Systemic lupus erythematosus-myositis overlap syndrome: report of 6 cases

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Abstract

The incidence of myositis in patients with systemic lupus erythematosus (SLE) is low among different series. Here we attempt to describe the main features of SLE/myositis overlap syndrome. We retrospectively reviewed the medical records of 174 patients with SLE seen over 15-year period. All the patients fulfilled the revised American Rheumatology Association criteria for SLE. Patients who met The Bohan and Peter criteria for definite myositis were included in this study. Among those patients, six patients had an associated myositis (3.4% overall). They were 6 women with a mean age of 29 years (20-41 years). At the initial evaluation, 3 patients (50%) were complained from myalgia, and all patients had symmetrical muscle weakness (proximal muscle weakness in 6 cases with distal muscle weakness in 2 cases). The muscle disease was severe in 1 case. Involvements of muscles of the pharynx and upper esophagus were noted in 4 patients (66.6%). The creatine kinase (CK) levels were elevated in 4 cases with a mean rate of 2153.5 UI/L. The electromyogram (EMG) revealed signs of myositis in 5 cases. Muscle biopsy, performed in 5 patients, revealed an inflammatory myopathy changes in 4 cases. Antinuclear antibodies (ANA) were positive in all cases. All our patients were treated with high doses of corticosteroids with favorable outcome. Relapse of SLE disease had occurred in 2 patients. The association SLE-myositis is rare with heterogeneous presentation. Through our observations and literature data we will specify the characteristics of this association.

Introduction

The term *overlap syndrome* includes a large group of conditions characterized by the coexistence of signs, symptoms and immunological features of 2 or more connective tissue diseases and occurring simultaneously in the same patient.[1] Myositis (polymyositis PM or dermatomyositis DM) identifies a group of patients in whom the mascular weakness is the principle clinical feature often associated with muscle pain, tenderness and wasting, or other form of connective tissue diseases; the muscle biopsy generally demonstrates areas of muscle fibre necrosis accompanied by interstitial and/or perivascular cellular infiltrates. Myositis associated with overlap syndromes is usually of paroxysmal variety and has been associated with one or another of connective tissue disorders [Systemic Sclerosis (SSc), Rheumatoid arthritis (RA), Sjögren's syndrome or systemic lupus erythematous (SLE)]. Pearson and Bohan found an incidence of 21% of this type of myositis.[2] Myositis is a rare complication of systemic lupus erythematous[3,4] occurring in almost 4-16% of cases of SLE[3,5,6] and such association is considered to be an heterogeneous condition, sometimes less severe,[7] sometimes similar[2,3] or even worse[8] than the primary disease.

Herein we report a survey of 6 patients who developed overlap syndrome of systemic lupus erythematosus and myositis. We attempt to analysis the epidemiological, clinical, immunological features and therapeutic management of this rare condition, which further elucidation.

Materials and Methods

We retrospectively reviewed the medical records of patients with SLE attending the Department of internal medicine of The University Hédi Chaker Hospital (Sfax, Tunisia) between January 1996 and December 2010. All these patients fulfilled The revised American Rheumatology Association criteria (ACR) for SLE.[9] Patients who had an associated myositis were included in this study.

For myositis diagnosis, we used the criteria proposed by Bohan and Peter for definite myositis [dermatomyositis (DM) or polymyositis (PM)],[10] including symmetrical muscle weakness, increase in serum muscle enzymes, characteristic electromyographic pattern, signs of myositis proven by muscle biopsy and in case of DM typical cutaneous rash.

For each case, we studied the demographic data (gender, age at onset, duration of symptoms), clinical features, investigations, treatment details, and the response to treatment.

Laboratory findings including levels of serum creatine kinase (CK), hematological details and renal function were obtained. For immunological data, antinuclear antibodies (ANA) using HEp2 cells, antibodies directed against native double stranded (ds) DNA, extractable antigens [Ro(SSA), La(SSB), RNP, Sm.] were recorded.

