CASE REPORT

Acquired haemophilia A complicating alemtuzumab therapy for multiple sclerosis

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SUMMARY

Alemtuzumab is a highly efficacious therapy used in the treatment of multiple sclerosis (MS), but uncoupling of T and B cell repopulation during immune reconstitution associates with an increasing range of secondary B cell-mediated autoimmune complications. A 34-year-old woman developed Graves' disease 11 months following an initial course of alemtuzumab treatment for MS. Nine months following the second treatment with alemtuzumab, the patient presented with spontaneous intramuscular and subcutaneous haemorrhage due to development of an inhibitory autoantibody to coagulation factor VIII. Acquired haemophilia A (AHA) is an extremely rare complication in patients treated with alemtuzumab. Treatment with rituximab may induce a rapid remission of AHA; however, the patient's high John Cunningham virus (JCV) antibody index and alemtuzumab-induced T cell lymphopenia may lead to an increased risk of progressive multifocal leucoencephalopathy, a potential complication which was unacceptable to the patient.

sclerosis (MS) is associated with improvement in disability, and a sustained reduction in both relapse rate and MRI disease activity for up to 5 years in 70% of patients.^{2,3} However, immune reconstitution following alemtuzumab treatment results in secondary autoimmune disease (AID) in up to 50% of patients at 7 years post-treatment.⁴ Alemtuzumab therapy has been associated with the development of a range of thyroid autoimmune diseases, immune-mediated thrombocytopenia (ITP) and Goodpasture's disease.⁴ Within Australia, a national surveillance programme exists to monitor for such complications (Bloodwatch). Here, we report a case of acquired haemophilia A (AHA) following alemtuzumab therapy due to development of autoantibodies directed against coagulation factor VIII. One previous case of AHA associated with alemtuzumab therapy in MS has been reported in abstract form in 2017.⁵ This case highlights the potential for emergence of unexpected and potentially life-threatening autoimmune complications of alemtuzumab which are not detected by existing screening protocols.

BACKGROUND

Alemtuzumab is a humanised IgG3 monoclonal antibody which targets CD52, and is approved for the treatment of relapsing–remitting multiple sclerosis (RRMS). Alemtuzumab is administered as an initial course of five daily infusions of 12 mg which is followed by a second course of three daily doses of 12 mg 12 months later. As CD52 is highly expressed on the surface of T and B lymphocytes treatment results in profound lymphopenia.¹ Alemtuzumab use in patients with multiple

CASE PRESENTATION

A 34-year-old woman of Bangladeshi ethnicity was assessed in September 2014 after presenting with an episode of right optic neuritis due to MS. The patient had originally presented with an episode of incomplete transverse myelitis at the age of 17 and had an episode of right optic neuritis in her early 20s. She had never received immunomodulatory treatment. The patient was on thyroxine for hypothyroidism following an episode of

Figure 1 (A,B) Sagittal postgadolinium FLAIR study demonstrates multifocal areas of signal change within the hemispheric deep white matter with a posterior callosal lesion demonstrating gadolinium enhancement (arrow).

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Figure 2 Extensive spontaneous ecchymoses of the right lower limb.

Hashimoto's thyroiditis at age 26 and cetirizine for dermatographic urticaria.

Examination revealed a right visual acuity of 6/9 and a 0.3 log unit right relative afferent pupillary defect. The remainder of the cranial nerve and neurological examination was normal.

An MRI study of the brain with gadolinium demonstrated a significant burden of supratentorial and infratentorial multifocal T2/Fluid attenuated inversion recovery (FLAIR) signal abnormality with many of the lesions demonstrating corresponding black holes on T1-weighted imaging. There was marked atrophy of the corpus callosum. Following administration of gadolinium, there was enhancement of the right optic nerve and a left posterior pericallosal lesion (figure 1A,B). MRI of the cervical spine was normal. Additional investigations included the presence of a cerebrospinal fluid-specific oligoclonal bands, a negative neuromyelitis optica-IgG and positive John Cunningham (JC) virus serology with an index of 3.113.

