Connective Tissue Disorders: An Update

Eddie Needham, MD, FAAFP

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Eddie Needham, MD, FAAFP

Program Director and Academic Chairman, Florida Hospital Family Medicine Residency, Winter Park; Associate Professor, University of Central Florida College of Medicine, Orlando; Clinical Associate Professor, Florida State University College of Medicine, Tallahassee

Dr. Needham practices full-service family medicine, providing care from “conception to resurrection.” In 2013, he received the Florida Academy of Family Physicians Exemplary Full-Time Educator award. Previous awards include the Georgia Academy of Family Physicians Teacher of the Year award in 2007 and the AAFP Foundation’s Parke-Davis Teacher Development Award in 1997. It is his joy and passion to teach students of medicine the wonders of the human body and spirit.

Learning Objectives

1. Recognize symptoms of connective tissue disorders through astute history and physical exam is vital when a CTD is suspected.
2. Apply appropriate diagnostic strategies to confirm diagnosis, when CTD is suspected.
3. Develop collaborative care plans emphasizing treatment monitoring and adherence to prescribed therapies.
4. Establish standardized processes for possible referral and coordination of care with a rheumatologist.

Audience Engagement System

Step 1
Step 2
Step 3
More About Dr. Needham

- Practices “conception to resurrection” family medicine
- Taught family medicine for two decades
- Joy and passion to teach the wonders of the human body and spirit.
- Married for 28 years with five grown children
- Adventure:
  - Rigors of triathlons, soccer, and volleyball
  - Wonder and surprise of fishing
  - Mountain top experiences with friends

General Comments re: CTD

- Pattern recognition is invaluable in assessing for potential CTDs
- Women are affected much more frequently than men for almost all CTDs
- Most CTD patients should be managed with the help of a rheumatologist when prescribing immunomodulators or biologic agents
Patient Case

- 37 yo female presents with progressive shortness of breath.
- Has given birth to 7 healthy children previously without difficulty.
- Other complaints include:
  - Knee and elbow pain
  - Patchy hair loss

Labs of note:
- ANA (+) at 1:320
- Platelet count of 96
- WBC 3.5
- Lymphocyte count of 1200

Exam notable for bilateral pleural effusions with (+) LE cell prep

AES POLL QUESTION

37 yo female with dyspnea, arthralgias, (+) ANA, mild pancytopenia, and pleural effusion. What is the most likely diagnosis?

A. Rheumatoid arthritis
B. Systemic lupus erythematosus
C. Wegener’s granulomatosis
D. Sarcoidosis

Lupus Erythematosus Prep
Systemic Lupus Erythematosus (SLE)

- SLE is a systemic inflammatory autoimmune disease with protean manifestations.
- Female: male incidence of 9:1
- Typically affects women of child bearing years
- US prevalence of 0.1% (1 per 1000)
- More prevalent and severe among blacks and Hispanics

SLE

- Estimated survival rates of 96% at 5 years, 93% at 10 years, and 78% at 15-20 years.
  - Previously, 50% at 5 years in the 1950s
- Major causes of mortality is premature coronary artery disease with a 50 fold increase over general population.
- Increased risk of osteoporosis
  - From disease and drugs (steroids)

SLE

- The diagnosis is clinical
- (+) ANA – not always helpful
- Must have 4 of 11 diagnostic criteria
- Lab tests cannot substitute for pattern recognition in the history and physical by the physician!

SLE Diagnostic Criteria

- Mucocutaneous signs – 4 of them
- Brain – neurologic involvement
- Lab – (+) ANA
- Lab – other immune criteria
- Arthritis – nonerosive (vs Rheumatoid Arthritis)
- Serositis
- Hematologic disturbances
- Renal disease

Mucocutaneous Signs

- Malar rash
  - Spares the nasolabial folds
- Discoid rash
  - Erythematous, raised, scaling plaque, central scar
  - Follicular plugging
- Photosensitivity
- Aphthous ulcers
  - Usually painless

Neurologic involvement

- Seizures
- Psychosis
- Of note, 80% of patients will have some form of cognitive impairment by 10 years after diagnosis.

