Juvenile scleroderma: experience in one institution

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Summary

Background: **Scleroderma is a chronic connective tissue disease characterized by hardened or scaly skin and widespread abnormalities of the viscera, which is rare in the pediatric age group.**

Objective: **In this study, we retrospectively reviewed 23 pediatric patients suffering systemic (SSc) and localized (LS) scleroderma.**

Methods: **Twenty-three patients were enrolled and were diagnosed with SSc or LS from March 1993 to September 2009 in the Department of Pediatrics at Mackay Memorial Hospital in Taipei, Taiwan. These diagnoses were based on the criteria of the American College of Rheumatology and the clinical manifestations of hard skin. Data recorded included sex, age-at-onset, age-at-diagnosis, laboratory data, family history, trauma history, treatment, and outcomes.**

Results: **Three patients suffered SSc and 20 patients had LS, including 16 girls and 7 boys. Mean age-at-onset was 6.55±3.28 years old. Antinuclear antibodies were positive in 15 patients. Tests for anti-Scl-70 antibodies were positive in 1 patient with SSc. One boy had *en coup de sabre* combined with a posterior fossa tumor. Twenty-two patients were treated with D-penicillamine. Oral prednisolone and methotrexate were added, if indicated. One girl with LS developed proteinuria after D-penicillamine treatment. All patients with localized disease ultimately documented a softening of their skin lesions.**

Conclusions: **While scleroderma is rare in children, the prognosis of SSc is poor but better than for adults. The prognosis for LS is usually benign, however, the skin may become progressively indurated and it may not only be a skin disease. No progression from LS to SSc was observed in our study. *(Asian Pac J Allergy Immunol 2010;28:279-86)***

Key words: *Juvenile scleroderma, linea, morphea,* en coup de sabre, *D-penicillamine*

Introduction

Juvenile scleroderma is an autoimmune rheumatic disease of unknown origin. The word "scleroderma" literally means "hard skin". Diseases grouped under this term can have other manifestations, but hardening of the skin is a feature common to all types of the disorder and is the signal characteristic of the disease. Although less common in children than in adults, these conditions are important causes of morbidity, and occasional mortality, when they occur in a pediatric population. The disease may range from limited skin involvement (localized scleroderma, LS) to diffuse cutaneous sclerosis and severe internal organ disease (systemic sclerosis, SSc). Juvenile SSc is further subdivided by the extent of the skin disease into diffuse cutaneous scleroderma (DCSS) and limited cutaneous systemic scleroderma (LCSS). There are 3 types of LS: plaque morphea, generalized morphea, and linear morphea. Children are more likely than adults to develop LS. By definition the onset of juvenile scleroderma happens before 16 years of age. Herein, we report on our experience with juvenile scleroderma.

Methods

A retrospective chart review was performed. There were 23 patients diagnosed with SSC and LS who were enrolled in our study. Diagnoses were made from March 1993 to September 2009 in the Department of Pediatrics at Mackay Memorial Hospital, Taipei, Taiwan. We divided these patients into 2 groups: group 1 comprised 3 SSc patients with visceral organ involvement and group 2 included 20 LS patients.

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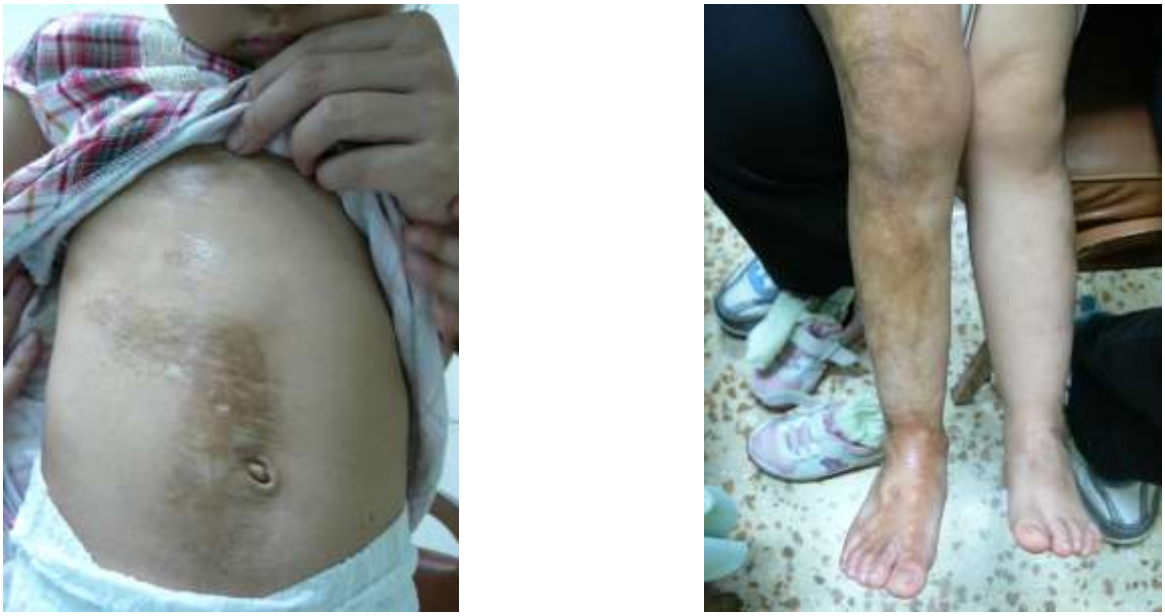

