# Resident's Curriculum
# Cardiovascular Pathology
# CCHS

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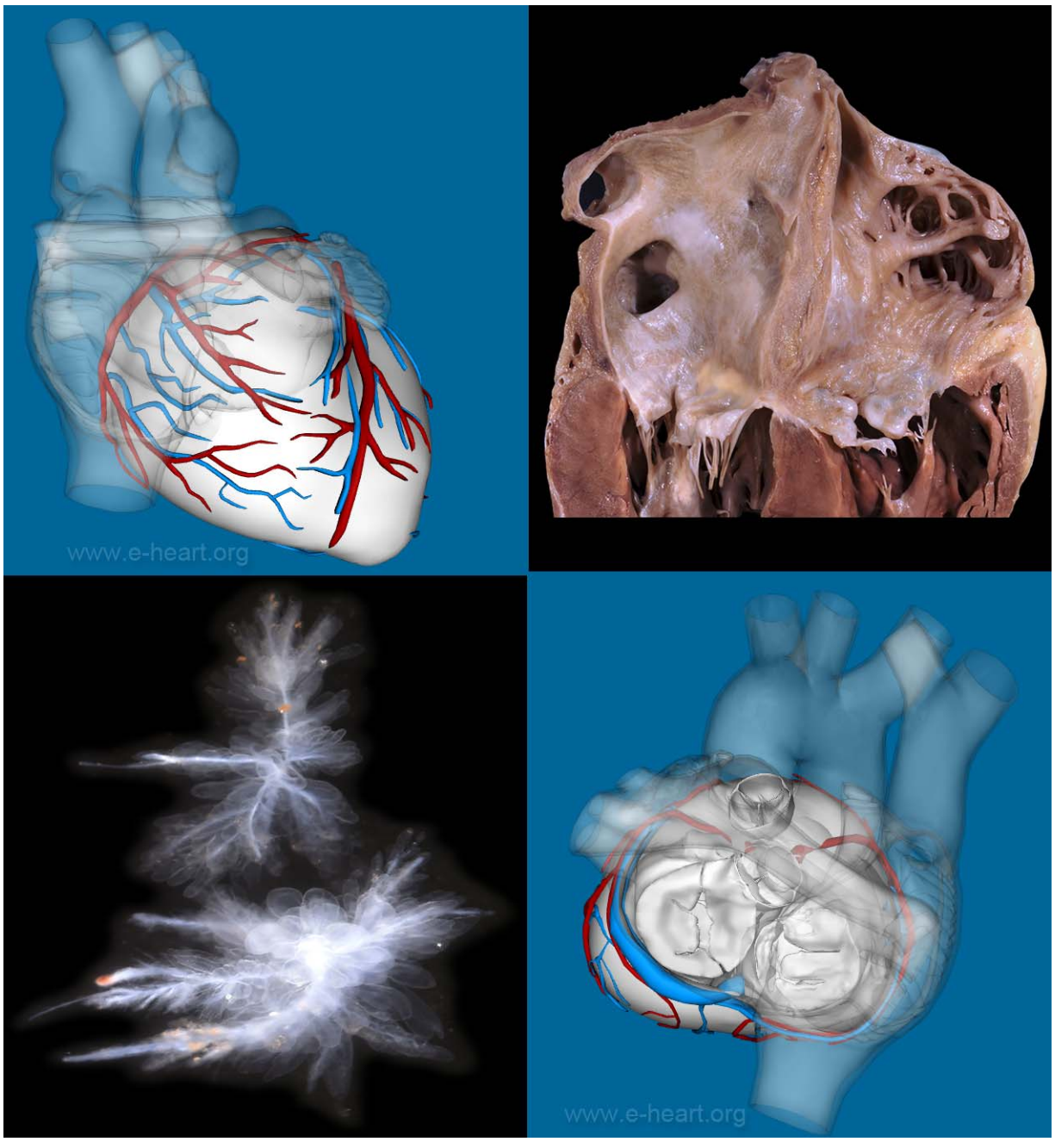

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# I. Pathology of the Heart

## Congenital Heart Disease

### General Information

- 0.6–0.8% of live births
- No identifiable cause in most cases
- Between 8-18% are associated with chromosomal abnormality; over 50 genes have been associated with congenital heart defects
- First trimester rubella infection can lead to patent ductus arteriosus and pulmonary stenosis
- Down syndrome associated with septal defects (atrial and ventricular), defects of atrioventricular valves
- Turner syndrome associated with coarctation of aorta
- Drugs, such as alcohol and thalidomide, can also lead to congenital heart abnormalities
- Clinical presentation include asymptomatic murmur, cyanosis, failure to thrive, heart failure, and shock
- Shunt lesions
    - Left-to-right shunts
        - Portion of oxygenated blood from the lungs is shunted back to the lungs
        - Most important complications are pulmonary hypertension due to increased pulmonary blood flow and eventual right ventricular hypertrophy
        - Increased pulmonary vascular resistance leads to reversal of shunt with cyanosis (Eisenmenger syndrome)
    - Right-to-left shunts
        - Portion of deoxygenated blood from systemic veins return to the systemic arterial circulation bypassing the lungs
- Obstructive lesions
    - Obstructions can occur at the level of the valves, ventricular outflow tracts or great arteries

Table 1. Incidence of Congenital Heart Disease

| Malformation | Incidence per million live births |
|---|---|
| Ventricular Septal Defect (VSD) | 4482 |
| Atrial Septal Defect (ASD) | 1059 |
| Pulmonary Stenosis | 836 |
| Patent Ductus Arteriosus (PDA) | 782 |
| Tetralogy of Fallot | 577 |
| Coarctation of the Aorta | 492 |
| Atrioventricular Septal Defect (AV Canal) | 396 |
| Aortic Stenosis | 388 |
| Transposition of the Great Arteries (TGA) | 388 |
| Hypoplastic left heart syndrome (HLHS) | 279 |
| Truncus Arteriosus (TA) | 136 |
| Total Anomalous Pulmonary Venous Connection | 120 |
| Bicuspid aortic valve | 13,817 |

*Source: Hoffman JIE, Kaplan S: The incidence of congenital heart disease. J Am Coll Cardiol. 2002;39:1890*

| Table 2. Congenital Malformations organized by type of physiology | | |
|---|---|---|
| Left-to-Right Shunts | Right-to-Left Shunts | Obstructive |
| ASD | TOF | Aortic coarctation |
| VSD | Truncus arteriosus | Aortic Stenosis / Atresia |
| PDA | Tricuspid atresia | Pulmonary Stenosis / Atresia |

*Modified from: Kumar V, et al. Robbins and Cotran Pathologic Basis of Disease, 9th Edition. 2015. Elsevier Saunders. Chapter 12 , pp 538*

## Aortic Stenosis

- Obstructive disease
- Approximately 6% of congenital heart abnormalities
- May assume valvular, subvalvular and supravalvular forms
- Most common cause is bicuspid aortic valve, with typical clinical presentation of valve failure in early middle age
- In the neonate, more commonly caused by unicuspid/unicommissural aortic valve; may result in the development of endocardial fibroelastosis and manifest as heart failure in infancy
- Williams-Beuren syndrome produces arterial wall thickening which effectively produces supravalvular stenosis of the aortic root and ascending aorta
- Subvalvular forms due to subaortic membrane

## Atrial Septal Defect (ASD)

- Produces a left-to-right shunt
- Comprises approximately 10% of congenital heart abnormalities
- Defects at the fossa ovalis are called ostium secundum (OS) defects
- Defects inferior to the fossa ovalis are called ostium primum (OP) defects, usually a component of atrioventricular canal defects and associated with mitral valve defects
- OS defect is much more common than OP defect
- OS defects often not detected in childhood because of lack of symptoms but may later present in adulthood

## Coarctation of the Aorta

- Obstructive disease
- Approximately 7% of congenital heart abnormalities
- More common in males
- Coarctation located usually as a discrete lesion proximal, distal or opposite the orifice of the ductus arteriosus
- May be a long-segment or tubular narrowing of the aortic arch
- Patients develop systemic hypertension in the upper body and collateral flow to the distal aorta
- Frequent (12%) in Turner syndrome
- 50% of cases associated with bicuspid aortic valve
- Approximately 60% will die (frequently of aortic rupture and dissection) by age 40 if not corrected

## Hypoplastic Left Heart Syndrome

- Obstructive disease
- Spectrum of cardiac anomalies with small left atrium, mitral valve atresia or stenosis, aortic atresia, underdeveloped left ventricle and ascending aorta
- Right atrium, right ventricle and pulmonary artery often dilated

- Interatrial communication through a patent foramen ovale (PFO) or ASD often present
- Aortic atresia with normal sized left ventricle is associated with the presence of a large ventricular septal defect (VSD)
- Male predominance
- Cyanosis from birth, with high mortality within the first month of life

## Patent Ductus Arteriosus (PDA)

- Left-to-right shunt
- Manifestations depend on the size of communication between aorta and pulmonary artery
- Small PDA results in a small left-to-right shunt with “machinery” murmur and mild symptoms
- Large PDA results in a large shunt leading to pulmonary hypertension, eventually evolving into a shunt reversal with cyanosis (Eisenmenger physiology)

## Pulmonary Stenosis and Atresia

- Obstructive disease
- Approximately 7% of congenital heart abnormalities
- Caused usually by a dome-shaped valve with central perforation or dysplastic pulmonary valve with thick myxoid cusps
- Leads to right ventricular hypertrophy and systemic venous congestion
- In case of pulmonary atresia, the valve is replaced by a fibrous membrane and the right ventricle will be hypoplastic, blood to the lungs is delivered through a PDA, rarely through multiple aorto-pulmonary collaterals

## Tetralogy of Fallot

- Right-to-left shunt through a VSD
- Most common cyanotic congenital anomaly
- Four classic anatomical findings
  - VSD
  - Dextroposition of the aorta that overrides the VSD and originates from both right and left ventricles
  - Right ventricular outflow obstruction (pulmonary or subpulmonary stenosis)
  - Right ventricular hypertrophy
- The degree of cyanosis is related to the severity of obstruction to the pulmonary circulation; increased right ventricular outflow obstruction augments right-to-left shunting
- Right-to-left shunt predispose patients to develop cerebral abscesses or stroke

## Transposition of Great Arteries

- Approximately 4% of congenital heart defects
- Aorta arises from morphologic right ventricle and is situated anterior and to the right of pulmonary artery (normal is situated posterior and to the right of pulmonary artery), pulmonary artery arises from morphologic left ventricle
- To survive, mixing of blood between the two parallel circulations occurs through a PFO, ASD, VSD or PDA
- Cyanosis at birth

## Tricuspid Atresia

- Right- to-left shunt through a PFO or ASD
- Tricuspid valve absent and associated with hypoplasia of right ventricle and pulmonary artery

- VSD may allow flow from left ventricle to pulmonary artery
- Cyanosis present from birth

### TRUNCUS ARTERIOSUS

- Right-to-left shunt
- Single arterial vessel arises from both ventricles above a VSD
- Presents with cyanosis from birth

### VENTRICULAR SEPTAL DEFECT (VSD)

- Left-to-right shunt
- Most common cardiac defect seen in children, approximately 20% of congenital heart defects
- May be divided into (1) small, usually muscular type defects that spontaneously close in the first few years of life; (2) small, usually perimembranous type defects with minor symptoms and do not cause pulmonary hypertension; (3) large hemodynamically significant defects
- Mostly occurs in perimembranous portion of the interventricular septum
- May predispose to infective endocarditis, aortic insufficiency if one of the aortic cusps prolapse into the VSD
- Large VSDs, if untreated, will produce volume overload and pulmonary hypertension, biventricular hypertrophy and congestive heart failure and may lead to Eisenmenger syndrome

## Acquired Diseases of the Myocardium

### ISCHEMIC HEART DISEASE

Ischemic heart disease is due to an imbalance between coronary perfusion and myocardial oxygen demand. It manifests as diverse clinical ischemic syndromes including stable and unstable angina, myocardial infarction (MI), chronic ischemic heart disease, and sudden cardiac death.

### *Acute Myocardial Infarction*

#### *Clinical*

- Most often due to coronary artery atherosclerosis in over 90% of cases; less often due to coronary vasospasm, coronary artery dissection, coronary thrombosis or embolism
- Plaque fissure or rupture may cause a totally occlusive thrombosis leading to acute ST-segment elevation MI or a non-occlusive thrombosis leading to unstable angina or non-ST-segment elevation MI
- Myocardial necrosis occurs in a wavefront phenomenon from the subendocardium to the subepicardial myocardium
- Extent of myocardial necrosis depends on length of time of occlusion and degree of collateral blood flow
- Complications of large transmural infarcts include:
  - Congestive heart failure – likely to develop if >40% of left ventricle is infarcted
  - Arrhythmia – conduction block, bradyarrhythmias, tachyarrhythmias
  - Infarct extension/reinfarction – development of new necrosis in the same area of a recent infarction as evidenced by recurrence of chest pain, elevated cardiac enzymes, and electrocardiographic changes
  - Infarct expansion and left ventricular aneurysm – infarcted zone becomes thin and stretched out, forming a regional left ventricular cavity dilatation

- Mural thrombosis/embolism – thrombi can form in expanded akinetic infarcted wall usually in the setting of large anteroapical MI, with risk of systemic embolization
- Right ventricular infarction – associated with posterior wall infarction and high pulmonary pressures
- Cardiac rupture
  - free wall rupture leading to hemopericardium, most often in the anterior wall
  - interventricular septal rupture leading to left-to-right shunt
  - papillary muscle rupture leading to acute mitral regurgitation
  - ruptures usually occur in the first 10 days of MI
- Pericarditis – may be seen in the area of acute infarction or represent a late postinfarction inflammation (Dressler syndrome) appearing weeks after infarction

***Macroscopic***

- Myocardial necrosis in an acute MI appear grossly as pale yellow areas in the myocardium
- If reperfusion has occurred, the infarcted areas may appear red
- May be either subendocardial, transmural or multifocal (Fig.1)

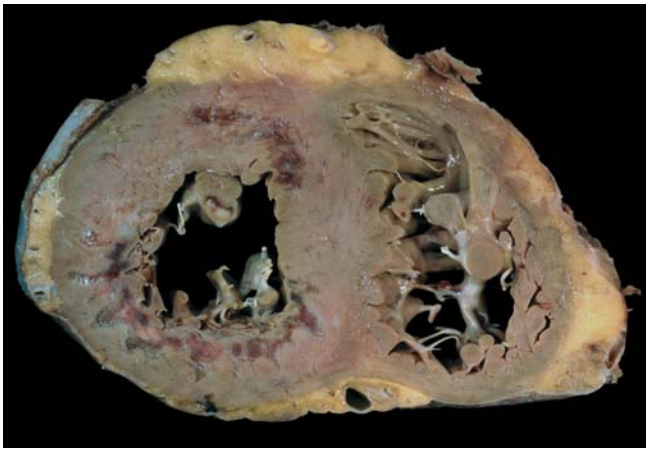

Fig. 1. Cross section of the ventricles showing subendocardial infarcts in the anterior and posterolateral walls that extend into the septum. The infarcts have a gelatinous texture and the red areas represent granulation tissue. Bordering the infarcts there are subtle areas of white gray discoloration which represent areas of early scar formation. Also note the infarct in the anterolateral papillary muscle..

- In the first 6-12 hours, usually no grossly detectable changes unless using tetrazolium incubation (Fig . 2)

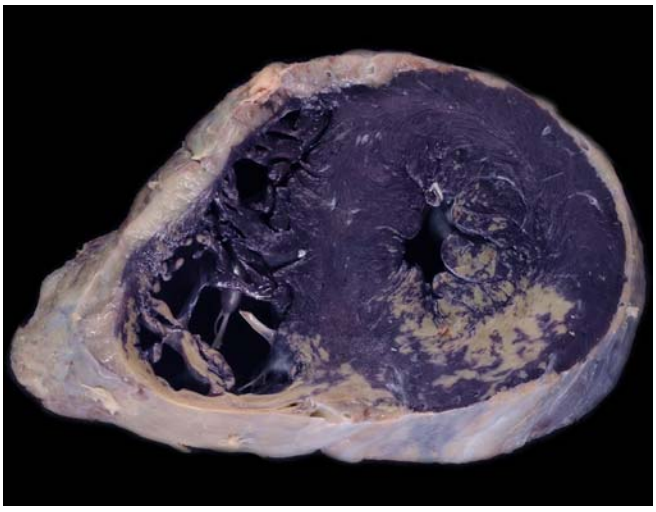

Fig. 2. Cross section of the ventricles fixed in formalin after incubation in nitroblue tetrazolium chloride. Nitroblue tetrazolium is transformed to blue/purple dye by lactic dehydrogenase, indicating viable tissue. This image shows two distinct infarcts (lack of blue/purple staining) in the posterior wall of the left and right ventricles. This stain accurately detects infarcts less than 4 hours in evolution, before any reliable histologic finding can be seen.

- After 18–24 hours, there may be either myocardial pallor or mottling
- In 2-3 days, the infarcted zone begins to appear yellow as polymorphonuclear leukocytes infiltrate the tissue, the pallor increases as more polymorphonuclear leukocytes continue to infiltrate the infarcted myocardium (Fig. 3)

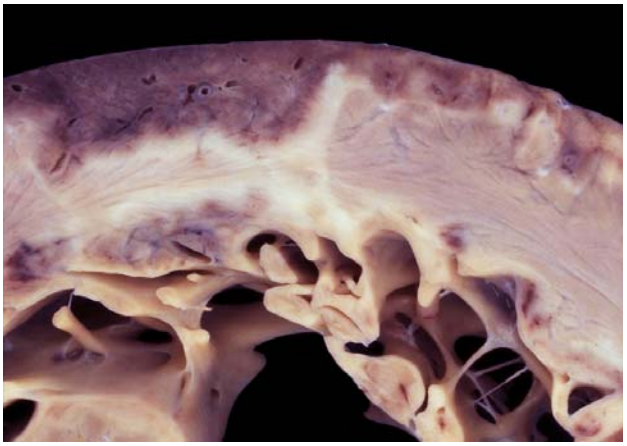

Fig. 3. The myocardium shows a yellow demarcation between the viable subepicardial myocardium and infarcted subendocardial myocardium on the left. The infarct becomes transmural on the right side of the field. The paler yellow border represents the zone of maximal infiltration of neutrophils at 2-3 days.

- At 7 days, distinct gelatinous early scar with red borders and depression on cut surface is present
- At 14 days, gelatinous change transitions to early white scar (Fig. 4)
- By 7–8 weeks, cicatrization may be complete (Fig. 4)

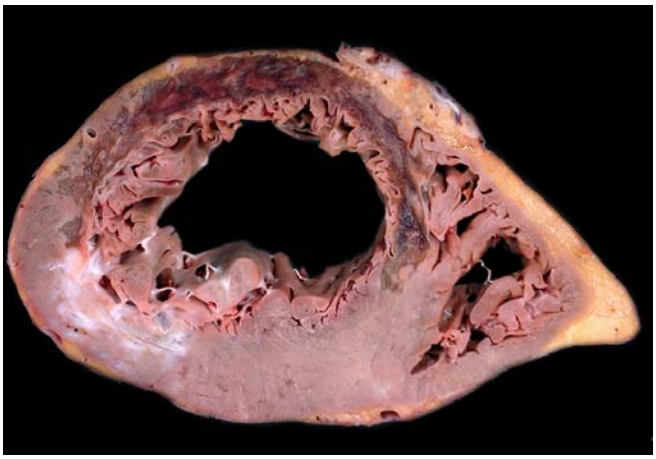

Fig. 4. An extensive transmural anteroseptal left ventricular infarct shows thinning of the myocardium with gelatinous change consistent with early scar formation between 7 to 14 days. Islands of necrotic myocardium may persist in large infarcts as seen in the anterior wall in this case. A healed infarct with white scar is present in the posterolateral wall.

- Complications with structural changes after myocardial infarction include rupture of papillary muscle (Fig. 5), ventricular rupture (Fig. 6), ventricular aneurysm or pseudoaneurysm (Fig. 7)

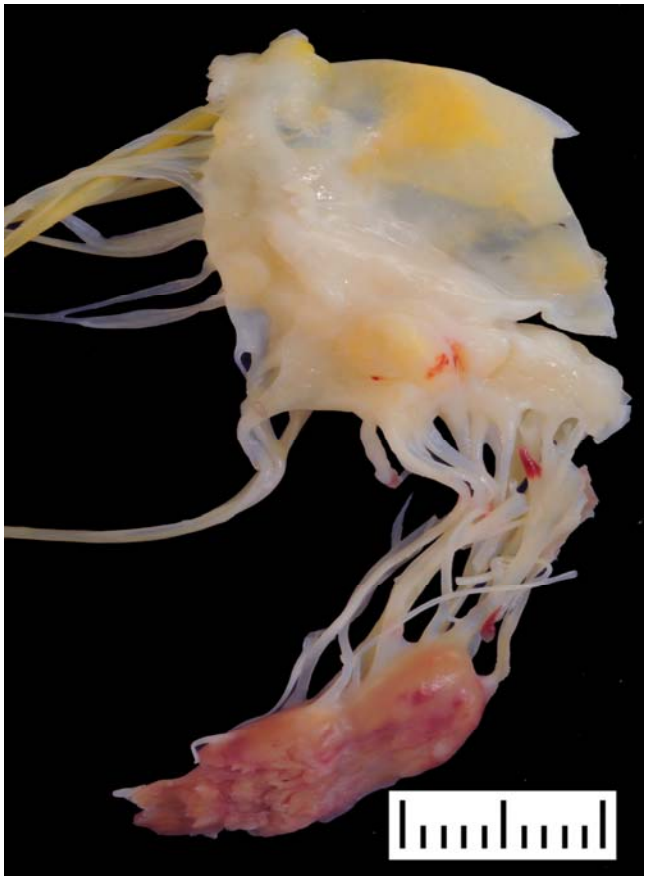

Fig. 5. Surgical specimen showing a segment of mitral valve and a ruptured papillary muscle secondary to myocardial infarction. Note the pale myocardium with hemorrhages and the ragged edges of the papillary muscle head.

