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**Case Report**

# Neuropsychiatric lupus: report of an interesting case with challenges in diagnosis and management

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## ABSTRACT

NPSLE, an array of neurological and psychiatric symptoms within systemic lupus erythematosus (SLE), poses diagnostic challenges due to negative serology and absence of systemic signs. We present a 54-year-old woman with anemia, musculoskeletal pain, recurrent pleural effusion, and erratic behavior. Despite delayed identification, extensive testing finally revealed NPSLE. This case underscores the difficulty in linking diverse symptoms to SLE, resulting in delayed treatment initiation and adverse outcomes upon presentation**.**

**Keywords:** Neuropsychiatric systemic lupus erythematosus, Autoimmune disease, Psychosis, Methylprednisolone

## INTRODUCTION

Asterion is the confluence of the temporal, occipital and parietal bones on the Systemic lupus erythematosus (SLE) is a multisystem autoimmune disease with protean clinical manifestations. Females are affected more than males, with a female-to-male ratio of 9:1.[1]

Neurological and psychiatric manifestations are hallmarks of Neuropsychiatric SLE (NPSLE).[2] Clinical symptoms of NPSLE range from several peripheral or central nervous system (CNS) findings with varying severity.[3] Skilled physicians find it difficult to diagnose NPSLE due to the lack of specific and sensitive laboratory cerebrospinal fluid and serum markers, neuroimaging deficits, and other formal criteria.[2]

Here, a 54-year-old female presented with recurrent symptoms of anemia, myalgias, proximal lower limb weakness, and acute encephalopathy, and later went on to get diagnosed with NPSLE.

## CASE REPORT

A total of 50 skulls (27 A 54-year-old lady presented to our hospital in an acute confusional state for two days. She presented first to a local hospital with complaints of progressive fatigue, and breathlessness for seven days where she required intensive care and mechanical ventilation for three days from which she was successfully weaned off. No other history was given. Her routine blood investigations done outside revealed anemia and elevated erythrocyte sedimentation rate (ESR) (Table 1). Computed tomography (CT) of the chest revealed moderate pleural effusion without any changes suggestive of pneumonia. The echocardiogram revealed an ejection fraction of 55% without any regional wall motion abnormality. RT PCR for COVID-19 was negative. Urinalysis revealed nephrotic range proteinuria (<3.5g/day) (Table 1). Investigations were, thus, suggestive of heart failure with preserved ejection fraction with nephropathy. She started experiencing multiple episodes of anxiety, panic attacks, and psychosis in the hospital, requiring psychiatric treatment and

behavioral management including benzodiazepines and anxiolytics. She was then transferred to our hospital for further care.

On examination, the woman was confused and not oriented to time, place, and person with incoherent speech. The blood pressure was 130/90 mmHg, pulse rate was 82 beats per minute respiratory rate was 20 cycles per minute and oxygen saturation was 94%. Upon questioning, she experienced visual hallucinations for the past two days as claimed by her family.

