SUCCESSFUL MANAGEMENT OF NATALIZUMAB-ASSOCIATED PROGRESSIVE MULTIFOCAL LEUKOENCEPHALOPATHY AND IMMUNE RECONSTITUTION SYNDROME IN A PATIENT WITH MULTIPLE SCLEROSIS

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Objective: To describe a case of successful clinical management of natalizumab-associated progressive multifocal leukoencephalopathy (PML) and immune reconstitution syndrome (IRIS) in a patient with multiple sclerosis.

Design: Case report.

Setting: University hospital.

Patient: A 41-year-old woman with relapsing-remitting multiple sclerosis developed PML after 29 natalizumab infusions.

Interventions: Immediate plasma exchange was combined for removal of natalizumab with application of mefloquine and mirtazapine to limit viral replication and oligodendrocyte infection. A subsequent IRIS was treated with glucocorticosteroids.

Results: After 3 months of treatment, cerebrospinal fluid tested negative for JC virus. There was a favorable outcome, and the Expanded Disability Status Scale score remained stable at 3.5 compared with before PML.

Conclusions: In the setting of early diagnosis and consequent treatment, natalizumab-associated PML can be well managed in some cases. This situation differs from the course of PML in other conditions, eg, after the application of depleting monoclonal antibodies, in which irreversible cellular effects are associated with very high mortality.


PROGRESSIVE MULTIFOCAL LEUKOENCEPHALOPATHY (PML) is a rare neurological disease caused by infection with a human polyoma JC virus (JCV). It is characterized by infection and lysis of oligodendrocytes and subsequent demyelination of the central nervous system white matter, predominantly involving the brain at multiple locations. While latent infection with JCV is widespread—about 70% of the general population harbors JC antibodies—PML is mainly observed in immunocompromised patients such as those receiving immunosuppressive medication after transplantation or chemotherapy or those with HIV infection but sometimes it is observed in patients with only occult immunosuppression. Recently, several PML cases were reported in patients with multiple sclerosis (MS) who were receiving long-term treatment with natalizumab. Since February 2005, at least 31 PML cases associated with natalizumab treatment of MS have been confirmed. The exact sequela of events leading to the development of PML while receiving natalizumab are still unknown. Although guidelines for patient selection and monitoring have been proposed and several experimental therapies have been described, there is no established treatment of PML and associated complications in these patients yet.

REPORT OF A CASE

At 21 years of age, a female patient was diagnosed with relapsing-remitting MS at an outside hospital. For more than 15 years, she was treated with different immunomodulatory therapies including intravenous immunoglobulins and interferon β 1a (30 µg once weekly). After experiencing breakthrough disease including repeated relapses with motor involvement,
EDSS progression, and magnetic resonance imaging (MRI) activity, the patient presented to our outpatient clinic and started receiving therapy with natalizumab. At this time, her Expanded Disability Status Scale (EDSS) score was 3.5. Control cerebral MRI studies after 1 and 2 years of natalizumab treatment did not detect new lesions. The patient remained relapse free with a stable EDSS of 3.5 and without any neuropsychological symptoms. After the 29th natalizumab application, the patient was hospitalized after 2 generalized seizures for the first time in her life. Immediately, a new cranial MRI was performed. T2-weighted imaging revealed a new, atypical white matter lesion in the left frontal lobe with faint gadolinium enhancement at the margin (Figure, A and D).

On neuropsychological evaluation, the patient was awake, alert, and oriented but showed signs of disinhibition and some attentional deficit. Motor function was not affected, and the patient only showed the preexisting mild right-sided hemiparesis and a mild gait ataxia. Her EDSS score was 4.0. Routine laboratory and cerebrospinal fluid testing did not reveal any significant findings, and results of HIV testing were negative. JC virus polymerase chain reaction in the CSF repeatedly tested positive, with copy detection of 1387/mL, while in the plasma, there were only 28/mL. In the urine, JC virus replication could not be detected.

After establishing a diagnosis of PML, the patient was treated with 5 courses of plasma exchange to accelerate removal of natalizumab from the blood circulation. In

Figure. Serial axial postcontrast T1-weighted (A-C) and T2-weighted (D-F) magnetic resonance images of the brain at the point of progressive multifocal leukoencephalopathy diagnosis (A and D), in the immune reconstitution syndrome phase (B and E), and after treatment (C and F).
addition, the patient received 60 mg per day of mirtazapine and a loading dose of 250 mg by mouth of melfloquine for 3 days.\textsuperscript{8} Subsequently, melfloquine was continued at a dose of 250 mg once per week. One week after completion of plasma exchange therapy, the patient showed progressive cognitive decline with somnolence and slowing of psychomotor function. A new cranial MRI scan revealed an increase of the left frontal lesion associated with mass effect and compression of the anterior horn of both lateral ventricles and persistent contrast enhancement compatible with an immune reconstitution syndrome (IRIS) (Figure, B and E). Methylprednisolone was given at a dosage of 500 mg/d for 5 days. Additionally, treatment of cerebral edema with mannitol at a dose of $4 \times 125 \text{ mL/d}$ was initiated and continued for a total of 4 days. During this regimen, with intensive care unit monitoring, the patient showed rapid amelioration of vigilance as well as cognitive function and was again awake and alert, with only some mild residual signs of frontal inhibition. Follow-up cranial MRI scans revealed a residual left frontal demyelinating lesion with persistent marginal contrast enhancement but no mass effect (Figure, C and F). In the further course, the patient clinically further improved with an EDSS of 3.5. After 1 month of treatment, polymerase chain reaction copy numbers for JCV in the cerebrospinal fluid had significantly decreased to 169/mL while numbers in the plasma were unchanged. After 3 months of treatment, JCV DNA was undetectable in the cerebrospinal fluid, plasma, and urine. At this time, melfloquine and mirtazapine were discontinued and the patient started receiving immunomodulatory therapy with glatiramer acetate.

