Juvenile Scleroderma

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Agenda

- **Definition and pathogenesis**
- Localized sclerodermas
- Systemic sclerosis

Juvenile Scleroderma

Definition

- Localized scleroderma (jLS)
  - fibrosis of skin and underlying tissue
  - without vascular or internal organ involvement
  - more common in children
  - incidence of 2.5/million children/yr (CI 1.8-3.1)

- Systemic sclerosis (jSS)
  - skin, vascular and visceral organ fibrosis
  - more common in adults
  - incidence of 0.27/million children/yr (CI 0.1-0.5)

“Hard skin” Pathology

- Inflammatory infiltrate

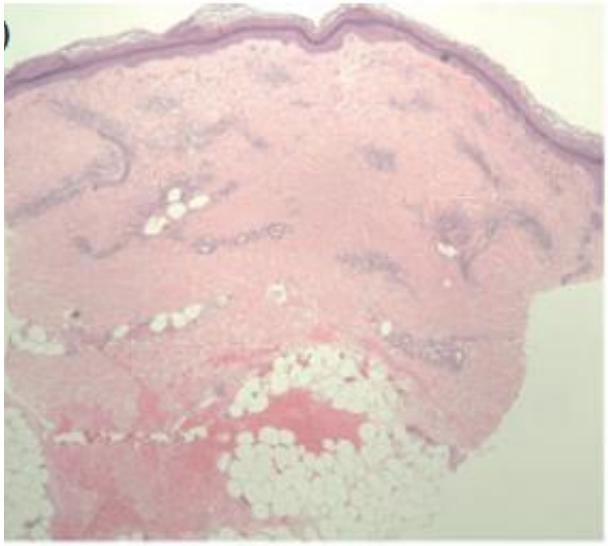
  lymphocytes, plasma cells, macrophages, eosinophils and mast cells

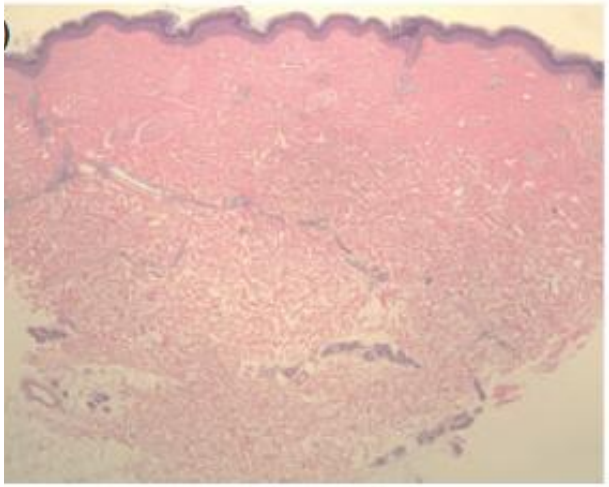
  hyalinization blood vessel walls, proliferation endothelial cells

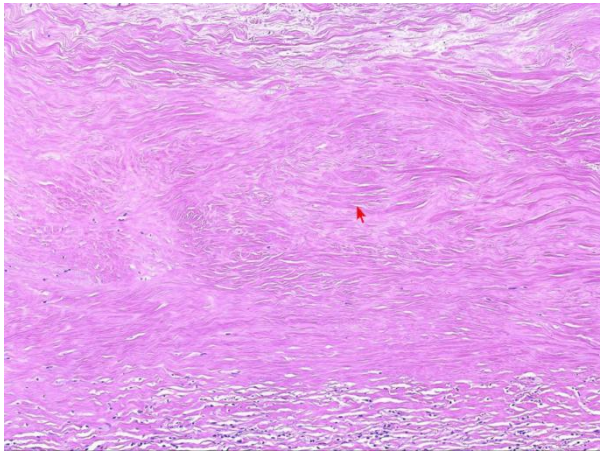
- Increase in fibroblasts and collagen < escalating sclerosis
- Entire dermis replaced by compact collagen fibers
- Thinning of epiderm, atrophy dermal appendiges

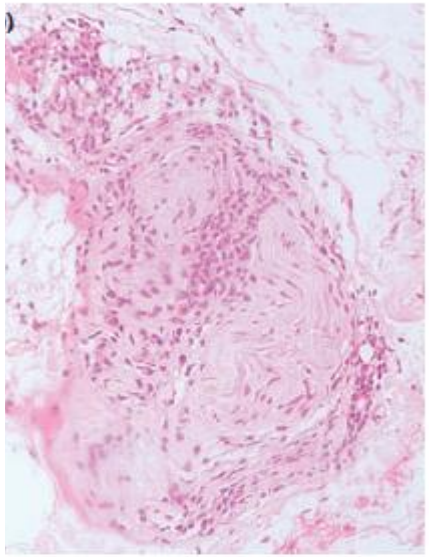
“Hard skin”

Pathology









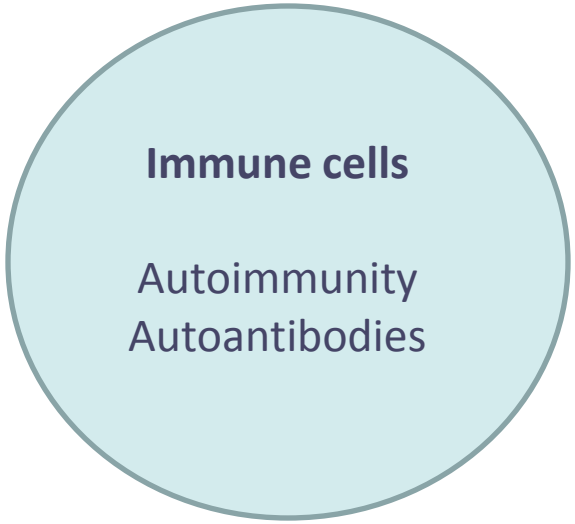
Dermal sclerosis (diffuse vs superficial)
Perivascular and peri-eccrine lymphocytes

jLS intense inflammation
prevalent diffuse dermal fibrosis
perineural inflammation

Succaria et al, J Eur Ac Derm Veneorol 2013

Juvenile scleroderma

Pathogenesis



Th1 and Th17 cells and Th-cytokines, chemokines, growth factors in serum and tissue

