Tough Cases in Rheumatology

Andrew Gross, MD
Rheumatology Clinic Chief
Associate Professor of Medicine

Teaching Objectives

• Learn the Importance of taking a Systematic Approach to the Patient with Complex Disease
• Recognize Patterns of Autoimmune Disease
• Choose Tests Wisely
Case I
A Systemically Ill Man and a Work-up with Some Dead-Ends

- The patient is a 70 year old man was transferred to our institution for work-up of ~4 weeks of myalgia and weakness.
- He was in his usual state of health until 1 month ago when he developed bilateral lower extremity edema and weakness such that he had difficulty climbing stairs.
- 5 days PTA he was evaluated at a local ED. In addition to weakness he noted intermittent fevers, mild dyspnea with exertion, and 10 lb weight loss over 2 weeks.
- He had been treated with a simvastatin for 5 years for hyperlipidemia without change in dose, and this was stopped.
OSH workup

- Laboratory Data:
  - WBC 14.7, ESR 93, CRP 210, ferritin 529,
  - CK 249 (normal 50-388)
  - negative ANA, RF, SSA, SSB, HIV, RPR
  - negative hepatitis panel, troponin, BNP,
  - Normal TSH, AM cortisol.
- Ultrasound of lower extremities negative for DVT
- Blood cultures were negative, and no antibiotics administered.
- Due to persistent fevers and weakness he was transferred to UCSF.

Past Medical History
- Elevated PSA
- Hyperlipidemia

Medications
- rosuvastatin (CRESTOR)
- aspirin 81 mg
- eszopiclone (LUNESTA)
- acetaminophen (TYLENOL)
- Ibuprofen
- calcium carbonate-vitamin D3
- Multivitamin

Other History
- Born in Greece (last traveled there 5 years ago)
- Moved to US age 18
- Retired as software engineer
- No family history of autoimmune or neuromuscular disease
Physical Examination

- Temp Max: 39.3°C, Pulse 105, BP 124/70, RR 19
- There is reduced breath sounds
- Heart sounds are tachycardic without murmur
- No organomegaly
- No skin rash
- No joint swelling or tenderness

Neurologic:
- No facial or tongue weakness; no dysarthria.
- There was very minimal weakness of the deltoid, biceps, and grip, perhaps 4+. There is more noticeable LE weakness: weakness of hip flexors 4-/4-, quadriceps 4+/4+, plantar flexors 4+/4+ and mild weakness of the left toe extensors and EHL (4+).
- Normal muscle tone. Reflexes were normal throughout. Babinski sign absent and normal finger/toe tapping.
- Sensation to light touch, pinprick, vibration, and proprioception is intact in the limbs

Laboratory Data

- WBC 17.5 (H)
- Hemoglobin 12.2
- MCV 89
- Platelet Count 654
- Neutrophil 14.53
- Lymphocyte 0.93 (L)
- Eosinophil 0.33
- Creatinine 0.85
- AST 97, ALT 109, Alk Phos 99, T-Bili 0.7
- Hep C Ab (-), Hep B sAg (-), Hep B sAb (-)
- Sedimentation Rate >100
- C-Reactive Protein 275.0 (nl <6.5)
- Creatine kinase, total 119
- Troponin I <0.05 ug/L
- HIV(-), PPD (-)

Urine Analysis
- Moderate heme
- Protein 30
- 11-20 WBCs
- 3-10 RBCs
Summary

Older man with:
• Mild Muscle weakness that is:
  – Symmetric
  – Proximal
  – Upper & Lower extremities
• Normal reflexes
• Normal sensation

Differential Diagnosis
• Inflammatory Myositis
  – Polymyositis (no rash to suggest dermatomyositis)
  – Necrotizing Myositis
  – Statin or other drug induced (alcohol)
• Mimickers of myositis
  – Polymyalgia Rheumatica
  – Endocrine disease
  – Neurologic Disease (ALS)
  – Steroid Myopathy
  – Systemic Illness

Normal CK

Weakness with a normal CK
Does this patient have Inflammatory Myositis?

