OVERVIEW

1. General approach to vasculitides
2. Large Vessel Vasculitides
3. Medium Vessel Vasculitides
4. Small Vessel Vasculitides
5. Vasculitides in one slide!
6. Cases
OBJECTIVES

1. Recall the approach to classification of the vasculitis syndromes using anatomic distinctions such as large, medium, and small vessel diseases.
2. Compare & contrast the general histopathological features of small, medium and large vessel vasculitis. Recognize that there is some overlap between them.
3. Compare & contrast the general clinical features of small, medium and large vessel vasculitis.
4. Recognize the histopathological and clinical differences between individual ANCA associated vasculitis syndromes (granulomatosis with polyangiitis, eosinophilic granulomatosis with polyangiitis, and microscopic polyangiitis)

RESOURCES

• Robbins textbook
• ACP Scientific American Medicine
• American College of Rheumatology Image Library
• www.rheumatology.org
• Other resources as applicable in corresponding slides
• Me: ROSTROWSKI@LUMC.EDU

DEFINITION OF VASCULITIS

1. Inflammation involving blood vessels
2. Typically arteries
3. Primary vs secondary
   1. Primary vasculitis is the focus of this lecture
4. When to suspect vasculitis
   1. Constitutional symptoms (fever, fatigue, weight loss)
   2. Symptoms suggestive of specific organ involvement
Raising Awareness of Auto-immune Disease
http://weishendopublications.com/diseases-g---h.html#gsa=7

INFLAMMATION

↓

OCCLUSION

↓

ISCHEMIA

GENERAL APPROACH TO VASCULITIS

1. Does the patient appear to have a systemic inflammatory condition?
   Systemic? Inflammatory?

2. What organs are involved?
   What type of blood vessels supply those organs?
   Large, Medium, Small

3. Can the vasculitis be explained by other conditions?
   Infection? Malignancy? Drug?

STEP BACK AND SEE THE BIG PICTURE
(A COUPLE APPROACHES)

Size of vessels involved (Scientific American Medicine)
- Large Vessel, Medium Vessel, Small Vessel

Pathogenesis (Robbins)
- Noninfectious
  - Immune complex deposition
  - Antineutrophil cytoplasmic antibodies
  - Anti-endothelial cell antibodies
  - Autoreactive T cells
LARGE VESSEL VASCULITIS

1. GIANT CELL ARTERITIS
2. TAKAYASU ARTERITIS

GIANT CELL ARTERITIS

- AKA: Temporal Arteritis
- Typically persons >50 years of age (mean: 70-75 years)
- 2/3 Female
- Most common primary vasculitis, annual incidence 2.4-32.8/100,000 people ≥50 years old
- Highest incidence rates in Scandinavian populations
GIANT CELL ARTERITIS

- Four general presentations (next slide)
- Polymyalgia Rheumatica (PMR) is common
  1. Significant stiffness in the proximal joints (shoulders, hips)
  2. Pain in proximal joints, and muscles
  3. Prolonged morning stiffness

Table 5 Giant Cell Arteritis

<table>
<thead>
<tr>
<th>No.</th>
<th>Description</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>Cranial arteritis&lt;br&gt;Headache&lt;br&gt;Temporal arteries up to 50%&lt;br&gt;Scalp and/or temporal tenderness&lt;br&gt;Classification of joint and tongue muscles</td>
</tr>
<tr>
<td>2</td>
<td>Polymyalgia rheumatica&lt;br&gt;80% of patients&lt;br&gt;Proximal upper and lower extremity myalgia&lt;br&gt;Common in disease relapse</td>
</tr>
<tr>
<td>3</td>
<td>Non-specific inflammatory disease&lt;br&gt;Fever, night sweats, malaise, weight loss&lt;br&gt;Anemia, leukocytosis, thrombocytosis&lt;br&gt;Elevated ESR and CRP normally very high</td>
</tr>
<tr>
<td>4</td>
<td>Larger vessel vasculitis&lt;br&gt;Vary frequent but usually asymptomatic&lt;br&gt;Signs of ischaemia (e.g., asymmetrical pulses and/or blood pressures limited) Not absent</td>
</tr>
</tbody>
</table>

