A young woman with HIV and hemiparesis

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Abstract

Progressive Multifocal Leucoencephalopathy (PML) is a rare and invariably fatal neurological disease that is seen patients with untreated HIV infection and as a complication of immune suppression with agents such as natalizumab. With the increasing occurrence of HIV, it is important to consider this condition in the differential diagnosis of patients with neurological features. We present the case of a young woman with a long history of HIV infection who presented with neurological symptoms; recognition of this diagnosis enabled identification of her poor compliance with treatment. The investigation and treatment of this condition is discussed.

Keywords

HIV, Progressive Multifocal Leucoencephalopathy, neurological, natalizumab, immunosuppressed.

Key Points

1. PML is a demyelinating disease that is usually seen as a complication of advanced, untreated HIV infection.
2. The diagnosis is confirmed by typical imaging findings and the presence of John Cunnigham (JC) virus DNA in CSF.
3. Early recognition is important as it can facilitate suitable interventions early in the course of the illness and improve survival.
4. In patients with HIV who develop PML there is no specific treatment but HAART improves prognosis.

Case report

A 22 year old woman was admitted to hospital with left sided weakness.

She was of Zimbabwean origin and had a background of vertically acquired HIV infection which was diagnosed at the age of 14. Previous complications of her HIV included Pneumocystis Carinii (PCP) Pneumonia in October 2010, oesophageal candidiasis leading to stricture formation and frequent vomiting that needed endoscopic dilatation in March 2010 and CMV retinitis that had led to a partial loss of vision in one eye in February 2011. She had been intolerant to a significant number of highly active anti retroviral therapy (HAART), mostly due to nausea and swallowing difficulties, leading to poor compliance with these drugs. She was also resistant to non nucleoside analogue reverse transcriptase inhibitors (NNRTIs), likely related to non compliance with previous therapy. She had been having difficulty coming to terms with her diagnosis and had a strained relationship with her mother who was healthy on HAART. She frequently missed her HIV clinic appointments.

Her current medications included a combination of the NRTIs zidovudine, lamivudine and abacavir with the integrase inhibitor raltegravir and valganciclovir, co-trimoxazole and fluconazole.

She had developed gradual onset weakness of the left upper limb about 8 weeks before inpatient admission. This manifested mostly as an inability to grasp objects with the left hand and was accompanied by a feeling of numbness in the left upper limb. There were no problems with her gait, and no other focal weakness. She denied headache, neck pain or radicular symptoms, and there was no history of fever or vomiting.

On examination, she appeared alert and comfortable but tended to give only one word answers to most questions. She had a temperature of 37 C, heart rate of 96, blood pressure of 96/56 mmHg and oxygen saturation of 99% when breathing room air. She was frail with a Body Mass Index (BMI) of 15. Neurological examination revealed a pronator drift on the left side with 3/5 power at the elbow and 2/5 distally, but no sensory deficit.

Her CD4 count was 10, and the viral load was 250,000 copies/ ml. Her CRP was <2 and WBC count was 0.9 (Neutrophils 0.4, Lymphocytes 0.1) An MRI scan of the brain revealed bilateral widespread, asymmetric areas of reduced signal on T1 weighted images and increased signal on T2 weighted images, with no contrast enhancement or oedema. These did not conform to a particular vascular territory. (Figure 1)

An MRI of the spine was unremarkable. Lumbar Puncture showed acellular cerebrospinal fluid (CSF) with positive JC virus DNA PCR, confirming the diagnosis of PML.

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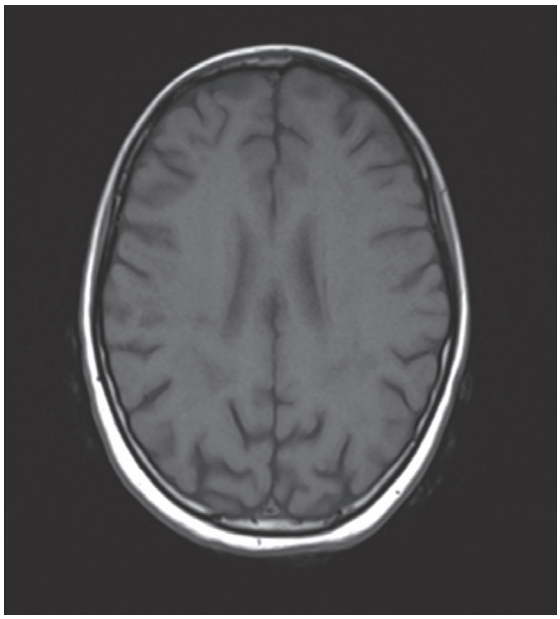