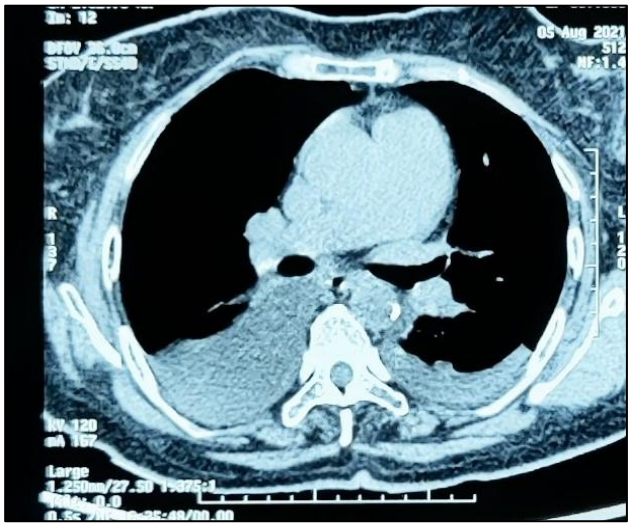

**Figure 1: CT chest (day 2) depicting pleural effusion (white arrows) without any changes of pneumonia.**

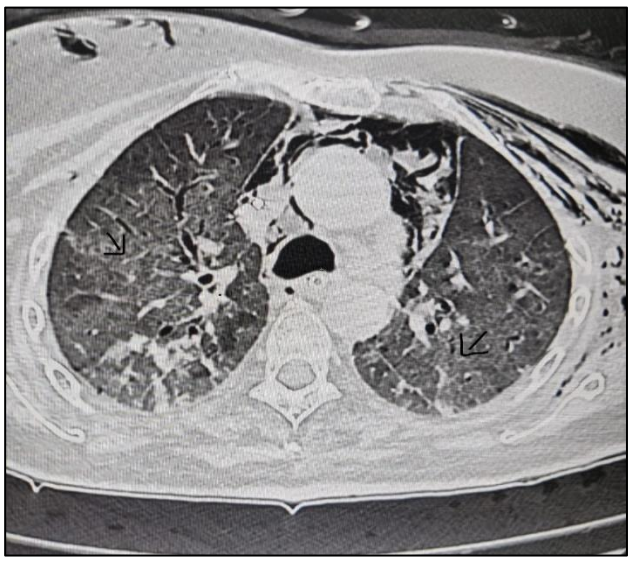

**Figure 2: CT chest (day 15) depicting ground glass opacities (black arrows).**

The patient also gives a history of pain in both lower extremities on several occasions for the past year. She has had difficulty getting up from her chair for 6 to 7 months. The relatives had also noticed a mild cognitive decline and intermittent behavioral disturbances in her over the past 8 to 9 months. The patient had a history of diabetes mellitus for 10 years controlled with oral medications. Her personal and family histories were unremarkable.

On further examination, the patient was found to be disoriented with incoherent speech. Muscle bulk and tone were normal with grade 4/5 power in both lower limbs. There was no rash, neck stiffness, papilledema, swelling of fingers or brittle nails, alopecia, or mouth ulcers. Deep tendon jerks were normal and both plantars were flexor. Her blood investigations (hemogram, biochemical, and thyroid hormone levels) revealed anemia, thrombocytopenia, and high ESR and creatinine levels. A lumbar puncture was performed with normal laboratory findings (Table 1). A repeat CT scan revealed mild bilateral pleural effusion which could not be tapped (Figure 1).

Because of a multisystem involvement and altered sensorium; infectious and immunological workups (Anti-Nuclear Antibodies and Blot, anti-N-Methyl-D-Aspartate Receptor antibodies) were sent. EEG did not reveal any epileptiform discharges. USG revealed a bright echotexture of both kidneys without any hepatosplenomegaly. MRI Brain was normal. Neuropsychiatric Systemic Lupus Erythematosus was diagnosed because of an acute confusional state, seizures, and positive serological markers (positive titers for ANA, dsDNA, and anti-Sn RNP) with normal neuroimaging findings. The hemoglobin of the patient dropped to 7.8 g/dl and further trended down to 6.7 g/dl on day 3 of admission requiring a blood transfusion. She also started complaining of sleep deprivation and increased fatiguability. Given the elevated creatinine level and almost borderline nephrotic range protein urea (3.5g/day), she was given intravenous methylprednisolone (1000 mg daily for 5 days) and oral mycophenolate mofetil (1g per day).

Anticoagulation and antiplatelet therapy were also started to prevent thrombosis, while antiphospholipid antibodies (APLA) profile was sent. After consequent injections of methylprednisolone, an improvement in serum creatinine, a decline in urine proteins was noted, and her sensorium improved. The psychosis was resolved. Following marked improvement, oral prednisolone was started and a renal biopsy was planned. On day 9, her mental status deteriorated and a confusional state recurred again. Serum electrolytes showed a sodium (Na+) level of 123 mmol/l (reference range 135-145) concomitant with urine spot sodium of 116 mmol/l (reference range 20-40). A diagnosis of Syndrome of Inappropriate Antidiuretic hormone secretion (SIADH) was attributed to her NPSLE. Fluid restriction, oral salt capsules thrice a day, and tablet Tolvaptan were commenced. On Day 13, her sodium levels gradually rose to a level of 136 mmol/l. On day 15, she developed a fever and chills and tested positive for COVID-19 (positive RT-PCR test). She was transferred to the COVID ICU. CT of the chest now revealed irregular dense areas of consolidation in bilateral lower areas with the remainder of the lung showing diffuse ground glass densities and interlobular septal thickening (Figure 2). Renal biopsy was deferred, and on day 21, she succumbed to her illness.

