Scleroderma in Childhood

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KPA 2016
Case presentation

- 8 yr old boy
- No significant medical or family history
- Presented at the age of 2 years with a whitish mark on his left cheek
- Lesion was initially labelled a birthmark by a dermatologist, but continued to grow in size
General Examination

- Slight frame, but appropriately grown for age
- No pallor, clubbing, oedema or lymphadenopathy
- Facial asymmetry with thickened skin over left side of face
- Loss of inferior left eyelashes
- Hypoplasia of left nostril, nasal deviation to left
- Malocclusion of teeth with hypoplasia of left mandible and maxilla
- Scar notably warmer than the rest of the face
Systemic Exam

MSS
- Mild benign hypermobility
- No evidence of arthritis
- No peripheral features of scleroderma

Resp
- Chest clear
- Equal air entry bilaterally

CVS
- Normal, no evidence of pulmonary hypertension.

Abdomen
- Soft, no organomegaly
- No epigastric tenderness.

CNS
- Cranial nerves intact
- Tone, power and reflexes normal and equal UL and LL
- Cerebellar function normal
- Sensation preserved though decreased sensitivity over area of skin thickening
Pediatric Scleroderma

Systemic sclerosis (SSc)
Multi-system disease

- Diffuse cutaneous (dcSSc)
  Cardiac, renal, pulmonary (ILD)
- Limited cutaneous (lCSSc)
  Gastrointestinal, pulmonary (PAH)
- Overlap SSc
  Cardiac, renal, pulmonary, myositis, arthritis

Localized Scleroderma (LS)
Cutaneous disease

- Linear scleroderma
  - Limbs/trunk
  - Head
  - Neurologic
- Circumscribed morphea
  - Superficial
  - Deep
- Generalized morphea
- Mixed
- Pansclerotic morphea
  Severe limitation joint ROM
Paediatric Scleroderma

- uncommon in children
- estimated annual incidence
  - LS being 1 to 3 per 100,000 children
  - SSc being 1 per million children.
- The mean age of onset for both: 7.3 - 8.8 years of age.
A large, multicentre, multinational study

Long term goal of developing uniform classification criteria

Collected information on the clinical and immunological features of patients with JLS

750 patients from 70 paediatric and dermatology centres
Classification

- Circumscribed morphea
- Generalised morphea
- Pansclerotic morphea
- Linear scleroderma
  - En Coup De Sabre
  - Parry Romberg Syndrome
- Mixed type
- Eosinophilic faciitis - controversial
Circumscribed ‘Plaque’ Morphea

- Localized, single or small areas involved
- Oval or round circumscribed areas of induration, surrounded by a violaceous halo
- Confined to the dermis
- Usually affects the trunk
Generalised Morphea

- 4 or more plaques, individually >3cm, that become confluent

- Involving at least 2 out of 7 anatomic sites
  - head-neck
  - right/left upper extremity
  - right/left lower extremity
  - anterior/posterior trunk
Pansclerotic Morphea

- Extremely rare, but severe
- Generalised full thickness involvement of the skin of the trunk, extremities, face and scalp
- Sparing of the fingertips and toes
- Deep and superficial involvement including muscles and tendons
- Symmetrical
Linear Scleroderma

- Most common subtype in children and adolescents
- One or more linear fibrous bands that can extend through dermis, subcutaneous tissue, muscle and bone
- Usually on extremities or face
- May cause significant atrophy of tissue, limiting joint mobility and causing growth deformities
- Involvement of scalp and upper face
  - En coup de sabre
Parry Romberg Syndrome

- Progressive hemifacial atrophy of the skin and tissue (bone, muscle, adipose) below the forehead
- Considered the severe end of the spectrum of ECDS
- Subcutaneous tissue is the primary target, the skin is affected secondarily
- Associated neurological and ocular problems
<table>
<thead>
<tr>
<th>Neurological</th>
<th>Ocular</th>
</tr>
</thead>
<tbody>
<tr>
<td>Seizures</td>
<td>Anterior uveitis</td>
</tr>
<tr>
<td>Headache</td>
<td>Episcleritis</td>
</tr>
<tr>
<td>Vascular malformation</td>
<td>Glaucoma</td>
</tr>
<tr>
<td>Behavioral changes</td>
<td>Keratitis</td>
</tr>
<tr>
<td>Neuroimaging abnormalities</td>
<td></td>
</tr>
<tr>
<td>EEG alterations</td>
<td></td>
</tr>
</tbody>
</table>
Mixed Type JLS

