Vascular Diseases

Vasculitis — Inflammation of the blood vessel walls.

Can be ***infectious*** or ***non-infectious***.

Clinical findings are diverse and depend on the organ(s) involved.
Generally have **constitutional symptoms** (fever, myalgias, malaise), +/- localized tissue damage due to **ischemia or bleeding** (leading to single or multiorgan dysfunction). **Elevated CRP and ESR**.

Classified mostly based on this size of the vessel usually involved and the organs involved.

Many systemic rheumatologic diseases (e.g., Rheumatoid arthritis, sarcoidosis, and Systemic Lupus Erythematosus) can have associated vasculitis.

Main immunological mechanisms of Non-infectious vasculitis:

1) Immune Complex-associated Vasculitis—Antigen-antibody/complement complexes deposit in the vessel wall→ recruit inflammatory cells. Seen with many systemic immunological conditions (e.g., SLE), drug hypersensitivity, and viral infections.

2) Antineutrophil Cytoplasmic Antibodies (ANCA) —Antibodies react with neutrophil cytoplasmic antigens (ANCAs)→ activate neutrophils → degranulate → damages vessels.
2 types of ANCA: *MPO-ANCA* (formerly p-ANCA) seen with microscopic polyangiitis and Churg-Strauss, and *PR3-ANCA* (formerly c-ANCA) seen in Wegner's.

3) Anti-endothelial Cell Antibodies — Antibodies to endothelial cells

Variable Vessels
Behçet's disease
Cogan's syndrome

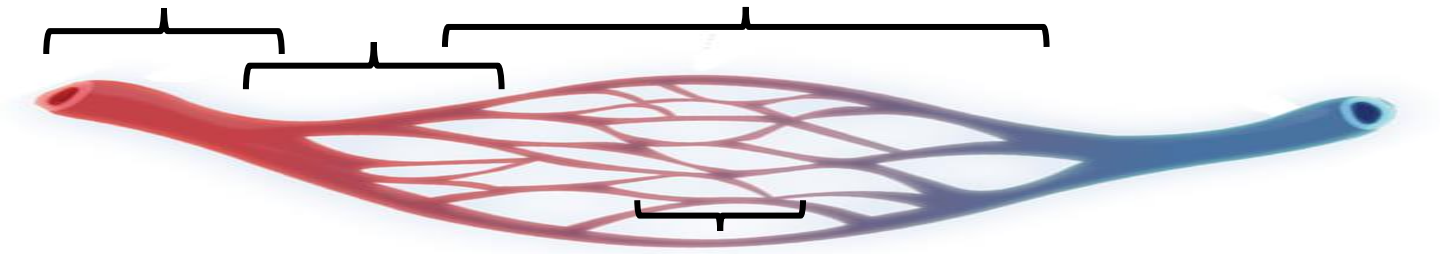
Small Vessels
Immune complex
IgA vasculitis (Henoch-Schönlein purpura)
Cryoglobulin vasculitis, SLE, Goodpasture disease

ANCA
Microscopic polyangiitis
Granulomatosis with polyangiitis (Wegner's)
Eosinophilic granulomatosis with polyangiitis (Churg-Strauss)

Medium Vessels
Immune complex
Polyarteritis nodosa

Anti-endothelial cell
Kawasaki disease

Large Vessels
Granulomatous
Giant-cell arteritis
Takayasu arteritis



Capillaries only
Anti-endothelial cell
Anti-GBM disease

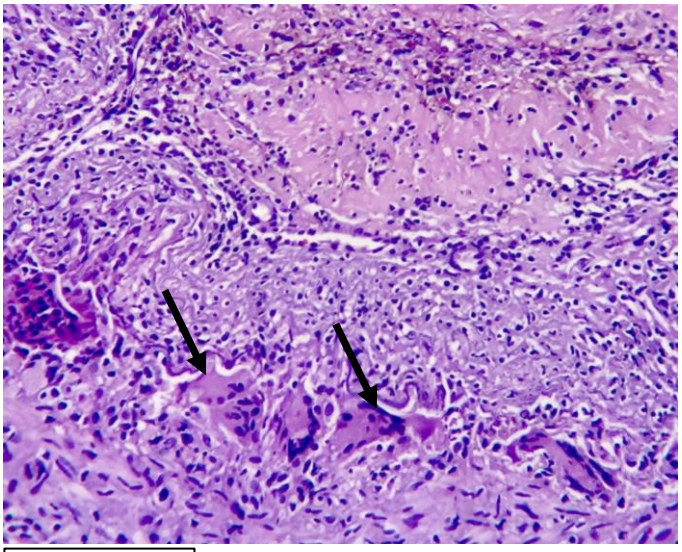
Based on the Chapel Hill Consensus Conference of 2012

Large Vessel Vasculitis

Involves large vessels (not inside of organs) with some medium-sized vessels
Histologically see **lymphohistiocytic inflammation of vessel wall with frequent granulomas/giant cells**.
Fragmentation of internal elastic lamina (IEL; best seen on EVG stain)
Patchy→ so get lots of levels and an EVG in biopsies. Nodular thickening of intima with medial scarring.

