

Systemic Sclerosis Sine Scleroderma With Pulmonary Arterial Hypertension in a 3-Year-Old Girl

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Systemic sclerosis sine scleroderma (ssSSc) is a rare variant of systemic sclerosis, with only one pediatric case reported in the medical literature to date. Pulmonary arterial hypertension as the presenting feature of ssSSc is extremely rare, even in adults, and so far has never been reported in children. We report, for the first time, a case of pediatric ssSSc in a 3-year-old girl, who presented with interstitial lung disease and pulmonary hypertension. The patient was prescribed early aggressive pulmonary vasodilators combined with anti-inflammatory medications. The clinical response was good, and her current condition at 12 years of age is remarkable, considering the high mortality rates reported in adults. We underscore the importance of early aggressive treatment in future cases of similar presentation.

Systemic sclerosis (SSc) is a multisystem disease characterized by functional and structural abnormalities of small blood vessels, immune system activation, inflammation, and fibrosis of the skin and internal organs. Over the last decade, differences with regard to clinical manifestations, organ involvement, and prognosis between the adult and juvenile diseases have come to light.^{1,2}

Systemic sclerosis sine scleroderma (ssSSc) is an extremely rare variant of this syndrome, first described in 1954.³ This subset is characterized by internal organ involvement and serological abnormalities, without skin changes. In children, only one case of ssSSc has been reported so far, which manifested with nocturnal seizures and Raynaud phenomenon (RP).⁴

Pulmonary arterial hypertension (PAH) as the presenting feature of ssSSc is extremely rare, even in adults,⁵ and to date has never been reported in children. We describe, for the first time,

a child with juvenile ssSSc, who presented with RP in addition to PAH secondary to interstitial lung disease.

CASE REPORT

A previously healthy 3.5-year-old Israeli girl of Yemenite origin was referred for the evaluation of a new 2-month onset of RP, in the absence of skin changes, dysphagia, or arthralgia. Her parents and 4 siblings were healthy, and family history for connective tissue diseases was negative.

Physical examination revealed RP of fingers with digital ulcers, without sclerodactyly or skin change, and exertional dyspnea (Fig 1). Capillaroscopy demonstrated capillary dropout and tortuous dilated loops. Physical examination was otherwise normal. Weight and height were in the sixth and 20th percentiles, respectively.

Complete blood cell count, muscle and liver enzymes, erythrocyte

abstract

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sedimentation rate, and C-reactive protein were within normal limits. The immunologic laboratory results were positive for antinuclear antibody at titer levels $\gg 1:160$, mixed pattern, and antitopoisomerase I (anti-Scl-70) antibody was 163 U/mL (0–15). Von Willebrand antigen was 181% (50–150). Anti-dsDNA, anti-Ro/SSA, anti-La/SSB, anti-RNP, anti-Sm, antihistone, anticentromere, anti-RNA polymerase, Rheumatoid factor, and antiphospholipid antibodies were all negative results. Complement levels (C3, C4) were normal.

Chest radiograph images revealed bilateral central infiltrates and an enlarged heart (Fig 2). Electrocardiography (ECG) was compatible with right ventricular hypertrophy (Table 1, Fig 3). There was clear evidence of severely elevated (near systemic) pulmonary hypertension and tricuspid regurgitation. No cardiac defects were noted, and the cardiac output was normal. A diagnostic right heart catheterization demonstrated moderate PAH (mean 30 mm Hg) and a normal pulmonary capillary wedge pressure of 10 mm Hg (Table 1). High-resolution computerized tomography revealed ground glass and mosaic perfusion and cardiomegaly. The inferior vena cava and hepatic veins were congested. Pulmonary arteries were enlarged (Fig 4). Pulmonary function tests were of limited value because of the patient's young age.

A diagnosis of SSc with interstitial lung involvement and pulmonary hypertension without skin changes was established.² Immunomodulatory treatment was initiated with monthly pulses of intravenous cyclophosphamide (750 mg/m² per month for 6 months). Glucocorticoids were avoided owing to the risk of scleroderma renal crisis. An endothelin receptor antagonist (31.25 mg of bosentan 2 times per day) and a phosphodiesterase type 5



FIGURE 1
A recent photo of the patient's fingers showing RP.

inhibitor (25 mg of sildenafil 4 times per day) were added.

