Update in Rheumatic Diseases
Scleroderma/Sjogren's/Myositis

• Intensive Review of Internal Medicine
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Outline
• Scleroderma: clinical patterns and newer
  treatment options
• Sjogren's syndrome: clinical manifestations and
  treatment options
• Myositis: classification, diagnosis and
  treatment

Systemic Sclerosis
(Scleroderma)
• Complex systemic disease that affects
  predominately the skin, lung, kidney, heart and GI
  tract
• Incidence of 19 cases per million.
• Pathophysiology due to a combination of factors
  that include vascular and endothelial dysfunction,
  autoimmunity, and fibroblastic activation and
  proliferation.
• Survival is 50% 10 years for diffuse disease, >70% for
  limited cases.

Classification of Scleroderma

- Localized scleroderma
  • Morphea
  • Linear scleroderma
  • “En coup de sabre”
- Systemic sclerosis
  • Diffuse cutaneous
  • Limited cutaneous
  • CREST syndrome
  • Systemic sclerosis sine scleroderma
- Overlap syndromes

Forms of SSc-Like Syndromes
• Toxin induced scleroderma (vinyl chloride,
  organic solvents, epoxy resins)
• Eosinophilic myalgia syndrome (L-
  tryptophan)
• Bleomycin
• Toxic oil syndrome
• Vibration injury
• Scleromyxedema
Scleroderma: clinical features

- Skin: more edematous early, thickened, hard later in disease. Proximal to forearm seen in diffuse disease
- Renal: hypertensive crisis, hemolysis, renal failure
- Interstitial lung disease
- Pulmonary hypertension
- Reflux, dysmotility and blind loop syndrome

Scleroderma: laboratory features

- ANA positive in nearly all cases
- Scl-70 antibody (anti-topoisomerase ab) noted in diffuse SSc, anti-centromere pattern
  ANA noted in limited SSC, but neither test very sensitive
- Anti-polymerase III (increased risk of renal crisis), anti Th/To
- Nucleolar pattern noted in scleroderma
- Other antibodies noted include anti-DNA polymerase, U3-RNP, and anti-PM-Scl often seen in overlap disease.

Raynaud’s phenomenon

- Episodic, reversible digital skin color change
  - white to blue to red
  - well-demarcated
- Due to vasospasm
- Usually cold-induced
- Primary (Raynaud’s disease) and secondary forms

Causes of secondary Raynaud’s phenomenon

- Connective tissue diseases
  - Scleroderma, systemic lupus erythematosus, MCTD, undifferentiated CTD, Sjogren’s syndrome, dermatomyositis
- Occlusive arterial disease
  - Atherosclerosis, anti-phospholipid antibody syndrome, Buerger’s disease
- Vascular injury; Frostbite, vibratory trauma
  - Beta blockers, vinyl chloride, bleomycin, ergot, amphetamines, cocaine
- Hyperviscosity/cold-reacting proteins
  - Paraproteinemia, polycythemia, cryoglobulinemia, cryofibrinogenemia, cold agglutinins
Dermatomyositis and scleroderma: periungual involvement (nailfold capillaroscopy)

Puffy hands of early scleroderma
Scleroderma: acrosclerosis and terminal digit resorption

CREST syndrome: calcinosis cutis, fingers

Scleroderma: Mauskopf, facial changes

Interstitial lung disease in SSc

Scleroderma: abnormal motility esophagus

Scleroderma: digital artery (photomicrograph)
**Treatment in scleroderma:**
There has been progress!

- Interstitial lung disease (modest improvement in lung function/skin scores with cyclophosphamide)
- Renal: ACE inhibitors
- Pulmonary hypertension: prostacyclin, endothelin antagonists, sildenafil
- Reflux: PPI high dose, anti-reflux surgery
- Raynauds: endothelin antagonists, sildenafil, prostacyclin, statins
- Stem cell transplant, lung transplant, tyrosine kinase inhibition

**New therapies in fibrotic diseases**

- Complications of scleroderma are increasingly better managed
- Recognize the presence of concomitant Raynauds and GERD as a possible clinical manifestation of underlying limited scleroderma and therefore the potential for longterm risk of pulmonary hypertension
- Pulmonary hypertension is a complication of long standing scleroderma of mostly the limited variant and treatment that improve morbidity and possible mortality are available now.
- Raynauds that develops in an adult after age 35 is a concern for the development of a rheumatic disease

**Key points in Scleroderma**

- 53 yo female with 20 year hx of Raynauds develops fatigue and dyspnea over the preceding 6 months
- On nifedipine
- BP 115/80
- Exam notable for prominent P2
- PFTs show DLCO 48% predicted
- O2 sat is 96% rest, 93% with activity
- Echo shows mild TR, systolic PAP est. 48 mmHg

**Board question**

- 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

- Correct answer: C
Board question

- 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 and legs. Lungs clear Heart RRR nml S1 S2. 1+ edema in legs.

Laboratory

- Hgb 9.8 Plt 101K BUN 32 Cr 1.4
- Urine: 2+ protein, no casts
- Smear: 2+erythrocyte fragment and schistocytes.
- Pt started on captopril 6.25 mg every 8 hrs,
- Captopril escalated to 25 mg every 8hrs
- 3 days later, BP 140/95, Cr now 2.1.
- UA shows 2+protein

Which of the following is the most appropriate next step?

- A Discontinue captopril, begin nifedipine
- B Continue to increase the captopril
- C. Perform plasmapheresis
- D. Perform angiography to assess for RAS

Correct answer: B

Sjogrens syndrome

- Autoimmune disorder characterized by salivary and lacrimal gland dysfunction and decreased production of tears and saliva. The disease is characterized by proliferation and infiltration of lymphocytes of exocrine glands. Autoantibody production and the role of B cells in the pathophysiology of this disease are the source of ongoing investigation.

