

Vasculitis

4th year MBBS

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Consultant Rheumatologist

Case 1

- A 45 man presents with 3 wk hx of fever, fatigue, malaise, abdo pain and polyarthralgia. He noticed a rash on both legs & pain & weakness of L foot.
- O/E: temp 39, abdo tender diffusely. Livedo reticularis & palpable purpura on legs, L foot drop

Investigations

- Hb↓, platelets↑, ESR 95 ↑ ↑
- ANA, ANCA, hep B&C negative
- Abdo x ray normal
- Skin biopsy: non granulomatous necrotising vasculitis
- NCS: L common peroneal nerve lesion
- Abdo angio: microaneurysms & stenoses in mesenteric arteries.

Diagnosis??

Objectives

- Definition & Classification
- Epidemiology
- Manifestations & differential diagnosis
- Large vessel vasculitis
- ANCA associated vasculitis
- Medium vessel vasculitis
- Small vessel vasculitis
- Other

Vasculitis

- A heterogeneous group of disorders linked by the primary finding of inflammation within blood vessel walls.
- At least 20 forms of systemic vasculitis are recognized
- Uncommon
- Cause significant morbidity and mortality

Classified by the size of blood vessel involved:

- **Small vessel**
 - (capillaries and postcapillary venules)
- **Medium vessel**
 - (muscular arteries and arterioles)
- **Large vessel**
 - (the aorta and its major branches).

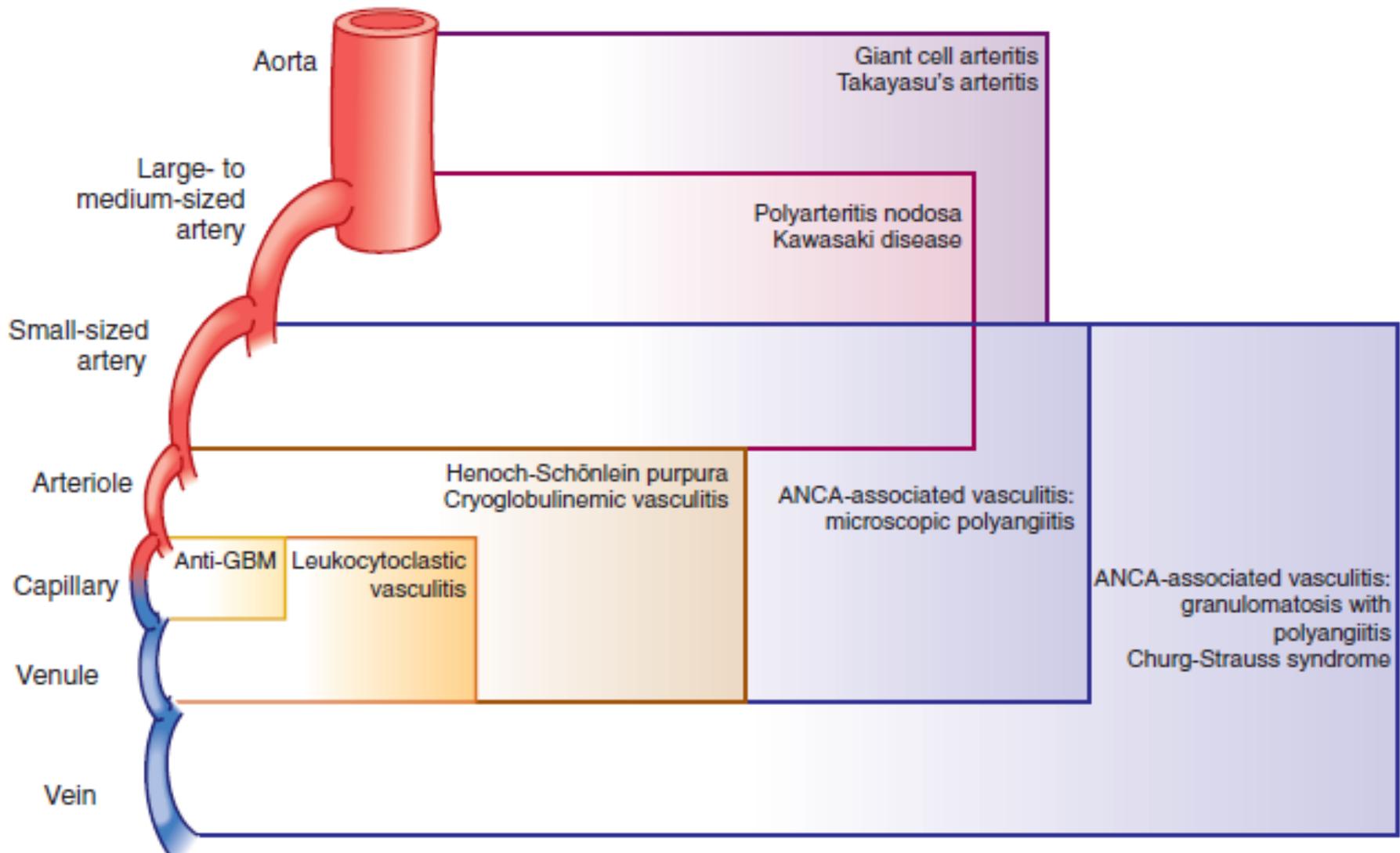
Vasculitis

- May be:
 - primary or
 - secondary

Dominant vessel involved	Primary	Secondary
Large arteries	Giant cell arteritis (GCA) Takayasu arteritis (TA)	Aortitis associated with RA Infection (e.g., syphilis, tuberculosis)
Medium arteries	Classical PAN Kawasaki disease	Hepatitis B virus associated PAN
Small vessels and medium arteries	Wegener's granulomatosis (WG) ^a Churg–Strauss syndrome (CSS) ^a Microscopic polyangiitis ^a	Vasculitis secondary to RA, SLE Sjögren's syndrome Drugs ^b Infection (e.g., HIV)
Small vessels (leukocytoclastic)	Henoch–Schönlein purpura (HSP) Cutaneous leukocytoclastic angiitis	Drugs ^c Infection Hepatitis C virus induced cryoglobulinemia

Drugs that may cause vasculitis:

