Vasculitis Lecture Handout

Please note, this handout serves two general purposes:

1) To complement in an outline form key information from the lecture
2) To give additional information that can fill in gaps (these are distinguished by light italicized font).

You will not be tested on material in this handout that is NOT on the powerpoint slides.

I. Overview
   a. General approach to vasculitides
      i. Large Vessel Vasculitides
         1. Giant Cell Arteritis
         2. Takayasu Arteritis
      ii. Medium Vessel Vasculitides
          1. Polyarteritis Nodosa
          2. Kawasaki Disease
      iii. Small Vessel Vasculitides
          1. ANCA Associated Vasculitis
             a. Granulomatosis with polyangiitis
             b. Eosinophilic granulomatosis with polyangiitis
             c. Microscopic polyangiitis

II. Giant Cell Arteritis (GCA)
   a. Epidemiology
      i. Most common large vessel vasculitis
      ii. Occurs at 50 years or old, and especially at 70-75 years
      iii. Most common primary vasculitis. annual incidence 2.4-32.8/100,000 people >/= 50 years old
      iv. Occurs more commonly in females
      v. Highest incidence in Scandinavians
   b. Presentation & Distribution
      i. Polymyalgia Rheumatica (PMR) is characterized by stiff and painful proximal joints, and painful proximal muscles. **PMR should not be confused with polymyositis (inflammation of the muscles which usually presents with muscle WEAKNESS, not pain)**
      ii. PMR very common as a manifestation of GCA but can also occur as a distinct disease by itself. **Many (not all) patients with GCA have PMR symptoms, but not all patients with PMR have GCA. Look for red flag symptoms of GCA to have a higher suspicion of GCA**
      iii. Non PMR Red flag symptoms of GCA
         1. Headaches, vision loss, scalp tenderness
         2. Claudication of jaw and tongue muscles (pain due to lack of blood flow caused by occlusion of the arteries)
         3. Fevers and chills
         4. Signs of ischemia
      iv. **Remember, GCA is also known as temporal arteritis, but should not lead one to be confused by the fact that the temporal artery is a ‘medium’ sized vasculitis. Giant cell arteritis is generally classified as a large vessel vasculitis but can involve both large and medium vessels (particularly the medium vessels that branch off of the arch of the aorta).**
      v. Aorta, subclavian, and iliac arteries would be classic large vessels involved in GCA, but the temporal, ophthalmic, and vertebral arteries are also involved even though they are technically medium sized vessels
   c. Pathogenesis
      i. Cause still unknown
      ii. Infectious triggers not identified
iii. Chronic, granulomatous inflammation of large (and some medium) arteries
iv. Both innate and adaptive immune system involved
v. Characteristic granulomatous inflammation suggests a dominant role of T cell mediated response
   1. Characteristic granulomatous inflammation suggests a dominant role of T cell mediated response; CD4 T cells particularly have been implicated
vi. Cytokines involved: TNF alpha, IL-6, IFN-gamma
   1. You might recognize these pro-inflammatory cytokines from Host Defense.
      Interleukin 6 (IL-6) has especially been the center of attention in more recent research, with the only FDA approved biologic therapy, tocilizumab (an anti-IL6 drug), now being used for treatment
vii. Additionally, other factors have been noted: HLA Class II (HLA-DR4 gene): this gene has been implicated in many autoimmune diseases including rheumatoid arthritis
viii. A hypothesized sequence of events is outlined below (summarized in UpToDate (https://www.uptodate.com/contents/pathogenesis-of-giant-cell-temporal-arteritis?source=related_link), from the following references:
      Piggott K et al. Vascular damage in giant cell arteritis. Autoimmunity 2009;42:596
      Weyand CM et al. IFN-γand IL-17: the two faces of T-cell pathology in giant cell arteritis.
      Curr Opin Rheumatol 2011;23:43-9
      1. Unknown initial factor (viral or other infection) activates dendritic cells located in the adventitia of medium and large vessel walls, initiating adaptive immune response
         a. Location of the activation is influenced by specific toll-like receptors (TLR) on the cells, which recognize the pathogenic factor
         b. Ligands to TLR4 recruit CD4 T cells that invade deeply into the wall, causing panarteritis, while ligands to TLR5 condition dendritic cells to support a perivascular infiltrates
         c. The age-changed vessel also influences inflammatory response.
      2. Activated monocytes then produce inflammatory cytokines (including IL-6), resulting in constitutional symptoms, elevated ESR and increase of other acute phase proteins
         a. Some activated monocytes infiltrate the adventitia of the walls of large arteries
         b. Within these vessels, infiltrating macrophages encounter antigen, which leads to recruitment of additional macrophages and lymphocytes.
      3. Interactions among recruited cells lead to production of further mediators of inflammation, tissue destruction, and induction of repair mechanisms. Cytokines subsequently promote intimal proliferation, thrombosis, and, possibly, vessel occlusion. In addition, damage of the smooth muscle of the media is followed by fibrosis, scarring, and narrowing or occlusion of the arteries.