Figure 1. T1 weighted image showing periventicular hypodensities

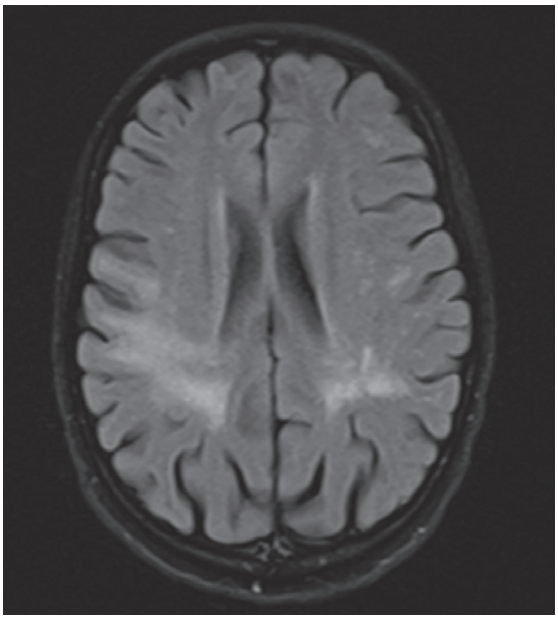


Figure 2. FLAIR- the same areas appear hyperdense

Subsequently, a massive stockpile of HAART drugs (several months' worth) was discovered at her home and in her bedside cabinet, indicating that she had not been taking her prescribed medication. After 4 weeks of supervised treatment in hospital, her viral load had decreased to 1400 from 260,000. Currently, 8 months since the diagnosis, she remains on supervised treatment, although there has been little change in her weakness. She remains ambulant and undergoes periodic oesophageal dilatation for her stricture. Her adherence to treatment has been better since undergoing psychological counselling and an improved relationship with her mother.

Discussion

PML is a disease of the brain resulting from infection of glial cells with John Cunningham (JC) virus in severely immunosuppressed patients and is often fatal[1] with a 3 month mortality rate of 20-50%.[2] Thankfully this condition is now uncommon owing to the success of modern treatment regimens for HIV / AIDS; however this may also mean that many clinicians may be unfamiliar with its features. In this case, recognition of the diagnosis helped to highlight the patient's poor compliance with her treatment, and closer supervision along with a multiprofessional approach to her ongoing care arrested progression of her weakness.

Infection with the neurotropic JC virus, the polyoma virus that causes PML is widespread and acquired during adolescence.[3] Evidence suggests that the initial site of infection is the tonsils, and spread leads to latency within the kidneys and gastrointestinal tract.[4] Studies have shown that 19-27% of healthy individuals excrete JC virus in their urine.[5,6] In the context of profound cellular immunosuppression, the JC virus can reactivate and spread to the brain, where it causes a lytic infection of the myelin producing oligodendrocytes leading to demyelination. The lesions in PML are preferentially localized to the gray-white junction of the cerebral hemispheres.[7]

First described in 1958 in patients with Chronic Lymphatic Leukaemia and Hodgkin's disease,[8] PML used to be a rare condition, seen only in immunosuppressed patients with haematological cancers and organ transplant recipients. With the advent of the HIV/AIDS epidemic, the prevalence of PML increased to as much as 5% in patients with AIDS.[9] Since the widespread use of HAART, the incidence of PML has decreased.[10,11] More recently, the monoclonal antibodies natalizumab, efalizumab, and rituximab—used for the treatment of multiple sclerosis, psoriasis, haematological malignancies, Crohn's disease, and rheumatic diseases—have been associated with PML.[1]

In a recent analysis of 9675 cases of PML using inpatient codes from 1998 to 2005 in the US, 82% had HIV, 8% haematological cancers, 3% had solid organ cancers and under 0.5% had rheumatological diseases.[12] Though typically a condition affecting patients with severe immunosuppression, PML has occasionally been described in individuals with minimal or occult immunosuppression including those with liver cirrhosis and renal failure, and even with no specific underlying diagnosis[13] and should therefore be considered in the differential diagnosis for patients with unexplained neurological features even those who are apparently immunocompetent.[1] When natalizumab is used for multiple sclerosis, the risk of PML is 1.56 cases per 1000 patients with 25-36 infusions.[1]

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The presenting symptoms can vary and, as the name implies, the condition is typically progressive, with multifocal symptoms that may include altered mental status, motor deficits (hemiparesis or monoparesis), limb ataxia, gait ataxia, and visual symptoms such as hemianopia and diplopia.[14] Sensory deficits, cognitive dysfunction and aphasia may occur but the disease does not usually involve the optic nerves or the spinal cord.[1] Seizures can occur in up to 18% of patients.[15] Affected individuals with HIV generally have CD4 counts < 200 per mm.[3]

The diagnosis of PML can be made on clinical and radiological grounds and confirmed by the detection of JC virus DNA in CSF.[14] The 'gold standard' for diagnosis is by brain biopsy, which has a sensitivity of 64-96% and specificity of 100%.[14] However, this procedure carries significant risk of morbidity (8.4%) and mortality (2.9%) in patients with HIV.[16] Further, some patients may be unable to tolerate the procedure and lesions may be inaccessible.[14]

The typical appearance of PML on neuroimaging is of symmetric or asymmetric multifocal areas of white matter demyelination that do not conform to cerebrovascular territories and exhibit neither mass effect nor contrast enhancement.[14] MRI is the imaging modality of choice and PML lesions appear hypointense in T1 weighted sequences and hyperintense on T2.[17]

