Dilemmas in Vasculitis

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Vasculitis: Classification

• Large vessel vasculitis:
  – Giant cell arteritis: more to follow
  – Takayasu’s arteritis: aortic arch and its branches, can involve any part of the aorta; claudication of upper > lower extremities, CNS events; granulomatous panarteritis

• Medium vessel vasculitis:
  – Polyarteritis nodosa: small and medium-sized arteries; may affect any organ: skin, joints, peripheral nerves, gut, and kidney are most commonly involved; focal but panmural necrotizing arteritis with a predilection for involvement at the vessel bifurcation
  – Kawasaki’s disease: small and medium-sized arteries; acute febrile illness primarily affecting infants and young children; fever, prominent mucocutaneous changes, cervical lymphadenopathy, polymorphous rash, erythema and edema of hands and feet, desquamation, myocarditis, coronary vasculitis; probable infectious vector resulting in cytokine-mediated endothelial damage
  – Primary angiitis of the CNS
• Small vessel vasculitis (ANCA positive):
  – Granulomatosis with polyangiitis (GPA) (formerly Wegener’s): small and medium-sized arteries; upper respiratory tract (sinuses), lungs, and kidneys, may affect other organs; pauci-immune, necrotizing, granulomatous arteritis usually associated with serum cytoplasmic-ANCA (c-ANCA)
  – Microscopic polyangiitis (MPA): arterioles, capillaries, and venules; pulmonary hemorrhage, glomerulonephritis, palpable purpura, peripheral neuropathy, joint and abdominal pain; pauci-immune, necrotizing vasculitis, serum perinuclear-ANCA (p-ANCA) common

• Small vessel vasculitis (ANCA positive):
  – Churg-Strauss syndrome: small arteries and venules; asthma, eosinophilia, multiorgan involvement – lungs, skin, peripheral nerves, gut, heart, renal (rare); necrotizing extravascular granulomas and vasculitis of small arteries and venules, eosinophils present in early stage

• Small vessel vasculitis (ANCA negative):
  – Henoch-Schönlein Purpura (HSP): arterioles and venules; palpable purpuric skin lesions lower extremities, arthritis, abdominal pain, hematuria; leukocytoclastic (neutrophilic perivascular/transmural infiltrate) or necrotizing vasculitis often with IgA deposition
  – Cutaneous leukocytoclastic angiitis (hypersensitivity vasculitis): arterioles and venules; palpable purpuric skin lesions, arthralgias, systemic symptoms may be present, usually secondary to an immune response [drugs, bugs (infections), connective tissue disease, malignancy]
• Small vessel vasculitis (ANCA negative):
  – Essential cryoglobulinemic vasculitis: cryoglobulins are immunoglobulins that are reversibly precipitated by reduced temperatures; cryoglobulins are deposited in small vessels including glomerulocapillaries; purpura, arthralgias, weakness, peripheral neuropathy, Raynaud's phenomenon, glomerulonephritis, pulmonary hemorrhage possible; often rheumatoid factor (RF) and hepatitis C antibody positive; cryoglobulins deposited on the vascular wall stimulate complement activation and a cellular inflammatory response.

Clinical Features Suggestive of Some Kind of Vasculitis (SKV)
• Constitutional symptoms: fever, anorexia, weight loss, weakness, fatigue
• Musculoskeletal symptoms: arthralgias, arthritis/synovitis, myalgias
• Palpable purpura: biopsy will show leukocytoclastic vasculitis – do immunofluorescence (IF) to rule out IgA deposition c/w HSP
• Mononeuritis multiplex or asymmetric polyneuropathy
• Pulmonary-renal involvement

Vasculitis: Diagnostic Approach
• History and Physical examination
• Laboratory:
  – ↑ ESR and CRP: if both negative low probability of vasculitis
  – AOCD, reactive thrombocytosis, ↓ albumin
  – ARF with hematuria/proteinuria
  – Low complement levels
  – ANA, RF, ANCA's with PR3 and MPO, cryos
  – Biopsy of affected organ
  – Angiography
Some Kind of Vasculitis
What is the appropriate initial approach?
62-year-old man is admitted with a 1-month h/o progressive
dyspnea, weakness/myalgias, and flu-like symptoms. He
denied hemoptysis but complained of sinus pressure and
right ear fullness. On exam: no synovitis, rash, or neuropathy.
Labs: Cr 0.9 with urine dip negative; 13/36/379; ESR 75; CRP
120 (<3); CT chest with diffuse ground glass opacities.
Bronchoscopy with diffuse alveolar hemorrhage (DAH);
cultures negative. Pending: ANA, RF, ANCAs, PR3, MPO, anti-
GBM antibodies.
1. Treat for community-acquired pneumonia (CAP)
2. Prednisone 40 mg/day
3. Prednisone 60 mg/day
4. Methylprednisolone 250 mg iv q6h x 3 days (pulse steroids)
5. Pulse steroids plus therapeutic plasma exchange (TPE)

