Progressive Multifocal Leukoencephalitis In A Patient With Systemic Lupus Erythematosus On Hydroxychloroquine

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Citation

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Abstract

Progressive multifocal leukoencephalopathy (PML) is a rare demyelinating disease of the central nervous system. Reactivation of the polyomavirus JC in immunosuppressed patients induces a lytic infection of oligodendrocytes. The disease is usually fatal in a few months and survivors experience severe neurologic deficits. It is well known to be associated with conditions such as HIV, malignancies, organ transplant recipients and those with chronic inflammatory diseases on immunosuppressive therapy. Review of the medical literature revealed only a few case reports of this disease occurring in minimally immunosuppressed patients (1,3,6). We report a patient with systemic lupus erythematosus on minimal iatrogenic immunosuppression that subsequently developed PML.

CASE REPORT

A 55 year old woman with a history of cutaneous herpes zoster, hypertension, and depression was diagnosed with systemic lupus erythematosus five months prior to presentation. She had a history of polyarthritis, photosensitive malar rash, Raynaud's syndrome, positive ANA, positive anti- Smith and RNP antibody but without any organ involvement . She was treated with hydroxychloroquine 400mg and low dose prednisone. Other medications included sertraline, clonazepam, gabapentin, oxycodone, simvastatin and omeprazole. She is a retired social worker with a 40 pack year tobacco history and denied any illicit drug or alcohol abuse in the past.

The patient presented to the hospital with a five day history of a sudden onset expressive aphasia and right arm weakness which was progressively worsening. On examination, her comprehension was impaired and she had expressive and receptive aphasia along with a labile affect. Muscle strength testing of the right upper extremity was 0/5 and right lower extremity was 2/5. Her general examination was otherwise unremarkable; reflexes were preserved and sensation was intact. An MRI revealed an abnormal T2 and FLAIR signal intensity in the frontoparietal subcortical region extending to periventricular margins with associated effacement of the gyri and sulci, but without significant edema or mass effect. After ruling out a cerebrovascular accident, a rheumatology consultation was requested to rule out lupus cerebritis.

Laboratory tests including complete blood count, comprehensive metabolic panel were normal. Further investigations revealed an erythrocyte sedimentation rate of 115mm/hr, ANA 1:320 (speckled) with anti-Smith and RNP antibody positivity. Other serologic tests such as lupus anticoagulant, anti-phospholipid antibodies, beta-2 glycoprotein, anti-neuronal and anti-ribosomal P antibodies and HIV were negative. Cerebrospinal fluid was positive for JC virus on polymerase chain reaction assay. Ultimately she underwent a brain biopsy to establish a definitive diagnosis, which confirmed severe leukencephalitis, evidence of glial inclusions and sections immunostained with an antibody to polyomavirus. The presence of JC virus-infected glial cells was confirmed by in situ hybridization for JC virus DNA. As there is no specific therapy for PML, her clinical course continued to deteriorate. Improved outcomes with the use of mirtazapine and mefloquine have been reported (7) and was tried in our patient, however she was left with devastating neurologic sequelae but continues on with intense rehabilitation efforts.