Over the next 6 months, the patient's RP greatly improved, and the digital ulcers healed. However, the dyspnea worsened, even during mild exercise (functional class II), and the patient failed to gain weight. Additionally, the patient complained of new episodes of presyncope and abdominal pain, occurring on a daily basis for almost 2 weeks. She was readmitted for evaluation. The physical examination was unchanged. Blood tests, including D-dimer and troponin levels, were within normal limits, and no changes in the ECG were observed. A continuous 24-hour ECG recording



FIGURE 2
Chest radiograph revealing bilateral central infiltrates and an enlarged heart shadow.

revealed 2 episodes of sinus tachycardia with ST depression and T wave inversion, followed by a sudden decrease in heart rate, which correlated with the episodes of weakness and presyncope, suggesting a cardiac etiology. Heart catheterization revealed normal coronary arteries and improvement of the pulmonary vascular resistance under nitric oxide and 100% oxygen. Because of these dramatic and life-threatening clinical events, treatment with intravenous epoprostenol (20 ng/kg per minute) was added. High-resolution computerized tomography demonstrated worsening of the interstitial lung disease and signs of pulmonary hypertension. Cyclophosphamide was switched to mycophenolate mofetil (400 mg 2 times per day). With triple drug therapy for PAH (sildenafil, bosentan, and epoprostenol) and the mycophenolate mofetil, the presyncope episodes ceased, and the patient's functional class improved from class III to class I-II (Table 2).

Over the last 8 years, the patient has been monitored closely by a pediatric multidisciplinary team (rheumatologists, cardiologists, and pulmonologists) at Schneider Children's Medical Center of Israel. Except for dosage adjustments to match her growth, the pharmacologic treatment remains unchanged.

Presyncope, arthralgia, and gastrointestinal complaints have not recurred, and no skin abnormalities have been noted to date. Weight and height correlated with the sixth and 20th percentiles, antitopoisomerase I (anti-Scl-70) antibody was 60 U/mL (0–15), and Von Willebrand antigen values were normalized at the last follow-up visit in 2019.

The pulmonary function was first assessed at the age of 8 years and revealed a restrictive pattern with a forced vital capacity of 63% predicted for age and body size. Repeated assessments at the age of

TABLE 1 Cardiac Catheterization at Presentation and at Evaluation for Syncope Events

Criterion	Cardiac Catheterization			
	At Presentation		Evaluation for Syncope	
	Baseline	After 80 ppm of Inhaled NO and 100% O ₂	Baseline	After 80 ppm of Inhaled NO and 100% O ₂
Mean pulmonary systolic pressure, mm Hg	30	—	26	—
Pulmonary capillary wedge pressure, mm Hg	10	—	11	—
Mean aortic systolic pressure, mm Hg	50	—	52	—
Calculated pulmonary vascular resistance, Woods units	5.5	3.2	4.5	2.5
Pulmonary resistance and systemic resistance	0.48	0.28	0.41	0.18

NO, nitric oxide. —, not applicable.

11 revealed a stable pattern with a forced vital capacity of 49%. The most recent high-resolution computerized tomography revealed a slight worsening in parenchymal findings compared with previous scans. However, signs of elevated pulmonary blood pressure significantly decreased. In recent echocardiography assessments, pulmonary arterial pressure was only mildly elevated. The ventricular function was normal, with a mild residual right ventricular dilation (Table 1).

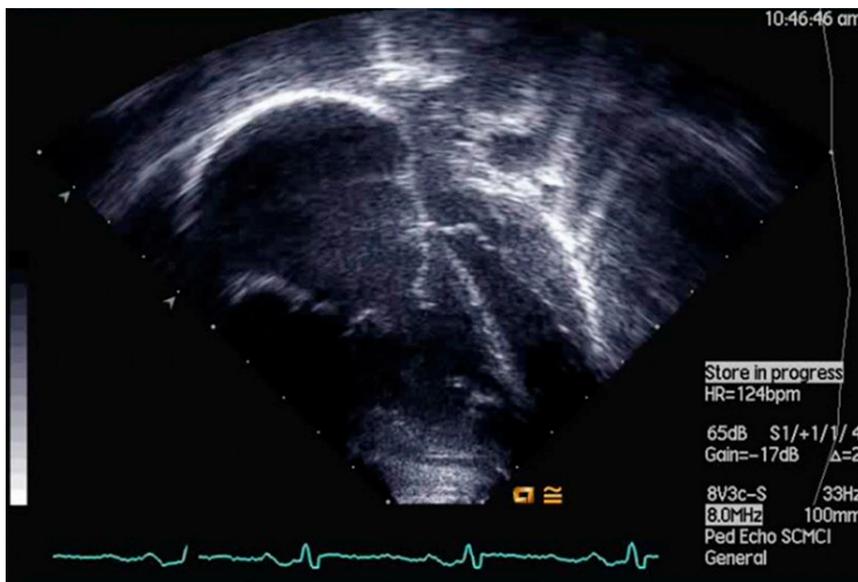
DISCUSSION

SSc rarely occurs in children younger than 16 years, with a reported annual incidence of 0.45 to 1.9 cases per 100 000 persons.⁶ In the largest series of patients with juvenile SSc ($n = 153$), no case of ssSSc was reported. Characteristic skin changes were the most common feature reported, followed by RP (~75%) and musculoskeletal symptoms (33%). Dyspnea and pulmonary hypertension occurred in 18% and 7% of patients, respectively.⁷