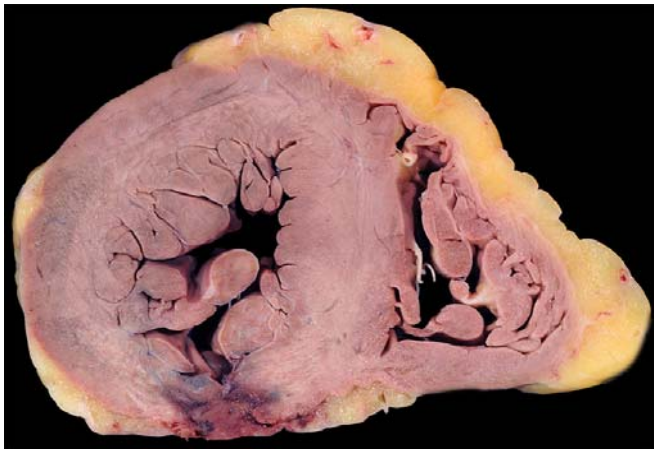

Fig. 6. Acute transmural infarction in the posterior wall evolved into a rupture site. The image shows a serpiginous hemorrhagic path of the blood dissecting through the necrotic myocardium.

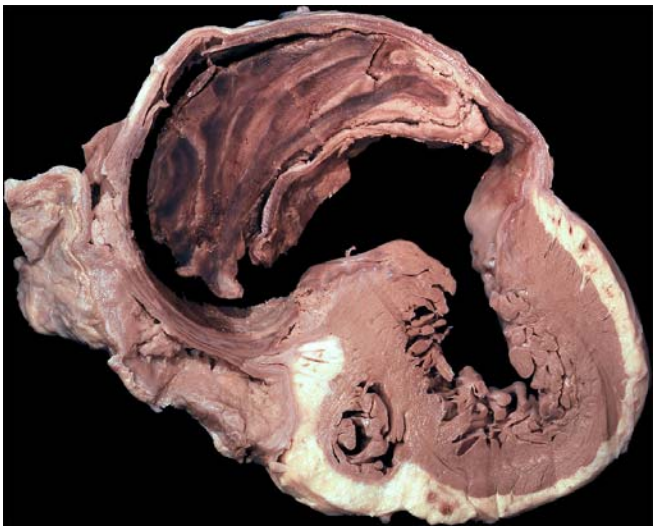

Fig. 7. A pseudoaneurysm with laminated thrombus is shown surrounded by fibrous tissue and pericardium. A pseudoaneurysm results from a contained rupture of the ventricular wall and communicates with the ventricular cavity through a narrow neck. In comparison, a true ventricular aneurysm results from dilatation of the scarred myocardium.

***Microscopic***

- Hypereosinophilia of myocyte sarcoplasm, nuclear pyknosis and karyolysis.
- Coagulation necrosis - hypereosinophilia with blurring or loss of the striated pattern of the myocyte sarcoplasm (Fig. 8)
- Colliquative myocytolysis (hydropic change of myocytes) (Fig. 9) in subendocardial location

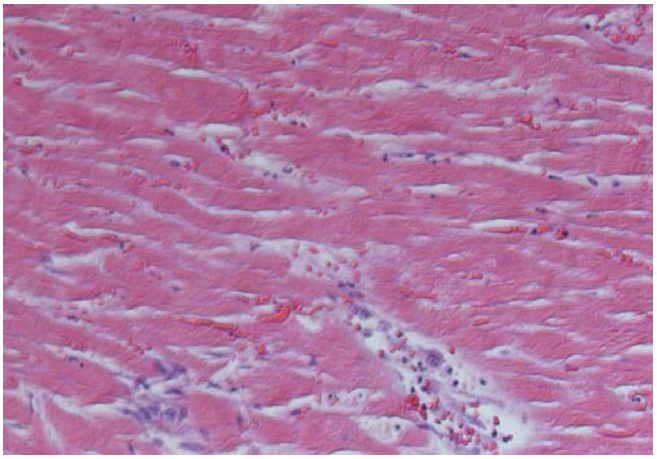

Fig. 8. Coagulation necrosis of the myocardium showing hypereosinophilic sarcoplasm of the myocytes with indistinct or frankly blurred striations and loss of nuclei.

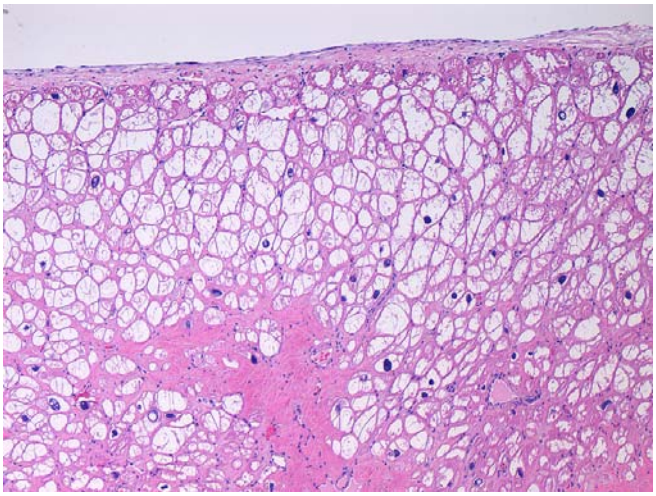

Fig. 9. Colliquative myocytolysis showing large vacuolated sarcoplasm of myocytes due to hydropic change. It usually occurs in subendocardial location. It may also be seen in areas of "hibernating" myocardium in chronic ischemic injury.

- Contraction band necrosis (which may be part of reperfusion injury including interstitial hemorrhage) is frequently present (Fig. 10)

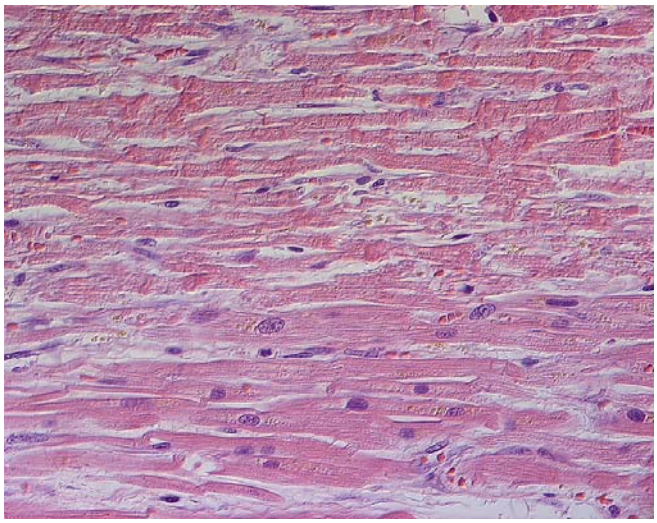

Fig. 10. Contraction band necrosis showing transverse hypereosinophilic bands alternating with pale granular spaces along the length of the myocytes. The transverse bands result from overlapping of hypercontracted sarcomeres within a myocyte. For comparison the myocytes in the lower portion of the field do not show contraction band necrosis.

- Wavy and thinned myocytes can also be seen, however wavy myocytes without thinning should not be interpreted as infarcted myocardium (Fig.11)

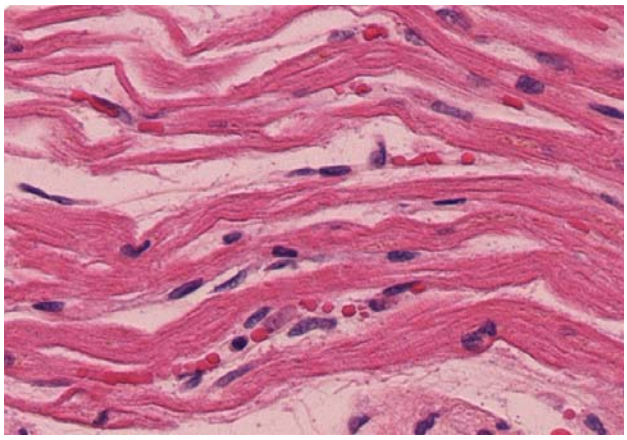

Fig. 11. An early morphologic change in acute myocardial infarction is the appearance of wavy and thinned fibers. Note the capillary congestion in these areas, lack of polymorphonuclear infiltration and presence of hypereosinophilic fibers in the myocytes.

- Inflammatory response starts at around 4 hours with margination and progresses as shown in Table 3
- If reperfusion occurs, contraction band necrosis is prominent with interstitial hemorrhages

**Table 3. Sequence of Certain Microscopic Changes in Acute Myocardial Ischemia (Approximate)**

| *Time after event* | *Histopathologic findings* |
|---|---|
| 4-6 hours | Margination of polymorphonuclear leukocytes (Fig. 12) |
| 8-12 hours | Diapedesis of polymorphonuclear leukocytes into the myocardial interstitial space (Fig. 13) |
| 1 day | Hypereosinophilic fibers, nuclear pyknosis, coagulation necrosis, colliquative myocytolysis, edema, interstitial hemorrhage, contraction band necrosis, increase in neutrophilic infiltration |
| 2-3 days | Marked polymorphonuclear infiltrate with extensive karyorrhexis, loss of myocyte nuclei (Fig. 14) |
| 4 days to 1 week | Macrophage infiltration, early granulation tissue with fibroblast response and capillary proliferation at the edges (Fig.15) |
| 7-14 days | Granulation tissue with hemosiderin-laden macrophages; variable amount of lymphocytes, rare plasma cells and eosinophils; polymorphonuclear leukocytes have disappeared |
| 2-8 weeks | Granulation tissue matures with increased collagen deposition, which becomes prominent and more dense (Fig. 16) |
| 2 months | Healed scar |

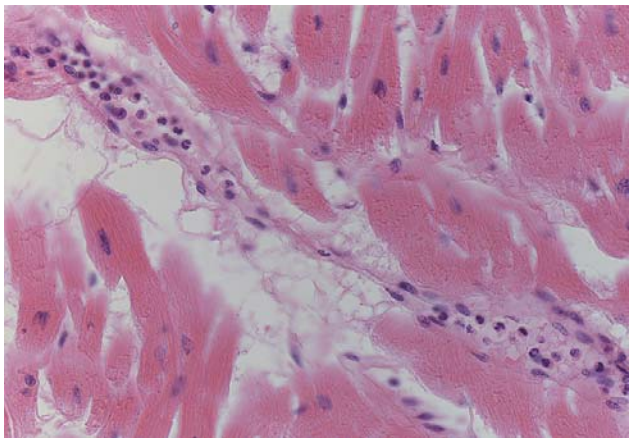

Fig. 12. Margination of polymorphonuclear leukocytes is one of the earliest unambiguous changes in myocardial infarcts. It is seen as early as 4 to 6 hours postinfarction.

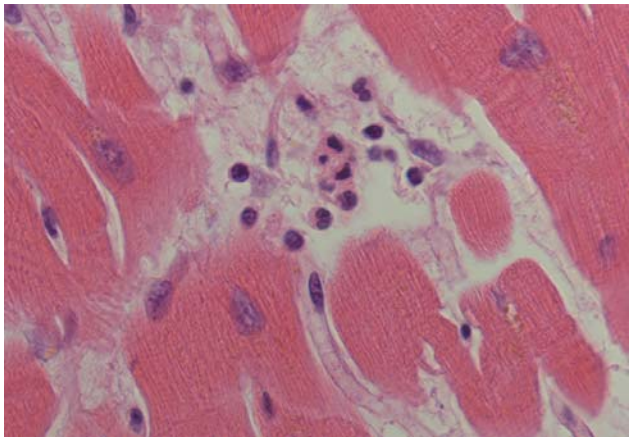

Fig. 13. Once the polymorphonuclear leukocytes marginate inside capillaries near the infarcted area, they begin to diapedese into the extracellular space and infiltrate the surrounding myocardium. This change usually starts at around 6-8 hours and increases with time as more polymorphonuclear leukocytes are chemoattracted to the infarcted myocardium.

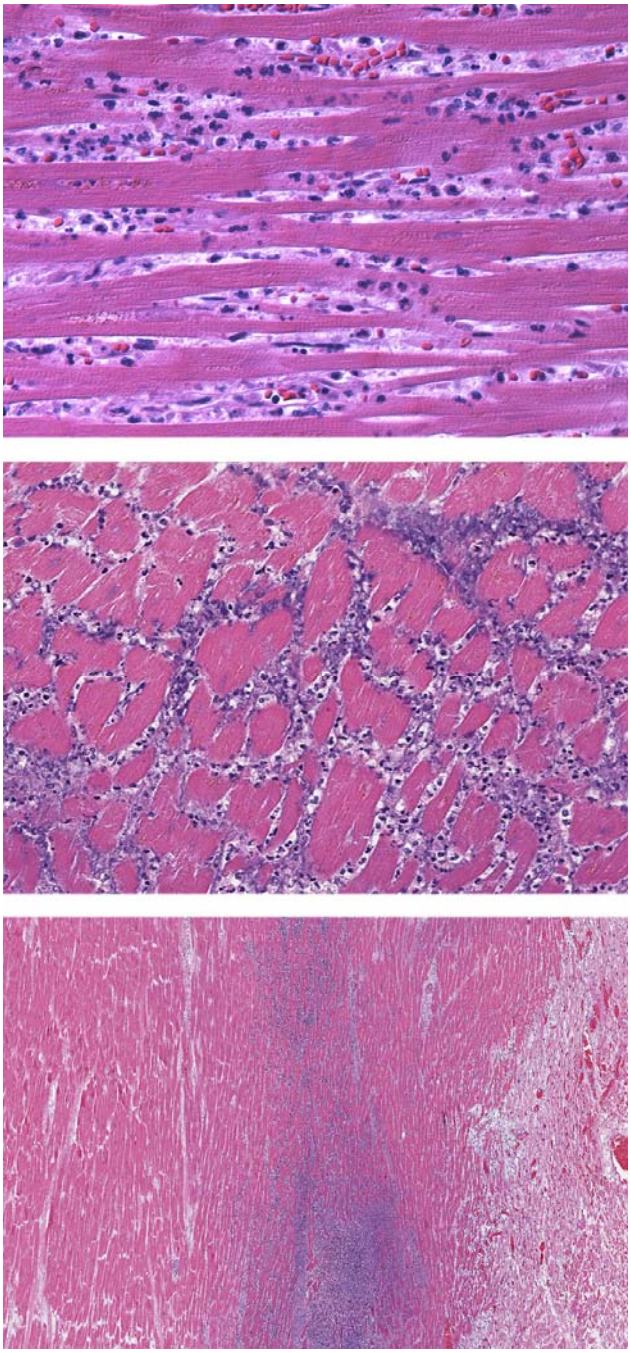

Fig. 14 The top panel shows frank infiltration of the interstitium by further diapedesis of polymorphonuclear leukocytes. The myocardium shows coagulation necrosis. This amount of polymorphonuclear leukocyte infiltration occurs at around 24 hour of evolution of the infarct. The nuclei of the myocytes are not staining but striations can still be identified in the sarcoplasm. The middle panel shows extensive karyorrhexis of the polymorphonuclear leukocytes, which imparts a "dusty" basophilic appearance and is observed at 3-4 days postinfarct. The lower panel shows a zone of basophilia representing polymorphonuclear cells undergoing karyorrhexis between the zone of coagulative necrosis on the left and viable myocardium on the right.

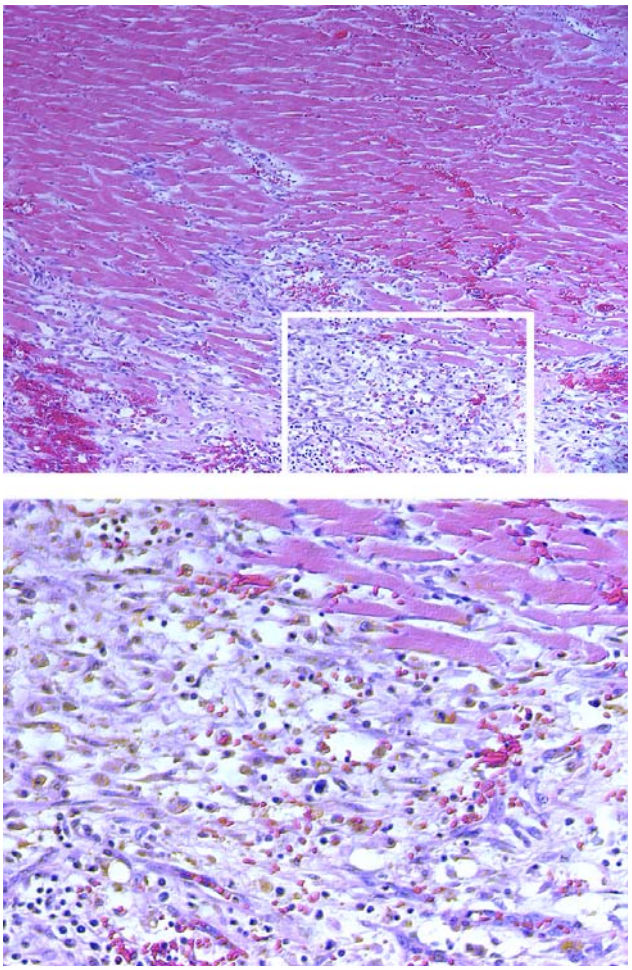

Fig. 15. In the deepest areas of a large infarct the acute inflammatory infiltrate may not reach, and promote lysis of the myocytes. Thus dead myocytes appear eosinophilic, but do not show nuclei (karyolysis). Similarly the endothelial cells of the capillaries undergo karyolysis. However as the repair response approaches this core it shows abundant fibroblasts and hemosiderin-and-lipofuscin laden become ubiquitous macrophages (inset and lower image). This infarct is about 7 days in in evolution.

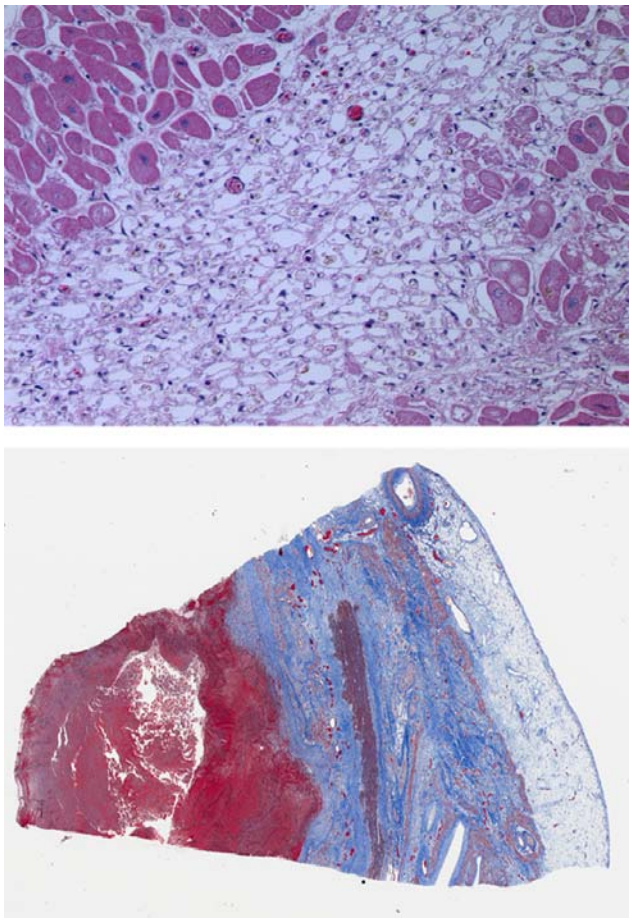

Fig. 16. Another pattern commonly seen is the disappearance of myofibrils from the sarcoplasm, which leaves empty spaces bounded by the sarcolemma resulting in an alveolar pattern with scattered macrophages. This pattern is usually seen in small areas of infarction or in the outer zone of a large infarct. The lower image shows a healing transmural infarct with pale and dark blue zones of collagen deposition. Note the mural thrombus with the red fibrin in a trichrome stain (red).

## *Chronic ischemic heart disease*

### *Clinical*

- Insidious onset of congestive heart failure due to progression of myocardial ischemic damage following previous MIs

### *Macroscopic*

- Chamber dilatation and hypertrophy
- Patchy interstitial fibrosis or healed MI (Fig. 17)

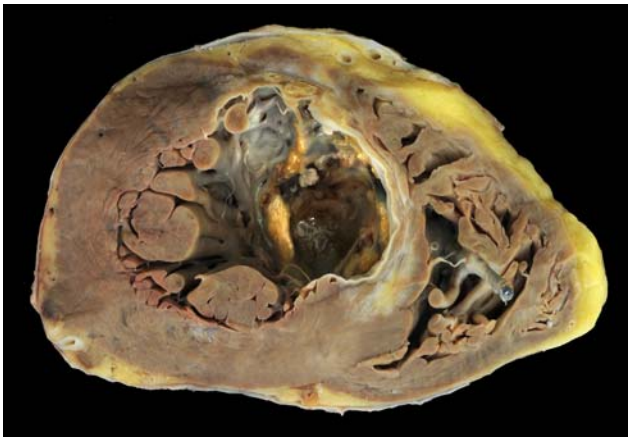

Fig. 17. A healed transmural infarct of the anterior septum and a small portion of the anterior left ventricular wall appears as dense white scar with focal calcification. There is an apical thrombus. Note the fine areas of grey white fibrosis in the non-infarcted myocardium. The right ventricle shows a segment of a pacing lead with a fibrous tissue cuff surrounding it.

