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Case Report

Anti-SRP myositis: a diagnostic and therapeutic challenge

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ABSTRACT

Background. Anti-signal recognition protein (anti-SRP) myopathy is a rare idiopathic inflammatory myopathy in children. Herein, a 3-year-old patient with severe anti-SRP myopathy showing a rapidly progressive disease course is presented in order to increase the awareness of pediatricians about idiopathic inflammatory myopathies.

Case Presentation. A previously healthy 3-year-old girl presented with progressive symmetrical proximal muscle weakness that caused difficulty in climbing stairs for two months prior to evaluation, and a marked elevation of the serum creatine kinase levels. A skeletal muscle biopsy revealed necrotic and regenerating processes, with mild inflammatory changes. Myositis-specific and associated autoantibodies tested by the immunoblot method were positive for anti-SRP. Pulse corticosteroid, intravenous immunoglobulin, and methotrexate were administered. However, muscle weakness progressed, respiratory distress and dysphagia developed. Rituximab was initiated. While on rituximab treatment, she was able to walk independently and muscle enzymes were within normal range at the 15th month of diagnosis.

Conclusion. Early diagnosis of patients with anti-SRP myositis is important to control inflammation and prevent disease progression and complications. To our knowledge, our patient is the youngest case reported in the literature and was successfully treated with rituximab added to conventional therapy.

Key words: anti-signal recognition protein myopathy, anti-SRP, rituximab, inflammatory myopathy, children.

Idiopathic inflammatory myopathies (IIM) are a heterogeneous group of disorders characterized by inflammatory changes in skeletal muscle with muscle weakness more prominent in proximal muscles. Juvenile dermatomyositis (JDM) is the most common subtype of IIM and is relatively easy to diagnose due to specific cutaneous signs. There are other subtypes of IIM, such as immune-mediated necrotizing myopathies (IMNM) and overlap myositis, which are rarer, have a worse prognosis, and are challenging to diagnose.[1]

Immune-mediated necrotizing myopathy is a rare and severe subtype of IIM in children. Anti-signal recognition protein (SRP) and 3-hydroxy-3-methylglutaryl-Co A reductase (HMCGR) antibodies are associated with IMNM.[2] Anti-SRP is a myositis-specific antibody (MSA) which has been well described in adults but rarely in children.[3] It is usually associated with a severe or fulminant course and poor response to therapy.[4] Pediatric patients have a similar clinical spectrum as adults, but only a few cases have been reported.[5-8]

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Herein, a 3-year-old patient with severe anti-signal recognition protein (SRP) myopathy showing a rapidly progressive disease course is presented in order to increase awareness of pediatricians about IIMs other than JDM and to draw attention to the differential diagnosis.

Case Presentation

A previously healthy 3-year-old girl presented with frequent falls, muscle weakness, and difficulty in climbing stairs for two months prior to evaluation. There was neither parental consanguinity nor a family history of muscle disease. Neurological examination revealed nasal speech and proximal muscle weakness which was more prominent in the lower extremities. Motor power measured by the Medical Research Council's (MRC) classification of bilateral proximal and distal upper extremities was 4/5 and 5/5, respectively. The proximal and distal muscle strength of her lower extremities were 3/5 and 4/5, respectively. She had hypoactive deep tendon reflexes and waddling gait pattern. There was no muscle wasting, muscle hypertrophy, or pseudohypertrophy. Our physical examination revealed no skin rash, joint swelling, or other systemic features such as respiratory distress or dysphagia.

Serum inflammatory markers and complete blood count were normal. Muscle enzymes were elevated (creatine kinase, CK: 13552 U/L, lactate dehydrogenase: 3149 U/L, aspartate aminotransferase: 427 U/L), as well as cardiac markers (troponin I: 1064 ng/L and CK-MB: 300 μg/L). Thyroid and parathyroid hormone levels were within the normal range. Metabolic screening (such as organic acids and amino acids) was normal. Ultrasonography of the neck and abdomen and thoracic tomography showed no pathologic findings. Bone marrow aspiration was normal. Electroneuromyography demonstrated an active myopathic process more prominent in the proximal muscles with intermittent spontaneous denervation. The electrocardiogram and cardiac ultrasound were normal. Muscle biopsy from the vastus lateralis revealed widespread variation in fiber size, rounding of fibers, necrosis and regeneration of muscle fibers. There were prominent foci of endomysial and perivascular inflammatory infiltrates, accompanied by endomysial and perimysial fibrosis (Fig. 1). HLA-ABC antigens were not expressed in the sarcolemma or sarcoplasm and most fibers were positive for neonatal myosin. Inflammatory cells were mainly T lymphocytes and macrophages, with rare B lymphocytes. MSA testing by immunoblot method was positive for anti-SRP and other autoantibodies were negative.

