TEN TOPICS IN RHEUMATOLOGY

Systemic Sclerosis

Early Diagnosis and Treatment

Gabriele Valentini

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Systemic Sclerosis
Morphological Features

- **Vasculopathy** obliterative/dilatative at microvessels; proliferative at small arteries
- **Interstitial fibrosis** by accumulation of matrix constituents
- **Perivascular mononuclear infiltrates** indicating, along with autoantibodies, an (auto)immune response
TWO-SUBSET CLASSIFICATION
EC LeRoy et al. J Rheumatol 1988

Diffuse cutaneous SSc (dcSSc)

- Onset of RP within 1 year of onset of skin changes
- Truncal and acral skin involvement
- Tendon friction rubs
- Early interstitial lung disease, oliguric renal failure, diffuse GI disease, and myocardial involvement
- Absence of anticentromere antibodies (ACA)
- Avascular areas

Limited Cutaneous SSc (lcSSc)

- Isolated RP for years (occasionally decades)
- Skin involvement limited to hands, face, feet
- Late pulmonary hypertension, trigeminal neuralgia, skin calcifications, telangectasia
- A high incidence of anticentromere antibodies (ACA, 60%)
- Dilated nailfold capillary loops without capillary dropout
PRELIMINARY ACR CRITERIA FOR THE CLASSIFICATION OF SSc

Major criterion  - Scleroderma proximal to MCP/MTF

Minor criteria    - Sclerodactily
                 - Digital pitting scars
                 - Bibasilar lung fibrosis (X-ray)

Fine et al. (Lancet 1996) designated “prescleroderma” any condition characterized by RP, digital ischemic changes and SSc marker autoantibodies and/or capillaroscopic findings typical of the scleroderma pattern.
CRITERIA FOR THE CLASSIFICATION OF “early” SSc

“early “ (limited) SSc

Raynaud’s phenomenon

plus any one of

- SSc type nailfold capillary pattern

or

- SSc selective autoantibodies

EC LeRoy, TA Medsger jr  J Rheumatol 2001
Diagrammatic representation of serologic subsets in SSc

Diffuse

- Anti-topoisomerase I (Scl-70)
- Anti-RNA polymerase I-III
- Anti-U3RNP
- Anti-U1RNP

Overlap

Limited

- Anti-centromere
- Anti-Th
- Anti-PM-Scl

Medsger TA and Steen VD, 2001
Definite SSc outcome in 586 patients with RP according to NCM profiles and SSc-specific autoantibodies at the first evaluation

<table>
<thead>
<tr>
<th>Predictors</th>
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<tr>
<td><strong>P</strong></td>
<td>-</td>
<td><strong>&lt;0.001</strong></td>
<td><strong>&lt;0.001</strong></td>
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</tr>
</tbody>
</table>

VEDOSS STUDY
J Avouac et al Ann Rheum Dis 2011

• CRITERIA FOR AN EARLY REFERRAL
   RP; PUFFY FINGERS; ANA

• CRITERIA WITH HIGH CLINICAL RELEVANCE FOR VEDOSS
   RP; PUFFY DIGITS *TURNING INTO SCLERODACTYLY*;
   SCLERODERMA PATTERN CAPILLAROSCOPIIC FINDINGS;
   ACA; ANTI-ScI70
### ACR/EULAR 2013 CRITERIA FOR THE CLASSIFICATION OF SSc


