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Two case reports of acquired haemophilia A as complications of alemtuzumab treatment for multiple sclerosis

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ABSTRACT

Objective To describe the case histories of two patients who developed acquired haemophilia A following treatment with alemtuzumab for multiple sclerosis.

Results Two patients, a 48-year-old woman and a 31-year-old woman, developed acquired haemophilia A 21 months after their second doses of alemtuzumab. Both presented with spontaneous bruising, and the second case reported menorrhagia. One patient required treatment to control bleeding. Both patients responded to treatment with prednisolone and cyclophosphamide to eliminate the inhibitor.

Conclusions Acquired haemophilia A is a rare complication following treatment with alemtuzumab. Activated partial thromboplastin time and prothrombin time should be performed in cases of abnormal bleeding in which the platelet count is normal, to facilitate timely diagnosis and prevention of major bleeding complications.

INTRODUCTION

Alemtuzumab is a humanised IgG3 monoclonal antibody used in a number of conditions, including multiple sclerosis, haematological conditions and transplant medicine. It targets the glycoprotein cluster of differentiation 52, which is expressed on lymphocytes, natural killer cells and monocytes.[1] It causes prolonged T-cell and short-lived B-cell depletion.[1]

Over an average of 7 years of follow-up, almost 50% of patients were found to develop secondary autoimmune disease after alemtuzumab treatment for multiple sclerosis.[1] Manifestations include thyroid autoimmune disease, immune-mediated thrombocytopenia, Goodpasture's disease, haemolytic anaemia and autoimmune neutropenia.[1] The development of autoimmunity may be related to expansion of naïve B cells, free from the controls of absent regulatory T cells, resulting in a group of autoreactive B cells.[1]

Acquired haemophilia A due to secondary autoimmune disease related to alemtuzumab treatment has been reported previously in four patients treated for multiple sclerosis and one treated for anti-neutrophil cytoplasmic antibodies-associated vasculitis.[2–6] Here, we report two further cases of acquired haemophilia A after alemtuzumab treatment with comparatively milder symptoms at presentation.

CASE I

The first case was a 48-year-old woman with multiple sclerosis who developed spontaneous bruising 21 months after initiation of alemtuzumab.

She was diagnosed with multiple sclerosis in April 2007 after developing a right internuclear ophthalmoplegia, on a background of several focal sensory symptoms between 2005 and 2007 and an episode of oscillopsia in February 2007. She declined treatment for several years, during which she experienced multiple relapses. She was commenced on pegylated interferon in April 2015; however, this was ceased in early 2016 due to intolerance.

Treatment was switched to alemtuzumab, and the patient received doses in July 2016 and July 2017. Following treatment, there was no clinical or radiological evidence of disease activity.

In April 2018, routine surveillance thyroid function tests and subsequent antibody testing showed features consistent with autoimmune thyroid disease. The patient was commenced on thyroxine replacement.

In late April 2019, the patient reported spontaneous bruising up to 5 cm in diameter over her arms and flanks. She also reported one episode of mucosal bleeding. Blood tests showed a prolonged activated partial thromboplastin time (APTT) of 85 s (normal 25–35 s), a normal prothrombin time, haemoglobin, platelet count, renal and

liver function tests. The APTT only partially corrected on mixing studies suggestive of an inhibitor. Lupus anticoagulant detection was initially inconclusive. Factor VIII coagulant (FVIIIc) activity was markedly reduced (<0.02 U/mL, normal 0.5–1.5 U/mL), with normal factor IX, XI and XII levels. A factor VIII inhibitor was detected with Bethesda assay at a level of 51.2 BU/mL.

She was diagnosed with acquired haemophilia A likely secondary to alemtuzumab. She was commenced on prednisolone 75 mg (1 mg/kg)/day and cyclophosphamide 50 mg/day in early May 2019. She noticed occasional diarrhoea following commencement of cyclophosphamide, and difficulty sleeping, cushingoid facies and weight gain with prednisolone.

After 2 weeks of treatment, her APTT had improved to 55 s; factor VIII level had improved to 0.39 U/mL, and inhibitor level had reduced to 14.4 BU/mL. APTT levels improved during this period; however, they remained around 40 s (normal 25–35 s). Repeat lupus anticoagulant testing was positive. FVIIIc levels normalised in June 2019. The prednisolone was gradually weaned over subsequent months to a point where both prednisolone and cyclophosphamide were ceased by November 2019. There was no clinical relapse during this period.

CASE II

The second case was a 31-year-old woman with multiple sclerosis who developed menorrhagia and easy bruising approximately 21 months after initiation of alemtuzumab.

She was diagnosed with multiple sclerosis in 2010 following a clinically isolated syndrome of right hemiparesis, gadolinium-enhancing lesions on MRI consistent with demyelination and cerebrospinal fluid positive for oligoclonal bands. She was commenced on fingolimod the following year after there was evidence of radiological progression. The patient developed significant neutropenia and lymphopenia in late 2017 and she was switched to alemtuzumab, receiving doses in May 2018 and May 2019.

In late January 2020, routine surveillance thyroid function tests and subsequent antibody testing showed features consistent with mild secondary autoimmune thyroid disease. She was managed expectantly and her thyroid stimulating hormone returned to the normal range over a month.