- Patchy endocardial fibrosis
- Severe atherosclerosis of coronary arteries

### *Microscopic*

- Colliquative myocytolysis – hydropic change in myocytes, most prominent in the subendocardial myocardium
- Interstitial and replacement fibrosis
- Compensatory myocyte hypertrophy

## CARDIOMYOPATHY

- Cardiomyopathies are a heterogeneous group of diseases of the myocardium associated with mechanical and/or electrical dysfunction that usually (but not invariably) exhibit inappropriate ventricular hypertrophy or dilatation.
- There is absence of coronary artery disease, valvular disease, congenital heart disease, and hypertension sufficient enough to explain the myocardial disorder.
- Etiology is varied but frequently are genetic.
- Cardiac involvement can be the primary manifestation of the disease (primary cardiomyopathies) or it may be part of generalized systemic disorders (secondary cardiomyopathies).
- The pathology of cardiomyopathies can be classified in three major practical categories which correlate the morphology and functional phenotype: dilated, hypertrophic and restrictive as shown in Table 4.
- Each phenotype can be further classified into familial/genetic or non-familial/non-genetic in etiology.

| Table 4. Morphologic and Clinical Physiologic Classification of Cardiomyopathies | | | | |
|---|---|---|---|---|
| Functional Pattern | LV ejection fraction | Mechanisms of failure | Causes of Phenotype | Differential diagnosis: Indirect Myocardial Dysfunction (Mimicking Cardiomyopathy) |
| Dilated | <40% | Impaired contractility (Systolic dysfunction) | Genetic, Inflammatory, Toxic, Idiopathic | Ischemic, valvular, hypertensive, congenital heart disease |
| Hypertrophic | 50-80% | Impairment of compliance (Diastolic dysfunction) | Genetic, Friedreich ataxia, Storage diseases, Infants of diabetic mother | Hypertensive heart disease, aortic stenosis |
| Restrictive | 45-90% | Impairment of compliance (Diastolic dysfunction) | Amyloidosis, radiation-induced fibrosis, Idiopathic | Pericardial constriction |

*Modified from: Kumar V, et al. Robbins and Cotran Pathologic Basis of Disease 9th Edition. 2015. Elsevier Saunders. Chapter 12 , pp 565.*

## *Dilated Cardiomyopathy*

### *Clinical*

- Can occur at any age
- Signs and symptoms of systolic heart failure – dyspnea, orthopnea, fatigue; evidence of low cardiac output on examination including hypotension, tachycardia, cool extremities, mental status changes; evidence of volume overload including weight gain, peripheral edema, jugular venous distension
- Genetic in at least 30% of cases
- Phenotype associated with pregnancy or the postpartum period (peripartum cardiomyopathy), alcoholism (alcoholic cardiomyopathy), myocarditis, muscular dystrophies, catecholamine excess, takotsubo "stress cardiomyopathy"

### *Macroscopic*

- Cardiomegaly with left ventricular cavity dilatation, often with four-chamber dilatation (Fig. 18)

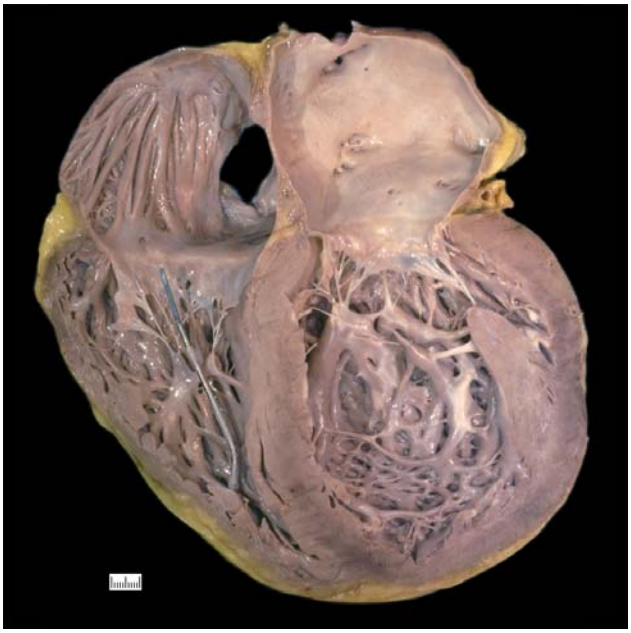

Fig. 18. A case of dilated cardiomyopathy with enlargement of all four chambers, most severe in the left ventricle which appears globular. The wall thickness may be normal as the hypertrophy is masked by the dilatation. The right ventricle shows a segment of a pacing lead well anchored in the apex of this chamber.

- Left ventricular wall thickness is increased but may be near normal as the hypertrophy is masked by chamber dilatation
- Valvular annulus dilated
- Mural thrombi can be present in the atrial appendages and ventricles
- Absence of significant coronary artery disease

### *Microscopic*

- Histologic changes are usually nonspecific as to the etiology of dilated cardiomyopathy
- Variable degrees of myocyte hypertrophy, degeneration and interstitial fibrosis
- Inflammatory infiltrates minimal and confined to areas of interstitial fibrosis
- Myocyte sarcoplasm vacuolization secondary to toxic drugs or other chemicals

## *Hypertrophic Cardiomyopathy*

### *Clinical*

- Left ventricular hypertrophy in the absence of hypertension and aortic valve disease
  genes encoding sarcomeric proteins mutated
- Mutations in β-myosin heavy chain, myosin binding protein C, and troponin T account for up to 80% of cases with genetic mutations
- Symptoms of left ventricular outflow obstruction in 25% of patients
- Associated with sudden death during exercise
- Treated by beta adrenergic blockage; septal myectomy if with obstructive physiology

### *Macroscopic*

- Asymmetric septal hypertrophy (basal, mid septal or apical subtypes exist) (Fig. 19)

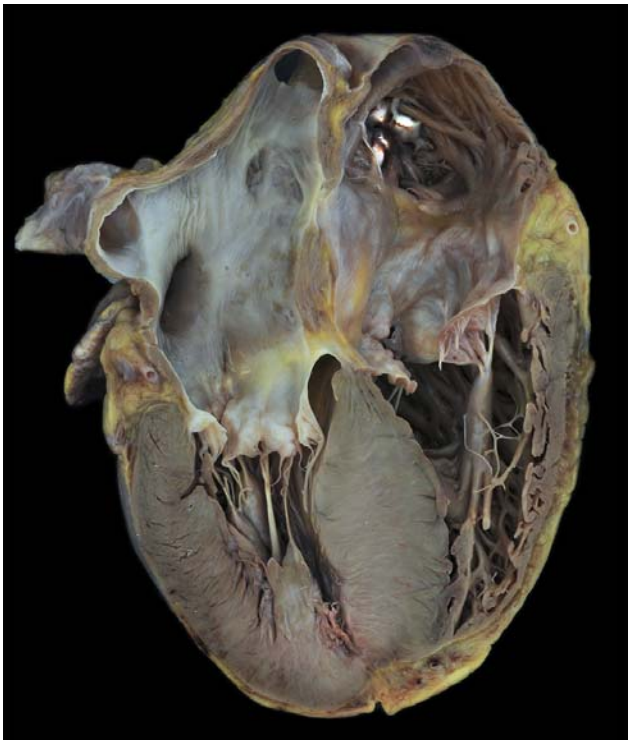

Fig. 19. This heart shows marked hypertrophy of the interventricular septum which is twice as thick as the left ventricular free wall. There is dilatation of the other chambers as well with a white organizing thrombus in the right atrial appendage.

- If obstructive, mitral valve thickening and focal endocardial thickening in the outflow tract as a result of contact with anterior mitral leaflet during systole
- Enlarged left atrium

***Microscopic***

- Myocyte disarray and hypertrophy (Fig. 20)

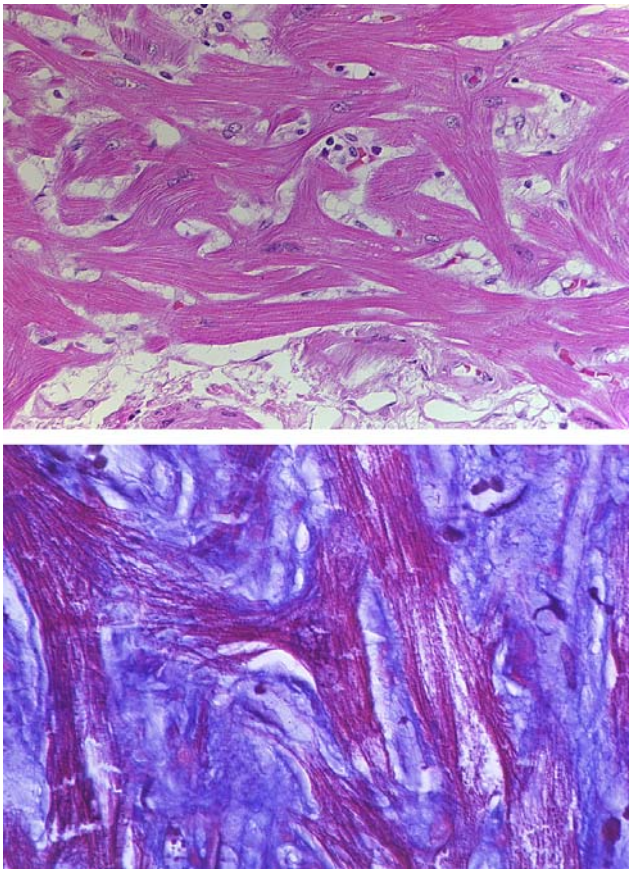

Fig. 20. In hypertrophic cardiomyopathy, the hallmark of the disease is "disarray". Disarray occurs at the fascicle level, myocyte level and sarcomere level. At the myocyte level, the myocyte sarcoplasm is disorganized forming branches in contrast to a normal parallel arrangement in sections taken from the interventricular septum. The disarray is also evident in the myofibrils within individual myocytes. This is often accompanied by interstitial fibrosis as shown in the trichrome stain.

- Small intramural coronary artery dysplasia (Fig. 21)

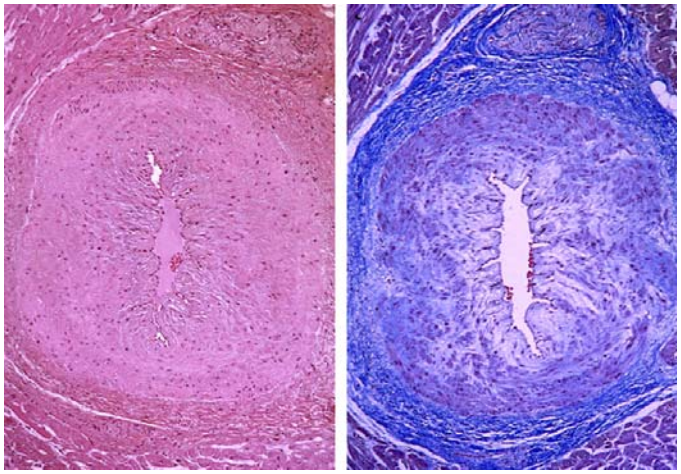

Fig. 21. The intramural coronary arteries in the septum of hearts with hypertrophic cardiomyopathy are often abnormal. The lumen is narrowed and the wall is thickened by an increase in the smooth

- Variable fibrosis (interstitial and replacement type)
- Endocardial fibroelastosis in the left ventricular outflow tract (Fig. 22)

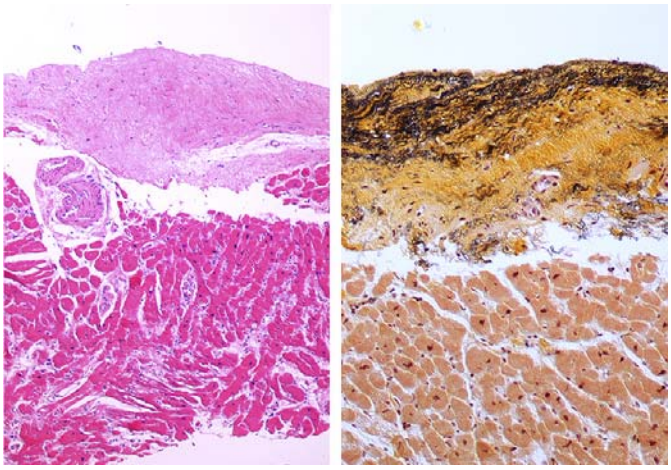

Fig. 22. The outflow tract of the left ventricle in the obstructive type of hypertrophic cardiomyopathy shows endocardial thickening with fibrosis and elastosis evident in the Movat stain.

***Differential Diagnosis***

- Amyloidosis, Fabry's disease, storage diseases, mitochondrial disorders, Friedreich's ataxia
- Hypertensive or valvular (especially aortic) heart disease, which may show concentric left ventricular hypertrophy

## *Arrhythmogenic Right Ventricular Cardiomyopathy*

### *Clinical*

- Global or regional dysfunction of the right ventricle that may progress to involve the left ventricle
- Associated with arrhythmias of right ventricular origin, heart failure, and sudden death
- Mutations in desmosomal protein encoding genes (plakoglobin, plakophilin-2, desmoplakin, desmocollin-2, desmoglein-2) are common; other mutations involving transmembrane protein 43, transforming growth factor-beta 3, desmin, and titin are reported

### *Macroscopic*

- Gross infiltration of right ventricular free wall with replacement of the compact zone myocardium by adipose and fibrous tissue (Figs. 23-25)

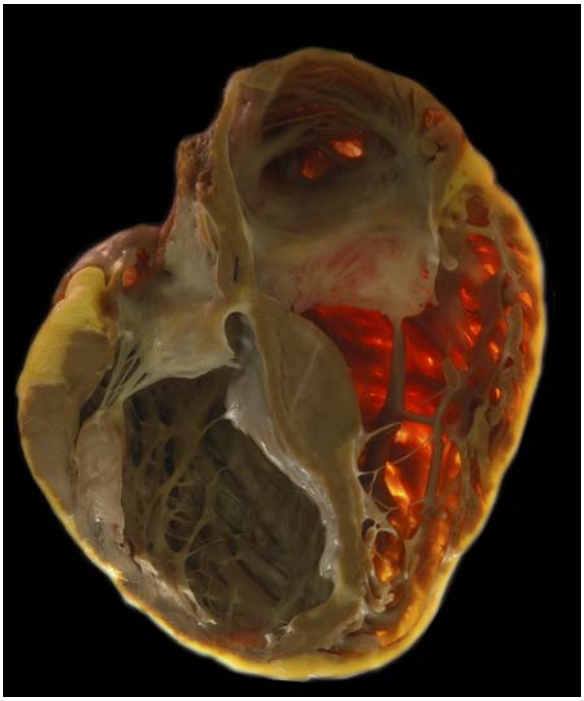

Fig. 23. Transilluminated specimen shows loss of the compact zone in the right ventricle which appears translucent in a case of arrhythmogenic right ventricular cardiomyopathy. Also note the thinning of the left ventricular wall and interventricular septum towards the apex due to fibrofatty replacement.

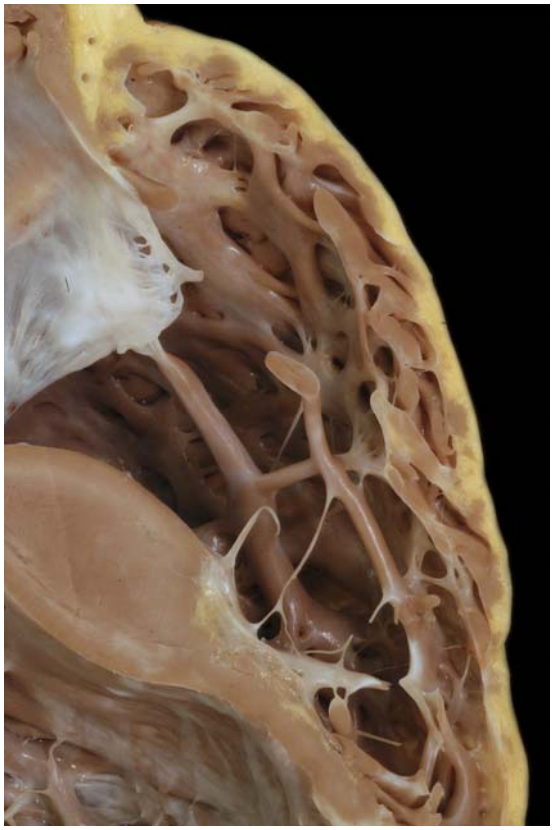

Fig. 24. The right ventricular wall of the same heart in Fig. 23 is shown. The compact zone is discontinuous with fatty infiltration and fibrous replacement. The trabecular myocardium is relatively spared.

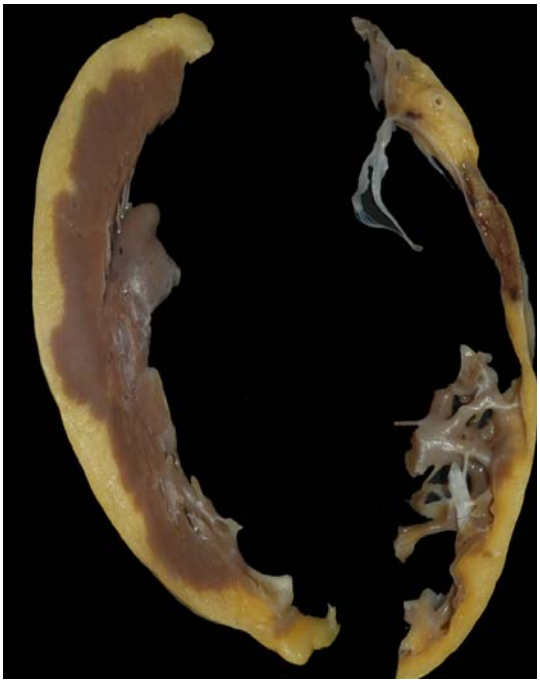

Fig. 25. In addition to the marked thinning of the wall of the right ventricle (shown on the right) due to fibrofatty replacement in arrhythmogenic right ventricular cardiomyopathy, involvement of the left ventricle with fatty infiltration producing a “moth eaten” appearance is seen in almost half of the cases. Note the irregular contour of the subepicardium of the left ventricle in this example.

### *Microscopic*

- Myocyte loss in the compact zone with transmural replacement by adipose and/or fibrous tissue (Fig. 26)
- Mononuclear leukocytic infiltrates can be present

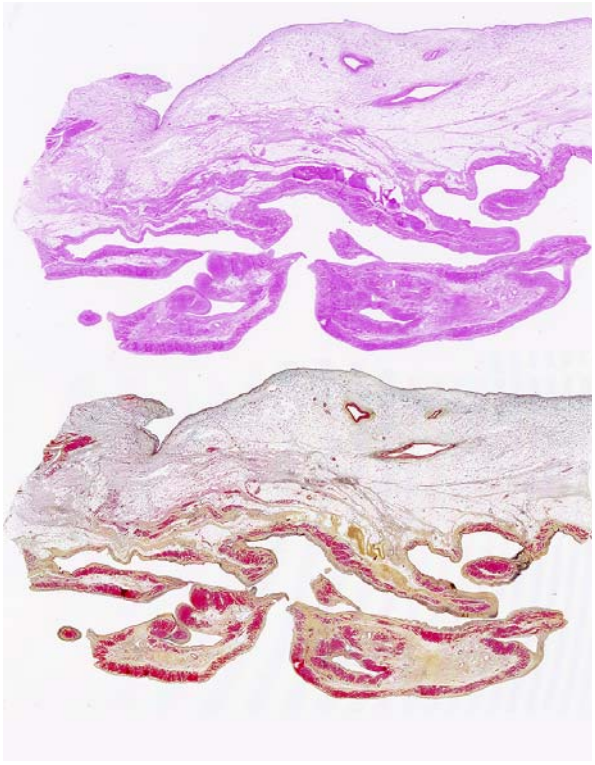

Fig. 26. Section of the right ventricular wall with extensive adipose tissue replacement of the compact zone and trabecular myocardium as shown in an H&E stain and corresponding Movat stain. The Movat stain highlights the fibrous tissue in yellow.

