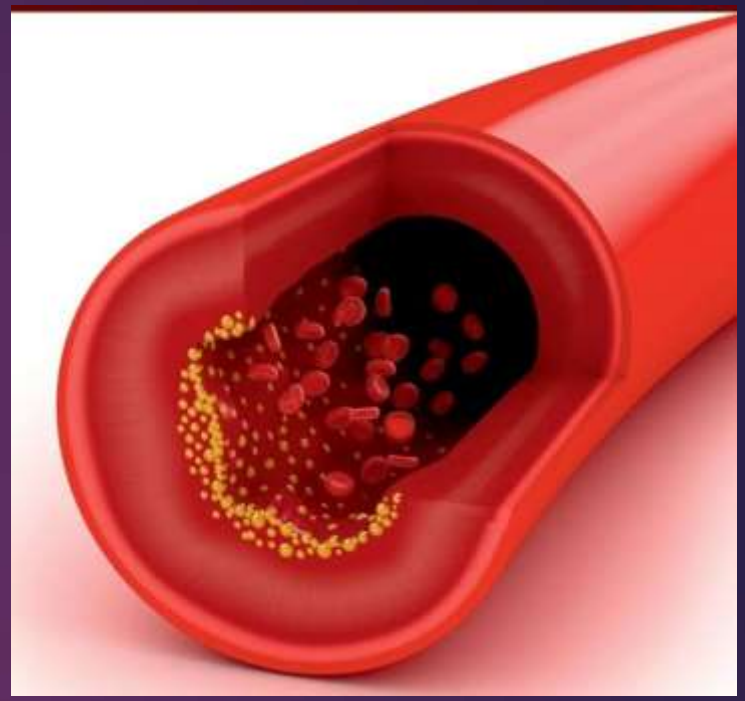
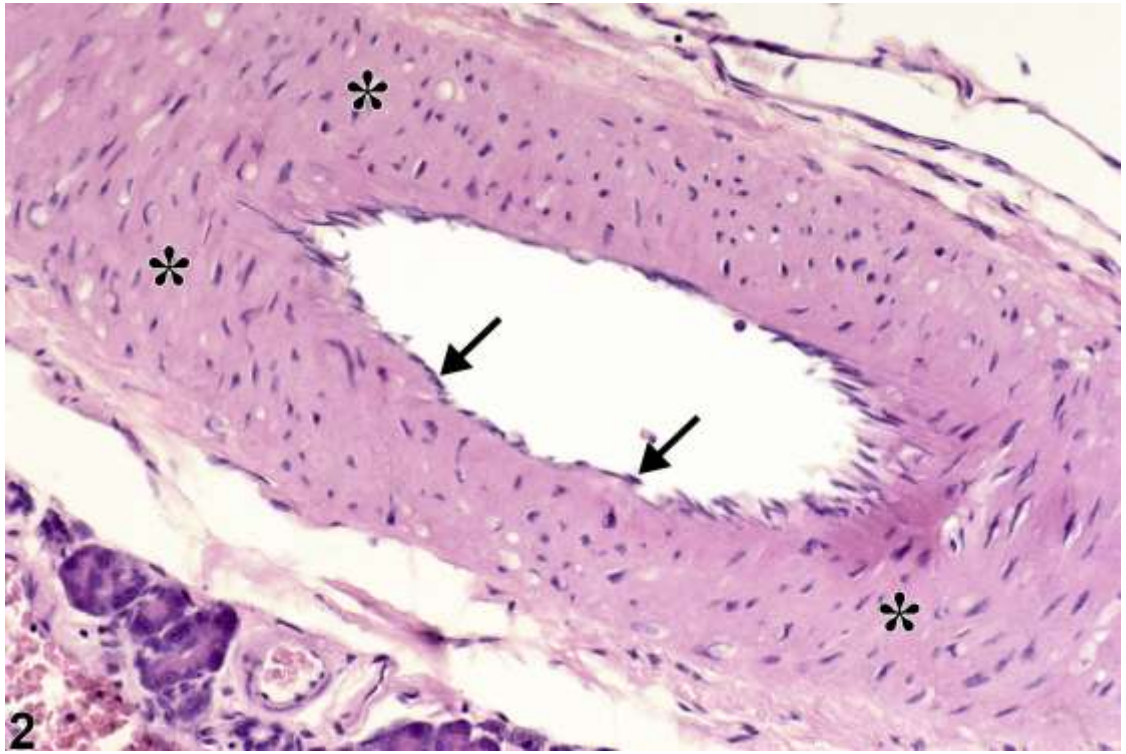
CVS module – 5
Vasculitis

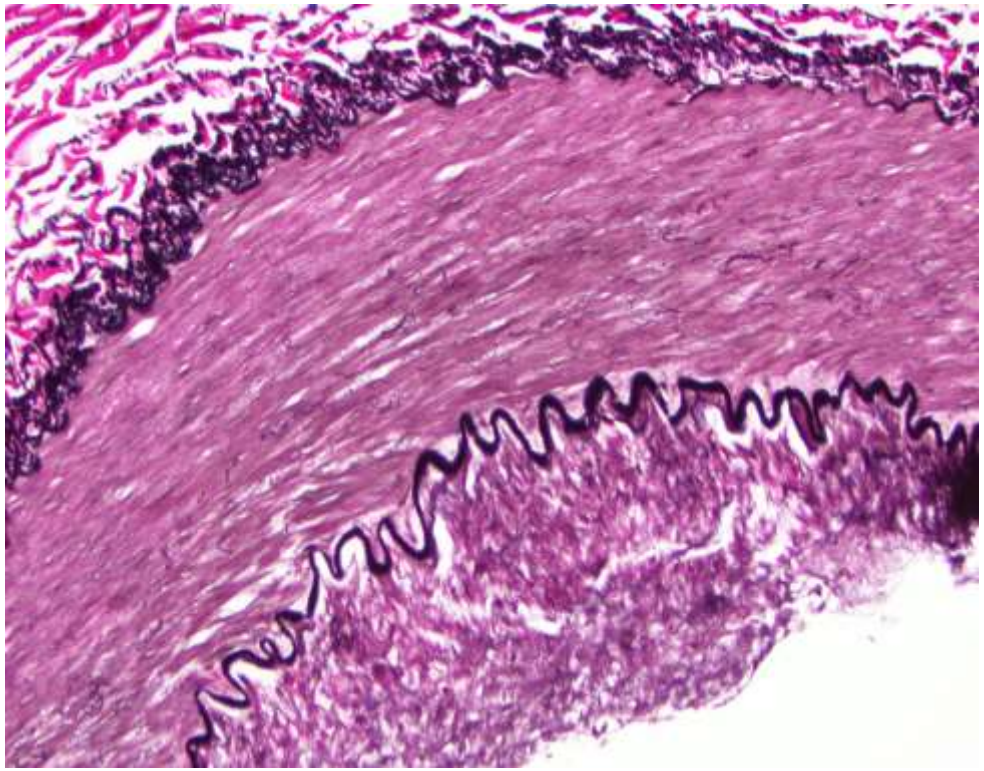


DR. EMAN KREISHAN, M.D

22-11-2023

Histology of normal blood vessel





Vasculitis

- General term for vessel wall inflammation.

