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Case Report

Spinal cord lesions of progressive multifocal leukoencephalopathy in an acquired immunodeficiency syndrome patient

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Progressive multifocal leukoencephalopathy (PML) is a deadly demyelinating disease of the central nervous system, which occurs in immunosuppressed individuals. This disease is caused by a reactivation of the polyomavirus JC (JCV). Clinical presentation can be variable from patient to patient as lesions can occur anywhere in the CNS white matter; however, they appear to spare the optic nerves and the spinal cord. The authors present a case of PML in the setting of acquired immunodeficiency syndrome (AIDS) who developed PML lesions in the spinal cord, discovered during the postmortem examination. This finding is significant because PML has recently been diagnosed in patients with multiple sclerosis (MS) treated with the novel immunomodulatory medication natalizumab. Indeed, spinal cord lesions are frequent in MS. Therefore clinicians should be aware that in addition to the brain, PML may also affect the spinal cord white matter. *Journal of NeuroVirology* (2007) **13,** 474–476.

Keywords: AIDS; demyelination; HIV; immunosupression; JC virus; multiple sclerosis; progressive multifocal leukoencephalopathy; spinal cord

Introduction

Progressive multifocal leukoencephalopathy (PML) is a demyelinating disease of the central nervous system caused by the polyomavirus JC (JCV). Asymptomatic primary infection is common in childhood and the virus remains quiescent throughout life in up to 86% of adults (Weber *et al*, 1997). Reactivation of the virus occurs most often in the setting of a severe suppression of the cellular immune response such as in patients with hematological malignancies, acquired immunodeficiency syndrome (AIDS), and in organ transplant recipients, resulting in a lytic infection of oligodendrocytes in the central nervous system (CNS) (Koralnik, 2006). More recently, PML has also been diagnosed in three cases of multiple sclerosis (MS) and Crohn's disease treated with the novel immunomodulatory medication natalizumab (Berger and Koralnik, 2005). Differentiating PML from MS lesions on neuroimaging studies may be challenging. PML lesions are often typically located in the subcortical hemispheric white matter. Nevertheless, like MS lesions, they can also involve other areas of the white matter as well as the cerebellum, brain stem, and cerebellar peduncles. Demyelination of axons has also been observed in deep gray structures, including basal ganglia, thalamus, and even cortical gray matter where U fibers may be affected. However, whereas MS frequently affects spinal cord and optic nerves, PML lesions have been seldom reported there (Koralnik, 2006). We present herein the case of an AIDS patient who had a rapid fatal outcome secondary to hemispheric PML, whose postmortem examination also showed PML lesions in the spinal cord.

Case report

A 38-year-old human immunodeficiency virus (HIV)-infected man presented with clumsiness and progressive weakness of the left hand in September 1998.

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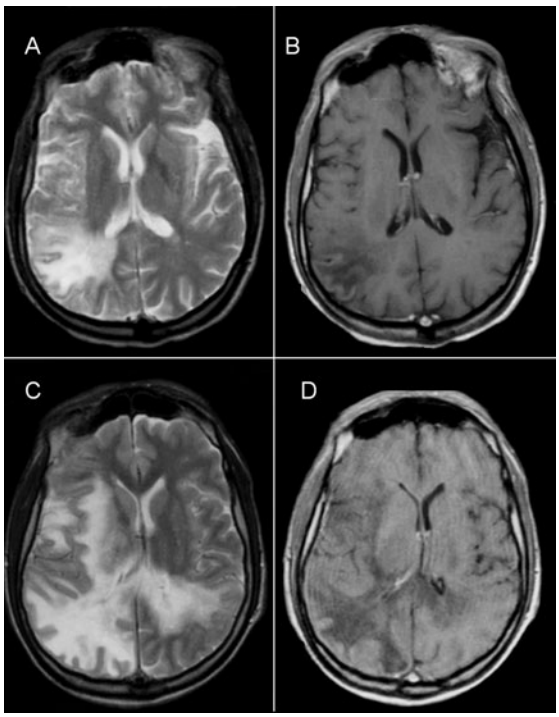

Figure 1 Extensive hemispheric PML lesions in a patient with AIDS. MRI images show right parietal white matter hyperintense lesions in T2-weighted images (**A**) that did not enhance following gadolinium injection on T1-weighted images (**B**). A repeat MRI done 2 months later showed progression of the lesions in the right hemisphere with extension through the splenium of the corpus callosum to the left parietal lobe white matter (**C**). Moderate mass effect is seen on the right lateral ventricle, without evidence of contrast enhancement (**D**).

His $CD4^+$ T-lymphocyte count was 38 cells/μl and the HIV viral load was 13,000 copies/ml; the patient was on ritonavir, zidovudine, and dideoxycytosine. His initial neurological examination showed marked deficit of attention and short-term memory, psychomotor slowing, and left-sided neglect, as well as a left inferior quadrantanopsia, a left central facial palsy, and a left hemiparesis. Head magnetic resonance imaging (MRI) showed a large right parieto-occipital lesion hyperintense in T2-weighted images with no enhancement or mass effect, consistent with PML (Figure 1A and B). He was started on anti-toxoplasmosis therapy and cerebrospinal fluid (CSF) analysis showed the presence of JC virus (JCV) DNA detected by polymerase chain reaction (PCR). Anti-toxoplasmosis therapy was discontinued. Antiretroviral therapy was changed to stavudine, nelfinavir, and dideoxycytosine. Two months later the patient had another brain MRI that showed progression of the lesions in T2-weighted images, with new involvement of the right hemisphere and further extension to the posterior limb of the internal capsule, thalamus, corpus callosum, restiform body, and upper pons. Again no contrast enhancement was seen. (Figure 1C and D) The patient was started on intravenous cidofovir 5 mg/kg weekly for 3 weeks without clinical improvement. He then developed respiratory failure and died 3 months after PML onset.