## *Restrictive cardiomyopathy*

### *Clinical*

- Diastolic dysfunction with impaired relaxation (must be distinguished from constriction)
- Least common type of cardiomyopathies
- Could be idiopathic or secondary due to stiff myocardium or thickened endocardium
- Endocardium-based restriction:
  - Endomyocardial fibrosis
  - Diffuse endocardial fibroelastosis
  - Loeffler (hypereosinophilic) endomyocarditis
- Myocardial interstitium-based restriction:
  - Amyloidosis (see below under Amyloidosis)
  - Post-radiation fibrosis
  - Fibrosing sarcoidosis

### *Macroscopic*

- The macroscopic features vary depending on the etiology of the restriction
- Heart size normal or only slightly enlarged
- Ventricular cavities normal or mildly dilated; atrial cavities moderately to severely dilated
- Left ventricular wall thickness may be normal
- Endocardial fibrosis that may obliterate the apices of the right and left ventricles and surround the papillary muscles
- Mural thrombi may be present in endomyocardial fibrosis

### *Microscopic*

- Primary restrictive cardiomyopathy show myocyte hypertrophy and interstitial fibrosis

- Severe fibrous thickening of the endocardium with or without eosinophils and organizing thrombi
- Elastic fiber proliferation in endocardial fibroelastosis seen in the pediatric age group often secondary to aortic stenosis

## INFILTRATIVE MYOCARDIAL DISEASES

### *Amyloidosis*

#### *Clinical*

- Depending upon the type and degree of involvement, it may be asymptomatic or present with congestive heart failure, arrhythmias, ischemic disease, and sudden death
- Light chains (Kappa or Lambda) are the most common amyloidogenic proteins (60%) found in the heart, followed by Transthyretin (TTR) (40%) in symptomatic patients
- Senile amyloidosis may be due to TTR or less commonly atrial natriuretic factor/peptide (ANF / ANP)

#### *Macroscopic*

- Extensive deposits may lead to pale, firm, and rubbery myocardium
- Left atrial endocardial and valvular deposits may appear waxy and shiny yellow/ochre fine nodules (Fig. 27)

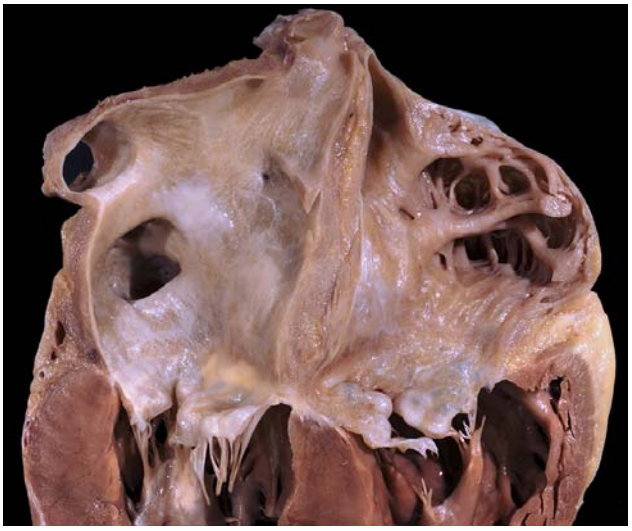

Fig. 27. In extensive cardiac amyloidosis, the atria are enlarged and the endocardium of both atria shows fine yellow-ochre granular surface due to amyloid deposition. These The ventricular myocardium shows subtle areas of pallor which correspond to amyloid deposits.

***Microscopic***

- Extracellular, eosinophilic homogeneous (also called "amorphous") material on hematoxylin and eosin (H&E) stained section (Fig. 28)
- Deposits can be interstitial surrounding myocytes or nodular
- Vascular wall involvement can be present, most commonly in light chain amyloidosis, and may cause vessel stenosis
- By definition, deposits are Congo red positive, with apple green birefringence when examined with polarized light microscopy(Fig. 29)

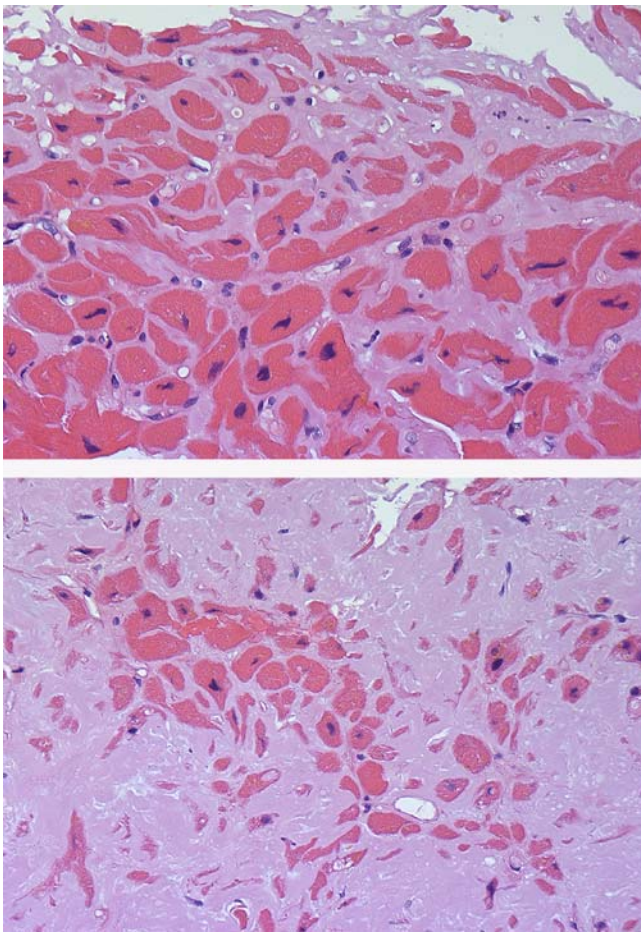

Fig. 28. Amyloid infiltration in the heart shows "amorphous" eosinophilic material accumulating in the extracellular space. The amyloid is deposited thoughout the interstitium surrounding individual myocytes (top panel). In advanced disease, there is more pronounced myocyte atrophy with accumulation of the interstitial deposits into a nodular pattern (bottom panel).

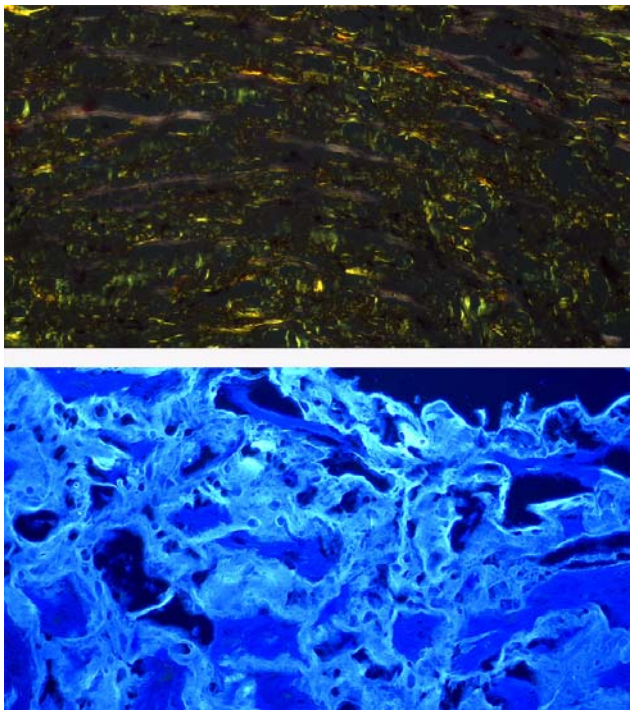

Fig. 29. Interstitial amyloid shows apple green birefringence on polarization microscopy (top panel) when stained with Congo Red. Amyloid deposits also appear fluorescent with thioflavin S or T staining viewed under fluorescence microscopy. This is a more sensitive and reproducible stain than Congo Red.

- Alternatively, sulfated Alcian blue stain has been used. However, Thioflavin-T and Thioflavin-S stains are very sensitive but require UV light microscopy
- Immunohistochemical identification of cardiac amyloid is specific for the common subtypes that affect the heart (Kappa light chains, lambda light chains, transthyretin, atrial natriuretic factor) (Fig. 30). Other subtypes may need mass spectroscopy for identification.

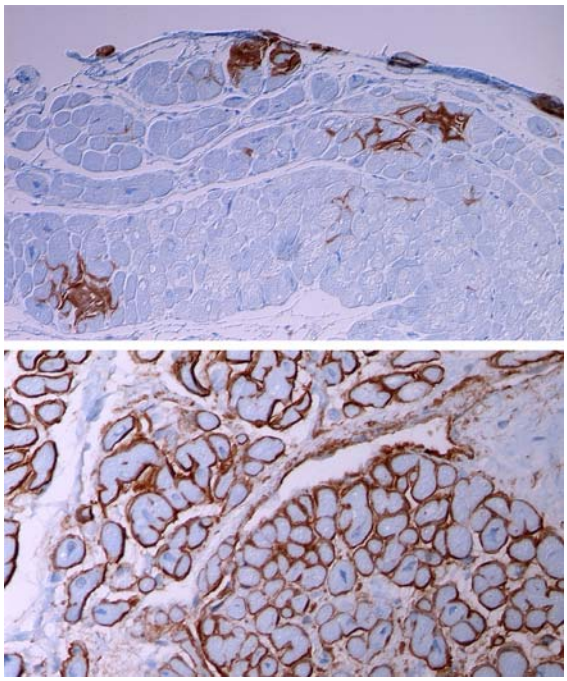

Fig. 30. Immunohistochemical staining is useful for typing of cardiac amyloidosis. The top panel shows focal deposits of transthyretin in a coarse interstitial pattern and forming small nodules. The bottom panel shows a diffuse interstitial perimyocytic pattern of deposition in light chain amyloidosis where lambda light chains are at least twice as frequently seen compared to kappa light chain deposition.

- Electron microscopy is also definitive (showing 10 nm extracellular fibrils) but rarely necessary

## *Glycogen Storage Diseases*

- Excess sequestration of various glycogen storage products in lysosomes or free in the sarcoplasm leads to heart failure
- Several glycogen storage diseases in infants (Pompe's disease) and adults (due to mutations in LAMP2 and PRKAG2) are well-known mimickers of hypertrophic cardiomyopathy (Figs. 31 and 32)

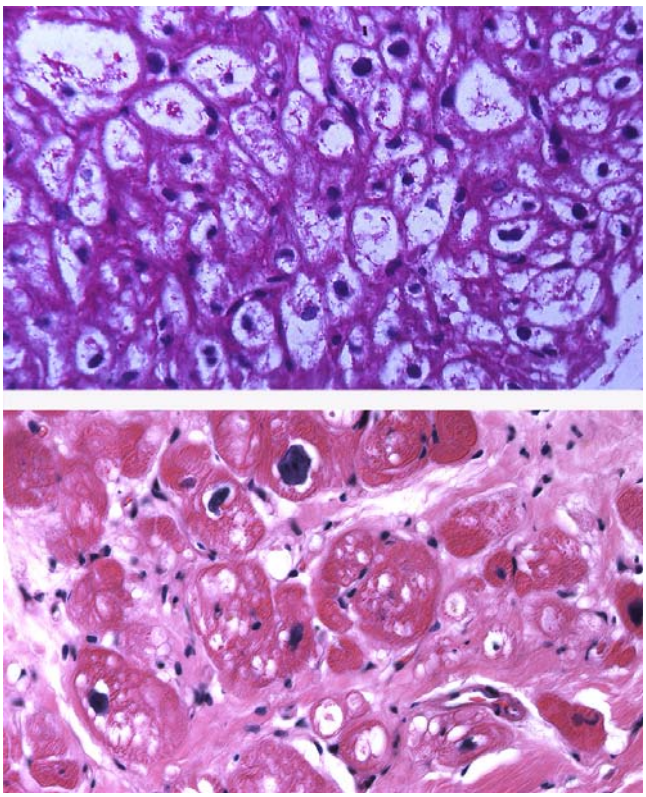

Fig. 31. The myocytes are enlarged with pale sarcoplasm due to massive accumulation of glycogen that stain PAS-positive in a case of Pompe's disease (top panel). In the adult, glycogen storage disease may appear as irregular vacuoles associated with interstitial fibrosis (bottom panel).

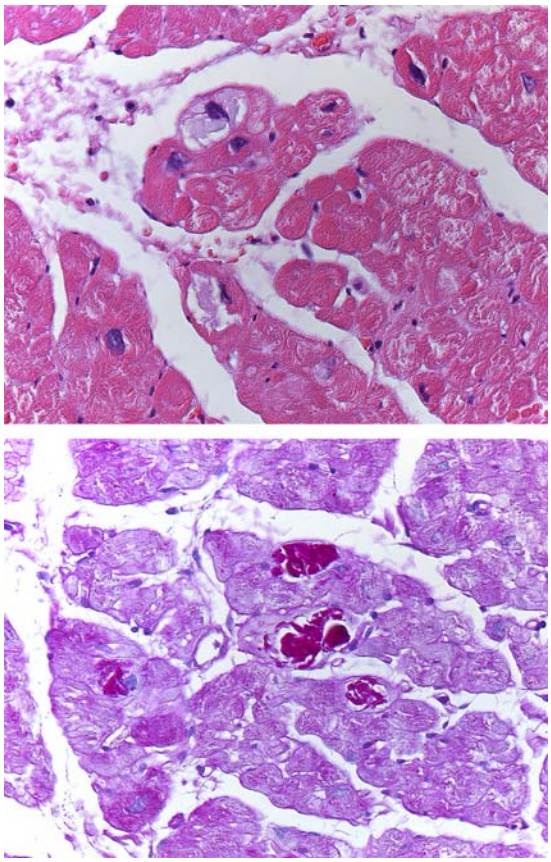

Fig. 32. A few myocytes show accumulation of basophilic material in the sarcoplasm that is intensely positive with PAS. This type of glycogen deposition can be seen in type IV glycogen storage disease and in hearts of patients older than 65 years of age (basophilic degeneration).

## *Hemochromatosis - Hemosiderosis*

- Systemic iron deposition with organ damage (usually in hemochromatosis)
- Iron stain to demonstrate iron in the myocyte sarcoplasm (Fig. 33)
- Morphology alone cannot differentiate hemochromatosis from hemosiderosis

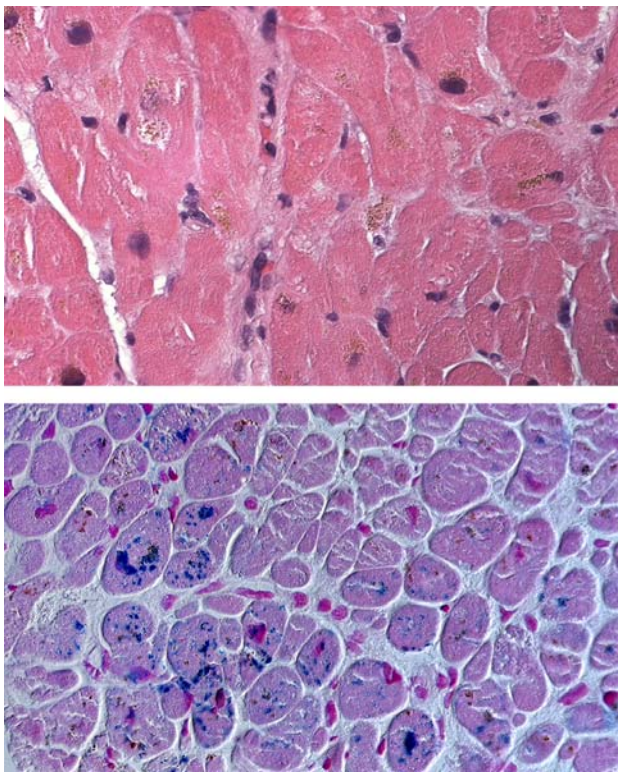

Fig. 33. The myocytes contain dark-yellow-to-brown granular deposits mostly in perinuclear location (top panel) which are readily identified as iron on a Prussian blue stain (bottom panel) in a case of hemosiderosis.

## *Angiokeratoma Corporis Diffusum Universale (Fabry's Disease)*

- X-linked recessive inheritance
- Deficiency of lysosomal alpha galactosidase leading to ceramide trihexoside accumulation
- Skin, cornea, kidney, and heart affected
- Microscopically, enlarged myocytes that appear vacuolated (Fig. 34)
- Intralysosomal concentric or parallel lamellae (myelin figures) by electron microscopy are the hallmark (Fig. 34)

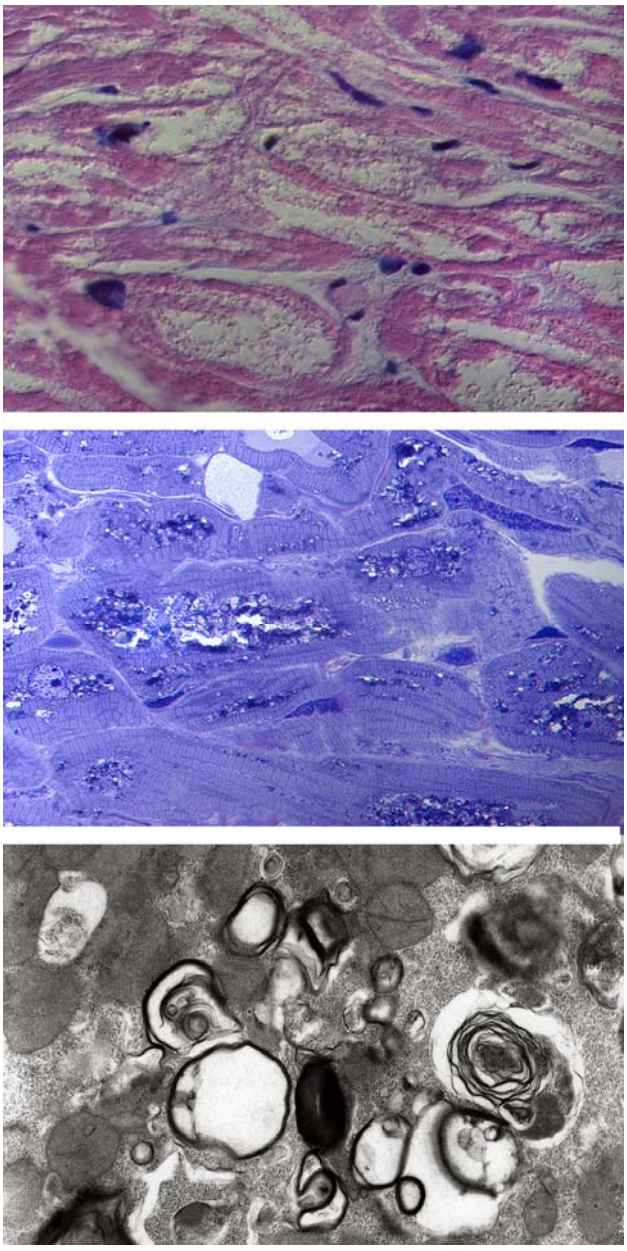

Fig. 34. In Fabry disease, there is marked vacuolation of the myocytes. The myofibrils are displaced to the periphery by the deposits occupying the central clear to finely granular area (top panel). On toluidine blue stain of a semithin section, the glycolipid deposits are evident as dark blue metachromatic deposits in Touluidine blue stained plastic section. Ultrastructural examination demonstrates that the metachromatic deposits are in fact the characteristic lamellar bodies seen in Fabry's disease.

- Differential diagnosis: chloroquine and hydroxychloroquine cardiotoxicity also shows myocyte vacuolization and presence of myelin figures, clinical history is very important to distinguish between these two entities

## MYOCARDITIS

### *Clinical*

- Associated with viral infections (most often coxsackie, echovirus, influenza, adenovirus, parvovirus B19), autoimmune diseases and drug reactions.
- Bacterial, fungal, protozoal and parasitic myocarditis are far less common
- Complications include congestive heart failure, conduction defects, arrhythmias, and sudden death

### *Macroscopic*

- Range from normal to biventricular dilatation/hypertrophy with pale "flabby" myocardium and fibrosis

### *Microscopic*

- Dallas criteria for the evaluation of myocarditis in biopsies: leukocytic infiltrate (usually lymphocytic) with myocyte degeneration/necrosis
- In most cases, a T-cell lymphocytic infiltrate admixed with histiocytes (Fig. 35), occasionally with eosinophils
- Myocyte injury can be spotty or geographic

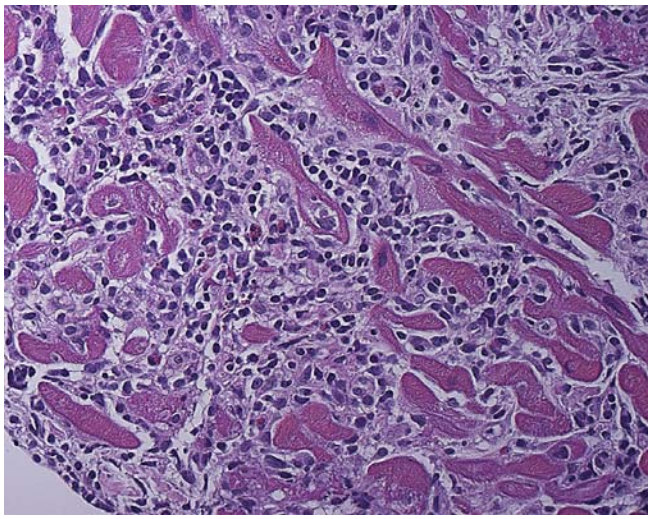

Fig. 35. Lymphocytic myocarditis showing dense infiltrates of lymphocytes, histiocytes and few eosinophils that expands the interstitial space. Myocyte injury is evident in the left lower corner of the field showing fragmentation and irregular borders of the myocytes.

