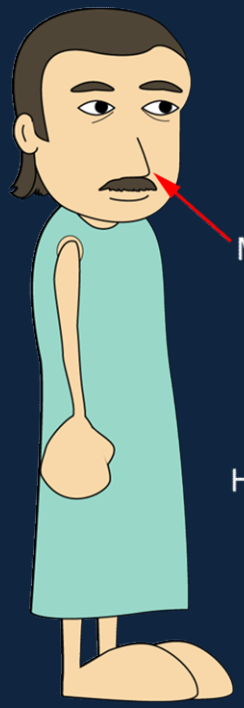
Recurrent sinusitis and dyspnea in a patient with microscopic hematuria

A 40 year old man presents with **recurrent sinusitis** for 2 years, associated with a bloody nasal discharge, **intermittent cough and breathlessness**. The response to antihistamines and antibiotics was poor. His medical and surgical histories are unremarkable and he is currently not on any medications. His full blood count shows a **Hb level of 10.1 g/dL**, and a leukocyte count of 13,500, with 85% neutrophils. His **ESR is 110 mm** in the first hour.



Afebrile
No lymphadenopathy

Multiple nasal polyps noted

Heart, lungs and abdomen:
No abnormalities

Select Relevant Investigations

♦ **Chest X-Ray**

*There is a **nodular pulmonary lesion** measuring ~3 cm in diameter in the upper lobe of the left lung. Multiple small nodular lesions are also seen in the right upper lobe. There is no evidence of hilar or mediastinal lymphadenopathy.*

♦ **Urinalysis**

*There is **microscopic hematuria** with **red cell casts** and **proteinuria**.*

♦ **Autoimmune Screen**

***c-ANCA: elevated** (1:64 titre)*
p-ANCA: negative
Anti-GBM Abs: negative
ANA, C3, C4: within normal ranges

♦ **Lung Biopsy**

*Biopsy of lesion in the left upper lobe reveals **granulomatous inflammation** accompanied by an inflammatory infiltrate, vasculitis, and parenchymal necrosis.*

Select Relevant Management

- **Corticosteroids**
- Resection of nodules
- Antituberculous therapy
- Radiotherapy

Diagnosis and reasoning

This middle aged gentleman has presented with a mix of upper and lower respiratory tract symptoms.

His examination is significant only for multiple nasal polyps, a non-specific finding which might just be due to chronic inflammation.

In the majority of such patients, these clinical findings are usually due to benign causes - most often asthma combined with rhinosinusitis.

However, this patient's basic investigations show several anomalies: mild anemia, neutrophilia, and, very importantly, a significantly elevated ESR. These findings suggest that a more sinister cause may be at play.

The differential diagnosis for an elevated ESR in conjunction with mixed upper and lower respiratory symptoms is quite broad. However, in practice, the causative etiologies can be classified into three main categories:

- Small vessel vasculitides (such as Wegener's granulomatosis, Churg-Strauss syndrome, and microscopic polyangiitis);
- Connective tissue disorders such as Sjogren's syndrome;
- Immunodeficiencies such as HIV/AIDS.

A careful history and examination and targeted investigations are crucial in differentiating between the above.

Wegener's Granulomatosis (WG) is well known to present in this manner and is a key diagnosis to keep in mind.

Churg-Strauss syndrome typically presents with asthma and peripheral blood eosinophilia, making this diagnosis less likely. Microscopic polyangiitis rarely manifests as otorhinolaryngologic disease.

The lack of musculoskeletal and skin manifestations (which are common presenting features of connective tissue diseases), makes this group of conditions less likely.

Immunodeficiencies are almost impossible to exclude on clinical grounds alone.

A chest x-ray is a good first step in his workup; this shows nodular pulmonary lesions in both lung fields. Considering the clinical context, these could very likely be granulomata (i.e. WG).

Simultaneous pulmonary and renal disease is common in WG - thus, urinalysis is a good next investigation. This reveals an active sediment suggestive of glomerulonephritis.

Given the strong suspicion of Wegener's Granulomatosis, the step after this should probably be an autoimmune assay; the presence of cytoplasmic antineutrophil cytoplasmic antibodies (c-ANCA) is almost confirmatory.

However, a tissue sample is required for definitive diagnosis (ΔΔ cancer), necessitating a lung biopsy. This reveals characteristic histological features of Wegener's Granulomatosis, confirming the diagnosis.

Corticosteroids and immunosuppressive therapy form the mainstay of treatment in these patients.

Note that resection of pulmonary nodules, antituberculous therapy, and radiotherapy are of no use these individuals.

Discussion

Wegener's granulomatosis (WG) is a rare ANCA (antineutrophil cytoplasmic antibodies) associated systemic vasculitis characterized by involvement of the upper and lower respiratory tract and glomerulonephritis.

The peak incidence of WG is in the fourth decade of life, although it can also present at any age; The condition is slightly more common in males.

Upper respiratory tract disease is the most common presenting feature in these patients. This includes sinusitis, epistaxis, rhinorrhea, otitis, hearing impairment and destructive lesions that might lead to saddle-nose deformity.

Pulmonary symptoms include cough, hemoptysis, chest pain and dyspnea. Diffuse alveolar hemorrhage and subglottic stenosis are other well known manifestations of WG.

Many patients ultimately develop renal disease, but this is less common than respiratory tract involvement at the initial presentation.

Constitutional symptoms such as fever, malaise and weight loss are often seen at the initial presentation. Vasculitis may also involve the musculoskeletal system, skin, nervous system and the coronary vessels.

The chest x-ray is frequently abnormal in these patients; this may demonstrate alveolar or interstitial infiltrates and nodular or cavitary disease.

Serum c-ANCA (anti-proteinase-3 ANCA) is found in most patients, and is highly sensitive (90% to 95%) and specific (90%) in detection of active systemic WG. Note however that c-ANCA alone is not sufficient to confirm or exclude the diagnosis.

Tissue biopsy from an affected site provides a definitive diagnosis; when the lung is affected thoracoscopic or open lung biopsy almost always confirms the diagnosis. A renal biopsy may be considered if the kidney is involved; note that while biopsies of the upper respiratory tract (i.e. sinuses) may also be obtained, their diagnostic yield is often very poor.

The treatment of WG has 3 phases; remission induction, maintenance of remission and treatment of relapse. The intensity of the initial treatment depends on the severity of the disease.

Induction of remission is usually with corticosteroids and cyclophosphamide. Other agents that are used in the management include azathioprine, methotrexate, plasma exchange and intravenous immunoglobulin.

Patients should be monitored during treatment for the development of drug toxicity, infection or disease relapse.

Poor prognostic factors include advanced age, more severe renal impairment and alveolar hemorrhage.

Take home messages:
1. Upper respiratory tract disease is the most common presenting feature in Wegener's granulomatosis.
2. Many patients ultimately develop renal disease, but this is less common than respiratory tract involvement at the initial presentation.
3. Tissue biopsy from an affected site provides a definitive diagnosis.

Vasculitis

Prevalence: 50 cases per 1 million persons

Vasculitis is defined as an inflammatory disorder of blood vessel walls, causing destruction (aneurysm/rupture) or stenosis. It can affect the vessels of any organ, and presentation depends on which organs are involved. It may be a primary condition or secondary to other diseases, eg SLE, RA, hepatitis B & C, HIV. It is categorized according to the main size of blood vessel affected:

- *Large:* Giant cell arteritis, Takayasu's arteritis (see p726).
- *Medium:* Polyarteritis nodosa, Kawasaki disease (*OHCS* p646).
- *Small:* •ANCA +ve vasculitis has a predilection for respiratory tract and kidneys. It includes p-ANCA associated microscopic polyangiitis, glomerulonephritis and Churg-Strauss syndrome (p710) and c-ANCA associated Wegener's granulomatosis (p728).
- ANCA -ve vasculitis includes Henoch-Schönlein purpura (p716), Goodpasture's syndrome (p714) and cryoglobulinaemia.

Three possible mechanisms of vascular damage:

- **immune complex deposition,**
- **ANCAs (humoral response)**
- **T-lymphocyte response with granuloma formation (cell-mediated)**

PREVALENCE OF RHEUMATIC DISEASES

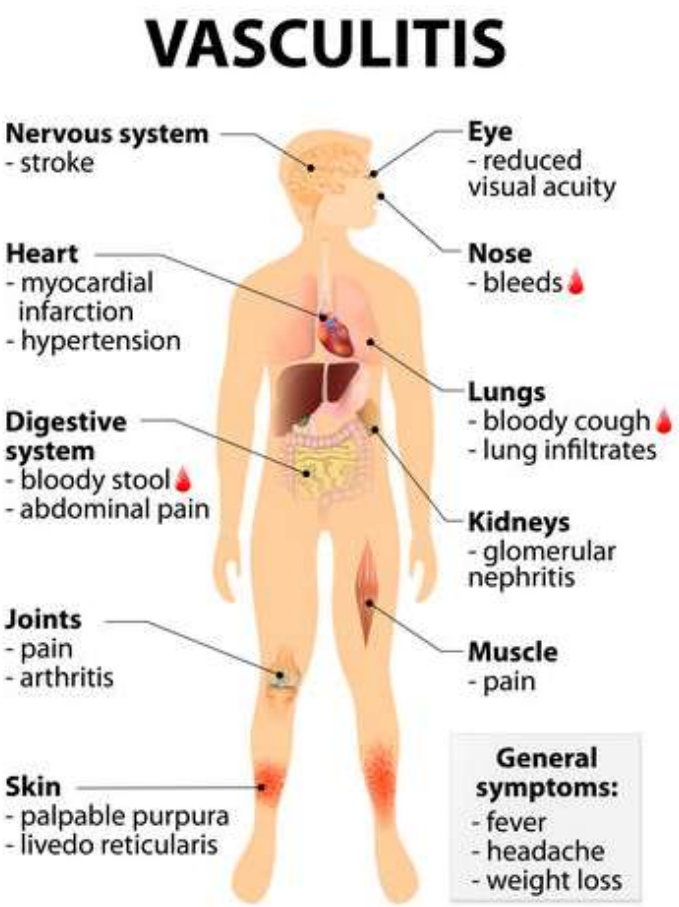
Rheumatoid arthritis	1 per 100
Spondyloarthropathy	1 per 100
Sjögren's syndrome;	1 per 100
Systemic lupus erythematosus	0.1 per 100
Systemic sclerosis	0.01 per 100
Vasculitis	0.01 per 100

Table 1. Classification of Primary Systemic Vasculitis (Chapel Hill Consensus Conference Nomenclature)

Adpated with permission from Jennette JC, Falk RJ, Andrassy K, et al. Nomenclature of systemic vasculitides. Proposal of an international consensus conference. Arthritis Rheum. *1994;37(2):189.*

Small vessel	
Churg-Strauss syndrome	Eosinophil-rich and granulomatous inflammation involving the respiratory tract; necrotizing vasculitis of small to medium vessels; associated with asthma
Cutaneous leukocytoclastic angiitis	Isolated cutaneous leukocytoclastic angiitis without systemic vasculitis or glomerulonephritis
Essential cryoglobulinemic vasculitis	Vasculitis, with cryoglobulin immune deposits, affecting capillaries, venules, or arterioles; associated with serum cryoglobulins; skin and glomeruli are often involved
Henoch-Schönlein purpura	Immunoglobulin A–dominant immune deposits, affecting capillaries, venules, or arterioles; typically involves skin, gut, and glomeruli; associated with arthralgias or arthritis
Microscopic polyangiitis	Necrotizing vasculitis, with few or no immune deposits, affecting capillaries, venules, or arterioles, but may involve small and medium arteries; necrotizing glomerulonephritis is very common; pulmonary capillaritis often occurs
Wegener granulomatosis	Granulomatous inflammation involving the respiratory tract, and necrotizing vasculitis affecting capillaries, venules, arterioles, and arteries; necrotizing glomerulonephritis is common
Medium vessel	
Kawasaki disease	Arteritis involving coronary arteries, but aorta and veins may be involved; associated with mucocutaneous lymph node syndrome
Polyarteritis nodosa	Necrotizing inflammation of medium or small arteries without glomerulonephritis or vasculitis in arterioles, capillaries, or venules
Large vessel	
Giant cell (temporal) arteritis	Granulomatous arteritis of the aorta and its major branches, with a predilection for the extracranial branches of the carotid artery; often involves the temporal artery; associated with polymyalgia rheumatica
Takayasu arteritis	Granulomatous inflammation of the aorta and its major branches

Symptoms: Different vasculitides preferentially affect different organs, causing different patterns of symptoms (see BOX 1), but the presentation may often be of only overwhelming fatigue with ↑ESR/CRP. ►►*Consider vasculitis in any unidentified multisystem disorder*. If presentation does not fit clinically or serologically into a specific category consider malignancy-associated vasculitis. A severe vasculitis flare is a medical emergency. If suspected, seek urgent help, as organ damage may occur rapidly (eg critical renal failure <24h).



