Vasculitis
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Objectives
- Participants should:
  - be able to categorize the various vasculitides by vessel size.
  - know that large vessel vasculitis causes symptoms related to ischemia but lack skin findings.
  - know that medium and small vessel vasculitis commonly have skin involvement.
  - be able to list the ANCA mediated vasculitides
  - know that treatment for vasculitis related to underlying infection or drug exposure primarily involves treating the infection or removing the offending agent.

Vasculitis: Definition
“The term vasculitis refers to a heterogeneous group of disorders characterized pathologically by evidence of blood vessel inflammation and clinically by a diverse set of symptoms and signs”

Vasculitis: Pathogenesis
- Complex, not fully understood
- Involves
  - Cellular immunity (T cells, B cells, monocytes/macrophages, endothelial cells)
  - Complement
  - Cytokines (IL-1, TNF, IFN, IL-6)
  - Autoantibodies (ANCA)
  - Antigens (drugs, infectious agents)
- Symptoms common to the different vasculitides are related to the inflammatory nature of the diseases
- Symptoms more specific to certain vasculitides correlate with the size of vessel involved.

Types of Vasculitis
- Giant cell arteritis
- Takayasu’s arteritis
- Polyarteritis nodosa
- Kawasaki syndrome
- Wegener’s Granulomatosis
- Churg-Strauss syndrome
- Microscopic polyangiitis
- Hypersensitivity vasculitis
- Urticarial vasculitis
- Henoch-Schonlein purpura
- Mixed cryoglobulinemia
- Leukocytoclastic vasculitis
- Others...

Classification Scheme
- ACR Classification Criteria (1990)
  - Classification criteria designed so that all who meet criteria have disease
  - Not always useful diagnostically
    - atypical presentation won’t meet criteria
    - MPA (among others) not included
- Chapel Hill consensus conference (1994)
  - Based on size of vessel involved
Classification Scheme

- Large vessel vasculitis
  - Giant cell arteritis, Takayasu's arteritis
- Medium vessel vasculitis
  - Polyarteritis nodosa, Kawasaki's disease
- Small vessel vasculitis
  - ANCA-associated: Wegener's Granulomatosis, Churg-Strauss syndrome, microscopic polyangiitis
  - Others: Henoch-Schonlein purpura, essential cryoglobulinemic vasculitis, cutaneous leukocytoclastic angiitis

Large Vessel Vasculitis
Giant Cell Arteritis

- Occurs almost exclusively in patients > 50 years of age
- Most common vasculitis
- Incidence varies with ethnic group
  - Southern US: 1.6 cases/100,000 people > 50 y old
  - Iceland: 25.4 cases/100,000 people > 50 y old
- Female > male
- Northern Europeans
  - "Elderly white female"

GCA: ACR criteria

- 3 of 5 of the following:
  - Age at onset > 50 y old
  - New headache
  - Temporal artery abnormality
  - Elevated ESR
  - Abnormal artery biopsy

Giant Cell Arteritis

- General symptoms
  - Fever, anorexia, weight loss
  - Can manifest as FUO
- Symptoms related to extra-cranial branches of carotid
  - Include temporal, vertebral, ophthalmic arteries, spares intracranial vessels
  - Headache, scalp tenderness, ischemic optic neuropathy ("amaurosis fugax"), jaw claudication, TIA
- Symptoms related to other large vessels
  - Arm claudication, pulselessness, aortic aneurysm (esp. thoracic), aortic insufficiency

Giant Cell Arteritis

- Examination may reveal scalp tenderness, swollen and/or tender temporal arteries
- Labs may show a mild anemia
- Markers of inflammation (ESR, CRP) almost always elevated
- For diagnosis, temporal artery biopsy
  - Easy, safe
  - Several cm – skip lesions
  - Granulomatous, with multinucleated giant cells
Polymyalgia Rheumatica
- Syndrome in elderly patients of constitutional symptoms and stiffness of shoulders and hips
- No true weakness
- Usually have elevated ESR or CRP, but not always
- Diagnosis is clinical – resolution of symptoms with low dose prednisone (usually trial of 15mg)
- 50% of pts with GCA have PMR
- 15% of pts with PMR have GCA

