Case Report

Progressive multifocal leukoencephalopathy in non HIV, splenectomised, 66 years old male – A rare case report

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Abstract

Progressive multifocal leukoencephalopathy (PML) is a rapidly progressive AIDS-defining disease of the central nervous system. PML affects up to 8% of patients with AIDS and in most cases is fatal within 3–5 months. We presented here a case of 66 years old male who is non HIV with past history of splenectomy, and diagnosed as progressive multifocal leukoencephalopathy which is very rare. Here, we presented this rare entity which may be difficult to diagnose although, histopathological examination helps greatly in the diagnosis of this condition but the specificity and sensitivity of JC virus DNA PCR in CSF are quite acceptable.

Key words

Multifocal leukoencephalopathy, Non HIV, Splenectomy.

Introduction

Progressive multifocal leukoencephalopathy (PML) is a rapidly progressive AIDS-defining disease of the central nervous system. It is caused by the infection and destruction of oligodendrocytes and perhaps other brain cells by the JC virus, a ubiquitous polyomavirus, resulting in multifocal demyelination. PML affects up to 8% of patients with AIDS and in most cases is fatal within 3–5 months [1, 2, 3]. Current treatment protocol is not much effective. Anecdotal case reports have recently suggested that highly active antiretroviral therapy (HAART) may improve survival in patients with

PML [4, 5, 6, 7]. The diagnosis of PML in two [4, 5] of these case reports, however, was solely based on clinical and radiological criteria and not confirmed histologically or virologically. In the other two patients, follow-up was relatively short [6, 7].

Case report

A 66 years old male came with complains of aphasia, right upper limb weakness, difficulty in walking, forgetfulness and he was bed ridden for last 4 months. Patient had past history of splenectomy 24 years ago and status epilepticus 1 year ago. Patient was recently diagnosed for Diabetes type II. Total leukocyte count, differential leukocyte count and CD4 count were within normal limit. EEG showed mild to moderate electrophysiological dysfunction without any epileptiform discharge. CSF examination for JC virus DNA PCR and BK virus DNA PCR was negative. HIV I and II by western blot technique were non reactive. Anti nuclear antibody by indirect immunoflourscence and anti neutrophilic cytoplasmic antibodies by indirect immunoflourescence was negative. Anti phospholipid antibody (IGG and IGM) by ELISA method was negative. Glycated haemoglobin by immunoturbidimetric (COBAS INTEGRA) was 6.1 % of total haemoglobin. Lupus anticoagulant test was negative.

MRI showed non-enhancing confluent white matter hyper intensity in subcortical and periventricular left frontal and temporo-parieto-occipital and right frontal region and small area in right parietal region. Similar area in left thalamus extending to left crus cerebri with small foci in right thymus, right peritrigonal white matter, spelnium of corpus callosum and postero-superior aspect of medulla. Findings were in favor of chronic atypitcal panencephalitis or progressive multifocal leukoencephalopathy. **(Photo – 1)** MRI angio of brain showed acute demyelination possibility of vascular dementia. **(Photo – 2)** USG abdomen showed situs inversus and dextrocardia. Left frontal lobe burr hole and biopsy was done and sent for Histopathological examination.

Photo – 1: MRI brain showed non-enhancing confluent white matter hyper intensity in subcortical and periventricular left frontal and temporo-parieto-occipital and right frontal region.

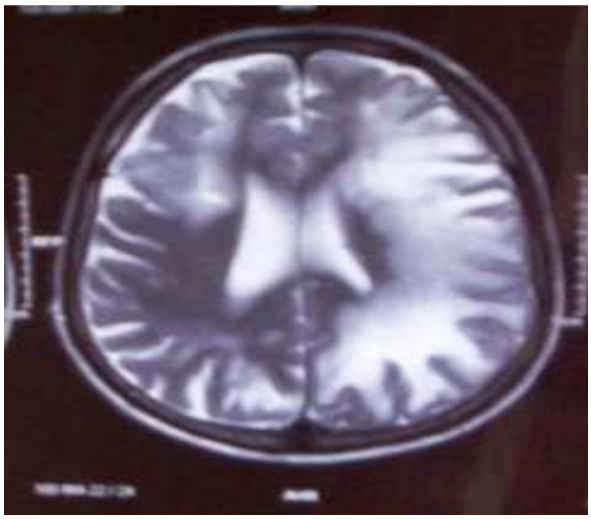
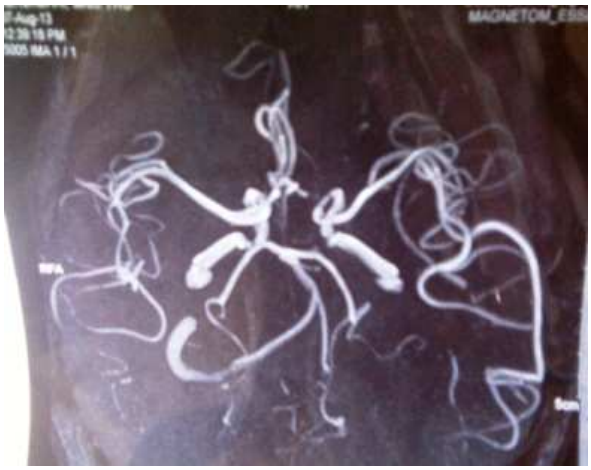


Photo – 2: MRI of brain with angio showed acute demyelination.