<table>
<thead>
<tr>
<th>Screening test(s)</th>
<th>n (%)</th>
<th>Sensitivity (95% CI)</th>
<th>Specificity (95% CI)</th>
<th>LR+</th>
<th>LR-</th>
</tr>
</thead>
<tbody>
<tr>
<td>CK &gt; 1000 IU/l</td>
<td>64 (100)</td>
<td>48 (30–66)</td>
<td>94 (87–102)</td>
<td>8.0</td>
<td>0.6</td>
</tr>
<tr>
<td>CK &gt; 500 IU/l</td>
<td>64 (100)</td>
<td>66 (48–83)</td>
<td>77 (63–91)</td>
<td>2.9</td>
<td>0.4</td>
</tr>
</tbody>
</table>

• Creatine Kinase has limited sensitive to detect inflammatory myositis
• LDH, Aldolase, Transaminases can be elevated when CK is normal
• Note: CK up to 500 can be normal, especially in African Amer. Men (Wong ET, et al, Am J Clin Path, 1983)

Cardy CM & Potter T, Rheumatology, 2007, PMID 17704522
Weakness with a normal CK
Does this patient have Inflammatory Myositis?

Electromyography and muscle MRI both have good sensitivity & specificity

Cardy CM and Potter T, Rheumatology, 2007, PMID 17704522

### Table 1. Predictive values of screening investigations for abnormal muscle biopsy

<table>
<thead>
<tr>
<th>Screening test(s)</th>
<th>n (%)</th>
<th>Sensitivity (95% CI)</th>
<th>Specificity (95% CI)</th>
<th>LR$^+$</th>
<th>LR$^-$</th>
</tr>
</thead>
<tbody>
<tr>
<td>CK &gt; 1000 IU/l</td>
<td>64 (100)</td>
<td>48 (30–66)</td>
<td>94 (87–102)</td>
<td>8.0</td>
<td>0.6</td>
</tr>
<tr>
<td>CK &gt; 500 IU/l</td>
<td>64 (100)</td>
<td>66 (48–83)</td>
<td>77 (63–91)</td>
<td>2.9</td>
<td>0.4</td>
</tr>
<tr>
<td>Abnormal EMG</td>
<td>50 (78)</td>
<td>74 (56–92)</td>
<td>67 (49–84)</td>
<td>2.2</td>
<td>0.4</td>
</tr>
<tr>
<td>Abnormal MRI</td>
<td>21 (33)</td>
<td>92 (76–107)</td>
<td>89 (68–109)</td>
<td>8.4</td>
<td>0.1</td>
</tr>
</tbody>
</table>

Electromyography and muscle MRI both have good sensitivity & specificity

Autoantibodies Testing is often not helpful

#### Table 3. Myositis-specific autoantibodies

<table>
<thead>
<tr>
<th>Autoantibody name</th>
<th>Antigen</th>
<th>Clinical association</th>
<th>Frequency in ILD</th>
</tr>
</thead>
<tbody>
<tr>
<td>Antibodies to aminoadenylyl-trNA synthetases</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Anti-Jo-1</td>
<td>Histidyl-tRNA synthetase</td>
<td>Anti-synthetase syndrome</td>
<td>20–25%</td>
</tr>
<tr>
<td>Anti-PL-7</td>
<td>Threonyl-tRNA synthetase</td>
<td>Anti-synthetase syndrome</td>
<td>5–10%</td>
</tr>
<tr>
<td>Anti-PL-12</td>
<td>Alanyl-tRNA synthetase</td>
<td>Anti-synthetase syndrome</td>
<td>~5%</td>
</tr>
<tr>
<td>Anti-EJ</td>
<td>Glycyl-tRNA synthetase</td>
<td>Anti-synthetase syndrome</td>
<td>5–10%</td>
</tr>
<tr>
<td>Anti-OJ</td>
<td>Isoleucyl-tRNA synthetase</td>
<td>Anti-synthetase syndrome</td>
<td>~5%</td>
</tr>
<tr>
<td>Anti-KS</td>
<td>Asparagyl-tRNA synthetase</td>
<td>Anti-synthetase syndrome</td>
<td>Rare</td>
</tr>
<tr>
<td>Anti-Ha</td>
<td>Tyrosyl-tRNA synthetase</td>
<td>Anti-synthetase syndrome</td>
<td>One patient</td>
</tr>
<tr>
<td>Anti-Zo</td>
<td>Phenylalanyl-tRNA synthetase</td>
<td>Anti-synthetase syndrome</td>
<td>One patient</td>
</tr>
</tbody>
</table>

