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CASE SERIES

Epidemiology, spectrum of clinical manifestations and diagnostic issue of acquired haemophilia: A case series

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Abstract

Introduction: Acquired haemophilia A (AHA) is a rare acquired bleeding disorder caused by polyclonal immunoglobulin G autoantibodies against clotting factor VIII (FVIII). The incidence was reported to be rare occurring in 0.2- 4 cases/million/year. Patients may present with different clinical manifestations to various specialties. Early recognition of the disease contributes to favourable clinical outcome. *Case Series:* Here, we reported five cases of this disorder with different clinical presentations from two tertiary hospitals in Kelantan state, Malaysia within a two year-period. Most of them were elderly, except for one who presented at the age of 36 years old. No direct or secondary cause was identified except for one patient who had developed from pregnancy-related at 3 weeks postpartum. These patients presented with spontaneous bleeding typically into skin, muscles, and mucous membranes but also at rare site in the epidural space. All patients denied previous history of bleeding or family history of bleeding disorder. FVIII activities were recorded between <1% to 19%, while the inhibitor titre levels were between 3.9 BU to 340 BU. The treatment approaches especially at presentation were complicated by unfamiliarity of managing this rare condition but all these patients received appropriate medical attention. *Discussion:* Prompt diagnosis and management in the right hand are critical. Awareness of this disorder by medical personnel at all levels in the community and in various specialties is important.

Keywords: Acquired haemophilia A, factor VIII inhibitor, haemophilia, bleeding

INTRODUCTION

Acquired haemophilia A (AHA) is a rare bleeding disorder due to the development of autoantibodies against factor VIII (FVIII) activity. The incidence ranges from 0.2-4 cases/ million/year and the mortality rate ranged from moderate to high (9.1% to 27.9%).[1,2] It has bimodal age distribution, majority of cases occur in patients more than 65 years of age while a small peak occurs at younger age group (between 20 and 30 years), associated with pregnancy or postpartum complication.[2] The disease developed later in life without a personal or family history of previous bleeding episodes.[3] Half of the AHA cases are idiopathic, while the other half is associated with the postpartum condition, autoimmune diseases, malignancy and drugs.[4]

Majority of patients present with haemorrhage into the skin, muscles or soft tissues, and mucous membranes. AHA may also present with gastrointestinal or urological bleeds, and retroperitoneal hematomas; sometimes they can have serious and life-threatening bleeding such as excessive postpartum or post-operative bleeding.[3] Diagnosis of AHA is often delayed due to unfamiliarity among clinician towards the condition and also interpreting laboratory findings of this rare acquired bleeding disorder.

Acute bleeding with unexplained isolated prolonged activated partial thromboplastin time (APTT) warrants further testing of the presence of AHA. This prolongation is not corrected when mixed with normal plasma; however, the presence of lupus anticoagulant (LA) needs to

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be excluded. The latter is not associated with bleeding tendency. Typically, AHA patients will show normal results of bleeding time, platelet count and prothrombin time (PT).

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A total of five patients were identified from two major hospitals in Kelantan (Hospital Universiti Sains Malaysia and Hospital Raja Perempuan Zainab II) from January 2015 till July 2017. Their age ranged from 36 years old to 69 years old. The median age at diagnosis was 67 years. Male-to-female ratio was 1.5:1. So far, no direct or secondary caused of FVIII inhibitor were identified except for one case who presented at 3 weeks postpartum due to pregnancy-related. All the clinical data of the 5 patients is summarised in Table 1.

Case 1

This patient presented with spontaneous bruises over left upper limb for one-week duration. The bruises became progressively worsen and associated with swelling of the left forearm due to haematoma. There was no fever or history of trauma. She was a known case of hypertension and ischaemic heart disease, on medication. No family history of a congenital bleeding diathesis or previous history of bleeding tendency. Blood tests showed mild anaemia with isolated prolonged APTT, and was not corrected by immediate and incubation mixing studies.

Her FVIII level was 2% and FVIII inhibitor titre was recorded 3.9 Bethesda units (BU). PT, fibrinogen, and platelet count were within the normal ranges. Connective tissue disease screening and tumour markers were all negative. Based on no previous history of bleeding disorder, together with the presence of prolonged APTT, and non-corrected with normal plasma, AHA was diagnosed and supported by the FVIII inhibitor assay (Bethesda assay). She was started with intravenous methylprednisolone, which later was converted to oral prednisolone. From day 3 hospitalisation, the patient showed a progressive improvement both clinically and from the coagulation parameter. She was discharged well after one week of hospitalisation.

