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Systemic lupus erythematosus-myasthenia gravis overlap syndrome: Presentation and treatment depend on prior thymectomy

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Abstract

In this study, we investigated four patients who met the diagnostic criteria for overlapping systemic lupus erythematosus (SLE) and myasthenia gravis (MG) but responded differently to treatment. All patients were acetylcholine receptor (AChR) and antinuclear antibody positive at the time of SLE diagnosis. Two patients presented with SLE who have been effectively treated with cholinesterase inhibitors for MG. These patients developed SLE with photosensitivity, rash, and arthritis post thymectomy, which had been performed 29 years and 40 years earlier, respectively. Two other patients were found to have AChR antibodies and MG in the context on new-onset SLE. These subjects were responsive to hydroxychloroquine and immunosuppression but failed cholinesterase inhibitors. The evolution of these cases is relevant for the role of thymus in lupus pathogenesis during aging and for treatment selection in SLE-MG overlap patients.

Keywords

myasthenia gravis; systemic lupus erythematosus; acetylcholine receptor antibody; antinuclear antibody; antiphospholipid antibody; thymectomy

1. Introduction

In this case series, we present four patients who were diagnosed with myasthenia gravis (MG) and subsequently met the criteria for systemic lupus erythematosus (SLE). The co-occurrence of SLE and MG is rare; nevertheless, MG has long been recognized as one of the

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CONFLICT OF INTEREST STATEMENT

We report no conflicts of interest.

19 neuropsychiatric manifestations of SLE (1). The prevalence of MG in a cohort of 1,300 patients diagnosed with SLE was reported as 1.3% (2). Another study followed 380 SLE patients for 7.5 years, and determined that the prevalence of MG in that population was 0.25% (3), which is substantially higher than the prevalence of 0.02% for MG in the general population (4). MG has been implicated as a mechanism underlying fatigue in a subset of patients with SLE (5). Typically, the first line of therapy for MG is an acetylcholinesterase inhibitor (6) such as pyridostigmine, because it is relatively safe and can be orally administered. Another approach to the treatment of MG is thymectomy (6) as the thymus is thought to be a major trigger of autoantibody production. The absence of the thymus is associated with increased regulatory T cells (7;8). Although the role of the thymus in lupus development has long been considered, its precise role appears to vary among lupus-prone mouse strains (9). Interestingly, thymectomy does not appear to influence the course of disease in established SLE (10). Thymectomy has been shown to precede the development of antiphospholipid antibody syndrome (APS) (11) and SLE in patients with MG (12;13). Here, we report four patients with SLE-MG overlap with two, radically different disease courses and responsiveness to treatment. The diagnosis of SLE (14;15) and MG were made on the basis of established criteria (16). The anti-nuclear antibody (ANA) titers have been provided for each patient based on immunofluorescence staining of HEp-2 cells (17). While SLE developed decades after the diagnosis of MG and thymectomy in two post-menopausal females, both of whom were dependent on treatment with pyridostigmine, MG developed in a male and a post-menopausal female patient after their diagnosis with SLE. In the case of the male patient, he was unresponsive to pyridostigmine, and the female patient developed MG-related symptoms after stopping hydroxychloroquine. These four cases have implications both for disease pathogenesis and selection of the most appropriate first line therapy in MG and SLE overlap patients.

2. Case series with SLE-MG overlap

2.1. Case #1

A 62-year-old female with a 29-year history of seropositive MG presented to her neurologist in 2013 with generalized muscle weakness, diplopia, left ophthalmoplegia, and difficulty with mastication (Table 1A) (16;18). She was diagnosed with MG in 1986 based on a positive test for anti-AChR antibodies (Table 1) and underwent a thymectomy the same year of her MG diagnosis. At the time of diagnosis, the patient was placed on pyridostigmine to manage her MG, which significantly improved her muscle weakness. In 2009, she was diagnosed with SLE (Table 1B) and placed on hydroxychloroquine. Upon physical exam it was determined that she had left upper eyelid weakness and facial asymmetry with right facial hemiparesis. She also exhibited bilateral ankle, knee, wrist, and proximal interphalangeal (PIP) joint swelling and tenderness. The patient's muscle weakness and SLE-related symptoms significantly improved after treatment with an increased dose of pyridostigmine and hydroxychloroquine.