**Table 1: Blood, urine, and immunological investigations of the patient done outside and at our hospital.**

| Investigations | Values | | | | Normal range |
|---|---|---|---|---|---|
| | Outside | Our hospital | | | |
| **Blood** | **Other hospital** | **On admission** | **Day 9 (Post admission)** | **Day 15 (Post admission)** | |
| Haemoglobin (mg/dl) | 9.9 | 9.1 | 7.6 | 8.6 | 11-16 mg/dl |
| Total leucocyte counts | 9,000 | 8,800 | 13,900 | 21,400 | 4000-11,000 cells/cumm |
| Platelet count | 98,000 | 87,000 | 99,000 | 99,000 | 1.5-4 lakhs/cumm |
| Blood urea | 40 | 37 | 42 | 45 | 10-45 mmol/l |
| Serum creatinine | 2.9 | 3.1 | 2.8 | 2.7 | 0.6-1.2 mg/dl |
| Serum sodium | 136 | 133 | 123 | 136 | 135-145 mmol/l |
| Serum potassium | 4.1 | 3.6 | 3.8 | 3.9 | 3.5-4.5 mmol/l |
| Erythrocyte sedimentation rate | 97 | 102 | 107 | 111 | 0-20 mm/hour |
| C- reactive protein | 96 | 92 | 149 | 230 | 0-10 mg/dl |
| Urine protein | ERROR | ERROR | ERROR | ERROR | nil |
| Urine red blood cells | 0-1/HPF | 2-3/HPF | 2-3/HPF | 2-3/HPF | 2-4/HPF |
| Urine sugar | Mild | Absent | Absent | Absent | nil |
| Urine pus cells | 3-4/HPF | 3-4/HPF | 4-5/HPF | 9-10/HPF | 3-5/HPF |
| Urine crystals/casts | Not seen | Not seen | Not seen | Not seen | nil |
| Urine bacteria | Not seen | Not seen | Not seen | Very few | nil |
| Urine 24-hour protein | 3341 | 3487 | 3347 | 3510 | 100 mg/day |
| Antibody | Outside | Our hospital | Normal Range | | |
| Antinuclear Antibody (ANA) | ERROR | ERROR | negative | | |
| SS-A autoantibody | Not done | Positive | - | | |
| SS-B autoantibody | Not done | Positive | - | | |
| anti-double stranded DNA antibody (anti-dsDNA) | Not done | Positive | - | | |
| Antinuclear ribonucleoprotein (anti-RNP) antibody | Not done | Positive | - | | |
| c-ANCA and p-ANCA | Not done | Negative | - | | |
| C3 levels | 66 mg/dl | 60.6 mg/dl | 90-180 mg/dl | | |
| C4 levels | 23 mg/dl | 17.7 mg/dl | 10-40 mg/dl | | |
| Anti NMDAR Ab | | Negative | - | | |
| HIV/HbsAg | Negative | Negative | - | | |

**Table 2: Case reports comparing clinical presentation and treatment options in patients with NPSLE.**

| Authors | Clinical presentations | Treatment offered | Results |
|---|---|---|---|
| **Ivania et al[14]** | Depression and aseptic meningitis | I.V. Dexamethasone followed by oral Dexamethasone for the first two days and then switched to oral Prednisolone | After days 3-5 of the initiation of steroids the patient was alert and interacting. Cognitive function improved substantially too. |
| **Iftikhar et al[15]** | Status epilepticus in the setting of cytopenia, malar rash, mouth ulcers, and arthritis | I.V. Midazolam, IV Methylprednisolone along with Rituximab followed with Prednisolone which was slowly weaned off. | Seizures subsided and the rash improved after treatment |

Continued.

| Authors | Clinical presentations | Treatment offered | Results |
|---|---|---|---|
| **Gosal et al[16]** | Altered mental sensorium with fever preceded by visual hallucinations | Prednisone, Hydroxychloroquine, and Mycophenolate. Quetiapine and Olanzapine for psychosis | Psychosis persisted with corticosteroids, immunosuppressants, and Quetiapine but improved upon transitioning to Olanzapine |
| **Chapra et al[17]** | acute fever along with generalized seizures evolving into symptoms such as confusion and combative behavior. | IV Dexamethasone Levetiracetam, Antipsychotics and Benzodiazepines. Finally switching to IV Methylprednisolone and IV Cyclophosphamide | The condition worsened and agitation was difficult to control despite using heightened doses of antipsychotics and benzodiazepines. Confusion and clinical state showed remarkable improvement upon starting with Methylprednisolone and Cyclophosphamide |