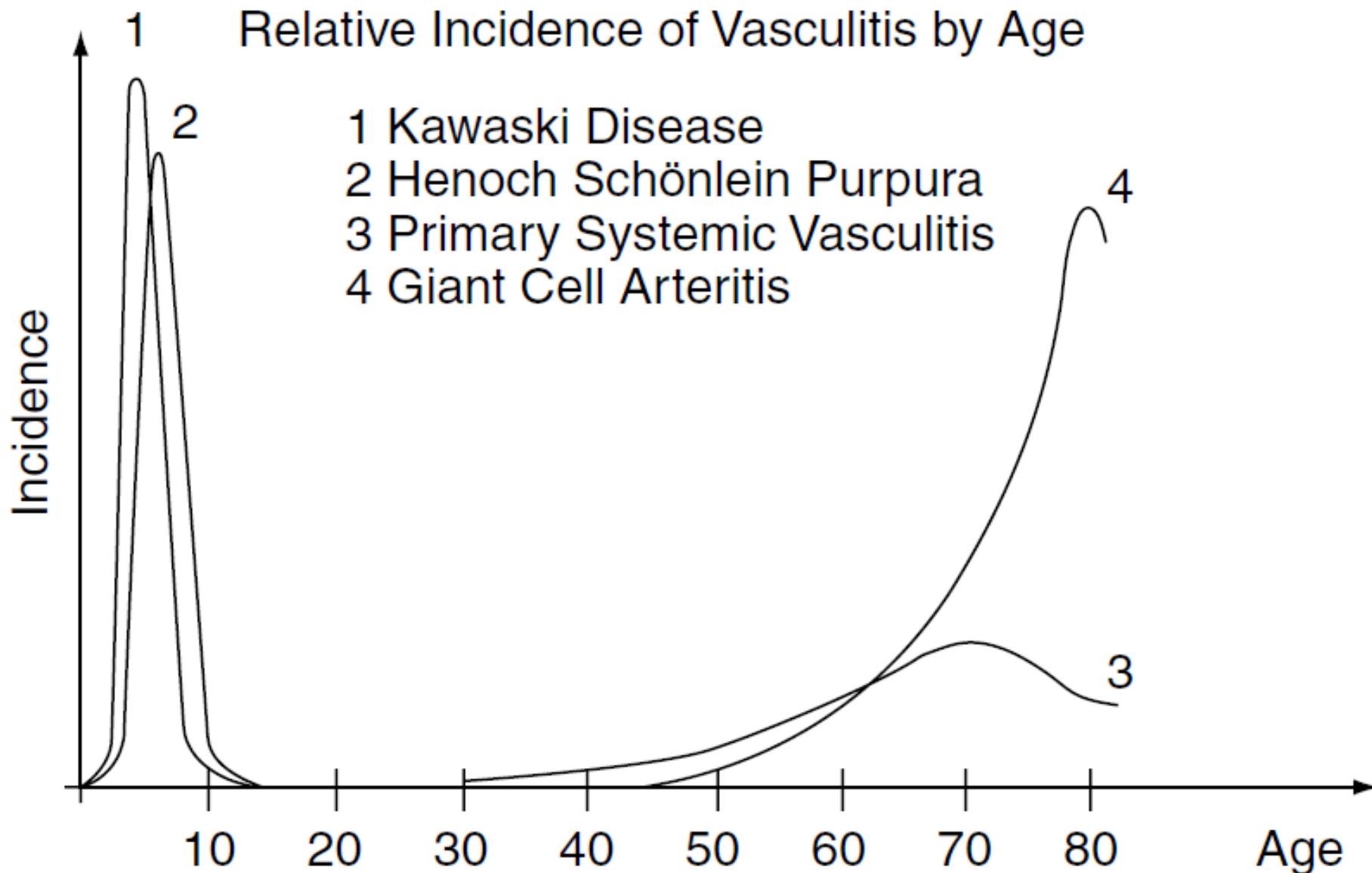
- **Prescribed**
 - Propylthiouracil
 - Hydralazine
 - Allopurinol
- **Abused**
 - Cocaine
 - Heroin
 - Amphetamine



Epidemiology

- Diseases of childhood or old age
- GCA most common Scandinavia and relatively uncommon in Africans and Japanese
- Takayasu more common in Japan
- AAV overall incidence (20/million/year)
- Cause unknown
- ? Environmental agent (unknown) in a genetically predisposed host

Relative Incidence of Vasculitis by Age



Typical clinical manifestations of large-, medium- and small-vessel involvement by vasculitis

Large	Medium	Small
Headache	Cutaneous nodules	Purpura
Limb claudication	Ulcers	Vesiculobullous lesions
Asymmetric blood pressures	abdominal pain	Urticaria
Absence of pulses	Livedo reticularis	Glomerulonephritis
Bruits	Digital gangrene	Alveolar hemorrhage
Aortic dilatation	Mononeuritis multiple	Cutaneous extravascular necrotizing granulomas
	Microaneurysms	Splinter hemorrhages
		Scleritis/episcleritis/uveitis

Constitutional symptoms: fever, weight loss, malaise, arthralgias/arthritis (common to vasculitides of all vessel sizes)

Clinical Features Suggesting Vasculitis

- Multisystem inflammatory disease
- Rapidly progressive major organ dysfunction
- Constitutional symptoms (fever, weight loss)
- Unexplained infarction in multiple vascular territories
- High ESR, severe anemia, thrombocytosis
- Evidence of small-vessel inflammation:
 - In the kidneys = active urinary sediment (RPGN)
 - In the lungs = hemoptysis, dyspnea (Diffuse alveolar hemorrhage)
 - In the skin = palpable purpura/hemorrhage
- Acute neurologic changes
 - Foot drop
 - Altered mental status

Differential diagnosis of vasculitis

Infection

- Bacterial endocarditis.
- Hepatitis B
- Hepatitis C
- HIV
- Occult abscess
- Syphilis

Malignancy

- Lymphoma
- Hodgkins disease.
- Hypernephroma
- Metastatic carcinoma
- Multiple myeloma Macroglobulinemia

Autoimmune disease

- Rheumatoid arthritis .
- Systemic lupus

Multiple emboli/, cholesterol emboli.

Drug allergy

Case 2

- A 48 year old man, IVDU, presented with a 4 week history of generally feeling unwell and purpuric rash over both legs. He looked ill, and there were several nail fold infarcts and vasculitic lesions over his fingers. Blood picture was in keeping with systemic inflammatory response. CXR showed cavitating lesions. Skin biopsy showed leucocytoclastic vasculitis. His illness was attributed to systemic vasculitis and specialist opinion was sought.

