

# Four Cases of Anti-PM/Scl Antibody-positive Juvenile Overlap Syndrome with Features of Myositis and Systemic Sclerosis

To the Editor:

Overlap syndromes of systemic sclerosis (SSc)/myositis are rare and have primarily been described in adults. Relatively few cases of childhood SSc/myositis overlap have been reported<sup>1,2,3,4,5,6,7</sup>. In our case series, 4 patients diagnosed with juvenile overlap syndrome of myositis with SSc are described (Table 1). All 4 cases were positive for anti-PM/Scl and eventually developed symptoms consistent with overlap SSc/myositis.

Patient 1 was an 8-year-old white male who presented with diffuse hand swelling, tight skin, and contractures of the metacarpophalangeal (MCP), proximal interphalangeal (PIP), and distal interphalangeal joints and wrists of 3-month duration. His muscle strength was normal. He had Gottron papules over his MCP and PIP joints, cracking of the tips of his fingers and toes (without ulceration), and erythema over his elbows and knees. He denied Raynaud phenomenon (RP), fatigue, dysphagia, or dyspnea. Myositis antibody panel demonstrated positive anti-PM/Scl antibodies, and he was diagnosed with overlap SSc/myositis syndrome. One year after diagnosis, he had substantial improvement in his functional ability while receiving therapy, but not complete symptom resolution.

Patient 2 was an African American female diagnosed with juvenile dermatomyositis (JDM) at age 6 when she presented with a 5-month history of arthralgias, proximal muscle weakness, heliotrope rash, periungual telangiectases, and Gottron papules. She experienced remission in the first year, and treatment was discontinued but later resumed owing to recrudescence of her disease. At age 9, despite ongoing treatment, she gradually developed

limited range of motion of her wrists with skin tightness and thinning of the subcutaneous digital tissue, raising suspicion for an overlap syndrome with SSc. She frequently experienced livedo reticularis, but not RP. Six years after initial diagnosis, myositis antibody profile was positive for anti-PM/Scl antibodies. Clinical remission was subsequently achieved, despite residual limited range of motion of her wrists and mild sclerodactyly. Treatment was discontinued at age 14. She had 7 years of followup after treatment discontinuation and remained asymptomatic.

Patient 3, a white female, was diagnosed with JDM at age 4 at an outside institution when she presented with proximal muscle weakness, elevated muscle enzymes, and characteristic rash. Her disease was complicated by calcinosis of her fingers and hands. She was transferred to our institution at age 12 and subsequently developed sclerodactyly and skin tightness around her mouth, raising concern for an overlap syndrome. At age 14, she tested positive for anti-PM/Scl antibodies, and her diagnosis was modified to overlap SSc/myositis. Her disease was resistant to treatment with intravenous immunoglobulin for 8 months [used in addition to methotrexate (MTX) and prednisone]. She received a course of rituximab, with eventual control of her symptoms. At age 17, she self-discontinued treatment. In followup 2 years later, she was doing well with only mild RP and residual sclerodactyly.

Patient 4, an African American female, was diagnosed with JDM at age 8 at an outside institution when she presented with muscle weakness, elevated muscle enzymes, Gottron papules, and a heliotrope rash. Her disease course was complicated by cataracts and glaucoma secondary to her steroid therapy. When she was transferred to our institution at age 11, her disease was clinically well controlled and her MTX was decreased. She subsequently developed bilateral parotid swelling (with nodularity and calci-

Table 1. Four pediatric patients with SSc/myositis overlap syndrome.

Characteristics	Patient 1	Patient 2	Patient 3*	Patient 4
Age at diagnosis and presenting symptoms	8 y/o M: Hand swelling and contractures, sclerodactyly, faint Gottron papules, rash, elevated muscle enzymes	6 y/o F: Heliotrope rash, Gottron papules, proximal muscle weakness, elevated muscle enzymes, periungual telangiectases, arthritis	4 y/o F: Proximal muscle weakness, elevated muscle enzymes, rash	8 y/o F: Heliotrope rash, Gottron papules, proximal muscle weakness, elevated muscle enzymes
Timing and manifesting symptoms suggestive of an overlap syndrome	At diagnosis	3 yrs after diagnosis developed hand/wrist skin sclerosis, sclerodactyly, livedo reticularis	9 yrs after diagnosis developed extremity calcinosis, sclerodactyly, skin tightness	3 ½ yrs after diagnosis developed localized facial scleroderma with hyperpigmentation, calcinosis
Laboratory tests	Aldolase 22.7 u/l, CK 343 u/l, ANA 1:640 (nucleolar), anti-Scl-70 (–), ENA panel (–), anticentromere (–), anti-PM/Scl+ by S-35 immunoprecipitation (obtained at diagnosis)	Aldolase 20 u/l, CK 519 u/l, ANA 1:2560 (speckled), anti-Scl-70 (–), ENA panel (–), anticentromere (–), anti-PM/Scl+ by immunodiffusion and S-35 immunoprecipitation (obtained 3 yrs after diagnosis)	ANA 1:160 (nucleolar), anti-Scl-70 (borderline), ENA panel (–), anti-PM/Scl+ by immunodiffusion and S-35 immunoprecipitation (obtained 10 yrs after diagnosis)	Aldolase 6.9 u/l, CK 2354 u/l, ANA 1:2560 (speckled), anti-Scl-70 (–), ENA panel (+) with SS-A (+), anti-RNP (–), anti-PM/Scl+ by immunodiffusion (obtained 4 yrs after diagnosis)
Treatment	PRED 2 mos, MTX 7 mos, MMF 1 yr	PRED 31 mos, MTX 24 mos, LEF 3 yrs	PRED many yrs, MTX many yrs, IVIG 8 mos, RTX 4 infusions	PRED 30 mos, MTX 7 yrs, HCQ 3 mos
Yrs of followup and current status	1.6 yr of followup, currently receiving MMF treatment	15 yrs of followup, received treatment for 8 yrs and remained in remission without treatment for 7 yrs	15 yrs of followup, received treatment for 13 yrs and remained in remission without treatment for 2 yrs	8 yrs of followup, received treatment for 6 yrs and remained in remission without treatment for 1 yr

