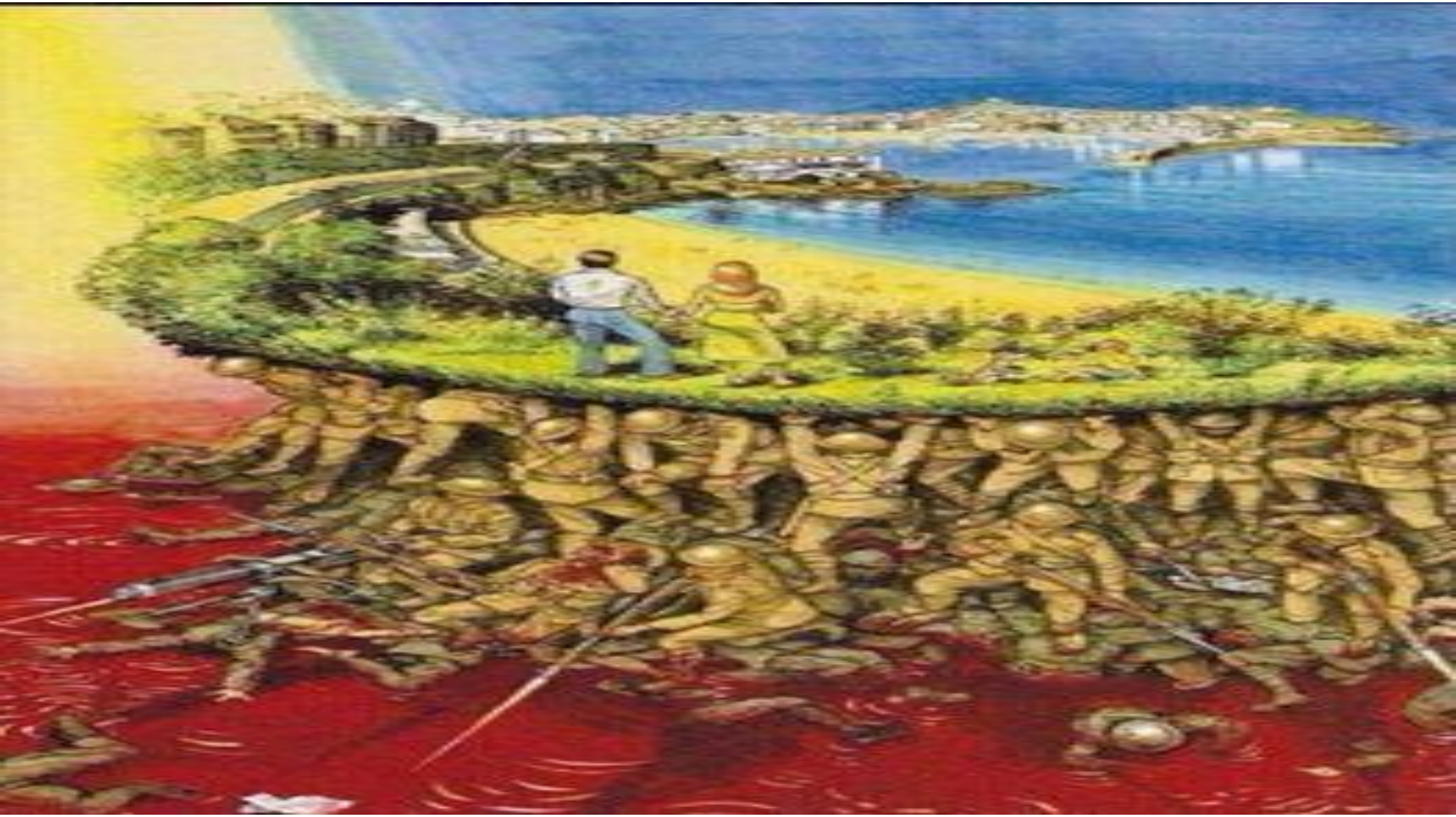
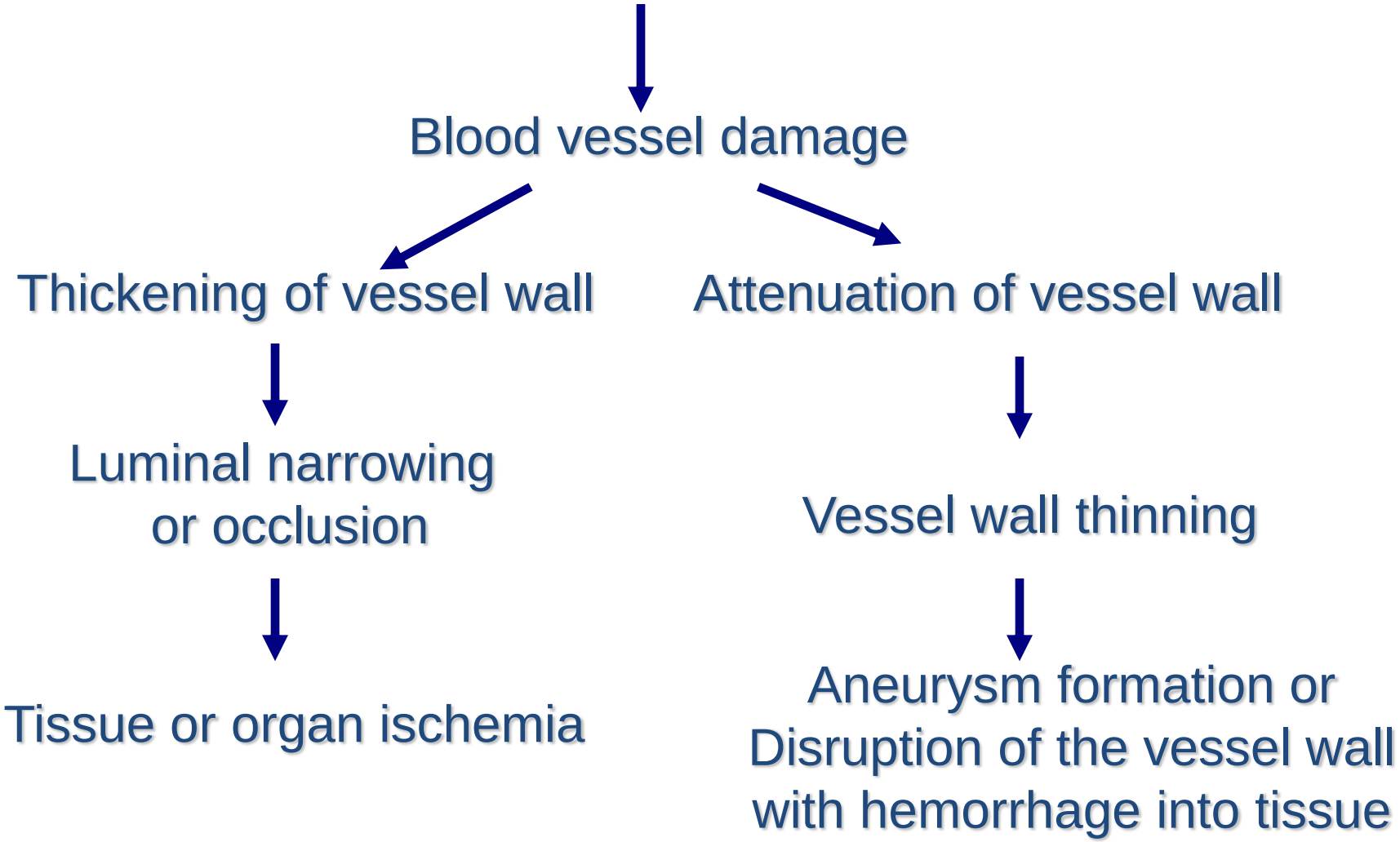
Vasculitis



