Vasculitis

• A heterogeneous group of disorders characterized by vascular inflammation leading to vessel occlusion and tissue ischemia and necrosis.
• Pathophysiology not well understood
• Difficult but improving treatment options
• Pattern recognition is key to early diagnosis and early therapeutic intervention.

Vasculitis: Outline

• Polyarteritis nodosa: abdominal pain, skin ulcers, neuropathy
• Microscopic polyangiitis: pulm/renal syndrome, MPO ANCA
• Granulomatosis with Polyangiitis (Wegener’s granulomatosis): upper and lower respiratory tract, pulm/renal syndrome, PR3 ANCA predominate
• Churg Strauss: asthma, eosinophilia, pulmonary infiltrates
• Cryoglobulinemic vasculitis: cutaneous vasculitis
• Behcets: oral and/or genital ulcers, rash, uveitis
• Takayasus arteritis: pulseless syndrome affected females.
• Giant Cell Arteritis: headache, jaw claudication, visual loss

Vasculitis: Classification

- Small vessels (venules, arterioles)
  - Drug-induced and serum sickness
  - Henoch-Schönlein purpura
  - Cryoglobulinemia
  - Vasculitis associated with systemic rheumatic diseases
  - Vasculitis associated with malignancy
  - Hypocomplementemic urticarial vasculitis
  - Vasculitis associated with infections

- Small and medium muscular arteries
  - Classic PAN
  - Microscopic polyangiitis
  - GPA (Wegener’s granulomatosis)
  - Churg Strauss vasculitis
  - Kawasaki syndrome
  - Rheumatoid vasculitis
  - SLE

- Large arteries
  - Giant cell or temporal arteritis
  - Takayasus arteritis

Vessel Size and Clinical Disease Correlates

- Large vessel (GCA, Takayasus)
- Medium vessel (PAN, Kawasaki) PAN is REALLY RARE
- Small vessel (ANCA disease (GPA, WG) or MPA, HSP, Goodpastures, SLE/RA/CTD, cryoglobulinemia)
- Small and Medium (Buerger’s, Cogan’s, Primary CNS vasculitis, sometimes ANCA vasculitis)
- Any or all types of blood vessels (Behcet’s, Relapsing Polychondritis, Cogan’s)
When to suspect vasculitis: clinical features

- Multisystem disease
- Unexplained constitutional signs and symptoms
- Skin lesions (palpable purpura)
- Ischemic vascular changes (gangrene, claudication, Raynaud’s phenomenon, livedo)
- Glomerulonephritis
- Mononeuritis multiplex
- Myalgia, arthralgia/arthritis
- Abdominal (intestinal angina) or testicular pain

Hard to classify vasculitis (Lamprecht, Clin Exp Rheum 2011)

- Goodpastures syndrome (Anti-glomerular basement membrane disease)
- Behcet’s disease
- IgG4 related systemic disease (autoimmune pancreatitis, chronic sclerosing cholangitis, orbital inflammatory pseudotumour, aortitis, and retroperitoneal fibrosis)
- Cogan’s syndrome (vestibulitis, hearing loss, vasculitis)
- Primary CNS vasculitis
- Intestinal vasculitis
- Chronic periaortitis
- Thromboangiitis obliterans (Burger’s disease)

Conditions that mimic systemic vasculitis

- Atheroembolic disease
- Cardiac myxoma
- Thrombotic disorders
  - Anti-phospholipid antibody syndrome
  - Thrombotic thrombocytopenic purpura
- Drug-induced vascular damage
  - Ergot derivatives
  - Cocaine
  - Amphetamines
- Infective endocarditis

Pathogenesis

- IC deposition (SLE, cryos, HSP)
- Ab vs vascular structures (antiGBM)
- Ab against no vascular structures (ANCA)
- Cell mediated tissue injury (GCA, TA)

What is this?