2.2. Case #2

A 56-year-old female presented with a history of MG diagnosed at 10 years of age. MG was based on the development of generalized body weakness, dysphagia, and bilateral ptosis

(Table 1A). She was found to have anti-AChR antibody (Table 2) and treated with pyridostigmine. At age 20, she underwent a thymectomy that improved her muscle weakness. Upon presentation in 2015, the patient was bed bound. Upon physical examination the patient was unable to move her lower extremities, but had minimal movement of her upper extremities. She exhibited abnormal muscle tone, muscle tenderness, and flexion contractures at both wrists. At the time of visit, the patient met five diagnostic criteria for SLE (Table 1B). The patient has been prescribed hydroxychloroquine for the SLE.

2.3. Case #3

A 57-year-old male presented with a 3-year history of MG based on positive AChR antibodies, ptosis, fatigue, respiratory dysfunction, and proximal muscle weakness (Table 1A). His muscle weakness typically worsened during the day, and it was triggered by minimal exertion. He reported dyspnea on exertion, diplopia, and gait instability. Upon physical examination, he had synovitis and tenderness in his metacarpophalangeal (MCP) and PIP joints. Of note, he also had a history of pulmonary embolisms. Following laboratory studies, he met the criteria for SLE (Table 1B), and APS (Table 2). Since the patient was positive for modulating and striated anti-AChR antibodies (Table 2) and his muscle weakness worsened with use, he was initially placed on a cholinesterase inhibitor, which failed to improve the muscle weakness. He was subsequently placed on mycophenolate mofetil and hydroxychloroquine resulting in improvement of his proximal muscle weakness, ptosis, fatigue, and synovitis.

2.4 Case #4

A 58-year-old female was referred by her primary care physician for a possible diagnosis of SLE. The patient had severe fatigue for the past year and morning stiffness in her MCP joints. She also stated that she had chest pain and shortness of breath upon exertion. She did not report any photosensitivity, oral ulcers, or alopecia. She has a history positive for seizures and a “mini-stroke.” Upon physical examination she did not have any joint pain or swelling, neurologic deficits, or any rashes. Her referring physician reported that upon physical examination the patient had a malar rash although none was present at the time of presentation. Following laboratory studies she met the criteria for SLE (Table 1B) and was placed on hydroxychloroquine. Approximately one year later the patient was no longer taking hydroxychloroquine and presented with ptosis that worsened throughout the day and diplopia that was initially attributed to her SLE. Two years later she was worked up for MG because of her ptosis/diplopia and APS based on her prior history of a stroke. She was eventually diagnosed with APS as evidenced by a positive hexagonal phase neutralization assay (Table 2), and MG based on her clinical presentation (Table 1A) as well as positive binding, blocking, and modulating anti-AchR antibodies (Table 2).

3. Discussion

Upon initial presentation, three of four patients had an established diagnosis of MG and were undergoing acetylcholinesterase inhibitor therapy. In cases 1 and 2, the acetylcholinesterase inhibitor treatment in combination with thymectomy was effective for

management of MG symptoms including ptosis and muscle weakness. In case 3, however, the acetylcholinesterase inhibitor failed to improve the patient's proximal muscle weakness. At the time of this case series, the patient in case 4 was not placed on an acetylcholinesterase inhibitor. The patient in case 3 only began to show signs of improvement of muscle weakness, which was attributed to myositis rather than MG; he was diagnosed with SLE-myositis overlap and received mycophenolate mofetil and hydroxychloroquine. However, the patient in case 4 began to show signs of MG after the removal of hydroxychloroquine. If we consider the timeline of the four patients' disease progression (Figure 1), it becomes apparent that the patients in cases 1 and 2 underwent a thymectomy after they were diagnosed with MG. It has been demonstrated in certain lupus-prone mouse strains that thymectomy can trigger systemic autoimmunity due to a breakdown in central tolerance and excessive production of autoantibodies (4;19;20). In contrast, the patient in case 3 may have had SLE that was manifesting itself in a way that was similar to MG. The muscle weakness that the patient in case 3 initially presented with could have been caused by SLE-associated myositis, a finding supported by his high CK levels upon presentation. The positive modulating and striated anti-AChR antibodies could be the result of muscle-breakdown-induced autoantibody production in the setting of SLE. Case 4 had a working diagnosis of SLE for approximately a year before she began experiencing MG symptoms that coincided with the discontinuation of hydroxychloroquine. The course of events that occurred in case 4 culminating with her diagnosis of MG is highly suggestive of MG driven by autoantibodies generated by SLE. Both cases 3 and 4, who developed AChR antibody in the setting of SLE also produced aPL, which raises the possibility of epitope spreading from circulating phospholipids to the complex of AChR and acetylcholine (21).

