Vasculitis

- Inflammation of the vessel wall.
- Signs and symptoms:
  1. local findings according to the involved tissue
  2. systemic manifestations (fever, myalgia, arthralgias, and malaise)
- vasculitis can be classified according to vessel size, immune complexes, specific autoantibodies, granuloma formation, etc
- considerable clinical and pathologic overlap among many of these disorders
1- immune-mediated inflammation
2- direct vascular invasion by infectious pathogens.

➢ It is critical to distinguish between infectious and immunologic mechanisms due to the huge difference in management.

3- Physical injury (radiation, mechanical trauma)
4- chemical injury (toxins)
Non-infectious vasculitis

- The main *immunologic mechanisms* underlying noninfectious vasculitis are
  - Immune complex deposition
  - Antineutrophil cytoplasmic antibodies (ANCA)
  - Anti-endothelial cell antibodies
  - Autoreactive T cells
Immune complex deposition

- is implicated in the following vasculitides:

1. **Drug hypersensitivity vasculitis.**
   - e.g., penicillin
   - vary from mild and self-limiting, to severe and even fatal
   - skin lesions are most common.
   - Treatment: discontinuation of the offending drug.

2. **Vasculitis secondary to infections.**
   - Antibody to microbial molecules form immune complexes
   - e.g. 30% of patients with PAN → immune complexes composed of (HBsAg) and anti-HBsAg antibody
Anti-Neutrophil Cytoplasmic Antibodies

- **ANCAs** = circulating antibodies that react with neutrophil cytoplasmic antigens (mainly enzymes)
- ANCAs blood levels are very useful markers for diagnosis, clinical severity, and as predictive of disease recurrence.
- two types are most important:
  1. **Anti-proteinase-3 (PR3-ANCA)** = c-ANCA.
     - is a neutrophil azurophilic granule constituent similar to numerous microbial peptides; e.g. Wegener granulomatosis.
  2. **Anti-myeloperoxidase (MPO-ANCA)** = p-ANCA.
     - MPO is a lysosomal granule constituent; e.g. microscopic polyangiitis and Churg-Strauss syndrome
     - MPO-ANCAs are also induced by several drugs, e.g. propylthiouracil.
Anti-Endothelial Cell Antibodies

- Antibodies to endothelial cells
- Associated with certain vasculitides, such as Kawasaki disease (discussed later).
Giant Cell (Temporal) Arteritis

- *is the most common form of vasculitis among the elderly in developed countries.*
- *chronic, granulomatous, inflammation of large arteries, mainly the temporal arteries.*
- Vertebral and ophthalmic arteries, as well as the aorta (giant cell aortitis), also can be involved.
- Ophthalmic artery involvement → sudden and permanent blindness (rapid diagnosis and treatment are mandatory)
Giant Cell (Temporal) Arteritis

- **Pathogenesis**: T cell-mediated immune response to unknown vessel wall antigen.

- **Morphology**:
  - changes are patchy along the length of affected vessels.
  - nodular intimal thickening & thromboses reduce the lumen diameter and cause distal ischemia.
  - granulomatous inflammation (75%) within the inner media centered on the internal elastic membrane ((lymphocytes and macrophages, with multinucleate giant cells))
  - fragmentation of the internal elastic lamina.
  - lesions at different stages of development are seen within the same artery
Giant Cell (Temporal) Arteritis- clinical picture

- rare before the age of 50.
- **Signs and symptoms:**
  - fever, fatigue, weight loss
  - facial pain or headache, (superficial temporal artery).
  - Ocular symptoms (ophthalmic artery) in 50% of patients; range from diplopia → → complete vision loss.
- **Diagnosis:**
  - biopsy and histology
- **Treatment:**
  - Corticosteroid or anti-TNF therapies
Giant Cell (Temporal) Arteritis
Takayasu arteritis

- a granulomatous vasculitis of medium-sized and large arteries
- **ocular disturbances + marked weakening of the pulses in the upper extremities** (= the *pulseless disease*).
- **scarring and thickening of the aorta - esp. the aortic arch with severe luminal narrowing of the major branch vessels.**
- the distinction from giant cell aortitis is made largely on the basis of a patient's age: >50 years → giant cell aortitis
  <50 years → Takayasu aortitis.
- **Pathogenesis:** An autoimmune etiology is likely
Takayasu arteritis - MORPHOLOGY

- affects the aortic arch and arch vessels (2/3)
- Pulmonary arteries (50% of patients)
- renal and coronary arteries also can be affected.