Features of vasculitis

The presentation of vasculitis will depend on the organs affected:

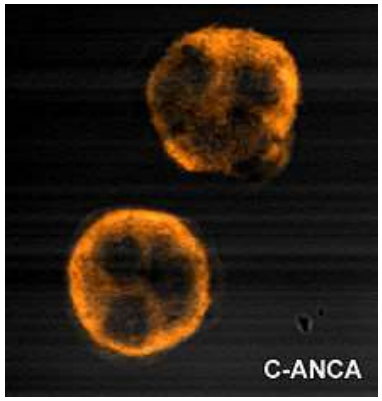
Systemic: fever, malaise, weight loss, arthralgia, myalgia.
Skin: purpura, ulcers, livedo reticularis (fig 1), nailbed infarcts, digital gangrene.
Eyes: episcleritis, scleritis, visual loss.
ENT: epistaxis, nasal crusting, stridor, deafness.
Pulmonary: haemoptysis and dyspnoea (due to pulmonary haemorrhage).
Cardiac: Angina or MI (due to coronary arteritis), heart failure and pericarditis.
GI: Pain or perforation (infarcted viscus), malabsorption (chronic ischaemia).
Renal: Hypertension, haematuria, proteinuria, casts, and renal failure (renal cortical infarcts; glomerulonephritis in ANCA +ve vasculitis).
Neurological: Stroke, fits, chorea, psychosis, confusion, impaired cognition, altered mood. Arteritis of the vasa nervorum (arterial supply to peripheral nerves) may cause mononeuritis multiplex or a sensorimotor polyneuropathy.[63]
GU: Orchitis—testicular pain or tenderness.

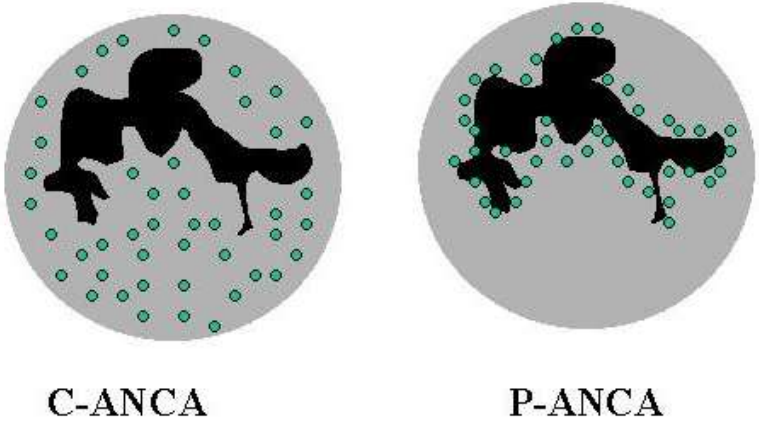
Tests: ESR/CRP↑. ANCA may be +ve. ↑Creatinine if renal failure. Urine: proteinuria, haematuria, casts on microscopy. Angiography ± biopsy may be diagnostic.

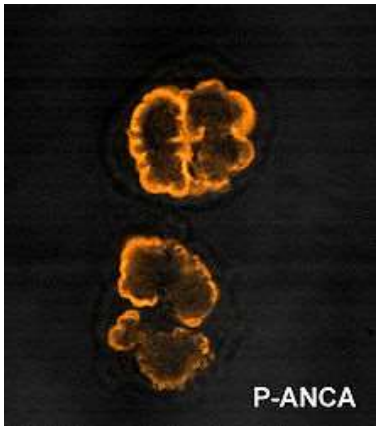
• *Small:* • ANCA +ve vasculitis has a predilection for respiratory tract and kidneys. It includes p-ANCA associated microscopic polyangiitis, glomerulonephritis and Churg-Strauss syndrome (p710) and c-ANCA associated Wegener's granulomatosis (p728).
• ANCA -ve vasculitis includes Henoch-Schönlein purpura (p716), Goodpasture's syndrome (p714) and cryoglobulinaemia.

Anti neutrophil cytoplasmic antibodies

- Most often, ANCA tests are performed using indirect immunofluorescence microscopy (IFA). Serum samples are mixed with neutrophils to allow autoantibodies that may be present to react with the cells. The sample is put on a slide and treated with a fluorescent stain. The slide is then examined under a microscope and the resulting pattern noted.
- The cytoplasmic pattern (**cANCA**) is associated with **proteinase 3 (PR3) antibodies** and the perinuclear pattern (**pANCA**) is associated with **myeloperoxidase (MPO) antibodies**. Another possible pattern is atypical ANCA.
- Myeloperoxidase antibodies and proteinase 3 (PR3) antibodies may be individually and specifically tested using an immunoassay method.
- Some laboratories will perform all three tests, ANCA, MPO and PR3, as a panel while others will perform MPO and PR3 only if an initial ANCA test is positive.



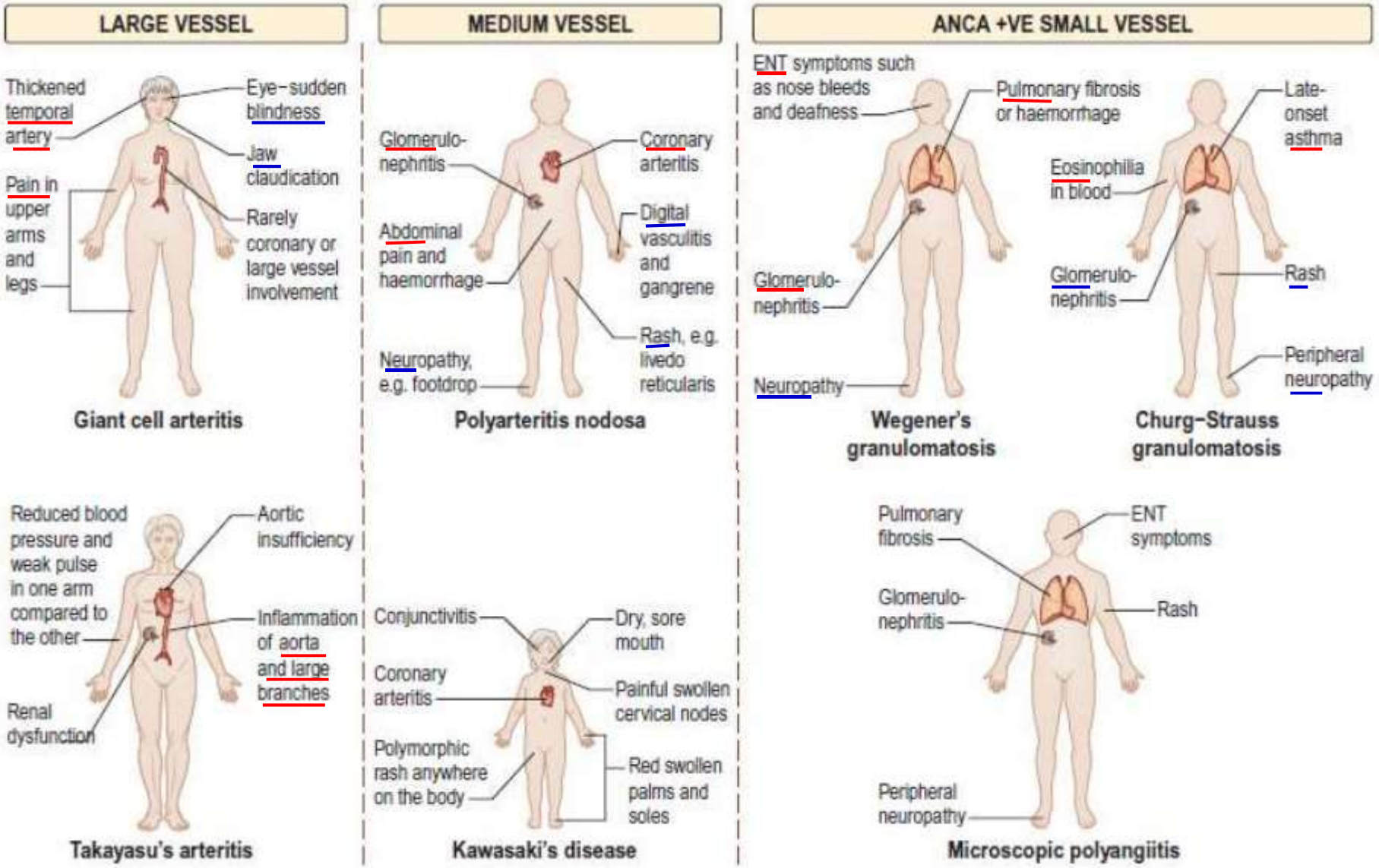




The granular, cytoplasmic staining pattern of c-ANCA

Perinuclear staining typical of p-ANCA

Clinical features



Management: Large-vessel vasculitis: steroids in most cases. Medium/small: standard therapy is steroids and IV *cyclophosphamide* (15mg/kg).[59] Azathioprine may be useful as steroid-sparing maintenance treatment.

Table 2. Clinical Features of Major Systemic Vasculitides

Vasculitis	*Organ involvement*	*Age (years)*	*Clinical features*
Small vessel			
Churg-Strauss syndrome	Respiratory tract, heart	50 to 60	Allergic rhinitis, asthma, peripheral eosinophilia
Cryoglobulinemic vasculitis	Skin, kidney	40 to 50	Recurrent palpable purpura, polyarthralgia, glomerulonephritis
Cutaneous leuko-cytoclastic angiitis	Skin	Any age	Palpable purpura, cutaneous infarcts, necrotic papules, urticaria
Henoch-Schönlein purpura	Skin, gastrointestinal tract, kidney, joint	3 to 8	Purpura, arthritis, abdominal pain, gastrointestinal bleeding, glomerulonephritis
Microscopic polyangiitis	Skin, lung, heart, kidney, liver, gastrointestinal tract	50 to 60	Palpable purpura, pulmonary hemorrhage, glomerulonephritis
Wegener granulomatosis	Upper and lower respiratory tracts, kidney	40 to 50	Pneumonitis with bilateral nodular and cavitary infiltrates, mucosal ulceration of nasopharynx, chronic sinusitis, glomerulonephritis
Medium vessel			
Kawasaki disease	Coronary arteries, aorta and its branches	2 to 4	Fever, conjunctivitis, desquamating skin rash, enlarged cervical lymph nodes
Polyarteritis nodosa	Renal and visceral organs, spares lung	30 to 40	Fever, weight loss, hypertension, abdominal pain, melena, peripheral neuritis, renal ischemia
Large vessel			
Giant cell arteritis	Extracranial branches of carotid artery, often involves temporal artery	50 to 60	Fever, visual disturbances, facial pain and headache (often along the course of superficial temporal artery)
Takayasu arteritis	Aorta and its major branches	30 to 40	More common in young Asian women Markedly lower blood pressure and weaker pulse in upper extremities, with coldness and numbness of fingers, visual disturbances, hypertension, neurologic deficit

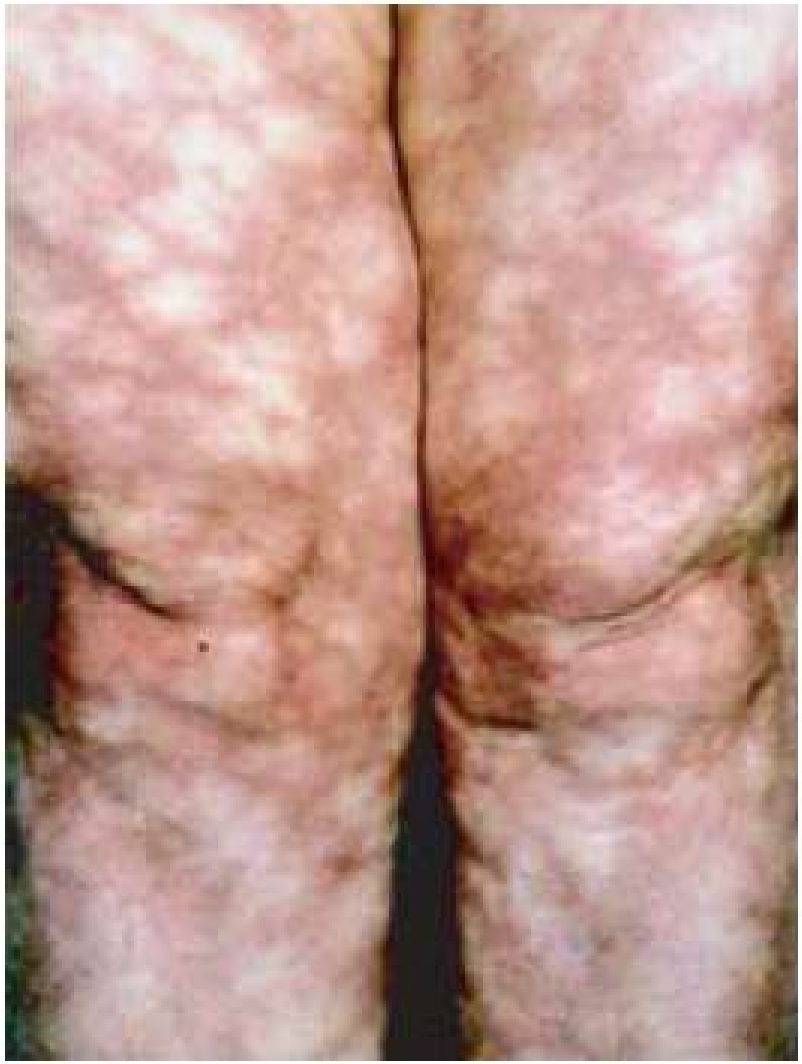
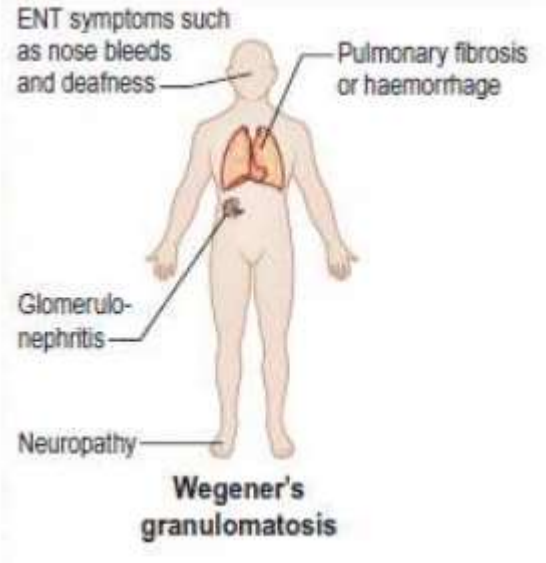


Fig 1. Livedo reticularis: pink-blue mottling caused by capillary dilatation and stasis in skin venules. Causes: physiological, eg cold, or vasculitis.

