LETTER / Neuroradiology

Immune reconstitution inflammatory syndrome in a patient treated with natalizumab presenting progressive multifocal leukoencephalopathy

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Immune reconstitution inflammatory syndrome (IRIS) is a phenomenon that can occur when a patient’s immune system recovers after a period of immunodeficiency. There are distinct types following the recovery periods from different kinds of immunodeficiency, e.g. a patient undergoing antiretroviral treatment for HIV, recovering from post-chemotherapy aplasia, or stopping an immunosuppressant treatment. We report a case of a patient who developed IRIS after progressive multifocal leukoencephalopathy within multiple sclerosis (MS) and on discontinuing natalizumab. We discuss the contribution made by the brain MRI in diagnosing IRIS.

Case report
A 33-year-old male patient had been under monitoring for MS for 8 years, and he had been treated with mitoxantrone, followed by interferon beta-1a, then natalizumab for the past year. Further to an episode when he was unable to recall words, a repeat brain MRI was carried out (Fig. 1). The white matter lesions were larger than they had been on the previous MRI scan (Fig. 2). A lumbar puncture was carried out and the polyomavirus JC virus was identified in the cerebrospinal fluid (CSF) on PCR, which suggested a diagnosis of progressive multifocal leukoencephalopathy (PML) and this meant that natalizumab had to be discontinued.

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The patient was treated with plasmapheresis for PML, in order to reduce the serum concentration of natalizumab and reduce his immunosuppression, and he also received mirtazapine and mefloquine. Shortly after the plasmapheresis, the patient presented status epilepticus and he needed to be admitted to hospital in the intensive care ward. In addition to aphasia, the clinical examination found frontal lobe syndrome, lower limb motor difficulties and sphincter dysfunction with urinary incontinence. Several differential diagnoses were considered: a progression of his PML, side effects due to mirtazapine and/or mefloquine toxicity, or IRIS.

A further brain MRI was carried out. It showed multiple high signal intensities on T2-FLAIR imaging in the peri-ventricular white matter bilaterally, which were nodular and presented enhancement after use of a contrast agent (Fig. 3), suggesting IRIS. Treatment was initiated with high-dose corticosteroids, which led to improvement in his clinical signs thus confirming the diagnosis of IRIS.

**Discussion**

IRIS is classically seen to develop in 23% of cases of HIV-positive patients with PML [1]. It occurs during the passage from a state of acquired and reversible immunodeficiency to a state of functional immunity and is caused by stopping an immunosuppressant treatment or starting a treatment for infection. IRIS seems to be the result of an explosive immune response caused by excessive stimulation of CD8+ T-lymphocytes. In this case of JC virus infection, the fall in the concentration of natalizumab induced by plasmapheresis led to a massive increase in the concentration of CD4+ and CD8+ T-lymphocytes in the CSF [2]. The strong inflammatory activity of the MS before natalizumab was initiated and may have encouraged IRIS to develop [3].

The brain MRI scan is an essential tool in the diagnosis of IRIS after discontinuation of natalizumab in a patient with PML. It demonstrates lesions in the peri-ventricular white matter producing high signal intensity on FLAIR imaging that are nodule-shaped and bilateral. These can be differentiated from the PML lesions because they are much more widespread, nodular, and they present a greater, patchier, and more diffuse uptake of contrast because the blood-brain barrier is disrupted. IRIS lesions are more often found

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**Figure 1.** Initial brain MRI. Transverse axial views using Fluid-Attenuated Inversion Recovery (FLAIR) and T1 SE (spin echo) sequences, both with and without gadolinium enhancement; a: bilateral areas of high signal intensity on FLAIR sequences in the bilateral frontal and parietal white matter; b: low signal intensity on T1 sequences from abnormalities in the white matter. Gadolinium-enhancing nodules present.

**Figure 2.** Previous brain MRI using Fluid-Attenuated Inversion Recovery (FLAIR) sequences — same views.
at the peripheries of the plaques of demyelination that existed before treatment [3]. The lesions only take up contrast temporarily and this phenomenon is not seen on repeat examinations. [4]. These signs may be accompanied by diffuse cerebral oedema that could lead to intracranial hypertension and life-threatening brain herniation. PML that develops after treatment with natalizumab can be differentiated from the classic presentation of PML in HIV-positive patients because the lesions are more invasive and contrast uptake occurs more frequently. Lesion enhancement can even be found before natalizumab is discontinued, and this phenomenon is considered to be early stage IRIS [5]. The treatment for IRIS is high-dose corticosteroid therapy [6].

Conclusion

This case report emphasises the value of close radiological monitoring of patients with MS who then develop PML after treatment with natalizumab is discontinued, and all the more so when there are clinical signs. Combined with the clinical examination and PCR analysis of the CSF (to look for JC virus), use of radiology can guide the diagnosis towards IRIS and is able to exclude a diagnosis of PML disease progression.

Disclosure of interest

The authors declare that they have no conflicts of interest concerning this article.

References