- “Vasculitis” is a heterogeneous group of disorders characterized by inflammation within the walls of affected blood vessels.

Vasculitis = Inflammation of the Blood Vessel



- **Vasculitis affects all ages**, although some types are restricted to certain age groups
- **Vasculitis tends to affect Caucasians**, although many African-Americans are affected
- **Vasculitis has a genetic component**, but is not heritable
- **Vasculitis is a chronic relapsing disease**, although some patients experience prolonged remission

Definition

Pathologist

Inflammatory destruction of blood vessels

- **Infiltration** of vessel wall with inflammatory cell,Leukocytoclasis,Elastic membrane disruption
- **Fibrinoid necrosis** of the vessel wall
- **Ischemia**, occlusion, thrombosis
- **Aneurysm** formation
- Rupture, hemorrhage

Rheumatologist

- A clinicopathologic process characterized by inflammatory destruction of blood vessels that results in occlusion or destruction of the vessel and ischemia of the tissues supplied by that vessel.
- “Systemic vasculitides”

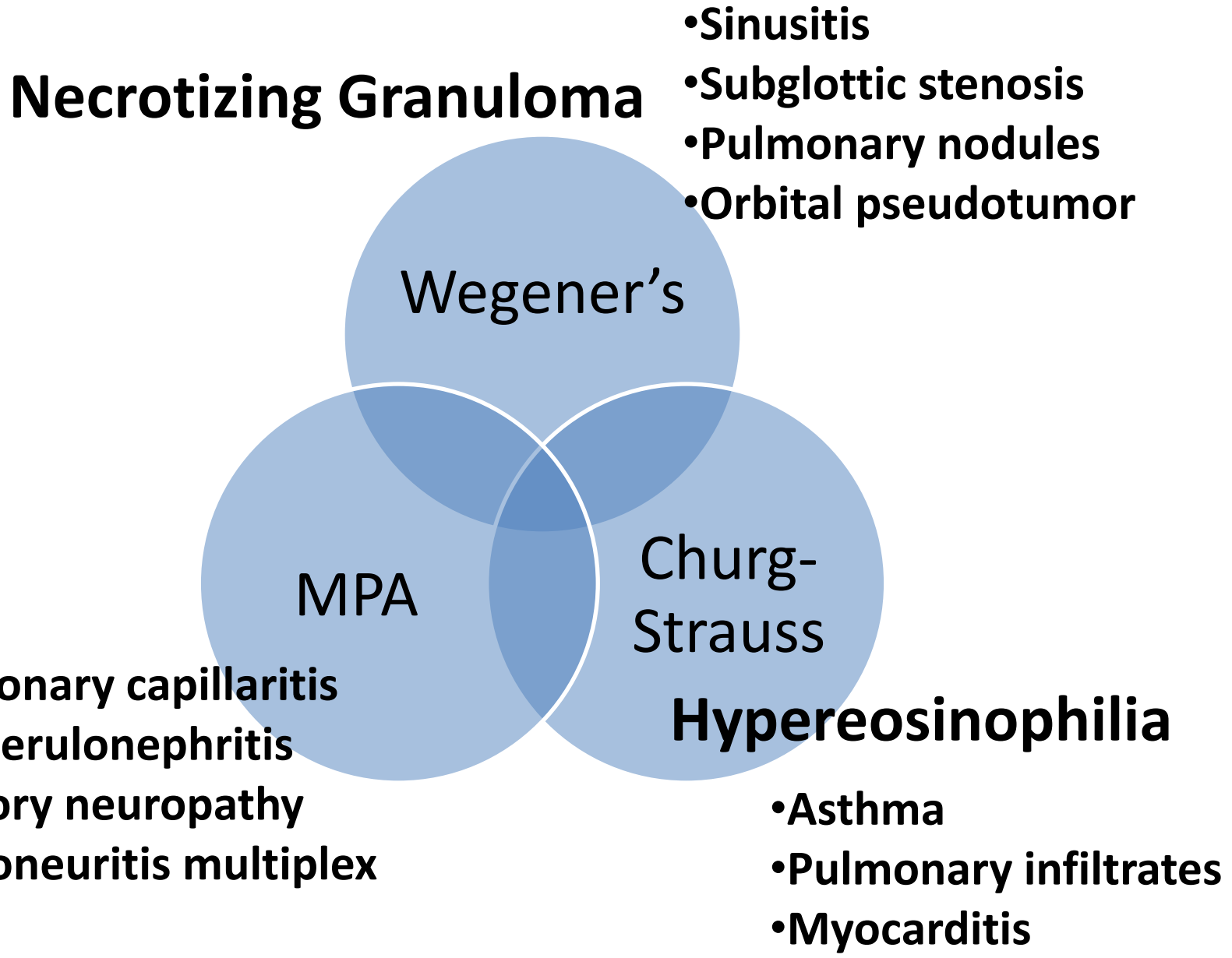
Classification

- Large-vessel vasculitis
  - Giant cell arteritis, Takayasu's arteritis
  - Behcet's disease, Cogan's syndrome
- Medium-vessel vasculitis
  - Polyarteritis nodosa
  - Buerger's disease, Central nervous system vasculitis, Kawasaki's disease, Rheumatoid vasculitis
- Small-vessel vasculitis
  - Wegener's, microscopic polyangiitis, Churg-Strauss
  - Cryoglobulinemic vasculitis, Henoch-Schönlein purpura,