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Other muscle's investigations including electromyography (EMG) and muscle biopsy findings were also noted.

Patients with an overlap syndrome were subclassified into those who had a monophasic illness (a single episode of active disease), relapsing-remitting disease (disease flares associated with disease-free periods), chronic progressive disease (evidence of active disease despite treatment) and remission.

Results

Among a large cohort of 174 SLE patients (whom 162 were females with a frequency of 93%) who had attended the Department of internal medicine, 6 patients were found to have overlap of SLE and idiopathic myositis giving a frequency of 3.4%. Although myalgia was found as a feature of SLE in 15.8% , a true myositis defined by the Bohan and Peter criteria was found in only 3.4% of our SLE patients.

The mean age at presentation was 29 years (range between 20 and 41 years) all the patients were females. SLE and myositis were diagnosed at the same time in 5 cases (83.3%). Myositis had occurred 9 months after SLE diagnosis in one case.

Clinical features

Four patients (66.6%) were symptomatic for more than 2 months prior to presentation (range between 2 and 8 months). Constitutional symptoms were the most common features at disease onset. They were present in 5 patients. Five patients (83.3%) had fever and 3 patients (50%). had general fatigue. At the time of SLE diagnosis, 4 of our patients (66.6%) had mucocutaneous involvements. They were photosensitivity in 4 cases (66.6%), mild mucosal ulceration in 3 cases (50%),

malar rash in 2 cases (33.3%) and discoid SLE rash in 1 case (16.6%). Upon examination, 2 patients (33.3%) had moderate arthritis (pain, swelling and tenderness in more than 2 joints with some loss of function range of movements), and 1 patient (16.6%) had pericardial effusion. Neurological involvement was noted in 3 patients (50%): seizure in 2 patients and documented cerebral vasculitis in 1 patient. Two patients were found to have urine abnormalities (33.3%).

At the time of initial evaluation, 3 patients (50%) were complained from myalgia, and all patients had symmetrical muscle weakness (proximal muscle weakness in 6 cases with distal muscle weakness in 2 cases). The muscle disease was severe in 1 case with complete proximal and distal deficit in 1 case. Involvements of muscles of the pharynx and upper esophagus were noted in 4 patients (66.6%). It was a rapidly progressive dysphagia in 4 cases and a dysphonia in 1 case. One patient had typical DM skin changes (heliotrope rash) leading to the diagnosis of DM. the other five patients were diagnosed as having PM.

Complementary investigations

Laboratory data

Hematological examinations were abnormal in all cases. Five patients (83.3%) had lymphocytopenia, 3 patients (50%) had thrombocytopenia and 2 patients (33.3%) had anemia.

Four patients (66.6%) had elevated creatine phosphokinase at initial examination with a mean serum CPK level at 2153.5 UI/L (range between 1003 and 3000 IU/L). Serum CPK level was within normal limits in the other 2 cases.

Antinuclear antibodies were positive in all cases (range between 1/320 and 1/1280). Anti-DNA native was positive in 3 cases. All patients had other anti-nuclear antibodies (ANA) specificities: 4 patients were positive for ribonucleoprotein antibodies (anti-RNP), anti SSA (n=4), anti-centromere (n=1), anti-Sm (n=3), anti-Scl70 (n=2), anti-histone (n=1), anti nucléosome (n=1), anti Ro52 (n=1), anti ECT (n=1). Of the disease-specific antibodies, anti-Jo-1 was detected in only one out of the 6 patients tested. For patients who had positive anti-RNP antibodies, none of them met the criteria for mixed connective tissue disease (MCTD).

Electromyography and biopsy data

EMG was parformed in all patients. It was suggestive of inflammatory myopathy in 5 cases, with spontaneous activity at rest, including fibrillation potentials, positive sharp waves, and complex repetitive discharges.

