- Vasculitis
- Means inflammation of the blood vessel wall.
  - May affect arteries, veins and capillaries.
- What causes the inflammation?
  - Immunologic hypersensitivity reactions:
    - Type II : complement dependent
    - Type III: immune complex mediated**
    - Type IV : cell mediated

- Direct invasion by micro-organisms

- Etiopathogenesis

Immunologic mechanisms

- Immune complexe deposition
  - Responsible for <u>most</u> cases***
  - Deposition of immune complex →
  - Activation of complement →
  - Release of C5a
  - C5a → chemotactic for neutrophil

- Neutrophils → damage endothelium and vessel wall → fibrinoid necrosis.
- Endothelial damage → thrombosis →
- Ischemic damage to tissue involved.
- Example of IC mediated Vasculitis = Henoch-Schonlein purpura

- Etiopathogenesis

  Immunologic mechanisms

- Type IV hypersensitivity: delayed type of hypersensitivity reaction

- implicated in some types of vasculitis due to presence of granulomas.
- Example: Temporal arteritis

- Direct Invasion:
  - by all classes of microbial pathogens
    - Rickettsiae
    - Meningococcus
    - Fungus

- Laboratory testing in vasculitis
- Antineutrophil cytoplasmic antibodies (ANCA)

- Erythrocyte sedimentation rate (ESR)

- Antineutrophil cytoplasmic antibodies (ANCAs)
- Are seen in some types of vasculitis esp small vessel vasculitis
- Are circulating ab reactive with neutrophil cytoplasmic ag = ANCA.
- The ANCAs activate neutrophils
  - Cause release of enzymes and free radicals resulting in vessel damage.

- ANCA titers correlate with disease activity.
- Detected by immunofluorescence

- Two types of ANCAs
- Cytoplasmic (c-ANCAs):
  - Ab directed against proteinase 3 in cytoplasmic granules.
  - Cytoplasmic staining pattern
  - Example: Wegener's granulomatosis.
- Perinuclear (p-ANCAs):

- Ab directed against myeloperoxidase.
- Perinuclear pattern of staining
- Example: Churg-Strauss syndrome, PAN.

- Classification of Vasculitis : based on vessel size
- <u>Large vessel Vasculitis:</u>
  - Giant cell arteritis *
  - Takayasu's arteritis *
- <u>Medium vessel Vasculitis</u>
  - Polyarteritis nodosa (PAN)*

- Kawasaki's disease*
- Thromboangitis obliterans (TAO)*

- <u>Small vessel Vasculitis</u>
  - Hypersensitivity vasculitis
    - Henoch Schonlein purpura*
  - Churg Strauss syndrome
  - Wegener granulomatosis *

- Clinical manifestations of vasculitis
- Clinical picture depends on the size and extent of the vessel involvement.

- Large vessel Vasculitis:
  - Presents with loss of pulse or
  - Stroke
- Medium vessel Vasculitis
  - Presents with infarction or aneurysm
- Small vessel Vasculitis
  - Presents with Palpable purpura*
- General features:
  - Fever, weight loss, malaise, myalgias

- What do you see??

- **Patient Profile # 1**

- Old female patient presents with
    - Headache in the temporal region
    - Pain in the jaw while chewing
    - Muscle aches and pains
    - Develops problems with vision.
- On examination:
    - Has nodular and palpable temporal artery.
- Labs:
    - elevated ESR
- Biopsy: (temporal artery)
    - granulomatous inflammation with giant cells
- Diagnosis:
    - Giant cell (temporal) arteritis

- Large vessel vasculitis
  Giant cell (temporal) arteritis
- Is the most common vasculitis**.
- Occurs in women > 50 years (Female > male)
- Vessel involvement::
  - Typically involves temporal artery and extra-cranial branches of external carotid.
  - Involvement of ophthalmic branch of external carotid → blindness.

- Etiopathogenesis:
  - Type IV hypersensitivity mediated reaction causing granulomatous inflammation.

