Topics to be discussed

- Introduction
- Pathogenesis
- ANCA patterns
- Other diseases associated with ANCA
  - Churg-Strauss syndrome,
  - Wegners granulomatosis.
- Microscopic polyangiitis.
- Miscellaneous
Vasculitis

- Clinicopathologic process characterized by inflammation of and damage to blood vessels.
- Vessel lumen is usually compromised → leading to possible ischemia and possible necrosis.
- This also leads to increase cytokine production and inflammation.
- It could be only confined to one single organ, such as the skin, or it may simultaneously involve several organ systems.
- The distribution of affected organs may suggest a particular vasculitic disorder, but significant overlap is observed.
- It is often a serious and sometimes fatal disease that requires prompt recognition and therapy.
Pathophysiology

- Likely that a number of factors are involved in the ultimate expression of a vasculitis syndrome.
  - genetic predisposition
  - environmental exposure
  - regulatory mechanisms associated with immune response to certain antigens
Conditions that can mimic vasculitis

**Infectious ds:**
- Bacterial endocarditis
- Disseminated gonococcal infection
- Pulmonary histoplasmosis
- Coccidioidomycosis
- Syphilis
- Lyme ds
- Rocky Mountain spotted fever
- Whipple’s ds

**Neoplasms**
- Atrial myxoma
- Lymphoma
- Carcinomatosis

**Drug toxicity**
- Cocaine
- Amphetamines
- Ergot alkaloids
- Arsenic

**Coagulopathies/thrombotic microangiopathies**
- Antiphospholipid antibody syndrome
- Thrombotic thrombocytopenic purpura

**Sarcoidosis**
- Atheroembolic ds
- Goodpasture’s syndrome
- Amyloidosis
- Migraine
Classification

Large-sized Vessels:
• Giant Cell Arteritis
• Takayasu’s Arteritis

Medium-sized Vessels
• Polyarteritis Nodosa
• Kawasaki’s Disease
• Primary Central Nervous system vasculitis
Classification

**Small-sized Vessels**

ANCA-Associated
- Wegener’s Granulomatosis
- Microscopic Polyangiitis
- Churg-Strauss Syndrome

Immune-Complex mediated:
- Henoch-Schonlein purpura
- Essential cryoglobulinemic vasculitis
- Hypersensitivity vasculitis
- Vasculitis secondary to connective tissue disease
- Vasculitis secondary to viral infection
ANCA-associated antibodies

- Directed against certain proteins in the cytoplasmic granules of neutrophils and monocytes.
- ANCA associated vasculitis syndromes include:
  - Wegeners granulomatosis
  - Church Strauss syndrome
  - Microscopic polyangiiitis.
Role of ANCA and PR3 and MPO

• PR-3 and MPO reside in azurophilic granules and lysosomes of resting neutrophils and monocytes (normally inaccessible to serum antibodies).

• When neutrophils or monocytes are primed by TNF alpha or IL-1 → PR3 and MPO translocate to the cell membrane → can interact with extracellular ANCA → neutrophils degranulate → production of reactive oxygen species that can cause tissue damage.

ANCA-activated neutrophils could:
• adhere to and kill endothelial cells.
• (and monocytes) induce release of proinflammatory cytokines such as IL-1 and IL-8.
C-ANCA

- Two patterns of ANCA: **cytoplasmic and perinuclear.**
- **C-ANCA: Cytoplasmic:** diffuse, granular cytoplasmic staining pattern observed by immunofluorescence microscopy when serum antibodies bind to indicator neutrophils.
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  - Proteinase-3 (PR-3): 29-kDa neutral serine proteinase present in neutrophil azurophilic granulues, is a major c-ANCA antigen.
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  - More than 90% of patients with typical active Wegener’s granulomatosis have detectable antibodies to PR3.
There is heavy staining in the cytoplasm while the multilobulated nuclei (clear zones) are nonreactive.
P-ANCA

• **P-ANCA**: Perinuclear refers to the more localized perinuclear or nuclear staining pattern of the indicator neutrophils.

