Case Report

# Progressive Multifocal Leuoencephalopathy(PML) in HIV Patient

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**Abstract:**

In the conservative Muslim community's lack of transparency and awareness to resultant bad consequences that mislead practicing doctors, delay in the diagnosis and increase in costs of treatment and worsen of morbidity of the disease is the ultimate consequence. Three phases are recognized in the natural history of infection by the human immunodeficiency virus (HIV): (a)An early or acute phase lasting several weeks with infectious mononucleosis-like symptoms, (b) an intermittent or chronic phase, with active low-grade viral replication, lasting several years and (c) the final stage or crises, which corresponds to the clinical phase of AIDS. The virus may enter the nervous system at the time of sero-conversion. However the clinical picture of dementia appears later, when there is marked immunodeficiency. There are many causes for CNS lesions in patients with HIV as vascular, viral, bacterial, myco-bacterial, fungal, parasitic, and neoplastic causes.

Human immunodeficiency virus leucoencephalopathy (HIVL) is an uncommon and rapidly progressive form of AIDS dementia complex (ADC) that has remained poorly understood.

Here we report a rare case of Progressive Multifocal Leuoencephalopathy (PML) in a case of HIV/AIDS who was not willing to disclose her diagnosis till late in the disease.

**Key words:** Progressive Multifocal Leucoencephalopathy (PML), HIV, HAART, Jc virus.

A 37 year old female, single from Hasahisa district was brought to the casualty of the Omdurman Military Hospital (OMH), suffering of fever and headache for four days.

HPI: A known HIV infected patient, diagnosed in Fedail Medical Centre in 2008, and was on Highly Active Antiretroviral Therapy(HAART) regularly, started in OMH several months ago, with the gap period due to the social stigma where no one of her first degree relatives knows about her disease. She used to have prodromal symptoms of flu and malaria now and then. When the suffering was at its maximum her elder brother insisted to bring her seeking medical care. At this stage she admitted to have been diagnosed and treated as a case of HIV/AIDS.

She presented complaining of high grade fever three days. The fever was associated with sweating but not chills, or convulsions. Fever was on and off with severe headache that prevent her to sleep and associated with nausea and vomiting which was stained with bile, 3-4 times a day. In Hisahisa Hospital, she was diagnosed to have malaria and received I.M injections, with-out improvement

One day prior to admission the patient developed right side weakness and drowsiness of sudden onset. She was admitted to Hisahisa Hospital in Elgazeera Estate, and then referred for brain imaging in Albaraha Medical City Khartoum. She developed loss of sphincter control, the mother mentioned that the right eye and mouth were deviated laterally and swallowing became difficult but has no other symptoms related to GIT or CNS.

Systemic inquiry:

Cardio-pulmonary system: no cough, chest pain, palpitation, shortness of breath or lower limb swelling.

Genito-urinary system: She has no burning micturition or change in urine colour.

Musculo-skeletal system and skin: no joint or bone pain or swelling, but has painful neck stiffness and generalized skin rash.

