

# Progressive Multifocal Leukoencephalopathy Associated with Pulmonary Tuberculosis in an Immuno-Compromised Indian Patient

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## Abstract

We present here a case of progressive visual loss and convulsions in a 45 year old male immuno-compromised patient with pulmonary tuberculosis. He was subsequently diagnosed as Progressive Multifocal Leukoencephalopathy (PML) based on Magnetic Resonance Imaging, cerebrospinal fluid and clinical findings.

**Keywords:** PML; HIV; AIDS; Tuberculosis

## Introduction

Progressive Multifocal Leukoencephalopathy (PML) is a rare syndrome which occurs in immune-compromised patients in about 2 to 5% of the cases. It occurs almost exclusively in people with severe immune deficiency, such as transplant patients on immunosuppressive medications, those on certain kinds of chemotherapy, receiving natalizumab for multiple sclerosis, on long-term efalizumab for psoriasis, brentuximab for Hodgkin's Lymphoma or those with Acquired Immuno Deficiency Syndrome (AIDS) [1-3]. The causative agent of the disease JC virus belongs to papovavirus family which has been divided into polyomavirus and papillomavirus. JC Virus is a Polyomavirus (JCPyV). Tuberculosis is another disease of major public health problem in India. Both these diseases namely HIV and tuberculosis are immune suppressive in nature. In this unique case report we describe an Indian patient who had HIV1 infection in association with PML and pulmonary tuberculosis.

## Case Report

A 45 years old male patient presented to our outpatient clinic in December 2012 with complaints of progressive visual loss in both eyes, headache, difficulty in walking, loss of memory and repeated generalised tonic-clonic seizures. He was a driver by profession and had studied up to undergraduate level. On close questioning he revealed contact with multiple commercial sex workers. He was an alcoholic and smoked 2 cigarettes a day. He also had cough with haemoptysis (small amount) and low grade fever (100°F/38°C) at the time of presentation. He had loose motions 3 to 4 times per day for the past 3 weeks and candidiasis of the tongue. Pulse rate was 100/min, respiration rate 20/min, blood pressure 120/86 mmHg in the left upper limb in supine posture. Weight of the patient was 56 kg and height 165 cm. Chest examinations revealed coarse crepitations bilaterally more marked in the right upper zone. Cardiovascular system examination was normal and so was the abdominal examination. Clinical examination of the eye revealed figure counting at about 2 feet. Other neurological examination revealed bilateral extensor planters. The Mini Mental Status Examination (MMSE) had a score of 20/30 thereby indicating features of moderate dementia. An ophthalmologist confirmed bilateral optic atrophy. The patient had dysmetria and a staggering gait but no hemiplegia. He had slurring of speech. Laboratory investigations revealed normal liver, renal function tests and complete blood count

except for a haemoglobin level of 9.0 gm/100 ml. HIV 1 was positive by two rapid kits and further confirmed by Enzyme Linked Immuno Sorbent Assay (ELISA) as per National AIDS Control Organisation (NACO) of India guidelines. The CD<sub>4</sub> count of the patient was 103/μl. Plasma viral load was >10000 copies/ml. Chest X-Ray postero-anterior view showed evidence of bilateral infiltrations in both the lungs more marked on the right (Figure 1). Most of the above clinical findings were attributable to HIV infection.



**Figure 1:** X-ray chest PA view showing patchy non-homogenous opacity more marked in the right mid and lower zone suggestive of tuberculosis infection.

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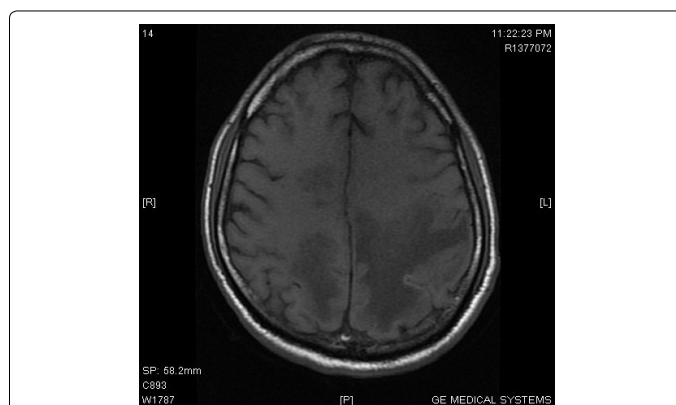
Received July 17, 2013; Accepted August 28, 2013; Published August 31, 2013