• Major target for p-ANCA is the enzyme myeloperoxidase. Other targets include: elastase, cathepsin G, lactoferrin, lysozyme and bactericidal/permeability-increasing protein.
• Staining is limited to the perinuclear region and the cytoplasm is nonreactive.
More on P-ANCA

- P-ANCA could be associated to certain medications (drug-induced) that include:
  - Hydralazine, propylthiouracil, minocycline.
- P-ANCA pattern or atypical pattern has been associated with rheumatic diseases, inflammatory myopathies, reactive arthritis, APS, autoimmune GI disorders, such as ulcerative colitis or chron's, also cocaine, infections.
- Typically anti-MPO antibody is helpful and if present, it is more suggestive of true vasculitis.
- (but it is not always the case, since reports of positive anti-MPO antibodies could also be found in any of the above-mentioned clinical presentations).
1990 Criteria for ANCA vasculitities

**Churg-Strauss syndrome**

- Asthma (a history of wheezing or the finding of diffuse high pitched wheezes on expiration)
- Eosinophilia of >10 percent on differential white blood cell 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

- The presence of 4 or more of these criteria yields a sensitivity of 85% and specificity of 99.7% for Churg-Strauss syndrome.
- Small artery in a patient with Churg Strauss syndrome showing intimal fibrinoid necrosis and mural infiltration by histiocytes consistent with a necrotizing granulomatous vasculitis. There is marked extravascular eosinophilia.
Churg-Strauss syndrome

- Allergic angiitis and granulomatosis.
- Characterized by asthma, peripheral and tissue eosinophilia, extravascular granuloma formation, and vasculitis of multiple organ systems.
- Uncommon ds with estimated annual incidence of 1-3/ 1,000,000.
- Can affect any age, except infants with mean age at onset at 48y/o.
- Female:male 1.2 :1
Churg-Strauss syndrome pathogenesis

- Necrotizing vasculitis involving small and medium-sized muscular arteries, capillaries, veins and venules.
- Granulomatous reactions present in tissues or even within the walls of the vessels themselves.
- Usually associated with infiltration of tissues with eosinophils.
- Can affect any organ, with predominance of lung involvement, but also skin, cardiovascular, kidney, peripheral nervous system, GI tract.
Churg-Strauss syndrome clinical presentation

- Fever, malaise, anorexia, weight loss (constitutional symptoms),
- **Most predominant: pulmonary:** severe asthmatic attacks with presence of pulmonary infiltrates.
- **Mononeuritis multiplex:** second most common manifestation (up to 72% pts).
- **Allergic rhinitis and sinusitis** (up to 61% pts).
- **Heart ds** (14% pts).
- **Skin lesions (51%):** purpura, cutaneous and subcutaneous nodules.
- **Kidney:** less common and generally less-severe than of WG or MPA.

**Labs:**
- Eosinophilia (>1000 cells/uL in >80%), elevated ESR, fibrinogen, Alpha2-globulins found in >81%. And then organ specific findings.
- About 48% pts have +ANCA, usually anti-MPO ab.
Churg-Strauss syndrome

Treatment

• Prognosis is poor, with reported 5-year survival of 25%.
• With treatment, prognosis is favorable, about 72%.
• Myocardial involvement is the most frequent cause of death and is responsible for 39% of pts’ mortality.
• Treatment is done with glucocorticoids, and if persistent high doses of glucocorticoids are needed, then cyclophosphamide or other immunomodulatory agents are used.
1990 Criteria for ANCA vasculitides

**Wegener granulomatosis (GPA)**

- Nasal or oral inflammation (painful or painless oral ulcers or purulent or bloody nasal discharge).
- Abnormal chest radiograph showing nodules, fixed infiltrates, or cavities.
- Abnormal urinary sediment (microscopic hematuria or red cell casts).
- Granulomatous inflammation on biopsy of an artery or perivascular area.