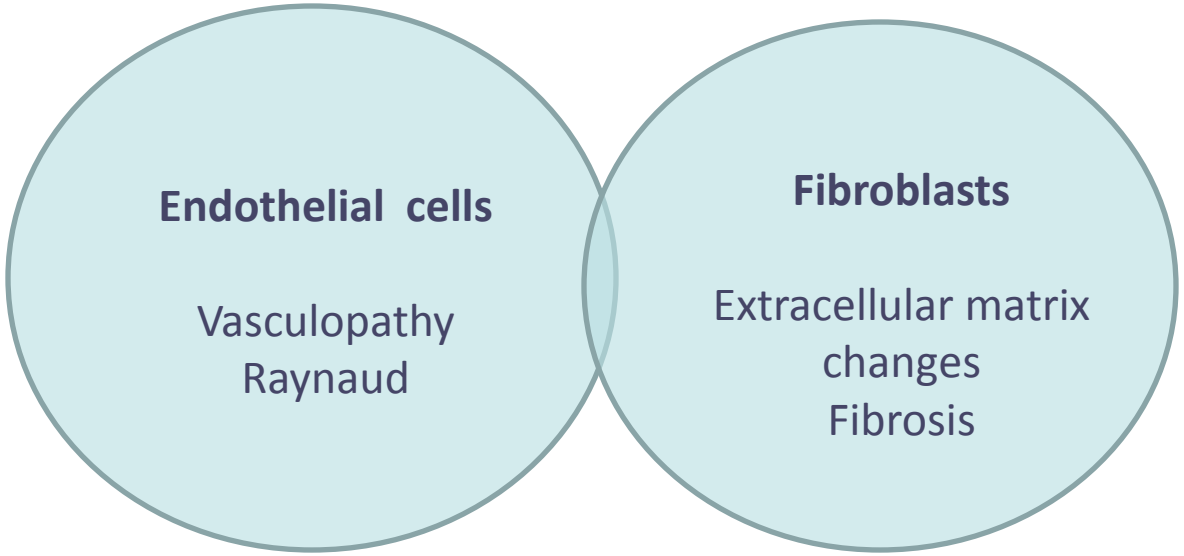
ANA (antihistone, anti-ssDNA) in 20 -73% of LS

ANA (anti-topoisomerase I > anti-centromere, anti-RNA polymerase III) in 95% SS

Concomitant autoimmune diseases (psoriasis, vitiligo, JIA, SLE, Sjogren)

Juvenile scleroderma

Pathogenesis



Infiltration of immune cells with release of cytokines, chemokines, growth factors affecting EC and fibroblasts

Increased expression of adhesion molecules mediating contact between immune cells, endothelial cells and fibroblasts

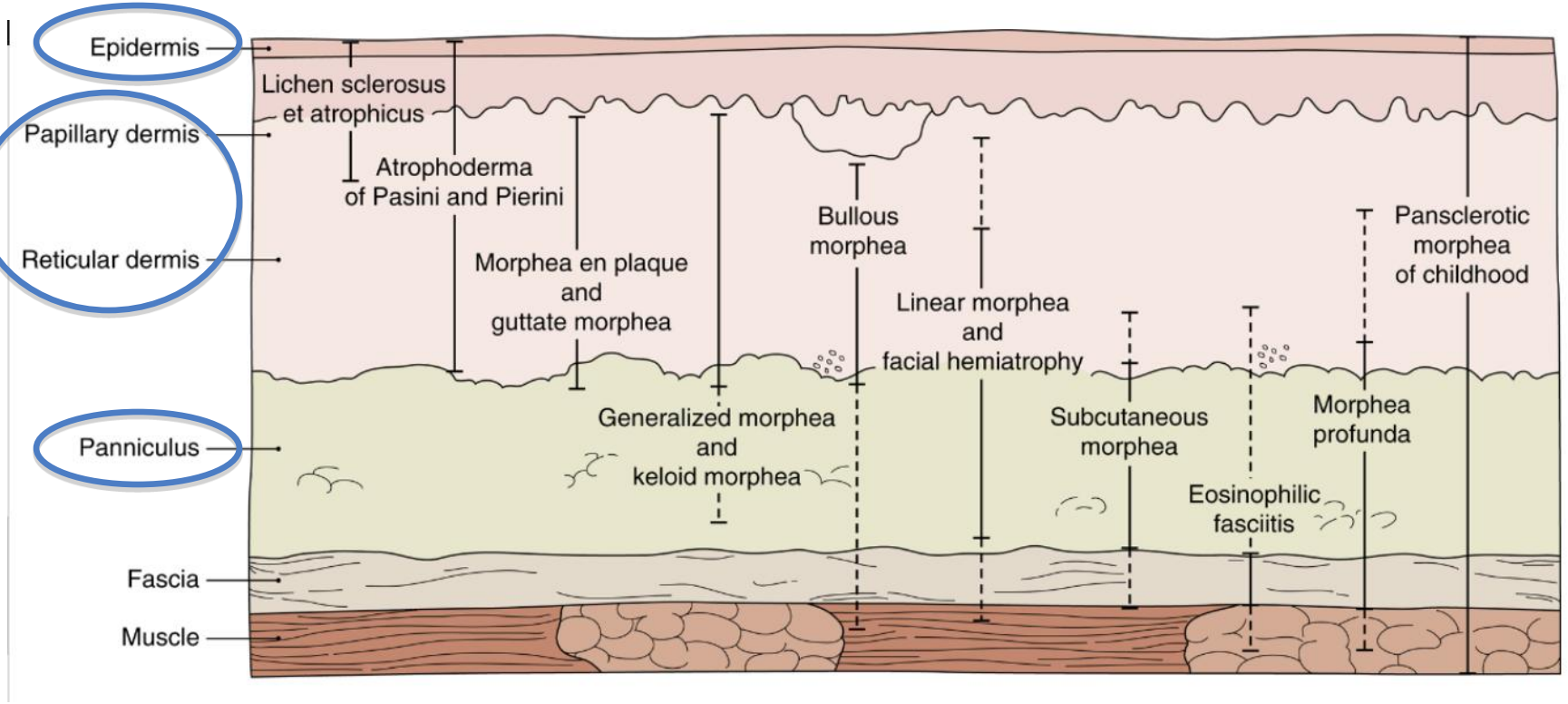
Abnormal control of collagen synthesis and regulation of fibroblast apoptosis

Localized scleroderma

- **Classification and clinical features**
- Assessment of activity and damage
- Treatment

Localized scleroderma

Classification



LS subtypes differentiated by depth of skin involvement

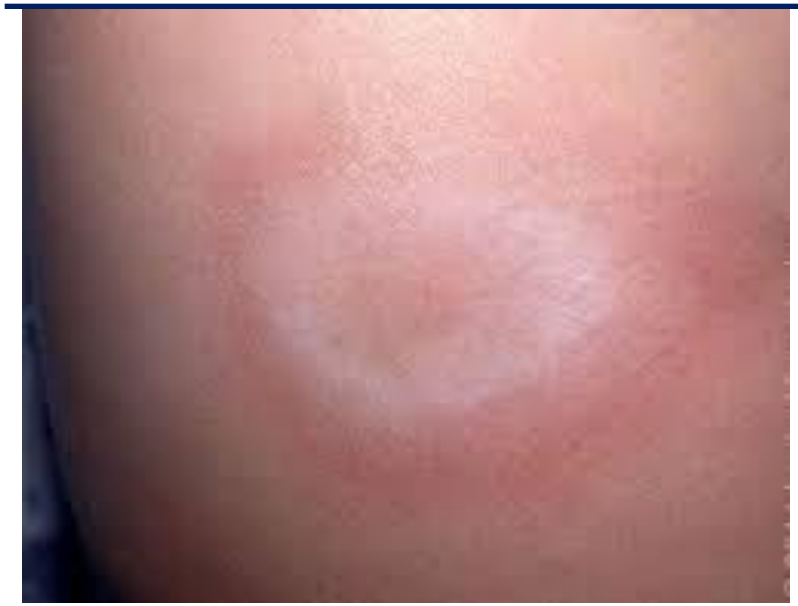
Localized scleroderma Classification

Main Group	Subtype/Definition
1. Circumscribed morphea	A, Superficial B, Deep
2. Linear scleroderma	A, Trunk/limbs B, Head c, En coup de sabre cc, Parry-Romberg or progressive hemifacial atrophy
3. Generalized morphea	Four or more plaques (>3 cm) and involves at least 2 of 7 anatomic sites
4. Pansclerotic morphea	Circumferential involvement of the limbs, affecting all tissue layers including the bone
5. Mixed morphea	Combination of 2 or more previous types