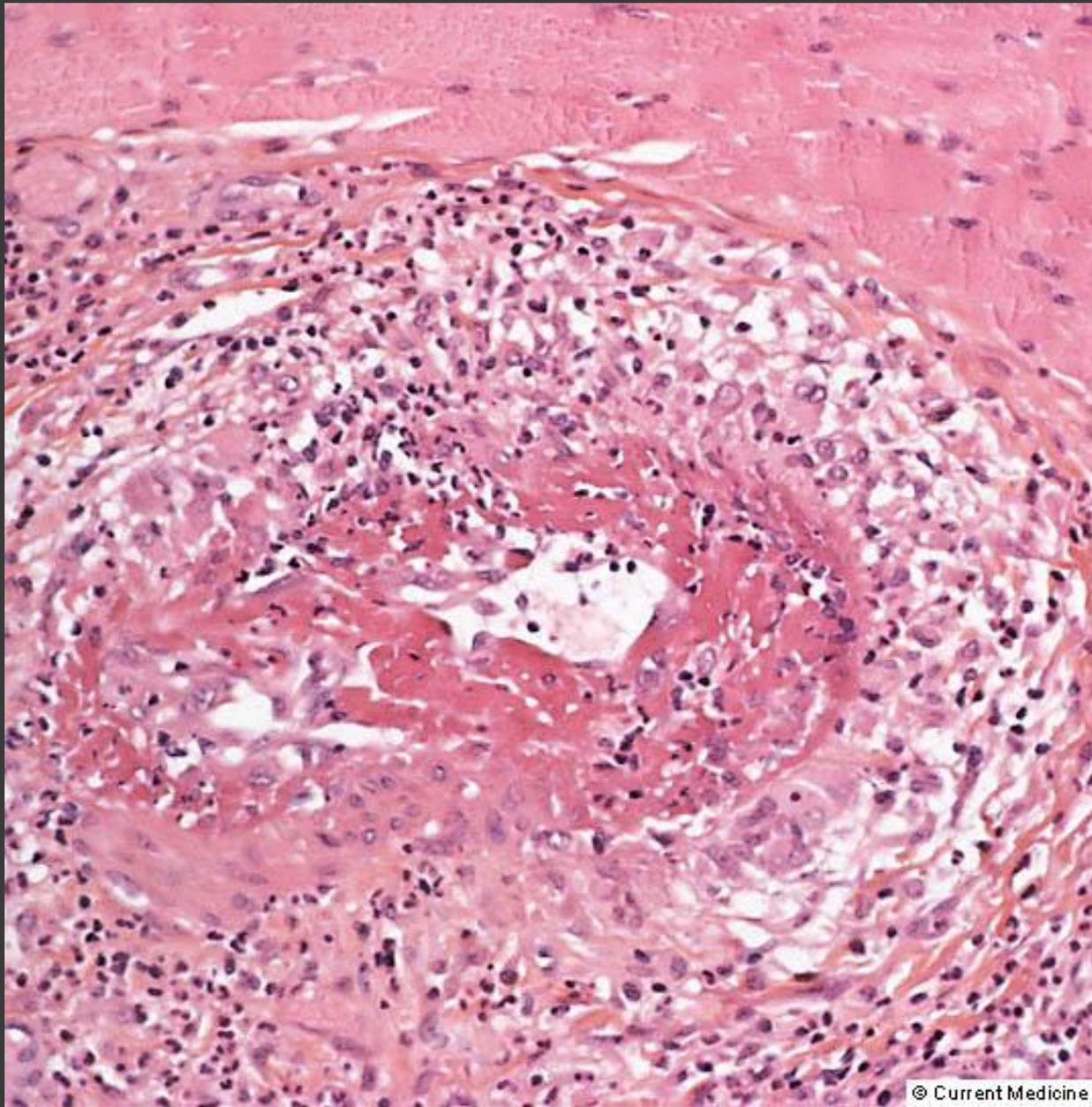


- Several days after admission serial blood cultures and echocardiogram were arranged. Blood cultures grew *Staphylococcus aureus* and TTE showed vegetations around the tricuspid valve consistent with right heart endocarditis. The cavitating lesions were lung abscesses secondary to septic emboli.



Because treatment of vasculitis entails the use of immunosuppressive drugs, the consequences of not recognising infection would be disastrous.

Thus, it is mandatory to perform a full infection screen in all patients with suspected vasculitis



Large vessel vasculitis

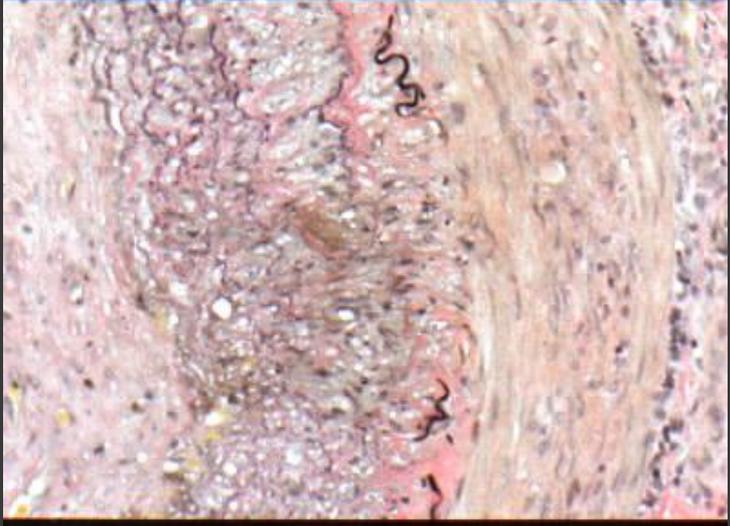
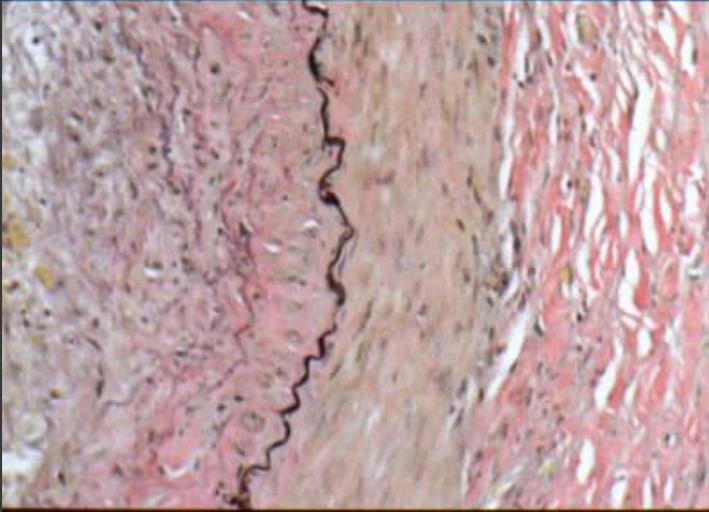
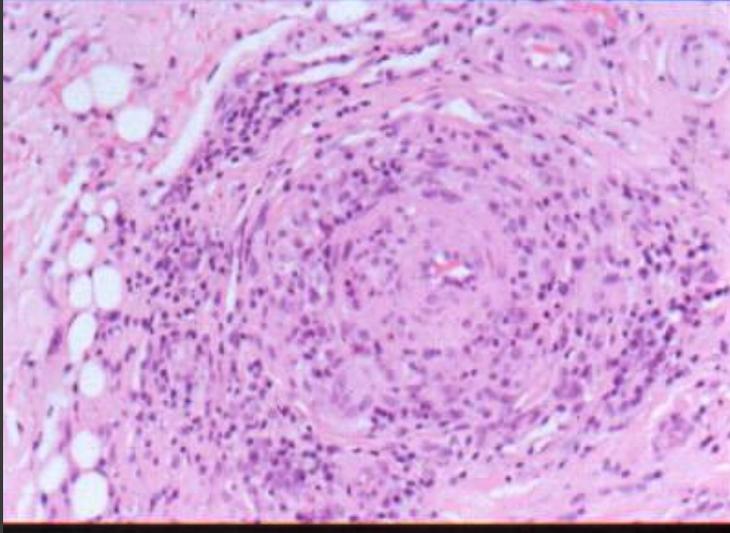
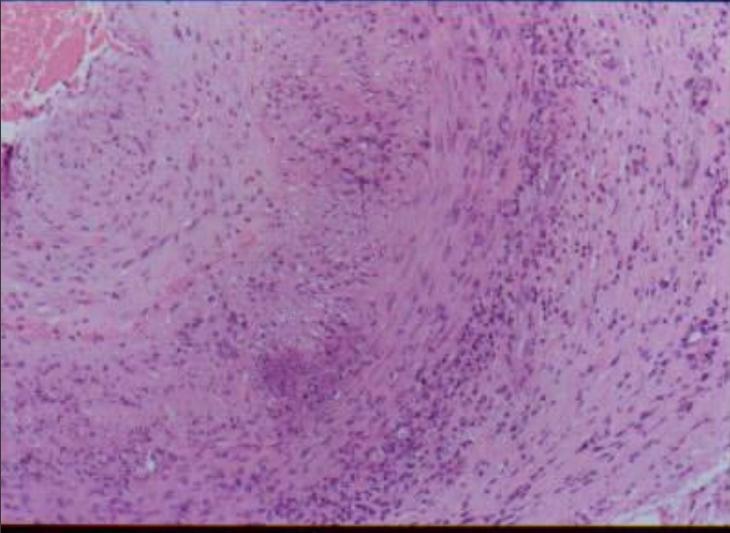
Giant cell arteritis (GCA)

