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CASE REPORT

Progressive multifocal leukoencephalopathy in idiopathic CD4+ lymphocytopenia

Rajeswari Aghoram[1] · Sunil K. Narayan[1]

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Abstract

Progressive multifocal leukoencephalopathy is a central nervous system demyelinating disease caused by infection with John Cunningham virus. It affects predominantly the subcortical white matter, producing progressive neurological deficits and large confluent white matter lesions on imaging. It is usually seen in immunodeficient individuals, such as those suffering from acquired immunodeficiency syndrome, those on treatment with monoclonal antibodies, and those following therapeutic bone marrow suppression. Here, we report a rare case of progressive multifocal leukoencephalopathy in an apparently immunocompetent adult, who was found to have idiopathic CD4 lymphocytopenia upon further investigation.

Keywords Progressive multifocal leukoencephalopathy · Idiopathic CD4 lymphocytopenia · Therapy · Stroke

Introduction

The John Cunningham Virus (JCV) is a ubiquitous human polyoma virus. It has high seroprevalence worldwide, but it is activated only in immunosuppressed patients to produce a devastating central nervous system demyelinating illness known as progressive multifocal leukoencephalopathy (PML) (Viscidi et al. 2011). PML presents with neurological deficits like progressive hemiparesis, ataxia, visual disturbances, and dementia. It is characterized by lytic lesions of myelin-producing oligodendrocytes, which appear as focal demyelination on neuroimaging. Acquired immunodeficiency syndrome (AIDS) is the most common predisposing condition for PML. In the absence of AIDS, PML is most often reported with other conditions, which suppress the immune system like therapy with monoclonal antibodies (natalizumab, infliximab, and rituximab), transplant recipients, and bone marrow suppression (Ferenczy et al. 2012). PML has rarely been reported in patients with minimal or occult immunosuppression. In a series of 38 such patients, Gheuens et al. documented 5 patients with idiopathic CD4 lymphocytopenia (Gheuens et al. 2010). Idiopathic CD4 lymphocytopenia (ICL) is a rare condition, and much of what is known about this condition is from case reports. Only around 18 patients with ICL and PML have been reported in the literature so far. Here, we describe the case of a young man with PML and ICL.

Case study

A 36-year-old man presented to us with a history of acute onset of left-sided weakness 2 months ago. His first magnetic resonance imaging (MRI) revealed T2 hyperintensity in the right parietal subcortical area with no diffusion restriction (Fig. 1a, b). He was a smoker and had recently been diagnosed to be hypertensive. There was no family history of similar illness. He was started on antiplatelet agents and investigated for causes of stroke in the young. His erythrocyte sedimentation rate (ESR) was elevated. An autoimmune antibody profile was negative. His serologies for human immunodeficiency virus (HIV) and syphilis were negative. Lumbar puncture revealed acellular cerebrospinal fluid (CSF) with mildly increased proteins (53 mg%). Vascular imaging including digital subtraction angiography was normal. Over the next few months, he developed progressive left-sided weakness, cognitive dysfunction, anarthria, dysphagia, stridor, and right-sided cerebellar signs. Further worsening resulted in a bedridden

✉ Rajeswari Aghoram
rajeswari.a@gmail.com; rajeswari.a@jipmer.edu

Sunil K. Narayan
sknarayan@gmail.com

[1] Department of Neurology, Jawaharlal Institute of Postgraduate Medical Education and Research (JIPMER), SS Block, D. Nagar, Pondicherry 605006, India

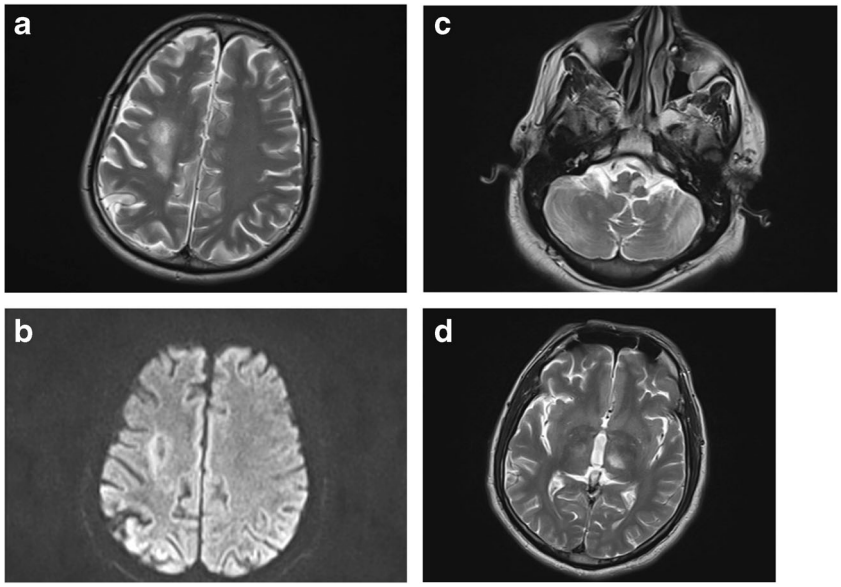

Fig. 1 Serial MRI images. **a**, **b** MRI at first presentation showing T2 hyperintensity right subcortical white matter with no diffusion restriction, contrast enhancement, or mass effect. **c**, **d** Repeat MRI after 7 months showing new T2 hyperintensities in the left medulla and left thalamus after 7 months

mute state within 7 months from onset of illness. Examination revealed a patient who was conscious, mute, and able to follow only simple commands. Left upper motor neuron facial palsy was present, with spasticity of the left upper and lower limbs. The right upper limb was rigid, with coarse tremors. Episodic dysautonomia, characterized by sweating, tachycardia, and tachypnea, was also noted.

