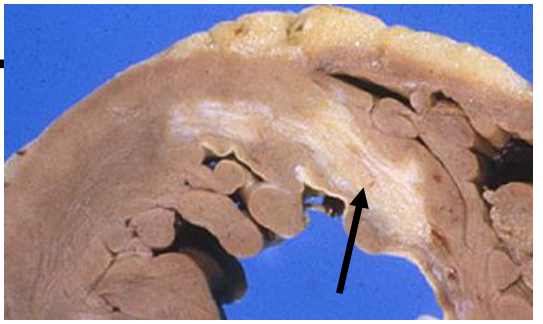
Cardiac Pathology

Myocardial/Vascular Conditions

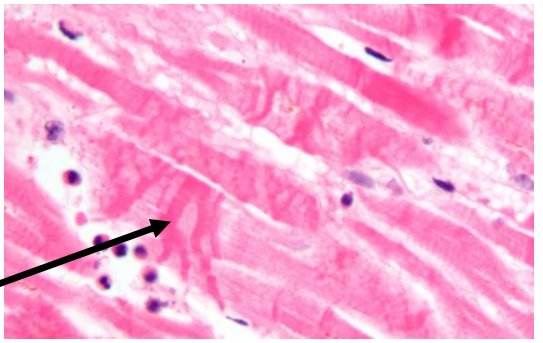
Myocardial Infarction *aka "MI"*



Ischemia → irreversible coagulative necrosis of myocardium
Usually due to acute thrombus overlying unstable atherosclerotic plaque (see below)

Necrosis of myocytes → leak troponins and other cardiac enzymes → detected in serum (distinguishes between angina and MI)

Timing of Pathologic Findings:
0-2 days → hypereosinophilic myocytes
<5 days → mostly neutrophilic inflammation and coagulative necrosis ("Acute"), Grossly: pale yellow
~1 week → starts healing with granulation tissue and fibrosis ("Subacute"), Grossly: pale with hyperemic border
~1-3 months → "healed" with dense fibrous scar

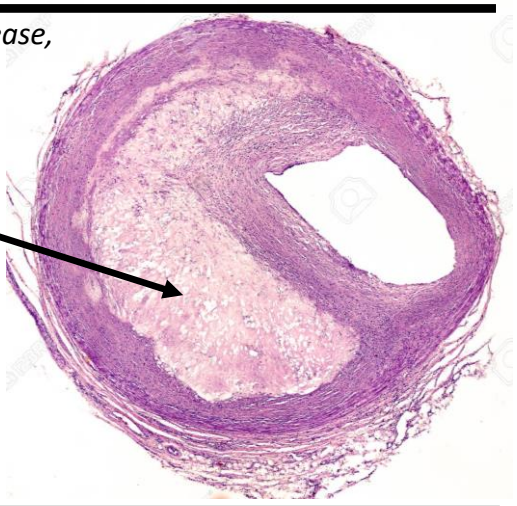


If ***reperfused***→ hemorrhage and prominent contraction bands

Arteries are in epicardium, so first/most impacted areas are subendocardial. Most fatal MI's are transmural.

Potential complications: Death (most often from arrythmia), Ventricular wall or papillary muscle rupture, Pericardial effusion (Dressler syndrome), Heart failure

Coronary Atherosclerosis *aka Coronary Artery Disease, "CAD"*

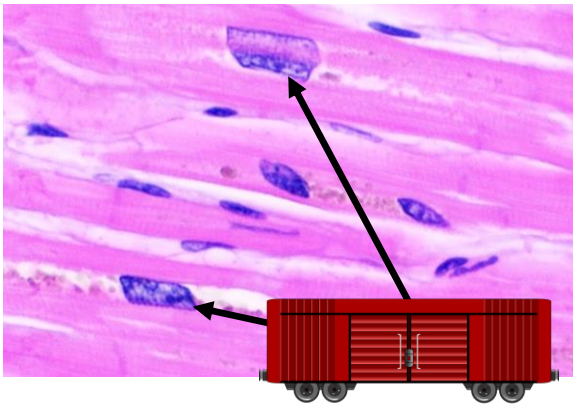


Development of **atheromatous plaques** in coronary arteries

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 → **myocardial infarction**

