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Letter to the Editor

Varicella-zoster virus vasculopathy in a multiple sclerosis patient on fingolimod

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Dear editor,

In the past decade, a variety of medications have come on the market to treat relapsing remitting multiple sclerosis (RRMS). Fingolimod, a functional antagonist of sphingosine 1-phosphate (S1P) receptors, reduces relapse frequency, MRI activity and disease progression. However, several side effects have been described – notably, heart block, macular edema, transaminitis, and infections. Varicella-zoster virus (VZV) cutaneous reactivation (shingles) is a well-known complication, but VZV vasculopathy has only been reported once [1].

We present the case of a 42-year-old woman with RRMS and a recent Expanded Disability Status Scale (EDSS) of 2.0 treated with fingolimod. She was diagnosed with RRMS 6 years prior and was initially treated with interferon-beta-1a and then teriflunomide, the former discontinued due to an undesirable cutaneous reaction and the latter due to lack of efficacy. She was subsequently stable on fingolimod for 3 years. The patient denied a history of VZV infection but anti-VZV IgG was positive prior to fingolimod initiation. There was no prior history of frequent infections to suggest a primary immunodeficiency nor past episodes of herpesvirus-associated disease.

Two months prior to her current presentation, she experienced a subacute onset of left proportional hemiparesis attributed to a MS relapse and was treated with five days of intravenous methylprednisolone without improvement. Two months later, she presented with acute onset left homonymous hemianopsia, left-sided hypoesthesia, hemineglect and encephalopathy. Her NIH Stroke Scale (NIHSS) score was 12. Fingolimod had been discontinued 10 days prior to presentation in anticipation of a transition to natalizumab in the context of the presumed recent relapse.

Brain MRI demonstrated an acute infarct of the right parieto-occipital region and a subacute infarct in the right corona radiata (Fig. 1a & b), likely responsible for the left sided hemiparesis two months prior. MR-angiography with and without gadolinium showed multifocal vessel irregularities (Fig. 1d) with stenoses of the right supra-clinoid internal carotid artery, right proximal middle and posterior cerebral arteries as well as the second segment of the left anterior cerebral artery. All vessel stenoses were associated with concentric vessel wall enhancement (Fig. 1c).

Fingolimod-associated lymphopenia (0.36×10^9/L) had been present in the last two years and persisted upon presentation. Cerebrospinal fluid (CSF) analysis demonstrated an elevated white blood cell count of 14×10 [6]/L (99% lymphocytes) and a protein level of 0.57 g/L (normal range 0.15–0.4 g/L), with a normal glucose. CSF VZV PCR was positive, confirming the diagnosis of VZV-vasculopathy. The patient did not exhibit any cutaneous manifestations of herpes zoster. Immunoglobulin levels and HLA typing were not obtained.

She was treated with 21 days of intravenous acyclovir and 5 days of oral prednisone (1 mg/kg). There was rapid resolution of her encephalopathy and she did not develop any additional deficits. Despite clear clinical improvement, CSF WBC count increased to 47×10 [6]/L after 14 days of acyclovir. This was attributed to an immune reconstitution reaction, as follow-up CSF VZV PCR was negative. At three-month follow-up, NIHSS had decreased from 12 to 5 and EDSS was 5.5. Glatiramer acetate was initiated to prevent further MS relapses.

To our knowledge, this is the first reported case of VZV-vasculopathy in the setting of fingolimod-induced lymphopenia and absence of concomitant cutaneous herpes zoster, with MRI evidence of multifocal intracranial stenosis and concentric vessel wall enhancement. The only other published case describes a patient with herpes zoster, VZV encephalitis and vasculopathy, normal magnetic resonance angiography, as well as exposure to natalizumab in the year prior to presentation [1].

Sudden onset neurological deficits are unusual in patients with RRMS and should prompt consideration of an alternative etiology, primarily one of vascular origin. In the neurovascular literature, however, VZV-vasculopathy is a well-known cause of cerebral ischemia, although strokes are often temporally associated with varicella infection or herpes zoster [2,3].

