

Update in Rheumatic Diseases: Scleroderma/Sjögrens/Myositis

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Disclosures

Up to Date

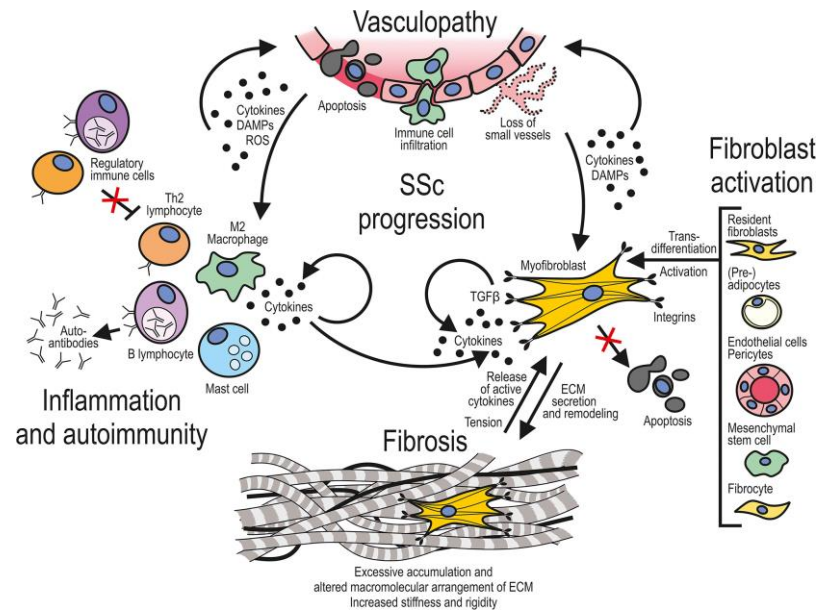
Outline

1. Scleroderma
2. Sjögren's syndrome
3. Myositis
 - Clinical manifestations and diagnosis
 - Treatment options

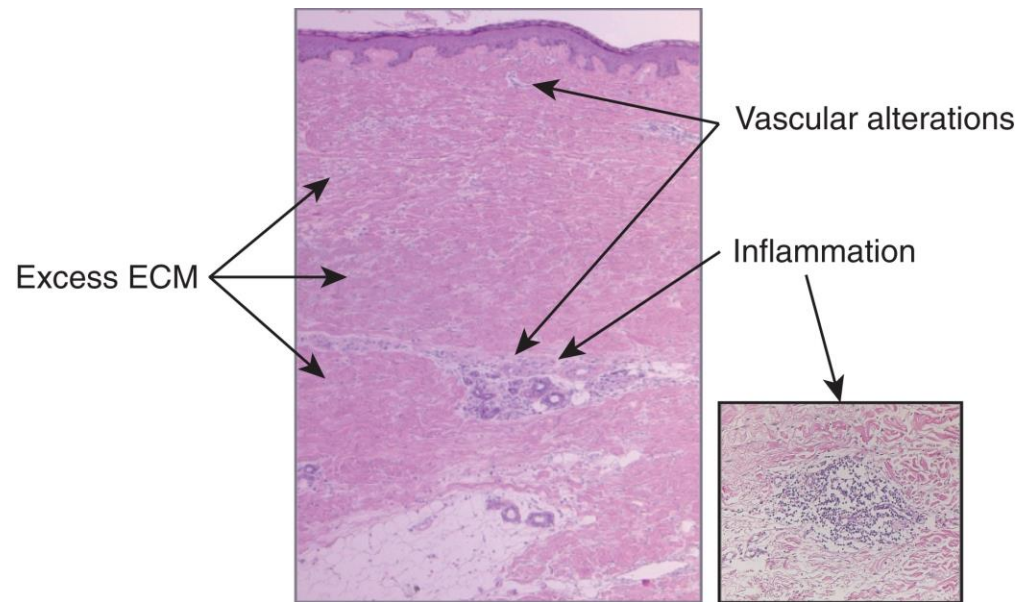
Systemic Sclerosis (SSc/Scleroderma)

- Complex systemic disease that affects the skin, lung, heart, GI tract, and kidney
- Pathophysiology
 - Vascular and endothelial dysfunction
 - Autoimmunity
 - Fibroblastic activation and proliferation

Pathophysiology of systemic sclerosis (scleroderma)



Pathophysiology of systemic sclerosis (scleroderma)



Scleroderma = Hardening of the Skin

Localized scleroderma

Morphea

Linear scleroderma

Systemic sclerosis

Diffuse

Limited (CREST)

Sine scleroderma

Overlap Syndrome



Limited Systemic Sclerosis: CREST

Calcinosis

Raynaud's

Esophageal Dysmotility

Sclerodactyly

Telangiectasias



Limited vs Diffuse SSc

	Limited	Diffuse
Skin thickening	Face, forearms, lower legs, hands and feet	Face, trunk, entire arms/legs, hands and feet; tendon friction rubs
Raynaud's phenomenon	Progressive disease following onset of RP	Rapid onset following RP: months to 3 years
Autoantibodies	Association with anti-centromere Ab (50-60%)	Association with anti-Scl 70 ab (30%)
Internal organ involvement	Late: primarily pulmonary HTN (10-30%), esophageal dysmotility	Early: ILD (75%), myocardial disease, diffuse GI involvement, scleroderma renal crisis (10-15%)
Prognosis	10-yr survival $\geq 70\%$	10-yr survival 40%