## DISCUSSION

An autoimmune disease like SLE presents with multiorgan involvement characterized by rash, extreme fatigue, joint pain, renal impairment, central nervous system, and vascular disease.[4] According to the 1999 American College of Rheumatology classification, neurological manifestations of SLE are as follows, seizures, aseptic meningitis, headache, cognitive dysfunction, cerebrovascular disorders, mood disorder, psychosis, movement disorders, Guillain-Barre syndrome, autonomic neuropathy.[5]

The mechanism behind NPSLE is of unclear etiology. Serologically, it is the autoantibodies that target self-proteins. Females are more commonly affected by SLE, and several observations of this difference have indicated an estrogenic effect.[6] 5% of patients diagnosed with lupus experience psychosis which can include confusion, sudden change in behavior, visual or auditory hallucination, lack of insight, and unkempt behavior.[7] Visual hallucinations characterized psychosis in our patient. The presentation of psychosis can be due to various aetiologies that need to be evaluated; these include drug use, infections, structural brain abnormalities, and metabolic abnormalities. The differential diagnosis of NPSLE is comprehensive, making the diagnosis challenging. The main mimics we excluded were CNS vasculitis, systemic diseases like granulomatosis with polyangiitis, Sjogren Syndrome, Neuro-Behcet's disease, viral infections, Hashimoto encephalopathy, Autoimmune encephalitis, and disseminated TB.[8]

Laboratory workup can help familiarize the diagnosis as enlisted in Table 1, but no test can confirm or rule out NPSLE. In our case, the MRI was unremarkable. According to previous studies, more than 50% of the patients with a clinical diagnosis of NPSLE have no obvious abnormality or only non-specific white matter hyperintensities on MRI independent of its diagnosis and severity.[9] As per a case study, hyponatremia can occur in patients with NPSLE by the mechanism of the Syndrome of Inappropriate Anti-Diuretic Hormone (SIADH).[10] On the management front, due to scarcity of controlled trials, specific NPSLE therapy remains relatively empirical. In such patients, the commencement of immunosuppressants such as corticosteroids is warranted alone or in combination with other immunosuppressive therapy, including azathioprine, cyclophosphamide, and mycophenolate mofetil.[11] Oral prednisolone is one of the only agents tested in NPSLE with positive results.[12] To support our case, other adjunctive therapies have been used, including prednisolone, statins, antiplatelet, and anticoagulation therapy to prevent arterial or venous thrombosis.[13] Possible reasons for this early higher incidence of thrombosis could be the high levels of circulating immune complexes, disease activity, cytotoxic antibodies, or a higher state of inflammation.[14] Table 2 depicts various studies revealing initial clinical presentations and subsequent treatment regimens offered in patients diagnosed with NPSLE.[15-18]

As our patient succumbed to COVID-19, there is also a riveting need to gauge the impact of COVID-19 on such patients diagnosed with an autoimmune disease as NPSLE. Reports have revealed that respiratory infections, especially the novel Coronavirus, are one of the most frequent causes of hospitalization and early death in patients with SLE.[19]

## CONCLUSION

In this intricate case of Neuropsychiatric Systemic Lupus Erythematosus (NPSLE), the diverse clinical manifestations underscore the challenges in both diagnosis and management. The patient's presentation, characterized by recurrent symptoms of anemia, myalgias, lower limb weakness, and acute encephalopathy, exemplifies the intricate nature of NPSLE. Despite the absence of specific and sensitive laboratory markers and neuroimaging deficits, the diagnosis was established based on a comprehensive evaluation, including clinical symptoms, serological markers (positive titers for ANA, dsDNA, and anti-Sn RNP), and exclusion of mimicking conditions. The patient's neuropsychiatric symptoms, including visual hallucinations and psychosis, added a layer of complexity to the diagnostic process. The management approach encompassed initiating immunosuppressive therapy, incorporating intravenous methylprednisolone, oral mycophenolate mofetil, and other adjunctive therapies.

Noteworthy improvements were observed in serum creatinine, urine proteins, and the resolution of psychosis following the administration of methylprednisolone. However, the emergence of the Syndrome of Inappropriate Antidiuretic Hormone secretion (SIADH) added an additional layer of complexity to the clinical course. Furthermore, the patient's unfortunate succumbing to COVID-19 highlights the critical intersection of autoimmune diseases, such as NPSLE, with infectious complications.

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