Mycophenolate-Associated Progressive Multifocal Leukoencephalopathy in a Woman with Systemic Lupus Erythematosus

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Background

- Systemic lupus erythematosus (SLE) is an autoimmune disease that affects one or multiple organs. It leads to the activation of the innate and adaptive immune responses, which cause B and T cell autoactivation. This leads to the formation of immune complex depositions in the tissue of a single organ or several organs resulting in systemic dysfunction (1).
- Mycophenolate mofetil (MM) is one of the immunosuppressants used in the treatment of SLE. It works by blocking the de novo purine synthesis via the noncompetitive inhibition of inosine monophosphate dehydrogenase (IMPDH). Lymphocytes lack the purine synthesis salvage pathway and are susceptible to mycophenolate inhibition, which interferes with their function and proliferation (2).
- Progressive multifocal leukoencephalopathy (PML) is a progressive and often fatal demyelinating disease caused by the JC virus. It preferentially affects the central nervous system in immunocompromised patients, such as those on long-term immunosuppressive therapy. JC virus is a DNA virus that is lays dormant in immunocompetent patients. However, it can reactivate in immunosuppressed hosts due to the host's poor cellular response. PML has been associated with immunosuppressants, such as MM (3).
- In this case report, we present PML in a patient with SLE after the long-term use of the immunosuppressant agent mycophenolate mofetil.

Images

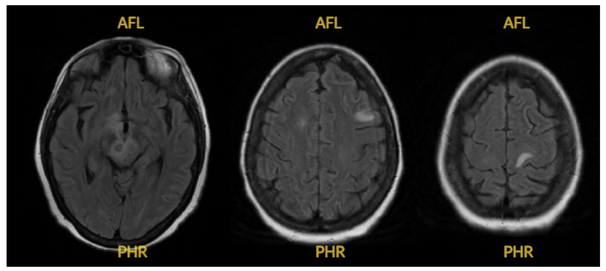

Figure 1: MRI of the brain showing marked signal abnormalities throughout the right hypothalamus and midbrain, as well as in the left subcortical region, likely related to demyelination. These lesions were not enhanced with contrast.

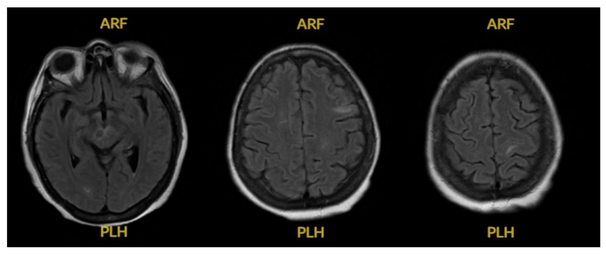

Figure 2: Repeat brain MRI showing significant improvement of the diffuse T2 signal abnormality along the right side of the 4th ventricle, bilateral superior cerebellar peduncles, mesencephalon, right thalamus and also of the patchy areas of increased T2 signal in both frontal lobes. These findings were most compatible with resolving demyelination.

Case Presentation

- This patient is a 48-year-old Hispanic female with a past medical history of SLE and hypothyroidism. She presented with gradually worsening generalized weakness and loss of balance, inability to ambulate, somnolence, and slurred speech for 5 days.
- Her condition has been managed with hydroxychloroquine 200mg BID, prednisone 10mg BID, and mycophenolate 500mg BID.
- Vital signs and physical exam: temperature 99.5F, HR of 118, respirations of 18, BP of 121/86. The patient was lethargic with waxing and waning mentation but was still arousable. Communication was limited by slurry speech and altered mentation. Extraocular movements were intact. There was symmetrical strength in the BUE (5/5), and symmetrical and diffuse weakness in the BLE (4 to 4+/5). Sensation and reflexes were intact.
- Labs: hyponatremia (124 mEq/L), elevated BUN/Cr 26/1.90, severe leukopenia (1.8 K/uL). TSH WNL. HIV, COIVD19, influenza A/B: negative.
- Lumbar puncture: The opening pressure was 23 (cmH2O). WBC of 610 (cell/uL), PMNs 78%, RBCs 2 (cell/uL), Lymph 7%. Protein level 205 (mg/dL); glucose level 31 (mg/dL). Gram stain was negative, and cultures did not show any growth.
- Additional workup: positive ANA (1:1280), slightly low C3 69 (mg/dL), C4 21 (mg/dL), cryoglobulin, anti-CCP, and ANCA were negative.
- Imaging: the first MRI of the brain showed marked signal abnormalities throughout the right hypothalamus and midbrain, as well as in the left subcortical region, likely related to demyelination, (Figure 1). These lesions were not enhanced with contrast.
- Immunosuppression with mycophenolate 500mg BID was continued for the first two days of admission and then was discontinued.

Outcome of treatment

- Following the discontinuation of mycophenolate, the patient's WBC slowly improved, and after 7 days following discontinuation, her WBC improved to 5.8 (K/uL) and to 8.2 (K/uL) after 11 days. The patient exhibited significant neurological improvement over the following two weeks. Her mentation and level of arousal improved dramatically. She was alert and oriented. Her speech returned to normal, and she was able to carry on a full conversation. Her BLE weakness slightly improved, allowing for an increased level of mobility from the initial presentation. Repeat MRI showed significant improvement of the diffuse T2 signal abnormality along the right side of the 4th ventricle, bilateral superior cerebellar peduncles, mesencephalon, right thalamus and also of the patchy areas of increased T2 signal in both frontal lobes. These findings were most consistent with resolving demyelination. (Figure 2).
- Eventually, the patient was deemed clinically stable and was discharged home.

Discussion

- PML is a CNS demyelinating disease of the CNS caused by reactivation of the JC virus in patients with HIV or undergoing immunosuppressive therapy. The patient is this case report was underdoing MM treatment for SLE, which severely decreased her lymphocyte proliferation, as evidenced by the severe leukopenia on the initial presentation. The profound cellular immunosuppression in this patient likely caused reactivation of JC virus causing oligodendrocytes dysfunction and leading to the demyelinating changes exhibited in initial neurological exam and MRI findings. After discontinuation of MM, and resolution of leukopenia, the patient made significant neurological recovery and showed reversal of demyelinating changes on the MRI.
- The current literature shows that autoimmune disorders are seen in 23% of PML cases. The high prevalence of the disease has been linked to immunosuppressive therapy in these patients. Furthermore, out of all rheumatological disease, SLE carries the highest risk factor for PML (4).
- Extensive workup was done to rule out other infectious etiologies and autoimmune causes in this case. The initial MRI findings showed a multifocal process that was limited to white matter, which did not enhance with contrast, did not conform to vascular territories, and did not exhibit mass effect. These findings along with severe leukopenia and all point to MM as the cause of reactivation of JC virus leading to development of PML in this patient.

Conclusion

- SLE patients treated with MM are susceptible to many of its side effects due to its immunosuppression. In these patients, PML should be considered in the differential diagnosis if new or progressive neurological symptoms develop. MM should be discontinued at the onset of symptoms in order to avoid further neurological deterioration. In such cases, alternative immunosuppressive agents may be attempted.

References

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