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Past medical history: She was not known to be diabetic or hypertensive, no past similar condition. She has no history of hospitalization, transfusion or operation before. Upper GI endoscopy was performed seven months ago for epigastric pain with meals. The latter symptoms resolved with medications and adjustment of dietary pattern.
Family history: Her mother is diabetic, no hypertension in family, and no similar condition.
Drug history: She was on artimether injections for five 5 days and i.v fluid and antibiotics the day before admission.
Social history: moderate socio-economic status
Gynecological history: Mother is not sure about it, but her daughter didn't complain of any problem with her cycle.
Physical examination: On arrival she was drowsy. Pulse rate 78beats/minute, regular, of average volume, not collapsing, synchronous, with palpable distal pulses and normal vessel wall. BP 140/80, RR 22 breath/minute, temperature 37.8$^{o}$C. She was not pale, jaundiced or cyanosed, but had whitish oral ulcerations, JVP was not raised, no thyroid enlargement, no cervical lymphadenopathy, but she had painful neck stiffness.
Skin showed generalized macular hyper-pigmented rash, and some papules with crusts.
Chest and pericordium: normal contour, trachea was central, apex beat in 5$^{th}$ Inter Costal Space within the Midclavicular line, normal air entry, breath sounds and normal heart sounds.
Abdomen: flat, no tenderness, no organomegaly.
CNS: patient was drowsy, not oriented to time place or person, with inappropriate sounds. However she was co-operative (obeying commands) with GCS 13.
There was weakness in the right lower part of the face (upper motor neuron facial palsy) but the other cranial nerves possible to examine were intact.
Upper limb examination: average equal muscle bulk in both sides, with normal skin. The right arm was adducted and medially rotated. It was hypertonic and hyperreflexic.
Lower limb exam: Right limb was externally rotated, hypertonic and hyperreflexic with bilateral equal average muscular bulk.
Sphincter control was lost hence she was catheterized.
Investigations: CBC showed normal morphology, TWBCs 4.400x10$^{9}$/l, Hb 10.1 g/dl, Platelets 300x10$^{9}$/l. RBG 64 mg/dl ESR 105 in 2 hours, CD4 count 60×10$^{6}$/l blood urea 25mg/dl creatinine 0.3mg/dl $K^{+}$ 3.4mmol/l $Na^{+}$ 142mmol/l
Blood film for malaria was negative. Widal test was negative for brucellosis
Urinalysis: pus cells 8-10 /HPF RBCS 15-17/HPF albumin +.
Urine culture and sensitivity showed no growth. Chest X-ray showed nothing significant.
Liver Function Test: total proteins 6.2gm\l, albumin 2.1gm\l, globulin 4.1gm\l, Alkaline phosphatase 207 U\l, SGOT 123U\l, SGPT 68U\l, Total billirubin 3mg\dl.
Antinuclear antibody (ANA) was negative, and screening for HIV were strongly reactive by ELISA.
CSF: proteins 400mg\dl, sugar 59mg\dl
PCR assay was negative for Mycobacterium tuberculosis.
ECG Showed normal lead pattern.
MRI showed features of multi-focal encephalitis with pre-ventricularleuco-encephalopathy (Figure1).

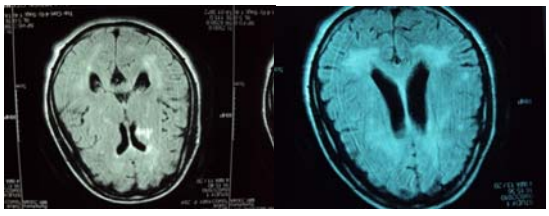

Figure1: MRI with pre-ventricularleuco-encephalopathy.

She was started on I.V, fluid, Mycostatin oral drops, antacid syrup, Ceftriaxone 2g 12 hourly, acyclovir 600mg in normal saline

8 hourly and ampiclox 5oo mg q.d.s, fluconazole infusion 200 mg b.d.
Input output fluid chart, and nursing of hemiplegic patient.
Patient discharged three weeks later in a good condition with improvement of the higher brain functions, motor and cranial nerves performance, on HAART, Fluconazole and Cefpodoxime to be followed in the referral clinic of the(voluntery counceling) VCT in OMH.

**Discussion:**

Although our patient was previously diagnosed as HIV/AIDS she did not disclose this serious information because of the social stigma of this disease in our conservative Muslim community though the disease is not uncommon (Table 1).