- Giant cell arteritis: Pathology
- Affected vessel are cordlike and show nodular thickening.
- Microscopy:
  - Focal Granulomatous inflammation of temporal artery
  - Fragmented internal elastic lamina

  - **Giant cells.**
- Temporal (giant cell) arteritis
- **Giant cell (temporal) arteritis**
- **Clinical features:**
  - **Fever, fatigue, weight loss**
  - **Temporal headache* (MC symptom), facial pain.**
  - **Painful, palpably enlarged and tender temporal artery***
  - **Generalized muscular aching and stiffness (shoulders and hip)**
  - **Temporary / permanent blindness***

- Giant cell (temporal) arteritis
- Investigations:
  - ESR: screening test of choice ; markedly <u>elevated</u>.
  - Temporal artery biopsy : definitive diagnosis (positive in only 60% cases)
- Treatment:
  - Corticosteroids (to prevent blindness)

- What do you see?
- Patient profile # 2

- Middle aged Asian woman presents with:
  - Visual disturbances
  - Marked decrease in blood pressure in upper extremity and
  - Absent radial, ulnar and carotid pulses.
- Angiography shows:
  - Marked narrowing of aortic arch vessels
- Biopsy:
  - Granulamatous inflammation with giant cells
- Diagnosis:

- Takayasu's arteritis (pulseless disease)

- Takayasu's arteritis (pulseless disease)
- Is an inflammatory disease of vessels affecting
  - the aorta and its major branches
- Seen in Asian women <50 years old.
- Vessel involvement:
  - Typically involves the aorta* and the aortic arch vessles* (carotids, subclavian).

- Can also involve: pulmonary, renal, coronary

- Etiopathogenesis:
  - Type IV hypersensitivity reaction causing granulomatous inflammation (granulomatous vasculitis)
- Takayasu's arteritis
- Takayasu's arteritis (pulseless disease)
- Pathology:
  - Thickening of vessels (aorta & branches) with narrow (stenosis) lumen →

  - decreased blood flow
- Microscopic
  - Similar to/indistinguishable from Giant Cell Arteritis

- Takayasu's arteritis (pulseless disease)
- Clinical:
  - Dizziness,syncope.
  - Absent upper extremity pulse (pulseless disease)**
  - Blood pressure discrepancy* between extremitis : low in upper and higher in lower
  - Visual disturbances

- Diagnosis:
  - angiography

- Patient profile # 3
- Young male IV drug abuser with history of Hepatitis (HBV) presents with
  - Hypertension, abdominal pain, melena, muscle aches and pains and skin nodulations.
- Biopsy of skin nodules:
  - Segmental transmural inflammation of blood vessels with fibrinoid necrosis.

- **Labs:**
  - **HBsAg +ve**
  - **pANCA +ve**
- **Diagnosis:**
  - **Polyarteritis nodosa (PAN)**
- **Polyarteritis nodosa (PAN)**
- **A systemic disease.**
- **Vessel involvement:**
  - **Affects medium sized & small muscular arteries*.**
  - **<u>Typically involves vessels of</u>**
    - **Kidney, heart, liver, GIT and skin**
    - **Spares the lung****
- **Etiology:**
  - **Mediated by type III hypersensitivity (ag-ab complex deposition).**

- Associations:
  - strong association with HBV antigenemia
  - hypersensitivity to drugs (IV amphetamines).
- Pathogenesis:
  - immunecomplex deposition (e.g. HBsAg / anti-HBsAg)
- PAN
- Pathology:
  - Transmural inflammation (involving all layers).
    - Lesion in the vessel wall may

  - involve entire circumference or part of it
  - Fibrinoid necrosis
- Consequences:
  - development of
    - Thrombosis → infarction
    - Weakening of vessel wall →Aneurysms (kidney, heart and GI tract)

- PAN: Clinical features
- More common in young to middle aged men
- Signs and symptoms: due to ischemic damage.

- Target organs:
  - Kidneys : Vasculitis/infarction → hypertension , hematuria, albuminuria.
  - GI tract: Bowel infarction → abdominal pain, melena.
  - Skin: Ischemic ulcers and nodules.
  - Coronary arteries: aneurysms, MI
- Systemic manifestation: fever, malaise and weight loss.
- Cause of death: Renal failure MC COD

- PAN
- Laboratory findings:
  - HbsAg positive in 30% of cases
  - Hematuria with RBC cast
- Diagnosis:
  - arteriography or biopsy of palpable nodulations in the skin or organ involved .
- Treatment:

  - Untreated cases: almost fatal
  - Good response to immunosuppressive therapy.

- Churg-Strauss Syndrome (Allergic granulomatous angitis)

- Is a systemic vasculitis that occurs in persons with asthma*.
- A variant of PAN.

