CASE REPORT

Rapidly progressive cerebellar ataxia in West Wales

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SUMMARY

Progressive multifocal leucoencephalopathy (PML) is a severe demyelinating disease of the central nervous system that is caused by the JC virus infection. It is often fatal or severely disabling. PML exclusively happens in the context of cell-mediated immunosuppression. Prior to the era of HIV, PML was mainly confined to patients with haematological malignancies and rheumatological diseases. The HIV epidemic in the early eighties led to massive expansion in the incidence and prevalence of the disease. PML has also been recognised to happen due to treatment with monoclonal antibodies such as natalizumab, which is used as a disease-modifying agent for relapsing remitting multiple sclerosis and other monoclonal antibodies used in dermatological and haematological conditions. The clinical picture is that of cognitive decline, visual disturbance and hemiparesis. The correct clinicroadiological picture combined with demonstrating the JC virus DNA in the cerebrospinal fluid (CSF) using PCR (PMR) is enough to establish the diagnosis. Brain biopsy is rarely needed. Immune reconstitution represents the mainstay in the treatment of PML. We present a case of a 47-year-old man who presented with progressive cerebellar ataxia. Investigations confirmed PML. He was found to be HIV positive. We also review the literature.

BACKGROUND

Progressive multifocal leucoencephalopathy (PML) was a rare neurological disease, which was mainly confined to people with impaired cell-mediated immunity secondary to haematological and rheumatological conditions, with the arrival of the HIV epidemic in the 1980s and the use of monoclonal antibodies to treat conditions such as multiple sclerosis and other medical conditions, PML gained considerable attention. The clinical picture is that of cognitive decline, visual disturbance and hemiparesis. The correct clinicroadiological picture combined with demonstrating the JC virus DNA in the cerebrospinal fluid (CSF) using PCR (PMR) is enough to establish the diagnosis. Brain biopsy is rarely needed. Immune reconstitution represents the mainstay in the treatment of PML.

We present a case of a 47-year-old man, who presented with progressive cerebellar ataxia. Investigations confirmed PML. He was found to be HIV positive.

HIV test should be considered in all patients with an atypical neurological presentation.

CASE PRESENTATION

A 47-year-old man was referred to the neurology department with a 6-week history of gait disturbance and clumsiness. He had initially noticed some

difficulty with his balance while dancing at a party, and over the next 2 weeks became aware that he was bumping into doors and walls. He attended his local hospital at this point and an MRI scan of the brain was performed. Following this, he developed progressive unsteadiness. Over the week prior to admission there was a marked deterioration in his clinical condition with worsening balance to the extent that he was unable to stand, severe slurring of his speech and double vision.

He had no medical history of note and was not on any medication. There was no significant family history. He was a keen surfer, and had travelled extensively. He stopped smoking 2 years ago and drank 6 units of alcohol daily.

On examination, he had a wide-spread erythematous scaly rash, suggestive of seborrhoeic dermatitis all over his body, the rest of his general examination was normal. His neurological examination showed bilateral gaze evoked nystagmus with upbeat nystagmus of the right eye. He had limited abduction of the right eye. He had a prominent cerebellar dysarthria and a severe truncal ataxia which rendered him bedbound. He had an asymmetric limb ataxia, being more prominent on the right. He had no other neurological abnormality.

INVESTIGATIONS

Full blood count, urea and electrolytes, liver function and thyroid function test were normal, he had a normal chest X-ray, his inflammatory markers were not raised with normal plasma glucose level. A repeat MRI scan of his brain was performed and compared with the original (figure 1).

His first MRI scan showed an area of signal change in the right cerebellar peduncle, being hyperintense on the T2 and fluid-attenuated inversion recovery (FLAIR) sequences, and hypointense on the T1-weighted imaging. The lesion showed a mild mass effect with some effacement of the right side of the fourth ventricle. Despite increased signal on the diffusion-weighted images, the ADC findings were not consistent with restricted diffusion. The lesion did not enhance. His second MRI scan showed an obvious progression with enlargement of the lesion on T2 and FLAIR sequences.

CSF examination showed 15 lymphocytes with CSF glucose 3.7 mmol/L with paired plasma glucose 5 mmol/L and CSF protein 0.37 g/dL. CSF oligoclonal bands were positive. Other neuroinflammatory blood tests were normal or negative (box 1). HIV test was positive. HIV viral RNA load was found to be 281 911 IU/mL with CD4 count of $84 \times 10^9/L$. JC virus DNA PCR demonstrated 1670 copies/mL in the CSF.

