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CASE REPORT

An unusual cause of bruising in an 80-year-old woman

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Abstract

Presentation: a previously fit 80-year-old woman presented with a 2-week history of spontaneous and extensive bruising affecting all four limbs. The severity was such that she required a transfusion of 8 units of blood.
Results of investigations: a markedly prolonged activated partial thromboplastin time which was only partially corrected with normal plasma; tests for lupus anticoagulant were negative. Factor VIII levels were reduced and the Bethesda assay indicated an acquired inhibitor to factor VIII. She was treated with a combination of intravenous immunoglobulin and immunosupression.
Outcome: the response to treatment was excellent, with a marked reduction in anti-factor VIII antibody levels and resolution of the bruising over the next few weeks.

Keywords: *acquired haemophilia, factor VIII inhibitor, spontaneous bruising*

Introduction

Acquired factor VIII inhibitors are very rare in patients who do not have haemophilia. This condition predominantly affects older people, and about one case presents every 2 years to an average-sized hospital. Recognition is important as morbidity and mortality are high, and effective interventions are available.

Case report

A previously well 80-year-old woman presented with a 2-week history of spontaneous bruising of all four limbs. The only important medical history was of hypertension, treated with felodipine and atenolol.

On examination, she was pale with extensive bruising, mainly affecting the arms and left leg. There was no evidence of retroperitoneal or gastrointestinal bleeding.

Chest x-ray and electrocardiogram were unremarkable. Full blood screen was within normal limits apart from a haemoglobin of 6.4 g/dl (normal range 11.5–16.5). Mean corpuscular volume was 87 fl (82–98). Prothrombin time and platelet count were normal. However, the activated partial thromboplastin time (APTT) ratio was 2.44 (0.8–1.2), falling to 1.69 after 50:50 correction with normal plasma. Screening tests for a lupus anticoagulant were negative.

She was transfused with 4 units of blood and transferred to a tertiary centre for further investigation and management. Factor VIII levels were 1.7 IU/dl (50–200). The Bethesda (anti-factor VIII) assay result was 136.7 BU/ml. A diagnosis of an acquired factor VIII inhibitor was made and she was treated with intravenous immunoglobulin (five doses of 0.4 g/kg/day), oral prednisolone (initially at 60 mg/day for 1 week with discontinuation after 3 weeks) and oral cyclophosphamide (100 mg one daily for 10 days, then ongoing at 50 mg once daily). She required a further 4 units of blood over the next few days.

Further investigations did not reveal any evidence of an underlying malignancy. However, anti-nuclear factor was positive at a titre of 1:1280. Anti-thyroglobulin and anti-smooth muscle antibodies were weakly positive. Other auto-antibodies, including rheumatoid factor and anti-nuclear cytoplasmic antibody, were negative.

She remains well at follow-up with almost complete resolution of the bruising. At 2 months, the APTT ratio had decreased to 1.6 and the inhibitor level had dropped to 9.2 BU/ml.

Discussion

Acquired inhibitors of factor VIII partially or completely inhibit its procoagulant activity, rarely affecting other activities of the factor VIII complex. They are classified

as either allo-antibodies, which occur in 8–14% of patients with severe haemophilia A, or auto-antibodies, which develop spontaneously in subjects with previously normal levels of factor VIII [1]. Auto-antibodies are very rare, developing in 0.2–1.0 people per million population per year [1]. The condition mainly affects older individuals and the sex ratio is equal [2].

The pattern of bleeding is different to that seen in hereditary haemophilia [2]. The bleeding is more severe than that expected from the levels of factor VIII [3]. Presentation is usually with severe soft tissue bleeding, which may lead to the development of a compartment syndrome. Retroperitoneal bleeding, haematuria, epistaxis, post-surgical and intracranial haemorrhage may also occur. In contrast to hereditary haemophilia, haemarthroses are rare [2].