Takayasu Arteritis

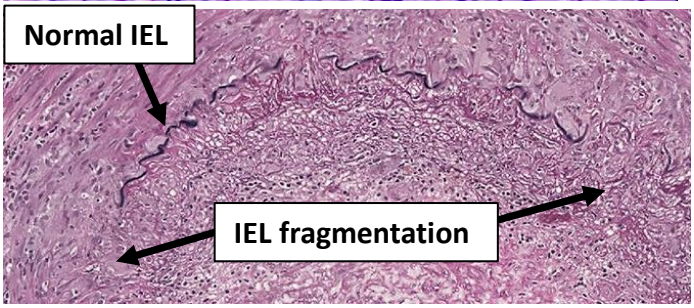
Predominantly impacts aorta (particularly the arch) and its major branches
Onset usually *before* age 50
Transmural fibrous thickening of aorta, with lumen narrowing, particularly of branching vessels→ loss of pulses in upper extremities.



Giant cell (Temporal) Arteritis

Usually impacts aorta and/or its major branches, with a predilection for the branches of the carotid and vertebral arteries, especially the temporal artery
Onset usually *after* age 50.
Most common vasculitis in elderly in US.
Often associated with polymyalgia rheumatica
Involvement of ophthalmic artery can cause *permanent blindness*, so considered a medical *emergency* requiring prompt Dx and treatment with corticosteroids.

As these processes are histologically *indistinguishable*, they are often identified clinically, primarily by age.

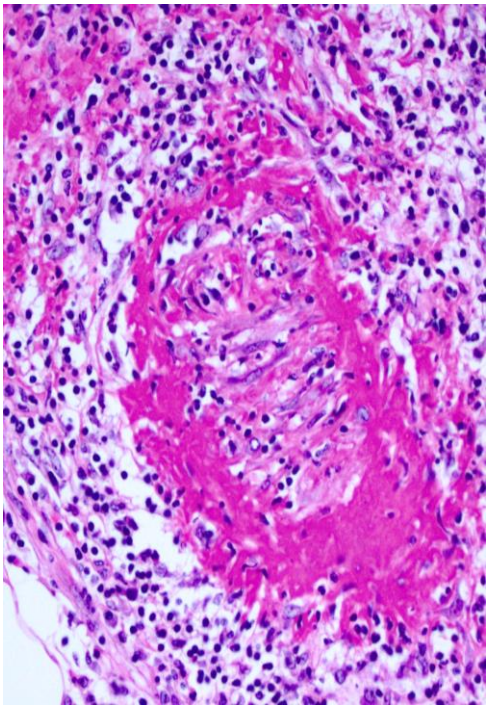


Medium Vessel Vasculitis

Involves main visceral arteries and their branches.
Inflammatory aneurysms and stenoses are common.

Polyarteritis Nodosa (PAN)

Transmural necrotizing arteritis of medium or small arteries (without glomerulonephritis or vasculitis of arterioles, capillaries, or venules) with mixed inflammation, fibrinoid necrosis, and thrombosis. Frequently involves renal artery and GI tract.
Often patchy/segmental.
Immune complex mediated.
~30% have chronic Hepatitis B

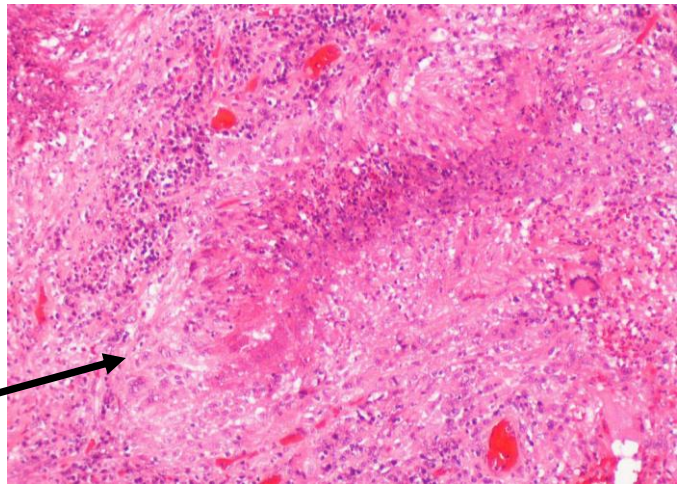


Kawasaki Disease *("Mucocutaneous lymph node syndrome")*

Arteritis impacts medium and small arteries.
Usually < 4 years old, presenting with oral, conjunctival and palmoplantar erythema ("strawberry tongue") with a desquamative rash and cervical lymphadenopathy. Often post-infectious.
Predominantly coronary arteries involved→ aneurysms & MI.
Autoantibodies to endothelial/smooth muscle cells.
Treat with IVIG and aspirin.

Small Vessel Vasculitis

Often neutrophil-predominant and **leukocytoclastic**→ fibrinoid necrosis, thrombosis, RBC extravasation.



