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FULL RECOVERY OVER ONE YEAR OF THE OVERLAP SYNDROME SCLEROMYOSITIS TO MAINTENANCE THERAPY WITH MYCOPHENOLATE MOFETIL AND RITUXIMAB, WHICH RELAPSED WITHIN 8 MONTHS OF DISCONTINUATION

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ABSTRACT

Scleromyositis (SM) is an emerging, distinct entity within the spectrum of diffuse systemic sclerosis (SSc) and autoimmune inflammatory myopathies. It can carry a poorer prognosis due to multisystem involvement and extramuscular complications, with no consensus on treatment strategies currently available.

We report on a 20-year-old woman with a history of recurrent infections over the past year, who presented with persistent myalgias for four months. On examination, she exhibited muscle weakness in the scapular and pelvic girdles, along with sclerodactyly. Laboratory results showed elevated creatine kinase (13,000 U/l), aldolase (15.6 U/l), lactate dehydrogenase (1,481 U/l) and myoglobin (4,400 ng/ml). Autoimmune screening was positive for antinuclear antibodies, anti-PM-scleroderma (anti-PM-Scl) 75 and 100, and anti-CENP-B antibodies. An MRI of the pelvic girdle indicated acute/subacute myositis, and electromyography revealed both distal and proximal myopathy. Muscle biopsy showed extensive necrosis with minimal inflammatory infiltration. Nailfold capillaroscopy demonstrated an early scleroderma pattern, while CT and spirometry revealed mild interstitial restrictive lung disease. Initial treatment involved intravenous immunoglobulin (IVIG), mycophenolate mofetil (MMF) and prednisolone. This was followed by maintenance therapy with MMF and rituximab (RTX) every six months for the first year. Over six months, the patient showed progressive improvement in muscle strength and normalisation of muscle enzyme levels.

In conclusion, SM presents with variable phenotypes, ranging from mild to extensive systemic involvement. This case underscores the importance of individualised patient stratification and highlights the need for structured induction and maintenance therapy due to the disease's extensive activity.

KEYWORDS

Scleromyositis, inflammatory myositis, systemic sclerosis, interstitial lung disease, digital sclerosis

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LEARNING POINTS

- Scleromyositis (SM) is a rare and poorly understood condition that combines features of systemic sclerosis and immune-mediated myositis, often linked to anti-PM-scleroderma antibodies.
- Despite efforts to classify SM, it demonstrates unique clinical patterns that distinguish it from other myositis subtypes.
- The management of SM remains challenging, as there are no established guidelines or standardised treatment protocols.

INTRODUCTION

Systemic sclerosis (SSc) is a rare autoimmune disease characterised by small vessel vasculopathy and fibroblast dysfunction leading to increase of fibrosis[1-3]. Most patients experience skin thickening and variable internal organ damage[1-3]. Two forms of SSc can be distinguished according to the extent of systemic involvement: limited or diffuse[1-3]. Autoimmune inflammatory myositis (AIM) encompasses a heterogeneous rare condition characterised by myopathy secondary to inflammation-driven damage and widely variable extramuscular features[1,2,4]. Subtypes that have been described in AIM are immune-mediated necrotising myopathy (IMNM), anti-synthetase syndrome, dermatomyositis, polymyositis (PM) and inclusion body myositis[1].

Clinical features and autoantibodies of SSc have been reported in up to 40% of AIM patients and AIM has been described in 96% of SSc patients, confirming a close relationship between them[1,5].

Scleromyositis (SM) has been a term used to define an independent entity between the AIM and the SSc spectrum[1,5]. Although well known, it is a harsh syndrome to characterise due to its changeable clinical severity that may vary from muscle weakness with limited skin involvement to having life-threatening pulmonary and cardiovascular complications[1,6].

Treatment of SM must be tailored and is distinctive from the management of SSc and AIM alone[1]. A thorough clinico-sero-pathological characterisation of these patients is crucial to predict clinical outcomes and guide individualised treatment, since no management guidelines are available for this entity[1].

CASE DESCRIPTION

A 20-year-old female presented to the emergency department with worsening myalgia on upper and lower limbs, accompanied by asthenia and exertional dyspnoea for the last four months. Over the past year she reported

Parameter	Day 1	Day 30 (MMF, IVIG, RTX, PDN)	Three months follow-up	Six months follow-up
Haemoglobin (g/dl)	12.6	12.3	11.6	12.5
Leucocytes (×10⁶/µl)	16.09	8.47	12.06	8.22
Neutrophils (%)	74	52	73	51
Lymphocytes (%)	19	29	19	37
C-reactive protein (mg/l)	8.5	7.5	0.9	0.5
Platelets (×10³/µl)	265	261	295	227
Aspartate aminotransferase (AST, U/l)	571	298	19	16
Alanine aminotransferase (ALT, U/l)	333	224	12	9
Bilirubin (mg/dl)	0.51	0.34	0.50	0.43
Creatinine (mg/dL)	0.34	0.27	0.53	0.53
Lactate dehydrogenase (U/l)	1,481	1,034	145	168
Creatine kinase (U/l)	13,104	5,386	61	62
Myoglobin (U/l)	4,393	3,264	14.2	-
Aldolase (U/l)	15.6	80.9	6.2	5.1

Table 1. Progression of analytical features.

