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CASE REPORT

Progressive multifocal leukoencephalopathy in a patient without apparent immunosuppression

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Abstract Progressive multifocal leukoencephalopathy (PML) is a viral demyelinating disease due to the reactivation of the JC virus (JCV), which usually occurs in the context of immunosuppression in HIV infection, malignancy, or in patients on disease modifying therapy for autoimmune diseases, such as multiple sclerosis (MS) and Crohn's disease. Notably, there is growing recognition that PML can occur in patients with transient immune dysfunction. Here, we present a case of a 55-year-old man without history of immunosuppression or evidence of ICL who was diagnosed with PML on brain biopsy. We will discuss the potential etiologies of mild and transient immunosuppression that can lead to PML with non-apparent immunosuppression.

Keywords Progressive multifocal leukoencephalopathy · Immunocompetent host

Introduction

Progressive multifocal leukoencephalopathy (PML) is a viral demyelinating disease due to the reactivation of the JC virus (JCV), which usually occurs in the context of immunosuppression in HIV infection, malignancy, or disease-modifying therapy for autoimmune diseases, such as multiple sclerosis (MS) and Crohn's disease. Notably, there is growing recognition that PML can occur in patients with immune dysfunction including idiopathic CD4 lymphocytopenia (ICL), as well as CD8 and CD40 ligand (CD40L) deficiency (Delgado-Alvarado et al. 2013; Haider et al. 2000; Johansen et al. 2013). PML without associated immunosuppression is rare. Although there have been some cases reported as early as the 1970s, it is unclear whether those patients underwent a thorough workup for immunosuppression (Bolton and Rozdilsky 1971; Fermaglich et al. 1970). In addition, there is a greater recognition of novel clinical presentations of JCV infection, such as JCV encephalopathy, JCV granule cell neuronopathy, and JCV meningitis (Tan and Koralnik 2010), which makes the diagnosis of neurological syndromes associated with JC virus more plausible in patients, regardless of the immune status. In this paper, we present the case of a 55-year-old man without history of immunosuppression or evidence of ICL who was diagnosed with PML on brain biopsy. We discuss the potential etiologies of mild and transient immunosuppression that can lead to PML with non-apparent immunosuppression.

Case report

Before the case report was begun, an application to the institutional review board was submitted, and it was determined to be exempt research. A 55-year-old man with a history of chronic obstructive pulmonary disease, hypothyroidism, and chronic alcoholism presented with progressive symptoms of diplopia, vertigo, weakness, urinary incontinence, and cognitive decline. He had a history of smoking and chronic

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alcoholism for 10 years, but no immune suppression or cancer. His symptoms started a year and a half prior to admission with dragging of his right foot leading to intermittent right-sided cramps and a right upper extremity tremor that interfered with activities of daily living (ADLs). Four months prior to admission, he noticed blurry vision and vertigo causing gait imbalance, as well as increasing forgetfulness. Two weeks prior to admission, his gait impairment became more pronounced with marked gait freezing and unsteadiness. His legs were stiff, and he had such difficulty initiating movements that he began requiring a wheelchair. He also developed urinary incontinence, constipation, and decreased speech output. He stopped feeding himself, and his cognition declined dramatically. Given this marked decline, he was taken to a local community hospital for evaluation. Upon further assessment, he was awake, but found to be confused and restless with poor insight and judgment. His examination was remarkable for cognitive impairment, aphasia, and gait imbalance.

Initial magnetic resonance imaging (MRI) of the brain showed multifocal non-enhancing, T2 hyperintense lesions with minimal mass effect involving the bilateral frontal lobes spanning across the anterior corpus callosum, right parietal lobe, the cerebral peduncles, and bilateral cerebellar hemispheres and pons. There was also evidence of partial effacement of the lateral ventricles. The lesions appeared hyperintense on fluid attenuation inversion recovery (FLAIR), but had no evidence of restricted diffusion to suggest ischemic insult (Fig. 1). A lumbar puncture yielded clear cerebrospinal fluid (CSF) with 0 WBCs, 0 RBCs, glucose of 50 mg/dL, and protein of 83 mg/dL (normal 15–45 mg/dL). Gram stain, acid-fast stain, bacterial, and fungal cultures were negative. IgG index was 0.5 mg/dL (normal 0.23–0.64), and there were two oligoclonal bands in the CSF without matching bands in the serum. The myelin basic protein was elevated at 17 μg/ml, suggesting an inflammatory process. B-cell rearrangement was reactive and oligoclonal. His HIV and autoimmune work-up were negative and no angiotensin converting enzyme (ACE) activity was noted. Hematologic and oncologic malignancies were ruled out with CT scans of the chest, abdomen, and pelvis with both intravenous and oral contrast. There were no abnormalities of the liver, adenopathy, or other granulomatous changes. Subsequently, he was referred to our institution due to marked decline in mental status, inability to ambulate, and strong concern for a primary or metastatic CNS tumor.

