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

Pathogenesis

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-Antiproteinase-3 (PR3-ANCA)= **c-ANCA**.

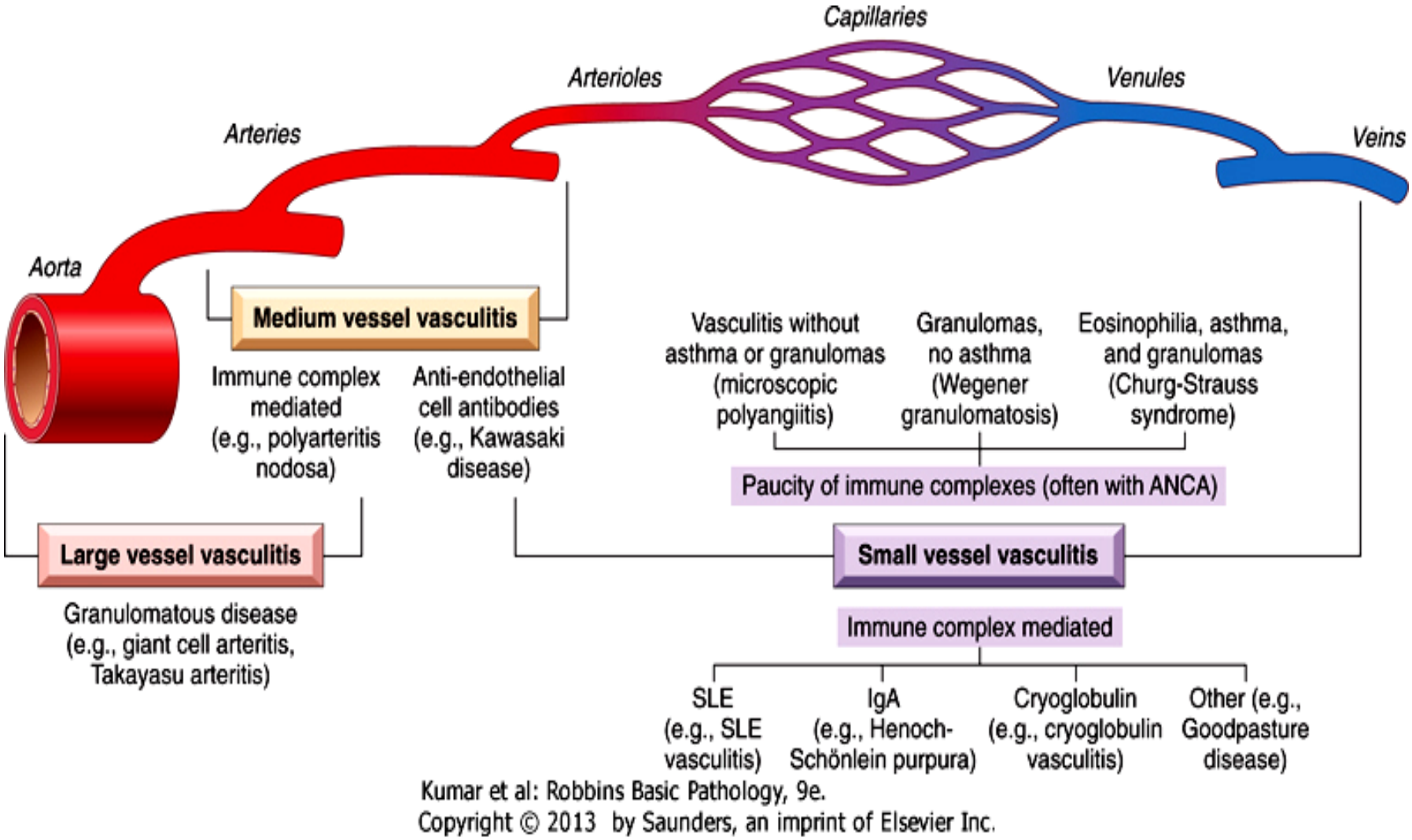
- is a neutrophil azurophilic granule constituent similar to numerous microbial peptides; e.g. Wegener granulomatosis.

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).



Kumar et al: Robbins Basic Pathology, 9e.