   d. Histology & Morphology
      i. “Patchy” or “Skip lesions”
         1. Important to know because this leads to false negatives on biopsies
      ii. Lumen occlusion which leads to thromboses, which then lead to ischemia
      iii. Granulomatous inflammation
         1. Within inner media centered on internal elastic membrane
         2. Infiltrate of lymphocytes, macrophages, multinucleate giant cells
         3. Granulomas & giant cells are considered classic, but not always present (up to 25%)
            a. Granuloma: collection of localized inflammatory cells (activated macrophages)
            b. Giant cells: union of multiple cells (macrophages)
      iv. Fragmentation of internal elastic lamina
1. **DESTRUCTION OF THE INTERNAL ELASTIC LAMINA** can lead to aneurysm formation. This characteristic is also a key distinction between GCA and other vasculitides. *Thoracic aortic aneurysms can occur as a late complication, even after treatment has been started.*

e. **Diagnosis**
   i. History and physical exam very important here
   ii. Temporal artery biopsy carries risk of false negatives because of skip lesions
   iii. No specific markers or serologies (antibodies)
   iv. Erythrocyte Sedimentation Rate (ESR) and C-reactive protein indicate elevated inflammation
   v. If large vessel involvement suspected, imaging is useful (MR Angiogram)
      1. Look for stenoses and complications such as aneurysms
      2. **Inflammation in the actual blood vessel walls can also be detected with MR angiogram, though not always**

III. **Takayasu Arteritis**

a. **Epidemiology**
   i. Giant cell arteritis and Takayasu arteritis can look very similar because they both involve primarily large vessels and some medium vessels. However, the big distinction, when you are presented with a case, is the age (Takayasu Arteritis patients are younger than 50 years old, most cases of GCA presented are patients older than 50 years and often in their 70s-80s)
   ii. *Earlier descriptions mostly in Japanese populations but has been described globally*
   iii. **VERY RARE:** 1 out of 2.6 million comes out to: 0.000038%!
   iv. *More common in females*

b. **Presentation & Distribution**
   i. Classically affects aorta and arch of aorta and arch vessels, including the subclavian artery. *This is similar to GCA, but involvement of arteries usually associated with GCA are not as commonly involved, like the temporal arteries. So even though technically Takayasu arteritis is very similar to GCA, patients are not expected to simply be a 'younger version' of GCA patients. For example, vision changes and temporal headaches are not classic presentations for Takayasu patients like they are for GCA patients.*
   ii. 1/3 of cases involve the remainder of the aorta & its branches
   iii. Skip lesions are common as they are in GCA
   iv. Renal and coronary arteries can be involved, *with renal being more common in Takayasu than in GCA (unclear why) which manifests in hypertension (decreased blood flow to the kidneys which are involved in blood pressure regulation). Not clear why the distributions of affected vessels are different, but some theories include differences in embryonic origin for different arteries and different portions of arteries*
   v. Also called pulseless arteritis because it manifests in loss of pulses (for example with involvement of the subclavian arteries)