Lab

- (+) ANA
  - 90% of patients with SLE have a (+) ANA
- Negative at < 1:40 serum dilutions
- Indeterminate at 1:40 – 1:160
- Clearly positive at > 1:320

Lab

- False (+) RPR
- Prolonged PTT (Lupus anticoagulant)
- (+) Anti-Smith antibodies
- (+) Anti-double stranded DNA antibodies
- (+) Anticardiolipin antibodies
- (+) Lupus erythematosus cell prep

Arthritis and Serositis

- Nonerosive polyarthritis
  - 2 or more joints
  - Tenderness
  - Swelling
  - Effusion
    - Consider arthrocentesis
- Serositis affecting the pleura or pericardium
  - Rub or effusion, EKG with pericarditis, pleurisy

Hematologic Involvement

- Leukopenia < 4000 WBCs
- Lymphopenia < 1500
- Thrombocytopenia <100
- Hemolytic anemia
  - Schistocytes, look at the blood smear
  - Elevated total and indirect bilirubin
  - Decreased haptoglobin

Renal Involvement

- Proteinuria > 0.5 grams/day
- > 3+ protein on dipstick
- Cellular casts indicative of renal disease
  - RBC casts suggest glomerulonephritis
  - Tubular casts suggest inflammation of the tubules

American College of Rheumatology Slide Set
AES POLL QUESTION
Which of the following is not a cause of an elevated ESR?
A. Acute gout flare
B. SLE/Lupus
C. Polymyalgia rheumatic
D. Fibromyalgia

Etiologies of elevated ESR > 100mm/hour
• Acute gout
• Polymyalgia rheumatica/temporal arteritis
• Rheumatoid arthritis
• SLE
• Infections:
  – Osteomyelitis, Subacute bacterial endocarditis, deep tissue abscess
• Cancer:
  – Carcinoma, leukemia, lymphoma, multiple myeloma


Diagnostic Tests for CTDs
• Antinuclear antibodies (ANA)
  – SLE, scleroderma, Sjogren’s, poly-/dermatomyositis, mixed CTD
• Anti-SSA (Ro), Anti-SSB (La): SLE and Sjogren’s syndrome
• Anti-Jo-1: Polymyositis
• ANCA (antineutrophilic cytoplasmic antibodies)
  – Wegener’s (c-ANCA) and vasculitides (p-ANCA)
    – Confirm Wegener’s with antiproteinase 3 Ab
    – Confirm vasculitis with antmyeloperoxidase Ab
• Anti-ribonucleoprotein (Anti-RNP): Mixed CTD
• Antitopoisomerase Ab (anti-Scl-70): diffuse scleroderma
• Anti-centromere antibodies
  – Limited scleroderma, CREST syndrome
ANA patterns

- Homogeneous:
  - DNA-protein complex Ag → SLE
- Diffuse:
  - Histone Antigen → Drug induced SLE
  - Topoisomerase-1 Ag → Scleroderma
- Speckled:
  - RNP Ag → mixed CTD
  - SSA/SSB Ag → SLE/Sjogren’s
  - Smith Ag → SLE

Tests specific for SLE

- Anti-double-stranded DNA antibodies
  - Present in 60% of SLE patients
- Anti-Smith antibodies
  - Present in 40% SLE patients
- C3 and C4 complement levels
  - Decrease with activity of SLE, esp. lupus nephritis

Tests specific for Rheumatoid Arthritis

- Rheumatoid factor
  - IgM antibody
  - Can be elevated in other conditions than RA
- Anticyclic citrullinated peptide antibodies

How to treat the wolf of Lupus

- NSAIDs
  - Can be used early in SLE treatment
  - Effective for arthralgias and serositis
  - Avoid with lupus nephritis and renal insufficiency
  - Avoid Cox-2 inhibitors in patients with an increased risk of CVD

SLE Treatment
AES POLL QUESTION
Which of the following non-selective NSAIDs is least likely to cause GI irritation/bleeding?
A. Ibuprofen  
B. Indomethacin  
C. Meloxicam  
D. Naproxen

SLE treatment
• Steroids
  - High dose steroids can be used to manage severe disease episodes
  - May serve as bridge therapy until slow-acting drugs become effective
  - Low dose (5mg daily) can be used in the treatment of mild SLE
  - Topical steroids for localized skin manifestations
  - Intra-articular steroids for joint disease
    • Rule out septic arthritis first

SLE treatment
• Hydroxychloroquine
  - All SLE pts should be on hydroxychloroquine unless not tolerated
  - Requires 6-12 weeks to show benefit.
  - Can be combined with NSAIDs for mild disease
    • Cutaneous manifestations and arthralgias

SLE treatment
• Other immunomodulatory drugs:
  • Methotrexate – some benefit
  • Mycophenolate mofetil (Cellcept)
  • Cyclophosphamide
    • Historically used for lupus nephritis
    • Recent data suggests use of mycophenolate may be preferable


SLE treatment
• The Tumor Necrosis Factor (TNF) inhibitors used in rheumatoid arthritis are not routinely used in SLE.
• These drugs increase autoantibody production and may potentially exacerbate SLE.
Scleroderma (Systemic Sclerosis)

- A chronic condition characterized by fibrosis of the skin and internal organs
- Raynaud’s phenomenon is present in most patients at some stage of the disease
- Prevalence between 20-250 patients per 10^6
- Women have a 5 fold increased risk
- Survival of 78% at 5 years, 55% at 10 years, 37% at 15 years, and 27% at 20 years
- 60% of patients die from pulmonary disease