**Citation:** Pandey K, Singh D, Das VR, Bimal S, Singh BK, et al. (2013) Progressive Multifocal Leukoencephalopathy Associated with Pulmonary Tuberculosis in an Immuno-Compromised Indian Patient. J AIDS Clin Res 4: 241. doi: 10.4172/2155-6113.1000241

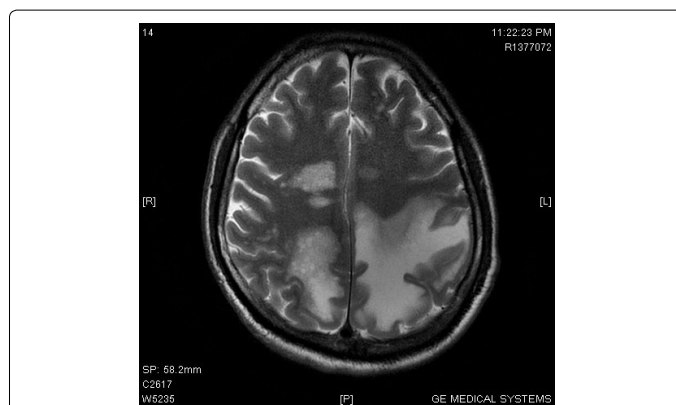
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Two sputum samples, one spot and one overnight were collected in sterile McCartney's bottles. Sputa were decontaminated by modified Petroff's method and then subjected to microbiological examination by Ziehl-Neelsen technique for acid fast bacilli and culture on solid Lowenstein-Jensen (L-J) medium for mycobacterium tuberculosis. The drug susceptibility test (DST) was performed by using a high-throughput, 1% proportional absolute concentration method of four first line anti-tuberculosis drugs namely Isoniazid (0.2 µg/ml), Rifampicin (40 µg/ml), Streptomycin (4 µg/ml), and Pyrazinamide (200 µg/ml) on L-J medium according to WHO guidelines [4]. The culture was sensitive to above mentioned four first line anti-tuberculosis drugs. *Mycobacterium tuberculosis* was identified by its special eugenic growth, colony morphology and biochemical tests such as niacin accumulation, nitrate reduction, and insertion sequence (IS6110) by polymerase chain reaction (PCR) [5,6]. This was confirmed with *M. tuberculosis* (H<sub>37</sub>Rv) reference strain. Streptomycin was added as the patient had visual difficulty thereby avoiding Ethambutol which can lead to retro bulbar neuritis.

Electroencephalogram showed evidence of diffuse slowing. A cerebrospinal fluid (CSF) examination was done and it was normal. However, PCR was positive for JC virus with a value of >3.64 log copies/ml [7]. Computerised tomography (CT) scan demonstrated multiple areas of non-enhancing lesions in white matter. In the magnetic resonance imaging (MRI) T<sub>1</sub> and T<sub>2</sub> weighted images showed increased signal intensity of the temporo-occipital white matter with relative cortical sparing (Figure 2 and 3).



**Figure 2:** T<sub>1</sub> weighted axial MRI of the brain showing increased signal intensity with lesions bilateral occipito temporal and "parietal" regions.



**Figure 3:** T<sub>2</sub> weighted axial MRI of the brain showing increased signal intensity with lucencies bilateral occipito temporal and "parietal" regions.