A B

Figure 1. Generalised scleroderma (Patient 19)
A. A central area of induration with a waxy, ivory-colored area surrounded by inflammation and hyperpigmentation over the abdominal area
B. Other skin appearance of the same patient over the right leg with a contracted ankle

In group 1, SSc was diagnosed according to criteria from the American College of Rheumatology (ACR).[1] The cutaneous involvement was graded according to LeRoy's classification as limited (hands, forearms, face, or feet) or diffuse (truncal and acral).[2] In group 2, LS patients were separated into subsets based on the clinical appearance of the lesions: subset 1 was plaque morphea, characterized by circumscribed hypo- or hyper-pigmented sclerotic plaques on the skin; subset 2 was general morphea, in which individual plaques of morphea become confluent or multiplied, affecting 3 or more anatomic sites and subset 3 was linear scleroderma, which involve 1 or more linear streaks that typically involve the upper or lower extremities. The lesions frequently follow a dermatomal distribution, and were unilateral in most cases. When linear scleroderma involves the face or scalp, it is referred to as *en coup de sabre* (ECDS). Combinations of subgroups were noted, with confirmatory histopathology examinations conducted, if necessary.

Data recorded included sex, age-at-onset, age-at-diagnosis, clinical manifestations, laboratory data, family history, trauma history, treatments and outcomes. Tests were performed for antinuclear antibodies (ANAs) and anti-Scl-70 antibodies and test for antibodies against double-stranded DNA (anti-dsDNA) were performed using double immuno-diffusion assays. Rheumatoid factors (RFs) were measured by Nephelometry tests. The disease course was assessed annually by reviewing medical records or via telephone interviews with the patients and their families.

Results

Records of the 23 patients diagnosed with scleroderma over the 16-year study period were retrieved. Three patients (13.04%, 2 girls and 1 boy) had SSc and 20 patients (86.96%, 14 girls and 6 boys) had LS, an LS to SSc ratio of 6.7:1. Two of the SSc patients had DCSS and one SSc patient had LCSS (patient 12). In the 20 patients in the LS group, 5 (25%) patients had plaque morphea, 5 (25%) had linear morphea, 5 (25%) had a combination of plaque and linear morphea and 5 (25%) had general morphea (Figure 1), while 7 (35%) patients had ECDS (Figure 2). In total, there were 16 girls and 7 boys (female to male ratio of 2.3:1). The mean age-of-onset was 6.55±3.28 years old. The mean age-at-diagnosis

Figure 2. En coup de sabre (Patient 18) A 16-year-old girl with involvement to the left midline from the forehead to the nose, resulting a depression and mild asymmetry of the forehead and nose