Immunosuppressive treatment with fingolimod was commenced in January 2015; however, in May 2015, the patient developed an episode of incomplete transverse myelitis. A progress MRI of the cervical and thoracic spine revealed interval

development of a T2 hyperintense lesion at the level of C4. Fingolimod was ceased in September 2015 and the lymphocyte count had risen to $1.6 \times 10^9/L$ when the first course of alemtuzumab was commenced on 16 November 2015. Other than an expected induction of lymphopenia, monthly Bloodwatch testing remained within normal limits and progress MRI studies demonstrated stable appearances of the brain and cervical spine.

Immediately prior to the second course of treatment in November 2016, surveillance thyroid function tests (TFTs) demonstrated an elevated free T4 (47.7 pmol/L, normal 11.0–22.0 pmol/L) with suppressed thyroid-stimulating hormone (TSH) (<0.02 mIU/L, normal 0.4–4.2 mIU/L). Thyroid receptor antibodies were 19 IU/L (normal <1.8 IU/L) and thyroid scintigraphy demonstrated diffuse moderate isotope uptake consistent with a diagnosis of Graves' disease. Treatment with carbimazole was commenced and the patient elected to continue treatment with alemtuzumab, with the second course administered in late November 2016. The patient has remained free of MS disease activity. The TSH receptor antibody continued to rise and in April 2017 was 82.1 IU, but the patient has remained euthyroid on a tapering dose of carbimazole.

On 19 August 2017, the patient was admitted to hospital following a 10-day history of progressive right leg pain, swelling, spontaneous bruising and palpable, non-purpuric masses of the left posterior thigh and arm. There had been no visceral bleeding. The patient had no prior history of spontaneous bruising and heavy menstrual bleeding and no abnormal bleeding following dental extractions or previous surgeries. There was no family history of a bleeding disorder. The patient had no symptoms to suggest occult malignancy and was not pregnant. Examination identified right thigh swelling with extensive subcutaneous ecchymoses of the lateral and lower portion of the leg (figure 2) and palpable deep muscular haematomas of the left posterior thigh and forearm. Right knee range of movement was limited by pain but no haemarthrosis was evident. There were no petechiae, oral cavity purpura and no lymphadenopathy or hepatosplenomegaly.

INVESTIGATIONS

Initial investigations demonstrated a haemoglobin of 9.9 g/dL, white cell count of $8.1 \times 10^9/L$, with a lymphocyte count of $1.4 \times 10^9/L$ and platelet count of $285 \times 10^9/L$. A biochemical profile, including creatinine kinase (CK), and thyroid function were normal. A coagulation profile revealed a normal prothrombin time (PT) (14 s) and fibrinogen (4.8 g/L), but a significantly prolonged activated partial thromboplastin time (APTT) of 71 s (24–38 s) that corrected to 38 s on an immediate mixing study. APTT-dependent factor levels identified a markedly reduced factor VIII level of 2 U/dL (40–180 IU/dL), with normal levels of factor IX (117 U/dL), factor XI (83 U/dL), factor XII level (47 U/dL) and normal von Willebrand studies. A factor VIII Bethesda assay confirmed the presence of an inhibitor with a titre of 5.7 Bethesda units (BU). Tests for antinuclear antibody, extractable nuclear antigen antibody, double-stranded DNA and antineutrophil cytoplasmic antibodies (ANCA) with PR3 and MPO antibodies were all negative and a lupus inhibitor was not detected. Beta subunit of human chorionic gonadotropin (b-HCG) was negative.

DIFFERENTIAL DIAGNOSIS

The clinical presentation and investigations were typical of AHA. TFTs were in the normal range and a normal CK excluded

Database Name	Search Strategy Used	Number of Records Retrieved	Number of Similar Cases
MEDLINE	MeSH Term: 'Hemophilia A' OR acquired haemophilia.mp OR acquired hemophilia.mp AND alemtuzumab.mp	0	0
Embase	EMTREE Search terms: 'Hemophilia A' OR 'Blood clotting factor 8 inhibitor' OR acquired hemophilia.mp OR acquired haemophilia.mp AND EMTREE search term 'alemtuzumab'	27	2

Figure 3 Search strategy flow chart.

myositis, which has been seen following alemtuzumab treatment (personal communication). ITP was excluded by a normal platelet count. Further investigations excluded pregnancy, malignancy and a primary autoimmune disease as causes of AHA. The temporal relationship to alemtuzumab therapy was felt to be significant and a B cell-mediated autoimmune complication of alemtuzumab therapy was considered the most likely underlying aetiology for AHA in this patient.