Histopathological examination showed small fragments of white matter. Some of the fragments showed active demyelination and sparse infiltration by lymphocytes and foamy histiocytes. There was florid reactive astrocytosis with numerous hypertrophic astrocytes, many with bizarre nuclei. Some of the enlarged nucleus showed smudged chromatin pattern and

identification of intra nuclear inclusion was difficult. However some of the oligodendrocytes were enlarged and contained intra nuclear basophilic inclusion. CD68 stain highlighted foamy macrophages within the demyelinated areas and hypertrophic reactive astrocytes were highlighted by GFAP stain. Immuno stain for JC virus (using both positive and negative controls) showed intra nuclear positivity in both oligo and astrocytic cells. Histological and immunological features were consistant with progressive multifocal leucoencephalopathy.

Discussion

Progressive multifocal leukoencephalopathy (PML) is a well-recognized demyelinating neurological disorder caused by a polyomavirus called JC virus infects the central nervous system. It results in a generally quick and fatal outcome. It is associated with cell mediated immune deficient diseases but some few cases were reported in immunocompetent hosts. Since 1981, it has been commonly associated with AIDS. PML occurs primarily in immunocompromised patients; the first case was reported in a patient with chronic lymphocytic leukemia [8]. PML has since been reported in patients with other haematological malignancies (such as lymphomas) or connective tissue diseases and in transplant patients and patients receiving long-term treatment with immunosuppressive agents. PML has been reported in 1%–4% of HIV infected patients and accounts for 1% of AIDS-defining illnesses [9].

Clinically, PML is characterized by variable but rapidly progressive neurological impairments, depending on the location of the cerebral lesions. Gross dementia, paralysis and loss of all senses represent the end stage of disease [10, 11]. The clinical and radiological signs of PML are non-specific, and other viral encephalitis, especially HIV encephalitis, can mimic PML [10, 11, 12, 13]. Reliable confirmation of the diagnosis is therefore mandatory when evaluating treatment responses. PCR-based tests detecting JCV DNA in CSF have become the diagnostic method of choice, because they are easily repeatable and minimally invasive compared with brain biopsy. In recent years, primers with sensitivities of 80% and specificities approaching 100% have been developed [14, 15, 16].

B cells are usually affected via JC virus infection and have been concerned in the reactivation and central nervous system (CNS) transmigration of the JC virus [17, 18]. A selective recruitment of B cells may be responsible for PML development by spread of JCV distribution. B cells also serve as a carrier that transports the JC virus to the CNS [19]. The most important reservoir of memory B cells is spleen. If spleen is tested positive for JCV DNA, then it harbors the highest variety of sequence rearrangements within the JCV regulatory region [17, 20, 21, 22]. Immune cell homeostasis mainly the B cell compartment is widely affected after splenectomy. The Percentage of CD19+ B cells may be elevated in some cases but not all post-splenectomy patients irrespective of the reason for splenectomy that is trauma or hematological disease [23, 24]. However, increase in the percentage of B cells is per se not considered a risk factor for infection in post-splenectomy patients. High percentage of B lymphocytes can be contributed to PML in some patients. Assessment of IgM memory B cell frequency is considered as potential parameter for evaluation of splenic function or risk of infection following splenectomy [23, 25, 26].

The prognosis of PML is grave, and the median survival from the onset of first symptoms is 3.5–5.5 months. In non-HIV-associated cases of PML, prolonged survival of up to 10 years is not uncommon, especially after withdrawal or dose reduction of immunosuppressive therapy [27, 28, 29, 30, 31, 32, 33]. Higher CD4 cell counts have been associated with prolonged survival in other studies [3, 11, 34]. The therapeutic options for PML are extremely limited. No single drug or combination has been shown to be effective for PML in a controlled clinical trial. Therapeutic trials using cytarabine, IFN-α, foscarnet, steroids, heparin, vidarabine, idoxuridine, or different immune stimulators such as tilorin or levimasol

have yielded conflicting or disappointing results [3, 27, 35, 36, 37, 38, 39, 40, 41, 42, 43, 44].

Conclusion

As PML is a rare in non HIV patient, here we presented this rare entity which was difficult to diagnose. Early diagnosis of PML will prompt efforts at immune reconstitution, which may be beneficial in improving survival rates. Early diagnosis before irreversible neurologic damage has occurred will be crucial for evaluation of the newer treatment modalities. Various diagnostic modalities are helpful for the diagnosis although it should be confirmed by histopathological examination of biopsy specimen because it is the gold standard for final diagnosis but the specificity and sensitivity of JC virus DNA PCR in CSF are quite acceptable.

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