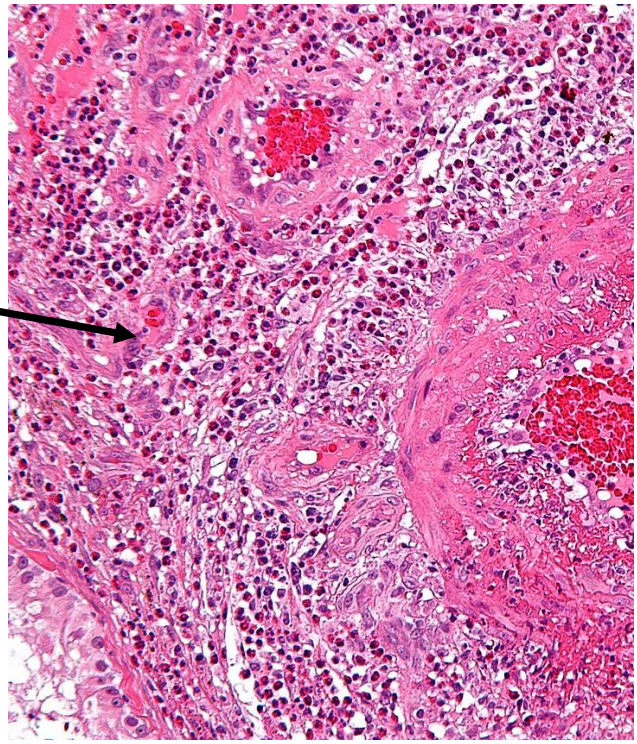
ANCA-mediated

Microscopic Polyangiitis (MPA)

Necrotizing vasculitis of small/medium vessels.
Mixed inflammation with fibrinoid necrosis
Very commonly involves kidney and lung.
MPO-ANCA usually positive.

Granulomatosis with Polyangiitis (Wegner's)

Necrotizing granulomatous inflammation.
Commonly impacts lung, nasal cavity, and kidney.
In lung/head see granulomas with geographic central necrosis and associated vasculitis→ form ulcers and nodules. In kidney can see crescentic glomerulonephritis.
PR3-ANCA positive.



Eosinophilic Granulomatosis with Polyangiitis (Churg-Strauss)

Eosinophil-rich and necrotizing granulomatous inflammation. Often impacts the lung. Associated with asthma and eosinophilia. MPO-ANCA usually positive.

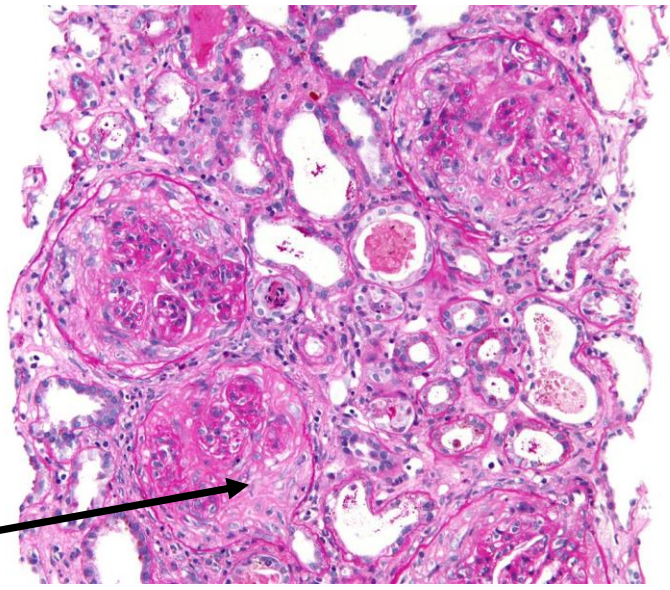
Immune complex-mediated

IgA Vasculitis (Henoch-Schönlein purpura)

Vasculitis with IgA1-dominiant immune deposits.
Often involves skin (palpable purpura), GI tract (abdominal pain), kidney, and joints (arthritis).
Most common systemic vasculitis in kids. Usually self-limited and post-infectious (often after URI).

Cryoglobulinemic Vasculitis

Serum cryoglobulins (Ig that precipitate out of solution at < 37°C)→ vessel deposits→ vasculitis. Often involves skin, kidney, and peripheral nerves. Highly associated with Hep C and monoclonal gammopathy.



Hypocomplementemic Urticarial Vasculitis (Anti-C1q)

Associated with anti-C1q antibodies. Immune complex→ activate complement cascade→ mast cell degranulation and neutrophil activation→ urticaria and small vessel vasculitis

Anti-Endothelial Cell Antibody-mediated

Anti-Glomerular Basement Membrane (GBM) Disease (Goodpasture Syndrome)

Impacts capillaries in kidney, lung, or both. In lung→ hemorrhage. In kidney→ crescentic glomerulonephritis.

