

# Vasculitis syndromes

# DEFINITION

Vasculitis is a clinicopathologic process characterized by inflammation of and damage to **blood vessels**.

The vessel lumen is usually compromised, and this is associated with **ischemia** of the tissues supplied by the involved vessel.

A broad and heterogeneous group of syndromes may result from this process, since any **type, size, and location** of blood vessel may be involved

# VASCULITIS SYNDROMES

## Primary Vasculitis Syndromes

- Granulomatosis with polyangiitis (Wegener's)
- Microscopic polyangiitis
- Eosinophilic granulomatosis with polyangiitis (Churg-Strauss)
- IgA vasculitis (Henoch-Schönlein)
- Cryoglobulinemic vasculitis
- Polyarteritis nodosa
- Kawasaki disease
- Giant cell arteritis
- Takayasu arteritis
- Behçet's disease
- Cogan's syndrome
- Single-organ vasculitis
- Cutaneous leukocytoclastic angiitis
- Cutaneous arteritis
- Primary central nervous system vasculitis
- Isolated aortitis

## Secondary Vasculitis Syndromes

- Vasculitis associated with probable etiology
- Drug-induced vasculitis
- Hepatitis C virus-associated
- cryoglobulinemic vasculitis
- Hepatitis B virus-associated vasculitis
- Cancer-associated vasculitis
- Vasculitis associated with systemic disease
- Lupus vasculitis
- Rheumatoid vasculitis
- Sarcoid vasculitis

# TYPICAL CLINICAL FEATURES BASED ON VESSEL SIZE

- **CONSTITUTIONAL SYMPTOMS** in all types are

- Fever
- Weight loss
- Malaise
- Anorexia
- Arthralgias
- Myalgias.

- **LARGE**

- Limb claudication
- Asymmetrical blood pressures
- Absence of pulses
- Bruits
- Aortic dilatation
- Aortic primary branch stenoses and/or aneurysms

# TYPICAL CLINICAL FEATURES BASED ON VESSEL SIZE

## • MEDIUM

- Cutaneous nodules
- Ulcers
- Livedo reticularis
- Digital gangrene
- Mononeuritis multiplex
- Microaneurysms of mesenteric and/or renal branch arteries

## • SMALL

- Purpura
- Vesiculobullous lesions
- Alveolar hemorrhage
- Glomerulonephritis
- Mononeuritis multiplex
- Cutaneous extravascular  
Necrotizing granulomas
- Splinter hemorrhages
- Scleritis, episcleritis,  
uveitis

# Conditions That Can Mimic Vasculitis

## ➤ Infectious diseases

- Bacterial endocarditis
- Disseminated gonococcal infection
- Pulmonary histoplasmosis
- Coccidioidomycosis
- Syphilis
- Lyme disease
- Rocky Mountain spotted fever
- Whipple's disease

## ➤ Coagulopathies/thrombotic microangiopathies

- Antiphospholipid syndrome
- Thrombotic thrombocytopenic purpura

## ➤ Neoplasms

- Atrial myxoma
- Lymphoma
- Carcinomatosis

## ➤ Drug toxicity

- Cocaine
- Levamisole
- Amphetamines
- Ergot alkaloids
- Methysergide
- Arsenic

## ➤ Sarcoidosis

## ➤ Atheroembolic disease

## ➤ Antiglomerular basement membrane disease (Goodpasture's syndrome)

## ➤ Amyloidosis

## ➤ Migraine

## ➤ Reversible cerebral vasoconstrictive syndrome



# Granulomatosis with Polyangiitis (GPA) (Wegener's Granulomatosis)

# Epidemiology - GPA

- an uncommon disease with an estimated prevalence of 3 per 100,000.
- It is extremely rare in blacks compared with whites.
- the male-to-female ratio is 1:1
- The disease can be seen at any age  
rarely does the disease occur before adolescence
- the mean age of onset is 40 years

# Pathology and Pathogenesis- GPA

- The histopathologic **hallmarks** of granulomatosis with polyangiitis (Wegener's) are **necrotizing vasculitis** of small arteries and veins together with **granuloma** formation, which may be either intravascular or extravascular
- **Lung involvement**  
multiple, bilateral, nodular cavitary infiltrates which on biopsy almost invariably reveal the typical **necrotizing granulomatous vasculitis**.