#### Other myositis-specific autoantibodies

<table>
<thead>
<tr>
<th>Autoantibody name</th>
<th>Antigen (putative)</th>
<th>Clinical association</th>
<th>Frequency in ILD</th>
</tr>
</thead>
<tbody>
<tr>
<td>Anti-P155/140</td>
<td>TIF1γ</td>
<td>Juvenile dermatomyositis, cancer in adult dermatomyositis</td>
<td>13–30%</td>
</tr>
<tr>
<td>Anti-CADM-140</td>
<td>MDA-5</td>
<td>CADM</td>
<td>50% of CADM</td>
</tr>
<tr>
<td>Anti-Mi-2</td>
<td>Mi-2α and Mi-2β</td>
<td>Dermatomyositis</td>
<td>8% of ILD generally, 15–20% of dermatomyositis</td>
</tr>
<tr>
<td>Anti-SRP</td>
<td>SRP</td>
<td>Necrotizing myopathy</td>
<td>4-6% of ILD</td>
</tr>
<tr>
<td>Anti-XK1/100</td>
<td>200KX1 and 100KX3 proteins</td>
<td>Necrotizing myopathy</td>
<td>40% of necrotizing myopathy</td>
</tr>
</tbody>
</table>

ANA (+) in <33%
Hochberg 1986

Zong M and Lundberg E, Nat Rev Rheumatol 2011, PMID 21468145
An EMG was obtained...

EMG interpretation

<table>
<thead>
<tr>
<th>EMG Steps</th>
<th>Normal</th>
<th>Myogenic Lesion</th>
</tr>
</thead>
<tbody>
<tr>
<td>Insertional Activity</td>
<td>Normal</td>
<td>Normal</td>
</tr>
<tr>
<td>Spontaneous Activity</td>
<td></td>
<td>Fibrillation</td>
</tr>
<tr>
<td>Motor Unit Potential</td>
<td>0.5-1.0 mV 5-10 msec.</td>
<td>Small Unit</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Early Recruitment</td>
</tr>
</tbody>
</table>

EMG findings

- **Procedure**: EMG studies of the right vastus intermedius, iliopsoas and cervical, thoracic, and lumbar paraspinal muscles were performed with concentric needle electrodes.
- **Impression**: Normal results for these electrodiagnostic studies apart from suprasegmental weakness.
- **Comment**: There is no electrodiagnostic evidence of a myopathic process. Suprasegmental weakness can occur in the context of pain, reduced effort, or CNS dysfunction.

Back to the drawing board...
• The patient remained febrile between 38°-39°C with a leukocytosis.
• Chest CT demonstrated a small ground glass nodule in the right lower lobe approximately 1 cm in diameter.
• He was treated with antibiotics without improvement in his fevers.

Fever of Unknown Origin
Modified definition from 1991

• Unexplained fever >38.3°C during
  – at least 3 outpatient visits or
  – at least 3 days of hospitalization

• Subsets of Patients
  – Classic FUO
  – Nosocomial FUO
  – FUO associated with immunodeficiency
  – FUO associated with HIV

Causes of FUO in 51 non-immunosuppressed Japanese patients age ≥65

- Unknown 19.6%
- Infection 23.5%
- Other 11.8%
- Malignancy 15.7%
- NIID 29.4%

(Ne-Non-Infectious Inflammatory Disease)

Naito T, et al, BMJ Open 2013, PMID 24362014

Fever of unknown origin in the elderly
Esposito AL, Gleckman RA: J Am Geriatr Soc 1978

**Bacterial**
- Mycobacterial (Tuberculosis)
- Mycoplasma
- Trichinella
- Legionella
- Whipple’s disease
- Spirochaete (Syphilis, Borrelia)
- Leptospirosis
- Bartonella (cat-scratch)
- Brucellosis
- Coxiella (Q-fever)
- Tularemia
- Entamoeba, Giardia

**Viral**
- Influenza, Coxsackie, Parvovirus
- HIV
- Herpes Viruses (CMV, HSV, EBV)
- Arboviruses (West Nile, Dengue, Chikungunya, Equine Encephalitis)

**Medications**

**Cancer**
- Hematogenous malignancy
- Hepatocellular
- Colon cancer
- Renal Cell
### Fever of unknown origin in the elderly

