Case Conference
April 1, 2014
Melissa Spera, MD
Chief Complaint

- Throat pain and neck swelling x 3 months
24 yr old man with no known past medical history who presented to ILH on 2/3/14 complaining of persistent throat and neck pain since November 2013.

The patient reports that in Nov 2013 he began to experience right ear pain with bilateral ear fullness.

He presented to OSH #1 at that time and was diagnosed with uvulitis and treated with a course of Amoxicillin/Clavulanate.
The patient reported slight improvement in his symptoms following antibiotics.

His symptoms then continued to progress to include dysphagia to solids then to liquids with associated odynophagia.

Other associated symptoms were night sweats, fevers, chills, fatigue and 30 lb weight loss attributed to decreased appetite and ability to eat.

He presented to OSH #2 for further evaluation on 12/31/13.

CT neck showed possible pharyngeal abscess and the patient was transferred to OSH #3 for ENT evaluation on 12/31/13.
On 1/3/14 he underwent bilateral tympanostomy tube placement with the finding of bilateral purulent otitis media.

During the procedure, the right tonsil was noted to be inflamed with evidence of parapharyngeal cellulitis.

Right sided tonsillectomy was also performed with exploration of the right upper parapharyngeal space.

No masses or abscesses were encountered.

Culture of ear drainage => slight coagulase negative staph.

The patient was treated with unknown IV antibiotics during hospitalization.
Repeat imaging of the neck was performed on 1/6/14 and showed possible mastoiditis with continued ill defined area of low attenuation in the right neck.

The patient was discharged 1/6/14 with PO antibiotics and prednisone taper prescribed.

Referral was sent to LSU ENT from OSH #3.
HPI

- The patient reported slight improvement in his symptoms following D/C with antibiotics and prednisone.
- Once treatment was completed his symptoms returned and progressed to include the following:
  - Bilateral conjunctivitis
  - Decreased vision in right eye
  - Difficulty opening his mouth with right facial droop
  - Nausea
  - Dysuria
  - Polyarthritis in his bilateral shoulders, knees, elbows and ankles
The patient was seen in LSU ENT Clinic on 2/3/14 for his head and neck symptoms.

Sent by ENT to the ED for admission to establish a diagnosis and direct therapy.
HPI

- Past medical history: as above
- Past surgical history: as above
- Family History
  
  Mother - alive - 50 yo with asthma, bronchitis
  
  Father - alive - 72 yo with CAD s/p stent placement
HPI-Social history

- Tobacco: 1 ppd x 5-10 years, quit Nov 2013
- ETOH: 1-2 beers/day on weekends
- Illicit drug use: Marijuana
- Employment: Previously employed as a crab fisherman on Lake Pontchartrain
- Sexual History: Previous monogamous relationship with woman
- Currently lives with his mother in Robert, La
- Hobbies include hunting and fishing
- No pets, sick contacts, recent travel or insect bites
HPI

- Allergies: NKDA
- Medications:
  - Hydrocodone acetaminophen 7.5-500mg syrup q6 hrs PRN pain
  - Promethazine 6.25mg/ 5ml syrup q6 hrs PRN nausea
- Health Care Maintenance-
  - Tdap, influenza - not up to date
- ROS - per HPI
Physical Exam

- BP 118/78  Pulse 107  Temp 99.5 °F  Resp 20  SpO2 99%
- Ht 1.88 m (6' 2")  Wt 107.049 kg (236 lb)  BMI 30.29 kg/m2
- BP 116/70  Pulse 95  Temp 100.0 °F  Resp 17  SpO2 97%
- General: AAOx4, appeared uncomfortable
- HEENT:
  - Ophtho: Bilateral mild ptosis, right pupil 3mm to 2mm, left 5mm to 3mm both reactive to light, bilateral conjunctivitis without exudate
  - No papilledema, no AV nicking, macula flat
  - OP: Evidence of right tonsillectomy, good dentition, no oral lesions noted, + trismus
  - Neck: Trachea midline, slight swelling of right neck, no masses palpated
  - Cardiac: Regular rate and rhythm, no murmurs, no rubs, no S3, no S4
  - Resp: Clear to auscultation bilaterally, no wheezes, no rhonchi, no crackles, symmetric chest expansion
Physical Exam continued