c. **Pathogenesis**
   i. This section is an easy one to remember: Pathogenesis is poorly understood.
   ii. The major cytokines involved are IL-6, IL-8, and IL-18. In fact, treatment for Takayasu includes anti-IL=6 therapy (tocilizumab), but despite this breakthrough in treatment, we still do not fully understand the pathogenesis of Takayasu arteritis.

d. **Histology & Morphology**
   i. Histology is characterized by granuloma formation, similarly to GCA
      1. Adventitial and transmural mononuclear infiltrates, giant cells, & patchy medial necrosis
   ii. Look for transmural scarring & thickening of the involved vessel, like the aorta

e. **Diagnosis**
   i. There are no specific markers or serologies
   ii. ESR and CRP would be the most useful blood tests as indicators of ongoing inflammation (similar to GCA), but are not 100% sensitive or specific
iii. As a result, we rely heavily on clinical presentation and imaging
iv. CT angiogram, MR angiogram, or PET scan is used to evaluate for active inflammation from vasculitis. Stenoses indicate areas of narrowing from the vasculitis, and collateral vessel formation as a result of chronic decreased blood flow is more common in Takayasu Arteritis than in GCA.
v. Unlike GCA, temporal artery biopsy is not used since the temporal artery is not commonly involved with Takayasu Arteritis as it is with GCA patients
vi. Skip lesions (like GCA)
vii. Not easy to obtain biopsies (often in crucial locations not easily amenable to removing tissue)

IV. Treatment for both GCA and Takayasu Arteritis
   i. Immunosuppression
   ii. Corticosteroids (prednisone)
   iii. Anti-Interleukin 6 (tocilizumab)
       1. Intravenous medication
   iv. Oral steroid sparing agents
       1. Methotrexate, azathioprine

V. Polyarteritis Nodosa (PAN)
   a. Epidemiology
      i. Annual incidence: 9-77 out of a million (wide range but still very rare)
      ii. Earlier data closely linked this condition to Hepatitis B virus, with up to 95% of an association in HBV endemic areas, but this association is much lower now with the decline in HBV
   b. Presentation & Distribution
      i. Medium vessels, and sometimes small vessels are affected
      ii. Thrombosis and aneurysms occur in affected vessels
      iii. Kidney (renal artery), heart (coronary artery), liver and gastrointestinal tract (mesenteric arteries) involved most commonly, but the skin and subcutaneous tissues are also involved
      iv. The pulmonary system is usually not involved
      v. Hypertension (kidney), bloody stools from mesenteric ischemia (GI tract), muscle pain, peripheral neuritis (mononeuritis multiplex), orchitis, ulcers/infarcts/livedo reticularis (skin)
   c. Pathogenesis
      i. Outside of the association with HBV (when it is present), little is known about the pathogenesis of PAN
   d. Histology & Morphology
      i. Focal, segmental (skip lesions—again—similar to GCA and Takayasu)
      ii. Transmural necrotizing inflammation: begins in the intimal layer and then progresses (inside → out) to transmural involvement (different from GCA which begins in the adventitia—outside → in)
      iii. Neutrophils and mononuclear cells are the predominant infiltrating cells
      iv. Fibrinoid necrosis
          1. Fibrinoid necrosis is noted on histology when the vessel wall is necrosed (has died) and this tissue, along with the inflammatory material that has been recruited in, takes on a pink “fibrin-ike” appearance. Hence the name “fibrinoid” because it is not actually all fibrin.
      v. Luminal thrombosis develops from the inflammation
      vi. Destruction of internal & external elastic lamina leads to aneurysm formation
      vii. Involve one part of the circumference (not the entire circumference) which is more common for PAN
   e. Diagnosis
      i. Constitutional symptoms (malaise, fever, weight loss)
      ii. ESR and CRP reflect systemic inflammation
      iii. Muscle or nerve biopsy (sural nerve) most feasible if involved, will show inflammation
iv. Abdominal angiography if GI involvement (look for areas of stenoses and aneurysms, called “beading”)

