

CASE REPORT

A case series of acquired haemophilia in a Malaysian hospital: unpredictably rare medical emergency

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Abstract

Acquired haemophilia (AH) is a rare bleeding disorder characterized by the presence of acquired inhibitors against Factor VIII causing disruption of coagulation cascade. It has no known genetic inheritance, and diagnosis remains a challenge. The peculiar presentations are later age of onset as acute pain in weight-bearing joints and spontaneous muscle haematoma with isolated prolonged activated partial thrombin time (APTT). Prevalence is 1 per million per year affecting both genders equally where blood product transfusion is seen in almost 87% of cases. The direct cause of AH is still unknown, and autoimmune dysregulation has been postulated, which predisposes to the development of the factor inhibitors. Being extremely rare, we are reporting two consecutive patients diagnosed by unusual bleeding episodes with isolated prolonged APTT due to Factor VIII inhibitors. AH deserves a special mention as high index of suspicion is required. More studies are required to provide better guidance in diagnosis and management of this condition.

INTRODUCTION

Acquired haemophilia (AH) is a rare disorder when compared with its congenital counterpart. There is neither any hereditary pattern nor gender preponderance. Incidence is 1.5 cases/million/year [1]. Mortality is 8–22% [2]. Majority of the cases affect the adult population unlike congenital haemophilia. Median age at presentation is 60–67 years [2]. AH is characterized by the presence of non-complement fixing autoantibodies against Factor VIII [3]. The severity of AH depends on the inhibitors' level measured in Bethesda Units (BU). In 50% of the cases, there is an association with other underlying medical conditions such as pregnancy (also post-partum state), solid tumours, autoimmune diseases (systemic lupus erythematosus, rheumatoid arthritis, Sjogren's syndrome), lymphoproliferative malignancies, skin disorders and drugs-induced or even graft-versus-host disease [2]. We are reporting two patients

who spontaneously developed Factor VIII inhibitors with one of the abovementioned underlying medical conditions.

CASE REPORTS

The first case was a 61-year-old male smoker with underlying diabetes mellitus, hypertension and hyperlipidaemia taking aspirin 75 mg daily, clopidogrel 75 mg daily, perindopril 4 mg daily, simvastatin 20 mg daily, metoprolol 25 mg bid, metformin 500 mg bid and nitroglycerine 1 tablet as required. He was electively admitted for angiogram, during which he developed spontaneous bruising and swelling over the left calf (Fig. 1) and the right buttock (Fig. 2). Initial blood investigations, haemoglobin (Hb) 13.5 g/dl, platelet $256 \times 10^9/l$, white blood cells (WBC) $8.0 \times 10^9/l$, international normalized ratio (INR) 0.82 and normal prothrombin time (PT)

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Figure 1: Haematoma over the left calf region.



Figure 2: Ecchymoses over the right buttock.

with prolonged activated partial thrombin time (APTT) at 72 s. He then developed per rectum bleeding with Hb dropped to 6.7 g/dl. Hence, antiplatelets were stopped, and packed red cells were transfused. However, repeated blood investigation shows worsening coagulation profile; INR becomes 1.12 and APTT 120 s. A mixing study was immediately performed, which did not show correction of the APTT. His fibrinogen level was normal. Factor VIII activity was reported at 1.2% (normal >25%), and Factor VIII inhibitors were reported to be 60 BU using Bethesda method. Therefore, intravenous (IV) methylprednisolone 500 mg OD was started, and multiple transfusions were given before his transfer to another haematology centre for commencement of immuno-suppressive therapy.

