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Hepatitis B virus-induced CD4 lymphocytopenia: A rare cause of progressive multifocal leukoencephalopathy

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ABSTRACT

Progressive multifocal leukoencephalopathy (PML) is a rare subacute-onset fatal demyelinating disease of the central nervous system caused by the John Cunningham (JC) virus. It usually occurs in impaired cell-mediated immunity settings such as lymphoproliferative disorders, chronic infective or granulomatous conditions on immunosuppressive medications, and human immunodeficiency virus infection. It also appears very rarely with idiopathic CD4 lymphocytopenia. We present a case of PML with visual field defect, progressive motor impairment, behavioral alteration, and dementia. Magnetic resonance imaging had features of asymmetric non-enhancing hyperintense subcortical white matter lesions in the background of chronic active hepatitis B infection. To the best of our knowledge, this is the first case report of CD4 lymphocytopenia associated PML following chronic hepatitis B infection.

Key words: Progressive multifocal leukoencephalopathy; Idiopathic CD4 lymphocytopenia; Human immunodeficiency virus; John Cunningham virus; Acquired immunodeficiency syndrome; Hepatitis B virus; Polymerase chain reaction; Translocator protein positron emission tomography

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INTRODUCTION

Progressive multifocal leukoencephalopathy (PML) is a subacute infective disease of the white matter of the brain and spinal cord caused by the John Cunningham (JC) virus. PML is characterized by JC virus-mediated destruction of oligodendrocytes that produce myelin. Asymptomatic primary infection occurs with the JC virus in childhood. By adult life, approximately 55-85% of the population is seropositive.[1] Following the primary infection, the JC virus becomes latent in the sites such as the kidney, bone marrow, and lymphoid organs, including the tonsils of healthy individuals. Its reactivation in the presence of immunosuppression may lead to PML.[2] The development of PML is typically opportunistic, particularly in acquired immune deficiency syndrome. In addition, it usually affects patients with profound immunodeficiency states, such as lymphoproliferative disorders and idiopathic CD4 lymphocytopenia (ICL).[2]

A definite diagnosis of PML requires neuropathological demonstration of the typical histopathologic triad (demyelination, bizarre astrocytes, and enlarged oligodendroglial nuclei) coupled with the techniques to show the presence of the JC virus. In addition, the clinical and imaging manifestations consistent with the diagnosis and not better explained by other disorders, coupled with the demonstration of JC virus by polymerase chain reaction (PCR) in cerebrospinal

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fluid (CSF), are also considered diagnostic.[3] Here, we report a case with features suggestive of PML in a background of lymphocytopenia induced by chronic active hepatitis B infection.

CASE REPORT

A fifty-year-old male, car driver by profession, with a history of addiction to alcohol, presented to us with a history of subacute-onset progressive difficulty in vision in both eyes and difficulty locating objects in the environment for 4½ months. He had no history of fever, headache, vomiting, visual hallucinations, or metamorphopsia. He also complained of fatigue, sleep disturbances, nausea, anorexia, generalized weakness, loss of interest, and significant weight loss of four kilograms in the past 3 months. The patient denied any history of multiple unprotected sexual intercourses or taking any immunosuppressive medication. 1½ months later, he noticed a gradual onset of complete left-sided weakness and stiffness.

The general survey revealed mild pallor and icterus. There were no stigmata of chronic alcoholism or features of portal hypertension. He had a normal sensorium with poor attention span, poor working memory, and altered behavior in the form of irritability, aggressiveness, and emotional lability. Later on, the patient developed an altered sensorium. There was a mild pallor of both optic disks without blurring the disc margin. Fundus had a normal number of peridiscal capillaries with no evidence of vascular sheathing. He had visual acuity of 6/18 in both eyes by Snellen's chart and bilateral homonymous hemianopia by confrontation perimetry. The color vision and pupillary reflexes were normal. There was no relative afferent pupillary defect. The motor system examination showed left-sided complete hemiparesis, brisk deep tendon reflexes, and gait ataxia.