- The presence of 2 or more of these criteria yielded a sensitivity of 88% and specificity of 92%.
- As a result, an abnormal chest radiograph or the findings of granulomatous inflammation on biopsy are not absolute requirements to distinguish patients with Wegener granulomatosis from those with other forms of vasculitis.
- Almost all patients with active systemic Wegener granulomatosis have a positive ANCA usually directed against PR3.
Wegner’s granulomatosis (GPA)

- Characterized by granulomatous vasculitis of the upper and lower respiratory tracts together with glomerulonephritis.
- Prevalence: 3/100,000,
- Extremely rare in blacks compared to whites.
- 15% pts are <19 y/o, mean age of onset is approximately 40y/o.
- Rarely occurs before adolescence
Wegner’s granulomatosis pathogenesis-1

- Necrotizing vasculitis of small arteries and veins together with granuloma formation.
- Usually affects upper and lower respiratory tracts and kidney.
- **Lung**: multiple bilateral nodular cavitary infiltrates (on biopsy almost always show necrotizing granulomatous vasculitis).
- **Upper airway**: sinuses and nasopharynx, reveal inflammation, necrosis, granuloma formation, with or without vasculitis.
Wegner’s granulomatosis pathogenesis-2

- **Kidneys**: earliest form presents with focal and segmental glomerulonephritis that may evolve into rapidly progressive crescentic glomerulonephritis. Granuloma formation is only rarely seen on renal biopsy. No immune complex deposition is found.

- Suggestion of cell-mediated immune response to an exogenous or even endogenous antigen that enters through or resides in the upper airway.
- Increased secretion of IFN-gamma and TNF-alpha and increased levels of CD4+ T cells.
Necrotizing glomerulonephritis

Light micrograph showing fresh segmental necrotizing lesions with bright red fibrin deposition (arrows). A necrotizing glomerulonephritis can be seen in a variety of inflammatory disorders including vasculitis and lupus nephritis. The latter has prominent immune complex deposition which is generally absent in vasculitis.
Wegner’s granulomatosis
Clinical presentation

Upper airway (95% pts):
• paranasal sinus pain and drainage, purulent or bloody nasal discharge
• possible nasal mucosal ulceration
• possible nasal septal perforation → could lead to saddle nose deformity
• serous otitis media from eustachian tube blockage
• subglottic tracheal stenosis from active ds or scarring in up to 16% of pts (could lead to severe airway obstruction).

Upper airway (85 to 90%):
• Cogh, hemoptysis, dyspnea, chest discomfort (present in 85-90%).
• Endobronchial ds (active or as a result of fibrous scarring, could lead to obstruction with atelectasis).

Eye involvement (up to 52%): may range from mild conjunctivitis to dacycystitis, episcleritis, scleritis, granulomatous sclerouveitis, ciliary vessel vasculitis, and retroorbital mass lesions, leading to proptosis.
Wegner’s granulomatosis saddle nose deformity
Wegner’s granulomatosis
ground glass opacities and
Wegner’s granulomatosi
Clinical presentation-2

Skin lesions (46% of pts) appear as papules, vesicles, palpable purpura, ulcers, or subcutaneous nodules (biopsy shows vasculitis, granuloma or both).

Cardiac involvement (8% of pts) as pericarditis, coronary vasculitis or cardiomyopathy.

Nervous system manifestations (23%) include cranial neuritis, mononeuritis multiplex, or cerebral vasculitis and/or granuloma.

Renal ds (77% of pts) presents with glomerulitis with protenuiria, hematuria, red blood cell casts, but if untreated, then rapidly progressive renal failure ensues.

Constitutional symptoms

Labs:
- Elevated ESR, mild anemia, leukocytosis, mild hypergammaglobulinemia (mostly IgA class), could have midly elevated RF, thrombosis.
- 90% of pts have +anti-PR3 ANCA.
- In the absence of active ds, the sensitivity drops to approximately 60 to 70%.
Wegner’s granulomatosis

Treatment

• Mortality reaches 90% in 2 years if untreated.
• With proper treatment, more than 75% remission.
• The most effective therapy for life-threatening, typically with pulmonary-renal involvement is cyclophosphamide 2mg/kg per day orally with glucocorticoids for 6 months.
• Glucocorticoids at 1mg/kg daily for one month or so, then with decreasing doses every month or so.
• Alternative to oral cyclophosphamide is IV cyclophosphamide monthly (1 g/m²).
• Cyclophosphamide-related toxicities include: cystitis (at least 30%), bladder cancer (6%), myelodysplasia (2%), high risk of infertility.
• Then, maintenance therapy is done with methotrexate or with azathioprine or cellcept.
• TMP-SMX for PCP prophylaxis and also to prevent upper respiratory relapse.
Wegner’s granulomatosis

Treatment

For mild ds: could use methotrexate.