TREATMENT

Recombinant factor VII was administered at a dose of 90 µg/kg to treat acute intramuscular bleeding with improvement in pain and stabilisation of anaemia. Prednisolone therapy at 1mg/kg was initiated with appropriate antimicrobial and gastric ulcer prophylaxis in order to suppress inhibitor formation. Factor VIII level remained low over the following 2 weeks. The patient developed a further intramuscular haematoma, requiring a repeat dose of recombinant factor VII. Consideration was given to the initiation of cyclophosphamide, but in the absence of critical organ bleeding and concerns regarding potential adverse effects on fertility, the patient elected to continue single-agent prednisolone therapy with regular monitoring. Our usual practice is to administer rituximab therapy (375 mg/m²) for four doses since clinical response is usually apparent within a week of the first dose.⁶ However, in the context of known high JC virus index and the potential for development of progressive multifocal leucoencephalopathy (PML) with rituximab therapy, this treatment option was not acceptable to the patient.

OUTCOME AND FOLLOW-UP

The patient was discharged following a 21-day hospital admission. Her mobility had returned to baseline and there was no evidence of active bleeding; however, her factor VIII level remained significantly reduced (3 IU/dL) with an improved but persistent factor VIII inhibitor titre (2.2 BU). The patient will undergo regular laboratory and clinical monitoring with an anticipated median time to complete remission on prednisolone therapy alone of approximately 5 weeks seen in 50% of patients. The patient will continue with Bloodwatch monitoring and regular clinical and MRI surveillance.

DISCUSSION

AHA is a rare autoimmune disorder with an estimated incidence of 1.3–1.5 cases/million/year.⁷ It is seen more

frequently with increasing age and may be drug-induced or arise in the setting of pregnancy, underlying autoimmune disease or malignancy.⁷ Up to 60% of patients will not have a predisposing condition.⁷ Medline and Embase searches were performed and two previous cases of alemtuzumab-induced AHA were identified (see figure 3). The first was a case of AHA occurring 5 years after alemtuzumab therapy for ANCA-associated vasculitis,⁸ and the second was the previously mentioned case following treatment for MS, published in abstract form.⁵

Alemtuzumab targets CD52, a lymphocyte-specific cell surface protein, inducing T and B cell depletion. It has been used historically for treatment of haematological malignancy and in organ transplantation.⁹ Pivotal licensing trials and real-world data^{2,3,10} suggest alemtuzumab is among the most effective disease-modifying treatments in relapsing MS. However, its use is complicated by secondary B cell-mediated autoimmunity that typically peaks 2–3 years post-treatment initiation.⁴ Following each course of treatment, T cell repopulation is driven by early homeostatic proliferation of predominately CD8+ memory T lymphocytes¹ followed by slower reconstitution of CD4+ cells with median recovery time to baseline of 61 months following a single infusion.¹¹ Conversely, early B cell hyperpopulation is seen at 3 to 6 months post-treatment, driven by an arrested cell phenotype.¹² Despite a rise in the proportion of T-regulatory lymphocytes (T-regs) following alemtuzumab therapy,¹³ absolute counts of T-regs remain below baseline during the period of B cell reconstitution.¹ Thus, it is proposed that hyperpopulation of naïve B cells regenerating in the absence of T-regs may allow the development of autoreactive populations.^{1,12} Elevated interleukin 21 levels, increased availability of antigen-presenting cells and a lower threshold for cell proliferation in response to self-antigen skews the T cell repertoire following alemtuzumab therapy¹⁴ and these factors also potentially contribute to the development of autoimmune disease.