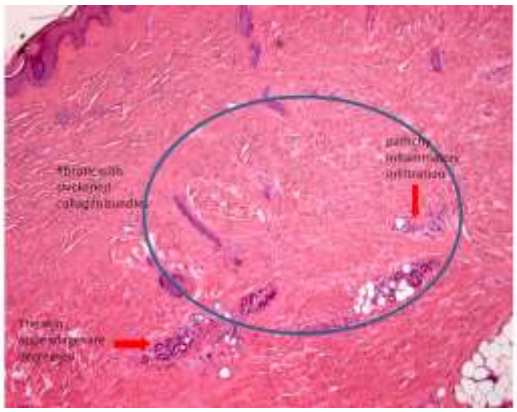

Figure 3. Histopathologic features of the cutaneous disease are visible in Patient 20 with localized scleroderma. The dermis and superficial subcutis are fibrotic with thickened collagen bundles and pathchy inflammatory infiltration. The skin appendages are decreased. (hematoxylin and eosin stain; magnification 40)

was 9.12±3.50 years old. The 3 patients with DCSS had the onset at ages 3, 5.5, and 7 years old. The mean age-of-onset of LS was 6.76±3.42 years old (range, 1.1 to 11 years old). The delay between onset and diagnosis was 2.62±2.18 years in the entire group, 4.9 to 6.2 years for the SSc group and 2.21±2.02 years for the LS group. Two (8.70%) of the children with LS (patient 5 and patient 7) had a history of trauma. Patient 5 was involved in a road traffic accident. Her morphea and operation scar were on the same anatomic site over left forearm. Patient 7 suffered abrasions over right little finger and the skin change began within the same year. One (4.34%) child with LS (patient 7) had an aunt who suffered rheumatoid arthritis. There were no other family histories of autoimmune disease among the other 22 children.

The 23 patients presented with a variety of symptoms and signs (Table 1). Skin tightening was present in all children and contracture was observed in 10 (43.48%) of them (Table 2). Given the prevalence of LS, the skin and musculoskeletal systems were mostly involved. Sclerodactyly was present in 9 (39.13%) patients, 3 with SSc and 6 with LS. Raynaud's phenomenon and digital pitting were present in 3 (13.04%) SSc patients. One SSc patient (patient 2) had an osteolytic lesion of the right index finger. Two (8.70%) patients with SSc had headaches. One child with SSc had proteinuria (patient 2), initially diagnosed as nephropathy of an unknown origin. One boy (patient 21) had linear scleroderma over the left face (ECDS) combined with a posterior fossa tumor, which is still under investigation. His initial presentations included headache and vomiting, and these symptoms happened after 3 years of skin changes.

Pulmonary function tests were performed in 17 patients. Among these 17 patients, one (5.88%) patient with SSc (patient 2) had mildly restrictive ventilation with diffusing capacity defects. Diffusing capacity of the lungs for carbon monoxide (DLco) was 64% of the predicted value. None of the 5 patients in whom an upper GI series were done had abnormalities. Four LS patients had skin biopsies to confirm their diagnoses (Figure 3). The findings were all compatible with scleroderma.

Antinuclaer antibodies were positive in 15 (65.21%) patients at titers of 1:40 to 1:10240. Among these 15 patients, 2 (13.33%) exhibited nucleolar patterns, 7 (46.67%) had speckled patterns, 4 (26.67%) had homogenous patterns and 2 (13.33%) had speckled-to-homogeneous patterns. Tests for anti-Scl-70 antibodies were positive in only 1 (4.34%) patient with SSc (patient 12). All tests for anti-ds-DNA antibodies were negative. Serum levels of rheumatoid factor ranged from <20 to 60.2 IU/ml including 2 (8.70%) children having positive levels (60.2 IU/ml in patient 2 with SSc; 45.6 IU/ml in patient 7 with LS whose aunt had rheumatoid arthritis). There is no association with arthritis in these two patients.

During the 16-year follow up period, all 22 patients were treated with D-penicillamine and documented softening of their skin lesions. Oral prednisolone and methotrexate were added, if indicated. Only 1 girl (patient 15) with LS received conservative therapy.

One girl (patient 20) with LS had nephrotic syndrome (proteinuria, hyperlipidemia, hypoalbuminemia and edema) after 10 months of treatment. She received D-penicillamine (300 mg BID), methotrexate (12.5 mg QW) and prednisolone as initial therapy. Prednisolone was gradually tapered, then stopped. After her nephrotic syndrome occurred, D-penicillamine was stopped and supportive treatment was given. No steroid or immunosuppressive agents were prescribed. No renal biopsy was performed and she was kept under observation. Her proteinuria and edema resolved three weeks after D-penicillamine was stopped. Her serum level of albumin and total cholesterol levels returned to normal ranges after 5 weeks. D-penicillamine nephropathy was highly suspected. There was no evidence of deterioration in renal function.

