. No extraluminal contrast extravasation on arterial phase nor pooling of contrast on portal venous and delayed phase was observed to suggest internal abdominal bleeding.

We ruled out any source of infection that could lead to sepsis causing Disseminated Intravascular Coagulation (DIC). There is no sign and symptoms of sepsis and afebrile. CRP was not raised. Fibrinogen degradation product was not significantly elevated, and D-dimers was negative. We checked any medications that could induce ecchymosis or purpura including steroids, NSAIDs, and anticoagulants such as warfarin. However, other than the intramuscular injection of Diclofenac for pain relief for his joint pain, the patient denied taking any medications.

TREATMENT

The patient was admitted for close observation of any worsening signs of bleeding. Our first priority is haemostatic treatment. We aimed at preventing further iatrogenic causes of bleeding in the ward and control of acute bleeding. Venepuncture only be taken by experienced medical officers and as indicated. Blood pressure cuff measured only as often as when deemed clinically relevant to prevent worsening of ecchymosis. We applied cold compression over the haematoma sites.

The patient was started intravascular Tranexamic acid 500mg three times a day and intravascular Hydrocortisone 100 mg three times a day, completed for 1 week. We also transfused 5-pint packed cells, 4 unit of Fresh Frozen Plasma (FFP), and 2 unit of Cryoprecipitates. After diagnosis, AHA is confirmed, and he was started immunosuppressant IV Cyclophosphomide 150 mg daily for 1 week. He was closely monitored for any signs of worsening bleeding. During the hospitalisation, he has no clinical evidence of worsening ecchymosis and haematoma. The bruises over bilateral upper limb were reducing in size and non-tender. Hb was static (Hb 9.7–10.8) after transfusion, and platelet count was within normal range (250– 290). aPTT was not worsening, ranging 48.3–50, PT 13–13.7, INR 0.98–1.03. Total protein 58.ALP 80 AST 23. Total bilirubin 22. He was discharged well after 10 days of hospitalisation.

During the follow-up at the clinic, he has neither new bruises nor bleeding. There are residual bruises over left thigh, but not increasing in size, and not limiting his range of motion.

DISCUSSION

The above case presentation showed sign of haemorrhage with typical isolated prolonged aPTT, which can be missed at a clinical setting. Prevalence and occurrence rates in Malaysia are still unknown. However, there are three reports found in the literature describing the same disease from 1995 till recent 2015.[3,5,6]

No exact aetiology could explain the condition, approximately half of patients with AHA have concomitant disorders, most often other autoimmune disorders or malignancy. Some literature revealed there is a relationship between genetic and environmental factors, which might lead to failure in immune tolerance and cause development of autoantibodies against FVIII. Some human leukocyte antigen (HLA) class II alleles and single-nucleotide polymorphisms of the cytotoxic T lymphocyte antigen 4 (CTLA-4) have been observed in a higher frequency in AHA.[2,7] In this case presentation, we can correlate the patient's recent flare-up of plaque psoriasis, which is an autoimmune condition that could possibly contribute to AHA.

AHA is frequently confused with other life-threatening conditions (e.g., disseminated intravascular coagulation) and typically occurs in an elderly population, thus can lead to severe morbidity and even mortality before it is correctly diagnosed. Estimates of the mortality associated with acquired haemophilia range from 8% to 22%, with most haemorrhagic deaths occurring within a few weeks of presentation.[8] If left untreated, bleeding was the cause of death in 9% of the cohort and remained a risk until the inhibitor had been eradicated.[9]