At follow-up in March 2020, the patient reported easy bruising over her back and left upper limb, as well as menorrhagia. She was found to have an APTT of 48 s (normal 22–35 s), normal prothrombin time, normal haemoglobin, normal platelets, and normal renal and hepatic function. FVIIIc was 0.22 U/mL (normal 0.5–1.5 U/mL), with a factor VIII inhibitor detected at a level of 1.0 BU/mL.

She was diagnosed with acquired haemophilia A secondary to alemtuzumab. Treatment included tranexamic acid, prednisolone 50 mg and cyclophosphamide 50 mg/day. Over the following month, her APTT and FVIIIc normalised. Her prednisolone dose was gradually weaned to cessation by June 2020.

DISCUSSION

Acquired haemophilia A is the most common form of acquired coagulation inhibition, characterised by antibody interference with factor VIII activity, resulting in a haemorrhagic diathesis. It is a rare condition with rates reported as 1.3–1.5 per million per year.[7] The spectrum of bleeding includes sizeable haematomas and ecchymoses, epistaxis, gastrointestinal bleeding and genitourinary bleeding.[8]

Coagulation studies in acquired haemophilia typically show a prolonged APTT, a normal prothrombin time and persistence of the prolonged APTT with a mixing study. Mixing studies are unable to distinguish lupus anticoagulant from factor inhibitors, although this is more likely to present with thrombosis than bleeding. A reduced FVIIIc and quantification of the inhibitor by Bethesda assay confirm the diagnosis of acquired haemophilia A.[8]

Treatment of acquired haemophilia A involves both control of bleeding and elimination of the inhibitor. Options to control bleeding include monotherapy or sequential therapy with recombinant activated factor VII, activated prothrombin complex concentrate or recombinant porcine factor VIII.[9]

Corticosteroids with or without cyclophosphamide are generally used as first-line immunosuppressants to eliminate factor VIII inhibitors. Should this not be successful in achieving remission, rituximab is often employed as a second-line option.[9]

Acute treatment to control bleeding was required in case II, and both were treated with prednisolone and cyclophosphamide to eradicate the inhibitor.

Acquired haemophilia A following alemtuzumab treatment for multiple sclerosis has been reported four times previously, and the six reported cases are summarised in table 1.[3–6] The mean time from administration of the second dose of alemtuzumab to onset of symptoms was 19.7 months (range 7–48 months). Most patients presented with spontaneous bruising, with four cases experiencing severe bleeding requiring pharmacological control. Other presenting symptoms included epistaxis and menorrhagia. The mean APTT was 75.8 s, and the mean factor VIII inhibitor activity was 39.7 BU/mL (range 1–128 BU/mL). Four of the six cases were treated with prednisolone and cyclophosphamide. One of these cases required a change of treatment to methylprednisolone and azathioprine. One case was treated initially with rituximab.

Our two cases of acquired haemophilia A presented with milder bleeding manifestations. This raises the prospect that acquired haemophilia A following alemtuzumab treatment may be under-reported or not recognised if patients are experiencing what they deem to be minor symptoms of bleeding.

Table 1 Summary of cases

Report	Age/sex	Symptoms	Months after second alemtuzumab dose	APTT (s)	FVIII activity	FVIII inhibitor activity (BU/mL)	Treatment to control bleeding	Treatment to eliminate the inhibitor
Pisa *et al*[5]	46/F	Abnormal bruising after minimal trauma: left palm, top of foot, right hand, popliteus haematoma	7	Ratio 2.95*	1%	128	Recombinant FVIIa	Prednisolone 75 mg and cyclophosphamide 100 mg; following relapse, switched to methylprednisolone and azathioprine
McCaughan *et al*[3]	37/F	Progressive right leg pain, swelling, bruising; left arm and thigh non-purpuric masses	9	71 (n 24–38)	2 U/dL	5.7	Recombinant FVIIa	Prednisolone 1 mg/kg
Madeley *et al*[4]	36/M	Easy bruising and epistaxis, then left thigh haematoma	48	88	<0.01 U/dL	7	Recombinant FVIIa	Prednisolone 1 mg/kg and rituximab
Brink *et al*[6]	42/M	Extensive gluteal haematoma	12	87	<0.1%	45	Factor VIII bypassing fraction	Prednisolone and cyclophosphamide
Gounder *et al* (current report)	48/F	Spontaneous bruising over arms and flanks	21	85 (n 25–35)	<0.02 U/dL	51.2	Not required	Prednisolone 75 mg and cyclophosphamide 50 mg
	31/F	Menorrhagia and easy bruising	21	48 (n 22–35)	0.22 U/dL	1	Tranexamic acid	Prednisolone 50 mg and cyclophosphamide 50 mg

APTT, activated partial thromboplastin time; F, female; FVIII, factor VIII; M, male.

Patients who receive alemtuzumab are generally aware to report any bleeding disorder to their treating clinician. Should the platelet count be normal, excluding immune-mediated thrombocytopenia, we suggest determining the APTT and prothrombin time. If a prolonged APTT is identified, factor VIII levels and lupus anticoagulant should be tested.

Although it is a rare complication of alemtuzumab, early recognition of acquired haemophilia A may potentially avoid a catastrophic bleeding manifestation.

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