On admission, he was abulic with diminished attention, impaired orientation, and inability to follow commands. He was able to respond to his name, but no other meaningful communication was present. Cranial nerves were intact. There was no obvious sign of weakness, but his motor exam was significant for hyperreflexia in bilateral lower extremities. Sensory and cerebellar exam were unremarkable. He was able to stand with physical and occupational therapy, but required maximum assistance to take a step. Additional work up revealed a negative paraneoplastic panel, nonreactive HIV antibody, and undetectable viral load. CD4 count was 1170 cells/μL with no evidence of lymphopenia. Serum JC virus-specific antibody testing was positive, but a JCV polymerization chain reaction (PCR) was not checked from the CSF. A repeat MRI, done 1 month after the initial MRI, showed enlarging lesions and increasing effacement of the lateral ventricles (Fig. 1). A brain biopsy was planned due to the uncertainty of the diagnosis, with a differential including atypical demyelinating disease, lymphomatosis cerebri, gliomatosis cerebri, and PML, despite lack of immunosuppression. In the interim, the patient received pulsed dose steroids for 5 days because of the strong suspicion of atypical inflammatory demyelinating disease. Due to the lack of a clinical response to the high dose steroids, he was given intravenous immunoglobulins (IVIG) and received one dose without changes in symptomatology. IVIG was terminated due to biopsy results, which showed lesions rich in macrophages with strong expression of CD163, as well as demyelination, atypical bizarre astrocytes, and oligodendrocyte viral inclusions, that were strongly reactive to Simian virus-40 (SV-40) antibody widely used in neuropathology, that cross react with JC virus and confirm the active stage of the JC virus cycle (Tan and Koralnik 2010) (Stoner et al. 1988; Hess et al. 1994; Bauer et al. 2015). Additional staining identified low expression of CD4 and few CD20 B cells at the site of the lesion (Fig. 2). The combination of low CD4, and very few B cells and high numbers of macrophages, SV-40 immunoreactivity, bizarre astrocytes, viral inclusions, and demyelination, were diagnostic for typical PML (Stoner et al. 1988; Hess et al. 1994; Bauer et al. 2015) and fulfilled the American Academy of Neurology histopathological criteria (Berger et al. 2013).

Given his poor prognosis and worsening cognitive function, the family elected comfort care and the patient was eventually discharged home with hospice. On discharge, the patient had global aphasia, abulia, and significant motor apraxia, which limited his ambulation and ability to perform any ADLs. The patient died weeks after discharge. An autopsy was not performed per the family's wishes.

Discussion

PML is the most frequent manifestation of a productive neurotropic infection with JC virus, while JCV-encephalopathy, JCV-granule cell neuronopathy, and JCV-meningitis occur with much less frequency (Tan and Koralnik 2010). PML is usually seen in the context of immunosuppression; approximately 79 % of PML patients have acquired immune deficiency syndrome (AIDS), 13 % have hematologic malignancies, 5 % have organ transplants, and 3 % have autoimmune diseases treated with immunosuppressive or immunomodulatory medications (Koralnik et al. 2004). Patients diagnosed with