- Raynauds/acral necrosis
- Antiphospholipid Ab
- Endocarditis
- Small vessel vasculitis (including RA)
- Medium vessel vasculitis

ACR 1990 criteria for classification of polyarteritis nodosa

- Must have at least 3 of the 10 criteria present.
  - Weight loss > 4 kg
  - Livedo reticularis
  - Testicular pain or tenderness
  - Myalgias, weakness, or leg tenderness
  - Mononeuropathy or polyneuropathy
  - Diastolic BP > 90
  - Elevated BUN/creatinine
  - Hepatitis B virus
  - Arteriographic abnormality
  - Biopsy of small or medium artery containing PMN
- Sensitivity 82.2% and Specificity 86.6%
Case

- 26 you presented in the spring 2010 with right flank pain, CT scan showed a right renal infarct. Pt treated with anticoagulation after an unremarkable evaluation for hypercoagulability and then developed a hematoma. He had mild fatigue but otherwise was well.
- An MRI/A was performed
ANCA associated vasculitis

- Include Granulomatosis with Polyangiitis (Wegener's Granulomatosis), microscopic polyangiitis and Churg Strauss and drug induced vasculitic syndromes (PTU, allopurinol), levamisole tainted cocaine
- Morbidity associated with these diseases typically related to renal failure due to glomerulonephritis or pulmonary hemorrhage.
- Mortality often related to disease progression but more often treatment associated infection. In fact, vasculitis that appears to be worsening should be considered an infection until proven otherwise.

ANCA Associated Vasculitis

- C-ANCA with PR3 reactivity most commonly found in GPA (Wegener’s), though p-ANCA-MPO has been noted in 10% of cases of WG (5,6)
- P-ANCA-MPO most often seen in microscopic polyangiitis. Occasionally ANCA and anti-GBM can be concurrent
- Very high titer ANCA (esp MPO) raises possibility of drug induced vasculitis (including cocaine)
- In initial treatment, the ANCA type is irrelevant, though mortality is higher with PR3 ANCA
- ANCA is useful diagnostically but does not necessarily predict relapse

Anticytoplastic autoantibodies

Granulomatosis with Polyangiitis (formerly Wegener's Granulomatosis)

- Classic patterns include upper respiratory symptoms, sinusitis, epistaxis, hearing loss, otitis media (remember, adults otherwise rarely get otitis media)
- Lower respiratory symptoms (bronchitis, hemoptysis due to capillaritis)
- Glomerulonephritis
- Mononeuritis multiplex, cranial neuropathy, orbital pseudotumor
- Constitutional symptoms (fever, weight loss) (8,9)
Histopathology

- When a renal biopsy is done, the presence of focal segmental necrotizing glomerulonephritis is not specific to differentiate between GPA(Wegener’s), SLE, microscopic polyangitis or Goodpastures. (10)

Immunohistopathology: Renal

- SLE: clumpy immune complex deposition
- GPA(Wegener’s): scant or no immune deposits
- Goodpastures: linear IgG deposition along the glomerular basement membrane
Microscopic polyangiitis

- Present with GN as major clinical finding
- Mononeuritis multiplex
- Alveolar hemorrhage
- Sometimes difficult to distinguish from GPA(WG)
- ANCA in pANCA pattern MPO

Churg Strauss Syndrome

- Asthma
- Eosinophilia
- Non fixed pulmonary infiltrates
- Paranasal sinus abnormality
- Extravascular eosinophils (biopsy)
- Mononeuropathy or polyneuropathy

Clinical features of CSS

- Phase I: adult onset asthma, most require steroids for control
- Phase II: eosinophilic infiltrates in the lung and GI tract. Lung infiltrates are typically peripheral, patchy and asymmetrical.
- Phase III: constitutional symptoms, peripheral neuropathy, CNS vasculitis, mesenteric ischemia, cutaneous vasculitis
- Cardiac involvement with myocarditis is the leading cause of death.
What could this be?

- PAN (necrotic lesions, often nodular)
- Cryoglobulinemia
- Cocaine associated ANCA disease (typically skin disease)

ACR classification criteria: Takayasu arteritis (13,14)

- Must have at least 3 of the 6 criteria present.
  - Age < 40 years at disease onset
  - Claudication of extremities
  - Decreased brachial artery pulse
  - BP difference > 10 mm Hg between arms
  - Bruit over subclavian arteries or aorta
  - Arteriogram abnormality: occlusion or narrowing in aorta or main branches

Criteria for diagnosis of Behçet’s disease (15,16)