- Large-vessel vasculitis
  - Aorta and the great vessels (subclavian, carotid)
  - Claudication, blindness, stroke
- Medium-vessel vasculitis
  - Arteries with muscular wall
  - Mononeuritis multiplex (wrist/foot drop), mesenteric ischemia, cutaneous ulcers
- Small-vessel vasculitis
  - Capillaries, arterioles, venules
  - Palpable purpura, glomerulonephritis, pulmonary hemorrhage

ANCA-associated vasculitides

- **Wegener's granulomatosis**: granulomatous inflammation involving the respiratory tract and necrotizing vasculitis affecting small to medium-sized vessels
- **Microscopic polyangiitis**: Necrotizing vasculitis affecting the small vessels.
- **Churg-Strauss Syndrome**: Eosinophil-rich and granulomatous inflammation involving the medium-sized vessels, and associated with asthma and eosinophilia


Necrotizing Granuloma
•Sinusitis
•Subglottic stenosis
•Pulmonary nodules
•Orbital pseudotumor
Wegener's
MPA
Churg-Strauss
•Pulmonary capillaritis
•Glomerulonephritis
•Sensory neuropathy
•Mononeuritis multiplex
Hypereosinophilia
•Asthma
•Pulmonary infiltrates
•Myocarditis

Vasculitis Is Not One Specific Disease

Blood vessel inflammation can be seen in a variety of settings

Primary Vasculitides

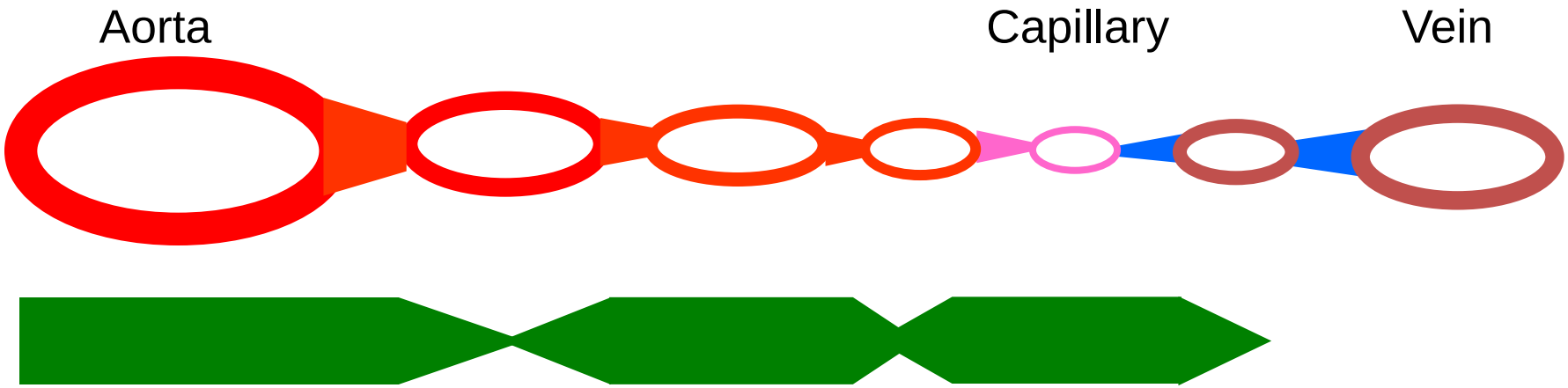
Unique disease entities without a currently identified underlying cause where vasculitis forms the pathological basis of tissue injury

- Giant cell arteritis
- Takayasu's arteritis
- Kawasaki disease
- Polyarteritis nodosa
- Wegener's granulomatosis
- Microscopic polyangiitis
- Churg-Strauss syndrome
- Henoch-Schönlein purpura

Secondary Vasculitides

Vasculitis occurring secondary to an underlying disease or exposure

- Medications
- Infection
- Malignancy
- Transplant
- Cryoglobulinemia
- Connective tissue disease
  (Rheumatoid arthritis, SLE
  Inflammatory myositis)



Large Vessel	Medium Vessel	Small Vessel
Giant cell arteritis	Polyarteritis nodosa	Wegener's granulomatosis
Takayasu's arteritis	Kawasaki disease	Microscopic polyangiitis
		Churg-Strauss syndrome
		Henoch-Schönlein purpura
		Isolated cutaneous vasculitis

Vessel size plays a role in:

Symptoms and signs

Methods of diagnostic evaluation

Diagnosis

- **Diagnosis of a systemic vasculitis is often a diagnosis of exclusion, based on recognition of the clinical syndrome**
  - e.g. Churg-Strauss: adult onset asthma x 2 years, followed by atypical pneumonias, followed by peripheral nerve involvement
- **Biopsy of involved organ is the most straightforward method of establishing a diagnosis**
  - Biopsy may be helpful to exclude infection/malignancy
- **Other tests may be suggestive, but not diagnostic**
  - ESR, CRP
  - CT: pulmonary hemorrhage, cavitary lesions
  - Bronchoscopy: pulmonary hemorrhage (hemosiderosis)
  - Urinalysis: for patients with kidney vasculitis
  - ANCA (antineutrophil cytoplasmic antibodies)
  - Angiogram (including MRA, CT-angiogram)

Treatment

- **Remission induction**:
  - Cyclophosphamide 2mg/kg po qd x 3-6 months
    [or 15 mg/kg IV q 2 wk x3 then q 3 weeks x 6-12 months]
  - Prednisone 1mg/kg po qd x 1 month, then taper
  - [Bactrim, Calcium, Vitamin D]
- **Remission maintenance** (minimum 2 years)
  - Methotrexate 20-25 mg po q week + folate
  - Azathioprine 2mg/kg po qd
  - Mycophenolate mofetil 1.5 g po BID
  - Leflunomide 20-30 mg po BID

