VASCULITIS

• Inflammatory Disease of blood vessels.
• The term “vasculitis” is usually applied to noninfectious, inflammatory diseases of blood vessels.
• Encountered in diverse clinical settings.
• Vessels of any type in virtually any organ can be affected.
• Clinical manifestations: constitutional signs and symptoms, i.e., fever, myalgia, arthralgia and malaise.
Vasculitis

- **Mechanisms of vasculitis:**
  1. Immune-mediated inflammation.
  2. Direct invasion of vascular walls by infectious pathogens.
Pathogenesis of Noninfectious Vasculitis

1. Immune complexes.
   * Immune reactants and complement can be detected in the serum or vessels of patients with vasculitis (e.g., DNA/ anti-DNA complexes in SLE. IgG, IgM and complement in cryoglobulinemic vasculitis).

   * Hypersensitivity to drugs causes approximately 10% of vasculitic skin lesions (deposits of immune complexes, e.g. penicillin, conjugate serum proteins), whereas others are foreign proteins.
Pathogenesis of Noninfectious Vasculitis

1. **Immune complexes**
   - HBsAg/anti HBsAg in PAN
   - HCV and GN.
     - Whether complexes found in vessel walls by deposition from the circulation, by in situ formation, or by a combination of these mechanisms is not known.
Pathogenesis of Noninfectious Vasculitis

2. Antineutrophil Cytoplasmic Antibodies.

ANCAs comprise a heterogeneous group of autoantibodies directed against enzymes mainly found within the azurophil or primary granules in neutrophils and in the lysosomes of mononcytes and in ECs.
2. Antineutrophil Cytoplasmic Antibodies.

- There are two main immunofluorescent patterns:
  - cytoplasmic localization of the staining (c-ANCA).
  - perinuclear staining (p-ANCA).

* ANCAs serve as useful quantitative diagnostic markers for these disorders. (ANCA associated vasculitis).
* The close association between ANCA titeres and disease activity, particularly c-ANCA in Wegener granulomaosis suggest its important role in pathogenesis.
Pathogenesis of Noninfectious Vasculitis

Antineutrophil Cytoplasmic Antibodies.

* Whether ANCAs are mere markers of vasculitides or play a role in tissue injury is not entirely clear.
Pathogenesis of Noninfectious Vasculitis

3. Antiendothelial cell antibodies.

Antibodies to ECs e.g. SLE and Kawasaki disease.
Classification of Vasculitis

according to size, anatomic site, histologic and clinical character

1. Large-vessel vasculitis:
   - Giant cell (temporal) arteritis
   - Takayasu arteritis

2. Medium-sized vessel vasculitis:
   - Polyarteritis nodosa
   - Kawasaki disease (mucocutaneous lymph node syndrome)

3. Small-vessel vasculitis:
   - Microscopic polyangitis (microscopic polyarteritis, hypersensitivity or leukocytoclastic angiitis)
   - Wegener granulomatosis
   - Thromboangiitis obliterans (Buerger disease)

4. Infectious arteritis.
GIANT CELL (TEMPORAL) ARTERITIS

- Most common of the vasculitides.
- Is an acute and chronic, often granulomatous, inflammation of arteries of large to small size.
- Arteries in the head, especially the temporal arteries, others e.g. vertebral and ophthalmic arteries.
- Other arteries throughout the body including the aorta (giant cell aortitis).
GIANT CELL (TEMPORAL) ARTERITIS

MORPHOLOGY

- Nodular thickenings with reduction of the lumen.
- Thrombosed.
- Fragmentation of the internal elastic lamina.
- Granulomatous inflammation of the inner half of the media centered on the internal elastic membrane.
GIANT CELL (TEMPORAL) ARTERITIS

• Less common pattern: rare or absent granulomas and giant cells and there is a nonspecific panarteritis with a mixed inflammatory infiltrate.

• The later healed stage of these patterns reveals collagenous thickening of the vessel wall.