- Inflammatory processes that affect capillaries, venules and small, medium and large sized vessels.

- The pathogenic mechanisms of vasculitis are include:
- immune-mediated .
- Infectious causes.
- Mechanical causes:
- Physical and chemical injury like: radiation, mechanical trauma, and toxins

Classification

- vessel diameter.
- role of immune complexes.
- presence of specific autoantibodies.
- granuloma formation.
- organ specificity.

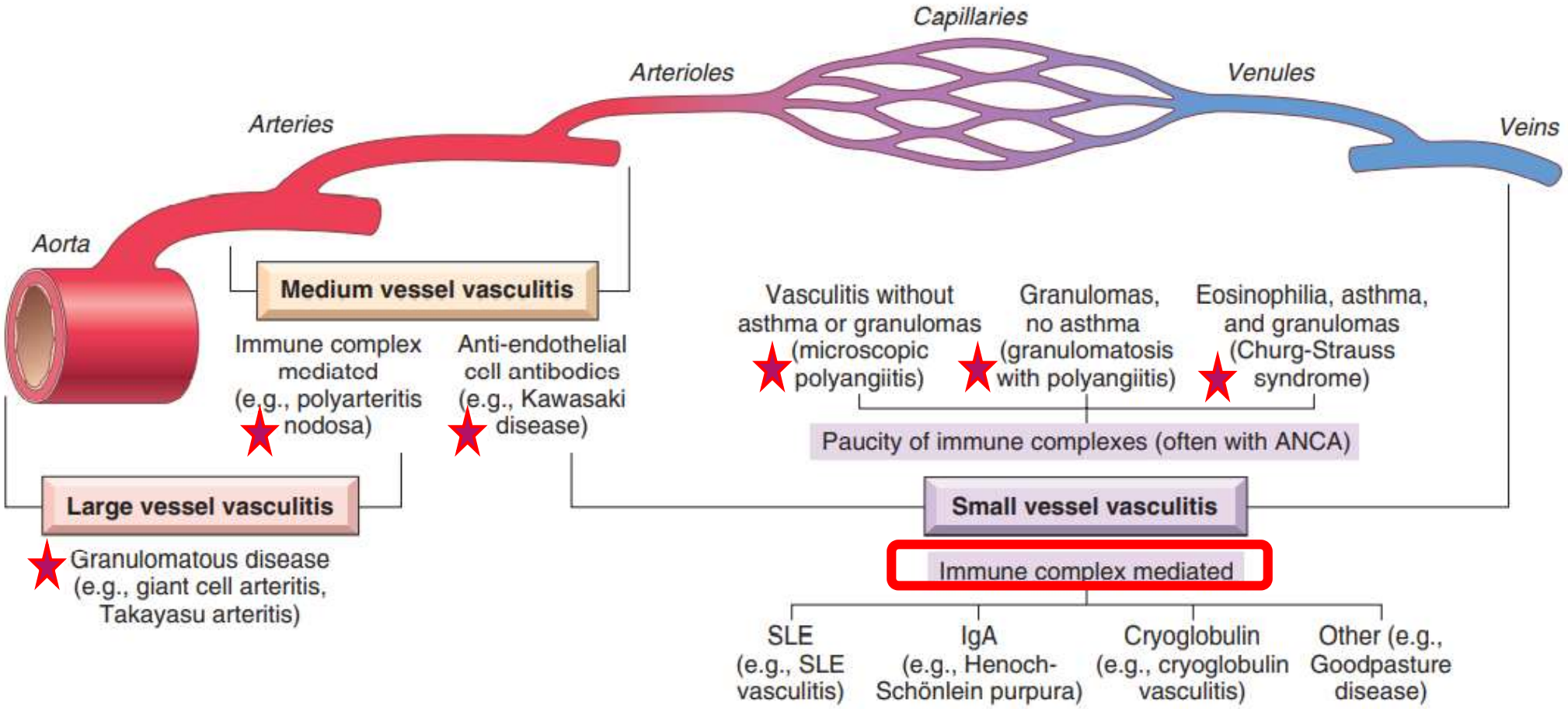
Table 10.4 Primary Forms of Vasculitis

	Giant Cell Arteritis	Granulomatosis With Polyangiitis	Churg-Strauss Syndrome	Polyarteritis Nodosa	Leukocytoclastic Vasculitis	Buerger Disease	Behçet Disease
Sites of Involvement							
Aorta	+	–	–	–	–	–	–
Medium-sized arteries	+	+	+	+	–	+	+
Small-sized arteries	–	+	+	+	+	+	+
Capillaries	–	–	–	–	+	–	+
Veins	–	–	–	–	+	+	+
Inflammatory Cells Present							
Lymphocytes	+	+	+	±	±	±	±
Macrophages	+	+	+	±	±	±	±
Neutrophils	Rare	+	+	±	±	±	Required
Eosinophils	Very rare	±	Required	±	±	±	±
Other Features							
Granulomas	±*	Required*	±	–	–	–	–
Giant cells	Often; not required	±	–	–	–	–	–
Thrombosis	±	±	±	±	±	Required	±
Serum ANCA positivity	–	+	+	±	–	–	–
Clinical history	>40 years of age, ± polymyalgia rheumatica	Any	Asthma, atopy	Any	Any	Young male smoker	Orogenital ulcers

*The granulomas of giant cell arteritis are found within the vessel wall as part of the inflammation comprising the vasculitis, but need not be present to render the diagnosis. The granulomas of granulomatosis with polyangiitis are larger, spanning between vessels, and associated with areas of tissue necrosis.

ANCA, Anti-neutrophil cytoplasmic antibodies.

From Seidman MA, Mitchell RN: Surgical pathology of small-and medium-sized vessels. In Winters, GL, ed., *Current concepts in cardiovascular pathology*, Philadelphia, 2012, Saunders.


Capillaries
Arterioles
Venules
Arteries
Veins
Aorta
Medium vessel vasculitis
Immune complex mediated (e.g., polyarteritis nodosa)
Anti-endothelial cell antibodies (e.g., Kawasaki disease)
Large vessel vasculitis
Granulomatous disease (e.g., giant cell arteritis, Takayasu arteritis)
Vasculitis without asthma or granulomas (microscopic polyangiitis)
Granulomas, no asthma (granulomatosis with polyangiitis)
Eosinophilia, asthma, and granulomas (Churg-Strauss syndrome)
Paucity of immune complexes (often with ANCA)
Small vessel vasculitis
Immune complex mediated
SLE (e.g., SLE vasculitis)
IgA (e.g., Henoch-Schönlein purpura)
Cryoglobulin (e.g., cryoglobulin vasculitis)
Other (e.g., Goodpasture disease)

- **Noninfectious Vasculitis :**

- **Immune complex deposition :**
- immunologic disorders, Drug hypersensitivity vasculitis, Vasculitis secondary to infections
- **Anti-neutrophil cytoplasmic antibodies :**
- granulomatosis with polyangiitis, microscopic polyangiitis and Churg-Strauss syndrome.
- **Anti-EC antibodies :** Kawasaki disease
- **Autoreactive T cells** : vasculitides characterized by formation of granulomas.

