

# A Case of Progressive Multifocal Leucoencephalopathy

Progressive multifocal leucoencephalopathy (PML) can present as an unusual complication of immunosuppressive states other than human immunodeficiency virus (HIV) infection. We present a case of PML affecting a patient with chronic lymphatic leukaemia (CLL), previously treated with chlorambucil. The case highlights the need to maintain a high index of suspicion in immunocompromised patients presenting with central or peripheral progressive neurological signs.

## Case report

A 61-year-old man was referred from an ophthalmology outpatient clinic complaining of progressive visual loss, affecting his right visual field, over the previous two to three weeks and occasional headaches, described as a pressure sensation over the occipital region. He was systemically well and denied any motor, sensory, sphincter, speech or cognitive symptoms. He had been diagnosed with CLL two and a half years previous following a routine blood test for an upper respiratory tract infection. Treatment started one year after diagnosis when his white cell count peaked at  $112.7 \times 10^9/l$ . He achieved remission after six courses of chlorambucil (10mg daily for 10 days, each) and prednisolone but had to be restarted on the same regime again one year later. Chlorambucil had been stopped two months prior to the current admission. He also had a past medical history of peptic ulcer disease and hypothyroidism.

On examination, his visual acuity was 6/36 on the right and 6/24 on the left, with a dense right-sided hemianopia involving the macula. His optic discs were pale and pupillary responses were normal. The remainder of the cranial nerve examination was normal. Motor examination revealed increased tone and reflexes in both lower limbs with sustained ankle clonus on the right and an extensor right plantar response. Sensation was preserved. On general examination, lymphadenopathy affecting the left supraclavicular area, both axillae and the inguinal region and a moderate splenomegaly were noted.

His white cell count on admission was  $150 \times 10^9/l$  with a predominant lymphocytosis ( $141 \times 10^9/l$ ), a haemoglobin of 14.7g/dl and a platelet count of  $117 \times 10^9/l$ . The remainder of his blood biochemistry, including creatinine, liver function tests and LDH was normal.

The initial differential diagnosis included an infiltrating occipital lesion, either CLL or a secondary neoplasm, or an opportunistic infection.

Magnetic resonance imaging (MRI) of the brain revealed bilateral high  $T_2$  signal in the occipital white matter, more on the left than the right, also involving the corpus callosum (Figure 1). The radiological differential diagnosis included progressive multifocal leucoencephalopathy (PML), reversible posterior leucoencephalopathy and infiltration with lymphoma. CSF examination was undertaken, showing less than five white cells per  $mm^3$ , no red cells, a protein of 0.56 g/l (normal range: less than 0.65g/l), glucose 4.5 g/l, normal cytology and negative oligoclonal bands.

The patient underwent a trial of dexamethasone for six days and was then re-imaged with Gadolinium. Repeat MRI remained unchanged.

Viral PCR for HIV, cytomegalovirus (CMV), Epstein-Barr virus (EBV), varicella zoster virus (VZV), herpes simplex virus (HSV) and human herpes virus (HHV)6 was negative but JC virus (JCV) polymerase chain reaction (PCR) of the CSF yielded a positive result, establishing the diagnosis of PML.

Management of JCV was discussed with infectious dis-

eases specialists and haematologists. Owing to the rarity of the disease in non-HIV patients, the patient was subsequently tested for HIV 1 and 2 antibodies, both of which were negative.

Following reports of success with a combination of mirtazepine and cytosine arabinoside,<sup>1</sup> oral mirtazepine was started but had to be discontinued after one week, due to confusion and the antimetabolite cytosine arabinoside was not added, as his CLL did not require any treatment at that stage. Meanwhile, his visual acuity had deteriorated and rendered him functionally blind. A trial of cidofovir was commenced (four doses). Two induction doses of 5mg/kg iv were administered, one week apart, without clinical improvement. The last two doses were not administered, as the patient's cognitive state rapidly declined with aggressive behaviour and confusion and he was transferred to a hospice for terminal care, where he died three months after the onset of his visual loss.