Large Vessel Vasculitis
Takayasu’s arteritis: ACR Criteria
At least 3 of 6 criteria:
- Age at onset < 40 years
- Claudication of extremities
- Decreased brachial artery pulse
- BP difference > 10 mm Hg
- Bruit over subclavian artery or aorta
- Arteriogram abnormality

Takayasu’s arteritis
- Clinical Characteristics
  - Young, usually < 40 years of age
  - Female > male (about 4:1)
  - Rare
  - Incidence about 2/1,000,000 in whites
  - Most predominant in Asia, next in parts of South America
  - “Young Asian female”

Takayasu’s arteritis
- General symptoms
  - Fever, weight loss, anorexia, myalgias
- Ischemic symptoms
  - Symptoms depend on artery affected
    - Carotid/vertebral
    - Subclavian
    - Aorta
    - Coronary (usually ostial lesions)

Pathology
- Large vessels, involvement can be patchy
- Early: granulomatous inflammation of adventitia and outer layers of affected artery
- Progression to panarteritis
- (But we only get tissue at autopsy)
- Angiography
Vasculitis: Skin involvement

- Large vessel vasculitides have no characteristic skin involvement
- Characteristic cutaneous lesion of other vasculitides is palpable purpura

Medium and small vessel vasculitides

- Medium vessel
  - 50-150 micrometers
  - Muscular wall
- Small vessel
  - <50 micrometers
  - Capillaries, glomeruli, post-capillary venules, nonmuscular arterioles
- Distinctions imprecise, much overlap

Medium vessel vasculitis

Polyarteritis nodosa: ACR criteria

At least 3 of 10 criteria:
- Weight loss > 4 kg
- Livedo reticularis
- Testicular pain or tenderness
- Myalgia, weakness, leg tenderness
- Mononeuropathy or polyneuropathy
- Diastolic BP > 90 mm Hg
- Elevated BUN (>40) or Cr (>1.5)
- Hepatitis B virus
- Arteriographic abnormality
- Biopsy of small or medium-sized vessel

Polyarteritis Nodosa

- Inflammation of medium- and small-sized arteries
- Nonspecific constitutional symptoms
- Specific organs targeted
  - Skin
    - Livedo reticularis
    - Subcutaneous nodules
    - Ulcers
    - Digital gangrene
Polyarteritis Nodosa

- Specific organs targeted (continued)
  - Peripheral nerves
    - Many have a mononeuritis multiplex
  - GI tract
    - Postprandial periumbilical pain ("intestinal angina")
  - Kidney
    - No symptoms, can cause renin-mediated HTN
  - Musculoskeletal
    - Myalgias, arthralgias
  - Testicular pain
  - Spares lung

Polyarteritis Nodosa

- Pathology
  - Patchy involvement
  - Minimal immune deposits
  - ANCA usually negative
  - Association with hepatitis B
    - Need not have hepatitis B to have PAN
- Diagnosis
  - Angiogram
    - not MRA
  - Biopsy of involved organ
    - Often sural nerve if mononeuritis multiplex
Small Vessel Vasculitis

- ANCA-associated (AAV)
  -Anti-neutrophil cytoplasmic antibodies
    -cytoplasmic ANCA (c-ANCA)
      -Wegener’s Granulomatosis
    -perinuclear ANCA (p-ANCA)
      -Churg-Strauss Syndrome
      -Microscopic polyangiitis
  - “Cutaneous” vasculitides
    -Not ANCA-associated

ANCA

- Anti-neutrophil cytoplasmic antibody
  -Ethanol-fixed neutrophils
  -Two patterns on IF
    -cANCA – cytoplasmic
      -Proteinase-3 specific antigen
    -pANCA – perinuclear
      -Myeloperoxidase specific antigen

Wegener’s Granulomatosis: ACR Criteria

At least 2 of 4 criteria:
- Nasal or oral inflammation
- Abnormal chest radiograph
- Urinary sediment
- Granulomatous inflammation on biopsy