- **Infectious Vasculitis**

1. Vasculitis due to Immune complex deposition

- Immunologic disorders, e,g SLE: Anti-double stranded DNA(dsDNA).

- Drug hypersensitivity vasculitis:
- antibodies directed against the drug which act as foreign molecules result in immune complex formation.
- Commonly seen with penicillin and streptokinase.

- Vasculitis secondary to infections:
- Antibodies to microbial constituents can form immune complexes that circulate and deposit in vascular lesions. E.g. polyarteritis nodosa, immune complexes composed of hepatitis B surface antigen (HBsAg) and anti-HBsAg antibody

2. Anti-Neutrophil Cytoplasmic Antibodies(ANCAs).

- ANCAs are a heterogeneous group of autoantibodies directed against constituents (mainly enzymes) of neutrophil primary granules and monocyte lysosomes.

- These are classified according to their antigen specificity:

1. **c-ANCA :Anti-proteinase-3 (PR3-ANCA).**

- PR3 is a neutrophil azurophilic granule constituent that shares homology with numerous microbial peptides.
- PR3- ANCAs are associated with granulomatosis with polyangiitis.

2. **p-ANCA: Anti-myeloperoxidase (MPO-ANCA).**

- MPO is a lysosomal granule constituent involved in oxygen free radical generation.
- MPO-ANCAs are associated with microscopic polyangiitis and Churg-Strauss syndrome.

Note

- The ANCA auto-antibodies are directed against cellular constituents and do not form circulating immune complexes; therefore ANCA-associated vasculitides often are described as “pauci-immune.”

- ANCAs are very useful diagnostic markers; their titers generally mirror clinical severity, and a rise in titers after periods of quiescence is predictive of disease recurrence.

Most common clinically important vasculitides

1. Giant Cell (Temporal) Arteritis

- It is the most common form of vasculitis among older adults in developed countries

- chronic inflammatory disorder, typically with granulomatous inflammation, that mainly affects large- to small-sized arteries in the head.

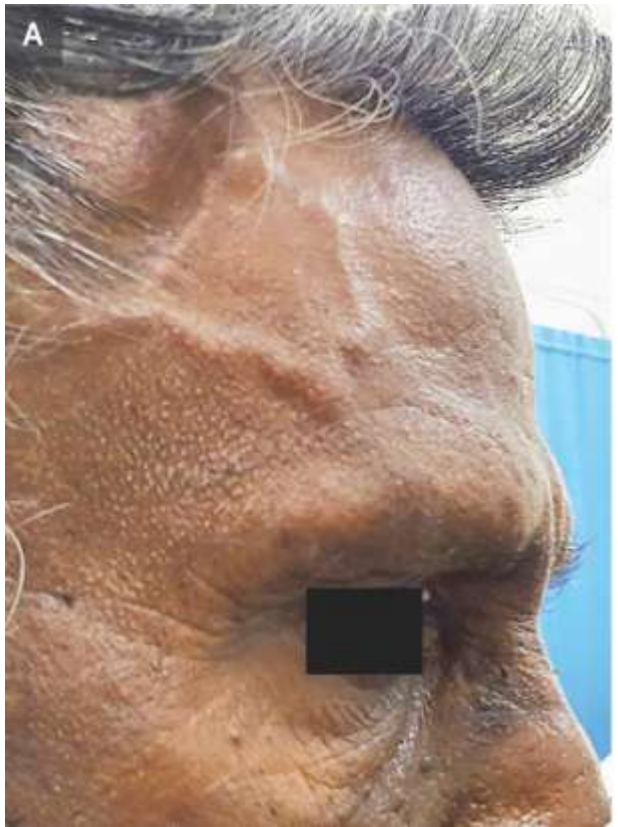
- common sites of involvement:
- temporal arteries
- Vertebral arteries.
- ophthalmic arteries (lead to sudden and permanent blindness).
- aorta .

- Giant cell arteritis likely occurs as a result of a T-cell– mediated immune response to unknown vessel wall antigen

Clinical Features

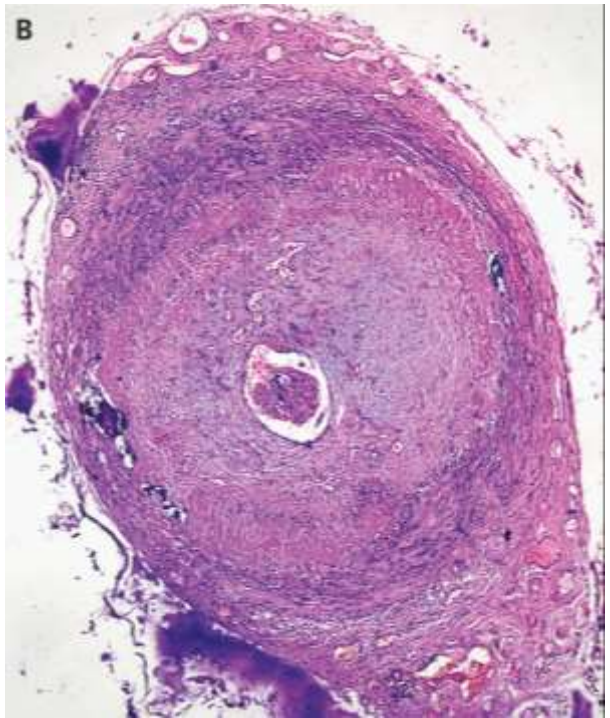
- vague and constitutional (e.g., fever, fatigue, weight loss).
- Facial pain or headache, most intense along the course of the superficial temporal artery.
- involvement of the ophthalmic artery with diplopia to complete vision loss.