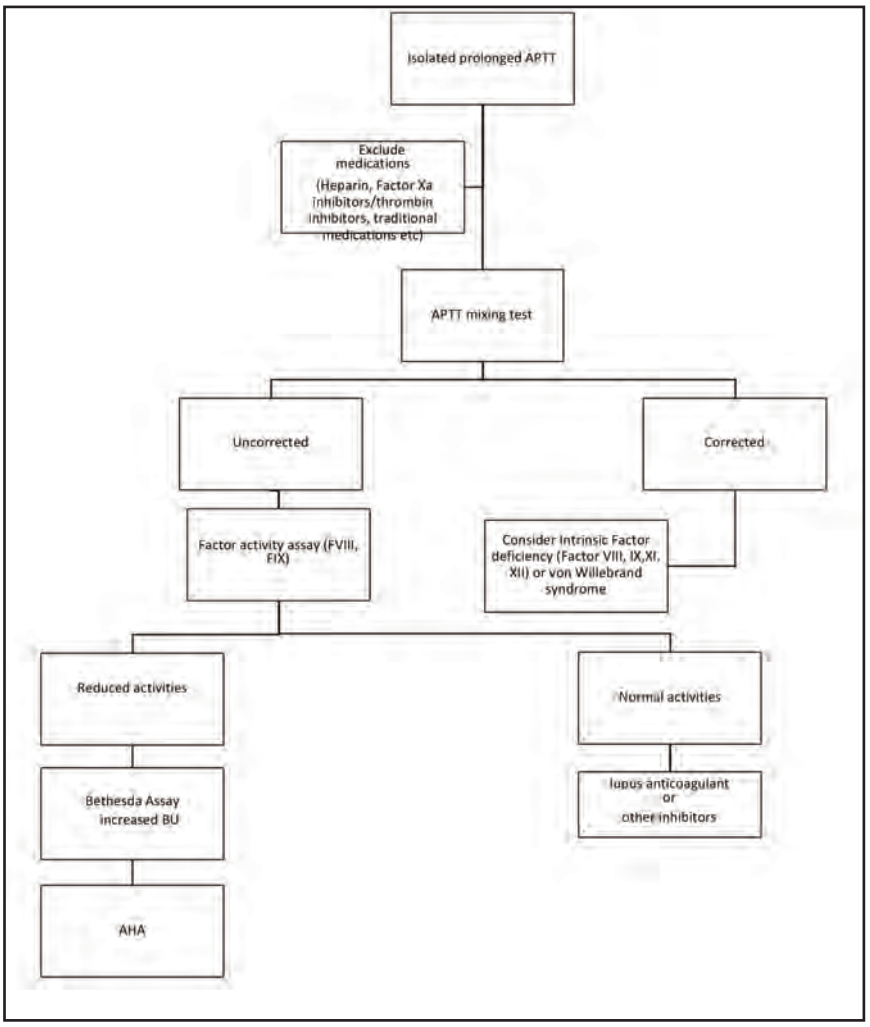
Typically, patients with AHA present with acute or recent bleeding symptoms, without a previous bleeding history, with laboratory investigation showing an isolated prolonged APTT. The bleeding pattern is characterised with subcutaneous bleeds being most common (observed in 80% of patients), followed by muscle, gastrointestinal, genitourinary, and retroperitoneal bleeds. Hemarthrosis, which is the hallmark of Congenital Haemophilia, is much less common in AHA.[4]

Coagulation factor deficiencies or coagulation factor inhibitors, including autoantibodies, LA, or pharmacological anticoagulants, may result in prolonged APTT. To distinguish a factor deficiency from the presence of an inhibitory substance, diagnostic aPTT mixing test is indicated. The diagnostic algorithm is shown in Table II.

In aPTT mixing test, varying amounts of patient plasma and pooled normal plasma are mixed, and the aPTT was measured. After mixing, measurement of the aPTT should be performed not only immediately but also after incubation at 37ºC for one to two hours. The second measurement is necessary to detect factor VIII inhibitors with slow reaction kinetics. Correction of the prolonged aPTT suggests a factor deficiency or VWD, while persistent prolongation of the aPTT indicates the presence of an inhibitor. The mixing test will establish whether an inhibitor is present but will not identify the inhibitor's specificity.

The Bethesda assay both establishes the diagnosis of a factor VIII inhibitor and quantifies the antibody titre. The Bethesda assay was developed to detect and quantify FVIII alloantibodies and thus useful in detecting FVIII inhibitors in AHA. A serial dilutions of patient plasma are incubated with pooled normal plasma at 37ºC for two hours; factor VIII activity is then measured using a clotting assay as one would in a patient with hereditary factor VIII deficiency. The

Table II: Blood investigations



reciprocal dilution of patient plasma that results in 50% factor VIII activity is defined as one Bethesda unit (BU). The stronger the inhibitor, the greater the dilution required to allow for factor VIII activity.

The first priority of management is to control acute bleeds and to prevent injury in the measure of limited iatrogenic cause of bleeding injury, haemostatic therapy, tranexamic acid, and blood transfusion if indicated. The second goal of treatment would be to reduce or to eliminate the inhibitor using bypassing agents, for example, APCC (FEIBA) or recombinant activated factor VII (NovoSeven).4 Corticosteroid therapy with prednisolone or prednisone 1 mg/kg/day PO for 4–6 weeks was suggested in the 2009 international AHA recommendations. In the Society for Thrombosis and Haemostasis Research e.V. study, it is recommended that patients not responding to steroids after 3 weeks were escalated to second-line therapy with cyclophosphamide, and later rituximab.[4]

In this case study, the bypassing agents such as APCC (FEIBA) or NovoSeven were not given due to the high-cost consideration. Despite this, the patient started corticosteroid therapy combined with cyclophosphamide and achieved recovery and remission as clinical outcomes.

The prognosis of patients with AHA depends on the patient's response to immunosuppression therapy. A meta-analysis of 249 patients with AHA found that three factors had an independent impact on overall survival and disease-free survival: related conditions (malignancy vs postpartum), complete remission status, and age at diagnosis (<65 y vs. ≥65 y).[10] Survival was greatest in patients with postpartum inhibitors, in those who achieved complete remission, and in those who were younger than 65 years.

Generally, there is variable consensus on management guidelines on management of AHA. Large, multinational collaborative randomised controlled trials are required for better assessment of treatment regimes in these patients with a rare, but devastating disorder. We hope this case report could shed some light on understanding of AHA.

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