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

Ventricular Hypertrophy



Adaptive response to increased load

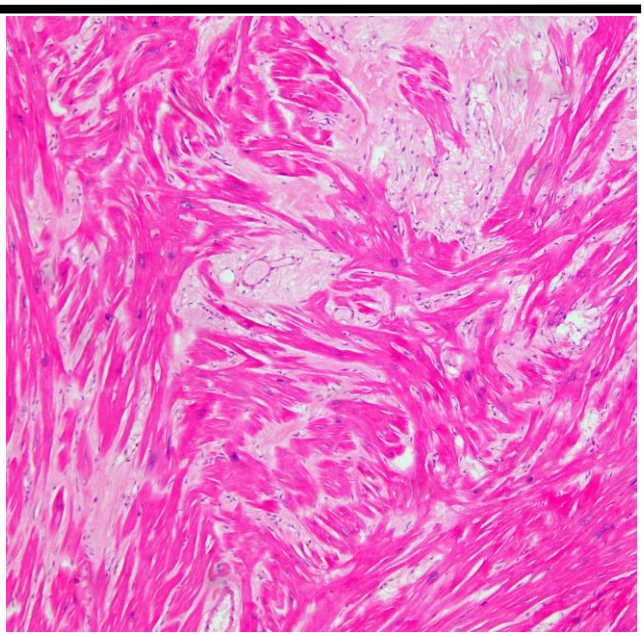
Common causes: Systemic hypertension, Aortic stenosis

Grossly: Wall thickness >1.5 cm

Microscopically: **Myocyte hypertrophy** (big cells with big "**box car**" square nuclei) with interstitial fibrosis

Increased risk of ventricular arrhythmias and sudden death

Hypertrophic Cardiomyopathy



Relatively common cause of **sudden cardiac death**, particularly in **young adults** with **exertion**

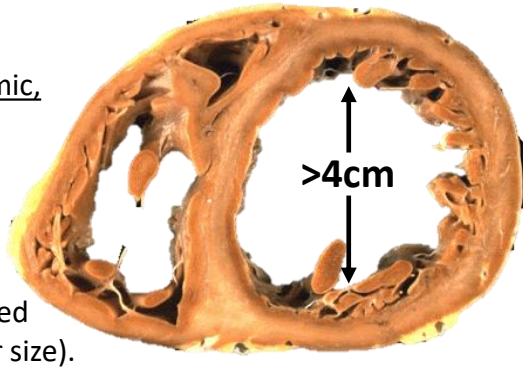
Frequently have mutations of sarcomere proteins. Often autosomal dominant with incomplete penetrance. Common (~1/500 people)

Grossly: Enlarged with **thickening** of the ventricular walls, particularly the interventricular septum

Microscopic: **Myocyte hypertrophy**, **myofiber disarray** (on taking cross sections of the ventricular septum), and interstitial (pericellular-type) **fibrosis**

→ Can lead to outflow obstruction ("hypertrophic obstructive cardiomyopathy," HOCM) and/or arrythmia

Dilated Cardiomyopathy

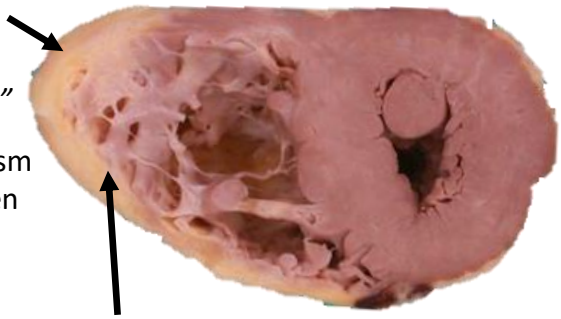


Four-chamber dilatation in the ***absence*** of significant valvular, ischemic, or hypertensive disease.

Can be **primary** (genetic/familial: multiple genes implicated) or **secondary** to other disorders (e.g., post-inflammatory, medication-induced, peripartum, endocrine, nutritional, or EtOH)

Left ventricular dilation >4cm. Dilated atria. Normal to mildly thickened walls. Nonspecific microscopic findings (Fibrosis and variation in fiber size).

Arrhythmogenic Cardiomyopathy



aka "arrhythmogenic right ventricular dysplasia/cardiomyopathy"

Classically, **right ventricle infiltrated by fat and scar** with aneurysm formation → arrhythmias and conduction disturbances → sudden cardiac death. (Actually, ***both*** ventricles often involved)

Multiple genes implicated (familial).

Left Ventricular Noncompaction

Prominent ventricular trabeculations, deep trabecular recesses, and a thin compacted layer, mostly involving the left ventricle.

Most common in infants/kids. Associated with other congenital heart problems.