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Figure 1 MRI of the brain T2 and fluid-attenuated inversion recovery (FLAIR) sequences (A and B) at 2 and weeks from onset (C and D) at 6 weeks. The scans demonstrate a lesion at the right cerebellar peduncle, the lesion shows increased signal at the T2 and FLAIR sequences. There is clear progression at 6 weeks images.

TREATMENT

He was treated with highly active antiretroviral therapy (HAART), his immune system recovered with drop in his viral load and raise of his CD4 count (figures 2 and 3).

OUTCOME AND FOLLOW-UP

His recovery so far has been complicated by an aspiration pneumonia, which required admission to the high dependency unit. Currently, 6 months following admission, he is slowly making some neurological recovery in a neurological rehabilitation unit. He is dysarthric with gaze-evoked nystagmus to the right with right-sided abducent nerve palsy, peripheral and central ataxia.

Box 1 The following blood test were either negative or normal

- ▶ FBC, U&E, LFTs, glucose
- ▶ CRP1, ESR 23
- ▶ B12, Folate
- ▶ TSH, Free T4
- ▶ ANA, ANCA, ENA
- ▶ Anti-cardiolipin antibodies
- ▶ C3, C4
- ▶ LDH
- ▶ Anti-Hu, Anti-Yo, Anti-Ri

ANA, antinuclear antibody; ANCA, antineutrophil cytoplasmic antibody; CRP, C reactive protein; ENA, extractable nuclear antigen; ESR, erythrocyte sedimentation rate; FBU, full blood count; LDH, lactate dehydrogenase; LFTs, liver function tests; TSH, thyroid stimulating hormone.

Figure 2 HIV viral RNA load: the graph demonstrates dramatic drop in the HIV viral load immediately after starting highly active antiretroviral therapy (HAART).

Figure 3 CD4 count: the graph showing improving CD4 count over the course of treatment with highly active antiretroviral therapy (HAART).

He can walk using a walking frame. Seborrhoeic dermatitis is known to happen in association with HIV infection.

DISCUSSION

PML is a severe, often fatal, demyelinating disease of the central nervous system that is caused by the JC virus. PML was first described in 1958 in two patients with haematological malignancies who developed severe progressive neurological disease leading to death.¹ It took until 1971 to isolate the JC virus in fetal brain cell cultures.² It is a small human polyomavirus, which is species specific, found only in humans, hampering efforts to study the virus in animal medium.³

Up until the 1980s PML mainly occurred in patients with profound immunosuppression, with hematological malignancies, solid tumours, systemic lupus erythematosus and rheumatoid arthritis all being associated with PML. The HIV epidemic led to a vast increase in the incidence and prevalence of the disease. In a large epidemiological study in the USA, 9675 cases of PML were analysed from 1998 to 2005; 82% were associated with HIV, 8.4% with haematological malignancies, 2.83% with solid tumours and 0.44% with rheumatological diseases.⁴

PML is thought to happen as a reactivation of a latent JC virus infection. The primary infection is probably caught in childhood. The method of transmission is not well established, but respiratory or gastrointestinal transmission has been suggested. After the initial infection which can cause mild respiratory illness, the virus remains dormant in the kidney epithelial cells, lymphoid tissue, bone marrow and possibly the brain cells.⁵ It is thought that conditions, which can lead to severe defects of the cellular-mediated immunity can lead to the

reactivation of the virus. The seroprevalence of the virus is variable depending on the technique used and the population studied. It is probably between 30% and 80% of the population.^{6–12}

PML is now being recognised to affect an increasingly variable population. In 2005 during the SENTINEL trial, where natalizumab (a monoclonal antibody) and Avonex were used as disease modifying agents for relapsing remitting multiple sclerosis, two patients developed PML.^{13 14} Another patient who was given natalizumab for Crohn's disease also developed PML.¹⁵ Since then a total of 305 cases with 66 fatalities have been reported.¹⁶ Other monoclonal antibodies were also reported to cause PML including rituximab,¹⁷ used to treat haematological malignancies and efalizumab,¹⁸ used to treat psoriasis.

As the name implies, PML is mainly a disease of the white matter, and the clinical manifestations are dependent on the location of the lesions. PML is not known to affect the optic nerves or the spinal cord. Although isolated lesions can occur, PML tends to be multifocal. There are some clinical and radiological differences between PML with HIV (classic PML) and natalizumab associated PML. The onset is subacute with a combination of cognitive and behavioural decline associated with motor weakness, language disturbance and visual symptoms.^{19–25} Interestingly seizures have been reported in 18% of patients. This is thought to be due to lesions very close to the grey matter and the U fibres.²⁶ In the case of natalizumab-associated PML, differentiating PML from multiple sclerosis symptoms can be challenging. A high index of suspicion is needed. Table 1 below shows the common symptoms associated with classic PML and natalizumab-associated PML.