Table 1 shows the blood, CSF, and urine investigation findings and interpretations.

Fibroscan of the liver was within normal limits (5KPa). Hepatoportal Doppler study showed non-reversal of portal blood flow pattern. Ultrasonography revealed decreased brightness, coarse echo pattern, and increased echogenicity of the liver. There was neither hypoechoic nodule nor hypertrophy of the caudate lobe.

EEG showed a focal slowing in the right frontoparietal region. Pattern shift visual evoked response study showed normal P100 latency and subnormal amplitudes on both sides. Electrocardiogram, echocardiogram, and roentgenogram of chest were normal.

Magnetic resonance imaging (MRI) of the brain, including T1 contrast and T2 FLAIR, showed a non-enhancing asymmetrical bilateral confluent subcortical white matter hyperintensity in the fronto-parieto-occipital region. MRI of the whole spine and orbit was normal.

Whole-body PET scan findings are shown in Figure 1. Liver histopathology is depicted in Figure 2.

The patient was managed conservatively with pharmacotherapy with tenofovir, mirtazapine ($5H_2A$ receptor antagonist) and supportive care. However, he had a rapid downhill course and succumbed to death following aspiration pneumonia within 6 months from the onset of the illness.

DISCUSSION

A few anecdotal case reports of PML in patients with ICL are present.[4] ICL is an extremely rare syndrome characterized by a CD4 cell count of <300 per/mL, or a CD4 count of <20% of the total T-cell count on two separate occasions with no evidence of human immunodeficiency virus (HIV) infection, absence of any defined immunodeficiency state, or any therapy that suppresses the CD4 level.[3] In ICL, there is lymphocytopenia with normal to low immunoglobulins and a normal CD8 count. Whereas in HIV, there is predominant hypergammaglobulinemia. Common conditions mimicking ICL to be excluded include SLE, sarcoidosis, RA, IRIS, lymphoproliferative disorders, chronic infective diseases (tuberculosis, hepatitis C, EBV, CMV, fungal infection etc.), and immune-suppressive therapy.[5]

The previous literature reviews did not show any case reported with PML in the background of CD4 lymphocytopenia with chronic hepatitis B infection. A few case reports of PML secondary to hepatitis C virus infection-related T-cell lymphocytopenia were present, but none with isolated hepatitis B virus.[6]

The reported pathology of the hepatitis B virus suggests a reduction of the CD4 T lymphocyte subset with an increase in the CD8 lymphocyte subset and an imbalance in the Th1/Th2 lymphocytes. PML affects immunocompromised hosts. Hepatitis B virus induces immunosuppressive cells such as MDSCs, NK-reg, and T-reg cells through an immune-suppressive cascade. Excessive immunosuppression could contribute to a hepatitis B virus persistent infection, leading to progressive liver fibrosis and hepatocellular carcinoma.[7]

The above-mentioned T lymphocyte change depends on the activity of the hepatitis B virus and the alanine aminotransferase (ALT) level. The ALT is an indicator

