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CASE REPORT

Spinal cord progressive multifocal leukoencephalopathy detected premortem by MRI

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Introduction

Progressive multifocal leukoencephalopathy (PML) is a rare and often fatal demyelinating disease caused by JC virus, a ubiquitous polyomavirus that seroepidemiological studies reveal is present in more than 50 % of the adult population (Berger 2014). The rarity of PML indicates that multiple barriers almost certainly exist to its development. Virtually, all predisposing illnesses are associated with an impairment of cell mediated immunity. From the time of its description in 1958 to the onset of the AIDS pandemic, underlying lymphoproliferative disorders, typically B cell diseases, were the most common predisposing disorders for PML (Brooks and Walker 1984). Currently, HIV is the most common predisposing disorder. Prior to the availability of antiretroviral therapies, as many as one in 20 HIV-infected individuals died with PML (Berger et al. 1987) and even in the era of effective antiretroviral therapy, 1.0 % of AIDS deaths are due to PML (Christensen et al. 2010). The gold standard for diagnosis is brain biopsy in which the characteristic histopathological triad of demyelination, enlarged bizarre astrocytes, and enlarged oligodendroglial nuclei can be found, coupled with the demonstration of the presence of JC virus by immunocytochemistry or electron microscopy. However, the diagnosis is more often established on clinical criteria which include an appropriate clinical picture, typical brain MRI findings, and detection of JC virus (JCV) DNA in the CSF by polymerase chain reaction (Berger et al. 2013).

Magnetic resonance imaging in PML typically shows multiple foci of demyelination in the supratentorial white matter, most commonly found in the subcortical parietal lobe. Subcortical lesions are the most common though periventricular lesions can occur as well and are often similar in appearance to multiple sclerosis. Less commonly, infratentorial white matter lesions can be found in the posterior fossa typically involving the middle cerebellar peduncle and cerebellar white matter. Both posterior fossa and supratentorial lesions are typically hyperintense on fluid-attenuated inversion recovery (FLAIR) imaging and do not enhance (Berger et al. 1987). Involvement of the spinal cord in PML is exceedingly rare, especially on imaging. To our knowledge, there has never been a report of spinal cord lesions in PML found on premortem imaging (Berger et al. 1987). In only a handful of cases, autopsies have revealed typical PML lesions in the spinal cord on histology (Yousry et al. 2012).

We present a patient with progressively worsening hemiparesis, ataxia, and diplopia, due to PML associated with idiopathic CD4 lymphopenia resulting in pan lymphocytopenia. Within 6 weeks of presentation, she exhibited extensive infratentorial lesions and a lesion in the cervical spinal cord. To the best of our knowledge, this is the first documented example of PML demonstrated in the spinal cord premortem.

Case report

A 58-year-old female with history of hypothyroidism and hyperlipidemia presented to an outside hospital with sudden onset of right-sided weakness. She fell while playing golf and had trouble articulating words. At the outside hospital, a brain

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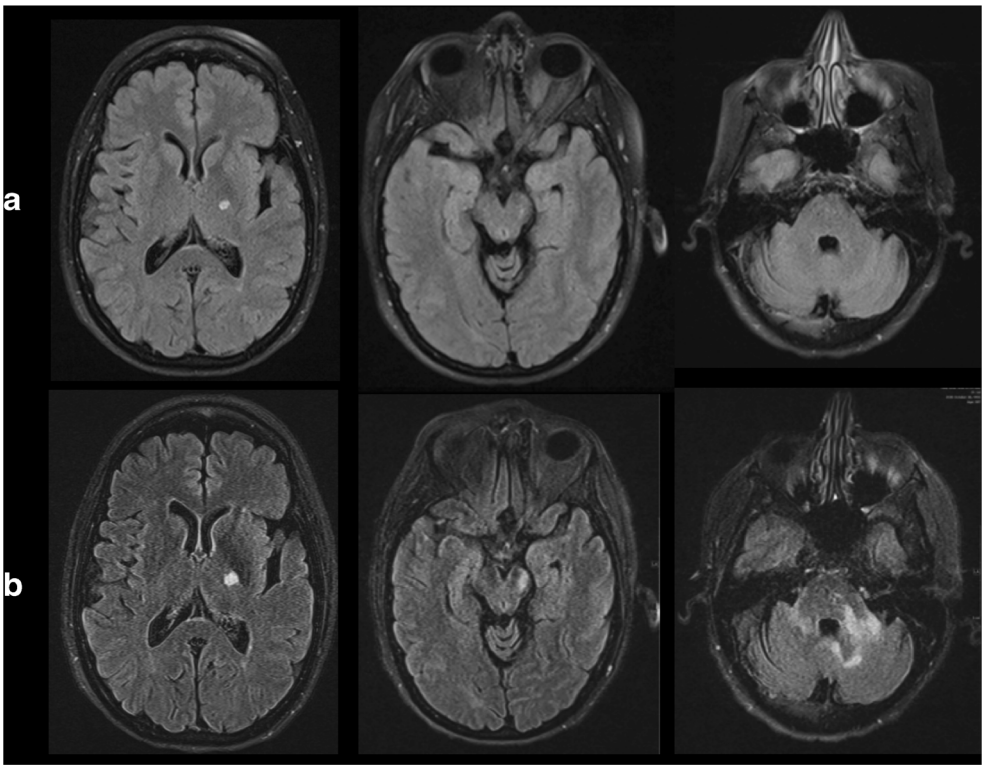