- Rare under age 50
- Headache: temporal / occipital
- Scalp tenderness
- ? Thickened, nodular, tender TA
- ? ↓ / absent TA pulse
- Jaw claudication: **internal maxillary artery**
- Tingling tongue: **lingual artery**
- Amaurosis fugax
- Unilateral permanent loss of vision → other eye affected within 1-2 wks
(**ophthalmic & posterior ciliary arteries**)

GCA

- **Diagnosis**
 - 1. Normocytic anaemia
 - 2. High ESR & CRP
 - 3. Temporal artery biopsy: skip lesions common
- **Complication**: sudden loss of vision if untreated
- **Treatment**: Steroids (good response)

GCA



Polymyalgia Rheumatica (PMR)

- Closely associated with GCA
- May be seen in 40–50% of patients With GCA
- Pain and stiffness in shoulder and pelvic girdles worse in morning
- Good response to steroids

Takayasu's Arteritis

- Affects young people <40
- Characterized by stenosis, occlusion, and sometimes aneurysm formation of large arteries
- Commonest in Asia, the Middle East and South America
- F:M = 9:1
- No autoantibodies

Takayasu's Arteritis

Clinical Features

- 3 phases:

1. **Systemic phase:**

- Fatigue, weight loss, night sweats, fever, arthralgia, and myalgia

2. **Vascular phase:**

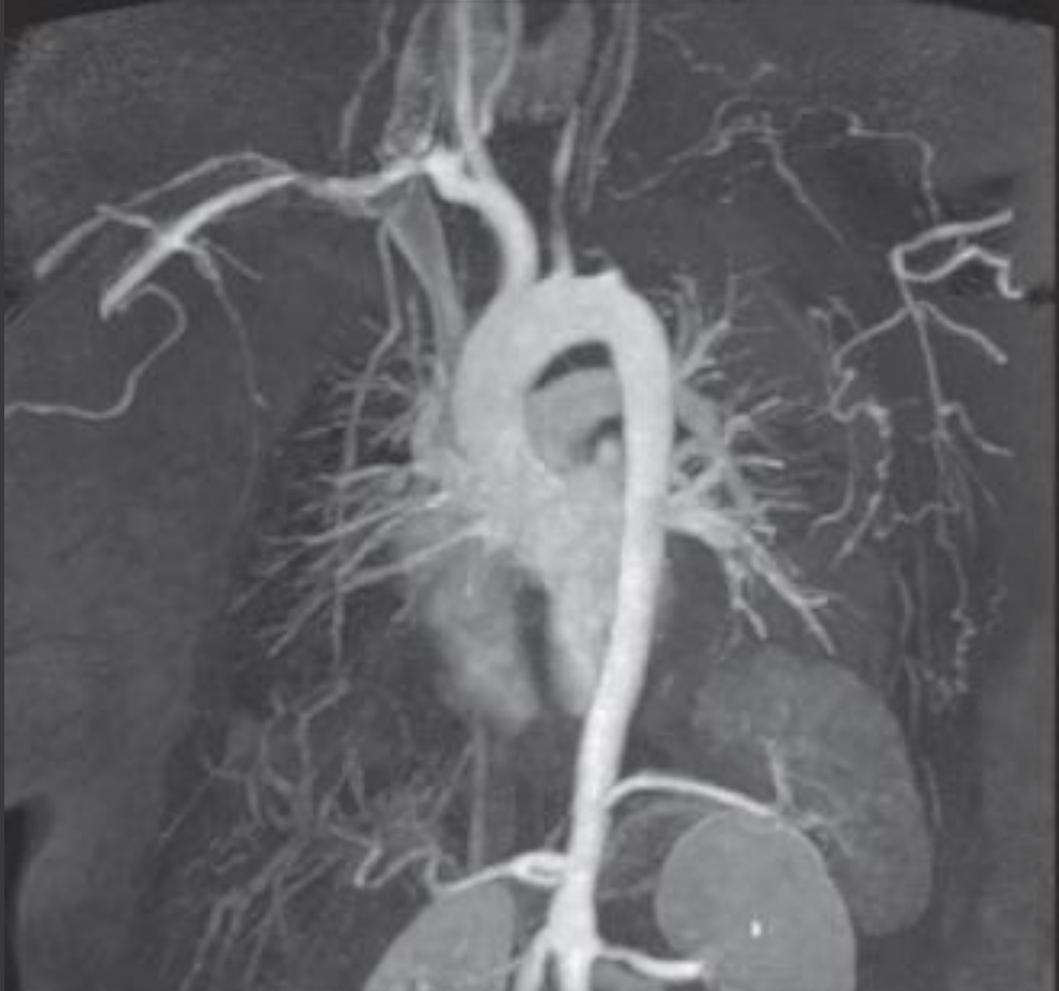
- asymmetry of peripheral pulses
- claudication of arm or legs
- transient visual disturbance, scotoma, blurring, or diplopia

3. **Burnt-out pulseless phase**

Takayasu's Arteritis: Examination

- Diminished or absent pulses
- Bruits
- Asymmetric blood pressure between extremities
- Carotidynia
- Hypertension

Takayasu's Arteritis: radiology



18F-fluorodeoxyglucose positron emission tomography (18F-FDG-PET)



18F-FDG is taken up by metabolically active cells including at sites of inflammation. Uptake can be visualized in the walls of inflamed large vessels

Takayasu's Arteritis: Treatment

- High-dose oral prednisolone at 0.5–1 mg/kg
- Steroid-sparing agents: Azathioprine, methotrexate
- Surgery

ANCA associated vasculitides

ANCA Associated Vasculitides (AAV)