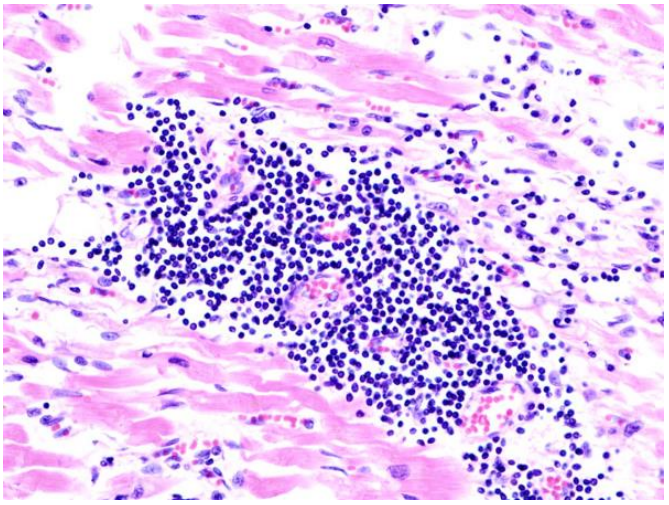
Can lead to heart failure, arrythmias, and embolic events.

Myocarditis

Inflammation of the myocardium with myocyte degeneration/necrosis not due to ischemic CAD.

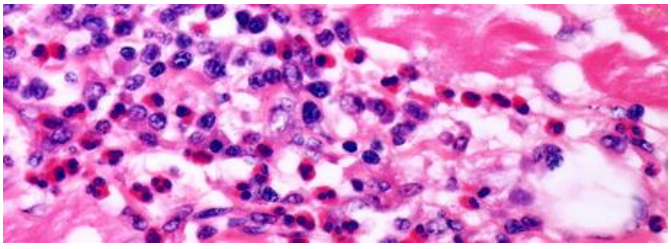
Lymphocytic myocarditis

Most common form of myocarditis. Usually children or young adults. Dx often made based on clinical findings. Usually attributed to **viruses**, most commonly coxsackieviruses and adenoviruses.
Often diffuse **infiltration of myocardium by T-cells**
Most patients respond to anti-inflammatory medication, but a subset progress to dilated cardiomyopathy. Can cause arrythmia→ sudden death.
DDX: Lyme disease, Collagen vascular disease



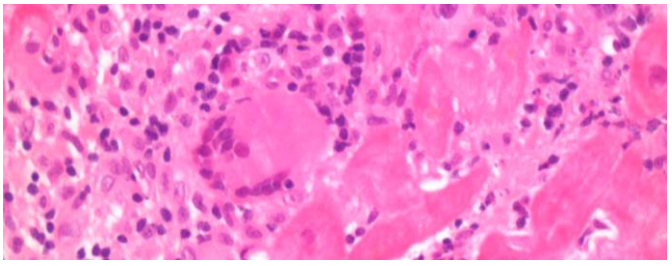
Eosinophilic myocarditis

Myocarditis with documented tissue or peripheral **eosinophilia**. Often **allergic** or **hypersensitivity**-associated. Rarely parasites. Minimal damage.
Usually attributed to mediations.



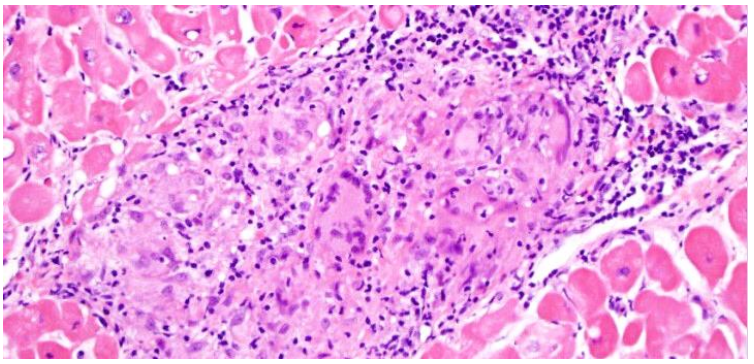
Giant cell myocarditis

Rare, idiopathic, likely autoimmune. Young adults.
Rapidly deteriorating course.
Diffuse infiltration of the myocardium by a mix of lymphocytes, eosinophils, occasional neutrophils, and **prominent giant cells** (*not* granulomas, as is seen in sarcoidosis). Diffuse necrosis.



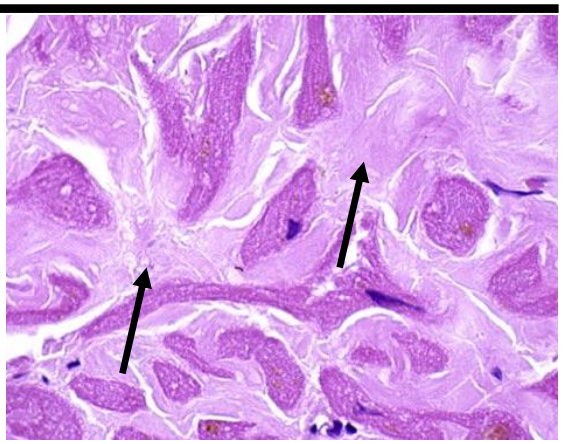
Sarcoidosis

Most have systemic involvement.
Well-formed, "hard," **granulomas** with fibrosis.
May have some associated lymphocytic inflammation.
→ Interrupt conduction→ heart block & arrythmias → sudden death