- Recent recognition as a distinct subgroup
- 15% of study population had linear lesions associated with circumscribed lesions
- In 64% of patients linear lesions appeared before or at the same time as the plaque lesions
Eosinophilic Fasciitis

- Fascia is the predominant site of involvement
- Usually involves extremities proximal to hands and feet
- Characteristic cutaneous features - pitting oedema, diffuse painful areas with peau d’orange appearance
- Lesion becomes fibrotic later in the disease course
- Associated eosinophilia, raised ESR and hypergammaglobulinaemia
Figure 2 - Band lesion in the left lower limb
Natural History of LS – Cutaneous manifestations

Severity

Activity

Time (years)

Disease transition from activity to damage

Erythema
New/Enlarging
Skin Induration

Damage

Skin Thickness
Dermal Atrophy
Subcutaneous Atrophy
Dyspigmentation

Usually when diagnosed

doi:10.1016/j.pcl.2012.03.011

Kathryn S. Torok,
A positive family history for rheumatic or autoimmune diseases was reported in 12% of patients.
Autoimmune parameters

ANA were positive in 42.3% of the patients
Anti-Scl70 antibodies and ACA antibodies, markers of SSc in many adults, were positive in 3.2 and 1.7% of patients, respectively
None of these patients presented signs or symptoms of internal organ involvement after a mean follow-up of 3.4 yr
Drug treatment of JLS

- Many treatments have been proposed
  - Topical and systemic corticosteroids
  - Methotrexate
  - D-penicillamine
  - UVA phototherapy
  - Vitamin D analogues (Calipotriol)
  - Topical tacrolimus
  - Cyclosporin

- Until recently there were no randomized controlled studies that had clearly established their efficacy in children
Methotrexate Treatment in Juvenile Localized Scleroderma

A Randomized, Double-Blind, Placebo-Controlled Trial

Francesco Zulian,1 Giorgia Martini,1 Cristina Vallongo,1 Fabio Vittadello,1 Fernanda Falcini,2 Annalisa Patrizi,3 Maria Alessio,4 Francesco La Torre,5 Rosa A. Podda,6 Valeria Gerloni,7 Mario Cutrone,8 Anna Belloni-Fortina,1 Mauro Paradisi,9 Silvana Martino,10 and Giorgio Perilongo1

• Patients were randomized (2:1) to receive oral MTX (15 mg/m2, maximum 20 mg) or placebo once weekly, for 12 months or until treatment failure
• Both groups received oral prednisone (1 mg/kg/day, maximum 50 mg) for the first 3 months
  • Target lesions were evaluated clinically, with infrared thermography and using a computerized scoring system with skin score rate (SSR) evaluation
Table 2. Change in the response parameters from baseline to the final visit in the intent-to-treat analysis

<table>
<thead>
<tr>
<th>Parameter</th>
<th>Methotrexate (n = 46)</th>
<th>Placebo (n = 24)</th>
<th>P</th>
</tr>
</thead>
<tbody>
<tr>
<td>Thermography changes, mean ± SEM ΔTh%*</td>
<td>−44.4 ± 7.4</td>
<td>−12.1 ± 13.0</td>
<td>0.024</td>
</tr>
<tr>
<td>Skin Score Rate, mean ± SEM</td>
<td>0.79 ± 0.05</td>
<td>1.1 ± 0.1</td>
<td>0.011</td>
</tr>
<tr>
<td>No. (%) of patients with new lesions</td>
<td>3 (6.5)</td>
<td>4 (16.7)</td>
<td>0.221</td>
</tr>
</tbody>
</table>