- Involves small* & medium vessels of
  - upper/lower respiratory tract*
  - heart, spleen, peripheral nerves, skin , kidney.
- Pathology:
  - Inflammation of vessel wall (eosinophils)
  - Fibrinoid necrosis
  - Thrombosis and infarction

- Churg-Strauss Syndrome (Allergic granulomatous angitis)

- Features very similar to PAN but patients with CSS have:
  - History of atopy
  - Bronchial asthma, allergic rhinitis and
  - peripheral blood eosinophilia.
- Microscopy:
  - Similar to PAN
- Labs:
  - peripheral eosinophilia , high serum IgE,
  - p-ANCA*

- Patient profile # 4

- A 4 year old Japanese child presents with
  - Fever, redness of eyes and oral cavity
  - Swollen hands and feet
  - Rash over the trunk and extremities
  - Peeling of skin and
  - Cervical lymphadenopathy.
- Labs:
  - ECG changes consistent with myocardial ischemia
- Diagnosis:
  - Kawasaki Disease (mucocutaneous lymphnode syndrome)

- Kawasaki's disease
- Is also known as <u>mucocutaneous lymphnode syndrome</u>.
  - Is an acute self limited febrile illness of infants and children (< 5 yrs).
    - Is endemic in Japan , Hawaii
  - One of the manifestations is vasculitis (coronary artery).
- In other words:
  - KD is a childhood vasculitis that mainly

targets coronary arteries.

- Coronary artery involvement:
  - can lead to coronary thrombosis or aneurysm formation and its rupture.

- Clinical features : Kawasaki's disease
- Clinical findings:
  - High fever
  - Erythematous rash of trunk and extremities with desquamation of skin.

  - Mucosal inflammation : cracked lips, oral erythema
  - Erythema, swelling of hands and feet.
  - Localized lymphadenopathy (cervical adenopathy)
  - MCC of an acute MI in children******
- Lab:
  - Neutrophilic leukocytosis
  - Thrombocytosis : characteristic finding
  - High ESR
  - abnormal ECG (e.g. acute MI)*****

- **Patient profile # 5**
- A young smoker male patient from Israel presents with C/O

  - Pain in the foot
    - Which is severe and present even at rest
- On examination:
  - Presence of ulcers and blackish areas over the fingers and toes.
  - Some missing digits.
- Biopsy from lower limb vessel:
  - Acute inflammation of vessel wall with Obliteration of vessel lumen by a thrombus.
- Diagnosis: Thromboangitis Obliterans (Buerger's Disease)
- Buerger's Disease
- Also known as Thromboangitis Obliterans.

- Is a peripheral vascular disease of smokers.
- Pathology:
  - Earliest change: Acute inflammation involving the small to medium sized arteries in the extremities (tibial, popliteal & radial arteries).
  - Inflammation of vessel → thrombus formation → obliterates lumen → ischemia · gangrene of extremity.

- Inflammation also extends to adjacent veins and nerves.
  - Involvement of entire neurovascular compartment.

- Buerger's Disease
- Buerger's Disease
- Clinical findings:
  - Young-middle age, male, heavy smoker*
    - Israel*, Japan, India.
  - Symptoms start between 25 to 40 years
  - Early manifestation:
    - Intermittent Claudication in feet or hands
      - Cramping pain in muscles after

exercise, relieved by rest

- Late manifestation:
  - Painful ulcerations of digits
  - Gangrene of the digits often requiring amputation.

- Buerger's Disease
- Diagnosis:
  - biopsy
- Rx:
  - early stages of vasculitis frequently cease on discontinuation of smoking.

- Small vessel vasculitis

- Small vessel vasculitis Hypersensitivity (leukocytoclastic) vasculitis
- Refers to a group of immune complex mediated vasculitides.
- Characterized by:
  - Acute inflammation of small blood vessels
  - Manifesting as palpable purpura***.
- Organs involved:

- Usually skin (other organs less commonly affected).

- Hypersensitivity (leukocytoclastic) vasculitis
- May be precipitated by
  - Exogenous antigens
    - Drugs
      - E.g. aspirin/penicillin/thiazide diuretics
    - Infectious organisms
      - E.g. strep/staph infections,TB,viral diseases

    - Foods
  - Chronic diseases
    - E.g. SLE, RA etc.

