Polymyalgia Rheumatica
Giant Cell Arteritis

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Disclosures

• None
Case

• 72 yo WM, previous smoker from south GA
  • 3 mo h/o nonproductive cough
  • Dyspnea, fever (102°F), and weight loss
  • Chest radiograph negative
  • No response to 2 courses of antibiotics
  • Sputum culture and PPD negative
CT Chest: Pulmonary nodule
Increased uptake:

- Carotid
- Subclavian
- Aorta
- Common iliac
- Femoral
Additional Information

- ESR: 112 mm/hr
- Recent temporal headaches and tenderness
- No jaw or peripheral claudication
- No visual changes

- Referred to Rheumatology for possible “inflammatory lung and blood vessel disease”
Physical Exam

• Vitals:
  • BP R: 140/80
  • BP L: 130/60
  • Pulse 72 and regular bilaterally

• Right temporal artery slightly thickened and mildly tender

• No synovitis, bruits, or vasculitic lesions
Laboratory Workup

- **Hgb/Hct**: 12.2/36; WBC: 5.8; Plt: 259

- **ESR**: 101 mm/hr; **CRP**: 75.2

- Rheumatologic panel negative
- CMP unremarkable
- U/A negative, without sediment
What is your next diagnostic or therapeutic decision?

a) Refer to cardiothoracic surgery for lung nodule biopsy/resection.

b) Treat empirically with prednisone 20 mg daily for a “connective tissue disease.”

c) Biopsy right temporal artery.

d) Obtain blood cultures and RPR for infectious aortitis.
Correct Answer: C

Right temporal artery biopsy
Treatment/Outcome

• Prednisone 60 mg daily
  • Slow taper over course of 2 years
  • Symptoms and lab abnormalities resolved

• No relapse to date
Outline

• Polymyalgia rheumatica
  • Background
  • Making the diagnosis
  • Treatment

• Giant Cell Arteritis
  • Background
  • Clinical presentations
  • Diagnostic tools
  • Treatment
PMR: Background

• Systemic inflammatory disease
• Patients > 50 yo
• Peak incidence age 70-80
• Risk of lifetime development 2\textsuperscript{nd} only to RA
• F:M 3:1
• Incidence highest in those of Northern Europeans

Behind the Scenes

- Genetic predisposition?
  - HLA DR4 and HLA DRB1
  - Circulating CD4+ T cells
  - Increase in IL-6
  - Interferon gamma-producing T cells not prominent → no prototypical arteritis!!!
Clinical Presentation

• Age ≥ 50
• Pain/stiffness bilateral shoulders/hip girdle
• Insidious or subacute onset
• Prolonged morning stiffness
• Constitutional symptoms

• Keep eye out for GCA symptoms!!!

Salvarani C, Arthritis Rheum. 1998
Myklebust G, Br J Rheumatol. 1996
Physical Exam Findings

• Muscle tenderness (bursitis?)

• Decreased ROM

• Nonerosive synovitis (about 25%)
  • Wrists → CTS
  • Sternoclavicular joint
  • Knees
Laboratory

- Elevation in ESR and CRP

- **Caution:** 7% may have normal or only mildly elevated (<40 mm/h) ESR

- Normocytic anemia, thrombocytosis
- Elevated alk phos (33%)
- Negative ANA, RF, CCP

Proven A, *J Rheumatol*. 1999
Imaging

- Ultrasound
- MRI
- $^{18}$FDG-PET
PMR: Ultrasound/MRI

- Case-control study 57 consecutive pts
- Subacromial/subdeltoid bursitis
  - 96% with PMR, 22% controls
- Bilateral findings
  - 96% with PMR, 4% controls
- MRI confirmed in 100% cases
- US sensitivity 92.9%, specificity of 99.1%, and PPV 98.1%

Cantini F. J. Rheumatol. 2001
PMR: Ultrasound/MRI

• Trochanteric bursitis most common hip lesion

• US less sensitive than MRI in assessment of hip synovitis and iliopsoas bursitis.

