

## Progressive multifocal leukoencephalopathy in an immunocompetent patient: A case report

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### Abstract

Progressive multifocal leukoencephalopathy (PML) is a progressive lethal demyelinating disease of the brain, caused by JC virus. Reactivation of JC virus due to reduction of cellular immunity especially in setting of AIDS, is the commonest underlying cause. PML has classically been described in individuals with profound cellular immunosuppression such as patients with AIDS, haematological malignancies, organ transplant recipients or those treated with immunosuppressive or immunomodulatory medications for autoimmune diseases. Rarely it has also been diagnosed in cases with no or minimal immunosuppression. Here, we report a 50 year-old man who presented with sudden onset multiple neurologic deficits. Neuroimaging, histopathology, and virology studies confirmed the diagnosis of PML. We could not however demonstrate any underlying immunodeficiency state. Our case suggests that absence of immunodeficiency does not exclude the possibility of PML and should be considered in immunocompetent patients with a typical clinical course and neuroimaging findings.

### INTRODUCTION

Primary infection with JC virus is usually asymptomatic. Progressive multifocal leukoencephalopathy (PML) is a rare, progressive and lethal demyelinating disease of the brain, caused by JC virus.<sup>1</sup> The term PML was first used in 1958 to describe extensive demyelination in brain associated with haematological malignancies.<sup>2</sup> PML is usually seen in patients with severe deficits in cell mediated immunity. AIDS is the commonest underlying cause (82%), followed by haematological malignancies (8%), solid organ transplants (3%), rheumatological diseases (0.44%), and immunosuppressive drugs.<sup>3,4</sup> However recent reports have revealed that transient or mild failure of cellular immunity might be sufficient for JC virus reactivation.<sup>5</sup> We report a case of PML in a 50 years old, immunocompetent male patient who presented with sudden onset neurological deficits.

### CASE REPORT

This fifty years old male presented with slurring of speech for 4 months, followed by sudden worsening for the last 2 weeks, with reduced word output, speaking in monosyllables, using gestures for communication, with relatively preserved comprehension. This was associated

with weakness of both hands, especially in performing fine work and difficulty in initiating gait with tendency to fall, without any weakness or gross incoordination. He also had coughing and choking while swallowing, especially with liquids. There was also change in behavior, with inappropriate laughter and crying spells and episodes of voiding in clothes.

There was no history of headache, vomiting, fever, loss of consciousness, seizure, visual symptoms, sensory complaints, delusions, or hallucinations. Patient had completed 6 months antitubercular therapy for pleural effusion 4 months back. No other significant past or personal history was obtained.

His general examination was normal. On neurological examination he was conscious, had reduced attention span, was slow to respond, with pseudobulbar affect. His speech was dysarthric, nonfluent, speaking in monosyllables, with impaired naming, reading and writing, but with relatively intact comprehension and repetition. His detailed higher mental function evaluation was not possible to perform. He also had slow saccades, optic ataxia, oculomotor apraxia, right UMN facial palsy, slow tongue movements, brisk gag, and jaw jerk. Motor examination revealed generalized hypertonia and hyperreflexia (right more than the left). Detailed sensory and cerebellar

examination was not possible. Gait was wide based with difficulty in initiation and turning. Other systems were normal.

His cerebrospinal fluid examination (CSF) was normal. MRI brain revealed diffuse mild cortical atrophy with multiple large areas of altered signal intensity appearing hypointense on T1W, hyperintense on T2W and FLAIR images, in subcortical white matter, right frontal, bilateral temporoparietooccipital and bilateral gangliothalamic complexes with minimal contrast enhancement. (Figure 1, 2)

The differential diagnoses of PML and central nervous system lymphoma were considered and he was subjected to stereotactic brain biopsy. Histopathology showed collection of foamy macrophages in the white matter with reactive astrocytosis. Some oligodendrocytes were enlarged with intranuclear inclusion. There were foci of demyelination with perivascular T lymphocytic cuffing. The cortex did not show any pathology. These findings were consistent with those of PML, and his brain tissue was positive for JC virus.

