Raynaud Phenomenon and Scleroderma

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Disclosures

• None

• Off-label use of medications
Case

• CP is a 69yo previously healthy female admitted with 9 months of fatigue and severe exertional dyspnea. A chest x-ray performed by her PCP was normal. Echocardiogram reveals an estimated pulmonary artery pressure of 55mmHg. She reports having 10 years of digital cold sensitivity with triphasic color changes (white → blue → red).
Case

• Workup identifies a positive ANA (>1280) and positive anti-centromere antibody (>8.0). PFTs reveal normal volumes with reduced DLCO (69%). Right heart catheterization reveals PA pressure of 80/38 with mean PAP of 52mmHg.
Case

• She is diagnosed with limited cutaneous systemic sclerosis (lcSSc or limited scleroderma) with pulmonary hypertension and started on continuous IV vasodilator therapy with minimal symptom improvement.
Objectives

1. Describe Raynaud’s phenomenon (RP) and how to differentiate primary from secondary RP.
2. Review the differential for secondary RP and findings concerning for rheumatic disease.
What is Raynaud’s phenomenon?

- An exaggerated response of the digital arterial circulation triggered by cold temperature and emotional stress
- Exaggeration of a “normal” response
- Present in 3-15% of the normal population
- More common in women (3-4:1)
- Often begins before age 20 years old
What is Raynaud’s phenomenon?

- Vasoconstriction can occur at the level of the digital arteries, precapillary arterioles and cutaneous arteriovenous shunts.

http://www.nhlbi.nih.gov
Thermoregulation

- The sympathetic nervous system regulates this process through arteriovenous (A-V) shunts in the skin.

- Nutritional flow to the skin is provided by a separate network of capillary vessels.
Identifying Raynaud’s

• “Do you have Raynaud’s?”
  – Rarely helpful
• Photos are very helpful – use the camera phone.

• Provocative testing

Images.rheumatolog.org
Identifying Raynaud’s

1. “Are your fingers unusually sensitive to the cold?”
2. “Do your fingers change color when exposed to cold temperatures?”
3. “Do they turn white, blue or both?”

Raynaud’s is confirmed with 3 positive responses and excluded with a negative response to 2 and 3.
Primary vs. Secondary Raynaud’s

• Raynaud’s is considered to be primary if there is no evidence of an associated disorder.

• Every patient should be carefully evaluated to determine if there is an underlying cause.
Primary Raynaud’s

- Median age of onset is 14 years
- Only 27% of cases begin after age 40 years
- Only 12% of patients reported having severe attacks
- About 25% of patients have a first-degree relative with Raynaud’s phenomenon

Primary Raynaud’s Characteristics

- Attacks precipitated by cold or emotional stress
- Symmetric attacks in both hands
- Generally milder symptoms and absence of necrosis, ulceration or gangrene
- Normal nailfold capillaries
- Negative ANA and normal ESR
- Absence of findings to suggest a secondary cause

Primary Raynaud’s

• Very low risk to progress to systemic sclerosis or another connective-tissue disease (<1%).

• Therapy is focused on conservative measures and dihydropyridine calcium channel blockers (amlodipine and nifedipine) when necessary.
Secondary Raynaud’s

1. Mechanical or external causes
2. Large artery disease
3. Systemic rheumatic disease
4. Other systemic disease
Features of Secondary Raynaud’s

- Later age of onset (greater than 40 years)
- Known precipitant
- Male gender
- Asymmetric attacks
- Painful attacks or signs of tissue ischemia
- Abnormal nailfold capillaries
- Abnormal laboratory studies suggesting vascular or autoimmune disease
Secondary Raynaud’s

- Findings suggesting rheumatic disease
  - Arthralgia and myalgia
  - Fever or rash
  - Muscle weakness
  - Telangectasia
  - Sclerodactyly or skin thickening
  - Dysphagia
  - Calcinosis
Case