Skin Thickening



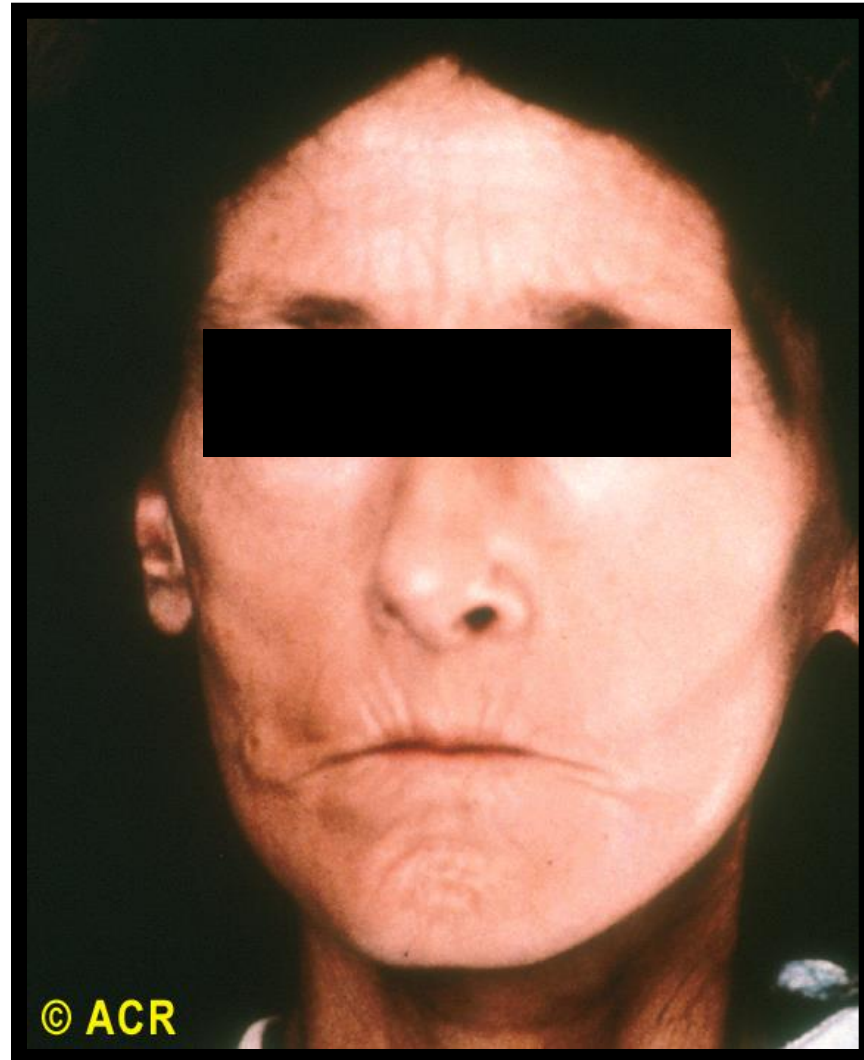
Puffy Hands of Early SSc



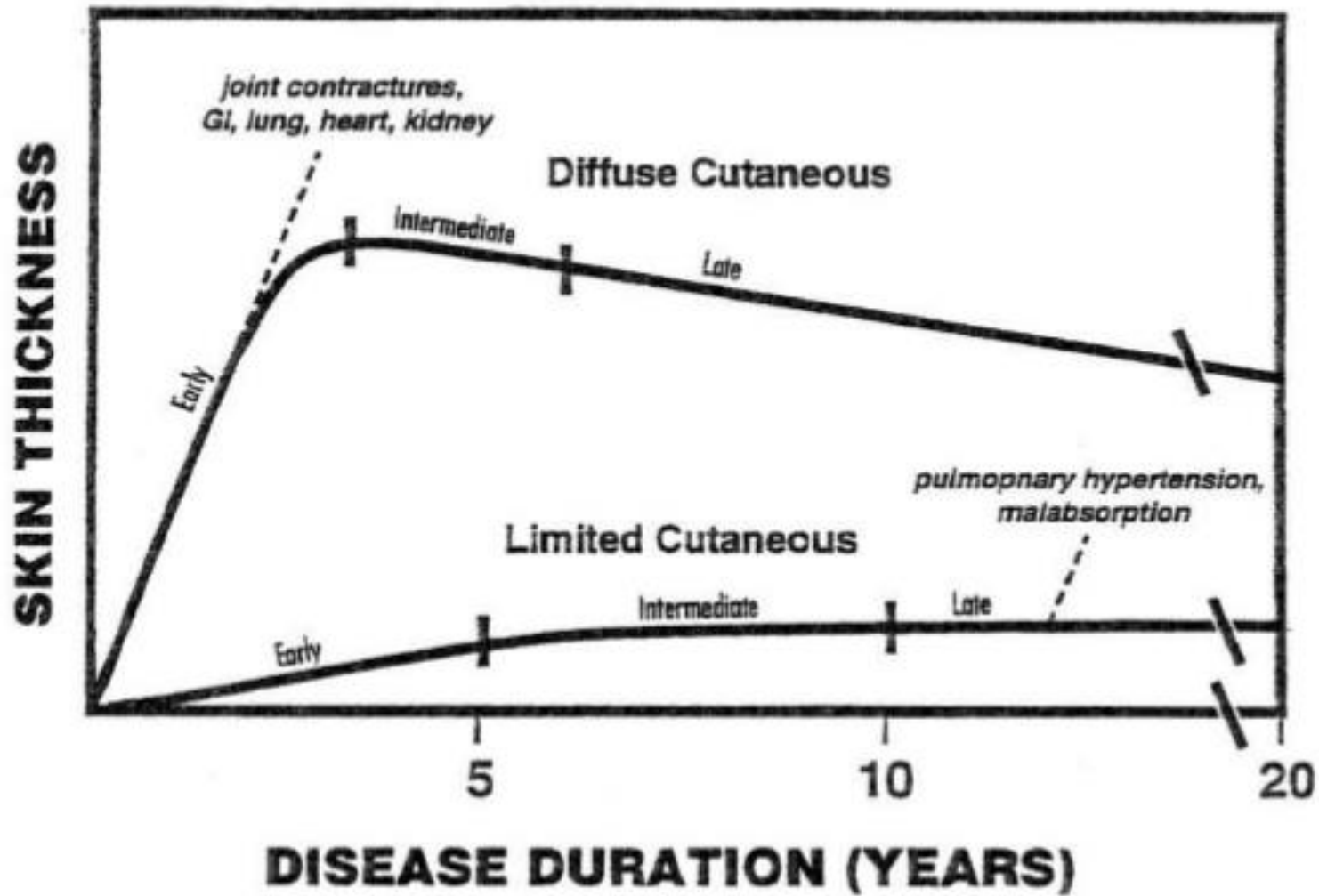
Sclerodactyly



Mauskopf Facies



Natural History of Skin Tightening in SSc



Raynaud's Phenomenon

Not an infrequent initial presentation of CTDs

Episodic, reversible digital skin color change

White to blue to red

Well-demarcated

Due to vasospasm

Usually cold-induced

Raynaud's Phenomenon



Raynaud's Phenomenon



Raynaud's Phenomenon

- **Primary Raynaud's**

- Common in young women (<age 30)
- Often have + family history
- ANA mostly negative

- **Secondary Raynaud's**

- Onset in > age 35
- Digital ulcers, pitting scars in fingers
- Abnormal capillary microscopy
- Presence of autoantibodies