**Esposito AL, Gleckman RA: J Am Geriatr Soc 1978**

<table>
<thead>
<tr>
<th>Autoimmune with Arthritis</th>
<th>Autoimmune with Arthritis</th>
</tr>
</thead>
<tbody>
<tr>
<td>Crystal Disease (especially CPPD)</td>
<td>Crystal Disease (especially CPPD)</td>
</tr>
<tr>
<td>Still's disease (systemic Juvenile Idiopathic Arthritis)</td>
<td>Still's disease (systemic Juvenile Idiopathic Arthritis)</td>
</tr>
<tr>
<td>Relapsing Polychondritis</td>
<td>Relapsing Polychondritis</td>
</tr>
<tr>
<td>Familial Periodic Fever Syndrome (e.g. FMF)</td>
<td>Familial Periodic Fever Syndrome (e.g. FMF)</td>
</tr>
<tr>
<td>(SLE &amp; Anti-Synthetase Syndrome)</td>
<td>(SLE &amp; Anti-Synthetase Syndrome)</td>
</tr>
</tbody>
</table>

- Vasculitis
  - small (ANCA associated, infection associated, HSP)
  - Medium (PAN)
  - Large (GCA, Takayasu's)
- Still's disease
- Behcet's Disease
- Relapsing Polychondritis
- SLE (not Scleroderma, Sjogren's)
- Kikuchi's disease (necrotizing lymphadenitis)
- Inflammatory myositis
- Granulomatous Disease

### Tips? – look at the CBC

<table>
<thead>
<tr>
<th>Leukocytosis, Thrombocytosis</th>
<th>Leukopenia, Thrombocytopenia</th>
</tr>
</thead>
<tbody>
<tr>
<td>Vasculitis</td>
<td>Lupus</td>
</tr>
<tr>
<td>Still's disease</td>
<td>(Sarcoidosis)</td>
</tr>
</tbody>
</table>

**Then Order Tests... but which ones??**
All of the following tests can be helpful for evaluation of FUO EXCEPT:

A. Biopsy of skin lesion or rash
B. Bone Marrow Biopsy
C. Sinus X-ray
D. Chest and/or Abdominal CT scan
E. FDG-PET scan

Diagnostic Tests in FUO
A prospective multicenter study on fever of unknown origin: the yield of a structured diagnostic protocol.