v. Test for Hepatitis B Virus

vi. The American College of Rheumatology Criteria from 1990 uses the following ten criteria (you do not have to memorize this), of which the presence of at least three criteria leads to the diagnosis of PAN:

1. Weight loss of 4 kg or more
2. Livedo reticularis
3. Testicular pain/tenderness
4. Myalgia or leg weakness/tenderness
5. Mononeuropathy or polyneuropathy
6. Diastolic blood pressure greater than 90 mm/Hg
7. Elevated blood urea nitrogen (BUN) or creatinine level unrelated to dehydration or obstruction
8. Presence of hepatitis B surface antigen or antibody in serum
9. Arteriogram demonstrating aneurysms or occlusions of the visceral arteries
10. Biopsy of small- or medium-sized artery containing polymorphonuclear neutrophils

f. Treatment

i. Immunosuppression
ii. Corticosteroids (prednisone)
iii. For severe disease, cyclophosphamide (cytotoxic agent)
iv. Long term steroid sparing agents
v. Methotrexate
vi. Treat Hepatitis B or C if present

VI. Kawasaki Disease

a. Epidemiology

i. Usually affects young children, <5 years of age
ii. Much higher prevalence in Japan 215.3/100,000 (0.22%) than US (0.017%) though still rare; peak ages in Japan were found to be at 9-11 months
iii. Occurs more in boys than girls (ratio 1.62:1)

b. Presentation & Distribution

i. Medium vessel disease, especially coronary arteries
ii. Usually self limited
iii. However, 1 out of 5 children not treated with IVIg early in disease course develop coronary artery aneurysms
   1. Coronary artery aneurysms can then lead to myocardial ischemia, infarction, and sudden death
iv. Coronary aneurysm in 25% of untreated patients

c. Pathogenesis

i. Unknown, but microbial agent is the likely trigger (mostly viral)
ii. Likely infection by a pathogen that usually cause asymptomatic or nonvasculitic condition in most children but results in Kawasaki in genetically predisposed children
iii. Possible delayed type hypersensitivity response directed against cross-reactive or newly uncovered vascular antigen (anti-endothelial cell antibodies)

d. Histology & Morphology

i. Similar morphology to polyarteritis nodosa (PAN)
ii. Transmural inflammatory infiltrate
iii. Destruction of elastin and collagen fibers
iv. Fibrinoid necrosis also present
v. REMEMBER: focal fibrinoid necrosis and transmural destruction can lead to coronary artery aneurysms as a complication

e. Diagnosis
   i. Diagnostic criteria
      1. Persistent fever (>5 days) PLUS at least four of the following:
      2. Nonpurulent bilateral conjunctivitis
      3. Oral mucosal involvement: erythematous pharynx, red or fissured lips, or strawberry tongue
      4. Soft tissue abnormalities of hands and feet: erythema, edema, or desquamation
      5. Polymorphous, nonvesicular rash
      6. Cervical adenopathy

   ii. Laboratory testing to demonstrate inflammation
      1. Complete blood count
         a. Lymphocyte counts can drop in the acute phase of disease and then rise
         b. Platelets are often high
         c. Normocytic normochromic anemia
         d. ESR, CRP are expected to be high
         e. Liver tests
            i. Transaminases (ALT and AST) can be high, though the cause of this is unknown

