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Case Study: Progressive Multifocal Leukoencephalopathy Presenting as Early Manifestations of HIV

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ABSTRACT

JC virus, a human polyomavirus that is the etiologic agent of progressive multifocal leukoencephalopathy (PML), is an important opportunistic pathogen in patients with AIDS. PML is the only known clinical manifestation of JC virus infection. It is a late manifestation of AIDS and is seen in ~1–4% of patients with AIDS. PML is a lesion of the subcortical white matter of the brain and exhibits signs and symptoms according to involvement of multiple regions of the brain. Ataxia, hemiparesis, visual field defects, aphasia, and sensory defects may occur. Headache, fever, nausea, and vomiting are rarely seen.

We are presenting a case of a 32-year-old male patient who presented with slurring of speech, unilateral weakness, aphasia and difficulty in swallowing.

Keywords: JCV; PML; Polyoma virus; Demyelination

INTRODUCTION

JC Virus causes a lytic infection of oligodendrocytes in the central nervous system causes progressive multifocal encephalopathy (PML) (CNS). Pathological cases such as PML were described by a German pathologist Hallervorden as early as 1930[1]. These researchers' descriptions matched the development of a multifocal distribution of tiny or confluent white matter lesions throughout the cerebellum, basal ganglia, thalamus, and brain stem. Although the cause of these lesions was unknown, the presence of inclusion bodies in the nuclei of injured oligodendrocytes suggested that a virus was involved in PML pathogenesis[2].

PML is a subcortical white matter disease of the brain that causes signs and symptoms in multiple areas of the brain[3-6]. Demyelination can occur in any position in the white matter[7], but it can also occur in other parts of the central nervous system, such as the brainstem and cerebellum, and is a multifocal process[7,8].

CASE STUDY

A 32-year-old patient presented to the Medicine Outpatient Department in our hospital with the complaints of Slurring of speech for 2 months followed by left sided upper limb weakness 45 days ago that was followed by left sided lower limb weakness in the last 15 days. The patient also complaint of fever in the past 15 days. This progressed to difficulty in swallowing and aphasia for 1 week and the patient was in drowsy state in the last 3 days.

The Patient history is unrevealing. The patient did not seek any medical advice in the past for any similar complaint. There is no history of TB, hypertension, thyroid disorders, psychiatric disorders or any major surgeries that lead to blood transfusion. The patient denied any drugs, alcohol, tobacco addiction. There is no complaint of similar symptoms in any family members.

INVESTIGATIONS

JC (John Cunningham) Virus PCR that has lower limit of sensitivity of 98 copies per ml showed 58926 copies per ml thus was positive. Quantitative test of JC DNA was performed by Standard procedure on Real time PCR. HIV I and II testing on initial evaluation when slurring of speech occurred was non-reactive. 5 weeks later when retested the test for HIV I and II it was reactive (Table 1).

Table 1: Complete Blood Count

Test	**Results (Initial)**	**Results (After 5 weeks)**	**Units**	**Normal**
Hb	12.9	14.20	Gm%	12.5 to 15.0
Total WBC	9200	**10660**	/cumm	4000 to 10000
Total RBC	**3.86**	4.37	mill/cumm	4.5 to 6.5
Platelet count	139000	194000	/cumm	1.5 lac to 4.5 lac
Polymorphs	**85**	**83**	%	60 to 70
Lymphocytes	**10**	**8**	%	20 to 40
Eosinophils	03	03	%	01 to 05
Monocytes	02	06	%	01 to 06
Basophils	00	00	%	00 to 01

CSF analysis revealed increased concentrations of Protein and Chloride with normal levels of CSF glucose. Gram staining revealed no pus cells and was negative for acid fast bacilli along with Negative staining for Cryptococcus.

IMAGE STUDIES

USG Abdomen and pelvis did not reveal any significant changes. Liver appeared to be normal with no evidence of focal or diffuse lesion. No evidence of dilated IHBR. No calculus or hydronephrosis. Urinary bladder was normal with no free fluid in peritoneal cavity.

Initial MRI of brain revealed Multiple, discrete altered signal intensity areas involving subcortical white matter of bilateral frontal, right parietotemporal lobes, bilateral cingulate gyrus, right insular region. Similar signal intensity areas also noted involving bilateral brachium pontis (left more than right) dorsal aspect of pons. Normal appearance of corpus callosum.
Later MRI of brain with orbit screening revealed Multiple ill-defined variable size altered signal intensity lesions in sub-cortical region of (bilateral frontal, bilateral cingulate gyrus, bilateral parietal lobe (more on right side), right temporal lobe and right insular cortex as well as in bilateral brachium pontis (more on left side) and posterior aspect of pons with signal characteristic thus suggesting a possibility of demyelination.

Optic nerve, retro orbital space and recti muscles appear normal on either side. Cerebral & cerebellar atrophic changes. No evidence of acute infarct, venous malformation or intra-cranial haemorrhage is seen. No definite changes of meningitis.

The last MRI was diagnostic and revealed Multiple discrete and confluent asymmetrical T2Wt and FLAIR hyperintense areas(Without any postcontrast enhancement are noted involving subcortical and deep white matter of bilateral fronto parietal and right temporal lobe, with possible involvement of bilateral frontal parasagittal cortex, Cingulate Gyrus and bilateral insular and perisylvian region. Similar signal intensity areas are also seen involving bilateral brachium pontis (left more than right) dorsal aspect of pons.
As compared to previous MRI there was significant increase in number and distribution of opacities suggestive of progression of disease.
It was then clinically differentiated as Progressive Multifocal Leucoencelopathy because of positive JC Virus PCR.