For pulmonary hemorrhage: seven sessions of plasma exchange over two weeks (60 mL/kg at each session).

- Fresh frozen plasma is the preferred replacement fluid, with one to two liters being given at the end of the procedure to reverse pheresis-induced depletion of coagulation factors.

- Among patients who develop severe infection in the setting of plasma exchange, a single infusion of IVIG (100 to 400 mg/kg) can be given to partially replenish antibody levels.

For subglottic stenosis: intraleisonal injection of glucocorticoids in combination with endoscopic dilation may avoid the need for more invasive surgical procedures.

Newly FDA approved 2011: rituximab (B-cell depletion anti-CD20 monoclonal Ab) for ANCA-associated vasculitis in non-inferiority study compared to cyclophosphamide.
1990 Criteria for ANCA vasculitities

Microscopic polyangiitis

- Pts have equivalent vasculitic lesions to those observed in WG, but, at least at presentation, do not typically have symptomatic or histologic respiratory involvement.
- Such individuals are considered to have microscopic polyarteritis. However, two observations suggest that this disorder is closely related to WG and should be considered similarly: some patients subsequently develop classic respiratory tract lesions.
- ANCA are typically present with anti-MPO ab.
- Absence of granulomatous inflammation differentiates it from WG.
Microscopic polyangiitis
Pathogenesis

• Vascular lesion in microscopic polyangiitis is histologically similar to that of PAN.
• But unlike PAN, it typically involves capillaries and venules in addition to small and medium sized arteries.
• Immunohistochemical staining: paucity of immunoglobulin deposition in the vascular lesion of microscopic polyangiitis (so no immune complex deposition).
• Renal lesion is identical to that of WG.
• Highly associated with +ANCA but typically with anti-MPO ab.
Microscopic polyangiitis clinical manifestation

- Constitutional symptoms
- **Glomerulonephritis occurs in 79%** pts and can be rapidly progressive, leading to renal failure.
- **Hemoptysis** may be the first symptom of alveolar hemorrhage, which occurs in 12% of pts.
- **Mononeuritis multiplex.**
- **GI tract.**
- **Cutaneous vasculitis.**
- Upper airway ds and pulmonary nodules are not typically found in microscopic polyangiitis (and if present, suggest WG).

**Labs:**
- Elevated ESR, anemia, leukocytosis, thrombocytosis,
- ANCA is present in 75% pts (typically with anti-MPO ab).
Microscopic polyangiitis treatment

- Treatment is similar to WG treatment, depending on severity.
- 5-year survival rate is about 74%.
- Disease-related mortality occurs usually from alveolar hemorrhage or GI, cardiac, or renal ds.
- Relapse is lower than WG with about 34% pts relapsing.
- Limited studies. Most information comes from WG pts treatment trials.
Difference between WG and MPA

• On histologic examination, the absence of granulomatous inflammation in MPA.
• Both disorders are typically ANCA-positive, but WG is primarily associated with PR3-ANCA, while MPA is primarily associated with MPO.
• According to some experts, a lower rate of significant upper respiratory tract involvement in MPA.
• After induction of remission with initial immunosuppressive therapy, a lower rate of relapse in MPA is seen.
Does negative ANCA exclude small vessel vasculitis?

- Up to 40% pts with limited WG and up to 10% of severe WG could have negative ANCA.
- Up to 30% of MPA and up to 50% of CSS could have negative ANCA.
Does increased ANCA titers predict a disease flare?

- Studies have shown that elevations in titers in ANCA do not predict disease flares.
- If a pt was ANCA-positive during a period of active disease, a persistently ANCA-negative status is consistent with, but not absolutely proof of remission.
- Absolute height of antibody titers does not correlate well with disease activity.
Should tissue biopsy be done?

