Vascular Pathology:
From Vasculitis to Vasculopathy to Vascular Rejection

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Part 1:
PATHOLOGY OF VASCULITIS
INFLAMMATORY VASCULAR DISEASES (VASCULITIDES)

Infectious Vasculitis (caused by vessel invasion by pathogenic microorganisms)
- Bacterial
- Rickettsial
- Viral
- Fungal

Noninfectious Vasculitis (not known to be caused by vessel invasion by pathogens)
- Large vessel vasculitis
- Medium-sized vessel vasculitis
- Small vessel vasculitis
- Phlebitis
- Atherosclerosis
CASE #1

A 30 year old white male developed headaches, myalgias and fever. He noticed the onset of an erythematous rash on his arms and hands that became predominantly petechial.

He got bad advice from a friend. He developed abdominal pain and vomiting. Physical examination revealed a fever of 40°C, a petechial rash on all extremities and the trunk, an enlarged liver and increased respiratory rate. He had hiked along the Blue Ridge Parkway during Spring break. Skin biopsy was diagnostic. He was treated but died two weeks after the initial onset of symptoms.
Diagnosis: Rocky Mountain Spotted Fever

Anti-R. rickettsia
Immunologic Pathogenic Mechanisms of “Noninfectious” Vasculitis

Immune Complex Mediated Vasculitis

Direct Antibody Attack Mediated Vasculitis

Anti-neutrophil Cytoplasmic Autoantibody (ANCA) Mediated Vasculitis (Pauci-immune Vasculitis)

Cell Mediated Vasculitis
Names Proposed by the Chapel Hill Nomenclature System

Large Vessel Vasculitis
- Giant Cell Arteritis
- Takayasu Arteritis

Medium-Sized Vessel Vasculitis
- Polyarteritis Nodosa
- Kawasaki Disease

Small Vessel Vasculitis
- Microscopic Polyangiitis
- Wegener’s Granulomatosis
- Churg-Strauss Syndrome
- Henoch-Schönlein Purpura
- Cryoglobulinemic Vasculitis
- Cutaneous small vessel vasculitis

Three general categories of systemic vasculitis are:

- Large vessel vasculitis (chronic granulomatous arteritis)
- Medium-sized vessel vasculitis (necrotizing arteritis)
- Small vessel vasculitis (necrotizing polyangiitis)

Large Vessel Vasculitis
(chronic granulomatous arteritis)
Large Vessel Vasculitis
(chronic granulomatous arteritis)
Large Vessel Vasculitis
(quiescent chronic granulomatous arteritis)
Takayasu Arteritis

Granulomatous inflammation of the aorta and its major branches. Usually occurs in patients younger than 50.
Takayasu arteritis (renal artery)
Takayasu arteritis (renal artery)
Takayasu arteritis (renal artery)
Takayasu arteritis (renal artery)
Takayasu arteritis (aortitis)
Takayasu arteritis (aortitis)
Giant Cell (Temporal) Arteritis

Granulomatous arteritis of the aorta and its major branches, with a predilection for the extracranial branches of the carotid artery. Often involves the temporal artery. Usually occurs in patients older than 50 and often is associated with polymyalgia rheumatica.
Giant Cell Arteritis
Giant Cell Arteritis
Giant Cell Arteritis (aortitis)
Giant Cell Arteritis (aortitis)
Giant Cell Arteritis (aortitis)
CASE #2

A 62 year old white woman developed progressive weight loss, fatigue, “morning stiffness” in her hips and shoulders and low grade fever. She also developed headaches and soreness over the right side of her face and scalp. A rheumatologist confirmed the fever and noted tenderness and slight nodularity of the right temporal artery, a faint bruit in the right neck, and reduced radial pulses bilaterally. Laboratory results included a markedly elevated ESR, mild anemia and slightly elevated platelet count. A segment of the right temporal artery was removed for pathologic evaluation.
Diagnosis: Giant Cell Arteritis
Giant Cell Arteritis
Takayasu Arteritis

granulomatous arteritis in a patient >50 yo

granulomatous arteritis in a patient <50 yo

Giant Cell Arteritis
Takayasu Arteritis

Chronic granulomatous arteritis

Large Vessel Vasculitis
Necrotizing arteritis begins as a segmental necrotizing inflammation of arteries with conspicuous infiltration of neutrophils and monocytes.

