The Complexities of Neuropsychiatric Lupus: Pathogenesis, Diagnosis, and Management

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Abstract

Background: Systemic Lupus Erythematosus (SLE) is a chronic autoimmune disease with widespread systemic involvement, including neurological manifestations that affect 10 to 80% of patients. Neurological symptoms in SLE can be diverse, ranging from headaches to severe conditions like CNS vasculitis. Methodology: We present a case of a 32-year-old female with a two-year history of SLE who had been non-compliant with her treatment for six months. She presented with new-onset symptoms, including low-grade fever, persistent headache, significant weight loss, tinnitus with hearing loss, and polyarthralgia. Laboratory tests and MRI were used for diagnosis. Results: Laboratory findings revealed elevated anti-dsDNA antibodies, decreased complement levels (C3 and C4), and increased serum Lactate Dehydrogenase (LDH). MRI of the brain showed diffuse T2 FLAIR hyperintensities, indicative of CNS vasculitis. The patient was diagnosed with CNS vasculitis secondary to SLE. Conclusion: The patient was treated with Mycophenolate Mofetil 500 mg twice daily, Hydroxychloroquine 200 mg nightly, and Methylprednisolone 8 mg daily. Significant improvement and resolution of symptoms were achieved within two weeks. This case highlights the importance of early diagnosis and aggressive treatment in managing SLE-related CNS vasculitis, emphasizing the need for adherence to treatment and regular follow-up to prevent disease progression.

Keywords: SLE, CNS vasculitis, anti-dsDNA, Mycophenolate Mofetil, Hydroxychloroquine, Methylprednisolone.

Significance | This case determines the critical need for early diagnosis and aggressive treatment of CNS vasculitis in SLE to achieve remission.

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Introduction

Systemic lupus erythematosus (SLE) is a chronic autoimmune disease with diverse clinical manifestations that affect multiple organ systems, including the central nervous system (CNS). Neuropsychiatric manifestations of SLE, often termed neuropsychiatric SLE (NPSLE), represent a broad spectrum of symptoms ranging from mild cognitive dysfunction to severe neurovascular complications, including CNS vasculitis and strokes. These neuropsychiatric syndromes are some of the most challenging aspects of lupus management due to their heterogeneity and the complexities involved in differentiating primary CNS involvement from other causes such as infections or medication side effects.

NPSLE can affect any part of the nervous system, including the brain, spinal cord, and peripheral nerves. It is believed that up to 75% of SLE patients may experience neuropsychiatric symptoms at some point during their illness. These symptoms range from mood disorders, psychosis, and cognitive impairment to more severe outcomes such as seizures and cerebrovascular events. This broad clinical spectrum poses diagnostic difficulties, especially in the absence of active systemic disease, as NPSLE can occur independently of other lupus manifestations.

One of the most serious manifestations of NPSLE is CNS

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vasculitis, which can occur in the absence of systemic disease activity, making diagnosis even more challenging. CNS vasculitis in lupus patients is rare but highly aggressive, often leading to severe neurological deficits or death if left untreated. Neuroimaging studies and cerebrospinal fluid analysis are crucial in detecting CNS involvement, but these tools are often not sufficient alone, requiring clinicians to rely on a combination of clinical, serological, and imaging findings. Additionally, autoantibodies, such as anti-ribosomal P and anti-NMDA receptor antibodies, have been implicated in the pathogenesis of NPSLE, but their clinical utility in diagnosis remains a subject of ongoing research (Abdel-Nasser et al., 2008; Arinuma et al., 2019; Eber et al., 2005).

The pathophysiology of NPSLE remains incompletely understood, but it is thought to involve immune-mediated damage to the nervous system. Mechanisms such as vasculopathy, autoantibody production, and inflammatory cytokine release have been implicated. In some cases, neuropsychiatric symptoms can precede the diagnosis of SLE, further complicating the clinical picture. Treatment of NPSLE is similarly challenging due to its diverse presentations. Immunosuppressive therapies, such as corticosteroids, cyclophosphamide, and rituximab, are commonly used, though treatment strategies must be individualized based on the severity and type of neuropsychiatric involvement. Early and aggressive treatment is crucial in preventing irreversible damage, particularly in cases involving CNS vasculitis or seizures (Aschman et al., 2021; Bertsias & Boumpas, 2010; Bertsias et al., 2010).

Given the complexity of NPSLE, a multidisciplinary approach to care is essential. Rheumatologists, neurologists, and psychiatrists must work together to manage these patients, with close monitoring for any signs of CNS involvement. Recent advances in neuroimaging and the identification of novel biomarkers hold promise for earlier and more accurate detection of NPSLE, which could improve clinical outcomes (Gelb et al., 2018; Fleetwood et al., 2018). However, more research is needed to fully understand the mechanisms underlying CNS involvement in lupus and to develop more effective treatments.