Monitoring

- Large-vessel vasculitis
  - **MRI/MRA** chest/abdomen/pelvis every 6-12 months
- Medium-vessel vasculitis
  - **Mesenteric angiogram** to assess disease activity
  - **EMG/NCV** to monitor nerve damage
  - **Wound care** for cutaneous ulcers
- Small-vessel vasculitis
  - **Chest CT** every 6-12 months
  - **Blood and urine tests** every 1-4 weeks

Long-term Damage

- Large-vessel vasculitis
  - **Blindness, Stroke**
  - **Claudication:** "Angina" of the arms
- Medium-vessel vasculitis
  - **Foot drop:** inability to lift a foot
  - **Wrist drop:** inability to lift a hand
  - **Cutaneous ulcerations**
- Small-vessel vasculitis
  - **Oxygen dependence**
  - **Renal insufficiency/failure**

Summary

- The systemic vasculitides are chronic diseases, characterized by relapse and remission
- Achieving remission requires intense monitoring by a multidisciplinary team with expertise in these diseases
- Even after achieving disease remission, patients will continue to suffer from the chronic, irreversible consequences of both the disease and its therapies
- Pain and fatigue are common consequences of vasculitis that are independent of disease activity and generally fail to respond to immunosuppression

- The major forms of primary systemic vasculitis are listed in Secondary livedo reticularis, now more properly known as livedo racemosa, occurs in association with diseases that cause vascular obstruction or inflammation

- **Livedo racemosa** resembles idiopathic livedo reticularis but has a wider distribution (often found on trunk and buttocks as well as extremities) and its lesions are more irregular,broken, and circular. Of particular importance is the link with antiphospholipid antibody syndrome(25%), vasculitides (particularly polyarteritis nodosa), cholesterol emboli syndrome,thrombocythemia, cryoglobulinemia, cold agglutinin disease, primary hyperoxaluria, and disseminated intravascular coagulation.

PMR & GIANT CELL ARTERITIS

- Age over 50 years.Markedly elevated ESR and CRP.
- **Polymyalgia rheumatica:** pain and stiffness in shoulders and hips lasting for several weeks without other explanation frequently in association with fever, malaise, and weight loss, without muscle weakness.
- **Giant cell arteritis(**systemic panarteritis affecting medium-sized and large vessels)**:** headache, jaw claudication, or throat pain, polymyalgia rheumatica, visual abnormalities, fever associated with rigors and sweats

The temporal artery is usually normal on physical examination but may be nodular, enlarged, tender, or pulseless.Blindness usually results from the syndrome of anterior ischemic optic neuropathy,

caused by occlusive arteritis.

Giant cell arteritis has affected the aorta or its major branches

- **Laboratory Findings**

1. Polymyalgia rheumatica—Anemia and elevated acute- phase reactants.

2. Giant cell arteritis—Nearly 90% of patients with giant cell arteritis have high ESR ,high CRP. Most patients also have a mild normochromic, normocytic anemia and thrombocytosis. The alkaline phosphatase (liver source) is elevated in 20%.

- **Differential Diagnosis**

rheumatic diseases (such as rheumatoid arthritis other systemic vasculitides, plasma cell myeloma, and other malignant disorders) and chronic

infections (such as bacterial endocarditis and osteomyelitis).

- **Treatment**

A. Polymyalgia Rheumatica

Patients treated with prednisone, 10–20 mg/day orallywith dramatic improvement within 72 hours. Usually after2–4 weeks of treatment, slow tapering of the prednisone can be attempted for a minimum 1 year Disease flares are common (50% or more) as prednisone is tapered. The addition of weekly methotrexate may increase the chance of successfully tapering prednisone in some patients.

- **B. Giant Cell Arteritis**

Once blindness develops, it is usually permanent. Visual loss, intravenous pulse methylprednisolone (eg, 1 g daily for 3 days) Therefore, therapy with prednisone (60 mg/day orally) should be initiated immediately.

Retrospective studies suggest that low-dose aspirin (~81 mg/day orally) may reduce the chance of visual los.

Diagnostic findings of giant cell arteritis may still be present 2 weeks (or even considerably longer) after

starting corticosteroids.

Typically, a positive biopsy shows inflammatory infiltrate in the media and adventitia with lymphocytes, histiocytes, plasma cells, and giant cells. An adequate biopsy specimen is essential (at least 2 cm in length is ideal), because the disease may be segmental. Unilateral temporal artery biopsies are positive in approximately 80–85% of patients, but bilateral biopsies add incrementally to the yield

- Imaging of the temporal artery with ultrasonography, MRI, or CT angiography can sometimes obviate the need for biopsy.

- Prednisone should be continued in a dosage of 60 mg/day orally for about 1 month, almost all patients will have a normal ESR.

The ESR often rises slightly as the prednisone is tapered, even as the disease remains quiescent.

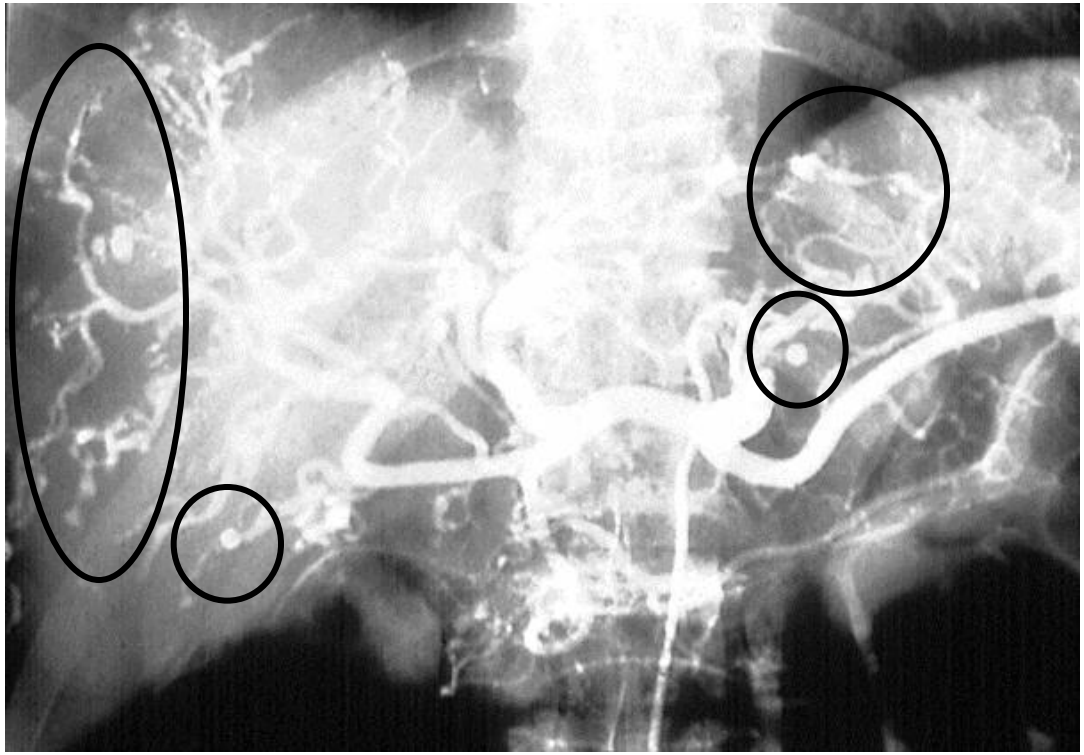
- Tocilizumab, an inhibitor of the IL-6 receptor, is FDA approved for giant cell arteritis that can reduce the prolonged use of prednisone and its side effects .After 1 year of treatment, tocilizumab achieves corticosteroid-free remission inapproximately 50% of patients.