\* Patient 3 was cared for at an outside institution for 8 years before transferring care to our institution, and less detailed records are available regarding her diagnosis and treatment during that period (including specific aldolase and CK values). SSc: systemic sclerosis; CK: creatine kinase; ANA: antinuclear antibodies; ENA: extractable nuclear antigen (containing anti-SSA, anti-SSB, anti-Sm/RNP, and anti-RNP antibodies); PRED: prednisone; MTX: methotrexate; MMF: mycophenolate mofetil; LEF: leflunomide; IVIG: intravenous immunoglobulin; RTX: rituximab; HCQ: hydroxychloroquine; PM: polymyositis; Scl: scleroderma.

fications confirmed by ultrasound) and tight, overlying hyperpigmented skin, recurrence of periungual telangiectases, and elbow calcinosis. She tested positive for anti-SSA and anti-PM/Scl antibodies, and her diagnosis was modified to overlap SSc/myositis. Treatment was discontinued at age 14 after she had been asymptomatic for 12 months. During 1 year of followup, she remained asymptomatic, and her parotid swelling gradually decreased.

The diagnosis of overlap SSc/myositis is often challenging. Indeed, these cases illustrate the extended period of time often needed to diagnose these patients and the key role of anti-PM/Scl antibodies in confirming the diagnosis. This antibody correlates strongly with the syndrome<sup>8,9</sup> and results in a nucleolar antinuclear antibody pattern<sup>8,10</sup>. Although it can be observed in isolated DM/JDM or SSc, 80% of patients with anti-PM/Scl antibodies will have overlap SSc/myositis syndrome<sup>4</sup>. PM/Scl antibodies persist regardless of disease activity, but do not appear to correlate with disease activity<sup>2</sup>. Despite being poorly characterized in children, the presentation of pediatric SSc/myositis overlap syndrome appears similar to adults with the exception of less visceral involvement<sup>11,12</sup>.

In this series of 4 pediatric patients, only patient 1 was diagnosed early with overlap SSc/myositis because he had features of both JDM and SSc at presentation. His diagnosis was confirmed when anti-PM/Scl antibodies were identified. The remaining 3 patients were initially diagnosed with JDM, and only years later after SSc-like features developed was the diagnosis of an overlap syndrome considered. Laboratory testing subsequently revealed the presence of anti-PM/Scl antibodies, confirming the diagnosis. SSc-associated myopathy can also present with mild myopathy and anti-PM/Scl antibodies<sup>13</sup>; however, the presence of a characteristic JDM rash and the development of sclerotic features only later in the disease course favors the diagnosis of SSc/myositis overlap.

Although antibodies are not included in the JDM diagnostic criteria, they frequently provide prognostic and clinical insight into the disease. Early recognition of antibodies may affect management, lead to an increased level of suspicion in regard to new symptoms, and allow diagnostic intervention and appropriate therapy before disease progression. Based on acquired experience, our center routinely obtains myositis-associated and myositis-specific antibodies in patients with JDM or SSc.

Overlap SSc/myositis has a relatively good prognosis<sup>2,6</sup> because of the typically mild myositis and good response to corticosteroids<sup>9</sup>. In our 3 patients with longer followup (an average of nearly 13 yrs), symptom control and eventually clinical remission were achieved (with normal muscle enzyme levels, normal muscle strength, and resolution of the JDM-associated rash), supporting a relatively favorable outcome.

Overlap SSc/myositis syndrome is a rare entity in adults and rarer still in childhood and adolescence. It is associated with the presence of anti-PM/Scl antibodies and features of SSc and dermatomyositis. In our case series of 4 pediatric patients, we highlight the key involvement of anti-PM/Scl antibodies in establishing the diagnosis and provide some evidence for a relatively good longterm prognosis, demonstrated by the achievement of disease remission in the 3 patients with longterm followup.

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