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Management approach including Pembrolizumab for Fingolimod-associated progressive multifocal leukoencephalopathy in a patient with relapsing remitting multiple sclerosis

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AWB provided clinical input, performed a review of the literature and drafted the article.
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Abstract

A 62 year-old man with relapsing remitting multiple sclerosis developed progressive multifocal leukencephalopathy (PML) after six years on Fingolimod. The Fingolimod was immediately discontinued and preexisting Mirtazepine increased. Three weeks later, with brain MRI appearances worsening and CSF JC virus titres increasing, Maraviroc was introduced. At six weeks, subtle punctate contrast enhancement raised the possibility of immune reconstitution inflammatory syndrome (IRIS), followed by a single focal-to-generalised tonic clonic seizure and a further deterioration in clinical disability. Mefloquine was commenced alongside three doses of Pembrolizumab administered a month apart. Serial CSF examinations and several imaging modalities including spectroscopy and fused FDG-PET-MRI were used to help distinguish between PML, PML-IRIS and MS activity and guide optimal management at each stage. A handful of small, enhancing ovoid lesions developed between the first two doses of Pembrolizumab, probably representative of a mild rebound phenomenon. A sustained improvement became obvious thereafter with CSF JCV-DNA undetectable 16 weeks following Fingolimod withdrawal. To our knowledge this is the first case of combined therapy and use of Pembrolizumab in a Fingolimod-associated PML.

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Progressive multifocal leukencephalopathy (PML) is a rare opportunistic infection, principally of oligodendrocytes, mediated by the polyoma JC virus (JCV) and arising in the context of underlying immune paresis associated with HIV, haematological malignancies, systemic autoimmunity or iatrogenic immunosuppression.\textsuperscript{1-3} PML has been increasingly encountered by neurologists over the past 15 years as a consequence of ever-expanding use of disease-modifying therapies (DMT) for multiple sclerosis (MS), particularly with Natalizumab which decreases immune surveillance of the central nervous system. Symptoms of PML usually include insidious accumulation of neurological deficits and occasionally seizures with MRI lesions typically expanding throughout white matter and myelinated deep grey matter structures and traversing vascular territories. Associated oedema or enhancement is perhaps more unusual but may be seen with concurrent rebound MS inflammatory activity or as part of an Immune Reconstitution Inflammatory Syndrome (IRIS).\textsuperscript{1} Aside from ameliorating the underlying cause of immunodeficiency, there remains no evidenced-based treatment for PML. Here we present a 62-year-old man with RRMS who developed PML in the rather infrequent setting of long-term Fingolimod for relapsing-remitting MS and discuss our management approach guided by sequential imaging and cerebrospinal fluid (CSF) analyses, and including novel use of the immune checkpoint T cell Programmed Cell Death Protein-1 (PD-1) inhibitor Pembrolizumab.

Case Report

The diagnosis of RRMS was made at the age of 45 years following a transverse myelitis three years previously. A long period of stability ensued until aged 53 when there was an optic neuritis followed by a cord relapse, with clinical presentation and radiological appearances remaining compatible with MS. Glatiramer acetate was commenced although a series of further relapses prompted a switch onto Fingolimod, at which point the Expanded Disability Status Scale (EDSS) was 6.0. Total blood lymphocyte count had remained above a long-held baseline of at least 800*10^6/L. Six years later an insidious left leg weakness, gait unsteadiness, slurred speech and double vision evolved over several months with asymmetric cerebellar ataxia, bilateral internuclear ophthalmoplegia and spastic paraparesis found on examination such that the EDSS had increased to 6.5. Blood lymphocytes
had also dipped to $200 \times 10^6$/L. On the suspicion of PML, Fingolimod was immediately withheld and the patient’s Mirtazepine dose increased from 30mg to 45mg daily. Urgent brain magnetic resonance imaging (MRI) demonstrated new, patchy, non-enhancing, hyperintense lesions within the white matter of the frontal lobes, right thalamus and brainstem (Fig.1 A-C) with PML confirmed on subsequent CSF analysis revealing a positive JCV polymerase chain reaction and 160 copies/ml of JCV-DNA. Despite clinical stability initially, MRI appearances and JCV-DNA copies worsened over the next 3 weeks followed by a further deterioration in gait bringing EDSS to 7.0. Maraviroc 300mg twice daily was then introduced empirically owing to uncertainty as to whether the deterioration might represent PML-IRIS. Six weeks after Fingolimod cessation, subtle punctate contrast enhancement suggestive of a mild IRIS was seen within the aforementioned areas of signal change of the midbrain and right frontal lobe (Fig.1 D-F), followed several days later by a single focal-to-generalised tonic clonic seizure. EDSS increased again to 8.0. Repeat contrast-enhanced brain MRI within 24 hours of the seizure no longer demonstrated enhancement. A fusion of brain FDG-PET and MRI was undertaken to help determine the likelihood of emergent PML-IRIS, but the established areas of PML demonstrated relative hypometabolism and thus reassured against PML-IRIS (Fig.1 G-I). Oral Mefloquine 250mg weekly was commenced and the first of three monthly doses of intravenous Pembrolizumab 200mg were administered. Serial CSF examination for quantification of viral load and brain MRI scans were undertaken (Fig.2). However, prior to the second dose of Pembrolizumab, a handful of small, enhancing ovoid lesions developed within the right parietal, right temporal and left midbrain raising the possibility of either PML-IRIS or rebound MS activity (Fig.1 J-O). Following the second dose of Pembrolizumab, a sustained but gradual improvement in imaging and examination parameters was observed alongside a steady reduction in CSF JCV-DNA (Fig.2). By 34 weeks after admission, the EDSS had improved to 6.5 and the Maraviroc was stopped. The patient currently remains clinically and radiologically stable off DMT, 36 months following his PML diagnosis and Fingolimod cessation.
Discussion