- It depends on the clinical presentation.
- Predictive value of ANCA testing depends heavily upon clinical presentation of the pt.
- If the presentation is highly suggestive of WG for example, and C-ANCA with anti PR3 ab is present, tissue biopsy is not necessary before initiation of treatment.
- However, the recommendation per ACR states that the biopsy should be obtained whenever possible, and it should be a biopsy of involved organ before starting pt on long-term potentially toxic therapy.
Classification

• Large vessel vasculitis
  – Giant cell arteritis
  – Takayasu’s arteritis

• Medium vessel vasculitis
  – Polyarteritis nodosa

• Small vessel vasculitis
  – Hypersensitivity vasculitis
Giant Cell Arteritis

- Affects the second- to fifth-order aortic branches, often in the extracranial aa of the head
  - AKA temporal arteritis, cranial arteritis
- Aged 50+ years, mean age is 72
- Women>men
- Epidemiology
  - Scandinavian countries/N Eur (15-25 cases/100,000)
  - Southern Europeans (6/100,000)
  - Blacks, Hispanics (1-2/100,000)
  - US-Olmsted County, Minnesota (17.8/100,000)
GCA-Pathophysiology

- Histology-mononuclear cell infiltrate dominated by T lymphocytes and macrophages
- Concentric intimal hyperplasia
- Affects all layers of the arterial wall
- Can be granulomatous (media) with infiltration of histiocytes and multinucleated giant cells
  - Multinucleated giant cells need not be present but may correlate with increased risk for ischemic complications
GCA-Pathophysiology

- Mononuclear cell infiltrate dominated by T lymphocytes and macrophages
  - Penetrate all layers of the arterial wall
  - Can be granulomatous
  - Giant cells are often absent but may indicate increased risk of ischemic complications
- T-cells gain entry into vessel wall from vasa vasorum in the adventitia
- DC strongly activated, produce chemokines, and express T-cell stimulatory ligands
Artery Anatomy

Artery and Vein

- Artery (lumen)
- Vein (lumen)
- Tunica Intima
- T. Adventitia
- Tunica Media
- T. Adventitia
Giant Cell Arteritis
GCA-Clinical Features

• Two major symptomatic complexes
  – Vascular insufficiency
    • Usually occlusion, aorta-arterial wall dilatation
  – Systemic inflammation

• Multiple variants/GCA-PMR syndrome
  – Cranial arteritis
  – Large-vessel GCA/aortitis
  – Fever/wasting syndrome
  – Isolated PMR
Cranial Arteritis

- Headaches - throbbing, sharp, or dull; unilateral or back of head
- Scalp tenderness
- Ischemic optic neuropathy → blindness (sudden, painless, irreversible)
  - Amaurosis fugax - intermittent visual blurring or diplopia with heat, exercise or postural changes
- Jaw claudication - talking, chewing illicit pain (50%)
- CNS ischemia → TIA, CVA (20-30%)
- PMR
Large-vessel GCA/Aortitis

- Large-vessel in 10-15% of pts, prefers carotid, subclavian, and axillary aa>femoral aa
  - Usually lack cranial involvement, 50% TA bx-neg
  - Aortic arch syndrome-claudication of the arms, absent or asymmetrical pulses, parasthesias, digital ischemia
- Aortitis-Aortic valve insufficiency, aortic aneurysm and dissection
  - Risk thoracic aortic aneurysm increased 17-fold
  - Ranges from silent aneurysm to dissection and rupture
Fever/Wasting Syndrome

- Fever and chills (occult presentation-GCA is cause of FUO in up to 15% elderly)
  - Need to exclude infection, malignancy
- Malaise, fatigue, anorexia, weight loss
- Night sweats
- Weakness
- Depression
- Dx: temporal artery bx
Isolated PMR

- Pain in shoulder and pelvic girdle muscles
- Stiffness
- Peripheral synovitis (uncommon)
- Malaise, weight loss, sweats, and low-grade fever
- Elevated ESR and/or CRP, anemia
- 2-3x more common than GCA, same population
GCA-1990 ACR Criteria