The disorder is most commonly idiopathic, although there are associations with auto-immune disease and malignancy (particularly head and neck carcinomas, chronic lymphocytic leukaemia and non-Hodgkin's lymphomas). In one study of 215 cases [4], just under half were idiopathic. Associated auto-immune disease (such as rheumatoid arthritis or systemic lupus erythematosus) was identified in 18% and malignancy (solid tumours and lymphoproliferative disorders) in 5%. Pregnancy (usually in the post-partum period) and drugs (e.g. penicillin, sulphonamides) are also recognized associations. In the series reported by Green and Lechner [4], 22% of patients died either directly or indirectly as a consequence of their disorder. About 30% of idiopathic cases remit spontaneously [4].

Patients have a prolonged APTT which does not correct or only partially corrects when incubated with normal plasma, indicating the presence of a coagulation inhibitor. Specific factor assays are performed and the presence of auto-antibody quantified by the Bethesda assay (where 1 Bethesda unit is the amount of antibody in the patient's serum permitting the detection of 50% residual factor VIIIc activity when mixed with normal pooled plasma [1]).

Other causes of a prolonged APTT include unfractionated heparin, lupus anticoagulant and deficiencies of factors V, IX, X, XI and XII. In the presence of a lupus anticoagulant, other phospholipid-dependent coagulation tests (such as the kaolin clotting time and dilute Russell's viper venom time) are prolonged and, like the APTT, fail to correct with the addition of an equal quantity of normal plasma. However, correction occurs with the addition of phospholipid-rich material [5].

Acquired von Willebrand disease, which may also be caused by a circulating inhibitor, usually presents with muco-cutaneous and post-surgical bleeding. The APTT is usually normal—unless the defect is severe, when an associated factor VIII deficiency may occur with prolongation of the APTT. The bleeding time is usually prolonged in this disorder [6].

Several treatments are available for patients with acquired factor VIII inhibitors. In patients with low titres of auto-antibodies (<10 BU), bleeding episodes are controlled with factor VIII in high enough doses to overwhelm the inhibitor. This may be given in combination with desmopressin, which releases factor VIII from storage sites, allowing a reduction in the dose of factor VIII given [7]. In patients with higher levels of factor VIII (>10 BU), options include porcine factor VIII, activated prothrombin complex concentrates (which include factors VII, IX and X and non-activated prothrombin) and recombinant factor VIIa. These may be used in combination with plasmapheresis (which is usually only transiently effective unless immunosuppressive therapy is given) or intravenous immunoglobulin. The latter complexes antibodies directed against factor VIII and, through modulation of the immune system, has a prolonged action on antibody synthesis [7].

Longer-term measures with the aim of reducing or eradicating production of the auto-antibody include steroids and cytotoxic agents, such as cyclophosphamide or azathioprine. In one study of 31 patients, one-third responded to a 3-week course of prednisolone and a further one-third responded with the addition or substitution of cyclophosphamide after the third week [8]. However, eradication and prevention of recurrence of the inhibitor generally requires immunosuppression for several months, which may be associated with an increased risk of life-threatening infection [1]. Given its complexity and expense, treatment should always be undertaken by a specialist, particularly when porcine factor VIII and intravenous immunoglobulin are used.

The high titre of anti-nuclear factor in this case is of interest. No clinical features of systemic lupus erythematosus have developed at follow-up and the patient does not satisfy the American Rheumatism Association 1982 revised criteria for this diagnosis [9]. Their relevance is therefore unclear and the patient is currently regarded as having an idiopathic factor VIII inhibitor.

Many patients with acquired auto-antibodies to factor VIII will present with a bleeding emergency, and the generalized nature of the bleeding diathesis may not initially be appreciated, leading to delays in diagnosis and referral [2]. Clinicians involved in the care of older patients should therefore be aware of this entity: the present case illustrates the excellent response to treatment which may occur.

Key points

- Acquired haemophilia, due to anti-factor VIII antibodies, is uncommon but should be considered in a patient with bruising in a prolonged activated partial thromboplastin time, which does not correct when incubated with normal plasma.
- If factor VIII levels are low, the Bethesda assay confirms the presence of a factor VIII inhibitor.

- It is associated with malignancy and auto-immune disease.
- Treatment can be effective but complex and should be undertaken by a specialist.

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