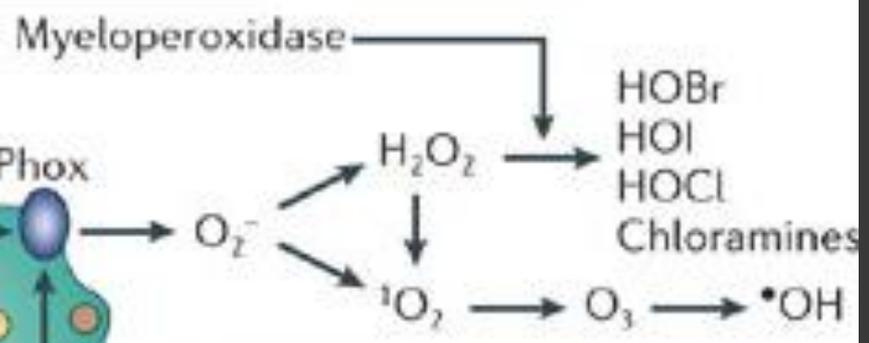
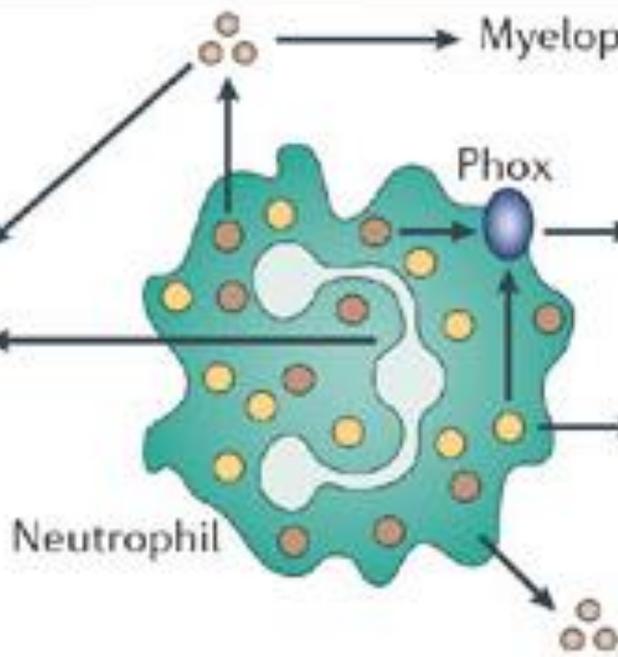
1. Microscopic polyangiitis (MPA)
2. Granulomatosis with polyangiitis (GPA, formerly Wegener's)
3. Eosinophilic granulomatosis with polyangiitis (EGPA, formerly Churg-Strauss)

Antineutrophil Cytoplasmic Antibodies (ANCA)

- Antibodies against azurophilic granules in neutrophils
- 2 types:
 - Cytoplasmic (cANCA): against proteinase 3. specific for Wegener's
 - Perinuclear (pANCA): against myeloperoxidase. Occur in CSS & MPA
- pANCA in diseases other than primary vasculitis in directed against other antigens (elastase, lactoferrin, cathepsin G)

Azurophilic (also known as primary) granules:
BPI, neutrophil elastase, cathepsin G, protease 3, azurocidin, myeloperoxidase

Nets that trap bacteria and neutrophil elastase

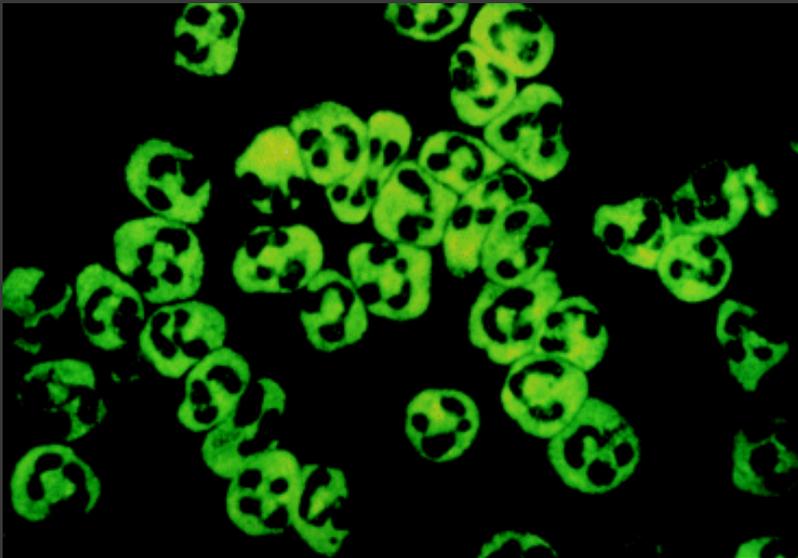


Specific and tertiary granules:
Lactoferrin, lipocalin, lysozyme, LL37, MMP8, MMP9 and MMP25

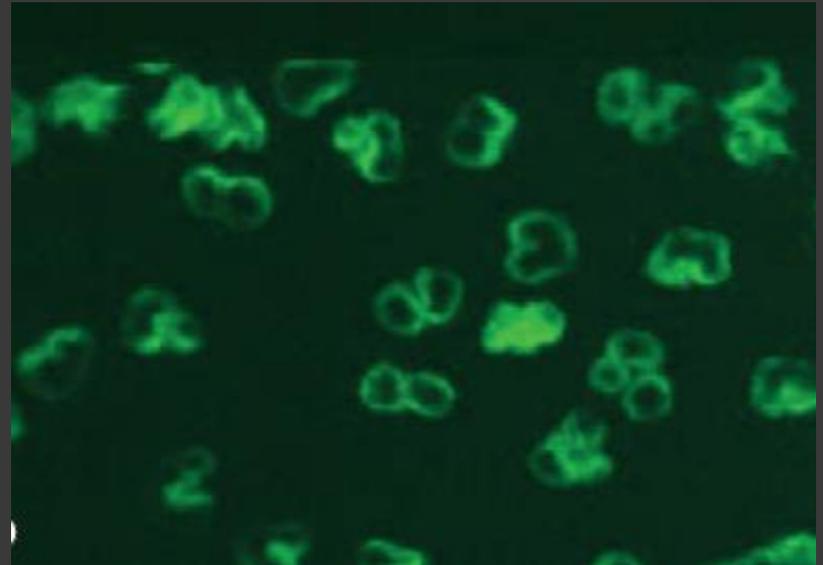
Calprotectin

ANCA

cANCA



pANCA



Microscopic Polyangiitis (MPA)

- Presents:
 - acutely with renal disease → RPGN, or
 - Pulmonary-renal syndrome
- Affect small vessels (arterioles, venules, capillaries)
- pANCA directed against MPO