The MRI findings in classic PML are of multiple lesions, typically affecting the white matter of the cerebral hemispheres, the U fibres, cerebellar peduncles and deep grey matter of the basal ganglia and the thalami, with no respect to vascular territory. The lesions look hyperintense on T2 and FLAIR images and hypointense on T1 images. They do not exhibit oedema, mass effect or gadolinium enhancement. On the other hand, in natalizumab-related PML, 30–40% of the patients show gadolinium enhancement, which is thought to be due to the ongoing host immune reaction against the JC virus.^{20–25 27 28}

The diagnosis of PML can be established by the detection of the JCV DNA in the CSF using PCR. The sensitivity of this test varies according to the laboratory, ranging between 75% and 95% with a specificity of 92–100%.^{23 25 29} The viral copy load in the CSF might be low, particularly in monoclonal antibody-associated PML, leading to a negative PCR test, and if the clinical suspicion is high, the PCR test should be repeated. JC virus antibodies in the CSF tend to be higher than in the blood indicating that these antibodies are produced from the CSF and are not crossed from the blood. This is called a high antibody index. This, combined with the classic clinicoradiological features and in the absence of alternative diagnosis, is sufficient to make the diagnosis of PML. Rarely the diagnosis can be established by the demonstration of JCV DNA or proteins by insitu hybridisation or by immunohistochemistry staining on brain biopsy. PML is the only human central nervous system demyelinating disease where there is a clear characteristic pathological agent. Pathologically there can be a varying degree of demyelination ranging from myelin pallor to severe demyelination associated with swollen oligodendrocytic nuclei, with bizarre-looking astrocytes.^{20 23–25}

Treatment trials of antiviral therapy with cidofovir, cytarabine, interferons, mirtazapine and mefloquine have all proved

Table 1 Clinical features of HIV-PML (classic PML) and natalizumab-associated PML²⁵

HIV-PML	Natalizumab-PML
<ul style="list-style-type: none"> ▶ Weakness 42% ▶ Speech abnormalities 40% ▶ Cognitive abnormalities 36% ▶ Gait abnormalities 29% ▶ Sensory loss 19% ▶ Visual impairment 19% ▶ Seizures, diplopia, limb incoordination ▶ Cerebellar features 	<ul style="list-style-type: none"> ▶ Cognitive features 48% ▶ Motor abnormalities 37% ▶ Language disturbance 31% ▶ Visual defects 26%

PML, progressive multifocal leucoencephalopathy.

disappointing. The mainstay of treatment involves reconstitution of the immune system, either through the use of HAART with a high CSF penetration score such as zidovudine and nevirapine in patients with HIV, or by stopping the responsible monoclonal antibody in monoclonal antibody-associated PML. The effect of natalizumab on the cell-mediated immune response can last for up to 3 months after stopping it because the antibody adheres itself to the $\alpha 4$ subunit of the adhesion molecule $\alpha 4 \beta 1$ integrin, leading to a continued immunosuppressive effect. Plasma exchange can be used to rapidly clear the natalizumab from the plasma.^{19 21–23}

Immune reconstitution can lead to a hyperimmune inflammatory reaction against the JC virus and the demyelinating lesions, known as immune reconstitution inflammatory syndrome (IRIS). IRIS develops within 1–109 weeks following treatment with HAART or stopping natalizumab. Those patients normally show a paradoxical deterioration of their PML symptoms despite apparently improving immunological status and reduction in the viral load. MRI changes in PML IRIS suggest enlarging PML lesions with mass effect and gadolinium enhancement leading to brain swelling, herniation and even death. The treatment of IRIS is difficult; steroids can be used in case of natalizumab-related PML, while in HIV cases, the risks of stopping antiretroviral treatment need to be balanced against the possibility of reactivation of the HIV virus.^{21–23}

PML is considered a fatal disease, in the era before the HAART, median survival rate was 3 months. This improved to 1.8 years after the introduction of HAART in 1996, with reports of many patients living an extended life.^{20 22} Remission of HIV-related PML has been reported.³⁰

Learning points

- Progressive multifocal leucoencephalopathy (PML) is a rare fatal demyelinating central nervous system disease.
- Patients with impaired cell-mediated immunity are at a high risk of PML.
- HIV test should be performed on patients with an atypical neurological presentation.

Contributors All the authors were involved in writing the case report and the subsequent discussion. KWA did the literature search. KGY and RP were the consultants looking after the patient.

Competing interests None.

Patient consent Obtained.

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