Table 1: Blood, CSF, and urine investigation reports

Parameter	Value	Interpretation
Hemoglobin	11 g/dL	Low
Platelet count	185000/μL	Normal
Total leukocyte count	3500/μL	Low
Lymphocyte count	750/μL	Low
CD4 count	102 and 104/μL (in two occasion 2 months apart)	Low
CD8 count	300/μL	Normal
CD4/CD8 ratio	<1	Low
Bilirubin	3 g/dL	High
Indirect bilirubin	2 g/dL	High
Direct bilirubin	1 g/dL	High
ALT	130 IU/L	High
AST	100 IU/L	High
GGT	40 IU/L	High
Albumin	3.8 g/dL	Normal
Globulin	2 g/dL	Normal
Prothrombin time	12 s	Normal
INR	1	Normal
Mantoux test, VDRL, anti-aquaporin4 antibody, anti-MOG antibody, paraneoplastic antibody profile, HIV serology including Western blot	Negative	Normal
Serum ACE, urine metabolic screen, serum VLCFA, serum immunoglobulin level, thyroid function, and renal function	within normal limits	Normal
Hepatitis virus panel		
HBsAg	Positive	Abnormal
anti-HBcIgM	Negative	Normal
HBV DNA	More than 10^5 copies/mL by PCR	Abnormal
HBe antigen	Negative	Normal
anti-HBe antibody	Positive	Abnormal
Hepatitis A, C, E	Negative	Normal
CSF study		
Cell count	4	Normal
Cell type	all mononuclear	Normal
Protein	50 mg/dL	high
Sugar	50 mg/dL	normal
Pan-neurotropic virus panel by multiplex PCR	Negative	normal
JC virus PCR	50 DNA target copies/mL	high

ACE: Angiotensin converting enzyme, ALT: Alanine aminotransferase, AST: Aspartate aminotransferase, CD: Cluster differentiation, GGT: Gama-glutamyl transferase, HBV: Hepatitis B virus, INR: International normalized ratio, IU: International unit, JC: John Cunningham, L: liter, mL: Milliliter, MOG: Myeline oligodendrocyte glycoprotein, PCR: Polymerase chain reaction, VDRL: Veneral disease research laboratory test, VLCFA: Very long chain fatty acid, CSF: Cerebrospinal fluid, PCR: Polymerase chain reaction, HIV: Human immunodeficiency virus

of hepatic inflammation and damage. It was seen that the CD4 changes occur when the ALT level rises above twice the normal value,[8] which is present in our case. Therefore, it appears that the chronic hepatitis B infection in our patient induced immunosuppression and activated the opportunistic JC virus causing PML.

The cirrhosis of the liver might be associated with minimal CD4 lymphocytopenia. On the other hand, hypersplenism and portal hypertension lead to sequestration of white blood cells in the spleen and hypogammaglobulinemia, which ultimately leads to occult CD4 lymphocytopenia.[9]

The symptoms of PML largely vary depending on the location and size of lesions. Still, most frequent clinical presentations are characterized by progressive motor deficits, visual field abnormalities, gait ataxia, behavioral changes, and altered sensorium. The presenting clinical features of our case largely corroborate with the classic focal symptoms of PML.

Fundoscopic examination revealed bilateral optic disc pallor with diminished visual acuity and subnormal amplitude of P100 in pattern shift visual evoked responses test. These features in the presence of bilateral hemianopic field defect without relative afferent pupillary defect suggest bilateral optic atrophy following transsynaptic degeneration of optic nerves associated with bilateral subcortical lesions in both occipital lobes.[10] The axons from the cell bodies in the lateral geniculate nucleus form the optic radiation and terminate at the visual cortex in the occipital lobe. Therefore, the PML lesions in the occipital subcortical white matter region have possibly involved optic radiation in our case.

MRI is the imaging modality of choice in PML. It shows multifocal hyperintense white matter lesion on T2W and

