Long-Term Remission in Progressive Multifocal Leukoencephalopathy Caused by Idiopathic CD4\(^+\) T Lymphocytopenia: A Case Report

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Progressive multifocal leukoencephalopathy is caused by JC virus, an opportunistic infection of the central nervous system. Antiretroviral treatment for progressive multifocal leukoencephalopathy in human immunodeficiency virus–infected patients is beneficial, but few data exist for patients who are not infected with human immunodeficiency virus. Idiopathic CD4\(^+\) T lymphocytopenia excludes human immunodeficiency virus infection. We describe a patient with progressive multifocal leukoencephalopathy with underlying idiopathic CD4\(^+\) T lymphocytopenia in whom functional recovery occurred without antiviral therapy.

Progressive multifocal leukoencephalopathy (PML) is an opportunistic, demyelinating neurological disorder caused by a ubiquitous polyomavirus called JC virus. The first case was described in a patient with chronic lymphocytic leukemia [1].

In the AIDS era, the incidence of PML has rapidly increased; persons with HIV infection account for ∼85% of all instances of PML, and ∼5% of patients with AIDS develop the disease [2]. Other patients with PML have immunosuppression due to leukemia or lymphomas, cancer chemotherapy, immunosuppressive medication, or chronic inflammatory disease [3]. Usually, the clinical outcome of patients with PML is poor, with an inexorable progression to death within 6 months after onset of symptoms; however, ∼7% to 9% of patients with PML demonstrate prolonged survival (>12 months) in the absence of specific therapy [4].

Idiopathic CD4\(^+\) T lymphocytopenia (ICL) is a syndrome defined by the Centers for Disease Control and Prevention [5] as having the following factors: (1) a CD4\(^+\) cell count < 300 cells/μL or ≤20% determined by >1 investigation, (2) no evidence of HIV infection, and (3) the absence of other known immune deficiency disease or therapy associated with lymphocytopenia. ICL is associated with numerous opportunistic infections [6].

**Case report.** A 39-year-old man presented with symptoms of vertigo and progressively unsteady gait. During the next month, he developed slurred speech and diplopia. He had no relevant past medical history, and he was without risk factors for immunosuppression, including HIV infection. On admission, the patient was afebrile; his systolic/diastolic blood pressure was 130/70 mm Hg and his heart rate was 82 beats/min. Neurological examination revealed spontaneous nystagmus and horizontal saccades to the left, dysarthria, general ataxia and dysmetria on the left side, and hyperactive deep tendon reflexes on the left side without abnormal reflexes. Ataxia was measured at an index of 21/35 using the methods of Klockgether et al. [7]. Neuropsychological deficits were absent, according to results from a series of tests (Mini–Mental State Examination, word list with delayed retrieval, semantic word generation task, Number Connection Test, Rey-Osterrieth Complex Figure Test, Digits Backwards Test, DemTect, and Phonemic Verbal Fluency Task); physical examination was otherwise unremarkable. Laboratory test results included a normal WBC count that showed a decrease of lymphocytes to 5%. The CD4\(^+\) T lymphocyte count was 80 cells/μL (13%) at admission, with a decline to 20 cells/μL (6%) within 1 month, and a CD4\(^+\) cell–CD8\(^+\) cell ratio of 0.5. Results of serological tests (EIA, immunoblot) for antibodies to HIV-1 and HIV-2, as well as HIV PCR, were negative. Syphilis serological test results (Veneral Disease Research Laboratory and *Treponema pallidum* hemagglutination assay) were negative. Analysis of CSF revealed normal parameters with respect to cell count and chemical analysis (cell count, 3 lymphocytes/μL; protein concentration, 49 mg/dL; lactate concentration, 1.3 mmol/L; glucose concentration, 58 mg/dL [61% of the serum glucose level]). There was a minor disturbance of the blood-brain barrier—suggested by the marginally elevated protein concentration—but there was no major intra-thecal synthesis of immunoglobulins. Isoelectric focusing revealed oligoclonal banding, most likely not specifically caused by CNS infection. IgG antibodies against varicella-zoster virus were detected in CSF, but PCR failed to detect varicella-zoster virus DNA. CSF was negative for IgG antibodies against rubella,
Figure 1. Findings from a multimodal imaging study of a 39-year-old patient with progressive multifocal leukoencephalopathy caused by idiopathic CD4+ lymphocytopenia. A, T2-weighted MRI scan shortly after the onset of the patient’s symptoms shows hyperattenuating lesions in the medial cerebellar peduncle and around the fourth ventricle in the parenchyma of the cerebellum. B, [11C]Methionin positron emission tomography scan does not show increased capillary density within the cerebellar lesions; therefore, a neoplastic process is not indicated. C, T2-weighted MRI scan 10 months after the first manifestation of symptoms shows regression of cerebellar lesions (the patient’s cerebellar symptoms had decreased). D, T2-weighted MRI scan 18 months after the first manifestation of symptoms shows further regression of cerebellar lesions without occurrence of new foci. E, Fluid-attenuated inversion recovery (FLAIR) MRI scan 10 months after the first manifestation of symptoms shows a new hyperattenuating lesion in the right temporo-occipital white matter (the patient had developed blurred vision). F, FLAIR MRI scan 18 months after the first manifestation of symptoms shows a regression of the supratentorial lesion (the patient’s visual symptoms had decreased).
measles, and *Borrelia* species infection; angiotensin-converting enzyme; and lysozyme. CSF PCR did not reveal herpes simplex virus RNA or cytomegalovirus RNA. Immunological findings (antinuclear antibodies, antineutrophil cytoplasmic antibody, double-stranded DNA, cardiolipin Ig antibodies, C3 T cell and C4 T cell complement components, and rheumatoid factors) were all within the reference range. There was no evidence of leukemia, lymphoma, or any other immune deficiency disease in bone marrow histological examination.