GIANT CELL ARTERITIS DISTRIBUTION

Illustration copyright 2001 Nucleus Communications, Inc. All rights reserved.

http://www.nucleusinc.com

Medicalook.com
http://www.medicalook.com/systems_images/Principal_Arteries_large.jpg

Note: selected texts have been blocked out from original image for teaching purposes.
GIANT CELL ARTERITIS

PATHOGENESIS

1. Cause still unknown
2. Chronic, granulomatous (usually) inflammation of large (and some medium) arteries
3. Both innate and adaptive immune system involved
4. Cytokines involved: TNF alpha, IL-6, IFN-gamma

Kumar V et al.  Ch 9, 327-63.e1

https://www-clinicalkey-com.archer.luhs.org/#!/content/book/3-s2.0-B978143771781500009X?scrollTo=%23s0225


GIANT CELL ARTERITIS

MORPHOLOGY

1. “Patchy” or “Skip lesions”
   1. Leads to false negatives on biopsies
2. Lumen occlusion, sometimes thromboses
3. Granulomatous inflammation
   1. Within inner media centered on internal elastic membrane
   2. Infiltrate of lymphocytes, macrophages, multinucleate giant cells
   3. Granulomas & giant cells are classic but not always present (up to 25%)
4. Fragmentation & destruction of internal elastic lamina
   1. Can lead to aneurysm formation

Kumar V et al.  Ch 9, 327-63.e1

https://www-clinicalkey-com.archer.luhs.org/#!/content/book/3-s2.0-B978143771781500009X?scrollTo=%23s0225

DESTRUCTION OF INTERNAL ELASTIC LAMINA, GIANT CELLS

American College of Rheumatology: Rheumatology Image Library
Image 99-12-0075

http://images.rheumatology.org/bp/#/search?q=giant%20cell%20arteritis&filters=%7B%22keyword%22%3A%5B%22vasculitis%22%5D%7D#2861651

American College of Rheumatology: Rheumatology Image Library
Image 99-12-0076

http://images.rheumatology.org/bp/#/search?q=giant%20cell%20arteritis&filters=%7B%22keyword%22%3A%5B%22vasculitis%22%5D%7D#2861652
GIANT CELL ARTERITIS
DIAGNOSIS

1. History and physical exam very important here
2. Temporal artery biopsy carries risk of false negatives
3. No specific markers or serologies
4. Erythrocyte Sedimentation Rate (ESR) and C-reactive protein indicate elevated inflammation
5. If large vessel involvement suspected, imaging is useful (MR Angiogram)

CAN CAUSE ANEURYSMS TOO

STENOSES (NARROWING) ON IMAGING FROM GCA
TAKAYASU ARTERITIS

1. AKA “Pulseless disease”
2. Also a granulomatous vasculitis
3. Affects large and medium vessels
4. Patients are younger than 50 years of age
5. Very rare: 2.6 / million
6. Earlier descriptions Japanese, but global distribution
7. 9:1 Female: Male ratio in Japanese series, but more equal in other populations

SIMPLE SUMMARY

https://www-clinicalkey-com.archer.luhs.org/#!/content/book/3-s2.0-B978143771781500009X?scrollTo=%23s0225

Kumar V et al.  Robbins Pathology. Ch 9, 327-63.e1

TAKAYASU ARTERITIS
DISTRIBUTION & DIAGNOSIS

- Classically affects aortic arch & arch vessels
- Renal and coronary arteries also affected
- 1/3 also involve remainder of aorta and its branches
- Hypertension (when renal artery involved)
- Occasional aortic root involvement
- Dilation and aortic valve insufficiency
- Pulseless manifestation, ischemia
- Pulmonary arteries in 50%
- Renal and coronary arteries also affected
- Hypertension (when renal artery involved)