TAKAYASU ARTERITIS

- Takayasu arteritis is a granulomatous vasculitis of the aorta and its major branches.
- Takayasu arteritis can present with nonspecific constitutional symptoms of malaise, fever, and weight loss or with manifestations of vascular inflammation and damage: diminished pulses, unequal blood pressures in the arms, carotidynia (tenderness over the carotid arteries), bruits over carotids and subclavian arteries, retinopathy, limb claudication, and hypertension.

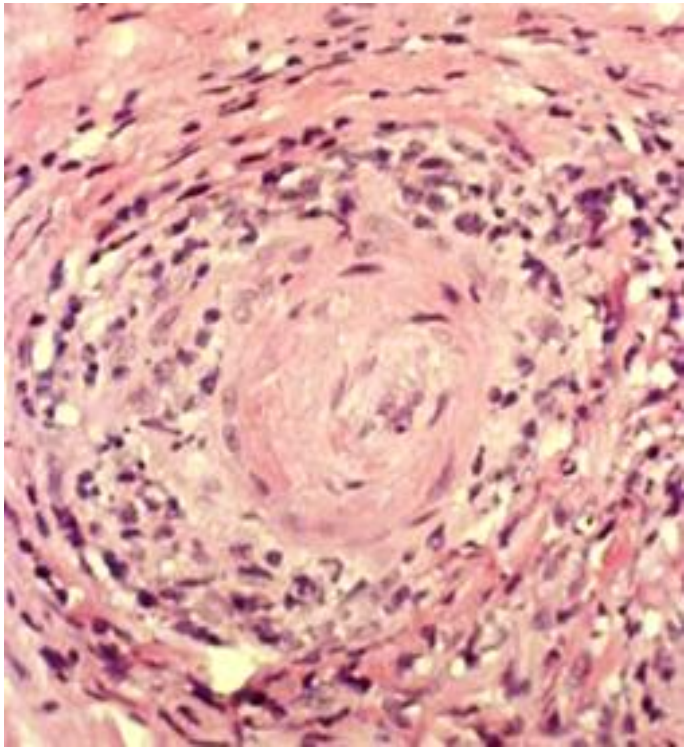
Medium Vessel Vasculitis

Mesenteric Arteriogram



Microaneurysms, stenoses, beading

Biopsy



Courtesy of Carol A. Langford

Vessel supplying sural nerve

Medium Vessel Vasculitis: Polyarteritis Nodosa

Mutation in adenosine deaminase 2,Hepatits B

Clinical Features:

Often presents with acute severe disease

– Systemic features	Fever, weight loss, arthralgias, night sweats
– Nerve	Mononeuritis multiplex (ie: foot drop, wrist drop)
– Renal	Hypertension, infarction
– GI tract.	Pain,nausea ,vomiting infarction, perforation, bleeding, acalculous cholecystitis or appendicitis.
– Skin	Purpura ,ulcers, nodules
– Digital infarction	Ischemic finger / toe

Polyarteritis Nodosa

Laboratories:

Elevated ESR
Anemia, mild elevations in WBC and platelets
May see LFT abnormalities, microscopic hematuria
A PAN-like vasculitis can occur with hepatitis B or C
ANCA-negative

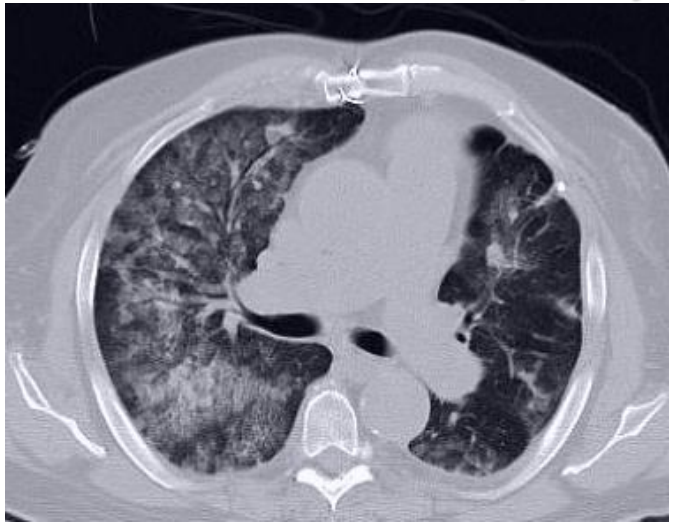
Diagnosed by: Arteriography, biopsies

Treatment:

Prednisone + cyclophosphamide, Methotrexate or azathioprine are used to maintain remissions induced by cyclophosphamide. Pulse methylprednisolone for patients who are critically ill at presentation
Antiviral treatment if hepatitis B or C are present