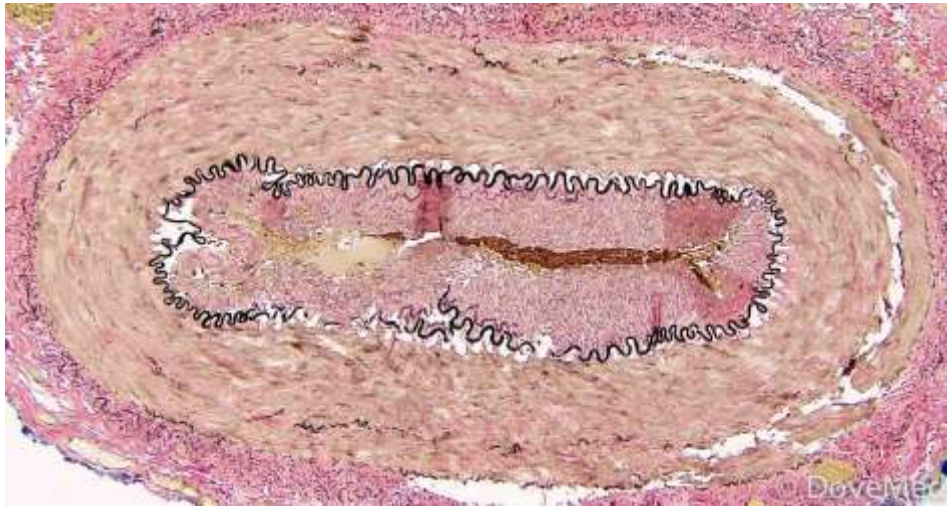
- Diagnosis is typically established by biopsy from temporal vessels.



Morphology

- Transmural inflammation pattern with lymphocytes, giant cells and macrophages arranged in concentric rings, surrounding the external and internal elastic lamina, the later is disrupted as viewed by- an elastic stain.





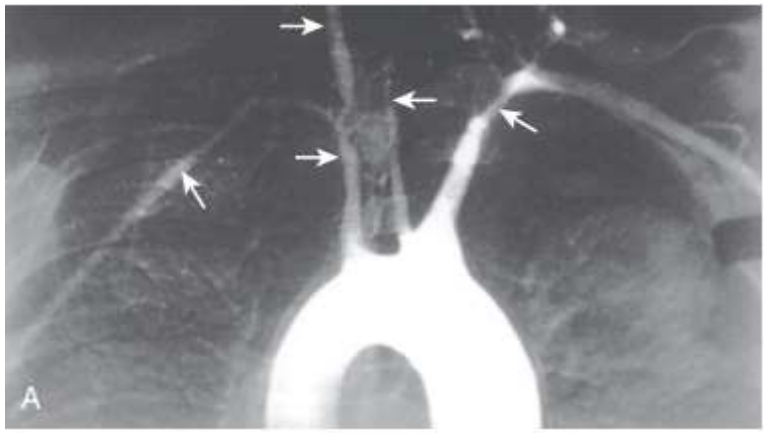
2. Takayasu arteritis (pulseless disease).

- Is a granulomatous vasculitis of medium- and large-sized arteries characterized principally by ocular disturbances and marked weakening of the pulses in the upper extremities.

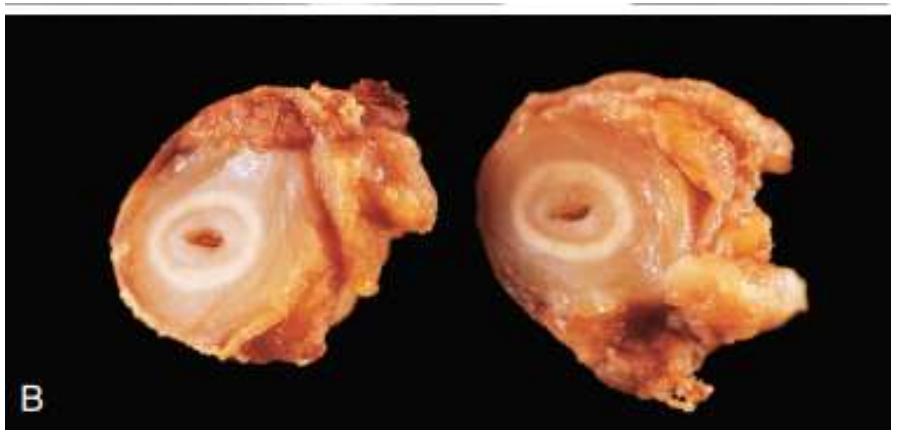
- This disorder manifests with transmural scarring and thickening of the involved vessel.

- It share many of the clinical and histologic features of giant cell aortitis. the distinction between the two entities is made largely on the basis of a patient's age;
- patient older than 50 years of age : giant cell aortitis.
- patient younger than 50 years of age : Takayasu aortitis.

Morphology



Aortic arch angiogram showing reduced flow of contrast material into the great vessels

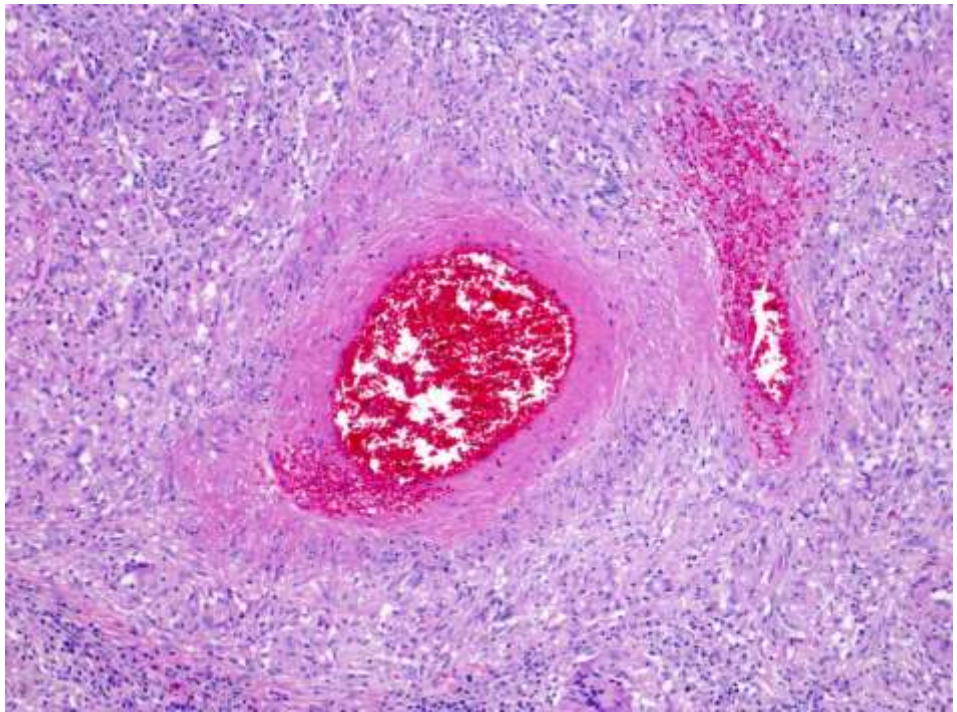


intimal thickening and luminal narrowing

Histology

- The histologic picture include a spectrum ranging from:

- intense transmural (including the adventitia) mononuclear inflammation.
- perivascular cuffing of the vasa vasorum.
- granulomatous inflammation with giant cells .
- patchy medial necrosis.