Fig. 1 Progressive brain lesions of PML. Axial FLAIR MR images from the first MRI (**a**) show a lesion in the left thalamus (*left*), but no abnormality in the cerebral peduncles (*middle*) or cerebellum (*right*). Axial FLAIR MR images (**b**) obtained 6 weeks later show slight progression of the left thalamic lesion (*left*), as well as new lesions in the left cerebral peduncle (*middle*) and bilateral cerebellum (*right*)

MRI revealed a small focus of T2 hyperintensity in the left thalamus abutting the internal capsule (Fig. 1a). No additional abnormalities were detected in her brain or cervical spinal cord, and she was diagnosed with a lacunar stroke.

Over ensuing 5 weeks, she continued to worsen, developing right-sided weakness precluding ambulation, diplopia on left gaze, vertigo, and increasing dysarthria. Repeat MRI showed multiple foci of hyperintense signal on FLAIR imaging within periventricular and subcortical white matter, bilateral cerebral peduncles, and left midbrain (Fig. 1b). The original left thalamic lesion had increased in size. The diagnostic impression was primary progressive multiple sclerosis; however, CSF studies, including oligoclonal bands and neuromyelitis optica antibody were normal. Lyme titers, HIV antibody, ANA, and other studies were also negative or normal. There was no improvement following a 7-day course of high-dose intravenous