Associated: lichen sclerosus et atrophicus, bullous morphea, eosinophilic fasciitis

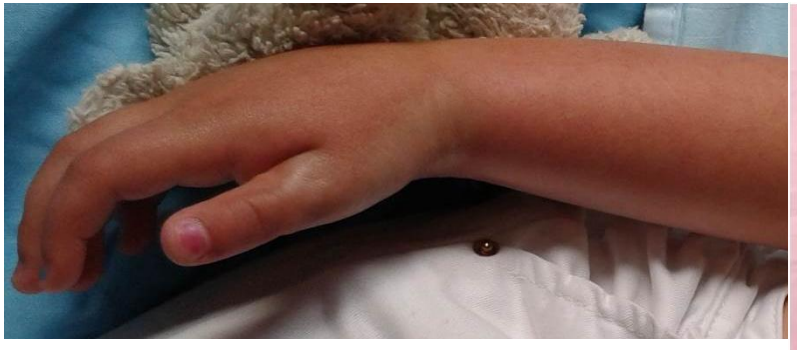
Padua classification, Laxer, Zulian, Curr Opin Rheumatol 2006

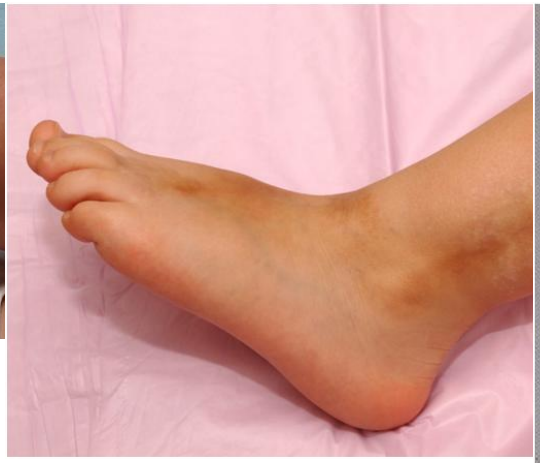
Circumscribed morphea

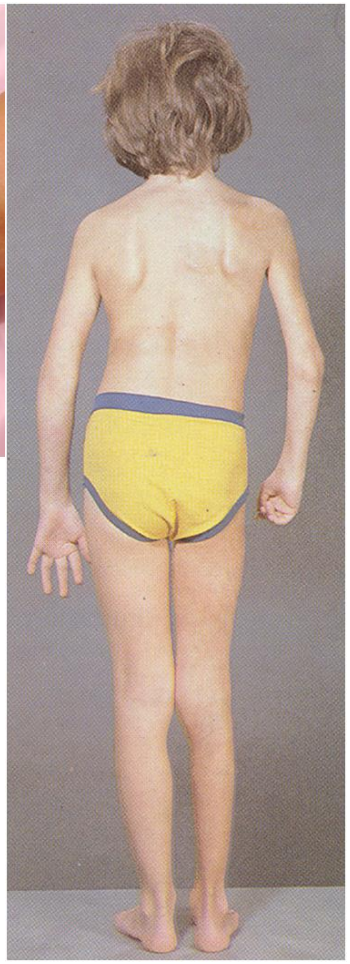


- Superficial « Plaque » — epidermis/dermis
- Deep morphea — dermis, subcutis, fascia, muscle
  also subcutaneous morphea
- Guttate morphea

Linear scleroderma







Most common subtype (50-60%)

One or more linear streaks or bands (mostly extremities)
- dermis, subcutis
- extension to muscle, tendons, bone

Cave joint contracture, muscle atrophy, limb shortening

Linear scleroderma en coup de sabre

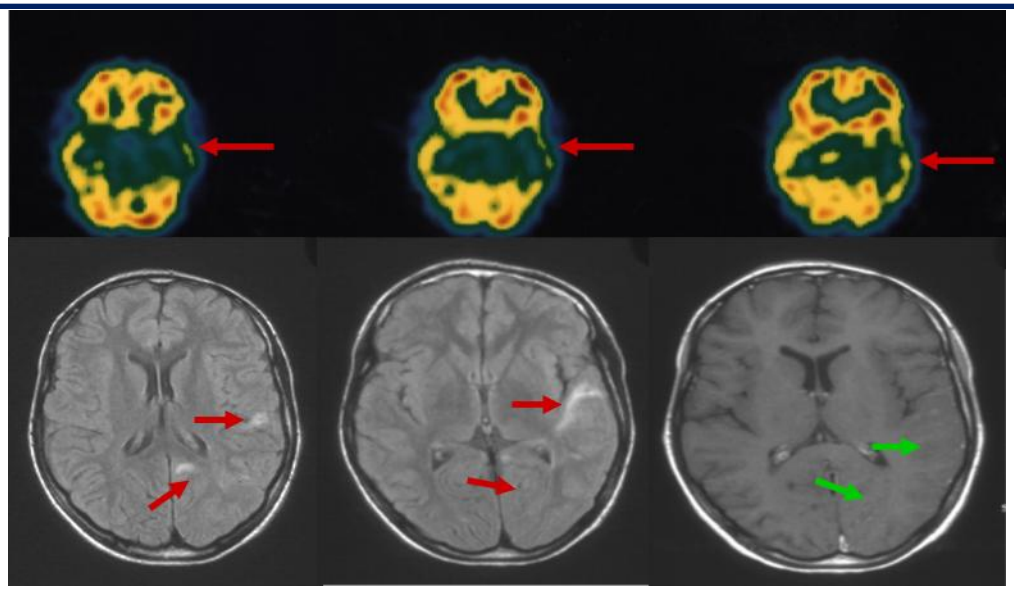
Linear induration of the skin, generally located at the frontoparietal scalp and/or paramedian forehead often resembling a stroke from a sword

LS en coup de sabre

Parry Romberg

Hemifacial atrophy of soft tissue of the cheek, progressing to chin and forehead, extending into underlying muscles and bone
mild/absent involvement of the superficial skin
provoking asymmetry of the face

LS en coup de sabre with encephalitis



- Coup de sabre since age 5 yrs
- Hemicranial migraine, complex partial seizures at age 12 yrs
  - MRI T2 hyperintense signals left subcortital white matter
  - SPECT hypoperfusion
  - ANA in serum and CSF
- Clinical remission, MRI stabilisation with MTX therapy