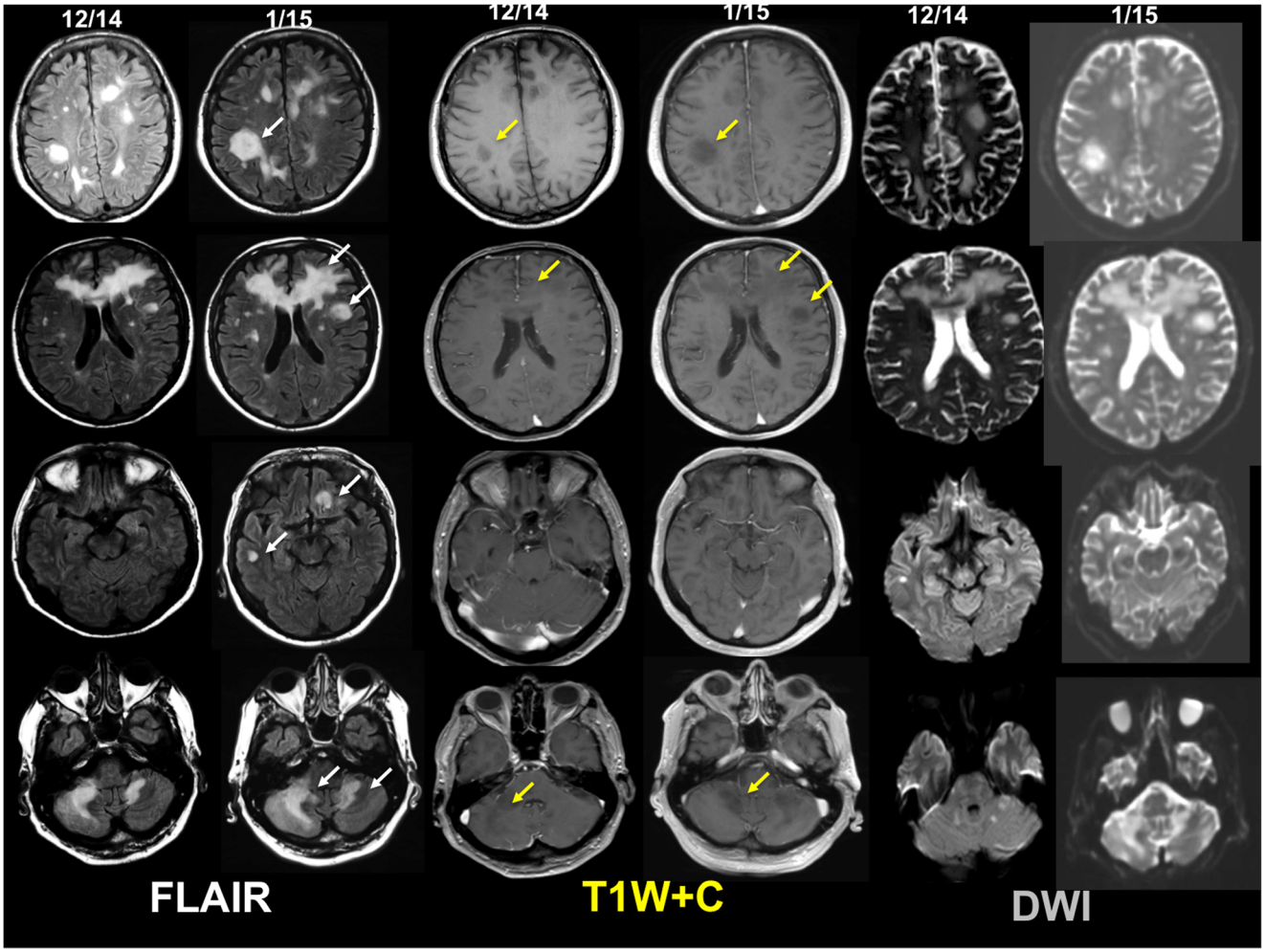

Fig. 1 MRI findings. Initial and 1-month follow-up brain MRI at multiple levels; from top to bottom, frontal, periventricular, temporal, and cerebellar sections from brain MRI 1 month prior and few days after admission showed progression of disease. Multifocal non-enhancing hyperintense lesions with minimal mass effect are seen in bilateral frontal lobes spanning across the anterior corpus callosum, right parietal lobe, bilateral cerebral peduncles, and cerebellar hemispheres (*arrow*). There is partial effacement of the lateral ventricles, but no true restricted diffusion to suggest ischemic insult. On the 1-month follow-up MRI, all lesions show progression in terms of size and effacement of the roof of the lateral ventricles. There continues to be a lack of enhancement and presence of FLAIR hyperintensity (*arrow*)

PML outside of these categories are rare. ICL has been implicated in such cases and is defined as "a documented absolute CD4 T lymphocyte count of less than 300 cells/μL, or of less than 20 % of total T cells on more than one occasion, no evidence of infection on HIV testing, and absence of any defined immunodeficiency or therapy associated with depressed levels of CD4 T cells." (Centers for Disease C. 1992). Patients with PML associated with ICL are often asymptomatic, but can develop sudden opportunistic infections at which time ICL is usually diagnosed (Zonios et al. 2008). These infections are similar to those seen in HIV patients with low CD4 counts (Walker and Warnatz 2006). Our case, however, did not fulfill criteria for ICL, since CD4 and CD8 counts were within normal range (1170 and 737 cells/μL, respectively) without evidence of lymphopenia.