Auto antibodies	Results
Anti-nuclear antibodies (ANAs)	> 1:640 (AC-8,9,10)
Anti-PM/Scl 75 antibodies	**Positive**
Anti-PM/Scl 100 antibodies	**Positive**
Anti-centromere B antibody (anti-CENP-B)	**Positive**
Anti-double stranded antibody (anti-dsDNA)	Negative
Anti-neutrophil cytoplasmic antibodies (ANCA)	Negative
Anti-cyclic citrullinated peptide antibodies (anti-CCP)	Negative
Rheumatoid factor	Negative
Anti-Jo-1 antibodies	Negative
Anti-RNP antibodies	Negative
Anti-Scl-70 antibodies	Negative
Anti-Sm antibodies	Negative
Anti-SSa antibodies	Negative
Anti-SSb antibodies	Negative

Table 2. Autoimmunity panel.

recurrent infections such as mild SARS-CoV-2 infection, a cutaneous abscess requiring drainage, vaginal candidiasis, herpes zoster, bacterial pneumonia, acute cystitis and mononucleosis. Physical examination revealed symmetrical proximal muscle weakness affecting both shoulder and pelvic girdles, more pronounced in the lower limbs, resulting in functional limitation. Sclerodactyly was observed predominantly on the right hand, with a Rodnan skin score of 3/51.

Initial laboratory results are shown on *Table 1*. We highlight the following findings: leukocytosis at 16,090/ul (74% neutrophils), C-reactive protein at 8.5 mg/l, lactate dehydrogenase at 1,481 U/l, creatine kinase at 13.104 U/l, myoglobin at 4.393 ng/mL, aldolase at 15.6 U/L and normal thyroid function.

The patient was admitted for further investigation. A full-body CT scan ruled out any neoplastic processes and additional tests, including blood and urine cultures, along with serologies for HIV, hepatitis B and C, Epstein-Barr virus, cytomegalovirus, *Coxiella*, *Rickettsia*, *Brucella*, *Bartonella* and *Leptospira*, were all negative. Immunoglobulin levels and protein profiles were within normal ranges. Autoimmune screening *(Table 2)* revealed positivity for antinuclear antibodies (ANAs), anti-PM/Scl 75/100, anti-DFS70 and anti-CENP-B antibodies.

Given the likely diagnosis of an autoimmune disease, further evaluation of systemic involvement and severity was conducted. An MRI of the lower limbs showed hyperintensity in the pelvic girdle muscles, consistent with acute/subacute myositis. Muscle biopsy revealed extensive necrosis with minimal inflammatory infiltration (isolated CD20 cells), supporting a diagnosis of IMNM *(Fig. 1)*. Electromyography confirmed proximal and distal myopathy with spontaneous muscle activity, without signs of neurological damage.

Although the presence of AIM was evident, some clinical manifestations, such as dermatological and respiratory symptoms, remained unexplained. Nailfold capillaroscopy demonstrated an early pattern of scleroderma (reduced capillaries, giant capillaries, microhaemorrhages). High-resolution chest CT revealed interstitial lung disease, with diffuse ground-glass opacities in the right upper and both lower lobes. Spirometry showed a mild restrictive lung disease pattern, with reduced total lung capacity and diffusing capacity for carbon monoxide. A transthoracic echocardiogram ruled out any cardiac dysfunction or valvular disease.

Given the diagnosis of SM with significant systemic involvement, induction therapy was initiated with intravenous immunoglobulin (IVIG) and mycophenolate mofetil (MMF). Due to a lack of clinical improvement after two weeks, likely due to the subacute nature of the disease, prednisolone (15 mg/day) and rituximab (RTX) were introduced. After four months of treatment, the patient showed significant improvement, both clinically (muscle strength and skin improvement) and analytically *(Table 1)*. This allowed for the tapering of steroids and discontinuation