Wegener's granulomatosis This has been renamed granulomatosis with polyangiitis (GPA), in part because of concerns over the suitability of Friedrich Wegener, a member of the Nazi party during WWII, to be the source of an eponym.[119] GPA is a multisystem disorder of unknown cause characterized by necrotizing granulomatous inflammation and vasculitis of small and medium vessels. It has a predilection for the upper respiratory tract, lungs and kidneys.

The American College of Rheumatology developed 4 criteria for WG, 2 of which have 88% sensitivity and 92% specificity for WG: (1) nasal or oral inflammation characterized by oral ulcers or bloody/purulent nasal discharge; (2) nodules, infiltrates, or cavitary lesions on chest radiograph; (3) microhematuria or red blood cell casts in the urine; and (4) intra-arteriolar or periarteriolar granulomatous inflammation on biopsy.[4]

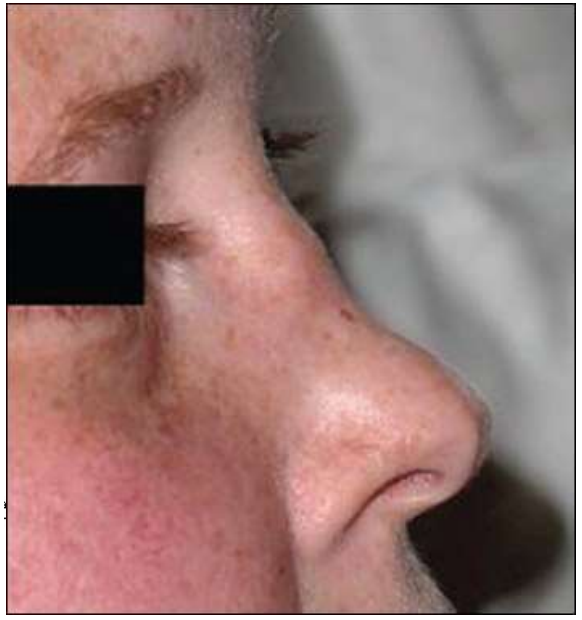


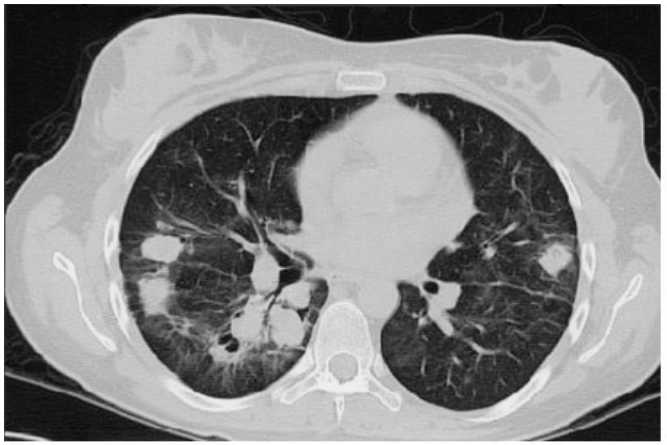
Wegener's granulomatosis

Tests:

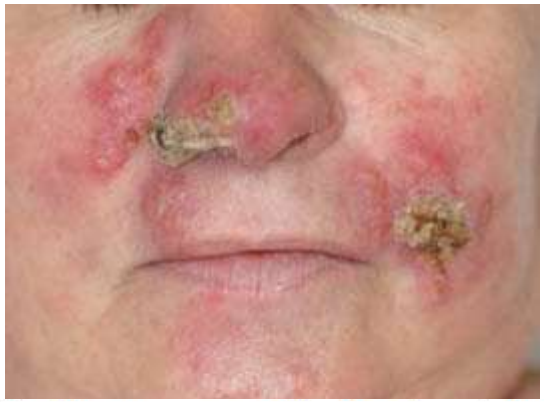
cANCA directed against PR3 is most specific and raised in the majority of patients (p555). Some patients express pANCA specific for MPO. ↑ESR/CRP. Urinalysis should be performed to look for proteinuria or haematuria. If these are present, consider a renal biopsy. CXR may show nodules ± fluffy infiltrates of pulmonary haemorrhage. CT may reveal diffuse alveolar haemorrhage. Atypical cells from cytology of sputum/BAL can be confused with bronchial carcinoma.[120]

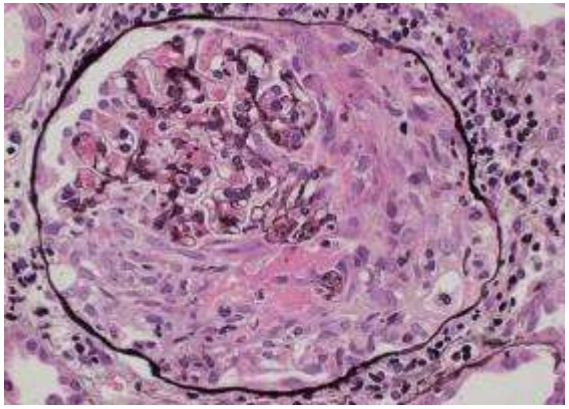
Mucosal thickening of the bilateral maxillary sinuses and a perforation of the nasal septum.





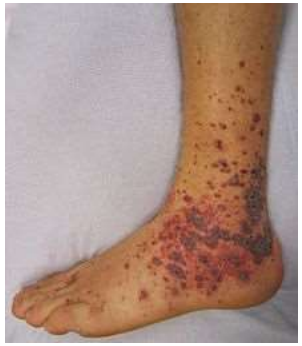
Bilateral nodular infiltrates seen on computed tomography of the chest





Nerve conduction studies

. *Features:* Upper airways disease is common, with nasal obstruction, ulcers, epistaxis, or destruction of the nasal septum causing a characteristic 'saddle-nose' deformity.[1] Sinusitis is often a feature. Renal disease causes rapidly progressive glomerulonephritis with crescent formation, proteinuria or haematuria. Pulmonary involvement may cause cough, haemoptysis (severe if pulmonary haemorrhage) or pleuritis. There may also be skin purpura or nodules, peripheral neuropathy, mononeuritis multiplex, arthritis/arthralgia or ocular involvement, eg keratitis, conjunctivitis, scleritis, episcleritis, uveitis.



Treatment: Depends on the extent of disease. Severe disease (eg biopsy-proven renal disease) should be treated with corticosteroids and ***cyclophosphamide*** (or ***rituximab***) to induce remission. ***Azathioprine*** and ***methotrexate*** are usually used as maintenance. Patients with severe renal disease (eg creatinine >500µmol/L) may benefit from plasma exchange in addition. ***Co-trimoxazole*** should be given as prophylaxis against *Pneumocystis jiroveci* and staphylococcal colonization.

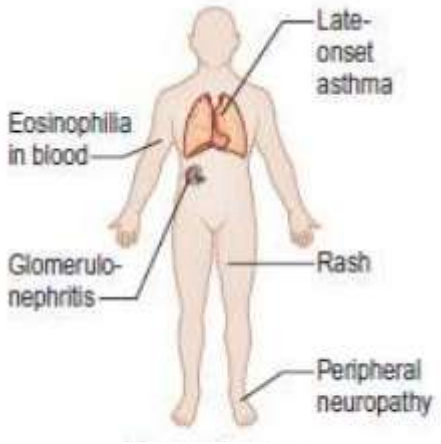
Friedrich Wegener, 1907–1990 (German pathologist)

Churg-Strauss syndrome A triad of adult-onset asthma, eosinophilia, and vasculitis (± vasospasm ± MI ± DVT), affecting lungs, nerves, heart, and skin. A septic-shock picture/systemic inflammatory response syndrome may occur (with glomerulonephritis/renal failure, esp. if ANCA +ve). *Rx*: Steroids; biological agents if refractory disease, eg *rituximab*.[24]

Jacob Churg, 1910–2005; Lotte Strauss, 1913–1985 (US pathologists)

Lanham diagnostic criteria for Churg Strauss syndrome.

Asthma
Blood eosinophilia exceeding 1500/mm^3
Evidence of vasculitis involving two or more organs.



Eosinophilic granulomatosis with polyangiitis (Churg-Strauss syndrome)

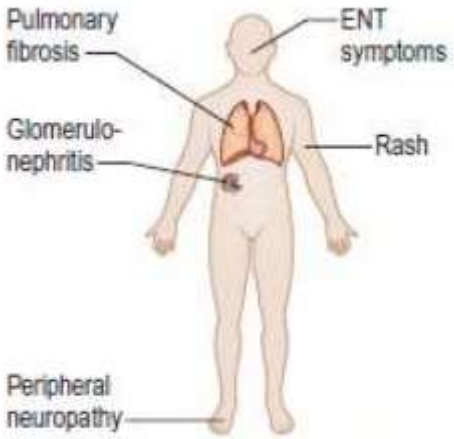
CHURG-STRAUSS SYNDROME

3 Clinical phases

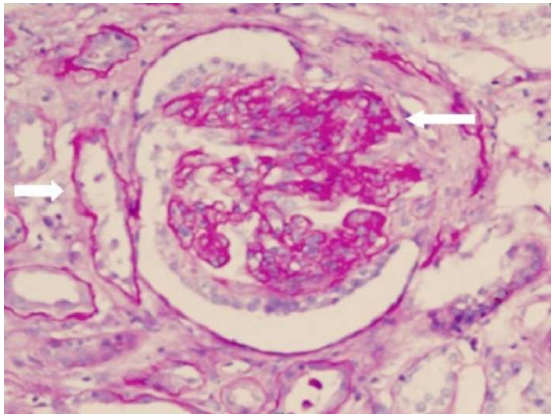
Prodromal Phase	Eosinophilic phase	Vasculitic phase
• Late onset allergic rhinitis and atopy* • Lasting for >10 years	• Marked blood eosinophilia • Eosinophillic infiltration of lung, GI tract or skin	• Vasculitis of the small and medium vessels • Vascular and extravascular granulomas • Constitutional symptoms • Worsening asthma symptoms

Microscopic polyangiitis

A necrotizing vasculitis affecting small- and medium-sized vessels. *Symptoms:* Rapidly progressive glomerulonephritis usually features; pulmonary haemorrhage occurs in up to 30%; other features are rare. *Tests:* pANCA (MPO) +ve (p555). *Treatment:* As for PAN.