LS with Parry Romberg and autoimmunity

Coeliac disease and bilateral uveitis at 5 yrs
ANA+, antigliadin ab+

Depigmentation, loss of eyelashes at right eye, CM lesion cheek at 6 yrs

Progressive hemifacial atrophy at 7 yrs

Bilateral wrist synovitis/tenosynovitis with carpal tunnel S at 8 yrs

Overlap between linear scleroderma, progressive facial hemiatrophy and immune-inflammatory encephalitis

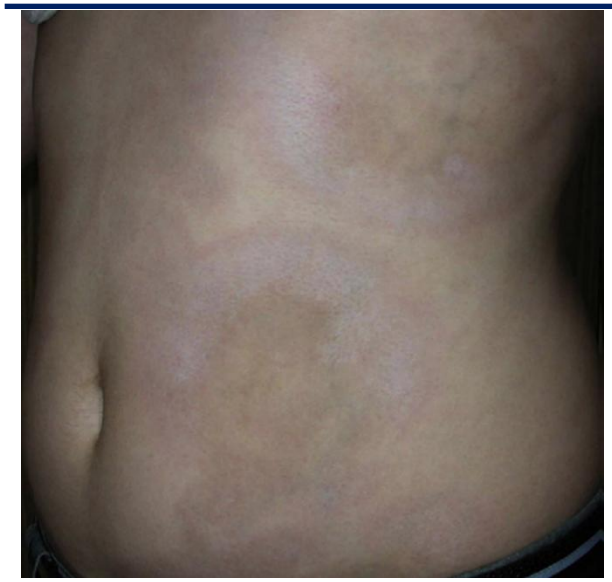
LSCS and PRS are the same disease entity with LSCS and superficial skin involvement at one end of the spectrum and PFH with involvement of subcutaneous deep tissues, at the other hand. Overlapping cutaneous features may occur with time

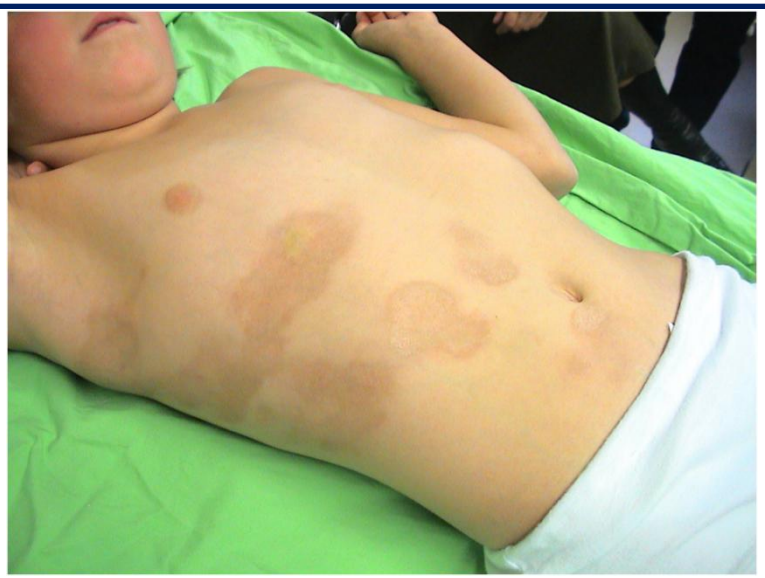
In both entities, **seizures and severe encephalitis mimicking Rasmussen encephalitis** can be observed

In both entities ocular and dental abnormalities and **autoimmune manifestations (arthritis, uveitis, ANA in serum/CSF)** may be present

De Somer, Eur J Pediatrics 2015; Lehman, J Rheumatol 1992

Generalized morphea

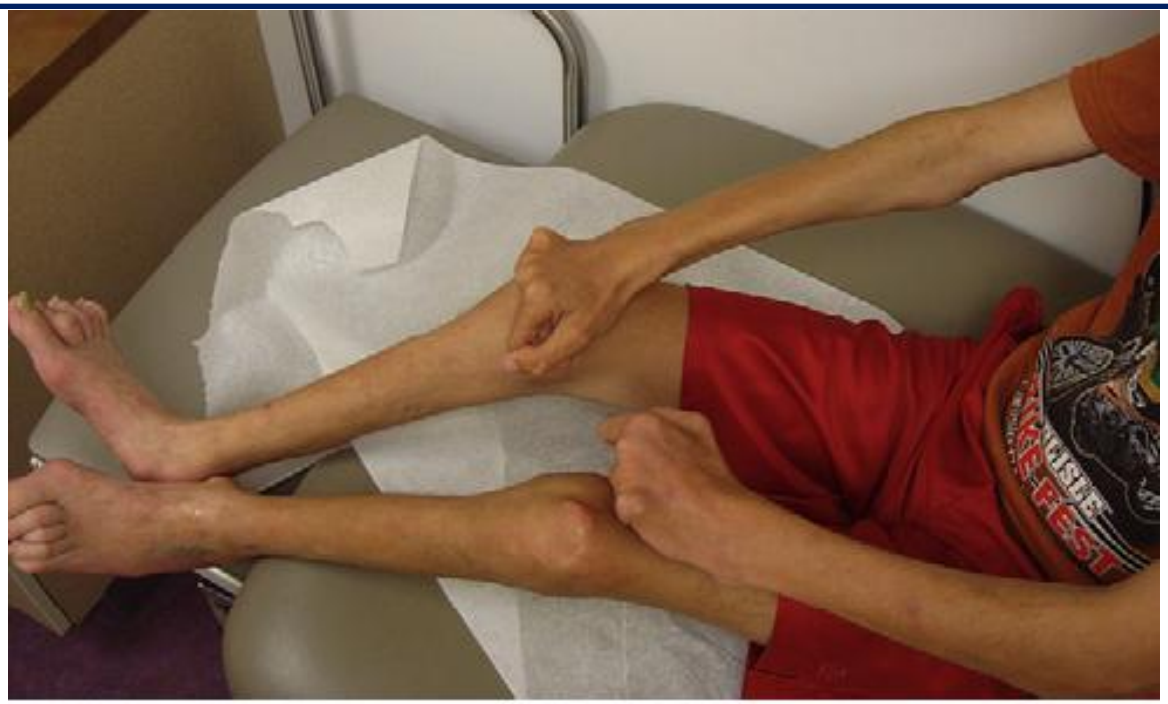




Four or more plaques, > 3 cm, becoming confluent and affecting several anatomic areas (most commonly trunk)

Uncommon (< 10% LS), often bilateral
Systemic symptoms: fatigue myalgia arthralgia

Pansclerotic morphea



Generalized circumferential full thickness involvement of skin, sc tissue, muscle and bone

Entire body, no internal organ involvement
Extremely rare (+-1% LS)
Cave contractures, chronic ulcers, (? evolution to squamous cell carcinoma)