• Tenosynovitis, especially extensor tendons, frequent in PMR

Cantini F, Clin Exp Rheumatol. 2005
PMR: $^{18}$FDG-PET

- Costly
- Can identify bursitis
- Subclinical large artery inflammation did not correlate with risk of relapse

- At this time, no proven clinical value in patients without any evidence for large vessel involvement
### Table 6. PMR classification criteria scoring algorithm—required criteria: age ≥50 years, bilateral shoulder aching, and abnormal CRP and/or ESR *

<table>
<thead>
<tr>
<th>Condition</th>
<th>Points without US (0–6)</th>
<th>Points with US (0–8) †</th>
</tr>
</thead>
<tbody>
<tr>
<td>Morning stiffness duration &gt;45 minutes</td>
<td>2</td>
<td>2</td>
</tr>
<tr>
<td>Hip pain or limited range of motion</td>
<td>1</td>
<td>1</td>
</tr>
<tr>
<td>Absence of RF or ACPA</td>
<td>2</td>
<td>2</td>
</tr>
<tr>
<td>Absence of other joint involvement</td>
<td>1</td>
<td>1</td>
</tr>
<tr>
<td>At least 1 shoulder with subdeltoid bursitis and/or biceps tenosynovitis and/or glenohumeral synovitis (either posterior or axillary) and at least 1 hip with synovitis and/or trochanteric bursitis</td>
<td>NA</td>
<td>1</td>
</tr>
<tr>
<td>Both shoulders with subdeltoid bursitis, biceps tenosynovitis, or glenohumeral synovitis</td>
<td>NA</td>
<td>1</td>
</tr>
</tbody>
</table>

* A score of 4 or more is categorized as polymyalgia rheumatica (PMR) in the algorithm without ultrasound (US) and a score of 5 or more is categorized as PMR in the algorithm with US. CRP = C-reactive protein; ESR = erythrocyte sedimentation rate; RF = rheumatoid factor; ACPA = anti–citrullinated protein antibody; NA = not applicable.
† Optional ultrasound criteria.
2012 EULAR/ACR Performance

- Single-center study over 6 years
- 136 cases and 149 controls (94 w/ RA)

- EULAR/ACR criteria
  - 93% sensitivity
  - 82% specificity
  - Inclusion of shoulder and hip US increased specificity to 91%

PMR: Treatment

- No universally accepted approach to initial glucocorticoid dosing, maintenance therapy, or dose reduction

- New proposed treatment recommendations forthcoming
PMR: Treatment

- Prednisone 15-20 mg/day x 2-4 weeks
- Prednisone taper by 2.5 mg every 3 weeks until at 10 mg daily
- Prednisone 10 mg daily x 4 weeks
- Prednisone taper by 1 mg/mo
- Monitor ESR/CRP/Clinical symptoms

Dasgupta B. *Rheumatology (Oxford)*. 2010
PMR: Treatment

- Increased risk of relapses
  - Higher initial steroid dose
  - Fast steroid taper
  - Persistently elevated CRP and IL-6
PMR: Treatment

• Managing relapses
  • The “Art of Medicine”
  • Bump prednisone to previously effective dose
  • Rule out other causes
  • Monitor closely
    • GCA
    • Seronegative inflammatory arthritis
    • Infections
    • Malignancy
PMR: Treatment
The “difficult patient”

• Methotrexate
  • Generally felt to be steroid-sparing
• Anti-TNF inhibitors
  • Infliximab unhelpful
  • Etanercept with some possible benefit.
• IL-6 inhibition (tocilizumab) showed promise

Kreiner F, Arthritis Res Ther. 2010
Corrao S, Clin Rheumatol. 2009
Catanoso MG, Arthritis Rheum. 2007
Caporali R, Ann Intern Med. 2004
Feinberg HL, J Rheumatol. 1996
Ferraccioli G, J Rheumatol. 1996
van der Veen MJ, Ann Rheum Dis. 1996
PMR
Take Home Points