# Pathology and Pathogenesis-GPA

- **Upper airway lesions**

sinuses and nasopharynx, inflammation, necrosis, and granuloma formation, with or without vasculitis

- **renal involvement**

focal and segmental glomerulitis

rapidly progressive crescentic glomerulonephritis

Granuloma formation is only rarely seen on renal biopsy

## Pathology and Pathogenesis - GPA

- any organ can be involved with vasculitis, granuloma, or both.
- The immunopathogenesis of this disease is unclear
- cell-mediated immune response to an exogenous or even endogenous antigen that enters through or resides in the upper airway.

# Clinical and Laboratory Manifestations-GPA

## Granulomatous vasculitis :

- the upper and lower respiratory tracts
- glomerulonephritis
- variable degrees of disseminated vasculitis involving both small arteries and veins.

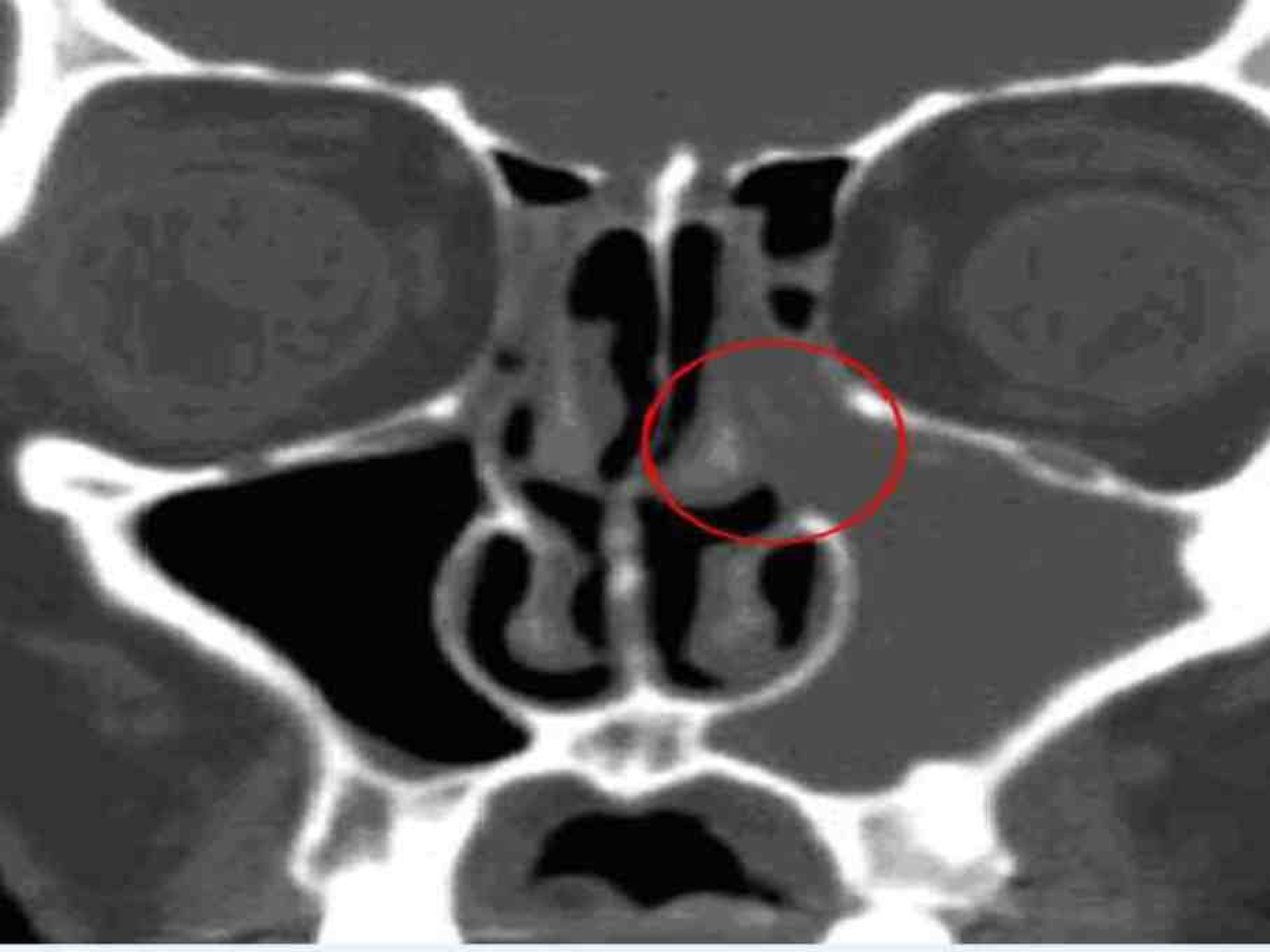
# Clinical and Laboratory Manifestations-GPA