- Age > 50 at onset
- New headache
- Temporal artery abnormality
- Elevated ESR (>50)
- Abnormal artery biopsy
  - +GCA if 3 of 5 criteria present
    - Sensitivity 93.5%, specificity 91.2%
GCA-Diagnosis

• Temporal artery Bx:
  – False-negative bx in 10% of pts
• Short-term steroids (up to 2 weeks) is unlikely to interfere with results
• Labs: elevated acute phase reactants (ESR, CRP), IL-6, normochromic or hypochromic anemia, thrombocytosis, elevated Alk phos
  • 25% of patients w/ + temporal bx had normal ESR
• Imaging-angiography (MRA, CTA, Doppler US)
This 60-year-old woman presented with weight loss, fevers, night sweats, carotidynia, and elevated inflammatory markers. The PET scan demonstrates increased 18F-fluorodeoxyglucose uptake in the aorta and its major branches consistent with active inflammation. Subsequent temporal artery biopsy confirmed giant cell arteritis.
GCA-Treatment

• Glucocorticoids
  – 60mg of prednisone or equivalent
  – Relief within 12 to 48 hours
  – Cannot reverse intimal hyperplasia, may decrease ischemic complications by decreasing edema
  – Once clinically stable, decrease dose by 10% q 1-2wks

• DMARDs, TNF blockers-results vary

• ASA 81-325mg/day may decrease risk of visual loss and CNS ischemia
  – ? Decreases IFN-gamma
PMR

• Affects same population but is 2-3x more common than GCA
• Activation of innate immune system-increased IL-1, IL-6, activated DC’s
  – IFN-gamma is absent (abundant in GCA)
  – Elevated ESR and/or CRP, anemia
• Exclude other diagnoses but is very steroid responsive which may help in diagnosis
• Signs of vascular insufficiency i.e. claudication, bruits over aa, and discrepant BP readings→high index of suspicion for GCA
PMR

• Treatment: steroids, 2/3 respond to prednisone < 20mg/day
  – Decrease by 2.5mg q 10-14 days until 8mg then slower tapering may be required
  – Higher required doses may indicate risk of developing GCA

• Prognosis good, disease self-limiting

• Some may develop seronegative RA-type picture requiring DMARDs
Takayasu’s Arteritis

• Chronic granulomatous vasculitis characterized by stenosis, occlusion, and sometimes aneurysm of the large elastic arteries, especially aorta and its main branches
  – May also affect coronary and pulmonary arteries
  – AKA Pulseless disease-complete occlusion of upper extremities
  – AKA Aortic arch syndrome
• Primarily affects adolescent girls and young women <40yo, can start >40 esp. in Asians
• Incidence highest in Asia followed by South Americans but occurs in all races
TA

• TA causes different aortic lesions in different countries
  – Japan, Korea, China-arch; India, Thailand, Middle East-abdominal aorta
• Etiology unknown, preceded by
  – External stress as a trigger ?microbial infection
  – Inflammatory mechanisms
  – Genetic factors
• CD8 T-cell-mediated cytolytic tissue injury
  – CD8 Tcells predominant in vascular infiltrate
  – Over-representation of HLA class I molecules, HLA-B52
TA-pathophysiology

• Granuloma formation and giant cells predominantly in the media
• Medial elastic smooth muscle is replaced with fibrotic tissue
  – Aortic involvement leads to dilation and aneurysm
• Intimal proliferation leads to tapering, narrowing or complete occlusion of the vascular lumen, sometimes with thrombosis
TA-Clinical Features

• Generalized inflammatory syndrome with fever, night sweats, malaise, anorexia, weight loss, diffuse myalgias

• Late consequences-ischemic complications
  – Carotid and vertebral- dizziness, tinnitus, HA, syncope, CVA, visual disturbances; facial muscle atrophy
  – Brachiocephalic and subclavian-arm claudication, pulselessness, and discrepant blood pressures, bruits
  – Aorta-Ischemic CAD, arrhythmia, CHF, AR
  – Coronary aa-angina pectoralis
  – Renal- renovascular HTN
  – Mesenteric aa-N/V, ischemic bowel disease
TA-Diagnosis

