Progressive Multifocal Leukoencephalopathy – As A Presenting Manifestation of AIDS


Abstract
Progressive multifocal leuкоencephalopathy (PML) is an opportunistic demyelinating disease caused by the ubiquitous, usually non pathogenic JC Polyomavirus. We report a case of PML as a presenting manifestation of AIDS in a forty five year old man on the basis of clinical features and neuroradiology.

INTRODUCTION
Progressive multifocal leuкоencephalopathy (PML) is a demyelinating disease of central nervous system. It is caused by JC virus, a human Polyomavirus (DNA virus) belonging to Papovaviridae group. PML is the result of reactivation of latent JC virus infection in the setting of cellular immunodeficiencies. Cases associated with HIV account for 85 % of all cases. PML is the only known clinical manifestation of JC virus infection. There is lysis of myelin producing oligodendrocytes. Perivascular inflammation is usually absent. Usually the outcome of patients of PML is poor with an inexorable progression to death within six months of symptom onset. Experimental treatments such as cytarabine, interferon or cidofovir have either failed to show any clinical benefit or their efficacy remains to be confirmed by randomized trials. In a cohort of HIV infected patients with recorded PML, significant survival benefit from highly active antiretroviral therapy (HAART) has been shown. This case is presented to enlighten the physicians regarding the clinical entity of PML to be suspected in HIV infected patients who present with focal neurologic deficits. To the best of our knowledge PML as a presenting manifestation of AIDS is not reported from Indian literature.

CASE REPORT
A forty five year old orchardist/horticulturist, right handed man was admitted in medical ward with two months history of progressive neurologic symptoms manifesting as dysarthria, ataxia, memory loss and delirium. Patient was apparently normal two months back when he developed slurring of speech. After a week patient started having difficulty in walking in the form that he used to sway to either side. He had a progressive decline of memory for recent as well as past events as narrated by attendants. For the last one day patient was having altered sensorium in the form of aggression, agitation and abnormal behaviour with history of urinary and fecal incontinence. There was no history of any motor weakness or sensory loss. No history suggestive of cranial nerves involvement. There was no history of seizures, fever, vomiting, headache, head injury, jaundice and ear discharge. There was no history of any prior medical illness. He was a smoker and a social drinker. He was married and having two children. On examination patient was afebrile. He was agitated, uncooperative and disoriented to time, place and person. Cranial nerve examination was normal. Speech appeared to be slurred. He was moving all the four limbs spontaneously. The tone and deep tendon reflexes were normal. The plantar reflex was bilaterally extensor. The patient was responding to painful stimulus. There were no meningeal signs present. Skull and spine examination was normal. Rest of the examination was normal.

The treatment records revealed that patient had attended medical OPD after becoming symptomatic and was advised CT head plain and contrast which showed hypodense area in left parietal region, left temporal region, which were nonenhancing after intravenous contrast (Fig. 1). Patient was thereafter started on statins and antiplatelets. One week later MRI Brain (plain) was also done from OPD which revealed multifocal poorly defined hyperintense lesions in left posterior temporoparietal subcortical white matter, left calcarine cortex and right thalamus on T2W and FLAIR images. No mass effect seen. The lesions were hypointense in T1W images (Fig. 2). The lesions were of undetermined nature. No further investigation were recommended and patient was continued on statins and antiplatelets.

The laboratory investigation after admission showed normal hemogram and biochemistry. CSF analysis revealed normal biochemistry and cytology. CSF was VDRL nonreactive as well as negative for cryptococcal infection. CSF was also found negative for tubercular antigen by

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polymerase chain reaction.

Contrast enhanced MRI brain done on second day of admission revealed asymmetrical, diffuse subcortical white matter demyelination without mass effect and contrast enhancement. The lesions were hypointense on T1W images, hyperintense on T2W images and on FLAIR images (Fig. 3a, 3b). Compared to previous MRI study of one and a half month earlier significant progression of the lesion was noted. MR spectroscopy revealed markedly reduced N-acetylaspartate (NAA) peak and increase in choline peak. The NAA/Creatine ratio was 1.45, the Choline/Creatine ratio was 1.34 and Inositol/Creatine ratio was 0.64 (Fig. 4). There was increase in lactate and lipid peaks.

Patient was a horticulturist and frequently traveled throughout major Indian metros so was tested for HIV infection by ERS (ELISA, rapid and simple) method and found HIV positive. CD4 count of the patient was 28/mm$^3$. Facilities of PCR for JC virus in CSF were not available. In view of above clinical features and investigations, patient was diagnosed to have progressive multifocal leukoencephalopathy. Patient was started on HAART along with prophylaxis of opportunistic infections.