Wegener’s Granulomatosis

-Granulomatous necrotizing vasculitis
  -Upper and lower airways
  -Kidney
- Clinical manifestations
  -Upper airways
    -Nasal: saddle nose deformity
    -Sinusitis
    -Laryngeotracheal
  -Pulmonary
    -cough, hemoptysis, pleuritis, infiltrates, nodules
  -Renal
    -Glomerulonephritis
      -if no involvement, called “limited”
  -Ocular: any compartment of the eye
  -Cutaneous
Wegener’s Granulomatosis

- Associated with c-ANCA
  - Specific antigen is proteinase 3 (PR3)
- Biopsy
  - Sinus biopsy usually nonspecific
  - Lung or kidney more useful
- Always check urine for renal involvement
- Special case
  - Cocaine induced midline granulomatous lesions may mimic Wegener’s and can be ANCA positive (anti-neutrophil elastase antibody)

Churg-Strauss Syndrome: ACR Criteria

- At least 4 of 6 criteria:
  - Asthma
  - Eosinophilia
  - Mononeuropathy or polyneuropathy
  - Pulmonary infiltrates, non-fixed
  - Paranasal sinus abnormality
  - Extravascular eosinophils

Churg-Strauss Syndrome

- Occurs in clinical setting of
  - asthma/allergic rhinitis
  - eosinophilia (blood and tissue)
  - pulmonary infiltrates
  - “new or worsening asthma”
  - skin involvement
  - mononeuritis multiplex
  - glomerulonephritis

Churg-Strauss Syndrome

- Lab tests
  - Peripheral eosinophilia
  - P-ANCA
    - Specific antigen myeloperoxidase (MPO)
  - Associated with leukotriene antagonists
Microscopic Polyangiitis

- Clinical manifestations
  - Renal
    - pauci-immune necrotizing glomerulonephritis
  - Pulmonary
    - Most serious is alveolar hemorrhage
    - Pathologically, pulmonary capillaritis
  - Skin, peripheral nerves, joints

- Differs from PAN
  - Involves lung
  - Glomerulonephritis
  - Associated with p-ANCA
  - Biopsy affected organ
    - Kidney or lung

ANCA Vasculitis

Drugs

- Cutaneous Necrotizing Vasculitis
  - Levamisole (cocaine adulterant)
  - Anthelminthic
  - Skin biopsy with vasculitis and thrombi
    - "occlusive necrotizing vasculitis"
  - Multiple antibodies present
    - Anti-Pr3, Anti-MPO, Anti-neutrophil elastase

Non-ANCA-associated Small Vessel Vasculitis

- Other small-vessel vasculitides
  - "Cutaneous vasculitis"
    - primarily skin manifestations, but not always limited to just skin
  - Leukocytoclastic angitis

Types

- Henoch-Schonlein purpura
- Mixed cryoglobulinemia
- Hypersensitivity vasculitis
- Urticarial vasculitis
- Infection or malignancy

Mixed Cryoglobulinemia

- Often associated with Hepatitis C infection
  - Patients will be RF positive (IgM antibody against Fc portion of IgG)
  - Minority of patients with cryoglobulinemia have vasculitis
  - Skin involvement most common
  - More rarely, nerve and kidney involvement
Drugs associated with hypersensitivity vasculitis

- NSAIDs (including ibuprofen, diclofenac, etodolac, piroxicam, naproxen)
- Antibiotics (including β-lactams, macrolides, sulfonamides, quinolones, antivirals)
- Growth factors (including G-CSF, GM-CSF)
- SSRIIs (including paroxetine, fluoxetine)
- Anti-thyroid drugs (propylthiouracil)
- Antihypertensive medications (including thiazides, β-blockers)
- Anti-convulsants (including phenytoin)
- Vaccinations
- Allopurinol
- Aspirin
- Acetaminophen
- Insulin
- Methotrexate
- Anti-TNF agents (etanercept, infliximab)

Treatment

- In general high dose steroids
  - 1mg/kg/day or 60mg po
- For GCA
  - Other immunosuppression doesn’t spare steroids
  - Alternate day dosing of prednisone doesn’t work
- Cytoxan for life or organ threatening involvement
  - Once in remission can be changed to methotrexate, azathioprine or other agent for maintenance
- Rituximab now approved for AAV
- If vasculitis related to underlying infection such as Hep B or Hep C, then treatment is targeted at the underlying infection.
  - Minimize immunosuppression
  - Consider plasmapheresis