* ΔTh% = percentage thermal change from baseline.
Figure 3. Kaplan-Meier analysis of the proportion of methotrexate-treated and placebo-treated juvenile localized scleroderma patients without disease flare, over time.
‘Findings demonstrate that a combination of methotrexate and a short course of prednisone is beneficial and well tolerated as treatment for localized scleroderma in children’
studied the prevalence and clinical features of extracutaneous manifestations in a large cohort of children with juvenile localized scleroderma
Extracutaneous manifestations developed in almost one quarter of the children.
- Often unrelated to the site of the skin lesions

Figure 1. Prevalence and distribution of extracutaneous involvement in patients with juvenile localized scleroderma.
Full clinical spectrum of Juvenile SSc developed in only 1 patient (0.13%) 6 months after the onset of linear scleroderma.
Study Conclusions

• Patients with juvenile localized scleroderma who have extracutaneous involvement are at low risk of developing SSc

• Organ impairment is milder than that seen in patients with SSc and is not life-threatening

• Juvenile localized scleroderma and juvenile SSc likely represent 2 ends of a continuous disease spectrum
<table>
<thead>
<tr>
<th>Parameter</th>
<th>Skin involvement only</th>
<th>Extracutaneous involvement</th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td>White blood cells</td>
<td>27/532 (5.1)</td>
<td>10/161 (6.2)</td>
<td>NS</td>
</tr>
<tr>
<td>Eosinophils</td>
<td>82/532 (15.4)</td>
<td>20/161 (12.4)</td>
<td>NS</td>
</tr>
<tr>
<td>Hemoglobin</td>
<td>20/535 (3.8)</td>
<td>16/161 (9.9)</td>
<td>&lt;0.05</td>
</tr>
<tr>
<td>Platelets</td>
<td>15/532 (2.8)</td>
<td>12/161 (7.5)</td>
<td>&lt;0.01</td>
</tr>
<tr>
<td>Erythrocyte sedimentation rate</td>
<td>78/504 (15.5)</td>
<td>45/159 (28.3)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>C-reactive protein</td>
<td>16/265 (6.0)</td>
<td>17/101 (16.8)</td>
<td>&lt;0.005</td>
</tr>
<tr>
<td>Creatine kinase</td>
<td>6/261 (2.3)</td>
<td>9/94 (9.6)</td>
<td>&lt;0.005</td>
</tr>
<tr>
<td>Serum IgG</td>
<td>48/280 (17.1)</td>
<td>29/101 (28.7)</td>
<td>&lt;0.05</td>
</tr>
<tr>
<td>Serum IgA</td>
<td>32/280 (11.4)</td>
<td>17/101 (16.8)</td>
<td>NS</td>
</tr>
<tr>
<td>Serum IgM</td>
<td>31/280 (11.1)</td>
<td>18/101 (17.8)</td>
<td>NS</td>
</tr>
<tr>
<td>Autoantibodies</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Antinuclear antibodies</td>
<td>203/514 (39.5)</td>
<td>81/157 (51.6)</td>
<td>&lt;0.01</td>
</tr>
<tr>
<td>Anti–double-stranded DNA</td>
<td>13/320 (4.0)</td>
<td>3/62 (4.8)</td>
<td>NS</td>
</tr>
<tr>
<td>Anti–Scl-70</td>
<td>9/303 (3.0)</td>
<td>3/75 (4.0)</td>
<td>NS</td>
</tr>
<tr>
<td>Anticentromere</td>
<td>2/169 (1.2)</td>
<td>2/71 (2.8)</td>
<td>NS</td>
</tr>
<tr>
<td>Anticardiolipin</td>
<td>12/100 (12.0)</td>
<td>2/11 (18.2)</td>
<td>NS</td>
</tr>
<tr>
<td>Rheumatoid factor</td>
<td>46/349 (13.2)</td>
<td>28/115 (24.3)</td>
<td>&lt;0.01</td>
</tr>
</tbody>
</table>

* Values are the no. positive/no tested (%). NS = not significant.
Box 1. 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, antitopoiso- merase 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%, and kappa statistic value of 0.86.

