Systemic Sclerosis: Case-based Update

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Disclosures

• Fellowship Program Grant Support
  • RRF Amgen Award

• Intellectual Property (with honoraria)
  • Hochberg, *Rheumatology, 6th ed*
  • Merck Manual
  • Rheumatic Disease Clinics of North America
  • Hospital Medicine

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- As is true for any ABIM candidate who has taken an exam for certification, I have signed the Pledge of Honesty in which I have agreed to keep ABIM exam content confidential.
- No exam questions will be disclosed in my presentation.
Discussion Points: Updates

• Classification criteria
• Clinical disease
  • Skin
  • Autoantibodies
  • Lung
  • Renal
Paul Klee
1879–1940

Gefangen 1940
“The Captive”

Slide courtesy of Kate Silver, MD
What We Know: The Triad

- Systemic Sclerosis (Scleroderma, SSc)
  - Excessive fibrosis
  - Endothelial dysfunction
  - Autoimmunity
Scleroderma Subsets: Definitions

• Limited cutaneous
  • Distal to the elbows and knees
  • Face

• Diffuse cutaneous
  • Proximal to the elbows and knees (truncal)
  • Face

• Systemic sclerosis *sine* scleroderma
  • No skin thickening
Scleroderma Subsets: Definitions

Limited and Diffuse SSc—Skin Involvement

Medsgen T. In Clements and Furst 2ND Edition, Systemic Sclerosis
Scleroderma Subsets: Natural History

• Skin disease progresses over a 2 year course
• Followed by skin softening, atrophy
  • May soften or normalize
• Predictors of diffuse skin involvement
  • Tendon friction rubs
  • Nailfold capillaroscopy changes
  • Anti-Scl-70 antibody
  • Anti-RNA Polymerase III antibody
ACR Criteria: 1980

- Major
  - Proximal scleroderma (proximal to the MCPs)
- Minor
  - Sclerodactyly
  - Digital pits
  - Basilar pulmonary fibrosis on CXR
- One major or two minor criteria
- Up to 10% of people would not meet criteria, though clinically have SSc-spectrum disease
- Patients with early SSc, and up to 20% of patients with limited cutaneous disease, do not meet criteria

46 yo woman with Raynaud’s (10 yrs), sclerodactyly, GER, pulmonary hypertension, ANA (centromere)

Would not fulfill criteria!

2013 Classification Criteria for Systemic Sclerosis

An American College of Rheumatology/European League Against Rheumatism Collaborative Initiative

This criteria set has been approved by the American College of Rheumatology (ACR) Board of Directors and the European League Against Rheumatism (EULAR) Executive Committee. This signifies that the criteria set has been quantitatively validated using patient data, and it has undergone validation based on an external data set. All ACR/EULAR-approved criteria sets are expected to undergo intermittent updates.

The American College of Rheumatology is an independent, professional, medical and scientific society which does not guarantee, warrant, or endorse any commercial product or service.
Table 1. The American College of Rheumatology/European League Against Rheumatism criteria for the classification of systemic sclerosis (SSc)*

<table>
<thead>
<tr>
<th>Item</th>
<th>Sub-item(s)</th>
<th>Weight/score†</th>
</tr>
</thead>
<tbody>
<tr>
<td>Skin thickening of the fingers of both hands extending proximal to the metacarpophalangeal joints (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 of the fingers (distal to the metacarpophalangeal joints but proximal to the proximal interphalangeal joints)</td>
<td>4</td>
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<td>Fingertip lesions (only count the higher score)</td>
<td>Digital tip ulcers</td>
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<tr>
<td></td>
<td>Fingertip pitting scars</td>
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</tr>
<tr>
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<td>SSc-related autoantibodies (anticentromere, anti-topoisomerase I [anti-Scl-70], anti–RNA polymerase III) (maximum score is 3)</td>
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* These criteria are applicable to any patient considered for inclusion in an SSc study. The criteria are not applicable to patients with skin thickening sparing the fingers or to patients who have a scleroderma-like disorder that better explains their manifestations (e.g., nephrogenic sclerosing fibrosis, generalized morphea, eosinophilic fasciitis, scleredema diabeticorum, scleromyxedema, erythromyalgia, porphyria, lichen sclerosis, graft-versus-host disease, diabetic cheiroarthropathy).
† The total score is determined by adding the maximum weight (score) in each category. Patients with a total score of ‡9 are classified as having definite SSc.
2013 Classification Criteria: Elements