Scleroderma

- Major criterion is symmetric sclerosis
  - Skin thickening
- Minor criteria
  - Sclerodactyly – thickening/tightening of the fingers
  - Digital pitting or loss of finger tip pad substance
  - Bilateral basilar pulmonary fibrosis

Scleroderma

- 2 forms of the disease
  - Limited
    - Morphea – localized thick, hardened skin patches
    - Linear scleroderma – bands of hard skin
    - CREST syndrome
    - Systemic sclerosis sine scleroderma
  - Diffuse

CREST syndrome

- Calcinosi
- Raynaud’s phenomenon
- Esophageal dysmotility
- Sclerodactyly
- Telangiectasia
Lab testing

- Most patients have a (+) ANA
- Nucleolar pattern is present in 30%
- Anti-topoisomerase-1 Ab (Scl-70) are associated with diffuse scleroderma  
  - Present in 40% of patients
- Anti-centromere Ab are present in 75% of patients with limited scleroderma and CREST

Routine monitoring every 6 months

- Complete blood count
- Creatinine level
- ESR
- Urinalysis
- ECG
- Echocardiogram
- PFTs: +/- DLCO to check for fibrosis

Clinical manifestations of Scleroderma

Raynaud’s Phenomenon

- "WBC"
- White
- Blue
- Carmine (Red)
- This is the order of color change with Raynaud’s Phenomenon
**Scleroderma Treatment**

- Arthralgias can be treated with:
  - NSAIDs, hydroxychloroquine, MTX, azathioprine, or mycophenolate
- Inflammatory episodes: steroids
- Any patient with scleroderma and HTN should be on an ACEI to preserve renal function
- Esophageal disease/reflux: PPI
- Pulmonary Disease: Cyclophosphamide

**Scleroderma Treatment**

- Raynaud’s phenomenon:
  - Calcium channel blockers: extended-release
    - Nifedipine or amlodipine
  - IV iloprost (prostacyclin analogue – vasodilator)
  - Sildenafil (phosphodiesterase inhibitor leading to vasodilation)

**Patient Case**

- 47 yo male with three year history of progressive weakness.
- He has trouble brushing his hair or reaching over his head.
- MRI brain and spine normal 3 years ago
- 6’ 5” male sitting in NAD
- Can’t get out of a chair without leaning far forward; cannot raise arms past 90 degrees

**AES POLL QUESTION**

47 yo male with shoulder girdle weakness and normal brain MRI. Most likely diagnosis?

A. Polymyositis
B. Poliomyelitis
C. Statin myopathy
D. Cushing’s syndrome with steroid myopathy
Polymyositis

Dermatomyositis

Patient Case
- Patient with similar complaints with:
  - Erythematous plaques on the dorsal MCPs and PIPs of both hands
  - Erythematous patches and plaques on the upper eyelid

Findings in both DM and PM
- Elevations in muscle enzymes
  - CPK, muscle aldolase, LDH, AST, ALT
- Symmetric proximal muscle weakness
- Characteristic EMG findings
- (+) anti-Jo-1 antibodies
- Muscle biopsy demonstrating active inflammation
- Additionally in DM
  - Heliotrope rash and Gottron’s papules

DDx for proximal muscle weakness
- DM/PM
- Polymyalgia rheumatica
- Temporal arteritis
- Endocrinopathy
  - Thyroid
  - Cushing’s disease
  - Parathyroid
- Infections
  - Toxoplasma
  - Inclusion
  - Viral
- Glucocorticoid myopathy
- Statin myopathy
- Neurologic disorders
  - Myasthenia Gravis
  - Eaton-Lambert
- Amyotrophic lateral sclerosis
- Muscular dystrophies
- Myopathies
- Electrolyte disturbances
Dermatomyositis

- Both DM and PM increase the risk of cancer, DM > PM
  - 3 fold increase in RR in DM; 2 fold increase with PM
  - 70% of cancers are peritoneal adenocarcinomas
- Recommend age appropriate cancer screening for patients (C-scope pts > 50 yo, etc...)
- In higher risk patients, consider CT Chest, Abdomen, Pelvis


DM/PM treatment

- Initial high dose steroids to placate the inflammatory myopathy: 60-80mg daily
  - Wean down over ~ 1 year
- Steroid sparing agents:
  - Azathioprine
  - Methotrexate
  - Hydroxychloroquine

Practice Recommendations

1. The astute history and physical exam is vital when a CTD is suspected. (Pattern recognition)
   (SORT C)
2. Order studies only as indicated, avoiding the "immune panels" that can give false (+) tests.
   (SORT C)
3. Work closely with a rheumatologist, when available, in diagnosing and treating our patients.
   (SORT C)

Questions
Thank you for your attention

- Eddie.Needham.MD@FLHosp.org