The development of SLE in MG patients several decades after thymectomy may hold mechanistic clues for the role of T cells in the development of systemic autoimmunity. A mechanistic relationship between SLE and MG is also suggested by a high prevalence of ANA in MG (22). Patients with MG show a paucity of CD4⁺CD25⁺FoxP3⁺ Tregs (8;23), which may be further depleted after thymectomy (24). In fact, the "accidental" removal of the thymus during cardiothoracic surgery appears to cause a depletion of T cells by itself (25). The proportion of FoxP3^{high} CD45RA⁻ memory-type Tregs have become depleted in a time-dependent manner up to 30 years after thymectomy (8). Interestingly, aging occurs with an overall increase of mechanistic target of rapamycin activity (26). In turn, the therapeutic blockade of mTOR reverses the depletion of Tregs and the aPL production in SLE (27–29). Overall, these findings suggest that MG patients unresponsive to cholinesterase inhibitors should be carefully evaluated for underlying SLE, myositis, and APS. Such patients may respond to mTOR blockade that has not been utilized in these cases.

4. Conclusion

The four patients with SLE-MG overlap syndrome discussed in this case series provides an opportunity to gain insight into the pathogenesis and potential treatment options for this rare subset of patients. Here, we report a correlation between prior thymectomy and response to treatment. Patients who had a thymectomy for MG prior to developing SLE responded to acetylcholinesterase inhibitors, while the patients that developed SLE prior to MG responded to immunomodulators such as hydroxychloroquine. Based on the response to

treatment in this study, we hypothesize that patients who have “classic” MG and underwent thymectomy develop SLE due a breakdown in central tolerance, while a subset of patients with SLE develop autoantibodies to the AChR within the scope of their systemic autoimmunity. Further studies are warranted to examine the impact thymectomy and its mechanism of action on autoimmunity both in humans and animal models.

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ABBREVIATIONS

AChR	acetylcholine receptor
anti-AChR	antibody anti-acetylcholine receptor antibody
ANA	antinuclear antibody
aPL	antiphospholipid antibody
APS	antiphospholipid antibody syndrome
anti-Sm	anti-Smith antibody
BUN	blood urea nitrogen
CBC	complete blood count
CK	creatine kinase
Cr	creatinine
CRP	C-reactive protein
dRVVT	diluted Russell viper venom time
anti-dsDNA	anti-double stranded DNA antibody
ESR	erythrocyte sedimentation rate
Hb	hemoglobin
HPPNA	hexagonal phase phospholipid neutralization assay
INR	international normalized ratio
MG	myasthenia gravis
MuSK	muscle specific kinase
MG	myasthenia gravis
NMJ	neuromuscular junction

PNP	platelet neutralization procedure
PT	prothrombin time
anti-RNP	anti-ribonucleoprotein antibody
SLE	systemic lupus erythematosus
SLE-MG	systemic lupus erythematosus and myasthenia gravis overlap
WBC	white blood cell count

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Figure 1.
Timeline of events in the four cases presented in this case series. Clinical course of each patient presented in this case report including year of diagnosis and administration of treatments.

Table 1A:

The most common findings in patients with myasthenia gravis (MG) that was used to initially establish the diagnosis of MG in these three cases. **1B:** Summary of the clinical and lab findings that led to the initial diagnosis of myasthenia gravis and eventually the diagnosis of systemic lupus erythematosus (SLE). Table 1B is the 2012 Systemic Lupus International Collaborating Clinics classification that was used to make the diagnosis of SLE in all cases. For a positive diagnosis, 4 out of 17 criteria including at least one clinical criteria and one immunologic criteria must be met; or a biopsy-proven lupus nephritis.

A)				
MG Criteria [14]	Case #1	Case #2	Case #3	Case #4
Edrophonium chloride test	N/A	N/A	N/A	N/A
Repetitive nerve stimulation	N/A	N/A	Negative	N/A
Single fiber electromyography	N/A	N/A	Negative	N/A
AChR antibody	Positive	Positive	Positive	Positive
MuSK antibody	N/A	Negative	N/A	N/A
Ice test	N/A	N/A	N/A	N/A
Ptosis	Positive	Positive in history	Positive	Positive
Fatigable chewing	Positive in history	Negative	Negative	Negative
Fatigue	Positive	Positive	Positive	Positive
Respiratory dysfunction	Positive in history	Positive in history	Positive	Positive
Proximal weakness	Positive	Positive	Positive	Positive
AChR modulating antibodies	Positive	N/A	Positive	Positive
Striated muscle antibodies	Negative	Negative	Positive	N/A
MG Composite Score	N/A	N/A	3	N/A
B)				
SLE Criteria (4 of 17 must be positive for a diagnosis) [15]	Case #1	Case #2	Case #3	Case #4
Acute cutaneous lupus	Positive	Positive	Positive	Positive in history
Chronic cutaneous lupus	Positive	Negative	Negative	Negative
Nonscarring alopecia	Negative	Negative	Negative	Negative
Oral or nasal ulcers	Negative	Negative	Negative	Negative
Joint disease (arthritis)	Positive	Positive	Positive	Positive
Serositis	Negative	Negative	Negative	Negative
Renal	Negative	Negative	Negative	Negative
Neurologic	Positive	Positive	Positive	Positive
Hemolytic anemia	Negative	Negative	Negative	Negative
Leukopenia or lymphopenia	Negative	Negative	Negative	Negative
Thrombocytopenia	Negative	Negative	Negative	Negative
ANA	Positive	Positive	Positive	Positive
Anti-dsDNA	Negative	Negative	Negative	Negative

