CREST and Systemic Sclerosis: What You Need to Know

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Objectives

• To recognize the differences between CREST and systemic sclerosis
• To learn about the pathophysiology of scleroderma
• To review the clinical features present in CREST and systemic sclerosis
• To identify risk factor associated with these diseases
• To identify current and future treatment options for patients
Pathophysiology of Scleroderma (SSc)

- Scleroderma is a rare connective tissue disease with unknown and complex pathogenesis. The exact etiology of Scleroderma is not completely understood, but both genetic and environmental factors are thought to play a part.

Genetic Association

- Very rare genetic association/more common in females/30-50 years
- The risks of Scleroderma and other autoimmune diseases are increased in relatives of people with SSc

Familial clustering: excess occurrence of a disease within a family compared to occurrence in the general population

- More common in African Americans and Native Americans
- Having family members with an autoimmune condition increases risk
- May be exposure to environmental factors shared by members of some families
Environmental Factors

- Several environmental triggers have been associated with development of SSc
- Infectious agents such as Cytomegalovirus (CMV), Epstein-Barr virus (EBV) and parvovirus B19.
- Exposure to silica dust
- Exposure to certain solvents (epoxy resins, organic solvents)
- Some drugs such as Bleomycin and cocaine have been associated with the development of SSc like illness (graft vs host disease, Werner’s syndrome)

Werner’s Syndrome

- Dramatic, rapid appearance of features associated with normal aging.
- Grow and develop normally until puberty
- Do not have a normal growth spurt
- Aged appearance begins in twenties (graying and loss of hair; a hoarse voice; and thin, hardened skin)
- Facial appearance described as “bird-like”
- As Werner syndrome progresses, cataracts, skin ulcers, diabetes infertility, severe hardening of arteries, osteoporosis, cancer
- Life expectancy 40-50
Systemic Sclerosis vs. CREST

- Scleroderma can be divided into two distinct forms, Localized Scleroderma or Systemic Sclerosis. These can be further be classified as either Limited Cutaneous Systemic Sclerosis (CREST syndrome) or Diffuse Cutaneous Systemic Sclerosis. Diagnosis is based on clinical and serological criteria (Adigun et al., 2020). It primarily affects women (female: male ratio of 4:1-10:1, depending on age and ethnicity).

CREST

- **CREST syndrome**, also known as limited or localized scleroderma, is a diffuse connective tissue disease which is differentiated by changes in the skin and subcutaneous tissue, blood vessels, skeletal muscles, and internal organs. Biopsy of the skin reveals dermal fibrosis like the changes seen in the thickened skin of Systemic Sclerosis. Although the skin changes approximate the changes with Systemic Sclerosis, Limited Scleroderma is not associated with some of the more serious pathology seen in Systemic Sclerosis.
CREST is an acronym for the clinical features that are identified in a patient with this disease.

- **Calcinosis**: Abnormal collection of calcium salts in or under the skin and in muscles or tendons. They appear frequently in dermatomyositis but also may be present in patients with overlapping autoimmune diseases, including systemic sclerosis, systemic lupus erythematosus, and mixed connective tissue disease. Calcinosis are hard, irregular nodules in or under the skin in any area of the body. They are very uncomfortable when they appear on the face, around joints, or on pressure points. They can cause functional disability, contractures, skin ulcers, and pain. They have a significantly negative impact on quality of life. Why nodules develop is not well-understood.

- **Raynaud’s phenomenon**: Tissue damage from inflammation and blood vessel changes.

- **Esophageal dysfunction**:

- **Sclerodactyly**:

- **Telangiectasias**:
Raynaud’s Phenomenon

- Secondary Raynaud’s phenomenon in Scleroderma
  - Caused by damage to blood vessels from SSe
  - Approximately 95 percent of those diagnosed with scleroderma have Raynaud phenomenon.

Esophageal Dysfunction

- Esophageal dysfunction is common
- The muscles and nerves that make up the wall of gastrointestinal organs are replaced with collagen
- Leads to stiffening of the wall and lessened motility in the junction of the esophagus and stomach
- Normally, the lower esophageal sphincter contracts producing a barrier to the reflux of gastric contents back into the esophagus.
  - Can cause GERD, esophagitis, ulceration, strictures, Barrett’s esophagus, and ultimately esophageal cancer
  - Gastroparesis associated with scleroderma makes GERD worse
    - Stomach remains filled with noxious materials after eating and prolongs time over which GERD can occur. The combination of GERD and gastroparesis can cause aspiration into the airway, which can be manifest as pneumonia and/or worsening lung function
Sclerodactyly