Table 1: HIV/AIDS in Sudan in 2007

| Subject | Number | Range |
|---|---|---|
| Population, 2008 | 42,300,000 | |
| Number of people living with HIV | 320 000 | 220 000 - 440 000 |
| Adults aged 15 to 49 prevalence rate | 1.4% | 1% - 2% |
| Adults aged 15 and up living with HIV | 290 000 | 190 000 - 420 000 |
| Women aged 15 and up living with HIV | 170 000 | 120 000 - 250 000 |
| Children aged 0 to 14 living with HIV | 25 000 | 18 000 - 33 000 |
| Deaths due to AIDS | 25 000 | 17 000 - 32 000 |
| Orphans due to AIDS aged 0 to 17: | Not available | Not available |

Source: Epidemiological Fact Sheet on HIV and AIDS, 2008 UNAID

HIV enters the nervous system carried in the macrophages, and usually infects the microglia but not the neurons. The physiopathology of dementia is not well known. It is thought that neuronal dysfunction may be mediated by viral proteins and cytokines synthesized by the infected cells and toxic to the neurones[1]. Tumour necrosis factor alpha (TNF alpha), which has been implicated in the pathogenesis of AIDS Dementia Complex (ADC), is localized in macrophages in the HIV infected brain[2]. PML is caused by reactivation of latent JC virus in the brain. It is the third major cause of focal CNS abnormalities in AIDS patients. Clinically, there is sub-acute onset of focal neurologic deficits with some accompanying cognitive decline. Seizures are uncommon[3]. These features are typical of our patient's presentation which was drowsiness, lack of orientation to time place or person associated with weakness in the right lower part of the face lack of sphincter control, adduction and medial rotation of right forearm and flaccid right lower limb.

PML is primarily a demyelinating disorder with a distinctive appearance on MRI (lesions confined to subcortical white matter).

Oedema and mass effect are unusual, although larger lesions may cavitate. In contrast in our patient MRI showed features of multi-focal encephalitis with pre-ventricularleuco-encephalopathy. The sub-acute presentation in combination with the radiologic findings is usually diagnostic. Sometimes the polymerase chain reaction (PCR) of the spinal fluid for the JC virus is helpful in making this diagnosis[3]. However this test is not available in our hospital at the time of presentation.

There are many potential causes for CNS lesions in patients with HIV being vascular, viral, bacterial, mycobacterial, fungal, parasitic and neoplastic. Vascular events include stroke that may occur in patients with HIV. Our patient's presentation is atypical for that of CNS lesions in HIV-positive such as CMV encephalitis, PML, or HIV. CMV encephalitis should be considered

there is evidence of enteritis as well as positive finding of CMV in the blood and the cerebrospinal fluid. A broad spectrum of CMV infection of the CNS includes polyradiculitis and periventriculitis, as well as mass lesions or abscesses[3]. However MRI in our case did not show the features of CMV. On the other hand, PML is caused by reactivation of latent JC virus in the brain. It is the third major cause of focal CNS abnormalities in AIDS patients

Bacterial infections may lead to embolic or mycotic aneurysms and should be considered in patients with history of S. aureus pneumonia or anaerobic abscess when the patient is febrile and appears toxic. In contrast associated cerebro-vascular events (stroke or hemorrhage) are common with metastatic infection. When these are present, MRI shows hypodense centre in the lesion associated haemorrhage. Neurosyphilis is a bacterial infection that also must be considered in patients with HIV since HIV accelerates the development of neurologic features of syphilis[3]. Also, Mycobacterium tuberculosis must be considered as a cause of the brain lesions because CNS infection is reported in 5%-10% of patients with HIV and tuberculosis[3]. In addition, fungi must be considered as Cryptococcus neoformans, Histoplasma-capsulatum,
Coccidioidesimmitis, however, aspergillus is uncommon but recognized opportunist in advanced HIV especially with neutropenia, high-dose steroids, chemotherapy, malignancy, or additional immune suppression[3]. CNS lesions, also, may be parasitic such as Toxoplasmosis caused by the obligate intracellular protozoan Toxoplasma gondii which reactivates, from its latent form, in immune compromised patients to cause multifocal with predilection for the basal ganglia. It appears as enhancing rings surrounded by oedema. However CT scan and MRI are not sufficient to distinguish the latter from primary CNS lymphoma. CNS toxoplasmosis with biopsy-proven toxoplasmosis may have negative Toxoplasma serology[4]. In contrast, the reported frequency of positive serology for toxoplasmosis in AIDS was 41% at 30 months vs 1.9% in seronegative patients. However, Raffi et al reported that 97% of patients with CNS toxoplasmosis were seropositive by enzyme-linked immune-electro-diffusion assay[5].