The second case was a 40-year-old post-partum lady with underlying pustular psoriasis who was on methotrexate for 4 years. She also has hypertension and gestational diabetes mellitus not on any treatment. She was admitted for relapsed pustular psoriasis after stopping her methotrexate during her pregnancy and intrauterine growth retardation at 38 weeks of gestation. She then underwent an emergency caesarean section following foetal distress. The procedure was uneventful, and estimated blood loss was only 200 ml. Her blood investigations 2 months before delivery showed Hb 12.8 g/dl, platelet $305 \times 10^9/l$, PT 12.1 s, INR 0.89 and APTT 36.1 s. However, during the post-partum period, the Hb dropped to 9.6 g/dl, platelet $496 \times 10^9/l$, PT 12.5 s, INR 0.93 and APTT 88.9 s. The coagulation profile was not corrected in the mixing study and the presence of Inhibitor Factor VIII 2BU. Her serum fibrinogen and von Willebrand factors were normal. She was started on prednisolone and cyclophosphamide; however, the inhibitors remain at 2 BU. She was then given rituximab. Three months later, her APTT increased to 110 s suggesting a relapse. Hence, she was reinduced with IV cyclophosphamide and T. prednisolone 40 mg OD, and at the same time, she developed retroperitoneal haematoma as seen on computed tomography scan with a drastic drop in Hb to 6.4 g/dl (baseline was 12.6 g/dl); therefore, blood products were given, and she was transferred to another tertiary facility for commencement of Recombinant Factor VIIa (rFVIIa). (Normal laboratory values: Hb 11.5–16 g/dl, WBC $4\text{--}11 \times 10^9/l$, platelet $150\text{--}450 \times 10^9/l$, PT 10–13 s, APTT 28–38 s and INR 0.9–1.2.)

DISCUSSION

These cases presented with typical clinical scenario of isolated prolonged APTT and major bleeding. Prevalence rate in Malaysia is unknown; however, there are two reports found in the literature describing the same disease from 1995 till 2013 [5, 6]. The exact aetiology is unknown but believed to be related to the development of autoantibodies against Factor VIII and hampering the coagulation cascade. Frequently, the isolated prolonged APTT could present long before any major bleeding. It is worth mentioning that inhibitor could develop during post-partum period either during labour or after parturition [2]. Transplacental transfer of inhibitor has been reported, which could lead to neonatal bleeding [7]. Fortunately, there was no neonatal bleeding noted in our case. The investigations include mixing study, which is done by mixing incubated patient's plasma with normal plasma; inhibitor is said to be present if APTT fails to normalize; and the level of inhibitor is then determined by the Bethesda method, which is measured in BU [8]. BU can also be used in monitoring disease activity. Treatment of AH is divided into two major parts [2, 4]. Firstly, securing haemostasis. rFVIIa is recommended as the first-line treatment regardless of inhibitor titre or residual Factor VIII activity. rFVIIa acts as Factor VIII bypassing agent to activate the coagulation cascade hence securing haemostasis, suggested dose is 90 µg/kg every

2–3 h until haemostasis is secured [4]. Other recommended agents are DDAVP (desmopressin), Factor VIII concentrates and activated prothrombin complex concentrates [2]. None of them is said to be superior to another.

Secondly, inhibitor elimination. The recommended first line is corticosteroid with or without cyclophosphamide [4]. The recommended dosage is prednisolone 1 mg/kg/day orally for 4–6 weeks [2, 4]. Elimination of inhibitors can be achieved in ~30% of patients [2]. The addition of cyclophosphamide 50–100 mg per day (or 1.5–2 mg/kg/day for up to 6 weeks) [4] could increase the inhibitor elimination rate to 60–70% [2]. Suggested second-line agent is Rituximab, which was used in our second case. Rituximab was used when failure of corticosteroid + cyclophosphamide to achieve a stable disease. Other suggested agents are azathioprine, vincristine, mycophenolate and cyclosporine [4]. The response rate of IV immunoglobulin is quoted differently. Alice *et al.* quotes 30% response rate over 2 or 5 days of usage [2]. Another author quotes only 10–12% in patients with low inhibitor titre (<5 BU); thus, its usage is not recommended [4]. In conclusion, coagulation profile derangement may occur before bleeding event; hence, isolated prolonged APTT should not be ignored especially for patient with bleeding tendency in post-partum period. Randomized controlled trials are needed to conclude a better standard of care.

CONFLICT OF INTEREST STATEMENT

None declared.

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