Serial imaging showed increasing T2 hyperintensities in the right parietal subcortical region with new lesions in both cerebellar hemispheres, left medulla, both thalami, and internal capsule (Fig. 1c, d). These did not restrict on diffusion or take up contrast, and there was no mass effect. The possibility of mitochondrial or metabolic disorders was considered. A series of investigations including tandem mass spectroscopy were done and found to be normal. Evoked potentials and oligoclonal bands in the CSF were also negative. At this point, PML was considered. CSF was submitted for JC virus polymerase chain reaction (PCR) and a brain biopsy was done simultaneously. PCR was performed using a validated JC virus specific primer (Ramalingam and Chakraborty 2016). This test was positive for JC virus, and the brain biopsy was also reported as consistent with PML. The patient's HIV serology and antigen assay (p24) was repeatedly negative. Underlying occult immunodeficiency was considered. No lymphocytopenia was present (absolute lymphocyte counts 1500–2000), and immunoglobulin (Ig) profile was normal except for elevated IgE. His CD4 count was 110/mm^3. Repeat CD4 count 2 weeks later was 87/mm^3. His CD3 and CD8 counts were 341/mm^3 and 241/mm CD4:CD8 ratio was 0.36. HTLV 1 and 2 serologies were negative. Hence, a diagnosis of idiopathic CD4 lymphocytopenia (ICL) with PML was made.

He was treated with supportive measures including mechanical ventilation. Cidofovir is not available in India and could not be used. Mefloquine was started. The patient's neurological status remained unchanged, until his sudden demise secondary to autonomic dysfunction, 11 months after the onset of illness.

Discussion

In India, diagnosis of PML is rare even in the presence of AIDS. One of the reasons suggested for this is that confirmation of PML diagnosis requires JC virus PCR and/or brain biopsy. In a resource poor setting like India, these techniques are often unavailable (Shankar et al. 2003). In the absence of AIDS, reports of PML are fewer still. One of the rare conditions that can underlie PML in apparently immunocompetent adults is ICL. The rarity of PML with ICL and our resource limited setting contributed to the delayed diagnosis in our patient.

ICL is diagnosed with absolute CD4+ T lymphocyte concentration < 300 cells/mm^3, or < 20% of total lymphocytes at a minimum of two separate time points with no serological evidence of HIV/HTLV infection; and the absence of any defined immunodeficiency or therapy associated with depressed levels of CD4 T cells (Smith et al. 1993). Our patient fit these criteria. ICL is believed to be a heterogeneous condition with uncertain pathogenesis, treatment and prognosis. While some patients with ICL may remain asymptomatic, others may develop life threatening opportunistic infections or autoimmune diseases. Ahmad et al. found 258 case reports of ICL published between 1989 and 2013. Among them most (88%) had at least one infection. They found ten patients with PML (Ahmad et al. 2013).

We were able to identify 18 patients with ICL and PML from the literature (Puri et al. 2010; Izaki et al. 2015; Aotsuka et al. 2016; Gupta et al. 2016; Nambirajan et al. 2017). All

were male, except for one 77-year-old woman. The patients' ages ranged from 30 to 82 years, with a mean of 62 years. Their CD4 counts varied from 87 to 298/mm^3. It is notable that the two cases reported from India (Puri et al. 2010; Nambirajan et al. 2017) and our own patient were relatively young (between 30 and 44 years). Over a variable follow-up period of up to 5 years, four patients died and six showed improvement.

These case reports documented use of methylprednisolone, mirtazapine, mefloquine, cidofovir, interferon, and IL-7. Although in vitro activity against JC virus has been demonstrated for cidofovir, mirtazapine, mefloquine, and interferon, there are only anecdotal reports of drug efficacy in vivo. The best therapy in HIV-associated PML is antiretroviral therapy, resulting in restoration of the immune system. A similar approach has been tried in PML associated with ICL, where IL-7 was given in three patients (Patel et al. 2010a; Alstadhaug et al. 2014; Miskin et al. 2016). IL-7 is believed to act by improving T cell proliferation, restoring T cell homeostasis and augmenting JC virus specific immune responses (Patel et al. 2010b). All three patients improved. In our setting, none of these drugs except mefloquine was available. We did not observe any clinical improvement with the use of mefloquine.

Conclusion

In conclusion, PML should be considered in the differential diagnosis even among apparently immunocompetent patients presenting with progressive neurological deficits and white matter lesions. These patients should be thoroughly investigated for underlying immunodeficiency states including ICL. Emerging therapies like IL-7 may improve the outcome of patients with ICL.

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