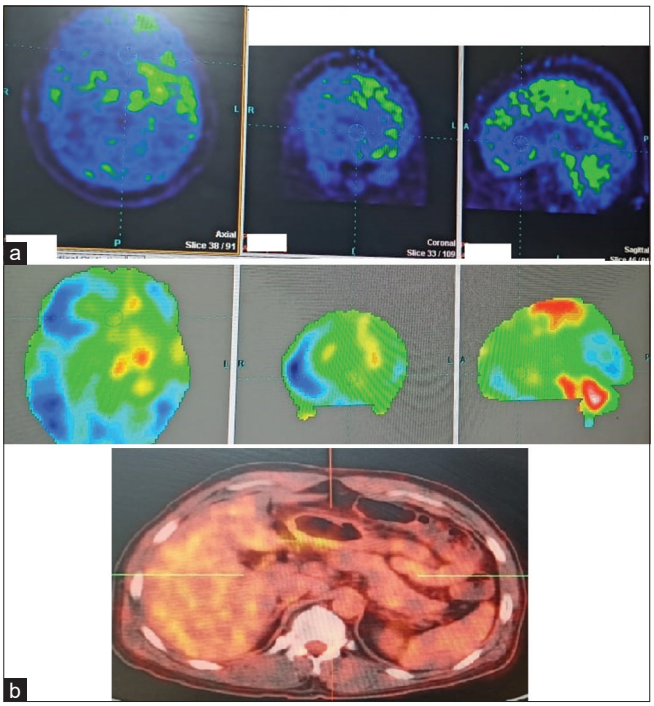

Figure 1: Whole-body positron emission tomography scan showed (a) severe hypometabolism in bilateral occipital, right angular, and supramarginal gyrus as well as right medial and inferior frontal gyrus. There was moderate hypometabolism in the bilateral cerebellum, bilateral cuneus, calcarine, lingual gyrus, and the whole of the right temporal lobe. It also showed diffuse hypermetabolism in the liver (b)

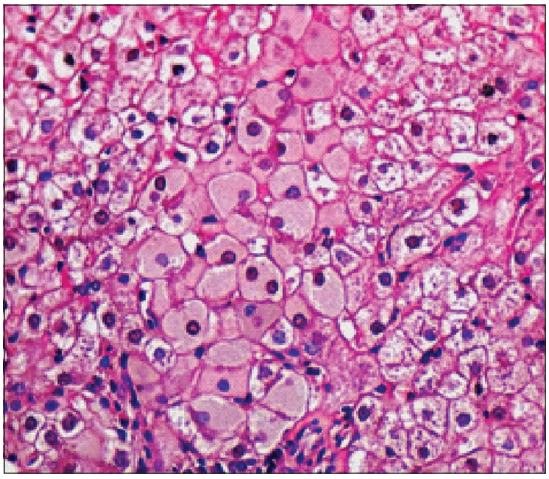

Figure 2: Liver biopsy showed lymphocytic portal inflammation, bridging necrosis, and ground-glass appearance of hepatocytes

FLAIR images, whereas hypointense on T1W images in the affected areas of the brain. These lesions do not enhance with contrast except for faint enhancement in 5–10% of cases. These lesions usually do not produce a mass effect. These lesions are typically bilateral and occur at the gray-white matter interface involving the U-fibers in fronto-parieto-occipital region but rarely with infratentorial and spinal involvement,[11] similar to our case.

The use of PET imaging in PML is rare. In PML lesions, the uptake of 18F-fluorodeoxyglucose is decreased, reflecting hypometabolism.[12] TSPO PET is an imaging tool for longitudinal monitoring of inflammation associated with PML and helps to differentiate MS activity from PML. Besides this, it might be utilized to detect PML in an asymptomatic state and before detection in MRI.[13] In our case, whole-body PET shows hypometabolism in multiple affected sites in the brain with hypermetabolism in the liver.

No PML case has been reported due to chronic hepatitis B-induced CD4 lymphocytopenia. We managed the patient conservatively with tenofovir, mirtazapine (5H2A receptor antagonist), and supportive care. However, he had a rapid downhill course and succumbed to death following aspiration pneumonia within 6 months from the onset of the illness. Further studies and observations are needed for establishing the causal role of hepatitis B in PML and its prognosis with antiviral treatment.[14]

Limitations of the study

Histopathological examination of the brain could not be done as the relatives were unwilling.

CONCLUSION

We present a case of PML with visual field defect, progressive motor impairment, behavioral alteration, and dementia. Magnetic resonance imaging had features of asymmetric, non-enhancing hyperintense subcortical white matter lesions in the background of chronic active hepatitis B infection. To the best of our knowledge, this is the first case report of CD4 lymphocytopenia associated PML following chronic hepatitis B infection.

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