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 arrhythmia), 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 arrhythmia → 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 mediators.

**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 & arrhythmias → 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**

**“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.

**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).

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

From PMID: 16297770

Transplant patients are frequently monitored with transjugular surveillance biopsies.

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

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

PMID: 24263017

<table>
<thead>
<tr>
<th>Grade</th>
<th>Definition</th>
<th>Findings</th>
</tr>
</thead>
<tbody>
<tr>
<td>pAMR 0</td>
<td>Negative for pathologic AMR</td>
<td>Both histologic and immunopathologic studies are negative</td>
</tr>
<tr>
<td>pAMR 1 (H+)</td>
<td>Histopathologic AMR alone</td>
<td>Histologic findings present and immunopathologic findings are negative</td>
</tr>
<tr>
<td>pAMR 1 (I+)</td>
<td>Immunopathologic AMR alone</td>
<td>Histological findings negative and immunopathologic findings positive (CD68+ and/or C4d+)</td>
</tr>
<tr>
<td>pAMR 2</td>
<td>Pathologic AMR</td>
<td>Both histological and immunopathologic findings are present</td>
</tr>
<tr>
<td>pAMR 3</td>
<td>Severe pathologic AMR</td>
<td>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.</td>
</tr>
</tbody>
</table>
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 **Mitr a l 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 → **Mitr a l 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**
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!

**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.


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. Arrhythmias→ sudden death.

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