Pulmonary haemorrhage in MPA



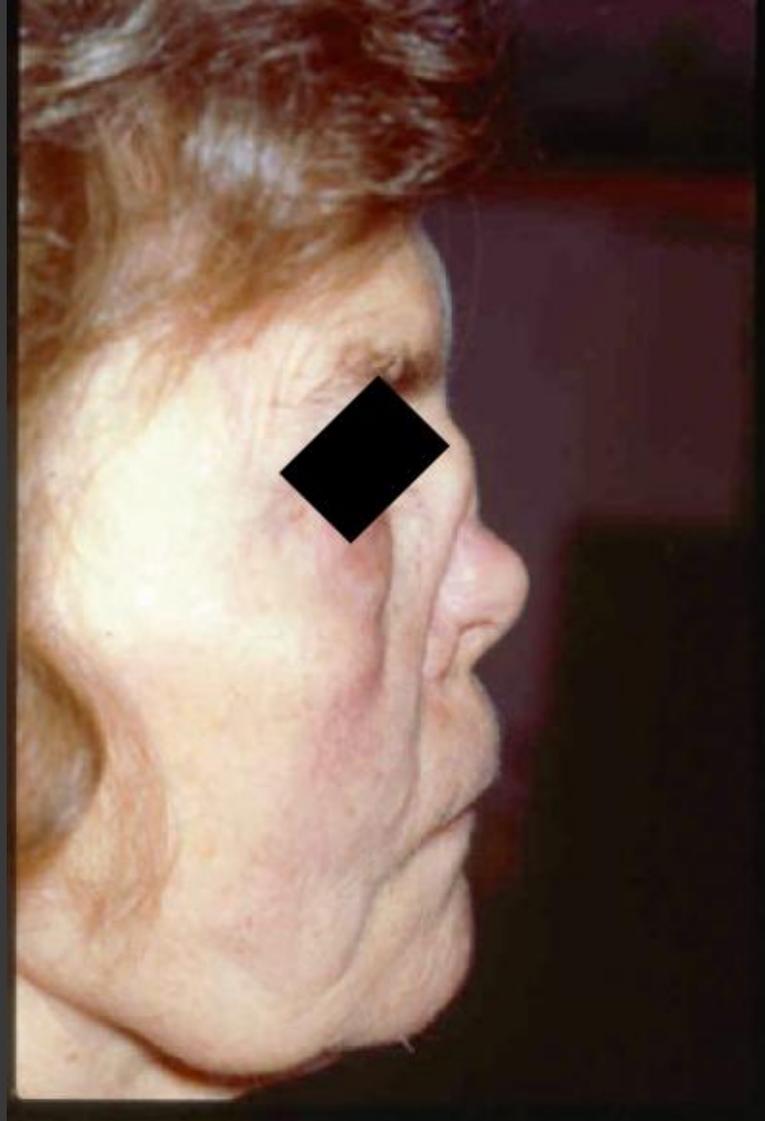
Granulomatosis with polyangiitis (GPA, formerly Wegener's)

- Granulomatous necrotising vasculitis affecting small to medium vessels
- Affects ENT, kidney & lung
- ANCA in >90% (mostly cANCA)
- 10/million/year
- Aetiology unknown

GPA features

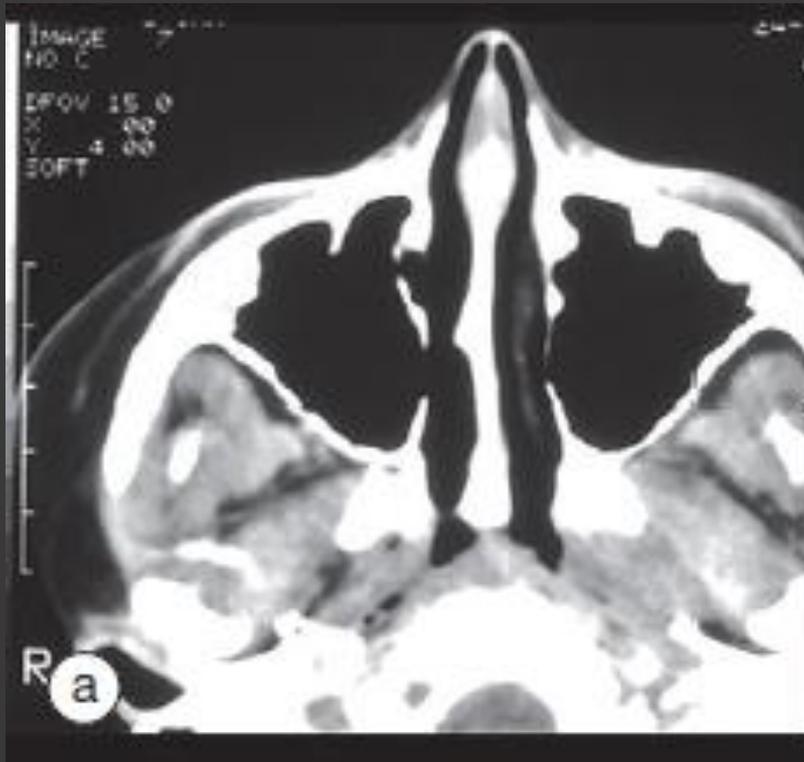
- **Systemic**: Fever, weight loss, myalgia, and arthralgia
- **Lung**: haemoptysis, dyspnoea
- **Skin**: purpura
- **ENT**: epistaxis, nasal crusting, sinusitis. nasal collapse
- **GI**: vasculitis
- **Neuro**: neuropathy
- **Renal**: RPGN (Paucimmune, crescentic)
- **Eye**: scleritis, proptosis due to retro-orbital mass

Saddle-nose in WG



Normal

GPA/Wegener's



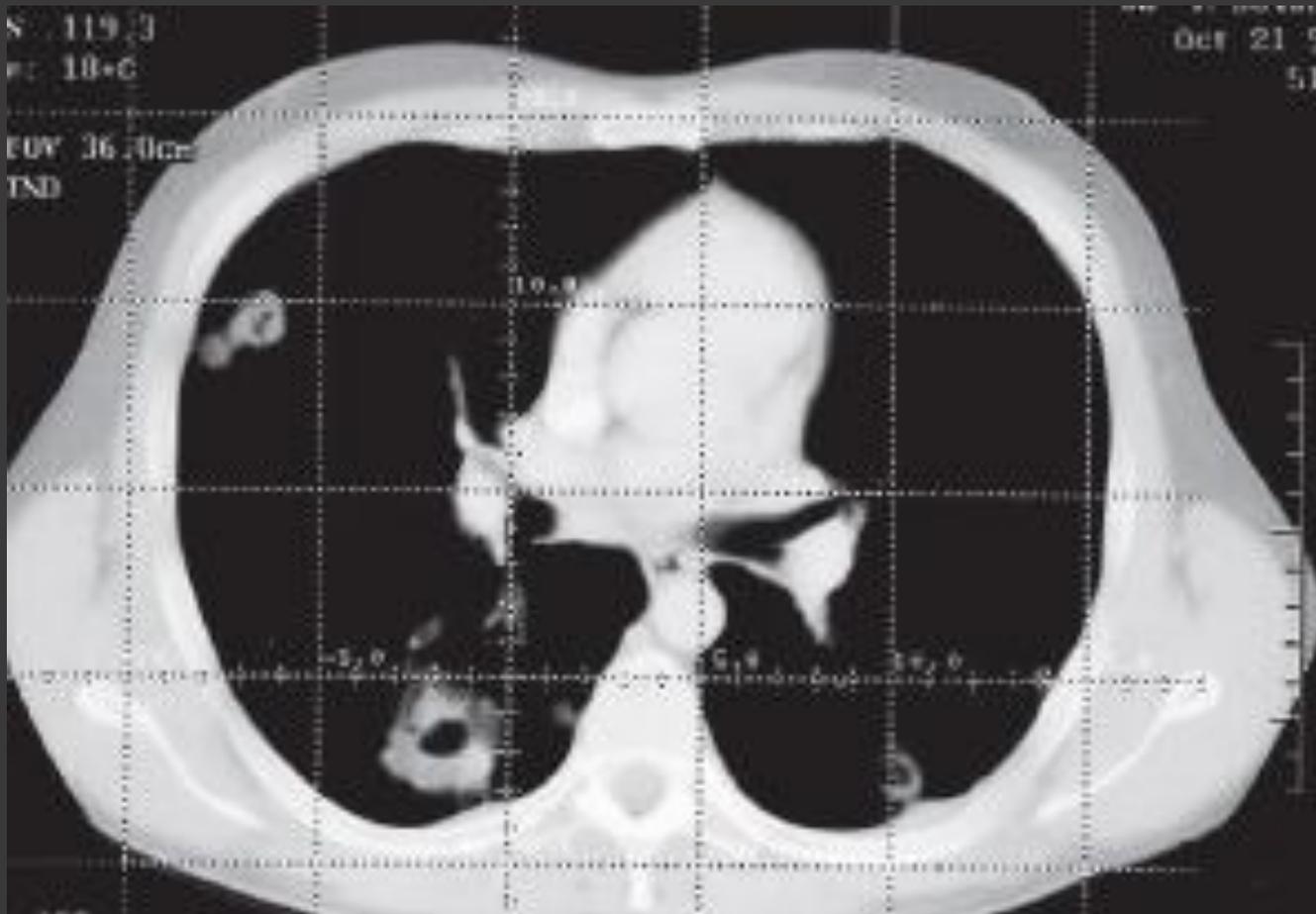
Exophthalmos due to orbital pseudotumors