### *Giant Cell Myocarditis*

- Occurs in young and middle-aged adults
- Presents with arrhythmias, conduction defects, cardiac failure, and sudden death (50%)
- Rapidly progressive and fatal; heart transplantation may be indicated
- Associated with thymoma, lupus, and inflammatory bowel disease

### *Microscopic*

- Geographic myocyte necrosis with lymphohistiocytic infiltration, eosinophils and plasma cells (Fig. 36)
- Lacks discrete granulomas
- Giant cells of both macrophage and myocyte origin are present

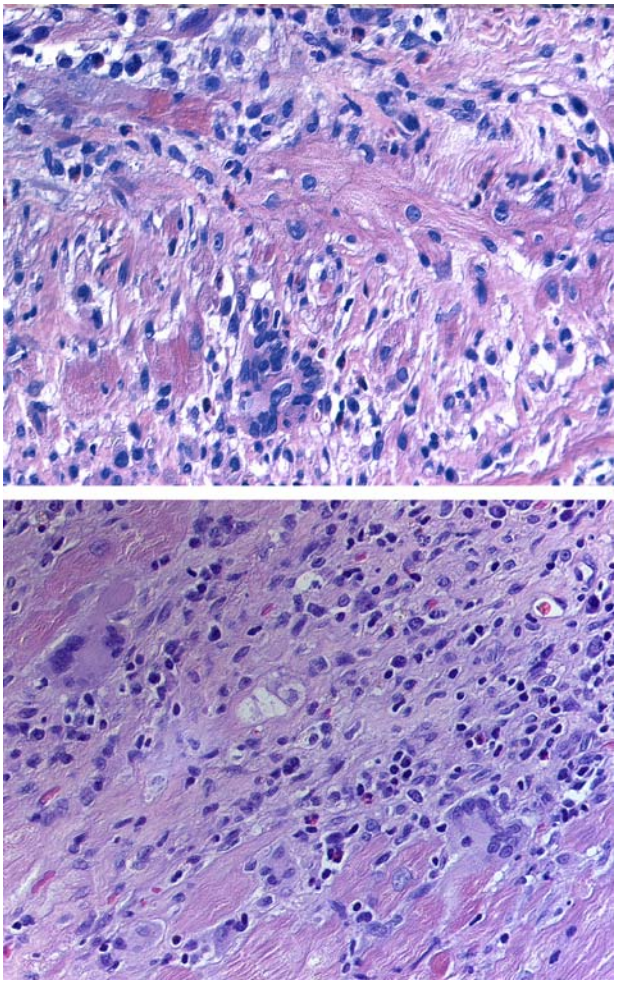

Fig. 36. Giant cell myocarditis showing an aggressive inflammatory infiltrate notable for the presence of multinucleated giant cells and variable amount of eosinophils in both images. Well-formed granulomas are absent.

### *Differential Diagnosis*

- Cardiac sarcoidosis
  - Cardiac involvement in sarcoidosis manifests as arrhythmias, congestive heart failure, and sudden death
  - On gross examination, sarcoidosis granulomata occur in the interventricular septum toward the base and spread towards the lateral walls of the right and left ventricle
  - The granulomata and the destroyed myocardium are replaced by dense fibrous tissue, producing firm to rubbery white to grey and glassy scars (Fig. 37)

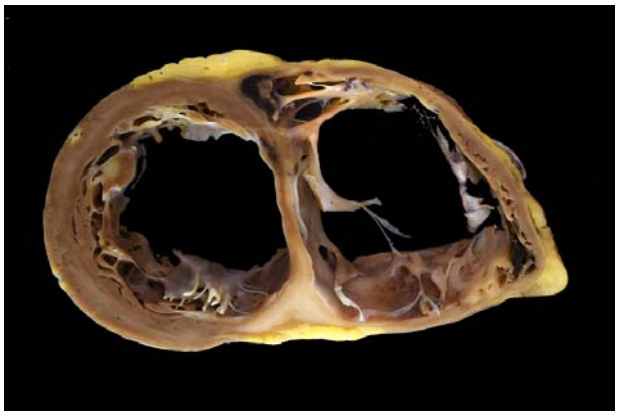

Fig. 37. A case of cardiac sarcoidosis with marked biventricular dilatation of the heart. There is sclerotic white "waxy" appearing formation of scars in the interventricular septum and posterior right ventricular wall. Mural thrombi are present in the right ventricle.

− Myocardial dropout associated with discrete non-necrotizing epithelioid granulomata with lymphocytes and eosinophils in the acute stages
- Once the myocardium is replaced by fibrous tissue, occasional granulomata remain (Fig. 38)

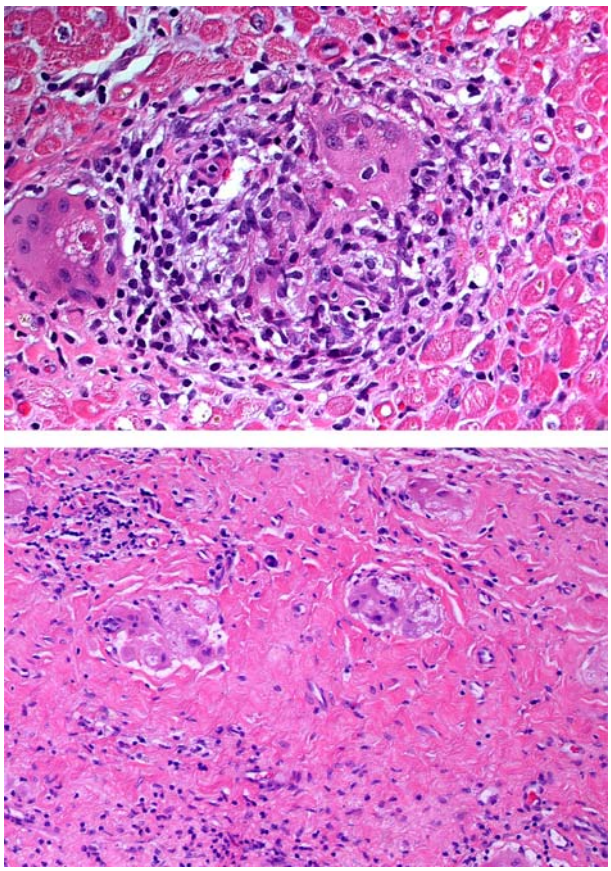

Fig. 38. Cardiac sarcoidosis showing discrete non-caseating granuloma in the myocardium (top panel). Small granulomas and multinucleated giant cells typically persist within dense fibrosis in areas of gross scarring (bottom panel).

- Most often due to drug hypersensitivity reaction, less commonly due to hypereosinophilic syndrome, eosinophilic granulomatosis with polyangiitis (Churg-Strauss syndrome), infection
- Eosinophil-rich infiltrate admixed with lymphocytes and histiocytes, commonly in perivascular location
- Myocyte necrosis rare and minimal

## Anthracycline Cardiotoxicity

- Includes cases associated with doxorubicin (adriamycin) and daunorubicin cardiotoxicity
- Earliest changes include myocyte vacuolization secondary to sarcoplasmic reticulum dilatation
- EM findings include sarcoplasmic vacuolization, sarcoplasmic reticulum system dilatation, and lysis of myofibrils
- Grading (0–3) is based on the percentage of cells affected in ten plastic-embedded blocks of tissue

## Hypertensive Heart Disease

- Secondary to longstanding systemic hypertension affecting the left ventricle
- Grossly, concentric left ventricular hypertrophy (Fig. 39)

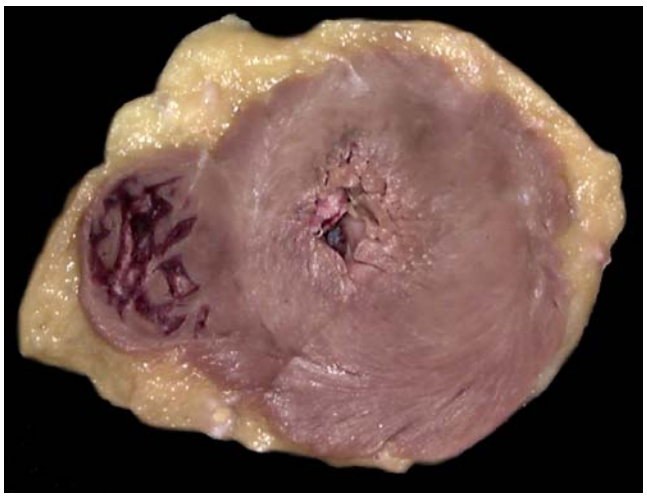

Fig. 39. Concentric left ventricular hypertrophy with a very small cavity.

- Must exclude the possible contribution of valvular and myocardial diseases to the hypertrophy
- If pulmonary hypertension is the cause, then right ventricular hypertrophy and dilatation occur

# Diseases of the Pericardium

## NORMAL PERICARDIUM

- Morphologically a parietal pericardium (the sac of fibrous tissue around the heart) and visceral pericardium can be recognized as distinct structures.
- Both are lined by mesothelial cells, thus forming a serosal layer that is continuous between the parietal pericardium and the visceral pericardium
- The mesothelial cell lining produces and reabsorbs pericardial fluid (Fig. 40)

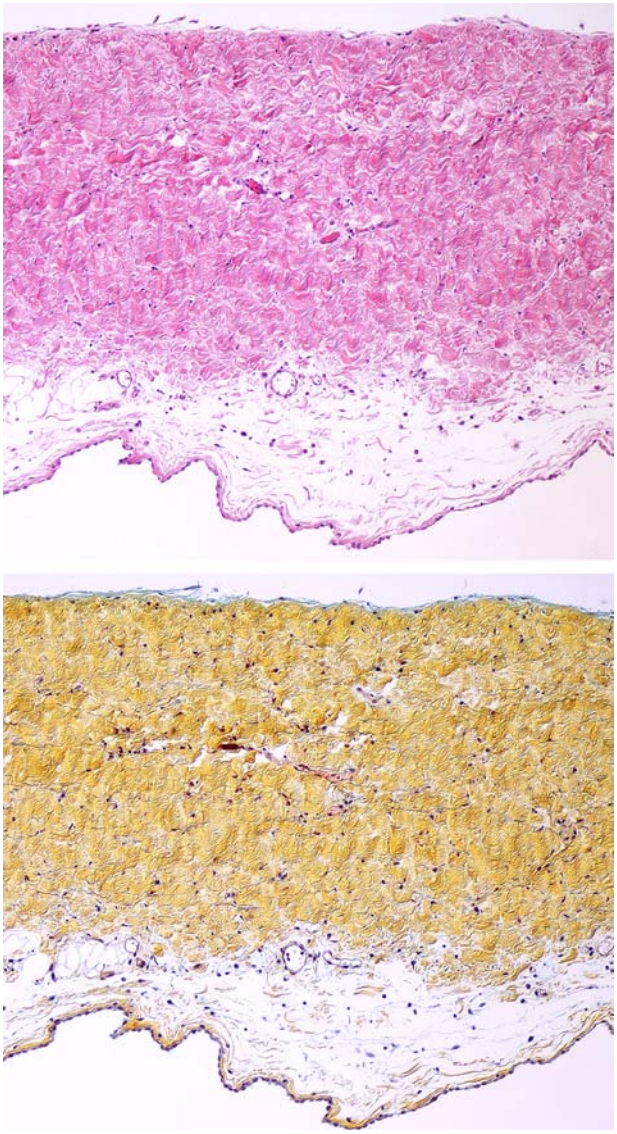

Fig. 40. Section of a parietal pericardium showing the fibrous pericardium consisting of compact layers of collagen bundles with a few small vessels and interspersed elastic fibers and serosal pericardium consisting of a layer of mesothelial cells.

## ACUTE PERICARDITIS

### *Clinical*

- Presents with chest pain, fever, friction rub
- Most are idiopathic; iatrogenic causes include cardiac surgery and radiation
- It may progress to chronic fibrous pericarditis

### *Macroscopic*

- Deposits on the parietal and visceral pericardium may be characterized as predominantly fibrinous, purulent or hemorrhagic (Fig. 41)

Fig. 41. In Fibrinous pericarditis, the strands of fibrin are organized between the parietal (fibrous pericardium) and the visceral pericardium (epicardium). This image shows fibrinous strands over the surface of atrial and ventricles giving the surface a coarse velvety appearance.

- Fibrinous: acute MI, post-MI (Dressler syndrome), uremia, radiation, trauma, lupus, and acute rheumatic fever
- Purulent: usually due to infections, but consider malignant effusion
- Hemorrhagic: usually due to malignancy in pericardium, also tuberculosis (TB) in other countries
- Caseating necrosis (rare!): TB until proven otherwise, infrequently fungi

### *Microscopic*

- Response to injury is manifested by fibrinous exudate, mesothelial hyperplasia, and inflammation (Fig. 42)

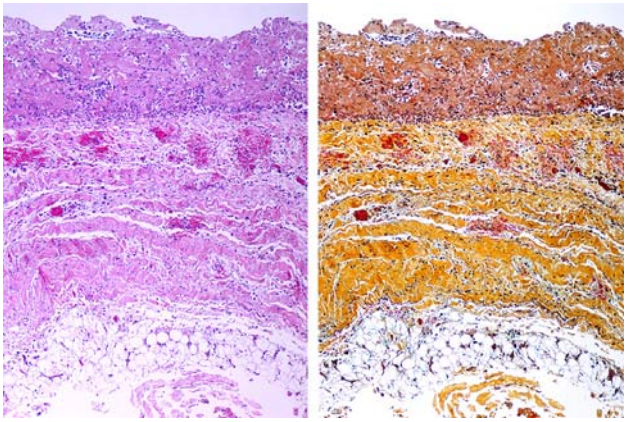

Fig. 42. Section of a parietal pericardium with fibrinous pericarditis showing a layer of fibrin with chronic inflammation and inconspicuous mesothelial lining.

- Organization may lead to fibrous adhesions with minimal thickening of the parietal and visceral pericardium
- Exuberant granulation tissue may lead to fibrous thickening of the pericardium

## Pericardial Effusion and Hemopericardium

### *Clinical*

- Accumulation of >50 mL fluid (serous, chylous, serosanguineous) and/or blood in the pericardial sac, respectively
- If volume is rapidly increasing, cardiac tamponade may result
- Large volume of effusion may be found in asymptomatic patients if the rate of fluid accumulation is slow

### *Macroscopic*

- Character of fluid can vary from serous, serosanguineous, fibrinous, or bloody
- Parietal pericardium can be thin or become thick and fibrotic with recurrent episodes of pericarditis
- Sometimes, effusions can be loculated and produce compression of only a particular cardiac chamber
- Serous exudate: usually noninfectious, common in congestive heart failure, hypothyroidism
- Hemopericardium: usually due to cardiac rupture secondary to MI or trauma and ascending aortic dissection / rupture (Fig. 43)

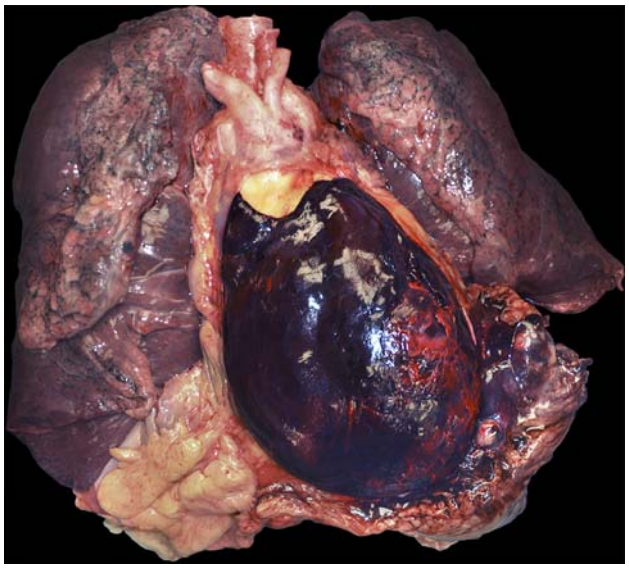

Fig. 43. Cardiopulmonary block showing that the anterior portion of the pericardial sac has been removed. This shows the pericardial cavity filled with clotted blood that obscures the heart in a patient who died of cardiac tamponade secondary to a ruptured anterior wall myocardial infarction.

- Chylous: idiopathic, congenital, iatrogenic injury to the thoracic duct, neoplastic obstruction of the thoracic duct
- Serosanguineous exudate: most often due to malignancy, but infection and renal failure (uremic pericarditis) need to be considered

## Constrictive Pericarditis

### *Clinical*

- Thick noncompliant pericardium does not allow sufficient diastolic filling of the ventricles, resulting in elevation of systemic venous pressures (hepatomegaly, ascites, peripheral edema, pleural effusion)

and low cardiac output (dyspnea, fatigue)
- Etiologies include idiopathic, cardiac surgery, radiation, infectious (viral, TB), collagen vascular diseases

***Macroscopic***

- Pericardial space is obliterated
- Parietal pericardium is stiff with fibrotic thickening and variable amount of calcifications (Fig.44)
- In some cases, visceral pericardium (epicardium) is also thickened

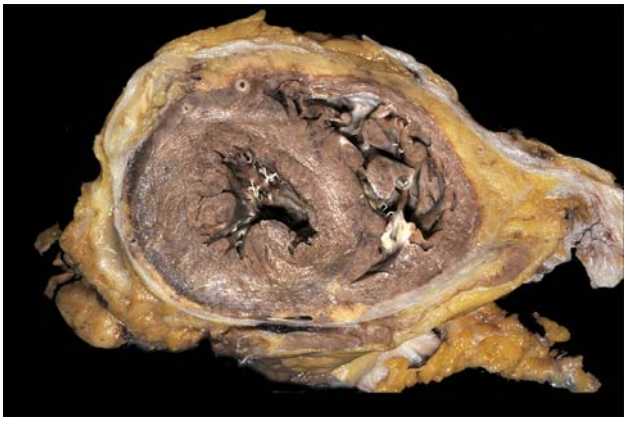

Fig. 44. The parietal pericardium is adherent to the heart with obliteration of the pericardial space. There are focal thickenings of the pericardium and calcification in the segment covering the anterior left ventricle.

***Microscopic***

- Different stages of organization can be seen varying from organizing pericarditis with fibroblastic proliferation and neovascularization to dense avascular fibrosis with or without calcifications (Fig. 45)
- Histology is generally not indicative of any specific etiology

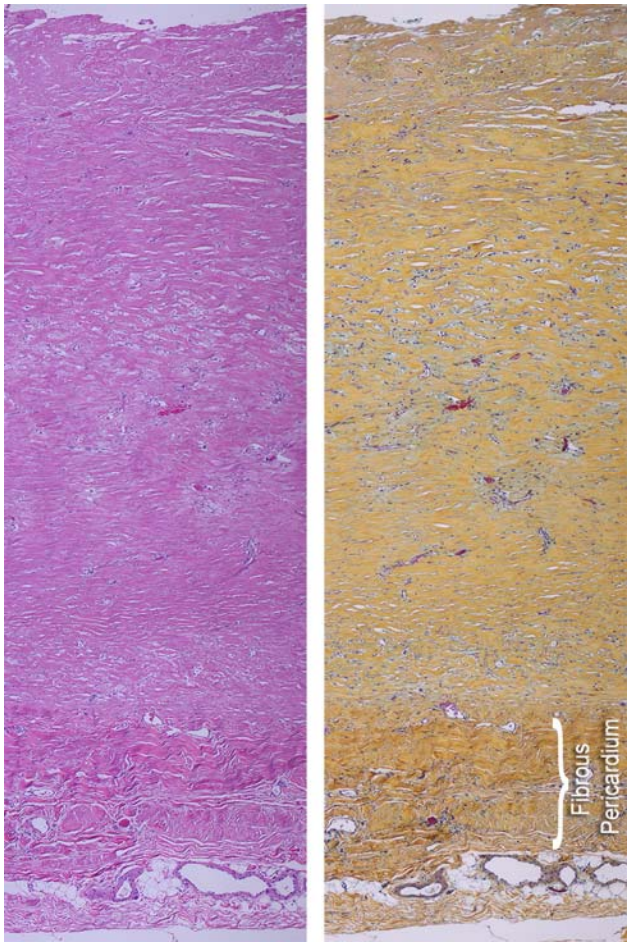


Fig. 45. Parietal (fibrous) pericardium (bracket) with marked fibrosis. The dense fibrous tissue is superimposed on the fibrous pericardium. This patient had multiple episode of pericarditis. There are fibroblasts and small capillary sized vessels without inflammation or exudate.

## PERICARDIAL TUMORS

- Pericardial cysts are considered congenital malformations and are thin-walled uniloculated cysts filled with serous fluid. These are usually incidental findings and most commonly located in the right costophrenic angle. (Fig. 46)

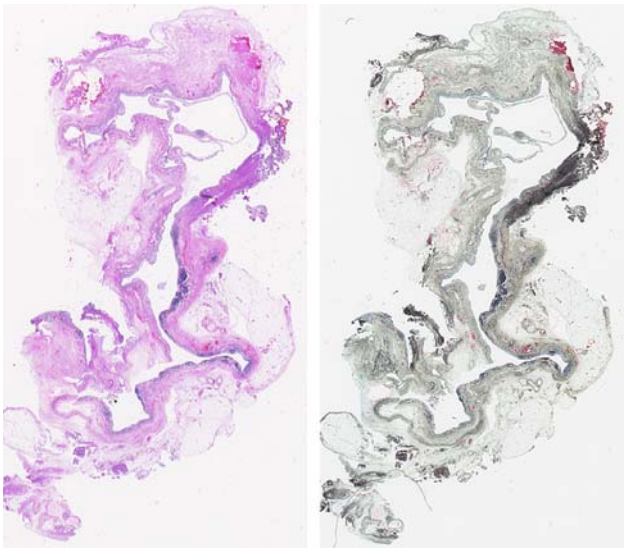

Fig. 46. Pericardial cyst are usually unilocular and are lined by mesothelial cells with a fibrous wall and focal aggregates of lymphocytes.