Small Vessel Vasculitis

Capillary, arteriole, venule



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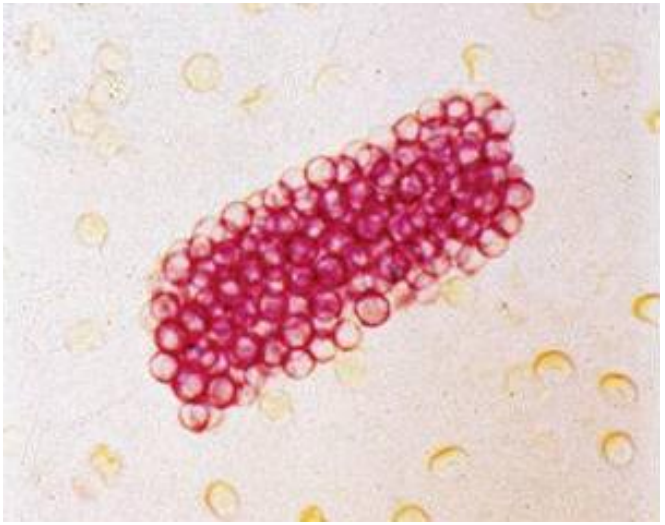
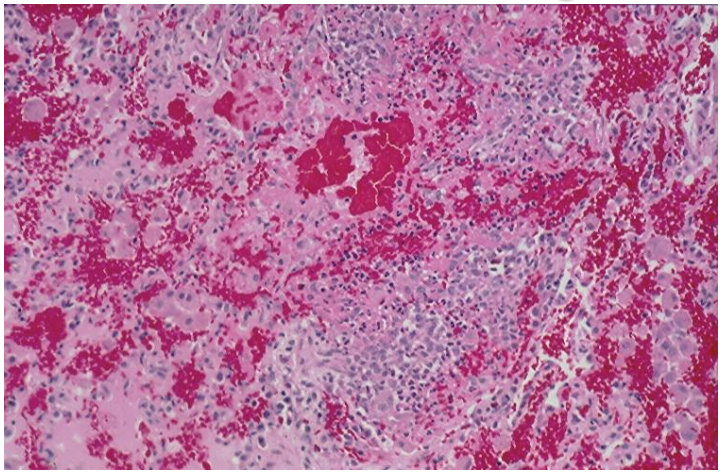


Alveolar hemorrhage



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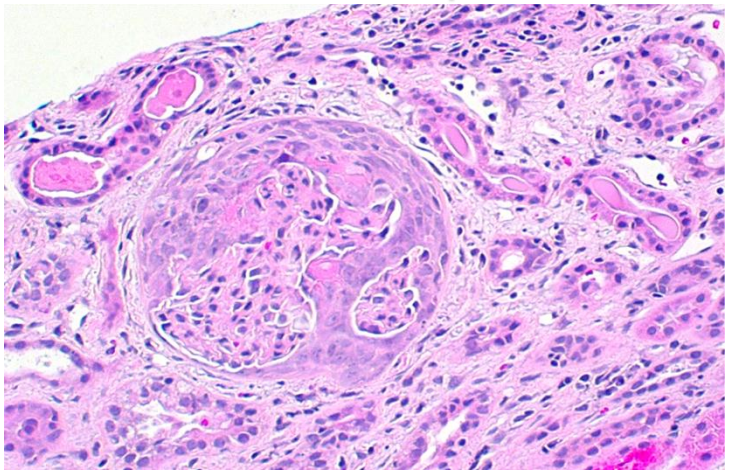
Glomerulonephritis



Courtesy of Carol A. Langford

Wegener's Granulomatosis

ANCAs (90% of patients), usually directed against proteinase-3 (less commonly

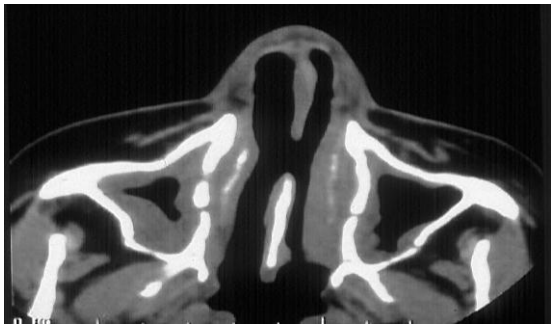
Necrotizing granulomatous lesions of both upper and lower respiratory tract, glomerulonephritis, and other organ manifestations.

Without treatment, generalized disease is invariably fatal, with most patients surviving less than 1 year after diagnosis.

It occurs most commonly in the fourth and fifth decades of life and affects men and women with equal frequency

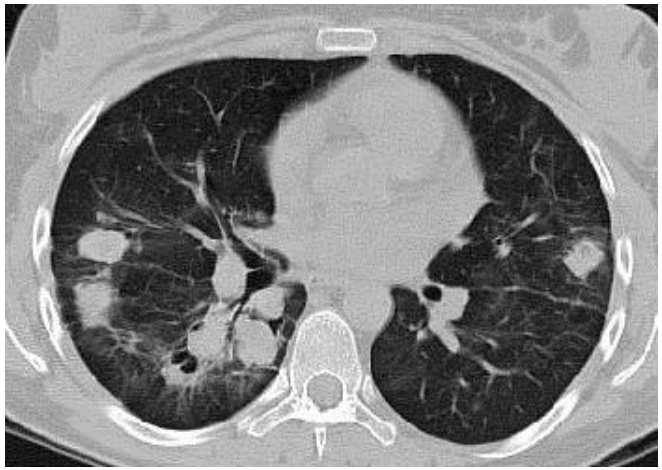
Small Vessel Vasculitis: Wegener's Granulomatosis

Sinus (>95%)



episcleritis, anterior uveitis, or peripheral ulcerative keratitis)

Lung (85%)



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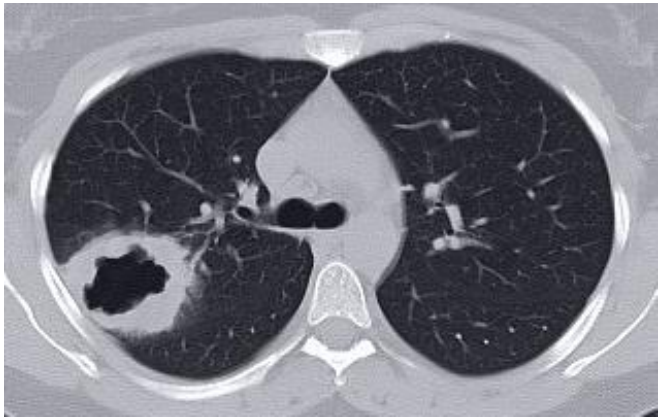


Courtesy of Carol A. Langford

Kidney (80%)