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

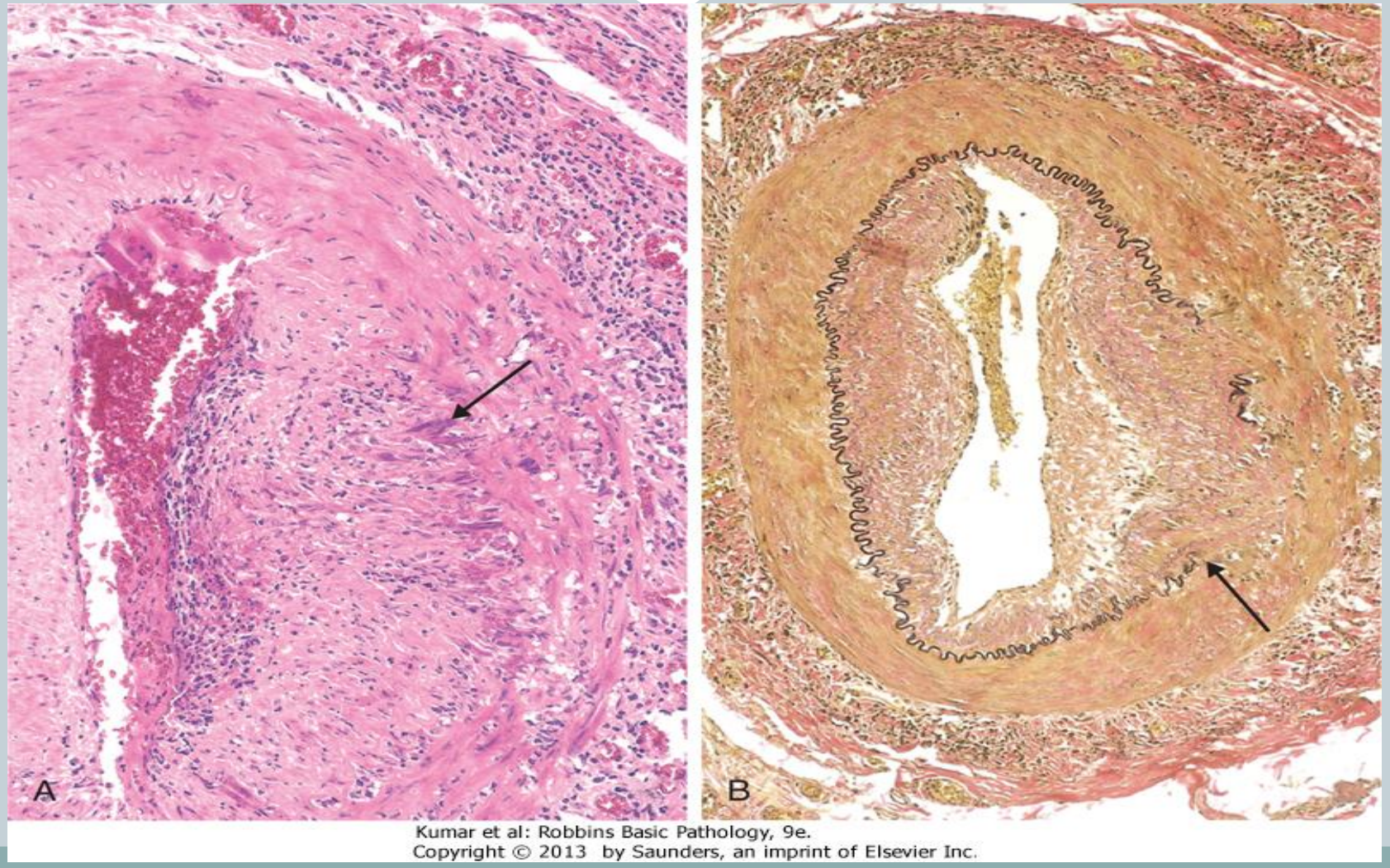
- rare before the age of 50.
- ***Signs and symptoms:***
- fever, fatigue, weight loss
- facial pain or headache, (superficial temporal artery).
- Ocular symptoms (ophthalmic artery) in 50% of patients; range from diplopia → → complete vision loss.
- ***Diagnosis***:

- 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**

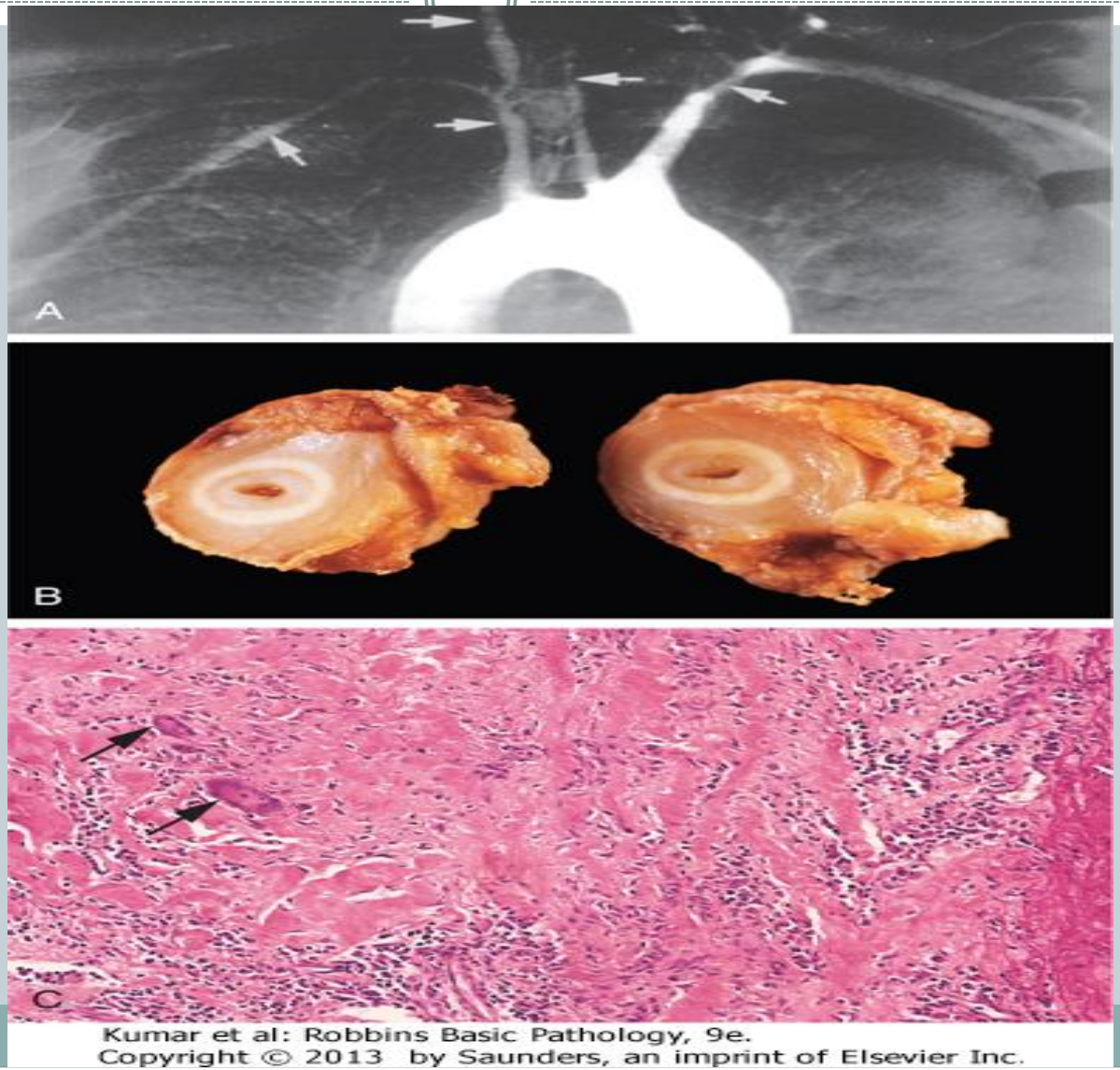
Takayasu arteritis -MORPHOLOGY

- **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.

Takayasu arteritis -MORPHOLOGY



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 ANCAs

- (1/3) chronic hepatitis B infection→ immune complexes containing hepatitis B antigens deposit in affected vessels.

- (2/3) →The cause is unknown

Polyarteritis nodosa (PAN)- morphology

- 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***➔ aneurysms → rupture or thrombosis→ 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) → →(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%.**

Wegener granulomatosis- clinical picture

- **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 granulomatosis and angiitis)
- **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