<table>
<thead>
<tr>
<th>CRITERION</th>
<th>Sub-CRITERION</th>
<th>WEIGHT/SCORE</th>
</tr>
</thead>
<tbody>
<tr>
<td>Skin thickening of the fingers of both hands extending proximal to the MCPs (sufficient criterion)</td>
<td>-</td>
<td>9</td>
</tr>
<tr>
<td>Skin Thickening of the fingers (only count the higher score)</td>
<td>Puffy fingers</td>
<td>2</td>
</tr>
<tr>
<td></td>
<td>Sclerodactyly</td>
<td>4</td>
</tr>
<tr>
<td>Fingertip lesions (only count the higher score)</td>
<td>Digital tip ulcers</td>
<td>2</td>
</tr>
<tr>
<td></td>
<td>Fingertip pitting scars</td>
<td>3</td>
</tr>
<tr>
<td>Telangectasias</td>
<td>-</td>
<td>2</td>
</tr>
<tr>
<td>Abnormal nailfold capillaries</td>
<td></td>
<td>2</td>
</tr>
<tr>
<td>PAH and/or ILD (maximal score 2)</td>
<td>PAH</td>
<td>2</td>
</tr>
<tr>
<td></td>
<td>ILD</td>
<td>2</td>
</tr>
<tr>
<td>Raynaud’s Phenomenon</td>
<td></td>
<td>3</td>
</tr>
<tr>
<td>Marker Abs (anti-Scl-70 or anti-CENP or anti-RNA pol III)</td>
<td></td>
<td>3</td>
</tr>
</tbody>
</table>

A patient is classified as affected by SSc if the sum of criteria is ≥9
PITFALLS IN USING CLASSIFICATION CRITERIA FOR THE DIAGNOSIS IN THE SINGLE PATIENT

- **Exclusion Criteria**
  nephrogenic fibrosis, generalized morphea, diffuse fasciitis, scleredema diabeticorum, scleromyxedema, porphyria, erythromyalgia, lichen sclerosis, GVH disease, diabetic cheiroarthropathy.

- **Systemic Sclerosis sine scleroderma**
Internal organ involvement consistent with SSc sine scleroderma I

Gastrointestinal involvement

*Distal esophageal hypomotility or aperistalsis (by either cineradioesophagography or esophageal manometry)* and/or

Typical small bowel radiographic abnormalities and/or

Characteristic colonic sacculations

Pulmonary involvement

Bilateral basilar interstitial fibrosis on chest radiograph and/or

Active pleuritis with pleural pain and either a pleural friction rub or pleural effusion and/or

DLCO <70% and/or

Pulmonary Arterial Hypertension

Cardiac involvement

*Pericarditis* and/or

Nodal or ventricular arrhythmias and/or

Congestive heart failure

H Poormoghin et al Arthritis Rheum 2000
Internal Organ Involvement consistent with SSc sine scleroderma II

Renal involvement
*Rapidly progressive renal failure with or without pulmonary hypertension*

Articular involvement
Arthritis ≥1 joint and/or
*Tenosynovitis (including carpal tunnel syndrome or tendon friction rubs)*

Skeletal muscle involvement
Proximal muscle weakness on physical examination
And any of the following:
Muscle biopsy showing myositis
Electromyography showing a myopathic pattern
Elevated serum enzymes reflecting muscle disease

H Poormoghin et al Arthritis Rheum 2000
REVISED DEFINITION

RP with typical capilaroscopic findings or marker autoantibodies or both

- Neither satisfying 2013 ACR/EULAR classification criteria for SSc
- Nor satisfying criteria for SSc sine scleroderma

Why underlining the case definition?
Demographic and clinical data of 469 patients with RP enrolled into the VEDOSS online database (T Minier et al Ann Rheum Dis 2013)