To the best of our knowledge, there is only one other case of childhood ssSSc reported,⁴ in a 6-year-old girl who was diagnosed during evaluation for refractory night convulsions for 3 years and found to have RP, minor skin changes, esophageal dysmotility, and PAH. The patient died within 4 months after being diagnosed with PAH. Our patient presented with RP, interstitial lung disease, and pulmonary hypertension, without gastrointestinal or skin involvement. Nailfold capillaroscopy and elevated antinuclear antibody and antitopoisomerase I titers strongly suggested the diagnosis of ssSSc. Antitopoisomerase I is considered to have a specificity of 95% and greater for SSc.⁸

Even in adults, ssSSc is a challenging diagnosis because of its rarity and the absence of the typical scleroderma skin changes.⁹ Considering the patient's young age, a genetic etiology was considered. Because of the lack of consanguinity or a family history of a connective tissue disorder, the possibility of a genetic disorder (eg, COPA) was considered to be low. Major features of the syndrome, such as arthritis or renal involvement, were absent. Moreover, RP and high antitopoisomerase were never described as being associated with COPA.^{10,11}

Because no guidelines for therapy of ssSSc in children are available, we followed the treatment guidelines for adults.^{12,13} The pulmonary hypertension in our patient warrants further discussion. We could find only one case of ssSSc diagnosed with pulmonary hypertension at first presentation in the medical literature.⁵ Associated PAH with connective tissue disease is rare in children, especially in the first decade of life. Early pulmonary hypertension in scleroderma lung is an unusual event. In patients with SSc, pulmonary hypertension may occur secondary to the interstitial lung disease or as primary arterial

**FIGURE 3**

Echocardiographic image of a moderately dilated and hypertrophied right ventricle. bpm, beats per minute; HR, heart rate; Ped, pediatric echocardiography; SCMCI, Schneider Children Medical Center of Israel.



FIGURE 4 High-resolution computed tomography showing lung tissue with matte glass and mosaic diffusion shape in both lungs, without pleural effusion.

hypertension. The latter is more common in long-standing limited scleroderma with positive anticentromere antibodies. PAH secondary to interstitial lung disease is usually less responsive to vasodilators and carries an ominous prognosis. Considering the generally poor prognosis,¹⁴ we opted for a more-aggressive initial treatment with a combination of 2 vasodilators to address the pulmonary hypertension and an immunomodulator to control

the inflammatory process and slow the progression toward fibrosis. Because clear treatment guidelines supported by randomized controlled trials were unavailable, we chose cyclophosphamide as an initial immunomodulatory therapy because of the large body of data from controlled trials in SSc-related lung disease.^{15,16} The initial treatment resulted in some clinical and hemodynamic improvement as assessed by echocardiography and

cardiac catheterization. However, because of the onset of cardiac syncope episodes, the pulmonary vasodilator therapy was supplemented with intravenous epoprostenol. Acknowledging the prognostic implications of SSc-related lung disease,^{17,18} we also addressed the lack of improvement in interstitial lung disease, and cyclophosphamide was switched to mycophenolate mofetil.¹⁹⁻²¹

At the time of writing, the patient continues to improve. Right ventricular function and size has normalized, and PAH is mild. This patient's good clinical response to therapy during several years of follow-up is encouraging, especially in light of the expected high mortality rate.

It is possible that the aggressive early pulmonary vasodilator treatment combined with anti-inflammatory treatment may have led to clinical and imaging improvement, which has been significantly better than the expected course, according to the adult literature.

CONCLUSIONS

We recommend that the pediatric community be aware of the possibility of SSc in children. Pulmonary hypertension in the presence of active inflammation should be diagnosed quickly and treated aggressively. Awareness and reporting of such cases will lead to a better characterization of the disease, enhance early diagnosis, and improve prognosis.

ABBREVIATIONS

ECG: electrocardiography
 PAH: pulmonary arterial hypertension
 RP: Raynaud phenomenon
 SSc: systemic sclerosis
 ssSSc: systemic sclerosis sine scleroderma

TABLE 2 Hemodynamics and Echocardiography Findings at Presentation, Evaluation for Syncope Events, and Most Recent Follow-up

	At Presentation	Evaluation for Syncope	Recent
Systemic blood pressure, mm Hg	100/60	100/60	100/60
Estimated right ventricular systolic pressure, mm Hg	80	80	<40
Right ventricle	Moderately dilated, hypertrophied	Mildly dilated	Mild residual dilation
Interventricular septum	Flattened in systole	Partial systolic flattening	Round in systole
Left ventricle systolic index, eccentricity index	2.0	1.4	1.1
Doppler flow in pulmonary arteries	Increased resistance	—	Normal

—, not applicable.

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