ANCAs: Cytoplasmic and Perinuclear

Antineutrophil Cytoplasmic Antibodies (ANCAs)

• Cytoplasmic-ANCA (cANCA):
  – Antibodies directed against a serine protease
called proteinase 3 (PR3); ELISA available
• Perinuclear-ANCA (pANCA):
  – Antibodies usually directed against
myeloperoxidase (MPO), ELISA available; also
lactoferrin, elastase, catalase, cathepsin G,
bactericidal permeability increasing protein,
lysozyme, and β-glucuronidase
  – Artifact of ethanol fixation of PMNs: positively
charged granule constituents rearrange around
the negatively charged nuclear membrane
  – ANA + individuals may have a false + pANCA
Conditions Associated with ANCAs

- Granulomatosis with polyangiitis (Wegener’s):
  - cANCA: sensitivity 64-90%, specificity 98% for active generalized WG (90% PR3+, remainder are MPO+)
  - Limited WG: 40% may be ANCA negative
  - cANCA plus anti-PR3: sens 73%, spec 99%; may obviate the need for tissue biopsy in the right clinical setting (Hagen EC et al. Kidney Int 1998;53:743)

- Microscopic polyangiitis (MPA):
  - pANCA: sensitivity 60-90%, specificity poor as can be seen in RA, SLE, IBD, PBC
  - pANCA plus anti-MPO: spec improves to >95%
  - True PAN: anti-PR3 and anti-MPO are negative

- Churg-Strauss: 50% ANCA positive; most MPO +
- Idiopathic pauci-immune GN: almost all ANCA + with 75-80% having MPO-ANCA
- Drug-induced ANCA-associated vasculitis:
  - Most are MPO-ANCA, often high titer
  - Strongest links:
    - Propylthiouracil (PTU): PR3, MPO, elastase
    - Hydralazine: MPO, elastase, lactoferrin
    - Minocycline: rarely MPO +
  - Other drugs: allopurinol, clozapine, phenytoin, and procaainamide

- Goodpasture’s: 10-40% ANCA+
- CTDs: pANCA have been reported in most inflammatory rheumatic conditions
- Ulcerative colitis and sclerosing cholangitis: pANCA 60-80%; often directed against a nuclear envelope protein
- Crohns: 10-27%, low titers
- Cystic fibrosis: non-MPO pANCA common; directed against bactericidal permeability increasing protein
- Others: autoimmune hepatitis, Buerger’s, SBE, cocaine-induced midline destructive lesions (human neutrophil elastase), cholesterol emboli syndrome, and chronic infections
Issues with ANCA Titers

• The disappearance of ANCA is usually associated with clinical remission
• Unfortunately, increases in ANCA titers do not predict disease relapses:
  – Prospective, observational cohort study of 156 patients with active GPA: only 40% of the increases in PR3-ANCA levels were followed by a relapse within 1 year (Finkielman JD et al. Ann Intern Med 2007;147:611-619)
  – Systematic review of 22 studies with ANCA-associated vasculitis was unable to conclude the clinical utility of following serial ANCA titers (Birck R et al. Am J Kidney Dis 2005;47:15-23)

Plasmapheresis

Therapeutic Plasma Exchange (TPE)

• Three subsets of ANCA-associated vasculitis that may benefit from TPE:
  – Concurrent anti-GBM antibody disease
  – Pulmonary hemorrhage
  – Presenting with dialysis-dependent renal failure
• TPE should be considered in mixed cryoglobulinemia syndrome with acute severe disease: progressive renal failure, DAH, distal necroses, and/or advanced neuropathy

TPE for ANCA-Associated Pulmonary Hemorrhage

• Randomized control trials have not been performed
• Klemmer PJ et al. Am J Kidney Dis 2003;42:1149:
  – UNC retrospective review of 20 pts with DAH and ANCA-associated vasculitis (17 MPA, 2 WG, and 1 CSS)
  – All received pulse steroids, TPE (alb and 2 units FFP), and IV cytoxan 0.5 gm/m²
  – DAH resolved in all patients
  – * Retrospective, lack of control group, and inability to assess role of TPE since all patients received the same treatment
**TPE for ANCA Renal Disease**