<table>
<thead>
<tr>
<th>Clinical characteristics</th>
<th>ANA+ patients (n=318)</th>
<th>ANA - patients (n=151)</th>
<th>p Value (ANA+ vs ANA- patients)</th>
<th>Patients with primary RP (n=80)</th>
<th>p Value (ANA+ vs primary RP patients)</th>
</tr>
</thead>
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<tr>
<td>DIGITAL ULCERS n (%)</td>
<td>19/316 (6.0%)</td>
<td>13/150 (8.7%)</td>
<td>0.290</td>
<td>0/80</td>
<td>0.018</td>
</tr>
<tr>
<td>PITTING SCARS, n (%)</td>
<td>18/316 (5.7%)</td>
<td>5/150 (3.3%)</td>
<td>0.362</td>
<td>0/80</td>
<td>0.031</td>
</tr>
<tr>
<td>PUFFY FINGERS, n(%)</td>
<td>122/317 (38.5%)</td>
<td>35/150 (23.3%)</td>
<td>0.001</td>
<td>0/80</td>
<td>&lt; 0.001</td>
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<td>SCLERODACTYLY, n (%)</td>
<td>32/304 (10.5%)</td>
<td>7/142 (4.9%)</td>
<td>0.051</td>
<td>0/77</td>
<td>&lt; 0.001</td>
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<td>TELANGECTASIA, n (%)</td>
<td>39/316 (12.3%)</td>
<td>2/148 (1.4%)</td>
<td>&lt; 0.001</td>
<td>1/79 (1.3%)</td>
<td>0.001</td>
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<td>OESOPHAGEAL SYMPTOMS n (%)</td>
<td>111/315 (35.2%)</td>
<td>27/147 (18.4%)</td>
<td>&lt; 0.001</td>
<td>16/77 (20.8%)</td>
<td>0.015</td>
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<td>TENDON FRIC. RUBS, n (%)</td>
<td>4/315 (1.3%)</td>
<td>1/149 (0.7%)</td>
<td>1.000</td>
<td>0/80 (0%)</td>
<td>0.587</td>
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<tr>
<td>CALCINOSIS (%)</td>
<td>8/316 (2.5%)</td>
<td>8/149 (5.4%)</td>
<td>0.117</td>
<td>4/80 (5.0%)</td>
<td>0.272</td>
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Review

Undifferentiated Connective Tissue Disease at risk for systemic sclerosis (SSc) (so far referred to as very early/early SSc or pre-SSc)☆

Gabriele Valentini *

Rheumatology Unit, Second University of Naples, Naples, Italy
Why UCTD at risk for SSc instead of very early-early SSc?
Definite SSc outcome in 586 patients with RP according to NCM profiles and SSc-specific autoantibodies at the first evaluation

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Early Systemic Sclerosis
Analysis of the Disease Course in Patients With Marker Autoantibody or Capillaroscopic Positivity or Both

During 12-102 months of follow-up
21 out of 60 strictly defined “early SSc” patients undergoing a twice yearly assessment satisfied the 2013 ACR/EULAR criteria for SSc

UCTD ar risk for SSc Subsets

1) RP with
   both serum marker autoantibodies
   ( anti-Scl70; ACA; anti-RNAplo III; anti-fibrillarin;
   anti- Th/To; anti-Pm-Scl)
   and typical capillaroscopic findings
   ( avascular areas; megacapillaries)

2) RP with serum marker autoantibodies without typical capillaroscopic findings

3) RP with typical capillaroscopic findings, but without any serum marker autoantibody
Why subsetting UCTD at risk for SSc?
Clinical and Functional Features and Relationships with serum activation markers profile

• Patients with a capillaroscopic scleroderma pattern (n = 55, 77.5%) had a higher prevalence of puffy fingers (P = 0.0001) and increased serum levels of soluble E-selectin (P = 0.0003) regardless of marker autoantibodies.

• Patients with marker autoantibodies (n = 48, 67.6%) had a higher prevalence of impaired diffusing lung capacity for carbon monoxide (P = 0.0217) and increased serum levels of carboxyterminal propeptide of collagen I (P = 0.0037), regardless of capillaroscopic alterations.

• During follow-up, 11/21 subset I (52.3%), 10/15 subset II (66.6%), 0/24 subset III and 0/44 UCTD patients satisfied the criteria (p=0.0001).

• The difference was significant between each of the 2 autoantibody-positive subsets (subsets I and II) and the capillaroscopic positive-autoantibody-negative subset (subset I versus III: p=0.0001; subset II versus III: p=0.0009).