Intractable pain and loss of vision
Refractory to therapy

WG: Left orbital mass causing proptosis and visual loss through compression of the optic nerve





Multiple bilateral pulmonary nodules, many of which have cavitated.

Eosinophilic granulomatosis with polyangiitis (EGPA, formerly Churg-Strauss)

- Eosinophil-rich granulomatous inflammation involving the respiratory tract, & necrotizing vasculitis affecting small to medium-sized vessels, associated with asthma & eosinophilia
- Cardiac involvement common: The principal cause of morbidity and mortality and accounts for 50% of deaths
- pANCA
- eosinophil count is useful in monitoring dis activity

EGPA: 3 phases

1. Prodromal phase

- may last for years: asthma, atopic features (e.g., allergic rhinitis, nasal polyposis).

2. Eosinophilic phase

- Peripheral blood eosinophilia and eosinophilic tissue infiltration of lung and GI tract.

3. Vasculitic phase

- The most severe phase: may only become apparent several years after prodromal phase.
- Malaise, lethargy, weight loss, fevers & vasculitis

Treatment of ANCA associated vasculitis

- Induction:
 - IV steroids +
 - IV cyclophosphamide OR rituximab
- Maintenance :
 - Oral steroids +
 - Oral MTX or azathioprine

Medium Vessel Vasculitis

Polyarteritis nodosa (PAN)

- A multisystem, necrotizing vasculitis of small- and medium-sized muscular arteries
- Involvement of the renal and visceral arteries is characteristic.
- *PAN does not involve lungs*
- No ANCA association
- Hepatitis B in 10-30%

PAN

CLINICAL MANIFESTATIONS RELATED TO ORGAN SYSTEM INVOLVEMENT IN CLASSIC POLYARTERITIS NODOSA

ORGAN SYSTEM	PERCENT INCIDENCE	CLINICAL MANIFESTATIONS
Renal	60	Renal failure, hypertension
Musculoskeletal	64	Arthritis, arthralgia, myalgia
Peripheral nervous system	51	Peripheral neuropathy, mononeuritis multiplex
Gastrointestinal tract	44	Abdominal pain, nausea and vomiting, bleeding, bowel infarction and perforation, cholecystitis, hepatic infarction, pancreatic infarction
Skin	43	Rash, purpura, nodules, cutaneous infarcts, livedo reticularis, Raynaud's phenomenon
Cardiac	36	Congestive heart failure, myocardial infarction, pericarditis
Genitourinary	25	Testicular, ovarian, or epididymal pain
Central nervous system	23	Cerebral vascular accident, altered mental status, seizure

Digital tip infarction in polyarteritis nodosa



Livedo reticularis in polyarteritis nodosa



Angiogram showing microaneurysms in polyarteritis nodosa



Mononuritis multiplex



Small Vessel Vasculitis

Hypersensitivity Vasculitis

Primary or secondary

Immune complex

Most common form of vasculitis.

Histology- leukocytoclastic vasculitis.

Almost invariably involves skin:-palpable purpura

Visceral involvement is infrequent , mild

Alveolar hemorrhage

Intestinal ischemia or hemorrhage

Glomerulonephritis.

Secondary:-

Autoimmune disease

Drugs.

Infection.

Allergy

Hematologic



Hypersensitivity vasculitis/ IgA vasculitis (HSP)

- Vasculitis with IgA-dominant immune deposits affecting small vessels
- Age at onset <20 years (majority <10)
- The most common vasculitis in children
- Follows upper respiratory infection
- involves alternate complement pathway & therefore C3 & C4 are normal

HSP: Clinical features

- Purpuric rash on legs & buttocks
- Colicky abdo pain
- Melaena
- Arthralgia: transient and self-limiting
- Haematuria & proteinuria
- Sometimes focal or diffuse proliferative glomerulonephritis develops
- Sometimes intussusception develops

HSP

- **Diagnosis:**
 - Skin biopsy: leucocytoclastic vasculitis
 - Immunofluorescence: IgA deposits
- **Treatment:** none
- Most have a self-limiting disease & settle within 2–3 weeks
- <5% of children develop chronic renal failure
- Renal failure is more common in adults

Henoch-Schönlein purpura (HSP)



Cryoglobulinaemia

- Cryoglobulins: immunoglobulins that precipitate at temperatures $<37^{\circ}$ C and redissolve on rewarming
- Associated with Hepatitis C virus infection
- Affects skin, kidneys & nerves
- Immune complex mediated
- Investigations:
 - Cryoglobulins
 - High RF
 - Low C4
 - Hep C serology

Cryoglobulinaemia: Clinical features

- Purpura
- Joint pain
- Raynaud's
- Neuropathy
- Renal: membranoproliferative GN

Cryoglobulinaemia: Treatment

- Interferon alpha + ribavirin + rituximab
- Plasma exchange for severe cases to remove cryoglobulins

Other

Behcet's disease

- Common along the silk route
- HLA-B51 association
- **Recurrent oral ulceration plus two of the following:**
 - Recurrent genital ulceration
 - Eye lesions
 - Skin lesions
 - Pathergy test
- Oral ulcers heal without scarring
- Genital ulcers leave scars
- No confirmatory blood or histological test, diagnosis clinical