• KA is a 28yo female referred for evaluation of possible lupus. She reports having 2 years of progressive fatigue and difficulty falling asleep. She has joint pain in the hands and feet without swelling or stiffness. She reports severe cold sensitivity in the hands and feet with intermittent blue and white color change. Once her right arm distal to the elbow was white and painful for 10 minutes.
Case

• Laboratory evaluation had revealed a normal CBC with differential, CMP, ESR and CRP
• ANA was mildly elevated, titer 1:40
• She tried amlodipine which was not helpful.
• She is currently taking an OCP and dextroamphetamine by prescription for ADHD.
## Primary vs. Secondary Raynaud’s

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<thead>
<tr>
<th>Primary (uncomplicated)</th>
<th>Secondary</th>
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<td>- Younger age (&lt;40)</td>
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<td>- Symmetric attacks</td>
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<td>- Absence of necrosis, ulceration or gangrene</td>
<td>- Severe attacks with ischemia and necrosis</td>
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<td>- Negative ANA</td>
<td>- Positive ANA or other laboratory studies</td>
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<td>- Other systemic disease or causal factors</td>
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Management of Raynaud’s

• Patient education and conservative measures are paramount.

• Placebo controlled trials are necessary due to a 10-40% placebo response.
Education and Conservative Measures

• Avoid cold temperatures and temperature shifts from warm to cold.
• Keep the body warm – gloves and base layers
• Avoid triggers and potentiating agents (smoking, CNS stimulants, decongestants, diet pills, estrogens, triptans, caffeine)
• Avoid fingertip trauma
• Limit stress
Pharmacotherapy for Raynaud’s

- 1st line – Dihydropyridine calcium channel blockers (CCBs)
  - Amlodipine 5-20mg daily
  - Nifedipine 30-180mg daily
  - Initiate low and titrate q2-4 weeks. Monitor BP.
Pharmacotherapy for Raynaud’s

• 2nd line options are often added to CCBs
  – Topical nitroglycerine (0.5 in of 2% ointment)
  – PDE-5 inhibitors (sildenafil 20mg daily up to TID)

• Alternatives to CCBs
  – Losartan, fluoxetine, and prazosin
Digital Ulceration and Critical Ischemia

- Uncontrolled pain and gangrene often represent a clinical emergency.
- Hospital admission to a single bed room for pain control and medication titration may be necessary.
- Digital sympathectomy (surgical or chemical), and IV prostacyclins (epoprostenol)
A 23yo woman seen in clinic reports joint pain and fatigue for 4 months. Pain is in the hands, wrists and ankles. She notes digital color change in the cold which resolves with rewarming. She has MCP tenderness.

Labs reveal mild anemia (Hgb 10.9) and an ANA of 1:80.
Question

• Which of the following findings would be most helpful in predicting evolution of this patient’s symptoms to a well-defined connective tissue disease?
  • A. Alopecia
  • B. Puffy hands
  • C. Nailfold capillary changes
  • D. Presence of anti-Ro/SS-A antibodies
Nailfold Capillary Changes

• Prospective studies have shown that patients with undifferentiated connective tissue disease (UCTD) and Raynaud’s more often evolved to systemic sclerosis if nailfold capillary changes are present.

• Approximately 20-30% of patients with Raynaud’s and nailfold capillary changes will develop features of scleroderma, typically within 2-3 years.
Nailfold Capillary Changes

Capillary telangiectasia and areas of dropout.

Changes can be seen at normal power when severe.
Nailfold Microscopy

http://archive.feedblitz.com/36640/~4000839
Poor Man’s Nailfold Capillaroscope

Nailfold capillary microscopy is performed by dropping oil on the periungual area and examining with an ophthalmoscope set at diopter 40 or with a dissecting microscope. Enlarged or distorted capillary loops and a relative paucity of loops suggest an underlying (or an increased likelihood of developing) connective tissue disease.