Variable Vessel Vasculitis

Behçet's Disease
Vasculitis involving arteries or veins of any size.
Recurrent oral and/or genital aphthous ulcers, accompanied by cutaneous, ocular, articular, GI, and/or CNS lesions. Can get thrombosis or aneurysms.
Most common along "ancient silk road" (Middle East→ Asia)

Cogan's Syndrome
Systemic vasculitis with predominantly ocular and inner ear findings. May also involve aorta & heart.

Infectious Vasculitis

Most often due direct extension of infected tissue. Can cause aneurysms→ "Mycotic" aneurysms

Examples where vasculitis is an important component of disease:

Syphilis→ luminal obstruction and perivascular infiltrate of lymphocytes and plasma cells.

Fungi→ Aspergillus and Mucor can cause disseminated infection with angioinvasion. Usually immunocompromised patients. Causes obstruction→ tissue necrosis.

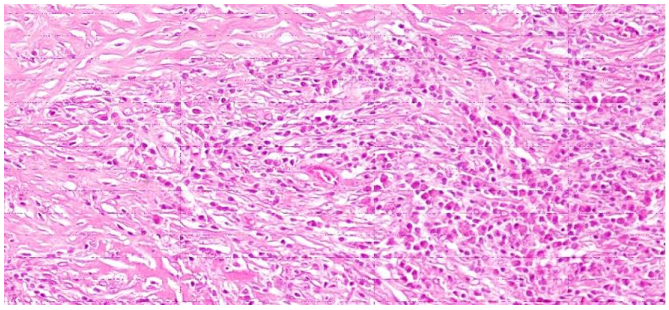
Other examples: Rocky mountain spotted fever, Q fever, Typhus, Meningococcus, Lyme disease

IgG4-related Aortitis/Periaortitis

Characteristic findings in adventitia: 1) Dense lymphoplasmacytic infiltrate, 2) Storiform-type fibrosis, 3) Obliterative phlebitis.

Must see >50 IgG4-positive plasma cells in a single HPF.

Most often older men.



Coagulopathic Disorders

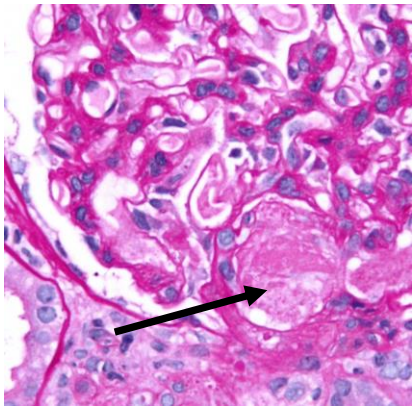
Look for "bland" (non-inflamed) thrombi in vessels

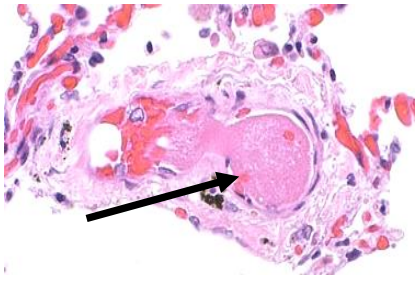
Disseminated Intravascular Coagulation (DIC)—Consumptive coagulopathy where systemic activation of the coagulation cascade leads to thrombosis of small vessels throughout the body (and also bleeding). Can occur in many settings (e.g., sepsis, trauma, etc…). See fibrin thrombi in small vessels.

Thrombotic Thrombocytopenic Purpura (TTP)—thrombotic microangiopathy with widespread platelet thrombi in small vessels→ hemolytic anemia, purpura, thrombocytopenia, renal dysfunction. Results from ADAMTS13 deficiency. See platelet-rich occlusive thrombi.

Hemolytic Uremic Syndrome (HUS)—Similar to TTP (thrombotic microangiopathy), but thrombi mostly limited to kidneys. Usually in Kids after eating *E. Coli* O157:H7 (makes Shiga-like toxin toxic to endothelial cells), which also causes bloody diarrhea.

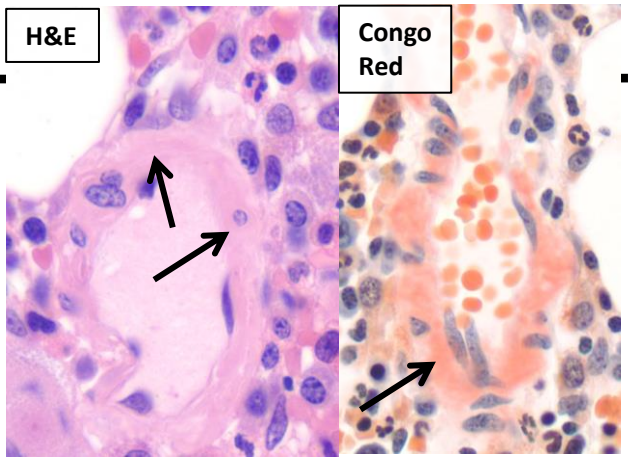
Heparin Induced Thrombocytopenia (HIT)—antibodies recognize heparin + platelet factor 4 complexes→ activate platelets→ thrombocytopenia and thrombus formation. Usually thrombi are in large vessels (e.g., DVT→ PE).