Neoplastic disease should be considered as primary CNS lymphoma is the most common CNS neoplasm in patients with AIDS. Primary CNS lymphoma has a subacute presentation, with symptoms evolving over weeks but 50% of its victims are diagnosed at autopsy. Radiologically, it appears as enhancing rings, space-occupying masses with associated edema. Although it appears pathologically multicentric, there is often a single dominant radiologic site. Elevated cerebrospinal fluid protein is common but cytology is usually negative. Progressive multifocal leukoencephalopathy (PML) is a rare, deadly demyelinating disease of the central nervous system, which is caused by a reactivation of the DNA polyomavirus JC and occurs in immunosuppressed individuals[6].
JCvirus is very common in the general population, infecting 70 to 90 percent of humans; most people acquire JCV in childhood or adolescence[7].
The initial site of JCV infection may be the tonsils, or possibly the gastrointestinal tract. The virus then remains latent in the gastrointestinal tract and can also infect the tubular epithelial cells in the kidneys, where it continues to reproduce, shedding virus particles in the urine. JCV can cross the blood-brain barrier into the central nervous system, where it infects oligodendrocytes and astrocytes, possibly through the 5-$HT_{2A}$ serotonin receptor[8].

JCV viruria was found as frequently in HIV-positive individuals as in control subjects, suggesting that its detection has no clinical value. JCV detection in the blood correlates with immunosuppression and not with PML. The presence of JCV in the CSF is highly sensitive and specific for PML, and a high CSF JC viral load was associated with poor clinical outcome in patients receiving antiretroviral therapy. JCV quantification in

the CSF constitutes a potentially important tool for monitoring clinical PML treatment trials[9]. JCV-specific T-cell and IgG responses may serve as prognostic markers for patients at risk because PML nonsurvivors had selectively impaired JCV-specific T-cell responses compared to CD4(+) T-cell-matched controls and failed to mount JCV-specific antibody responses[10].

Immune reconstitution inflammatory syndrome (IRIS) following initiation of combined antiretroviral therapy may lead to activation of an inflammatory response to detectable or latent JC virus infection. Early and prolonged treatment with steroids may be useful in these patients but requires further investigation[11].

There is a strong relationship between PML and monoclonal antibodies (MAbs), especially when used in autoimmune diseases. PML is becoming a crucial issue of MAbs, since they can cause severe adverse drug reaction (ADRs) through the imbalance of the immune system. Based on these results, patients treated with MAbs should be carefully monitored for early signs and symptoms of PML[12].

HAART-associated immune reconstitution seems to play a role on development of a substantial number of PML cases. Although the authors could not demonstrate a directly deleterious effect of HAART on PML progression, prompt initiation of HAART after diagnosis of PML and subsequent successful response were often associated with bad PML outcome[13].

For patients with HIV/AIDS, highly active antiretroviral therapy (HAART) is currently the only effective therapy for progressive multifocal leukoencephalopathy (PML), a viral-induced demyelinating disease caused by polyomavirus JC. Immune reconstitution inflammatory syndrome (IRIS) following initiation of HAART can cause paradoxical clinical deterioration in patients with established PML[14].

Rituximab improves outcomes for persons with lymphoproliferative disorders and is increasingly used to treat immune-mediated illnesses. Awareness is needed of the potential for PML among rituximab-treated persons[15].

Conclusion:

HIV is common disease in Sudan. Patient may present with neurological features of PML. Treating doctors should be transparent and raise their patients' awareness to resultant bad consequences of delay the diagnosis that lead to increase costs of treatment and worsen morbidity of the disease.

Recommendations:

PCR assay for Jc virus is recommended to be performed in our country to increase awareness about the disease and to complete the unclear picture of the mechanism and the pathophysiology of PML.

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