Associated conditions

Lichen sclerosus et atrophicus

superficial skin layers

< shiny white plaques, epidermal atrophy

Bullous morphea

can occur with most subtypes (esp linear/deep)

> localized trauma, lymphatic obstruction

Eosinophilic fasciitis

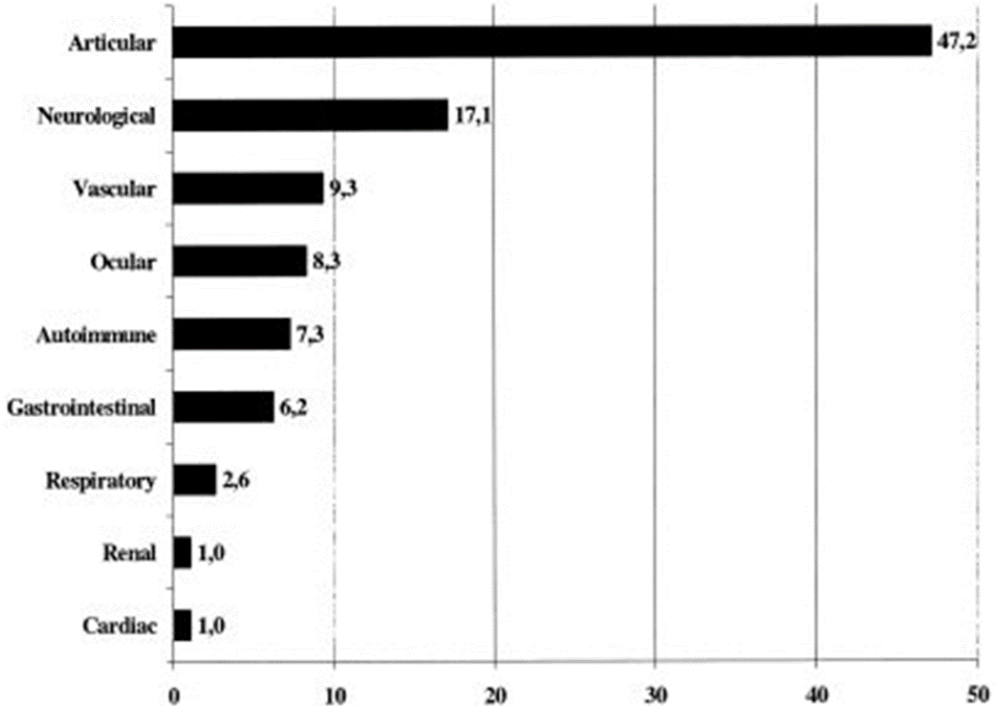
inflammation/sclerosis deep sc tissues, sparing dermis

mostly extremities, also hands and feet

« peau d'orange »

eosinophilia and hypergammaglobulinemia

Extracutaneous manifestations LS



In one quarter of LS patients (mostly linear scleroderma)

CNS and ocular especially in coup de sabre LS

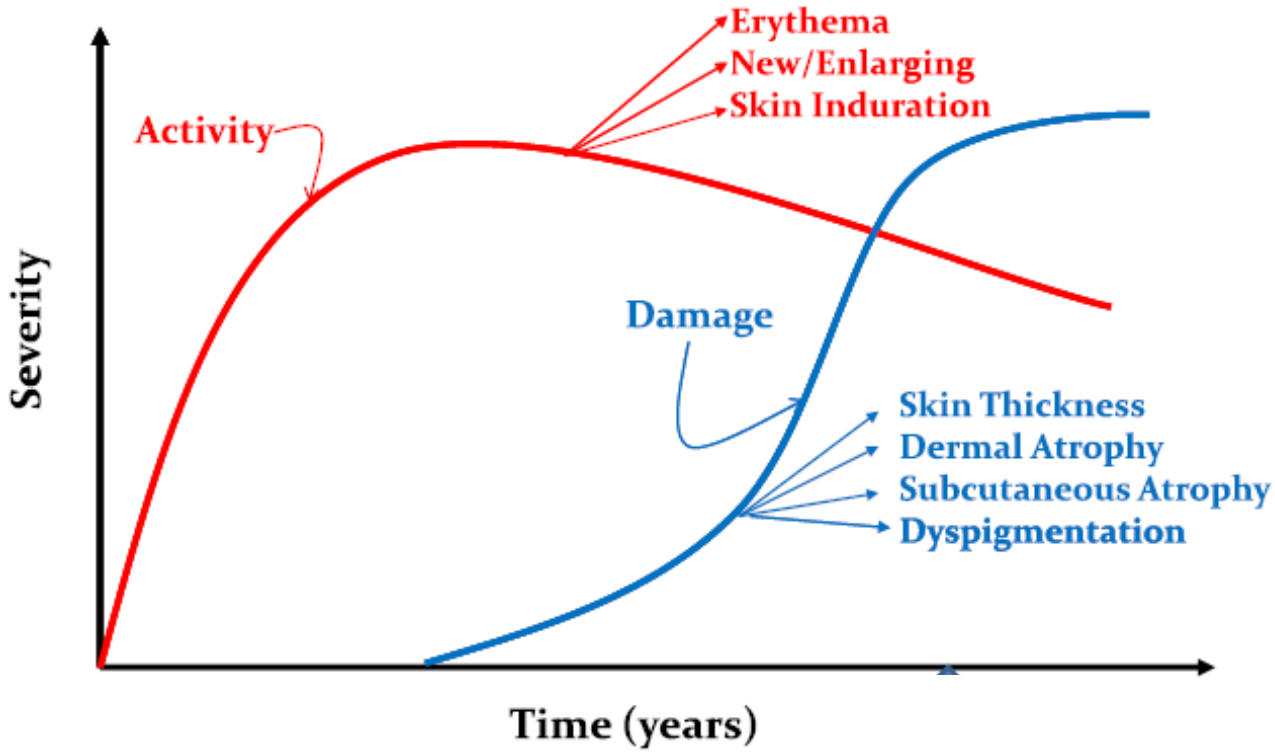
Multiple extracutaneous features in one third

Zulian, A&R 2005

Localized scleroderma Assessment

- Clinical skin scores
  - Modified Rodnan skin score
  - Localized scleroderma cutaneous assessment tool
  - Computerized skin score
- Measurement tools
  - Durometer (hardness)
  - Cutometer (elasticity)
- Imaging
  - Infrared Thermography
  - Laser Doppler flowmetry
  - Optical coherence tomography
  - Ultrasonography
  - MRI

Localized scleroderma: transition with time



Active disease: erythema, skin induration/edema, new/enlarging lesions

Disease damage: hypo- and hyperpigmentation, dermal and sc atrophy

Localized Scleroderma Cutaneous Assessment Tool (LoSCAT)

- Localized Scleroderma Skin Severity Index (LoSSI):
  erythema, thickening, new/extension lesion
  + Physician VAS global assessment of disease activity

- Localised Scleroderma Skin Damage index (LoSDI):
  dermal and subcutaneous atrophy, hypo/hyperpigmentation
  + Physician VAS global assessment of disease damage