• Organization of the luminal thrombus sometimes transforms the artery into a fibrous cord.
FIG. 15. Subacute temporal arteritis. The intimal fibrous tissue has a loose texture, and there is some residual inflammation.
GIANT CELL (TEMPORAL) ARTERITIS
PATHOGENESIS

• Unknown
• T cell mediated immune response to an unknown antigen, possibly vessel wall antigen
• Inherited pleomorphism in gene encodes intercellular adhesion molecule
GIANT CELL (TEMPORAL) ARTERITIS

CLINICAL FEATURES

• Older individuals and is rare before the age of 50.
• Symptoms: fever, fatigue, weight loss, facial pain or headache.
• Superficial temporal artery – painful to palpation.
• Ocular symptoms.
• Diagnosis depends on biopsy.
• Because of segmental nature of the involvement, adequate biopsy requires at least a 2- to 3- cm length of artery and a negative biopsy result does not rule out.
GIANT CELL (TEMPORAL) ARTERITIS

Diagnosis

• The five major diagnostic criteria selected by the American College of Rheumatology were
  1. age 50 years
  2. recent localized headache
  3. temporal artery tenderness
  4. Raised erythrocyte sedimentation rate (ESR; 50 mm/h)
  5. a positive temporal artery biopsy

If three or more of these criteria are present, there is more than 90% chance that cranial arteritis is the correct diagnosis
Granulomatous angiitis of CNS
Takayasu Vasculitis

- GRANULOMATOUS VASCULITIS
- Characterized principally by ocular disturbances and marked weakening of the pulses in the upper extremities (pulseless disease)
- related to fibrous thickening of the aorta with narrowing or virtual obliteration of the origins or more distal portions.
- Pathogenesis are unknown, although immune mechanisms are suspected.
Takayasu Vasculitis

**Morphology**

- Involves the aortic arch.
- One third of cases also affects the remainder of the aorta and its branches.
- Half of the cases, the pulmonary arteries are involved.
Takayasu Vasculitis
Histologic features

• The changes ranged from an adventitial mononuclear infiltrate with perivascular cuffing of the vasa vasorum to intense mononuclear inflammation in the media, to granulomatous inflammation, with giant cells and patchy necrosis of the media (similar to giant cell arteritis but younger patient)

• Later, there is collagenous fibrosis involving all layers of the vessel wall but, particularly the intima, accompanied by lymphocytic infiltration.
Takayasu Vasculitis

CLINICAL FEATURES

• Early nonspecific including fatigue, weight loss and fever.
• With progression, vascular symptoms appear:
  markedly lower blood pressure and weaker pulses in the upper extremities than in the lower extremities.
• Ocular disturbances.
• Neurologic deficits.
• Pulmonary arteries may lead to pulmonary hypertension.
• Renal artery narrowing in 50%.
POLYARTERITIS NODOSA

• A systemic vasculitis of small or medium-sized muscular arteries.

• Typically, involving renal and visceral vessels (kidneys, heart, liver and gastrointestinal tract followed by pancreas, testis, skeletal muscles, nervous system and skin).

• Sparing pulmonary circulation
POLYARTERITIS NODOSA
MORPHOLOGY

- Segmental transmural necrotizing inflammation of arteries of medium to small size in any organ.
- Weakening of the arterial wall.
- Impairment of perfusion.
- Fibrous thickening of the vessel wall.
- Characteristic of PAN is that all stages of activity may coexist in different vessels or even within the same vessel.
POLYARTHTERITIS NODOSA
POLYARTERITIS NODOSA

CLINICAL COURSE

- PAN is a disease of young adults.
- Malaise, fever of unknown cause and weight loss, hypertension, usually developing rapidly, abdominal pain and melena.
- Renal involvement (major cause of death)
- About 30% of patients with PAN have hepatitis B antigen in their serum.
- There is no association with ANCA.
- If untreated, the disease is fatal in most cases.
KAWASAKI DISEASE
(Mucocutaneous lymph node syndrome)

• An acute febrile illness of infancy and childhood that is associated with an arteritis affecting large, medium sized and small vessels.
• Involvement of coronary arteries.
• Epedemic in Japan
• 20% of untreated patients develop cardiovascular sequelae (asymptomatic vasculitis of the coronary arteries, coronary artery ectasia, or formation of giant coronary artery aneurysms).
KAWASAKI DISEASE

MORPHOLOGY

• The vasculitis is PAN-like with necrosis and pronounced inflammation affecting the entire thickness of the vessel wall.

