

Scleroderma - Systemic Sclerosis

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
 - ANA – nucleolar pattern is relatively specific for systemic sclerosis (seen in ~95% of patients)
- Antibody testing
 - Scl-70 (DNA anti-topoisomerase 1) 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 (pulmonary fibrosis)
 - Anticentromere antibody (ACA)
 - Associated with limited systemic sclerosis
 - Prevalence of 60-80% in limited scleroderma, including CREST
 - High incidence of pulmonary hypertension
 - 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 rapid diffuse skin involvement and high risk for renal involvement
 - Most patients who are positive are negative for anticentromere and anti-Scl-70
 - Anti-U1-RNP
 - High titers are associated with SSc/SLE/polymyositis overlap syndromes
 - Anti-Th/To (7S/8S RNA)
 - 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 mellitus
- Porphyria cutanea tarda
- Nephrogenic fibrosing dermopathy
- Scleromyxedema
- Scleredema
- Neoplasm (carcinoid in particular)
- Raynaud phenomenon
- Other connective tissue diseases
 - Mixed connective tissue disease
 - Inflammatory myopathies

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

Classification of scleroderma (systemic sclerosis) and scleroderma-like disorders

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 exist

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 and Automated Differential 0040003 Method: Automated Cell Count/Differential	Assess for presence of eosinophilia if morphea present		
Anti-Nuclear Antibodies (ANA), IgG by ELISA with Reflex to ANA, IgG by IFA 0050080 Method: Qualitative Enzyme-Linked Immunosorbent Assay/Semi-Quantitative Indirect Fluorescent Antibody	First-line test for connective tissue disease screening If ANA antibodies are detected, IFA titer is added		
Connective Tissue Diseases Profile 0051668 Method: Semi-Quantitative Multiplex Bead Assay	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: Semi-Quantitative Enzyme-Linked Immunosorbent Assay	Assess risk for renal crisis, diffuse cutaneous systemic sclerosis		

PM/Scl-100 Antibody, IgG, by Immunoblot with Reflex to ANA IFA 2003040 Method: Semi-Quantitative Immunoblot/Semi-Quantitative Indirect Fluorescent Antibody	Aid in identifying specific form of scleroderma		
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Additional Tests Available

Test Name and Number	Comments
Smith (ENA) Antibody, IgG 0050085 Method: Semi-Quantitative Multiplex Bead Assay	
Double-Stranded DNA (dsDNA) Antibody, IgG by ELISA with Reflex to dsDNA Antibody, IgG by IFA 0050215 Method: Qualitative Enzyme-Linked Immunosorbent Assay/Semi-Quantitative Indirect Fluorescent Antibody	dsDNA antibodies are screened using an ELISA assay If dsDNA antibodies are detected, then dsDNA Antibody IgG by IFA (using <i>Crithidia lucilliae</i>) will be performed
Anti-Nuclear Antibody (ANA), IgG by ELISA with Reflexes to ANA by IFA and to dsDNA, RNP, Smith, SSA, and SSB Antibodies 0050317 Method: Qualitative Enzyme-Linked Immunosorbent Assay/Semi-Quantitative Indirect Fluorescent Antibody/Semi-Quantitative Multiplex Bead Assay	If ELISA screen is positive, then IFA using HEp-2 substrate will be added; if confirmed by IFA, titer and pattern will be reported and testing for dsDNA antibody and ENA antibodies will be added
RNP (U1) (Ribonucleic Protein) (ENA) Antibody, IgG 0050470 Method: Semi-Quantitative Multiplex Bead Assay	Order as secondary screen based on results of ANA testing
Scleroderma (Scl-70) (ENA) Antibody, IgG 0050599 Method: Semi-Quantitative Multiplex Bead Assay	Order as secondary screen based on results of ANA testing
Extractable Nuclear Antigen Antibodies (RNP, Smith, SSA, & SSB) 0050652 Method: Semi-Quantitative Multiplex Bead Assay	
Extractable Nuclear Antigen Antibodies (RNP, Smith, Scleroderma, SSA, & SSB) 0050653 Method: Semi-Quantitative Multiplex Bead Assay	

SSA (Ro) (ENA) Antibody, IgG 0050691 Method: Semi-Quantitative Multiplex Bead Assay	
SSB (La) (ENA) Antibody, IgG 0050692 Method: Semi-Quantitative Multiplex Bead Assay	
Centromere Antibody, IgG 0050714 Method: Semi-Quantitative Multiplex Bead Assay	Order as secondary screen based on results of ANA testing
Histone Antibody, IgG 0050860 Method: Semi-Quantitative Enzyme-Linked Immunosorbent Assay	
Ribosomal P Protein Antibody 0099249 Method: Semi-Quantitative Multiplex Bead Assay	
ssDNA Antibody, IgG 0099528 Method: Semi-Quantitative Enzyme-Linked Immunosorbent Assay	
Jo-1 Antibody, IgG 0099592 Method: Semi-Quantitative Multiplex Bead Assay	

Guidelines

Avouac J, Fransen J, Walker UA, Riccieri V, Smith V, Muller C, Miniati I, Turner IH, Randone SB, Cutolo M, Allanore Y, Distler O, Valentini G, Czirjak L, Muller-Ladner U, Furst DE, Tyndall A, Matucci-Cerinic M. Preliminary criteria for the very early diagnosis of systemic sclerosis: results of a Delphi Consensus Study from EULAR Scleroderma Trials and Research Group. *Ann Rheum Dis.* 2011; 70 (3) :476-481.

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General References

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Diagnostic Algorithm(s)

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

Connective Tissue Disease Testing Algorithm

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Inflammatory Myopathies

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