Secondary Raynaud's Phenomenon

Connective tissue diseases

SSc, SLE, MCTD, Undifferentiated CTD,
Sjogren's syndrome, Dermatomyositis

Occlusive arterial disease

Atherosclerosis, Antiphospholipid Syndrome,
Buerger's disease

Vascular injury

Frostbite, vibratory trauma

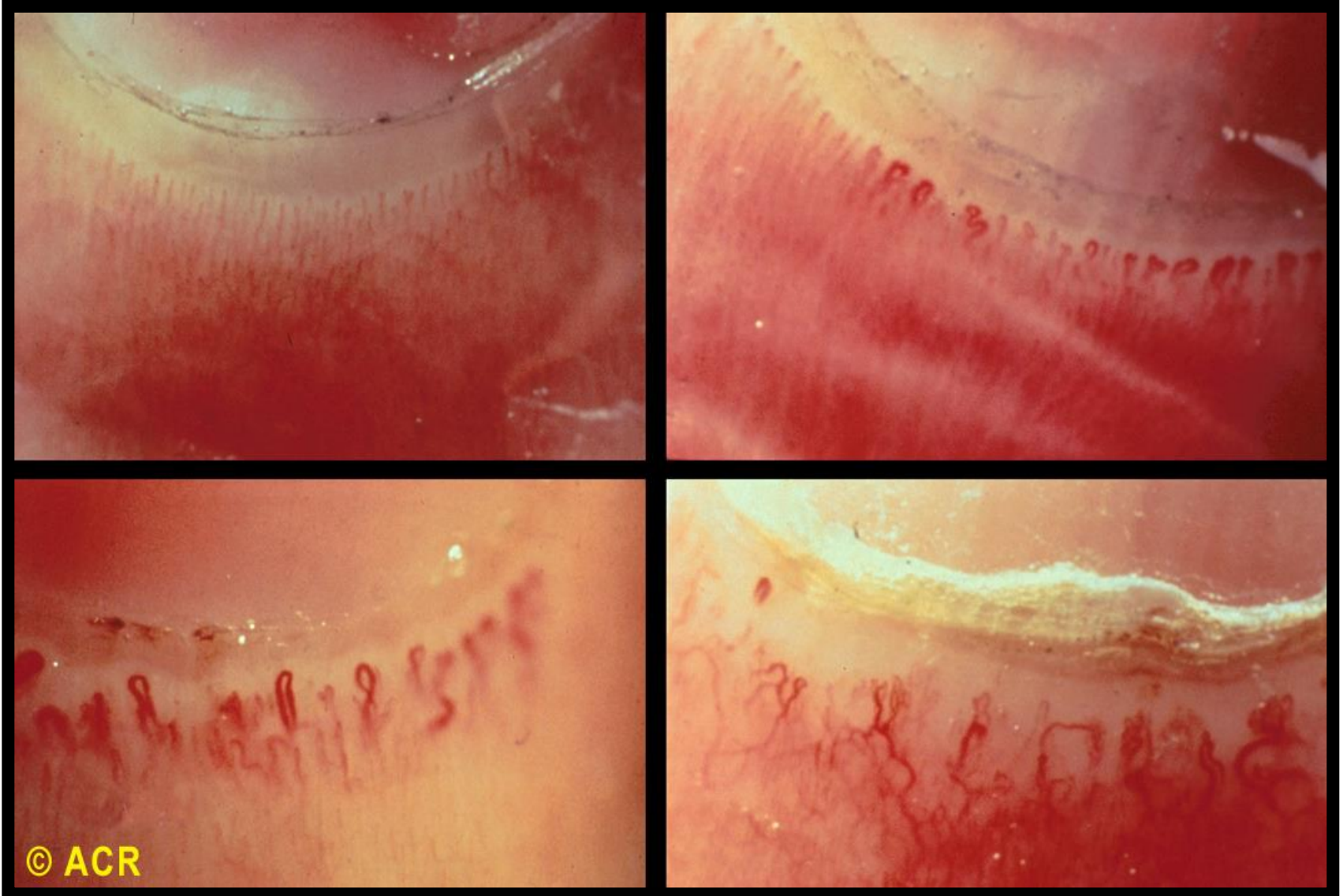
Vinyl chloride, bleomycin, amphetamines,
cocaine

Hyperviscosity/ cold-reacting proteins

Digital Ulcer in SSc



Nailfold Capillaroscopy: Periungual Changes



SSc: Autoantibodies

▶ ANA + in most but not all cases

- Often nucleolar

▶ Anti-centromere

- 50-60% limited SSc (high risk PH>ILD)

▶ Anti-Scl-70 (anti-topoisomerase ab)

- 30% diffuse SSc (high risk ILD)

▶ Anti-RNA polymerase III

- Associated with increased risk of renal crisis and increase risk of malignancy

▶ Other antibodies: anti-DNA polymerase, anti-U3-RNP, anti-PM-Scl and Th/To (ILD)

Autoantibody	Autoantigens	Representative Physiologic Functions of Autoantigens	Prevalence	Associated Clinical Phenotypes
Traditional SSc-Specific ANAs				
Anti-centromere	Centromeric protein	Contains histone H3 and involves epigenetic process	10%–50%	Limited cutaneous SSc PAH CREST DU in late phase
Anti-topoisomerase I	Topoisomerase I	Enzyme that cuts, relaxes, and reanneals one of the two strands of double-stranded DNA.	20%–30%	Diffuse cutaneous SSc ILD DU in early phase
Anti-RNA polymerase	RNA polymerase	Transcription	5%–30%	Diffuse cutaneous SSc Rapid progression of skin-thickening, renal crisis, GAVE, and cancer
Novel SSc-Specific ANAs				
Anti-U3 RNP	Fibrillarin complexed with small nucleolar RNA U3	Pre-rRNA processing localized in the fibrillar region of the nucleolus.	<10%	Both limited and diffuse cutaneous SSc ILD, PAH, renal crisis, and lower GI involvement in early phase
Anti-Th/To	Human RNase MRP complex	Mitochondrial RNA processing; Pre-rRNA processing	<10%	Limited cutaneous SSc ILD PAH
Anti-U11/U12 RNP	Small nucleolar RNA U11/U12	Noncoding RNA in the minor spliceosome complex that activates the alternative splicing	<5%	Both limited and diffuse cutaneous SSc ILD
Novel Functional SSc Antibodies				
Anti-PDGFR	Platelet-derived growth factor receptor	PDGF receptor on fibroblasts	NA	Vasculopathy and ILD
Anti-M3R	Type 3 muscarinic receptor	Acetylcholine receptor on myenteric neurons and visceral smooth muscles	NA	GI dysmotility
Anti-ICAM-1 or AECA	ICAM-1 or endothelial cells	Adhesion molecules on endothelial cells	NA	Vasculopathy
Anti-AT1R	Angiotensin II type 1 receptor	Receptor for angiotensin on visceral smooth muscles	NA	Vasculopathy, ILD
Anti-ETAR	Endothelin-1 type A receptor	Receptor for endothelin A on visceral smooth muscles	NA	Vasculopathy, ILD