<table>
<thead>
<tr>
<th>Investigation</th>
<th>No. of Patients</th>
<th>Helpful</th>
<th>False Positive</th>
<th>% Sensitivity (95% CI)</th>
<th>% Specificity (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Chest X-ray</td>
<td>73 (100)</td>
<td>8 (11)</td>
<td>2 (0)</td>
<td>90 (66-86)</td>
<td>87 (77-94)</td>
</tr>
<tr>
<td>Bone X-ray</td>
<td>22 (49)</td>
<td>0</td>
<td>2 (0)</td>
<td>NC</td>
<td>NC</td>
</tr>
<tr>
<td>Orthopantomogram</td>
<td>22 (39)</td>
<td>0</td>
<td>2 (0)</td>
<td>NC</td>
<td>NC</td>
</tr>
<tr>
<td>Barium enema</td>
<td>10 (17)</td>
<td>0</td>
<td>1 (10)</td>
<td>NC</td>
<td>NC</td>
</tr>
<tr>
<td>Enteroclysis</td>
<td>2 (5)</td>
<td>0</td>
<td>0</td>
<td>NC</td>
<td>NC</td>
</tr>
<tr>
<td>Abdominal ultrasound</td>
<td>58 (72)</td>
<td>6 (10)</td>
<td>18 (31)</td>
<td>86 (82-100)</td>
<td>68 (60-78)</td>
</tr>
<tr>
<td>Abdominal CT</td>
<td>60 (82)</td>
<td>12 (20)</td>
<td>17 (28)</td>
<td>92 (64-100)</td>
<td>63 (48-77)</td>
</tr>
<tr>
<td>Chest CT</td>
<td>46 (63)</td>
<td>9 (20)</td>
<td>8 (17)</td>
<td>82 (48-98)</td>
<td>77 (60-90)</td>
</tr>
<tr>
<td>FDG-PET</td>
<td>27 (96)</td>
<td>22 (33)</td>
<td>10 (14)</td>
<td>92 (74-99)</td>
<td>78 (63-89)</td>
</tr>
<tr>
<td>Coloculography</td>
<td>19 (29)</td>
<td>0</td>
<td>4 (22)</td>
<td>NC</td>
<td>NC</td>
</tr>
<tr>
<td>Bronchotomy</td>
<td>5 (7)</td>
<td>1 (20)</td>
<td>0</td>
<td>NC</td>
<td>NC</td>
</tr>
<tr>
<td>Gastricopy</td>
<td>21 (20)</td>
<td>0</td>
<td>3 (14)</td>
<td>NC</td>
<td>NC</td>
</tr>
<tr>
<td>Colonoscopy</td>
<td>19 (20)</td>
<td>1 (5)</td>
<td>2 (10)</td>
<td>NC</td>
<td>NC</td>
</tr>
<tr>
<td>Temporal artery biopsy</td>
<td>14 (19)</td>
<td>1 (7)</td>
<td>0</td>
<td>NC</td>
<td>NC</td>
</tr>
<tr>
<td>Bone marrow biopsy</td>
<td>19 (20)</td>
<td>2 (11)</td>
<td>1 (5)</td>
<td>NC</td>
<td>NC</td>
</tr>
<tr>
<td>Liver biopsy</td>
<td>7 (10)</td>
<td>1 (14)</td>
<td>2 (13)</td>
<td>NC</td>
<td>NC</td>
</tr>
<tr>
<td>Duodenal biopsy</td>
<td>12 (16)</td>
<td>0</td>
<td>1 (8)</td>
<td>NC</td>
<td>NC</td>
</tr>
<tr>
<td>Colonic biopsy</td>
<td>31 (38)</td>
<td>0</td>
<td>2 (15)</td>
<td>NC</td>
<td>NC</td>
</tr>
<tr>
<td>Lymph node biopsy</td>
<td>11 (15)</td>
<td>5 (46)</td>
<td>3 (27)</td>
<td>NC</td>
<td>NC</td>
</tr>
<tr>
<td>Skin biopsy</td>
<td>8 (11)</td>
<td>5 (63)</td>
<td>0</td>
<td>NC</td>
<td>NC</td>
</tr>
<tr>
<td>Laparotomy</td>
<td>4 (1)</td>
<td>2 (50)</td>
<td>1 (25)</td>
<td>NC</td>
<td>NC</td>
</tr>
</tbody>
</table>

**FDG-PET in evaluation of FUO**

<table>
<thead>
<tr>
<th></th>
<th>70 FDG-PET</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>23 positive</td>
</tr>
</tbody>
</table>

**FDG-PET: good for detecting infection & cancer less helpful for autoimmune disease**


---

**FDG-PET results:**

**IMPRESSION:**

1. Diffuse radiotracer uptake at the level of the right abdominal wall. Correlation with cross-sectional imaging is recommended.
2. Focal FDG avid foci in the retroperitoneal region. These foci may represent either lymph nodes or bowel. Correlation with the cross-sectional imaging is recommended.
3. Focal faint FDG avidity in the left inguinal region.

Recommendation with cross-sectional imaging is recommended

**Not helpful**
Now what?

Rheumatologists look for patterns
In this patient's case
• workup of the muscle weakness was a dead end
• workup of the fever was a dead end.

Looking for other patterns:
• he had a pulmonary process & abnormal urine test with blood and protein
• On repeat urine testing, he continued to have large hemoglobin in the urine with 100 protein and a protein creatinine ratio of 1.2 (normal <0.2).
Chest CT showed....
Diffuse Alveolar Hemorrhage

Vasculitis/Capillaritis
- ANCA-associated vasculitis (GPA, MPA, drug)
- SLE
- Anti-GBM disease (Goodpasture’s)
- Cryoglobulinemic Vasculitis
- Anti-phospholipid Antibody Syndrome
- Thrombotic Thrombocytopenia Purpura (TTP)

Other causes
- Pulmonary Embolism
- Idiopathic Pulmonary Hemosiderosis
- Pulmonary Alveolar Proteinosis
- Pulmonary Venous-occlusive disease
- Infection
- Cancer

Other causes
- Pulmonary Embolism
- Idiopathic Pulmonary Hemosiderosis
- Pulmonary Alveolar Proteinosis
- Pulmonary Venous-occlusive disease
- Infection
- Cancer
Chest CT results

- The non-calcified pulmonary nodule in right lower lobe has grown in size to 1.8 x 1.8 cm
- In addition, a 9mm round, non-calcified, well-defined nodule is present in the left lower lobe adjacent to the pleura.
- Additional subtle areas of ground glass opacity surround the peribronchovascular bundles in the left lower lobe and left upper lobe.