- Benign primary pericardial tumors include teratoma, lipoma, fibroma, hemangioma, lymphangioma , inflammatory pseudotumor and paraganglioma
- The two most common primary malignant tumors of the pericardium are malignant mesothelioma and angiosarcoma.
- Less common are synovial sarcoma, fibrosarcoma, liposarcoma , undifferentiated sarcoma, primitive neuroectodermal tumor and lymphoma
- Metastatic tumors are more common and frequently due to metastatic lung and breast carcinoma and lymphoma (Fig. 47)

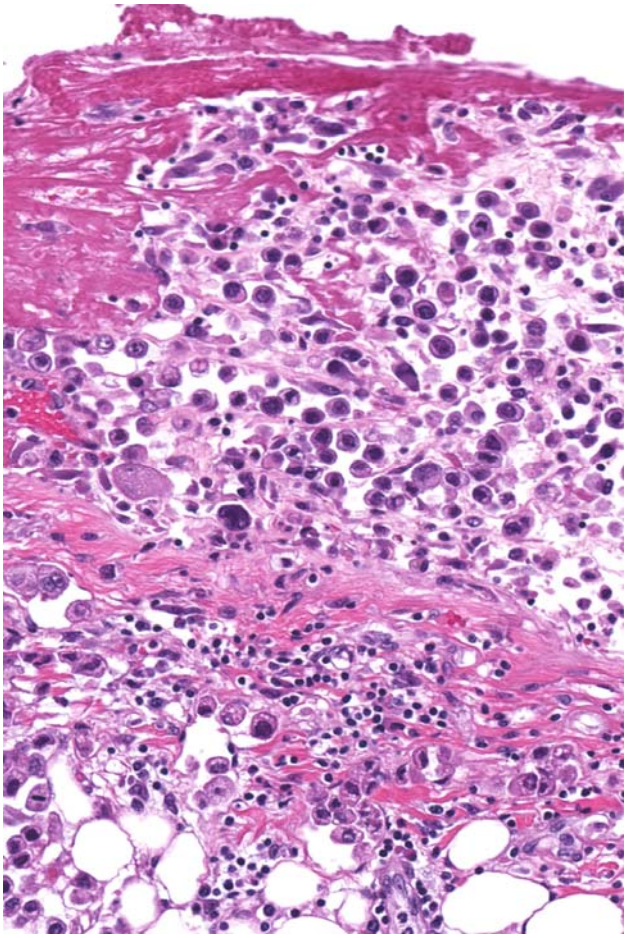

Fig. 47. Metastatic adenocarcinoma and fibrinous pericardial exudate in a pericardial biopsy of a patient with recurrent pericardial effusion.

# Diseases of the Valves and Endocardium

## VALVULAR STRUCTURE

### *Semilunar Valves*

- Trilaminar architecture (Fig. 48)
  - Fibrosa or Arterialis
  - Spongiosa
  - Radialis or Ventricularis

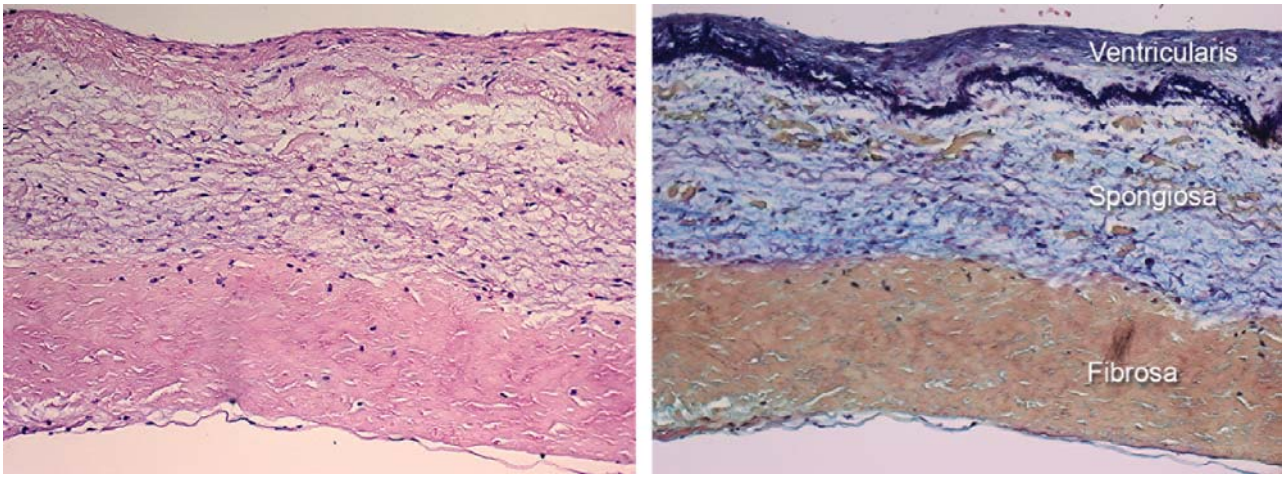


Fig. 48. Histology of a normal aortic valve shows three layers as identified from the top to the bottom: ventricularis, spongiosa and fibrosa.

### *Atrioventricular Valves*

- Trilaminar architecture (Fig. 49)
  - Atrialis
  - Spongiosa
  - Fibrosa

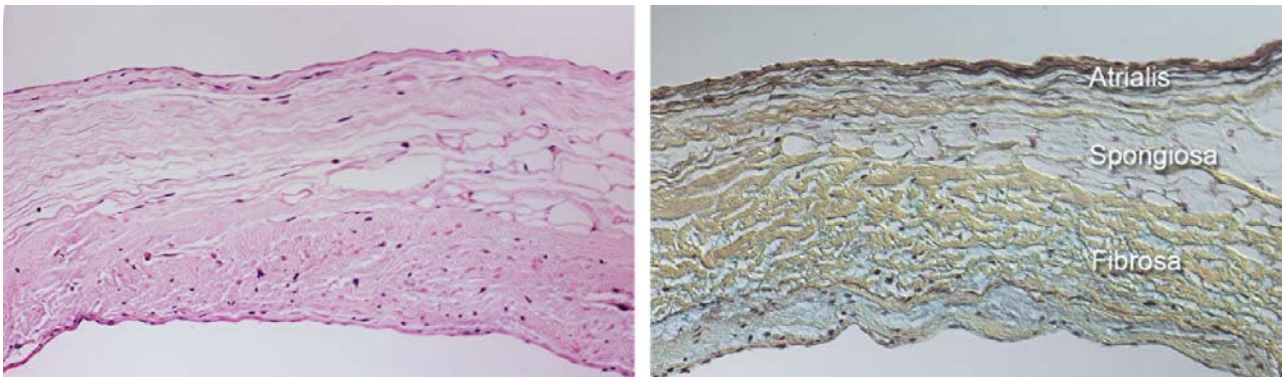


Fig. 49. Histology of a normal mitral valve shows three layers corresponding to the atrialis, spongiosa and fibrosa.

## Rheumatic Fever and Rheumatic Heart Disease

- Rheumatic fever can affect valves as well as myocardium and/or pericardium, but long-term sequelae in survivors are predominantly valvular

### *Clinical*

- Recurrent acute febrile disease of children following streptococcal pharyngitis (group A Streptococcus)
- Etiology is due to an autoimmune mechanism
- Most common cause of mitral stenosis

### *Macroscopic*

- Small valvular vegetations may be present during the acute episodes
- Valves affected in decreasing order of frequency: mitral, aortic, tricuspid, pulmonic
- In chronic form, there is diffuse valvular fibrosis and thickening, calcification, commissural fusion, and thickened, fused, shortened chordae (Fig. 50)

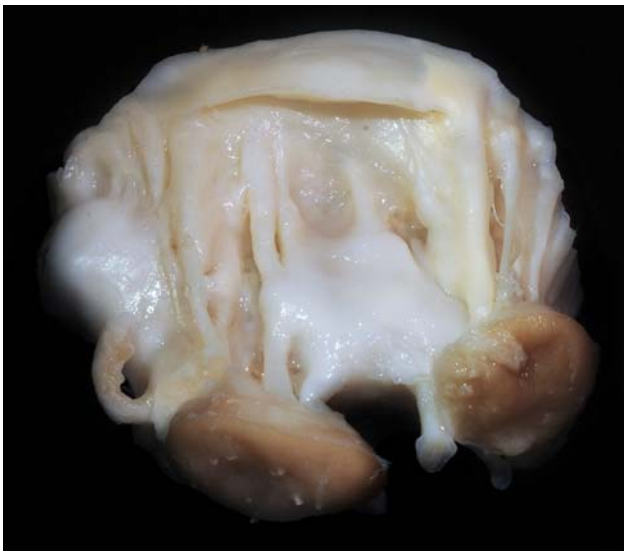

Fig. 50. Ventricular view of an excised mitral valve specimen showing shortening of the chordae due to marked fibrosis and fusion. This is a common sequelae of rheumatic valvular disease.

### *Microscopic*

- Subendocardial/perivascular areas of fibrinoid necrosis in acute form
- Later, lymphocytic then histiocytic infiltrates that may become granulomatous
- Granulomas are called Aschoff bodies, and they may contain characteristic “caterpillar cells”

## Aortic Valve Stenosis

### *Clinical*

- Most common cause of left ventricular outflow obstruction
- Associated with congestive heart failure and sudden death
- Most commonly a consequence of congenital bicuspid aortic valve (in persons younger than 70), and degenerative fibrosis and calcification (senile-type) in persons older than 70
- Other etiologies of aortic valve stenosis include congenital unicuspid valve and postinflammatory (rheumatic) valve disease, which occurs usually in association with mitral valve involvement

## *Congenital Bicuspid Aortic Valves*

- Most common valvular malformation, affecting approximately 2% of the population

- Rarely stenotic at birth
- Tend to prematurely develop fibrosis and calcification with increasing age, resulting in stenosis
- Prevalence of stenosis is proportional with age (Fig. 51)

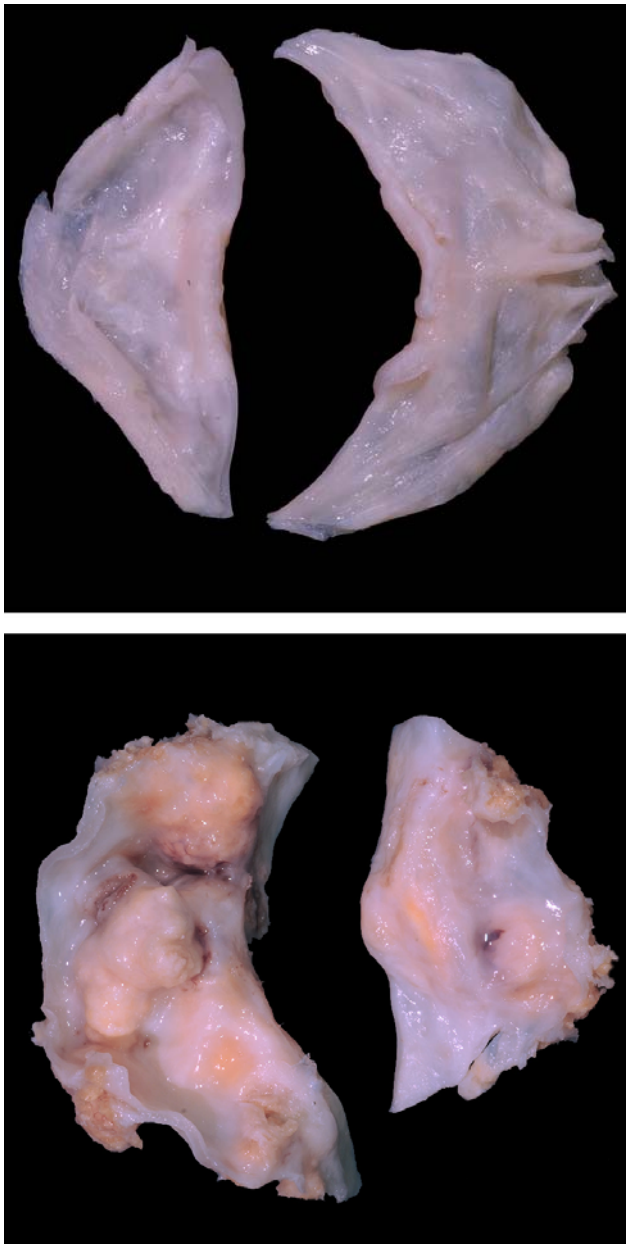

Fig. 51. Cephalad view of a bicuspid aortic valve without calcification (Top) shows asymmetry of commissure to commissure distance of the leaflets. A split raphe mimicking a commissure is seen in the cusp on the right. The lower image shows asymmetric leaflets with extensive calcification. The leaflet on the left shows a raphe in the center.

- Other associated complications are aortic insufficiency, infective endocarditis, ascending aortic aneurysms and dissection
- Gross cusps are oriented either anterior–posterior, or right–left
- A median raphe usually present in the conjoined cusp

## *Degenerative Fibrosis and Calcification (Senile-Type)*

- Occurs in three-cusped aortic valves
- Usually affects patients older than 60 years
- Gross calcification and fibrosis of valve cusps, with calcific deposits that may fill sinuses of Valsalva (Fig. 52)

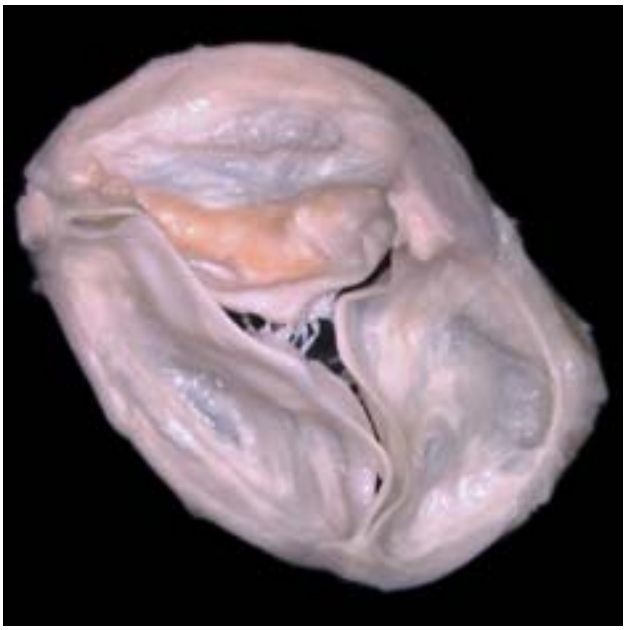

Fig. 52. Cephalad view of three-leaflet aortic valve with calcification of a leaflet. The posterior (non-coronary) cusp is (top) shows a yellow area of calcification. The commissures are normal (thin, delicate and non-fused). There are Lambl excrescences protruding from the ventricularis layer of the mid portion of the anatomical right cusp (shown on the left of the image).

- Senile-type calcification and fibrosis may be associated with fusion of one or more commissures, making the distinction from congenital bicuspid valve difficult at times
- Helpful features are summarized in Table 5

**Table 5. Helpful Distinguishing Features of Congenital Bicuspid Aortic Valves**

| *Acquired commissural fusion* | *Congenital bicuspid valve* |
|---|---|
| Combined length of the fused cusps is longer than the free cusp | Length of fused cusp is about equal that of the other cusp |
| Intercommissural distances are nearly equal in the three cusps | Intercommissural distance of each fused cusp is smaller than the non-fused cusp |
| Cephalad height of fused commissure is equal to non-fused commissures | Cephalad height of raphe is lower than the height of the unfused commissures |
| Fusion site is wide and extends to the cusp margin | Raphe does not extend to the cusp margin |

### *Rheumatic aortic stenosis*

- Fusion of the commissures results in a central stenotic orifice
- Diffuse fibrosis with thickening and retraction of the free edges
- Calcification is often mild

## AORTIC VALVE INSUFFICIENCY

- May result from a lesion of valvular cusps or dilation of aortic root itself
- Cusp lesions may include postinflammatory rheumatic changes, infective endocarditis, and congenital bicuspid valve
- Diseases causing aortic dilatation include aneurysms, aortitis, dissection and traumatic laceration of the aortic root
- Cuspal abnormalities usually associated with myxoid degeneration
- In cases of aortic diseases, the aortic valve may be normal or show thickened rolled up edges

## CARCINOID HEART DISEASE

### *Clinical*

- Occurs in setting of metastatic carcinoid tumor
- Left-sided lesions are associated with carcinoid tumors in the lung
- The valvular lesions may cause pulmonary stenosis and tricuspid regurgitation, but rarely pure tricuspid stenosis

### *Macroscopic*

- White endocardial or valvular fibrous plaques, usually of right atrium and/or ventricle
- Valve leaflets are thickened and retracted; valve annulus is constricted

### *Microscopic*

- Fibrous plaques are deposited predominantly on the ventricular aspect of tricuspid valve and arterial aspect of the pulmonic valve
- Fibrous plaques are composed of smooth muscle and myofibroblastic proliferation in proteoglycan-rich matrix
- No evidence of elastic lamellae accumulation in the plaque (Fig. 53)

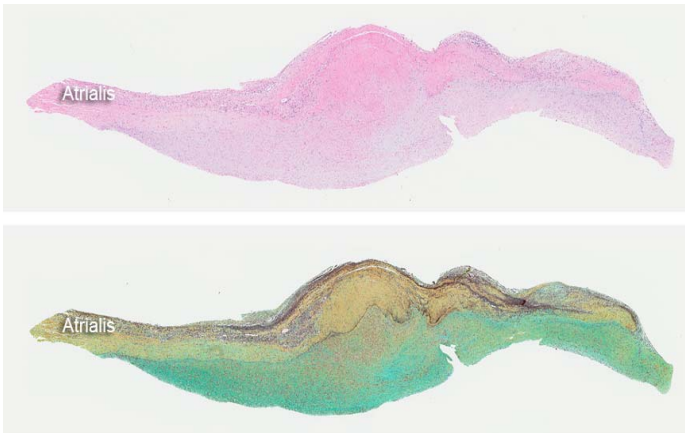


Fig. 53. Light micrographs of a tricuspid valve showing a carcinoid plaque encasing the fibrosa (ventricular) layer. The H&E stain shows an indistinct layer of connective tissue on the ventricular surface of the leaflet. The Movat stain (lower image) shows the distinct atrialis layer with abundant elastic fiber (black). The carcinoid plaque is shows proteoglycan rich extracellular matrix (green). Typically carcinoid plaques do not show elastic lamellae. This is a very useful feature to distinguish these plaques.

- Neovascularization and chronic inflammation may sometimes be present

***Differential Diagnosis***

- Endocardial fibroelastosis, which occurs in infants and children (typically not adults)

## ENDOCARDITIS: INFECTIVE

- Predisposing factors include: degenerative valve disease, rheumatic valve disease, congenital heart disease, prosthetic cardiac valves, intravenous drug use, invasive procedures, hemodialysis, chronic intravenous access and intravascular devices
- Fever is the most important symptom, half of patients develop new cardiac murmur due to valve insufficiency or less commonly stenosis
- Peripheral embolization occurs in approximately 40% of patients
- The modified Duke criteria for the diagnosis of infective endocarditis is most widely used for clinical diagnosis. These are listed in Table 6.
- Most common causes of bacterial endocarditis in native valves are staphylococci, viridans streptococci and enterococci.
- Staphylococci are the most common cause of prosthetic valve endocarditis and right-sided endocarditis
- Fungal endocarditis rare but often fatal, most commonly caused by Candida, Aspergillus and Histoplasma

| Table 6. Modified Duke Criteria for the Diagnosis of Infective Endocarditis (IE) | |
|---|---|
| Definite IE<br>Any of (1) or (2) | |
| | (1) Pathologic criteria:<br>Microorganisms demonstrated by culture or histologic examination of a vegetation, a vegetation that has embolized;<br>or an intracardiac abscess specimen; or<br>Pathologic lesions - vegetation or intracardiac abscess confirmed by histologic examination showing active endocarditis |
| | (2) Clinical criteria:<br>Any of 2 major criteria; or<br>1 major criterion and 3 minor criteria; or<br>5 minor criteria |
| Possible IE | 1 major criterion and 1 minor criterion;<br>or 3 minor criteria |
| Rejected | Firm alternative diagnosis explaining evidence of IE; or<br>Resolution of IE syndrome with antibiotic treatment for 4 or less days; or No pathologic evidence of IE at surgery or autopsy with antibiotic therapy for 4 or less days; or<br>Does not meet criteria for possible IE |
| **Major criteria:** | (1) Positive blood culture for IE:<br>(a) Typical microorganisms consistent with IE from 2 separate blood cultures: Viridans streptococci, Streptococcus bovis, HACEK group; Staphylococcus aureus or community-acquired enterococci in absence of a primary focus<br>(b) Microorganisms consistent with IE from persistently positive blood cultures defined as:<br>At least 2 positive blood cultures drawn more than 12 hours apart; or<br>All of 3, or a majority of 4 or more blood cultures with first and last sample drawn at least 1 hour apart<br>(c) Single positive blood culture for Coxiella burnetii or anti-phase I IgG antibody titer >1:800<br>(2) Evidence of endocardial involvement:<br>(a) Positive echocardiogram for IE:<br>Oscillating intracardiac mass on valve or supporting structures, in the path of regurgitant jets or on implanted material in the absence of an alternative anatomic explanation; or Abscess; or<br>New partial dehiscence of prosthetic valve; or<br>New valvular regurgitation (worsening or changing of pre-existing murmur not sufficient) |
| **Minor criteria:** | (1) Predisposition - predisposing heart condition or injection drug use<br>(2) Fever - temperature of 38 ° C or more<br>(3) Vascular phenomena - major arterial embolism, septic pulmonary infarcts, mycotic aneurysm, intracranial hemorrhage, conjunctival hemorrhages, Janeway lesions<br>(4) Immunological phenomena - glomerulonephritis, Osler's nodes, Roth spots, rheumatoid factor<br>(5) Microbiological evidence - positive blood culture but does not meet a major criterion as noted above or serological evidence of active infection with organism consistent with IE) |

***Macroscopic***

- Bulky friable vegetations on the side of direct flow, ie., atrial surface of atrioventricular valves and ventricular surface of semilunar valves (Fig. 54)

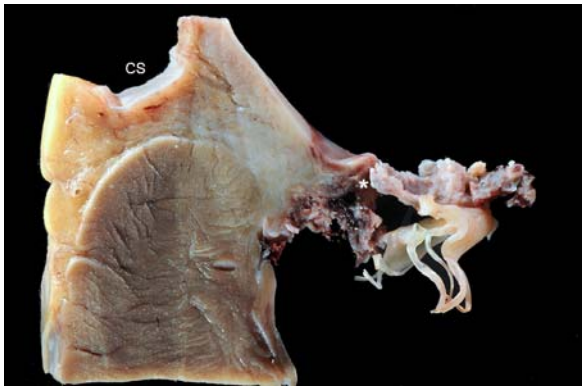


Fig. 54. Posterior leaflet of the mitral valve. The coronary sinus (CS) is shown. The mitral leaflet shows fibrinous vegetations on the atrial as well as on the ventricular surfaces. These vegetations communicate through a perforation site on the leaflet (*).