SSc: Internal Organ Involvement

► Interstitial lung disease

- ▶ Leading cause of mortality
- ▶ Occurs in 75% diffuse SSc
- ▶ Often within the first 4 years

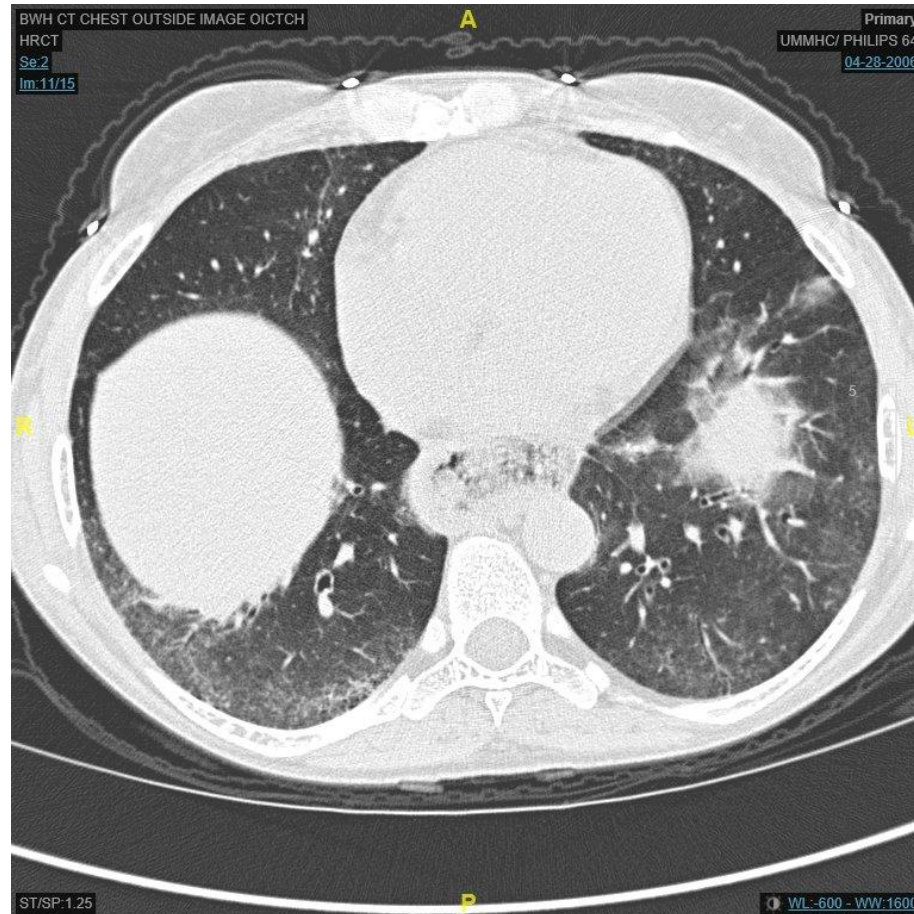
► Pulmonary hypertension

- ▶ More common in limited SSc (10-30%)
- ▶ Usually occurs years into illness
- **Concomitant pulmonary hypertension and ILD**
 - ▶ Extremely challenging clinical scenario
- **Increased rate of malignant lung neoplasms**

SSc: Internal Organ Involvement

- Renal Disease
 - 60-80% diffuse SSc in autopsy studies
 - Microalbuminuria, HTN, mild Cr rise ~ 50%
 - Renal crisis 10-15% (early diffuse SSc)
- Cardiac Involvement
 - Congestive heart failure, myocardial fibrosis (poor prognosis)
 - Pericarditis (10-20%)
 - Arrhythmias
- GI Involvement (90%)
 - Esophageal hypomotility/ LES incompetence
 - Gastroparesis
 - Watermelon stomach (vascular ectasia in the antrum)

Interstitial Lung Disease in SSc



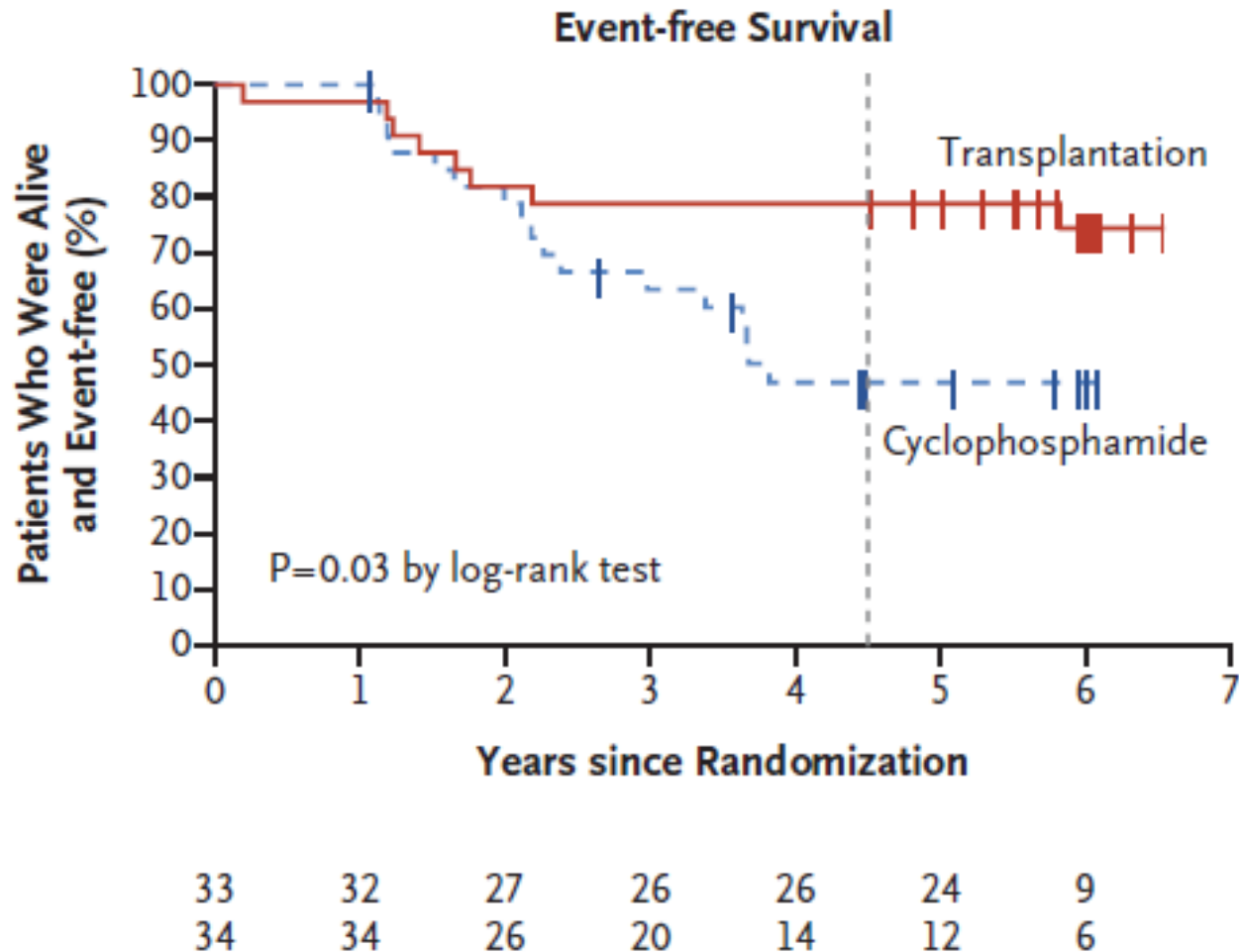
SSc: Esophageal Dysmotility (?Role in ILD)