- Recurrent oral ulceration plus two of the following:
  - Recurrent genital ulceration
  - Eye lesions (anterior/posterior uveitis or cells in vitreous or retinal vasculitis)
  - Skin lesions (E. Nodosum, pseudofolliculitis, papulopustular lesions or acneiform nodules)
  - Positive pathergy test
- Sensitivity 91% and specificity 96%
Behçet’s syndrome: ulceration, tongue

Cryoglobulinemia
• 3 types (I, II, III) with Type II and III mostly associated with hepatitis C (rarely hep B).
• Immune complex mediated vasculitis with complement consumption (low C4)
• Mixed cryo associated with both IgG and IgM
• IgM is often monoclonal and specific for Fc of the IgG (presence of rheumatoid factor)
• Nerve, skin and rarely renal and lung involved.
• Need to treat the Hep C infection long term to control the vasculitis

Cryoglobulinemia: ear necrosis

Treatment regimens: Vasculitis
• May need to start Treatment prior to having a clear diagnosis. Always rule out infection!
• Rituxan effective in ANCA associated disease; non inferior compared to CYC in both new onset and relapsing disease (RAVE trial NEJM 2010)
• Prednisone 1 mg/kg/day or daily bolus methylprednisolone 1 g per day x 3 days (RAVE protocol)
• Oral cyclophosphamide 2mg/kg/day adjusted for renal function in severe cases or intravenous CYC 5 mg/m2 q3-4 weeks, which may be safer
• Fulminant and rapidly progressive disease may be treated with higher doses of cyclophosphamide
• Plasmapheresis may be useful in ANCA associated disease and in cryoglobulinemia where standard regimen is not effective or disease is rapidly progressive
• Other therapies include mycophenolate, azathioprine, methotrexate
• Antiviral therapy in Hep C associated cryoglobulinemia
Board Question

- 74 yo male is hospitalized with diffuse alveolar hemorrhage over a period of a few days. He had a prodrome of malaise and arthralgia for several weeks. In the ICU his serum creatinine is 7.4 mg/dl, urinalysis shows 3+ protein, many RBCs, scattered red cell casts. He is intubated with copious bloody secretions evident from the ETT.

Which of the following antibodies is the patient most likely to have

- A. AntiSm antibodies
- B. AntiGBM antibodies
- C. p-ANCA MPO (myeloperoxidase)
- D. c-ANCA PR3
- E. all of the above

Correct answer

- E is correct

Board Review

- 45yo male with long standing asthma is evaluated for new onset fever, fatigue, skin rash and worsening dyspnea. He had been using his albuterol inhaler more frequently and requiring more oral steroids and was recently started on a leukotriene antagonist. He complains of diffuse abdominal pain and his CXR shows bilateral patchy infiltrates, and WBC count is 15,000/ul with 25% eos.

Which of the following is the correct next step

- A. Increase inhaled steroids
- B. Begin plasmapheresis
- C. Increase the prednisone from 10 mg to 20 mg orally per day
- D. Begin intravenous corticosteroids.
- E. perform an open lung biopsy

Correct answer is D
**Giant Cell Arteritis**

- Systemic vasculitis of large and medium vessels of unknown etiology characterized by transmural inflammation, granuloma formation, and luminal occlusion of the cranial blood vessels (16).
- Annual incidence in North America is 19-32 per 100,000 in persons > 50 yrs (17)
- IL-6, IL-1β, VEGF, PDGF play an important role in pathogenesis (16)

**Giant Cell Arteritis: other manifestations**

- Weight loss
- Fever (including FUO)
- Polymyalgia rheumatica
- Ischemia of the head, neck or extremities due to occlusive disease of the carotid, subclavian and vertebral arteries
- Carotidynia
- Cough

**Giant Cell arteritis: Diagnosis**

- Age greater than or equal to 50 years at time of disease onset
- Localized headache of new onset
- Tenderness or decreased pulse of the temporal artery
- Erythrocyte sedimentation rate greater than 50 mm/h (Westergren)
- Biopsy which includes an artery, and reveals a necrotizing arteritis with a predominance of mononuclear cells or a granulomatous process with multinucleated giant cells

**Headache in GCA**

- Scalp pain
- Location can be temporal, posterior, occipital
- “My hair hurts to brush”
- Tongue pain
- Ear, nose pain, jaw pain, trismus
- “throat pain”
**Retinal ischemia due to GCA**