  0-3 score in 18 anatomic surface areas

Arkachaisri, Rheumatology 2010

Localized scleroderma Imaging

- High frequency ultrasonography with Doppler
  - evaluation of superficial and deep soft tissues
  - Ultrasound Disease Activity (U-DA) composite score
  - vascularity, echogenicity vs contralateral side

Li, Arthr Care & Res 2011

- MRI
  - CNS or orbital involvement
  - true depth of lesions in deep or generalized morphea

Localized scleroderma Treatment

Systemic treatment for moderate and severe LS

linear and deep subtypes: risks disability
deeply involved subcutis, fascia, muscle, transversing joint
linear lesions affecting face/scalp
rapidly progressive or widespread active disease

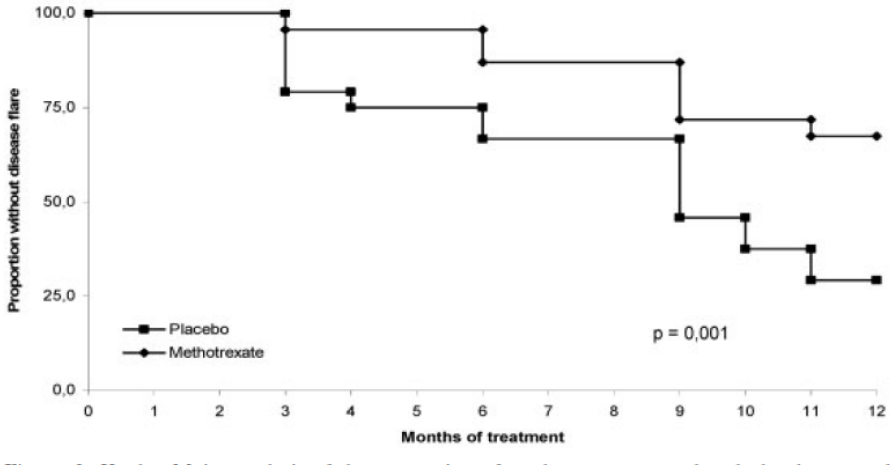
Methotrexate 10-15 mg/m2/week
+ Prednisone 0.5-1 mg/kg/d
+ IV MP 20-30 mg/kg monthly

Mofetil mycophenolate

Methotrexate Treatment in Juvenile Localized Scleroderma

Zulian, Arthr Rheum 2011

70 Juvenile LS patients with linear, generalized or mixed forms
oral MTX (15mg/m2) or placebo weekly for 12 months
prednisone (1 mg/kg) for three months



- Improvement infrared thermography, skin score (size target lesion), less new lesions with MTX therapy

- Less disease flare with MTX therapy

Juvenile Systemic Sclerosis

- Classification and clinical features
- Assessment of activity and damage
- Treatment

Juvenile Systemic Sclerosis Classification

- **Diffuse cutaneous systemic sclerosis**

  widespread rapidly progressive skin thickening

  and early visceral disease

- Limited cutaneous systemic sclerosis

  skin thickening limited distal extremities

  and late visceral disease

  includes CREST syndrome

- Overlap scleroderma

  diffuse or limited SSc with features of another connective tissue disease eg dermatomhyositis, SLE

Juvenile Systemic Sclerosis — Major criterion

Skin induration or sclerosis proximal to metacarpal phalangeal or metatarsophalangeal joints

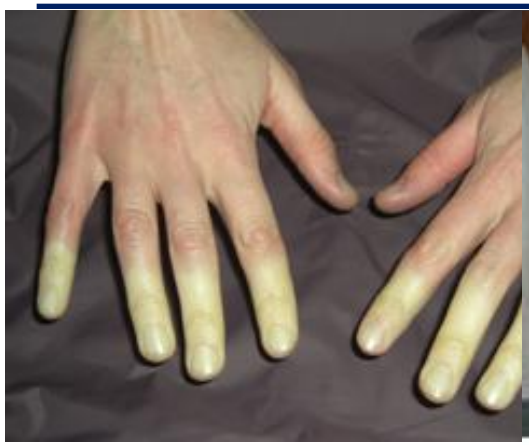
PReS/ACR/EULAR endorsed provisional classification criteria for jSS
Zulian, Arthr Rheum 2007

Juvenile Systemic Sclerosis — Minor criteria

Cutaneous	sclerodactyly
Peripheral vascular	Raynaud, digital tip ulcers, nailfold capillary changes
Gastrointestinal	dysphagia, gastroesophageal reflux
Cardiac	arrythmias, heart failure
Renal	renal crisis, new-onset arterial hypertension
Respiratory	pulmonary fibrosis (CT/XRays), decreased diffusion, pulmonary arterial hypertension
Neurologic	neuropathy, carpal tunnel syndrome
Muskuloskeletal	tendon friction rubs, arthritis, myositis
Serology	ANA, SS-selective antibodies (anticentromere, anti-topoisomerase I, antifibrillarin, anti-PMScl, antifibrillin, anti-RNA polymerase I or III)

Diagnosis : one major and at least two minor criteria

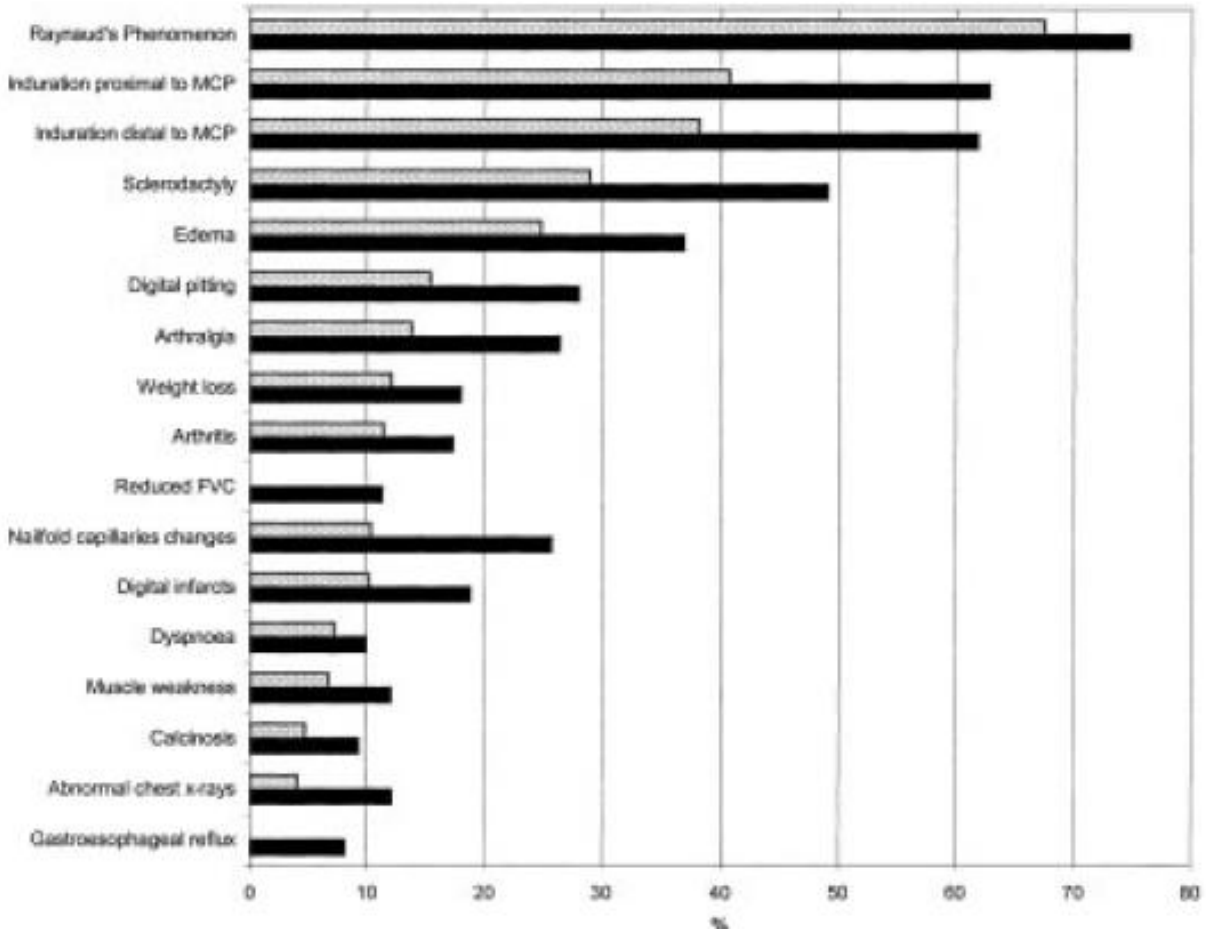
Juvenile Systemic Sclerosis Presenting symptoms