“PulmonaryRenal Syndrome”
Lung Manifestations

- **Diffuse alveolar hemorrhage**
- Acute pneumonitis
- Organizing pneumonia
- Pulmonary nodules
In a patient with a pulmonary-renal syndrome, all for the following diseases should be considered EXCEPT:

a) ANCA associated vasculitis
b) Systemic Lupus Erythematosus (SLE)
c) Polyarteritis Nodosa (PAN)
d) Cryoglobulinemic vasculitis
e) anti-GBM disease

<table>
<thead>
<tr>
<th>Table 1. Classification of the pulmonary-renal syndrome (pulmonary hemorrhage and glomerulonephritis)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Goodpasture's syndrome or antiglomerular basement membranes</td>
</tr>
<tr>
<td>Immune complex-induced</td>
</tr>
<tr>
<td>Systemic lupus erythematosus</td>
</tr>
<tr>
<td>Rheumatoid arthritis</td>
</tr>
<tr>
<td>Systemic sclerosis</td>
</tr>
<tr>
<td>Antineutrophil cytoplasmic antibody–associated vasculitis</td>
</tr>
<tr>
<td>Microscopic polyangiitis</td>
</tr>
<tr>
<td>Wegener's granulomatosis</td>
</tr>
<tr>
<td>Churg-Strauss syndrome</td>
</tr>
<tr>
<td>Drug-induced vasculitis</td>
</tr>
<tr>
<td>Pauci-immune necrotizing and crescentic glomerulonephritis</td>
</tr>
<tr>
<td>Non-antineutrophil cytoplasmic antibody–associated vasculitis</td>
</tr>
<tr>
<td>Henoch-Schönlein purpura</td>
</tr>
<tr>
<td>Essential cryoglobulinemia</td>
</tr>
<tr>
<td>Behçet's disease</td>
</tr>
<tr>
<td>Immunoglobulin A nephropathy</td>
</tr>
<tr>
<td>Antiphospholipid syndrome</td>
</tr>
<tr>
<td>Others</td>
</tr>
</tbody>
</table>
While we wait for the ANCA, dsDNA Ab, GBM Ab, what is the most helpful test:

a) Kidney biopsy  
b) ANA  
c) WBC  
d) complement levels  
e) CRP  
f) Rheumatoid Factor

<table>
<thead>
<tr>
<th>Table 1. Major Causes of Acute Nephritis*</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Low Serum Complement Level</strong></td>
</tr>
<tr>
<td>---------------------------------</td>
</tr>
<tr>
<td><strong>Systemic Diseases</strong></td>
</tr>
<tr>
<td>Systemic lupus erythematosus (focal, approximately 75%; diffuse, approximately 90%)</td>
</tr>
<tr>
<td>Cryoglobulinemia (approximately 85%)</td>
</tr>
<tr>
<td>Subacute bacterial endocarditis (90%)</td>
</tr>
<tr>
<td>&quot;Shunt&quot; nephritis (90%)</td>
</tr>
<tr>
<td><strong>Renal Diseases</strong></td>
</tr>
<tr>
<td>Acute poststreptococcal glomerulonephritis (approximately 90%)</td>
</tr>
<tr>
<td>Membranoproliferative glomerulonephritis</td>
</tr>
<tr>
<td>Type 1 (approximately 50%-80%)</td>
</tr>
<tr>
<td>Type 2 (approximately 80%-90%)</td>
</tr>
<tr>
<td></td>
</tr>
</tbody>
</table>

Madaio M & Harrington JT, Arch Intern Med 2001, PMID 11146695
Additional Laboratory Data

- ANA 1:40 speckled
- dsDNA Ab <15
- C3 120 (nl 71-159)
- C4 18.7 (nl 13-30)

- ANCA IF 1:80 in a cytoplasmic pattern
- Proteinase 3: 118 (nl <21)
- Myeloperoxidase <10

Kidney Biopsy results

Focal crescentic and necrotizing glomerulonephritis, pauci-immune

- Two glomeruli have cellular crescents one is associated with a necrotizing lesion.
- No glomerular intracapillary hypercellularity
- The glomerular capillary walls are of normal thickness.
- No mesangial matrix accumulation and/or mesangial hypercellularity
- Immunofluorescence Microscopy (IF) negative for Ig, complement
Normal Kidney