- Methylprednisolone versus Plasma Exchange (MEPLEX) trial: Methylprednisolone 1 gm/d x 3 versus Plasma Exchange (7 sessions in 2 weeks)
- Randomized trial of 137 patients with GPA, MPA, or necrotizing GN with a Cr > 5.7 mg/dl
- All received pred 1mg/kg/d and oral CTX 2.5 mg/kg/day x 3 months then AZA
- Three-month rate of dialysis-free survival:
  - TPE: 69%
  - Methylprednisolone: 49%
- 24% reduction in risk to ESRD with TPE at one year


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**Initial Immunosuppressive Therapy for GPA and MPA**

- Aggressive therapy is indicated: mortality rate in untreated GPA approaches 90% at 2 years (respiratory or renal failure)
- Initial treatment:
  - Corticosteroids: pulse IV methylprednisolone if critically ill versus prednisone 1mg/kg/day (max 60-80 mg/day)
  - Cyclophosphamide (CTX): IV or PO?
  - Rituximab (anti-CD20 B cell antibody): a possible alternative to CTX?

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**Cyclophosphamide: IV or PO?**

  - Meta-analysis of 11 studies: sparse data suggesting pulse CTX is more effective than oral CTX in inducing remissions but is less effective in preventing relapses
  - Pulse IV CTX vs oral cytoxan: treated until clinical remission then an additional 3 months followed by maintenance AZA with pred 5 mg/day for 18 months
**CYCLOPS**

**Pulse versus Daily Oral CTX**

- Pulse CTX was associated with a higher relapse risk than daily oral CTX (DO).
- Not associated with increased mortality or morbidity.
- Pulse CTX resulted in less cumulative dose vs DO.
- Increased risk of leukopenia with DO regimen.
- Base treatment decision on risk of relapse and risk of adverse effects.


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**Rituximab for GPA and MPA**

  - 197 pts (GPA 75%, MPA 25%); 49 pts new diagnosis with remainder relapses.
  - Rituximab 375mg/m^2/wk x 4 vs oral CTX (6 months).
  - Pulse steroids followed by oral prednisone.
  - Rituximab noninferior to CTX in inducing remission but superior to CTX in relapsing disease.

- **RITUXVAS trial** (Jones RB et al. N Engl J Med 2010;363:211)
  - 44 pts with new ANCA-assoc renal vasculitis.
  - Rituximab as above with 2 pulses CTX vs IV CTX for 3-6 months followed by AZA.
  - At 12 months, no diff in rate of remission (76% vs 82%).

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**ANCA-Associated Vasculitis**

**Points to Remember**

- PR3-ANCAs are more specific than MPO-ANCAs.
- Increases in ANCA titers do not predict disease relapses.
- Initial therapy includes high-dose steroids and CTX; rituximab should be considered in patients with contraindications or who refuse CTX.
- Indications for TPE: pulmonary hemorrhage, severe renal disease, and concurrent GBM antibody disease.
- Experts recommend IVIG (400 mg/kg dose x1) replacement after TPE to decrease infection risk.
Back to the Case of DAH
What is the appropriate treatment option?

- Pulse steroids and TPE were initiated
- Labs returned with negative ANA and RF; negative anti-GBM abs; p-ANCA < 1:20 with negative MPO; c-ANCA 1:640 with PR3 27 (<3.5)
- Dx: GPA – started IV CTX and pred 60 mg/day
  1. No further treatment aside from osteoporosis prophylaxis
  2. Trimethoprim-sulfamethoxazole
  3. Dapsone
  4. Atovaquone
  5. Aerosolized pentamidine

Prevention of Pneumocystis Pneumonia (PCP) in Non-HIV-infected Patients

- The name of the species of Pneumocystis that infects humans has been changed from *carinii* to *jirovecii* to distinguish it from the species that infects rats
- Asymptomatically present in scarce quantities in the lungs of up to 62% of adults (Ponce CA et al. Clin Infect Dis 2010;50:347-353)
- Leads to clinical disease and tissue damage in the setting of cell-mediated immune dysfunction (CD4+ T cells)

Pneumocystis Pneumonia (PCP) in CTD

- Incidence of PCP infection in patients with CTD is 1-2% which increases to > 6% in patients with GPA
- Staggering mortality rate of 39-59% in CTD patients with PCP compared to 10-20% in patients with HIV who develop PCP
- PCP in non-HIV patients often has a rapid, fulminant course requiring mechanical ventilation and ICU care
- Mortality rates are likely due to an immune-driven inflammatory response more than a pathogen-driven response