Vascular Deposition Disorders

Amyloidosis



Deposits of **abnormally folded protein** (rich in **β-sheets**) in vessels and tissues→ obstructs flow and makes rigid (impaired vasoreactivity) → ischemic injury; Also make vessel brittle→ hemorrhage.

Extracellular eosinophilic amorphous material (H&E)
Congo Red Stain → "Apple green" birefringence
Trichrome → greyish (vs Fibrosis→ bright blue)

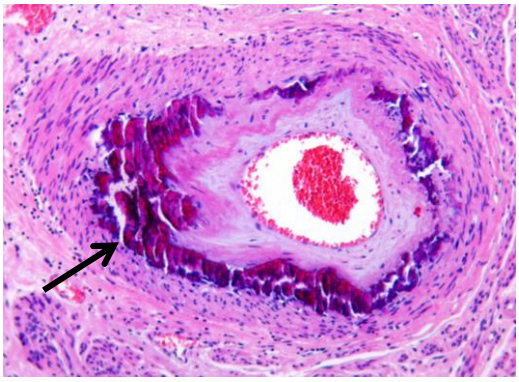
Can subtype (see below) to determine etiology using IF, Mass spectrometry, immunoblotting, IHC, etc…

Category	Associated Disease	Amyloid Protein	Precursor Protein
Systemic Amyloidosis			
Plasma cell dyscrasia (1°)	Multiple myeloma	AL	Immunoglobulin light chain (usually λ)
Reactive systemic amyloidosis (2°)	Chronic inflammatory conditions	AA	SAA
Hemodialysis-associated	Chronic Renal Failure	$A\beta_2m$	B_2-microglobluin
Localized Amyloidosis			
Senile Cerebral	Alzheimer disease	A*b*	APP
Endocrine	Type 2 Diabetes Medullary thyroid CA	AIAPP A Cal	Islet amyloid peptide Calcitonin
Isolated atrial		AANF	ANP
Hereditary			
Familial Mediterranean Fever		AA	SAA
Familial amyloidotic neuropathy		ATTR	Transthyretin
Systemic Senile		ATTR	Transthyretin

Modified from: Robbins and Cotran's Pathologic Basis of Disease,

Vascular Calcification (Mönckeberg's Arteriosclerosis)

Calcification of arterial media layer.
Common and often incidental in older patients.
Associated with age, diabetes, renal failure, and hyperparathyroidism.



Note: Calcification of the *intima* (and subsequently the media) is very common in *Atherosclerosis* (discussed separately)

Other Deposition Disorders

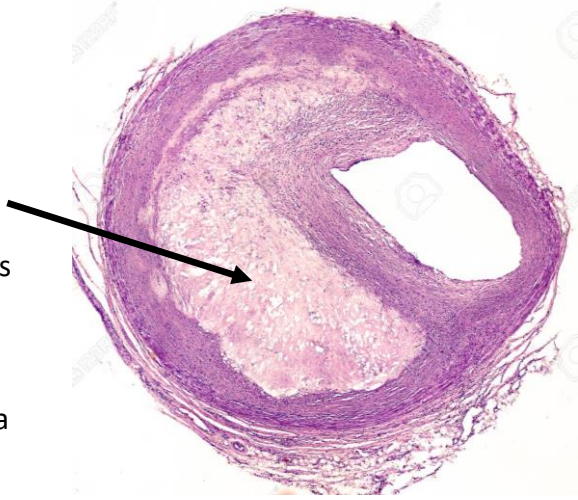
Light-Chain Deposition Disease—Immunoglobulin light chains deposit in tissue in *non*-amyloid form. Seen with immunoglobulin-producing neoplasms. Looks similar to amyloid on H&E, but not Congo red positive with Apple-green birefringence. Often due to κ light chains.

Calciphylaxis—progressive skin necrosis due to calcification of small and medium-sized vessels. Usually a result of hyperparathyroidism seen with chronic renal failure. Also see thrombi, soft tissue calcifications, panniculitis, necrosis, and ulceration.

Oxalosis– Deposition of calcium oxalate crystals in vessels and tissues→ occlude lumen→ ischemia. Can be 1° (due to enzyme deficiency) or 2° (due to ingestion of oxalates or ethylene glycol—antifreeze!). Birefringent crystals associated with foreign body giant cell reaction.