Microscopic polyangiitis



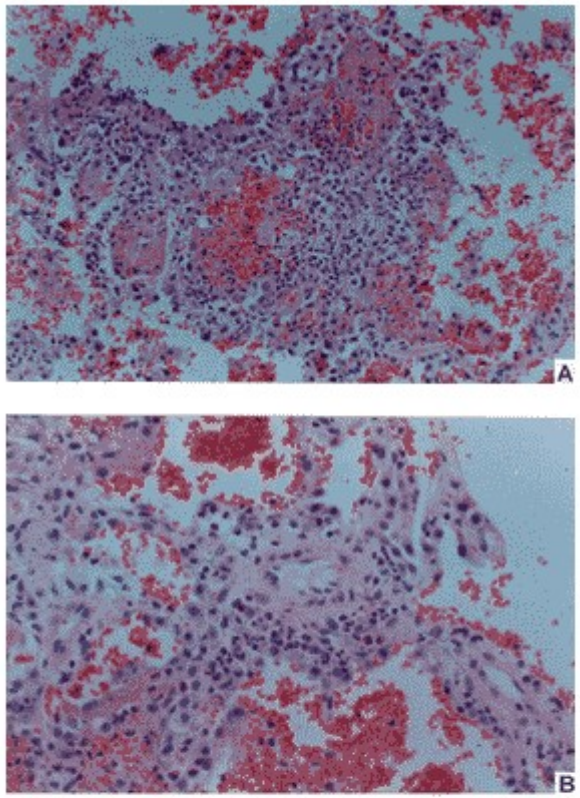
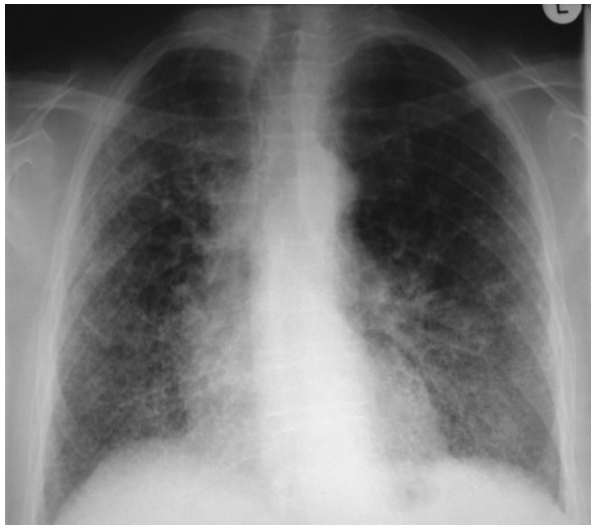


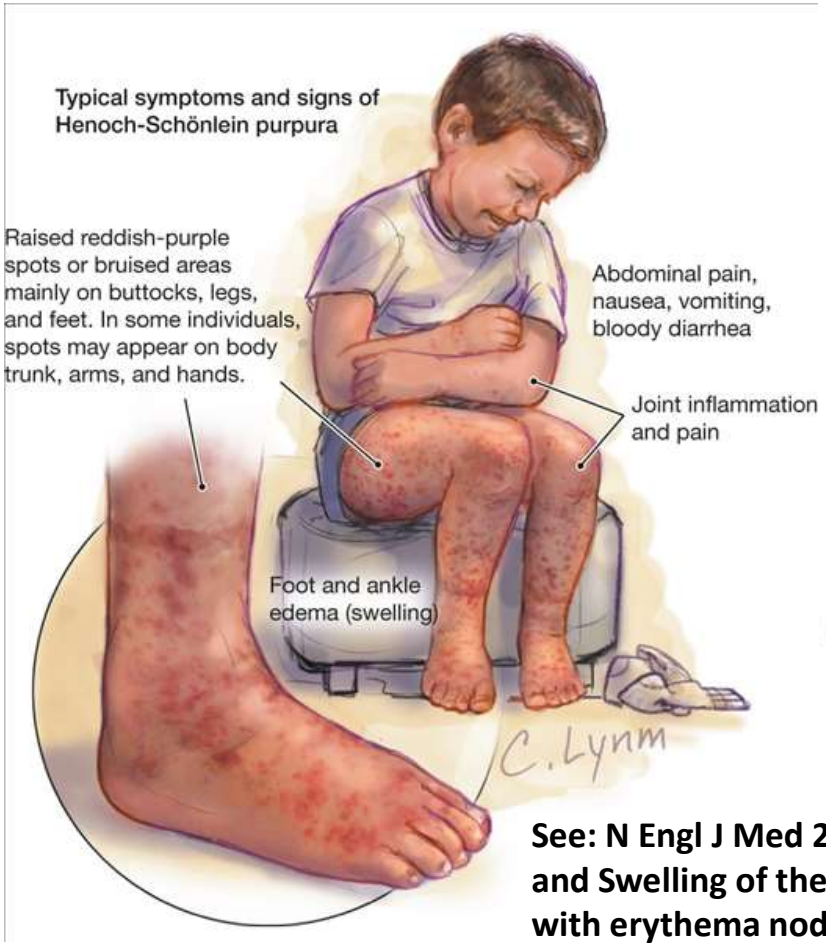
Figure 2 – A. Evidence of capillaritis and leukocytoclastic vasculitis in lung tissue, also showing areas of edema and hemorrhage (H&E – 100x) B. Detail of capillaritis: thickening of the alveolar septa due to accumulation of neutrophils (H&E – 400x).

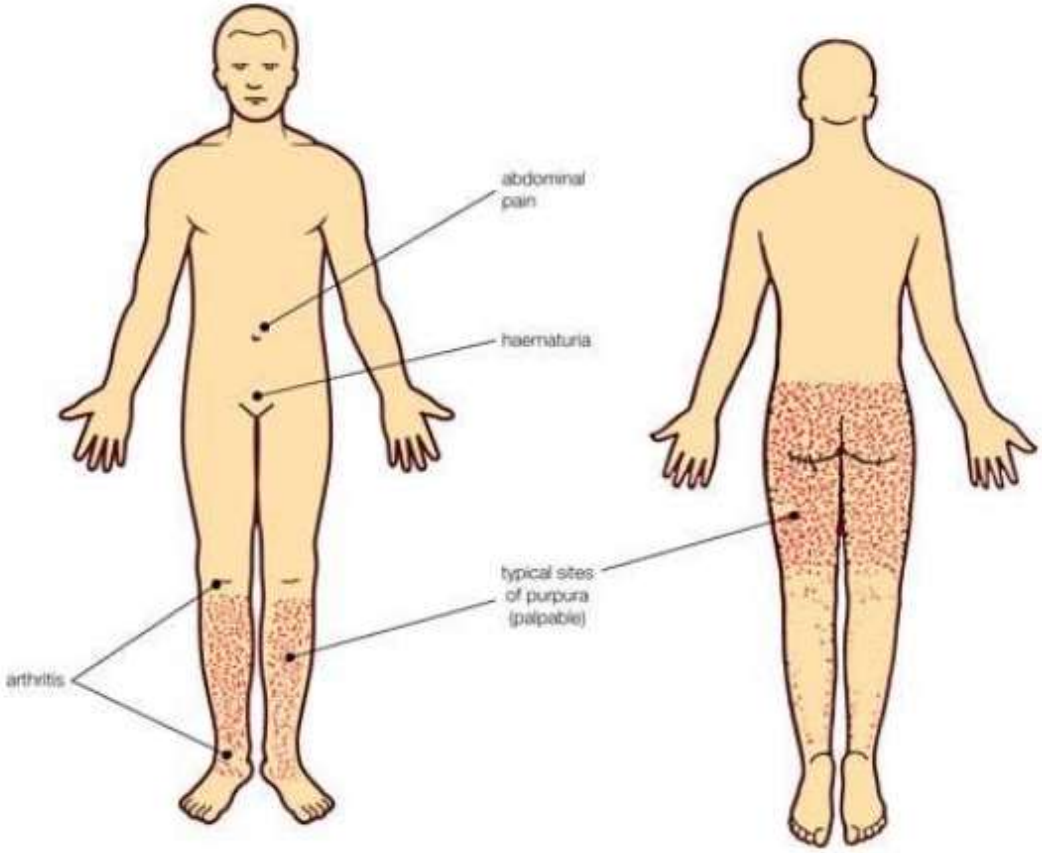


pulmonary fibrosis

Henoch-Schönlein purpura (HSP) (fig 2) A small vessel vasculitis, presenting with purpura (non-blanching purple papules due to intradermal bleeding), often over buttocks and extensor surfaces, typically affecting young ♂. There may be glomerulonephritis (p300), arthritis, and abdominal pain (±intussusception), which may mimic an 'acute abdomen'. ℞: Mostly supportive.

Eduard H Henoch, 1820–1910 (German paediatrician); Johann L Schönlein, 1793–1864 (German physician)





See: N Engl J Med 2017;376:1868-77. Case 14-2017: A 20-Year-Old Man with Pain and Swelling of the Left Calf and a Purpuric Rash. IgA vasculitis and Crohn's disease with erythema nodosum.

Table 1. Features of Small-Vessel, Medium-Vessel, and Large-Vessel Vasculitides.*

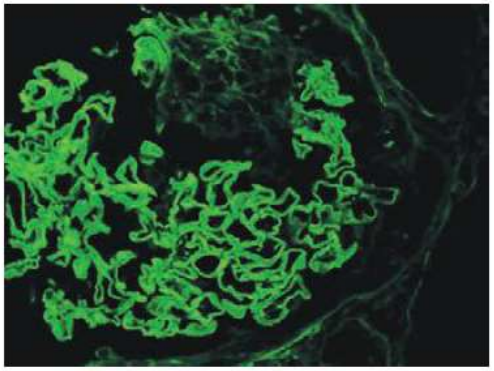
Vasculitis	Unique Clinical Features	Markers	Pathological Features
Large-vessel vasculitis			
Takayasu's arteritis	Diminished pulses and claudication of the arms and legs	None	Granulomatous inflammation and giant cells
Giant-cell arteritis	Headache, claudication of the jaw and of the arms and legs, scalp tenderness, and polymyalgia rheumatica	None	Granulomatous inflammation and giant cells
Medium-vessel vasculitis			
Polyarteritis nodosa	Cutaneous ulcers, nodules, renal infarcts, and testicular involvement; can be associated with hepatitis B virus	None	Necrotizing medium-vessel vasculitis without granulomas
Small-vessel vasculitis			
Granulomatosis with polyangiitis	Granulomatous manifestations (e.g., nasal crusting, destructive sinusitis, pulmonary nodules, and retroorbital mass)	ANCA (most commonly PR3), which is present in >90% of those with renal involvement and approximately 60% of those without renal involvement	Necrotizing small-vessel vasculitis that may be granulomatous and pauci-immune immunofluorescence staining
Microscopic polyangiitis	Interstitial lung disease	ANCA (most commonly MPO), which is present in approximately 70% of cases	Necrotizing small-vessel vasculitis without granulomas and pauci-immune immunofluorescence staining
Eosinophilic granulomatosis with polyangiitis	Asthma, eosinophilia, and cardiac involvement	ANCA (most commonly MPO), which is present in approximately 50% of cases	Necrotizing small-vessel eosinophilic vasculitis that may be granulomatous
Cryoglobulinemic vasculitis	Associated with hepatitis B and C viruses, systemic lupus erythematosus, and Sjögren's syndrome	Type II or III cryoglobulins, low C4, and rheumatoid factor	Necrotizing small-vessel vasculitis and positive immunofluorescence staining (types of immunoglobulin deposition depend on type of cryoglobulin); cryoglobulin deposits may be present
IgA vasculitis	Rare in the absence of skin lesions	None	Leukocytoclastic vasculitis and positive immunofluorescence staining for IgA

* Data are from Hoffman et al.,[2] Finkielman et al.,[3] and Jennette et al.[4] ANCA denotes antineutrophil cytoplasmic antibody, and MPO myeloperoxidase.

N Engl J Med 2017;376:1868-77. Case 14-2017: A 20-Year-Old Man with Pain and Swelling of the Left Calf and a Purpuric Rash. IgA vasculitis and Crohn's disease with erythema nodosum.

Goodpasture's disease[1] (a pulmonary-renal syndrome). Acute glomerulonephritis + lung symptoms (haemoptysis/diffuse pulmonary haemorrhage) caused by antiglomerular basement membrane antibodies (binding kidney's basement membrane and alveolar membrane). *Tests:* CXR: infiltrates due to pulmonary haemorrhage, often in lower zones. Kidney biopsy: crescentic glomerulonephritis. *Rx:* ►► Treat shock. Vigorous immunosuppressive treatment and plasmapheresis.

Ernest William Goodpasture, 1886–1960 (US pathologist)



B

FIGURE 62e-17 Anti–glomerular basement membrane antibody-mediated glomerulonephritis. There is segmental necrosis with a break of the glomerular basement membrane (*arrow*) and a cellular crescent (***A***), and immunofluorescence for IgG shows linear staining of the glomerular basement membrane with a small crescent at –1 o'clock (***B***). *(ABF/Vanderbilt Collection.)*

Anti-glomerular basement membrane (GBM) disease (figs 1 and 2): Also known as Goodpasture's disease, caused by auto-antibodies to type IV collagen, an essential component of the GBM. Type IV collagen is also found in the lung and pulmonary haemorrhage can occur, especially in smokers. Present with haematuria/nephritic syndrome, AKI may occur within days of onset of symptoms. If Rx (plasma exchange, steroids ± cytotoxics) is started early, full recovery is possible and relapses are rare. Renal prognosis is poor if dialysis-dependent at presentation.