One case series and literature review examined the laboratory and imaging features of patients with VZV-vasculopathy [4]. CSF pleocytosis was present in 67% and anti-VZV IgG antibodies were more sensitive than positive CSF VZV DNA, notably when associated with a reduced anti-VZV IgG serum/CSF ratio. Additionally, imaging findings were present in 97% of patients in the series, with angiographic abnormalities noted in 70%. More recently, high resolution MRI with vessel wall imaging has been used to evaluate patients with VZV

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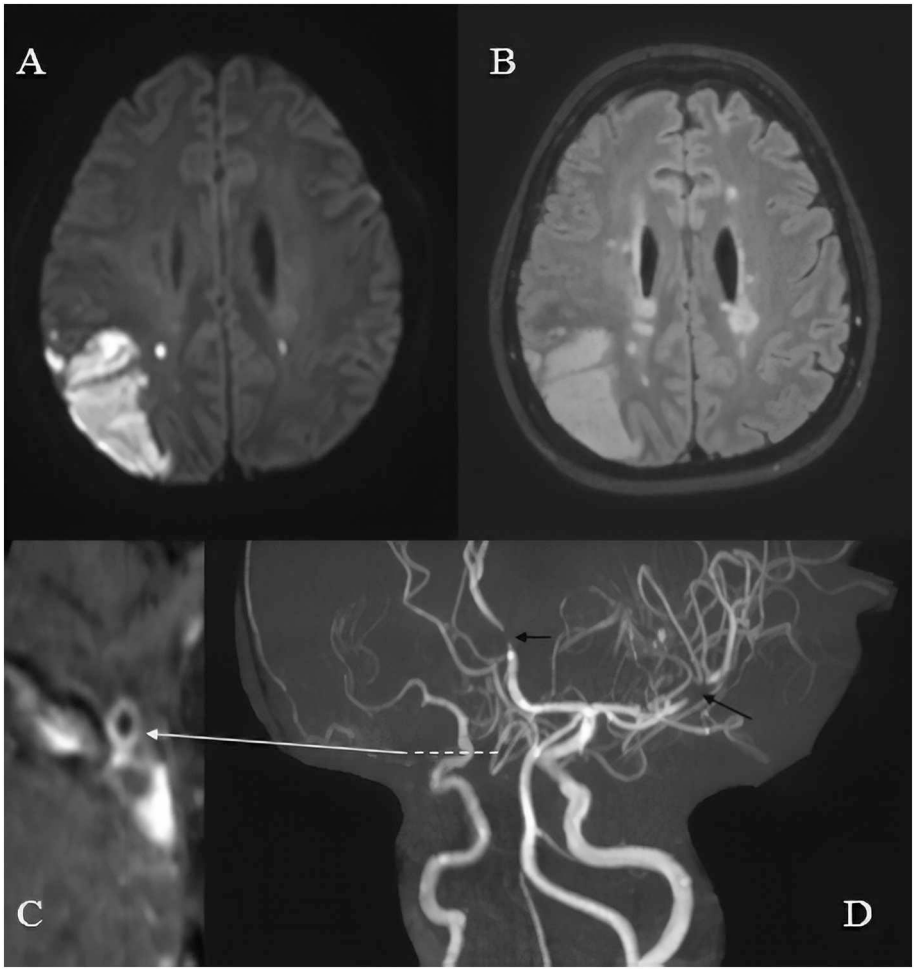

Fig. 1. A. MRI diffusion-weighed imaging reveals acute infarction of the right parieto-occipital region. B. MRI FLAIR sequence shows periventricular white matter lesions and infarction of the right parieto-occipital region. C. MRI vessel wall imaging demonstrates concentric enhancement of the right supraclinoid carotid artery (white arrow). D. MRA with gadolinium reveals multifocal intracranial arterial irregularities and stenoses (black arrows).

vasculopathy and one series of six patients illustrated a variety of stenosis and enhancement patterns, with predominant involvement of the terminal internal carotid artery and proximal middle cerebral artery segments [5].

