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## **Myasthenic syndrome in systemic lupus erythematosus successfully treated with plasma exchange: through one of the unexplored faces of neuropsychiatric involvement**

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## **Summary**

Neuropsychiatric systemic lupus erythematosus (NPSLE) encompasses a wide range of neurological manifestations, including, though rarely, myasthenia gravis (MG).

We report the case of a 47-year-old woman with long-standing SLE who developed diplopia and fluctuating muscle weakness. Electromyography revealed a decremental response to low-frequency stimulation in the absence of MG-specific autoantibodies. These neurological features were interpreted as manifestations of NPSLE and were initially treated with azathioprine and then rituximab, the latter discontinued due to an adverse reaction. Several years later, immunosuppressive therapy with mycophenolate mofetil and voclosporin was initiated following a renal flare. Although renal remission was achieved, the patient experienced a concomitant relapse of neurological symptoms. After multidisciplinary consultation with neurologists, the patient underwent three monthly cycles of plasma exchange combined with corticosteroid pulses, resulting in marked clinical improvement of neurologic symptoms and sustained serological and clinical stability during the follow-up.

The coexistence of SLE and MG is uncommon; distinguishing between an overlap syndrome or lupus-related myasthenic manifestations and choosing the optimal therapeutic strategy remain challenging. In this case, plasma exchange proved to be an effective rescue therapy, highlighting the importance of a multidisciplinary approach and individualized treatment strategies in managing complex NPSLE presentations.

## Introduction

Neuropsychiatric systemic lupus erythematosus (NPSLE) refers to the broad spectrum of neurological and psychiatric manifestations that can be directly attributed to SLE. In 1999, the American College of Rheumatology (ACR) described nineteen distinct syndromes included in this definition, reflecting the clinical heterogeneity of this entity (1). The prevalence of NPSLE ranges from 6 to 40% of adult SLE patients according to literature, indicating that the rates vary widely across different studies. The underlying pathophysiology is multifactorial and incompletely understood; the two proposed mechanisms involve an inflammatory pathway, characterized by autoantibody-mediated neuronal injury, complement activation, cytokine-driven inflammation, and a thrombotic pathway, often associated to antiphospholipid antibodies (2).

Within this complex spectrum, myasthenia gravis (MG) occupies a particular position. MG is an antibody-mediated autoimmune disorder of the neuromuscular junction characterized by fatigable weakness, typically affecting ocular, bulbar and proximal limb muscles, and in severe cases leading to respiratory compromise. Although rare, epidemiological studies suggest that the coexistence of MG and SLE occurs more often than would be expected. However, whether it represents a co-occurring autoimmune disease or a direct manifestation of NPSLE is still matter of debate.

## Case Report

This report describes the case of a 47-year-old woman with a diagnosis of SLE since the age of 21. Disease onset was primarily characterized by articular and hematologic involvement, with serological tests showing complement consumption, positivity for antinuclear antibodies (ANA), anti-Smith/ribonucleoprotein P (anti-Sm/RNP) and anti-double-strand DNA (anti-dsDNA) antibodies. The disease showed a mild clinical course in the first years and was successfully treated with glucocorticoids (GC), hydroxychloroquine (HCQ) and methotrexate.

At the age of 37, she developed diplopia and progressive muscle weakness. Laboratory tests showed normal muscle enzymes, inflammatory markers and complement levels, while immunological tests confirmed the previous positivity for ANA, anti-dsDNA and anti-Sm/RNP. Antiphospholipid antibodies resulted repeatedly negative.

A neurological evaluation was required for suspected MG. Anti-acetylcholine receptor (AChR) and anti-muscle specific kinase (MuSK) antibodies were negative, while electromyography showed a decremental response on repetitive nerve stimulation at low frequency (3 Hz). Other causes of muscular weakness, such as thyroid dysfunction, metabolic disorders, primary myopathies and steroid myopathies, were excluded through clinical and laboratory evaluation.

A brain magnetic resonance imaging revealed non-specific gliotic areas in the frontal white substance, while a single-photon emission computed tomography showed a reduced cerebral perfusion in the frontal-parietal left area and in the occipital right area.

The myasthenic-like symptoms were attributed to a manifestation of NPSLE and treatment with GC associated to azathioprine was initiated, the last one rapidly discontinued due to intolerance. Subsequently, rituximab 1000 mg, two courses two weeks apart, was prescribed; however, treatment was discontinued after the first infusion due to urticaria. Finally, symptomatic treatment with pyridostigmine was started upon neurological recommendation with stabilization of symptoms.