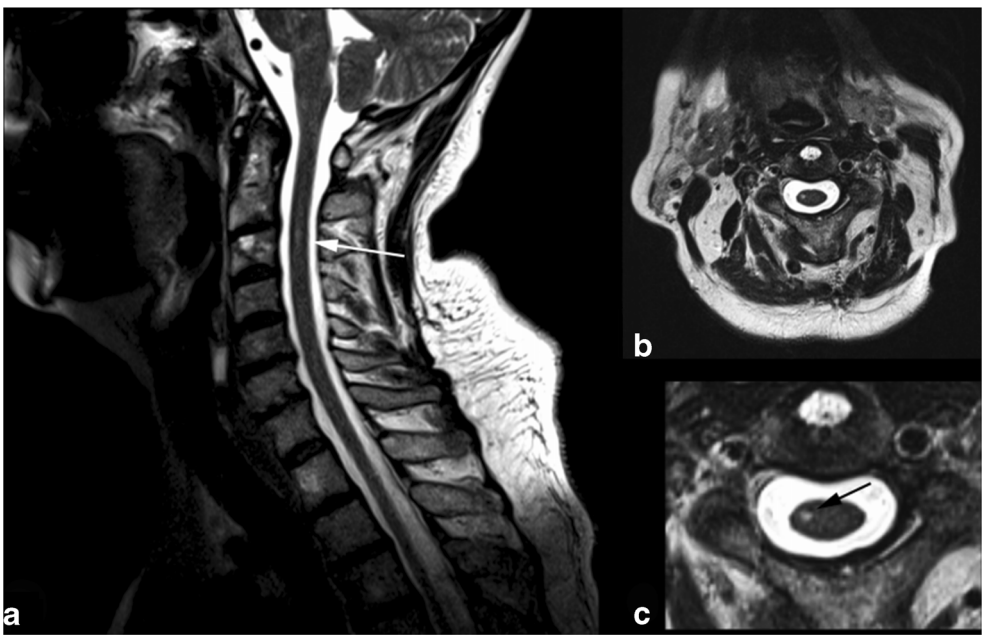

Fig. 2 Cervical cord lesion in PML. The sagittal T2-weighted MR image (**a**) shows a faint intramedullary hyperintense signal focus in the cord at the C3 level (*arrow*). The axial T2-weighted MR image (**b**, magnified in **c**) at this level confirms the lesion in the right lateral cord (see *arrow*, **c**)

methylprednisolone. She was transferred to the Hospital of the University of Pennsylvania 7 weeks from the onset of her illness. At presentation, she had incomplete abduction of the left eye, dysarthria, and severe right hemiparesis (strength 1/5). Repeat brain and cervical spine MRI revealed progression of the lesions, especially in the posterior fossa, and non-enhancing, T2 hyperintense foci in the right spinal cord at the C3 and C4 levels consistent with demyelination (Fig. 2). Repeat CSF studies were remarkable for a positive PCR for JCV DNA. This CSF examination revealed 2 WBCs/uL, protein 37 mg/dL, glucose 70 mg/dL, normal immunoglobulins, and no oligoclonal bands. Herpes simplex virus PCR, immunoglobulins for varicella zoster virus, bacterial and fungal cultures, cryptococcal antigen, and cytology were also negative in the CSF. An effort to determine whether she had an underlying immunological disorder demonstrated a profound lymphopenia with an absolute lymphocyte count of 0.57 cells/μL (normal 1.0–5.0), CD4 count of 137 cells/μL (normal 560–1840), CD8 count of 145 cells/μL (normal 260–1230), and CD3 count of 345 cells/μL (normal 900–3245). HIV antibody was repeatedly negative and additional studies revealed no evidence of malignancy. She was discharged to a nursing home and died shortly afterwards.

Discussion

PML lesions on MR imaging in the brain are typically hypointense on T1 and hyperintense on T2 and FLAIR. Although traditionally described as non-enhancing, the largest series of AIDS-associated PML found that 10 % were contrast enhancing on CT scan and 15 % on MRI (Berger et al. 1998). In natalizumab-associated PML, contrast enhancement is approximately 40 % (Yousry et al. 2012). Lesions are generally multiple, but need not be. They predominate in the parieto-occipital and frontal lobes, but are not uncommonly observed in the posterior fossa (Whiteman et al. 1993). The spinal cord appears to be remarkably resistant to the lesions of PML (Richardson and Webster 1983), although a handful of cases have been previously reported. Generally, these lesions have been small and scanty (Takeda et al. 2008), but more extensive lesions have been described at postmortem examination (Takeda et al. 2008; Bauer et al. 1969; Bernal-Cano et al. 2007; Shintaku et al. 2000; von Einsiedel et al. 1993). All prior reports of spinal cord PML had overwhelming brain involvement; none had recognized clinical features of myelopathy, and none were reported to have MRI abnormalities of the spinal cord (Bauer et al. 1969; Bernal-Cano et al. 2007; Shintaku et al. 2000; von Einsiedel et al. 1993; Takeda et al. 2009). To the best of our knowledge, spinal cord lesions of PML have never been documented by premortem imaging previously. This observation is exceptionally important in the context of natalizumab-associated PML as multiple sclerosis frequently involves the spinal cord, and spinal cord lesions resulting from PML may be overlooked in this context.

Conflict of interest Roger Murayi has no relevant financial interest to declare.

James Schmitt has no relevant financial interest to declare.

John H. Woo has no relevant financial interest to declare.

Joseph R. Berger is or has been a consultant to Genentech, Genzyme, Incyte, Inhibikase, Johnson & Johnson, and Novartis. He serves or has served on the PML Adjudication Committees of Amgen, AstraZeneca, Bristol-Myers Squibb, Eisai, Janssen, Millennium, PAREXEL, Pfizer, Roche, and Takeda, and has received grants from the PML Consortium and Biogen Idec.

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