

CASE REPORT

Multiple sclerosis reactivation postfingolimod cessation: Is it IRIS?

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SUMMARY

Although few recent studies have reported efficacy and safety data among patients with multiple sclerosis (MS) switching between immunotherapies, data on the mechanism of rebound activity postwithdrawal of fingolimod in patients with MS is scarce. A 36-year-old woman developed severe reactivation of her disease within 7 weeks of fingolimod's withdrawal despite the absence of breakthrough disease during the 8-week natalizumab washout period previously. The clinical presentation and radiological features were described indicating the diagnostic challenge given the potential risk of developing progressive multifocal leucoencephalopathy. The severe reactivation postwithdrawal of fingolimod could be due to the immune reconstitution inflammatory syndrome (IRIS) given the abrupt rise in lymphocyte count. Patients who discontinued fingolimod might be at risk of developing IRIS resulting in disease reactivation in the washout period.

relapsing-remitting MS. Yet, a controversy concerning the appropriate washout period between fingolimod and natalizumab arose, given the potential risk of rebound disease activity once the immunological effects of natalizumab cease. Immune reconstitution inflammatory syndrome (IRIS) describes the paradoxical deterioration in clinical status following immune system recovery, and it has been increasingly seen in patients following the removal of the immune suppressive or immune-modulatory drugs.¹¹ One such condition, which has recently received wide attention, is in the context of treatment of individuals with MS.^{12–14} We report a case of a patient with aggressive MS who was controlled on natalizumab and later switched to fingolimod due to John Cunningham (JC) virus seropositivity where she developed severe disease reactivation on discontinuation of fingolimod due to possible IRIS.

BACKGROUND

Patients with multiple sclerosis (MS) may be switched between different disease modifying therapies (DMTs) based on several factors such as breakthrough disease, adverse events or risk stratification of certain safety concerns. There is no consensus on washout periods between different DMTs. Most practice recommendations were based on retrospective data analysis. Immunological data suggested that potent DMTs such as natalizumab continue to exert the expected biological effects after their cessation, hence a notion of "drug-holiday" was proposed to decrease the long-term risk of serious safety concerns such as progressive multifocal leucoencephalopathy (PML).^{1–2} However, it was soon learnt that the risk of disease recurrence or rebound activity after the cessation of potent DMTs such as natalizumab could pose a critical management controversy.^{3–5} Several treatment strategies were advocated, which included bridging therapy with monthly pulsed intravenous methylprednisolone^{6–7} or de-escalation to less potent DMTs such as β -interferons (IFN) or glatiramer acetate (GA).^{8–9} A randomised, partially placebo-controlled study to evaluate the effect on MS disease activity of a 24-week interruption in natalizumab treatment showed that disease activity began after 12 weeks and peaked at around 16 weeks after discontinuation of natalizumab in 167 of 175 patients regardless of whether on a drug holiday or if bridging or de-escalation therapy to IFN or GA was instituted.¹⁰ Fingolimod appeared as a promising switching therapy after its approval in 2010, especially in patients with highly active

CASE PRESENTATION

A 36-year-old woman, who was diagnosed with MS in 1998, continued to have breakthrough disease manifested by relapses despite being on IFN β -1a subcutaneously. She was escalated to natalizumab in February 2011. She remained in remission with an Expanded Disability Status Scale of 3.0. On completion of 24 infusions of natalizumab in February 2013 and due to JC seropositive status with a titre of 1.230, she elected to switch to fingolimod after a washout period of 2 months. A follow-up of MRI of the brain and cervical spine while on natalizumab showed no evidence of disease activity. She started to develop lymphopaenia in the first 6 months postfingolimod institution necessitating the interruption of the dosing regimen for 1 month and a subsequent gradual resumption of fingolimod with every other day dosing. After reinstatement of daily dose of fingolimod in November 2013, lymphocyte count was monitored closely on a monthly basis. However, she developed severe lymphopaenia of $0.1 \times 10^9/L$ in February 2014 and fingolimod was discontinued. At the same time, a follow-up MRI of the brain revealed no evidence of disease activity (figure 1). The patient was counselled on the available treatment options and it was decided to resume natalizumab after the normalisation of lymphocyte count. She started to have slight imbalance and cognitive decline 7 weeks postfingolimod discontinuation. Natalizumab was started as the lymphocyte count was $1.2 \times 10^9/L$. Three days later, she was admitted to the hospital after developing dysarthria and right-sided pyramidal weakness, which rapidly progressed to drowsiness and coma within few days. She was unresponsive to verbal and pain stimuli. Her pupillary and corneal