A three-day pulse intravenous (IV) methylprednisolone (30 mg/kg/day), followed by oral prednisolone (2 mg/kg/day twice daily) was initiated. Intravenous immunoglobulin (IVIG; 2 g/kg/month) and methotrexate (15 mg/m^2/week) were added. Although CK levels decreased to 1880 U/L in the 2nd week of the treatment, muscle weakness progressed, as she became non-ambulatory, unable to lift her thighs and get up from a supine position. Respiratory distress and dysphagia developed. Rituximab (375 mg/m^2 four times weekly) was initiated. In the first month of treatment, she received the second course of a 3-day IV pulse methylprednisolone. Methotrexate was switched to mycophenolate mofetil (600 mg/m^2/day) because of elevated transaminases. After 2 months of hospitalization, she was discharged with oral prednisolone (1 mg/kg/day), IVIG (2 gr/kg/month), and mycophenolate mofetil. She showed a clinically significant improvement and achieved regain of ambulation in the 5th month of treatment. A second dose of rituximab was given 6 months after the first dose. Oral steroid therapy was tapered. IVIG was discontinued 11 months after the onset of the disease.

At the fifteenth month of diagnosis, she was able to walk independently and climb stairs with mild limitation in jumping and running activities alone. On neurological examination, she had mild proximal muscle weakness in the lower extremities (MRC 4+/5) with hypoactive