Behcet

Oral ulcers



Behcet skin lesions

Genital ulcers



Acneiform lesions



Erythema nodosum-
like



Superficial thrombophlebitis



Pathergy



Behcet

Eye lesions



Anterior uveitis & hypopyon

Vascular manifestations of Behcet's

- **Arterial**

- Aortic aneurysm
- Carotid aneurysm
- Pulmonary aneurysm

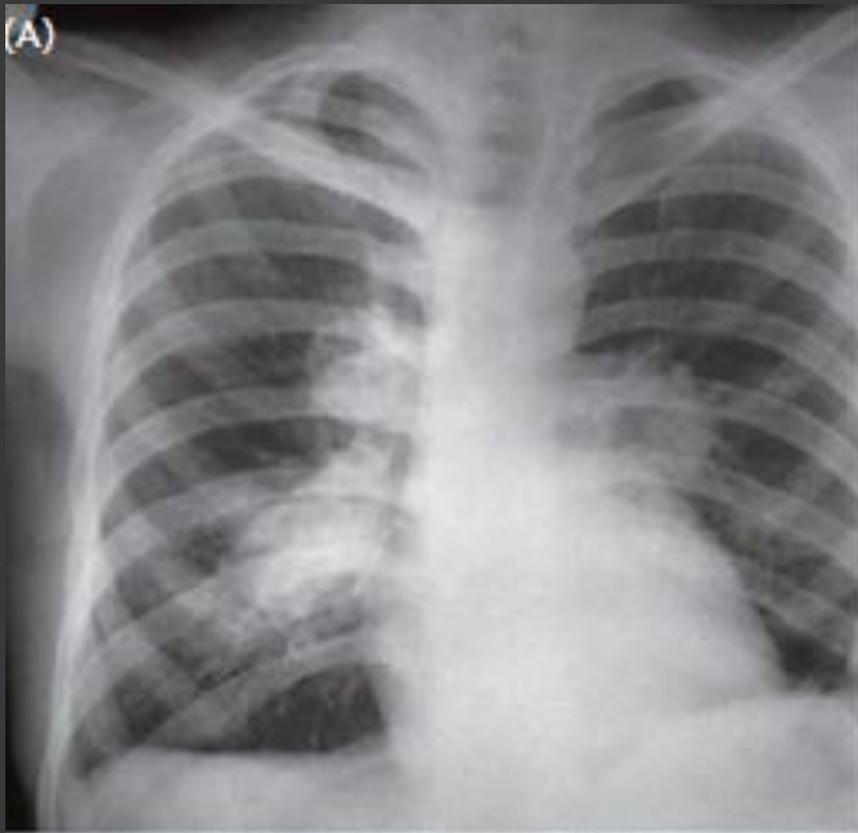
- **Venous**

- superficial venous thrombosis
- DVT
- Vena cava thrombosis
- Cerebral venous thrombosis
- Budd-Chiari syndrome
- Portal vein thrombosis

Carotid aneurysm



Pulmonary artery aneurysm



Behcet: Nervous system involvement

1. Brainstem or corticospinal tract syndromes (neuro-Behçet's syndrome)
2. Venous sinus thrombosis
3. Aseptic meningitis
4. Isolated behavioral symptoms, or isolated headache
5. Cranial and Peripheral neuropathy
6. Optic neuritis
7. Vestibular involvement
 - Poor prognosis is associated with a progressive course, parenchymal or brainstem involvement, and cerebrospinal fluid abnormalities

Behcet's Treatment

Depends on manifestations

- **Oral lesions:**
 - Colchicine
 - Azathioprine
 - Thalidomide
- **Arthritis:**
 - Colchicine
- **Eye:**
 - Steroids
 - Azathioprine
 - Interferon alpha
 - MMF
 - Infliximab
 - Rituximab
- **Vasculopathy:**
 - Steroids & cyclophosphamide
- **Neurological:**
 - Steroids
 - Interferon alpha
 - Anti-TNF

Last Case

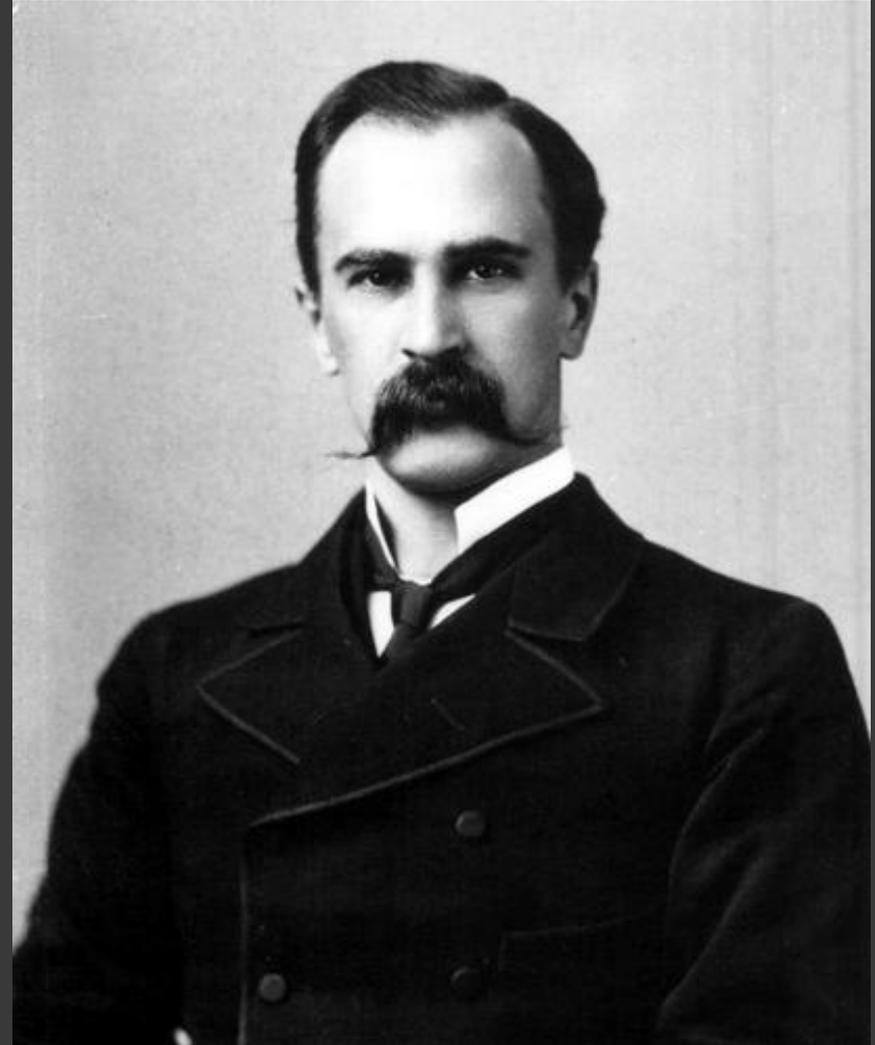
- A 52-year-old woman has had arthralgias and occasional purple spots on her legs for several years. She now presents with florid small, nonblanchable, palpable lesions on her legs and black fingers and obvious synovitis of multiple small joints. Some of the skin lesions have centers of necrosis. Radiographs of the hands and wrists show no erosions. In the past, she has been diagnosed at different times with RA and SLE, because of markedly positive RF, ANA, low C4, but normal C3 and Raynaud's. 30 years ago, she had a complicated but safe delivery of her only pregnancy, a breech presentation, which necessitated the transfusion of multiple units of blood.





- What further investigations
- What s the diagnosis?

He who studies
medicine without
books sails an
uncharted sea, but
he who studies
medicine without
patients does NOT
go to sea at all



Questions?

Vasculitis pearls

1. GCA is the most common vasculitis
2. Secondary vasculitis is more common than primary vasculitis
3. In GPA, the lung infiltrates are fixed, in EGPA, they are not fixed
4. renal and lung involvement is a negative prognostic factors in GPA or MPA
5. in EGPA most deaths occur from cardiac involvement.

6. Medium to small vessel respond to steroids + immunosuppressives
7. Large vessel respond to high dose steroids
8. Small vessel respond to low dose steroids
9. The appearance of active urinary sediment or rise in serum Cr in vasculitis is an indication for prompt aggressive treatment
10. Urinalysis is the most important investigation as prognosis is determined by the extent of renal involvement