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Systemic lupus erythematosus followed by myasthenia gravis: a rare association

Case Report

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Abstract: Systemic lupus erythematosus (SLE) and myasthenia gravis (MG) are autoimmune diseases, their association in the same patient being rarely described. Here, we report a case of SLE in a 19-year-old girl who within 2 years of the diagnosis of SLE developed MG, and underwent thymectomy for a benign thymoma immediately thereafter.

Keywords: *Systemic lupus erythematosus • Myasthenia gravis • Thymectomy*

1. Introduction

Systemic lupus erythematosus (SLE) is an autoimmune disease characterized by the production of antinuclear antibodies (ANA) in association with diverse clinical manifestations. SLE can affect any organ system, but it mainly involves the skin, joints, kidneys, serosa, lungs, heart and the nervous system.

The coexistence of SLE and other autoimmune diseases has been reported previously [1-4]. A retrospective study of 215 SLE patients showed that 30% of patients had another autoimmune disease, the most common being Sjogren's syndrome, followed by rheumatoid arthritis, autoimmune thrombocytopenia, antiphospholipid syndrome, and hypothyroidism [4].

Furthermore, the association between SLE and MG has been revealed [5]. Myasthenia gravis is a chronic autoimmune disease characterized by fatigue and proximal muscular weakness, which results from an immune-mediated destruction of acetylcholine receptors at the neuromuscular junctions. SLE can precede or follow the development of MG [6]. Moreover, it was described that SLE may develop in patients with MG who have undergone thymectomy [7-9]. Both conditions have common characteristics of autoimmune pathogenesis; these affect mainly young women and display alternate exacerbation and remission periods where both present with antinuclear antibody (ANA) [6].

The aim of this paper is to describe a rare case of MG in a young female patient who within 2 years of the diagnosis of SLE developed MG and underwent thymectomy for a benign thymoma immediately thereafter.

2. Case report

A 19 year-old female patient, previously diagnosed with SLE, was admitted to the County Emergency Hospital Timisoara, Department of Nephrology, in July 2010, with bulbar symptoms (aphonia, dysphagia), proximal

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muscle weakness, palpebral ptosis with complete eye closure failure, diplopia, and acute respiratory failure. Her condition progressively deteriorated rapidly and she developed acute respiratory insufficiency, which required mechanic respiratory support and subsequent admission to the intensive care unit.

The respiratory symptoms occurred a week before her admission, initially with dysphonia that was mistaken for acute laryngitis for which she received symptomatic treatment. She evolved gradually towards aphonia and acute respiratory failure.

Her medical history was significant for chronic glomerulonephritis with nephritic syndrome since 2007 with nospecific etiological framing of the disease. Furthermore, the patient presented chronic hepatitis B, with repeatedly undetected viremia.

During the course of the disease she had suffered from arthritis involving the small joints of hands, minimal pericardial effusion, and high titres of anti-dsDNA and ANA (2008). The diagnosis of SLE was established on 4 out of 11 criteria of The American College of Rheumatology. Renal biopsy was performed in 2009 and revealed membranous lupus nephropathy (Class V ISN/RPS-2003) (Figure 1). Induction therapy was started with pulse methylprednisolone at a dose of 1g/day and a total of three doses, followed by prednisolone 60 mg/day for four weeks. Cyclophosphamide 600 mg monthly was also started. After 2 pulses the medication was withdrawn due to patient's lack of compliance.

Upon admission, her physical examination revealed the following data: pallor of skin and mucosae, "full moon" face, butterfly rash, cyanosis, and bilateral eyelid ptosis. Her blood pressure was 130/80 mmHg and her heart rate was 110 beats/min. The Sp O_2 (spontaneous breathing) was 84% and the Sp O_2 (O_2 mask) was 88-90%. She complained of difficulty in swallowing both liquids and solids.