- Abdomen: Non distended; normoactive bowel sounds; soft, non tender, no rebound, no guarding
- GU: Negative for penile lesions, and discharge. No testicular masses or lesions
- Rectal: Good rectal tone, no stool in the vault, no masses palpated, no blood or melena present
- Lower extremities: No clubbing, cyanosis or edema, 2+ DP pulse bilaterally
- Neuro: Intact eye closure, head turn and shoulder shrug, smile limited by trismus, tongue midline, intact sensation in V1, 2, 3, 5/5 strength in bilateral upper and lower extremities
- Skin: No rashes, wounds, or jaundice
- Lymph: No cervical, axillary or inguinal lymphadenopathy
# Laboratory Findings

<table>
<thead>
<tr>
<th>Test</th>
<th>Value</th>
<th>Reference Range</th>
</tr>
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<tbody>
<tr>
<td>Na</td>
<td>132 mEq/L</td>
<td>(135-146 mEq/L)</td>
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<tr>
<td>K</td>
<td>4.5 mEq/L</td>
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<tr>
<td>Cl</td>
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<tr>
<td>CO2</td>
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<tr>
<td>BUN</td>
<td>15 mg/dL</td>
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</tr>
<tr>
<td>Cr</td>
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<tr>
<td>Gluc</td>
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<tr>
<td>Ca</td>
<td>9.2 mg/dL</td>
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<tr>
<td>Laboratory Findings</td>
<td>Value</td>
<td>Reference Range</td>
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<tr>
<td>---------------------</td>
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</tr>
<tr>
<td>WBC</td>
<td>9.8 K/uL</td>
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<tr>
<td>Hemoglobin</td>
<td>11.8 g/dL (13.5-17.5 g/dL)</td>
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<tr>
<td>Hematocrit</td>
<td>35.2% (40-51%)</td>
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<tr>
<td>Platelets</td>
<td>565 K/uL (130-400 K/uL)</td>
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<tr>
<td>MCV</td>
<td>88.7fL</td>
<td></td>
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<tr>
<td>RDW</td>
<td>12.6%</td>
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</tr>
<tr>
<td>Neutrophils</td>
<td>78%</td>
<td></td>
</tr>
<tr>
<td>Bands</td>
<td>0%</td>
<td></td>
</tr>
<tr>
<td>Lymphocytes</td>
<td>10%</td>
<td></td>
</tr>
<tr>
<td>Monocytes</td>
<td>6%</td>
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</tr>
<tr>
<td>Eosinophils</td>
<td>5% (AEC &gt;450)</td>
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</table>
# Laboratory Findings

<table>
<thead>
<tr>
<th>Test</th>
<th>Result</th>
<th>Reference Range</th>
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<tbody>
<tr>
<td>Total protein</td>
<td>7.2 g/dL</td>
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<tr>
<td>Albumin</td>
<td>3.0 g/dL</td>
<td>(3.4-5.0 g/dL)</td>
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<tr>
<td>Total bilirubin</td>
<td>1.2 mg/dL</td>
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<tr>
<td>AST</td>
<td>19 IU/L</td>
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<tr>
<td>Alkaline Phosphatase</td>
<td>70 IU/L</td>
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<tr>
<td>ALT</td>
<td>25 IU/L</td>
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</tr>
<tr>
<td>PT</td>
<td>16.1 sec</td>
<td>(9.2-12.5 sec)</td>
</tr>
<tr>
<td>INR</td>
<td>1.5</td>
<td>(0.9-1.2)</td>
</tr>
<tr>
<td>CRP</td>
<td>21.9 mg/dL</td>
<td>(&lt;0.90 mg/dL)</td>
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<tr>
<td>LDH</td>
<td>139 IU/L</td>
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</table>
Laboratory Findings

Urinalysis
- pH 8.0
- SG 1.008
- Clear, yellow
- Protein 25
- Glucose normal
- Ketones negative
- Blood 250
- Nitrites negative
- Uro bilinogen 4.0
- Leukocytes negative

Urine Microscopic
- > 100 RBC
- 6-10 WBC
- Sqam. epithelial cells 2-20
- Bacteria negative
- Casts 0-2
CT head with IV contrast
Hospital Course

- Admitted to ENT on the evening of 2/3/14
- General Medicine Consult Service, Infectious Disease, Hematology Oncology, Ophthalmology and IR consulted
Hospital Course 2/4/14

- IR felt the mass was too ill defined for ultrasound or CT guided tissue biopsy
- All services agreed tissue biopsy was necessary to establish diagnosis
Hospital Course 2/4

