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Case Report Open Access

An Unusual Case of Progressive Multifocal Leukoencephalopathy in a Patient with Non-traditional Risk Factors

Liebowitz JE*, Zeiger W, Sotirchos E and Pardo-Villamizar C

Johns Hopkins Bayview Medical Center, Baltimore, USA

Abstract

Progressive multifocal leukoencephalopathy (PML) is a frequently fatal demyelinating condition of the central nervous system in which reactivation of the human polyomavirus JC (JCV) leads to lytic infection of oligodendrocytes. JCV reactivation typically occurs in the setting of profound impairment of cellular immunity seen in conditions such as human immunodeficiency virus infection and acquired immune deficiency syndrome (HIV/AIDS), hematologic malignancies, autoimmune diseases, and treatment with immunosuppressive medications. However, an emerging body of literature suggests that minimal or occult immunosuppression may be sufficient for the development of PML in certain cases. We report the case of a 52 year old man diagnosed with PML without history of or risk factors for immunocompromise, with absolute number of CD4 + T cells below the lower limit of normal but not meeting criteria for idiopathic CD4+ lymphocytopenia (ICL), who was subsequently found to have evidence of hepatic cirrhosis of unclear etiology. This is only the eighth case published of hepatic cirrhosis as the main identifiable risk factor for the development of PML and informs the ongoing discussion on mechanisms of moderate immunocompromise sufficient to allow for occurrence of this disease.

Keywords: Progressive multifocal leukoencephalopathy; Lymphopenia; Hepatic cirrhosis; Seizure

Case Report

Mr. A is a 52 year old man from Qatar with a past medical history of hypertension, diabetes mellitus type 2, hyperlipidemia, diverticulitis status post hemicolectomy, and cervical stenosis of C5-7 who began experiencing intermittent headaches, episodes of slurred speech, and decreased appetite from April to October 2014. In November 2014, he developed progressive weakness of his right lower extremity over three days, to the extent that he was unable to control his right lower extremity or walk properly. The weakness was associated with intermittent leg pain as well as numbness in both feet. He had no associated bowel or bladder symptoms. He presented to the emergency department of a local institution where an MRI of the brain demonstrated focal atrophy of the left post central and adjacent superior frontal gyri at the vertex with mild white matter T2 hyperintensity. His symptoms persisted and he was transferred to a higher level of care for further evaluation. During that admission he developed he developed new onset right upper extremity weakness in addition to his right lower extremity weakness. The following day, he experienced a focal motor seizure of the right upper and lower extremities. Phenytoin was prescribed and after he had a second seizure and levetiracetam was later added. Repeat MRI of the brain with and without contrast showed a non-enhancing T2 hyperintense lesion involving the left posterior frontal and parietal pre- and post-central gyri without significant mass effect. Unfortunately, the patient experienced multiple recurrent focal seizures that were resistant to multiple anti-epileptics and was intubated due to declining level of consciousness. A third MRI of the brain showed increased size of the left frontoparietal lesion and expansion into the occipital cortical and subcortical regions, with mild increase in mass effect, and intralesional dark foci on susceptibility weighted imaging concerning for petechial hemorrhage. Viral and bacterial cultures from the patient's cerebrospinal fluid (CSF) showed no growth. The patient was then transferred to our institution for further diagnostic evaluation.

Shortly after arrival, the patient underwent repeat lumbar puncture. CSF analysis was notable for positive JC virus polymerase chain reaction. To make a more definitive diagnosis, brain biopsy was performed. Immunohistochemical stains of the biopsy tissue demonstrated SV40 positivity, relative axonal preservation, and CD68 labeled macrophages. Considering the totality of the patient's clinical and radiographic findings, a diagnosis of PML was made.

Extensive investigation was undertaken to evaluate potential sources of immunodeficiency as the patient had no known history of or risk factors for immunocompromise. Of note, records from the patient's initial evaluation in Qatar indicated the presence of pancytopenia, with a white blood cell count of 2.5 k/mm^3, a hemoglobin of 8.5 g/dL, and a platelet count of 100 k/mm^3. At the time of admission to our institution these had improved to 11.03 k/mm^3, 8.8 g/dL, and 197 k/mm^3, respectively. Further analyses revealed lymphopenia (1200 cells/mm^3) with an absolute number of CD4+ T cells of 352 cells/mm^3 and normal percentages of CD8+ and CD3+ T cells (33.2% and 51.2%, respectively). Interestingly, the absolute number of CD4+ T cells varied significantly over the hospital stay, from a nadir of 352 cells/mm^3 to a peak of 451 cells/mm^3. The patient had no prior exposure to corticosteroids or immunomodulatory medications. HIV-1 and HIV-2 antigen and antibodies were nonreactive and HIV-1 RNA PCR was negative as well. Serology was also negative for HTLV-1, HTLV-2, and hepatitis virus types B and C. Purified protein derivative was negative for tuberculosis. Bone marrow biopsy demonstrated hypercellularity but no evidence of lymphoma or other malignancy. Serologic testing was significant for positive antinuclear antigen with titer >1:640 (homogenous, speckled pattern), anti-Ro positivity, low titer anti-smooth muscle antibody positivity (1:20), and a mild C3 hypocomplementemia of 71. Serum paraneoplastic antibody panel was negative.