Amyloidosis

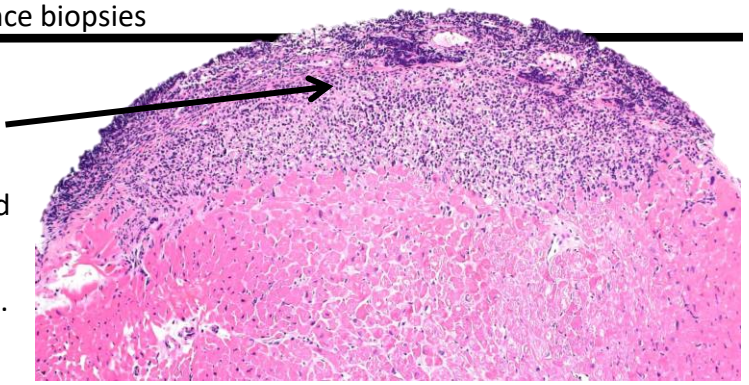
Usually part of **systemic disease**.
Deposition of misfolded protein → **restrictive cardiomyopathy,** arrhythmias, conduction disturbances, and/or CHF
Grossly: Large, firm, rubbery or waxy heart
All amyloid→ highlighted by **Congo Red stain** with "Apple Green" birefringence. On Trichrome stain it appears greyish.
Subtyping (via Mass Spec or IF) can help to determine the cause to potentially treat underlying disease



Transplant Pathology

Transplant patients are frequently monitored with transjugular surveillance biopsies

"Quilty Effect"



Nodular endocardial infiltrates.
Seen in ~10-20% of transplant biopsies.
Predominantly **lymphocytic** with **central B cells** and dendritic cells

Not rejection, but weekly associated with rejection.

As opposed to rejection (which is T cells within the myocardium), this is endocardial with B cells and dendritic cells.

Fun Fact: This was named after a patient who often had these in their biopsies!

Acute Cellular Rejection

Usually **weeks to months** after transplantation, but can occur years after if insufficiently immunosuppressed.

Infiltration by T lymphocytes with myocyte damage (must be within muscle or in a perivascular location)

May be asymptomatic or present with graft dysfunction.

IHC panel to further evaluate rejection: CD3, CD4, CD8, CD20, CD68
Acute cellular rejection: infiltrate is CD3+ T cells including both CD4+ and CD8+ with occasional macrophages (CD68+) and rare eosinophils

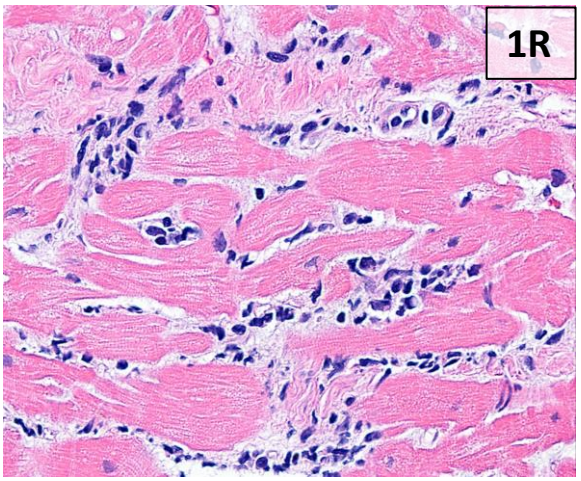
Quilty effect: Mixed in B cells with CD21+ dendritic cells

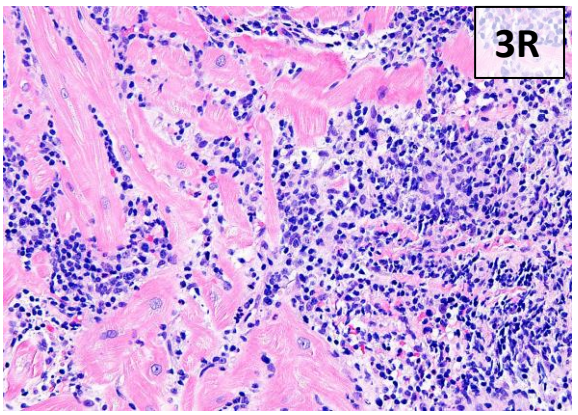
Ischemic changes: mostly PMNs and histiocytes (few lymphocytes)

Biopsy site: Mostly macrophages with B and T cells and disorganized myocytes with scarring.