Kumar V et al. Robbins Pathology Ch 9, 327-63.e1
https://www-clinicalkey-com.archer.luhs.org/#!/content/book/3-s2.0-B978143771781500009X?scrollTo=%23s0225


TAKAYASU ARTERITIS
DIAGNOSIS

- Clinical diagnosis
- No specific markers
- ESR & CRP (not always elevated)
- Arterial imaging (CT angiogram, or MR angiogram)
- Skip lesions (like GCA)
- Most tissue biopsy obtained during procedures or postmortem, so not often used

TAKAYASU PATHOGENESIS

- Pathogenesis poorly understood
- Major cytokines (IL-6, IL-8, IL-18) (lots of research needed)*

Kumar V et al. Robbins Pathology Ch 9, 327-63.e1
https://www-clinicalkey-com.archer.luhs.org/#!/content/book/3-s2.0-B978143771781500009X?scrollTo=%23s0225


TAKAYASU HISTOLOGY & MORPHOLOGY

- Granuloma formation
- Transmural scarring and thickening of the aorta (or other involved vessels)
- Similar changes to GCA
- Adventitial and transmural mononuclear infiltrates
- Giant cells and patchy medial necrosis
- Irregular thickening of the vessel wall, intimal hyperplasia, adventitial fibrosis

TAKAYASU ARTERITIS

Note the narrowed lumen
Thickening of the vessel wall
Inflammatory infiltrate

ARTERIAL STENOSES IN TAKAYASU ARTERITIS

Collateral vessel formation is more common in Takayasu than in Giant Cell Arteritis
MEDIUM VESSEL VASCULITIS

1. POLYARTERITIS NODOSA
2. KAWASAKI

MEDIUM VESSEL VASCULITIS #1

POLYARTERITIS NODOSA

SIMPLE SUMMARY
POLYARTERITIS NODOSA
EPIDEMIOLOGY, PATHOGENESIS
- Annual incidence 9-77/million
- Earlier data: higher incidence in Hepatitis B patients
  - Up to 95% associated with HBV in HBV endemic areas
  - Outside of HBV associated cases, cause is unknown
- Little known about pathogenesis


POLYARTERITIS NODOSA
PRESENTATION & DISTRIBUTION
- Medium (and sometimes small) sized arteries
- Thrombosis, aneurysms, ischemia
- Kidney, heart, liver and gastrointestinal tract involved
- Constitutional symptoms (malaise, fever, weight loss)
- Hypertension (kidney), bloody stools from mesenteric ischemia (GI tract), muscle pain, peripheral neuritis (mononeuritis multiplex), orchitis, ulcers/infarcts/livedo reticularis (skin)

Kumar V et al. Robbins Pathology. Ch 9, 327-63.e1
https://www-clinicalkey-com.archer.luhs.org/#!/content/book/3-s2.0-B978143771781500009X?scrollTo=%23s0225

POLYARTERITIS NODOSA
HISTOLOGY & MORPHOLOGY
1. Focal, segmental (skip lesions—again)
2. Transmural necrotizing inflammation
3. Neutrophils and mononuclear cells
4. Fibrinoid necrosis
5. Luminal thrombosis
6. Older lesions show fibrosis
7. Involve one part of the circumference

Kumar V et al. Robbins Basic Pathology. Ch 9, 327-63.e1
https://www-clinicalkey-com.archer.luhs.org/#!/content/book/3-s2.0-B978143771781500009X?scrollTo=%23s0225
POLYARTERITIS NODOSA

DIAGNOSIS

- No specific blood test
- Negative ANCA (anti-neutrophil cytoplasmic antibody)
- ESR and CRP reflect inflammation
- Muscle or nerve biopsy (sural nerve) most feasible if involved
- Abdominal angiography if GI involvement
- Test for Hepatitis B Virus
- Fatal if untreated

Kumar V et al. Ch 9, 327-63.e1 in Robbins Basic Pathology 9thed. https://www-clinicalkey-com.archer.luhs.org/#!/content/book/3-s2.0-B978143771781500009X?scrollTo=%23s0225