DIFFERENTIAL DIAGNOSIS

1. Other Opportunistic Infections like Tuberculosis, Cryptococcosis.
2. Multiple Sclerosis
3. Acute disseminated encephalomyelitis (ADEM) or acute demyelinating encephalomyelitis
4. Autoimmune Encephalopathy

TREATMENT

After making the diagnosis of HIV associated JC virus infection with Progressive Multifocal Leukoencephalopathy, therapy with aggressive anti-Retroviral was started according to NACO guidelines preceded by proper Renal function testing. The patient was in drowsy state thus RT was inserted for feeding. Surgical Consult was taken for multiple raw areas in the sacral and peri anal regions.

Antimicrobial therapy was initiated with Vancomycin 1gm in 100ml NS BD along with Ceftriaxone and Acyclovir. Followed by Methylprednisolone. Fluconazole and Azithromycin were later added to the antimicrobial regimen.

DISCUSSION

Progressive multifocal encephalopathy (PML) is a deadly demyelinating illness of the central nervous system (CNS) caused by a human polyomavirus, JC virus, infecting oligodendrocytes and causing lytic infection (JCV). PML is a rare disease that typically occurs in people with underlying immunosuppressive conditions such as Hodgkin's lymphoma, lymphoproliferative diseases, antineoplastic therapy, and AIDS[9]. Electron microscopy revealed the presence of viral particles resembling polyomavirus structures in the enlarged nuclei of infected oligodendrocytes[10,11]. Numerous attempts were made to isolate the putative virus, but its peculiar biological features, such as narrow host-range and tissue-specificity, rendered isolation challenging at the time. Padgett and colleagues isolated JCV for the first time from long-term cell cultures of glial cells in 1971, utilising brain samples from a PML patient as an inoculum source[12].

According to Sero epidemiological data, the majority of the human population (75-80%) is infected with JCV, and approximately half of this infection occurs during childhood. Individuals' first exposure to the viral infection does not appear to be associated with any known clinical manifestations[13-15].

The most prevalent symptom of PML is visual impairment, which accounts for 35 to 45% of patients. Other but damaging symptoms of PML include emotional liability, memory trouble, and dementia, which are observed in around one-third of cases. Another sign and symptom of PML is motor weakness, which is observed in a significant proportion of patients, accounting for 25 to 33% of cases[3]. The disease progresses slowly, with death occurring within 4-6 months; however, clinical signs and symptoms may occasionally remain stable for considerably longer periods of time[3,15,16]. Destruction of these cells causes microscopic lesions at first[15,17], but as the disease advances, demyelinated patches expand and may consolidate, making them evident on gross examination of cut sections[18]. JCV infects astrocytes as well, causing them to become larger, lobulated, and strange-looking nuclear structures[3-6].

Active macrophages are typically detected in demyelinating regions. They are most likely recruited into the CNS because of an immune response to phagocytize the by-products of myelin breakdown. As PML is linked to AIDS, a substantial proportion of HIV-infected macrophages are also detected in extremely widespread necrotic lesions[19]. Yet, it is unclear how these immune cells got into the demyelination sites.

Although magnetic resonance imaging (MRI) can detect PML lesions produced by both lytic infection of oligodendrocytes and neuronal death[20], some other CNS-related viral infections may make this diagnosis challenging. As a result, the identification of JCV in significant numbers of PML patients' brain samples would be solid proof for the disease's full diagnosis. Previously, antibodies against JCV were used; however, the specificity of this approach was always called into question due to cross-reactivity with other viral proteins. Using tissue samples taken from diverse PML patients, nucleic acid procedures such as in situ hybridization of JCV DNA were successfully done[21]. The polymerase chain reaction (PCR) has, however, been shown to be the most reliable approach for detecting JCV DNA in PML cases. PCR is a simple method for testing cerebrospinal

fluid (CSF) for infectious JCV[22]. The development of new effective PML medicines is urgently required. Targeting multifunctional viral proteins like large T antigen (LT-Ag) and agnoprotein could open up new pathways for PML medication research. Because these proteins are necessary for cell cycle progression and viral replication, targeted blocking of their activity may impede PML progression. Agnoprotein is of particular relevance because it has no major similarity to other biological proteins, making it an interesting target in PML medication research[23-25].

PML is an uncommon but fatal CNS illness characterised by neuronal cell demyelination, resulting in severe neurological deficits. There is currently no viable pharmacological treatment for PML. JCV, a human polyomavirus that was isolated about 38 years ago and latently infects the majority of the human population, causes the disease. When viral DNA undergoes particular changes in its regulatory region in a small group of immune compromised individuals, a virulent variant of the virus appears to arise. Although significant progress has been made in understanding its biology, further research is needed to properly characterise its life cycle, with a focus on investigations of the regulatory activities of viral specific regulatory proteins. Characterization of the involvement of agnoprotein and Sm t-Ag in viral replication and virion formation, in particular, will contribute to a better understanding of JCV biology, notably the viral reactivation process and the start of PML[9].

CONCLUSION

Thus, a case with initially non-reactive HIV patient with clinical manifestations of neurological deficits due to JC virus Infection was encountered. With series of multiple testing over a period of 6 weeks was done after which the patient had a seroconversion from non-reactive to reactive HIV status and then testing for JC virus was done. Thus, PML which is itself rare in HIV can present as the earliest manifestation of the same even before diagnosing retroviral status. These patients should be judiciously screened for the Virus status which can eventually lead to early initiation of ART and ultimately better prognosis.

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