AIDS–related progressive multifocal leukoencephalopathy

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ABSTRACT

A case of progressive multifocal leukoencephalopathy associated with human immunodeficiency virus infection with a fatal outcome is presented. The disease has not been reported from our region before. The patient presented initially with hemiparesis and non-enhancing lesion on computed tomography scan that was thought to be an infarct. After a delay of 4 months, the diagnosis was made by brain biopsy. This delay probably contributed to his unfortunate outcome. The case is described, and methods of diagnosis and treatment are discussed.

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Progressive multifocal leukoencephalopathy (PML) is a subacute demyelinating disease of the central nervous system caused by the human polyomavirus JC virus (JCV). Astrom et al[1] first identified PML as a separate clinical entity in 1958. Before the AIDS epidemic, PML was a rare disease, usually developing as a terminal illness in patients with lymphoma and leukemia.[2] A few cases have been reported in patients with sarcoidosis, tuberculosis, carcinomatosis, and organ transplant recipients.[3] Miller et al[4] reported the first AIDS-associated PML in 1982; one year after the new AIDS was recognized. Since the onset of the AIDS epidemic, HIV infection has become, by far the most common risk factor for the disease and currently more than 60% of cases of PML occur in patients with AIDS.[5] Studies suggest that the prevalence of PML in AIDS patients approaches 4%.[2,5] The outlook for patients with PML was until recently poor, leading invariably to death within 1-6 months after diagnosis,[5] however recent reports indicate that the use of antiretroviral therapy (ART) has led to improved outcome.[6] Herein we report the first case of AIDS associated PML in Qatar and review pertinent literature.

Case Report. A 49-year-old male Eritrean patient was admitted with the complaint of an increasing left sided body weakness of 2 months duration. He had no headache, seizure, and no change in level of consciousness. His past history was unremarkable. He did not consume alcohol and was a non-smoker. One month prior to admission, magnetic resonance imaging (MRI) carried out in a private clinic revealed right parietal lesion, which was considered to be an infarct. On admission, he was fully conscious with normal vital signs. General examination was unremarkable. Neurologic examination revealed normal cranial nerves; weakness in both left upper and lower limbs more marked in the upper limb. Reflexes were exaggerated on the left side. Laboratory investigations revealed white blood cell count 3500/mm^3 (58% neutrophiles, 29% lymphocytes, 9% monocytes, and 4% eosinophiles), platelets

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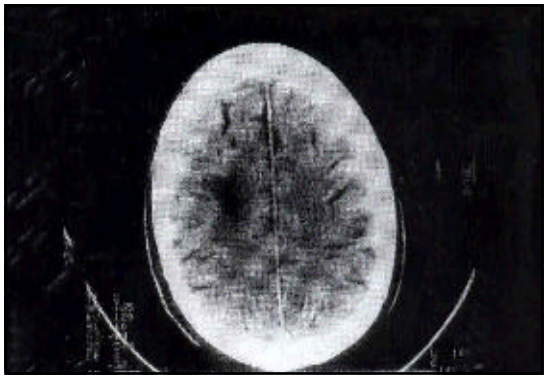

Figure 1 - Computed tomographic (CT) scan of the brain, axial view, showing low attenuation lesion in the right centrum-semioval extending to the gray white matter junction with no mass effect or calcification.

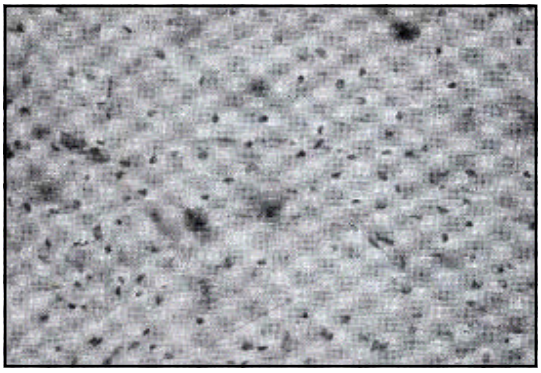

Figure 3 - Hematoxylin and eosin stain; original magnification x 200. The photomicrograph shows foamy macrophages, bizarre astrocytes and occasional oligodendrocytes with viral inclusions.