Muscle biopsy, performed in 5 patients, showed myopathy signs (necrosis and regeneration of muscle fibers with perivascular infiltration of mononuclear cells) in 4 cases. It was normal in one case.

Renal biopsy was performed in 2 cases. It disclosed aggressive diffuse proliferative lupus nephritis (type IV) according to the World Health Organization WHO classification in one case (case n°4), and showed type II lupus nephritis in the second case (case n°6).

Treatment and clinical course

All of our patients had been treated with oral prednisone (1 mg/kg/day) for 6 weeks. Then, the dose was gradually tapered to 10 mg/day. Three patients had received intravenous pulse of methylprednisolone (1g per day for 3 days consecutively followed by high dose of oral prednisone. The main indication being severe neurological involvement (cerebral vasculitis) in one case, severe myositis in one case and proliferative lupus nephritis (type IV according to the WHO classification) in one case. The latter has also been treated with monthly intravenous Cyclophosphamide pulses in association with corticosteroid therapy.

Over a mean follow up of 6 years (6 months -9 years), the disease was monophasic illness in 3 cases with complete remission of both SLE and myositis, relapsing–remitting SLE in 2 cases and chronic progressive SLE in 1 case. Full remission of myositis had been obtained for all cases.

The demographical, clinical characteristics, therapeutic management and outcomes of the six patients are given in Table 1.

Discussion

The existence of patients with signs and laboratory tests results suggestive of a systemic autoimmune disease but fulfilling more than one classification criteria for well-defined connective tissue disease is a more and more frequent situation in clinical practice and define an *overlap syndrome*. In the literature, and because of the diversity of clinical symptoms, reliable data concerning the prevalence of overlap syndromes are not available.[11,12] However, those patients appear to occur less frequent than patients with SLE, more frequent than patients with systemic sclerosis (SSc) or idiopathic inflammatory myositis (IIM).[12] In a longitudinal study of 100 patients with IIM, Troyanov *et al.* found a frequency of 24% of myositis associated with connective tissue disease according to the original classification.[13] When using its novel classification of myositis, the author found that 60% of their patients were classified as having *overlap myositis*,[13] and that Systemic sclerosis was the most common disease associated with IIM. In the literature, SLE associated with myositis occurs in 4-16% of cases.[14] In contrast to myalgia which can affect nearly half of patients with SLE, true myositis is relatively rare as shown also by our study.[15] Myositis can occur before, after SLE (case 2), or sporadically both diseases can be present simultaneously (cases 1, 3, 4, 5 and 6 in our series).[14]

Several published studies had described the clinical characteristics of myositis in patients with SLE in some series[3,5,6,16] or in cases reports.[4,14,17,18] Our lupus myositis patients were all female which is concordant to the previous studies.[3,7,14,17,19] The study reported by Foot *et al.*[6] suggested that lupus myositis was very similar to primary disease, in contrast to the milder descriptions of Fessel[16] and Tsokos *et al.*[5] were less than rigorous: all but one of their patients with alleged myositis had a normal serum CK, and only 5/18 subjects had a confirmatory muscle biopsy. Although it remains unclear, some reports have indicated that this overlap syndrome follows a benign course and that the prognosis of myositis associated with SLE is reputed to be better than primary myositis in terms of morbidity and response to therapy.[20-22] However, there have been some controversies in the literature. Garton and Isenberg[3] have indicated, in a review of 30 cases that there is no significant difference between patients with overlap myositis /SLE and patients with primary myositis. There were no substantial deferences in morbidity or mortality on prolonged follow-up, and the clinical course was generally similar for both groups. Antibodies to Jo-1 were of low prevalence in this group, although anti-56 kDa nRNP antibodies were seen with high frequency. Anti-56 kDa nRNP antibodies are associated with myositis occurring together with SLE; the presence of this antibody can help to predict muscle involvement in this group of patients.