There was no history suggestive of immunocompromised state, even after detailed review of history. Routine blood investigations including haemogram, total and differential white blood cell count, erythrocyte sedimentation rate, peripheral smear, blood sugar, liver and renal function, serum proteins including globulins were all normal. HIV ELISA and Western blot done thrice were nonreactive. His absolute CD4+ cells count was 552/mm<sup>3</sup> (400 – 1600), absolute CD8+ cells count was 365/mm<sup>3</sup> (220 – 1300), and CD4+/CD8+ ratio was 1.5 (0.9- 1.9), which were all normal. Other investigations including immunoglobulin levels, HBsAg, HCV-RNA, VDRL, ANA, RA factor, ultrasonography of the abdomen with pelvis, X-ray chest, were all normal.

The patient was diagnosed as PML in an immunocompetent state. During the hospital stay the patient's clinical condition deteriorated as he became mute, akinetic, incontinent and was bedridden. He was given a trial of pulse therapy of injection methyl prednisolone for 3 days, and his clinical condition stabilized. After 4 weeks of hospital stay he was discharged on oral steroids in the same neurological status. He died after one month of discharge with pneumonia as a probable cause of death.

## DISCUSSION

PML typically presents with incoordination, motor

weakness, visual deficits, confusion, dementia and personality changes. Less common features include speech disturbances, seizures, vertigo and headache.<sup>6</sup> Histopathology shows multiple demyelinating foci in the cerebral, cerebellar, and brainstem at the gray-white matter junction. In severe cases confluent lesions, inflammatory infiltrates, necrotic and cystic lesions may be present. Nuclear inclusions containing viruses may be seen in large ballooned oligodendrocytes. The CSF picture in PML patients is normal in the majority except slight protein elevation.<sup>5</sup> MRI brain shows single or multiple confluent T2 hyperintense lesions in subcortical white matter predominantly in parietooccipital area or cerebellar peduncles; without edema or contrast enhancement. Rarely gray matter structures such as the basal ganglia, thalamus and spinal cord may be involved.<sup>7</sup>

The definitive diagnosis is by DNA PCR for JC virus in CSF or brain tissue, which has a sensitivity of 74-92% and specificity of 92-99%. There is no specific treatment for PML. A few antiviral, immunosuppressive, and immunomodulatory medications have been tried without much success. Role of steroids in treatment of PML is unclear except some beneficial effect in inflammatory PML (IRIS-PML).<sup>8,9</sup>

In a review of 38 cases of PML with minimal or occult immunosuppression by Sarah *et al*<sup>5</sup> 19 (50%) patients were HIV negative, CD4 count was found to be low in 5 and normal in 9 cases; in the other 5 cases, CD4 count was not done. The remainder 19 (50%) cases were not tested for HIV and CD4 count. The common underlying medical conditions were idiopathic CD4+ T-lymphocytopenia (ICL), chronic liver and renal disease. Psoriasis, Sjogren's syndrome, dermatomyositis, sarcoidosis and pregnancy were also postulated to be associated with mild immunocompromised state. The clinical, histological, radiological and CSF picture of PML in immunocompetent patients is similar to that of classical PML associated with immunocompromised states.<sup>7</sup>

In patients with HIV associated PML the median survival time has increased from 0.4 years in pre HAART era to 1.8 years in post HAART era.<sup>10</sup> The outcome of patients with HIV-negative PML has not been evaluated. In a recent review of PML associated with minimal immunosuppression, the outcome was fatal in 27 out of 38 cases (71.1%) within a period of 1.5-120 months (median 8 months).<sup>5</sup> The survival rate (71%) has been better in cases of PML associated with natalizumab use, probably reflecting early diagnosis and the ability

to achieve immune reconstitution. Many of the patients who survived (20 out of the total 28) however had serious morbidity and substantial and permanent disability. Prognosis may be related to the location of lesions and JC viral titres in the CSF.<sup>11</sup>

The clinical, radiological and histopathological findings in our patient confirmed diagnosis of PML. The only associated medical illness in our patient was pulmonary tuberculosis. Whether or not tuberculosis was responsible for reactivation of JC virus in our patient is not clear. Also this case highlights the fact that clinical profile, CSF, neuroimaging, histopathological picture as well as prognosis of PML is similar in immunocompetent and immunocompromised patients.

In conclusion, our case suggests that absence of immunodeficiency does not exclude the possibility of PML, and should be considered in immunocompetent patients with a typical clinical course and neuroimaging findings.

## DISCLOSURE

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