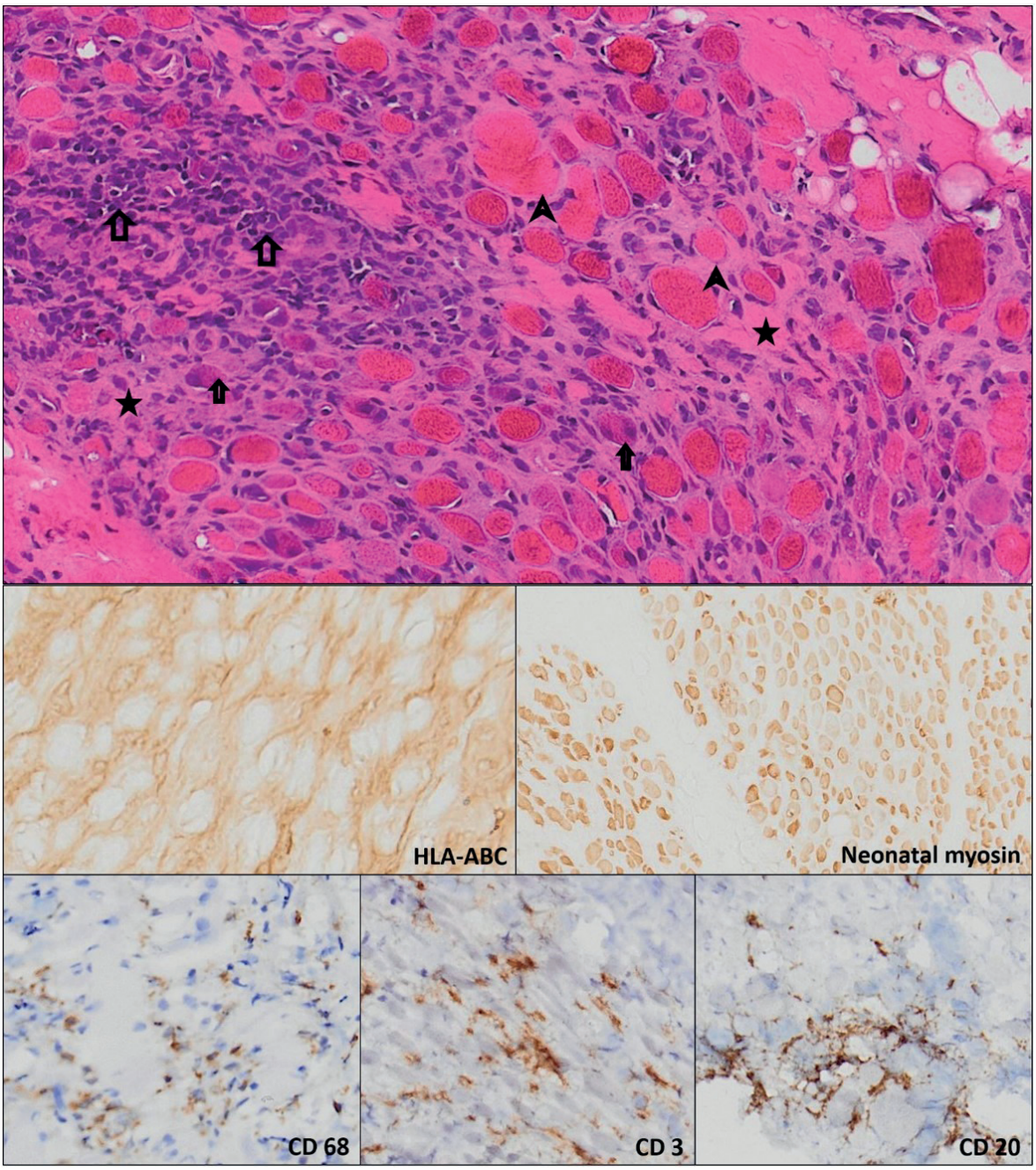

Fig. 1. Top: Muscle biopsy showing many necrotic (arrow head) and regenerating (solid arrow) fibers, prominent inflammatory infiltration (arrow), and severe endomysial and perimysial fibrosis (star), H&E stain. **Middle row:** HLA-ABC is not expressed. Neonatal myosin is expressed in majority of fibers. **Bottom row:** CD 68 and CD 3 positive mononuclear cells are more widespread, while CD 20 positive cells are fewer, in small foci.

patellar deep tendon reflexes. Her muscle enzymes were in the normal range. Asummary of treatment is shown in Fig. 2.

An informed consent was received from the patient's family for the publication of this report.

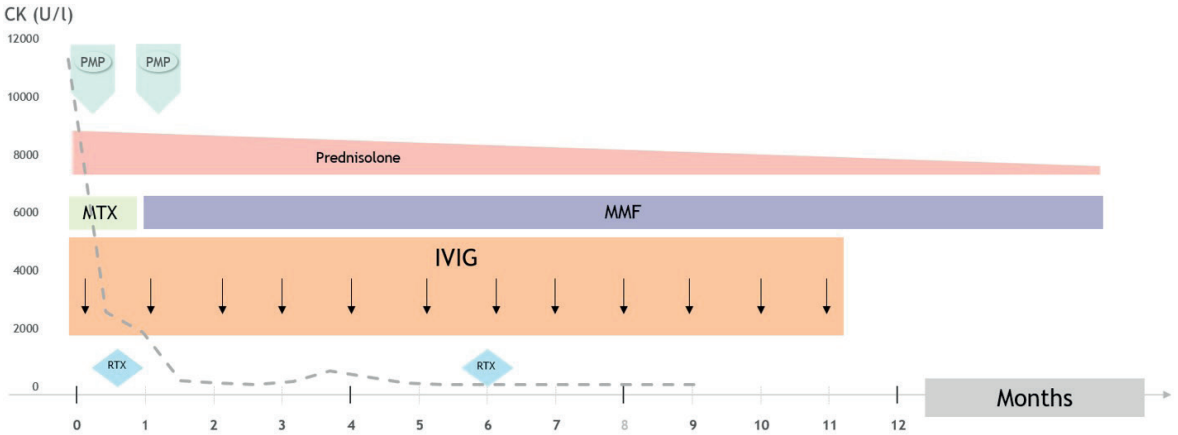

Fig. 2. Summary of treatment. Dashed lines show serum CK levels.

CK, creatine kinase; IVIG, Intravenous immunoglobulin; MMF, Mycophenolate mofetil; MTX, Methotrexate; PMP, Pulse methylprednisolone; RTX, Rituximab.