## upper airways

- 95% of patients with granulomatosis with polyangiitis (Wegener's).

severe upper respiratory tract findings :

- paranasal sinus pain and drainage
- purulent or bloody nasal discharge
- nasal mucosal ulceration



## Clinical and Laboratory Manifestations-GPA

- **Nasal septal perforation** may follow, leading to saddle nose deformity.
- **Serous otitis media** may occur as a result of eustachian tube blockage.
- **Subglottic tracheal stenosis** resulting from active disease or scarring occurs in 16% of patients and may result in severe airway obstruction.

# Saddle nose deformity



# Subglottic tracheal stenosis



# Clinical and Laboratory Manifestations-GPA

## **Pulmonary involvement (85–90%)**

- asymptomatic infiltrates
- clinically expressed as cough, hemoptysis, dyspnea, and chest discomfort.

## **Eye involvement (52%)**

- mild conjunctivitis
- dacryocystitis
- Episcleritis
- scleritis
- granulomatous sclerouveitis.

# Pulmonary involvement - GPA

## Lung cavities in CXR



## Lung cavities in CT Scan



Source: Longo DL, Fauci AS, Kasper DL, Hauser SL, Jameson JL, Loscalzo J: *Harrison's Principles of Internal Medicine*, 18th Edition: [www.accessmedicine.com](http://www.accessmedicine.com)

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# Clinical and Laboratory Manifestations-GPA

## **Skin lesions (46%)**

- appear as papules, vesicles, palpable purpura, ulcers, or subcutaneous nodules;
- biopsy reveals vasculitis, granuloma, or both.

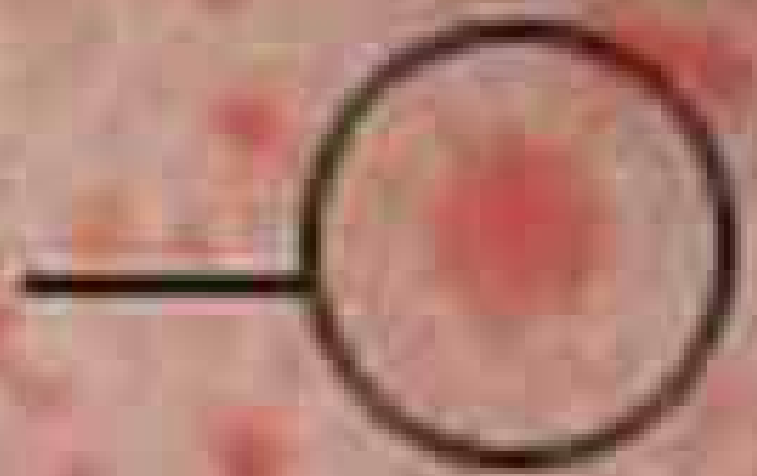
## **Cardiac involvement (8%)**

- pericarditis, coronary vasculitis, or, rarely, cardiomyopathy.