- Begins with edema
- Tapering deformity of the bones of the fingers
- Tight, stretched, wax like, hardened skin causing fingers to curl inwards (clawed position)
- Digital ulcerations
- Underlying soft tissues atrophy and can cause disability

Telangiectasias

- May develop on the face, mucous membranes and hands
- Become more numerous over time
- Cause is unknown
  - Some believe they are a manifestation of body’s attempt to increase blood flow to tissues
  - May be a marker of ongoing vascular injury and failed repair
- The total number correlates with disease duration
- Also correlates to the risk of developing pulmonary artery hypertension
- Associated with the presence of the centromere antibody (the antibody that is active in cell division)
CREST

• At least two of the preceding five features need to be present to be diagnosed
• Immune system appears to stimulate the production of too much collagen which builds up in the skin and internal organs
  • Fibroblasts produce excess amounts of collagen which causes progressive fibrosis of tissues
  • While collagen normally is produced to heal wounds, in Sse, collagen is produced even when it is not needed
  • Forms thick bands of connective tissue around cells of skin, blood vessels, and internal organs
• No cure.
  • Treatment: Relieving signs and symptoms and preventing complications

Diagnosis

• Can be difficult
• S & S vary widely and often resemble those of other connective tissue and autoimmune diseases
• Can occur with other autoimmune conditions — such as polynmyositis, lupus and rheumatoid arthritis
Diagnosis

- Laboratory findings: ANA and anticentromere
  - Not definitive—not everyone with limited scleroderma has these antibodies
- Skin biopsy: Helpful but cannot definitively diagnose CREST
- Additional tests: try to identify underlying lung, heart or gastrointestinal complications
- Calcinosis and esophageal motility issues are confirmed with imaging studies

Symptom Relief-Calcinosis

- Corticoids oral or injected inside the lesion (intralesional)
- Probenecid
- Diltiazem
- Warfarin
- Aluminum hydroxide
- Bisphosphonate
- Minocycline
- Colchicine
- Intravenous immunoglobulin therapy
- Surgical removal if too painful or infection/ulceration/can lead to amputation
Symptom Relief: Raynaud’s

- Reduce/remove risk factors/triggers:
  - Smoking, beta-blockers
- Keep hands and body warm
- Calcium channel blockers
  - Relax and open small blood vessels
  - Heal skin ulcers
  - Nifedipine, Procardia, Norvasc
- Vasodilators
  - Topical nitroglycerin paste
  - Cozaar, Viagra, Prozac, prostaglandins

Symptom Relief: Esophageal Dysmotility/GERD

- Same as in patients without SSe
- Behavior changes
  - Healthy weight, avoid tight clothing, elevate head of bed, stay upright after eating
- H2 blockers
  - Reduce the amount of acid produced by the cells in the lining of the stomach
    - Cimetidine, famotidine, nizatidine, ranitidine
- Botulinum Toxin injection in lower esophageal sphincter
- Esophageal dilatation
  - Can help if severe feeding difficulty or regurgitation occur due to esophageal narrowing
Symptom Relief-Sclerodactyly

- Corticosteroids, nonsteroidal anti-inflammatory drugs, D-penicillamine, IFN-gamma, cyclosporine, and cytostatic drugs
- Physical and occupational therapy-early in disease
  - Specialized therapists can make casts to wear which will allow the patient to carry out activities. Useful if hands harden, take shape that is most useful for carrying out ADL’s
- Ultraviolet light
  - Helps decompose collagen in the middle layer of the skin
- Skin involvement in CREST syndrome typically is not severe; therefore, treatment is not necessary in many cases

Symptom Relief-Telangiectasia

- Cosmetic camouflage (bothersome but not harmful)
- Pulsed-dye laser treatment (face)
  - In Sse, telangiectasia are more resistant to laser therapy; may need multiple treatments.
  - Does not prevent new telangiectasia
- Laser ablation
- Sclerotherapy
  - Solution injected into blood vessel; causes inflammation and disappearance over time
  - Should only use for severe cases
Lastly…Tell CREST Patients

- Wear gloves and mittens—even if not very cold
- Dress in layers, hat, thermal socks, and boots
  - Maintain the body’s core temperature to reduce Raynaud’s symptoms
- Eat soft, moist foods, chew food well, small, frequent meals; avoid spicy or fatty foods, chocolate, caffeine, and alcohol
- Avoid exercising immediately before or after eating to improve symptoms of acid reflux.
- Use skin moisturizers and humidifier to ease skin and breathing symptoms