This typically induces fibrinoid necrosis characterized by accumulation of plasma proteins in injured tissue, including coagulation factors that are converted to fibrin.
Necrotizing arteritis
A “large artery” in a small biopsy is in fact a small artery.

Necrotizing arteritis in a small biopsy specimen does not distinguish between a medium-sized vessel vasculitis (e.g. PAN) and a small vessel vasculitis (e.g. MPA).
Sclerotic Necrotizing Arteritis
All necrotizing vasculitis enters a final common pathway of chronic inflammation and scarring.

The transformation to sclerotic lesions with a predominance of infiltrating T-lymphocytes and macrophages occurs as quickly as one or two weeks after the initiation of injury.
If the necrotizing inflammation extends through the vessel wall into the perivascular tissue, inflammatory aneurysms (pseudoaneurysms) will develop.
Nomenclature History of Necrotizing Arteritis

Kussmaul & Maier 1866

Pseudoaneurysm

Polyarteritis nodosa
Microscopic polyangiitis

Nomenclature History of Necrotizing Arteritis

Kussmaul & Maier 1866

Arkin 1930
Davson 1948
Zeek 1952
Chapel Hill 1994

Microscopic polyangiitis
Polyarteritis nodosa

COPY
Nomenclature History of Necrotizing Arteritis

Kussmaul & Maier 1866

- Arkin 1930
- Davson 1948
- Zeek 1952
- Chapel Hill 1994

- Microscopic polyangiitis
- Wegener's granulomatosis

- Polyarteritis nodosa

Davson & Churg 1954

Klinger 1931

Wegener 1939

Chapel Hill 1994

Microscopic polyangiitis

Wegener's granulomatosis

Polyarteritis nodosa

Kussmaul & Maier 1866
Nomenclature History of Necrotizing Arteritis

Kussmaul & Maier 1866

Churg & Strauss 1951

Polyarteritis nodosa

Churg-Strauss syndrome

Wegener's granulomatosis

Microscopic polyangiitis

Chapel Hill 1994

Klinger 1931

Wegener 1939

Arkin 1930

Davson 1948

Zeek 1952
Polyarteritis Nodosa

Necrotizing inflammation of medium-sized or small arteries without glomerulonephritis or vasculitis in arterioles, capillaries, or venules.
Nomenclature History of Necrotizing Arteritis

Kussmaul & Maier 1866

- Arkin 1930
- Davson 1948
- Zeek 1952
- Chapel Hill 1994

- Klinger 1931
- Wegener 1939
- Churg & Strauss 1951
- Churg & Churg 1954

- Kawasaki 1967
- Tanaka 1971

- Kawasaki Disease
- Polyarteritis nodosa
- Microscopic polyangiitis
- Wegener’s granulomatosis
- Churg-Strauss syndrome

Microscopic polyangiitis (Chapel Hill 1994)
Kawasaki Disease

Arteritis involving large, medium-sized and small arteries, and associated with mucocutaneous lymph node syndrome. Coronary arteries are often involved. Aorta and veins may be involved. Usually occurs in children.
Kawasaki Disease

Arteritis involving large, medium-sized and small arteries, and associated with mucocutaneous lymph node syndrome. Coronary arteries are often involved. Aorta and veins may be involved. Usually occurs in children.
Kawasaki Disease
Kawasaki Disease