Complete remission of skin lesions occurred in 1 boy (patient 10) and 1 girl (patient 15) who had LS after 4 years and 2 years of treatment, respectively. Patient 10 received prednisolone (0.5mg/kg/day) and D-penicillamine (10mg/kg/day). Prednisolone was used for initial

Table 1. Demographic and clinical characteristics of 23 patients with juvenile scleroderma

Patient	Sex	Symptoms and signs	ANA/Anti-Scl70 Ab	RF	Trauma history/ Family history	PS/ D-PC / MTX
1^, 6y/o	M	Generalized morphea, Raynaud's phenomenon*, Headache*	1:640(H)/-	-	-/-	+/+/+
2^, 9y/o	F	Generalized morphea, Proteinuria*	1:640(S)/-	+	-/-	+/+/+
3^^, 6y/o	F	Plaque morphea*	1:40(S/H)/-	-	-/-	-/+/-
4^^, 6y/o	M	Plaque morphea*	1:160(S)/-	-	-/-	-/+/-
5^^, 12y/o	F	Plaque and linear morphea*	1:160(S)/-	-	+/-	-/+/-
6^^, 8y/o	F	Plaque and linear morphea*,	1:640(S)/-	-	-/-	+/+/+
7^^, 10y/o	F	Plaque and linear morphea*, Contracture*	1:640(H)/-	+	+/+ (aunt: RA)	-/+/-
8^^, 9y/o	F	Plaque and linear morphea*, En coup de sabre	1:160(S)/-	-	-/-	+/+/-
9 ^^, 12y/o	M	General morphea*,	<1:40/-	-	-/-	+/+/-
10^^, 9y/o	M	Plaque morphea*	1:40(S/H)/-	-	-/-	+/+/-
11^^, 7y/o	F	Plaque morphea*	<1:40/-	-	-/-	+/+/-
12^, 12y/o	F	Proximal scleroderma over hands*, Raynaud's phenomenon*, Digital pitting*,	1:10240(H)/+	-	-/-	-/+/-
13^^, 13y/o	F	Linear morphea*, En coup de sabre	1:320(N)/-	-	-/-	+/+/-
14^^, 13y/o	M	Plaque morphea*,	<1:40/-	-	-/-	+/+/-
15^^, 1.2y/o	F	Linear morphea*, En coup de sabre	1:40(S)/-	-	-/-	-/-/-
16^^, 9y/o	F	Plaque morphea*	<1:40/-	-	-/-	-/+/-
17^^, 13y/o	F	Linear morphea*, En coup de sabre	1:320(H)/-	-	-/-	+/+/-
18^^, 16y/o	F	Linear morphea*, En coup de sabre	<1:40/-	-	-/-	+/+/+
19^^, 3y/o	F	General morphea*	1:320(N)/-	?	-/-	+/+/+
20^^, 6y/o	F	Plaque and Linear morphea*, Proteinuria due to D-penicillamine	1:2560(S)/-	-	-/-	+/+/+
21^^, 4y/o	M	Plaques and Linear morphea*, En coup de sabre, Posterior fossa tumor	<1:40/-	-	-/-	+/+/+
22^^, 8y/o	M	General morphea*	<1:40/-	-	-/-	+/+/+
23^^, 14y/o	F	Linear morphea*, En coup de sabre	<1:40/-	-	-/-	+/+/+

*Initial manifestation, ^ Group 1: systemic scleroderma, ^^ Group 2: localized scleroderma, PS: Prednisolone, D-PC: D-penicillamine, MTX: Methotrexate, ANA=Antinuclear antibodies, normal range (<1:40), RF=Rheumatoid factors, normal range (<20 IU/mL), RA=Rheumatoid arthritis, (S): Speckled pattern, (H): Homogenous pattern, (N): Nucleolar pattern, (S/H): Speckled-to-homogenous pattern