   iii. Echocardiogram, to evaluate cardiac function and coronary arteries

VII. ANCA Positive Vasculitides:
   - Granulomatosis with polyangiitis (GPA) formerly known as Wegener’s granulomatosis
   - Eosinophilic granulomatosis with polyangiitis (EGPA) formerly known as Churg Strauss syndrome,
   - Microscopic polyangiitis (MPA)

   a. First, What is ANCA anyway?
      i. Anti-neutrophilic cytoplasmic antibody
         1. Antibodies directed against components of neutrophil granules (mostly against enzymes)
         2. There are two patterns: perinuclear (p-ANCA), and cytoplasmic (c-ANCA).
            a. Perinuclear pattern correlates with presence of anti-myeloperoxidase Antibodies
               i. Anti-myeloperoxidase (anti-MPO, p-ANCA)
                  1. Lysosomal granule involved in oxygen free radical generation
               ii. When a patient with suspected small vessel vasculitis has a positive p-ANCA/MPO, you should think of MPA or EGPA
            b. Cytoplasmic pattern correlates with anti-proteinase 3 antibodies
               i. Anti-proteinase 3 (anti-PR3, c-ANCA)
                  1. Serine protease in the ‘azurophilic’ granule that shares homology with several microbial peptides
               ii. When a patient with suspected small vessel vasculitis has a positive c-ANCA/PR3, think of GPA

   b. Theory on How ANCA Works
      i. ANCA formation induced by drug or cross reactive microbial antigen (an example of a drug that can is associated with ANCA formation is prophylthiouracil, used to treat hyperthyroidism)
         1. Remember molecular mimicry from host defense? Similar concept
         2. Another possibility is leukocyte expression of PR3 or MPO during infection in a susceptible individual leads to ANCA formation
      ii. During subsequent infection or stimulus, inflammatory cytokines like TNF increase neutrophil surface expression or release of PR3 and MPO
      iii. ANCA binds these cytokine- activated cells, further activating neutrophils
iv. ANCA activated neutrophils release granule contents and reactive oxygen species leading to vascular damage

v. IMPORTANT: THIS PROCESS IS NOT THE SAME AS IMMUNE COMPLEX MEDIATED DISEASE (which is what lupus is).
   1. The ANCA auto-antibodies don’t form immune complexes which is what we see in lupus, cryoglobulinemic vasculitis, or subacute bacterial endocarditis
   2. Also, the vascular lesions don’t usually contain antibody and complement deposits, so ANCA-associated vasculitides often are described as “pauci-immune” on biopsies

c. Other causes of positive ANCA
   1. Other rheumatic autoimmune diseases
   2. Inflammatory bowel disease (40-80% in ulcerative colitis)
   3. Autoimmune liver disease
   4. Infections
   5. Malignancies
   6. Myelodysplastic processes

   ii. Drugs: Levamisole (more on this later), allopurinol, hydralazine, propylthiouracil, minocycline


   http://ovidsp.tx.ovid.com.archer.luhs.org/sp-3.21.1b/ovidweb.cgi?&S=JKKPFPBCKMDDFDNCNCIKMAIBKIEAAA00&Link+Set=S.sh.20%7c1%7csl_10

   iii.

d. ANCA Vasculitis Pathogenesis
   i. Evidence that PR3 and MPO Antibodies are involved in pathogenesis
      1. Closely associated with corresponding vasculitis
         a. Higher levels correspond with active disease and relapses
      2. In-vitro studies show that ANCA stimulate neutrophils to produce reactive oxygen species and release lytic enzymes
         a. Adherence to endothelial cells, and lysis or detachment of endothelial cells
      3. Animal studies demonstrate renal and pulmonary disease when IgG MPO antibodies are introduced


e. ANCA Associated Vasculitis Presentation in General

   i. Small vessel vasculitides
   ii. Distribution of inflammatory manifestations
      1. Classical Triad: Lungs, Kidneys, Skin
      2. Skin: specifically palpable purpura (leukocytoclastic vasculitis)
      3. Neurologic involvement not uncommon