**DISCUSSION**

Progressive multifocal leukoencephalopathy (PML) was first diagnosed by a German neuropathologist, Hallervorden.
<table>
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<th>CNS Involvement</th>
<th>Clinical Features</th>
<th>CT/ MRI</th>
<th>Investigations CSF</th>
<th>Serology</th>
<th>Other</th>
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<tr>
<td><strong>Toxoplasmosis</strong></td>
<td>Symptoms and signs both diffuse and focal. Focal neurological signs (69%), headache (55%), confusion (52%), seizures (29%). The meninginal signs are present in 30% cases. Presentation may be subtle and nonspecific, including malaise, fever, nausea &amp; vomiting, accompanied by headache. Less frequent are cranial nerve palsies, psychiatric abnormalities, speech disturbance &amp; seizure.</td>
<td>Single or multiple ring enhancing lesions of cortex and deep grey matter MRI more sensitive. Often shows more lesions than CT.</td>
<td>Nondiagnostic. Can be normal, show mononuclear pleocytosis and elevated protein.</td>
<td>Serum antitoxoplasma antibodies by ELISA or IFA</td>
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<td><strong>Cryptococcus</strong></td>
<td>Presents as subacute meningitis. Headache &amp; fever (65-90%), acute confusion (20%), seizure/focal deficit (&lt;10%). The meninginal signs are present in 30% cases.</td>
<td>Normal or only atrophy</td>
<td>Normal / mononuclear pleocytosis, elevated agglutination. high opening pressure.</td>
<td>CRAG (CSF Cryptococcal Antigen) by Latex</td>
<td>- CSF India Ink staining - CSF culture</td>
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<td><strong>AIDS Dementia Complex</strong></td>
<td>Subcortical dementia. Symptoms are cognitive, motor &amp; behavioural: Cognitive-forgetfulness associated with slowed motor and mental abilities, loss of balance, leg weakness. Behavioural apathy, social withdrawal, organic psychosis. Absence of focal neurological deficit.</td>
<td>Cortical atrophy, Enlarged ventricles. Diffusely, symmetrical decreased attenuation of deep white matter, involves periventricular areas and do not involve arcuate (U) fibres. Lesions are isointense on T1W images. On MR spectroscopy NAA and NAA/Creatine is decreased and Choline/Creatine significantly increased.</td>
<td>Normal cytology and biochemistry</td>
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<td><strong>CNS Lymphoma</strong></td>
<td>Confusion, lethargy, memory loss, headache, focal neurological signs like hemiparesis, hemisensory loss, ataxia and aphasia. Seizures are less common.</td>
<td>Single or multiple contrast enhancing lesions. Primary CNS lymphoma can be indistinguishable radiologically from toxoplasmosis, however, a single lesion on MRI with negative antitoxoplasmal antibody favour lymphoma</td>
<td>Mild pleocytosis, protein elevation. Tumor cells identified in &lt; 25%</td>
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<td>Definitive diagnosis is by biopsy</td>
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<td><strong>CNS Tuberculosis</strong></td>
<td>The spectrum of presentation varies from acute, subacute to chronic. The symptoms due to associated tuberculoma are fever, altered sensorium, headache, seizures and behavioural changes. The signs are of meningeal irritation, papilloedema, cranial nerve palsies, hemiplegia. Hydrocephalus is common. Generally HIV status does not alter the clinical manifestation.</td>
<td>Thickening and enhancement of basal meninges, hydrocephalus, infarction, edema (often periventricular) and mass lesions or tuberculosis abscess. Common sites of exudates are basal cisterns. MRI is superior to CT scan in detection of basal meningitis and small tuberculomas.</td>
<td>Predominantly lymphocytes, predominant of neutrophils in the early stage, raised protein, low glucose. Normal CSF is more frequent in HIV+ve cases. AFB seen on direct smear of CSF sediment in 20% cases CSF culture diagnostic upto 80% cases.</td>
<td>Mycobacterial antibody by ELISA, radio-immunoassay and immunoblot Mycobacterial antigen by ELISA and latex agglutination PCR in CSF.</td>
<td>CXR consistent with pulmonary TB in 25-50% cases.</td>
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<td><strong>PML</strong></td>
<td>Focal neurologic deficit with rapid progression of symptoms</td>
<td>Focal, discrete, asymmetrical hypointensity of lesions on T1W and hyperintense on T2W &amp; Flair images with involvement of the subcortical arcuate (U)</td>
<td>Normal cytology and biochemistry.</td>
<td>Detection of JC virus by PCR in CSF.</td>
<td>Definitive diagnosis by brain biopsy.</td>
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in 1930. It was described as a syndrome in 1958 by Astrom and Richardson and identified as a viral disease in 1965 by ZU-Rhein. The JC virus was isolated in 1971 by Padgett and Walker which is a DNA containing Polyomavirus.1 Seroepidemiologic studies show that infection with the JC virus is common and usually occurs during childhood. The JC virus has been shown to persist in the kidneys and is shed in the urine. More than 80% of the human adult population is seropositive for JC virus specific IgG antibodies.3,4 Despite this high prevalence of infection, JC virus induced disease is rare, occurring almost exclusively in immunosuppressed individuals.6 Since the onset of 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.1,2 PML has been estimated to affect 4% of patients with HIV infection.3 India has over 5 million people living with HIV/AIDS at present. The expected incidence of PML in Indian HIV infected population should be significantly large. But PML is uncommon in India and was reported only in three recently diagnosed patients with AIDS from a neurological centre in India.5 Limited data is available regarding true incidence of PML while studying neurological manifestation of HIV disease in Indian literature.6 Thorat et al found PML in 3.9% of patients while studying neurological manifestation in patients having HIV infection.7 The non AIDS population affected by PML is middle aged and usually harbors either an underlying lymphoproliferative, myeloproliferative, granulomatous disorder or is receiving immunosuppressive therapy.1 The neurologic signs and symptoms of PML result from the viral destruction of the myelin producing oligodendrocytes in the CNS. The main pathologic features are atypical astrocytes with enlarged multilobulated nuclei and intranuclear inclusions in oligodendrocytes which are JC virus particles on in situ hybridization.1 The clinical feature are of progressive focal neurological dysfunction. Commonly aphasia/dysarthria, monoparesis, hemiparesis, ataxia, cortical blindness or visual field defects are reported. Mental status changes like confusion, dementia and even coma are seen. Seizures are infrequent (< 10%). There are no clinical features of raised intracranial pressure or of systemic infection.1