20% at diagnosis
80% during course

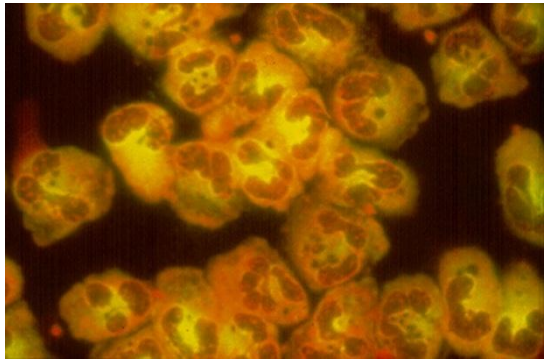
Can be rapidly progressive
Typically asymptomatic
May lead to renal failure

Detected by urinalysis:

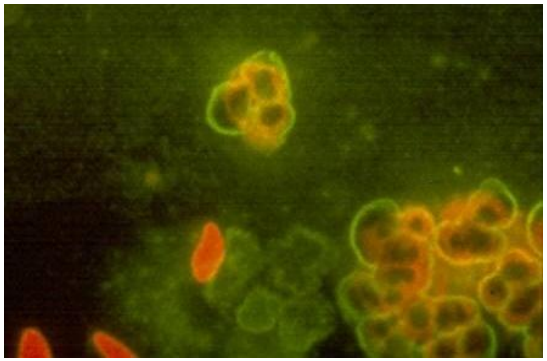
Proteinuria,
Hematuria
Red blood cell casts

Antineutrophil Cytoplasmic Antibodies (ANCA)

cANCA
cytoplasmic staining



pANCA
perinuclear staining



Target Antigens In Vasculitis

Proteinase 3 (PR3)

Myeloperoxidase (MPO)

	PR3-ANCA	MPO-ANCA	ANCA (-)
Wegener's granulomatosis	75-90%	5-20%	up to 20%
Microscopic polyangiitis	10-50%	50-80%	up to 20%
Churg-Strauss syndrome	3-20%	2-40%	up to 60%

Key Clinical Issues Regarding ANCA

- Can ANCA be used to diagnose Wegener's granulomatosis?

  Usually no – because of the toxicity of therapy and the need for diagnostic precision biopsy still required in most people

  ANCA can be helpful but is not necessary for diagnosis

- Do high ANCA levels indicate active vasculitis?

  No - In large cohorts, ANCA levels are higher overall in active disease but…..

  In individual patients ANCA does not correlate with disease activity and should not be used alone to guide treatment

Diagnosed by: Typically biopsy:vasculitis,granulomatous inflammation,geographic necrosis,acute and chronic inflammation.

Treatment: Prednisone + cyclophosphamide
Prednisone + methotrexate (non-severe disease)

C. Imaging CT is more sensitive than chest radiography; lesions include infiltrates, nodules,masses, and cavities.Pleural effusions are uncommon

Outcome: Survival:Untreated: 5 months .Treatment: 80% survival
Challenges:
- Damage from prior disease
- Treatment related toxicity
- 50-70% relapse

Treatment

Inducing remission:corticosteroids and either AntiCD20 or cyclophosphamide.

Maintenance of Remission

azathioprine, methotrexate , or rituximab

MICROSCOPIC POLYANGIITIS

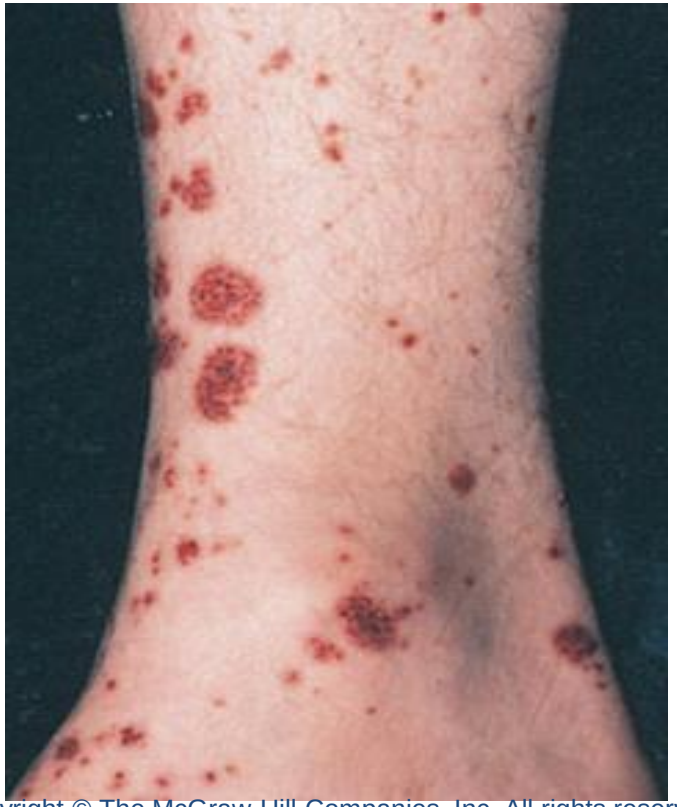
- Microscopic polyangiitis is a pauci-immune nongranulomatous necrotizing vasculitisthat affects small blood vessels (capillaries, venules, or arterioles), often causes glomerulonephritis and pulmonary capillaritis, and is often associated with ANCA
- Palpable and other signs of cutaneous vasculitis (ulcers, splinter hemorrhages, vesiculobullous lesions).
- Interstitial lung fibrosis, pulmonary hemorrhage may occur.
- Vasculitic neuropathy (mononeuritis multiplex) is also common

- **Laboratory Findings**
- **Traetment**

patients with severe disease, typically involving pulmonary hemorrhage and glomerulonephritis, require urgent induction treatment with corticosteroids and either cyclophosphamide or rituximab.

Azathioprine, or methotrexate (provided the patient has normal kidney function).