Polarizing dermatoscope

Uptodateonline.org
Nailfold Capillary Changes

NORMAL

EARLY

ACTIVE

LATE
Scleroderma

- A heterogeneous group of conditions which in almost all cases are linked by having thickened and sclerotic skin lesions.
- There is great diversity in the other manifestations among subtypes with regard to the extent of skin disease and internal organ involvement.
Scleroderma Classification

• Localized Scleroderma
  – Morphea
  – Linear scleroderma
  – Scleroderma en coup de sabre

• **Systemic Scleroderma** (systemic sclerosis, SSc)
  • As the name implies, systemic manifestations are expected with systemic sclerosis.
    – Limited cutaneous disease (lcSSc)
    – Diffuse cutaneous disease (dcSSc)
Systemic Sclerosis

• “Pre-scleroderma” or “very early scleroderma”

• Patients with Raynaud’s phenomenon, nailfold capillary changes and/or autoantibodies (ANA or scleroderma specific autoantibodies) but without cutaneous or visceral organ involvement.
Pathophysiology

**Vascular Injury**
- Endothelial dysfunction
- Endothelial cell activation
- Endothelin-1 release
- Platelet activation

**Leukocyte Activation, recruitment**
- Activated Th2 cells (CD4+ CD8+)
- Monocytes/macrophages
- Activated B cells

**TGF-β**
- Th2 cytokines
- CTGF, PDGF
- Chemokines

**Fibroblast activation**
- Collagen accumulation
- ECM molecule deposition
- Adhesion, matrix remodeling, contraction

**Collagen accumulation**
- Extracellular matrix reorganization
- Impaired matrix degradation

**Fibrosis**

**Vascular damage**
- Neointima formation
- Medial hypertrophy
- Peri-adventitial fibrosis
- Luminal narrowing
- Thrombosis

**Obliterative Vasculopathy**
- Tissue Hypoxia

**Defective vasculogenesis**

**Autoantibodies**
- Myofibroblast differentiation
- Pericyte differentiation
- Bone-marrow derived mesenchymal progenitor cells

Klippel J. Primer on the Rheumatic Diseases
Clinical Manifestations

- Scleroderma is the hallmark feature of systemic sclerosis
  - Hardening and thickening of the skin
- *Fibrosing* process is responsible for thickened skin, pulmonary parenchymal disease and GI dysmotility.
- Malaise, fatigue, arthralgia and myalgia are frequent general manifestations.
Clinical Manifestations

- Obliterative small vessel vasculopathy
- *Vasculopathy* is responsible for Raynaud’s phenomenon, scleroderma renal crisis and pulmonary artery hypertension.
More Feared Manifestations

• Scleroderma renal crisis was the leading cause of death in systemic sclerosis before the development of ACE-in.
• Pulmonary disease including pulmonary artery hypertension and interstitial lung disease is now the leading cause of death.
• Small pericardial effusion is very common. Tamponade is considered rare, but can occur.
Disease Timeline

- Interstitial lung disease
- Myocardial involvement
- Skeletal myopathy
- Joint contractures
- "renal crisis"
- Raynaud's digital ischemia
- Esophageal disease
- Pulmonary hypertension
- Malabsorption

Time

Skin thickness

LIMITED CUTANEOUS

DIFFUSE CUTANEOUS

Varga et al, Scleroderma, Springer 2012
Diffuse Cutaneous vs. Limited Cutaneous

• Limited Cutaneous
  – To the hands, distal forearm, face and neck
  – More prominent vascular manifestations
  – Many have “CREST syndrome”

• Diffuse Cutaneous
  – Involves chest, abdomen, upper arms and shoulders
  – More likely to have significant internal organ involvement due to ischemia and fibrosis
Update on the profile of the EUSTAR cohort: an analysis of the EULAR Scleroderma Trials and Research group database

Florian M P Meier,1 Klaus W Frommer,1 Robert Dinser,1 Ulrich A Walker,2 Laszlo Czirjak,3
Christopher P Denton,4 Yannick Allanore,5 Oliver Distler,6 Gabriela Riemekasten,7
Gabriele Valentini,8 Ulf Müller-Ladner,1 EUSTAR Co-authors