## Discussion

Progressive multifocal leucoencephalopathy (PML) is an acquired demyelinating disorder of the CNS caused by the human papovavirus JC,<sup>2</sup> which is invariably fatal. PML has been described as a complication of various conditions which result in impaired cellular immunity, including lymphoproliferative disorders,<sup>2</sup> chronic granulomatous disorders such as sarcoidosis, iatrogenic immunosuppression,<sup>3</sup> cancer chemotherapy and autoimmune disorders.<sup>4,5</sup>

The case presented is unusual in that PML is rare in patients not affected by the human immunodeficiency virus (HIV). Since the onset of the AIDS epidemic in 1981, the incidence of PML has increased significantly and now HIV-associated cases account for up to 85% of all cases of PML.<sup>2</sup>

Clinically, PML usually presents as a progressive neurological deficit resulting in a monoparesis, hemiparesis or ataxia. However, the disease is not restricted to cerebral white matter and may present, although less commonly, with cortical deficits such as dysphasia, seizures and hemianopia,<sup>2</sup> as in this case. Typically, patients do not exhibit signs of raised intracranial pressure or sepsis.

Lymphoproliferative diseases and immunosuppressive treatment are two independent risk factors in the development of PML. Reports describing CLL as the only predisposing factor for PML are rare. Two of the earliest reported cases of PML were described in two CLL patients



**Laura Mantoan** is an SHO in Neurology at Frenchay Hospital, Bristol. Born in Italy, she graduated in Austria, where she completed an MD investigating caspase inhibition in a rat model for Multi System Atrophy. As an SHO, she trained in Bristol and Cambridge. Her special interests lie with epilepsy, cognitive neurology and neurophysiology.

## Correspondence to:

L Mantoan,  
119 North Rd,  
Bristol,  
BS6 5AH, UK.  
Email: lauramantoan@  
doctors.org.uk

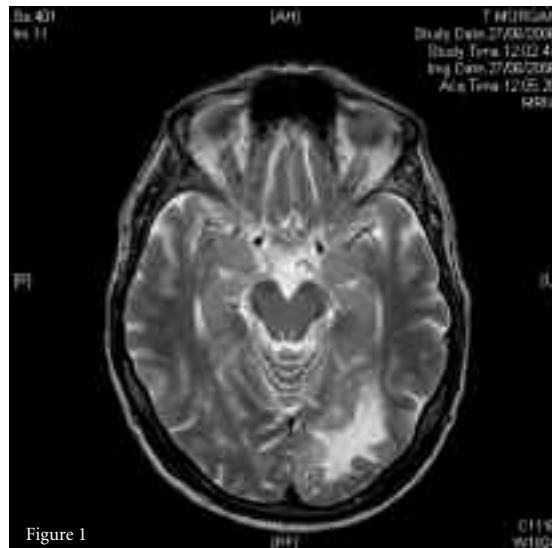


Figure 1

in the 1930s<sup>6</sup> and a more recent German case describes a 44-year-old patient with CLL and secondary antibody deficiency syndrome presenting with dysarthria and left-sided hemiparesis. In this case papova-like virions were found in glial cells on electron microscopy.<sup>7</sup>

Whereas PML as a consequence of fludarabine treatment is encountered relatively frequently in the literature,<sup>8,10</sup> there are only a few case reports linking treatment with chlorambucil and PML.<sup>5,11</sup> The reasons behind this may be twofold: fludarabine is becoming the initial therapy for low-grade lymphoproliferative malignancies such as CLL and follicular lymphoma, thus replacing chlorambucil.<sup>12,13</sup> Secondly, fludarabine is more toxic than chlorambucil; patients receiving single-agent flu-

darabine have more severe neutropaenia, more major infections and herpes virus related infections compared with chlorambucil-treated patients.<sup>14,15</sup>

It is possible that PML develops in patients with CLL due to a combination of primary CLL-related immunosuppression worsened by iatrogenic immunosuppression with cytotoxic drugs and prednisolone.