**New JSSc Classification Criteria**

- Consensus by PRES, ACR, EULAR 2007
- First paediatric criteria

<16yrs
Need 1 major and 2 minor criteria
90% sensitivity, 96% specificity
Skin sclerosis score

Modified Rodnan Skin score

<table>
<thead>
<tr>
<th>Location</th>
<th>Score</th>
</tr>
</thead>
<tbody>
<tr>
<td>Face</td>
<td>3</td>
</tr>
<tr>
<td>Neck</td>
<td>3</td>
</tr>
<tr>
<td>Anterior chest</td>
<td>3</td>
</tr>
<tr>
<td>Abdomen</td>
<td>3</td>
</tr>
<tr>
<td>Back - upper</td>
<td>3</td>
</tr>
<tr>
<td>Back - lower</td>
<td>3</td>
</tr>
<tr>
<td>Upper arm</td>
<td>3</td>
</tr>
<tr>
<td>Forearm</td>
<td>3</td>
</tr>
<tr>
<td>Hand</td>
<td>3</td>
</tr>
<tr>
<td>Fingers</td>
<td>3</td>
</tr>
<tr>
<td>Thigh</td>
<td>3</td>
</tr>
<tr>
<td>Leg</td>
<td>3</td>
</tr>
<tr>
<td>Foot</td>
<td>3</td>
</tr>
</tbody>
</table>

Maximum (17 site)  51
20 site            60
HIV-associated juvenile systemic sclerosis: A case report

Lawrence O. Okong’o, MMed (Paed)*, Kate Webb, MMed, FCPaed (SA), Christian Scott, FCPaed (SA), Grad Cert Paed Rheum (UWA)

Red Cross War Memorial Children’s Hospital, University of Cape Town, Cape Town, South Africa
Table 3. Pharmacotherapy of SSc disease manifestations.

<table>
<thead>
<tr>
<th>Disease manifestation</th>
<th>Pharmacotherapy</th>
</tr>
</thead>
<tbody>
<tr>
<td>Raynaud’s phenomenon</td>
<td>Calcium channel blockers, sildenafil and related phosphodiesterase type-5 inhibitors, intravenous iloprost</td>
</tr>
<tr>
<td>Digital ulcers</td>
<td>Bosentan, statins, intravenous iloprost, aspirin</td>
</tr>
<tr>
<td>Scleroderma renal crisis</td>
<td>ACE inhibitors plus calcium channel blockers and addition of beta adrenergic blockers or nitrate infusions as warranted to control hypertension</td>
</tr>
<tr>
<td>Esophageal dysmotility</td>
<td>Proton pump inhibitors</td>
</tr>
<tr>
<td>Delayed gastric emptying</td>
<td>Pro-motility drugs (metoclopramide domperidone, erythromycin)</td>
</tr>
<tr>
<td>Small bowel dysmotility (blind loops)</td>
<td>Ooctreotide, antibiotics</td>
</tr>
<tr>
<td>Colonic dysmotility</td>
<td>Erythromycin, prucalopride, octreotide</td>
</tr>
<tr>
<td>Coronary artery vasospasm</td>
<td>Calcium channel blockers, ACE inhibitors, dipyridamole</td>
</tr>
<tr>
<td>Progressive pulmonary fibrosis</td>
<td>Cyclophosphamide, ? mycophenolate mofetil</td>
</tr>
<tr>
<td>Pulmonary arterial hypertension</td>
<td>Prostacyclin analogs (epoprostiol, treprostolin, iloprost), bosentan, sitaxsentan, ambrisetan, phosphodisterase type-5 inhibitors</td>
</tr>
<tr>
<td>Arthritis</td>
<td>DMARDs (hydroxychloroquine, methotrexate, sulfasalazine)</td>
</tr>
<tr>
<td>Osteoporosis</td>
<td>Calcium, vitamin D, intravenous bisphosphonates</td>
</tr>
</tbody>
</table>

Pharmacotherapy of systemic sclerosis

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†University of Tennessee Health Science Center, Department of Connective Tissue Disease, 956 Court Avenue, Room C326, Memphis, TN 38163, USA
Conclusion

- Scleroderma in Children is a rare, complex disease with many faces
- Early diagnosis and therapy is important to avoid disease progression
- Screening for associated complications is essential
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