PTLD: Mostly B cells; Infection: Mixture of T and B cells.

Grade using **ISHLT grading system** (see below).





Grade	Findings
0 R	No infiltrates or necrosis (No rejection)
1 R	Interstitial and/or perivascular infiltrate with up to 1 focus of myocyte damage
2 R	Two or more foci of infiltrate with associated myocyte damage
3 R	Diffuse infiltrate with multifocal myocyte damage, ± edema, ± hemorrhage, ± vasculitis

From PMID: 16297770

Antibody-mediated Rejection

Complement-mediated endothelial damage.

Endothelial activation (big, swollen endothelial cells) with immune complement deposition.

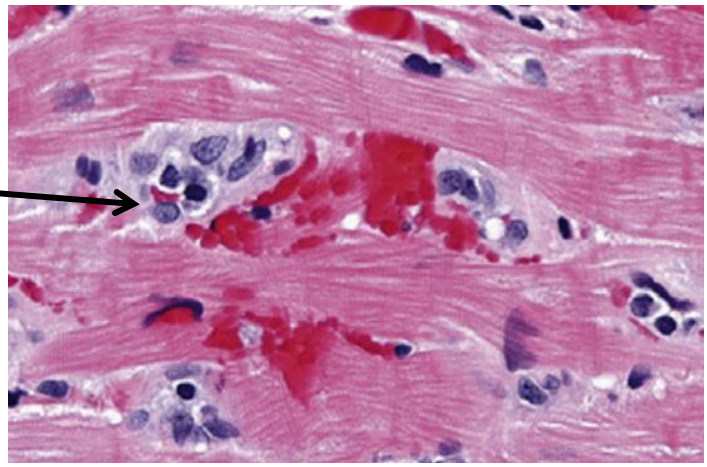
Intravascular macrophages (CD68+)
No significant lymphocytic inflammation.

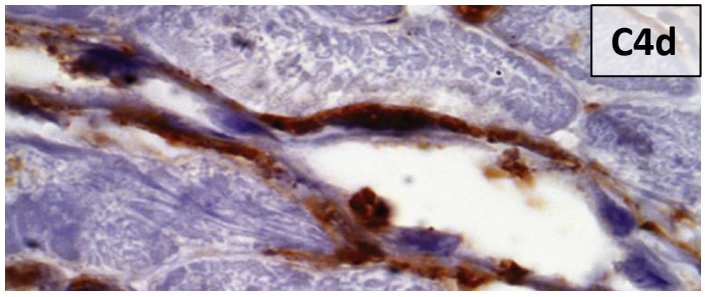
Can identify complement deposition in capillaries with **C4d** IHC (or IF)→ looking for diffuse subendothelial capillary positivity

Can coexist with acute cellular rejection!

Clinically have donor-specific antibodies.

Usually first month after transplant, but can get later too.





Grade	Definition	Findings
pAMR 0	Negative for pathologic AMR	Both histologic and immunopathologic studies are negative
pAMR 1 (H+)	Histopathologic AMR alone	Histologic findings present and immunopathologic findings are negative
pAMR 1 (I+)	Immunopathologic AMR alone	Histological findings negative and immunopathologic findings positive (CD68+ and/or C4d+)
pAMR 2	Pathologic AMR	Both histological **and** immunopathologic findings are present
pAMR 3	Severe pathologic AMR	Rare. Histologic findings of interstitial hemorrhage, capillary fragmentation, mixed inflammatory infiltrates, endothelial cell pyknosis, and/or karyorrhexis and marked edema **and** immunopathologic findings are present. Poor outcome.

PMID: 24263017

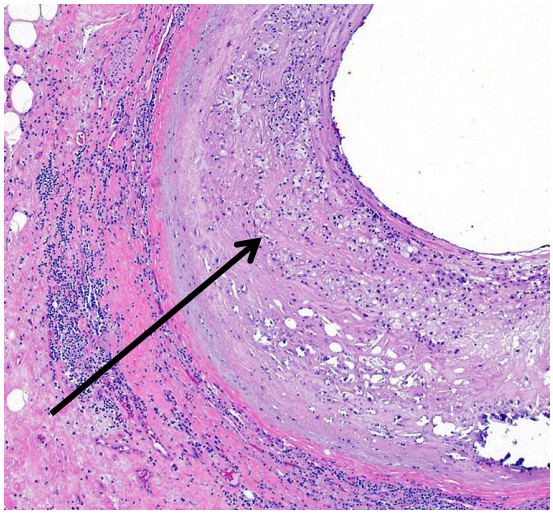
Allograft Vasculopathy

Essentially cardiac version of **chronic rejection**.
Mainly impacts **arteries** (only seen at autopsy/explant)

Concentric, diffuse, vessel wall thickening (and lumen narrowing) by **intimal hyperplasia** with smooth muscle with mild **chronic inflammation**. IEL intact. Inflammation involves all layers of vessel.

