

Two Cases of Juvenile Systemic Sclerosis and Literature Review

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Abstract Juvenile scleroderma is a rare disease and rarely reported in the literature. We report two cases with different sex and age groups; one had limited dermatological involvement while the other one had wide systemic involvement. Discussions and literature review were made on the different types and management of juvenile scleroderma.

Key words Juvenile systemic sclerosis; Raynaud's phenomenon

Case Reports

Case 1

A seven years old boy presented with progressive skin tightening of hands and face for one year and Raynaud's phenomenon (RP) of fingers for one month. No symptoms were noted for gastrointestinal, pulmonary or cardiovascular systems. There is no family history of autoimmune disease.

Physical examination showed a thin boy with skin tightening and thickening of bilateral hands, atrophic changes were noted over all knuckles. Ranges of movement for flexion and extension were significantly reduced over the interphalangeal joints and there was flexion contracture over those joints (Figure 1). Functional abilities of the hands were mildly affected e.g. pencil work and use of chopstick. Hypopigmented lesions were noted over multiple sites including anterior chest, thigh, back and posterior auricular

area. No calcification or ulcers were noted at presentation. There was no skin rash or telangiectasia and the nailfolds were normal. The pulmonary, cardiovascular and neurological systems were all normal.

Clinically, the diagnosis of limited cutaneous type of juvenile systemic sclerosis (jSSc) was made. Further investigations showed that he was not anaemic. ESR and C3 were normal. Antinuclear antibodies (ANA) titre was 1/2560 (normal <1/80) while anti-dsDNA, Rheumatoid factor (RF), Antineutrophil cytoplasmic antibodies (ANCA), anticentromere antibodies (ACA) and anti-Scl 70 were all negative.

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Figure 1 Hands of case 1.

Systemic evaluation showed that the disease was limited to skin involvement alone. The lung function test, high resolution computerised tomography (HRCT) of the thorax, echocardiogram, renal function and urinalysis were all normal. Skin biopsy was not performed because of parent's refusal.

Amlodipine and dipyridamole were initiated for his RP. Skin tightening gradually improved but the RP persisted. Ramipril was then added and his RP gradually improved. Oral methotrexate was given at a dose of 10 mg per week for immunomodulation. Two years after presentation, he only experienced RP in winter while the skin tightening remained minimal.

Case 2

A 12 years old girl presented with RP of the hands for a month and digital ulcers of both hands for one week. She did not have any pulmonary, cardiac or gastrointestinal symptoms but there was progressive weight loss of around 5 kg. There was no history of joint pain or malar rash. Family history was unremarkable.

Physical examination showed a thin and anxious girl. Generalised alopecia was noted. The skin over both hands was atrophic, cyanotic and shiny. Multiple ischaemic ulcers were found over the fingers (Figure 2). Ranges of movement of flexion and extension were reduced over the interphalangeal joints. Upper limbs pulses were all normal. The toes were not involved. There was no clubbing of fingers. No other skin rashes or oral ulcers were found. Telangiectasia was present over the face (Figure 3). Dilated capillaries were noted in the nailfolds. There were bilateral basal crepitations in the chest while cardiovascular,



Figure 2 Digital ulcers in case 2 at presentation.

neurological examinations were unremarkable.

Clinical diagnosis of diffuse cutaneous type of jSSc was made. Investigations showed that the girl has normochromic normocytic anaemia with haemoglobin of 9.4 g/dL (normal 12.0-15.0 g/dL), globulin was markedly raised to 60 g/L (normal 23-36 g/L) with a low albumin of 31 g/L (normal 36-48 g/L). ESR was raised to 114 mm/hr (normal <31 mm/hr), and C3 decreased to 0.55 g/L (normal 0.79-1.52g/L). There was a rise in ANA titre to 1/2560 with homogenous pattern, anti-Scl 70 was positive while ACA was negative. RF and anti-Ro were positive, and anti-cardiolipin IgM and IgG antibodies were slightly raised. Anti-dsDNA was negative.

Systemic evaluation showed multiple organ involvement. CXR showed bilateral lower zone haziness, lung function test showed a restrictive pattern with marked decreased in FEV1/FVC ratio. HRCT thorax showed honeycomb lungs (Figure 4). Echocardiogram revealed pericardial effusion



Figure 3 Telangiectasia over face in case 2 at presentation.

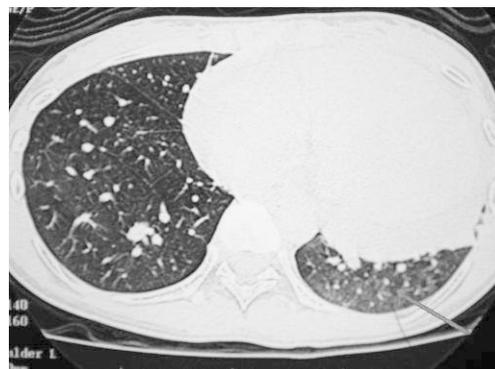


Figure 4 HRCT thorax of case 2 showing honeycomb lungs.

of five mm. Otherwise, urinalysis, doppler ultrasound of kidneys and 24 hour pH probe study were normal.