The cryoglobulinaemias

Lancet 2012; 379: 348–60

- **Cryoglobulins are immunoglobulins that precipitate in vitro at temperatures less than 37°C and produce organ damage through two main pathways:**
  - **vascular sludging (hyperviscosity syndrome, mainly in type I cryoglobulinaemia)**
  - **immune-mediated mechanisms (principally vasculitis, in mixed cryoglobulinaemia).**
- **More than 90% of cases of cryoglobulinaemia are associated with many illnesses, which can be broadly grouped into infections, autoimmune disorders, and malignancies; the most common cause is infection with hepatitis C virus.**
- **Nearly 10% of cases of mixed cryoglobulinaemia are regarded as idiopathic or essential**
- **Mixed cryoglobulinaemic syndrome is diagnosed when a patient has typical organ involvement (mainly skin, kidney, or peripheral nerve) and circulating cryoglobulins. Cutaneous purpura and ulcers are the most common manifestation of cryoglobulinaemic vasculitis. The most frequently affected internal organs are the peripheral nerves, kidneys, and joints. The course varies widely and prognosis is infl uenced by both cryoglobulinaemic damage to vital organs and by comorbidities associated with underlying diseases.**

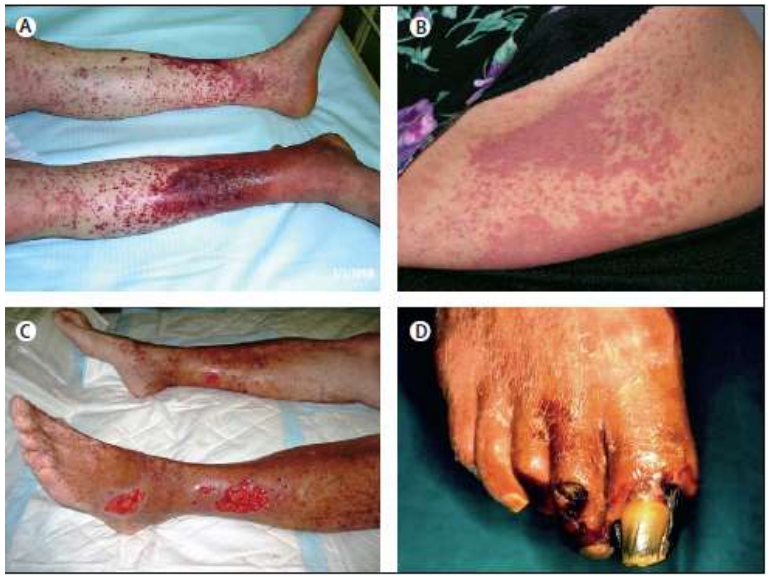


Figure 3: Cutaneous involvement in cryoglobulinaemia
(A) Purpura in legs, (B) atypical purpura, (C) cutaneous ulcers, (D) digital necrosis.

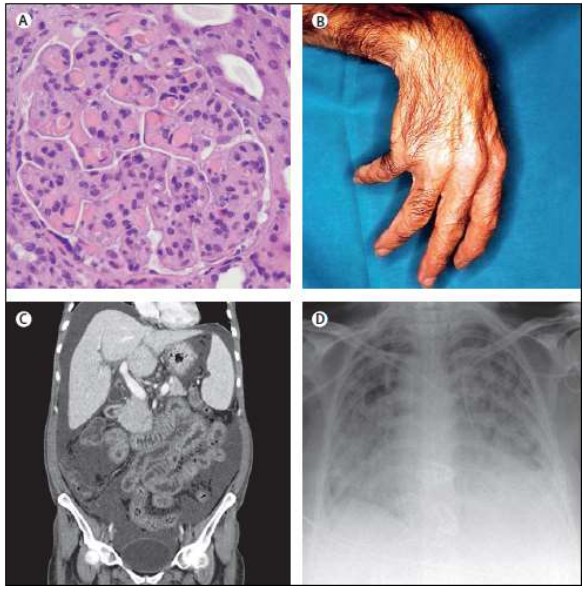


Figure 4: Systemic cryoglobulinaemic vasculitis
(A) Membranoproliferative glomerulonephritis associated with HCV-related type II cryoglobulinaemia. A glomerulus shows proliferative changes and subendothelial deposits within capillary loops (pink). These lesions resemble pseudothrombi. (B) Multineuritis (radial and cubital paralysis), (C) intestinal ischaemia (diffuse oedema of intestinal wall), (D) pulmonary haemorrhage.

Panel 1: Clinical, laboratory, and histopathological red flags advising cryoglobulin testing

Regard cryoglobulinaemia as highly probable when at least two features of different subsets are present

Clinical findings

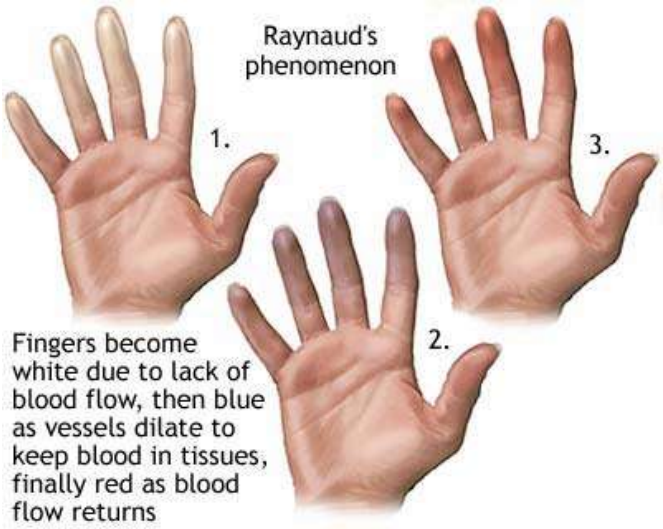
- Skin purpura in adults
- Cutaneous necrotic ulcers
- Glomerulonephritis
- Peripheral neuropathy
- Non-erosive arthritis
- Acral ischaemia
- Cold-induced acrocyanosis
- Raynaud's phenomenon

Laboratory abnormalities

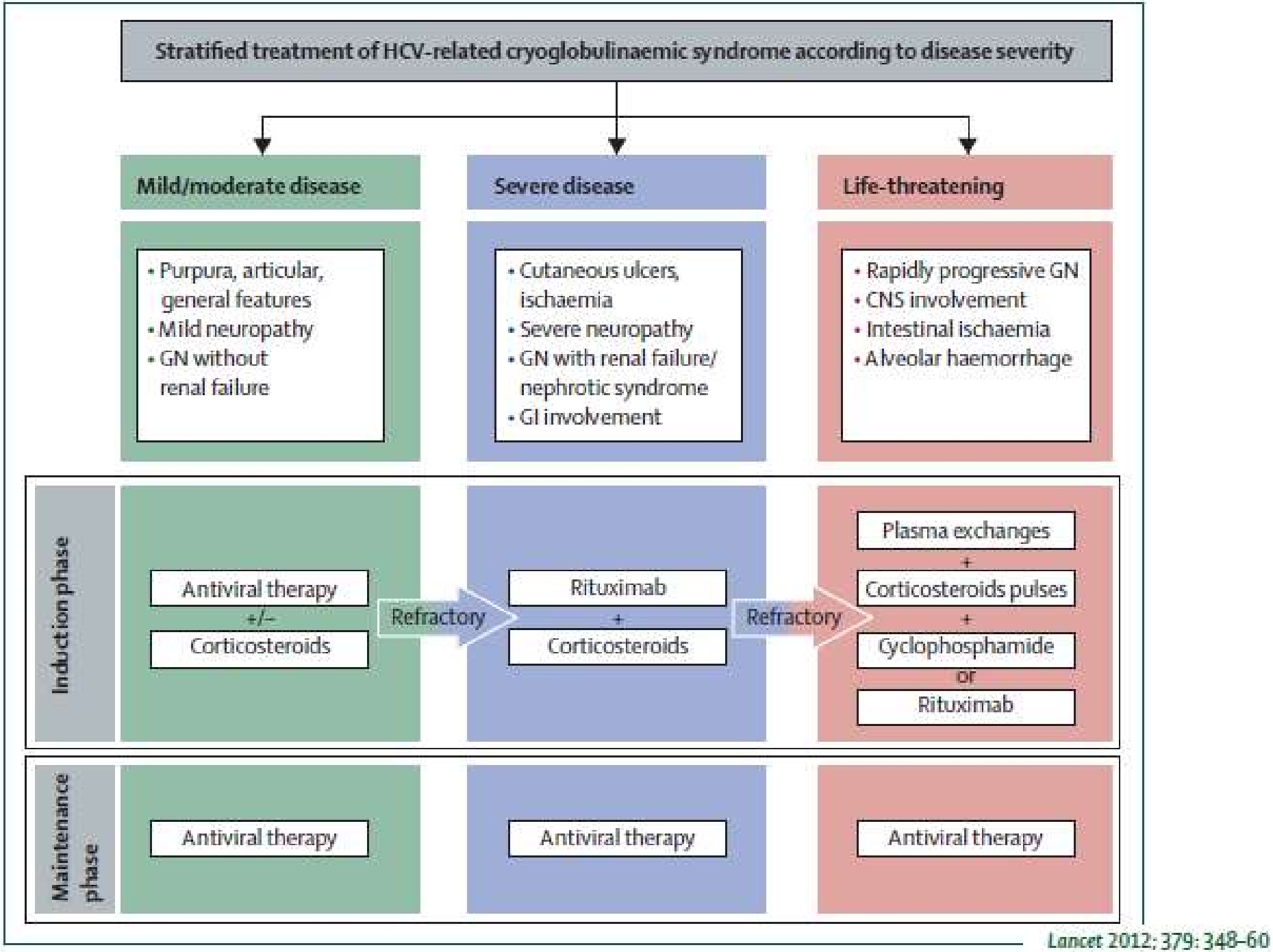
- Monoclonal gammopathy, particularly of IgM isotype or with hyperviscosity
- Unexplained low concentrations of complement (especially C4)
- Unexplained high titres of rheumatoid factor
- Pseudothrombocytosis
- Formation of erythrocyte *rouleaux*

Histopathological findings

- Leukocytoclastic vasculitis in adults
- Membranoproliferative glomerulonephritis
- Hyaline thrombi in capillaries in context of glomerulonephritis or small-vessel vasculitis
- Endoneural vasculitis
- Unclassified systemic necrotising vasculitis involving small–medium-sized vessels



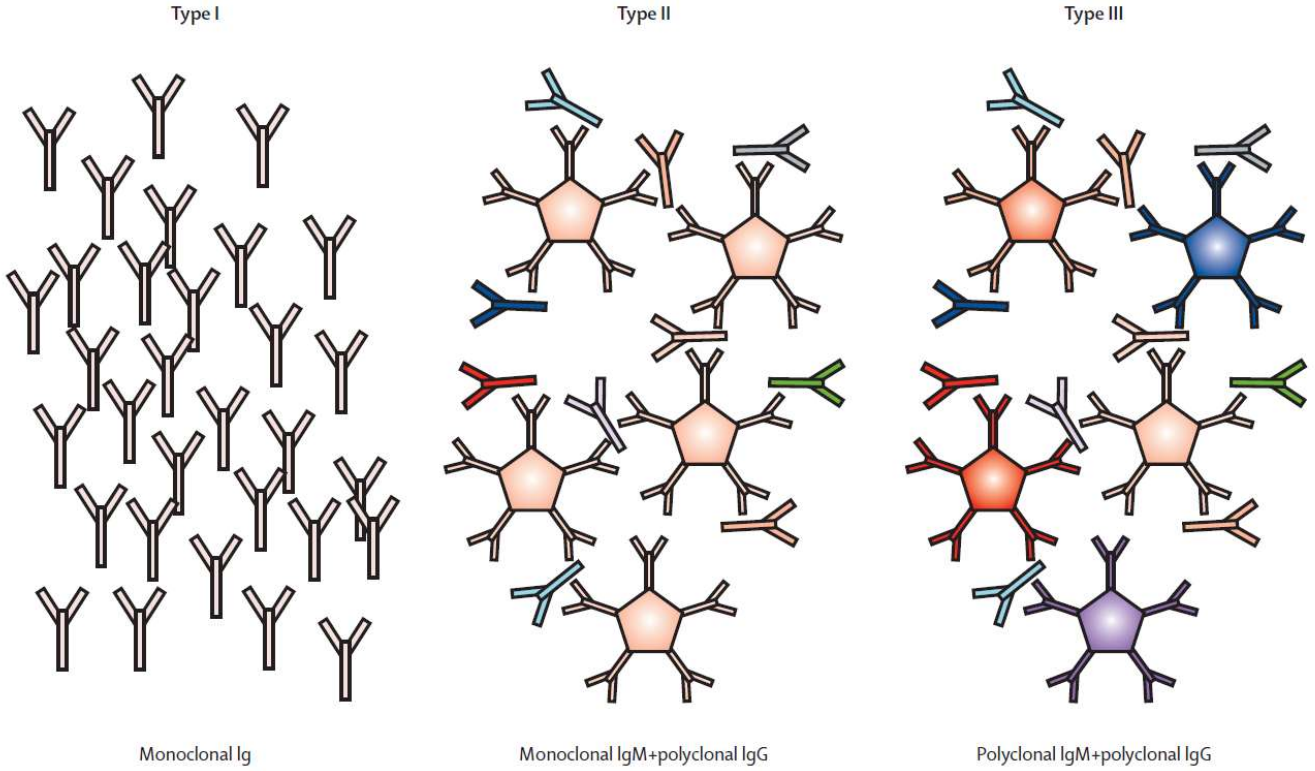
Lancet 2012; 379: 348–60



Lancet 2012; 379: 348–60

Cryoglobulins are generated by the monoclonal or polyclonal expansion of B cells, in the context of either lymphoproliferative disorders or persistent immune stimulation triggered by chronic infections or autoimmune diseases. Types I (IgG) and II (IgM) cryoglobulinaemias result from the monoclonal expansion of a clone. By contrast, B-cell expansion is polyclonal in type III cryoglobulinaemia.