Clinical Features

- Nonspecific symptoms including fatigue, weight loss, and fever.
- reduced upper-extremity blood pressure and pulse strength.
- ocular disturbances, including visual field defects, retinal hemorrhages, and total blindness.
- pulmonary artery involvement can cause pulmonary hypertension.
- Narrowing of the coronary ostia can lead to myocardial infarction.
- involvement of the renal arteries causes systemic hypertension .

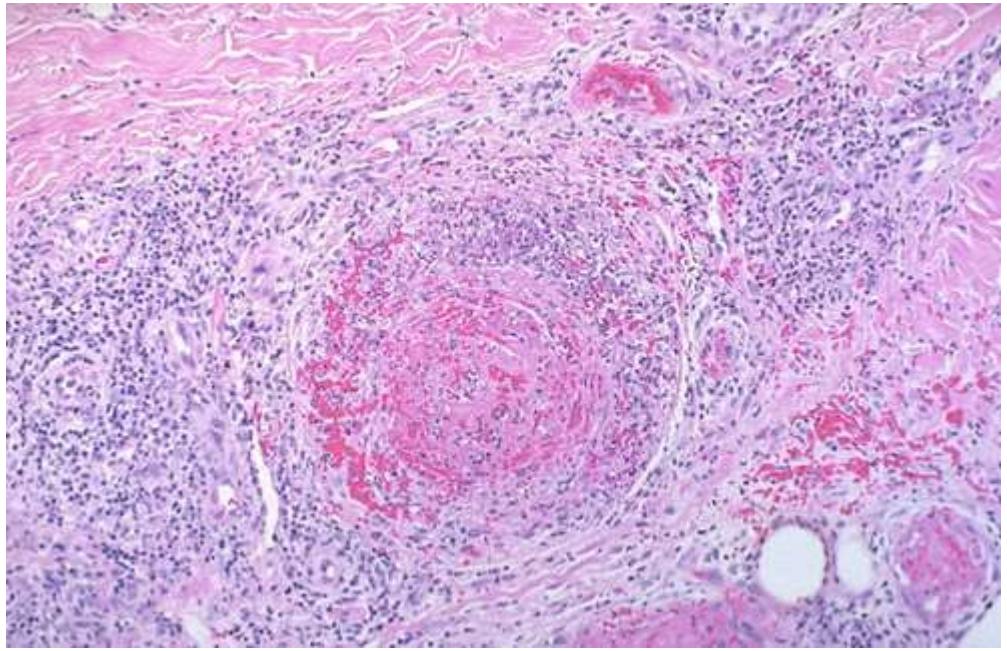
3. Polyarteritis Nodosa

- systemic vasculitis of small- or medium-sized muscular arteries; it typically involves the renal and visceral vessels and spares the pulmonary circulation.
- There is no association with ANCAs, but one third of patients have chronic hepatitis B infection, which leads to the formation of immune complexes containing hepatitis B antigens that deposit in affected vessels.
- PAN is primarily a disease of young adults but can occur in all age groups.
- Kidney, heart, liver, and gastrointestinal tract vessels are affected in descending order of frequency.

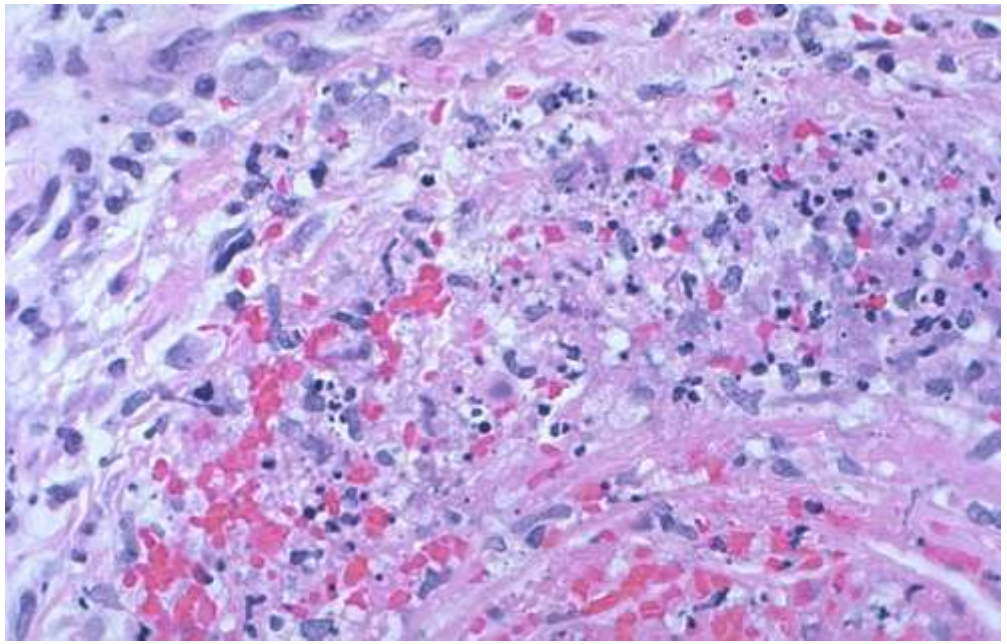
MORPHOLOGY

- PAN is a segmental transmural necrotizing inflammation of small- to medium-sized arteries, often with superimposed thrombosis.
- In the acute phase, there is transmural mixed inflammatory infiltrate composed of neutrophils and mononuclear cells, frequently accompanied by fibrinoid necrosis and luminal thrombosis.
- Older lesions show fibrous thickening of the vessel wall extending into the adventitia.
- The inflammatory process also weakens the arterial wall, leading to aneurysms and rupture.

PAN MORPHOLOGY



transmural necrotizing inflammation



necrosis of the vascular wall.

Clinical Features

- The clinical course typically is episodic, with long symptom-free intervals.

- Non specific systemic findings like malaise, fever, and weight loss.
- Impaired perfusion may lead to ulcerations, infarcts, ischemic atrophy, or hemorrhages in the distribution of affected vessels:

- renal artery involvement : rapidly accelerating hypertension.
- gastrointestinal vessels involvement: abdominal pain and bloody stools.
- motor nerves involvement: diffuse muscular aches and pains; and peripheral neuritis.

