38 year old woman presents with 3 months of progressive fatigue and dyspnea that limits her ability to climb the steps in her two story house. Her past medical history is remarkable for a ten year history of Raynaud’s phenomenon which is treated with nifedipine.

Blood pressure – 130/75, Pulse 90, Respiratory Rate 14, Pulse oximetry 92% on Room Air.

Physical exam reveals clear lungs bilaterally, and an S3. Skin is remarkable for palmar and facial telangiectasias and thickening of the skin overlying the fingers.
Pretest

- Chest radiograph, EKG, and CBC are normal
- What additional test would you order for the patient?
- Consider your Diagnosis
Overview

- Definitions
- Manifestations of Scleroderma
  - Cutaneous
  - Extracutaneous
- Treatment
Scleroderma

- Skleros derma – hard skin
- Prevalence 150/1,000,000
- Women:Men::3:1
- Etiology Unknown
  - Possible genetic predisposition with environmental trigger
- Treatment - evolving
  - 1753 – ‘bloodletting, warm milk, and small doses of quicksilver’
Pathophysiology

- **Autoimmunity**
  - Autoantibody production (ANA, SCI-70, anti-centromere), B and T cell activation

- **Fibrosis**
  - Increased production of collagen, glycosaminoglycan and fibronectin
  - Scleroderma fibroblasts contain a higher percentage of fibroblasts resistant to anti-Fas-mediated killing - ?apoptosis defect
Pathophysiology

Vascular changes
- Endothelial injury
- Intimal proliferation
- Alterations in vasoactive substances
- Platelet aggregation – induced by cooling
Cross Section of Pulmonary Arteriole in a Patient with Scleroderma
HYPOTHETICAL SCHEME OF THE PATHOGENESIS OF SYSTEMIC SCLEROSIS

Endothelial activation and injury → Inciting events → Immune cell activation

- Autoantibodies
- B cells
- LAK cells
- T-cells
- IL-2
- Macrophages
- TGF-β
- PDGF
- Fibroblasts and smooth muscle cells
- Extracellular matrix substances

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Classification

- Diffuse Scleroderma/systemic sclerosis
- Limited Scleroderma or CREST Syndrome
  - Calcinosis, Raynaud’s, Esophageal dysmotility, Sclerodactyly, Telangtasia
- Scleroderma *sine* Scleroderma
- Morphea or Linear Scleroderma
Antibodies in Scleroderma

- Anti-nuclear antibody (ANA)
  - Present in 90% of SSc pts

- Anti-DNA topoisomerase I (Scl-70)
  - Present in 20-40% of dSSc pts

- Anti-centromere antibodies
  - Present in 50-96% of ISSc pts
Cutaneous Manifestations

- Puffy hands – seen in early stages of disease
- Pruritis
Cutaneous Manifestations

- Sclerodactyly – skin thickening distal to metacarpal-phalangeal joints
- Telangiectasias
Cutaneous Manifestations

- Hypopigmentation
Cutaneous Manifestations

- Calcinosis cutis
Extracutaneous Manifestations of Scleroderma

- Vascular
- GI
- Renal
- Cardiac
- Pulmonary
Vascular Manifestations

Raynaud’s

- Hypoperfusion of digits secondary to
  - Vascular hyperreactivity
  - Underlying vasculopathy
  - Platelet activation
- Typical sequence – white, blue, red
- Severe cases can progress to ulceration/amputation
- Primary Raynaud’s – typically benign
Raynaud’s
Raynaud’s with digital ulcers and amputation
Raynaud’s Treatment

- Environmental Modifications
  - Smoking cessation
  - Cold avoidance

- Vasodilators
  - Calcium channel blockers
  - Nitroglycerin
  - Hydralazine
  - Minoxidil
  - Sildenafil
  - Bosentan

- Antiplatelet agents
  - Aspirin
  - Dypiradimole

- Anticoagulation
  - Heparin
  - Coumadin

- Sympathectomy
GI Manifestations

- Gastroesophageal Reflux
- Esophageal strictures
- Barrett’s esophagus

- Watermelon stomach
GI Complications

- Widemouth diverticula
- Bacterial overgrowth
- Chronic constipation
Renal Manifestations

Scleroderma Renal Crisis

- Seen in rapidly progressing diffuse disease
- Can be precipitated by corticosteroids