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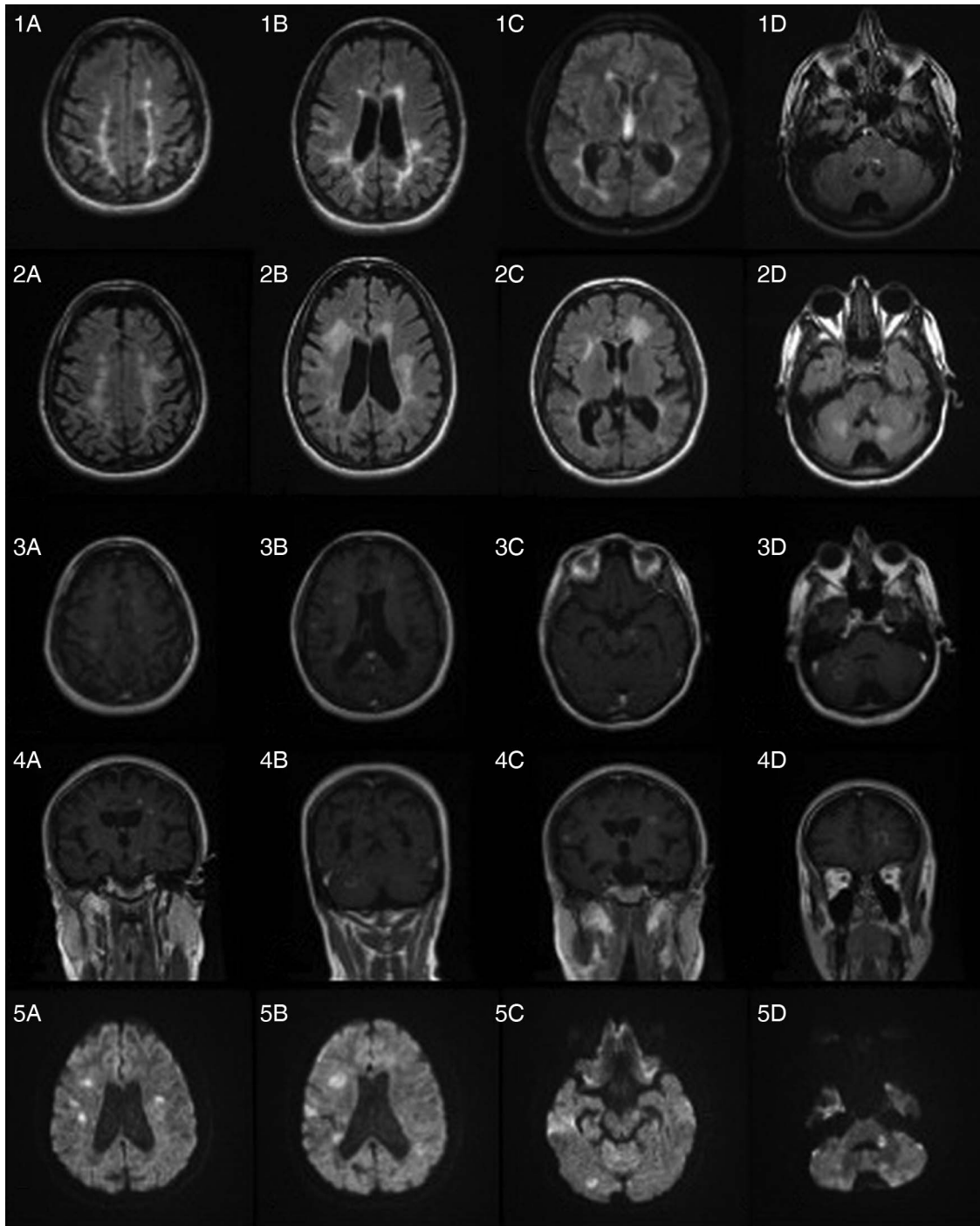


Figure 1 MRI—1(A–D) baseline axial fluid-attenuated inversion recovery (FLAIR) at the time of fingolimod’s withdrawal; 2(A–D) axial FLAIR images 8 weeks after fingolimod’s withdrawal; 3(A–D) axial T1 with gadolinium; 4(A–D) coronal T1 with gadolinium and 5(A–D) axial diffusion-weighted images.

reflexes were preserved but her oculocephalic reflexes were suppressed. She had localising pain on the left upper and lower extremities and her deep tendon reflexes were asymmetrically brisker on the right side with bilateral upgoing plantars.

INVESTIGATIONS

The initial septic work up was negative including blood and urine cultures. MRI of the brain with gadolinium was performed on day 2 of admission, which revealed significant increase in T2/fluid-attenuated inversion recovery lesions in subcortical white matter, juxtacortical areas, brainstem and

cerebellum when compared with the previous MRI (figure 1), along with at least 20 gad-enhancing lesions (figure 1). A lumbar puncture was performed the next day. Cerebrospinal fluid parameters revealed lymphocytic pleocytosis of 5 with normal protein and glucose. JC virus DNA was negative.

DIFFERENTIAL DIAGNOSIS

Given the unusual clinical presentation and MRI findings, a diagnosis of PML was suspected. The differential diagnosis was reactivation of MS (relapse).