Case 2

A para-4 female patient presented with excessive vaginal bleeding with blood clots on day 23 post spontaneous vaginal delivery. She had uneventful pregnancy and delivery. However, there were significant skin bruises which developed following body massage during this recent pregnancy. Isolated prolonged APTT and non-correction immediate APTT mixing test was noted with normal fibrinogen and FDP levels. Postpartum acquired haemophilia (PAH) was suspected only when the laboratory results were reviewed by the Medical team. The factor VIII activity level was less than 1% with a FVIII inhibitor detected at a concentration of 340 BU; thus, confirming the diagnosis of AHA secondary to pregnancy-related after autoimmune screening test was negative. Methylprednisolone and cyclophosphamide were prescribed to the patient and she responded with an appropriate declined in APTT results. She responded to the treatment and the inhibitor level on follow-up was undetectable.

Case 3

This patient presented with prolonged bleeding from uncomplicated tooth extraction for 4 days duration. He had intermittent bruises and hematoma of upper and lower limbs for the past 2 months. He had leech bite recently and the bleeding at the bite site only stopped after 2 days. He was a known case of hypertension, hyperlipidaemia and ischaemic heart disease. He was on aspirin treatment; however, it was stopped one week prior to tooth extraction. He had no family history or previous history of bleeding disorder. His coagulation screen test showed isolated prolonged APTT and not corrected by adding normal plasma on mixing test. Other coagulation parameters and connective tissue screening test were all normal. FVIII assay showed reduced FVIII activity (6%) and there was presence of factor VIII inhibitor (7.7BU). He was given oral prednisolone, together with rituximab and cyclophosphamide. He was discharged well after one week of hospitalisation and no record of return due to bleeding manifestation after that.

Case 4

The patient presented to the emergency department with sudden onset of bilateral lower limb weakness one day prior to the presentation. At the same time, he also had anal and bladder incontinence. There was no previous history or family history of bleeding disorders. APTT result was elevated and platelet count was mildly low. Immediate and 2 hours incubation mixing study of APTT was not corrected. Urgent computed tomography scan (CT scan) followed by magnetic resonance imaging (MRI) showed epidural

TABLE 1. Summary of the clinical and laboratory characteristics of patients with acquired haemophilia A.

	Case 1	Case 2	Case 3	Case 4	Case 5
Age (years)	59	30	67	69	69
Gender	F	F	M	M	M
Clinical presentation	spontaneous upper limb bruises	excessive per vaginal bleeding	prolonged bleeding from tooth extraction	Bilateral lower limb weakness	generalised skin bruises
Underlying risk factors	No	postpartum	No	No	No
Treatment	Prednisolone	Methyl prednisolone, cyclophosphamide	Methyl prednisolone, rituximab, cyclophosphamide	FEIBA, Prednisolone, rituximab	Defaulted
Patient outcome	Discharge well, no recurrent bleeding	Discharge well, no recurrent bleeding	Discharge well, no recurrent bleeding	Discharge, no recurrent bleeding	Unknown
Laboratory investigations at presentation					
PT (s)	13.5 (N)	11.9 (N)	12.1 (N)	12.6 (N)	12.5 (N)
APTT (s)	77.7	110.0	63.6	60.4	96.9
Mixing APTT	Not corrected	Not corrected	Not corrected	Not corrected	Not corrected
Fibrinogen (g/L)	Normal	Normal	Normal	Normal	Normal
FDP (ug/ml)	Normal	Normal	Normal	Normal	Normal
FVIII level (%) (N: 50 -100)	2.0	<1.0	6.0	14.0	<1.0
FVIII Inhibitor level (BU)	3.9	340	7.7	16.8	30
Hb (g/dL) (N: 12.5 – 15)*	9.6	6.0	11.2	11.2	9.0
Plt ($x10^9$/L) (Normal: 150 – 400)	276	312	195	129	210
LA study	Not detected	Not detected	Not detected	Not detected	Not detected
ANA	Normal	Not done	Normal	Normal	Normal

PT=Prothrombin time, APTT=Activated partial thromboplastin time, Hb=Haemoglobin, Plt=Platelet, F=Female, M=Male, FDP=Fibrin degradation products, ANA=Antinuclear antibody, FEIBA=Factor VIII inhibitor by passing agent, s=Second, N=Normal, *Standard adult reference range for both genders

haematoma with spinal cord compression. Multiple extradural and intradural bleeds were also reported. These findings contributed to the neurologic bladder and anal dysfunction.

AHA was suspected after APTT and mixing test findings were reviewed by medical team. FVIII assay recorded 14% and factor VIII inhibitor was detected (16.8 BU). Factor VIII anti-inhibitor coagulant complex FEIBA® 75 U/kg (Baxter Healthcare Corporation, Westlake Village, CA) was administered every eight-hourly as well as prednisolone 1 mg/kg prescribed once daily. However, factor VIII inhibitor test showed no reduction in the level and hence intravenous rituximab was added to his treatment regimen. He completed 4 cycles of rituximab and no further bleeding episode was recorded after that and his hospitalisation course was otherwise uneventful.