Fingolimod binds to and down-regulates the sphingosine-1-phosphate receptor on lymphocytes sequestering them inside lymphoid tissue and thereby reducing their entry to the central nervous system. The overall risk of Fingolimod-associated PML is approaching 1 in 10,000, with older patients particularly susceptible and those who have been on Fingolimod for at least 18-24 months, although the degree of lymphopaenia bears an unclear relationship and prior DMT use is not a prerequisite. Withholding the fingolimod, as with other presumed causative therapies in cases of PML, remains the only consistent management approach with consensus agreement - the ultimate aim being to restore cell-mediated immunity and temper the magnitude of any IRIS which may lead to a paradoxical symptom deterioration. There are otherwise no evidence-based or targeted treatments for PML or, indeed, PML-IRIS, with almost as many permutations of putative approaches as there are reported cases. Mirtazepine and Mefloquine are commonly prescribed to patients with PML owing to their ease of availability and limited in vitro evidence that they may prevent JCV infection or replication. However, there are only anecdotal indications of possible clinical benefit in vivo, including in patients with fingolimod-associated PML.

PML-IRIS also remains tricky to identify confidently against the backdrop of advancing PML infection or, in the case of MS, a resurgence of (rebound) neuroinflammatory activity. There are no specific tests for PML-IRIS and so one must primarily rely on a combination of the change in clinical status, coupled with those of contrast-enhanced imaging (albeit not always sensitive to the presence of histologic IRIS) and CSF JCV load. However, in real time, the receipt of such results, particularly the CSF viral load, may be several weeks into the future and, as is evident only in retrospect from the brain FLAIR imaging in this case (see Fig.2), the PML-associated signal abnormalities may lag somewhat behind a decreasing CSF viral load. Furthermore, the use of steroids to dampen the excessive effects of PML-IRIS (or, at least, what is believed to be IRIS) is considered reasonable and beneficial in many cases, but may come at the expense of exacerbating the PML itself. Limited class IV evidence suggests that chemokine receptor type 5 (CCR5) antagonist Maraviroc may be able to alleviate Natalizumab-associated PML-IRIS with equivocal benefit in fingolimod-associated PML. Our patient had been on Maraviroc for over three weeks at the point of the
transient punctate enhancing lesions seen on MRI and subsequent generalized seizure, but PML-IRIS remained a definite concern. Seizures are often considered to be more representative of PML-IRIS, and yet they have been reported in up to 9% of the HIV positive PML population, who are untreated with anti-retroviral therapy, and thus presumably harbouring no IRIS. A fused brain FDG-PET-MRI study was undertaken in our patient with a view to help inform the likelihood of either advancing PML or PML-IRIS, reported to associate with either hypo- and hypermetabolism, respectively. It was felt that the relative hypometabolism seen within the established areas of PML-associated signal change would be less supportive of an ongoing and/or significant PML-IRIS reaction or, indeed, inflammatory relapse activity, whilst acknowledging the undetermined sensitivity of FDG-PET-MRI to confidently rule in or rule out IRIS. In view of the patient’s clinical downturn, further encroachment of PML-associated MRI FLAIR signal abnormality and (the so far available) worsening CSF JCV load, use of steroids was not felt ideal at this point – although would have been the authors’ treatment of choice if PML-IRIS was strongly suspected.