Diagnosis of PML can be difficult, particularly in cases presenting in unusual ways and where the index of suspicion is low. Before the AIDS epidemic, a definitive diagnosis of PML was only possible by brain biopsy.<sup>2</sup> Serological tests for the JC virus are not useful as 80-90% of the population will have been exposed to the virus in childhood. CSF identification of JC virus by DNA

amplification techniques is useful. Polymerase Chain Reaction (PCR) has a sensitivity of 95% and specificity of 90-99%. MRI findings are typical in this condition, with a high T<sub>2</sub> signal and a low T<sub>1</sub> signal, which does not enhance with gadolinium and has no mass effect.

PML should be considered in all patients with an underlying disease process associated with altered cell-mediated immunity. Despite cessation of the immunosuppressive agent and treatment, the prognosis remains poor. Since the AIDS epidemic, however, the increase in numbers of patients with PML has led to significant progress in research into the pathophysiology of PML.<sup>16,17</sup> This will hopefully be of benefit to both HIV and non-HIV patients affected by this devastating disease.

## References

- Vulliemoz S, et al. *Favourable outcome of progressive multifocal leucoencephalopathy in two patients with dermatomyositis*. JNNP 2006;77:1079-82.
- Manji H, Miller RF. *Progressive multifocal leucoencephalopathy: progress in the AIDS era*. J Neurol Neurosurg Psychiatry 2000;69:569-71.
- Review of progressive multifocal leucoencephalopathy and natalizumab*. Neurologist 2006 Nov;12(6):293-8.
- White R P, et al. *Progressive multifocal leucoencephalopathy isolated to the posterior fossa in a patient with systemic lupus erythematosus*. Rheumatology 2002;41:826-7.
- Sponzilli EE, et al. *Progressive multifocal leucoencephalopathy: a complication of immunosuppressive treatment*. Neurology 1975 Jul;25(7):664-8.
- Åström et al. *Progressive Multifocal Leuco-Encephalopathy a Hitherto Unrecognized Complication of Chronic Lymphatic Leukaemia and Hodgkin's Disease*. Brain 1958;81(1):93-111.
- Hofeler H, et al. *Progressive multifocal leucoencephalopathy. Late complication in chronic lymphatic leukemia*. Dtsch Med Wochenschr. 1987;Jun12;112(24):963-6. [Article in German].
- Brynjar V, et al. *Progressive multifocal leucoencephalopathy after fludarabine therapy for low-grade lymphoproliferative disease*. Am J Haematol 2002;70(1):51-4.
- Saumoy M, et al. *Progressive multifocal leucoencephalopathy in chronic lymphocytic leukemia after treatment with fludarabine*. Leuk Lymphoma. 2002Feb;43(2):433-6.
- Cid J, et al. *Progressive multifocal leucoencephalopathy following oral fludarabine treatment of chronic lymphocytic leukemia*. Ann Hematol 2000Jul;79(7):392-5.
- Hahn J S, et al. *Progressive Multifocal Leucoencephalopathy in a 15-Year-Old Boy With Scleroderma and Secondary Amyloidosis*. Pediatrics 1998;102(6):1475-9.
- Rai R K, et al. *Fludarabine Compared with Chlorambucil as Primary Therapy for Chronic Lymphocytic Leukemia*. NEJM 2000;343:1750-7.
- Leporrier M. *Role of fludarabine as monotherapy in the treatment of chronic lymphocytic leukemia*. Hematol J. 2004;5Suppl1:S10-9.
- Intergroup Study Cancer and Leukemia Group B 9011. *Impact of Therapy With Chlorambucil, Fludarabine, or Fludarabine Plus Chlorambucil on Infections in Patients With Chronic Lymphocytic Leukemia*. Journal of Clinical Oncology 2001;19(16):3611-21.
- Chlorambucil Is Still an Appropriate First-Line Therapy for Chronic Lymphocytic Leukaemia*. Drug Ther Perspect 2001;17(20):8-12.
- Progressive multifocal leucoencephalopathy in a haploidentical stem cell transplant recipient: A clinical, neuroradiological and virological response after treatment with risperidone*. Antiviral Res. 2006Nov27;[Epub ahead of print].
- Martinez J V, et al. *Immune reconstitution inflammatory syndrome associated with PML in AIDS: A treatable disorder*. Neurology 2006;67:1692-4.