- *Proximal skin thickening (to MCPs)
- Sclerodactyly
- Puffy fingers
- Digital ulcers, *digital pits*
- Telangiectasias
- Abnormal nailfold capillaroscopy
- PAH and/or *ILD*
- Raynaud phenomenon
- Autoantibodies

* Scores a 9 and meets criteria for diagnosis

*Van den Hoogen et al, Arthr and Rheum, 2013*
Case 1: 42 yo woman with 4 weeks of swelling in her hands and feet

- New onset Raynaud phenomenon
- Puffy fingers, telangiectasias
  - No synovitis
- “Active” nailfold capillaries
  - Capillary dilatation and avascularity
- ANA 1:320 speckled
- (+) Anti-RNA Polymerase III antibody

She would not be classified as having scleroderma using 1980 Classification Criteria

Absence of sclerodactyly, digital pits, pulmonary fibrosis
### Classification Criteria 2013

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† The total score is determined by adding the maximum weight (score) in each category. Patients with a total score of ≥9 are classified as having...
Systemic Sclerosis: Autoantibodies

Systemic Sclerosis
- ANA, nucleolar pattern
  - Systemic sclerosis (either limited or diffuse)
- ANA, centromere
  - Limited cutaneous
  - Longstanding Raynaud’s
  - Pulmonary hypertension
- Th/To
  - Limited cutaneous
  - Pulmonary hypertension
  - Could have ILD or renal crisis

- Anti-Scl-70 (anti-topoisomerase I)
  - Diffuse skin disease
  - ILD
- Anti-RNA Polymerase III
  - Diffuse skin disease
  - Scleroderma renal crisis
  - “Protective” from ILD
  - Malignancy association
  - Gastric antral vascular ectasia (GAVE)
Case 1: 42 yo woman with 4 weeks of swelling in her hands and feet

- New onset Raynaud phenomenon
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*She would not be classified as having scleroderma using 1980 Classification Criteria*

Absence of sclerodactyly, digital pits, pulmonary fibrosis

- Daily blood pressure checks
- Routine CBC, BMP, urinalysis
- Malignancy screening
Case 2

- 35 yo woman with 3 years of diffuse cutaneous SSc, positive ANA, positive anti-Scl-70.
- 2 months DOE
- Lungs with basilar crackles
- CXR clear
- PFTs:
  - FVC 65%, DLCO 60%
  - TLC 70%
- Request HRCT
Interststitial Lung Disease

• 40% of patients with SSc will develop clinical evidence of ILD

• Most likely to occur in first 4 years from disease onset
  • African American men in 5th and 6th decades most likely

• Poor survival if moderate to severe ILD at baseline

Interstitial Lung Disease

• Pulmonary function testing
  • Reduced lung volumes (restrictive pattern)
  • Reduced DLCO

• High resolution CT scan
  • Ground glass opacification (GGO)
  • Increased interstitial markings
  • Subpleural cysts

• Bronchoalveolar lavage—rarely needed
  • Elevated PMNs and/or Eos

• Open lung biopsy—rarely needed
Screening Strategy in Patients With SSc

Annual Screening

Consider every 2 year exam if DLCO > 70% and FVC/DLCO ratio < 1.6
Interstitial Lung Disease

• Treatment options
  • Daily oral cyclophosphamide (CYC)
  • Monthly IV cyclophosphamide (less studied)
  • Mycophenolate mofetil (MMF)
  • Home O₂
  • Lung transplantation
• Avoid high dose glucocorticoids
  • Increased risk for normotensive renal crisis
Interstitial Lung Disease
Scleroderma Lung Study I (SLS I)