POLYARTERITIS NODOSA

Wrist Drop

Kumar V et al. Ch 9, 327-63.e1
https://www-clinicalkey-com.archer.luhs.org/#!/content/book/3-s2.0-B978143771781500009X?scrollTo=%23s0225

Livedo reticularis

POLYARTERITIS NODOSA

IMAGING

Aneurysmal changes, accompanied by stenotic areas (narrowing). “Beading” often described.
POLYARTERITIS NODOSA
TREATMENT

- Immunosuppression
- Corticosteroids (prednisone)
- For severe disease, cyclophosphamide (cytotoxic agent)
- Long term steroid sparing agents
  - Methotrexate
- Treat Hepatitis B or C if present


KAWASAKI DISEASE

SIMPLE SUMMARY
KAWASAKI DISEASE

EPIDEMIOLOGY

- Infants and young children (usually <5 years)
- Japan: 215.3/100,000 in 2007 (age 0-4 years)
- US: 20/100,000 in 2006 (<5 years old)
- Occurs more in boys:girls (1.62:1 ratio)
- Rare, but it is the most common vasculitis in children
- Former name “Mucocutaneous lymph node syndrome”

Huang WC et al.  Kawasaki disease is the leading cause of acquired heart disease in children worldwide … Pediatrics 2009;123:e401

KAWASAKI PRESENTATION & DISTRIBUTION

- Medium vessel disease, especially coronary arteries
- Usually self limited (see next slide for symptoms)
- However, 1 out of 5 children not treated with IVIg early in disease course develop coronary artery aneurysms
- Reports as much as 25% of untreated patients develop coronary aneurysm


KAWASAKI DISEASE

DIAGNOSIS

- Diagnostic criteria
- Laboratory testing to demonstrate inflammation
  - Complete blood count, ESR, CRP, Liver test, Albumin
  - Echocardiogram

<table>
<thead>
<tr>
<th>Table 4</th>
<th>Diagnostic Criteria for Kawasaki Disease</th>
</tr>
</thead>
<tbody>
<tr>
<td>Persistent fever (&gt;3 days) plus at least 3 of the following conditions:</td>
<td></td>
</tr>
<tr>
<td>1. Non-purulent bilateral conjunctivitis</td>
<td></td>
</tr>
<tr>
<td>2. Oral mucosal involvement: erythema, pharynx, red or fissured lips, or strawberry tongue</td>
<td></td>
</tr>
<tr>
<td>3. Symmetrical involvement of hands and feet: edema, erythema, or desquamation</td>
<td></td>
</tr>
<tr>
<td>4. Polymorphous, nonscarlet rash</td>
<td></td>
</tr>
<tr>
<td>5. Cardiovascular pathology</td>
<td></td>
</tr>
</tbody>
</table>

KAWASAKI DISEASE PATHOGENESIS & PATHOLOGY

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

Kumar V et al.  Ch 9, 327-63.e1 in Robbins Basic Pathology, 9th Ed

https://www-clinicalkey-com.archer.luhs.org/#!/content/book/3-s2.0-B978143771781500009X?scrollTo=%23s0225

Direct link to PDF: http://www.ncbi.nlm.nih.gov/pmc/articles/PMC1798473/

KAWASAKI HISTOLOGY & MORPHOLOGY

1. Similar morphology to polyarteritis nodosa (PAN)
2. Transmural inflammatory infiltrate
3. Destruction of elastin and collagen fibers
4. Fibrinoid necrosis also present (less severe than PAN)
5. REMEMBER: focal fibrinoid necrosis and transmural destruction can lead to coronary artery aneurysms as a complication

Kumar V et al.  Ch 9, 327-63.e1 in Robbins Basic Pathology, 9th Ed

https://www-clinicalkey-com.archer.luhs.org/#!/content/book/3-s2.0-B978143771781500009X?scrollTo=%23s0225

Direct link to PDF: http://www.ncbi.nlm.nih.gov/pmc/articles/PMC1798473/

American College of Rheumatology Image Library
http://images.rheumatology.org/rglp/research/kawasaki/image1024x768/226274
SMALL VESSEL VASCULITIS

1. ANCA POSITIVE VASCULITIDES (GPA, MPA, CSS)
2. HENOCH SCHONLEIN PURPURA
3. CRYOGLOBULINEMIA
4. “OTHERS”

ANCA ASSOCIATED VASCULITIS

SIMPLE SUMMARY
WHAT'S ANCA ANYWAY?