Petechiae



Purpura



# Clinical and Laboratory Manifestations-GPA

## **Nervous system (23%)**

- cranial neuritis, mononeuritis multiplex, or, rarely, cerebral vasculitis and/or granuloma

## **Renal disease (77% )**

- generally dominates the clinical picture and
- most of the mortality rate in this disease.
- mild glomerulitis with proteinuria, hematuria, and red blood cell casts
- rapidly progressive renal failure.

# Clinical and Laboratory Manifestations-GPA

## Nonspecific symptoms and signs

- Malaise, weakness, arthralgias, anorexia, and weight loss.
- Fever may indicate activity of the underlying disease **but** more often reflects secondary infection, usually of the upper airway

## laboratory findings - GPA

- markedly elevated ESR
- mild anemia and leukocytosis
- mild hypergammaglobulinemia (particularly of the IgA class)
- mildly elevated rheumatoid factor
- Thrombocytosis
- 90% have a positive antiproteinase-3 ANCA.

# Diagnosis- GPA

**necrotizing granulomatous vasculitis** on **tissue biopsy** in a patient with compatible clinical features.

**Pulmonary tissue** offers the highest diagnostic yield, almost invariably revealing granulomatous vasculitis.

Biopsy of **upper airway tissue** usually reveals granulomatous inflammation with necrosis but may not show vasculitis.

## Diagnosis - GPA

- **Renal biopsy** can confirm the presence of pauci-immune glomerulonephritis
- The **specificity** of a positive **antiproteinase-3 ANCA** for granulomatosis with polyangiitis (Wegener's) is very high, especially if active glomerulonephritis is present.
- However, the presence of ANCA should be **adjunctive** and, with rare exceptions, should not substitute for a tissue diagnosis



# **Eosinophilic Granulomatosis with Polyangiitis ( EGPA )**

## **Churg-Strauss Syndrome (CSS)**

## Definition & Epidemiology - EGPA

- asthma, peripheral and tissue eosinophilia, extravascular granuloma formation, and **vasculitis** of multiple organ systems.
- uncommon disease with an estimated annual incidence of **1–3 per million**.
- The disease can occur at **any age** with the possible exception of infants.
- The mean age of onset is **48 years**
- female-to-male ratio of **1.2:1**

## Pathology and Pathogenesis - EGPA

- The **necrotizing vasculitis** of Churg-Strauss syndrome involves small and medium-sized muscular arteries, capillaries, veins, and venules.
- A characteristic histopathologic feature of Churg-Strauss syndrome is **granulomatous reactions** that may be present in the tissues or even within the walls of the vessels themselves.
- These are usually associated with **infiltration of the tissues with eosinophils**.

# Clinical and Laboratory Manifestations - EGPA

- **Nonspecific manifestations** such as fever, malaise, anorexia, and weight loss, which are characteristic of a multisystem disease.
- The **pulmonary** findings in Churg-Strauss syndrome clearly dominate the clinical picture with **severe asthmatic attacks** and the presence of **pulmonary infiltrates**.
- **Mononeuritis multiplex** is the second most common manifestation and occurs in up to 72% of patients
- **Allergic rhinitis** and **sinusitis** develop in up to 61% of patients

# Clinical and Laboratory Manifestations - EGPA

- heart disease occurs in 14% of patients and is an important cause of **mortality**.
- Skin lesions occur in 51% of patients and include **purpura** in addition to **cutaneous and subcutaneous nodules**.
- The renal disease in Churg-Strauss syndrome is less common and generally less severe than that of granulomatosis with polyangiitis (Wegener's) and microscopic polyangiitis.