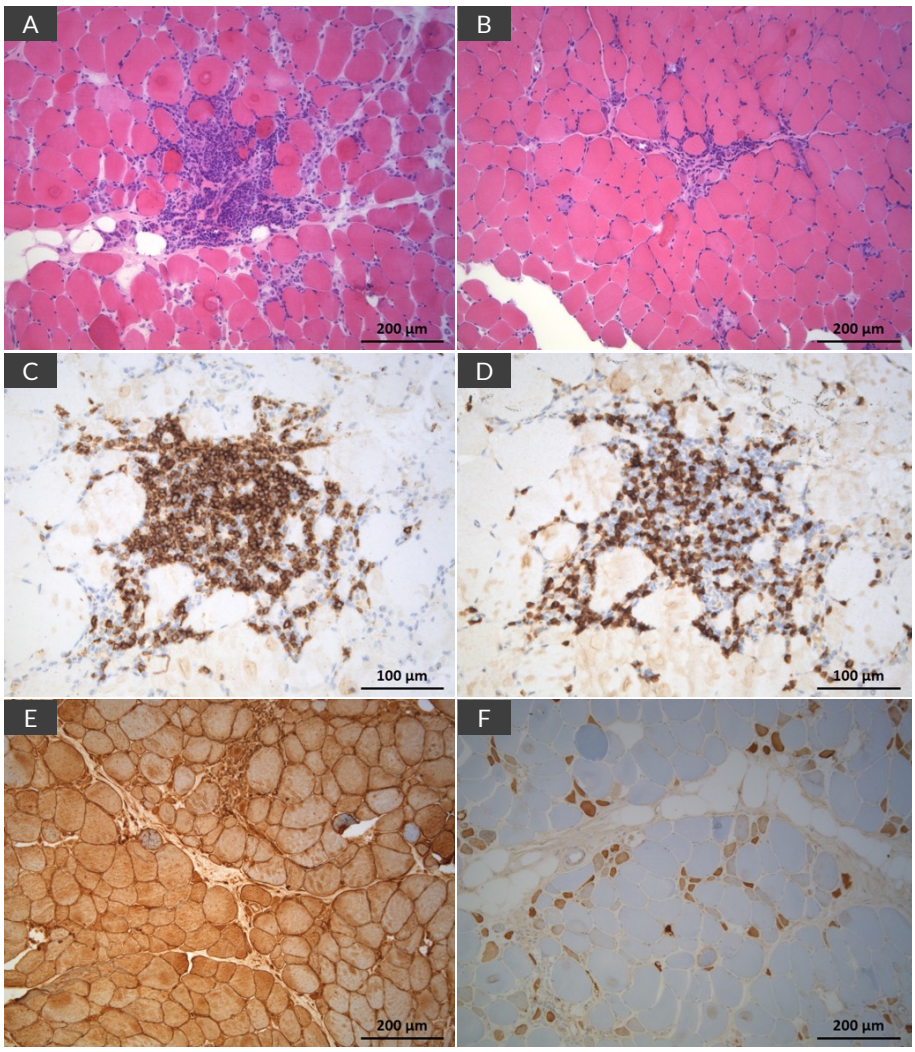


Figure 1. Histopathological findings on muscle biopsy: A) Inflammatory infiltrate located in the perimysium and in a perivascular location, with extension to the endomysium and damage to adjacent muscle fibres; B) Muscle with a myopathic profile where frequent fibres stand out in different phases of the necrosis process, dispersed throughout the fascicles, and some basophil fibres. There is no perifascicular predominance of these changes; C and D) Mononuclear inflammatory infiltrates are composed of T lymphocytes, with an important population of associated B lymphocytes co-existing; E) Overexpression of MHC-I products is observed in an intense and diffuse manner, without perifascicular predominance; F) Numerous regenerating fibres, without any perifascicular predominance.

of IVIG. Maintenance therapy with MMF and RTX continued every six months. After one year, with a full clinical recovery, the patient decided to discontinue treatment. The following eight months, we saw a clear worsening of sclerodactyly (Rodnan 6), progression of interstitial disease *(Fig. 2)* and myositis.

DISCUSSION

SSc and AIM are two heterogeneous entities with well-established diagnostic criteria[1,5]. Controversy arises when these two entities overlap, resulting in a condition designated as SM. Although there is literature supporting SM as a unique connective tissue disease with specific pathology and worse prognosis, the European Neuromuscular Centre has still not recognised it as an independent entity[1,5,7,8].

Having a highly variable clinical presentation without known pathognomonic signs or symptoms, diagnosis of SM relies mostly on muscle biopsy findings and serological profiling[2,4]. Distinct systemic involvement and extramuscular complications stand out as major clinical differences to other entities: interstitial lung disease (ILD) is detected in up to 90% of cases, followed by gastrointestinal (65%) and cutaneous (40%) involvement[2,4,5]. In SM patients, ILD seems to have better prognosis than in SSc-associated myopathy; as demonstrated in our case, where even after voluntary suspension of treatment, there was a minimal ILD progression[8]. We believe that pulmonary changes in SM are secondary to inflammatory response rather than generalised fibrosis (as in SSc), explaining the disparity of prognosis[8].