In summary, these findings are characteristic for ICL. A T2-weighted MRI scan revealed hyperattenuating lesions in the medial cerebellar peduncle and around the fourth ventricle in the parenchyma of the cerebellum (figure 1A). 

The patient underwent a stereotactic biopsy of the lesion in the right cerebellar peduncle. Histological examination of the biopsy sample showed infiltration of the brain tissue by foamy macrophages and mature lymphocytes with perivascular clustering (figure 2A). Luxol fast blue staining revealed a loss of myelin as well as residual myelin fragments within macrophages (figure 2B). Within the lesion, astrocytes were reactive and exhibited polymorphic nuclei, prominent nucleoli, and protein p53 expression (figure 2C). Immunocytochemical examination revealed JC virus antigen in oligodendrocytes (figure 2D). Results of CSF PCR specific for JC virus were positive, and JC virus–specific antibodies were found in CSF. Both of these findings are in line with a diagnosis of PML. In addition, JC virus DNA was detected by PCR in a cell-free serum sample as well as in gradient, purified PBMCs, demonstrating highly active peripheral infection and increased viral load in the course of PML not associated with HIV. The rate of PCR amplification for serum samples and PBMCs in our patient, compared with the rates of amplification in patients with PML associated with HIV (HIV PML), suggests that the circulating viral load in our patient was comparable to that regularly found in persons with HIV PML [8]. Because of our patient’s overall good condition and because of the lack of data regarding antiretroviral therapy for patients without HIV infection with PML, we refrained from the introduction of a specific drug therapy; instead, treatment for symptoms with amantadine (200 mg per day) to improve the patient’s mobility was initiated.

**Follow-up.** One year after the onset of disease, severity of ataxia had decreased (Klockgether score, 16/35). The patient reported a new symptom of blurred vision in the left visual...
field. Furthermore, neuropsychological testing revealed new, severe cognitive deficits in information processing and semantic fluency (assessed by the semantic word generation task, number connecting test, and Phonemic Verbal Fluency Test). The patient’s T cell percentage (CD4⁺ lymphocytes, 10%) was identical to his initial percentage, and the results of HIV ELISA and HIV PCR also revealed identical results to initial findings. In CSF, IgG antibodies against varicella-zoster virus were no longer detectable, but oligoclonal banding was still present. A T2-weighted MRI scan revealed a new, hyperattenuating lesion in the right temporo-occipital white matter but regression of the infratentorial lesions (figure 1C and 1E). Specific antiviral therapy was not recommended, but prophylaxis with cotrimoxazole was initiated against opportunistic Pneumocystis jiroveci pneumonia. Twenty months after the occurrence of the patient’s first symptoms, he reported a complete restoration of visual function. Ataxia was still notable but had further improved (Klockgether score, 13/35). Results of neuropsychological tests showed an improvement in cognitive function. The patient’s T cell percentage (CD4⁺ lymphocytes, 12%) as well as the results of HIV ELISA and HIV PCR were still characteristic for ICL. Cerebral MRI revealed partial regression of all known lesions without the occurrence of new foci (figure 1D and 1F).

Discussion. Currently, PML is most commonly associated with HIV infection, and clinical progress of the disease is usually quite fulminant, but cases of partial remission or even resolution associated with HAART for HIV infection have been described [9–11]. However, few data exist about antiviral treatment for patients without HIV infection with PML. Only 3 cases of PML caused by ICL have been reported in the literature so far, and they describe patients who were very gravely affected by the disease [12–14]. To our knowledge, our patient is the first with PML not associated with HIV to show functional improvement without receiving specific antiviral therapy. Haider et al. [13] used cidofovir for the treatment of PML caused by ICL and described a poor therapeutic outcome. Salmaggi et al. [15] reported the disappearance of the JC virus genome from CSF after treatment with cidofovir in a patient with PML caused by systemic lupus erythematosus, without effect on the clinical state of the patient. In general, the benefit of cidofovir in the treatment of PML is rather controversial; different clinical studies show either clinical improvement [16] or no effect of cidofovir on PML [17, 18]. Because of these observations, the potential adverse effects of treatment, and poor outcomes described in literature, we propose that the decision to initiate antiviral treatment for patients without HIV infection with PML should be very carefully evaluated.

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References