SSc Treatment: ILD

- Current standard of care
 - Mycophenolate (MMF) :preferred agent
 - Tocilizumab (IL-6) FDA approved in SSc ILD
 - Cyclophosphamide: used less frequently
 - Emerging therapy: **Inhaled treprostinil** for PH-ILD (Waxman et al NEJM 2021)
- Anti-fibrotics in IPF: FDA approved 2014
 - Pirfenidone approved in IPF
 - **Nintedanib: now approved in Scleroderma**
 - **Stem cell transplant in selected patients**

Myeloablative Autologous Stem-Cell Transplantation for Severe Scleroderma



SSc Treatment: There Has Been Progress!

- Renal: ACE inhibitors
- Skin: MTX, MMF, RTX, IL6
- PAH: Prostacyclin, Endothelin antagonists, Phosphodiesterase inhibitors
- Reflux: PPI high dose, anti reflux surgery
- Raynaud's: CCB, Endothelin antagonists, Prostacyclin, Phosphodiesterase inhibitors, Surgery, Botox
- Lung: MMF, antifibrotics, IL-6 RTX and stem cell and lung transplant
- Cell based therapies CAR T Therapy
- Newer antifibrotics (Neramdomilast)

Checkpoint inhibitor- Systemic Sclerosis

Less Raynaud's

Often ANA negative

Scleroderma specific antibody
negative (Anti-Scl-70, RNA
Polymerase III, Centromere)

No particularly known
association with pulmonary
hypertension or ILD

Primary Systemic Sclerosis

Raynaud's very common

Vast majority ANA positive

More often scleroderma specific
antibody positive (Anti-Scl-70,
RNA Polymerase III, Centromere)

Morbidity of pulmonary
hypertension and ILD

Microstomia

Sclerodactyly

Body skin
thickening

ANA: Antinuclear antibody, Anti-Scl-70: Antibody to the scleroderma 70kD extractable immunoreactive fragment from topoisomerase antigen, RNA: Ribonucleic acid, ILD: Interstitial lung disease

Pharmaceuticals
2023, 16(2),
259; <https://doi.org/10.3390/ph16020259>

Key Points in Scleroderma

- ILD remains the leading cause of mortality
- Pulmonary HTN is a complication of long standing limited SSc; screening is essential as treatments are available that improve morbidity
- Renal Crisis requires early recognition and prompt initiation of ACE inhibitor
- **Raynaud's that develops > age 35 raises concern for a rheumatic disease**
- The presence of concomitant Raynaud's and GERD should raise suspicion for limited SSc
- Therapies exist to help control disease progression but better therapies are needed.

Sjögren's Disease

- Autoimmune disorder characterized by salivary and lacrimal gland dysfunction
 - Decreased production of tears and saliva
- Primary and secondary
- Prevalence primary SS = 2-10 per 10,000
- Pathophysiology
 - Proliferation and infiltration of lymphocytes in exocrine glands
 - Autoantibody production: ANA positive in most cases though Ro (inc Ro 60 kD and Ro 52 kD) and La antibody + in about 60% of cases

Sicca Syndrome Manifestations

Keratoconjunctivitis sicca

Ocular dryness

Corneal injury

Xerostomia

Oral dryness, dysphagia

Dental caries, thrush

Nasal dryness and epistaxis

Vaginal dryness

Dyspareunia

Classification Criteria for Primary SjD

Item	Weight/Score
Labial salivary gland with focal lymphocytic sialadenitis and focus score of ≥ 1 foci/4 mm ²	3
Anti-SSA/Ro positive	3
Ocular Staining Score ≥ 5 in at least 1 eye	1
Schirmer's test ≤ 5 mm/5 min in at least 1 eye	1
Unstimulated whole saliva flow rate ≤ 0.1 mL/min	1

Score of ≥ 4 needed to establish dx

* exclusions: active hepatitis, head/neck xrt, sarcoidosis AIDS, amyloidosis, IgG4-related disease

