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Case report

B cell depletion therapy resulting in sustained remission of severe autoimmune complications following Alemtuzumab treatment of Multiple Sclerosis

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ABSTRACT

Secondary autoimmune disorders (AID) are a recognised complication of alemtuzumab treatment for multiple sclerosis. We have previously reported two female multiple sclerosis patients treated with alemtuzumab who developed rare but severe secondary AID; acquired haemophilia A and autoimmune encephalitis with seizures. Both cases proved to be refractory to treatment with conventional immuno-therapy. However, treatment of the patients with anti-CD20 therapy resulted in sustained remission. This observation validates anti-CD20 therapy as a potential treatment option in patients with autoimmune complications of alemtuzumab that are postulated to arise as a result of B cell hyperpopulation.

Alemtuzumab is a pan-lymphocyte ablating anti CD-52 monoclonal antibody licensed for the treatment of relapsing remitting multiple sclerosis (RRMS). Despite being classified as a high efficacy therapy, clinical application of alemtuzumab has been hampered by the frequent occurrence of secondary autoimmune disease (AID), with clinical trials and single-centre follow up cohorts estimating an incidence of up to 50% at seven years post treatment (Tuohy et al., 2015). Alemtuzumab has been associated with a range of antibody-associated AIDs including thyroid autoimmunity, immune-mediated thrombocytopenia (ITP) and Goodpasture's disease, and published case reports have highlighted the potential for additional rare, humorally-mediated complications. Following T and B cell ablation, early B cell hyperproliferation in the absence of circulating regulatory T cells is believed to be a causal factor in the development of humoral autoimmunity (Baker et al., 2017). Additionally, non-humoral autoimmunity is being reported as a complication of the immune reconstitution process. In addition to the aforementioned complex interplay between B cells and T regulatory cells it is postulated that the immunology may also involve an expanded oligoclonal population of antigen specific T memory cells developing during the period of lymphopenia induced proliferation post-alemtuzumab (Ruck et al., 2018). Despite the establishment of pharmacovigilance programs to monitor for common complications of alemtuzumab, EMA recommendations around the involvement of multi-disciplinary specialist care in patients treated with the drug and consensus statements from regional groups on the management of prototypical secondary AID post-alemtuzumab (Decallonne et al., 2018; Lambert et al., 2018), management guidelines for many rare and significant secondary AIDs are lacking. We have previously reported two female RRMS patients treated with alemtuzumab who developed rare but severe secondary AID (McCaughan et al., 2017; Giarola et al., 2019). Following publication of details of these presentations, both cases proved to be refractory to treatment with conventional immuno-therapy and the purpose of this article is to report the sustained remission of these severe autoimmune disorders following administration of anti-CD20 therapy.

1. Case one

The history of this 34-year-old woman with a background of hypothyroidism following Hashimoto's thyroiditis, has previously been reported (McCaughan et al., 2017). In brief, the patient was diagnosed with RRMS in 2014 following two episodes of optic neuritis and an episode of incomplete transverse myelitis in her teens and twenties.

The patients have given informed consent for publication of this case. A signed consent form can be provided if required.

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Immunosuppressive treatment with fingolimod was commenced in January 2015; however, in May 2015 the patient developed an episode of incomplete transverse myelitis resulting in an EDSS of 3. In November 2015 the patient commenced treatment with alemtuzumab and was diagnosed with Graves disease immediately prior to the second course of treatment in November 2016. The patient was a non-smoker, with no other medical history.

In August 2017 the patient was admitted to hospital following a ten day history of progressive right leg pain, swelling, spontaneous subcutaneous bruising and intramuscular haematomas of the left posterior thigh and arm. Haematological investigations identified the presence of a Factor VIII inhibitor and a diagnosis of acquired haemophilia A (AHA) was made. The condition was refractory to prednisolone therapy (1 mg/kg) and the patient initially declined rituximab therapy, the preferred second line agent, due to her concerns about the risk of developing progressive multifocal leukoencephalopathy. The patient also elected not to receive cyclophosphamide due to concerns about reduced fertility. In view of emerging data demonstrating the potential efficacy of bortezomib therapy in AHA, and other autoimmune conditions (McFadyen et al., 2017), two cycles (eight doses) of Bortezomib (1.3 mg/m^2) were administered between 24 October and 7 November 2017.