Common Aging-associated Disorders

Atherosclerosis

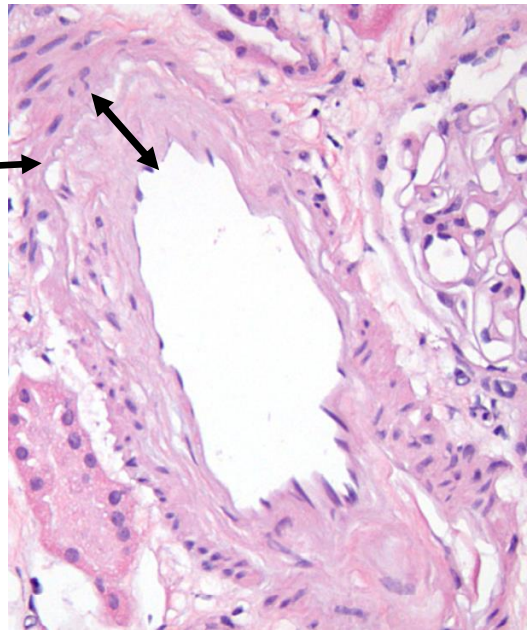


Development of **atheromatous plaques** in arteries.
Often most noteworthy in coronary arteries→ Myocardial infarction or cerebral arteries→ Stroke.
Can also cause peripheral vascular disease.

Endothelial injury/inflammation → accumulation of lipoproteins → ingested by macrophages → foamy macrophages in intima ("Xanthoma") with a fibrous cap, calcifications, and smooth muscle proliferation → gradually grows and narrows lumen → can **rupture** → triggers **thrombosis** of rest of lumen → ischemia → **infarction**

Risk factors: obesity, diabetes, smoking, hypercholesterolemia, men, hypertension, inflammation

Hypertensive Changes



Most commonly associated changes with "Benign" hypertension (but also generally seen with aging!).

1) Intimal fibroplasia of small arteries *(Arteriolosclerosis)*
Deposition of collagenous extracellular matrix and vascular smooth muscle cell growth between endothelium and IEL → thickening of intima → narrowing of vessel lumen

2) Hyalinization of arterioles *(Hyalinosis)*
Amorphous eosinophilic material (PASd+, Congo red -) made up of plasma proteins with matrix. Also associated with diabetes.

In "malignant" hypertension→ see hyperplastic arteriolosclerosis → small arteries have thickened "onion skin-like" intima (concentric layers) with fibrinoid necrosis and thrombosis.

Intimal Proliferative Disorders

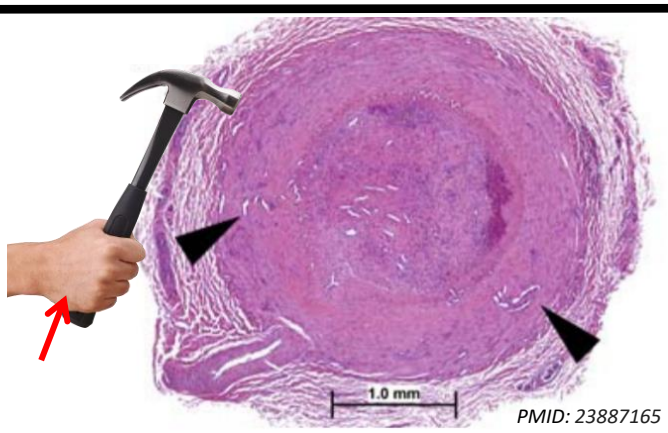
Expansion of intima by smooth muscle cells and myofibroblasts. This is a common consequence of vascular injury and vascular activation (i.e., a common endpoint of many diseases).

Hypothenar Hammer Syndrome

Direct mechanical injury of superficial vessels

(classically of ulnar artery on hypothenar surface of hand from overuse of a hammer)

→Lumina occlusion/thrombosis with scarring and ingrowth of capillaries into the media
→ Present with signs of vascular insufficiency (e.g., cold pale or cyanotic hand)



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Moyamoya Disease

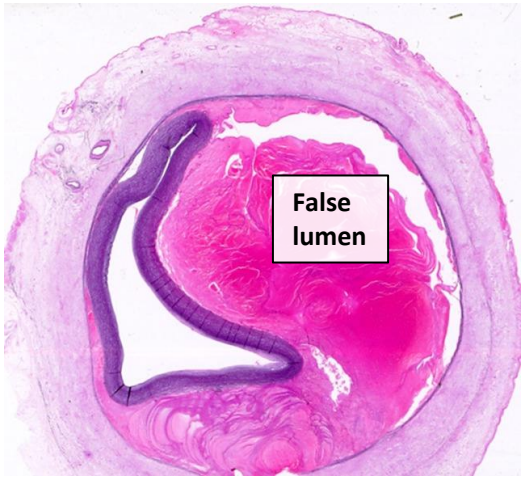
Most common in **Japan**. Idiopathic. Multiple spontaneous occlusions of cerebral arteries. Secondary development of adjacent net-like systems of collaterals→ Looks like a "puff of smoke" on angiography → can rupture → stroke