- Raynaud phenomenon
- Skin changes of hands
  - edema
  - induration proximal to MCP, sclerodactyly
  - digital ulceration/pitting

In almost all (>95%) jSS patients throughout course of disease

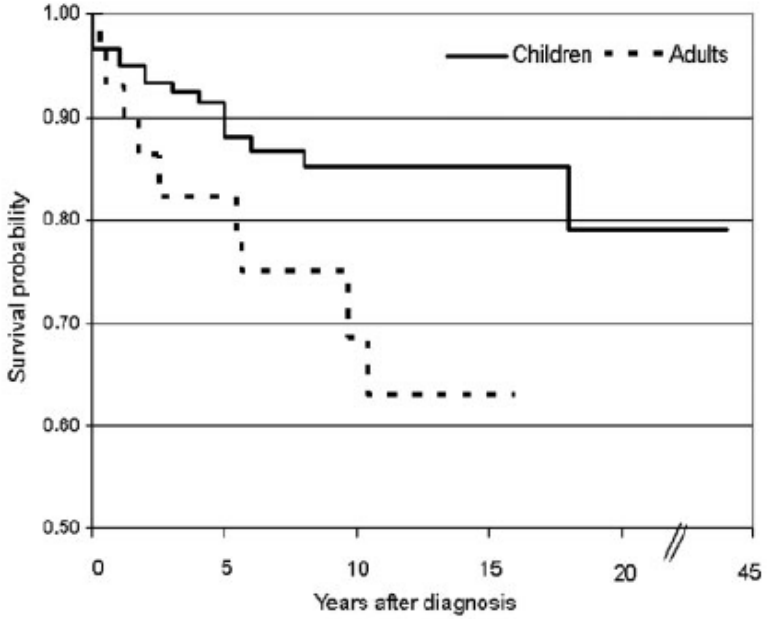
Juvenile Systemic Sclerosis Clinical features



Clinical features at onset (stippled) and at diagnosis (solid) in 153 children with jSS

Martini, A&R 2006

Juvenile Systemic Sclerosis — Outcome



Survival rates (5 to 20 yrs) significantly higher than in adult-onset SS

Causes of death: cardiac failure, pulmonary HT, renal insufficiency, respiratory failure

Subset with rapid development of internal organ failure and early fatality versus majority of slow insidious course with lower mortality