In other hand, in a recent study, the authors had compared clinical and laboratory features in 10 patients with SLE complicated by myositis with 290 patients with SLE without myositis. The results suggested that patients with an overlap of myositis and SLE are more likely to have alopecia, oral ulcers, erosive joint disease and pulmonary disease but less likely to have renal disease. They found that those SLE/myositis patients were likely to die at a younger age and that their overall disease evolution seems to be influenced by the presence of antiRNP autoantibodies.[23] Our lupus myositis patients are characterized by a frequent mild form of myositis with the presence on anti-RNP antibodies (66.6%), the frequency of hematological (100%), mucocutanous (66.6%) and central neurological involvement (seizure and cerebral vasculitis in 50%) for SLE with a good response to corticosteroid therapy in all cases. However, our study is small and potential confounding influences must be considered.

In the primary autoimmune myositis, the

Table 1. Summary of the demographical, clinical characteristics, therapeutic management and outcomes of our patients with systemic lupus erythematosus /myositis overlap syndrome.

	Case #1	Case #2	Case #3	Case #4	Case #5	Case #6
Age at onset (years)/gender	20/F	23/F	24/F	30/F	41/F	39/F
SLE symptoms	Hematological: Anemia/lymphopénia Arthritis/ Pericarditis	Constitutional symptoms: fever/ Cuttaneous: Malar rash/ photosensitivity/ Hematological: Anemia/lymphopenia Arthritis	Constitutional symptoms: fever/Oral ulcer/ Hematological: Anemia/lymphopenia/ thrombocytopenia/ Neurological symptoms: seizure	Constitutional symptoms: fever/ Cuttaneous: Malar rash/ photosensitivity Hematological: Anemia/ lymphopenia/ thrombocytopenia/ Nephritis (type IV)/ Neurological symptoms: seizure/ Pericarditis	Constitutional symptoms: fever/Oral ulcer/ Hematological: Anemia Neurological symptoms: cerebral vasculitis	Constitutional symptoms: fever/ Cutaneous: discoid SLE rash/ Hematological: Anemia/lymphopenia/ thrombocytopenia/ Nephritis (II)
Myositis symptoms	PM: Proximal muscle weakness	PM: Dysphagia/ Proximal and distal weakness	PM: Dysphagia/ Myalgies/ Proximal muscle weakness	PM: Dysphagia/ Myalgias/ Proximal muscle weakness	DM: heliotrope rash/ Dysphagia/ Dysphonia/ Proximal muscle weakness Proximal and distal weakness	PM: Myalgias/
Time of onset of myosits/SLE symptoms	concomitant	After 9 months	concomitant	concomitant	concomitant	concomitant
Laboratory findings	Baseline CK level (U/L): 19381	Baseline CK level (U/L): 54	Baseline CK level (U/l): 1003	Baseline CK level (U/L): 2673	Baseline CK level (U/L): 334	Baseline CK level (U/L): 3000
Immunological findings	Positive ANA 1/1280 Positive anti-RNP Positive anti-SSA	Positive ANA 1/320 Positive anti-RNP Positive anti-SSA Positive anti-Scl70	Positive ANA 1/320 Positive anti-RNP Positive anti-Sm	Positive ANA 1/1280 Positive anti-DNA Positive anti-SSA Positive anti-SSB Positive anti-Histones Positive anti-Ro52	Positive ANA 1/1280 Positive anti-DNA Positive anti-RNP Positive anti-Scl70 Positive anti-ECT	Positive ANA 1/1280 Positive anti-DNA Positive anti-JO1 Positive anti-SSA
Initial treatment	Prednisone 1mg/kg/day for 6 weeks then tapered to 30 mg/day	Prednisone 1 mg/kg/day for 6 weeks then tapered to 10 mg/day	Methylprednisolone pulses 1 g/day for 3 days Prednisone 1 mg/kg/ day for 6 weeks then tapered to 10 mg/day	Methylprednisolone pulses 1 g/day for 3 days Prednisone 1 mg/kg/day for 6 weeks then tapered to 10 mg/day Cyclophosphamide pulses (SLE nephritis)	Methylprednisolone pulses 1 g/day for 3 days (neurological symptoms) Prednisone 1 mg/kg/day for 6 weeks then tapered to 10 mg/day	Methylprednisolone pulses 1 g/day for 3 days Prednisone 1 mg/kg/day for 6 weeks then tapered to 10 mg/day
Outcomes (relapse)	relapsing-remitting disease/ Initial improvement/ Relapse of SLE after 2 months , under prednisone 30 mg/day (fever, anemia, pericarditis, myocarditi)	Improvement of SLE and myositis symptoms infectious complications: Tuberculosis	- relapsing-remitting disease - Initial improvement - 4 relapses of SLE symptoms	chronic progressive disease Complete remission of myositis with normalization of muscle function and levels serum CK Persistent fever and Anemia	monophasic illness Improvement with complete remission of both diseases	monophasic illness Improvement
Mean duration of follow up	3 years	9 years	8 years	6months	6 years 1 month	8 years and 9 months