However, the FVIII inhibitor titre continued to rise and the patient presented with left hip pain due to haemarthrosis on 24 December 2017. The acute hip pain settled rapidly with administration of 45 mcg/kg recombinant Factor VIIa. Given this worsening of clinical symptoms and the persistent risk of life-threatening bleeding, the patient agreed to treatment with rituximab and 375 mg/m^2 (700 mg) was commenced weekly for four weeks. By the end of January 2018 the inhibitor titre had started to decline (see Fig. 1) and there were no further bleeding episodes. The prednisolone dose had been weaned to 20 mg daily by March 2018 and the inhibitor titre continued to decline, but the patient did not demonstrate a rising FVIII level until the FVIII inhibitor became undetectable in July 2018. The patient achieved complete remission with no detectable inhibitor and a normal FVIII level in August 2018. No further rituximab has been administered and in March 2019 the lymphocyte count was 1.1 × 10^9/L with a CD19+ count of 110 × 10^6/L (80–430). As of March 2019 the patient remains in complete remission following weaning and cessation of steroid therapy. Her MS remains quiescent, with no evidence of disease activity (NEDA) following treatment with alemtuzumab and rituximab.

2. Case two

As previously reported (Giarola et al., 2019), a 20-year-old female was diagnosed with RRMS in February 2014 and received the first course of alemtuzumab in August 2016 following clinical and MRI progression despite treatment with teriflunomide, fingolimod and dimethyl fumarate. The patient is a non-smoker and her EDSS was 1 at time of commencement of alemtuzumab. In May 2017 the patient developed autoimmune hypothyroidism and proceeded to the second course of alemtuzumab in November 2017. In March 2018 the patient developed ITP which responded to multiple courses of treatment with dexamethasone and intravenous immunoglobulin (ivIg).

In April 2018 the patient developed a march of parasthesiae in the right arm which resolved spontaneously in two hours. The following day she developed left hemifacial myoclonus and epilepsy partialis continua (EPC) of the right genioglossus. The patient was diagnosed with presumed autoimmune encephalitis (AE) after recurrent subsequent generalised tonic-clonic seizures and eventual status epilepticus requiring prolonged intubation and ventilation. Serial MRI studies demonstrated multiple cortical/subcortical foci of T2/FLAIR and DWI hyperintensity in both hemispheres without true diffusion restriction or contrast enhancement. Both serum and CSF were serially negative for antibodies to cell surface neuronal antigens (NMDA, AMPA, GABA(A), GABA(B), mGluR1, and mGluR5 receptors, LGI1 and Caspr2, DPPX, Neurexin3 and Iglon5) when evaluated with cell-based assays (Hospital Clinic, University of Barcelona). Following an initial response to immunosuppression with eight doses of 1 g intravenous methylprednisolone, seven plasma exchanges and five doses of ivIg (0.4 g/kg/day), the patient was maintained on monthly ivIg and a reducing course of Prednisolone. However, the patient represented with a generalised tonic-clonic seizure on 2 September 2018 and an MRI confirmed recurrence of autoimmune encephalitis. Despite a further course of intravenous Methylprednisolone, plasma exchange and ivIg the patient developed polymorphic seizures manifesting with visual symptomatology, focal motor seizures of the right ankle and speech arrest with an MRI study of the brain on 24 September disclosing

