

## Scleroderma - Systemic Sclerosis

### Clinical Background

Systemic sclerosis is a chronic multisystem autoimmune disorder characterized by thickening of the skin and accumulation of connective tissue in various organs.

#### Epidemiology

- Incidence – 3-20/1,000,000
- Age – peak onset 20s-30s
- Sex – M<F, 1:3-8
- Ethnicity – overall slight increase in frequency for African Americans compared to Caucasians
  - 10-fold increase in Choctaw Indians (southern Oklahoma)

#### Classification of Scleroderma (Systemic Sclerosis) and Scleroderma-like Disorders

- Systemic sclerosis
  - Limited cutaneous disease – CREST syndrome variant
  - Diffuse cutaneous disease
  - Sine scleroderma
  - Undifferentiated connective tissue disease – multiple serologic and clinical features that do not meet American College of Rheumatology (ACR) criteria for rheumatic disease
  - Overlap syndromes – systemic sclerosis plus polymyositis, rheumatoid arthritis (RA) or systemic lupus erythematosus (SLE)
- Localized scleroderma
  - Plaque morphea
  - Generalized morphea
  - Bullous morphea
  - Deep morphea
  - Linear scleroderma
- Chemical-induced scleroderma-like disorders
  - Toxic-oil syndrome (rapeseed oil)
  - Vinyl chloride-induced disease
  - Bleomycin-induced fibrosis
  - Pentazocine-induced fibrosis
  - Epoxy- and aromatic hydrocarbons-induced fibrosis
  - Eosinophilia-myalgia syndrome
  - Nephrogenic system fibrosis ( gadolinium-based contrast agents)
- Other scleroderma-like disorders
  - Scleredema adultorum of Buschke
  - Scleromyxedema (papular mucinosis)
  - Chronic graft-vs-host disease
  - Eosinophilic fasciitis
  - Digital sclerosis in diabetes
  - Primary amyloidosis and amyloidosis associated with multiple myeloma
  - Paraneoplastic syndromes

#### Pathophysiology

- Pathologic remodeling of connective tissues is typified by 3 cardinal features
  - Fibrosis due to excessive collagen production
  - Vascular damage
  - Inflammation or autoimmune processes
- Pathologic antibodies

- Commonly identified antibodies
  - Anti-centromere (ACA)
  - Anti-topoisomerase (Scl-70)
- Less frequent antibodies
  - Anti-RNA polymerase I/III
  - Anti-Th/To, anti-PM/SCL
  - Anti-U1-ribonucleoprotein (RNP)
  - Anti-fibrillarin/anti-U3-ribonucleoprotein (RNP)

#### Clinical Presentation

- Morphea
  - Skin manifestations of systemic sclerosis without sclerodactyly or organ involvement
  - Morphea classifications
    - Plaque – guttate, generalized, nodular, lichen sclerosis, atrophoderma
    - Bullous
    - Linear
    - Deep – subcutaneous, profunda, eosinophilic, pansclerotic of children
- Systemic sclerosis
  - Dermatologic – thickening of skin, telangiectasis, hair loss, calcium deposits, Raynaud phenomenon, digital ulcers, sclerodactyly
  - Gastrointestinal – esophageal dysmotility, reflux, gastroparesis, malabsorption, constipation
  - Pulmonary – interstitial fibrosis, pulmonary hypertension
  - Musculoskeletal – arthralgia, myalgia, arthritis, myopathy, weakness (usually proximal muscles)
  - Cardiovascular – myocardial fibrosis, pericarditis, valvular abnormalities, conduction problems (arrhythmias)
  - Renal – glomerulonephritis, scleroderma renal crisis
  - Head and neck – Sicca syndrome, hypothyroidism, Sjögren syndrome, blepharitis
  - Central nervous system – cranial and peripheral neuropathies, carpal tunnel syndrome
  - Genitourinary – erectile dysfunction, sexual dysfunction
  - Pediatric population
    - CREST unusual
    - Arthritis seen more often
    - Diffuse variant occurs most often (79%)

#### Treatment

- Remittive agents – cyclophosphamide
  - May alter the course of the disease; however, no definitive studies as yet

### Diagnosis

- Indications for testing – clinical presentation is characteristic for disease and should prompt lab confirmation
- Laboratory testing
  - Initial testing – Anti-nuclear antibodies (ANA) for both morphea and system sclerosis; CBC for morphea
  - Antibody testing
    - Scl-70 (anti-topoisomerase antibodies) is a specific marker of scleroderma when it is the only autoantibody present

- Prevalence ranges from 20-60% in adult scleroderma
- Low frequency in pediatric populations
- Correlates with higher risk of interstitial lung disease
- Anticentromere antibody (ACA)
  - Associated with limited systemic sclerosis
  - Prevalence of 60-80% in limited scleroderma including CREST
- Other less frequent antibodies include the following
  - Anti-fibrillarin/anti-U3-RNP
    - May predict skeletal muscle involvement and pulmonary arterial hypertension
    - Some studies suggest higher prevalence in individuals of African American descent
  - Anti-PM/SCL
    - Polymyositis and scleroderma overlap disease
  - Anti-RNA polymerase I/III
    - Invariably coexists with higher specificity than anti-RNA polymerase II
    - Predictive of diffuse skin involvement and high risk for renal involvement
  - Anti-U1-RNP
    - High titers are associated with SSc/SLE/polymyositis overlap syndromes
  - Anti-Th/To
    - May predict development of pulmonary hypertension
- Negative antibody test result does not exclude systemic sclerosis
- Histology
  - Anti-fibrillarin/anti-U3-RNP – associated with internal organ involvement
  - Anti-Th/To – associated with pulmonary fibrosis
  - Morphea – early lesions characterized by dense infiltrate of lymphocytes, macrophages, plasma cells and occasionally eosinophils
  - Systemic sclerosis – biopsy rarely required for diagnosis