Pembrolizumab is a monoclonal antibody immune checkpoint inhibitor (ICI) which blocks the PD-1 receptor on T cells in order to facilitate effector cell responses, typically against neoplastic entities. The PD-1 receptor is up-regulated in PML providing a plausible case for its use clinically, albeit that the handful of case reports in non-MS-related PML have demonstrated a range of outcomes. More work is required to explore whether patient subgroups with particular immune profiles may benefit specifically but, interestingly, PML-IRIS was not reliably encountered after Pembrolizumab. To the authors’ knowledge, this is the first described use of Pembrolizumab in Fingolimod-associated PML. However, it was administered as part of a combined therapy approach alongside Mirtazapine, Mefloquine and Maraviroc, and (perhaps most importantly) the discontinuation of Fingolimod itself, so no conclusion can be drawn regarding its apportioned contribution to the observed improvement in this patient’s symptoms. Although, in retrospect, the JCV viral load had already begun to decline at Week 7 when the first Pembrolizumab infusion was given, the MRI appearances of PML had heralded a generalized seizure and downturn in EDSS to 8.0. Likewise, gradual clinical and MRI improvement were not manifest until after the second
Pembrolizumab infusion at Week 11. It is, therefore, not a foregone conclusion that the Pembrolizumab was surplus to requirements.

The small ovoid areas of enhancement observed on MRI between the first two doses of Pembrolizumab posed a diagnostic conundrum as they may have been representative of several phenomena: rebound MS inflammatory activity (owing to Fingolimod cessation approximately 70 days earlier); progressive PML; PML-IRIS; or Pembrolizumab-induced inflammation which has been rarely reported following this and other ICI therapies.\textsuperscript{15} However, as the patient had shown no new impairment in function, close clinical monitoring rather than intervention was preferred and the ovoid lesions had resolved on subsequent surveillance MRI several weeks later. This does, however, highlight the importance of the judicious use of Pembrolizumab and of thorough informed consent processes owing to the potential for usually mild infusion-related reactions or immune-related adverse effects, including pneumonitis, colitis, hepatitis, nephritis, skin reactions and endocrinopathies.

In summary, we present our management approach and real-time clinical deliberations for a patient with RRMS and Fingolimod-associated PML. Treatment included novel use of the immune checkpoint T cell PD-1 inhibitor Pembrolizumab in the face of symptom deterioration with indistinct pointers towards either worsening PML infection versus PML-IRIS. Nevertheless, the authors candidly acknowledge that its contribution to the subsequent clinical and radiological improvement is uncertain and that, in a highly heterogenous PML population, discontinuation of the causative DMT remains the most important contributor to immune restoration and optimal long term outcome. Close monitoring for PML particularly in older RRMS patients on Fingolimod for several years and worsening lymphopaenia under 200 cells per microlitre would also be advised.
Figure 1. MR Brain FLAIR images at baseline showing new hyperintensities (red arrows) without oedema or enhancement within both frontal lobes (A, B), right posterior cingulum (B), midbrain and right occipital lobe (C) suggestive of PML. Prior to the 1st Pembrolizumab infusion, MRI showed worsened appearances with patchy enhancement (yellow arrows) in the posterior frontal region (D) and brainstem (F and E [sagittal]) raising possibility of PML-IRIS. Fused FDG-PET-MRI following the generalised seizure at Week 7 demonstrates relative hypometabolism within established areas of PML (green arrows G-I) reassuring against PML-IRIS. At week 10, between 1st-2nd Pembrolizumab infusions, appearances of the fluffy hyperintense areas on FLAIR ascribed to PML had worsened (red arrows J-L) with new adjacent ovoid lesions demonstrating contrast enhancement on T1-weighted sequences with gadolinium (yellow arrows M-O).
Figure 2. Sequential axial MR Brain FLAIR images (a-g) and CSF analyses at each epoch. Appearances of PML on imaging worsened until week 10 (e) although JCV DNA began to decrease from between weeks 5-7 and prior to Pembrolizumab and Mefloquine. Samples analysed at different labs returned JCV viral loads with differing sensitivities and units of measurement: *Public Health England, Colindale, London, NW9 5HT in international units per millilitre; and **UniLabs, Copenhagen, Denmark in viral copies per millilitre. WCC=white cell count; RCC=red cell count; PCR = polymerase chain reaction; OCBs=oligoclonal bands.
References