CD68
Polyarteritis Nodosa

Kawasaki Disease

necrotizing arteritis without MCLN syndrome

necrotizing arteritis with MCLN syndrome

Medium-Sized Vessel Vasculitis

Aorta

Arteries

Arteriole

Capillary

Venule

Vein

Aorta Arteries Arteriole Capillary Venule

Necrotizing arteritis

Polyarteritis Nodosa

Kawasaki Disease
CASE #3

A 43 year old male noted worsening arthralgias, myalgias, abdominal pain, migrating “tingling” in both lower extremities, and marked weakness in his left leg and foot. Physical examination revealed livido reticularis on his left lower extremity. Nerve conduction studies indicated a peripheral neuropathy. Laboratory data included mildly elevated LFTs, mildly increased CPK, positive stool occult blood, negative ANCA, negative rheumatoid factor, negative serology for hepatitis B and C, negative cryoglobulins, normal serum complement, negative ANA, normal CBC and unremarkable urine analysis. A biopsy of sural nerve and adjacent skeletal muscle was performed.
Diagnosis: necrotizing arteritis, differential diagnosis includes polyarteritis nodosa, and microscopic polyangiitis and other vasculitides that cause necrotizing arteritis (recommend ANCA serology)
A 3 year old child became irritable and febrile. The parents noticed that the baby had a red tongue and throat, and swollen “glands” in the neck. They were worried about “strep throat”. After the baby did not improve over several days, they took the baby to see a pediatrician. The baby became extremely agitated on the way to the doctor and went into cardiopulmonary arrest soon after arriving at the office. The baby could not be resuscitated. A forensic autopsy was ordered by the medical examiner.
Diagnosis: Kawasaki Disease
Small Vessel Vasculitis (Necrotizing Polyangiitis)

- Aorta
- Arteries
- Arteriole
- Capillary
- Venule
- Vein
- Arteritis
- Arteriolitis
- Capillaritis
- Venulitis
- Phlebitis

- Medium vessel vasculitis
- Large vessel vasculitis
Small vessel vasculitis (necrotizing polyangiitis) often has clinical and pathologic evidence for involvement of capillaries (e.g., glomerulonephritis and pulmonary capillaritis) and venules (e.g., dermal leukocytoclastic venulitis), although arteries may be affected (e.g., epineural arteries causing peripheral neuropathy and intraparenchymal arteries causing abdominal pain).
Small Vessel Vasculitis

Immune Complex Small Vessel Vasculitis
  Henoch-Schönlein Purpura
  Cryoglobulinemic Vasculitis
  Serum Sickness Vasculitis
  Goodpasture’s Syndrome
  Lupus Vasculitis
  Rheumatoid Vasculitis
  Hypocomplementemic Urticarial Vasculitis
  Drug-Induced Immune Complex Vasculitis
  Infection-Induced Immune Complex Vasculitis

Pauci-immune (ANCA) Small Vessel Vasculitis
  Microscopic Polyangiitis
  Wegener’s Granulomatosis
  Churg-Strauss Syndrome
  Organ-limited Disease (e.g. Pauci-immune Crescentic GN)
Immune Complex Vasculitis
One of many clinical presentations of small vessel vasculitis is palpable purpura.
Henoch-Schönlein Purpura
Schönlein-Henoch Purpura

Abdominal pain
Arthralgias
(Nephritis)

Edward Henoch
Johann Lukas Schönlein
Henoch-Schönlein Purpura

Vasculitis with IgA-dominant immune deposits affecting small vessels, i.e. capillaries, venules, or arterioles. Typically involves skin, gut, & glomeruli, and is associated with arthralgias or arthritis.
Cryoglobulinemic Vasculitis

Vasculitis with cryoglobulin immune deposits affecting small vessels, i.e. capillaries, venules, or arterioles, and associated with cryoglobulins in serum. Skin and glomeruli are often involved.
Cryoglobulinemic Glomerulonephritis
Anti-GBM Disease

(Anti-GBM crescentic glomerulonephritis and Goodpasture’s syndrome)
Small Vessel Vasculitis

Immune Complex Small Vessel Vasculitis
  Henoch-Schönlein Purpura
  Cryoglobulinemic Vasculitis
  Serum Sickness Vasculitis
  Goodpasture’s Syndrome
  Lupus Vasculitis
  Rheumatoid Vasculitis
  Hypocomplementemic Urticarial Vasculitis
  Drug-Induced Immune Complex Vasculitis
  Infection-Induced Immune Complex Vasculitis

