

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.

Test Name and Number	Recommended Use	Limitations	Follow Up
CBC with Platelet Count & Automated Differential 0040003 Method: Automated Cell Count with Flow Cell Differential	Determine presence of morphea		
Anti-Nuclear Antibodies (ANA), IgG Screen with Reflex to IFA Titer 0050080 Method: Enzyme-Linked Immunosorbent Assay/Indirect Fluorescent Antibody	First-line test for connective tissue disease screening		
Connective Tissue Diseases Profile 0051668 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 2001601 Method: Enzyme-Linked Immunosorbent Assay	Asses risk for renal crisis, diffuse cutaneous systemic sclerosis		
PM-Scl Antibody, ID 0099591 Method: Immunodiffusion	Order as secondary screen based on results of ANA testing		

Additional Tests Available

Test Name and Number	Comments
Smith (ENA) Antibody, IgG 0050085 Method: Multi-Analyte Fluorescent Detection	
NOT FOUND 2002500 Method: NOT FOUND	

<p>Anti-Nuclear Antibody (ANA), IgG Screen with Reflex to ANA IFA Titer, dsDNA, RNP, Smith, SSA, & SSB Antibodies 0050317</p> <p>Method: Enzyme-Linked Immunosorbent Assay/Indirect Fluorescent Antibody/Multi-Analyte Fluorescent Detection</p>	
<p>RNP (U1) (Ribonucleic Protein) (ENA) Antibody, IgG 0050470</p> <p>Method: Multi-Analyte Fluorescent Detection</p>	Order as secondary screen based on results of ANA testing
<p>Scleroderma (Scl-70) (ENA) Antibody, IgG 0050599</p> <p>Method: Multi-Analyte Fluorescent Detection</p>	Order as secondary screen based on results of ANA testing
<p>Extractable Nuclear Antigen Antibodies (RNP, Smith, SSA, & SSB) 0050652</p> <p>Method: Multi-Analyte Fluorescent Detection</p>	
<p>Extractable Nuclear Antigen Antibodies (RNP, Smith, Scleroderma, SSA, & SSB) 0050653</p> <p>Method: Multi-Analyte Fluorescent Detection</p>	
<p>SSA (Ro) (ENA) Antibody, IgG 0050691</p> <p>Method: Multi-Analyte Fluorescent Detection</p>	
<p>SSB (La) (ENA) Antibody, IgG 0050692</p> <p>Method: Multi-Analyte Fluorescent Detection</p>	
<p>Centromere Antibody, IgG 0050714</p> <p>Method: Multi-Analyte Fluorescent Detection</p>	Order as secondary screen based on results of ANA testing
<p>Histone Antibody, IgG 0050860</p> <p>Method: Enzyme-Linked Immunosorbent Assay</p>	
<p>Ribosomal P Protein Antibody 0099249</p> <p>Method: Multi-Analyte Fluorescent Detection</p>	

ssDNA Antibody, IgG 0099528 Method: Enzyme-Linked Immunosorbent Assay	
Jo-1 Antibody, IgG 0099592 Method: Multi-Analyte Fluorescent Detection	

Guidelines

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General References

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References from the ARUP Institute for Clinical and Experimental Pathology®

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Reviewed by

Hill, Harry R., MD. Group Medical Director, Laboratory of Immunology, ARUP Laboratories, and Executive Director of the ARUP Institute for Clinical and Experimental Pathology; Professor and Division Head, Pathology (Clinical), University of Utah

Tebo, Anne E., PhD. Assistant Medical Director, Immunology at ARUP Laboratories; Assistant Professor of Pathology (Clinical), University of Utah

Diagnostic Algorithm(s)

PDF algorithm(s) available at www.arupconsult.com.

Connective Tissue Disease Testing Algorithm

Related Content

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Vasculitis - ANCA

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