Considering the clinical as well as the CSF, CT and MRI findings a diagnosis of PML with pulmonary tuberculosis in an immuno-compromised patient was made (WHO clinical stage IV). The patient was continued on anti-tuberculosis therapy with oral rifampicin (450 mg), isoniazid (300 mg), pyrazinamide (1500 mg) with pyridoxine 20 mg/day and streptomycin (1000 mg) intra muscular. Tablet Moxifloxacin (400 mg/day) was added due to the fact that it has shown a very good response when used in combination with the first line drugs [8]. After 2 months only rifampicin and isoniazid was continued for a further period of four months. He was started on phenytoin sodium (300 mg/day) at bedtime for seizures. Antiretroviral therapy (ART) was initiated with Zidovudine (300 mg) twice daily, Lamivudine (150 mg) twice daily and Efavirenz (600 mg) once daily at bedtime orally, two weeks after initiation of antituberculous therapy. Efavirenz has less drug interaction with Rifampicin as compared to Nevirapine [9,10]. Candidiasis was treated with tablet fluconazole (150 mg) once daily orally. Tablet memantine (NMDA receptor blocker) and donepezil (acetyl cholinesterase inhibitor) combination was added for memory loss. The patient is being monitored and is improving slowly. He has been followed up to six months; CD<sub>4</sub> count has increased to 152/µl and weight has increased to 60 kg. Phenytoin sodium, ART, memantine and donepezil are being continued. Signed informed consent was obtained from the patient prior to initiation of investigations and treatment.

## Discussion

PML is difficult to diagnose and treat particularly in a poor country like India. The main basis of diagnosis is a high level of suspicion in an immunocompromised person. The confirmation of diagnosis can be made by classical CT, MRI findings as well as by the demonstration of papovavirus (JC virus) by brain biopsy or PCR from CSF in a HIV positive patient. The PCR for JCV is not specified. While diagnostic PCR is somewhat standard technique, there is no widely available commercial kit for JCV and choice of primers/probes and amplification conditions are important. The simian virus (SV) 40 and BK virus (BKV) share significant homology with JCV and the wrong choice of primers could amplify non-specifically. Equally controls in this assay are extremely important since this is the final diagnostic criteria for PML [11,12]. Eosinophilic intracytoplasmic inclusion bodies are seen in the oligodendroglial cells at the periphery of the lesions in PML. Electron microscopy studies have shown these inclusion bodies to be composed of papovavirus cells. There is multifocal demyelination in the cerebellum, brain stem and spinal cord white matter with perivascular infiltration. The clinical features include visual loss, convulsions, hemiplegia, cranial nerve palsies, focal neurological deficits, ataxia, convulsions and progressive dementia [13]. Bad prognostic indicators include a CD<sub>4</sub> count of less than 100/µL associated with other opportunistic infections [14]. There is no effective treatment for PML but with the advent of ART, the prognosis may be better [15-17]. Cidofovir and camptothecin are two new drugs which are being used in controlled clinical studies. Camptothecin, an alkaloid cytostatic inhibits topoisomerase 1 which is required for DNA of JC Virus replication [18]. Cidofovir, a nucleotide analogue is used for treatment of cytomegalovirus (CMV) has also been found to be effective in a few patients but can lead to nephro toxicity [19]. However in a retrospective analysis of 35 patients it was not found to be as effective and is no longer used for the treatment of PML [20]. In the recent years 5-HT<sub>2a</sub> inhibitors/serotonin receptor antagonists have been proposed for PML treatment [21]. Experimental case studies for some agents such as risperidone and mirtazapine, serotonergic receptor blockers are being tried [22,23]. The best treatment option at present is focused on antiretroviral agents like Zidovudine, Emtricitabine, Abacavir, Nevirapine and Lopinavir.

Currently as per NACO guidelines Protease inhibitors are regarded as the second line treatment for HIV. No prophylaxis is available. As per the previous records death usually occurs within 9 to 12 months in 80% of the cases but again it depends on the time of initiation of ART and the viral load [24,25]. A previous study determined JCV DNA loads in patients with HIV and tuberculosis but did not present MRI findings [26]. This case report is of special interest because it uses both PCR and MRI to diagnose PML in a HIV positive patient with tuberculosis.

#### Acknowledgements

The authors are extremely thankful to Dr. Vishwa Mohan Katoch, Secretary, Department of Health Research, Ministry of Health and Family Welfare, Government of India and Director General, Indian Council of Medical Research (ICMR), New Delhi, for the establishment of Tuberculosis Research (MDR/XDR) and Antiretroviral Therapy Center at Rajendra Memorial Research Institute of Medical Sciences (ICMR), Patna, Bihar, India.

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