***Corresponding author:** Jason Evan Liebowit, Johns Hopkins Bayview Medical Center, Baltimore, USA, Tel: 240676-5999; E-mail: jliebow3@jhmi.edu

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Of particular note, CT of the abdomen with intravenous contrast revealed cirrhosis of the liver, and hepatic function testing demonstrated an AST level of 119 U/L, ALT level of 42 U/L, albumin of 2.2 g/dL, and INR of 1.3. He denied history of any alcohol consumption. Liver biopsy was performed for further analysis, but tissue sample was inadequate for analysis. Wedged hepatic venous pressure was 22 mmHg, consistent with severe portal hypertension.

The patient's hospital course was complicated by failure to wean from mechanical ventilation, and thus tracheostomy and percutaneous endoscopic gastrostomy tube placement were performed. He intermittently experienced focal seizures with impaired consciousness, for which levetiracetam was continued. He was also prescribed rifaximin for prophylaxis against hepatic encephalopathy. He was transferred to a ventilator rehabilitation facility, where he has continued to participate in physical, occupational, and speech language pathology rehabilitation over several months, but he remains dependent on total assistance in all activities of daily living.

Discussion

PML is a frequently debilitating and, in most cases, rapidly fatal disease. For many years it has been understood as a condition affecting patients with severe immunocompromise, such as those with HIV/AIDS. However, a recent review of the literature identified 38 cases of PML in patients with minimal or occult immunosuppression from conditions including renal failure, hepatic cirrhosis, pregnancy, and dermatomyositis. Specifically among patients with hepatic cirrhosis and portal hypertension, hypersplenism was often observed and may result in leukopenia, lymphopenia, or CD4+ lymphocytopenia due to splenic sequestration. Even in patients with cirrhosis but no evidence of decreased leukocyte counts, immune dysfunction in the form of abnormal cytokine production, vascular disturbances, and altered cellular immune responses may be adequate for the development of PML [1].

We first considered autoimmune mediated mechanisms as a predisposing factor. In particular, the high titer antinuclear antigen positivity, slight C3 hypocomplementemia, and anti-Ro positivity suggested the possibility of systemic conditions such as systemic lupus erythematosis (SLE) and Sjogren's syndrome. However, the patient denied premorbid sicca symptoms and did not meet any other diagnostic criteria for either SLE or Sjogren's syndrome. Autoimmune disease as related to occult malignancy was also unlikely as his paraneoplastic antibody panel was negative.

More likely contributory was the patient's hepatic cirrhosis with concurrent portal hypertension, although the cause of his cirrhosis remained unclear. He denied a history of alcohol consumption, his hepatitis serologies were all negative, and his anti-smooth muscle antibody titer was low and unlikely to be sufficient to cause auto-immune hepatitis. Other considerations for causes of cirrhosis included hemochromatosis, Wilson's disease, alpha-1-antitrypsin deficiency, amyloidosis, and sarcoidosis, but the liver biopsy sample was unfortunately insufficient to evaluate for these conditions. Given the patient's obesity, it was felt that the most likely cause of hepatic cirrhosis was nonalcoholic steatohepatitis,

In addition to hepatic cirrhosis, the patient reported here was also found to have a low CD4+ T cell count, with a nadir of 352cells/mm^3 measured at our institution. One differential diagnostic consideration we entertained was the possibility of idiopathic CD4+ T lymphocytopenia (ICL). Although rare, it has been hypothesized as the etiology of PML in 11 cases reported in the literature to date [2]. The Centers for Disease Control and Prevention (CDC) define ICL as follows: "A documented absolute CD4 T lymphocyte count of less than 300 cells/cubic millimeter or of less than 20% of total T cells on more than one occasion, no evidence of infection on HIV testing, and the absence of any defined immunodeficiency or therapy associated with depressed levels of CD4+ T cells [3]. Our patient's measured CD4+ T cell count did not meet these criteria. However, his lymphopenia was significantly worse prior to transfer to our institution, suggesting his true CD4+ T cell nadir may well have been below 300 cells/mm^3. Ultimately, the cause of his transient pancytopenia was never identified.

Conclusion

In conclusion, while this patient did not have any of the traditional risk factors for PML, his idiopathic systemic autoimmunity, hepatic cirrhosis, and transient lymphopenia likely contributed in a multi-factorial fashion to cause immunocompromise sufficient to lead to JCV reactivation. His case typifies the growing body of evidence that such non-traditional risk factors may lead to the development of PML in select cases.

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