

Acquired haemophilia A: a case report and literature review

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ABSTRACT

Acquired factor VIII deficiency is a very rare bleeding disorder and can be life threatening and most physicians are not aware of it. This disorder should be suspected if a patient with no prior history of bleeding presented with spontaneous bleeding and unexplained prolonged activated partial thromboplastin time (aPTT). We report a case of a 73-year-old man who presented with spontaneous bleeding secondary to acquired Factor VIII deficiency.

Keywords: Factor deficiency, bleeding, haemophilia, acquired, haemostasis

INTRODUCTION

Acquired factor VIII deficiency or acquired haemophilia A is very rare bleeding disorders caused by autoantibodies against clotting factor VIII.^{1-4, 5-7} These autoantibodies referred to as "inhibitors", leads to reduce the factor VIII and its subsequent pro-coagulant activities.² The incidence is reported to be between one and four cases per million populations per year.¹⁻⁴ The distribution is biphasic with predominant peak of patients over the age of 60 years old. There is no difference in incidence between sexes reported.¹⁻⁴

Approximately 50% of the cases are idiopathic.^{2, 3} However, this disorder can be associated with malignancies, other autoimmune diseases, postpartum state, infections

and medications (e.g. penicillin, phenytoin, methyldopa).¹⁻⁴ Clinical features include spontaneous bleeding into skin, muscles, soft tissue, epistaxis, gastrointestinal bleeds or urogenital bleeds.¹⁻⁴ Severe bleeding can occurs in up to 90% of the affected individuals and this contribute to the high rate of morbidity and mortality.³ In contrast to congenital haemophilia, haemarthroses is uncommon in acquired Factor VIII deficiency and is also very rare for patient to present with intracerebral haemorrhage.¹⁻³

We report a rare case of acquired haemophilia A in a 73-year-old man who presented with multiple spontaneous haematoma.

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CASE REPORT

A 73-year-old Malay man presented to the Emergency Department with spontaneous haematoma of the right shoulder of three

days and spontaneous haematoma on the left thigh a day before presentation. His past history was relevant for type 2 diabetes mellitus, hypertension and dyslipidaemia. His medications consisted of gliclazide 160mg BD, aspirin 100mg OD, atenolol 50mg OD, enalapril 10mg OD, metformin XR 1gm OD and atorvastatin 20mg OD.

On presentation, the full blood count revealed anaemia of 7.8g/dL (normal range of 12.5-16.3 g/dL) but otherwise normal white blood cell count (WBC) of $8.7 \times 10^9/L$ (3.6-10.0) and platelet count of $235 \times 10^9/L$ (150-450). The coagulation profile showed prolonged activated partial thromboplastin time (aPTT) of 75.1 sec (25.6-41.5), partially corrected to aPTT to 44.7 sec with 50% correction study and normal prothrombin times of 11.7 sec (10.5-13.5) and INR of 1.04 (0.9-1.5).

Acquired factor VIII deficiency was suspected and the patient was transfused with a unit of packed red blood cells and given Factor Eight Inhibitor Bypassing Agent (FEIBA) at 100U/kg to control the bleeding. Factor VIII and Factor IX levels which were done prior to initiating treatment were low at 3.8% (50-150%) and 109.5% (65-150%) respectively. In addition, Factor VIII inhibitor was sent abroad and this was detected at 32 Bethesda u/ml. On the fifth day of admission, oral prednisolone was started at 1mg/kg daily along with cyclophosphamide at 100mg daily.

Hepatitis B and C serologies were non-reactive. The autoimmune screen was sent as well where ANA, dsDNA, extractable nuclear antigen (ENA) and ANCA were all negatives. Imaging that include a computed to-

mography scan of the thorax, abdomen and pelvis excluded any malignancy but revealed the left intramuscular pectus haematoma.

After two weeks of the treatment, the aPTT reduced to 57.8 sec. He was discharge home with follow up in the Haematology clinic. On 19th day, the aPTT reduced to 42.7 sec and went down to 35.3 sec on 34th days. The prednisolone was planned to be tapered off and cyclophosphamide for at least three months.

DISCUSSION

Acquired Factor VIII deficiency is a very rare autoimmune disorder and can be misdiagnosed and unrecognised. This can be fatal as it has mortality rate of up to 33%. It is vital to make a rapid diagnosis based on the clinical finding and prolonged aPTT as the disorder carries high mortality. Hence prompt treatment is important.