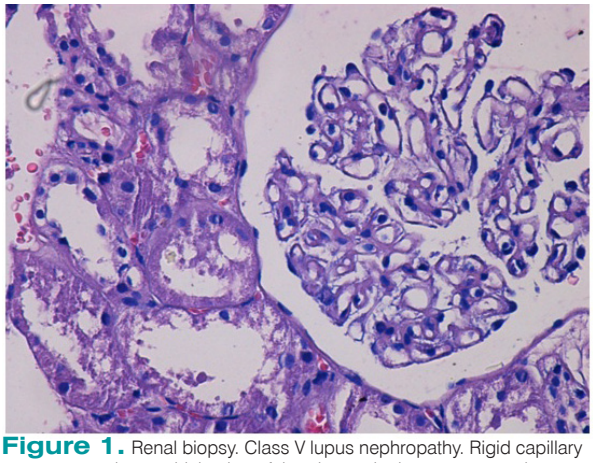

Figure 1. Renal biopsy. Class V lupus nephropathy. Rigid capillary loops, thickening of the glomerular basement membrane (PAS stainx400)

Her neurological exam showed bilateral incomplete eyelid ptosis, peripheral facial palsy, weakness of the nape muscles, and proximal weakness of the scapular and pelvic girdle.

These clinical findings prompted suspicion of circulating immune complex (CIC)- or anti-neutrophil cytoplasm antibody (ANCA)-associated vasculitis, secondary to SLE. Furthermore, the possibility of an anti-phospholipid syndrome with cerebral determination was taken into consideration but ruled out later on. Further laboratory tests and imaging investigations were recommended. Laboratory tests on admission are presented in Table 1. The cerebral angio-MRI revealed no changes of the cerebral blood vessels. Abdominal ultrasound was normal. Chest X-Ray showed a mediastinal mass. Subsequently, mediastinal CT scan confirmed the presence of a solid mass (4.2/1.7/4.6cm), which engulfed the ascending aorta and the pulmonary artery trunk.

Based upon the clinical presentation, the laboratory and the imaging findings we raised the suspicion of myasthenia gravis, which was confirmed by the significant response to Myostin and Atropine. It should be noted that after 10 minutes of Myostin administration, the patient performed eyelid occlusion, raised her arms vertically, performed thigh flexion on the pelvis, and was disconnected from the respiratory device, being able to breathe spontaneously. Corticotherapy was restarted.

After introducing this treatment, the patient evolved with episodes of aggravation and remission. Therefore, treatment with intravenous immunoglobulins 0.4g/kg/day for 5 days, was started. After five days of immunoglobulin therapy, the clinical and biochemical status improved significantly with disappearance of symptoms.

Immunosuppressive treatment was restarted using pulse methylprednisolone at a dose of 1g/day and a total of three doses, followed by oral Prednisolone at a dose of 80 mg daily and Cyclophosphamide 600 mg monthly (6 months).

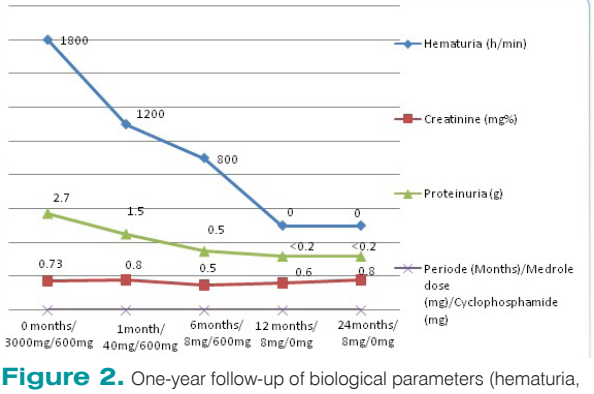

Figure 2. One-year follow-up of biological parameters (hematuria, creatinine, proteinuria)

The patient was discharged with Mestinon 60 mg three times daily and Prednisolone 40mg/day for four weeks, tapered progressively to 8mg/day. Additional medication included Esomeprazole 40 mg oral daily and supplementation with Calcium + Vitamin D daily. The patient's outcome in the following 2 years was uneventful and favourable (Figure 2), and after the last pulse of cyclophosphamide she was switched to Azathioprine 2x50 mg/day. The patient underwent thymectomy with positive outcome.

3. Discussion

The coexistence of SLE and MG has been reported in the literature, but controlled clinical trials have not been performed to prove a real association between these two diseases [9].

Hereby, we describe a case of SLE in a 19-year-old girl who within 2 years of the diagnosis of SLE developed MG and underwent thymectomy for a benign thymoma immediately thereafter.

In most cases reported in the literature, MG occurred before SLE; in these cases thymectomy was a precipitating factor for the development of SLE. Moreover, thymectomy is indicated in all patients with generalized MG between the age of puberty and around 55 years.