Fingolimod, a S1P receptor modulator, acts on lymphocytes via a complex mechanism leading to the prevention of their egress from lymphoid tissue. As a result, fingolimod induces a reduction in lymphocyte counts within 2 weeks of initiation, notably of naïve T cells and central memory T cell, without affecting their function [6,7]. This relative lymphopenia results in an increased risk of VZV infection – a large cohort suggesting the risk in those treated with the S1P analogue versus placebo to be 11 versus 6 per 1000 patient-years [8]. Furthermore, the rate was significantly higher in patients treated with fingolimod than with any other disease modifying therapy. Fortunately, the proportion of serious herpes zoster infections was quite low, with only 2 fatal cases. Similarly, VZV-vasculopathy was not reported in this large systematic review and has only been documented once in the setting of fingolimod use [1].

The MS literature recommends establishing VZV immune status prior to initiation of fingolimod and vaccination in those who lack varicella immunity [8]. Furthermore, as corticosteroids may increase risk for VZV reactivation, it is suggested that acute treatment of relapses in patients taking fingolimod should be limited to a short course of steroids without taper [8]. Although routine antiviral prophylaxis is not indicated in all patients receiving steroids, in those requiring a prolonged or repeated course, longer term antiviral treatment should be considered [8]. Should signs or symptoms of varicella or herpes zoster develop, antiviral treatment should be implemented immediately to decrease the risk of further complications, including meningoencephalitis and vasculopathy.

Stroke in an RRMS patient treated with fingolimod may be secondary to VZV vasculopathy, even in the absence of cutaneous herpes zoster. Clinicians should consider infectious vasculopathies in the presence of sudden-onset symptoms in this patient population, particularly in the setting of fingolimod induced lymphopenia. This rare complication should be rapidly recognized to allow introduction of antiviral agents rather than escalation of immunosuppressive therapy.

Ethics approval and consent to participate

Written informed consent for participation was obtained from the patient.

Consent for publication

A copy of the consent form is available for review by the editor of this journal.

Availability of data and material

All data and material supporting our findings are contained within the manuscript.

Competing interests

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Authors' contributions

AM and AN contributed equally to data collection and analysis as well as to drafting and editing the manuscript. ML, CO, MG and AP all participated in editing the manuscript.

References

[1] J.N. Ratchford, K. Costello, D.S. Reich, et al., Varicella-zoster virus encephalitis and vasculopathy in a patient treated with fingolimod, Neurology 79 (19) (2012) 2002–2004.
[2] S. Lanthier, D. Armstrong, T. Domi, et al., Post-varicella arteriopathy of childhood: natural history of vascular stenosis, Neurology 64 (4) (2005) 660–663.
[3] K. Sundström, C.E. Weibull, K. Söderber-Löfdal, et al., Incidence of herpes zoster and associated events including stroke - a population-based cohort study, BMC Infect. Dis. 15 (2015) 488.
[4] M.A. Nagel, R.J. Cohrs, R. Mahalingam, et al., The varicella zoster virus vasculopathies: clinical, CSF, imaging and virologic features, Neurology 70 (11) (2008) 853–860.
[5] E. Cheng-Ching, S. Jones, F.K. Hui, et al., High-resolution MRI vessel wall imaging in varicella zoster virus vasculopathy, J. Neurol. Sci. 351 (1–2) (2015) 168–173.
[6] G. Francis, L. Kappos, P. O'Connor, et al., Temporal profile of lymphocyte counts and relationship with infections with fingolimod therapy, Mult. Scler. 20 (4) (2014) 471–480.
[7] M. Mehling, V. Brinkmann, J. Antel, et al., FYT720 therapy exerts differential effects on T cell subsets in multiple sclerosis, Neurology 71 (16) (2008) 1261–1267.
[8] A.M. Arvin, J.S. Wolinsky, L. Kappos, et al., Varicella-zoster virus infections in patients treated with fingolimod: risk assessment and consensus recommendations for management, JAMA Neurol 72 (1) (2015) 31–39.

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