Multiple B cell autoimmune diseases (AIDs) have been reported following alemtuzumab treatment in MS which interestingly occur at much higher rates than when the same treatment is administered for haematological malignancy.¹⁵ In addition to thyroid disorders, nephropathy and idiopathic thrombocytopenic purpura, cases of haemolytic anaemia⁴ and autoimmune neutropenia¹⁶ have recently been reported. The current monitoring programme for emergence

of AIDs following alemtuzumab treatment in Australia involves TFTs, full blood count (FBC), serum creatinine (Cr) and urinalysis with microscopy prior to treatment and then monthly FBC, Cr and urinalysis and three monthly TFTs until 48 months after the last infusion.¹⁷ We suggest that given the two reported cases of AHA complicating alemtuzumab therapy in MS, that standard coagulation testing, APTT and PT, should be added to existing monitoring protocols in these patients as early recognition may prevent fatal haemorrhage.

Early recognition of AHA is critical in order to initiate treatment and prevent development of life-threatening haemorrhage. Management of patients with factor VIII inhibitors involves therapy to both control bleeding and to eliminate the inhibitor. Typically, corticosteroids are used for inhibitor eradication, with or without the addition of cyclophosphamide and/or rituximab therapy. We sought to avoid cyclophosphamide therapy initially in this patient because of fertility concerns and inconsistent evidence of improved efficacy. In addition, given that alemtuzumab treatment has resulted in T cell lymphopenia and the patient is seropositive for JC virus with a high antibody index, there is a potential risk for development of PML with use of rituximab. A review in 2009 reported 76 cases of confirmed or suspected PML in the setting of rituximab therapy, although

these cases occurred predominantly in the setting of malignancy,¹⁸ and it is currently not possible to accurately quantify the risk of PML in the setting of JC virus antibody positivity, as the available data are extremely limited.^{19–21} In this instance, the patient deemed even a small risk of PML to be unacceptable.

Encouragingly, in the CAMMS223 and CARE-MS studies, all patients with immune thrombocytopenic purpura (apart from the index case who suffered a fatal haemorrhage) had a sustained response to therapy, with 70% having a complete response to first-line therapy (corticosteroids, intravenous immunoglobulin or anti-Rh(D)).²² A proportion of those who relapsed on tapering of first-line therapy received rituximab to good effect. It is possible that our patient will have inhibitor eradication on corticosteroid therapy alone. However, if this fails, another therapeutic consideration would be bortezomib therapy, which has recently been described as inducing factor inhibitor eradication in a patient with AHA refractory to cyclophosphamide and rituximab.²³

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Patient's perspective

I was diagnosed with acquired haemophilia, 9 months after being treated with alemtuzumab for my relapsing–remitting multiple sclerosis (MS), as an unexpected adverse effect of the treatment. When I thought about whether I would have gone ahead with the treatment, knowing that I would have been impacted such, I came to the conclusion that I would have. This is because the treatment has stopped the MS progression completely and I feel that the unknown risks associated with the progressive MS relapses were far greater.

Learning points

- ▶ Alemtuzumab is a highly efficacious therapy in the treatment of multiple sclerosis (MS), but uncoupling of T and B cell repopulation during immune reconstitution is associated with an increasing range of secondary B cell-mediated autoimmune conditions, including bleeding diatheses.
- ▶ Acquired haemophilia A (AHA) is a potentially life-threatening antibody-mediated complication that can be observed following alemtuzumab administration for the management of MS.
- ▶ Screening for development of AHA or other inhibitors of specific coagulation factors, using simple and cheap coagulation studies, activated partial thromboplastin time (APTT) and prothrombin time (PT), should be incorporated into existing protocols for monitoring patients with MS following administration of alemtuzumab. Early recognition and treatment may prevent life-threatening haemorrhage.
- ▶ Treatment of AHA following alemtuzumab therapy in this instance is complicated by T cell lymphopenia and positive John Cunningham virus serology with an associated but unquantifiable risk of progressive multifocal leucoencephalopathy.

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