- Anti-neutrophil cytoplasmic antibody
- Antibodies directed against components of neutrophil granules (mostly against enzymes)
- Anti-myeloperoxidase (anti-MPO, p-ANCA)
  - Myeloperoxidase: lysosomal granule involved in oxygen free radical generation
  - Microscopic polyangiitis (MPA) & Eosinophilic Granulomatosis with Polyangiitis (EGPA) (AKA Churg-Strauss Syndrome)
- Anti-proteinase 3 (anti-PR3, c-ANCA)
  - Serine protease in the ‘azurophilic’ granule that shares homology with several microbial peptides
  - Granulomatosis with polyangiitis (AKA Wegener granulomatosis)

THEORY ON HOW ANCA WORKS

1. ANCA formation induced by drug or cross reactive microbial antigen
   - Another possibility is leukocyte expression of PR3 or MPO during infection in a susceptible individual leads to ANCA formation
2. During subsequent infection or stimulus, inflammatory cytokines like TNF increase neutrophil surface expression or release of PR3 and MPO
3. ANCAs bind these cytokine-activated cells, further activating neutrophils
4. ANCA activated neutrophils release granule contents and reactive oxygen species leading to vascular damage

**IMPORTANT: THIS PROCESS IS NOT THE SAME AS IMMUNE COMPLEX MEDIATED DISEASE** (which is what lupus is)
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
7. Drugs: Levamisole (more on this later), allopurinol, hydralazine, propylthiouracil, minocycline

ANCA VASCULITIS PATHOGENESIS

• Immune complex deposits generally not present
  • Unlike IgA vasculitis and cryoglobulinemic vasculitis, which we discuss later
• Evidence that PR3 and MPO Antibodies are involved in pathogenesis
  1. Closely associated with corresponding vasculitis
     • Higher levels correspond with active disease and relapses
  2. In-vitro studies show that ANCAs stimulate neutrophils to produce reactive oxygen species and release lytic enzymes
     • 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

ANCA VASCULITIS PRESENTATION (IN GENERAL)

• Small vessel vasculitides
• Distribution of inflammatory manifestations
  • Classical Triad: Lungs, Kidneys, Skin
  • Skin: specifically palpable purpura (leukocytoclastic vasculitis)
  • Neurologic involvement not uncommon
• ANCA usually (but not always) positive
GPA

SIMPLE SUMMARY

GPA EPIDEMIOLOGY, PATHOGENESIS

- Males and Females affected, any age
- Annual incidence 1.3-14.4 per million
- Cell-mediated hypersensitivity response to an environmental trigger
- PR-3 Antibodies present in 95% and likely play major role in tissue injury
- T cell activation
GRANULOMATOSIS WITH POLYANGIITIS

- Formerly known as Wegener’s Granulomatosis
- C-ANCA positive, PR3 (proteinase) Ab positive
- Upper airway disease (ear, nose, throat involvement)
  - Unique to GPA (vs MPA and EGPA)
  - Recurrent sinusitis (80%), recurrent nasopharyngeal ulcers (75%), septal perforations, saddle nose deformities, subglottic stenosis, cilia media
- Lower respiratory disease (95%)
  - Nodules→ cavitating lesions, diffuse alveolar hemorrhage
  - Must exclude other etiologies i.e) infection
- “Limited” form only involves respiratory tract

SADDLE NOSE

NODULAR INFILTRATES


American College of Rheumatology: Image Library: Image 01-12-0033 http://images.rheumatology.org/bp/#/search?q=anca&filters=%257B%257D#2862324