Pauci-immune (ANCA) Small Vessel Vasculitis
  Microscopic Polyangiitis
  Wegener’s Granulomatosis
  Churg-Strauss Syndrome
  Organ-limited Disease (e.g. Pauci-immune Crescentic GN)
Circulating anti-GBM antibodies with linear capillary IF staining

Vascular immune complex localization with granular IF staining

Little or no vascular IF immunoglobulin staining

ANTIBODY MEDIATED GLOMERULONEPHRITIS AND VASCULITIS

Anti-GBM disease

Immune complex disease

Pauci-immune (ANCA) disease
Henoch-Schonlein Purpura
Cryoglobulinemnic Vasculitis
Microscopic Polyangiitis
Wegener’s Granulomatosis
Churg-Strauss Syndrome

IgA immune complexes
Cryoglobulinemia
No granulomatous inflammation or asthma
Granulomatous inflammation but no asthma
Granulomatous inflammation, asthma, and eosinophilia

Immune complex necrotizing vasculitis, Pauci-immune (ANCA) necrotizing vasculitis

Small vessel vasculitis

Aorta
Arteries
Arteriole
Capillary
Vein
Venule
## FREQUENCY OF DIFFERENT IMMUNOPATHOLOGIC TYPES OF CRESCENTIC GLOMERULONEPHRITIS RELATIVE TO AGE

<table>
<thead>
<tr>
<th>Age</th>
<th>Immune Complex</th>
<th>Anti-GBM</th>
<th>Pauci-immune *</th>
<th>Other</th>
</tr>
</thead>
<tbody>
<tr>
<td>All ages</td>
<td>24%</td>
<td>15%</td>
<td>60%</td>
<td>1%</td>
</tr>
<tr>
<td>Age 1-20</td>
<td>45%</td>
<td>12%</td>
<td>42%</td>
<td>0%</td>
</tr>
<tr>
<td>Age 21-60</td>
<td>35%</td>
<td>15%</td>
<td>48%</td>
<td>3%</td>
</tr>
<tr>
<td>Age 61-100</td>
<td>6%</td>
<td>15%</td>
<td>79%</td>
<td>0%</td>
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</table>

* Of patients with pauci-immune crescentic glomerulonephritis, ~80% have ANCA and ~75% have systemic vasculitis

## Anti-neutrophil Cytoplasmic Autoantibodies (ANCA)

<table>
<thead>
<tr>
<th></th>
<th>Staining of Alcohol-fixed Neutrophils</th>
<th>Staining of Formalin-fixed Neutrophils</th>
<th>Immunoassay Antigen Specificity</th>
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<tbody>
<tr>
<td><strong>C-ANCA</strong></td>
<td>Cytoplasmic</td>
<td>Cytoplasmic</td>
<td>Proteinase 3 (PR3-ANCA), BPI, others</td>
</tr>
<tr>
<td><strong>P-ANCA</strong></td>
<td>Perinuclear</td>
<td>Cytoplasmic</td>
<td>Myeloperoxidase (MPO-ANCA), elastase, others</td>
</tr>
</tbody>
</table>
Pauci-Immune (ANCA) Small Vessel Vasculitis

Necrotizing Venulitis

Necrotizing Arteritis

Glomerular Capillaritis

Pulmonary Capillaritis
Pauci-Immune (ANCA) Small Vessel Vasculitis
Acute ANCA Renal Vasculitis

Necrotizing Glomerulonephritis
Necrotizing Medullary Angiitis
Necrotizing Arteritis

Segmental Fibrinoid Necrosis
Microscopic Polyangiitis

Necrotizing vasculitis with few or no immune deposits affecting small vessels, i.e. capillaries, venules, or arterioles. Necrotizing arteritis involving small and medium-sized arteries may be present. Necrotizing glomerulonephritis is very common. Pulmonary capillaritis often occurs.
Wegener's Granulomatosis