Table 2. Organ system involvement

Organ System	Present/Examined
Skin	
Subcutaneous calcification	0/23
Digital Pitting	3/23 (13.04%)
Telangiectasias	3/23 (13.04%)
Pigmentation	23/23 (100%)
Digital arteries (Raynaud's phenomenon)	3/23 (13.04%)
Musculoskeletal	
Arthralgia	4/23 (17.40%)
Contractures	10/23 (43.48%)
Muscle weakness	5/23 (21.74%)
Muscle atrophy	23/23 (100%)
Nervous system	
Headache	2/23 (8.70%)
Numbness of extremities	3/23 (13.04%)
CNS tumor	1/23 (4.34%)
Gastrointestinal tract	
Abnormal esophageal motility	0/5
Lung	
Abnormal diffusion	1/17 (5.88%)
Heart	
Cardiomegaly	0/8
ECG abnormalities	0/6
Kidney	
Proteinuria	2/11 (18.18%)
Impaired renal function	0/11

one month, and gradually tapered. D-penicillamine was prescribed for 4 years until his skin lesions disappeared. The linear morphea of patient 15 was mild and she received conservative therapy. She also had atopic dermatitis and was treated with emollient and intermittent topical steroid. There were no reports of progression from LS to SSc in our study.

Discussion

SSc is rare in children. In Japan, in a primary survey, 0.9% of children with a rheumatic condition had scleroderma.[3] Because of the small number of reports on children with SSc, and the small number of patients in each report, determining precise percentages of clinical manifestations, courses, and outcomes is difficult. However, the disease does seem similar to its counterpart in adults. The incidence of juvenile SSc (JSSc) is around 0.05 per 100,000 children.[4] The onset of JSSc occurs at a mean age of 8.1 years old, with a peak age between 10- and 16-years-old.[3,5] The disease occurs almost 4 times more frequently in girls.[5]

LS is also relatively uncommon, but is far more common than SSC in childhood by a ratio of at least 10:1.[6] The condition has an estimated incidence of 0.4 to 1 per 100,000 individuals.[7] Juvenile LS (JLS) has a mild female predilection (female to male ratio 2.4: 1) with mean age-at-onset of 7.3 years old.[5] In our study, the mean age-at-onset of LS was 6.76±3.42 years, and the female-to-male ratio of LS was 2.3:1. These figures are similar to previous reports.

Although the etiology of juvenile scleroderma is unknown, viral, environmental, and metabolic stimuli should be considered. There is a significant association of trauma with childhood-onset scleroderma**,** which is not observed in the adult-onset disease.[8] In an international study of 750 JLS cases, 91 patients (12%) had a positive family history for rheumatic or autoimmune diseases, and 100 (13.3%) reported environmental events as possible triggers.[9] In our report, 2 (8.70%) of our children with LS had a history of trauma and 1 (4.34%) girl with LS had an aunt with rheumatoid arthritis.

The first presenting signs and symptoms of JSSc are often characterized by the development of Raynaud's phenomenon and the tightening, thinning, and atrophy of the skin. In an international database, Raynaud's phenomenon was the most frequent symptom in 75% of the patients, followed by skin induration in 74% of the patients.[10] Other common signs of skin involvement included sclerodactyly in 66% of patients, edema in 46%, and calcinosis in 19%.[10] In another study, Zulian reports skin tightening occurring in 84% of children and Raynaud's phenomenon in around 72%.[11] Telangiectases, the distorted capillary architecture of the periungual nailfold and digital pitting, sometimes with ulceration, were characteristic signs of JSSc.[11] In our study, all 3 SSc patients endured Raynaud's phenomenon, skin induration, and sclerodactyly. One girl with SSc had an osteolytic lesion on her right index finger. There was also telangiectases, digital pitting, and a tortuous dilated periungual nailfold capillary seen in our 3 SSc children.

At the time of diagnosis, the children exhibited significantly less frequent involvement of all organs than the adults.[10] Involvement of other internal organs included the respiratory (42%) and gastrointestinal (GI) systems (30%), arthritis (27%), and cardiac involvement (15%). Rarely reported were sclerodermal renal crisis (0.7%), renal failure (5%), and central nervous system (CNS) involvement (3%).[5] Other reports show similar results with pulmonary involvement found in 41%-50% and renal involvement in 10%,

Table 3. Preliminary classification criteria for juvenile systemic sclerosis

Major criterion - proximal sclerosis/induration of the skin
Minor criteria
Skin
sclerodactyly
Vascular
Raynaud's phenomenon
Nailfold capillary abnormalities
Digital tip ulcers
Gastrointestinal
Dysphagia
Gastro–esophageal reflux
Renal
Renal crisis
New-onset arterial hypertension
Cardiac
Arrhythmias
Heart failure
Respiratory
Pulmonary fibrosis (high resolution computed tomography/radiograph)
Diffusing lung capacity for carbon monoxide
Pulmonary hypertension
Musculoskeletal
Tendon friction rubs
Arthritis
Myositis
Neurological
Neuropathy
Carpal tunnel syndrome
Serology
Antinuclear antibodies.
SSc-selective autoantibodies (anticentromere, antitopoisomerase I, antifibrillarin, anti-PM-Scl, ant-fibrillin or anti-RNA polymerase I or III)