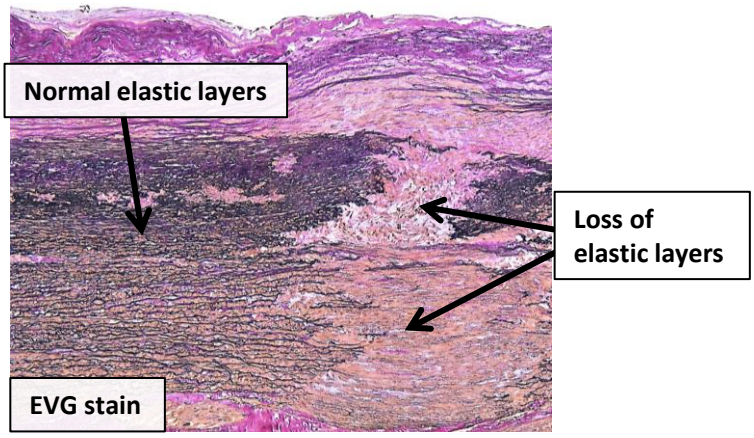
Arterial Dissections

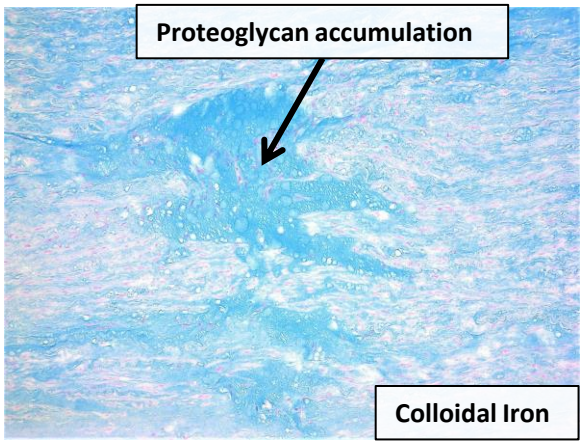
Disruption of vessel lumen→ blood can enter "false lumen" and dissect between layers or rupture. Frequently caused by trauma, but can be sporadic.

Common sites:
Cervical (carotid/vertebral arteries): Often younger adults.
Coronary arteries

Aorta: Often older males with history of hypertension. Also associated with Marfan Syndrome and bicuspid aortic valve.
Stanford Type A: involves *a*scending aorta (more common).
Stanford Type B: only descending aorta.
With sporadic cases, microscopically often see "Cystic Medial Degeneration" with 1)Marked loss of elastic lamellae (best seen with elastic stain) and 2)Deposition of proteoglycans (best seen with colloidal iron stain)

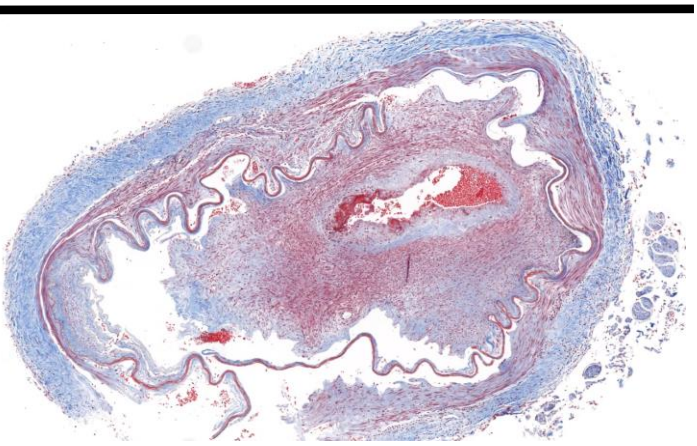






Miscellaneous Disorders

Fibromuscular Dysplasia



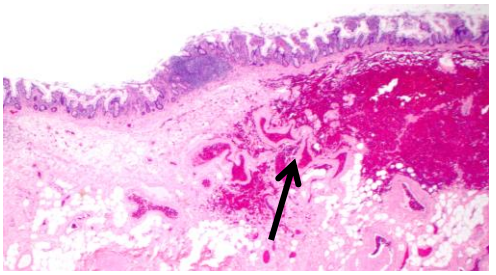
Replacement of normal component (usually smooth muscle) by loose fibrous tissue → causes narrowing and weakening/aneurysm formation (like beads on a string).

Often involves large to medium-sized blood vessels, especially renal arteries (causing hypertension due to renin/angiotensin system). Often middle-aged women.

Thromboangiitis Obliterans *aka "Buerger disease"*

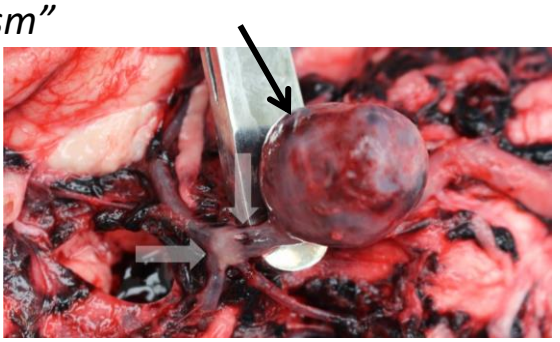
Almost exclusively in middle-aged males who are ***heavy smokers***.
(Thought to be a pathologic response to smoking)
Acute thrombosis of peripheral vessels→ invokes inflammatory response (not a true vasculitis, IEL intact)

Angiodysplasia of the Gastrointestinal Tract



Arteriovenous malformation, often in the cecum of elderly patients.
Causes GI bleed. Thought to be degenerative.
Dilated capillaries and veins in submucosa/mucosa.
Sometimes called "vascular ectasia."