Due to rarity of this disorder, it can be mistaken with other disorders with prolonged aPTT. Prolongation of the aPTT can be due to either deficiency of clotting factors or the presence of inhibitors to the clotting factors. Mixing study will differentiate between these two main causes. If the aPTT is corrected, this is due to clotting factor deficiency. However, if the test is not corrected, this is due to inhibiting factors, and it can be caused by various disorders such as lupus anticoagulants, von Willebrand disease (vWD), heparin, direct thrombin inhibitors and inhibitory antibodies to factors VIII, IX, V or X. However, lupus anticoagulant presents as thrombosis rather than bleeding symptoms and this will help to differentiate from this disorder. Acquired factor VIII deficiency can be confirmed

by performing Factor VIII level and by confirming the presence of Factor VIII inhibitors by using the Bethesda assay.⁸

Approximately 50% of acquired factor VIII deficiency cases are idiopathic. The next common cause is the postpartum state, which accounts for two to 21% of all the cases. This typically presents between the third and 150th day postpartum with mean of 89 days.⁸ Interestingly, the haemorrhagic potential is often low and the inhibitors often spontaneously disappear.² In addition, the relapse rate of pregnancy-associated factor VIII inhibitors appears to be lower. Other associated disorders include autoimmune diseases such as systemic lupus erythematosus, rheumatoid arthritis, myasthenia gravis, multiple sclerosis, thyroid dysfunction, autoimmune haemolytic anaemia, inflammatory bowel disease, pemphigus and graft versus host disease (GVHD).² In addition, they can present with autoimmune disorder in 20% of patients. Hence the autoimmune disorder needs to be excluded.

The diagnosis should be suspected in patients with no previous history of bleeding disorder presenting with spontaneous bleeding. The aPTT will always be prolonged with normal prothrombin time (PT), normal international normalised range (INR), normal platelets counts and normal von Willebrand factors (vWF). The aPTT will not be corrected in mixing study due to presence Factor VIII inhibitor.¹⁻⁴ The diagnosis is confirmed by low Factor VIII level and the presence of Factor VIII inhibitor.^{1-4, 9} The inhibitor titre does not directly indicate the severity or frequency of bleeding symptoms, or mortality. However, the titres are very useful as marker of the

efficacy of the inhibitor elimination.¹⁻⁴

The management of the disorder consists of two very important aspects. First is to control the active bleeding, and second to eradicate the inhibitor by using immunosuppression.^{1, 9} Usually the treatment of the bleeding in acquired Factor VIII deficiency is by using a bypassing agent and it has been reported in several literatures that bypassing agent is proven to be more effective.^{1-4, 9}

Available bypassing agents include recombinant activated factor VII (rFVIIa Novoseven) and activated prothrombin complex concentrate (aPCC, Factor Eight Inhibitor Bypassing activity-FEIBA). Both agents have been reported to have similar rates of bleeding control and overall efficacy rate.¹ Due to risk of fatal bleeding, Factor VIII inhibitor needs to be eliminated urgently by using immunosuppression for normalisation of haemostatic function and prevention of the risk of haemorrhage. The aim of the treatment is to reduce the inhibitor titre. The existing recommendations include corticosteroid in combination of cyclophosphamide.³ Other treatments available to eliminate the inhibitor include rituximab, high dose intravenous immunoglobulins, exchange plasmapheresis, calcineurin inhibitors (e.g. cyclosporine), azathioprine or vincristine.¹ However, the best available treatment reported is the combination of corticosteroids and cyclophosphamide.³

Immunosuppression is the mainstay treatment. Current recommendation consists of corticosteroids in combination with other cytotoxic agents (i.e. cyclophosphamide, cyclosporine, azathioprine and vincristine). The combination of corticosteroids and cyclophos-

phamide is effective in eradicating the Factor VIII inhibitors in up to 70% of patients with acquired Factor VIII deficiency.¹⁰ It was also reported that corticosteroids alone achieved 58% to 76% of inhibitor eradication and 77% to 89% in combination therapy of corticosteroid and cytotoxic agents.⁸ However the overall survival is similar in both group and this most likely due to the side effects of the cytotoxic agents (e.g. infection).

Rituximab, a chimeric human monoclonal antibody targeting the CD20 antigen on B-cell surface has been reported to be effective in reducing the inhibitors titers in patients not responding to prednisolone and cyclophosphamide.¹⁰ It is reported to be effective in 42% to 87% of the cases with good safety profiles.⁸ However, there are currently no randomised control trials to assess its efficacy due to rarity of this disorder.

Another treatment that is reported to be of some benefit is intravenous immunoglobulin (IVIg).^{3, 11} Complete remission can be achieved in 10% to 25% of cases in very low titre inhibitors only.⁸ However, the responses are variable, with decline in the inhibitors seen within several days to weeks or months. In addition, treatment often required multiple courses. Therefore, IVIg is not recommended to be used as first line treatment.

In conclusion, acquired Factor VIII deficiency is a very rare condition and the

clinical suspicion should be high in patients presenting with spontaneous bleeding and prolonged aPTT. The subsequent management is vital as this disorder can be life threatening if not suspected earlier.

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