A)				
MG Criteria [14]	Case #1	Case #2	Case #3	Case #4
Anti-Sm	Negative	Negative	Negative	Negative
Antiphospholipid	Negative	Positive	Positive	Positive
Low complement	Negative	Negative	Negative	Negative
Direct Coombs' test	Negative	Negative	Negative	Negative

Table 2

Lab values with reference values for both cases that were used to help establish the initial diagnosis of myasthenia gravis and the diagnosis of systemic lupus erythematosus in each case presented.

Laboratory tests	Case #1	Case #2	Case #3	Case #4
ANA	6250 Speckled	6250 Homogeneous	250 Speckled	250 Homogeneous
Anti-ACh Receptor Ab	6.13	0.43	Negative	14.80
Negative < 0.25 nmol/l				
Borderline 0.25–0.40 nmol/l				
Positive 0.40 nmol/l				
Ach Receptor (Muscle) Modulating Ab (0–20% reported as % loss of AChR)	26	N/A	28	32
Ach Receptor Blocking Ab	41	N/A	N/A	38
Negative: 0–25%				
Borderline: 26–30%				
Positive: > 30%				
Striational (Striated Muscle) Ab (Positive titer < 1:60)	N/A	Negative	1:960	N/A
CK (20–200 U/)	154	13	282	68
C3 - Complement (90–180 mg/dl)	148	50	137	162
C4 - Complement (10–40 mg/dl)	44	10	22	28
Complement Total Activity (42–62 U/ml)	63	N/A	55	N/A
CBC:Hb (Male: 13.5–18 g/dl) (Female: 11.5–15.5 g/dl)	13.9	11.7	16.9	N/A
WBC (4000–10,000 /ul)	3800	3400	5900	5300
Platelets (150,000–400,000 /ul)	161,000	156,000	207,000	295,000
BUN (6–20 mg/dl)	15	20	15	12
Cr (0.5–1.2 mg/dl)	1.1	1	1.2	0.6
ESR (0–20 mm/h)	11	67	3	43
CRP (1.0–3.0 mg/l)	N/A	10.8	0.7	N/A
Cardiolipin IgA Ab (0–11 APL Negative)	< 9	3	0	< 9
Cardiolipin IgG Ab (0–14 GPL Negative)	< 9	11	0	8.7
Cardiolipin IgM Ab (20–80 MPL Low to Moderately Positive)	< 9	39	5	4.8
B2 Glycoprotein IgG (20 SGU)	< 9	< 9	< 9	6.7
B2 Glycoprotein IgM (20 SMU)	< 9	14	< 9	3.6
B2 Glycoprotein IgA (20 SAU)	< 9	21	< 9	N/A
dRVVT Ratio (< 1.20)	0.99	0.95	1.48	1.18
HPPNA (< 10.0 s)	2.5	7.5	5.0	18.4
PNP (< 1.0 s)	0.0	1.0	0.0	0.0

Normal values of each test are shown in the parentheses.

ANA, antinuclear antibody; dsDNA, double-stranded DNA; anti-Sm, anti-Smith; RNP, ribonucleoprotein; anti-AChR antibody, anti-acetylcholine receptor antibody; CK, creatine kinase; CBC, complete blood count; Hb, hemoglobin; WBC, white blood count; BUN, blood urea nitrogen; Cr, creatinine; HIV, human immunodeficiency virus; UA, urinalysis; ESR, erythrocyte sedimentation rate; CRP, C-reactive protein; dRVVT, diluted Russell's viper venom time; HPPNA, hexagonal phase phospholipid neutralization assay; PNP, platelet neutralization procedure.