CASE REPORT

Successful immunoadsorption of life-threatening bleeding in factor VIII inhibitor disease, but no long-term remission with anti-CD20 treatment

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Accepted 27 July 2015

SUMMARY

A 62-year-old man and a 64-year-old woman presented to our institution with acquired haemophilia A. They both developed life-threatening bleeding. Immunoadsorption using protein A columns was used to rapidly lower factor VIII inhibitor levels. Immunosuppression with steroids and the anti-CD20 antibody, rituximab, was instituted. Yet their effects were either partial or complicated by an early relapse. Repetitive cyclophosphamide administration led to a sustained immunological response. While immunoadsorption appears effective and safe to lower factor VIII inhibitor levels, it seems that further preferably randomised controlled trials are needed to establish the value of rituximab versus the standard immunosuppressive regime comprising cyclophosphamide.

BACKGROUND

Acquired haemophilia A is a rare disorder with an estimated prevalence of 0.2–1 cases/million persons/year.¹ Factor VIII inhibitors in this entity consist of polyclonal IgG autoantibodies directed against binding domains of the light and heavy chain of factor VIII.² In contrast to congenital haemophilia A, patients with autoantibodies against factor VIII typically present with haemorrhages of the skin, mucous membranes, muscles and soft tissues.³ Both sexes seem to be equally affected, and besides during the postpartum period, the disease tends to occur in people over 60 years of age.⁴ There is an association with autoimmune diseases, malignancies and drugs, but approximately 30–50% of cases are idiopathic.⁵

Initial management consists of preventing or stopping life-threatening bleeding with the help of rhVIIa (Novoseven), factor VIII inhibitor bypass activity and blood transfusions. If no precipitating cause can be identified, patients are treated with immunosuppressive therapy. Prednisone and cyclophosphamide are the mainstay of therapy. However, several case reports have described the use of cyclosporine, azathioprine, cladribine, intravenous immunoglobulin (IVIG) or, more recently, the anti-CD20 antibody, rituximab.^{6–10} Previously, plasmapheresis or immunoadsorption had only been rarely used to treat factor VIII inhibitors despite proven effectiveness, rapid removal of antibodies and likely lower cost compared to repetitive doses of recombinant blood products.^{10–12} We describe two cases of acquired haemophilia A

where immunoadsorption was successfully used to stop severe bleeding and where immunosuppression with rituximab and steroids was insufficient to achieve long-term remission and necessitated addition of cyclophosphamide.

CASE PRESENTATION

Patient A: A 64-year-old Caucasian woman presented to the emergency department with spontaneous haematomas on her extremities and incessant bleeding from small wounds on her forearm. The patient's medical history was remarkable for chronic obstructive pulmonary disease, hypertension, type II diabetes and resection of a caecal adenocarcinoma together with a tubulovillous sigma adenoma 2 years previously. Follow-up colonoscopy 1 month before this admission had been uneventful.

Patient B: A 62-year-old Caucasian man was referred from the department of dermatology, with epistaxis, multiple haematomas and bleeding from venipuncture sites while receiving dapsone and prednisone to treat p200 pemphigoid. Until the diagnosis of p200 pemphigoid, shortly before this admission, the patient's medical history was only remarkable for hypertension and type II diabetes.

INVESTIGATIONS

Patient A: A spontaneous partial thromboplastin time (PTT) of 73 s (normal 23–36 s) with normal international normalised ratio (INR) of 0.85, normal platelet count and haemoglobin (Hb; 238 000/μL and 13.3 g/dL, respectively) were the most notable laboratory findings. A coagulation screen revealed factor VIII activity <1% and a factor VIII inhibitor of 258 Bethesda Units (BU)/mL.

Patient B: Laboratory values were unremarkable except for a PTT of 124 s (normal INR of 0.99), anaemia (Hb 8.5 g/dL), thrombocytopenia (108 000/μL) and markedly elevated γ-GT (1141 U/L, normal <66 U/L). A coagulation screen showed factor VIII activity <1% and a factor VIII inhibitor of 600 BU/mL. Lupus anticoagulant was negative and phospholipid β₂-glycoprotein IgM antibody was slightly elevated (15 U/mL, normal <12 U/mL).