## Clinical and Laboratory Manifestations - EGPA

- laboratory finding eosinophilia, which reaches levels >1000 cells/L in >80% of patients
- Approximately 48% of patients with Churg-Strauss syndrome have circulating ANCA that is usually antimyeloperoxidase ( MPO )

# Diagnosis - EGPA

- **biopsy** in a patient with the characteristic clinical manifestations
- histologic confirmation can be challenging as the pathognomonic features often do not occur simultaneously.
- a patient should have evidence of **asthma, peripheral blood eosinophilia, and clinical features consistent with vasculitis**



# **Polyarteritis Nodosa ( PAN )**

# Definition & Epidemiology - PAN

- multisystem, necrotizing vasculitis
- small and medium-sized muscular arteries
- renal and visceral arteries is characteristic.
- PAN **does not** involve pulmonary arteries, although bronchial vessels may be involved;
- granulomas, significant eosinophilia, and an allergic diathesis **are not observed**.
- **very uncommon disease**

# Pathology and Pathogenesis - PAN

- involvement of venules **is not seen** in PAN and, if present, suggests microscopic polyangiitis .
- **Aneurysmal dilations** up to 1 cm in size along the involved arteries are characteristic of PAN.
- The pathology in the kidney in classic PAN is that of arteritis **without** glomerulonephritis.
- PAN associated with **Hepatitis B** and **Hairy cell Leukemia**

# Clinical and Laboratory Manifestations - PAN

- Nonspecific signs and symptoms are the **hallmarks** of PAN.
- **Fever, weight loss, and malaise** are present in over one-half of cases.
- **vague symptoms** such as weakness, malaise, headache, abdominal pain, and myalgias that can rapidly progress to a fulminant illness.
- hypertension, renal insufficiency, or hemorrhage due to microaneurysms.

# Clinical and Laboratory Manifestations - PAN

- No diagnostic serologic tests for PAN
- >75% Elevated leukocyte count/PMN
- anemia of chronic disease
- elevated ESR
- screening for hepatitis B.
- Antibodies against myeloperoxidase or proteinase-3 (ANCA) are rarely found in patients with PAN.

# Diagnosis

- The diagnosis of PAN is based on the demonstration of characteristic findings of vasculitis on **biopsy material of involved organs**.
- In the absence of easily accessible tissue for biopsy, the **arteriographic demonstration of involved vessels**, particularly in the form of **aneurysms of small and medium-sized arteries in the renal, hepatic, and visceral vasculature**, is sufficient to make the diagnosis.
- **Biopsy of symptomatic organs** such as nodular skin lesions, painful testes, and nerve/muscle provides the highest diagnostic yields.







# **Microscopic Polyangiitis ( MPA )**

# Definition & Epidemiology - MPA

- **Necrotizing vasculitis** with few or no immune complexes affecting **small vessels** (capillaries, venules, or arterioles).
- **Glomerulonephritis** is very common in microscopic polyangiitis
- **pulmonary capillaritis** often occurs.
- The absence of granulomatous inflammation differentiate it from granulomatosis with polyangiitis (Wegener's)
- The mean age of onset is **57 years** of age, and **males** are slightly more frequently affected than females

## Pathology and Pathogenesis - MPA

- involve **capillaries and venules** in addition to small and medium-sized arteries.
- **The renal lesion** seen in microscopic polyangiitis is identical to that of granulomatosis with polyangiitis (Wegener's).
- Like granulomatosis with polyangiitis (Wegener's), microscopic polyangiitis is highly associated with the presence of **ANCA**.

# Clinical and Laboratory Manifestations - MPA

- Because of its predilection to involve the small vessels, microscopic polyangiitis and granulomatosis with polyangiitis (Wegener's) **share similar clinical features**.
- Disease onset may be **gradual**
- **initial symptoms** of fever, weight loss, and musculoskeletal pain.
- **Glomerulonephritis** occurs in at least **79%** of patients and can be rapidly progressive, leading to **renal failure**.