Results In June 2011, 7655 patients (2838 with diffuse cutaneous (dc) and 4481 with limited cutaneous (lc) SSc who fulfilled the American College of Rheumatology diagnostic criteria had been registered in 174 centres, mainly European. The most prominent hallmarks of disease were Raynaud’s phenomenon (96.3%), antinuclear antibodies (93.4%) and a typical capillaroscopic pattern (90.9%). Scleroderma was more common on fingers and hands than on any other part of the skin. Proton pump inhibitors (65.2%), calcium channel blockers (52.7%), and corticosteroids (45.3%) were most often prescribed. Among the immunosuppressant agents, cyclophosphamide was used more often in dcSSc than in lcSSc.
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RP Impacts Quality of Life

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## Autoantibodies

**Predictive of disease phenotype**

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<th>Prevalence (%)</th>
<th>Clinical association</th>
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<td>20–30</td>
<td>Limited scleroderma, Crest syndrome, pulmonary hypertension</td>
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<tr>
<td>Antitopoisomerase (anti-Scl-70)</td>
<td>15–20</td>
<td>Diffuse scleroderma, interstitial lung disease</td>
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<tr>
<td>Anti-PM-Scl</td>
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<td>Polymyositis/scleroderma overlap</td>
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<td>Anti-RNA polymerase</td>
<td>20</td>
<td>Diffuse scleroderma</td>
</tr>
<tr>
<td>Antifibrillarin</td>
<td>4</td>
<td>Diffuse scleroderma, myositis, pulmonary hypertension, renal disease</td>
</tr>
<tr>
<td>Anti-Ku, anti-Sm, anti-U1RNP</td>
<td>Rare</td>
<td>Overlap syndromes with features of scleroderma</td>
</tr>
<tr>
<td>Anticardiolipin antibodies</td>
<td>20–25</td>
<td>Limited/diffuse subsets, features of secondary antiphospholipid antibody syndrome rare</td>
</tr>
</tbody>
</table>
Autoantibodies

- **Anti-centromere-Ab**
  - Strongly associated with limited cutaneous systemic sclerosis (seen in up to 50% of cases)
  - Commonly associated with “CREST syndrome”
    - The term CREST has been somewhat superseded by lcSSc to emphasize the occurrence of systemic manifestations.
  - Female predominance
  - Increase risk for progressive Raynaud's and digital ischemia
  - Increased risk of isolated PAH

Varga et al, Scleroderma, Springer 2012
Autoantibodies

• Anti-topoisomerase-1 Ab, Scl-70-Ab
  – More likely to have diffuse cutaneous disease
  – Less likely to have isolated pulmonary hypertension
  – Patients with early diffuse SSCc and anti-Scl70-Ab have high risk of severe ILD (23%) and lower risk of renal crisis (10%). Monitoring with PFTs q3-6mo is recommended.

Varga et al, Scleroderma, Springer 2012
Autoantibodies

• Anti-RNA polymerase III-Ab
  – Present in 3.4-23% of patients with SSC
  – Rapidly progressive skin thickening which can predate the onset of Raynaud's
  – SRC develops in 24-33% of patients, a marked increase compared to all SSC patients (up to 5X)
  – All such patients should perform vigilant ambulatory BP monitoring
  – Only 7% of patients develop significant ILD
  – Most strongly associated with cancer

Emille S et al. Scan J Rheumatol 2011 40(5) 404-6
Varga et al, Scleroderma, Springer 2012
Autoantibodies and Early Detection

- Scleroderma specific autoantibodies are often present before the onset of clinical manifestations.
- Early identification and phenotyping of scleroderma or “pre-scleroderma” patients provides the opportunity for adequate screening, detection and intervention for the more severe manifestations of scleroderma.
Treatment

*Pre-treatment Evaluation
Take Home Points

• Every patient with Raynaud’s should be carefully evaluated to determine if there is an underlying cause.
• Patients with Raynaud’s and high risk features should be closely monitored for the development of scleroderma.
• In scleroderma patients, autoantibodies can predict disease phenotype and provide guidance on monitoring for systemic complications.