In August 2024, at the age of 47, the patient experienced an SLE flare characterized by arthralgias, elevated inflammatory markers, low complement levels and proteinuria exceeding 1 g/24 hours, with preserved kidney function. A renal biopsy was performed and revealed a class V lupus nephropathy. In October 2024, the patient received intravenous methylprednisolone pulses (500 mg/day for 3 days), followed by oral prednisone 25 mg/day. Immunosuppressive therapy with mycophenolate mofetil (MMF) 2 g/day and voclosporin 47,4 mg/day was initiated with a rapid decline in proteinuria, resulting in a complete renal response after four months of treatment.

However, during prednisone tapering up to 2.5 mg/day, she reported asthenia, ptosis and muscle fatiguability. Blood exams showed ANA 1:160 speckled, anti-SmRNP 44 U/mL, anti-dsDNA 46 U/mL, normal complement levels and normal inflammatory markers.

Considering the worsening of neurological symptoms, she received three pulses of intravenous methylprednisolone (500 mg/day for 3 days) followed by oral prednisone 25 mg/day, which led to only partial improvement in neurological and muscular symptoms. Different treatment strategies were evaluated and, after a multidisciplinary discussion with the neurology department, we opted for plasma exchange (PLEX).

She underwent three sessions of PLEX followed by a single pulse of methylprednisolone 500 mg administered three days after the final session. The same therapeutic scheme was repeated monthly for three consecutive months. Treatment with MMF, voclosporin and HCQ was continued.

Right after the first cycle, she reported a significant improvement in her neurological symptoms, including resolution of diplopia and substantial reduction of muscle weakness. ANA and Sm-RNP positivity was confirmed after treatment, while dsDNA resulted negative. Routine exams and complement levels were persistently normal. Oral prednisone was gradually tapered to 5 mg/day.

The patient is currently followed-up in our day hospital, showing clinical and laboratory stability.

## Discussion

This clinical case gave us the opportunity to explore MG as an infrequent manifestation of NPSLE. A prospective analysis of neuropsychiatric (NP) events in the SLICC cohort reported no cases of MG (3), while a cross-sectional study in 524 patients with peripheral nervous system involvement described MG in 7 (1.3%) patients (4). Data from smaller cohorts and case series suggest a frequency of MG in SLE between 0.2% and 1%, higher compared to the general population. The temporal relationship reported between the two diseases is variable: MG may precede the diagnosis of SLE, develop concurrently, or appear years later in the disease course. In the first case, SLE patients developing MG seem to have higher prevalence of arthritis, while cutaneous and renal involvement are less frequent. Diagnosis of MG relies on the same principles as in isolated MG, anti-AChR antibodies are positive in the majority of cases and electromyography shows characteristic findings (5-7).

The “seronegative” MG accounts for approximately 10-15% of patients who are negative for anti-AChR antibodies and an additional 5-8% who are also negative for anti-MuSK antibodies (often referred to as double-seronegative MG). In these cases, single-fiber electromyography is usually required, and additional antibodies may be detected only with specialized assays (8, 9).

A more recent nationwide population-based study confirmed a statistically significant association between MG and SLE, with MG patients having more than 10 times higher risk to develop SLE compared to the general population. Moreover, MG patients undergoing thymectomy reported an increased risk of developing SLE. Those with both diseases were more likely to be women, African American and younger compared to subjects with isolated MG (10).

Table 1 summarizes the main literature reports describing the association between MG and systemic lupus erythematosus

Comparing our patient with literature findings, she was atypical due to absence of MG-specific autoantibodies and presence of renal involvement. Published reports of SLE associated with MG describe patients with definite MG, supported by positive MG serology, whereas truly antibody-negative myasthenic presentations are rarely reported. Finally, only isolated cases have been described with a myasthenic syndrome in the setting of active lupus nephritis.

These specific characteristics led both us and the neurologists to interpret the clinical manifestations as a myasthenic syndrome occurring in the context of active SLE, rather than as a concomitant diagnosis of MG. This idea was further confirmed through the Italian algorithm for the attribution of NP events in SLE (11). In our patient, the MG onset occurred after SLE diagnosis, in the absence of minor/non-specific NP events; confounding factors were excluded; and two positive factors were present, particularly responsiveness to GC and active concomitant disease, achieving a score of 9.