• Systemic inflammatory process in patients ≥ 50 yo with neck, bilateral shoulder and hip girdle stiffness accompanied by inflammatory marker elevation

• Peripheral arthritis and bursitis may be present

• Initial treatment with prednisone 15-20 mg daily remains foundation of treatment with slow taper
Bayard T. Horton
1895-1980

- Ophthalmologic manifestations
- Jaw claudication
- Large vessel involvement
- Pathologic findings
- 26 cases published by 1946

Horton:

• “The physician should be aware of headache in the senior citizen. It may forebode, among many things, the insidious onset of temporal arteritis, a disease that can be easily overlooked in its early stages.”

• The headache of temporal arteritis can vary—“But all patients agree that it differs from any other headache they may have previously experienced.”
GCA: Background

- Granulomatous vasculitis of aorta and branches
- Age ≥ 50
- Female (3:1)
- Female smokers
- HLA-DR-4
- Highest prevalence in Northern European populations
GCA: Physical Exam

- Physical exam
  - Arterial
  - Ophthalmologic
  - Joints

- Labs
  - Elevated ESR, thrombocytosis
  - Normochromic anemia
  - Elevated AST/Alk phos
GCA: Beware

- Population-based study of 167 cases
  - ESR < 50 mm/hr 11%
  - ESR < 40 mm/h in 5%
- Another series of 173 cases
  - ESR < 46 mm/hr in 5.8%

- Risk of visual loss indistinguishable from those in patients with a higher ESR

Liozon E, Arthritis Rheum. 2002
Salvarini C, Arthritis Rheum. 2001
GCA: ACR Classification Criteria

- Age at onset > 50 years old
- New headache
- Temporal artery abnormality
- Elevated ESR
- Positive temporal artery biopsy

3 or more of these has been shown to have a sensitivity of 93.5% and specificity of 91.2%
GCA & PMR

Large-vessel GCA

GCA aortitis

Cranial GCA

FUO & wasting

Heterogeneity of IR

Cytokine profiles

Mφ effector functions

Diverse clinical manifestations
### Giant Cell Arteritis
#### Clinical Manifestations in 100 Patients

<table>
<thead>
<tr>
<th></th>
<th>1980</th>
<th>2000</th>
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<tbody>
<tr>
<td>Headache</td>
<td>68</td>
<td>67</td>
</tr>
<tr>
<td>PMR</td>
<td>39</td>
<td>19</td>
</tr>
<tr>
<td>Fever</td>
<td>42</td>
<td>34</td>
</tr>
<tr>
<td>FUO</td>
<td>15</td>
<td>11</td>
</tr>
<tr>
<td>Weight loss/anorexia</td>
<td>50</td>
<td>51</td>
</tr>
<tr>
<td>Malaise/fatigue</td>
<td>40</td>
<td>38</td>
</tr>
<tr>
<td>Transient visual sx</td>
<td>16</td>
<td>20</td>
</tr>
<tr>
<td>Permanent visual loss</td>
<td>14</td>
<td>12</td>
</tr>
<tr>
<td>Myalgias</td>
<td>30</td>
<td>26</td>
</tr>
<tr>
<td>Jaw claudication</td>
<td>45</td>
<td>67</td>
</tr>
</tbody>
</table>

Clinical Manifestations
Cranial Arteritis

- Ischemic optic neuropathy (ION)
- Amaurosis fugax
- Diplopia
- Headaches
- Jaw claudication
- Scalp tenderness
- CNS ischemia
- Maxillary Pain

- Dysphasia
- Cough
- Sore throat/sore tongue
- Tender throat
- Hoarseness
- Choking sensation
- Chest pain
Features of Arteritic Ischemic Optic Neuropathy

- Older patients
- Systemic symptoms
- High ESR

- Ocular findings:
  - Amaurosis fugax
  - Cup to disc ratio >0.2
  - Marked pallor optic disc ("chalky white")
  - Early massive or bilateral simultaneous visual loss

