
Peer reviewed version

Link to published version (if available): 10.1177/1352458519898113

Link to publication record in Explore Bristol Research

PDF-document

This is the author accepted manuscript (AAM). The final published version (version of record) is available online via Sage Publications at https://journals.sagepub.com/doi/10.1177/1352458519898113. Please refer to any applicable terms of use of the publisher.

**University of Bristol - Explore Bristol Research**

**General rights**

This document is made available in accordance with publisher policies. Please cite only the published version using the reference above. Full terms of use are available: http://www.bristol.ac.uk/red/research-policy/pure/user-guides/ebr-terms/
Alemtuzumab-related Eosinophilic CNS Vasculitis

Leach OA, Department of neurology, University Hospitals Plymouth NHS Trust, Plymouth, UK
Hilton D, Department of Neuropathology, University Hospitals Plymouth NHS Trust, Plymouth, UK
Adams WM, Department of Neuroradiology, University Hospitals Plymouth NHS Trust, Plymouth, UK
Love S, Department of Neuropathology, North Bristol NHS Trust, Bristol, UK.
Straukiene A, Department of Neurology, Torbay and South Devon NHS Foundation Trust. Torquay, Devon, UK

Corresponding author :

Oliver Leach
Dept of Neurology
Derriford Hospital
Derriford Road
Plymouth PL6 8DH

Oliver.leach@nhs.net
@oliveraleach

01752 432028
fax:

keywords:
multiple sclerosis
vasculitis
autoimmune
alemtuzumab
eosinophilic
Abstract

A 36 year old woman with relapsing remitting MS presented with right sided spasms, focal seizures and neuropsychiatric symptoms 10 months after her first course of alemtuzumab. MRI brain imaging revealed multiple foci of T2 hyperintensity. Subsequent blood and CSF testing for PML, vasculitis and infective causes was negative. A brain biopsy was performed, revealing a prominent perivascular inflammatory infiltrate with multiple immune cells including eosinophils, suggesting eosinophilic vasculitis. The patient was treated successfully with cyclophosphamide. The potential sequelae of alemtuzumab treatment are discussed; this treatable complication should be considered when tests for JC virus are negative.

Background to case

A 36 year-old female presented in 2005 with right arm clumsiness, and was diagnosed with relapsing remitting multiple sclerosis after imaging and CSF analysis (fig 1A). Three relapses occurred over the next five years, including optic neuritis and right-sided weakness, which responded well to steroids. Surveillance MRI in 2011 revealed new lesions, and glatiramer acetate was commenced in 2012. Due to adverse effects treatment was stopped, but after further relapses dimethyl fumarate was commenced in July 2014. In December 2014 she experienced another relapse; MRI demonstrated new cervical lesions. After MDT discussion, treatment was escalated to alemtuzumab, and she
received the first 5-day course in March 2015 with routine antiviral prophylaxis. Surveillance MRI in December 2015 demonstrated a new lesion in the anterior medulla but no clinical relapses were reported (Fig 1B).

In January 2016, she presented to urgent care with right-sided spasms and was treated with gabapentin. Three weeks later she contacted the MS service, describing a 10-day history of events consistent with partial seizures comprising dysgeusia, speech arrest and left head version. Levetiracetam was started and she was admitted for investigation; MRI brain showed multiple foci of poorly defined high T2 signal involving the left insular and perisylvian cortex, bilateral temporal poles and the left inferior parietal lobe. The appearances were considered highly suggestive of progressive multifocal leukoencephalopathy (PML).

Three MRI scans, including contrast, were performed over the next two weeks, showing evolving abnormalities of the left temporal and parietal lesions (Fig1C-D). Routine blood tests did not show any evidence of a systemic inflammatory response. Three CSF samples were sent for JC virus PCR to laboratories in the UK and Copenhagen; each was negative. CSF protein, glucose and cell counts were normal. CSF PCR was negative for HSV 1&2, mumps, parechovirus, enterovirus, VZV, HHV6 and TB. CSF flow cytometry showed small numbers of reactive lymphocytes with a CD4:CD8 ratio of 1:1. Flow cytometry of blood showed reduced CD4+ and CD8+ T-cell numbers as follows: CD4+ 203 cells/ul (450-1700); CD8+ 121 cells/ul (250-1100). The ratio was 1.69, within the normal range, as were B-lymphocyte and natural killer cell numbers. Serum was
negative for antibodies to NMDA receptor, VGKC complex, Ma1, CV2/CRMP5, amphiphysin, fix1, zic4, TR, Hu, Yi, Ro. Serology for Hepatitis B/C, HIV, toxoplasma, Cryptococcus and aspergillus was negative. ANA, ANCA and thyroid antibodies were negative.

The patient declined with progressive disinhibition, euphoria and dysphasia, and required escalating doses of antiepileptics. A brain biopsy was performed, which showed demyelination within the white matter and cortical gliosis, astrocytosis and microvacuolation associated with neuronal loss. Within the cortex and leptomeninges a predominantly perivascular inflammatory cell infiltrate was observed, comprising lymphocytes, macrophages, eosinophils and plasma cells (Fig 2). In places this extended into the vessel wall, without evidence of necrosis or thrombosis. There was no evidence of bacteria, fungi, CMV, toxoplasma, HSV, VZV, measles or polyoma virus. The appearances were considered suggestive of a non-necrotising vasculitis; the presence of eosinophils raised the possibility of an allergic vasculitis, or vasculitis in the context of more widespread connective tissue disease. However, there was no evidence of systemic involvement and the patient had not been on regular medication at the time of onset.