Search strategy

We screened PubMed/MEDLINE by using the following keywords: "juvenile idiopathic inflammatory myopathy", "pediatric", "anti-signal recognition protein", and "rituximab" and searched the literature from database inceptions to December 31, 2023. The search was limited to English articles. Case reports, original research articles, editorials, and review articles about IIM were analyzed. Two authors independently screened full texts of all relevant articles (Fig. 3). The following parameters were assessed within the included studies: gender, age at diagnosis, clinical and laboratory findings, treatment, and outcome.

Discussion

Immune-mediated necrotizing myopathy is a rare and severe subtype of IIM in children. IMNM has 3 subtypes: anti-SRP myositis, anti- 3-hydroxy-3-methylglutaryl-coenzyme A reductase myositis, and seronegative myositis. Although all subtypes of IMNM are associated with muscle weakness, anti-SRP myositis is associated with more severe muscle weakness and atrophy.[1]

The diagnosis of IIM is based on a combination of medical history, serum muscle enzyme levels, muscle biopsy findings and at times auto-antibodies.[1,9] The broad differential diagnosis of IIM causes diagnostic challenges. The differential diagnosis of muscle weakness includes infectious myopathies, muscular dystrophies, metabolic myopathies, endocrinopathies (such as hypo-hyperthyroidism, hypo-hyperparathyroidism), drug-induced myopathies, and malignancy, in addition to inflammatory myopathies.[9] Metabolic and endocrine tests were normal in this case. There was no drug exposure and no evidence of malignancy. Infective myositis is an acute, self-limiting condition seen in children with a recent history of viral infection; it was most commonly reported in those with influenza, although other viral infections can also cause myositis.[10] Our patient had progressive muscle weakness and no history of previous infections. Muscular dystrophies (MD) are a group of inherited degenerative muscle diseases characterized by progressive muscle weakness and dystrophic findings on muscle biopsy. Muscle weakness can occur at various stages of the clinical course. Congenital MD is characterized by severe and progressive muscle weakness from the neonatal

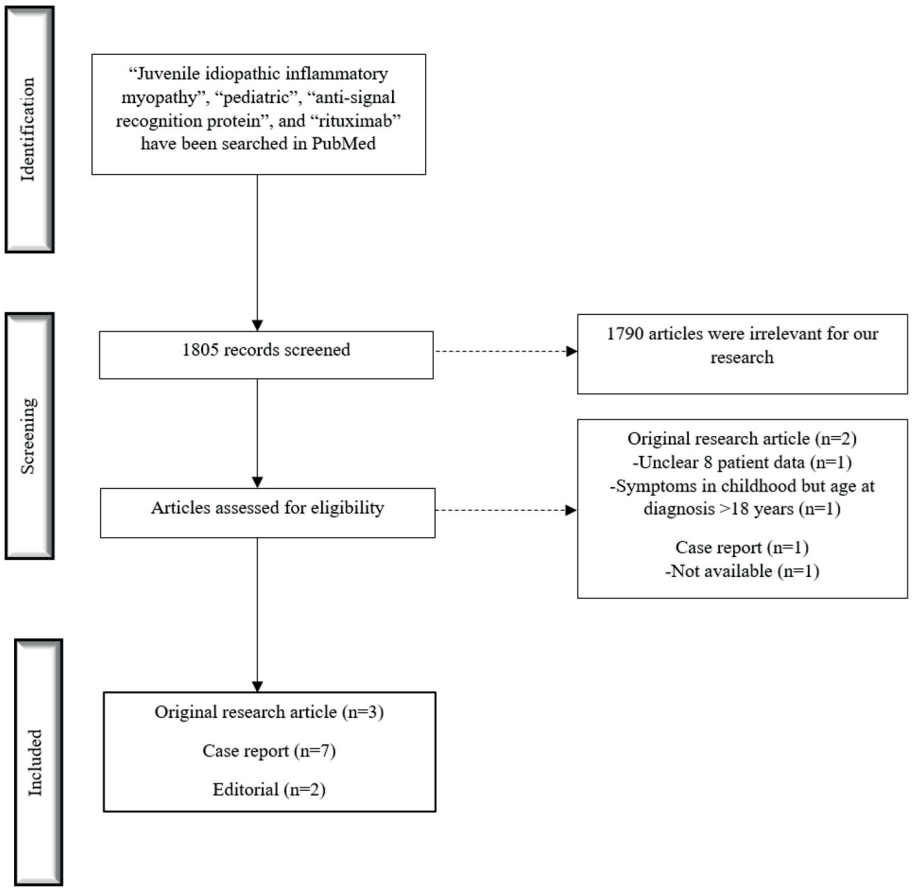

Fig. 3. Search strategy for literature review.