Granulomatous inflammation involving the respiratory tract, and necrotizing vasculitis affecting small to medium-sized vessels, e.g. capillaries, venules, arterioles, and arteries. Necrotizing glomerulonephritis is common.
ANCA Pulmonary Venulitis and Microabscess
Churg-Strauss Syndrome

Eosinophil-rich and granulomatous inflammation involving the respiratory tract and necrotizing vasculitis affecting small to medium-sized vessels, and associated with asthma and blood eosinophilia.
Churg-Strauss Syndrome
Churg-Strauss Syndrome
Pauci-Immune (ANCA) Small Vessel Vasculitis

- **Organ-limited Pauci-Immune Vasculitis**
- **Microscopic Polyangiitis**
- **Wegener’s Granulomatosis**
- **Churg-Strauss Syndrome**

- **Organ-limited Pauci-Immune Vasculitis**
- **No granulomatous inflammation or asthma**
- **Granulomatous inflammation, but no asthma**
- **Granulomatous inflammation, asthma, and eosinophilia**

- **vascular predilection**

- **Aorta**
- **Arteries**
- **Arteriole**
- **Capillary**
- **Venule**
- **Vein**
Approximate Frequency of ANCA in Active, Untreated Pauci-immune Small Vessel Vasculitis

<table>
<thead>
<tr>
<th></th>
<th>WC</th>
<th>MPA</th>
<th>CSS</th>
<th>GN alone</th>
</tr>
</thead>
<tbody>
<tr>
<td>PR3-ANCA</td>
<td>75%</td>
<td>40%</td>
<td>10%</td>
<td>20%</td>
</tr>
<tr>
<td>MPO-ANCA</td>
<td>20%</td>
<td>50%</td>
<td>60%</td>
<td>70%</td>
</tr>
<tr>
<td>Negative</td>
<td>5%</td>
<td>10%</td>
<td>30%</td>
<td>10%</td>
</tr>
</tbody>
</table>
CASE #5-1

A 54 year old white male developed a “flu-like” illness with fever, arthralgias and myalgias that cleared after about a week, but was followed by the onset of sinusitis and runny red eyes. Two weeks later, he developed a rash on his ankles and lower legs bilaterally. He visited a physician who identified palpable purpura on both lower extremities. The patient was refereed to a dermatologist who performed a skin biopsy. A diagnosis of severe leukocytoclastic angiitis consistent with hypersensitivity vasculitis was made.
He developed massive hemoptysis. Physical examination revealed new and old crops of purpuric skin lesions on the lower extremities, nasal crusting and ulceration, and grossly bloody sputum. Radiographs showed severe sinusitis and extensive pulmonary infiltrates. Laboratory results included serum creatinine 2.1 mg/dl, 3+ proteinuria, 2+ hematuria with dysmorphic erythrocytes, and negative serology for anti-GBM, ANCA, cryoglobulins, and ANA. A nasal biopsy showed “nonspecific” acute and chronic inflammation with no granulomatous inflammation.
CASE #5-3

An open lung biopsy showed acute inflammation and hemorrhage but no granulomatous inflammation. A kidney biopsy showed focal necrotizing glomerulonephritis with 40% crescents but no granulomatous inflammation.
CASE #5-4

A diagnosis of “presumptive” Wegener’s granulomatosis was made by the clinicians and the patient was begun on treatment with high dose corticosteroids and cyclophosphamide.

Pathologic Diagnoses: Cutaneous leukocytoclastic angiitis, acute and chronic sinusitis, pulmonary capillaritis and focal necrotizing glomerulonephritis, most consistent with microscopic polyangiitis but can not rule out Wegener’s granulomatosis.
 важным

A negative ANCA result does not rule out any of the ANCA-associated vasculitides.
# Causes of Pulmonary-Renal Syndrome