- Ophthalmology evaluation
- Conjunctivitis likely due to blepharitis vs Dry Eye Syndrome
- Could not rule out iritis
- Artificial tears with erythromycin ointment started
- Anisocoria - Idiopathic vs due to pharyngeal mass involvement
Hospital Course evening 2/5

- Temperature of 101.7°F recorded
- Vancomycin and piperacillin-tazobactam started
- Blood cultures drawn 2/3 were NGTD
- Patient with persistent eosinophilia:
  - >450 absolute eosinophil count on 2/4 and 2/5
- Further imaging including MRI orbit, face and neck performed
MRI Head with and without IV contrast
Hospital Course 2/6/14

- Taken to OR on 2/6/14 by ENT for full neck exploration
- Reactive parapharyngeal lymph nodes and parapharyngeal fat were noted
- No obvious abscess found
- Tissue specimens sent to pathology
  - Samples included parapharyngeal mass, lymph nodes and medial pterygoid
- JP drain was left in place
Pathology from neck exploration
Lymph node, reactive lymphoid hyperplasia, sinus histiocytosis, presence of neutrophils and eosinophils.
Lymph node, reactive lymphoid hyperplasia, high-power view, abundant eosinophils in the sinuses.
Pterygoid muscle, eosinophilic myositis, skeletal muscle with eosinophilic infiltration, muscle destruction and regeneration.
Pterygoid muscle, eosinophilic myositis, high-power view, abundant eosinophils evidence of muscle destruction
Parapharyngeal mass. Fibroadipose tissue with mixed inflammation including plasma cells and abundant eosinophils.
Parapharyngeal mass. High-power view. Mixed inflammatory infiltrate with abundant eosinophils.
Hospital Course 2/7/14

- Preliminary comments from pathology => possible vasculitis
- Further work up for vasculitis initiated
- Tissue cultures and blood cultures remained NGTD; AFB smear negative
Hospital Course 2/7/14

- Renal function worsened overnight from Cr 0.81 to 1.99
- Work up for AKI was initiated
- FENA was 0.43 => thought to be pre renal azotemia from decreased PO intake vs contrast induced
- UA was repeated and hematuria was still present
- No urine eosinophils were present
- Renal ultrasound => non specific echo texture of the renal parenchyma likely due to medical renal disease.
Hospital Course 2/8/14

- Creatinine continued to worsen => increasing from 1.99 to 2.63 despite IVF
- Vancomycin and piperacillin-tazobactam discontinued
- Renally dosed imipenem-cilastatin was initiated at 250mg IV q 8 hours
- Nephrology was consulted
Hospital Course 2/9/14

- Creatinine peaked at 3.28
- Urine specimen centrifuged by Nephrology
  - Too numerous to count RBC’s with dysmorphic RBC’s present
- Serologic work up to further evaluate renal failure was initiated
Creatinine trend

Creatinine trend graph showing the values over a specified date range.
Hospital Course 2/10-2/11

- Worsening creatinine, proteinuria and hematuria
- Patient consents to renal biopsy
- INR found to be 1.8
- Patient received FFP and vitamin K
- INR decreased to 1.5
- IR plans for renal biopsy
Hospital Course 2/11

- Anti proteinase 3 antibody returns as positive
- Concern for underlying ANCA associated vasculitis
- Patient is questioned further
- He reports recurrent sinusitis symptoms which began at age 18 yrs
- History of nasal crusting
- Occasional epistaxis
- No history of asthma, nasal polyps, or necrotizing nasal lesions
Hospital Course

- Methylprednisolone 1 gram IV daily was started × 3 days by renal on 2/11 to prevent further worsening of renal function
- Renal biopsy performed 2/12
Renal Biopsy

Slides courtesy of S Meleg-Smith, MD, Tulane nephropathology
Glomerulus

tubules

HE stain
ATN
RBC
Granular cast
Epith necrosis

HE stain
Loops OK

Epithelial proliferation

Inflammation

Fibrin

necrosis

HE stain
Antiserum to human fibrin

Crescent

Negative glomerulus
Fibrin Positive
In
Segmental necrosis of glomerulus
suggestive of fibrin thrombi in glomerulus
cannot rule out segmental necrosis
Loops with well preserved foot processes
R-83-14

Final diagnosis:

Focal segmental necrotizing glomerulonephritis

"pauci"-IC, i.e. neg IC
Laboratory Findings

C3 complement 160mg/dl
C4 complement 12mg/dl (18-55mg/dl)
Anti streptolysin O titer 61 IU/mL
ANA Screen Negative
Anti mitochondrial antibody 5.7 Units
Anti proteinase (PR-3) antibody >8 AI (<1.0 AI)
Anti myeloperoxidase antibody <0.2 AI (<1.0 AI)
Anti GBM antibody <0.2 AI
Rheumatoid Factor 948 IU/mL (<20 IU/mL)
TP/Creatinine ratio 849mg/g (<200mg/g)
Serum protein electrophoresis Negative
Urine protein electrophoresis Negative
**Laboratory Finding**

- **C-ANCA**: 1:80 (<1:20)
- **P-ANCA**: <1:20
- **Atypical ANCA**: <1:20
- **Serum IgG**: 839 mg/dL
- **IgG1**: 412 mg/dL (422-1292 mg/dL)
- **IgG2**: 355 mg/dL
- **IgG3**: 55 mg/dL
- **IgG4**: 94 mg/dL
- **T Spot TB**: Negative
- **IgE**: 723 IU/mL
Once renal biopsy preliminary results known => Rheumatology was consulted

“ANCA associated vasculitis”

Eosinophilic Granulomatosis Polyangiitis (EGPA) vs Granulomatosis Polyangiitis (GPA)

Patient underwent echo to evaluate for EGPA cardiac involvement

Echo 2/14 showed left ventricular enlargement with normal valves, normal systolic and diastolic function, LVEF > 55%, PAP < 35 mm Hg
Treatment 2/13

- The patient was started on prednisone 60mg PO q 24 hours with plans to taper with azathioprine 50mg PO q 12 hours

- The patient was discharged 2/14/14 with follow up
Hospital Follow up 2/26-2/27

- Follow up in Rheumatology and Renal Clinics
- Patient reports feeling better with improved swallowing
- He has noticed facial and lower extremity edema and a 30lb weight gain
- He was noted to have 2+ pitting edema on physical exam
Laboratory Findings 2/26

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<td>Na</td>
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<tr>
<td>Cl</td>
<td>106 mEq/L</td>
</tr>
<tr>
<td>CO2</td>
<td>29 mEq/L</td>
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<tr>
<td>BUN</td>
<td>47mg/dL</td>
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<td>Cr</td>
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<tr>
<td>Gluc</td>
<td>115 mg/dL</td>
</tr>
<tr>
<td>Ca</td>
<td>8.9 mg/dL</td>
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</table>
Follow up 2/26-2/27

- Nephrotic range proteinuria with protein/creatinine ration 4235 mg/g
- Azathioprine was increased to 100mg BID
- Prednisone continued at 60mg daily
- Furosemide 40mg daily initiated
Follow up 3/6-3/10

- Labs drawn 3/6/14 shows creatinine increased from 2.32 to 2.44 mg/dl
- Worsening TP/Cr ratio from 4235 to 5221 mg/g
- Rituximab infusion was initiated on 3/10/14, second dose received 3/17/14, and third dose on 3/24/14
Final Diagnosis

- ANCA associated vasculitis
ANCA Associated Vasculitis

- ANCA are highly specific for a group of disorders associated with vascular inflammation
- Include the following:
  - Granulomatosis Polyangiitis (GPA)
  - Microscopic polyangiitis (MPA)
  - Churg-Strauss syndrome.
- The term "ANCA-associated vasculitis" may be misleading since NOT all patients with clinical (and even histopathologically proven) diagnoses have ANCA.
  - 85% with GPA have ANCA
  - 70% with MPA have ANCA
  - 50% with Churg-Strauss syndrome have ANCA
Granulomatous Polyangiitis (GPA)

- Complex, immune-mediated disorder
  - Tissue injury results from:
    - Interplay of an initiating inflammatory event and
    - Highly specific immune response.
      - Part of this response is directed against previously shielded epitopes of neutrophil granule proteins
        - Leading to autoantibodies known as antineutrophil cytoplasmic antibodies (ANCA).
        - ANCA are directed against antigens present within the primary granules of neutrophils and monocytes
          - The most commonly identified and evaluated antigens in GPA are:
            - Proteinase 3 (PR3)
              - Observed in 70 to 80 percent of patients
            - Myeloperoxidase (MPO)
              - Observed in 10 percent of patients
      - These antibodies produce tissue damage via interactions with primed neutrophils and endothelial cells.
Granulomatous Polyangiitis (GPA)