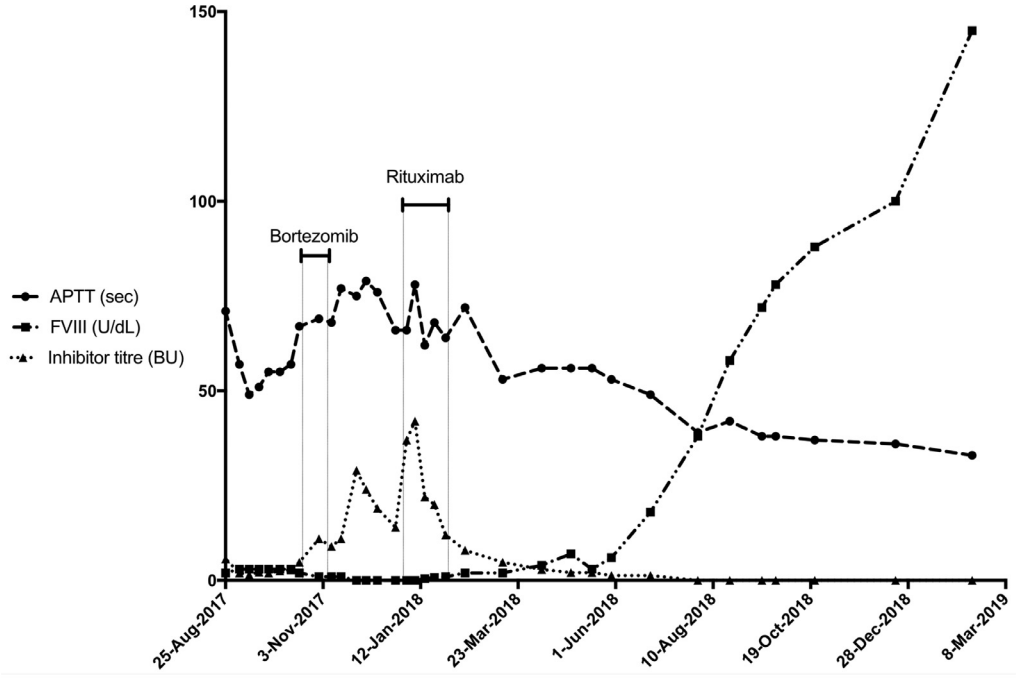

Fig. 1. Disease course of AHA. The patient's APTT, factor VIII level and factor VIII inhibitor levels were tracked following initial presentation with AHA. There was no improvement in disease parameters following administration of bortezomib therapy, but the inhibitor titre rapidly declined and remained suppressed following treatment with rituximab leading to a rise in factor VIII level and normalisation of the APTT.