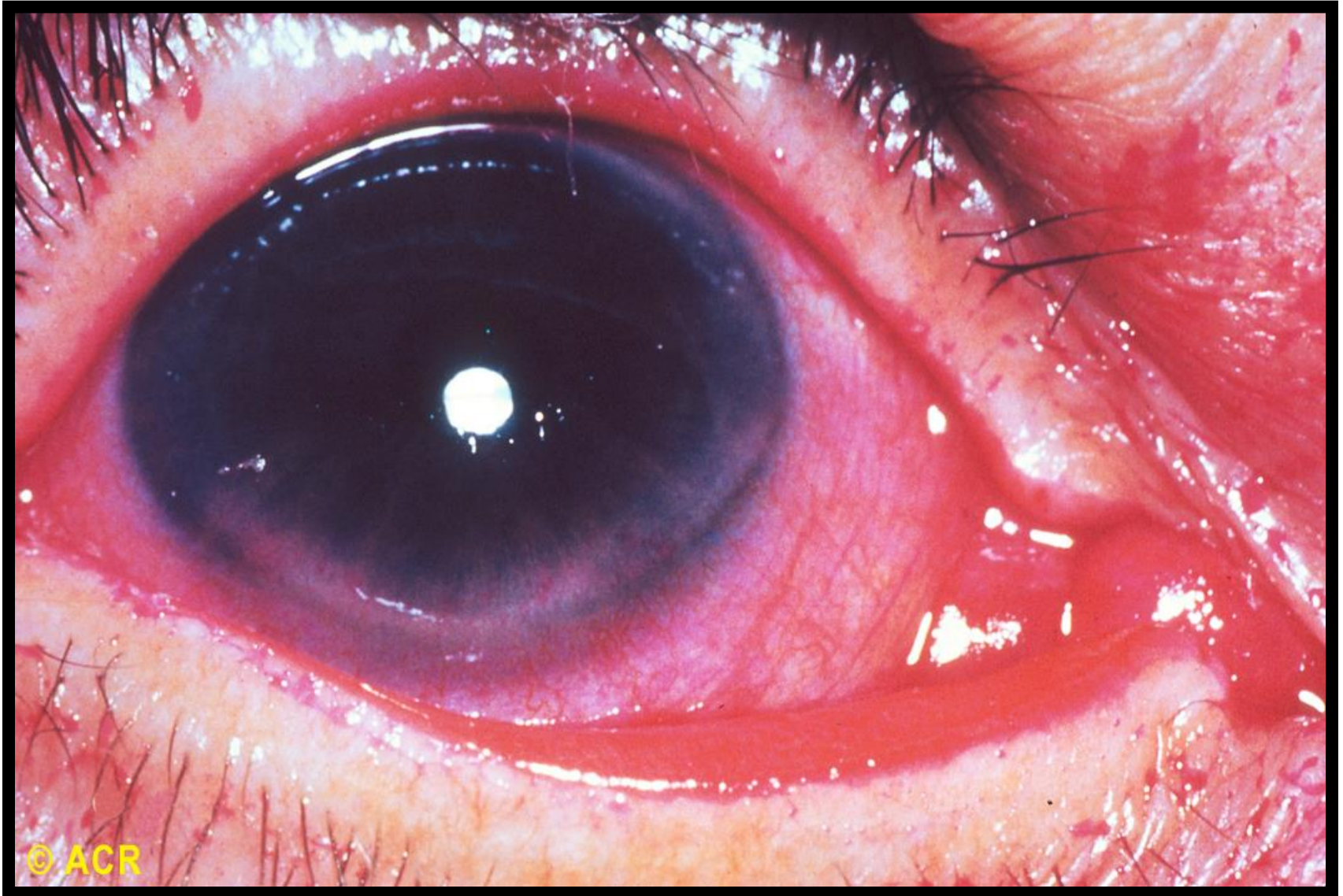
SjD: Parotid Gland Enlargement



In patients with sicca and/or salivary and lacrimal gland enlargement: other considerations

- Lymphoma
- Hepatitis C
- HIV infection
- Sarcoidosis
- IGG4 disease
- Graft versus host disease

SjD: Corneal Abrasions



SjD: Salivary Hypofunction



Primary SjD :Extraglandular Disease

- Peripheral neuropathy
- Vasculitis
- Interstitial lung disease (LIP, NSIP)
- Synovitis
- Risk factors for more aggressive disease: +RF, low C4, cryoglobulinemia
- Increased risk of lymphoma

50 yo with Known SjD with 8 lb Weight Loss
Lung biopsy c/w Marginal Zone Lymphoma



SjD: Associated Conditions

Connective tissue diseases

SLE

RA

Systemic sclerosis

Hypothyroidism

Cryoglobulinemia

Autoimmune hepatitis

Sjögren's Disease/Syndrome: Treatment

- Exocrine gland dysfunction
 - Xerostomia: oral hygiene and agents to stimulate salivary secretion (pilocarpine/muscarinic agonist)
 - KCS: cellulose products to augment tear replacement and topical cyclosporine
- Treatment of extraglandular disease is difficult
 - Trials are ongoing
- Hydroxychloroquine may be useful in those with fatigue and arthralgias

Key Points About Sjögren's Disease

- Higher risk of non-Hodgkins lymphoma in primary Sjögrens (up to 44 fold or 5% lifetime)
- ANA positive in most cases though Ro (Ro 60 and Ro 52) and La antibody + in about 60% of cases
- Most cases are secondary to other rheumatic diseases
- Treatment geared towards managing sicca symptoms and promoting oral hygiene
- Treatment of extraglandular disease is challenging
- Patients with low titer ANA, fatigue, and eye or mouth dryness are a significant challenge diagnostically
- Novel treatments are emerging



CD40 ligand antagonist dazodalibep in Sjögren's disease: a randomized, double-blinded, placebo-controlled, phase 2 trial

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Scientific Abstracts
Late Breaking Abstracts

LBA0010 EFFICACY AND SAFETY OF NIPOCALIMAB, AN ANTI-FcRn MONOCLONAL ANTIBODY, IN PRIMARY SJOGREN'S DISEASE: RESULTS FROM A PHASE 2, MULTICENTER, RANDOMIZED, PLACEBO-CONTROLLED, DOUBLE-BLIND STUDY (DAHLIAS)

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Inflammatory Myopathies

- Group of autoimmune disorders
 - Common feature = immune-mediated muscle injury
 - Usually present with muscle weakness and elevated muscle enzymes (CK/aldolase)
- Disorders include
 - Dermatomyositis (DM)
 - Polymyositis (PM)
 - Overlap myositis (with another systemic rheumatic disease)
 - Inclusion body myositis (IBM)
 - Necrotizing autoimmune myositis (NAM)
- Histopathologic and clinical distinctions

