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Progressive multifocal leukoencephalopathy in a patient with systemic lupus erythematosus, not receiving any immunosuppressant medication

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Progressive multifocal leukoencephalopathy (PML) is a rare central nerves system (CNS) disease that is almost always fatal. It is caused by John Cunningham virus (JCV). PML causes rapidly progressive multifocal neuropsychiatric symptoms and the diagnosis is made with brain magnetic resonance imaging (MRI), and cerebrospinal fluid (CSF) polymerase chain reaction (PCR) testing.[1,2]

There are two main theories regarding its pathophysiology; one considers reactivation of latent virus in the CNS as the causative etiology. The other one is based on entry of virus by lymphocytes or independently due to blood-brain barrier (BBB) permeability.[2]

It is generally accepted to be the result of immunosuppression [e.g., human immunodeficiency virus (HIV), acquired immunodeficiency syndrome (AIDS), natalizumab].[3,4] Old age, pregnancy, chronic illness, and autoimmune disease especially systemic lupus erythematosus (SLE) alone have been proposed as causative factors.[5] Surprisingly, there has been rare incidence of PML in immunocompetent patients.[3-7]

Here, we describe PML in a patient with a history of inactive SLE not under immunosuppressive therapy.

In September 2020, a thirty-year-old woman with past medical history (PMH) of SLE was taken to her rheumatologist due to diarrhea, dizziness, generalized weakness, abdominal pain, and thrombocytopenia.

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She had been diagnosed with SLE from the age of seven years, with signs including skin involvement, abdominal pain, diarrhea, and decreased white blood cells (WBCs) and platelets, and had been treated with prednisolone; but she had not shown any sign of SLE disease activity for the past 18 years, and was not taking any immunosuppressive medication. She had left school at the age of 12 years. No other important medical condition was mentioned in her past history. Her family history was also negative.

Considering lupus activation, her rheumatologist prescribed oral prednisolone (six 5 mg tablets, q.i.d), hydroxychloroquine (200 mg, b.i.d), and azathioprine (50 mg, q.i.d). Her symptoms progressed and after two weeks manifested urinary and fecal incontinence and insidious behavioral alteration. She was admitted and took one gram of intravenous (IV) methylprednisolone.

After the brain MRI, the patient was referred to our hospital for more evaluation.

General physical examinations were unremarkable except for cachexia and agitation. She had normal vital signs. Neurological examination showed abnormal mental state. She followed simple commands partially and slowly and did not speak. There was no apparent cranial nerve palsy; there was a mild symmetric generalized weakness, associated with decreased tendon reflexes and down-going toes, and she had an ataxic gait. Sensory examination was not conclusive.

Written informed consent was acquired from the patient's family. Research Ethics Committees of Neuroscience Institute, Tehran University of Medical Sciences, Tehran, Iran, approved the use of humans for this study and the related ID is IR.TUMS.NI.REC.1400.074. This study conforms to the requirements of the Declaration of Helsinki (1989).

A young woman with history of SLE who has rapidly progressive dementia has many differential diagnoses (DDx). Considering lupus activation, neurovascular diseases such as cerebral vasculitis and recurrent strokes due to it should be evaluated. Inflammatory CNS diseases including autoimmune, Hashimoto, viral [e.g., HIV, herpes simplex virus (HSV), and JCV] and bacterial encephalitis should be considered. Metabolic etiologies (e.g., electrolyte imbalance, hepatic encephalopathy, B12 deficiency, and uremia) and other diseases (e.g., neoplasia, recurrent seizures, psychiatric disorders, and substance abuse) are other DDxs.[8]

She had leukopenia, positive antinuclear antibodies (ANA) and anti-double-stranded deoxyribonucleic acid (anti-dsDNA), and elevated erythrocyte sedimentation rate (ESR) which were consistent with SLE. Platelet numbers were normal and no schistocytes were detected. Liver function tests, thyroid function tests, creatinine, blood urea nitrogen (BUN), electrolytes, and B12 levels were normal. Anti-thyroid peroxidase, serum antibody (Ab) to HIV, and antigen of HIV were negative. Results of routine CSF analysis included normal protein and sugar content, 3 white blood cells (one lymphocyte and two polynuclear cells), and no red cells. Brain MRI fluid-attenuated inversion recovery (FLAIR) showed patchy areas of abnormal, hypersignal foci in the white matter of both cerebral hemispheres (centrum semiovale) (Figure 1, a), involving U fibers, as well as in pons and middle cerebellar peduncles, without restriction in diffusion-weighted images (DWI) (Figure 1, b and c) and without post contrast enhancement (Figure 1, d).