Kumar V et al. Ch 9, 327-63.e1. Robbin’s Basic Pathology https://www-clinicalkey-com.archer.luhs.org/#!/content/book/3-s2.0-B978143771781500009X?scrollTo=%23s0225
**GPA, PRESENTATION**

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

- **Arthritis, arthralgias**

- **Mononeuritis multiplex, polyneuropathy, Central nervous system involvement**

- **Conjunctivitis, uveitis, scleritis, orbital pseudotumor**

- **Palpable purpura, panniculitis, skin ulcers**

---

**NECROTIZING SCLERITIS**

---

**PALPABLE PURPURA**

- Non-itchy
- Palpable rash
- Dorsal aspects of feet and ankles
- Which is non-blanching
- Dark
- Erythematous
GPA MORPHOLOGY

- Respiratory
  1. Sinuses: Granulomatous sinusitis
  2. Lungs:
     1. Necrotizing granulomatous vasculitis with surrounding fibroblastic proliferation
     2. Coalescence of multiple granulomata → central cavitation
     3. Vascular destruction leads to hemorrhage and hemoptysis

- Renal
  1. Focal and segmental necrotizing glomerulonephritis
     1. Glomerular necrosis
     2. Thrombosis of isolated glomerular capillary loops
     3. Crescentic glomerulonephritis in more advanced disease

- Skin
  - LEUKOCYТОCLASTIC VASCULITIS (classically)
    1. Neutrophilic infiltrate surrounding and disrupting small vessels
    2. Fibrin deposits and nuclear debris (leukocytoclasia)
    3. Extravasated red blood cells in the adjacent dermis.

GPA, LUNG MORPHOLOGY

CRESCENTIC GLOMERULONEPHRITIS


NORMAL GLOMERULUS


PAuci-IMMUNE
GLOMERULONEPHRITIS

Goldblatt CS and Bastacky S. University of Pennsylvania Dept of Pathology. http://path.upmc.edu/cases/case51/dx.html

LEUKOCYTOLASTIC
VASCULITIS

Derm101.com

GPA SUMMARY

- Small vessel vasculitis (think of the triad)
  - Add upper respiratory tract to the triad
  - C-ANCA, PR3 positive vasculitis
- Remember key features of morphology/histology
  - Granulomas, giant cells (though these are not always seen), if you can get a skin biopsy: leukocytoclastic vasculitis, and
EGPA

SIMPLE SUMMARY

EOSINOPHILIC GRANULOMATOSIS WITH POLYANGIITIS (EGPA)

EPIDEMIOLOGY, PRESENTATION

- Formerly known as Churg Strauss Syndrome
- Annual incidence 0-2.7/million
- Another ANCA associated vasculitis
  - p-ANCA, MPO positive
- Three phases
  1. Atopic phase, allergic rhinitis & asthma
  2. Eosinophilia
     1. Eosinophilia is striking (≥ 1k/uL vs GPA 500/uL)
  3. Systemic vasculitis


EOSINOPHILIC GRANULOMATOSIS WITH POLYANGIITIS

1. Pulmonary infiltrates
   1. Can be fleeting (like GPA)
   2. Nodules unlikely to lead to cavitating lesions (unlike GPA)
2. Mononeuritis multiplex
   • More common in EGPA (>60%)
3. Ischemic bowel disease
4. Ocular inflammation
5. Nasal perforations
6. Glomerulonephritis
7. Cutaneous nodules
8. Palpable purpura

• ASTHMA
• Cardiomyopathy
• Coronary arteritis (medium v)
• Leading cause of death
• Eosinophilic gastroenteritis

EGPA

MPA
**SIMPLE SUMMARY**

**MICROSCOPIC POLYANGIITIS (MPA)**

- Small vessel vasculitis
- Annual incidence 1-11.6 / million
- p-ANCA positive (anti-MPO positive)
- **MUST BE DISTINGUISHED FROM POLYARTERITIS NODOSA**
  - Remember the characteristics of PAN (medium v vasculitis)
  - Similar to GPA BUT much less likely to involve upper respiratory tract
- Glomerulonephritis, alveolar hemorrhage, polyneuropathy, palpable purpura