Criteria for the classification of SS

- Ocular Symptoms, Oral Symptoms (sicca)
- Ocular Signs
  - Schirmer ≤ 5 mm/Rose Bengal score ≥ 4
- Histopathology ≥ 1 agglomeration of 50 or more mononuclear cells/4mm
- tissue (focus score)
- Objective evidence of salivary gland involvement
- Autoantibodies (4 or > high sensitivity and specificity)SSA/Ro, SSB/La, ANA, RF
- Exclusions: lymphoma, sarcoid, GVH, acquired immune deficiency
Sicca syndrome manifestations
- Keratoconjunctivitis sicca
  - Ocular dryness, corneal injury
- Xerostomia
  - Oral dryness, dysphagia
  - Dental caries, thrush
- Nasal dryness and epistaxis
- Vaginal dryness
  - Dyspareunia
  - Candidiasis

Systemic manifestations of primary SS
- Peripheral neuropathy
- Vasculitis
- Interstitial lung disease
- Synovitis

Sjögren’s syndrome: associated conditions
- Connective tissue diseases
  - SLE
  - RA
  - Systemic sclerosis
- Hypothyroidism
- Cryoglobulinemia
- Autoimmune hepatitis
Key points about Sjogrens

• Higher risk of non Hodgkins lymphoma in primary Sjogrens (up to 44 fold)
• Most cases are secondary to other rheumatic diseases
• Treatment is geared to oral hygiene and agents to stimulate salivary secretion ( pilocarpine/muscarinic agonist ) and cellulose products to augment tear replacement, topical cyclosporine
• Treatment of systemic manifestations of SS are difficult and the source of ongoing trials, mostly in the area of B cell directed therapy.
• Patients with low titer ANA, fatigue, and eye or mouth dryness are a significant challenge diagnostically.

Inflammatory myositis

• Polymyositis
• Dermatomyositis
• DM sine myositis
• Inclusion body myositis

Proposed diagnostic criteria for polymyositis and dermatomyositis

• PM diagnosed as definite with 4 out of 5 of the below criteria or probable with 3 out of 5
• DM diagnosed as definite with rash plus 3 out of 4 of the below criteria or probable with rash plus 2 out of 4 criteria
  — Symmetric proximal muscle weakness
  — Elevated muscle enzymes (CPK, aldolase, transaminases, LDH)
  — Myopathic EMG abnormalities
  — Typical changes on muscle biopsy
  — Typical rash of dermatomyositis

Inflammatory myositis: differential diagnosis

• Polymyositis and dermatomyositis
• Hypothyroidism
• Drug-induced myopathies (steroids, colchicine, statins, hydroxychloroquine,alcohol,zidovudine)
• Infections
  — Viral, toxoplasmosis, trichinosis, bacterial pyomyositis
• Connective tissue disorders
  — Lupus, scleroderma, MCTD
• Systemic vasculitis
  — PAN, Wegener’s granulomatosis

Polymyositis: differential diagnosis, cont’d

• Metabolic myopathies
  — Disorders of carbohydrate and lipid metabolism
• Electrolyte disturbances
  — Hypernatremia, hypotremia, hypokalemia, hypophosphatemia, hypocalcemia
• Inclusion body myositis
• Sarcoid myopathy
• Amyloid myopathy
• Neurologic disorders
  — Myasthenia gravis, motor neuron disease, muscular dystrophy

Pathophysiology

• DM: humoral based immunity. Inflammation is typically located near vascular structures. Complement deposition
• PM: T cell mediated. Inflammation within muscle fibers
Inflammatory myopathy

(photomicrograph)

Inclusion body myositis

• Males affected more than females
• Age of onset usually greater than 50
• Slowly progressive
• Distal and asymmetric muscle weakness
• Myopathic and neuropathic changes on EMG
• Mononuclear cell infiltrates and vacuoles

Inclusion body myositis

(photomicrograph)

Steroid myopathy: muscle

(photomicrographs)

Newer classification

• Inclusion body myositis (IBM)
• DM (prob or definite)
• PM (prob or definite)
• Amyopathic DM
• Nonspecific myositis
• Necrotizing myopathy

Gottrens papules
Dermatomyositis: heliotrope rash

Dermatomyositis: diffuse facial erythema

Dermatomyositis: erythematous lesions, hands

Dermatomyositis: nailbed
Dermatomyositis: “mechanic’s hands”

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Antisynthetase syndrome

- Fever
- Raynauds
- Inflammatory Arthritis
- Mechanics hands
- ILD

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ILD in patient with DM

Deforming arthropathy in DM

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Diagnosis

- Physical examination
- MRI (increased signal on fat suppressed images)
- EMG (spont fibrillations, low amp/short duration motor and complex repetitive discharges)
- Muscle biopsy
- Skin biopsy
- Laboratory testing (elevated CK, aldoalse, sometimes liver enzymes)

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Localized nodular myositis: thigh (MRI)
Treatment Regimens in IMM

- Corticosteroids (sometimes alone but often in combination with DMARD)
- Methotrexate
- Calcineurin Inhibition (tacrolimus)
- Azathioprine
- Cyclophosphamide (ILD)
- Rituximab (recent trial efficacy unclear)
- IVIG (useful in refractory cases $$$)
- Abatacept (T cell co stimulatory inhibitor)

References

5. Connors GR, Christopher-Stine L, Oddis CV, Danoff SK. Interstitial lung disease associated with the idiopathic inflammatory myopathies: what progress has been made in the past 35 years. Chest 2010;138(3):864-74