Small Vessel Vasculitis: Cutaneous Vasculitis



Cutaneous vasculitis represents the most common vasculitic manifestation encountered in clinical practice

Small Vessel Vasculitis: Cutaneous Vasculitis

< 30% no identified cause or disease outside of the skin

Treatment of isolated cutaneous vasculitis:

- Do not overtreat: recognize that this is not threatening
- Avoid the use of toxic immunosuppressive agents

> 70% occur in the setting of an underlying process:

- Medication
- Infection
- Malignancy
- Connective tissue disease
- Heralding feature of a primary systemic vasculitis

HENOCH-SCHÖNLEIN PURPURA

- The most common systemic vasculitis in children, occurs in adults as well.
- Typical features are palpable purpura, arthritis, and hematuria,abdominal pain espetially in children.
- Pathologic features include leukocytoclastic vasculitis with IgA deposition, with unknown cause.
- The purpuric skin lesions are typically located on the lower extremities but may also be seen on the whole body.
- The knees and ankles being most commonly involved joints.
-

- Abdominal pain secondary to vasculitis of the intestinal tract is often associated with gastrointestinal bleeding.
- Hematuria signals the presence of a renal lesion that is usually reversible, may progress to chronic kidney disease especially in adults.
- Biopsy of the kidney reveals segmental glomerulonephritis with crescents and mesangial deposition of IgA.
- Chronic courses occur in adults than in children.
- The value of corticosteroids has been controversial. Severe disease is often treated with aggressive immunosuppressive agents, such as mycophenolate mofetil

CRYOGLOBULINEMIA

Cryoglobulinemia can be associated with an immunecomplex mediated, small-vessel vasculitis. Chronic infection with hepatitis C is the most common underlying condition; can occur also with other chronic infections (such as ubacute bacterial endocarditis, osteomyelitis, HIV, and hepatitis B), with connective tissues diseases (especially Sjögren syndrome), and with lympho-proliferative disorders.

- **Clinical Findings**

recurrent palpable purpura(predominantly on the lower extremities) and peripheral neuropathy. A proliferative glomerulonephritis can develop and can manifest as rapidly progressive, abdominal pain, digital gangrene,

and pulmonary disease may also occur.

The diagnosis is based on a compatible clinical

picture and a positive serum test for

cryoglobulins.

The presence of a low C4 level

- **Treatment**

-Antiviral regimens for hepatitis C

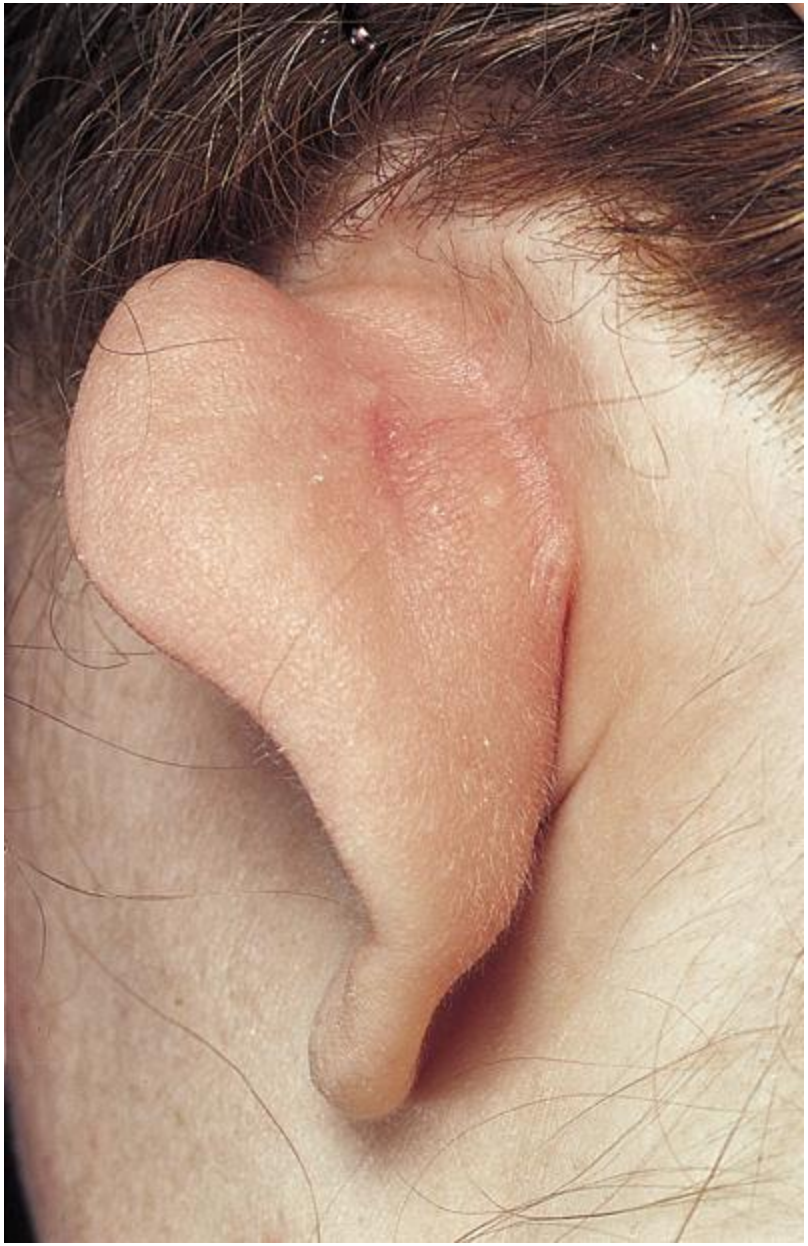
-Patients with severe vasculitis (eg, extensive digital gangrene,extensive neuropathy, and rapidly progressive glomerulonephritis) and hepatitis C should receive immunosuppressive therapy with corticosteroids and either rituximab or Cyclophosphamide

Plasma exchange

RELAPSING POLYCHONDRITIS

- This disease is characterized by inflammatory destructive lesions of cartilaginous structures, principally the ears, nose, trachea, and larynx. Nearly 40% of cases are associated with another disease, especially immunologic disorders (such as SLE, rheumatoid arthritis, or Hashimoto thyroiditis) or cancers (such as plasma cell
- myeloma) or hematologic disorders (such as myelodysplastic syndrome).
- The disease, which is usually episodic, affects males and females equally. The cartilage is painful, swollen, and tender during an attack and subsequently becomes atrophic, resulting in permanent deformity.

- Laryngotracheal and bronchial chondritis can lead to life-threatening airway narrowing and collapse. Noncartilaginous manifestations of the disease include fever, episcleritis, uveitis, deafness, aortic regurgitation, and rarely glomerulonephritis. In 85% of patients, a migratory, asymmetric, and seronegative arthropathy occurs,affecting both large and small joints and the costochondral junctions.
- Prednisone, is often effective. Dapsone or methotrexate . Involvement of the tracheobronchial tree may respond to inhibitors of TNF.



Polychondritis of the ear


هل أنت مع
التيار العلماني
أم مع التيار الاسلامي ؟
أنا مع
التيار الكهربائي !!!