- The events that MAY lead to the initiation of GPA are obscure and include:
  - Infection
  - Genetic factors
    - Met with limited success
  - Environmental factors
    - Exact relationships between environmental exposures and vasculitis are complicated by difficulties in obtaining reliable measurements of exposures
  - Drugs
    - Rifampicin, allopurinol, hydralazine, propylthiouracil, aminoguanidine reported to cause ANCA seroconversion
    - Particularly thiol and hydrazine containing compounds
  - Combo of all
Granulomatous Polyangiitis (GPA)

- GPA and MPA have similar clinical presentations
  - Mostly occur in older adults and both genders are equally affected.
  - Far more common among white individuals.
  - Typically present with constitutional symptoms including:
    - Fever, migratory arthralgias, malaise, anorexia and weight loss.
    - Prodromal symptoms may last for weeks to months without evidence of specific organ involvement.
Granulomatous Polyangiitis (GPA)

- Specific Organ System involvement
  - Ears, Nose, and Throat manifestations include:
    - Crusting, sinusitis, otitis media, persistent rhinorrhea, and purulent/bloody nasal discharge
    - More common in patients with GPA
      - Estimated frequency 90% in GPA versus 35% in MPA
    - GPA more typically have evidence of:
      - Bony and cartilage destruction resulting in saddle nose deformity
      - Upper airway and orbital masses
      - Cranial nerve entrapment and
      - Subglottic disease
Granulomatous Polyangiitis (GPA)

- Pulmonary manifestations
  - Either GPA or MPA may present with involvement of airways or pulmonary parenchyma causing:
    - Hoarseness, cough, dyspnea, stridor, wheezing, hemoptysis or pleuritic pain
    - Sometimes accompanied by signs of tracheal or subglottic stenosis, pulmonary consolidation and/or pleural effusion.
  - The chest x-ray findings are variable.
    - Common manifestations include nodules, patchy or diffuse opacities and fleeting pulmonary infiltrates, and hilar adenopathy
Granulomatous Polyangiitis (GPA)

- Renal manifestations is common in GPA and MPA
  - Can present as:
    - Asymptomatic hematuria or
    - Acute kidney injury with hematuria and cellular casts,
    - Variable degree of proteinuria that is usually subnephrotic.
  - Histologically, renal biopsy findings in GPA and MPA generally parallel the severity of the clinical presentation ranging from:
    - Mild focal and segmental glomerulonephritis in
      - Patients with asymptomatic hematuria and normal or near-normal renal function
    - Diffuse necrotizing and crescentic glomerulonephritis
      - Patients with acute kidney injury
    - In most patients, the glomerulonephritis is associated with few or no immune deposits in the glomeruli
      - Pauci-immune glomerulonephritis
Granulomatous Polyangiitis (GPA)

- Cutaneous manifestations occur in about one-half of patients with GPA or MPA.
  - The most common skin lesion is leukocytoclastic angiitis
    - Causes purpura involving the lower extremities
      - May be accompanied by focal necrosis and ulceration.
  - Skin lesions may also include urticaria, livida reticularis, and tender nodules

- Other manifestations include:
  - Eyes
    - Conjunctivitis, corneal ulceration, episcleritis/scleritis, optic neuropathy, nasolacrimal duct obstruction, proptosis, diplopia, retinal vasculitis, and uveitis
  - Nervous system
    - Mononeuritis multiplex, cranial nerve abnormalities, central nervous system mass lesions, external ophthalmoplegia, hearing loss
  - Patients with ANCA vasculitis have a high incidence of DVT.
Granulomatous Polyangiitis (GPA)

- Prompt diagnosis of GPA or MPA is important to permit initiation of therapy that may be life saving and organ sparing.
  - Diagnosis of vasculitis is strongly suggested in patients with:
    - Suggestive clinical findings
    - Positive ANCA test
    - False positive and negative results may be obtained.
  - Ultimately histologic examination of tissue is needed to make definitive diagnosis
    - Obtained by biopsy of an affected organ
    - Generally either skin, kidney or lung.
- Patients should be treated empirically if:
  - Clinical suspicion for ANCA vasculitis is high and
  - Tissue diagnosis cannot be obtained in a timely manner.
Granulomatous Polyangiitis (GPA)

Several attempts made to standardize the classification and diagnostic criteria for small vessel vasculitis.