A patient, aged less than 16 years, shall be classified as having juvenile systemic sclerosis if the one major and at least two of the 20 minor criteria are present. This set of classification criteria has a sensitivity of 90%, a specificity of 96%,

lower than in adult cohorts.[12] Proteinuria was the most frequent (28.6%) symptom and an early sign of renal damage in patients with scleroderma.[13] In our patients, proteinuria was diagnosed as nephrotic syndrome in the initial presentation of the girl with SSc, without renal function impairment. Children showed signs of interstitial lung involvement and gastroesophageal dysmotility less frequently than in adults.[10] Pulmonary involvement was manifested by reduced forced vital capacity (FVC) and DLco. Our 3 SSc patients did not have any GI involvement, but one did have dyspnea and decreased DLco.

Around 90% of JSSc have a diffuse subset.[4] The organ involvement of JSSc differs from that of adult patients. The duration between onset and diagnosis of JSSc takes a long time, from 1-4 years with a range of 0-26 years.[14] There is no special classification criteria for JSSc, so the criteria for adult SSc from the ACR may be used.[1] The adult ACR criteria was established in 1980, and includes the presence of one major criterion, namely "symmetrical thickening of the skin proximal to the metacarpophalangeal or metatarsophalangeal joints" or 2 or more minor criteria, including sclerodactyly, digital pitting scars, or the loss of substance from the finger pad, and bibasilar pulmonary fibrosis.

The new provisional classification criteria for JSSc are the first proposed criteria for pediatric-onset patients.[15] A patient, younger than 16-years-old, shall be classified as having JSSc if the one major criteria (proximal skin sclerosis/induration) and at least 2 of the 20 minor criteria are present (Table 3, grouped in 9 main categories). This criterion is prospectively not yet validated, but has the potential to make the diagnosis of JSSc earlier in the disease course and create a larger and more clearly defined patient population.[14] Compared with the ACR criteria, the JSSc criteria have the advantage of not being limited to only pulmonary symptoms as an indication of internal organ involvement, but also includes other scleroderma-specific organ involvement or antibody profiles that can define the disease for classification purposes.[14]

LS is a disorder of cutaneous induration. The duration between the first sign of LS to definitive diagnosis ranges from 1 mo to 8 y with a mean of 1.2 y.[7] In our report, the delay between onset and diagnosis was 2.62±2.18 years. Plaque morphea was the most common form and linear scleroderma affected children much more frequency than adults.[16] These patients may have 1 or more associated non-cutaneous manifestations. In a large cohort of children with juvenile LS, articular symptoms were the most extra-cutaneous manifestations.[7] Four (17.40%) of our patients complained of arthralgia.

Linear scleroderma ECDS is characterized by a clinical presence over the forehead and scalp with skin lesions resembling the stroke of a sabre. In our study, a 4-year-old boy had ECDS concurrent with a CNS tumor. Neurological abnormalities have been described in association with linear scleroderma ECDS. Epilepsy has been reported most frequently.[18] Kristen, *et al.*, described 3 pediatric patients with linear scleroderma ECDS who presented with neurologic abnormalities (including partial

complex seizures and palsy of the facial nerve) before or concurrent with the diagnosis of their skin disease.[19] Bergler-Czop, *et al.*, reported a 33-year-old patient with an ECDS scleroderma and a CNS tumor.[20]

Laboratory results are suggestive, but not specific enough for diagnosis. Antinuclear antibodies are present in 81% of patients with JSSc and anti-Scl-70 antibodies are present in 34% of such patients.[10] In our series, all 3 of our SSc patients tested positive for ANAs, and one was positive for anti-Scl-70 antibodies. Rosenberg reported positive ANAs in 63% of patients and 4% of patients reacted with anti-Scl-70 antibodies in juvenile LS.[21] In our study, 12 (60%) LS patients tested positive for ANAs and none were positive for anti-Scl-70. In children with LS, rheumatoid factors are present in 16%.[9] Two (10%) patients in our study had RFs of 45 and 60 IU/mL, one of whom had a family history of rheumatoid arthritis. Several auto-antibodies, including anti-centromere, anti-RNP I/III, anti-fibrillarin, and anti-Th/To, have been found to be specific for scleroderma and may help differentiate this disease from other connective diseases.[22]