Case 5

This patient presented with extensive skin bruises over the chest and both upper and lower limbs for one-week duration. He experienced periodic bruises for the past one month, otherwise no other complaints. He was a known case of myocardial infarction and was prescribed antiplatelet therapy. There was no family or personal history of a congenital bleeding diathesis. He had marked isolated prolonged APTT (96.6 second), which was not corrected with normal plasma at 2-hour post incubation. FVIII activity recorded 0.8% with presence of FVIII inhibitor (30 BU). While waiting for the diagnosis, this patient requested for discharge but did not turn up despite the advice to be seen again. Until this review was made, it is uncertain whether he went to other hospitals for treatment.

DISCUSSION

This report summarises that AHA is a heterogeneous condition which has different spectrum of clinical presentation. Diagnosis of acquired bleeding disorder may not be straight forward and requires many causes to be considered, including review of laboratory data. AHA is a rare condition and unfamiliarity among the treating teams toward this condition may contribute to delay in the diagnosis. In addition, the diagnosis of AHA is totally relied on laboratory confirmation. Some of the clinical presentations can be due to patient underlying medical diseases and treatment, which need to be excluded. Aspirin, for instance, is a common drug prescribed and known to be associated with platelet dysfunction, which can cause easy bruising. Hence initiating early specific investigation and treatment for AHA requires high index of suspicion set from the beginning. Most of the patients were elderly, which has similar findings with the two largest available cohorts, the prospective UK study[1] and the European Acquired Haemophilia (EACH2) registry.[2] They found more than 80% of patients being 65 years or older. The development of AHA is believed due to breakdown of immune tolerance mechanisms that regulate normal immune response to FVIII.[5]

AHA may manifest with different clinical presentation and severity, as seen in our patients. Some of them only presented with localised or generalised skin bruises while the other with severe bleeding manifestation such as postpartum haemorrhage and spinal cord compression due to epidural hematoma. In post-partum state, FVIII inhibitor develops commonly between three and 150 days after delivery.[6] AHA is more common in first pregnancy, however our patient only developed the disease after fourth pregnancy. Pregnancy-related AHA commonly shows better prognosis with low mortality rates (0-6%).[7]

Three of our patients presented to general physician while the other two presented to gynaecologist and emergency physician respectively, indicating patients with AHA may present to different specialties, who may not have experience with this rare condition. Thus, there were consensus recommended that the diagnosis of AHA be considered whenever an acute or recent onset of bleeding symptoms is accompanied by unexplained prolonged APTT.[8] To diagnose AHA, measurement of FVIII level is essential, followed by determination of FVIII inhibitor titre by the Bethesda assay (BA), Nijmegen Bethesda assay (NBA), or by an enzyme-linked immunosorbent assay (ELISA).[9] It is essential for the laboratory to have the expertise to perform these relevant tests to diagnose AHA. Failure to do this, there may be a delay in making the diagnosis if the sample needs to be outsourced far away.

DIC may have similar bleeding presentation and need to be excluded. Usually this condition shows both PT and APTT prolongation with other medical causes predispose to its development. In view of isolated prolonged APTT is relative to LA, the test for LA may be performed. However, antiphospholipid syndrome with LA is a clinical condition closely associated with hypercoagulable state and shows a predilection to

venous thromboembolism. Unless accompanying with factor deficiency (for example factor II and X) or thrombocytopaenia, bleeding tendency is not seen in patients with LA.

The severity of bleeding is highly variable due to the autoantibodies act as a second-order non-linear inactivation pattern.[10] Therefore, quantitation of the in-vitro inhibitor titre may underestimate the in-vivo inhibitor potency, due to non-linear reaction kinetics. This could explain that inhibitor titre or percentage of residual FVIII activity do not correlate with the severity of bleeding, as seen in this series. The management involve prevention and control of bleeding, as well as replacement therapy using bypassing agents. Recombinant activated FVII or activated prothrombin complex concentrate is the haemostatic treatment of choice followed by inhibitor eradication using corticosteroid alone, or corticosteroid and cyclophosphamide, or corticosteroids and rituximab as first-line therapy.[11]

As the confirmation from laboratory is critical for AHA, the laboratory should provide the related tests directed towards diagnosing this condition. It is also recommended that the laboratory perform a stat reflex testing by performing immediate and 2-hour incubation mixing tests after an isolated prolonged APTT is detected in all patients with new or recent spontaneous bleeding manifestation. Inhibitor assay should be arranged immediately in all suspected AHA cases. Communication between clinician and laboratory personnel on the bleeding presentation and arrangement of appropriate laboratory tests should be made urgently. These could prevent the delay in the diagnosis of this condition and prevent inappropriate management.

CONCLUSION

Our data agrees with the estimated general prevalence of AHA but showed spectrum of heterogeneous clinical manifestations in our series. Since AHA is rare and associated with high morbidities including fatality, high index of clinical suspicion is required to provide better guidance in early management of this condition. The tertiary centres or referral hospitals in each state should have the laboratory facility to diagnose AHA and receive immediate referral for all acute bleeding manifestation with prolonged APTT, irrespective of severity when acquired bleeding disorder is encountered.

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