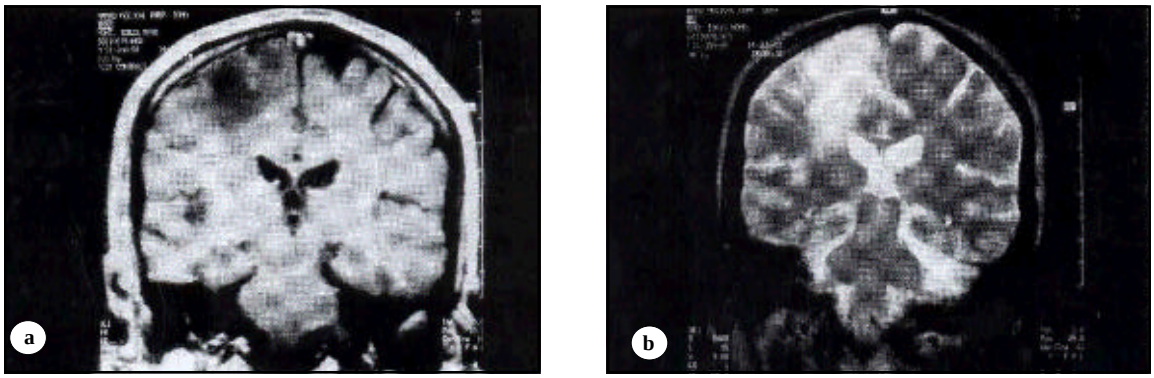

Figure 2 - Magnetic resonance imaging (MRI) of the brain, coronal view, T1 and T2. **(a)** T1 is showing low signal intensity lesion in the right fronto-parietal region with no mass effect. **(b)** T2 post contrast showing homogenous bright signal in the same region with no enhancement.

197,000 /mm^3, and erythrocyte sedimentation rate 36 mm/hour. Liver and kidney function tests, serum cholesterol, triglycerides and transthoracic echocardiogram all were normal. Computed tomographic (CT) scan of head showed a low attenuation area in the right frontal region, subcortical with no abnormal enhancement after intravenous contrast (**Figure 1).** Magnetic resonance imaging of brain revealed an area of high signal intensity in T2, and low signal in T1 in the right parietal lobe posteriorly, subcortical with no significant mass effect. No evidence of abnormal enhancement was detected after intravenous contrast **(Figure 2a & b)**. Both the CT scan and MRI were read as subcortical infarcts. The patient was given clopidogrel and physiotherapy and then discharged home. He was readmitted one month later with worsening weakness, numbness in his left side, headache, and difficulty in speech and swallowing. Physical examination revealed left facial palsy, weakness, exaggerated reflexes, and positive Babinski sign in the left side of his body. A CT scan revealed increase in the right temporo-parietal hypodense lesion with no contrast enhancement. An HIV ELISA test was positive, which was confirmed by western blot. Toxoplasma antibodies were negative. Brain biopsy was performed. Multiple biopsies were taken from the lesion and submitted for frozen section as well as for permanent sections. All the biopsies were fixed in formalin and embedded in paraffin blocks with standard hematoxylin and eosin stain. The sections showed a destructive process replacing the brain tissue. There were abundant foamy macrophages with interspersed large and bizarre astrocytes, as well as perivascular lymphocytic infiltrates. Scattered large oligodendroglial cells were also seen with ground glass nuclei secondary to viral inclusions. Immunoperoxidase stains were performed including S-100 and CD-68 (KP-1). The CD-68 showed staining of the macrophages and S-100 protein highlighted the large astrocytes cells, confirming the inflammatory nature of the process and ruling out the possibility of glial neoplasm. This morphologic

pattern in conjunction with the HIV status of the patient was consistent with PML **(Figure 3)**. Shortly after the biopsy was carried out, the patient left to his country where he died a few days after arrival.