Therefore, our DDx were narrowed down to autoimmune encephalitis and viral causes such as HIV and JCV. No antineuronal Ab or Ab against surface antigens [except for glutamic acid decarboxylase Ab (GAD Ab)] was detected. No onconeural Ab was detected in CSF although for serum, anti-Recoverin Ab was positive. CSF HIV PCR and other bacterial and viral causes were negative. Due to patient's MRI, clinical manifestations, and lab data, we considered PML as patient diagnosis. She was discharged on mirtazapine 15 mg one oral tablet daily, while waiting for the result of JCV-DNA PCR in the CSF.

Four days later, she was re-admitted because of one episode of generalized tonic-clonic seizure. The result of CSF JCV-DNA PCR was prepared and reported as positive. We added levetiracetam 500 mg oral tablets twice a day to patient's regimen, and referred her for home care management.

In the monthly follow-ups, the patient's condition gradually regressed and she became bedridden and ultimately died after one and a half years.

It is not uncommon for JCV to exist in body of asymptomatic persons. PML is mostly caused by JCV due to immunosuppression. Very rarely, it is possible for immunocompetent persons to suffer from JCV and this can be very challenging for physicians to diagnose due to lower suspicion. Pathophysiology of PML is still not wholly known. Recent cases of immunocompetent patients with PML cause many questions regarding its pathophysiology and it should be answered in the future studies.[2]

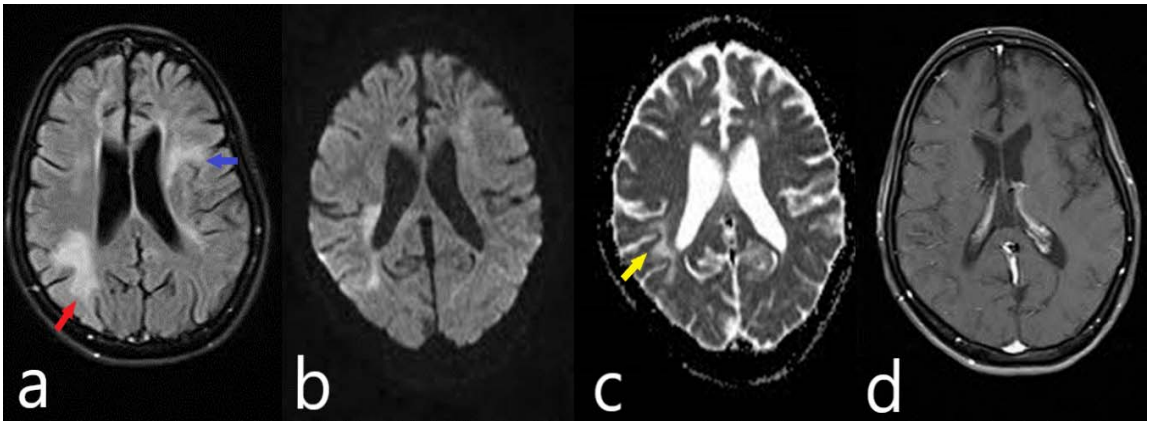

Figure 1. Brain magnetic resonance imaging (MRI) of patient, which is in favor of progressive multifocal leukoencephalopathy (PML); a) Fluid-attenuated inversion recovery (FLAIR) sequence showed patchy areas of abnormal hypersignal foci in the white matter of both cerebral hemispheres (red arrow shows subcortical lesion and blue arrow points to periventricular lesion); b) Diffusion-weighted imaging (DWI) sequence shows increased signal; c) Apparent diffusion coefficient (ADC) shows no restriction; however, U fibers involvement (yellow arrow) was observed; d) No post-contrast enhancement was noted.

Considering the entry of JCV into human brain neurons through 5HT2 receptors, mirtazapine has been proposed as a useful agent in management of PML. Mechanism of action of mirtazapine is shown to be blockage of 5HT2R receptors.[7]

Because of PML's fatality, its misdiagnosis as an autoimmune response can lead to inflicting more immunosuppression on the patients and it can be unforgiving.[4] It should be considered as an important DDx in a rapidly progressive dementia with multifocal neurological symptoms.[2]

We imply that contrary to generalized belief, PML is possible in the absence of immunosuppression, and therefore physicians must reevaluate their understanding of this disease.

Conflict of Interests

The authors declare no conflict of interest in this study.

Acknowledgments

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