As understanding of NPSLE continues to evolve, it is clear that early detection and individualized treatment are critical in improving patient outcomes. With advances in diagnostic tools and a better understanding of the pathogenesis of CNS involvement in lupus, there is hope for improved management strategies that can reduce the morbidity and mortality associated with this challenging disease (Bravo-Zehnder et al., 2015; Cieślik et al., 2022; Cohen et al., 2017; Donnellan et al., 2021; Delunardo et al., 2016; Kakati et al., 2017; Rowshani et al., 2005; Bialas et al., 2020; Fanali et al., 2012; Everett et al., 2008).

Case report

Patient History

The patient is a 32-year-old female with a known diagnosis of Systemic Lupus Erythematosus (SLE) for the past two years. She had been non-compliant with her treatment regimen for the past six months. Recently, she presented with a range of new symptoms. Over the past three months, she experienced a low-grade intermittent fever that was not associated with chills or rigors. She also reported a persistent headache for the last two months, which was not accompanied by visual disturbances, photophobia, or vertigo.

Additionally, the patient noted significant weight loss of over 15 kilograms during the past six months, accompanied by a marked loss of appetite. She described tinnitus in her right ear, which was associated with hearing loss. The patient also experienced polyarthralgia, predominantly affecting the bilateral interphalangeal joints and knees.

She denied any history of skin rashes, seizures, decreased urine output, chest pain, palpitations, or dyspnea. The patient had no other comorbid conditions.

Clinical Examination

On examination, the patient was conscious and oriented but febrile, with a recorded temperature of 99.8°F. Other vital signs were within normal limits. Systemic examination did not reveal any significant abnormalities.

Laboratory and Imaging Findings

The patient's laboratory results revealed significant abnormalities consistent with active SLE and its neurological complications. The Complete Blood Count (CBC) showed neutrophilia and a decreased red blood cell count, indicating inflammation and potential anemia. Erythrocyte Sedimentation Rate (ESR) was markedly elevated at 82 mm/h, reflecting systemic inflammation, while C-Reactive Protein (CRP) remained within normal limits at 1.2 mg/dl. Complement levels C3 and C4 were notably low at 60 mg/dl and 9.1 mg/dl, respectively, indicative of ongoing disease activity. Serum Lactate Dehydrogenase (LDH) was elevated at 305 U/L, suggesting tissue damage (Table 1). The Anti-double-stranded DNA (Anti-dsDNA) antibody level was elevated at 60 IU/ml, reinforcing active lupus. Anticardiolipin antibodies and lupus anticoagulant were negative, and D-Dimer was elevated at 1.18 mcg/ml, reflecting possible thrombotic activity. Imaging studies, including Magnetic Resonance Imaging (MRI) of the brain, revealed diffuse and multiple punctate T2 FLAIR hyperintensities in the bilateral brain parenchyma, suggestive of vasculitis and confirming the diagnosis of CNS involvement.

Diagnosis and Treatment

Based on the clinical presentation, laboratory results, and imaging findings, the patient was diagnosed with central nervous system (CNS) vasculitis secondary to Systemic Lupus Erythematosus (SLE). This diagnosis was supported by the presence of diffuse T2 FLAIR hyperintensities on MRI (Figure 1), alongside elevated anti-dsDNA levels and low complement C3 and C4 levels. The treatment

Table 1. The summary of investigations

Investigations	Values
ESR	82 mm
CRP	1.2 mg/dl
LDH	305 U/L
D-DIMER	1.18
ANA (IFA)	POSITIVE
LUPUS ANTICOAGULANT (DRVVT METHOD)	0.8 (NEGATIVE)
ANTICARDIOLIPIN ANTIBODIES: IgM: IgG	NEGATIVE 3 U/ml 3.3 U/ml
COMPLEMENT C3	60 mg/dl
COMPLEMENT C4	9.1 mg/dl
Anti-dsDNA	60 IU/ml