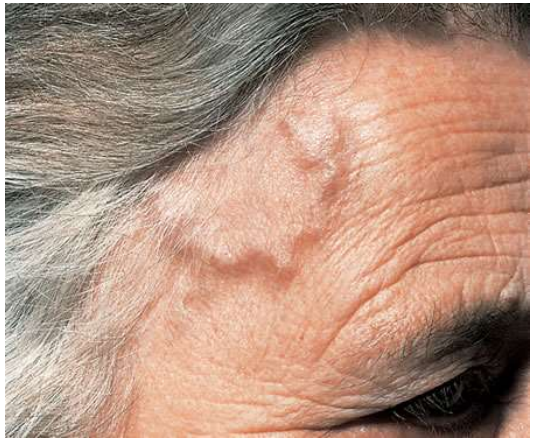
Type I and type II are encuntered in patients with a plasma cell dyscrasia such as multiple myeloma or Waldenström macroglobulinemia. Types II and III are associated with infection by the hepatitis C virus. Types III are associated with autoimmune disease such as systemic lupus erythematosus and rheumatoid arthritis.

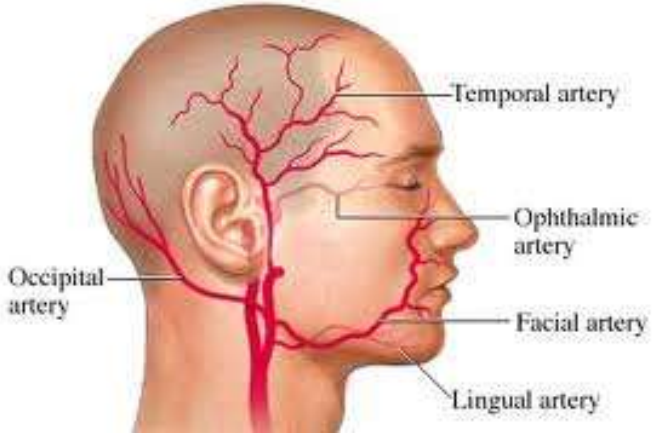


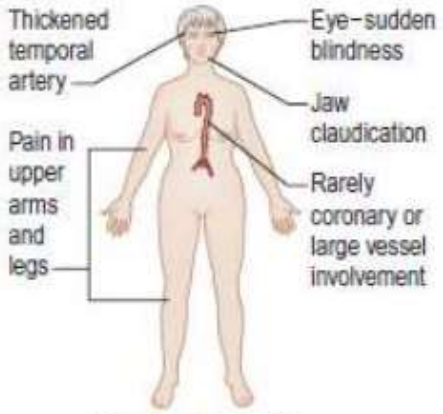
A 73-year-old woman presented with sudden **pain and stiffness of her shoulder muscles**. She had become increasingly depressed over the preceding 3 months, with anorexia and loss of weight. On examination, there was limitation of movement of both shoulders with muscle tenderness; neurological examination was normal. The **temporal arteries were extremely tender on palpation**. On investigation, her haemoglobin was 121g/l with a raised CRP of 68mg/l. A diagnosis of ***polymyalgia rheumatica and temporal arteritis*** was made and a **temporal artery biopsy** taken. . Treatment was started immediately with 60mg of **prednisolone** daily and within 24h the patient was markedly improved; she became more alert and her muscle stiffness lessened. The temporal artery biopsy showed a vasculitis with infiltration by lymphocytes, macrophages and giant cells. Improvement continued over the next few days. Steroids were gradually withdrawn over 2 months but her polymyalgia relapsed a year later and she again improved on steroids.

Giant cell arteritis (GCA)[60] = cranial or temporal arteritis

It is common in the elderly—consider Takayasu's if under 55yrs (p726). It is associated with PMR in 50% (see BOX 2). *Symptoms:* Headache, temporal artery and scalp tenderness (eg when combing hair), jaw claudication, amaurosis fugax, or sudden blindness, typically in one eye. Extracranial symptoms may include dyspnoea, morning stiffness, and unequal or weak pulses.[61] ▶▶If you suspect GCA, do ESR and start *prednisolone* 60mg/d PO *immediately*. The risk is irreversible bilateral visual loss, which can occur suddenly if not treated (some advocate IV methylprednisolone for 3d if visual symptoms—ask an ophthalmologist). *Tests:* ESR & CRP↑↑, plateletsꜛ, alk phosꜛ, Hb↓. Get a temporal artery biopsy within 7 days of starting steroids. Skip lesions occur, so don't be put off by a negative biopsy (up to 10%). *Prognosis:* Typically a 2-year course, then complete remission. Reduce prednisolone once symptoms have resolved and ↓ESR; ↑dose if symptoms recur. The main cause of death and morbidity in GCA is long-term steroid treatment so consider risks and benefits! Give gastric and bone protection (PPI & bisphosphonate).







Giant cell arteritis

Polymyalgia rheumatica (PMR)[64]

PMR is not a true vasculitis and its pathogenesis is unknown. PMR and GCA share the same demographic characteristics and, although separate conditions, the two frequently occur together.

Features: Age >50yrs; subacute onset (<2 weeks) of bilateral aching, tenderness and morning stiffness in shoulders and proximal limb muscles ± mild polyarthritis, tenosynovitis, and carpal tunnel syndrome (10%). Weakness is not a feature. There may be associated fatigue, fever, weight↓, anorexia and depression.

Investigations: CRP ↑, ESR typically >40 (but may be normal); ALP is ↑ in 30%. Note creatinine kinase levels are normal (helping to distinguish from myositis/myopathies).

Differential diagnoses: Recent onset RA, polymyositis, hypothyroidism, primary muscle disease, occult malignancy or infection, osteoarthritis (especially cervical spondylosis, shoulder OA), neck lesions, bilateral subacromial impingement (*OHCS* p664), spinal stenosis (*OHCS* p674).

Management: *Prednisolone* 15mg/d PO. Expect a dramatic response within 1 week and consider an alternative diagnosis if not. ↓dose slowly, eg by 1mg/month (according to symptoms and ESR). Investigate apparent 'flares' during withdrawal—recurrent symptoms may be attributable to another condition (above). Most need steroids for ≥2yrs, so give gastric and bone protection. NSAIDs are not effective and trials with steroid-sparing agents have been inconsistent. Inform patients to seek urgent review if symptoms of GCA develop.

	Systemic Activity
Prednisone	4–5
Triamcinolone	5
Triamcinolone acetonide	5
Dexamethasone	30–120
Betamethasone	30
Betamethasone valerate	—
Methylprednisolone	5
Fluocinolone acetonide	—
Flurandrenolide	—
Deflazacort	3–4

[1]Hydrocortisone = 1 in potency.

Conversione degli Steroidi

Idrocortisone **flebocortid**	20	40	60	80	100	120	140	160	200	400	625	2.500	5.000	10.000
Prednisone **deltacortene**	**5**	10	15	20	25	30	35	40	50	100	156	625	1.250	2.500
Prednisolone	5	10	15	20	25	30	35	40	50	100	156	625	1.250	2.500
Triamcinolone **ledercort**	4	8	12	16	20	24	28	32	40	80	125	500	1.000	2.000
Metilprednisolone **depo-medrol** **solu-medrol** **medrol** **urbason**	4	8	12	16	20	24	28	32	40	80	125	500	1.000	2.000
Betametasone **bentelan** **celestone**	0.75	1.5	2.25	3	3.75	4.5	5.25	6	7.5	15	23.5	94	188	375
Desametasone **soldesam**	0.7	1.5	2.25	3	3.75	4.5	5.25	6	7.5	15	23.5	94	188	375
Deflazacort **flantadin** **deflan**	6	12	18	24	30	36	42	48	60	120	188	750	1.500	3.000

Management of patients receiving systemic corticosteroids.

Recommendations for prescribing

- Do not administer corticosteroids unless absolutely indicated or more conservative measures have failed.
- Keep dosage and duration of administration to the minimum required for adequate treatment.

Monitoring recommendations

- Screen for tuberculosis with a purified protein derivative (PPD) test or chest radiograph before commencing long-term corticosteroid therapy.
- Screen for diabetes mellitus before treatment and at each clinician visit.
  - Have patient test urine weekly for glucose.
  - Teach patient about the symptoms of hyperglycemia.
- Screen for hypertension before treatment and at each clinician visit.
- Screen for glaucoma and cataracts before treatment, 3 months after treatment inception, and then at least yearly.
- Monitor plasma potassium for hypokalemia and treat as indicated.
- Obtain bone densitometry before treatment and then periodically. Treat osteoporosis.
- Weigh daily. Use dietary measures to avoid obesity and optimize nutrition.
- Measure height frequently to document the degree of axial spine demineralization and compression.
- Watch for fungal or yeast infections of skin, nails, mouth, vagina, and rectum, and treat appropriately.
- With dosage reduction, watch for signs of adrenal insufficiency or corticosteroid withdrawal syndrome.

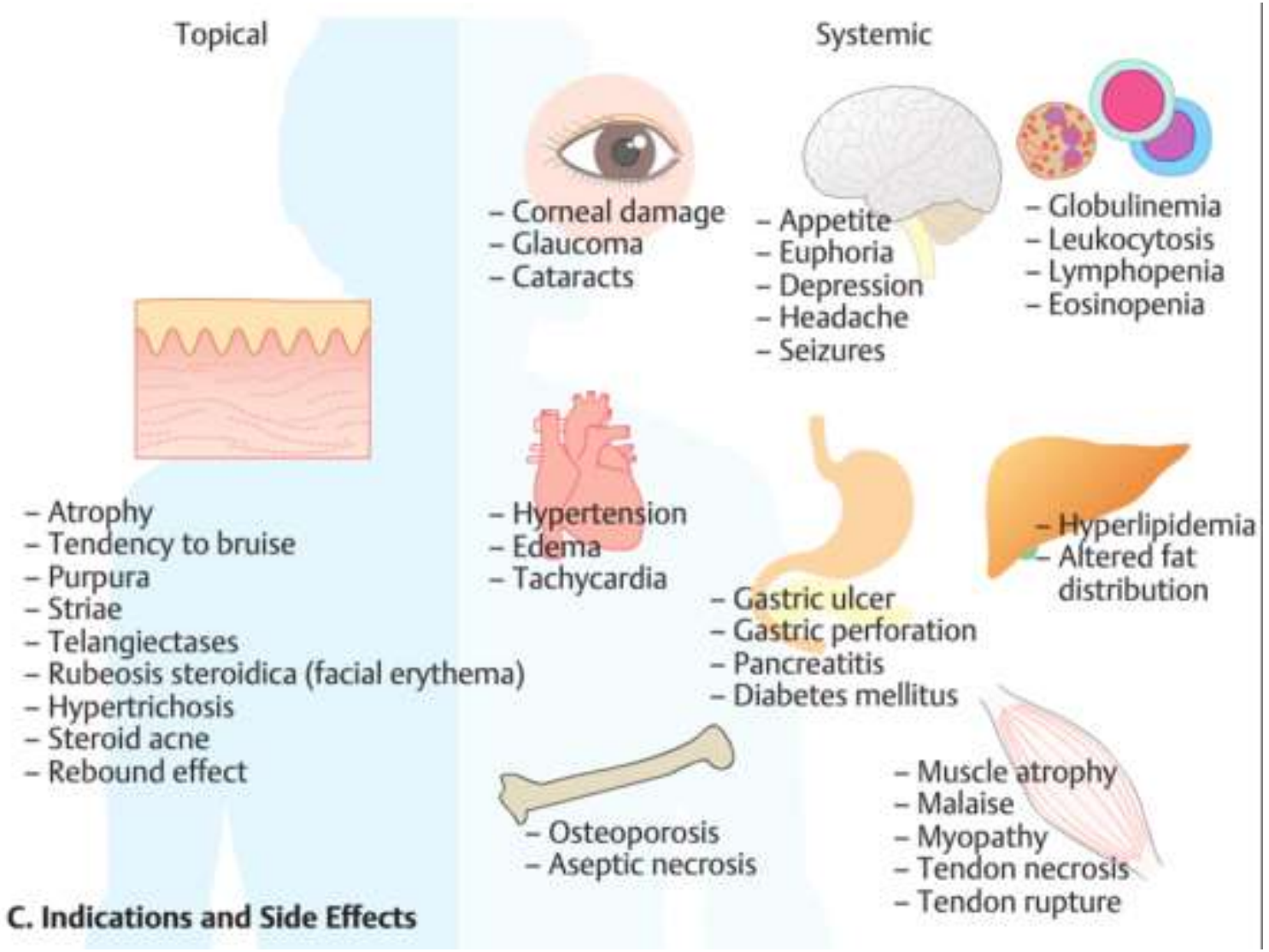
Patient information

- Prepare the patient and family for possible adverse effects on mood, memory, and cognitive function.
- Inform the patient about other possible side effects, particularly weight gain, osteoporosis, and aseptic necrosis of bone.
- Counsel to avoid smoking and excessive ethanol consumption.