High dose Prednisolone (0.8 mg/kg/day) was started shortly after diagnosis and pulse cyclophosphamide was given monthly for six doses (500 mg/m² for first three doses and 750 mg/m² for last three doses) followed by oral azathioprine (2 mg/kg/day). Amlodipine and dipyridamole were given for her RP and Ramipril was added later for better control of the symptoms.

Her symptoms gradually improved. Globulin gradually dropped to 43 g/l two months after presentation. Pericardial effusion resolved in three months. Haemoglobin, ESR and C3 were normal three months after the start of therapy. Two years after presentation, there was no digital ulcers and the skin thickening was much resolved (Figures 5 & 6). RP was mild in the winter time. Repeated lung function test showed improvement with a mild restrictive pattern. HRCT thorax was not repeated for an improving lung function.

Discussion

Juvenile scleroderma syndrome is a multi-system autoimmune disease which is characterised by the presence of hardened skin and onset before 16 years of age. It is a spectrum of syndrome which are mainly divided into localised scleroderma and systemic sclerosis. There is no uniform classification of scleroderma yet and it is previously mainly established for the adult population as shown in Table 1.^{1,2} Localised scleroderma is the predominant form



Figure 5 Remaining mild dustiness of digits in case 2 two years after presentation.

of childhood sclerosis but juvenile systemic sclerosis (jSSc) causes significant morbidity.

The latest criteria for the diagnosis of jSSc were established in 2007 by a multi-center multinational group representing the Paediatric Rheumatology European Society (PRES), the American College of Rheumatology (ACR) and European League Against Rheumatism (EULAR) (Table 2). jSSc is diagnosed if the major criterion and at least two of 20 minor criteria are met.¹

Our two cases demonstrated the different spectrum of jSSc. They are classified as the limited cutaneous systemic sclerosis (LCSS) and diffuse cutaneous systemic sclerosis (DCSS) respectively.

Clinical manifestations of jSSc mainly lie on skin disease at presentation. It is usually in a sequence of oedema, induration, sclerosis and finally atrophy. Digits and face were the first to be involved. Telangiectasia is characteristic for DCSS, especially in the periungual nailfolds. RP occurs in 70 to 90% of patients with DCSS and it is the most frequent initial symptom. In our two cases, RP were the presenting symptoms as well. Subcutaneous calcification may occur over the elbows, metacarpophalangeal joints and knees.³⁻⁵

There are a wide range of systemic involvements in jSSc. Musculoskeletal symptoms may include arthralgia, muscle pain and muscle atrophy. Gastrointestinal involvement is



Figure 6 Improvement of appearance in case 2 two years after presentation.

Table 1 Classification of scleroderma

Localised scleroderma	<ul style="list-style-type: none"> - Morphea - Generalised morphea - Linear scleroderma - Eosinophilic fasciitis 	<ul style="list-style-type: none"> - one or more circumscribed skin lesion in 2 or less anatomical sites - widespread skin lesions affecting 3 or more anatomical sites - skin changes follow a dermatomal distribution; lesion on face or scalp are called en coup de saber
Systemic scleroderma	<ul style="list-style-type: none"> - Diffuse cutaneous systemic (DCSS) - Limited cutaneous systemic (LCSS) - Overlap syndromes 	<ul style="list-style-type: none"> - truncal and acral skin involvement - nailfold capillary dilatation and capillary drop-out - early and significant incidence of visceral involvement - skin sclerosis distal to wrist or ankles, over face and neck - nailfold capillary dilatation but usually no capillary drop-out - 10-15% late incidence of CREST syndrome or interstitial lung disease

Table 2 Diagnostic criteria for juvenile systemic sclerosis (jSSc)

Major criteria	Proximal sclerosis/induration of skin
Minor criteria	<ul style="list-style-type: none"> Skin – sclerodactyly Vascular – Raynaud phenomenon, nailfold capillary abnormalities or digital tip ulcers Gastrointestinal – dysphagia or GER Renal – renal crisis or new onset arterial hypertension Cardiac – arrhythmia or heart failure Respiratory – evidence of pulmonary fibrosis, abnormality of DLCO, or pulmonary hypertension Musculoskeletal – tendon friction rubs, arthritis, or myositis Neurological – neuropathy or carpal tunnel syndrome Serology – presence of ANA or SSc selective autoantibodies

Major criterion and at least 2 of 20 minor criteria for diagnosis of jSSc.

reported to occur in 30 to 74% of jSSc patients, and pathologies include mucosal telangiectasia and dysmotility. Esophagus was involved in the majority of DCSS children and often quite early in the disease course. Patients with esophageal involvement usually present with heartburn, dysphagia, delayed emptying and regurgitation. Small bowel disease develops in up to 50% of patient. Cardiac disease is the main cause of mortality and it manifests as pericardial effusion and ischaemic heart disease. Pulmonary involvement is frequently asymptomatic, it is much less reported in children than adult series. There are two types of pulmonary disease in jSSc, namely fibrosing alveolitis and pulmonary vascular disease. Renal involvement was found to be less in paediatric patient, and proteinuria is the most frequent initial finding. Rarely, cranial nerve was

involved, for example, the sensory branch of the trigeminal nerve. Sicca syndrome with xerostomia and keratoconjunctivitis sicca are also quite common in DCSS.³⁻⁵