Features
- Rapidly progressive hypertension
- Schistocytes
- +/- proteinuria

Treatment – ACE Inhibitors

- 24% 1 yr mortality
Cardiac Manifestations

- Common
  - Seen in 80% autopsy cases
  - Clinically evident in 20-25%
- Often asymptomatic until advanced disease
  - 2 year survival 40%
  - 3 year survival 25%
- Collagen infiltration of myocardium
- Microvascular disease
Intramyocardial arteriole with intimal proliferation and surrounding myocarditis
Cardiac Manifestations

- **Arrhythmias**
  - Premature ventricular contractions
    - most common
  - Premature atrial contractions
  - Supraventricular tachycardia
  - Intraventricular conduction delays

- **Pericardial Disease**
  - Pericarditis
  - Pericardial effusion
Cardiac Manifestations

Myocardial Involvement

- Myocardial fibrosis
  - Secondary to ischemia/reperfusion vs. collagen infiltration
- Diastolic dysfunction
- Myocarditis
  - Can be associated with inflammatory muscle disease
- Congestive heart failure
Pulmonary Manifestations

- Interstitial Lung Disease (ILD)
- Pulmonary Fibrosis
- Pulmonary Artery Hypertension (PAH)
  - Primary
  - Secondary
Pulmonary Manifestations

- Aspiration pneumonitis
- Endobronchial telangiectasias
- Pulmonary Hemorrhage
- Bronchiolitis Obliterans with Organizing Pneumonia
Interstitial Lung Disease

- Pulmonary symptoms can parallel progression of skin disease
- Dyspnea, dry cough
- ‘velcro’ rales on auscultation
- Chest radiograph insensitive in early disease
- Spirometry with diffusion capacity and lung volumes most sensitive for early detection
Interstitial Lung Disease

- High resolution CT
  - Ground glass appearance

- Bronchoclar alveolar lavage
  - Neutrophils and eosinophils
Interstitial Lung Disease

- Can progress to pulmonary fibrosis and secondary PAH
Interstitial Lung Disease

**Treatment**

- **Scleroderma Lung Study**
  - Cyclophosphamide + prednisone
    - Improved exercise capacity
    - Attenuation of FVC decline
    - No improvement in overall survival
    - Considerable toxicity

- **Mycofenalate mofetil**
  - Pilot study (2/06) demonstrating improvement in breathlessness, diffusion capacity, vital capacity, and ground glass appearance on CT
Pulmonary Arterial Hypertension

- PAH seen in 12% of SSc patients
- PAH/SSc survival
  - 1 yr – 45%
  - 2 yr – 35%
  - 3 yr – 28%
- Insidious progression of dyspnea and fatigue
Pulmonary Arterial Hypertension

Physical findings
- Loud pulmonic component of S2
- S3 gallop
- Signs of right sided heart failure
  - Increased jugular venous distention, hepatomegaly, edema

Diagnosed with Doppler echocardiogram and confirmed with right sided coronary catheterization
PAH Treatment

- Calcium Channel Blockers
- Anticoagulants
- Endothelin antagonists
  - Nonselective
  - selective
- Phosphodiesterase type 5 inhibitors
- Prostacyclin analogs

- Atrial septostomy
- Transplant
  - Single lung transplant
  - Heart-lung transplant
PAH Treatment

Prostacyclins analogs
- Induces vascular smooth muscle relaxation via cAMP production
- Inhibits smooth-muscle cell growth
- Inhibits platelet aggregation

Flolan (epoprostanol)
- Continuous intravenous infusion

Remodulin (treprostinil sodium)
- Continuous subcutaneous infusion
PAH Treatment

- Bosentan (Tracleer)
  - Endothelin receptor analog
  - Inhibits endothelin mediated vasoconstriction of pulmonary circulation
  - Inhibits vascular remodeling, cellular proliferation, and fibrosis
PAH Treatment

- Bosentan (Tracleer)
  - Increases exercise capacity
  - Reduces pulmonary vascular resistance
  - Open label extension studies
    - SSc/PAH survival
      - 1 yr – 82%
      - 2 yrs – 66%
      - 3 yrs – 65%
PAH Treatment

Endothelin Receptor Antagonist-receptor blockers
- Sitaxsentan
- Ambrisentan

Pilot studies (12-18 weeks)
- improvement in exercise capacity, functional class, cardiac index and pulmonary vascular resistance
Summary

- Scleroderma is a multisystem autoimmune disorder
- Pulmonary hypertension and interstitial lung disease are the primary cause of death
- Early diagnosis and treatment can effect long term outcome
The End

1. Proceed to the post test
2. Print the post test
3. Complete the post test
4. Return the post test to:
   1. Dr. S.K. Oliver
   2. 407i TAMUII
What additional test would you order for the patient described in slide 2?

What is your diagnosis?