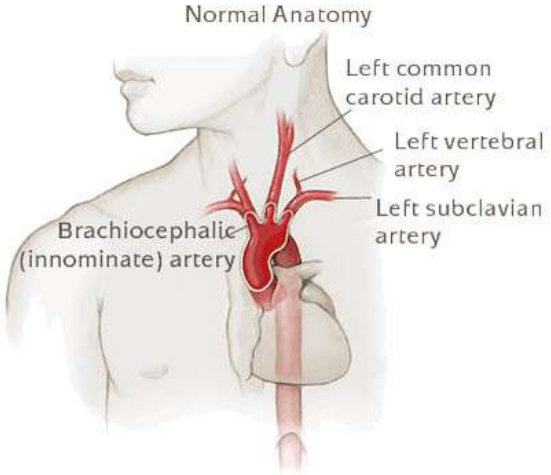
Prophylactic measures

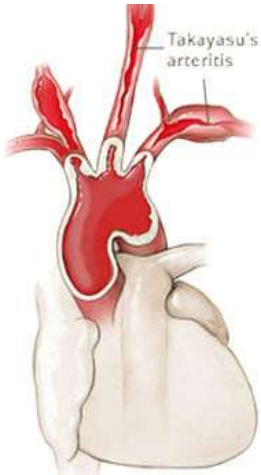
- Institute a vigorous physical exercise and isometric regimen tailored to each patient's disabilities.
- Administer calcium (1 g elemental calcium) and vitamin D_3, 400–800 international units orally daily.
  - Check spot morning urines for calcium; alter dosage to keep urine calcium concentration < 30 mg/dL (< 7.5 mmol/L).
  - If the patient is receiving thiazide diuretics, check for hypercalcemia, and administer only 500 mg elemental calcium daily.
  - Consider a bisphosphonate such as alendronate (70 mg orally weekly) or periodic intravenous infusions of pamidronate or zoledronic acid.
- Avoid prolonged bed rest that will accelerate muscle weakness and bone mineral loss. Ambulate early after fractures.
- Avoid elective surgery, if possible. Vitamin A in a daily dose of 20,000 units orally for 1 week may improve wound healing, but it is not prescribed in pregnancy.
- Avoid activities that could cause falls or other trauma.
- For ulcer prophylaxis, if administering corticosteroids with nonsteroidals, prescribe a proton pump inhibitor (not required for corticosteroids alone). Avoid large doses of antacids containing aluminum hydroxide (many popular brands) because aluminum hydroxide binds phosphate and may cause a hypophosphatemic osteomalacia that can compound corticosteroid osteoporosis.
- Treat hypogonadism.
- Treat infections aggressively. Consider unusual pathogens.
- Treat edema as indicated.

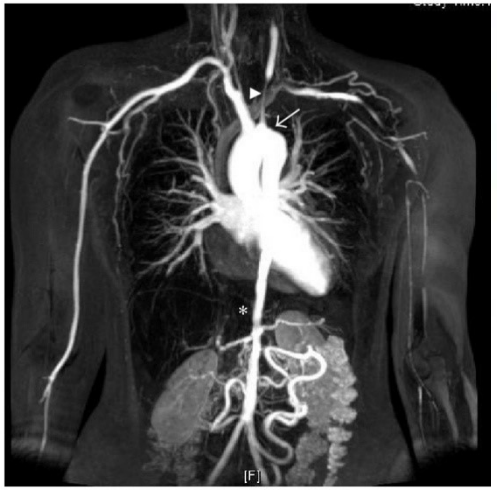
Steroid Adverse Effects



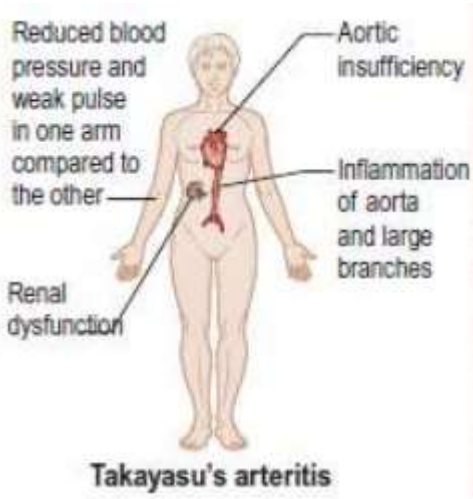
Takayasu's arteritis (aortic arch syndrome; pulseless disease) Rare outside of Japan, this systemic vasculitis affects the aorta and its major branches. Granulomatous inflammation causes stenosis, thrombosis and aneurysms. It often affects women aged 20–40yrs. Symptoms depend on the arteries involved. The aortic arch is often affected, with cerebral, ophthalmological and upper limb symptoms, eg dizziness, visual changes, weak arm pulses. Systemic features are common—eg fever, weight loss and malaise. ↑BP is often a feature, due to renal artery stenosis. Complications include aortic valve regurgitation, aortic aneurysm and dissection; ischaemic stroke (↑BP and thrombus); and ischaemic heart disease. *Diagnosis:* ↑ESR and CRP; MRI/PET allows earlier diagnosis than standard angiography. *℞:* Prednisolone (1mg/kg/d PO). Methotrexate or cyclophosphamide have been used in resistant cases. BP control is essential to ↓risk of stroke. Angioplasty ± stenting, or bypass surgery is performed for critical stenosis. *Prognosis:* ~95% survival at 15 years. *Mikito Takayasu, 1860–1938 (Japanese ophthalmologist)*







MR angiography



See: New Engl J Med 2017;376:1973-81. Case 15-2017: A 27-Year-Old Woman with Anemia, Thrombocytosis, and Skin Lesions after Travel Abroad. DD: systemic granulomatous disease. Takayasu's arteritis.

A 64-year-old man developed **diplopia** due to a right sixth nerve palsy, lethargy, weight loss and skin lesions on the right leg which were thought to be **erythema nodosum**. Six weeks later, he presented with aches and pains in his shoulders, which his doctor thought were due to **polymyalgia rheumatica**. He improved dramatically on steroids but unfortunately they had to be withdrawn because of hypertension. On investigation, he had an **ESR** of 104 mm/h, a polymorphonuclear leucocytosis and some **proteinuria** (1.5 g/24h) with occasional granular casts. Biopsy of a skin lesion showed non-specific changes. A **renal biopsy** was normal. *No diagnosis was possible*.

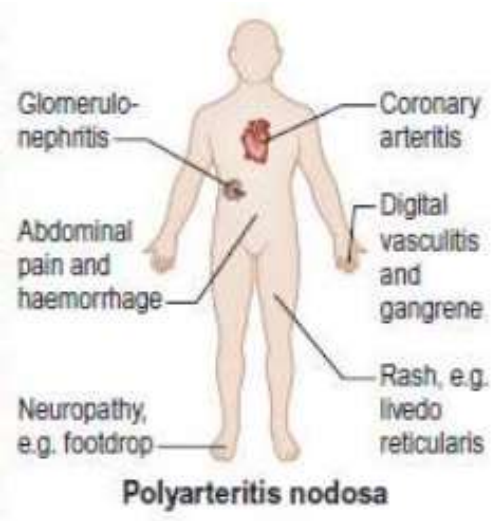
Four weeks later, he developed profound malaise with fever, marked muscle weakness and anaemia. His haemoglobin was 77g/l with a CRP of 70mg/l, a negative direct Coombs' test and a reticulocyte count of 5.4%. His blood urea, serum creatinine and creatinine clearance were normal, as was his serum creatine kinase level. His ANA, dsDNA binding and antineutrophil cytoplasmic antibodies (ANCA) were negative, with normal C3 and C4 complement levels. **Biopsy of an affected calf muscle** showed a florid arteritis. All the medium-sized arteries showed reduction of their lumens or complete occlusion. On the basis of this muscle biopsy, a firm diagnosis of **polyarteritis nodosa** was made. The patient was started on 60mg of prednisolone per day. Over the next few days his temperature fell and his symptoms improved.

A 70-year-old man presented with acute onset of **profuse bleeding per rectum**. An urgent colonoscopy showed blood throughout the colon and distal ileum but failed to localise the source. Subsequent visceral arteriography revealed **pseudoaneurysms** of the branches of the superior **mesenteric artery** and left **gastric artery**. The bleeding stopped spontaneously and the aetiology of the bleeding was later found out to be secondary to polyarteritis nodosa (PAN). The presence of profuse gastrointestinal bleeding as the sole manifestation at presentation in PAN is under-reported. Early diagnosis of PAN in patients with haemodynamically significant bleeding is necessary as prompt initiation of immunosuppressive therapy helps prevent relapses. With this case report, we highlight one of the unusual presentations of PAN and the favourable response to **immunosuppression with pulsed dose steroid**s.

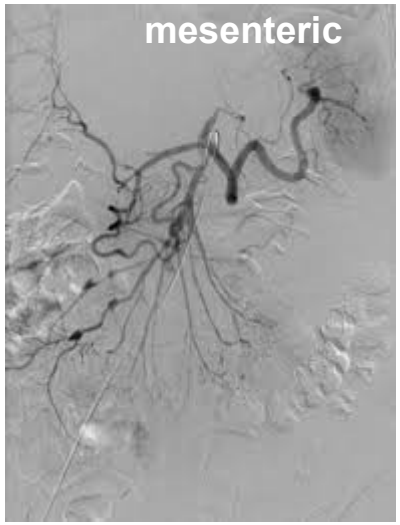
A 34-year-old man presented to our facility with a two-week history of **slow-resolving pneumonia**. On physical examination he had panniculitic type **tender skin nodules** with background **livedo reticularis**. A **skin biopsy** was suggestive of a small and medium vessel vasculitis compatible with polyarteritis nodosa. He was tested positive for hepatitis C antibodies. Serum cryoglobulin test and perinuclear antineutrophilic cytoplasmic antibody test were negative. Serum complement levels were reduced. He was diagnosed as having classic polyarteritis nodosa associated with hepatitis C infection. He later developed **left-sided radiculopathy involving both upper and lower limbs** and an **ischemic cardiac event**. His hepatitis C infection was managed with polyethylene glycol-interferon 2α combined with oral ribavirin. Simultaneously, his classic polyarteritis nodosa was treated with **prednisolone and cyclophosphamide**. He made a good recovery.

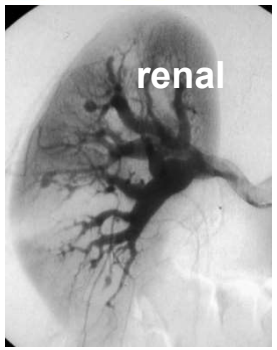
Polyarteritis nodosa (PAN)

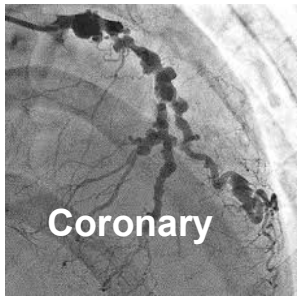
PAN is a necrotizing vasculitis that causes aneurysms and thrombosis in medium-sized arteries, leading to infarction in affected organs (fig 2), with severe systemic symptoms. ♂:♀≈2:1. It may be associated with hepatitis B, and is rare in the UK. *Symptoms:* Typically systemic features, plus predominantly skin (rash and 'punched out' ulcers), renal (main cause of death, though glomerulonephritis is not seen), cardiac, GI and GU involvement. See BOX. Coronary aneurysms occur in Kawasaki disease (childhood PAN variant, *OHCS* p646). *Tests:* Often WCC↑, mild eosinophilia (in 30%), anaemia, ESR↑, CRP↑, ANCA -ve. Renal or mesenteric angiography, or renal biopsy can be diagnostic. *Treatment:* Control BP meticulously. Refer to experts. Most respond to corticosteroids and cyclophosphamide. Hepatitis B should be treated with an antiviral (p407) after initial treatment with steroids.[62]