Classification algorithms have important limitations.

None of the algorithms reliably distinguish between GPA and MPA in all patients.

Alternative approach to classification based upon ANCA serology uses the terms:

"proteinase 3 ANCA disease," "myeloperoxidase ANCA disease," and "seronegative ANCA disease."

With this approach, no diagnostic criteria are needed other than serological findings.

Proteinase 3 ANCA and myeloperoxidase ANCA have more prognostic significance than the terms MPA and GPA with respect to response to therapy, propensity for relapse, and patient outcome.
Granulomatous Polyangiitis (GPA)

- **The American College of Rheumatology (ACR) 1990 criteria**
- **Chapel Hill Consensus Conference (CHCC) criteria**
- **European Medicines Agency algorithm**

The distinction of ANCA vasculitis from other systemic rheumatic diseases is a frequent clinical problem.

- Includes diseases with similar general clinical features, similar lung and/or renal signs, and/or positive ANCA serologies
- Evaluation must be undertaken to assess other potential diagnoses
Granulomatous Polyangiitis (GPA)

- Induction of complete remission is the goal of immunosuppressive therapy in GPA or MPA
- Defined as the absence of active disease.
  - Approach to initial therapy depends upon the severity of the disease and the organ systems involved.
  - From an initial therapeutic perspective, there are essentially two groups:
    - **Mild disease**
      - No evidence for "active" glomerulonephritis
      - Normal serum creatinine and no red cell casts or proteinuria
      - No organ-threatening or life-threatening manifestations
        - Absence of pulmonary hemorrhage, cerebral vasculitis, progressive neuropathy, orbital pseudotumor, gastrointestinal bleeding, pericarditis, or myocarditis
    - **Moderate to severe disease**
      - Other patients with GPA or MPA are classified into this group for the purposes of initial therapy.
      - May have organ-threatening or life-threatening manifestations, including (but not limited to) marked pulmonary hemorrhage or rapidly deteriorating renal function.
Granulomatous Polyangitis (GPA)

Choice of Therapy

Mild disease

- Glucocorticoids in combination with methotrexate (Grade 2C).
- Rather than other therapies or glucocorticoids alone
- Failure to respond to methotrexate or who have progressive disease should be treated with:
  - Either cyclophosphamide or rituximab.
Granulomatous Polyangiitis (GPA)

- **Choice of Therapy**
  - **Moderate to severe disease** -
    - Glucocorticoids in combination with either cyclophosphamide (oral or intravenous) or rituximab (Grade 1A).
    - Rather than other therapies or glucocorticoids alone
    - Cannot take or refuse to take cyclophosphamide then initial immunosuppressive therapy with rituximab and glucocorticoids (Grade 1B).
    - Plasma exchange in addition to cyclophosphamide and glucocorticoid therapy (Grade 2C) for patients with GPA or MPA who have one or more of the following:
      - Serum creatinine above 5.7
      - Requirement for dialysis
      - Pulmonary hemorrhage
      - And/or a positive anti-glomerular basement membrane (anti-GBM) antibody.
  - Consider prophylaxis against opportunistic infections during induction therapy
    - Suggested regimen varies with the regimen used for initial immunosuppression.
Eosinophilic Granulomatosis with Polyangiitis (EGPA/Churg-Strauss)

- Previously called the Churg-Strauss syndrome (CSS) or allergic granulomatosis and angiitis
- Multisystem disorder characterized by:
  - Allergic rhinitis
  - Asthma
  - Prominent peripheral blood eosinophilia.
    - $\geq 1500$ cells/microL and/or $>10\%$ eosinophils on differential leukocyte count
- The most commonly involved organ is the lung, followed by the skin.
- Can affect any organ system, including:
  - Cardiovascular, gastrointestinal, renal, and central nervous systems.
    - Vasculitis of extrapulmonary organs is largely responsible for the morbidity and mortality associated with EGPA.
Eosinophilic Granulomatosi with Polyangiitis (EGPA/Churg-Strauss)

- The exact etiology is unknown.
- ANCA is detected in about 40 to 60 percent of patients.
- EGPA is classified among the ANCA-positive vasculitides.
  - Least common of the three (MPA and GPA)
- Several other abnormalities in immunologic function occur, including:
  - Heightened Th1 and Th2 lymphocyte function
    - Determined by prominence of allergic features (allergic rhinitis, asthma, and positive skin tests) and pulmonary angiocentric granulomatosis respectively
  - Increased eosinophil recruitment and
  - Decreased eosinophil apoptosis.
Eosinophilic Granulomatosis with Polyangiitis (EGPA/Churg-Strauss)

- Genetic factors
  - HLA class and certain interleukin-10 polymorphisms may play a role in pathogenesis.