Cerebral Aneurysms *aka "Berry Aneurysm"*



Saccular aneurysm from localized structural degeneration (loss of IEL and muscle layers)
Typically occur in **circle of Willis**
Relatively common (~5% of population)
Associated with connective tissue disorders, polycystic kidney disease, hypertension, etc…

→ **rupture→ subarachnoid hemorrhage**

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Aortic Aneurysms

Abdominal Aortic Aneurysm (AAA): Associated with atherosclerosis. Most common in older, male smokers (screen this population with ultrasound). Often just above bifurcation with plaque, thinned media, and bland, laminated mural thrombus. If rupture→ massive fatal hemorrhage (risk is proportional to size).

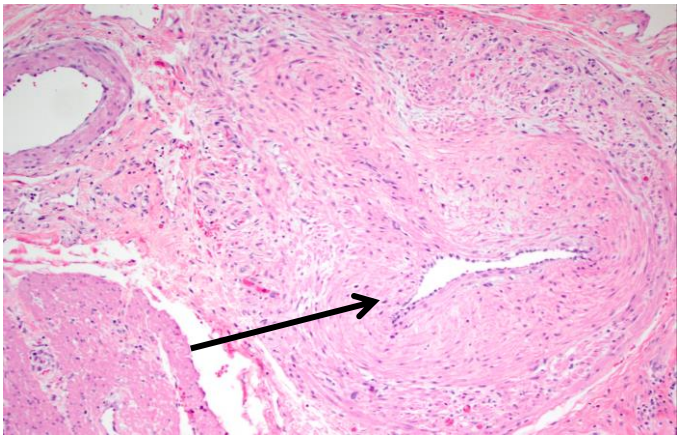
Thoracic Aortic Aneurysm: Usually associated with hypertension (and sometimes Marfan syndrome). As dilates→ encroaches on nearby structures (harder to swallow/breathe) and leads to aortic valve insufficiency. Can rupture→ massive hemorrhage

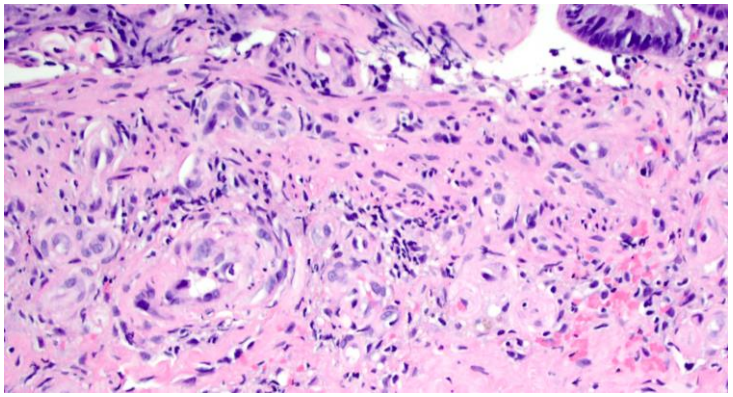
Idiopathic Myointimal Hyperplasia of Mesenteric Veins

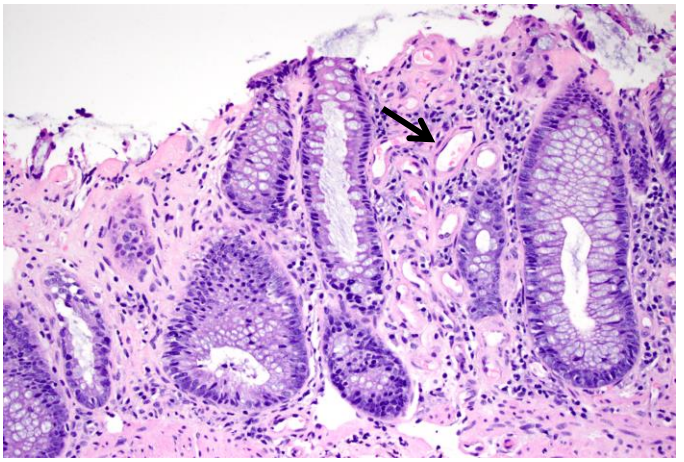
Rare.
Usually young to middle-aged men with GI pain and/or bleeding. Most common in left colon.
Can clinically look like IBD.

<u>On resection</u>: mural mesenteric veins have concentric proliferation of smooth muscle cells in the intima and media. (Arteries normal)

On biopsy: Arteriolized capillaries, subendothelial fibrin deposits, fibrin thrombi, and perivascular hyalinization. Reactive epithelium (mucin-depleted). +/- usual ischemic changes.







Enterocolic phlebitis

Localized lymphocytic perivenular circumferential cuff of inflammation → venous engorgement, hemorrhage, and necrosis.
Usually right-sided in middle-aged or elderly.
Can be necrotizing and/or granulomatous.