Until reaching endogenous control of virus replication via reconstitution of the immune system, pharmacologic approaches may further help limit JC virus infection of oligodendocytes. In most cases, evidence of efficacy is either only anecdotal or first positive reports were later refuted in more comprehensive analyses. Recently, in vitro studies revealed that the serotonin receptor 5-HT(2A)R acts as a cellular receptor for JCV on human glial cells.\textsuperscript{13} While small case series and case reports describe beneficial effects of the serotonin reuptake inhibitor mirtazapine in patients with PML,\textsuperscript{14,15} another article suggests that this regimen added little value to patient survival.\textsuperscript{16} Moreover, an in vitro screening assay of 2000 approved drugs and biologically active molecules for their anti-JCV activities revealed that melfloquine efficiently inhibited viral replication in cells after viral entry.\textsuperscript{9} In our case, combination therapy including mirtazapine and melfloquine at a dosage used in malaria prophylaxis was well tolerated. In the future, systematic studies of the efficacy and optimal dosage of these compounds in the treatment of PML are highly warranted.

In the setting of immune reconstitution after natalizumab removal, a paradoxical transient worsening of symptoms may occur. This immune reconstitution syndrome is associated with a pathological inflammatory response and may lead to substantial short-term morbidity and even mortality. Although the incidence of IRIS in HIV-associated PML has not been systematically studied, it may occur in at least 30% of patients with HIV after highly active antiretroviral therapy initiation. Risk factors include a low CD4 count, the presence of latent infections, and a strong response to highly active antiretroviral therapy.\textsuperscript{17,18} Cases of IRIS are also reported in patients with HIV who have PML.\textsuperscript{19,20} Here, worsening of neurological symptoms, increase in viral load, and MRI changes including cerebral edema and contrast enhancement of lesions may occur within 4 weeks after immune reconstitution. This course is consistent with the worsening of symptoms in our patient after plasma exchange. Apparently, this IRIS phase critically determines the outcome of PML cases while taking natalizumab. In this condition, intensive care management and even mechanical ventilation may be needed.\textsuperscript{3,4} In the case of suspected worsening, MRI may reveal signs of IRIS. For treatment of IRIS in patients with HIV who have PML, a series of 12 patients described a beneficial outcome in 58% of cases treated with steroids.\textsuperscript{20} In our patient, the rapid amelioration of symptoms after treatment with high-dose methylprednisolone underscores the use of anti-inflammatory and antiedematous treatment of PML-associated IRIS. Further studies are needed to determine the optimal duration and dose of steroids in this setting.

In classic PML, MRI contrast enhancement at baseline is rarely described. The situation may differ in natalizumab-associated PML in which contrast enhancement was observed in 12 of 28 patients (43%),\textsuperscript{21} as also seen in our present case. While in some HIV-PML studies, contrast enhancement may be a predictive factor for patient survival, the prognostic value in natalizumab-associated PML is not clear to date.

In summary, natalizumab-associated PML is a severe, potentially life-threatening adverse effect of natalizumab therapy in MS. Yet, in the early diagnosis and ac-

**COMMENT**

Here we describe the successful clinical management of natalizumab-associated PML and IRIS in a patient with relapsing-remitting MS. We combined plasma exchange for removal of natalizumab, melfloquine, and mirtazapine to limit viral replication or cellular JCV infection and applied glucocorticosteroids for the treatment of IRIS and concomitant edema. This regimen yielded a favorable outcome. In the present case, the good outcome may relate to the location of the lesion in a noneloquent region, the lack of immunosuppressive pretreatment before natalizumab, and, most importantly, the early comprehensive treatment of PML and IRIS.

While there is no established therapy for PML, observation of patients with HIV reveals that rapid reconstitution of the immune system is most favorable for controlling JCV replication.\textsuperscript{10} Recently, it has been shown that natalizumab clearance might be associated with restored leukocyte function.\textsuperscript{11} Hence, rapid natalizumab elimination seems a prerequisite to limit JCV-associated tissue damage. In a setting where suspected PML is not easy to delimit from MS relapse and diagnostic procedures for PML need further time, a rapid decision for plasma exchange may be made on an empirical basis and will also be beneficial for controlling eventual MS-related inflammatory activity.\textsuperscript{12}
tive treatment of IRIS phase, there may be a favorable outcome.

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REFERENCES


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