In recent years, evidence has emerged of systemic autoimmune disorders including SLE, Hashimoto's thyroiditis, cutaneous vasculitis, and antiphospholipid syndrome occurring many years after thymectomy in patients with MG or other immunological diseases.

The long-term thymectomized MG patients had mild T-cell lymphopenia, which was associated with hypergammaglobulinemia and B cell hyperreactivity. In addition, many of these patients had high titres of a variety of autoantibodies, including anti-dsDNA, and anti-cardiolipin antibodies [10,11].

In the present case report, investigations were initially directed towards ANCA- associated vasculitis secondary to SLE. This interpretation was supported by the presence of p-ANCA antibodies (anti-lactoferrin and anti-elastase antibody). The lack of cerebral vessels changes on angio-MRI ruled out this hypothesis.

Table 1. Laboratory data on admission

Variable	Mean Values	Reference range
White blood cell count, cells/mm^3	25600	4000-9000
Neutrophiles, %	89,8	52-74
Monocites, %	2,5	1-8
Red blood cell count, million/μL	5,64	4-5,5
Hemoglobin, g/dl	18,1	12-15.5
Hematocrit, %	52,4	36-45
Platelet count, cells/mm^3	575000	150000-400000
Erythrocyte sedimentation rate, mm/h	17	2-13
Glucose, mg/dl	232	65-115
Urea mg/dl	32	27-40
Creatinine mg/dl	0,73	0,5-1,3
Antinuclear antibodies	Positive	Negative
Double-stranded DNA	1:160	Negative
Antiphospholipid IgG, GPL units	3	<10
Antiphospholipid IgM, MPL units	1,5	<10
Anticardiolipin IgG, GPL units	4,8	1-10
Anticardiolipin IgM, MPL units	0,8	1-7
Acetylcholine receptor antibody, nmol/l	20,47	<0,45
p-antinuclear cytoplasmic antibody	Positive	Negative
Anti-lactoferrin antibody, U/ml	27,5	<10
Anti-elastase antibody, U/ml	26	<10
AgHBs	Positive	Negative
PCR AND HBV	Undetectable	Negative
Proteinuria/24h	2,7	0,010-0,150g/24h
Addis sediment	L: 600/min, H:2800/min	L:1000/min, H:1000/min

We have also discussed the possibility of an antiphospholipid syndrome (APS) since this may occur in more than 50% of SLE patients. APS is an autoimmune, hypercoagulable state caused by antibodies against cell-membrane phospholipids that provokes blood clots (thrombosis) in both arteries and veins. Moreover, APS occurs within the confines of other autoimmune diseases, such as SLE, in which case the term "secondary antiphospholipid syndrome" is used. Clinical symptoms are dominated by arterial/venous blood clots in any organ system (neurological, cardiac, hepatic, renal etc.). Our patient was negative for anti-cardiolipin and antiphospholipid antibodies.

The high titre of acetylcholine receptors antibodies and the positive response to the pharmacological test (with Myostin and Atropine) pleaded for MG. In SLE, myopathies may be part of the disease's clinical condition or associated with other autoimmune disorders, mainly polymyositis or dermato-polymyositis. Symmetric proximal muscle weakness of the scapular and pelvic girdle is encountered also in polymyositis, but extraocular and bulbar muscles are particularly affected in MG. Furthermore, we have not registered elevated muscle enzymes.

Several medications (chloroquine/hydroxychloroquine, colchicine, corticosteroids, D penicillamine, cyclosporin, simvastatin etc.) have been associated with the occurrence of muscle dysfunction. Antimalarials (chloroquine/ hydroxychloroquine) act as neuromyotoxins, affecting both the nervous system and the striated musculature. Drug-induced myotoxicity is characterized by symmetrical proximal muscle weakness, proximal myopathic potentials on EMG, and presence on optical microscopy of vacuoles within muscle specimens obtained by biopsies [12]. In this case no consumption of drugs inducing myotoxicity was noted.

Our case is characterized by several features:

a. the onset of the disease as chronic glomerulonephritis with nephritic syndrome followed by the development of SLE;
b. the onset of MG after SLE;
c. diagnosis of a thymic tumour that required thymectomy, within two years of the diagnosis of SLE and MG.

Reports concerning thymoma-myasthenia are well known in the literature. Less usual are the associations between autoimmune diseases (SLE or MG) and thymoma before surgery, as illustrated in our case.

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