**MPA MORPHOLOGY**

1. Segmental fibrinoid necrosis of media
2. Focal transmural necrotizing lesions
3. Granulomatus inflammation absent
4. Similar to PAN except it spares medium/large vessels
5. Leukocytoclastic vasculitis
   - This is seen in any of the small vessel vasculitides
   - "What you see under the microscope for palpable purpura"
ANCA VASCULITIS, HISTOLOGY

TREATMENT OF ANCA ASSOCIATED VASCULITIS

- Steroid therapy (immunosuppression)
- Severe disease: Rituximab for induction
- Maintenance therapy: Azathioprine, Methotrexate
- Limited disease: Methotrexate

NON-ANCA SMALL VESSEL VASCULITIDES

- IgA vasculitis
- Cryoglobulinemic Vasculitis
- Urticarial vasculitis
- Leukocytoclastic vasculitis
  - Can be seen in setting of multiple conditions
- Vasculitis secondary to other autoimmune disease
  - Systemic lupus erythematosus, Rheumatoid arthritis
IGA VASCULITIS

SIMPLE SUMMARY

IGA (IMMUNOGLOBULIN A) VASCULITIS

• Also known as Henoch Schonlein Purpura
  1. Palpable purpura
  2. Arthritis
  3. Gastrointestinal disease
     • Abdominal pain, vomiting, GI bleed, intussusception in children
  4. Glomerulonephritis
     • Hematuria, proteinuria

**IGA VASCULITIS**

1. Mostly in children 3-15 years of age, peak age 4-6 years
2. 20/100,000 children <17 years of age
3. Vascular and renal deposition of IgA immune complexes
4. If significant renal involvement (rare), usually in adults
5. Precipitated by medications or infections
   - Streptococcal or viral
6. Usually self-limited & does not require treatment


**IGA VASCULITIS MORPHOLOGY**

- Skin biopsy
  - Classical leukocytoclastic vasculitis with IgA deposition that is pathognomonic of HSP
- Kidney biopsy
  - Range from isolated mesangial proliferation to severe crescentic glomerulonephritis

**REMEMBER IMMUNE COMPLEX DISEASES?**

- You learned this in Host Defense
- Immune complexes form (i.e., systemic lupus erythematosus, infections—including subacute bacterial endocarditis, IgA vasculitis, cryoglobulinemic vasculitis)
- Immune complex formation leads to complement activation
  - C3b formation (opsonization & in this case most importantly, chemotactic factor attracting macrophages and neutrophils)
  - MAC formation (lysis of cells)
- Serves a purpose when needed, but in autoimmune disease, it causes destructive inflammation
CRYOGLOBULINEMIC VASCULITIS

**SIMPLE SUMMARY**

- Prevalence dependent on endemic areas of Hepatitis C infection
- Overall rare
- 15-30% of HCV patients, 5-10% of HIV patients
- Viral triggered, immune complex disease
  - Like IgA vasculitis (unlike ANCA associated vasculitis)

CRYOGLOBULINS

- Immunoglobulins that precipitate at <37°C (dissolve on rewarming)
- Three types of cryoglobulinemia
  - Type I: Monoclonal Ig, immunoproliferative disorders (Waldenstrom macroglobulinemia or multiple myeloma)
  - Type II: Mixed (poly & monoclonal), chronic infection
  - Type III: Mixed, autoimmune disorders
- Cryoglobulinemic vasculitis typically mixed (Type II/III)
  - Most common: underlying Hepatitis C

CRYOglobulinemic Vasculitis

1. Palpable purpura present in almost all patients
2. Weakness
3. Arthralgias
4. Liver involvement
5. Raynaud phenomenon
   - Decreased blood flow to fingertips caused by vasospasm induced by cold
6. Multiplex mononeuritis
   - Sensory and motor deficit


CRYOglobulinemic Vasculitis Morphology

Skin biopsy of palpable purpura

1. Leukocytic 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