<table>
<thead>
<tr>
<th>Condition</th>
<th>Percentage</th>
<th>Count</th>
</tr>
</thead>
<tbody>
<tr>
<td>ANCA Vasculitis</td>
<td>54.5%</td>
<td>48/88</td>
</tr>
<tr>
<td>ANCA &amp; Anti-GBM Vasculitis</td>
<td>8.0%</td>
<td>7/88</td>
</tr>
<tr>
<td>Anti-GBM Vasculitis</td>
<td>6.8%</td>
<td>6/88</td>
</tr>
<tr>
<td>Other</td>
<td>30.7%</td>
<td>27/88</td>
</tr>
</tbody>
</table>

* 8 Wegener’s granulomatosis
* 40 microscopic polyangiitis

Conclusion: ANCA vasculitis, especially microscopic polyangiitis, is the most common cause for pulmonary-renal vasculitic syndrome

*Niles et al, Arch Int Med 156:440-5, 1996*
Immune Complex Disease

MPO-ANCA Disease

PR3-ANCA Disease

Anti-GBM Disease
CASE #6

A 23 year old male developed lower extremity palpable purpura, arthralgias and abdominal pain. He visited his family physician who made a diagnosis of HS purpura. Urine analysis revealed 2+ proteinuria and 1+ hematuria; consistent with HS purpura nephritis. The physician scheduled him for a return visit in two weeks. At that time, the patient reported the added feature of nausea and a “funny feeling” in his hands and feet. Urine analysis revealed 4+ proteinuria and 3+ hematuria. He had a serum creatinine of 3.5 mg/dl. The patient was referred to a nephrologist who obtained additional laboratory data and performed a renal biopsy.
Diagnosis: Cryoglobulinemic Vasculitis
Diagnosis: Cryoglobulinemic Vasculitis
COPY

Summary
Large Vessel Vasculitis
Medium Vessel Vasculitis
Small Vessel Vasculitis

Aorta
Arteries
Arteriole
Capillary
Vein
Venule

Microscopic images of vasculitis in different vessel types.
Granulomatous arteritis in a patient >50 yo

- Giant Cell Arteritis
- Takayasu Arteritis
Large Vessel Vasculitis
- Takayasu Arteritis
- Giant Cell Arteritis
- Kawasaki Disease

Medium Vessel Vasculitis
- Polyarteritis Nodosa
- Necrotizing arteritis without MCLN syndrome

Small Vessel Vasculitis
- Necrotizing arteritis with MCLN syndrome
Large Vessel Vasculitis
- Giant Cell Arteritis
  - granulomatous arteritis in a patient >50 yo
- Takayasu Arteritis
  - granulomatous arteritis in a patient <50 yo

Medium Vessel Vasculitis
- Polyarteritis Nodosa
  - necrotizing arteritis without MCLN syndrome
  - necrotizing arteritis with MCLN syndrome

Small Vessel Vasculitis
- Wegener's Granulomatosis
  - granulomas and no asthma
- Churg-Strauss Syndrome
  - eosinophilia, asthma and granulomas
- Cryoglobulinemic Vasculitis
  - cryoglobulins in blood and vessels
- H-S Lupus/Rheumatoid Vasculitis
  - IgA-dominant vessel wall deposits
  - SLE or rheumatoid arthritis
- Microscopic Polyangiitis
  - vasculitis with no asthma or granulomas
  - granulomas and no asthma
- Other Im Cx Vasculitis
  - other sources for immune complexes
What is the diagnosis?

Skeletal Muscle Biopsy

Nerve Biopsy
What is the diagnosis?

Skeletal Muscle Biopsy  Nerve Biopsy

What major category of vasculitis can be ruled out?
What is the diagnosis?

Skeletal Muscle Biopsy  Nerve Biopsy  Lung Biopsy

What major categories of vasculitis can be ruled out now?
What is the diagnosis?

What major categories of vasculitis can be ruled out now?
What is the diagnosis?

Muscle

Nerve

Lung LM

Lung IM

What is the diagnosis?
What is the diagnosis?

**Diagnosis:** pauci-immune small vessel vasculitis, most consistent with *microscopic polyangiitis* but cannot rule out Wegener’s granulomatosis or Churg-Strauss syndrome without additional data.
Though we name the things we know, we do not necessarily know them because we name them.

Homer W. Smith
Nephrologist