Crescentic Glomerulonephritis with Necrotizing Lesion
Crescentic Glomerulonephritis

Crescentic Glomerulonephritis with Necrotizing Lesion

Courtesy of Jean Olson
Diagnosis:
ANCA associated pauci-immune glomerulonephritis with pulmonary nodules

Granulomatous Polyangiitis
(Formerly Wegener’s granulomatosus)

- Upper Respiratory involvement
  - Sinuses (nasal crusting)
  - Orbits (proptosis)
  - Hearing Loss (sensory neuronal or mechanical)
  - Subglottic stenosis
- Lower Respiratory Involvement
- Kidney Disease
- Arthralgia/Myalgia
- Fever
- Mononeuropathy multiplex

Laboratory Data
- ANCA or proteinase 3 present in >90% of severe GPA, 60% limited GPA
- Leukocytosis, anemia, thrombocytosis

Hoffman GS, Ann Intern Med 1992, PMID 1739240
Chauhan S, D’Cruz S, NEJM 2007
Pearl: Once Renal Involvement by GPA Begins, Organ- or Life-threatening Disease May Ensue Swiftly

Treatment of ANCA Associated Vasculitis

- High Dose Corticosteroids
  SoluMedrol 1000 mg/d x 3 days, then
  Prednisone 1 mg/kg/d (~60 mg/d), tapered off over 5-6 mo.
- Oral Cytoxan 2 mg/kg/d
  Fauci AS, et al, NEJM 1979, PMID 36563
- Rituximab (RAVE Study)
  Specks U, et al, NEJM 2013, PMID 23902481
- Plasmapheresis for:
  - Acute Renal Failure
  - Diffuse Alveolar Hemorrhage
Treatment Course

- The patient was treated with corticosteroids and then 2 doses of rituximab.
- He does well with resolution of fevers, improvement in weakness, and improvement in proteinuria and hematuria.
- 2 months later he returns to our ED with fever to 39°C, somnolence and confusion, mild dyspnea.
- Laboratory data: creat 0.8, LFTs normal, WBC 7.1, Hgb 10.5, PLT 103, ESR >100, CD19+ B cells undetectable.

**TIP: Refractory GPA is an Opportunistic Infection until proven otherwise**

- CSF Studies: protein 131, glucose 64, WBC 320 (90% lymphs)
- VZV PCR 1,900,00 DNA copies/ml
Monoarticular arthritis
Clinical Case

A 75 year old man with a history of diabetes, CKD, and gout is admitted with 1 day of acute swelling and pain in the right ankle. His temp is 101.4. The ankle is warm and swollen. The other joints seem unremarkable. Arthrocentesis in the ED demostrates negatively birefringent crystals. Cell count shows 85,000 WBC – 91% PMNs.

What do you do next:
A. Inject corticosteroids into the joint
B. Prescribe a prednisone taper
C. Prescribe colchicine every 30 min.
D. Prescribe IV antibiotics and wait for
The results of the gram stain & Cx

Differential Diagnosis of monoarticular arthritis

• Septic Arthritis
  – Staph
  – Lyme disease
  – Tb
  – Fungal

• Crystal Arthritis
  – Gout
  – Pseudogout

• Reactive Arthritis
• Trauma (Fracture)
• Exacerbation of OA
Risk factors for septic arthritis

- Diabetes
- HIV
- Rheumatoid arthritis
- Recent joint surgery
- Prosthetic joint (recent)
- Local wound/skin infection
- Immunosuppression (esp. TNF inhibitors)
- IV drug use

Margaretten ME, et al, JAMA 2007, PMID 17405973

The Value of a Careful Joint Exam

Tid bits

- WBC <10,000 has a strong negative predictive value
- WBC >100,000 has a strong positive predictive value
- Gram stain is 40-60% sensitive
- Cultures are 90% sensitive

Margaretten ME, et al, JAMA 2007, PMID 17405973

Synovial Fluid Analysis

WBC
- Gout & Septic arthritis 20,000 – 100,000
- Inflammatory Arthritis 2,000 – 20,000
- Non-inflammatory <2000
Acute Gouty Arthritis

• Provocation: trauma, ethanol, exercise, new medication

• First Attack:
  – fourth to sixth decade of life
  – 90% Monoarticular
  – 50% Podagra