- Choroidal nonfilling on fluorescein angiography
- Vast majority from narrowing or occlusion of the posterior ciliary arteries

Schäuble B. *J. Neuroophthalmol*. 2000
Clinical Manifestations
Musculoskeletal

• Isolated PMR

• Peripheral manifestations
  • Synovitis
  • Distal swelling w/ pitting edema (RS$_3$PE)
  • Distal extremity swelling, no pitting
  • Tenosynovitis
  • Carpal tunnel syndrome

Salvarani. 1999
Clinical Manifestations
Fever of Unknown Origin

- Chills, Anorexia, Weight loss
- Night sweats, Weakness, Depression

Bone marrow examination
- Normal
- Hyperplasia
- Hypocellular
- Diminished iron stores
- Plasmacytosis, vasculitis
- Granuloplasmatosis
- Plasma-megakaryocytosis
Clinical Manifestations
Large Artery Involvement

- Extremity claudication
- Decreased or absent pulses
- Paresthesia
- Bruit
- Raynaud’s phenomenon
- Aortic aneurysm/dissection
- Aortic insufficiency
Large artery disease in GCA

• Patients with GCA were found to have a > 17-fold higher risk of thoracic aortic aneurysm c/w general population.

Evans, *Ann Internal Medicine*. 1995
GCA: Imaging Modalities

• CT/CTA

• MRI/MRA

• $^{18}$FDG-PET

• Ultrasonography of temporal artery
GCA CTA aorta

A

B

An

Agard, Arth Care & Res. 2008
MRI & MRA in GCA

Stenosis
Aneurysm
Thickening
Edema
Uptake

Salvarani, NEJM. 2002
MRA in GCA

Temporal Artery Ultrasound
$^{18}$FDG PET Scans in GCA

Before treatment

After treatment

Potential Uses for $^{18}$FDG PET in Vasculitis

• FUO
• Negative TA Bx (40%)
• Early subclinical disease
• Measurement of disease activity
• Response to treatment
• Prognosis: aortic dilatation later

GCA: Temporal Artery Biopsy

- Gold standard for diagnosis

- Isolated PMR symptoms: no need for bx
  - Monitor for s/s of developing GCA

- Biopsy most symptomatic side first

- Biopsy length ≥ 0.5 cm length
GCA
Temporal Artery Biopsy: Pathology

• 50% “classic”
  • Granulomatous inflammation with giant cells and mononuclear infiltrate focused in intima-media border
  • Elastic lamina fragmentation
  • Partial or complete arterial lumen occlusion from intimal hyperplasia → ischemic complications

• 50% without granulomas/giant cells
  • Nonspecific panarteritis
  • Mixed inflammatory infiltrate
GCA: Treatment

- Prednisone 40-60 mg/day x 1 month
  - Reduce by 10 mg each month
    - Reduce by 2.5-5 mg monthly below 20 mg/day
      - Reduce by 1 mg monthly below 10 mg/day
- Baseline BMD and osteoporosis prophylaxis
- GERD prophylaxis
- Monitor for recurrent symptoms
- Monthly ESR
GCA: Treatment

- Low dose ASA
  - No RTCs

- Methotrexate and anti-TNFs
  - Meta-analysis demonstrated no benefit
GCA: Treatment with tocilizumab

• Humanized IL-6 receptor antibody

• Several case series show promise

• Need for controlled trials and long-term follow up studies

Giant Cell Arteritis
Take Home Points

• Large vessel vasculitis involving aorta and branches

• May lead to clinical symptoms of fever, headache, visual loss, claudication

• TABx is gold standard for diagnosis, but advanced imaging (CTA/MRA/PET) may be useful when biopsy negative

• Initial treatment with prednisone 60 mg daily with slow taper, but new agent blocking IL-6 pathway has shown promise in difficult cases
Thank you