Interestingly, studies have shown that detection of JC virus DNA by PCR in blood correlates with immunosuppression but not with PML. On the other hand, the presence of JC virus in the CSF is highly sensitive and specific for PML[18] and CSF PCR for JC virus carries a sensitivity of 74-93% and specificity of 92-99%.[19] However, It must be emphasized that a negative test for JC virus DNA in CSF does not exclude the diagnosis of PML. False negative results may result from differences in PCR protocols amongst laboratories, and genome variability.[20] Sensitivity of PCR testing for patients with a clinical presentation of PML who are on HAART can be as low as 57.5%.[21] Based on a consensus for PML terminology, these patients should be considered as "possible PML" cases and managed accordingly after exclusion of other conditions like HIV encephalopathy, lymphoma and toxoplasmosis.[22]

Differential diagnosis

When patients with HIV present with neurological deficit, it is important to consider a wide differential diagnosis (see Table 1). In patients with HIV and CD4 counts < 200, this includes HIV encephalopathy, primary CNS lymphoma (PCNSL) and toxoplasma encephalitis (TE). Lesions in the HIV Encephalopathy tend to be symmetric and periventricular, and associated with an increased CSF viral load. This may present with cognitive impairment but no focal deficit. PCNSL can present with similar symptoms as PML but MRI shows cortical involvement, oedema and diffuse post-contrast enhancement. TE presents more acutely with headache, altered mental state and focal features/ seizures. Lesions may involve the posterior fossa and usually tend to be multiple, ring enhancing with oedema. Lesions over 4 cm in size, and those that are callosal or periventricular are more likely to represent PCNSL than TE.[14]

Treatment and prognosis

Usually, the clinical outcome of patients with PML is poor with an inexorable progression to death within 6 months of symptom onset.[24] In patients without HIV infection, median survival is only 3 months.[14]

There is no specific antiviral drug against the JC virus.[1] Reconstitution of the immune system with HAART affords the best prognosis for this condition. Several case series have shown prolonged survival for patients receiving HAART.[24] JC Virus DNA load in cerebrospinal fluid has been found to be

Table 1. Differential Diagnosis of Neurological Deficit in patients with HIV.

	Onset	Features	MRI	CSF
PML	weeks	Focal deficits	Asymmetric, circumscribed white matter lesions with no oedema/ mass effect	Pleocytosis and raised protein JC virus DNA
PCNSL	weeks	Fever, wt loss Focal deficits, seizures	May be > 4 cm, single or multiple, ring enhancing with oedema/ mass effect	Pleocytosis and raised protein Positive cytology in 15%
TE	days	Fever, headache, focal signs	Usually multiple, ring enhancing lesions with oedema/ mass effect	Pleocytosis and raised protein
HIV encephalopathy	weeks	Cognitive impairment	Symmetric and poorly demarcated, periventricular	Increased CSF HIV viral load

PCNSL: primary CNS lymphoma; TE: toxoplasma encephalitis

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a strong predictor of patients' survival and HAART leads to a partial immune-mediated control of JCV replication.[25] Studies have found that survival in HIV infected patients with PML can go up from 66 days without HAART to 245 days with treatment.[26] One year survival has increased from 10% before HAART to 50% with HAART.[14] In a case series of 118 patients from Spain, almost 64% survived for a median of 2.2 years.[27] A third of the patients died despite HAART. Of the remainder, over half (40 patients) remained stable neurologically and just under half (33 patients) improved. A large Swiss cohort study found that PML attributable mortality had fallen from 82.3 deaths per 100 per year during the pre HAART era to 37.6 in the HAART era.[10]

Some patients, particularly those who display a marked increase in CD4 counts in response to HAART, may develop the Immune Reconstitution Inflammatory Syndrome (IRIS) due to an inflammatory reaction in PML lesions as demonstrated by contrast enhancement on MRI due to breakdown of the blood-brain barrier.[28] Time of onset can range from 1 to 104 weeks after starting HAART.[29] The development of IRIS does not appear to alter survival in PML[30] and it is treated with high-dose steroids without interruption of HAART.[14]

Various agents have been used in studies to treat PML, without success. These include the antiviral drug cidofivir, which conferred no survival benefit in a multi-cohort analysis,[31] the chemotherapeutic drug cytarabine (shown to inhibit JC virus replication in vitro) which showed no benefit in a randomised controlled trial,[32] and the serotonin receptor blocker mirtazepine which again showed no survival difference in a cohort study.[33] The antimalarial drug mefloquine has some anti-JCV activity in vitro but a randomised controlled trial evaluating it was stopped before completion as the drug failed to reduce levels of JCV in CSF.[34]

Natalizumab associated PML is treated by discontinuation of the drug and plasma exchange accompanied by treatment with mirtazepine. IRIS is likely to develop in these patients in 3 to 6 weeks and is treated with high dose steroids.[14]

Declaration of competing interests: Nothing to declare

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