TREATMENT

Patient A: Immunosuppression with prednisone 150 mg/day was started initially. After 1 week of steroid therapy, there was no improvement in the

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To cite: Grahammer F, Fischer K-G. *BMJ Case Rep* Published online: [please include Day Month Year] doi:10.1136/bcr-2015-210034

patient's coagulation status; PTT (66 s) and factor VIII inhibitor (251 BU/mL) remained high. Therefore, anti-CD20 antibodies (rituximab) were added to the treatment regimen at a dose of 375 mg/m². On the 13th hospital day, the patient developed a life-threatening soft tissue bleed requiring administration of packed red blood cells and rhVIIa (Novoseven). The inhibitor was still detectable at 180 BU/mL. We decided to start immunoadsorption to rapidly lower inhibitor levels. After the first treatment, the inhibitor was reduced to 44 BU/mL and the acute bleeding was stopped. An AS-Tec 204 plasma centrifuge (Fresenius, Bad Homburg, Germany) was used in conjunction with two Immunosorba protein A columns (Fresenius), where one column was loaded with IgG while the other was regenerated, these processes being controlled through a Citem 10 system (Fresenius). 3000 International Units (IU) heparin was provided into the circuit to coat all surfaces. After flush-out of heparin, circulating blood was regionally anticoagulated with citrate. 6.1 L of plasma were treated in each session (ie, twice the patient's plasma volume). After two further treatments on the 17th and 20th hospital day, the inhibitor had dropped to 3.8 BU/mL, factor VIII was detectable at 32.5% and PTT was nearly normal (38 s). Three further doses of rituximab were administered (figure 1A).

Patient B: Prednisone dose was increased to 150 mg/day and oral antidiabetics were substituted for insulin. Initially, the patient's coagulation status improved under high-dose steroids, and his factor VIII inhibitor level fell to 140 BU/mL on the 14th day. His diabetes was exacerbated due to steroid treatment, and increasing doses of subcutaneous insulin were needed. After one such injection, he developed a life-threatening abdominal wall haematoma of approximately 60×40 cm requiring transfusion

of packed red blood cells and application of rhVIIa (90 µg/kg twice within 48 h). Despite these measures, the haematoma continued to enlarge. Factor VIII inhibitor rose again to 375 BU/mL and PTT remained high at 105 s. Immunoadsorption performed with the same technique as described for patient A was started. By the 31st hospital day, the patient had received six treatments. PTT declined to 80 s and his factor VIII inhibitor fell to 30 BU/mL with factor VIII activity still <1%. On the 29th day, the patient received the first of six rituximab infusions (375 mg/m²). After the 12th immunoadsorption treatment on the 52nd day, factor VIII rose to 25%, PTT diminished to 51 s, the inhibitor decreased to 1.5 BU/mL and the patient could be discharged with close outpatient monitoring (figure 1B).

OUTCOME AND FOLLOW-UP

Patient A: Tumour screening was negative and the patient was discharged on the 31st hospital day. Three weeks later, in the outpatient clinic, her inhibitor had dropped below the detection limit of the test and factor VIII had risen to 265%. She was admitted 5 months later to the intensive care unit because of respiratory insufficiency. At that time, the inhibitor had risen again to 3 BU/mL and factor VIII was reduced to 38.5% with no overt bleeding. The patient was subsequently lost to follow-up.

Patient B: A tumour screen was negative. The patient had to be readmitted 6 weeks later when his factor VIII had dropped to 2% and PTT had risen to 63 s during steroid tapering. He received steroid pulses and was given four doses of cyclophosphamide (1000 mg) every 2 weeks. With this additional treatment, factor VIII normalised (105.1%), although the inhibitor was still measurable at the detection threshold 1 year after initial presentation.

Figure 1 Decisive laboratory parameters and treatments for patient A and patient B. The symbols in the figure mark the following events: ■ course of PTT values in s; ▲ course of inhibitor level in Bethesda Units (BU)/mL; ○ course of factor VIII level in % of normal; / administration of rituximab; × immunoadsorption treatment.