## Clinical and Laboratory Manifestations - MPA

- **Hemoptysis** may be the first symptom of alveolar hemorrhage, which occurs in 12% of patients

Other manifestations include:

- mononeuritis multiplex
- gastrointestinal tract
- cutaneous vasculitis.

## Clinical and Laboratory Manifestations - MPA

- Upper airway disease and pulmonary nodules **are not typically found** in microscopic polyangiitis and, if present, suggest granulomatosis with polyangiitis (Wegener's).
- elevated ESR, anemia, leukocytosis, and thrombocytosis.
- **ANCA** are present in **75%** with **antimyeloperoxidase** antibodies being the predominant ANCA.



# **Takayasu's arteritis ( TAK )**

# Definition & Epidemiology - TAK

- medium- and large-sized arteries
- strong predilection for the aortic arch and its branches.
- uncommon disease
- annual incidence rate of 1.2–2.6 cases per million.
- It is most prevalent in adolescent girls and young women.
- it is more common in Asia

# Clinical and Laboratory Manifestations - TAK

- The **generalized symptoms** include malaise, fever, night sweats, arthralgias, anorexia, and weight loss, which may occur months before vessel involvement is apparent.
- **Pulses are commonly absent** in the involved vessels, particularly the **subclavian artery**.
- **Hypertension** occurs in 32–93% of patients and contributes to renal, cardiac, and cerebral injury.
- **laboratory findings** include an elevated ESR, mild anemia, and elevated immunoglobulin levels

# Diagnosis

should be suspected strongly in a young woman who develops a decrease or absence of peripheral pulses, discrepancies in blood pressure, and arterial bruits.

The diagnosis is confirmed by the characteristic pattern on arteriography:

- irregular vessel walls
- stenosis
- poststenotic dilation
- aneurysm formation
- occlusion
- increased collateral circulation





# **Giant Cell Arteritis (GCA) & Polymyalgia Rheumatica (PMR)**

## Definition

- Giant cell arteritis, also referred to as **cranial arteritis** or **temporal arteritis**, is an **inflammation of medium- and large-sized arteries**.
- It characteristically involves **one or more branches of the carotid artery**, particularly the **temporal artery**.
- However, it is a systemic disease that can involve arteries in multiple locations, particularly the **aorta and its main branches**.

- Giant cell arteritis is closely associated with **polymyalgia rheumatica**
- stiffness, aching, and pain in the muscles of the neck, shoulders, lower back, hips, and thighs.
- Most commonly, polymyalgia rheumatica occurs in isolation, but it may be seen in **40–50%** of patients with giant cell arteritis

## Epidemiology - GCA

- In addition, **10–20%** of patients who initially present with features of isolated polymyalgia rheumatica later go on to develop giant cell arteritis
- Giant cell arteritis occurs almost exclusively in **individuals >50 years**. It is more common in **women** than in men and **is rare in blacks**.
- The annual incidence rates in individuals 50 years range from **6.9 to 32.8 per 100,000** population
- **Pathology is the same as is in takayasu's arteritis.**

# Clinical and Laboratory Manifestations - GCA

Giant cell arteritis is most commonly characterized clinically by the complex of **fever, anemia, high ESR, and headaches in a patient over the age of 50 years.**

**features of systemic inflammation** including malaise, fatigue, anorexia, weight loss, sweats, arthralgias, polymyalgia rheumatica, or large-vessel disease.

In patients with involvement of the cranial arteries, **headache** is the predominant symptom and may be associated with a **tender, thickened, or nodular artery**, which may **pulsate** early in the disease but may become **occluded** later.