- **The histologic picture**: a spectrum ranging from:
  - Mild WBC infiltrates
  - intense transmural inflammation
  - granulomatous inflammation, with giant cells and patchy medial necrosis
  - irregular thickening of the vessel wall
  - intimal hyperplasia
  - adventitial fibrosis.
Clinical Features of Takayasu Aortitis

- Initially, nonspecific: fatigue, weight loss, and fever.
- With progression:
  - reduced upper limb B.P. and pulse; neurologic deficits
  - Ocular: visual defects, hemorrhages, blindness.
  - leg claudication → distal aorta involvement
  - pulmonary hypertension → pulmonary artery involvement
  - MI → Narrowing of the coronary ostia
  - Hypertension → renal arteries (50% of patients).
- **Disease evolution:**
  - rapidly progressive in some cases
  - quiescent after 1 to 2 years (visual or neurologic deficits) in others
Polyarteritis nodosa (PAN)

- a systemic vasculitis of *small or medium-sized muscular arteries*
- typically involves the **renal** and visceral vessels and **spares** the pulmonary circulation.
- There is **no** association with ANCA$^{-}$s
  - (1/3) chronic hepatitis B infection $\rightarrow$ immune complexes containing hepatitis B antigens deposit in affected vessels.
  - (2/3) $\rightarrow$ The cause is unknown
Kidney (most common site), heart, liver, and GIT vessels are affected in descending order of frequency.

Segmental transmural necrotizing inflammation of small to medium-sized arteries, often with superimposed thrombosis.

Ulcerations, infarcts, ischemic atrophy, or hemorrhages in the affected tissues.

Inflammation→weakens arterial wall→aneurysms and rupture.

Lesions have different stages at the same vessel and at any given time.
PAN - The clinical course

- a disease of young adults but can occur in all age groups.
- episodic, with long symptom-free intervals.
- malaise, fever, and weight loss
- the vascular involvement is widely scattered.
- A "classic" presentation can be: a combination of:
  - malignant hypertension (renal artery) → a major cause of death
  - abdominal pain and bloody stools (GIT lesions)
  - muscular aches and pains
  - peripheral neuritis.

- Treatment: untreated → fatal
  - immunosuppression → remission or cure in 90% of the cases
Kawasaki disease

- acute, febrile, usually self-limited illness of infancy and childhood (80% of cases < 4 years)
- arteritis of mainly large to medium-sized vessels.
- Its clinical significance: involvement of coronary arteries \(\rightarrow\) aneurysms \(\rightarrow\) rupture or thrombosis \(\rightarrow\) myocardial infarction.
- Originally in Japan, the disease is now recognized worldwide
- Pathogenesis: anti-endothelial cell antibodies
- Treatment:
  - intravenous immunoglobulin therapy and aspirin
  - Nowadays, symptomatic coronary artery disease < 4%.
Kawasaki disease

- acute phase= dense transmural inflammatory infiltrate
- Chronic phase= aneurysm formation, intimal thickening.
- Also called *mucocutaneous lymph node syndrome*:
  - conjunctival and oral erythema and blistering
  - erythema of the palms and soles
  - a desquamative rash
  - cervical lymph node enlargement.
- cardiovascular disease (20% of untreated patients): ranging from asymptomatic coronary arteritis ➔ coronary artery aneurysms (7 to 8 mm) with rupture or thrombosis, MI, and sudden death.
Microscopic Polyangiitis