Discussion. Progressive multifocal leukoencephalopathy is a subacute demyelinating disease of the central nervous system caused by reactivation of the latent polyomavirus (JCV) in the presence of immunosuppression.[5] The JC virus infects up to 90% of the general population, usually acquired asymptomatically in childhood or early adulthood.[5] Since the onset of the AIDS epidemic, HIV infection has become the most common condition predisposing to PML.[5] Progressive multifocal leukoencephalopathy is a late manifestation of HIV infection with more than 90% of patients having CD4 cell count less than 200 cells/μL at the time of presentation.[5] Pathologically, the cardinal feature of PML is demyelination, which is typically a multifocal process and is rarely unifocal. Lesions may occur in any location in the white matter with predilection for the parieto-occipital region.[7] The clinical features of PML depend on the part of brain involved and include cognitive, and speech deficits, hemiparesis, difficulty with gait, and incoordination of limbs.[7] Visual disturbances occur in 30-50% of patients.[7] Radiographic imaging can strongly support the diagnosis of PML, but definitive diagnosis requires brain biopsy. Computed tomographic scan of the brain usually reveals hypodense lesions of the affected white matter that generally are neither enhanced with contrast nor exhibit mass effect. An MRI is more sensitive. It shows increased signal intensity on T2-weighted images in the affected region. On T1-weighted images lesions are typically hypointense.[5] Involvement of the gray matter may occur, but only in conjunction with white matter disease.[5] The JC virus DNA can be detected by means of polymerase chain reaction (PCR) of cerebrospinal fluid with a high degree of sensitivity and specificity.[5] Due to the relatively high positive predictive value of the test, a patient with a positive PCR result who has a compatible radiologic picture can be assumed to have PML. Conversely, a negative test does not rule out PML.[5] There is no proven effective treatment for PML. Cytosine arabinoside has been tried but failed to demonstrate clinical benefit.[5] Several anecdotal reports have suggested a benefit of cidofovir, a nucleotide analogue with in vitro anti-JCV activity among patients with PML.[8] Recent reports have documented improved survival among patients with PML who receive ART,[5,9] although cases paradoxical of worsening after treatment with ART due to immune reconstitution have been reported.[5]

We report this case on several accounts. The present case represents the first case of PML seen in Qatar. A total of 190 cases of HIV infection have been diagnosed in Qatar since 1984. Various HIV related neurologic complications have been diagnosed in these patients including toxoplasma encephalitis, cryptococcal meningitis, tuberculomas and tuberculous meningitis, primary central nervous system lymphoma, and AIDS related dementia, however, no case of PML was diagnosed in these patients. To our knowledge, no similar case has been reported before from the Gulf region. The prevalence of PML in AIDS patients has been reported to be 4%. However, this figure is quoted from studies in the United States and Europe.[2,5] Human immunodeficiency virus largely infects populations in Africa and Asia; however, cases of PML have been rarely reported in the literature in the AIDS or non-AIDS populations from these regions. Since infection with the JC virus is ubiquitous, the reason for the low prevalence of PML in these regions is not clear. Under reporting, viral strain differences, as well as HIV and JCV interactions may account for this low prevalence. Our patient fulfilled the 1993 Centers for Disease Control criteria for the diagnosis of AIDS. Although CD4 cell count was not carried out in this patient, however, he was HIV positive and had PML, this makes the diagnosis of AIDS confirmed. Progressive multifocal leukoencephalopathy as the first AIDS-defining illness occurs in up to 1% of all HIV infected individuals, which is approximately one quarter of patients with PML and AIDS.

Our case demonstrates the difficulties encountered in making the diagnosis of PML, which can prove to be a vexing problem. This is especially the case when the HIV status of the patient is unknown or when PML is the initial manifestation of AIDS. The diagnosis in our patient was delayed for approximately 4 months after the start of his symptoms. He denied risk factors for HIV infection, so PML was not considered in the differential diagnosis of his brain lesion in spite of suggestive neuroradiologic findings; this in turn led to delayed diagnosis. This delay probably contributed to his unfortunate outcome. The differential diagnosis in our patient includes in addition to PML, brain tuberculoma, toxoplasma encephalitis, brain abscess, and intracranial mycotic infections such as Aspergillus, Cryptococcus neoformans and Ramichloridium machenziei. The outcome in our patient conforms to that reported in the literature before the introduction of ART, which indicates that most patients die within 1-6 months from diagnosis.[5,6] If the diagnosis was made earlier in our patient, and ART treatment given, the disease course could have been modified and survival prolonged.

Recent World Health Organization statistics indicate that the number of cases of HIV infection in our region is increasing.[10] More cases of AIDS

associated PML may will be seen in the future. This case is being reported to alert physicians in our region to this disease in order to avoid delayed diagnosis with its grave consequences.

In conclusion, PML remains a very rare manifestation of HIV infection in our region. Diagnosis should be suspected in any HIV patient presenting with a focal neurologic disease. Clinical features, lumbar puncture findings, CT and MRI are relatively nonspecific. Diagnosis requires brain biopsy; however, newer techniques such as CSF for JCV may obviate the need for biopsy. Antiretroviral therapy has improved the prognosis of HIV-related PML.

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