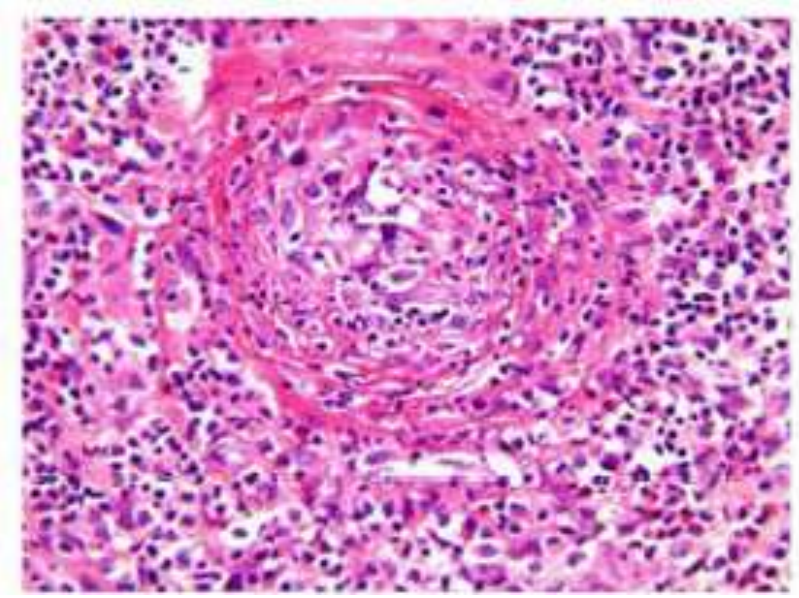
4. **Kawasaki Disease**

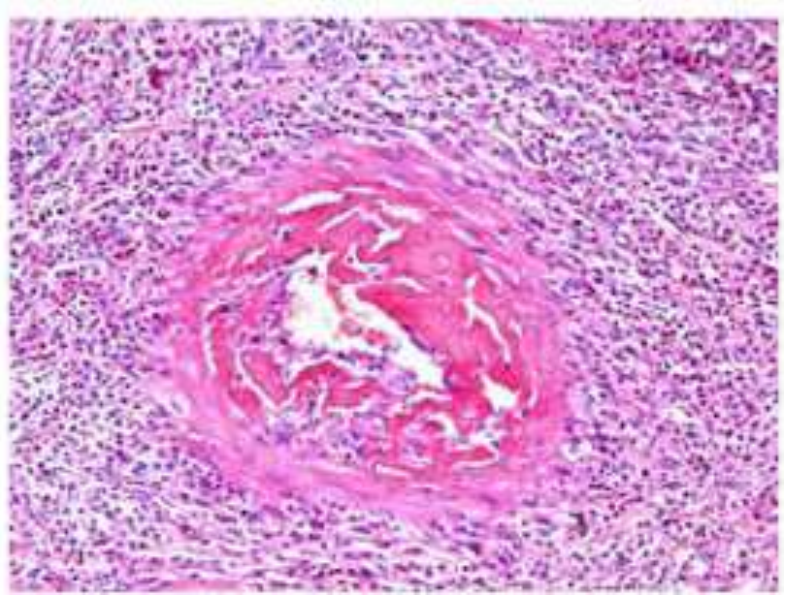
- Acute, febrile, usually self-limited illness of infancy and childhood (younger than 4 years) associated with an arteritis of mainly large- to medium-sized vessels.

- In genetically susceptible individuals, a variety of infectious agents (mostly viral) have been claimed to trigger the disease.
- Subsequent cytokine production and polyclonal B cell activation result in auto-antibodies to ECs and SMCs that precipitate the vasculitis.

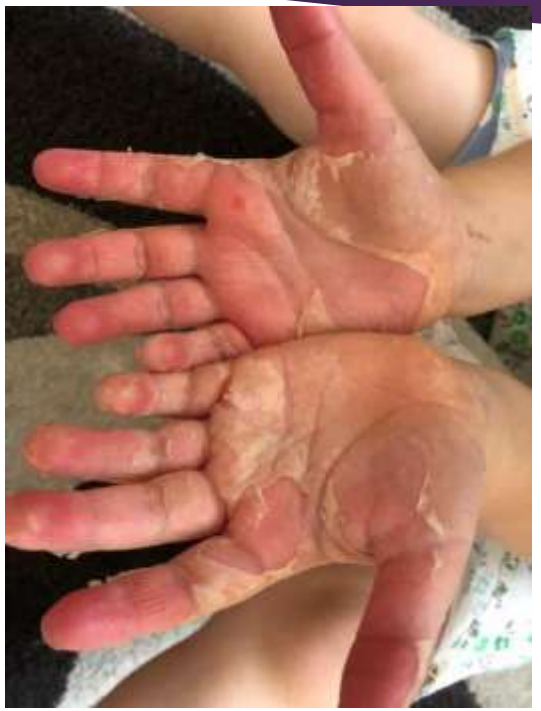
MORPHOLOGY

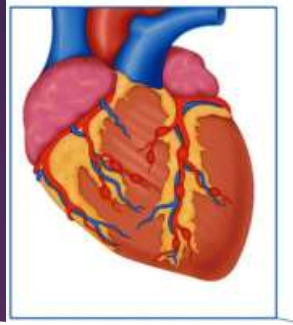
- Histological features resembles that seen in polyarteritis nodosa.
- There is a dense transmural inflammatory infiltrate, but less prominent fibrinoid necrosis.