- Tissue destruction lead to saccular outpouching and perforation of the valve
- Perivalvular abscess, especially of the aortic valve, may lead to fistula formation, conduction abnormalities, pericarditis (Fig. 55)

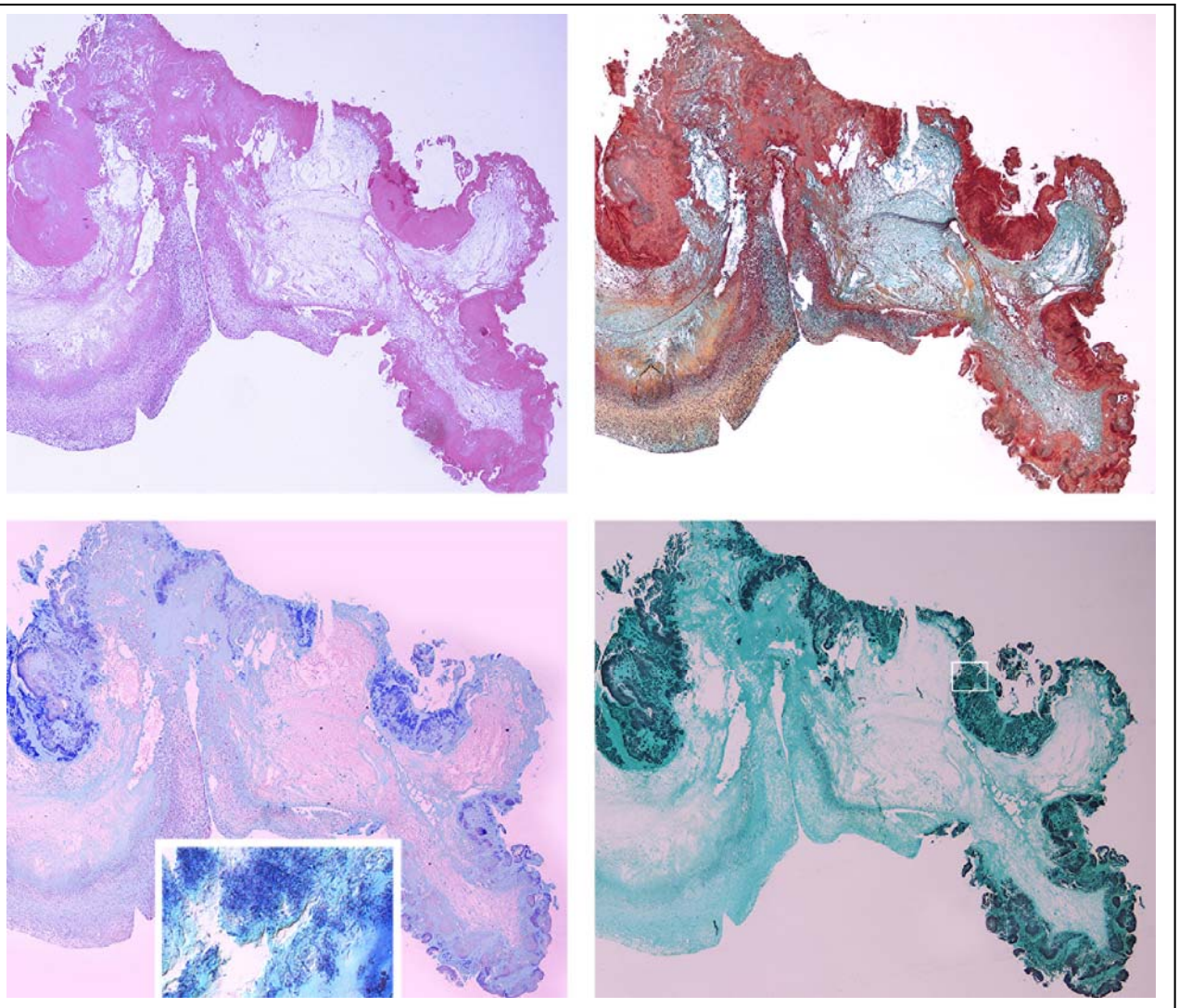

Fig. 55. Mitral valve with perforation by fibrinous vegetation. The perforation site is marked by the asterisk. The Movat stain (upper right) shows the loss of continuity of the leaflet at the perforation site. The fibrinous vegetation is shown in red and part of the vegetation shows organization with proteoglycan rich connective tissue (green). The fibrosa of the valve is yellow. The lower panels show the bacterial colonies formed by cocci. Gram stain (lower left and inset) show these cocci. The cocci are also visible as black bacteria in the GMS stain (lower right).

- Embolized vegetations may cause parenchymal abscess and mycotic aneurysms
- Infection of prosthetic valves may result in ring abscess and suture dehiscence

***Microscopic***

- Vegetations are composed of thrombus with bacteria or fungi (Fig. 56)

- Valvular inflammatory infiltrates consists of neutrophils, lymphocytes, histiocytes and occasionally multinucleated giant cells
- With organization, neovascularization and fibroblastic proliferation ensues
- Gomori methenamine silver stain is very useful to demonstrate not only fungi but also bacteria that have lost their Gram staining quality secondary to antibiotic therapy

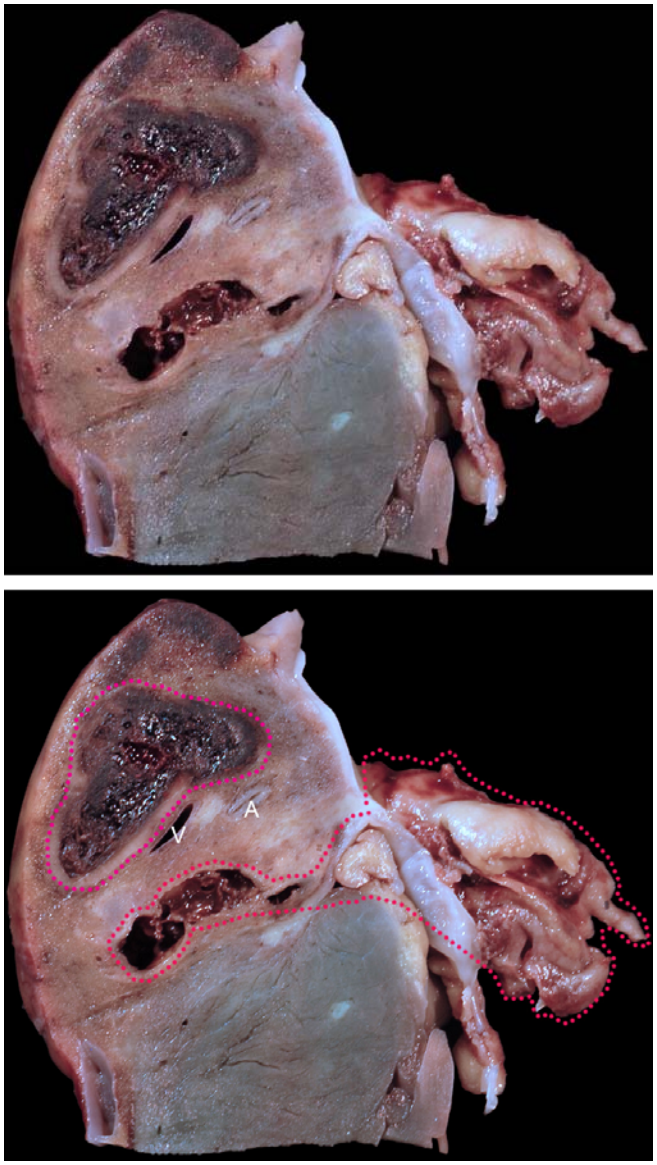


Fig. 56. Posterior leaflet of the mitral valve with a perivalvular abscess extending past the fibrous annulus of the valve into the adipose tissue in the atrioventricular groove. The red dotted line in the lower image delineates the massive vegetation and the abscess with also surrounds the circumflex coronary artery (A) and the great cardiac vein (V) on its path to become the coronary sinus.

## ENDOCARDITIS: NONINFECTIOUS

### *Nonbacterial Thrombotic Endocarditis (Marantic Endocarditis)*

- Occurs in setting of cancer (especially mucinous adenocarcinoma) or other systemic wasting illness
- May embolize
- Grossly, small vegetations that typically involve more than one valve along lines of closure (Fig. 57)

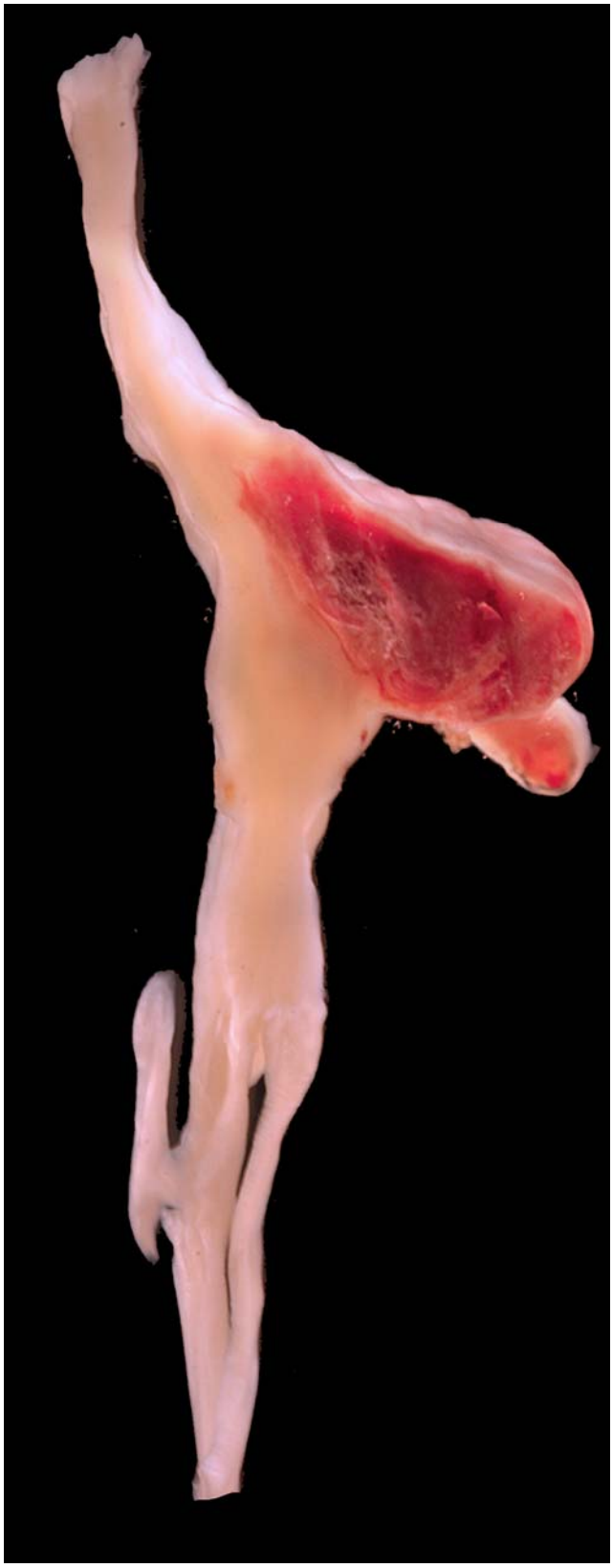

Fig. 57. Mitral valve leaflet with a red thrombotic vegetation on the atrial side of the leaflet consistent with non-bacterial thrombotic (marantic) endocarditis.

- Microscopically, fibrin thrombi without organisms (Fig. 58)
- Does not induce inflammation in the valve tissue

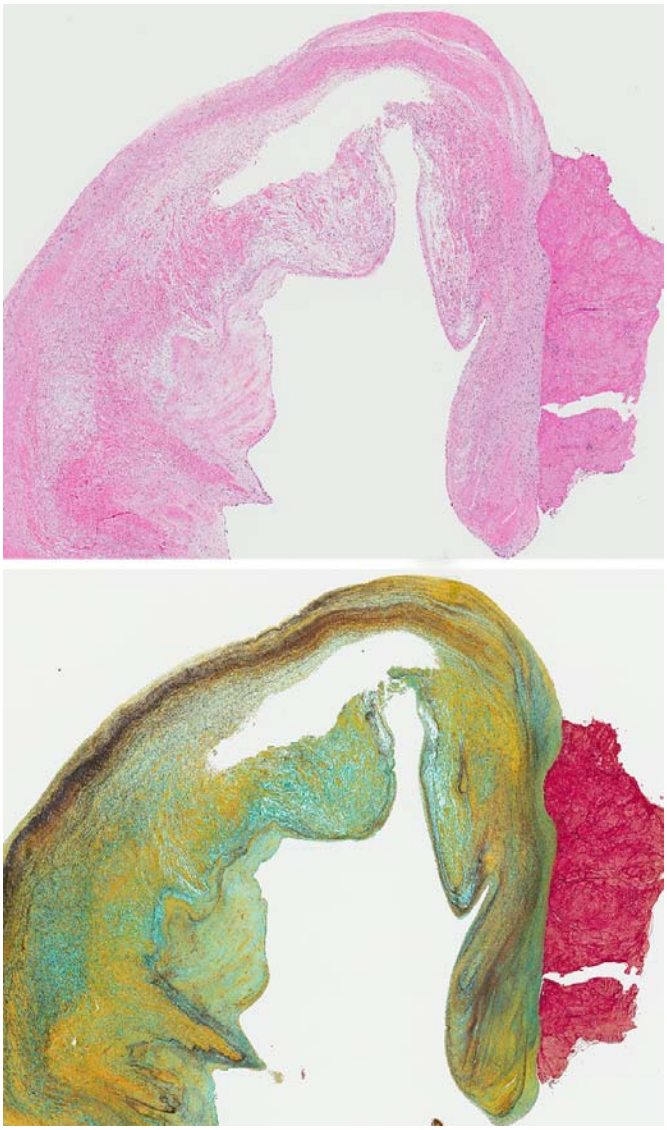

Fig. 58. The vegetations of non-bacterial thrombotic endocarditis are usually devoid of any significant inflammatory infiltrate in the thrombus. The Movat stain shows the trilaminar architecture of this mitral leaflet and the nil organization of the thrombotic vegetation (red).

## *Libman–Sacks Endocarditis (Verrucous Endocarditis)*

- Seen in systemic lupus erythematosus (SLE)
- Multiple small to medium size vegetations that can be seen on either the flow side or the non-flow side of the atrioventricular valves
- Microscopically, fibrin intermixed with cellular debris and scant inflammatory cells

# MITRAL REGURGITATION

## *Floppy Mitral Valve/Mitral Valve Prolapse*

### *Clinical*

- Most common cause of mitral regurgitation affecting predominantly middle-aged adults
- Can be seen in association with connective tissue diseases (Marfan syndrome, Loeys-Dietz, osteogenesis imperfecta)
- Mitral valve leaflets displaced into the left atrium during systole
- Complications include spontaneous chordal rupture, infective endocarditis, thromboembolism, arrhythmias, and sudden death

### *Macroscopic*

- Posterior leaflet is most frequently affected
- Valve is thick and hooded with excess valve cusp material (Fig. 27.59)
- Chordae are elongated, usually with thick and thin segments; ruptured chorda with frayed edges may be identified

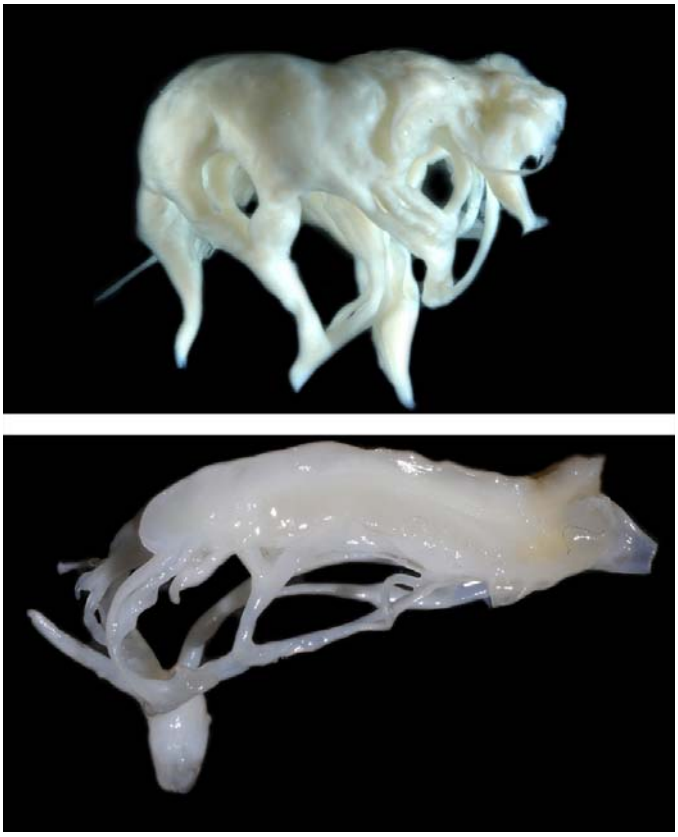

Fig. 27.59. Myxomatous degeneration of the mitral valve produces distinct changes on the leaflet architecture. The atrial surface shows from slight bumps which protrude into the atrial cavity to frank billowing. These changes are secondary to the massive infiltration of the spongiosa layer by mucopolysaccharides. These infiltration also affects the chordae tendineae producing irregular thickening which shows a "beaded" appearance of the chordae. This should not be confused with chordal fusion. The lower image shows a section perpendicular to the atrialis layer. The infiltration of the spongiosa by mucopolysaccharides imparts a gelatinous appearance to the leaflet. The chordae show the distinct irregular thickening.

***Microscopic***

- Accumulation of proteoglycan material expanding the spongiosa layer (Fig. 27.60)
- Proteoglycan infiltration of the chordae tendineae which weakens the chordae and allows elongation and rupture
- Variable elastosis of the atrialis layer

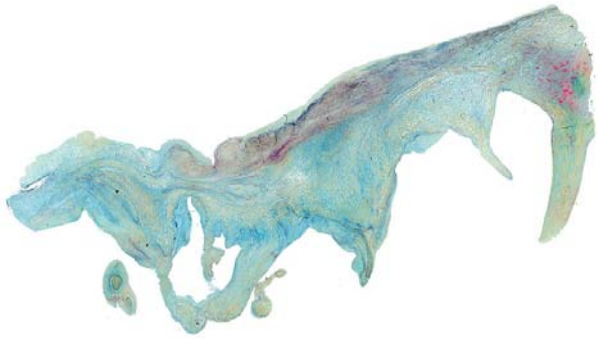

Fig. 60. Microscopic examination of a Movat stain shows the massive infiltration of the spongiosa layer by mucopolysaccharides (green). The atrialis layer shows prominent elastosis (black elastic lamellae). The chordae tendineae show that the dense fibrous tissue (yellow) is infiltrated also by mucopolysaccharides.