PCP Prophylaxis in Patients with CTDs

- No published guidelines for patients with CTDs receiving immunosuppressive drugs
- PCP prophylaxis is not routinely prescribed in patients treated with high-dose steroids for GCA or sarcoidosis; PCP is rarely reported
- PCP infections can occur in patients with SLE who are on no immunosuppressive therapy (Godeau B et al. J Rheumatol 1994;21:246-251)
- Lymphopenia (low CD4) obviously contributing

PCP Prophylaxis in Patients with CTDs

- PCP has been associated with other immunosuppressive medications including CTX (can result in prolonged lymphopenia), MTX, AZA, CSA, TNF inhibitors, and rituximab
- Other risk factors include lymphopenia and underlying lung disease:
  - Increased risk of PCP with CD4 counts < 350 cells/mm$^3$: need further studies to determine if low CD4 count or absolute lymphocyte count (ALC) can predict PCP risk
  - Underlying ILD is strongly associated with ↑ risk of PCP (GPA, Dermatomyositis, CTD-ILD)

Risk Factors for PCP in Patients with CTDs

1. Corticosteroids ≥ 20 mg for > 4 weeks
2. Simultaneous immunosuppressive medications
3. Severe lymphopenia
4. Underlying parenchymal lung disease
   
   **Suggest PCP prophylaxis if ≥ 2 of 4 risk factors**
### PCP Prophylaxis: Management Options

- **Trimethoprim-sulfamethoxazole (TMP/SMX):**
  - First line agent: dose 1 double-strength tablet three times a week ($9.00/week); > 90% reduction in PCP
  - TMP/SMX prophylaxis not contraindicated in patients on MTX; fatal cytopenias reported with MTX and high therapeutic dose of TMP/SMX
  - Sulfonamide allergic reactions reported in SLE patients: rash, cytopenias, and lupus flares
- **Dapsone:**
  - Dose 100 mg/day ($1.40/day)
  - Need to screen for G6PD deficiency: dapsone can precipitate hemolytic anemia even if G6PD negative

### PCP Prophylaxis: Points to Remember

- PCP: low incidence but high mortality
- Strong consideration for PCP prophylaxis with ≥ 2 of the following: 1) long term corticosteroids ≥ 20 mg/day, 2) simultaneous immunosuppressive meds, 3) severe lymphopenia, and 4) underlying parenchymal lung disease
- Maintaining or increasing corticosteroid dose may be of benefit in treating PCP in patients with CTDs (immune-driven response)
- Risk may persist after lower doses or cessation of immunosuppressive therapy: consider checking CD4 cell counts

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Another Case of SKV
What is the appropriate initial approach?
• 76-year-old woman was admitted for weight loss and failure-to-thrive. She reports a 2-month h/o frontal headache sometimes lateralizing to the left temple. She also c/o a scalp burning sensation which she attributed to a new Perm. Further history reveals occasional double vision and some jaw soreness with chewing. PE with cachexia and TA tenderness. Labs: 5/38/361; Cr 0.9, ESR 71.
1. Analgesics for tension headache
2. Elective TA biopsy followed by pred 60 mg/day
3. Methylprednisolone 1000 mg/day iv x 3 days
4. Pred 60 mg/day with TA biopsy within 1 week
5. Pred 60 mg/day and ASA 81 mg/day with TA bx within 1 week

Giant Cell Arteritis (GCA)
• GCA should be considered in anyone > age 50 with:
  – New headache
  – Acute onset of visual disturbances
  – Symptoms of PMR
  – Jaw claudication
  – Unexplained fever or anemia
  – High ESR and/or CRP: ESR may be < 50 in 10% of patients; CRP will be elevated

GCA: Clinical Presentations
• Gradual > acute onset 2:1
• Cranial symptoms (40%):
  – Superficial headache (80%)
  – Scalp tenderness; scalp necrosis
  – Jaw claudication (40%)
  – Tender temporal arteries (25%)
  – Associated low-grade fever (40%), weight loss (50%), and malaise (40%)
• Cranial symptoms and PMR (40%)
GCA: Other Presentations

- FUO with temps to 39-40°
- Cough/URI (10%)
- Arteritis of aorta/branches:
  - Claudication UE>LE (10%): bruits and BP changes
  - Stroke due to carotid/vertebral artery involvement (does not affect intracranial vessels which lack an internal elastic lamina)
  - Mesenteric ischemia
- Arteritis of medium arteries:
  - Coronary, audiovestibular, ischemic neuropathies
  - Ocular: diplopia to visual loss – vasculitis of posterior ciliary arteries; diplopia predictive of GCA