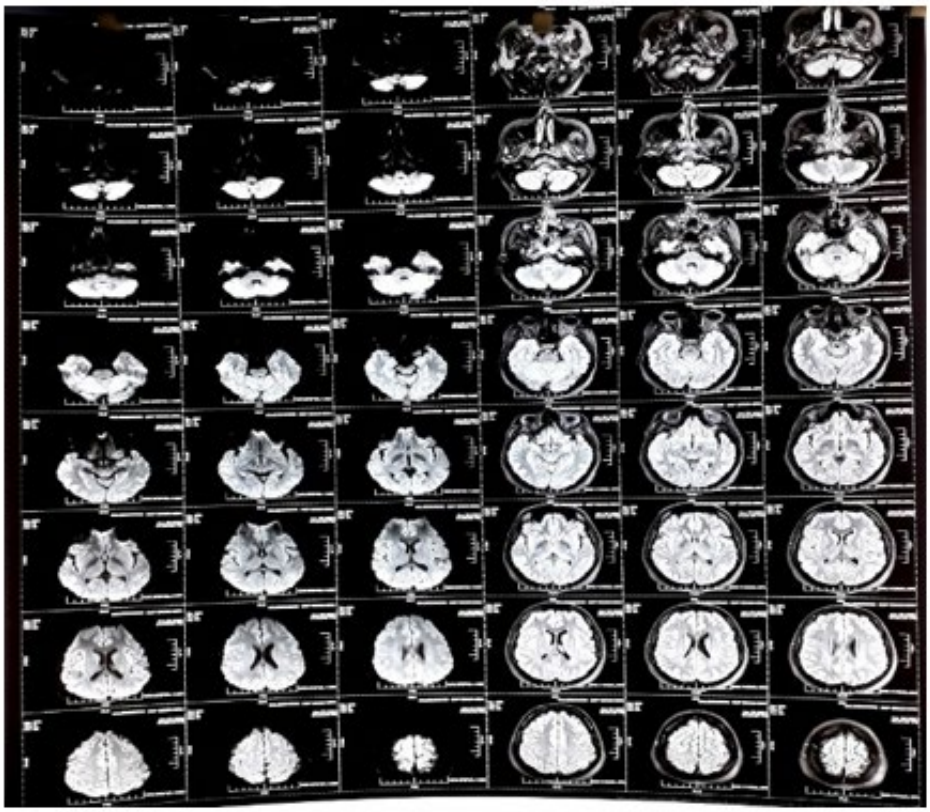

Figure 1. An MRI of brain diffuse and multiple punctuate T2 FLAIR hyperintensities in bilateral brain

regimen was promptly initiated to address the active vasculitis and manage SLE symptoms. The patient was started on Mycophenolate Mofetil 500 mg twice daily to provide immunosuppressive therapy, Hydroxychloroquine 200 mg at bedtime for its antimalarial and immunomodulatory effects, and Methylprednisolone 8 mg once daily to reduce inflammation. This combination of therapies aimed to control the disease activity and induce remission. The patient's condition improved significantly, with resolution of symptoms within two weeks of starting treatment, highlighting the effectiveness of this therapeutic approach.

Outcome

The patient showed significant improvement following the commencement of treatment. Her symptoms, including fever, headache, and tinnitus, subsided completely within two weeks. Regular follow-up and monitoring were advised to ensure sustained remission and manage any potential complications**.**

Discussion

Central nervous system (CNS) vasculitis is a rare yet serious complication of Systemic Lupus Erythematosus (SLE), occurring in only about 7% of SLE patients. This condition can present with a range of symptoms including recurrent fever, severe headache, and acute confusional states, which may rapidly progress to more severe manifestations such as psychosis, seizures, and coma (Everett et al., 2008). The pathophysiology of CNS vasculitis in SLE is often associated with systemic inflammation and vascular damage, driven by both autoimmune mechanisms and inflammatory mediators.

In this case, the patient exhibited typical symptoms of CNS vasculitis, including persistent headache, fever, and significant weight loss. Laboratory findings supported active SLE with hypocomplementemia, elevated anti-dsDNA levels, and increased LDH, all indicative of systemic disease activity. MRI findings of diffuse T2 FLAIR hyperintensities were consistent with vasculitis, confirming CNS involvement.

The differentiation between CNS vasculopathy and true vasculitis is crucial for appropriate management. CNS vasculopathy in SLE may result from underlying disease activity or secondary factors, whereas true CNS vasculitis involves direct inflammation of the cerebral vessels (Kakati et al., 2017). Accurate diagnosis requires a combination of clinical assessment, laboratory investigations, and imaging studies. In cases of rapid disease progression, aggressive treatment with intravenous cyclophosphamide and methylprednisolone is often recommended. For patients who cannot tolerate these agents or do not respond adequately, second-line treatments such as azathioprine and mycophenolate mofetil are utilized (Rowshani et al., 2005). Emerging therapies like Rituximab, an anti-CD20 monoclonal antibody, have also shown efficacy in refractory cases.

In this case, the patient responded well to a combination of mycophenolate mofetil, hydroxychloroquine, and methylprednisolone, leading to a complete resolution of symptoms. This outcome underscores the importance of early diagnosis and prompt, effective treatment in managing SLE-related CNS vasculitis.

Conclusion

This case highlights the complexity of managing Systemic Lupus Erythematosus with neurological involvement. Accurate diagnosis of CNS vasculitis is critical and relies on a combination of clinical, laboratory, and imaging findings. Early intervention with aggressive immunosuppressive therapy is essential for managing active disease and preventing progression. This case demonstrates that a tailored treatment approach, incorporating both standard and novel therapies, can lead to significant improvements and resolution of symptoms. Regular follow-up and monitoring remain vital to ensure sustained remission and address any potential complications.

Author contributions

RTV, GA, ZS, and VKP provided essential guidance and supervision throughout the study. All authors actively participated in discussing the results and contributed to the writing and revision of the manuscript.

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Competing financial interests

The authors have no conflict of interest.

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