#### Prognosis

- Markers not useful in prognostication

#### Differential Diagnosis

- Thyroid disorders
- Amyloidosis
- POEMS syndrome (Crow-Fukase syndrome)
- Diabetes
- Porphyria cutanea tarda
- Nephrogenic fibrosing dermopathy
- Scleromyxedema
- Scleredema
- Neoplasm (carcinoid in particular)
- Raynaud phenomenon

## Lab Tests

### Indications for Laboratory Testing

Tests generally appear in the order most useful for common clinical situations. For test-specific information, refer to the test number in the ARUP Laboratory Test Directory on the ARUP Web site at [www.aruplab.com](http://www.aruplab.com).

Test Name and Number	Recommended Use	Limitations	Follow Up
CBC with Platelet Count & Automated Differential <b>0040003</b> Method: Automated Cell Count with Flow Cell Differential	Determine presence of morphea		
Anti-Nuclear Antibodies (ANA), IgG Screen with Reflex to IFA Titer <b>0050080</b> Method: Enzyme-Linked Immunosorbent Assay/Indirect Fluorescent Antibody	First-line test for connective tissue disease screening		
Connective Tissue Diseases Profile <b>0051668</b> Method: Multi-Analyte Fluorescent Detection	Aid in identifying specific connective tissue disease  Panel consists of Smith (ENA), RNP, SSA, SSB, Jo-1, RPP, Centromere and Scl-70 antibodies		
RNA Polymerase III Antibody, IgG <b>2001601</b> Method: Enzyme-Linked Immunosorbent Assay	Asses risk for renal crisis, diffuse cutaneous systemic sclerosis		
PM-Scl Antibody, ID <b>0099591</b> Method: Immunodiffusion	Order as secondary screen based on results of ANA testing		

### Additional Tests Available

Test Name and Number	Comments
Smith (ENA) Antibody, IgG <b>0050085</b> Method: Multi-Analyte Fluorescent Detection	

<p>Double-Stranded DNA (dsDNA) Antibody, IgG by ELISA with Reflex to dsDNA Antibody, IgG by IFA  <b>0050215</b>                      Method:                      Enzyme-Linked Immunosorbent Assay/Indirect Fluorescent Antibody</p>	<p>dsDNA antibodies are screened using an ELISA assay                      If dsDNA antibodies are detected, then dsDNA Antibody IgG by IFA (using <i>Crithidia luciliae</i>) will be performed</p>
<p>Anti-Nuclear Antibody (ANA), IgG Screen with Reflex to ANA IFA Titer, dsDNA, RNP, Smith, SSA, &amp; SSB Antibodies  <b>0050317</b>                      Method:                      Enzyme-Linked Immunosorbent Assay/Indirect Fluorescent Antibody/Multi-Analyte Fluorescent Detection</p>	
<p>RNP (U1) (Ribonucleic Protein) (ENA) Antibody, IgG  <b>0050470</b>                      Method:                      Multi-Analyte Fluorescent Detection</p>	<p>Order as secondary screen based on results of ANA testing</p>
<p>Scleroderma (Scl-70) (ENA) Antibody, IgG  <b>0050599</b>                      Method:                      Multi-Analyte Fluorescent Detection</p>	<p>Order as secondary screen based on results of ANA testing</p>
<p>Extractable Nuclear Antigen Antibodies (RNP, Smith, SSA, &amp; SSB)  <b>0050652</b>                      Method:                      Multi-Analyte Fluorescent Detection</p>	
<p>Extractable Nuclear Antigen Antibodies (RNP, Smith, Scleroderma, SSA, &amp; SSB)  <b>0050653</b>                      Method:                      Multi-Analyte Fluorescent Detection</p>	
<p>SSA (Ro) (ENA) Antibody, IgG  <b>0050691</b>                      Method:                      Multi-Analyte Fluorescent Detection</p>	
<p>SSB (La) (ENA) Antibody, IgG  <b>0050692</b>                      Method:                      Multi-Analyte Fluorescent Detection</p>	
<p>Centromere Antibody, IgG  <b>0050714</b>                      Method:                      Multi-Analyte Fluorescent Detection</p>	<p>Order as secondary screen based on results of ANA testing</p>
<p>Histone Antibody, IgG  <b>0050860</b>                      Method:                      Enzyme-Linked Immunosorbent Assay</p>	

Ribosomal P Protein Antibody <b>0099249</b> Method: Multi-Analyte Fluorescent Detection	
ssDNA Antibody, IgG <b>0099528</b> Method: Enzyme-Linked Immunosorbent Assay	
Jo-1 Antibody, IgG <b>0099592</b> Method: Multi-Analyte Fluorescent Detection	

**Guidelines**

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**Diagnostic Algorithm(s)**

PDF algorithm(s) available at [www.arupconsult.com](http://www.arupconsult.com).

Connective Tissue Disease Testing Algorithm

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