From a pathophysiological perspective, several mechanisms may account for the myasthenic syndrome observed in our patient. Anti-dsDNA antibodies are described in nearly 80% of NPSLE patients, while anti-Sm/RNP antibodies have been associated with NP manifestations in 18-60% of

cases (12). Although data demonstrating their direct involvement in SLE-related myasthenic syndromes are not available, we can speculate that they could contribute to neuronal and neuromuscular dysfunction through immune-complex deposition and cytokine dysregulation. Moreover, other autoantibodies directed against components of the neuromuscular junction are probably still unidentified. Management is complex and requires an integrated multidisciplinary approach.

Symptomatic treatment for MG typically includes acetylcholinesterase inhibitors, such as pyridostigmine, but its efficacy appears limited in presence of SLE, requiring immunosuppressive treatment. GC are the first line therapy, while maintenance treatment relies on immunosuppressants, such as azathioprine or mycophenolate, indicated in both diseases (13). For acute exacerbations, IVIG or PLEX is indicated. Targeted therapies like rituximab or complement inhibitors (eculizumab) may be considered in refractory cases, though data in the overlap setting are scarce. Only one case report in the literature described an SLE patient developing MG characterized by rapidly progressive muscular weakness, successfully treated with PLEX in the acute phase (14).

A small number of case reports raised the possibility that HCQ might exacerbate or unmask neuromuscular transmission disorders, since rare reversible myasthenia-like symptoms have been reported with its use. Available literature data from small case series do not support any association, describing only few patients under HCQ treatment developing MG and no exacerbations in MG patients taking HCQ (7). Therefore, we can state that no causal relationship has been demonstrated, although more robust evidence from literature is needed to support this conclusion. In our patient, HCQ was continued, as the overall benefit-risk profile in SLE was considered favorable and there was no temporal correlation between HCQ exposure and myasthenic flares.

According to treatment choice, rituximab was excluded due to previous reported adverse event. Cyclophosphamide was considered for its role in NPSLE treatment, but it was excluded considering the need for rapid clinical response, the low evidence for its efficacy in MG and in SLE-related myasthenic syndromes. Moreover, the absence of life-threatening neurological manifestations and the effective control of renal disease through MMF and voclosporin led us to maintain the current treatment, considering alternative rescue therapies for the neurological symptoms.

PLEX and IVIG treatment were evaluated as the main options. After a multidisciplinary discussion, PLEX was preferred over IVIG, with a significant and rapid clinical improvement. Currently, there is no standardized PLEX regimen for SLE. Therapeutic schedules are heterogeneous, varying in number and frequency of sessions, individually defined through multidisciplinary consultation. According to the American Society for Apheresis guidelines, therapeutic PLEX regimens should be tailored to each patient depending on the severity of the clinical presentation and the therapeutic response (15).

In our patient, the frequency of PLEX was determined in collaboration with transfusion medicine specialists and modulated according to severity of symptoms and rapid clinical response.

The next challenge will be to avoid disease relapses without maintaining long-term GC treatment. The first option could be raising MMF to 3 g/day until GC discontinuation. Among the biologics approved for SLE, belimumab is not recommended as first-line treatment for active NPSLE, while experience with anifrolumab is limited.

## **Conclusions**

In conclusion, this case confirms that the myasthenic syndrome is a possible, although rare, manifestation of NPSLE. The clinical case appears also unique for the negativity of myasthenic-specific antibodies, the presence of concomitant renal involvement and the confirmed efficacy of PLEX as a rescue therapy, while further clinical experience is required to establish the optimal maintenance treatment.