The most characteristic radiologic findings on hand are marked by a decrease in soft tissue and resorption of the tufts of the distal phalanges (acro-osteolysis, particularly in patients with severe Raynaud's phenomenon). Resorption of the distal tufts is particularly common in children.[23] This finding was present in patient 2 in our series. Radiologic studies of the GI tract often demonstrate abnormalities, even in the absence of symptoms. None of the 5 in whom an upper GI series was performed had any abnormalities.

The histologic findings include increased numbers of T-lymphocytes, plasma cells, and macrophages in the deep dermis and subcutaneous tissue as well as around the small blood vessles, nerves, pilosebaceous apparatus, and sweat glands.[24] Later in the course of the disease , biopsies document homogenization of collagen fibers with a loss of structural detail and an increased density and thickness of collagen deposition.[25] In the advanced stages, the entire dermis may be replaced by compact collagen fibers.

There is no single therapy for SSc or LS that has proven to be very effective or significantly disease modifying. If there is a significant risk of disability from LS, improvement using methotrexate and corticosteroids have been confirmed.[26] In SSc, indications for glucocorticoids include the treatment of myositis, arthritis, and tenosynovitis.[5] According to expert pediatric opinions, methotrexate may be the treatment of choice for skin manifestations for children with JSSc, especially in its early phase. D-penicillamine (D-PC) is widely used for both LS and SSc, because of its ability to inhibit the disulfhydryl cross-linkages in collagen.[27] Besides a significant reduction in skin involvement, D-PC causes a statistically significant improvement in renal, cardiac, and pulmonary involvement.[28] However, D-PC nephropathy was suspected in one LS patient. D-PC treatment may be associated with some adverse effects. Reactions may occur after 3 months (or at most 6 months), due to an immunological response and renal toxicity. In one study, 33 patients who developed proteinuria during treatment with oral D-PC were studied throughout their renal illness. In all the patients whose nephropathy was due solely to treatment with D-PC, their proteinuria resolved completely when the drug was withdrawn (median duration: 8 months, range: 1-21 months) and their renal function did not deteriorate. The study concluded that corticosteroids were unnecessary[29].

Microvascular abnormalities and fibrosis are important targets for therapy in SSc. Calcium channel blockers, ACE inhibitors, sartans, phosphodiesterase-5 inhibitors, and serotonin re-uptake blockers are used for Raynaud's phenomenon.[27] New interventions such as autologous stem cell transplants and cytokine-directed therapies are under investigation as potential treatments for this complex disease.[30]

The prognosis of SSc in children appears to be better than in adults. Most patients who die in the first 5 years of the disease are from a diffuse subset. Most showed a very rapid progression with early signs of internal organ involvement. The survival rates of childhood-onset SSc at 5-, 10-, 15-years-old after diagnosis are 89% to 90%, 80%, and 74%, respectively, and are significantly higher than for adult-onset disease.[14,31] In children with SSc, fibrosis on chest X-rays, raised creatinine levels, and pericarditis are strongly and independently predictive of death.[32] Cardiac involvement as a prominent feature associated with fatal outcomes was previously described by other authors.[31,33] In adults, transitions from LS to

SSc was reported in 0.9% of patients,[34] but in children this is less common (0.13%).[17] LS often remits spontaneously after 3 to 5 years.[35] In our experience, all patients with LS experienced a documented softening of their skin lesions after treatment. Complete remission occurred to 1 boy and 1 girl after 4-years and 2-years of treatment, respectively.

In our series, juvenile scleroderma was rare in children, and characterized by the thickening and hardening of the skin. Most presented as a localized form of the disease. The prognosis of SSc appears to be poor, but better than in adults. In contrast, the prognosis in LS is usually benign. However, LS may become progressively more indurated and can extend through the dermis, subcutaneous tissue, and muscles to the underlying bone. If disease showed progressing clinically, it should be treated aggressively even when the skin lesion are localized initially. LS may not be limited to the skin and one of our patients had a concurrent CNS tumor. D-penicillamine nephropathy happened in one girl with LS in our study, but this resolved spontaneously after stopping treatment without any deterioration in renal function to date. All of our patients had documented skin softening.

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