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LETTER TO THE EDITORS

Acute posterior multifocal placoid pigment epitheliopathy after alemtuzumab treatment for relapsing–remitting multiple sclerosis

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Dear Sirs,

Alemtuzumab, a monoclonal antibody against CD52, is a highly effective treatment of relapsing–remitting multiple sclerosis (RRMS), but it is known to cause secondary autoimmunity in 40% of patients [1]. We present a case of a RRMS patient treated with alemtuzumab who developed acute posterior multifocal placoid pigment epitheliopathy (APMPPE).

A 34-year-old male patient, diagnosed with RRMS aged 26, experienced multiple disabling relapses per year whilst on treatment with interferon β-1a (Rebif) and was enrolled in a clinical trial for alemtuzumab (CAMMS 32400507). Six months after his first cycle of treatment, he had experienced no new relapses, but in the context of an enterococcal urinary tract infection with exacerbation of his RRMS symptoms, he awoke one morning to discover a 'multicoloured blob' obscuring the central field of his left eye.

On examination, visual acuity was 6/9, pinholing to 6/6, on the right and better than 6/6 on the left. Three left-eye scotomata were evident on Amsler grid plotting and fundoscopy revealed numerous pale-yellow lesions bilaterally at the level of the retinal pigment epithelium and choriocapillaris, with some showing early hyperpigmentation (Fig. 1a). Fluorescein angiography showed early hypofluorescence and late hyperfluorescence of some lesions (Fig. 1b).

Inflammatory markers were normal and a full blood count showed only a marginally low lymphocyte count (0.95×10^9/L). An autoimmune screen showed normal immunoglobulin, serum angiotensin converting enzyme (ACE) and complement levels, and was negative for antinuclear antibodies. Infection was ruled out by serological testing (including for syphilis), analysis of aqueous humour obtained by anterior chamber paracentesis, and a T-spot test for tuberculosis. Additionally, a CT of the chest, abdomen and pelvis was unremarkable, making lymphoma unlikely.

Over the next weeks, he demonstrated continual evolution of chorioretinal lesions bilaterally (Fig. 1a). There were no symptoms of neurological involvement. Accordingly, an MRI scan of the head showed no new lesions and a lumbar puncture was unremarkable. An empirical course of acyclovir treatment was commenced even though his presentation was not typical of herpetic disease and his symptoms began resolving after 2 months.

APMPPE is a self-limiting idiopathic inflammatory chorioretinopathy, believed to be secondary to a hypersensitivity-induced obstructive vasculitis affecting the choriocapillaris [2, 3]. Associations of the disease with preceding viral infections and vaccinations, as well as with human leukocyte antigen (HLA) haplotypes DR2 and B7, support an immune aetiology for APMPPE [4].

There is no single diagnostic investigation, but the exclusion of other causes and the characteristic appearance make APMPPE the most likely diagnosis in this case. Moreover, the timing of the occurrence of symptoms coincides with the earlier stages of B-cell reconstitution following alemtuzumab: the time period during which patients are at highest risk of autoimmune disease [5]. The coincident timing of

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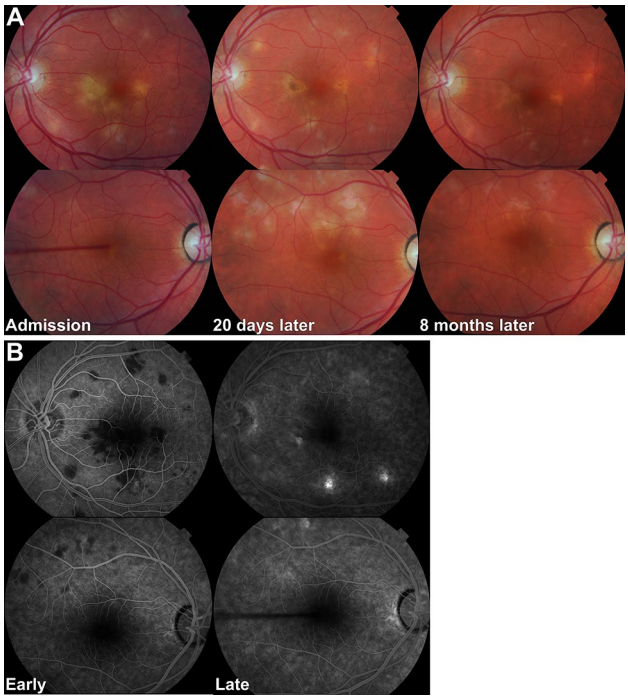

Fig. 1 Ophthalmological findings. **a** Fundus photography of the left (top) and right (bottom) eyes, showing numerous pale-yellow lesions at the level of retinal pigment epithelium and the choriocapillaris, evolving over time. **b** Fluorescein angiography of the left (top) and right (bottom) eyes, showing early hypofluorescence and late hyperfluorescence

symptom resolution and acyclovir treatment is thought to be insignificant given the negative aqueous humour analysis and the fact that APMPPE is expected to self-resolve within a similar period. Thus, an association between alemtuzumab treatment and APMPPE may be presumed, although causality cannot be proven.

This is the first report linking alemtuzumab treatment to APMPPE that we know of and raises interesting questions regarding the aetiology of the disease. In addition, although APMPPE is generally self-limiting with good visual outcomes, more serious cases involve neurological and systemic complications [4]. Therefore, it is important for neurologists to be aware of the spectrum of autoimmune diseases occurring after treatment with alemtuzumab.

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Compliance with ethical standards

Conflicts of interest Alasdair Coles received honoraria and travel expenses from Genzyme (Sanofi), up until 2017.

Ethical approval The patient provided informed written consent in accordance with the ethics standards laid down in the 1964 Declaration of Helsinki and its later amendments.

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