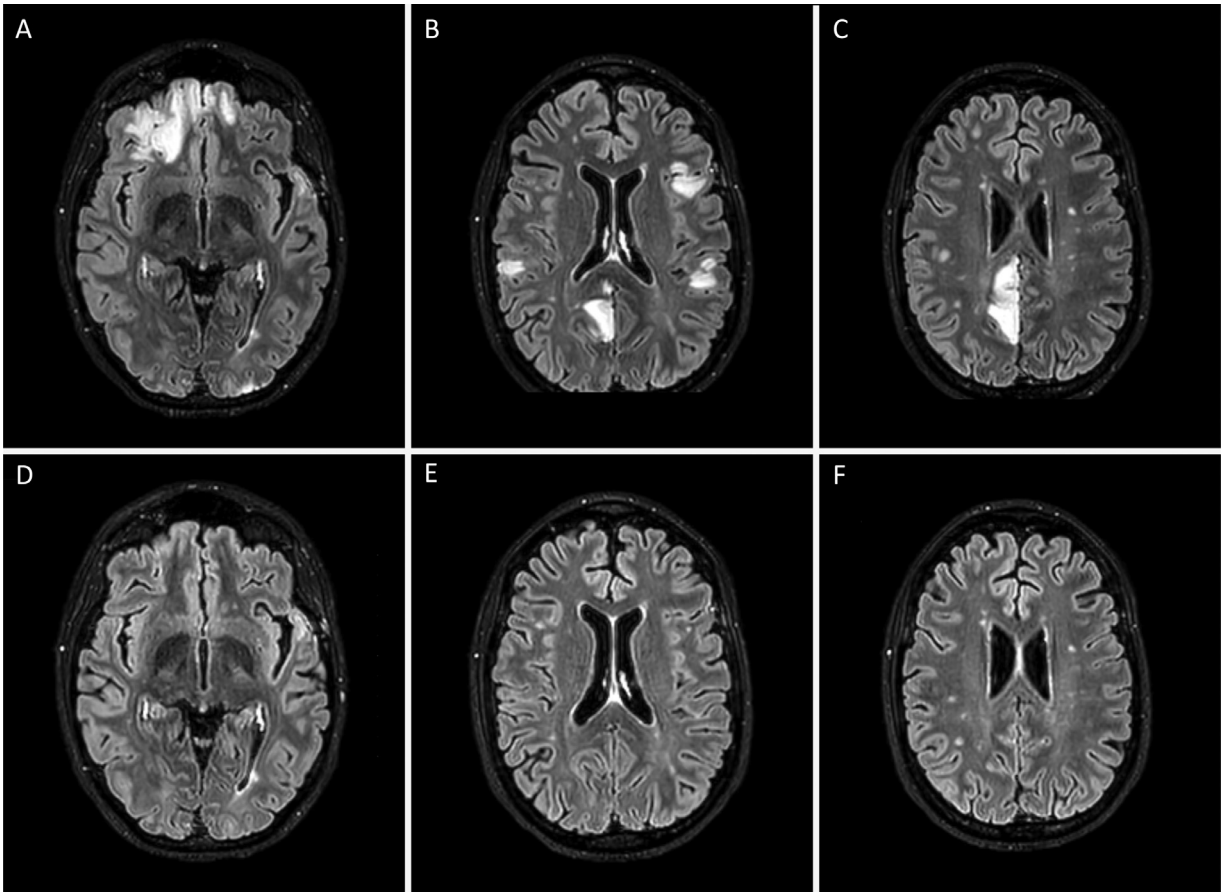

Fig. 2. Disease course of AE. (A – C) MRI from 24 September 2018 demonstrates large areas of T2/FLAIR hyperintensity involving the cortical and subcortical white matter of both frontal, parietal and occipital lobes. (D – F) Progress imaging following treatment with ocrelizumab showing complete resolution of these changes. Resolution of MRI change correlated with induction of a sustained clinical remission.

progressive multifocal cortical and subcortical signal change (see Fig. 2). A 300 mg dose of ocreluzimab was administered on 27 September and following an MRI study of the brain on 11 October, which demonstrated improved appearances, a second 300 mg ocreluzimab dose was given. An MRI on 11 November demonstrated complete resolution of the cortical / subcortical change (see Fig. 2) and it was possible to cease a reducing dose of prednisolone and withdraw all antiepileptic drug treatment by mid-December 2018.

On 29 January 2019 the lymphocyte count was 0.92×10^9/L with flow cytometry demonstrating re-emergence of CD19+ *B* cells (0.24×10^6/L). In February 2019 the patient remained asymptomatic and a progress MRI demonstrated stable appearances of the lesion load due to MS, and no recurrence of the MRI changes associated with the autoimmune encephalitis. The patient received a further dose of 600 mg ocreluzimab in March 2019 and continues to meet MS NEDA criteria.

3. Discussion

In both cases a B cell-mediated autoimmune complication of alemtuzumab therapy was considered the most likely underlying aetiology. Due to the potentially life-threatening nature of both AHA and AE, immunosuppression was initiated early in the patients' clinical presentations, however disease remission was not achieved until B cell depleting therapy was used. This observation supports the current understanding of alemtuzumab associated AIDs, which occur in a time frame in which B-cell hyperpopulation and peripheral expansion occurs in the absence of adequate T cell regulation following initial lymphoablation (Baker et al., 2017; Hill-Cawthorne et al., 2012). Thus, we suggest that B-cell depletion therapy should be considered early in the treatment course of patients presenting with severe humoral autoimmune complications of alemtuzumab. Clinicians should remain vigilant when caring for patients undergoing alemtuzumab treatment due to the potential for both B and T cell mediated immune reconstitution pathology, in addition to the significant risk of infectious or malignant complications.

No firm conclusions can be made regarding the duration of B cell depleting therapies. The patient with AHA has demonstrated sustained disease remission with re-emergence of B cell populations and it is relatively straightforward to monitor the APTT and for recurrence of the Factor VIII inhibitor. In the case of autoimmune encephalitis we have elected to continue with B cell depletion in the short term. In the absence of a defined antibody biomarker withdrawal of B cell depleting therapy will necessitate regular clinical and MRI surveillance for disease recurrence to facilitate early re-initiation of ocrelizumab.

Declaration of interests - Statement

Dr. Massey reports honoraria from Biogen, Merck, Genzyme and Teva, outside the submitted work. Dr. Massey has received a postgraduate research scholarship from MS Research Australia and clinical research support from the St. Vincent's Clinic Foundation.

Dr. Curnow reports honoraria from Novonordisk, outside the submitted work.

Dr. Sutton reports honoraria from Biogen, Merck, Genzyme and Teva, outside the submitted work.

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