In prior PML cases without associated ICL or immunosuppression, several patients were reported to have low-normal CD4 counts in the range of 80–559 cells/μL, suggesting a tendency towards immunosuppression (Vaklavas et al. 2010), which was not seen in our case. Additionally, in a study of 33 cases of PML in the absence of classic risk factors for immunosuppression, 18 patients had ICL, lymphopenia, or underlying conditions that were thought to cause a transient immunosuppression (Gheuens et al. 2010). Transient immune dysfunction can be seen in the setting of hepatic cirrhosis caused by alcoholism or hepatitis C infection, malnutrition, kidney failure, dermatomyositis, and pregnancy. In the aforementioned case series, the remaining 15 patients had no such conditions. However, 12 of these 15 were not tested for HIV. Thus, only three cases may truly be considered idiopathic cases of PML, but even this is questionable, because there was evidence of possible underlying immune dysfunction in each case due to psoriasis, sarcoidosis, chronic gastritis, sepsis, or 40 % body surface burns. Others have reported low

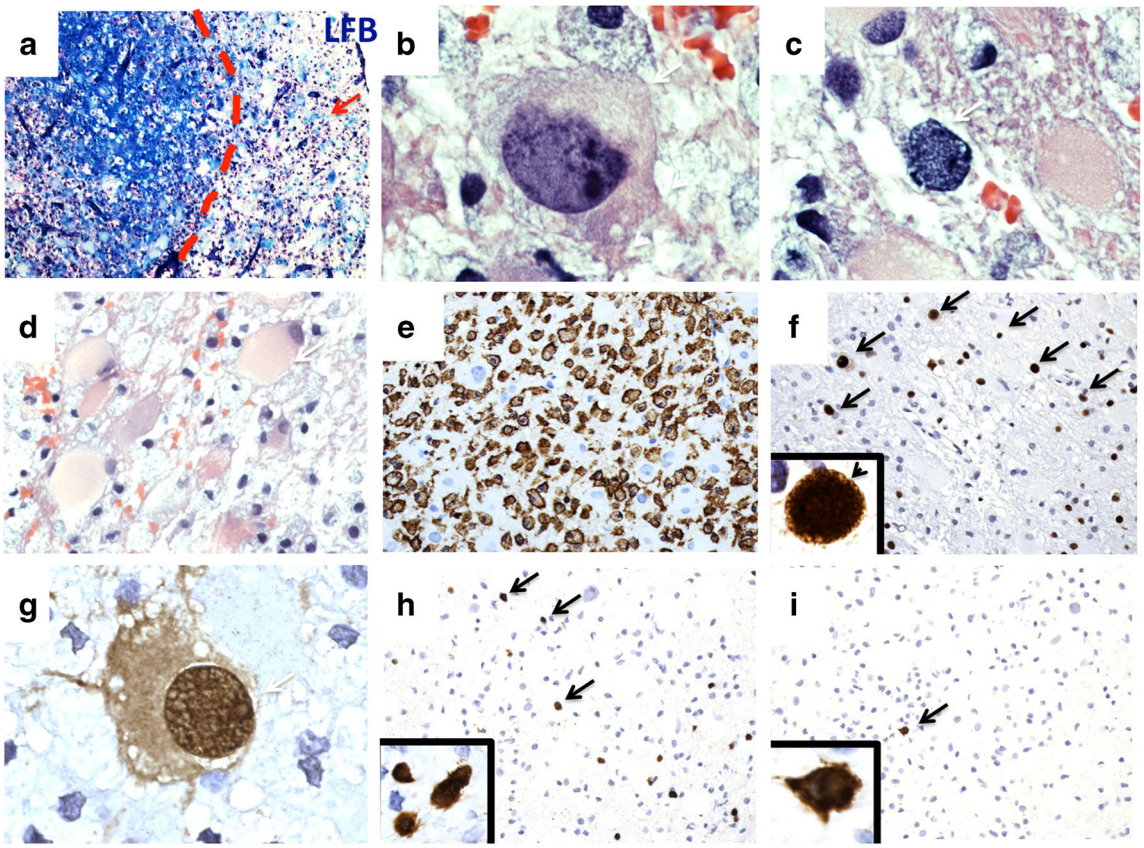

Fig. 2 Pathology findings on brain biopsy. **a** Areas of active demyelination (*dotted red line*) shown as loss of luxol fast blue (LFB) staining in an inflammatory background. **b** Magnified view of a hypertrophic astrocyte and myelin pallor in a lymphocytic background on Hematoxylin and Eosin (H & E) stain. **c** Oligodendrocyte with nuclear viral inclusions (*arrow*). **d** Magnified view of bizarre astrocytes with peripheral nuclei (*arrow*). **e** Intense infiltration of macrophages and microglia demonstrated by CD163 immunoreactivity (brown). **f** Intense SV40 immunoreactivity in rows of multiple cells with small round nucleus typical of oligodendrocytes (*arrows*). **g** Magnified astrocyte with SV40 both in nucleus and cytoplasm (*arrow*). **h** Scattered CD4 staining (*arrows*) and **i** rare CD20 positive B cell (*inset*)

serum immunoglobulins (Haider et al. 2000; Snyder et al. 2005), recent zoster infection (Delgado-Alvarado et al. 2013), and rheumatologic disease with minimal immunosuppressive treatment, as clinical indicators of underlying immune dysfunction that could potentially increase the risk of PML (Calabrese et al. 2007). There has also been one case report of PML in a patient on dimethyl fumarate for 2 years for psoriasis without associated severe lymphocytopenia (Nieuwkamp et al. 2015). Though the lymphocytopenia was only classified as grade I (792 cells/mm^2), and there was no evidence of leukopenia (4000 cells/μL), the duration of lymphopenia was pronounced. Thus, in cases where a clear history of immunosuppression or lymphopenia is absent, continued monitoring of leukocyte and lymphocyte counts could reveal a downward trend indicating a possible risk for developing PML.