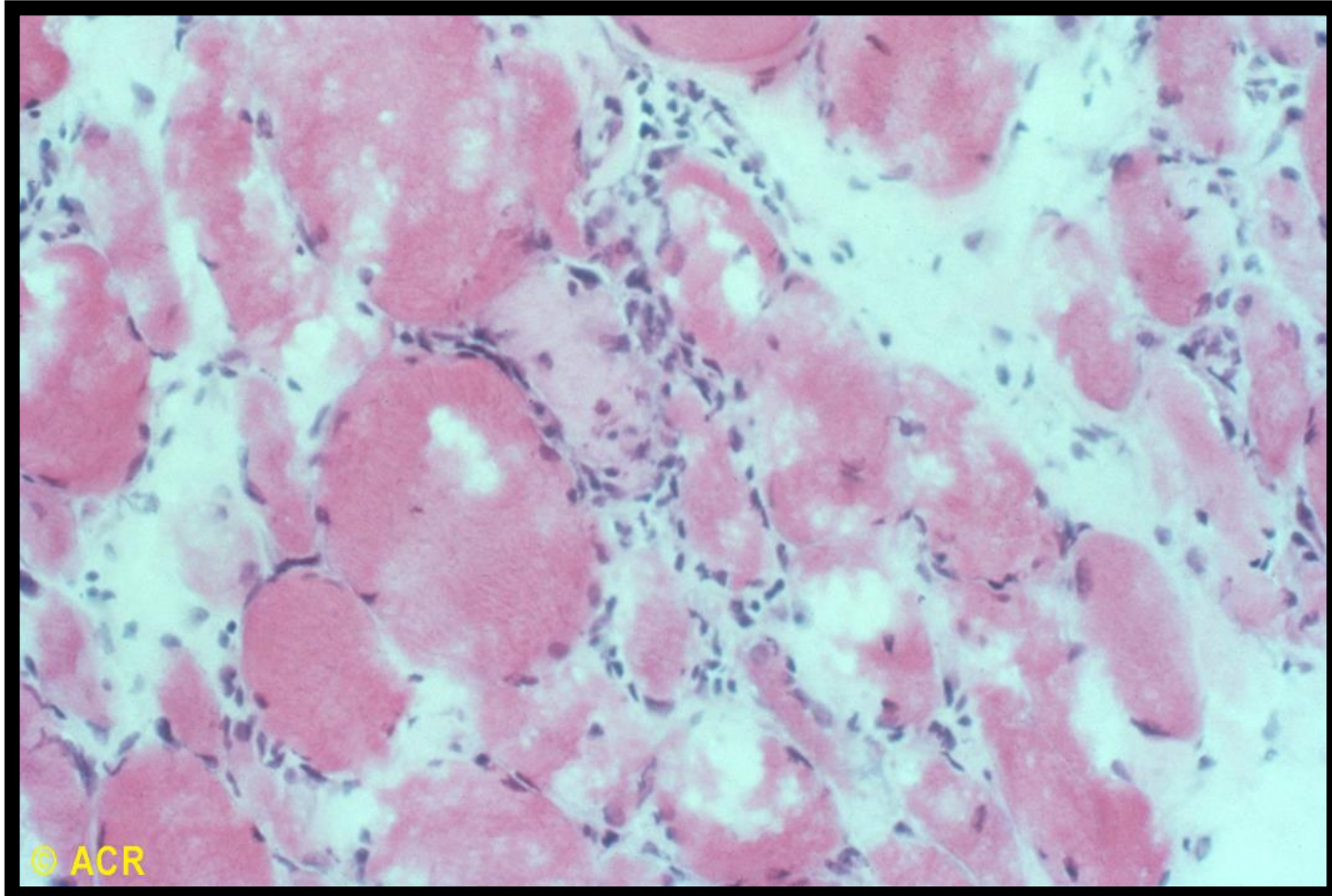
Inflammatory Myopathies: DDx

- Inflammatory myopathies
- Drug-induced myopathies
 - Steroids
 - Statins
 - Colchicine
 - Hydroxychloroquine
 - Alcohol
 - Zidovudine
- Infections
 - Viral
 - Toxoplasmosis
 - Trichinosis
 - Bacterial pyomyositis
- Systemic vasculitis
 - PAN, GPA, eGPA
- Amyloid myopathy
- Sarcoid myopathy
- Metabolic myopathies
 - Disorders of carbohydrate and lipid metabolism
- Hypothyroidism
- Electrolyte disturbances
 - Hyper/hyponatremia
 - Hypokalemia
 - Hypophosphatemia
 - Hypocalcemia
- Neurologic disorders
 - Myasthenia gravis
 - Motor neuron disease
 - Muscular dystrophy

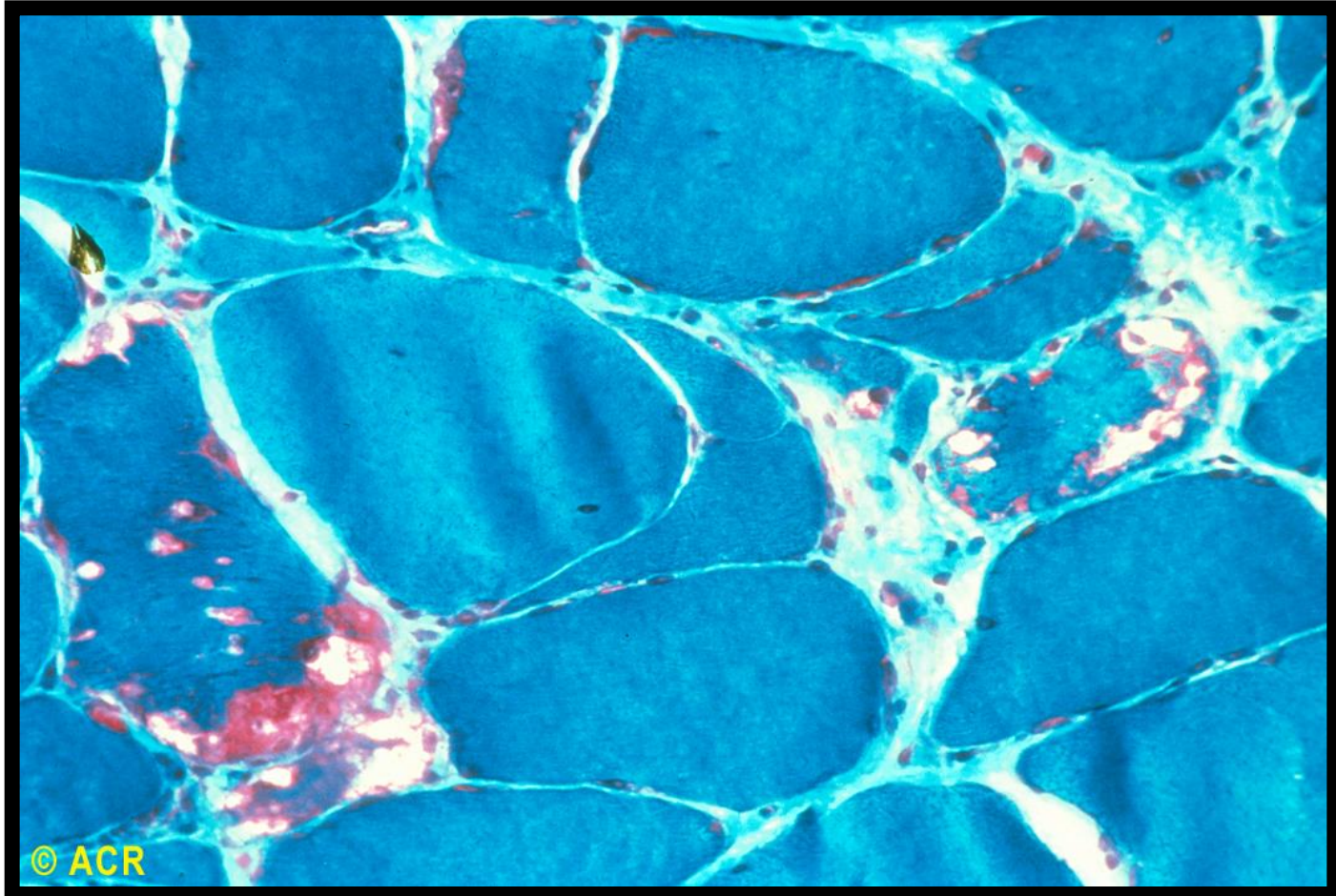
Inclusion Body Myositis v Idiopathic Inflammatory Myopathy