   iii. ANCA usually (but not always) positive

VIII. Granulomatosis with Polyangiitis (GPA)

Formerly known as Wegener’s Granulomatosis

a. Epidemiology
   i. Males and Females affected, any age
   ii. Rare
      1. Annual incidence 1.3-14.4 per million (rare!) (0.00013-0.00144%)

b. Presentation & Distribution
   i. C-ANCA positive, PR3 (proteinase) Ab positive
   ii. Upper airway disease (ear, nose, throat involvement)
      1. Unique to GPA (vs MPA and EGPA)
      2. Recurrent sinusitis (80%), recurrent nasopharyngeal ulcers (75%), septal perforations, saddle nose deformities, subglottic stenosis, otitis media
   iii. Lower respiratory disease (95%)
1. Nodules→ cavitating lesions due to necrosis in areas affected by vasulitis, diffuse alveolar hemorrhage
2. There is a “Limited” form that only involves respiratory tract

iv. Kidneys: Glomerulonephritis
1. Usually aggressive, may lead to end stage renal disease over course of weeks if untreated
2. Proteinuria (elevated protein in the urine), and hematuria (red blood cells or red blood cell casts on urinalysis)

v. Joints: Arthritis, arthralgias
vi. Nerves: Mononeuritis multiplex
vii. Eyes: Conjunctivitis, uveitis, scleritis
viii. Skin: Palpable purpura (on biopsy, remember palpable purpura will be seen as ‘leukocytoclastic vasculitis,’ ulcers

c. Pathogenesis
i. Cell-mediated hypersensitivity response to an environmental trigger
ii. PR-3 Antibodies present in 95% and likely play major role in tissue injury
iii. T cell activation
iv. See above: ANCA Vasculitis Pathogenesis & Theory on How ANCA works

d. Histology & Morphology
i. Respiratory
1. Sinuses: Granulomatous sinusitis (aka, granulomas present, see slides for images of granulomas with giant cells)
2. Lungs:
   a. Necrotizing granulomatous vasculitis with surrounding fibroblastic proliferation
   b. Coalescence of multiple granulomata will lead to central cavitation (see slides for a gross pathology picture of the lung with cavitation; these can be seen on xray and CT imaging of the lungs of a patient with active ANCA vasculitis)
   c. Vascular destruction in the lung tissue leads to hemorrhage and hemoptysis

ii. Renal
1. Focal and segmental necrotizing glomerulonephritis
   a. Glomerular necrosis
   b. Thrombosis of isolated glomerular capillary loops
2. Crescentic glomerulonephritis occurs in more advanced disease, with the word “crescentic” being a key phrase indicating the formation of ‘crescents’
   a. Diffuse necrosis
   b. Parietal cell proliferation forming epithelial crescents
3. Remember, this is going to be ‘pauci-immune’ on immunofluorescence (lacking in deposits of immunoglobulin and complements—which distinguishes it from other forms of glomerulonephritis like lupus)

iii. Skin
1. LEUKOCYTOCLASTIC VASCULITIS (classically)
   a. Neutrophilic infiltrate surrounding and disrupting small vessels
   b. Fibrin deposits and nuclear debris (leukocytoclasis)
   c. Extravasated red blood cells in the adjacent dermis.