# Clinical and Laboratory Manifestations - GCA

- Scalp pain and claudication of the jaw and tongue may occur.
- in untreated patients, ischemic optic neuropathy, which may lead to serious visual symptoms, even sudden blindness in some patients.
- Manifestations of large-vessel disease can include subclavian artery stenosis that can present as arm claudication or aortic aneurysms

# Clinical and Laboratory Manifestations - GCA

- Characteristic **laboratory findings** in addition to the **elevated ESR** include a **normochromic or slightly hypochromic anemia**.
- Liver function abnormalities are common, particularly **increased alkaline phosphatase levels**.
- Increased levels of IgG and complement have been reported.

# Diagnosis

- can often be suggested clinically by the demonstration of the complex of fever, anemia, and high ESR with or without symptoms of polymyalgia rheumatica in a patient >50 years.
- The diagnosis is confirmed by biopsy of the temporal artery.
- Since involvement of the vessel may be segmental, positive yield is increased by obtaining a biopsy segment of 3–5 cm together with serial sectioning of biopsy specimens.

# Diagnosis

- **Ultrasonography** of the temporal artery has been reported to be helpful in diagnosis.
- A temporal artery biopsy should be obtained **as quickly as possible** in the setting of ocular signs and symptoms,
- under these circumstances **therapy should not be delayed pending a biopsy.**
- it has been reported that temporal artery biopsies may show vasculitis **even after 14 days of glucocorticoid therapy.**

# PMR

**Isolated polymyalgia rheumatica** is a clinical diagnosis made by the presence of:

- typical symptoms of stiffness, aching, and pain in the muscles of the hip and shoulder girdle,
- increased ESR
- the absence of clinical features suggestive of giant cell arteritis
- prompt therapeutic response to low-dose prednisone



IgA Vasculitis

( Henoch–Schönlein Purpura )

# Pathology - HSP

- The histopathologic features of IgAV (Henoch–Schönlein purpura) are leukocytoclastic vasculitis or necrotizing small-vessel vasculitis.
- The characteristic direct immunofluorescence finding is predominantly **IgA deposition** in affected blood vessels.
- Persons of any age can be affected, but IgAV occurs primarily in children between the ages of **2 and 10 years**.

## Clinical Manifestations - HSP

- The **classic tetrad** of **palpable purpura, arthritis, abdominal pain, and renal disease** occurs in up to 80% of cases.
- **The rash** may begin as macular erythema and urticarial lesions, but may progress rapidly to purpura.
- The lower extremities and buttocks are the most common sites for the rash .

# PALPABLE PURPURA



# Clinical Manifestations - HSP

- **The joint** involvement is symmetrical and most commonly involves the **ankles and knees**, which are usually swollen, warm, and tender.
- **GI lesions** may cause severe cramping, abdominal pain, intussusception, hemorrhage, and, rarely, ileal perforation.
- **Renal involvement** usually manifest as asymptomatic proteinuria and hematuria.



# **CRYOGLOBULINEMIA**

## Definition

Mixed cryoglobulinemia is an immune-complex mediated **small-vessel** vasculitis commonly associated with :

- Chronic **hepatitis C** virus infection
- Systemic autoimmune diseases (especially Sjögren's syn )
- Lymphoproliferative disorders

## Definition

**Cryoglobulins** are immunoglobulins or immunoglobulin-containing complexes that spontaneously precipitate from serum and plasma at low temperatures and become soluble again with rewarming .

## Clinical Manifestations

- Cutaneous

**Palpable purpura** is the most common manifestation, being seen in up to 100% of cases during the course of disease.

**Urticarial vasculitis** can also occur.

Lesions typically affect the **lower extremities**, but can involve the trunk and upper extremities.

# Clinical Manifestations

- **Renal**

Type 1 membranoproliferative glomerulonephritis is the most common histologic pattern (80% of cases).

- **Neurologic**

painful sensory polyneuropathy is the most common finding.

It can be symmetrical or asymmetrical  
insidious or abrupt in onset.

Motor involvement can also occur