TREATMENT

Plasma exchange was initiated and six sessions were completed over 12 days in order to rapidly remove natalizumab since PML was the initial working diagnosis for her clinical deterioration. Subsequently, a course of intravenous methylprednisone 1 g once daily for 5 days was instituted and followed by oral prednisone (1 mg/kg) when IRIS was suspected.

OUTCOME AND FOLLOW-UP

The patient improved in terms of temporal orientation as she was responding to two-step commands, vocalising a few words and performing purposeful movements. She remained hemiplegic on the right side and continued to be dependent on her daily activities. She was transferred to a rehabilitation centre.

DISCUSSION

There are no established guidelines on the proper washout period between potent immunotherapies such as natalizumab and fingolimod. Two recent studies examined the risk of short-term relapse in patients switching from natalizumab to fingolimod.^{15 16} A French prospective cohort recommended a 3-month wash out period,¹⁵ while data derived from a large prospective international registry advised a maximum 2-month treatment gap for switches to fingolimod to decrease the hazard of relapse.¹⁶ The return to pretreatment disease activity should be differentiated from rebound phenomenon. Reactivation of MS can be worrisome and may lead to significant disabilities in patients who were initially escalated to second-line therapies due to their breakthrough disease.⁵ Miravalle *et al*¹² studied a cohort of 32 patients who stopped natalizumab after 1 year under a planned suspension protocol where 38% of the patients with relapsing MS had at least moderately severe relapses within a mean of 4 months and they were worse than the relapses in the prenatalizumab period. With the accumulation of postmarketing data, several cases of rebound disease activity were reported after the discontinuation of fingolimod.^{17–19} The mechanism of rebound phenomenon is controversial and may differ depending on the stage of the disease, duration of prior remission and, most importantly, the drug's mechanism of action and the way the immune system is being targeted. In an Experimental Autoimmune Encephalomyelitis model, Yoshida *et al*²⁰ found that a relapse postfingolimod's discontinuation was associated with infiltration of a clonal selection of myelin oligodendrocyte glycoprotein-specific T lymphocytes in secondary lymphoid tissue.

Ours is the first case reported in the literature to have had a severe rebound disease activity within 7 weeks of fingolimod's discontinuation despite the absence of any breakthrough disease activity during the natalizumab washout period. This highlights several observations. First, the differences in the mode of actions of the two drugs may play important roles in the time and mode of rebound activity. Second, despite the absence of breakthrough disease in the first washout period, rebound activity may appear with a second washout period. Third, the clinical presentation and radiological appearance of rebound phenomenon might be challenging to physicians in terms of diagnosis and symptomatic treatment.

We believe that our case had features suggestive of IRIS, given the abrupt rise in the lymphocyte count postfingolimod's withdrawal, which was associated with concurrent rapid clinical and radiological deterioration. The degree of inflammation postwithdrawal was indicative of a rapid influx of certain immune cells directing the inflammatory response. Although the term 'IRIS'

was first introduced to describe a phenomenon of clinical deterioration despite successful immunological recovery in HIV-infected patients following treatment with antiretroviral therapy, it has been increasingly implicated in patients with rebound activity postnatalizumab interruption.^{11 12} IRIS is likely the consequence of lymphocyte redistribution to the target tissues following the recovery of immune function, cell numbers and prior defects in regulatory function.^{21 22} It may be challenging to differentiate IRIS from usual disease activity especially in patients who had received natalizumab, as PML could be in the differential diagnosis.¹⁴ This challenge translates into a therapeutic dilemma as to whether to rapidly remove the offending drug or to initiate the treatment of IRIS. Corticosteroids in the form of intravenous methylprednisolone for 3–5 days followed by an oral taper for 6–8 days remain the recommended treatment for acute IRIS based on retrospective studies.^{11 23} Although corticosteroids are not the most ideal drug for controlling IRIS because of the lack of specificity, they remain the most effective class of drugs in patients with severe inflammation.¹¹ In our opinion, it might be practical to reduce the washout period to 4–6 weeks when switching from fingolimod to another DMTs to minimise disease reactivation and to avoid the acute stage of IRIS. Future studies are needed to examine the risk of disease reactivation in the setting of IRIS postwithdrawal of potent immunotherapies while consensus recommendations are urgently required to guide the treating physicians on the appropriate washout periods.

Learning points

- ▶ Reactivation of multiple sclerosis may occur during the washout period of potent immune-modulatory drugs, which may lead to severe rebound of previously halted disease activity.
- ▶ Progressive multifocal leucoencephalopathy is a potential diagnostic challenge in patients who were prescribed natalizumab and experienced deterioration of their neurological condition or in those suspected to have relapses.
- ▶ Discontinuation of fingolimod may lead to abrupt rise of lymphocyte count within 4–8 weeks, which could be implicated in fingolimod-associated IRIS (immune reconstitution inflammatory syndrome).

Competing interests None.

Patient consent Obtained.

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