IX. Eosinophilic Granulomatosis with Polyangiitis (EGPA)
Formerly known as Churg Strauss Syndrome
a. Epidemiology
i. Rare: Annual incidence 0-2.7/million—even more rare than GPA! (0-0.00027%)
ii. Another ANCA associated vasculitis which is p-ANCA, MPO positive
b. Presentation & Distribution
   i. Three phases of presentation
      1. Atopic phase, allergic rhinitis & asthma
      2. Eosinophilia
         a. Eosinophilia is striking (>1k/uL vs GPA 500/uL)
      3. Systemic vasculitis
         a. By this, I mean, think of similar symptoms that are common to the other
            vasculitides like constitutional symptoms caused by elevated levels of
            inflammatory cytokines (fevers, fatigue, weight loss, etc)
         b. Then, think of symptoms expected of ANCA vasculitis in general, including
            the classic triad (lungs, kidneys, skin)
   ii. Respiratory
      1. Pulmonary infiltrates which can be fleeting (like GPA)
      2. Nodules which are unlikely to lead to cavitating lesions (unlike GPA)
      3. ASTHMA is a classic symptom of EGPA, particularly longstanding difficult to treat
         asthma
   iii. Mononeuritis multiplex—sensory and motor deficit
      1. Can happen with any of the ANCA vasculitides BUT is more common in EGPA (>60%)
   iv. Eosinophilic gastroenteritis
   v. Ocular/eye inflammation
   vi. Glomerulonephritis
   vii. Skin
      1. Cutaneous nodules
      2. Palpable purpura—AKA Leukocytoclastic vasculitis (see above for more on
         leukocytoclastic vasculitis)
   viii. Cardiac
      1. Cardiomyopathy
      2. Coronary arteritis (medium vessel—remember, this is an exception to the rule of
         ‘small vessels’ involved)
         a. Leading cause of death for EGPA patients

c. Pathogenesis
   i. See ANCA vasculitis pathogenesis
   ii. Many patients are not ANCA positive, so the thought is that some of these patients may be
      responding to an antigen that normally should not elicit an inflammatory/eosinophilic
      response

d. Histology & Morphology
   i. Similarly to GPA, you will see small vessel vasculitis (inflammatory infiltrate) and granulomas
   ii. But the big difference here is that you will see an abundance of eosinophils

X. Microscopic Polyangiitis (MPA) –the last of the 3 ANCA associated vasculitides
a. Epidemiology
   i. Small vessel vasculitis
   ii. Rare: Annual incidence 1-11.6 / million
   iii. p-ANCA positive (anti-MPO positive)
b. Presentation & Distribution
   i. Similar to GPA clinically except
      1. Much less likely to involve upper respiratory tract
   ii. Glomerulonephritis, alveolar hemorrhage, polyneuropathy, palpable purpura

c. Pathogenesis
   i. See ANCA vasculitis pathogenesis

d. Histology & Morphology
   i. Segmental fibrinoid necrosis of media
   ii. Focal transmural necrotizing lesions
iii. Granulomatous inflammation absent (unlike GPA & EGPA), and abundance of eosinophils is also absent (unlike EGPA)

iv. Similar to PAN except it spares medium/large vessels

v. Leukocytoclastic vasculitis
   1. Remember, this is seen in any of the small vessel vasculitides
   2. When you see palpable purpura, this is typically the histological diagnosis that you would see under the microscope

vi. Diagnosis
   1. As discussed earlier, clinically MPA can look very similar to GPA
   2. Keep in mind two major differences when making the diagnosis
      a. Clinically, MPA is less likely to involve the upper respiratory tract (sinuses, trachea)
      b. p-ANCA/ positive MPO will distinguish this from GPA (which is c-ANCA/ positive PR3)
      c. Granulomatous changes on histology are less likely than the other two ANCA vasculitides

XI. Treatment of ANCA Vasculitis
   a. Steroid therapy (immunosuppression)
   b. Severe disease: Rituximab for induction (Rituximab is an anti-CD20 biologic agent given as an infusion)
   c. Maintenance therapy: Azathioprine, Methotrexate (both oral drugs often used in other autoimmune diseases; azathioprine is also used as a transplant drug to prevent organ rejection)
   d. Limited disease: Methotrexate

XII. Non-ANCA Vasculitides
   a. IgA vasculitis
   b. Cryoglobulinemic Vasculitis
   c. Urticarial vasculitis
   d. Leukocytoclastic vasculitis
      i. Can be seen in setting of multiple conditions like hypersensitivities (to drugs), infections (for example viral infections, but also subacute bacterial endocarditis)
   e. Vasculitis secondary to other autoimmune disease
      i. Systemic lupus erythematosus, Rheumatoid arthritis