period, whereas in the most common form, Duchenne MD, muscular dystrophy remains relatively stable until approximately 7 years of age.[11] MSAs are powerful diagnostic tools in the slowly progressive form of IMNM that can mimic muscular dystrophy. Suzuki et al.[12] reported that the diagnosis of anti-SRP myositis was confirmed by RNA immunoprecipitation in a patient with childhood-onset myopathy in whom the differential diagnosis of IIM or muscular dystrophy could not be made for 21 years, despite repeated muscle biopsies. It was also shown that none of the 105 patients with various MDs (e.g., Duchenne MD, Becker MD, limb-girdle MD, facioscapulohumeral MD, or Fukuyama-type congenital MD) had anti-SRP antibodies detected in serum samples.[12] In this case, anti-SRP antibody was positive and there were no histopathological findings of muscular dystrophy. Therefore, no further investigation was performed for the diagnosis of MD.

Cardiac symptoms such as chest pain, palpitations, and congestive heart failure are observed in some patients with anti-SRP myositis.[1] Although our patient had no cardiac symptoms or cardiac ultrasound or ECG findings, her cardiac enzymes were quite high, which was accepted as subclinical cardiac involvement. Dysphagia occurred in the 2nd week of follow-up with our patient's, and she had difficulty swallowing solid foods in the swallowing test. A recent study reported dysphagia in 30–69% of anti-SRP myositis cases.[13] The frequency of dysphagia is significantly more common than in other types of myositis. Therefore, dysphagia should

be investigated in IMNM cases to avoid life-threatening respiratory complications.

High-dose corticosteroids, IVIG, and methotrexate are the first-line treatments for patients with juvenile IIM. Similar to adults, cyclosporine, azathioprine, mycophenolate mofetil, and cyclophosphamide can also be used to treat refractory disease in children.[9] It has been shown that pediatric patients without clinical improvement with IVIG, methotrexate, infliximab, or cyclophosphamide have been successfully treated with rituximab.[3] A recent review reported that rituximab is the best alternative biologic agent when combinations with conventional drugs are inadequate in IIM.[14]

In our literature search, we reviewed 31 pediatric cases of anti-SRP myositis reported to date. The majority of the patients were girls (80.7%). The age range at diagnosis was 4-16 years (minimum-maximum). Only 4 patients had nonspecific skin manifestations. Cardiac and pulmonary evaluation results were obtained in 28 and 27 patients, respectively. 7 (25%) patients had abnormal electrocardiograms or echocardiograms and 18 (66.7%) patients had abnormal pulmonary function tests. In addition, three patients had thoracic computed tomography findings compatible with interstitial lung disease. Dysphagia was described in 13 patients. All patients received IVIG or at least one cytotoxic drug in addition to corticosteroid treatment. Despite intensive treatment, 14 patients used wheelchairs. Clinical, laboratory, treatment, and outcome data of anti-SRP myositis patients are summarized in Table I.

Early diagnosis of patients with anti-SRP myositis is important to control inflammation and prevent disease progression and complications. To our knowledge, our patient is the youngest case reported in the literature and was successfully treated with rituximab added to conventional therapy.

Ethical approval

Informed consent was obtained from the parents of the child.

Author contribution

The authors confirm contribution to the paper as follows: Study conception and design: NŞ, DA, EÇ; data collection: MCP; analysis and interpretation of results: MCP, BT, BÇA; draft manuscript preparation: MCP, EÇ. All authors reviewed the results and approved the final version of the manuscript.

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Conflict of interest

The authors declare that there is no conflict of interest.

Table I. Clinical characteristics of pediatric anti-SRP myositis patients.