• The cause of the condition is uncertain, but there is evidence that the vasculitis is characterized by T-cell and macrophage activation in response to an unknown antigen.
KAWASAKI DISEASE
(Mucocutaneous lymph node syndrome)

CLINICAL FEATURES

• Present as an acute fever, conjunctival and oral erythema and erosion, edema of the hands and feet, erythema of the palms and soles, a rash often with desquamation, and enlargement of cervical lymph nodes.
MICROSCOPIC POLYANGIITIS
(Microscopic polyarteritis, hypersensitivity or leukocytoclastic angiitis)

• Necrotizing vasculitis generally affects arterioles, capillaries and venules of skin, mucous membranes, lungs, brain, heart, gastrointestinal tract, kidneys and muscle.

• Necrotizing glomerulonephritis (90% of patients) and pulmonary capillaritis are particularly common.

• Clinical features are hemoptysis, hematuria and proteinuria, bowel pain or bleeding, muscle pain.
MICROSCOPIC POLYANGIITIS

MORPHOLOGY

- Segmental fibrinoid necrosis of the media with neutrophils (Leukocytoclastic angiitis) affecting post capillary venules.

- All lesion tend to be at the same age in a single patient

- p-ANCAs are present in over 80% of patients.
MICROSCOPIC POLYANGIITIS

• Disseminated vascular lesions of hypersensitivity angiitis may also appear in Henoch-Schonlein purpura, mixed cryoglobulinemia, vasculitis associated with some of the connective tissue disorders and vasculitis associated with malignancy.

• ANCAa are not present in these conditions.
In allergic granulomatosis and angitis (Churg-Strauss syndrome), vascular lesion is similar to microscopic polyangiitis, patient present with allergic rhinitis, bronchial asthma and eosinophilia.
WEGENER GRANULOMATOSIS

- Necrotizing vasculitis
- characterized by the triad:
  - acute necrotizing granulomas of the upper respiratory tract (ear, nose, sinuses, throat) or the lower respiratory.
  - necrotizing or granulomatous vasculitis affecting small to medium sized vessels of the lung.
  - renal disease in the form of focal necrotizing, often crescentic, glomerulonephritis.
WEGENER GRANULOMATOSIS
MORPHOLOGY

• Inflammatory sinusitis resulting from mucosal granulomatous to ulcerative lesions of the nose, palate or pharynx, rimmed by necrotizing granulomatous and accompanied vasculitis.

• Renal lesions, acute focal proliferation and necrosis in the glomeruli with thrombosis of isolated glomerular capillary loops and crescentic glomerulonephritis.
WEGENER GRANULOMATOSIS

PATHOGENESIS

• Hypersensitivity, possibly to an inhaled infectious or other environmental agent.
• Immunologic mechanism
• c-ANCA in 95%
WEGENER GRANULOMATOSIS

CLINICAL FEATURES

• Males are affected more often than females
• about 40 years.
• Persistent pneumonitis (95)
• Chronic sinusitis (90%)
• Renal disease (80%).
• Other features: rashes, muscle pains, articular involvement, mononeuritis or polyneuritis.
WEGENER GRANULOMATOSIS

CLINICAL FEATURES

• If untreated, 80% of patients die within 1 year
• c-ANCAs are present in the serum in up to 95% of patients with active generalized disease.