XIII. IgA (Immunoglobulin A) Vasculitis
   Also known as Henoch Schonlein Purpura
   a. Epidemiology
      i. Mostly in children
      ii. Rare. 20/100,000 children <17 years of age
      iii. If significant renal involvement (rare), usually in adults
      iv. Usually self limited & does not require treatment
   b. Presentation & Distribution
      i. Palpable purpura (AKA leukocytoclastic vasculitis—remember, whenever you see palpable purpura on physical exam, it typically correlates with leukocytoclastic vasculitis on histology of a skin biopsy)
      ii. Arthritis
      iii. Gastrointestinal disease
         1. Abdominal pain, vomiting, GI bleed, intussusception in children
      iv. Glomerulonephritis
         1. Hematuria, proteinuria
   c. Pathogenesis
      i. Vascular and renal deposition of IgA containing immune complexes
      ii. Precipitated by medications or infections
         1. Streptococcal or viral infections
   d. Histology & Morphology
i. Skin biopsy
   1. Classical leukocytoclastic vasculitis like the other small vessel vasculitides (including ANCA vasculitis) BUT IgA deposition is pathognomonic of HSP

ii. Kidney biopsy
   1. Range from isolated mesangial proliferation to severe crescentic glomerulonephritis with IgA deposition

XIV. Remember Immune Complex Disease?
   a. Immune complexes form (ie systemic lupus erythematosus, infections—including subacute bacterial endocarditis, IgA vasculitis, cryoglobulinemic vasculitis)—this is a different mechanism from ANCA associated vasculitis
   b. Excessive immune complexes formed antigens and antibodies either as a result of infection or autoimmune process
   c. Immune complex formation activates the classical complement pathway
      i. C3b is formed through the activated complement pathway (C3b facilitates opsonization & in this case most importantly, chemotactic factor attracting macrophages and neutrophils which then lead to inflammation)
      ii. MAC (C5-9) formation also results from complement activation and leads to lysis of cells (which is good if it is targeting pathogens like bacteria—but in vasculitis, it targets innocent bystanders such as normal tissue)
   d. Serves a purpose when needed, but in autoimmune disease, it causes destructive inflammation

XV. Cryoglobulinemic Vasculitis
   a. Epidemiology
      i. Most often associated with Hepatitis C infection
         1. Prevalence dependent on endemic areas of Hepatitis C infection
      ii. Overall rare
         1. 15-30% of HCV patients, 5-10% of HIV patients
   b. Presentation & Distribution
      i. Palpable purpura present in almost all patients
      ii. Weakness
      iii. Arthralgias
      iv. Liver involvement
      v. Raynaud phenomenon
         1. Decreased blood flow to fingertips caused by vasospasm induced by cold
      vi. Multiplex mononeuritis
         1. Sensory and motor deficit
   c. Pathogenesis
      i. Viral triggered, immune complex disease
         1. Like IgA vasculitis (unlike ANCA associated vasculitis)
      ii. Cryoglobulins: Immunoglobulins that precipitate at <37° (dissolve on rewarming)
         1. Three types of cryoglobulinemia
         2. Cryoglobulinemic vasculitis is typically of the mixed type (Type II or III)
            a. Most common: underlying Hepatitis C infection
   d. Histology & Morphology
      i. Skin biopsy of palpable purpura
         1. Leukocytoclastic vasculitis
         2. Cryoglobulins can be identified in the skin blood vessels (but not always seen)
         3. Immunofluorescence microscopy on the skin biopsy should show immunoglobulin and complement deposits
   e. Treatment
      i. Treatment: treat the underlying the disease (hepatitis C virus)
      ii. Immunosuppression with rituximab (anti-CD20), plasma exchange