There was no difference between the 2 autoantibody positive subsets (p=0.454).
SSc Pathogenesis

PERMISSIVE GENETIC BACKGROUND

TRIGGERS

VASCUATURE
- Endothelial Injury
- Intimal Proliferation
- Vascular Remodeling
- Vasoconstriction
- Hypoxia, ↑ROS
- PAH
- Defective Angiogenesis
- ↑Platelet Aggregation

FIBROBLASTS
- ↑Myofibroblasts
- ↑ECM deposition
- ↓MMP-1

INNATE/ADAPTATIVE IMMUNE SYSTEM
- ↓M1 Macrophages, ↑M2 Macrophages
- ↓Th1 cytokines, ↑Th2 cytokines
- ↓Th17 cytokines, ↑Treg function
- ↑Mast cell activation, ↑Inflammatory cytokines,
  ↑Activated B cells, and ↑autoantibody production

S1P, LPA, Endocannabinoid System

ET-1, IL-6, IL-8

Platelet contents

IL-4, Cytotoxic CD4⁺ T cells, ADCC, Anti-EC antibodies

D Pattanaik et al. Front Immunol 2015
Chemokines in early and definite SSc

Cytokines in early and definite SSc

![Box plots showing cytokine levels in HC, early SSc, lcSSc, and dcSSc groups](image)

**IL-13**
- HC: **
- early SSc: 
- lcSSc: 
- dcSSc: 

**IL-33**
- HC: 
- early SSc: **
- lcSSc: 
- dcSSc: 

**TGF-β**
- HC: 
- early SSc: **
- lcSSc: **
- dcSSc: **

Serum levels of collagen metabolites increase in SSc subsets along with the presence and extension of skin sclerosis

A baseline CXCL4 value > 8.3 ng/ml identifies patients evolved into definite SSc during follow-up with a 30% sensitivity and 86% specificity (AUC 0.69).

Figure Legend

Figure 2. Receiver Operator Curve showing the relationship between baseline serum CXCL4 and evolution into definite SSc.
EARLY DIAGNOSIS

• Assessing capillaroscopic alterations and autoantibody profile

• Investigating **Criteria Manifestations**: Puffy fingers, Skin sclerosis involving fingers, Telangectasia, ILD/PAH

• Investigating **NON-Criteria Manifestations**: Esophageal-Stomach-Intestinal Involvement; Tendon Friction Rubs; Serositis and Heart disease

• Investigating the presence of preclinical internal organ involvement
ANA-negative Systemic Sclerosis

• 208/3249 patients enrolled in the Scleroderma Family Registry (6.4%)
• Higher male prevalence
• Higher percentage of diffuse disease, but lower skin score
• Lower prevalence of telangectasias and digital ulcers
• Higher DLCO values and lower PAH prevalence
• Higher prevalence of malabsorption

GA Salazar et al. Semin Arthritis Rheum 2015
**Prevalence of functional cardiac, lung and esophageal alterations in 115 RP patients subdivided into three groups**

<table>
<thead>
<tr>
<th></th>
<th>Early SSc</th>
<th>2013 ACR-definite SSc</th>
<th>UCTD</th>
<th>P1</th>
<th>P2</th>
<th>P3</th>
</tr>
</thead>
<tbody>
<tr>
<td>E/A ratio &lt; 1</td>
<td>1/19</td>
<td>1/51</td>
<td>1/45</td>
<td>0.5</td>
<td>0.5</td>
<td>0.9</td>
</tr>
<tr>
<td>FVC &lt; 80 %</td>
<td>0</td>
<td>3/51</td>
<td>0</td>
<td>0.5</td>
<td>-</td>
<td>0.5</td>
</tr>
<tr>
<td>DLCO &lt; 80 %</td>
<td>7/19</td>
<td>26/51</td>
<td>10/45</td>
<td>0.4</td>
<td>0.2</td>
<td>0.006</td>
</tr>
<tr>
<td>DLCO &lt; 70%</td>
<td>5/19</td>
<td>15/51</td>
<td>5/45</td>
<td>0.9</td>
<td>0.1</td>
<td>0.04</td>
</tr>
<tr>
<td>Basal LES pressure &lt; 15 mmHg</td>
<td>4/18</td>
<td>24/43</td>
<td>4/25</td>
<td>0.02</td>
<td>0.7</td>
<td>0.001</td>
</tr>
<tr>
<td>Plus distal esophageal hypomotility</td>
<td>0/4</td>
<td>10/24</td>
<td>2/4</td>
<td>0.2</td>
<td>0.4</td>
<td>0.9</td>
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In addition to marker autoantibody positivity, preclinical lung or heart involvement was associated with an increased risk to satisfy the criteria during follow-up.