Our patient's clinical history and course exhibited none of the above causes of transient immunosuppression. Nevertheless, it could be hypothesized that his history of hypothyroidism and chronic alcoholism might have decreased his immune defenses (MacGregor 1986). However, our patient had no abnormalities on physical exam, CT scan of the abdomen, liver function tests, or coagulopathy labs to suggest cirrhosis or portal hypertension. Nonetheless, it is possible that our patient, despite having no leukopenia or lymphopenia, had a functional immune deficiency that could not be detected using our current diagnostic tests. Two such factors that could have played a role in this functional immune deficiency are interferon gamma and BCL-2-associated athanogene 3. Both of these factors are associated with JCV replication, thus deficiency or mutations of these factors could lead to development of PML in cases without apparent immunosuppression (Van der Kolk et al. 2016).

Although frank immunosuppression highly increases the risk of PML, it may be that mild or transient immune dysfunction impairs the ability to mount a T cell response against the JCV, which can predispose to JCV neurotropic infection (Tan and Koralnik 2010). These observations posit the question whether productive infection requires multiple alterations in the immune surveillance of the JC virus. Differences in the virus infectivity and host immune response may lead to a

variation in the productive infection that leads to rare cases of an already rare disease. JCV exists in two different forms: the one that is transmitted between individuals producing infection during early childhood (archetype) and the one that evolves from the archetype and produces PML (neurotropic). The transformation of this virus to neurotropic is due to mutations or deletions in the noncoding control region (NCCR) that may occur in hematological cells that migrate to the brain (Wollebo et al. 2015). Therefore, a variable degree of dysfunction in the immune surveillance during different aspects of the virus evolution results in transformation and productive infection, which may help to explain rare cases of PML in individuals with no apparent immunosuppression.

In conclusion, the increasing identification of PML in patients without classic immunosuppression, and the recognition of the expanded spectrum of JCV-associated diseases, will increase the early diagnosis and treatment of patients at risk. Clinicians with patients at risk should have a high index of suspicion for JCV-associated disease. Special attention to CD4 and CD8 numbers and MRI imaging looking for features of new T2 hyperintensities and changes in cerebellum is critical. Lastly, JCV PCR in CSF and biopsy can aid in diagnosis. The occurrence of neurological syndromes suggestive of progressive cortical, subcortical, or meningeal symptoms in patients who are immunocompetent yet at high risk should alert clinicians to promptly investigate JCV-associated neurological diseases.

Compliance with ethical standards

Conflict of interest The authors declare that they have no conflict of interests.

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