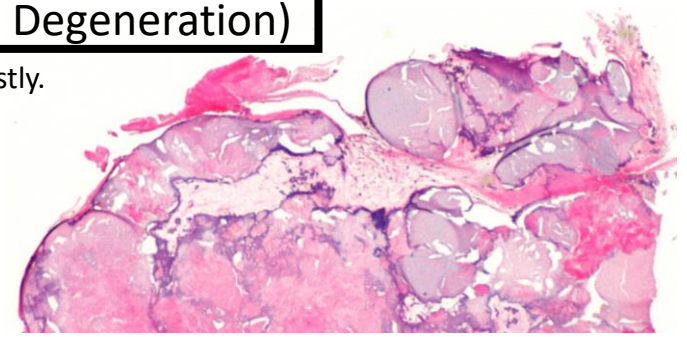
Can lead to thrombosis and/or chronic ischemia or infarction with fibrosis.

Main limitation to long-term success of transplantation



Valvular Disorders

Degenerative Valve Disease (Calcific Degeneration)

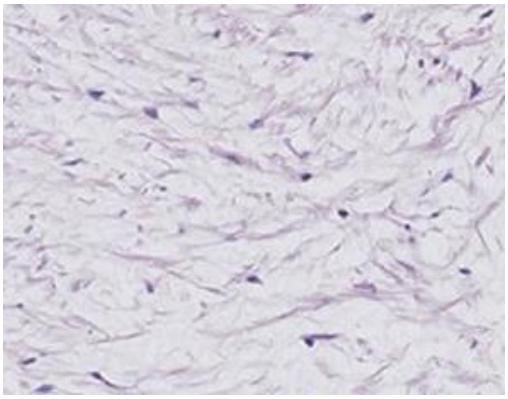


Impacts **aortic valve** and mitral annulus (left-sided) mostly.
Clinically present with **stenosis** ± insufficiency

Fibrotic thickening and nodular calcifications
May see sparse chronic inflammation

Esp. common if bicuspid aortic valve.
Treat with valve replacement

Myxomatous/Myxoid Degeneration



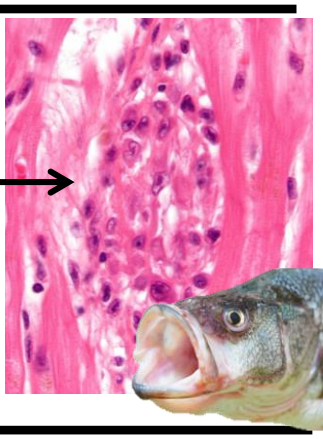
Impacts **Mitral valve** and aortic valve (left-sided).

Replacement of collagen with mucopolysaccharides, particularly in the central spongiosa layer. Grossly: floppy, translucent leaflets

→ **mitral valve prolapse (MVP) and insufficiency** and regurgitation
Aortic myxoid degeneration is often associated with/secondary to a dilated aortic root

Unclear etiology, genetics, and pathogenesis. MVP seen in F > M.

Rheumatic disease

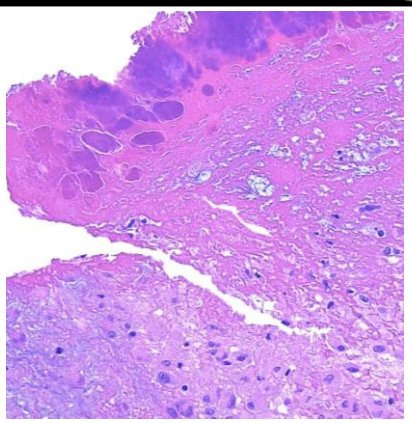


During acute rheumatic fever (due to group A streptococci infection)→ **Pancarditis** (all layers involved)
Classic finding: **Aschoff nodules**—round histiocyte-rich lesions with myocardium →

Afterwards, **scarring** of the mitral and aortic valve occurs secondary to an autoimmune reaction → **Mitral stenosis** ± insufficiency → Pulmonary hypertension → Right Ventricular hypertrophy

Marked valve fibrosis with commissural fusion and thickened chordae
Looks like a "fish-mouth" grossly. Nonspecific histologic findings.