• The 3 preclinical alterations detected by us with a similar prevalence in early SSc and UCTD patients likely depend on vascular disease.

• These evidence induce to hypothesize that vascular and fibrotic abnormalities detectable in SSc patients are driven by mechanisms, at least in part, independent each other and that the fibrotic process is correlated to the autoimmune response.

• In that regard, it has long been known that despite most patients present RP as the first manifestation of SSc, some develop skin sclerosis first and a few do not present RP ever.
EARLY TREATMENT

Identifying patients with so far undefined distinct cell activation and ongoing collagen overproduction
### LINKING PATHOGENESIS TO THERAPEUTIC TARGETS

<table>
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<th>CANDIDATE PERTURBED PATHWAYS</th>
<th>POTENTIAL TARGETS FOR THERAPY</th>
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<tbody>
<tr>
<td>Peptide and small molecule mediators</td>
<td>Lysophosphatic Acid</td>
</tr>
<tr>
<td></td>
<td>Cannabinoids</td>
</tr>
<tr>
<td>Immune cell subpopulations</td>
<td>CD20</td>
</tr>
<tr>
<td>Co-stimulatory molecules</td>
<td>CD80, CD86</td>
</tr>
<tr>
<td>Cytokine and growth factors</td>
<td>CCL2, IL-17, IL-13, IL-6, PDGF, TGFβ, CTGF</td>
</tr>
<tr>
<td>Integrin signalling</td>
<td>αvb6 integrin</td>
</tr>
<tr>
<td>Morphogen pathways</td>
<td>WNT, Hedgehog</td>
</tr>
<tr>
<td>Intracellular signalling</td>
<td>PPARy agonists, Phoshodiesterase, Jak, STAT, Smad</td>
</tr>
<tr>
<td>Epigenetic mechanisms</td>
<td>DNA methylation; miR29</td>
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### MAIN ONGOING TRIALS DEVOTED TO CONTRAST THE FIBROTIC PROCESS IN SSc

<table>
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<tr>
<th>DRUG</th>
<th>TARGET</th>
<th>PATIENTS</th>
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<tbody>
<tr>
<td>Tocilizumab</td>
<td>IL-6R</td>
<td>Early dc-SSc, SSc-ILD</td>
</tr>
<tr>
<td>Rilonacept</td>
<td>IL-1</td>
<td>dc-SSc</td>
</tr>
<tr>
<td>Rituximab</td>
<td>CD-20</td>
<td>SSc-PAH, SSc-Polyarthritis</td>
</tr>
<tr>
<td>IVIG</td>
<td>Fc receptor ?</td>
<td>dc-SSc</td>
</tr>
<tr>
<td>IVA337</td>
<td>PPARs</td>
<td>Early dc-SSc</td>
</tr>
<tr>
<td>Terguride</td>
<td>5-HT2</td>
<td>Early dc-SSc</td>
</tr>
<tr>
<td>Riociguat</td>
<td>sGC</td>
<td>Early-dc-SSc</td>
</tr>
<tr>
<td>Nintedanib</td>
<td>Signal trasduction</td>
<td>SSc-ILD</td>
</tr>
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JHW Distler et al. Arthritis Rheumatol 2017
Opening the way to a SSc “window of opportunity” is a suitable target!