- necrotizing vasculitis affects **capillaries**, as well as small **arterioles** and **venules**.
- called **hypersensitivity vasculitis** or **leukocytoclastic vasculitis**.
- **all lesions tend to be of the same age in any given patient.**
- The skin, mucous membranes, lungs, brain, heart, **GIT**, kidneys, and muscle
- **necrotizing glomerulonephritis** (90% of patients)
- **pulmonary involvement is common.**
- Pathogenesis: unknown

- can be a feature of a number of immune disorders (e.g. Henoch-Schönlein purpura..etc); drugs; or infections…
Microscopic polyangiitis- morphology

- segmental fibrinoid necrosis of the media with focal transmural necrotizing lesions
- *granulomatous inflammation is absent.*
- infiltrating *neutrophils* frequently undergo fragmentation, hence the term *leukocytoclastic vasculitis.*
- most lesions are "*pauci-immune*" (i.e., show little or no antibody or immune complexes)
Clinical Features of Microscopic Polyangiitis

- Depending on the vascular bed involved:
  - Hemoptysis → lung
  - hematuria, proteinuria → kidney
  - abdominal pain or bleeding → GIT
  - muscle pain or weakness → muscles
  - palpable cutaneous purpura → skin

- Treatment:
  - immunosuppression
  - removal of the offending agent
Wegener granulomatosis

- is a necrotizing vasculitis
- specific triad of:
  1. *Granulomas* of the lung and/or the upper respiratory tract (ear, nose, sinuses, throat)
  2. *Vasculitis* of small to medium-sized vessels (capillaries, venules, arterioles, and arteries) mostly in lungs and upper respiratory tract
  3. *Glomerulonephritis:* (FSGS) \(\rightarrow\) \(\rightarrow\) (crescentic glomerulonephritis)
Wegener granulomatosis - pathogenesis

- cell-mediated hypersensitivity response against inhaled infectious or environmental antigens.
- PR3-ANCAs (c-ANCA) > 95% of cases
  - are useful markers of disease activity (After immunosuppressive therapy, ANCA levels fall dramatically, while rising titers are predictive of relapse)
- The typical patient is >40 year old and male, although women and all ages can be affected.
- If untreated, the mortality rate at 1 year is 80%.
Rash, myalgias, articular involvement, neuritis, and fever
bilateral pneumonitis, nodules and cavitary lesions (95%)
chronic sinusitis (90%)
mucosal ulcerations of nasopharynx (75%)
renal disease (80%) → hematuria, proteinuria → rapidly progressive renal failure.

Treatment: steroids, cyclophosphamide, TNF inhibitors and anti-B cell antibodies
Most patients with Wegener granulomatosis now survive, but remain at high risk for relapses that can ultimately lead to renal failure.
Churg-Strauss syndrome

- (also called allergic granulomatosi
  and angiti
- is a small vessel necrotizing vasculitis
- classically associated with asthma, allergic rhinitis, lung infiltrates, peripheral eosinophilia, necrotizing granulomas, infiltration by eosinophils.
- extremely rare disorder.
- purpura, GIT bleeding, and renal disease (FSGS) are the major associations.
- Cardiomyopathy: due to eosinophils (in 60% of patients) → a major cause of morbidity and death.
- Pathogenesis: Unknown
Thromboangiitis obliterans (Buerger disease)

- a disorder of severe vascular insufficiency and gangrene of the extremities.
- focal acute and chronic inflammation of medium-sized and small arteries, especially the tibial and radial arteries, associated with thrombosis
- secondary extension into adjacent veins and nerves may be seen.
- **Pathogenesis**: almost exclusively in heavy tobacco smokers and usually < age 35.
- The etiology is unknown:
  - components of tobacco- ? Direct endothelial cell toxicity
  - ? an immune response.
  - ? A genetic predilection → increased prevalence in certain ethnic groups
Thromboangiitis obliterans (Buerger disease) – clinical manifestations

- Early: Raynaud phenomenon, foot pain induced by exercise, superficial nodular phlebitis (venous inflammation).
- Severe pain – even at rest → neural involvement.
- Chronic ulcerations
- Gangrene of fingers and toes
- **Treatment**: Smoking abstinence in the early stages of the disease