Reference	Number of patients	Gender	Age at disease onset	CK levels (U/L)	Cutaneous involvement	Cardiac involvement	Pulmoner involvement	Dysphagia	Treatment	Clinical course
Binns et al.[3]	3	F	14 years	23111	-	-	Abnormal PFTs	+	CS, MTX, IVIG, CYC, RTX	She was at school full-time and able to re-join her physical education and dance classes.
		F	13 years	25937	Periorbital swelling, RP	-	-	-		She had returned to school.
		F	11 years	19808	-	-	Abnormal PFTs, Ground glass opacification on thorax CT	-		NA
Luca et al.[5]	1	F	12 years	8826	RP	-	Abnormal PFTs	+		She was able to participate in dance classes.
Suzuki et al.[6]	2	F	10 years	2467						Wheelchair use
		F	6 years	4629	NA	NA	NA	NA		Not able to get up from a supine position
Rouster-Stevens et al.[7]	3	F	16 years	22155	RP	Abnormal ECHO	Abnormal PFTs, Honeycombing at both bases on thorax CT	-		Wheelchair use
		F	14 years	22857	-	-	Abnormal PFTs, Linear opacities at the bases on thorax CT	-		Wheelchair use
		F	11 years	33000	RP	Abnormal ECHO	Not tested	+		She was unable to run well, but otherwise had normal function.
Kawabata et al.[8]	1	F	15 years	20375	-	-	-	-		She recovered sufficiently to resume normal daily activities.
Kishi et al.[15]	8	5F; 3M	14.9 (10.7-16) years*	NA	RP (50%)	Abnormal ECG or ECHO (50%)	Abnormal PFTs (75%)	50%	NA	Wheelchair use (75%), Devices for mobility (62.5%)

*,Median (IQR).

AZA, Azathioprine; CK, Creatine kinase; CS, Corticosteroid; CYC, Cyclophosphamide; CT, Computed tomography; DLCO, Diffusing capacity of lungs for carbon monoxide; ECG, electrocardiogram; ECHO, Echocardiogram; F, Female; Hq, Hydroxychloroquine; IFX, Infliximab; IVIG, Intravenous immunoglobulin; LFM, Leflunomide; M, Male; MMF, Mycophenolate mofetil; MTX, Methotrexate; NA, Not available; PE, Plasma exchange; PFT, Pulmonary function test; RP, Raynaud's phenomena; RTX, Rituximab; TAC, Tacrolimus.

Table I. Continued.

Reference	Number of patients	Gender	Age at disease onset	CK levels (U/L)	Cutaneous involvement	Cardiac involvement	Pulmoner involvement	Dysphagia	Treatment	Clinical course
Della Marina et al.[16]	1	F	8 years	10710	-	-	Abnormal PFTs	+	CS, MTX, IVIG, RTX	She was able to stand up from the sitting position unsupported, but had to hold onto a railing when climbing stairs.
Momomura et al.[17]	1	F	15 years	20375	-	NA	NA	+	CS, AZA, CYC, PE	She was able to jog.
Zhao et al.[18]	3	F	4 years	4020				-	CS, IVIG	She was able to get up from the floor without assistance.
		F	11 years	4660	NA	-	-	-		She was able to walk without assistance
		F	12 years	13265				+		
Kobayashi et al.[19]	1	M	8 years	5896	-	-	-	-	CS, MTX, IVIG, TAC	He had no weakness.
Rider et al.[20]	1	F	10 years	8316	Erythema of cheeks	-	Abnormal PFTs	NA	CS, MTX, IVIG	NA
Rider et al.[21]	6	4F; 2M	15.1 (12.1-16.2) years*	18544 (9111-22857)*	Edema (16.7%) Cuticular overgrowth (16.7%) RP (50%)	Abnormal ECG or ECHO (50%)	Abnormal PFTs (83.3%)	50%	NA	Wheelchair use (83.3%)
Present case	1	F	3 years	13552	-	-	-	+	CS, IVIG, MTX, MMF, RTX	She was able to walk independently and climb stairs with mild limitation in jumping and running activities

*,Median (IQR).
AZA, Azathioprine; CK, Creatine kinase; CS, Corticosteroid; CYC, Cyclophosphamide; CT, Computed tomography; DLCO, Diffusing capacity of lungs for carbon monoxide; ECG, electrocardiogram; ECHO, Echocardiogram; F, Female; Hq, Hydroxychloroquine; IFX, Infliximab; IVIG, Intravenous immunoglobulin; LFM, Leflunomide; M, Male; MMF, Mycophenolate mofetil; MTX, Methotrexate; NA, Not available; PE, Plasma exchange; PFT, Pulmonary function test; RP, Raynaud's phenomena; RTX, Rituximab; TAC, Tacrolimus.

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