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Short communication

Progressive multifocal leukoencephalopathy in an immunocompetent patient

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ABSTRACT

A 69-year old man presents with a subacute history of worsening confusion, anxiety and abnormal gait. Brain MRI revealed an extensive non-enhancing signal abnormality of parieto-occipito-temporal white matter. CSF PCR was positive for JC virus, suggestive of progressive multifocal leukoencephalopathy (PML). Extensive workup for occult immunosuppression was negative. Although PML in an immunocompetent patient is exceedingly rare, biopsy confirmed the diagnosis. Mirtazapine and mefloquine therapies were initiated and JCV DNA titre decreased by 100-fold at six months. One year later, his clinical course had stabilized and neuroimaging was improved. Our case suggests that PML can rarely afflict immunocompetent individuals and that serotonin receptor targeting pharmacological therapy may improve the outcome.

1. Introduction

Progressive multifocal leukoencephalopathy (PML) is a fatal demyelinating disease of the brain caused by JC polyomavirus (JCV) that typically afflicts immunosuppressed individuals. The incidence is estimated at 4.4 cases per 100,000 despite nearly 50–90% of the adult population having antibodies to JCV [1,2]. PML pathogenesis is thought to result from reactivation of latent JCV in patients with profound cellular immune suppression. PML was initially described in patients with hematologic malignancies or systemic inflammatory diseases, but the HIV epidemic has led to a dramatic increase in incidence [1,2]. However, PML in HIV-patients has become increasingly common following increased immunosuppressant use [1,2]. Several medications have been investigated to treat PML, although none have been validated in clinical studies [1,2]. The mainstay of treatment for PML is immune reconstitution; highly active antiretroviral therapy (HAART) for HIV+ patients and discontinuing immunosuppressing agents in HIV-patients [1,2]. Unfortunately, prognosis is poor, with 3-month-mortality rates estimated to be 30–50% [2]. Often treatment is directed at preventing progression of disease rather than reversing deficits. There have been isolated case reports of PML in patients with minimal or occult immunosuppression, and treatment in this population is controversial [3–5]. Here we present the case of a patient with no identifiable immunosuppression who presented with clinical, radiographic, laboratory and histological evidences of PML with a favorable outcome on treatment with mefloquine and mirtazapine.

2. Case report

A 69-year-old Caucasian man with type 2 diabetes mellitus and hyperlipidemia presented to Yale-New Haven Hospital emergency room with confusion and abnormal gait. He had a two month history of worsening anxiety, memory loss, personality changes and odd behavior. On presentation to the emergency room, he was oriented only to person and was unable to answer simple questions or follow commands. He had a wide based, unsteady gait and could ambulate only with assistance. Cranial nerves were intact and the musculoskeletal examination was unremarkable. Vitals were within normal limits, comprehensive metabolic panel and urine toxicology screen were negative. Magnetic resonance imaging (MRI) of the brain demonstrated a prominent non-enhancing signal abnormality with water diffusion restriction involving the left parieto-occipito-temporal white matter with extension into the splenium of the corpus callosum and a satellite lesion in the right parietal lobe (Fig. 1). Multivoxel magnetic resonance spectroscopy of the lesion revealed an increase in the lactate and choline peak and decreased *N*-acetyl-aspartate. Based upon these findings, etiologies including lymphoma, glioblastoma and tumefactive multiple sclerosis were deemed unlikely, and low-grade glioma was suspected.

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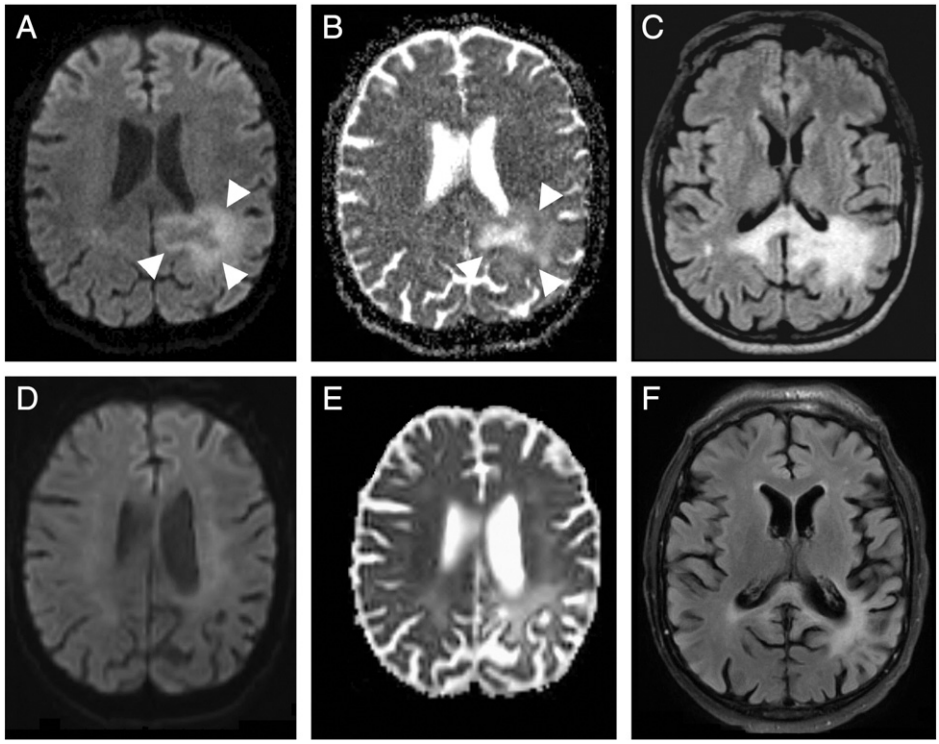