- Association with Medications
  - Leukotriene modifying agents, inhaled glucocorticoids, and omalizumab
  - Appears association most likely due to unmasking of the underlying disease or intensification of therapy in a patient with escalating EGPA, rather than a causal relationship.

- Cocaine
  - EGPA-like illness can rarely occur after the use of free base cocaine.
  - ANCAs associated with cocaine use recognize different target proteases than the typical ANCAs associated with EGPA.
Eosinophilic Granulomatosis with Polyangiitis (EGPA/Churg-Strauss)

- The major histopathologic findings of EGPA from any affected organ include the following:
  - May not all be present
  - Eosinophilic infiltration
  - Prominent and sometimes extensive areas of necrosis
  - Eosinophilic, giant cell vasculitis
    - Especially of the small arteries and veins
  - Interstitial and perivascular necrotizing granulomas
Eosinophilic Granulomatosis with Polyangiitis (EGPA/Churg-Strauss)

- Clinical features typically develop in several sequential phases
  - Although these phases are not always clearly distinguishable
  - Prodromal phase
    - Occurs in the second and third decades of life
    - Characterized by atopic disease, allergic rhinitis, and asthma.
  - Eosinophilic phase
    - Features include peripheral blood eosinophilia and eosinophilic infiltration of multiple organs
      - Especially the lung and gastrointestinal tract.
    - Almost 40 percent of patients with EGPA present with pulmonary opacities, asthma, and peripheral eosinophilia prior to the development of a systemic vasculitis (polyangiitis).
  - Vasculitic phase
    - Third and fourth decades of life
    - Life-threatening systemic vasculitis of the medium and small vessels
      - Often associated with vascular and extravascular granulomatosis.
    - May be heralded by nonspecific constitutional symptoms and signs
      - Especially fever, weight loss, malaise, and lassitude.
Eosinophilic Granulomatosis with Polyangiitis (EGPA/Churg-Strauss)

- **Pulmonary disease**
  - Asthma is the cardinal clinical feature and present in more than 90% of patients
    - Usually precedes the vasculitic phase by approximately 8 to 10 years
    - Suspect in patients whose asthma is poorly controlled on moderate doses of inhaled glucocorticoids
    - Prolonged treatment of asthma with glucocorticoid therapy may partially or totally suppress the usual clinical signs of untreated EGPA.
      - Disease may therefore not become evident until glucocorticoids are reduced or stopped
  - Other pulmonary findings are reported in 50 to 70 percent of patients include:
    - Pulmonary opacities with eosinophilia, pleural effusion (often eosinophilic), nodules that are rarely cavitary, and alveolar hemorrhage
Eosinophilic Granulomatosis with Polyangiitis (EGPA/Churg-Strauss)

- **Other organ involvement**
  - **Ears, Nose and Throat**
    - Serous otitis, allergic rhinitis, nasal obstruction, recurrent sinusitis, and nasal polyposis, is reported in 48 percent of patients
  - **Neurologic**
    - A peripheral neuropathy, usually mononeuritis multiplex, is seen in up to 75 percent of patients with EGPA.
  - **Skin**
    - Two-thirds of EGPA patients have skin involvement ranging from palpable purpura to subcutaneous nodules.
    - Skin biopsy is often helpful for confirming the diagnosis.
  - **Renal**
    - Varies in studies with largest having 22% involvement
  - **GI**
    - Can have eosinophilic gastroenteritis
  - **Cardiac**
    - One of the more serious manifestations, accounting for approximately one-half of deaths attributable to EGPA.
    - Suspected in the presence of refractory dyspnea, clinical evidence of heart failure, or cardiac rhythm abnormalities, but can also be asymptomatic.
Eosinophilic Granulomatosis with Polyangiitis (EGPA/Churg-Strauss)

- Labs
  - There are no laboratory tests that are specific for EGPA
    - Although eosinophilia is characteristic
  - Obtain a complete cell count with differential, a total eosinophil count, and an IgE level.
  - Also usually obtain an ANCA test
    - Although the sensitivity and specificity are low