Anterior Ischemic Optic Neuropathy (AION)

- Arteritic (GCA):
  - Mean age 70
  - F>M, HA, scalp tenderness
  - Pale or blurred disc; cotton wool spots
  - Normal disc cup
  - ESR 70
  - Steroids: rare improvement

- Nonarteritic (NAAION):
  - Mean age 60
  - M=F, HTN, DM, sildenafil: awaken with no vision
  - Hyperemic > pale disc with edema
  - Small disc cup: no cotton wool spots
  - ESR 20-40
  - ASA: 40% improve

GCA: Laboratory

- Elevated ESR usually > patient's age
  - Frequently > 100 mm/hr
  - ESR < 50 in 10% of pts; not a better prognosis
- Elevated C-reactive protein (CRP):
  - Frequently > 10 x ULN
  - Always abnormal
- CBC:
  - Anemia of chronic disease (AOCD)
  - Possible reactive thrombocytosis
  - Normal leukocyte count
### GCA: Laboratory

- **Chemistries:**
  - ↑ alkaline phosphatase (25-33%)
  - CPK normal
  - Renal function and urinalysis normal
- **SPEP:** ↑ α₁ and α₂; no spike
- **Serologies:**
  - ANA negative
  - ANCA negative
  - RF negative

### GCA: Diagnosis

- Temporal artery biopsy is gold standard:
  - Constitutional symptoms, jaw claudication, visual changes, and abn TA predicts positive biopsy (Gonzalez-Gay MA et al. Semin Arthritis Rheum 2001;30:249)
  - Large artery presentation: < 60% + TA biopsy
- **Bx size:** 3-5 cm and sliced at 1 mm increments
- **Unilateral versus bilateral TA biopsy?**

### Temporal Artery Biopsy

- NEVER hold prednisone therapy waiting for a biopsy if the suspicion of GCA is high
- Ideally would like to obtain TA biopsy within 1 week after starting prednisone therapy
GCA: Treatment

- Prednisone 60 mg/day and low-dose ASA 81 mg/day:
- New onset visual loss is unusual once on therapy
- Acute visual loss: suggest solumedrol 1 gram iv daily (split dose) x 3 days as further visual loss may occur within 6 days; visual recovery is uncommon (Danesh-Meyer H et al. Ophthalmology 2005;112:1098)
- Failure of symptoms to resolve within one week of high-dose steroids argues against the dx of GCA

GCA: Points to Remember

- Get ESR/CRP in an older patient with new onset headache, jaw claudication, or visual loss
- Beware of atypical presentations of GCA
- Tissue is the issue: start prednisone and ASA immediately; try to biopsy within 1 week; consider screening for TB
- Visual loss is rare (< 1%) after prednisone is started but rarely reversible
- Be mindful of steroid side effects

What is the Diagnosis?

- 45-year-old man presents initially with nodular skin lesions followed by painful necrotic purpura affecting his ears and extremities. WBC 1.2.
  1. Granulomatosis with polyangitis
  2. Cutaneous polyarteritis nodosa
  3. Levamisole-adulterated cocaine
  4. Henoch-Schönlein purpura
  5. Weber-Christian disease
Cutaneous Vasculopathy in Users of Levamisole-Adulterated Cocaine

- **Levamisole:**
  - Immunomodulatory properties: used to treat RA in the 1970s and colon ca with 5-FU in the 1990s
  - Removed from the US market in 2000 because of the potential for agranulocytosis
  - Veterinary use as an antihelminth agent
- **USA 2009:** 69% of cocaine adulterated with levamisole to enhance euphoric and addictive effects

Levamisole-Adulterated Cocaine Vasculopathy

- Retiform purpura with propensity to involve the ears
- Hypercoagulability: transient antiphospholipid antibodies (aPLs)
- Leukopenia or neutropenia: > 50% cases
- + ANCAs (high titer) reactive to multiple target antigens:
  - p-ANCA and/or c-ANCA
  - Myeloperoxidase (MPO) and/or Proteinase 3 (PR3)
  - Absent anti-neutrophil elastase characteristic of cocaine-induced midline destructive lesion

Levamisole-Adulterated Cocaine Vasculopathy

- Skin biopsy: leukocytoclastic vasculitis
- Utox for cocaine (2-3 day window)
- Treatment:
  - Cocaine cessation (smoking and snorting) and supportive care
  - Low to high dose steroids
  - Extensive skin necrosis reported with cocaine re-challenge

Ultrich K et al. J Clin Rheumatol 2011;17:193
Milman N et al. Arthritis Care Res 2011;63:1195