Figure 1

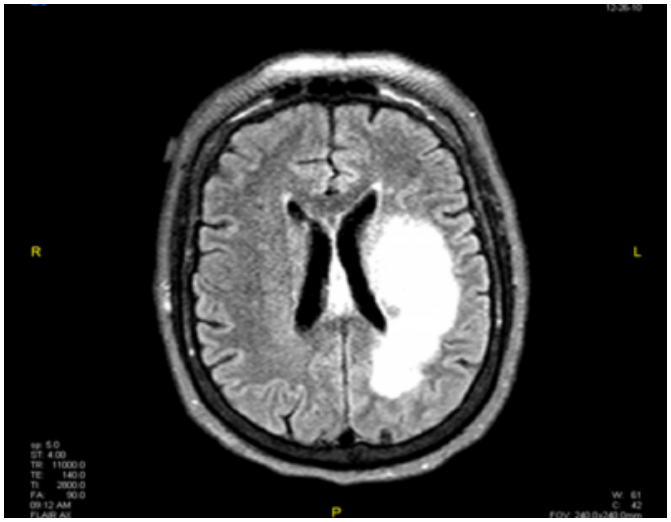
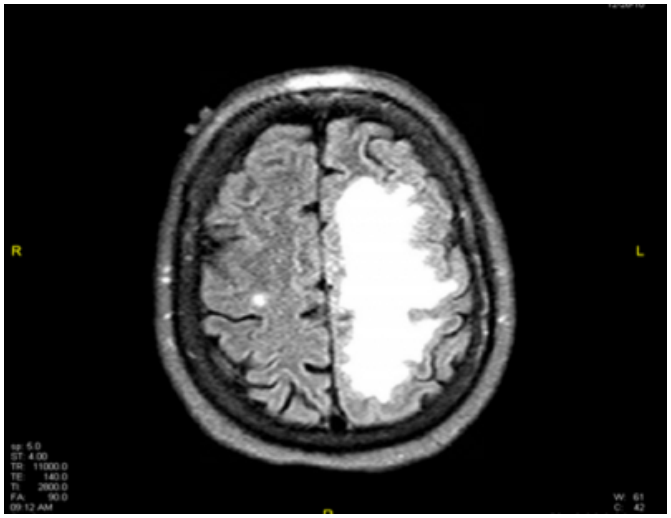


Figure 2



DISCUSSION

Progressive multifocal leukoencephalopathy is a frequently fatal demyelinating disease of the CNS. It is a reported complication of a variety of disease states including rheumatic conditions. In a study among patients with rheumatic diseases by Molloy et al, 32 out of 50 cases with PML, had occurred in patients with SLE (1). Of these patients, 28% were either on low dose prednisone and/or antimalarial or no immunosuppressive agents at all. The development of PML is not entirely attributable to the intensity of immunosuppressive therapy and there is growing evidence that SLE patients may have a unique susceptibility to the development of PML. It also may be more frequently encountered in the current era of biologic therapy as both synthetic and biologic immunosuppressive agents have been implicated in its development.

PML usually presents clinically with subacute neurologic deficits including altered mental status, speech, motor or visual deficits, and seizures. On neuroimaging, PML typically appears as multifocal areas of white matter demyelination that does not enhance with contrast, exhibit mass effect or conform to particular vascular territories. The diagnosis of PML can be established by polymerase chain reaction (PCR) of the cerebrospinal fluid, however the gold standard for diagnosis is a brain biopsy. Furthermore, in clinical practice, distinguishing PML from neuropsychiatric manifestations of SLE is difficult without biopsy or PCR testing, suggesting it may be under-diagnosed. Establishing a diagnosis is critical as the treatment approaches are significantly different. In regards to treatment of PML, there has been no proven effective therapy although a wide variety of agents have been tried. The serotonin receptor, 5HT2a, has been identified as a cellular receptor that the JC virus uses to infect cells(7), providing the basis for the use of mirtazapine in its treatment. There has also been some in vitro evidence of anti-JCV properties of mefloquine which is currently being investigated in a clinical trial for therapeutic use. Despite therapy with these two agents, our patient did not significantly improve neurologically.

CONCLUSION

In summary, PML is an opportunistic infection by the JC virus, which in a susceptible host, leads to central demyelination and a very devastating clinical syndrome. Lessons learned from review of available literature suggest that all patients treated with immunosuppressive therapy for rheumatic disease should be considered at risk for PML(1,3,4,6). Although rare, it should be included in the differential diagnosis in patients with an otherwise unexplained neurological decline. A patient with PML will almost always demonstrate characteristic white matter lesions on an MRI of the brain, and PCR testing of the cerebrospinal fluid should be considered in these patients an accurate diagnosis.

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