Neuropathologic examination demonstrated broad involvement of the brain by PML. White matter lesions were characterized by extensive loss of oligodendrocytes, numerous macrophages, and

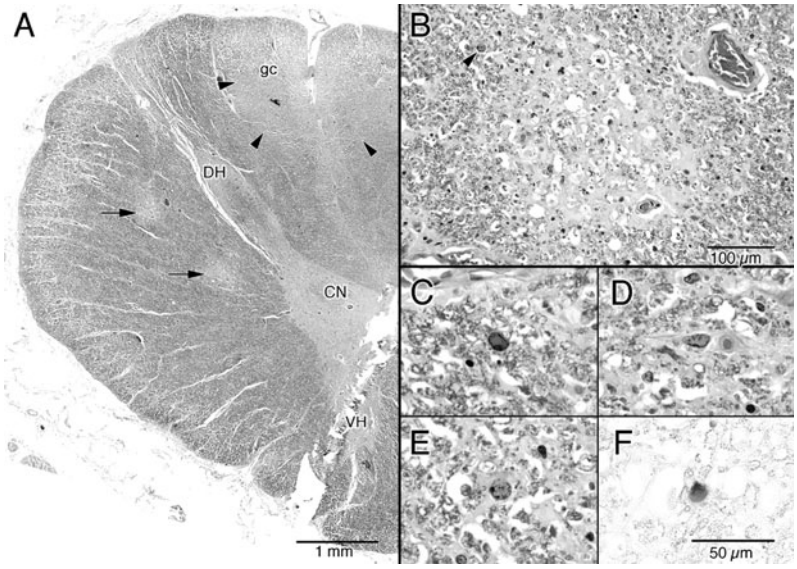

Figure 2 Isolated PML lesions in spinal cord. Pictures in **A** to **E** are hematoxylin and eosin stains with Luxol fast blue (H&E/LFB). (**A**) A field view of the thoracic spinal cord, showing two PML plaques (*arrows*) and the more diffuse wallerian degeneration in the gracilis columns (*arrowheads*). (**B**) A higher magnification view of the upper lesion, showing loss of myelin staining and atypical nuclei in the penumbra (*arrowhead*). (**C–E**) At the highest magnification, the atypical oligodendrocyte nuclei from both lesions show a characteristic spectrum of changes, including enlargement, coarsened chromatin, peripherally marginated chromatin, and glassy central changes. (**F**) Positive immunohistochemistry staining of enlarged, atypical oligodendrocyte nucleus, using an antibody against SV40 that cross-reacts with JCV VP1 major capsid protein (counterstained with hematoxylin). gc = gracilis column; CN = Clarke's nucleus; DH = dorsal horn; VH = ventral horn.

reactive gliosis, including bizarre astrocytes. Oligodendroglial nuclei at the edges of the demyelination had a characteristic spectrum of enlargement, peripherally marginated chromatin, and glassy inclusions. JCV infection significantly involved the brainstem and were found in 2/5 noncontiguous random samples of the thoracic spinal cord (Figure 2A, *arrows*). Spinal cord lesions similarly showed loss of myelin staining centrally (Figure 2B) and characteristic nuclear changes at their periphery (Figure 2C–E). Changes were distinct from the patient's more diffuse and nonspecific wallerian degeneration in his gracilis columns (Figure 2A, *arrowheads*). Enlarged nuclei of oligodendrocytes stained positively by immunohistochemistry with an SV40 antibody, which cross-reacts with JCV VP1 major capsid protein (Figure 2F). These results indicate that these cells were productively infected by JCV.

Discussion

To our knowledge, there are only five published cases of PML wherein the occurrence of independent foci of demyelination in many sites of the spinal cord is described (Bauer *et al*, 1969; Von Ensiedel *et al*, 1993; Shintaku *et al*, 2000). All these cases had PML lesions in the brain and none mentioned clinical symptoms of spinal cord dysfunction, perhaps because of the overwhelming brain involvement by the disease. Finally all those patients were severely immunosupressed in context of AIDS (Von Einsiedel *et al*, 1993), systemic lupus erythematosus, and common variable immunodeficiency (Bauer *et al*, 1969; Shintaku *et al*, 2000). Why PML seems to spare the spinal cord in most cases remains unclear. One hypothesis is that spinal lesions are under diagnosed in patients presenting with florid cerebral symptoms of PML. Another possibility may be that hematogenous spread of JCV favors cerebral over spinal cord seeding, or that immune clearance of the virus may be more efficient in the spinal cord. In any event, our finding is significant in light of the recent development of PML in patients with multiple sclerosis (MS) treated with the novel immunomodulatory medication natalizumab (Langer-Gould *et al*, 2005; Kleinschmidt-Demasters and Tyler, 2005; Berger and Koralnik, 2005). Indeed, spinal cord lesions frequently occur in MS patients. Therefore clinicians should be aware that in addition to the brain, PML may also affect the spinal cord white matter, and should consider this entity in the differential diagnosis of all individuals at risk of PML.

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