• High index of suspicion-vaso-occlusive disease and systemic inflammation in a young pt
• Dx: Angiography-long, smooth taperings of involved vessels, with collateralization in advanced cases
  – MRI/MRA for serial assessments
  – Doppler US for cervical vessels
  – CTA for aorta and proximal vessels
TA-1990 ACR Criteria

- Age at onset <40
- Claudication of extremities
- Decreased brachial artery pulse
- BP difference >10mm Hg
- Bruit over subclavian arteries or aorta
- Arteriogram abnormality
  - +TA if 3 of 6 criteria are present
    - Sensitivity 90.5%, specificity 97.8%
TA-Treatment

- Some cases TA “burn out” while others have progressive or relapsing/remitting course
- Glucocorticoids: prednisone 40-60mg/day then taper 5mg/day q2wks until 10mg/day
  - Monitor ESR, CRP but 50% of patients had progressing disease despite normal values
- ASA or other antiplatelet agent
- MTX up to 25mg/wk help improve remission and decrease steroids (no randomized trials)
  - Azathioprine, MMF, cyclosporine, TNF-blockers also success but no controlled studies
- Stenotic lesions are irreversible-no tx if collaterals
- Prognosis much improved; death d/t CHF, ischemic HD
Polyarteritis Nodosa

- Systemic vasculitis affects medium-sized arteries that supply the skin, gut, nerve, and kidney, but may affect multiple organs
- Incidence 2-9 cases per million annually
- M=F, all races and ages (mostly 40-60)
- May be p-ANCA positive but PR3- and MPO-ANCA negative
  - Not associated with glomerulonephritis or pulmonary involvement
PAN

• Presents insidiously with nonspecific symptoms
  – Fever, fatigue, malaise, myalgias, arthralgias
  – Cutaneous involvement possible
  – Diagnosis made when other systemic manifestations occur

• Associated w/ Hepatitis B infection and possibly hairy cell leukemia
  – 77 per 1 million in a Hep B-hyperendemic Alaskan Eskimo population
PAN-Diagnosis

• Based on characteristic symptoms, PE findings, and lab, angiography and pathologic findings
  – Abdominal angiography or biopsy recommended
• Differentiate from ANCA-associated vasculitis, cryoglobulinemia, and Buerger’s disease
  – R/O viral hepatitis, bacterial endocarditis, or other embolic disease; CTD-SLE, RA, SSc
• Lab-nonspecific: elevated acute phase reactants, anemia, renal insufficiency
• EMG/NCV-useful for confirming mononeuritis multiplex
PAN-Diagnosis

• Imaging-guided by symptoms; abdominal arteriography reveals strictures and aneurysms (beading)

• Biopsy-skin bx from center of lesion or edge of an ulcer
  – PAN need full thickness bx to capture larger vessels (aa within the fat of subq tissue often involved)
PAN-1990 ACR Criteria

- Weight loss >4kg
- Livedo reticularis
- Testicular pain or tenderness
- Myalgias, weakness, or leg tenderness
- Mononeuropathy or polyneuropathy
- Diastolic BP>90mm Hg
- Elevated BUN (>40 mg/dL) or creatinine (>1.5 mg/dL)
- Hepatitis B virus
- Arteriographic abnormality-aneurysms or occlusions
- Biopsy of small or medium-sized vessel-granulocytes or leukocytes in the artery wall
  - +PAN if 3 of 10 criteria are present
    - Sensitiviyt-82.2%, specificity-86.6%
1994 Chapel Hill Consensus

• 1990 ACR criteria do not differentiate between PAN an MPA
• PAN-necrotizing inflammation of medium-sized or small arteries without glomerulonephritis, or vasculitis in arterioles, capillaries or venules
• MPA-necrotizing vasculitis, with few or no immune deposits, affecting small vessels (i.e. capillaries, venules or arterioles)
  – Necrotizing arteritis involving small- and medium-sized vessels may be present. Necrotizing glomerulonephritis is very common. Pulmonary capillaritis often occurs
PAN-Pathophysiology