The CSF biochemistry and cytology is normal. In CSF, detection of JC virus by PCR is diagnostic. The sensitivity is 70 % and specificity is 90-100 %. In negative PCR for JC virus repeat CSF examination or brain biopsy is advocated which is confirmatory for diagnosis.1 Recent improvements in newer imaging techniques like MR spectroscopy are replacing the older invasive methods for diagnosing PML.3,8 In the appropriate clinical setting MRI brain has following characteristic features. The lesions are focal, discrete and asymmetrical if bilateral. They are predominantly subcortical white matter lesions involving arcuate (U) fibres. The lesions spare periventricular regions and are dominantly located in parieto-occipital lobes. The lesions are hypointense on T1W and hyperintense on T2W and FLAIR images. Typically no mass effect is seen and contrast enhancement is rare. Both cortical and subcortical atrophy is not seen.3 On MR Spectroscopy there is decreased N-acetylaspartate (NAA) with significantly decreased NAA/Creatine ratio with increased choline and increased lactate peak.3,8 The common differential diagnosis5,10 of PML are presented in Table 1.

Currently there is no proven therapy for AIDS related PML. Cytosine arabinoside either intravenous or intrathecally did not improve the prognosis of patients with PML. Studies with subcutaneous use of interferon-α have not shown clinical improvement.

Cidofovir (an antiviral agent with activity against JC Virus) appears to have no additional benefit over HAART administration alone. HAART at present is the most effective treatment for PML. It is postulated that HAART reduces the viral load and thus improving the immune function.1

**Summary**

PML is a fatal demyelinating CNS infection disease that exclusively affects immunocompromised individuals. JC virus, the etiologic agent for PML is ubiquitous in the general population but rarely cause disease in immunocompetent hosts. PML is most commonly seen in patients with a known diagnosis of AIDS, but it can be the presenting AIDS defining illness. Diagnosis can be confidently made on clinico-neuroradiologic basis. MRI brain and MR spectroscopy assume diagnostic significance in the appropriate clinical setting of PML where facilities for JC virus isolation by PCR are not available.

**REFERENCES**


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**Announcement**

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Venue: Le Meridien Hotel and International Convention Centre, Maradu, NH Bypass, Kochi.
Dates: 10th to 13th January 2008

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