- Imaging
  - Chest radiographic abnormalities are variable and diverse.
  - High resolution computed tomography (HRCT) of chest findings include:
    - Patchy parenchymal consolidation or ground glass opacification; nodules may also be noted
Eosinophilic Granulomatosis with Polyangiitis (EGPA/Churg-Strauss)

- The ACR has established six criteria for the classification of EGPA in a patient with documented vasculitis

- The presence of four or more of these criteria had a sensitivity of 85 percent and a specificity of 99.7 percent:
  - Asthma (a history of wheezing or the finding of diffuse high pitched wheezes on expiration)
  - Greater than 10 percent eosinophils on the differential leukocyte count
  - Mononeuropathy (including multiplex) or polyneuropathy
  - Migratory or transient pulmonary opacities detected radiographically
  - Paranasal sinus abnormality
  - Biopsy containing a blood vessel showing the accumulation of eosinophils in extravascular areas
Five-factor score in eosinophilic granulomatosis with polyangiitis (Churg-Strauss)

<table>
<thead>
<tr>
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<tbody>
<tr>
<td>Cardiac involvement</td>
<td>Age &gt;65 years</td>
</tr>
<tr>
<td>Gastrointestinal disease (bleeding, perforation, infarction, or pancreatitis)</td>
<td>Cardiac insufficiency</td>
</tr>
<tr>
<td>Renal insufficiency (plasma creatinine concentration &gt;1.6 mg/dL [141 mmol/L])</td>
<td>Renal insufficiency (stabilized peak creatinine 1.7 mg/dL [150 micromol/L])</td>
</tr>
<tr>
<td>Proteinuria (&gt;1 g/day)</td>
<td>Gastrointestinal involvement</td>
</tr>
<tr>
<td>Central nervous system involvement</td>
<td>Absence of ENT manifestations (presence is associated with a better prognosis)</td>
</tr>
</tbody>
</table>

The presence of each factor is given one point. The FFS score ranges from 0 to 2: a score of 0 is given when none of the factors is present, a score of 1 for one factor, and a score of 2 for two or more factors.

FFS: five-factor score; ENT: ear, nose, and throat.

Data from:
Eosinophilic Granulomatosis with Polyangiitis (EGPA/Churg-Strauss)

- The diagnosis of EGPA is typically suspected based on the clinical findings
  - Eosinophilia $\geq 1500$/microL, asthma, allergic rhinitis.
- Confirming the diagnosis is often difficult because of the following confounding factors:
  - Individual manifestations of the syndrome can occur in isolation.
  - Lung parenchymal involvement is not universal.
  - Some manifestations can exist for many years before additional features become clinically apparent.
  - Classified as a vasculitis but only 40 to 60% have ANCA.
    - Many biopsies do not show a necrotizing vasculitis or granuloma, but rather an apparently nondestructive infiltration of vessel walls by eosinophils.
Eosinophilic Granulomatosis with Polyangiitis (EGPA/Churg-Strauss)

- EGPA patients with evidence of systemic vasculitis
  - Systemic glucocorticoid therapy (Grade 1A) daily for 6 to 12 weeks, or until disease remission is attained, and then gradually tapered.
  - Patients with fulminant disease may require initial therapy with intravenous glucocorticoids.

- For patients with severe disease manifest by a FFS of 2:
  - Addition of cyclophosphamide to systemic glucocorticoid therapy (Grade 1B).

- For patients with a FFS of 1
  - Especially with cardiac or central nervous system involvement
  - Addition of cyclophosphamide to systemic glucocorticoids (Grade 2C).
**Eosinophilic Granulomatosis with Polyangiitis (EGPA/Churg-Strauss)**

- After induction of remission with cyclophosphamide
  - Transition to maintenance therapy with azathioprine to sustain the remission (Grade 1B).
  - Methotrexate and leflunomide are alternative agents that can be used if azathioprine is not tolerated or is not effective.
  - These drugs are preferred to long-term cyclophosphamide therapy
    - Associated with significantly greater toxicity
  - Continue maintenance immunosuppressive therapy for 12 to 18 months.
    - Longer term or indefinite maintenance therapy may be warranted in patients with multiple relapses
- Concurrent glucocorticoid therapy (prednisone or equivalent) (Grade 1C) is recommended for maintenance therapy.
  - Glucocorticoid is gradually tapered to the lowest dose required for control of symptoms and signs of active EGPA
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