DISCUSSION

Despite recent advances in the production of recombinant human coagulation factors and the availability of modern immunosuppressive agents, autoantibodies in acquired haemophilia A remain a therapeutic challenge, and the disease still bears a high mortality, estimated at between 8% and 22%.¹ Most deaths occur in the first weeks after diagnosis, and result from acute haemorrhage.³ Therefore, immunosuppressive therapy should be started immediately, once the diagnosis is established, to inhibit further production of autoantibodies. In patients with high inhibitor levels, this might not be sufficient, as illustrated in these two cases. Bleeding patients must be treated more aggressively to significantly reduce mortality. In the two patients presented, immunoadsorption was an effective and safe procedure that allowed for efficient reduction of factor VIII inhibitor levels (figure 1).¹⁰

We used double lumen femoral Shaldon catheters as vascular access, placed under ultrasound guidance to prevent accidental puncture of the femoral artery. Although some bleeding occurred around the insertion site in both patients, this bleeding stopped during treatment or could be managed with external pressure banding. Shaldon catheters have a major advantage over smaller peripheral access devices, being that immunoadsorption is virtually uninterrupted by blood flow stops; this increases the effectiveness of the procedure.

Immunoadsorption, as such, was well tolerated, and besides oral calcium substitution, no other treatment-related medication needed to be given. IVIG was given to prevent infectious complications. Two days after the last treatment, patient A had a urinary tract infection, which was treated with fluoroquinolones. Patient B developed symptomatic *Staphylococcus aureus* bacteraemia between the seventh and eighth treatments. No *S. aureus* was cultured from the tip of the catheter. The patient responded well to cefuroxime.

Although there have been no prospective trials comparing immunoadsorption with other treatments in acquired haemophilia A, it seems that in patients with high inhibitor levels and bleeding, a dual approach consisting of immunosuppression to prevent the production of autoantibodies and immunoadsorption to rapidly reduce circulating inhibitor levels is warranted to stop severe active bleeding. Furthermore, compared to expensive recombinant blood products, the economic advantage of immunoadsorption is obvious. Immunoadsorption is to be preferred to conventional plasmapheresis and delays in initiating immunoadsorption should be avoided.¹⁰ Despite the rareness of acquired haemophilia A, two publications reported on case series of 35 and 67 patients, respectively, who were treated with the so called 'Modified Bonn-Malmö Protocol'.^{13 14} In this protocol, immunoadsorptive treatment is combined with immunosuppressive therapy (prednisone and cyclophosphamide) as well as with immunomodulatory agents (IVIG and FVIII). Using this multimodal treatment approach, approximately 90% of patients achieve complete remission.

Since several case reports and one small study optimistically reported on the use of rituximab in acquired haemophilia, we decided to use it in conjunction with steroids and immunoadsorptive treatments as first-line therapy in our patients.^{9 15 16} At first, both patients seemed to attain remission, but they relapsed after 6 weeks and 5 months, respectively. Hence, despite adequate dosage of rituximab, no long-term remission could be achieved, and we would caution against its use as a first-line agent in high-titre patients, and would recommend the proven combination of cyclophosphamide and prednisone as initial treatment, instead.⁶ Our observations and conclusions are in

agreement with recently published evidence from European registry data.¹⁷

Learning points

- ▶ Acquired haemophilia A in the elderly is a life-threatening disease.
- ▶ Immunoadsorption seems to be a safe procedure to effectively reduce antibody titres and to eventually stop bleeding.
- ▶ Despite the severity of acquired haemophilia A, multimodal treatment protocols such as the 'Modified Bonn-Malmö Protocol' can achieve remission in approximately 90% of patients.
- ▶ To conclusively judge the role of the anti-CD20 antibody, rituximab, as the immunosuppressive component in such a multimodal approach, further preferably prospective trials are necessary.

Acknowledgements The authors would like to thank the technicians of the coagulation laboratory for reliable determination of coagulation factors, and Angelika Bockstaller and Ralph Landau, from the dialysis unit, for expert help with immunoadsorptive treatments.

Competing interests None declared.

Patient consent Obtained.

Provenance and peer review Not commissioned; externally peer reviewed.

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