Regarding the immunological profile, antibodies with frequent and strong association with SM include anti-PM/Scl (31%), anti-Ku, anti-U1-RNP, anti-U3-RNP and anti-SMN[1,2], unlike antibodies specifically associated with SSc that do not appear to be linked to SM[1,2]. Those serological differences might explain the disparities of clinical features, treatment response and prognosis between SSc and SM[1,2].

Histological findings of SM were reviewed in 559 muscle biopsies[5], showing necrosis in 56% and IMNM pattern in 16% of patients. Analysing the subgroup with positivity for anti-PM-Scl 75/100, as our patient, inflammatory infiltrates (85%) and necrosis (44%) were found.

Without official recommendations, treatment decisions in SM should be made on a case-by-case basis by a multidisciplinary group. In our opinion, in severe cases like ours, induction followed by maintenance therapy is mandatory due to the clinical severity[1,2]. We chose MMF first due to the high level of evidence demonstrated in pulmonary and skin involvement in other autoimmune diseases[1]. In general, corticosteroid therapy is the treatment of choice to control muscular manifestations, especially

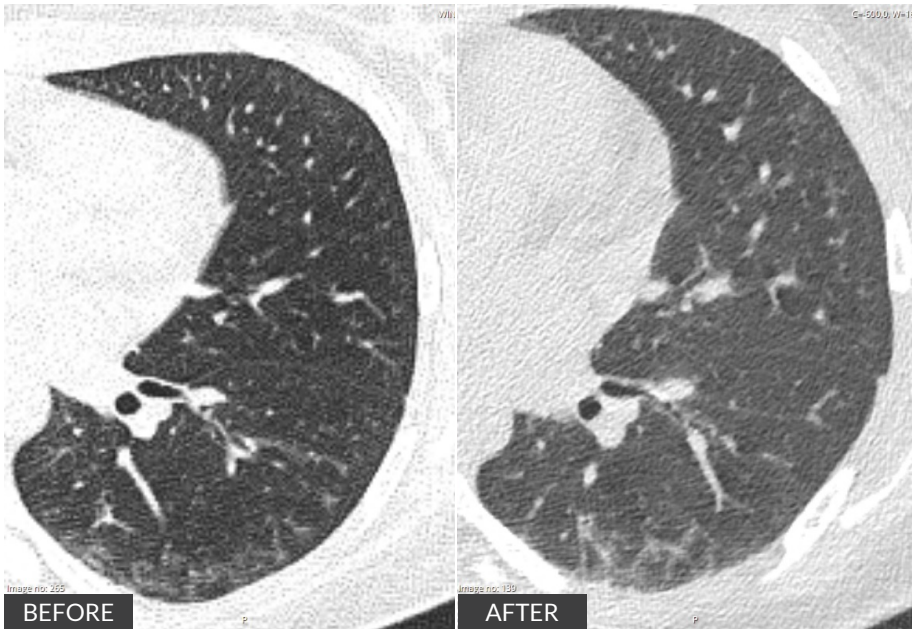


Figure 2. High-resolution chest CT before and after treatment discontinuation with progression of ground glass opacities in the right lower lobe.

if inflammatory changes (rather than fibrosing forms) are present[4]. The balance between treating muscle disease and the risk of developing a scleroderma renal crisis, as well as infectious complications, is always a concern[1,2,9]. Therefore, we recommend not exceeding prednisolone dosage of 15 to 20 mg daily[1,2,9]; IVIG should be added due to its steroid-sparing effect shown in case of muscle involvement[1]. As a last-line treatment, we consider the use of RTX in refractory cases, based on the favourable treatment response documented in patients with overlap of SSc and myositis[1]. In our SM patient, due to the clinical and analytical severity observed, there was a need for rapid escalation of treatment lines, anticipating the poor prognosis.

Two case reports with similar clinical severity were found in literature. One reports a 60-year-old female with anti-PM/Scl-positive SM with skin, muscle, pulmonary and gastrointestinal involvement treated with prednisone 1 mg/kg/day and azathioprine: she died 24 days after admission. Clinical improvement was transitory; she progressed with dysphagia and muscle weakness deterioration, followed by urinary septic shock in need of renal replacement therapy and vasopressors[2]. The second report describes a 28-year-old patient with anti-PM/Scl-positive SM with (skin) calcinosis, articular (arthritis), muscular, pulmonary and cardiac (myocarditis) involvement that showed therapeutic refractoriness to steroids, MMF, IVIG and RTX; clinical improvement was only achieved when adding tofacitinib 5 mg twice daily, without adverse effects[10].

CONCLUSION

Despite being a heterogeneous entity under study, there are clear arguments supporting its distinction from other overlap syndromes: its immunology, histopathology and treatment response. We consider SM to be a subtype of myositis with features associated with SSc, highlighting the need for this entity to be discussed and included in current guidelines for inflammatory myositis.

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