Endocarditis



Infectious Endocarditis: Bacterial or fungal infection of the endocardium
Most cases primarily involve valves. Most common : Staph and Strep

Vegetations consist of fibrin with neutrophils and microorganisms ± valve destruction

If you see PMNs and fibrin on a valve→ order bug stains!!

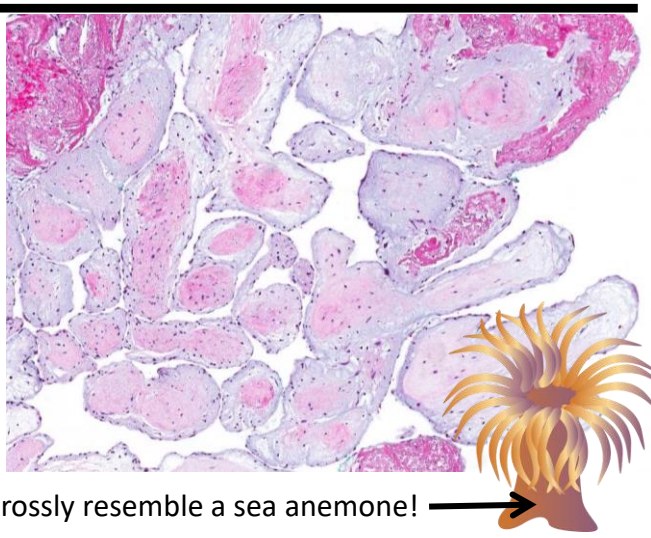
Nonbacterial thrombotic (marantic) endocarditis refers to the presence of sterile thrombi on heart valves due to abnormal flow and/or hypercoagulable states

Carcinoid Heart Disease—due to secretion of serotonin (and related products) from a well-differentiated neuroendocrine tumor. Usually from a small bowel tumor with liver metastases. Causes right-sided fibrous endocardial plaques on the leaflets of tricuspid and pulmonary valves→ Right-sided heart failure

Tumors

Primary heart tumors are **rare**. Even though the majority are *benign*, they can interfere with the heart's mechanical or electrical functions and present with sudden death!

Papillary Fibroelastoma



Benign endocardial neoplasm.

Papillary branching fronds covered in endothelium.
Avascular core with collagen and elastin.

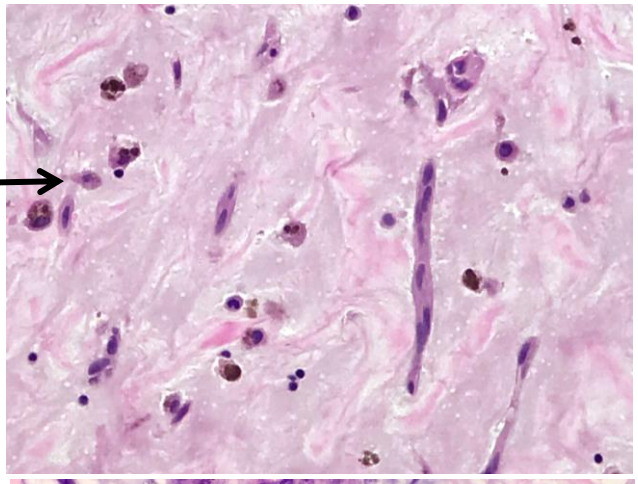
Most common cardiac tumor.
Usually arises on **valves** on **left side** of heart.

A subset have KRAS mutations (so seem to be neoplasms, previously thought to be reactive as most common in areas of relative trauma).

May be incidental. If symptomatic, may be due to obstruction or embolization.

Grossly resemble a sea anemone!

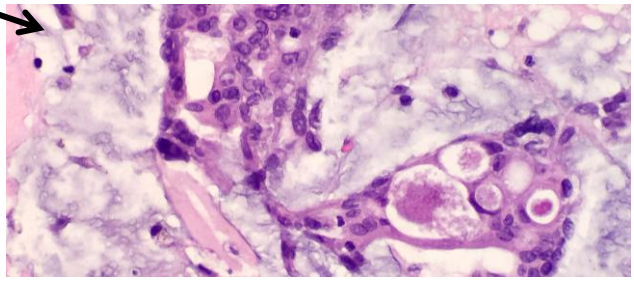
Cardiac Myxoma



Benign intracavitary endocardial lesions.
Usually in **left atrium**. Second most common heart tumor.

Bland stellate to plump spindled cells "myxoma cells" within a vascular myxoid matrix.