	Inclusion Body Myositis	IIM
Sex	Male > female	Female > male
Age	Usually > 50	Common before 50
Onset	Slowly progressive	Acute or sub-acute
Weakness	Distal and asymmetric muscle weakness	Proximal and symmetric
EMG	Myopathic and neuropathic changes	Myopathic changes
Muscle biopsy	Mononuclear cell infiltrates and vacuoles containing amyloid	Inflammation, fiber necrosis
Response to immunosuppression	Generally poor	Generally good

IIM (Photomicrograph)



Inclusion Body Myositis (Photomicrograph)



DM and PM: Clinical Features

- Proximal muscle weakness
 - > 90% PM patients
 - 50-60% DM patients at presentation; skin features may precede weakness
 - Amyopathic DM
- Skin findings
 - Classic DM
 - Not found in PM

DM: Gottron's Papules



DM: Heliotrope Rash





DM: Poikiloderma (Shawl and V Signs)



DM: Nailbed



DM and PM: Clinical Features

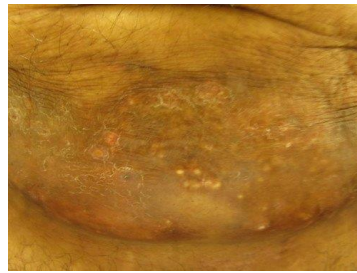
- Interstitial Lung Disease
- Cardiac disease
 - Myocarditis—frequently subclinical
 - 3-4x increased risk MI
- Esophageal disease
 - Weakness of striated muscle of upper 1/3rd of esophagus → aspiration

DM and PM: Autoantibodies

~ 80% ANA +

Myositis-specific autoantibodies	Clinical syndrome	Prevalence
Antisynthetase antibodies, including anti-Jo-1	Antisynthetase syndrome	20%
Anti-signal recognition particle (SRP)	Severe myopathy, aggressive disease that may be difficult to control	5%
Anti-Mi-2	Acute onset DM, classic skin findings, good prognosis	7-30%
<i>Anti-MDA-5</i>	<i>Rapidly progressive ILD, cutaneous ulceration involving Gottron's papules, arthritis, alopecia, oral ulcers, amyopathic</i>	

Phenotype skin MDA 5: high risk of rapidly progressive ILD inc AIP pattern



Narang et al
Arthritis Care
2015;67(5)



Antisynthetase syndrome: look for this in folks with “recurrent pneumonia”

Fever

- Raynaud's
- Inflammatory arthritis
- ILD (can be severe)
- *Mechanics hands*



Teaching Phenotypes: Look at the hands! Look at the skin!



Antisynthetase Syndrome



Fever
Raynaud's
Inflammatory
Arthritis
Mechanics



Solomon et al (2011) ⁽¹⁰⁾

Required: Presence of anti-aminoacyl tRNA synthetase antibody

PLUS two major or one major and two minor criteria:

Major:

1. Interstitial Lung Disease (not attributable to another cause)
2. Polymyositis or dermatomyositis by Bohan and Peter criteria

Minor:

1. Arthritis
2. Raynaud's phenomenon
3. Mechanic's hands

Treatment Regimens in IIM

- ▶ Corticosteroids (often with DMARD)
- ▶ DMARDs
 - Methotrexate
 - Calcineurin inhibition (Tacrolimus)
 - Azathioprine
 - Mycophenolate
- ▶ Cyclophosphamide (mostly in ILD)
- ▶ Rituximab (recent trial efficacy unclear but may be useful in antisynthetase syndrome)
- ▶ IVIG (FDA approved PRODERM trial)
- ▶ Abatacept (T cell co-stimulatory inhibitor)
- ▶ JAK inhibitors in MDA 5 ILD. Emerging as a primary Rx option given data focusing on targeting interferon

- **Scleroderma**

- Recognize clinical patterns
- Major morbidity/mortality = lung disease
- There are newer treatment options!

- **Sjögrens syndrome**

- Recognize clinical manifestations
- Sometimes marked by systemic disease
- Higher risk for lymphoma

- **Inflammatory myopathy**

- Recognize clinical patterns
- Newer antibodies may help with diagnosis
- Major morbidity = lung disease

Board Question #1

- ▶ 53 yo female with 20 year hx of Raynaud's develops fatigue and dyspnea over the preceding 6 months
- ▶ On Nifedipine
- ▶ BP 115/80
- ▶ Exam notable for prominent P2
- ▶ Scattered telangectasias on hands and face
- ▶ PFTs show DLCO 48% predicted (low)
- ▶ O₂ sat is 96% rest, 93% with activity (abnormal)
- ▶ Echo shows mild TR, est RVSP 48 mmHg

Board Question #1

What is the appropriate next test for this patient?

- A. CT angiogram of the chest
- B. HRCT of the chest
- C. Pulmonary artery catheterization
- D. Exercise stress test

Board Question #1

- Correct answer: C
- The longstanding history of Raynaud's raises the question of a CTD and the telangiectasias are seen in CREST
- Given the decline in DLCO and echo findings, PAH remains the greatest concern and the patient needs to get a right heart catheterization to confirm the diagnosis.

Board Question #2

- 51 yo man with diffuse cutaneous SSc is admitted with new onset hypertension associated with anemia and thrombocytopenia
- On admission: BP 180/105; skin thickening over face, chest, hands, legs; lungs clear; heart RRR normal S1 S2; 1+ edema in legs

Board Question #2

- Hgb 9.8 Plt 101K Cr 1.4
- UA 2+ protein, no casts
- Smear: 2+ schistocytes
- Started on captopril 6.25mg every 8hrs
- Captopril escalated to 25 mg every 8hrs
- 3 days later, BP 140/95, Cr now 2.1
- UA 2+ protein

Board Question #2

Which of the following is the most appropriate next step?

- A. Discontinue captopril, begin nifedipine
- B. Continue to increase the captopril
- C. Start plasmapheresis
- D. Angiography to assess for RAS
- E. Order the RNA polymerase III ab

Board Question #2

- Correct answer: B
- This patient has systemic sclerosis with diffuse skin disease and is at significant risk for renal crisis which is the case here. Despite the continued increase in creatinine, the ACE inhibitor should be continued.
- The RNA polymerase III ab confers increased risk for renal crisis

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