## References

1. The American College of Rheumatology nomenclature and case definitions for neuropsychiatric lupus syndromes. *Arthritis Rheum* 1999; 42: 599-608.
2. Kivity S, Agmon-Levin N, Zandman-Goddard G, Chapman J, Shoenfeld Y. Neuropsychiatric lupus: a mosaic of clinical presentations. *BMC Med* 2015; 13: 43.
3. Hanly JG, Urowitz MB, Su L, Bae SC, Gordon C, Wallace DJ, et al. Systemic Lupus International Collaborating Clinics (SLICC). Prospective analysis of neuropsychiatric events in an international disease inception cohort of patients with systemic lupus erythematosus. *Ann Rheum Dis* 2010; 69: 529-35.
4. Toledano P, Orueta R, Rodríguez-Pintó I, Valls-Solé J, Cervera R, Espinosa G. Peripheral nervous system involvement in systemic lupus erythematosus: Prevalence, clinical and immunological characteristics, treatment and outcome of a large cohort from a single centre. *Autoimmun Rev* 2017; 16: 750-5.
5. Minchenberg SB, Chaparala G, Oaks Z, Banki K, Perl A. Systemic lupus erythematosus-myasthenia gravis overlap syndrome: Presentation and treatment depend on prior thymectomy. *Clin Immunol* 2018; 194: 100-4.
6. Castrejón I, Shum K, Tseng CE, Askanase A. Association between myasthenia gravis and systemic lupus erythematosus: three case reports and review of the literature. *Scand J Rheumatol* 2011; 40: 486-90.
7. Jallouli M, Saadoun D, Eymard B, Leroux G, Haroche J, Le Thi Huong D, et al. The association of systemic lupus erythematosus and myasthenia gravis: a series of 17 cases, with a special focus on hydroxychloroquine use and a review of the literature. *J Neurol* 2012; 259: 1290-7.
8. Meriggioli MN, Sanders DB. Autoimmune myasthenia gravis: emerging clinical and biological heterogeneity. *Lancet Neurol* 2009; 8: 475-90.
9. Gilhus NE. Myasthenia gravis. *N Engl J Med* 2016; 375: 2570-81.
10. Igoe A, Merjanah S, Harley ITW, Clark DH, Sun C, Kaufman KM, et al. Association between systemic lupus erythematosus and myasthenia gravis: a population-based National Study. *Clin Immunol* 2024; 260: 109810.
11. Bortoluzzi A, Scirè CA, Bombardieri S, Caniatti L, Conti F, De Vita S, et al. Development and validation of a new algorithm for attribution of neuropsychiatric events in systemic lupus erythematosus. *Rheumatology* 2015; 54: 891-8.
12. Manca E. Autoantibodies in neuropsychiatric systemic lupus erythematosus (NPSLE): can they be used as biomarkers for the differential diagnosis of this disease? *Clin Rev Allergy Immunol* 2022; 63: 194-209.
13. Wiendl H, Abicht A, Chan A, Della Marina A, Hagenacker T, Hekmat K, et al. Guideline for the management of myasthenic syndromes. *Ther Adv Neurol Disord* 2023; 16: 17562864231213240.
14. García-Alfonso C, Bernal-Macías S, García-Pardo Y, Millán SP, Díaz MC. Coexistence of systemic lupus erythematosus and myasthenia gravis: an unusual case of polyautoimmunity. *Reumatol Clin* 2020; 16: 502-5.
15. Connelly-Smith L, Alquist CR, Aqui NA, Hofmann JC, Klingel R, Onwuemene OA, et al. Guidelines on the use of therapeutic apheresis in clinical practice—evidence-based approach from the writing committee of the American Society for Apheresis: the ninth special issue. *J Clin Apher* 2023; 38: 77-278.

**Table 1. Summary of reports describing the association between myasthenia gravis and systemic lupus erythematosus.**

Study	Sequence (MG↔SLE)	Clinical manifestation	MG serology	EMG findings	Treatment	Outcome
Castrejón <i>et al.</i> (2011) - case series	MG → SLE	Proximal weakness, ocular/bulbar	anti-AChR + in 11/16	Diagnostic in 9/16	Pyridostigmine, GC + thymectomy	Variable
Jallouli <i>et al.</i> (2012) - case series	Both directions (MG→SLE, SLE→MG)	Limb weakness, ocular	anti-AChR + in 94%	n.r.	HCQ, GC, immunosuppressives	Generally favorable; one MG exacerbation
Minchenberg <i>et al.</i> (2018) - case series	Both directions (MG→SLE, SLE→MG)	Muscular weakness; joint symptoms	Anti-AChR+ in 4/4	n.r.	Pyridostigmine, HCQ, MMF	Improvement
García-Alfonso <i>et al.</i> (2020) - case report	SLE→MG	Acute muscular weakness	n.r.	Diagnostic EMG	PLEX, GC, AZA, pyridostigmine	Improvement
Edrees (2022) - case report	SLE → MG	Proximal limbs weakness, ptosis, dyspnea	anti-AChR +	Diagnostic EMG	GC, AZA, pyridostigmine + thymectomy	Improvement

n.r., not reported; MG, myasthenia gravis; SLE, systemic lupus erythematosus; AChR, anti-acetylcholine receptor; GC, glucocorticoids; HCQ, hydroxychloroquine; MMF, mycophenolate mophetil; PLEX, plasma exchange; AZA, azathioprine; EMG, electromyography.