May see: inflammatory cells, giant cells, hemorrhage, hemosiderin-laden macrophages, calcifications, bone, and glandular-appearing elements

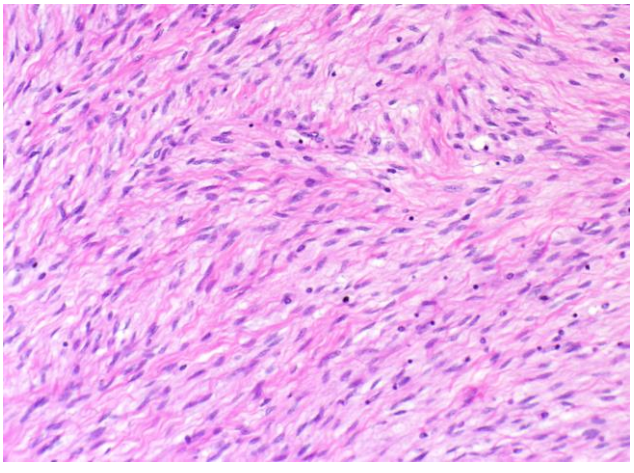


Matrix stains with PAS and Alcian blue.
Myxoma cells stain with calretinin.

May be pedunculated, sessile, or villiform
Can arise in the setting of Carney complex.

If symptomatic, usually due to obstructing blood flow or embolization. Recurrence after resection is relatively rare.

Cardiac Fibroma



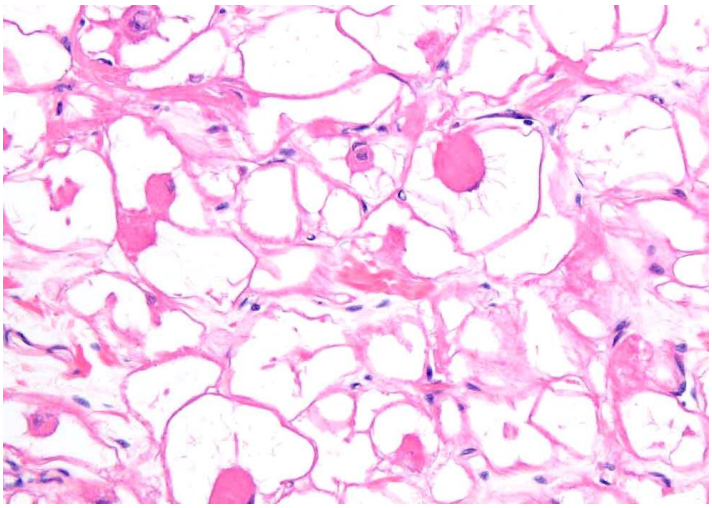
Benign. Usually in **ventricular septum** of **children.**

Bland fibroblasts in variably collagenized stroma.
Although grossly circumscribed, microscopically may infiltrate myocardium. Microcalcifications common.

IHC: (+) smooth muscle actin
Often large→ can interrupt conduction/contraction

Associated with **Gorlin syndrome** (Nevoid basal cell carcinoma syndrome) due to germline PTCH1 mutations.

Cardiac Rhabdomyoma



Benign. Most common in **ventricular myocardium** of **children**.

Vacuolated large "spider" cells with radial sarcoplasmic extensions from the nucleus to the membrane.

Most common cardiac tumor in children.
Thought to be a **hamartoma** of developing myocytes
IHC: (+)Desmin, Actin; PAS highlights glycogen

Often arises in setting of tuberous sclerosis (germline TSC1 or TSC 2 mutations)

Other Tumors

Metastases: *Most common by far*! Most commonly lung cancer.
Also frequent: melanoma, sarcoma, renal cell carcinoma.

Other tumors that can be seen in the heart:

Lipoma—benign, encapsulated proliferation of mature adipose tissue. If in atrial septum with brown fat + mature fat + atrial myocytes = lipomatous hypertrophy of atrial septum.

Adult cellular rhabdomyoma—Just like in the head and neck. Benign neoplasm of striated muscle. Cellular proliferation of round/spindled cells with prominent vascularity. Adults. No tuberous sclerosis.

Hemangioma—benign proliferation of thin-walled vascular spaces without atypia

Angiosarcoma—Malignant cells with vascular differentiation. Most common cardiac sarcoma.

Leiomyosarcoma

Undifferentiated pleomorphic sarcoma

Diffuse large B-cell Lymphoma

Very RARE cardiac tumors:

Lipomatous hamartoma of the atrioventricular valve—unencapsulated fat in AV valve

Hamartoma of mature cardiac myocytes—discrete nodular collection of disorganized myocytes forming a mass

Mesenchymal cardiac hamartoma—discrete collection of mature mesenchymal tissues in the heart

Conduction system hamartoma—collections of pale, eosinophilic Purkinje cells distributed along endocardium. Usually identified in kids. Arrythmias→ sudden death.

Cystic tumor of the atrioventricular node—endodermal inclusion forming a cystic lesion within the AV septum