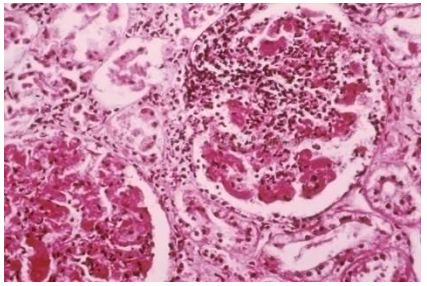
Polyarteritis nodosa







Necrotizing Arteriolitis and Glomerulitis →



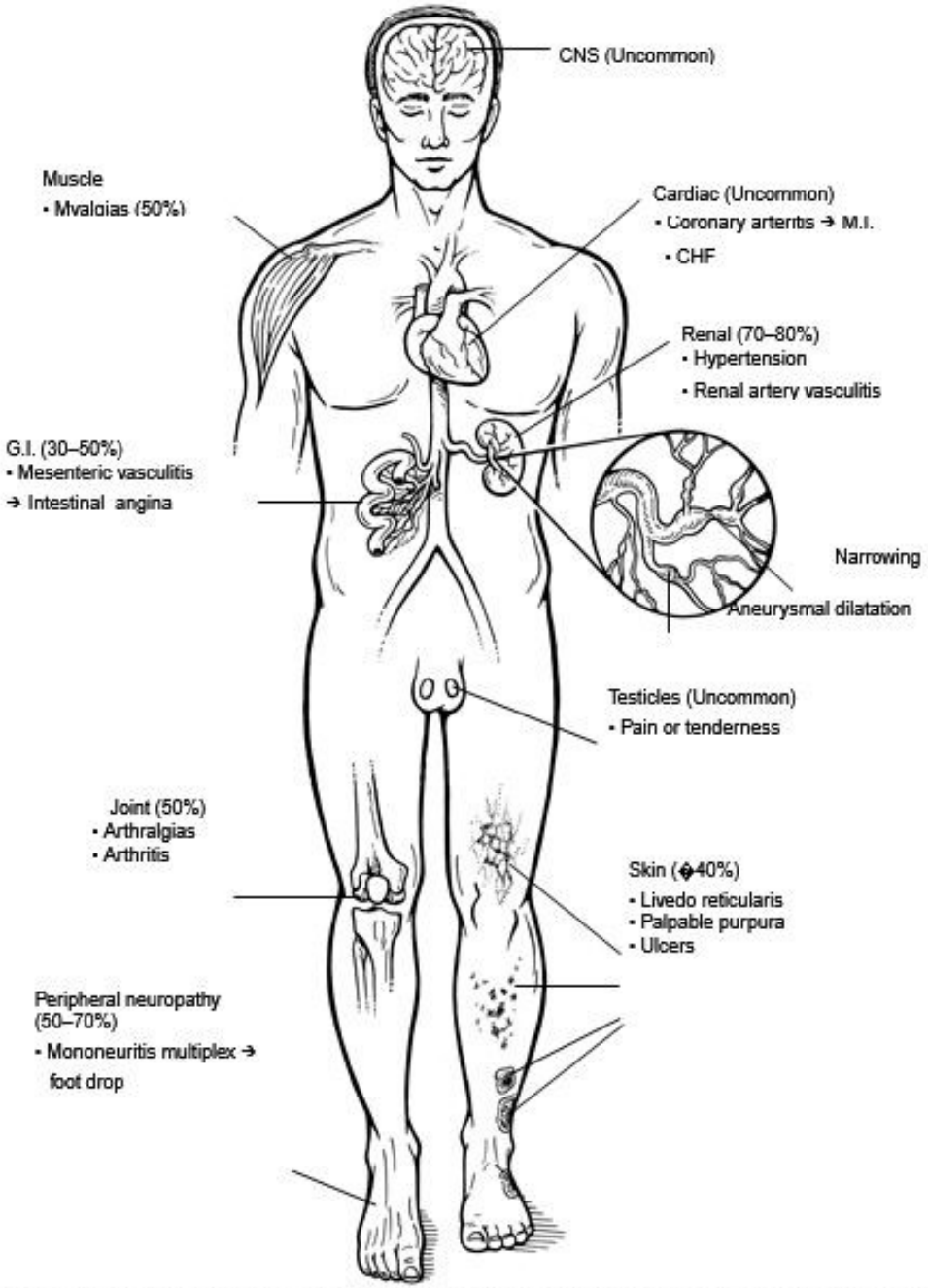
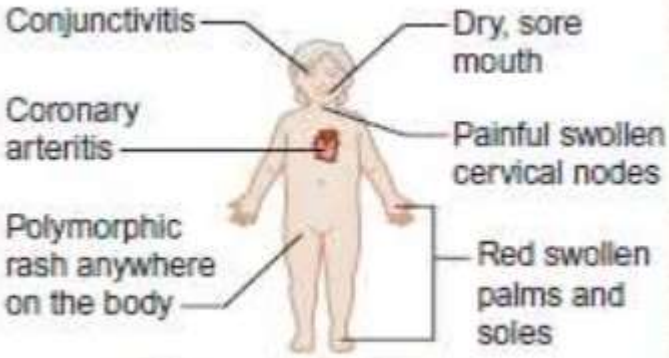


Figure 7. Manifestations of polyarteritis nodosa. Drawing of a visceral angiogram with classic vasculitis findings.

Fig 2. Renal angiogram showing multiple aneurysms in PAN.

KAWASAKI DISEASE



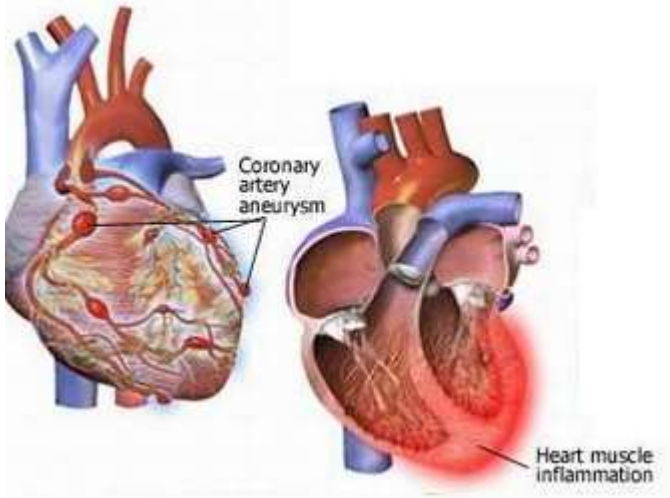
Kawasaki's disease

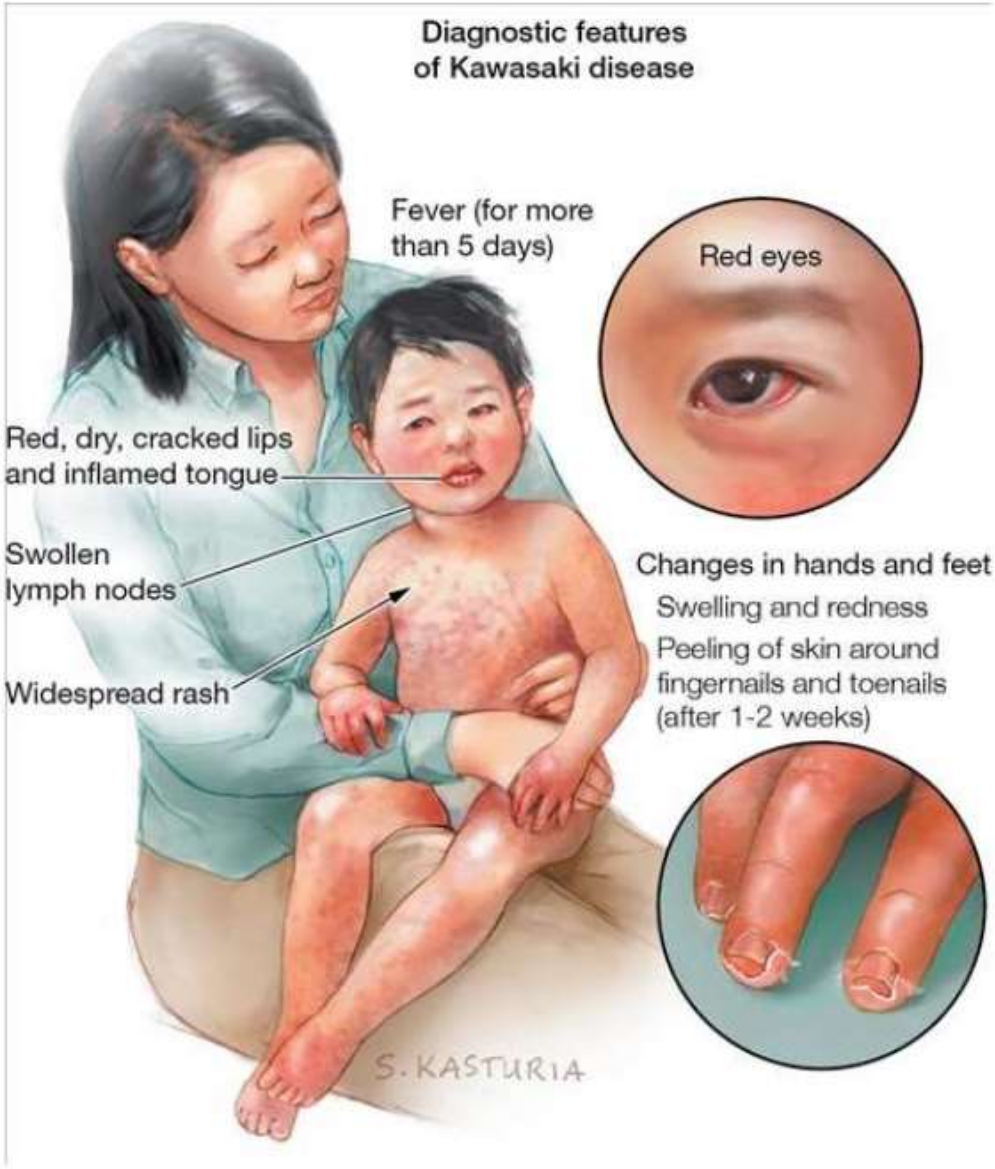
Kawasaki disease is a worldwide multisystemic disease. It is also known as the "mucocutaneous lymph node syndrome." It occurs mainly in children between the ages of 3 months and 5 years but can occur occasionally in adults as well. Kawasaki disease occurs significantly more often in Asians or native Pacific Islanders than in whites.

Kawasaki disease. It is an acute, self-limiting, mucocutaneous vasculitis characterized by the infiltration of vessel walls with mononuclear cells and later by IgA secreting plasma cells that can result in the destruction of the tunica media and aneurysm formation. Several infectious agents are implicated in its pathogenesis.

- Fever, conjunctivitis, oral mucosal changes, rash, cervical lymphadenopathy, peripheral extremity changes.
- Elevated erythrocyte sedimentation rate and C-reactive protein levels.

Major complications include arteritis and aneurysms of the coronary vessels, occurring in about 25% of untreated patients (and slightly over 10% of treated patients in a recent Danish review), on occasion causing myocardial infarction. The "incomplete" form appears more frequently




Diagnostic features
of Kawasaki disease
Fever (for more
than 5 days)
Red eyes
Red, dry, cracked lips
and inflamed tongue
Swollen
lymph nodes
Widespread rash
Changes in hands and feet
Swelling and redness
Peeling of skin around
fingernails and toenails
(after 1-2 weeks)
S. KASTURIA

Rheumatological emergencies:

- Acute SLE 556
- Acute systemic vasculitis 314 & 558
- Acute cord compression 470 & 545
- Methotrexate-induced pneumonitis 549
- Neutropenic sepsis 346
- Scleroderma: pulmonary hypertensive or renal crisis 314 & 554
- Septic arthritis 546

Skin manifestations of systemic diseases

Erythema nodosum (fig 1) Painful, blue-red, raised lesions on shins (± thighs/arms). *Causes:* sarcoidosis, drugs (sulfonamides, the Pill, dapsone), streptococcal infection. *Less common:* Crohn's/UC, BCG vaccination, leptospirosis, *Mycobacterium* (TB, leprosy), *Yersinia* or various viruses and fungi. Cause unknown in 30–50%.

Erythema multiforme (see *OHCS* p588) (fig 3) 'Target' lesions: symmetrical ± central blister, on palms/soles, limbs, and elsewhere. *Stevens–Johnson syndrome* (p724): a rare, severe variant with fever and mucosal involvement (mouth, genital, and eye ulcers), associated with a hypersensitivity reaction to drugs (NSAIDs, sulfonamides, anti-convulsants, allopurinol) or infections (herpes, *Mycoplasma*, orf—). Also seen in collagen disorders. 50% of cases are idiopathic. Get expert help in severe disease.

Erythema migrans (fig 7) Presents as a small papule at the site of a tick bite which develops into a spreading large erythematous ring, with central fading. It lasts from 48h to 3 months and there may be multiple lesions in disseminated disease. *Cause:* The rash is pathognomonic of Lyme disease and occurs in ~80% of cases (p430).

Erythema marginatum Pink coalescent rings on trunk which come and go. It is seen in rheumatic fever (or rarely other causes, eg drugs). See fig 1, p137.

Pyoderma gangrenosum (fig 2) Recurring nodulo-pustular ulcers, ~10cm wide, with tender red/blue overhanging necrotic edge, purulent surface, and healing with cribriform scars on leg, abdomen, or face. *Associations:* UC/Crohn's, autoimmune hepatitis, Wegener's*, myeloma, neoplasia. ♀>♂. *Treatment:* Get help. Oral steroids ± ciclosporin should be 1st-line therapy.[78]

Vitiligo (fig 4) *Vitellus* is Latin for *spotted calf:* typically white patches ± hyperpigmented borders. Sunlight makes them itch. *Associations:* autoimmune disorders; premature ovarian failure. Treat by camouflage cosmetics and sunscreens (± steroid creams ± dermabrasion). UK Vitiligo Society: 0800 018 2631.