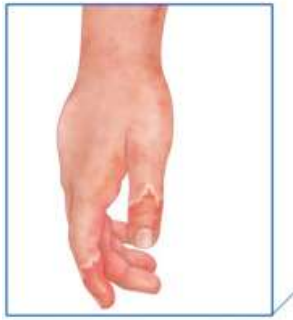


Diagnostic features of Kawasaki disease

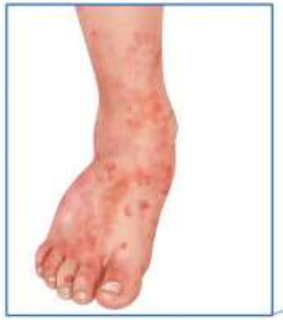




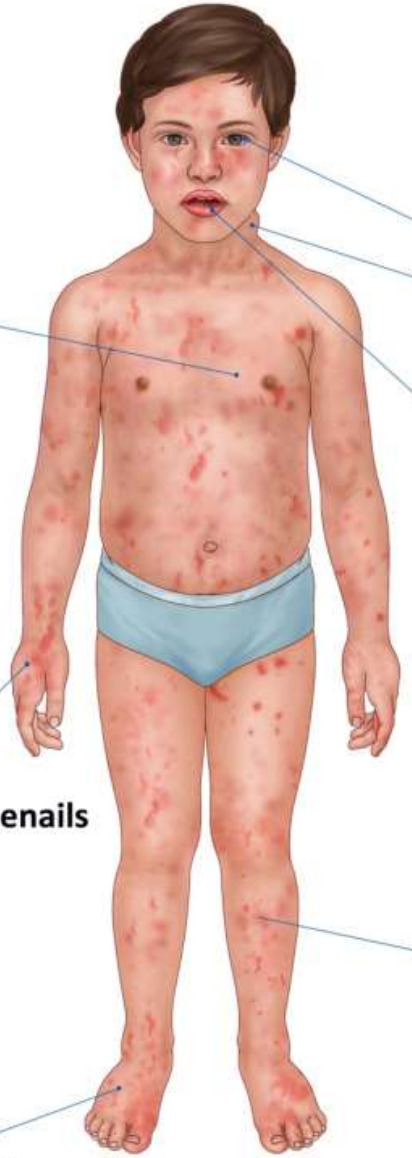
Coronary artery aneurysms



Peeling of skin around fingernails/toenails

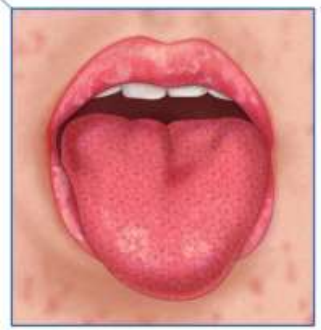


Swelling and/or eryhthema of palms/soles



Red eyes

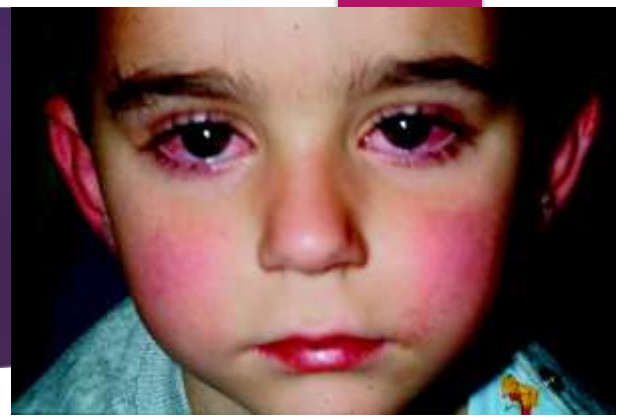
Swollen lymph nodes

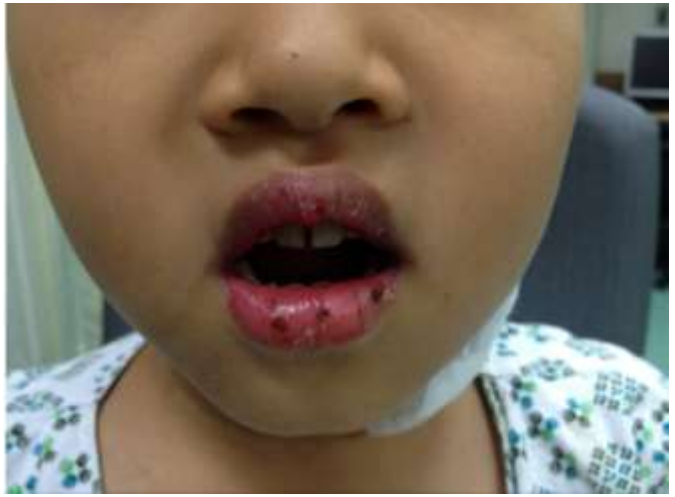


Red, dry, cracked lips and imflamed tongue

Widespread rash

Fever (for more than 5 days)





Prognosis

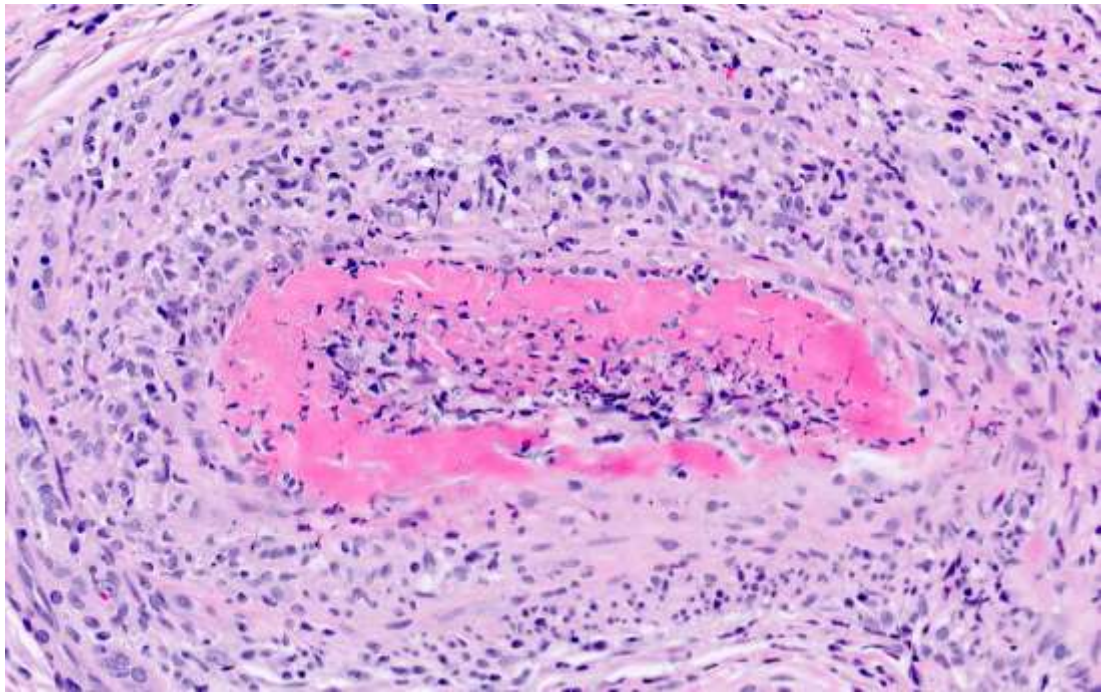
- Its clinical significance stems from the involvement of coronary arteries.
- Coronary arteritis can result in aneurysms that rupture or thrombose, causing myocardial infarction.
- The vasculitis typically subsides spontaneously or in response to treatment, but aneurysm formation due to wall damage may supervene.

5. **Microscopic polyangiitis (**leukocytoclastic vasculitis.)

- Necrotizing vasculitis that generally affects capillaries, small arterioles and venules.
- Necrotizing glomerulonephritis and pulmonary capillaritis are particularly common.
- Also involve the skin, mucous membranes, brain, heart, gastrointestinal tract, and muscle .
- Pathogenesis :
- immune complex deposition seen in immune disorders, such as Henoch-Schönlein purpura, essential mixed cryoglobulinemia.
- antibody responses to antigens such as: drugs (e.g., penicillin), microorganisms (e.g., streptococci), heterologous proteins, or tumor proteins

Morphology

- Characterized by segmental fibrinoid necrosis of the media with focal transmural necrotizing lesions; granulomatous inflammation is absent.



Clinical Features

- Recruitment and activation of neutrophils within affected vascular beds is probably responsible for the disease manifestations.

- Depending on the vascular bed involved, major features include:

- Hemoptysis.
- Hematuria.
- proteinuria.
- abdominal pain or bleeding.
- muscle pain or weakness.
- palpable cutaneous purpura.