- Hypersensitivity (leukocytoclastic) vasculitis
- Pathology:
  - acute inflammation of small blood vessels (arterioles, capillaries, venules)
  - Neutrophilic infiltrate in vessel wall.
  - Leukocytoclastic refers to nuclear debris from disintegrating neutrophils

    - The neutrophils undergo karyorrhexis.
  - Erythrocyte extravasation
- Hypersensitivity (leukocytoclastic) vasculitis
- C/F:
  - The disease typically presents as palpable purpura* involving the skin principally of lower extremities.
  - May also involve other organs
    - Lungs→ hemoptysis
    - GIT→ abdominal pain

- Kidneys → hematuria and
- Musculoskeletal system → arthralgia
- brain, heart

- Hypersensitivity (leukocytoclastic) vasculitis
- Diagnosis:
  - Skin biopsy is often diagnostic.
- Treatment:
  - removal of offending agent
- Patient profile # 6

- A 14 year old child with history of URT infection develops:
  - Polyarthritis
  - Colicky abdominal pain
  - Hematuria with RBC casts
  - Palpable purpura localized to lower limbs and buttocks.
- Lab:
  - Neutrophilic leukocytosis
  - Deposition of IgA-C3 immune complex : in skin and renal lesions

- Henoch Schonlein purpura (HSP)
- A variant of hypersensitivity vasculitis.
- Seen in children** (MC vasculitis in children) , rare in adults.
- Etiopathogenesis:
  - Usually occurs following an upper respiratory infection*.
  - Caused by deposition of IgA-C3 immune complexes in vessel wall.
- Vessels involved:

- Arterioles, capillaries and venules of
  - Skin, GIT,Kidney,musculoskeletal system.
- Henoch Schonlein purpura (HSP)
- Clinically characterized by:
  - Palpable purpura over extensor aspects of arms and legs.
    - commonly limited to lower extremities/ buttocks.
  - Involvement of

- GIT → colicky abdominal pain, melena
- Musculoskeletal system · Arthralgia (non migratory), and myalgias
- Kidneys · hematuria due to focal proliferative GN.
- Lung → rare

- Henoch Schonlein purpura (HSP)
- Lab:
  - Neutrophilic leukocytosis

  - Deposition of IgA-C3 immune complexes : in skin and renal lesions
- Rx: steroids

- Wegener Granulomatosis (WG)
- Is characterized by:
  - Necrotizing granulomatous inflammation of URT and LRT and
  - Granulomatous vasculitis of the same areas plus kidneys.
- Therefore patients have:

    - Lesions of the nose, sinuses and lungs* (upper & lower respiratory tract) and
    - Kidney*
- Highly associated with c-ANCA**

- Wegener Granulomatosis
- Pathology: two different types of lesions
    - Granulomatous Vasculitis

  - involving small vessels of URT and LRT and kidneys.
- Necrotizing granulomatous lesions
  - in the above sites.
  - Granuloma formation with giant cells
  -

- Wegener Granulomatosis
- Clinical features
- Persons most commonly affected by WG are
  - middle aged 40-50 yrs (Peak incidence)

  - Male> females
- Respiratory tract signs and symptoms dominate the clinical picture:
  - Upper respiratory tract (nasopharynx, sinuses, trachea)
    - Chronic Sinusitis, ulcers of nasopharyngeal mucosa.
    - Saddle nose deformity* : Nasal cartilage destroyed
  - Lower respiratory tract
    - Recurrent pneumonia with
    - Nodular lesions which undergo cavitation
- Kidney: Crescentric glomerulonephritis → can cause renal failure.

- Lab:
  - c-ANCA* present in 90% of patients with active disease (good marker of disease activity)
    - Specific for WG
- Chest radiograph:
  - bilateral nodular infiltrates or cavitary lesions.
- Diagnosis:
  - biopsy
- Treatment:
  - Cyclophosphamide

    - Danger of hemorrhagic cystitis and Transitional cell carcinoma
  - Steroids
  - Without treatment 80% die within 1 year
- Infectious vasculitis
- Fungal vasculitis: vessel invading fungi
  - Mucor, Aspergillus ,Candida.
- Rocky Mountain spotted fever
  - Rickettsia rickettsiae
- Disseminated meningococcemia:

  - Small vessel vasculitis → petechial hemorrhages
- Infective endocarditis*
  - Roth's spots in retina
  - Janeway's lesions on hands (painless)
  - Osler's nodes on hands (painful)
  - Glumerulonephritis