The diagnosis mainly lies on clinical features. There is often a delay of years between diagnosis and onset of symptoms because of the subtle nature of presentation. In a multi-center retrospective study of 153 children with jSSc, the median age of onset was 8.1 years and the mean duration of symptom onset to diagnosis was 1.9 years.⁵ Diagnosis of jSSc requires the presence of the major plus at least two minor criteria in Table 2.¹

As in our two cases, there was a significant delay in medical consultation from the onset of symptoms. In case 1, the boy had skin tightening for one year but he looked for medical help only when RP and painful digits

occurred. In case 2, although the history seems to be short, physical findings of significant skin atrophy suggested that the disease had developed for a period of time without being noticed.

Investigations for jSSc have limited use in diagnosis but they are important for the evaluation of systemic involvements. Autoantibodies and skin biopsy are rarely helpful for confirmation of diagnosis. Further systemic evaluations will include HRCT thorax, lung function test including pulmonary diffusion (DLCO), echocardiogram and urinalysis.

Anticentromere antibodies (ACA) and anti-Scl-70 (anti-topoisomerase-I) are classically associated with jSSc. However, ACA was present only in 7 to 8% of jSSc patients. It is associated with a higher risk of calcinosis, ischaemic digital loss and pulmonary hypertension but a lower risk of interstitial pulmonary fibrosis. Anti-Scl-70 is present in 9 to 30% of jSSc patients and is highly specific and classically associated with DCSS. Both ACA and anti-Scl-70 have no role in the monitoring of disease activity. ANA was reported to occur in 80 to 95% of SSc patients while other autoantibodies, including antiphospholipid antibodies (e.g. anticardiolipin antibodies), occur in 20 to 25% of patient with SSc.^{5,6}

Management of jSSc is challenging, and most of the treatment options had not undergone large randomised controlled trials. We mainly target on the treatment of its specific complications and will consider using disease-modifying agents for individual patients early if indicated.

Physiotherapy and the use of splints for improving functional ability and joint movement are beneficial. Education and psychological support are important. Therefore, multidisciplinary approach is warranted in the management of jSSc patients.

RP is an important complication to treat because it may lead to digital ulcers. Non-pharmacological methods are useful to prevent or avoid exacerbation. They include the use of gloves; avoidance of cold and stress; avoidance of nicotine, caffeine and sympathomimetic medications. Calcium channel blockers are the first line agents for RP. Nifedipine is most widely recommended, because there are several controlled trials showing its effectiveness in reducing RP as well as digital ulcers. Amlodipine is another agent of choice.⁷ Antithrombotic agent e.g. dipyridamole is used for its anti-platelet and vasodilating effects, however, it was not shown to have major impact on severe RP. Other vasodilators e.g. hydralazine or angiotensin converting enzyme inhibitors were used when the patient was not responding to calcium channel blockers. In very severe

attack of RP, prostaglandin and anticoagulation with aspirin will be considered.

Fibrosing alveolitis must be treated aggressively because of its high morbidity and mortality. It is generally recommended to use monthly intravenous pulse cyclophosphamide (500-750 mg/m²/dose) with low dose prednisolone (0.2-0.4 mg/kg/day) for at least a six to nine month period. The aim is to prevent the development into fibrosis from alveolitis, however, whether established fibrotic process can be reversed is not known.⁸ Azathioprine is an alternative agent but it was found to be inferior to cyclophosphamide.^{9,10} For the treatment of pulmonary hypertension, they include endothelin receptor antagonist e.g. bosentan, phosphodiesterase-5 inhibitor e.g. sildenafil and various prostacyclin analogs (e.g., epoprostenol, treprostinil, iloprost). For case 2, we treated the girl with high dose Prednisolone and monthly intravenous cyclophosphamide because of severe systemic involvement including lung fibrosis and pericardial effusion. Azathioprine was used as the maintenance therapy to prevent relapse.

There is no agent proven to be very effective in disease modifying in either children or adults. Since many of these drugs have significant side effects, careful consideration must be made before use. Methotrexate has some proven effect on the disease process of scleroderma. A randomised controlled trial in early diffuse scleroderma in adult patients showed that methotrexate produces a slight favorable effect particularly on the skin scores. However, it is not sustained after 12 months.¹¹ Methotrexate is well tolerated and therefore it may be considered in patients with significant skin involvement as in case 1.

Autologous haematopoietic stem cell transplantation was being used for various autoimmune disorders and it was shown to have significant improvement in the skin condition of systemic sclerosis recently by an U.S. multicenter pilot study.¹²

In summary, we have demonstrated two cases of different spectrum of jSSc. They are rare but can cause significant morbidities. Update on the classification and treatment options were discussed.

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