• Randomized placebo controlled double blind study
  • 158 patients at 13 US centers
  • 12 months CYC vs. Placebo and 2 year follow-up
  • ILD based on HRCT and/or BAL abnormalities
  • 145 patients completed ≥ 6 months

Tashkin DP et al, NEJM, 2006
Interstitial Lung Disease
Scleroderma Lung Study I (SLS I)

• Significant improvement
  • FVC % predicted
    • Modest 2.53% (p<0.03)
  • Dyspnea
  • Skin thickening
  • Quality of life
• Daily oral cyclophosphamide (CYC) was superior to placebo at one year in terms of lung function

Tashkin DP et al, NEJM, 2006
Effects of 1-year Treatment with Cyclophosphamide on Outcomes at 2 years

14-center, randomized, controlled, double-blind study of oral MMF, up to 1.5 g twice daily for 2 years, versus oral CYC, 2 mg/kg once daily for 1 year (followed by placebo for a 2nd year), for active SSc-ILD.

Scleroderma Lung Study 2
Mycophenolate vs. Cyclophosphamide

FVC % predicted

Skin Score

Scleroderma Lung Study 2
Mycophenolate vs. Cyclophosphamide

Time to premature withdrawal from study medication or treatment failure by treatment arm

Case 3

• 33 yo woman with dcSSc x 4 years presents for routine follow-up. She notes recent ankle swelling. She otherwise feels well.
Case 3

- 33 yo woman with dcSSc x 4 years presents for routine follow-up. She notes recent ankle swelling. She otherwise feels well.

- Physical exam
  - BP 185/102, HR 78
  - Lungs, CV, Abdomen unremarkable
  - Extremities with 1+ pre-tibial edema
  - Skin with diffuse skin thickening
Case 3

What should be done next?

Labs

WBC 4.8K
Hb 9.1
Plts 102K
Creat 0.8 (this is baseline)
Urinalysis with 1+ protein, 2-5 RBCs/hpf
Case 3

What should be done next?
Inpatient vs. outpatient management?
Which ACE-I?
What if her blood pressure does not respond?
Case 3

What should be done next?

Inpatient vs outpatient management?
- Review of peripheral smear
- Inpatient management with frequent uptitration of the ACE-inhibitor

Which ACE-I?
- Captopril-short-acting
  - Once controlled, then switch to longer acting agent

What if her blood pressure does not respond?
- Add whatever it takes!
Case 3(b)

• 33 yo woman with dcSSc x 4 years presents for routine follow-up.

• One year ago she was treated for post-viral reactive airways disease with a methylprednisolone dosepack; she then required a longer prednisone taper from 60 mg daily to discontinuation over 4 months.
Case 3(b)

• 33 yo woman with dcSSc x 4 years presents for routine follow-up. She has a h/o prednisone use.

• Physical exam
  • BP 125/72, HR 78
  • Lungs, CV, Abdomen unremarkable
  • Extremities without edema
  • Skin with diffuse skin thickening
Case 3(b)

Labs

- WBC 4.8K
- Hb 9.1
- Plts 102K
- Creat 1.0 (creat 0.7 is baseline)
- Urinalysis with 1+ protein, 2-5 RBCs/hpf

Normal blood pressure
History of glucocorticoids
Microangiopathy
Abnormal urine sediment
Creatinine increase by 30%
Renal

• Normotensive Renal Crisis
  • Normal blood pressures
  • Oliguric renal failure
  • Microangiopathy
• Clinical pearl
  • Previous high dose glucocorticoid treatment (≥15 mg daily)

Summary

- New classification criteria
  - Facilitates diagnosing patients with SSc
  - Facilitates screening for visceral involvement
- Prognosis with autoantibodies
  - Scl-70, RNA Polymerase III, centromere
- Earlier diagnosis ➔ Earlier intervention
- Mycophenolate mofetil for management of skin and interstitial lung disease (ILD)
- Avoidance of high dose glucocorticoids due to risk of normotensive renal crisis
Questions?

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