• Focal segmental necrotizing vasculitis of medium- and small-sized arteries
  – Capillaries and large-vessels less common
• Fibrinoid necrosis of the media and pleomorphic cellular infiltration (but no granulomas)
• Microaneurysms of arteries to or within the kidneys, liver, or GI tract; thrombosis can also occur
• Coexistence of necrotizing vasculitis and a healed lesion or normal arteries in different tissues or different parts of the same tissue is characteristic of PAN
PAN

• Predelection for certain organs:
  – Arteries to the kidney (70-80%)
  – GI tract (50%)
  – Peripheral nerves (50%)
  – CNS (10%)
  – Skin- livedo reticularis, nodules, ulcerations, ischemia of digits
    • Cutaneous PAN-nodules and ulcers, primarily of lower legs, in crops and very painful
This 37 year old woman presented with low-grade fever, abdominal pain, arthralgia, myalgia, anemia, and elevated ESR and C-reactive protein. There are numerous aneurysms in the hepatic, splenic, renal, celiac, superior mesenteric and inferior mesenteric arteries.
PAN-Treatment

• Glucocorticoids-prednisone 1 mg/kg/day
  – Will treat milder forms of the disease
• Rapidly progressive or organ-threatening cyclophosphamide is added to steroids
  – Daily oral or monthly pulsed IV for 6 to 12 months
  – Maintenance with azathioprine or MTX x 18 mos
Hypersensitivity Vasculitis

- AKA leukocytoclastic vasculitis, hypersensitivity angiitis
- Small-vessel vasculitis localized to the skin or may manifest in other organs, most commonly the joints, GI tract and kidneys
  - Can be acute or chronic
- 10-30 persons per million persons per year
- M=F, whites more common, any age (HSP in children)
Hypersensitivity Vasculitis

• Immune complex-mediated vasculitis with antigen-antibody complex deposition in capillaries, postcapillary venules, and arterioles

• Serum sickness-systemic illness with fever, rash and arthralgias, occurs 1-2 weeks after exposure to drug or foreign antigen
LCV-Etiology

- Drugs: antibiotics, NSAIDs, and diuretics; foreign proteins such as streptokinase and those found in vaccines
- Infections: URIs, viral hepatitis, HIV, bacterial endocarditis, HCV (?virus or cryoglobulins)
- Foods, additives
- CVD in 10-15% of vasculitis cases
  - RA, Sjögren syndrome and SLE; may indicate active dz
- Inflammatory bowel disease: Crohn’s, UC
- Malignancy (< 1%) lymphoproliferative diseases are more common, esp. hairy cell leukemia; however, any tumor type
  - Treatment of malignancy improves
LCV-Etiology

• Part of a larger-vessel vasculitis such as WG, PAN, MPA, Churg-Strauss
• No cause is identified in up to 50% of patients
• ½ to 1/3 cutaneous vasculitis cases are idiopathic
LCV-PE

- Cutaneous vasculitis-itching, burning, or pain, or they may have asymptomatic lesions
  - May occur in the absence of systemic disease
- Palpable purpura-most common
  - Round and 1-3 mm or coalesce to form plaques and may ulcerate
  - Symmetric, dependent areas
- Urticarial lesions can burn more than itch
- Other rashes: Livedo reticularis, nodular
LCV-Diagnosis

- Biopsy is method of choice
- Light microscopy of H&E stain shows inflammatory infiltrate and signs of vasculitis: leukocyte diapedesis, karyorrhexis, leukocytoclasia
- Direct immunofluorescence (DIF) recommended in cases of immune complex-mediated vasculitis
  - Evaluate type of reactants (Ig, complement proteins)
LCV-1990 ACR Criteria

- Age at onset > 16y
- Medication at disease onset
- Palpable purpura
- Maculopapular rash
- Biopsy including arteriole and venule (histology showing granulocytes in a perivascular or extravascular location)
  - +LCV if 3 of 5 criteria are present
    - Sensitivity-71.0%, specificity-83.9%
LCV-Treatment

• Removal of inciting agent, usually resolves in 1-2 weeks
  – May need to stop many meds simultaneously then re-start them gradually
• Reserve glucocorticoids for patients with fulminant systemic disease
• May have relapsing/remitting course but restricted to the skin not requiring immunosuppressive tx
References


• www.emedicine.com-vasculitis