• c-ANCAs are useful marker for generalized activity in Wegener granulomatosis, microscopic polyangiitis, Churg-Strauss syndrome (ANCA associated small vessel vasculitides).
**THROMBOANGIITIS OBLITERANS**  
(Buerger Disease)

- Characterized by segmental, thrombosing, acute and chronic inflammation of medium-sized and small arteries, principally the tibial and radial arteries and sometimes extending to veins and nerves.
- Almost exclusively in men who were heavy smokers of cigarettes.
- Direct endothelial cell toxicity by some tobacco products or hypersensitivity to them.
- Impaired endothelium-dependent vasodilatation when challenged with acetylcholine.
- Anti-endothelial cell antibodies have also been found.
THROMBOANGIITIS OBLITERANS
(Buerger Disease)
MORPHOLOGY

- Sharply segmental acute and chronic vasculitis of medium sized and small arteries.
- Thrombus contains small microabscesses.
- Surrounded by granulomatous inflammation.
THROMBOANGIITIS OBLITERANS
(Buerger Disease)
CLINICAL FEATURES

• Cold sensitivity of the Raynaud type in the hands, and pain in the instep of the foot induced by exercise.
• Chronic ulcerations of the toes, feet or fingers, gangrene.
BUERGER DISEASE
VASCULITIS ASSOCIATED WITH OTHER DISORDERS

- Vasculitis resembling hypersensitivity angiitis or classical PAN may sometimes be associated with an underlying disorder such as rheumatoid arthritis, systemic lupus erythematosus, malignancy and systemic illnesses e.g. mixed cryoglobulinemia
Radiation induced vasculitis
INFECTIOUS ARTERITIS

- Direct invasion of infectious agents, usually bacteria or fungi.
- Mycotic aneurysms.
- Induce thrombosis.
- Infarction.
Vasculitis

- Surgical pathologist must ask four specific questions:
  1. Are the microscopic changes the result of a true vasculitis, or are they a reaction to inflammation in surrounding tissues?
  2. What size of vessel is predominantly involved? Small vessels (arterioles, capillaries, veins, and venules), medium-sized arteries, or large arteries and the aorta?
  3. Are there clinical features that point to a specific diagnosis? For example, is there a characteristic skin rash as in Henoch–Schönlein purpura, a history of asthma or eosinophilia or respiratory tract involvement?
  4. Do other laboratory tests or biopsies indicate a specific diagnosis [e.g., proteinuria or other evidence of renal impairment, antineutrophil cytoplasm antibody (ANCA) positivity, immune deposits of immunoglobulin A (IgA) in skin or renal biopsies?]
### Differential diagnosis of reactive and vasculitic disorders of vessels

<table>
<thead>
<tr>
<th>Reactive changes</th>
<th>Vasculitis</th>
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<tbody>
<tr>
<td>Dense interstitial inflammation contrasts with paucity of vascular changes; completely normal vessels may be identified in densely inflamed tissue; inflammatory cells usually confined to adventitia or outer media.</td>
<td>Density of interstitial inflammation highly variable</td>
</tr>
<tr>
<td>Fibrous intimal thickening frequently develops</td>
<td>Transmural inflammation</td>
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<tr>
<td>Fibrinoid necrosis is uncommon</td>
<td>Vessel wall necrosis is common</td>
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<tr>
<td>may affect any BV</td>
<td>affected BV is according to underlying disease</td>
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SUMMARY

Large vessel vasculitis

Giant cell (temporal arteritis): Usually in patients older than 50 years and often associated with polymyalgia rheumatica

Takayasu’s arteritis: Granulomatous arteritis of the aorta and branches. Usually in patients younger than 50

Medium-sized vessel vasculitis

Polyarteritis nodosa: Necrotizing inflammation of medium-sized or small arteries

Kawasaki disease: Associated with mucocutaneous lymph node syndrome Coronary arteries often involved. Usually occurs in children

Granulomatous angiitis of CNS: Florid vasculitis of intracranial vessels. Can be associated with amyloid angiopathy
Small-vessel vasculitis

Wegener’s granulomatosis: Predilection for respiratory tract. ANCA positive. Glomerulonephritis common

Churg–Strauss syndrome: Eosinophil-rich granulomatous inflammation, often involves respiratory tract. Asthma with eosinophilia. ANCA positive

Microscopic polyangiitis: Necrotizing glomerulonephritis. Pulmonary involvement. No immune deposits. ANCA positive


Cutaneous leukocytoclastic vasculitis: Isolated vasculitis of cutaneous vessels, often in lower leg. Good prognosis