Progressive Multifocal Leukoencephalopathy and Idiopathic CD4+ Lymphocytopenia: A Case Report and Review of Reported Cases

Progressive multifocal leukoencephalopathy (PML) is a well recognized demyelinating neurological disorder caused by JC virus. Idiopathic CD4+ lymphocytopenia (ICL) is a syndrome first described by the Centers for Disease Control and Prevention as a CD4+ count <300 cells/mm³ or a CD4+ count that is <20% of the total T cell count on 2 occasions, with no evidence of human immunodeficiency virus (HIV) infection on testing, and absence of any defined immunodeficiency or therapy that depresses the levels of CD4+ T cells. To the best of our knowledge, this is the third reported case of PML and ICL, and also the first reported case of the use of cidofovir to treat PML in a patient not infected with human immunodeficiency virus.

Progressive multifocal leukoencephalopathy (PML) is a well-recognized demyelinating neurological disorder caused by a polyomavirus called JC virus. PML occurs primarily in immunocompromised patients; the first case was reported in a patient with chronic lymphocytic leukemia [1]. PML has since been reported in patients with other hematologic malignancies (such as lymphomas) or connective tissue diseases and in transplant patients and patients receiving long-term treatment with immunosuppressive agents. PML has been reported in 1%-4% of HIV infected patients and accounts for 1% of AIDS-defining illnesses [2]. Idiopathic CD4+ lymphocytopenia (ICL) is a syndrome that is defined by the Centers for Disease Control and Prevention as a CD4+ count <300 cells/mm³ or a CD4+ cell count that is <20% of the total T cell count on 2 occasions, with no evidence of HIV infection on testing, and absence of any defined immunodeficiency or therapy that depresses the level of CD4+ T cell levels [3]. ICL has been reported to occur along with numerous opportunistic and nonopportunistic infections [4]. To our knowledge, our case is the third reported case of PML with ICL [5, 6], and the first case report of the use of cidofovir to treat PML in a patient not infected with HIV [7–9].

A 49-year-old man presented in July 1999 with symptoms of diplopia. Over the next 2 months, he developed weakness in the right upper extremity, along with paresthesias of hands and feet, and marked decline in cognitive function.

By August 1999 his speech was impaired, and he was unable to carry out activities of daily living. He had no risk factors for HIV disease. His only relevant past history was a remote diagnosis of chronic lymphocytic leukemia in the early 1980s, from which he was asymptomatic and never required any treatment.

On admission the patients was afebrile, his blood pressure was 152/86 mm Hg, his pulse was 88/min, and his respiration rate was 20 breaths/min. He appeared agitated at times and had a nonfluent aphasis marked by profanity. Findings of a neurological examination were remarkable for a right hemianopsia, right-sided hemiparesis, flaccid right upper extremity, and a positive Babinski sign on the right side. The other findings of the physical examination were unremarkable.

Laboratory results included a normal WBC count, with normal neutrophil and lymphocyte counts on the differential. T2-weighted images from an MRI disclosed multiple hyperattenuating lesions in the subcortical, thalamic, and cerebellar regions (figure 1). The patient had a stereotactic biopsy of 1 of these lesions, which contained portions of cortical gray matter and white matter. The lesion consisted of focal demyelination, in association with a brisk reactive astrocytosis displaying atypical nuclei, and with frequent histiocytes. Many oligodendrocyte nuclei were enlarged, and several contained nuclear inclusions. In these nuclei, the chromatin was pushed to the periphery, and the nucleoplasm was replaced by an amphiphilic, finely granular material, giving the appearance of “ground glass” (figure 2). These findings are characteristic of PML.

Serological tests for HIV-1 by ELISA were negative, as was PCR analysis for HIV-1 DNA. Serological tests by ELISA were also negative for antibodies to HIV-2, human T cell leukemia virus (HTLV) type 1, and HTLV-2. CD4+ T cell counts were as follows: on September 22, 202 cells/mm³; on September 27, 115 cells/mm³; and on October 21, 270 cells/mm³. Serum immunoglobulin levels were IgG, 202 mg/dL; IgA, 104 mg/dL; and IgM, 21 mg/dL.

Our patient was treated with cidofovir in a manner similar to ACTG 363, “A Pilot Study of Effect of Cidofovir for the Treatment of Progressive Multifocal Leukoencephalopathy with Acquired Immune Deficiency Syndrome” (National Institute of Allergy and Infectious Diseases, unpublished data). A dose of 5 mg/kg (540 mg) iv was administered 3 times (on September 24, October 15, and October 29). He was pretreated with 0.9% normal saline and probenecid. His neurological status progressively worsened, despite the treatment, and he required intubation following an episode of aspiration. On November 6, he was extubated, because he no longer responded to deep stimuli, and he died later that day.

Only 2 cases of progressive multifocal leukoencephalopathy and ICL have been reported in the literature. Both patients were older males (aged >45 years) with a spectrum of clinical presentations that included gait abnormalities, severe dementia, bulbar palsy, dysphasia, and tetraparesis [5, 6]. The clinical course varied from a few months to 3 years. Both patients tested negative for HIV-1, HIV-2, HTLV-1, and HTLV-2 and had...
characteristic, persistently low CD4$^+$ counts. In both cases the diagnosis of PML was confirmed by examination of a biopsy specimen, which in both cases showed evidence of reactive astrocytosis with atypical nuclei; however, no swollen oligodendrocytes with inclusion bodies were noted. JC virus was identified either by a combination of PCR and restriction endonuclease analysis or by in situ hybridization from pathology specimens.

In conclusion, our case meets the diagnostic criteria of isolated CD4$^+$ lymphocytopenia (i.e., a persistent low CD4$^+$ T cell count and absence of HIV disease or other immunodeficiency state). The low levels of serum immunoglobulins in our patient are characteristic of ICL [4]. The association of PML with ICL remains an uncommon entity.

Our case is also the first reported HIV-negative patient to receive cidofovir for the treatment of PML, and the therapeutic outcome was poor. Cidofovir has been shown to be the most selective antipolyomavirus agent in a mouse polyomavirus model [10]. Clinical use of cidofovir has been limited to case studies in HIV-positive patients with PML, with variable results. These cases illustrate the rapidly progressive clinical course of PML and point out the need for further research into the pathogenesis of isolated CD4$^+$ lymphocytopenia and available treatments for PML.

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References


Figure 2. A hematoxylin and eosin stain of a stereotactic biopsy specimen from the brain of a patient with progressive multifocal leukoencephalopathy. The small hyperchromatic nucleus at 9 o’clock is a normal oligodendrocyte. Enlarged oligodendrocytes with expanded cytoplasmic compartment and intranuclear inclusions (“ground glass”) are visible at the center and at 4 o’clock of the picture (large arrow). A reactive astrocyte is also visible (small arrow). A myelinated axon courses across the upper third of the figure. (Original magnification, ×200).