Diffuse Systemic Sclerosis

- More heart involvement
- More kidney involvement
- Large joint contractures
- Disability, MSK pain

Diffuse vs Limited Scleroderma -Distinguishing Features-

<table>
<thead>
<tr>
<th>Diffuse</th>
<th>Limited</th>
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<tr>
<td>Lung fibrosis (severe in 15%)</td>
<td>Lung fibrosis (severe in 15%)</td>
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<tr>
<td>Heart (severe in 10%)</td>
<td>Minimal heart</td>
</tr>
<tr>
<td>Kidney (severe in 15-20%)</td>
<td>Minimal kidney</td>
</tr>
<tr>
<td>Large joint contractures</td>
<td>Late: Pulmonary hypertension (~15%)</td>
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<tr>
<td>Disability, fatigue, MSK pains</td>
<td>Late: Primary biliary cirrhosis (6-8%)</td>
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Modified Rodnan Skin Score (MRSS)

Standard outcome measure for skin disease in SSc and calculated by summation of skin thickness in 17 different body sites (total score = 51)

- Used as measure of disease severity and mortality risk
- An increase in skin thickening is associated with involvement of internal organs and increased mortality rates
- Improvement in the skin thickness score is associated with a more favorable outcome
Fine wrinkles; No thickness appreciated

“Mild” skin thickness; easily able to detect a thickened skin fold between 2 fingers
“Moderate” skin thickness; difficulty in making a skin fold and unable to appreciate fine wrinkles

“Severe” skin thickness; inability to make skin folds between 2 fingers
Rodnan Skin Score

• An individual with skin thickening restricted to the face, forearms, hands and fingers would be said to have **systemic sclerosis with limited scleroderma** or CREST syndrome.

• Skin thickening above the elbows and knees and on the chest and would be classified as having **systemic sclerosis with diffuse scleroderma**.

As you can see...

• Diffuse involves much more skin and internal organs than limited scleroderma.
Diffuse Scleroderma

- Raynaud phenomenon followed, within one year, by puffy or hidebound skin changes.
- Truncal and acral skin involvement; tendon friction rubs
- Nailfold capillary dilation and capillary drop-out
- Early and significant incidence of renal, interstitial lung, diffuse gastrointestinal, and myocardial disease
- Anti-Scl-70 (30-70 percent) (seen in 10-18% of CREST) and anti-RNA polymerase-I, II, or III antibodies (12 to 15 percent) - highly associated with SSc

Laboratory Findings

- **ANA**: present in about 95% of those with scleroderma, typically with a speckled, centromere, or – more rarely – nucleolar pattern test result.
- **Scl-70 antibody** (Scleroderma antibody, Anti-topoisomerase I antibody) – positive in up to 70% of adults with systemic sclerosis
- **Centromere antibody (ACA)/centromere pattern** – present in 50-96% of people with limited cutaneous scleroderma and strongly associated with CREST syndrome
- Anti-fibrillarin (U3RNP), anti-PM/Scl, anti-RNA polymerases I/III, anti-Nor-90, anti-PM-Scl, anti-B23, anti-U1-RNP, AHAs (anti-histone), and anti-Th/To (5-10%)
Prognosis for SSe

- Diffuse more serious
- May worsen rapidly and become fatal
- May only affect the skin for decades before affecting internal organs
  - Some damage to internal organs (such as the esophagus) is almost inevitable
  - Course is unpredictable; 92% of people who have limited systemic sclerosis and 65% of people who have diffuse systemic sclerosis live for at least 10 years after diagnosis
  - Prognosis worse for males, those who develop the disease later in life, have diffuse systemic sclerosis, or have heart, lung, or, particularly, kidney damage.
  - Prognosis for CREST syndrome more favorable.

Conclusion

- Systemic sclerosis (SSc) is a systemic autoimmune disease in which inflammation and fibrosis play a crucial role and lead to severe damage and failure of multiple organs such as the skin, joints, tendons, gastrointestinal tract, lungs, heart, blood vessels, and kidneys. It may lead to major disabilities due to vascular complications, cardiopulmonary involvement, inflammatory myopathy, and arthritis; likewise, it can cause malnutrition due to gastrointestinal tract involvement, and it can decrease quality of life as a consequence of the psychological and social impact. Additionally, it can be fatal, with a 3-year survival rate of 47-56% in cases of serious pulmonary or cardiac involvement. It is the single connective tissue disease with the worst survival prognosis.
References