Fig. 1. MRI on presentation (A, B, C) and sixteen months later (D, E, F). On presentation (A, B, C), a large T2/FLAIR (C) hyperintense, non-enhancing lesion was seen involving the left parieto-occipito-temporal region, splenium of the corpus callosum, and the deep white matter of the right parietal lobe. Its margin displayed relative restriction of water diffusion as evidenced by hyperintense signal on diffusion-weighted imaging (A) and iso- to hypointense signal on apparent diffusion coefficient mapping (B), which are characteristics for PML. Follow-up MRI (D, E, F) showed gliosis and encephalomalacia in the area of prior acute infection with hydrocephalus e vacuo (F). There was no restriction of water diffusion noted at the margin, indicating absence of acutely infected oligodendrocytes (D, E).

A lumbar puncture was performed and cerebrospinal fluid (CSF) analysis was unremarkable. Cytology revealed scattered mononuclear cells and small lymphocytes, with no evidence of malignant cells. Fungal and bacterial staining was negative on the smear. Lyme disease, VDRL and cryptococcal studies were negative as were tests for the presence of common viruses. JC virus (JCV) PCR was positive at cycle threshold of 35, which was confirmed at 34.

The presence of JCV in the CSF prompted a full immunological workup. Comprehensive blood count (CBC) revealed a white blood cell count of 10,800 cells/μL with a normal differential. Serum immunoglobulin assay was unremarkable and a T-cell profile was within normal limits. Serum protein electrophoresis revealed a mild hypoalbuminemia (albumin 3.4 g/dL) but no abnormal bands. A comprehensive review of systems demonstrated no previous iatrogenic or pathologic immune compromise.

Given the positive CSF JCV titre and atypical clinical presentation for PML, a stereotactic biopsy of the left parietal occipital area was performed. Histological analysis revealed focal loss of myelin, numerous macrophages as well as reactive astrocytes and microglial cells positive for SV40 protein (Fig. 2), consistent with PML. The patient was started on mefloquine 250 mg for 3 days followed by 250 mg weekly. During his hospital stay, he was seen by psychiatry for recurrent panic attacks and was started on clonazepam (0.5 mg twice daily) and mirtazapine (30 mg daily). Upon discharge, he was oriented only to self, and had an unstable gait, requiring a wheelchair.

One month after discharge, the patient's neurological state remained largely unchanged. Follow-up MRI was performed which revealed some interval progression of the leukoencephalopathy and his mirtazapine was increased to 45 mg daily.

Two months after discharge, he was noted to have right-sided weakness and neglect. Right facial weakness was seen as well as right pronator drift. Mefloquine was discontinued and he was started on cytosine arabinoside (10 mg/kg daily for 5 days).

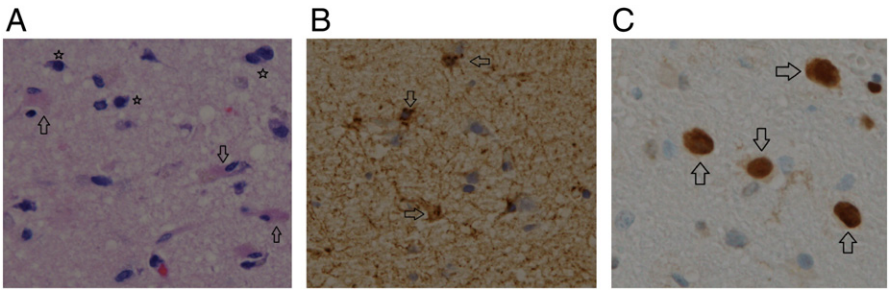

Fig. 2. Left parietal parenchymal biopsy. Hematoxylin & eosin stain (A) of white matter showed focal loss of myelin, numerous macrophages, oligodendrocytes with enlarged nuclei (stars) and bizarre atypical astrocytes (arrows). Immunohistochemistry showed glial fibrillary acidic protein positive reactive astrocytes (B, arrows), and enlarged oligodendroglial nuclei with viral inclusions staining for simian virus 40 (C, arrows).