6. Granulomatosis With Polyangiitis

- Previously called Wegener granulomatosis, granulomatosis with polyangiitis (GPA) is a necrotizing vasculitis characterized by a **triad** of the following:

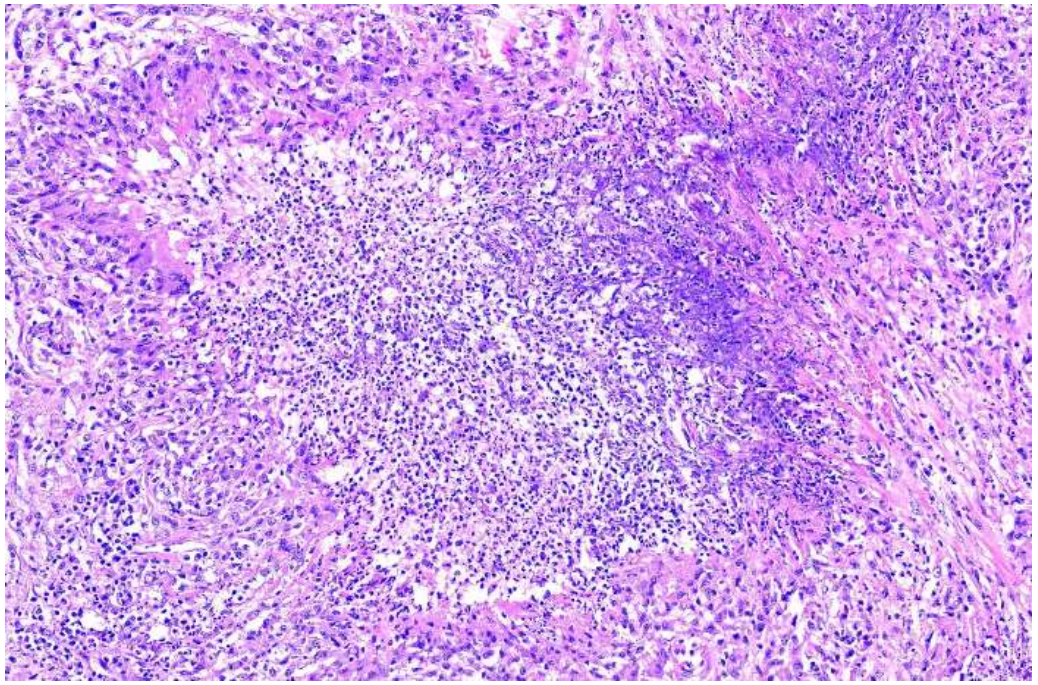
1. Necrotizing granulomas of the upper or lower respiratory tract .

2. Necrotizing or granulomatous vasculitis affecting small- to medium-sized vessels (e.g., capillaries, venules, arterioles, and arteries), most prominently the lungs and upper airways.

3. Focal necrotizing, often crescentic, glomerulonephritis

MORPHOLOGY

- 1. Respiratory :
- Upper respiratory tract lesions range from granulomatous sinusitis to ulcerative lesions of the nose, palate, or pharynx.
- lung findings ranging from diffuse parenchymal infiltrates to granulomatous nodules.

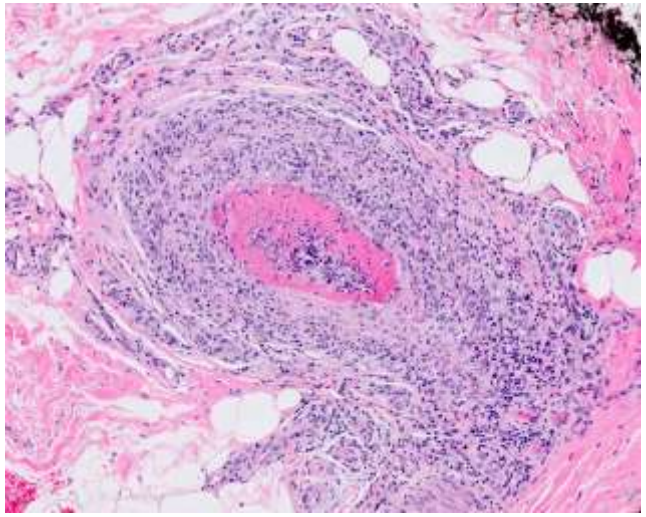


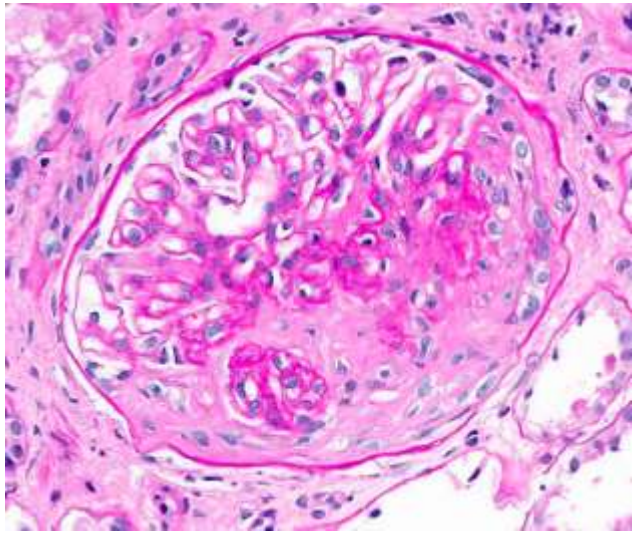
Morphology cont.

- 2. Multifocal necrotizing granulomatous vasculitis with a surrounding fibroblastic proliferation.

- 3. kidney:

- focal glomerular necrosis associated with thrombosis (focal and segmental necrotizing glomerulonephritis).
- crescentic glomerulonephritis.





Clinical Features

- The typical patient is a middle aged man.

- Non specific symptoms like Rash, myalgias, articular involvement, neuritis, and fever .
- Classic presentations include:
- bilateral pneumonitis with nodules .
- chronic sinusitis.
- mucosal ulcerations of the nasopharynx .
- renal disease: either mild such as hematuria and proteinuria or severe as renal failure

7. Churg-Strauss syndrome

- small-vessel necrotizing vasculitis classically associated with asthma, allergic rhinitis, lung infiltrates, peripheral eosinophilia, extravascular necrotizing granulomas, and a striking infiltration of vessels and perivascular tissues by eosinophils.

- Cutaneous involvement (with palpable purpura), gastrointestinal bleeding, and renal disease (primarily as focal and segmental glomerulosclerosis) are the major associations.

- Churg-Strauss syndrome may stem from "hyperresponsiveness" to some normally innocuous allergic stimulus.

- Cardiac involvement in form of cardiomyopathy resulting from cytotoxicity produced by the myocardial eosinophilic infiltrates.

Infectious Vasculitis

- Vasculitis caused by the direct invasion of arteries by infectious agents, usually bacteria or fungi, and in particular Aspergillus and Mucor spp.
- Vascular infections may weaken arterial walls and culminate in mycotic aneurysms or may induce thrombosis and infarction.