**Aortic dissection:** a rare complication of GCA

**Diagnosis: GCA**
- Laboratory markers: ESR, CRP, alkaline phosphatase, IL-6 though inflammatory markers may be normal or low
- Whenever there is a reasonable suspicion of GCA, a temporal artery biopsy should be performed. The morbidity of a biopsy is low
- It is preferable to obtain a biopsy prior to starting therapy but pathologic findings can persist for up to several weeks after starting steroids, so therapy should not be delayed if a biopsy cannot be obtained promptly
- Other imaging modalities include US, MRA, PET

**Treatment of GCA**
- Prednisone 40-80 mg per day for 4-8 weeks
- Reduce to 20 mg per day by third month
- Reduce by 5 mg every 2-4 weeks and then at 10 mg reduce by 1 mg every 4-6 weeks, total therapy up to 2 years
- Benefit of intravenous corticosteroids with visual symptoms is unclear but reasonable to consider
- Methotrexate as steroid sparing is controversial
- No evidence that TNF blockade is effective
- Low dose ASA may reduce ischemic events in GCA
- ?role of IL-6 inhibition and other biologic agents
Board question

- 82 year old healthy female (no meds) is evaluated for a 2 week history of headache and neck pain. She also complains of achingness of the shoulders, neck, and lower back. She had two episodes of blurriness in her right eye transiently last week but none now.
- On exam the scalp is diffusely tender, carotidynia noted, ROM limited due to pain in shoulders. Vision normal. Reflexes normal in UEs.
- ESR 24 mm/h, CRP 1.0 Hgb 11.7 CK 150

Which of the following is the most appropriate next step at this time?

- A MRI of head
- B EMG
- C Prednisone 1 mg/kg per day
- D Prednisone 15 mg per day
- E Doppler of the carotid artery
- F Temporal artery biopsy

Pearls : GCA

- GCA is a strong consideration in the elderly with new onset headache, neck ache, visual changes or unexplained fatigue or anemia
- Jaw claudication is the most specific sign of GCA, followed by visual loss and TA tenderness
- A more robust inflammatory response is correlated with a lower risk for visual loss.
- Patients with a low or normal ESR and CRP can have GCA if one biopsy is negative, the additional yield of a contralateral biopsy is modest but is reasonable to consider performing.
- A rising ESR in a treated for GCA does not necessarily suggest that GCA is returning

Correct answer C

Polymyalgia Rheumatica

- Age>50
- 1 month duration of morning stiffness in 3 or more areas (shoulders, hips, thighs and neck)
- ESR >40 mm/hr
- Exclusion of other diseases

RELATION OF POLYMYALGIA RHEUMATICA TO TEMPORAL ARTERITIS

- Polymyalgia Rheumatica
- Symptomatic Temporal Arteritis (Biopsy Positive)
- Biopsy Negative
PMR: Differential diagnosis

- Rheumatoid arthritis
- Polymyositis
- Rotator cuff tendonitis
- Parkinson's disease
- Giant cell arteritis
- Fibromyalgia
- Malignancy

PMR treatment

- Corticosteroids should result in substantial and often gratifying improvement in symptoms in low dose (≤20 mg/day prednisone). If response is underwhelming reconsider diagnosis
- With resolution of symptoms and normalization of ESR (typically 1-2 months), taper steroids by 2.5 mg every 2-4 weeks until 10 mg/day and then taper by 1 mg per month. Typical duration of treatment is up to 2 years or longer. Relapse is not uncommon.
- Calcium, Vitamin D and assessment for osteoporosis with bone densitometry

PMR treatment

- In patients with high clinical suspicion of disease where prednisone is not effective, consider the use of methylprednisolone, as some patients do not metabolize prednisone.
- Other agents, including MTX, hydroxychloroquine, other DMRDS may be helpful but limited trials
- Trial using TNF inhibitors showed no benefit

PMR pearls

- Synovitis of the hands can occur in PMR
- A normal ESR does not exclude the diagnosis
- 15-20% of patients with PMR will develop GCA
- Consider a temporal artery biopsy where response is suboptimal to low dose steroids, or persistent constitutional symptoms or inflammatory markers remain high.

References