• Sites:
  – 1st MTP
  – Instep, mid-foot, ankle, knee
  – wrist, fingers, elbow

• Extra-articular Sites
  – bursitis: MTP, olecranon, prepatellar

http://images.rheumatology.org/image_dir/album75676/md_99-14-0009.tif

Acute Gouty Arthritis

• Provocation: trauma, ethanol, exercise, new medication

• First Attack:
  – fourth to sixth decade of life
  – 90% Monoarticular
  – 50% Podagra

• Sites:
  – 1st MTP
  – Instep, mid-foot, ankle, knee
  – wrist, fingers, elbow

• Extra-articular Sites
  – bursitis: MTP, olecranon, prepatellar

### Acute Gouty Arthritis

**Differential Diagnosis**
- Crystal arthritis
- Septic arthritis (Source?)
- Trauma/fracture
- Dactylitis (spondyloarthropathy)
- Cellulitis
- Reflex sympathetic dystrophy

**Workup**
- Laboratory Studies
  - Uric Acid
  - Renal Function
  - CBC
  - TSH
  - ESR
- X-rays
- Joint aspiration of synovial fluid

### Test Your Knowledge...

All of the following are reasonable treatments for gout except:

a) **NSAIDS** (naproxen 500mg BID, indomethacin 50mg TID)

b) **Prednisone**: 40-60 mg/d, tapered over 6-18 days

c) **Intra-muscular corticosteroid injection**. (Triamcinolone 60-80 mg IM; may need to repeat in a couple of days)

d) **Intra-articular steroid injection** (Triamcinolone 20-40 mg)

e) **Colchicine**: 0.6 mg every 30 minutes until resolution or diarrhea/vomiting

f) **Anakinra** (IL-1 receptor antagonist), once daily for 3 days.
Treatment of Acute Gout

All of the following are reasonable treatments for gout except:

a) NSAIDS (naproxen 500mg BID, indomethacin 50mg TID)
b) Prednisone: 40-60 mg/d, tapered over 6-18 days
c) Intra-muscular corticosteroid injection. (Triamcinolone 60-80 mg IM; may need to repeat in a couple of days)
d) Intra-articular steroid injection (Triamcinolone 20-40 mg)
e) Colchicine: 0.6 mg every 30 minutes 1.2 mg then 0.6 mg 1 hour later. Do not repeat for 2 weeks if Pt has CKD.
f) Anakinra (IL-1 receptor antagonist), once daily for 3 days.
Treatment of Acute Gout

NSAIDs are problematic in patients with CKD

NSAIDs use was associated with increased risk of CKD in patients with hyperuricemia or gout (matched case-control study).

<table>
<thead>
<tr>
<th></th>
<th>Case (n/Tot)</th>
<th>Control (n/Tot)</th>
<th>[Risk of CKD] OR* (95% C.I.)</th>
<th>P value</th>
</tr>
</thead>
<tbody>
<tr>
<td>No previous renal disease or gout/hyperuricemia</td>
<td>6/43</td>
<td>25/143</td>
<td>0.57 (0.29, 1.16)</td>
<td>0.3</td>
</tr>
<tr>
<td>Previous renal disease, but no gout/hyperuricemia</td>
<td>14/38</td>
<td>2/20</td>
<td>6.6 (1.08, 37.5)</td>
<td>0.089</td>
</tr>
<tr>
<td>Gout/hyperuricemia, but no previous renal disease</td>
<td>8/17</td>
<td>4/21</td>
<td>7.1 (1.3, 39.7)</td>
<td>0.027</td>
</tr>
<tr>
<td>Previous renal disease and gout/hyperuricemia</td>
<td>4/12</td>
<td>0/5</td>
<td>82.2 (4.1, 1661.3)</td>
<td>0.004</td>
</tr>
</tbody>
</table>


Withdrawal of NSAIDs for 1 year (along with control of hyperuricemia) resulted in improved renal function in patients.


Mechanism of Inflammation in Gout

Neogi T, NEJM 2011, PMID 21288096
IL-1 and gout

All patients received anakinra (IL-1 receptor antagonist)
Treated with 100 mg SQ injection daily for 3 days.
All 10 patients with acute gout responded rapidly to anakinra.
No adverse effects were observed.

Thanks

- Dawn Gross, MD, PhD
- UCSF Rheumatology Division