While awaiting histopathology she was treated with five-days’ plasma exchange and prednisolone was started (60mg daily). In light of the histological analysis she was given a 1g bolus of cyclophosphamide, and two weeks later started on oral cyclophosphamide, 2.5mg/kg/day, in addition to oral steroid maintenance. Lymphopaenia necessitated GCSF and a short break from cyclophosphamide, but she was discharged for rehabilitation 6 weeks after presentation, with
expressive and receptive dysphasia, right sided weakness and left hemianopia. Five months after starting cyclophosphamide she undertook a graded return to work, with full recovery of vision and power and almost complete resolution of her dysphasia.

**Discussion**

Alemtuzumab is a monoclonal antibody directed against the CD52 antigen expressed on B-cells and T-cells of the adaptive immune system; administration causes long-lasting depletion of these cells via antibody-dependent and complement-dependent mechanisms. The lymphocyte niche is gradually repopulated via haematopoietic precursors, with CD8+ and CD4+ T-cell populations taking up to 60 months to reach previous numbers (1, 2). As seen in this case, the B-cell population is quicker to recover.

In trials, Alemtuzumab reduced the annualized relapse rate by up to 69% compared with interferon-β, as well as reducing accumulation of disability (3). The reduction in immune cells does not appear to result in a greater susceptibility to significant infections, but mild and moderate infections are reported with greater frequency. The major adverse effect is emergence of secondary autoimmunity (4), which may be associated with excess repopulation of B-cells (5). Most common is autoimmune thyroid disease, but other recognized complications include immune thrombocytopenia, and renal disease including anti-glomerular basement membrane disease and membranous glomerulonephritis. These complications usually respond well to
immunotherapies including corticosteroids, plasma exchange and cyclophosphamide (4).

The first case of alemtuzumab-related PML in the context of multiple sclerosis treatment has recently been reported (6). The patient made a good recovery following treatment with steroids. Hitherto, PML had reportedly only occurred following alemtuzumab in other settings. A lung transplant recipient, previously treated with multiple immunosuppressants, developed PML thirteen months after a single 30mg dose (7), and a patient with chronic lymphocytic leukaemia developed PML while undergoing a 12-week course of high dose alemtuzumab (8). The patient died in both cases.

A recent report describes two cases of inflammatory CNS disease occurring 6 months following alemtuzumab for MS, with ring-enhancing lesions on MRI. A prompt response to Rituximab was observed, leading the authors to propose that the pathology was due to the emergence of B-cell driven autoimmunity (9). Histology was not obtained in either of these patients, and the MRI appearances are markedly different to our case. There are two recent case reports of vasculitis in the context of alemtuzumab treatment for MS, the first a case of leukocytoclastic vasculitis that responded promptly to steroids (10), and the second a case of systemic MPO-ANCA positive polyangiitis that was also effectively treated with steroids alone (11). CNS vasculitis has been reported as a consequence of Daclizumab monotherapy in MS (12), but not other DMTs, suggesting that this is a treatment induced condition rather than a general propensity of MS patients to other autoimmune disease.

To our knowledge this is the first case of eosinophilic CNS vasculitis in the context of alemtuzumab. There was no evidence of systemic connective tissue
disease, and the improvement with cyclophosphamide after 2 months’ progression lends credence to the histological diagnosis. Angiography may have helped in this case; however, initially vasculitis was not high on the list of differential diagnoses, and angiography was felt to be unnecessary once the histological diagnosis was made.

Eosinophilic vasculitis is most commonly recognized in the context of systemic eosinophilic granulomatosis with polyangiitis (EGPA). In our case, granulomas were not seen, which is unusual but not unprecedented (13). The role of granulocytes and the mechanism of autoimmunity remain unclear; post-alemtuzumab autoimmunity appears to be mainly B-cell dependent, whereas the inflammatory infiltrate in this patient was dominated by T-cells, as in ANCA-associated vasculitis (14). Furthermore, B-cell ‘hyper-repopulation’ was not seen in our case, where flow cytometry revealed normal numbers of peripheral B-cells and a preserved CD4+/CD8+ T-cell ratio. The rapid response to immunotherapy and good outcome should prompt neurologists to consider the possibility of CNS vasculitis in this setting.

**Conflict of interest**

The Authors declare that there are no conflicts of interest.

**Acknowledgements**

We acknowledge and provide thanks to the patient and her family. We also acknowledge the contributions of Professor Jeremy Hobart and Dr Omar Al-Masri.

**Consent**
Patient consent was obtained.

**References**

10. Garten LE, K; Lezcano, C; Spiro, J; Siuta, J; Belcher, S. Case report: Leukocytoclastic vasculitis in an MS patient following alemtuzumab treatment. *Neurology* 2017; 88 (16 Supplement):P5.403;.
Figure 1. MRI brain imaging. A. Axial T2 prior to alemtuzumab. B. Sagittal FLAIR: multifocal T2 hyperintense lesions affecting cortex and underlying white matter. C. Axial T2: new left temporal lobe lesion. D. Post-contrast scan showing enhancement of left temporal lesion.
Figure 2. Brain Biopsy. Small cortical blood vessel showing prominent perivascular and transmural inflammation including scattered eosinophils. Haematoxylin/Eosin stain. Magnification x 200.