Martini, Rheumatology 2009

Juvenile systemic sclerosis

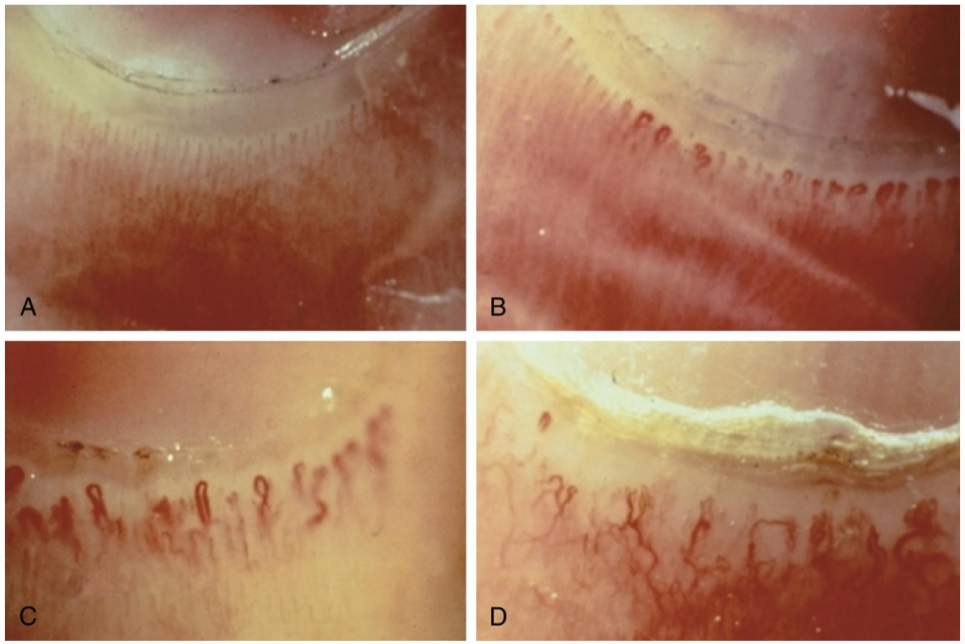
Predictors of outcome

	At diagnosis			Overall course		
	Alive Positive/tested (%)	Deceased Positive/tested (%)	*P*	Alive Positive/tested (%)	Deceased Positive/tested (%)	*P*
Skin						
Sclerodactily	74/116 (63.8)	7/16 (43.8)	NS	87/116 (75.0)	10/16 (62.5)	NS
Induration proximal to MCP	78/114 (68.4)	12/16 (75.0)	NS	96/115 (83.5)	14/16 (87.5)	NS
Induration distal to MCP	79/113 (69.9)	12/16 (75.0)	NS	92/114 (80.7)	13/16 (81.3)	NS
Peripheral vascular system						
RP	92/117 (78.6)	15/16 (93.8)	NS	101/117 (86.3)	15/16 (93.8)	NS
Digital infarcts	27/107 (25.2)	7/16 (43.8)	NS	36/107 (33.3)	9/16 (56.3)	NS
Positive capillaroscopy	44/81 (54.3)	4/10 (40.0)	NS	67/81 (82.7)	6/10 (60.0)	NS
Respiratory system						
Dyspnoea	12/115 (10.4)	4/15 (26.7)	NS	19/115 (16.5)	6/15 (40.0)	0.03
Basal crackles	3/116 (2.6)	3/16 (18.8)	0.02	8/116 (6.9)	6/16 (37.5)	0.001
Abnormal chest X-rays	14/105 (13.3)	5/15 (33.3)	NS	31/105 (29.5)	12/15 (80.0)	0.0001
Reduced DL_{CO}	13/69 (18.8)	1/12 (8.3)	NS	32/70 (45.7)	8/12 (66.7)	NS
Reduced FVC	19/88 (21.6)	2/14 (14.3)	NS	49/90 (54.4)	10/14 (71.4)	NS
Cardiac involvement						
Pericarditis	4/116 (3.4)	3/16 (18.8)	0.03	8/117 (6.8)	8/16 (50.0)	0.0001
Heart failure	0/114 (0.0)	4/16 (25.0)	<0.001	4/115 (3.5)	8/16 (50.0)	0.0001
Arrythmias	1/117 (0.9)	2/16 (12.5)	0.03	4/116 (3.4)	4/16 (25.0)	0.008
Pulmonary hypertension	2/84 (2.4)	2/14 (14.3)	NS	5/83 (6.0)	6/14 (42.9)	0.001
Muskulo-skeletal system						
Muscle weakness	17/114 (14.9)	5/16 (31.3)	NS	30/114 (26.3)	7/16 (43.8)	NS
Arthritis	27/115 (23.5)	6/16 (37.5)	NS	35/115 (30.4)	8/16 (50.0)	NS
Arthralgia	34/117 (29.1)	6/15 (40.0)	NS	47/117 (40.2)	9/15 (60.0)	NS
Gastrointestinal system						
Dysphagia	13/115 (11.3)	3/16 (18.8)	NS	24/115 (20.9)	9/16 (56.3)	0.002
Gastroesophageal reflux	11/110 (10.0)	5/16 (31.3)	0.03	30/110 (27.3)	12/16 (75.0)	0.0001
Diarrhoea	4/115 (3.5)	0/16 (0.0)	NS	11/115 (9.6)	4/16 (25.0)	NS
Weight loss	22/116 (19.0)	3/15 (20.0)	NS	33/116 (28.4)	7/15 (46.7)	NS
Renal system						
Raised serum creatinine	1/115 (0.9)	1/16 (6.3)	NS	3/115 (2.6)	4/16 (25.0)	0.004
Hypertension	2/116 (1.7)	0/16 (0)	NS	4/116 (3.4)	1/16 (6.3)	NS
Nervous system						
Seizures	1/116 (0.9)	0/16 (0.0)	NS	1/116 (0.9)	2/16 (12.5)	0.04

Comparison of clinical features at diagnosis/during course in surviving and deceased JSS patients

Juvenile Systemic Sclerosis

Assessment



Capillaroscopy

Enlarged capillaries

Giant capillaries

Microhemorrages

Loss of capillaries

Disorganized microvascular array

Capillary ramifications

Sulli, Arthr Rheum 2012

Capillary density and width are age related
Atypical morphology (tortuosity, bizar shapes) in healthy children

Lower linear density, increased capillary width, > 3 abnormal capillaries in at least 2 nailfolds indicative connective tissue disease
Avascularity specific for connective tissue disease

Dolezalova, Ann Rheum Dis 2003

Juvenile Systemic Sclerosis Assessment

Organ system	Components of the severity index
General	Body mass index
	Hemoglobin
Vascular	Raynaud's phenomenon requiring vasodilators
	Number of digital scars
	Number of ulcers/gangrene
Cutaneous	Modified Rodnan skin thickness score
Osteoarticular	Arthritis
	Limited range of motion
	Tendon friction rubs
Muscular	Childhood Myositis Assessment Scale
Gastrointestinal	Symptoms of gastroesophageal reflux
	Abnormal esophageal transit
	Malabsorption
Respiratory	Forced vital capacity
	Diffusing capacity for carbon monoxide
	Pulmonary artery systolic pressure by Doppler echocardiography
	Standard chest radiography
	High-resolution computed tomography of the chest
Cardiac	Electrocardiogram
	Echocardiogram
	Clinical signs of congestive heart failure
Renal	Creatinine clearance (glomerular filtration rate)

Juvenile Systemic Sclerosis Severity Score (J4S)

La Torre, Arthr Rheum 2012

Juvenile Systemic Sclerosis — Assessment

Organ system	Components of the severity index
General	Body mass index
	Hemoglobin
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Gastrointestinal	Symptoms of gastroesophageal reflux
	Abnormal esophageal transit
	Malabsorption
Respiratory	Forced vital capacity
	Diffusing capacity for carbon monoxide
PAH	Pulmonary artery systolic pressure by Doppler echocardiography
	Standard chest radiography
	High-resolution computed tomography of the chest
Cardiac	Electrocardiogram
	Echocardiogram
	Clinical signs of congestive heart failure
Renal	Creatinine clearance (glomerular filtration rate)

Risk: ILD, Scl-70 & ACA, older (2-3 yearly)

Risk: Diffuse SS, Scl-70, later onset (yearly)

La Torre, Arthr Rheum 2012

JSS assessment

Autoantibodies

ANA in 95% jSS patients, stable from onset

identification clinical/prognostic subsets

Topoisomerase (Scl-70)	Centromere	RNA-polymerase III	PM-Scl, U1-RNP
Diffuse SS	Limited SS	Diffuse SS	Overlap scleroderma
ILD Pulmonary fibrosis Cardiomyopathy	PAH GI involvement	Renal crisis Severe skin	Dermatomyositis, ILD Arthritis

Juvenile Systemic Sclerosis — Treatment

General supportive measures

Avoidance
- cold and trauma
- excessive sun exposure and heat
- drying or irritating local substances

Daily application of lanolin, water-soluble cream as emollient

Physical activity (active and gentle passive range of motion)

NSAIDS for musculoskeletal symptoms (cf renal function)

Organ/system	Treatment
Digital vasculopathy (RP, digital ulcers)	Calcium channel blockers (nifedipine) IV Prostanoids (Iloprost) Endothelin receptor antagonist (Bosentan)
Skin	MTX, + MMF if progressive disease
Muskuloskeletal	Low dose corticosteroids (cave renal crisis) MTX
Gastrointestinal	Proton pump inhibitors, prokinetic drugs, rotating antibiotics
Interstitial lung disease	Cyclophosphamide (active alveolitis) Corticosteroids
Pulmonary arterial hypertension	Endothelin receptor antagonists (bosentan, sitaxsentan) IV prostanoids: refractory PAH
Renal disease (renal crisis)	Angiotensin converting enzyme inhibitors (enalapril) Hemodialysis (renal failure)

Evidence from literature and epert opinion, Kowal biliecka, Ann Rheum Dis 2009