SLE, systemic lupus erythematosus; F, female; PM, polymyositis; DM, dermatomyositis; anti-RNP, antibody to a ribonuclease-sensitive ribonuclear protein; ANA, antinuclear antibody.

ANA were less commonly positive and the presence of a strongly positive ANA may lead to a more diligent search for an associated autoimmune rheumatic disease.[3] However, patients can have a high frequency of specifically associated autoantibodies to nuclear and cytoplasmic antigens, termed myositis specific antibodies (MSA).[24] MSA are found almost in patients with DM/PM and associated overlap syndromes. Autoantibodies detected in myositis associated overlap syndromes also include anti-U1 RNP, anti-Ro/SSA, anti-La/SSB, and anti-Sm. In general, the picture of overlap syndromes is complex and heterogeneous. The presence of specific autoantibody profiles is certainly a useful tool in the diagnosis evaluation of such patients.[20]

Sometimes, it seems difficult to distinguish myositis associated with SLE from

musculoskeletal involvement related to SLE and/or from muscle weakness occurring in patients with SLE that may be caused by many other disorders (includind infections, metabolic abnormalities or drug induced myositis). Generally, true myositis differs slightly in its clinical presentation. Enzymatic testing and additional testing (electromyography and muscle biopsy) would confirm the diagnosis. Furthermore, the presence of antibodies such as anti-RNP or PM-Scl is suggestive of an overlap myositis.[13]

The treatments used are basically the same, as many of the treatments used for myositis are applied to the different autoimmune diseases. Corticosteroids were used usually as a first-line therapy and additional immunosuppressive agents were commonly used. In our series, pulses of corticosteroid were indicated for lupus symptoms in 2 cases (cerebral vasculitis and nephritis type IV) and for severe myositis in 1 case. Immunosuppressive agent (cyclophosphamide in our series) was indicated for severe lupus nephritis in 1 case. The prognosis of myositis varies greatly and factors that affect prognosis in IIM should be considered the same in overlap syndrome SLE/myositis. These include the patient's age, the severity of myositis, the presence of dysphagia or cardiopulmonary disease and the initial response to corticosteroid therapy.

Conclusions

In the present study, we have tried to analyze the epidemiological and the clinical features concerning overlap syndrome of SLE and myositis. Our data confirm the rarity of this association, the female predominance, and the variety of clinical presentation and the benign course of myositis. Certainly, there are differences between overlap myositis/SLE and non-overlap patients and SLE/ myositis should not be considered as a mild disease and should be treated as aggressively as primary myositis. Many other questions need further study and investigations: what mechanisms induce and sustain myositis overlaps? What are the genetic and environmental risk factors that lead to myositis overlaps? And what new better therapies can block these mechanisms?

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