## *Mitral Regurgitation: Other Causes*

- Papillary muscle dysfunction secondary to ischemic heart disease or papillary muscle rupture
- Left ventricular dilatation causes annular dilatation and/or displacement of the papillary muscle with leaflet tethering, preventing coaptation of the leaflets
- Infective endocarditis may cause leaflet perforation or chordal rupture
- Chronic rheumatic valvular disease causes leaflet fibrosis and retraction, chordal shortening
- Congenital such as cleft mitral valve

## Mitral Stenosis

### *Clinical*

- Most common cause is rheumatic fever, followed by a latent period of several years and progressive stenosis
- Can be due to severe annular calcification that is more common in women
- Sequalae included left atrial enlargement, atrial fibrillation and thrombosis, pulmonary hypertension, risk of infective endocarditis

### *Macroscopic*

- Fibrous thickening and retraction of the leaflets, fusion of commissures which often become calcified and ulcerated, chordae fused and shortened
- New subendocardial blood vessel formation on the atrialis layer of the valves themselves may be seen

### *Microscopic*

- Fibrosis with loss of normal trilaminar architecture, neovascularization with thick-walled blood vessels, calcification

## Prosthetic Valves

- Can be divided into mechanical prosthesis, bioprosthesis and homografts
- Indications for prosthetic valve replacement include
  - − Mechanical fatigue of components
  - − Tissue failure of the bioprosthetic valve – calcification, tears, perforations
  - − Thrombosis and thromboembolism
  - − Tissue overgrowth (pannus)
  - − Infection (most commonly Staphylococcus)
  - − Perivalvular leaks in suture area or dehiscence

# Cardiac Neoplasms

## General Considerations

- Cardiac tumors can be clinically silent until they reach a large size so as to obstruct flow or interfere with valve function, but small tumors may become clinically significant because of systemic embolism or arrhythmias
- Invasive tumors can cause chest pain, arrhythmias, conduction blocks or sudden death
- The left atrium is the most common site of benign and malignant primary cardiac tumors
- Clinical detection is most commonly through echocardiography

## Benign Tumors

### *Myxoma*

#### *Clinical*

- Most common primary benign cardiac tumor in the adult that are surgically resected
- Mostly sporadic and usually affects middle-aged women
- Familial types seen in less than 10% of cases, usually in younger patients with multiple tumors, associated with risk of recurrence and presence of extracardiac lesions (Carney complex/myxoma syndrome)
- Can cause constitutional symptoms (fever, malaise, and weight loss) due to interleukin-6 production
- Associated with systemic embolism of tumor fragments; embolized tumor may sometimes remain viable for

months to years and form arterial aneurysms

***Macroscopic***

- Most commonly solitary left atrial (approximately 75%) or right atrial mass
- Located in the fossa ovalis in atrial septum
- Attached to the endocardium without deeper infiltration
- Can have a broad base or a pedicle
- Surface is smooth or with friable papillary fronds that tend to embolize
- Most are gelatinous, commonly with hemorrhages, sometimes with calcifications and cystic spaces (Fig. .61)

***Microscopic***

- Myxoma cells (also called lepidic cells) have abundant eosinophilic cytoplasm with indistinct cell borders, ovoid nuclei, nucleoli variably present (Fig. 61)
- Singly-scattered cells may appear polygonal to stellate
- Myxoma cells typically form trabeculae, syncytia, canaliculi and rings surrounding vascular channels in a myxoid and/or fibrous matrix
- Hemosiderin is present in macrophages and sometimes myxoma cells
- Inflammation is common, both in the tumor and in the subjacent myocardium, extramedullary hematopoiesis may be present
- Immunohistochemically, positive staining with calretinin, vimentin, alpha-1 antitrypsin, and alpha-1 antichymotrypsin
- Occasionally it may show well-developed mucin-producing glands (with glandular structures), which may be confused with metastatic adenocarcinoma
- Glandular areas are positive for CK7, CK20, CEA, and EMA

***Differential Diagnosis***

- Myxoid sarcoma
  - Lacks lepidic cells that form syncytia, canaliculi, trabeculae, cords and ring-like structures
  - Nuclear atypia and mitotic figures favor malignancy
- Mural (organized) thrombus
  - May rarely be indistinguishable with myxoma especially if heavily calcified

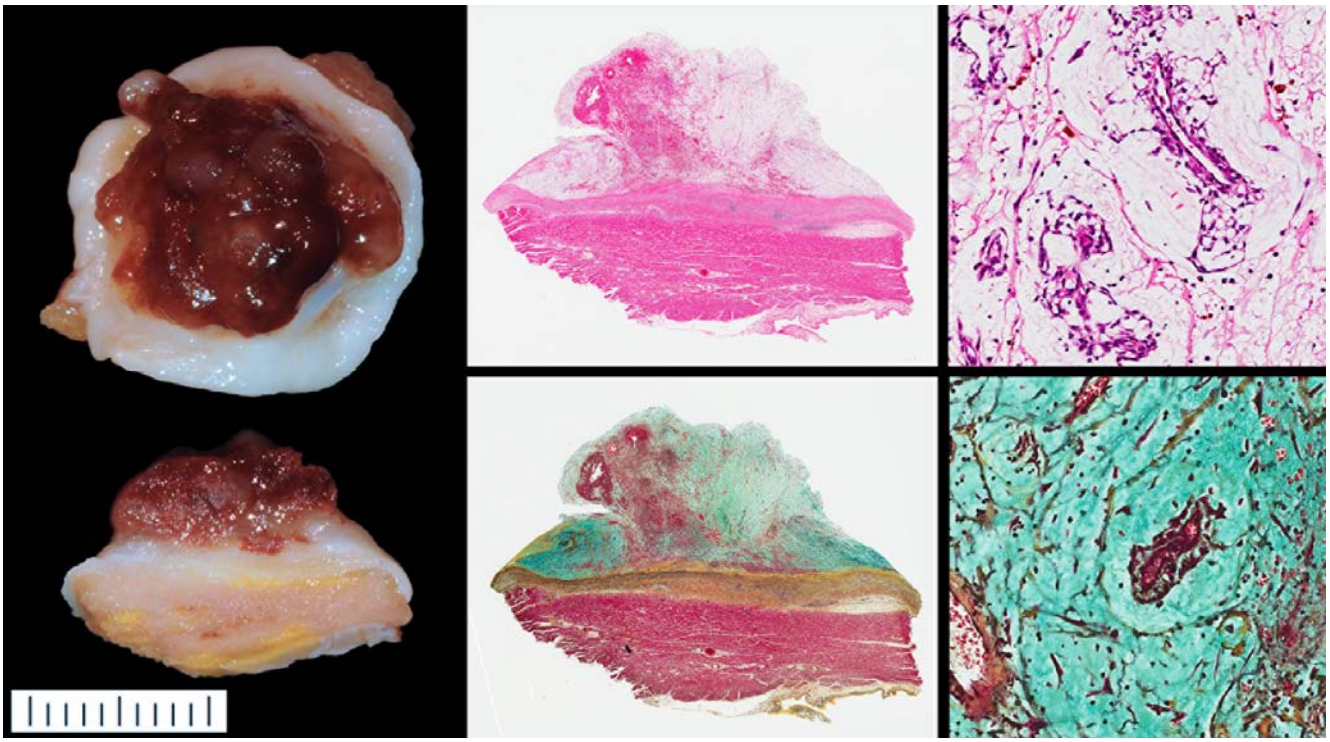

Fig. 27.61. Cardiac myxoma. The images on the left show a myxoma on the surface of a left atrium (the endocardium is thick and white). The tumor is well vascularized, gelatinous and intensely red. A perpendicular section to the atrial surface shows the gelatinous tumor on the endocardial surface of the atrial muscle. The Atrial muscle shows a tan appearance with yellow adipose tissue, indicating that this is interatrial septal muscle. The H&E stain mid panel (top) show a pale myxomatous stroma and in its mid portion is well vascularized and even hemorrhagic. The bottom mid panel shows the matching Movat stain. This stain shows the myocardium in red. The intervening endocardium in yellow and the tumor with its prominent myxoid stroma in green. Higher magnification (right images) show the myxoid stroma with canaliculi of lepidic (myxoma) cells. The Movat stain shows the mucopolysaccharide rich matrix.

## *Papillary Fibroelastoma*

### *Clinical*

- Asymptomatic, incidental finding during surgery, on imaging or at autopsy
- May give rise to symptoms including stroke or transient ischemic attacks due to embolism of surface thrombi or portions of the tumor to the cerebral circulation, rarely myocardial ischemia because of obstruction of a coronary ostium, and sudden death

### *Macroscopic*

- Gelatinous to fibrotic papillary structure attached on the surface of valves, commonly the aortic valve, best appreciated when the tumor is examined under water
- May also occur on other endocardial locations and occasionally multiple (Fig. 27.62)

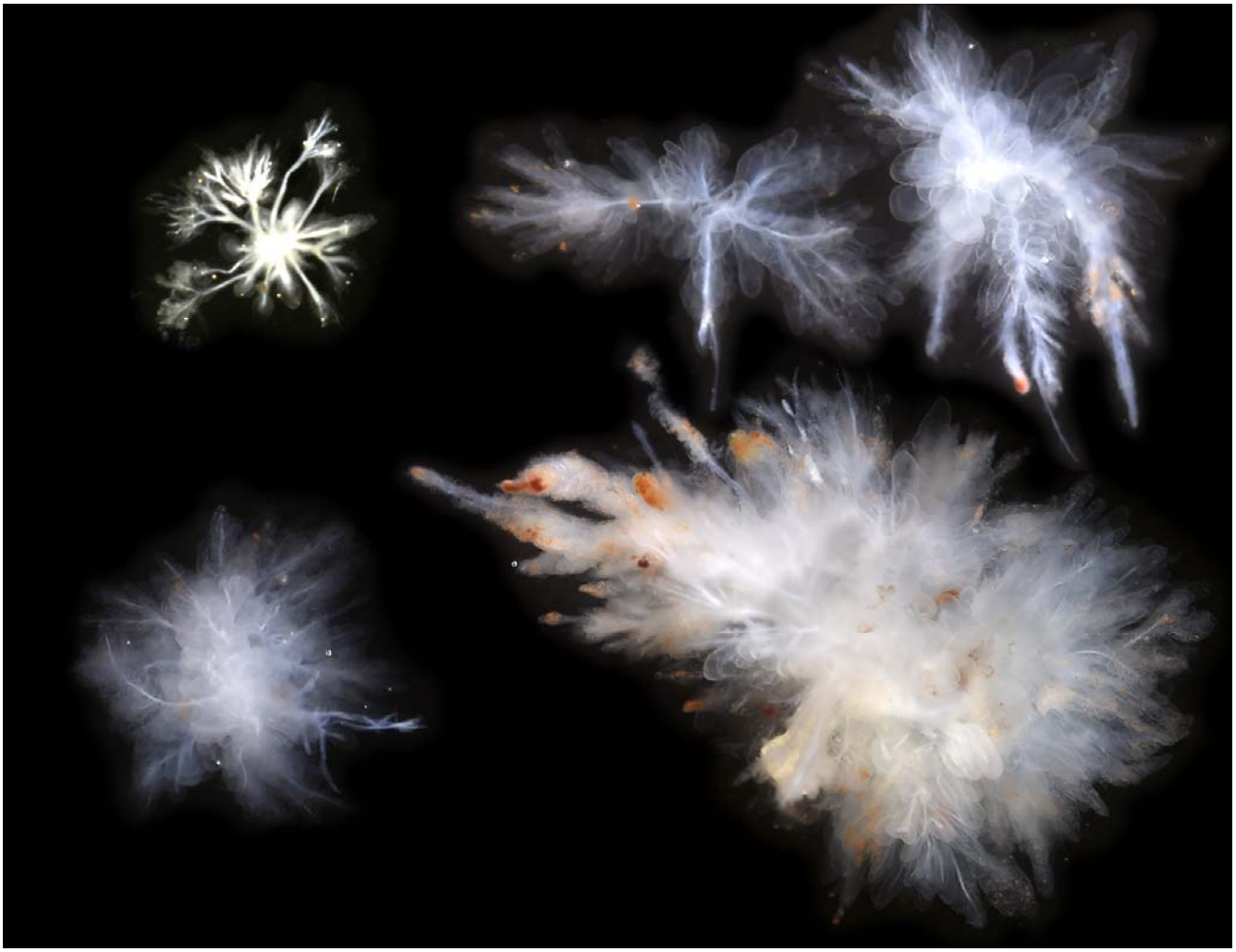

Fig. 62. Papillary fibroelastomas usually show a stem from which branches, smaller fronds and actual villi form. The only way to appreciate this architecture is by examining the tumor while immersed in fluid. Commonly there is a swelling of mucopolysaccharide rich matric around individual villi. This gives the tumor an appearance of “bunches of grapes”. In other tumors the villi are just straight. Minute thrombi are trapped between the villi.

***Microscopic***

- Papillary formation with a dense fibrous core and concentric fragmented elastic fibers, in turn, covered by endothelial cells (Fig. 63)

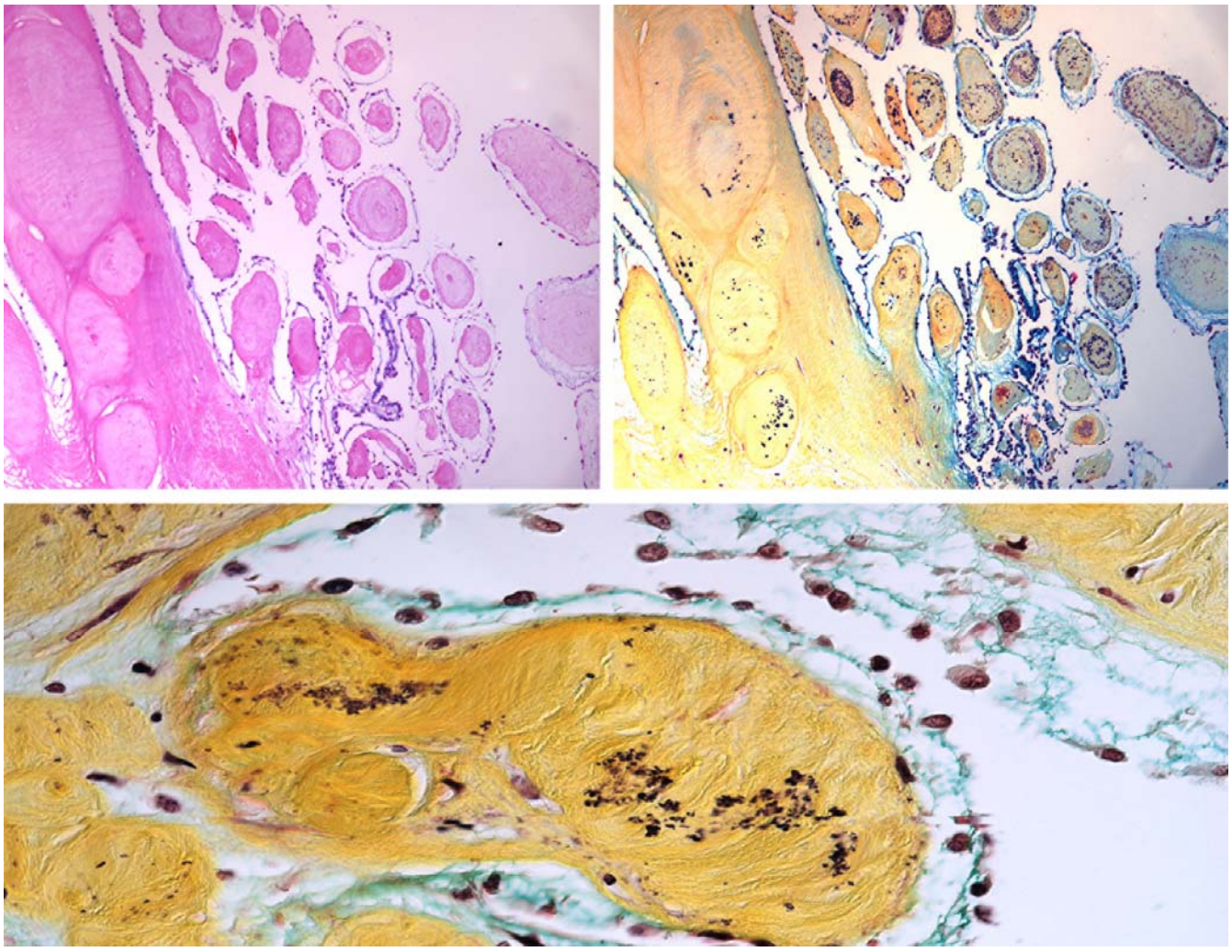

Fig. 63. Microscopic examination the papillary fibroelastoma shows the fibrous stem and the braches and villi. The villi show a fibrous stroma shown in the H&E on the left and stained yellow in the Movat stain on the right and lower panel. The fibrous core of the villi shows concentric layers of fragmented elastic lamella (black). The mucopolysaccharide translucent layer shown around the villi in Fig. 27.62 is shown in the Movat stain as green extracellular matrix.

***Differential Diagnosis***

- Lambl excrescences
  - Filiform projections occurring along the lines of closure (linea alba) and free cuspal edge of valves (Fig. 64)

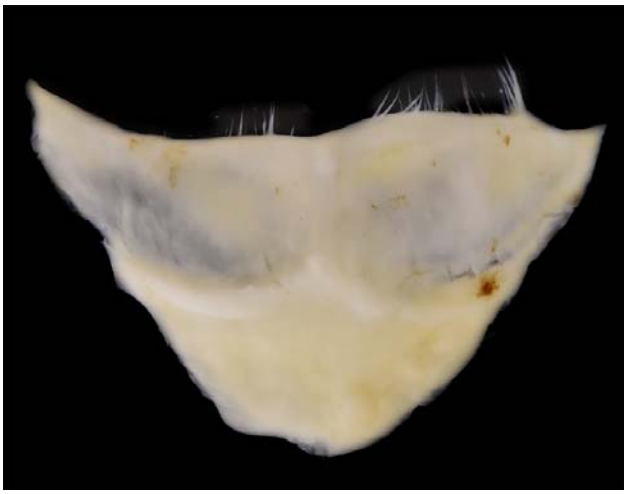

Fig. 64. Lambl excrescences are morphologically similar to papillary fibroelastomas. They can be single, but commonly they are multiple. They usually do not arborize and do not show a bulging translucent layer surrounding their core. They appear on the free border of the aortic leaflets or on the coaptation border at the level of the linea alba. Less commonly they may be seen the coaptation site near the free border of mitral valve leaflets.

  - Histologically similar to papillary fibroelastomas, but much smaller in size and less complex in structure

## *Rhabdomyoma*

***Clinical***

- Most common cardiac tumors diagnosed in the first decade of life
- Detection of these tumors in utero is highly associated with tuberous sclerosis complex
- Sporadic cases are often single, patients with tuberous sclerosis complex typically have multiple tumors
- Also seen in patients with congenital heart disease
- No sex predilection
- It may represent a hamartoma of myocyte origin
- May present with arrhythmias or congestive heart failure
- Tumors are known to regress with age

***Macroscopic***

- Single or multiple, firm, pale tan-to-white, well-circumscribed nodules
- The most common locations are the left ventricle and ventricular septum

***Microscopic***

- "Spider cells" are large vacuolated cells with central nuclei and radial sarcoplasmic extensions (Fig. 65)
- Absent calcifications, necrosis or mitoses
- Cells are positive for periodic acid-Schiff stain due to abundant glycogen content
- Immunohistochemical positivity for myoglobin, actin, desmin

***Differential Diagnosis***

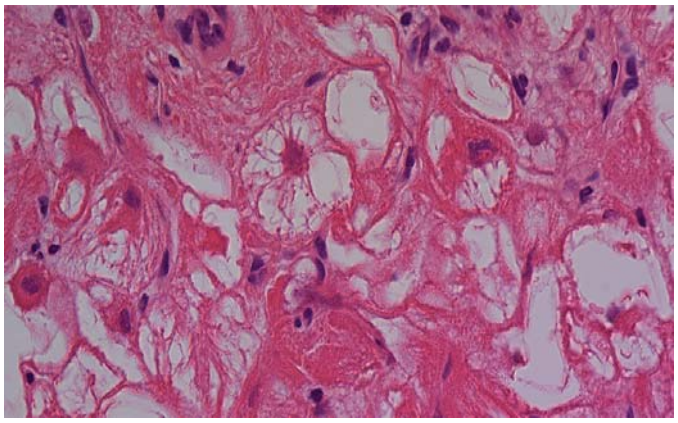

Fig. 65. Rhabdomyoma. The cardiac myocytes have a somewhat polygonal shape and vacuolated appearance with disruption of the myofilaments which imparts a "spider" like branching pattern to the sarcoplasm of the myocytes when seen in cross section.

- Glycogen storage disease
  - Vacuolated myocytes do not form distinct mass lesions
- Granular cell tumor
  - Found in the atria and epicardial surface
  - Cytoplasmic granules are PAS-positive, diastase-resistant
  - Cells are positive for CD68 and S-100
- Histiocytoid cardiomyopathy (Oncocytic cardiomyopathy, Purkinje cell hamaratoma)
  - Multiple yellow-tan lesions often found in the subendocardium
  - Polygonal myocytes with granular sarcoplasm due to mitochondrial proliferation

## *Fibroma*

### *Clinical*

- Second most common tumor in children
- Occurs in infants and children, often <1 year old
- May present with congestive heart failure, arrhythmias or cardiomegaly
- No sex predilection
- Probably represents a hamartomatous lesion
- May be part of nevoid basal cell carcinoma syndrome (Gorlin syndrome)

### *Macroscopic*

- Usually single, large, well-circumscribed, “fibroid”-like tumors of the myocardium
- Most often located in the ventricular septum
- No hemorrhage or necrosis
- Calcifications may be present

***Microscopic***

- Cellular tumors composed of fibroblasts in a collagen-rich extracellular fibrous stroma (Fig. 66)
- Sparse elastic fibers and sparse mononuclear inflammatory cells
- No necrosis or significant cellular pleomorphism; mitotic figures rare
- Microscopically not encapsulated, tumor interdigitates with the surrounding myocardium

***Differential Diagnosis***

- Inflammatory pseudotumors (inflammatory myofibroblastic tumor)
  - Endocardial polypoid lesions composed of myofibroblasts with variable amount of inflammation (lymphocytes, plasma cells and eosinophils), areas of myxoid and collagenous stroma
- Fibrosarcoma (also called myxofibrosarcoma, myxosarcoma)
  - Frequent mitotic figures
  - Usually occurs in adults as left atrial mass
- Organized mural thrombi and involuted fibrosed myxomas
  - Follow the contour of the endocardium, unlike intramural location of fibroma

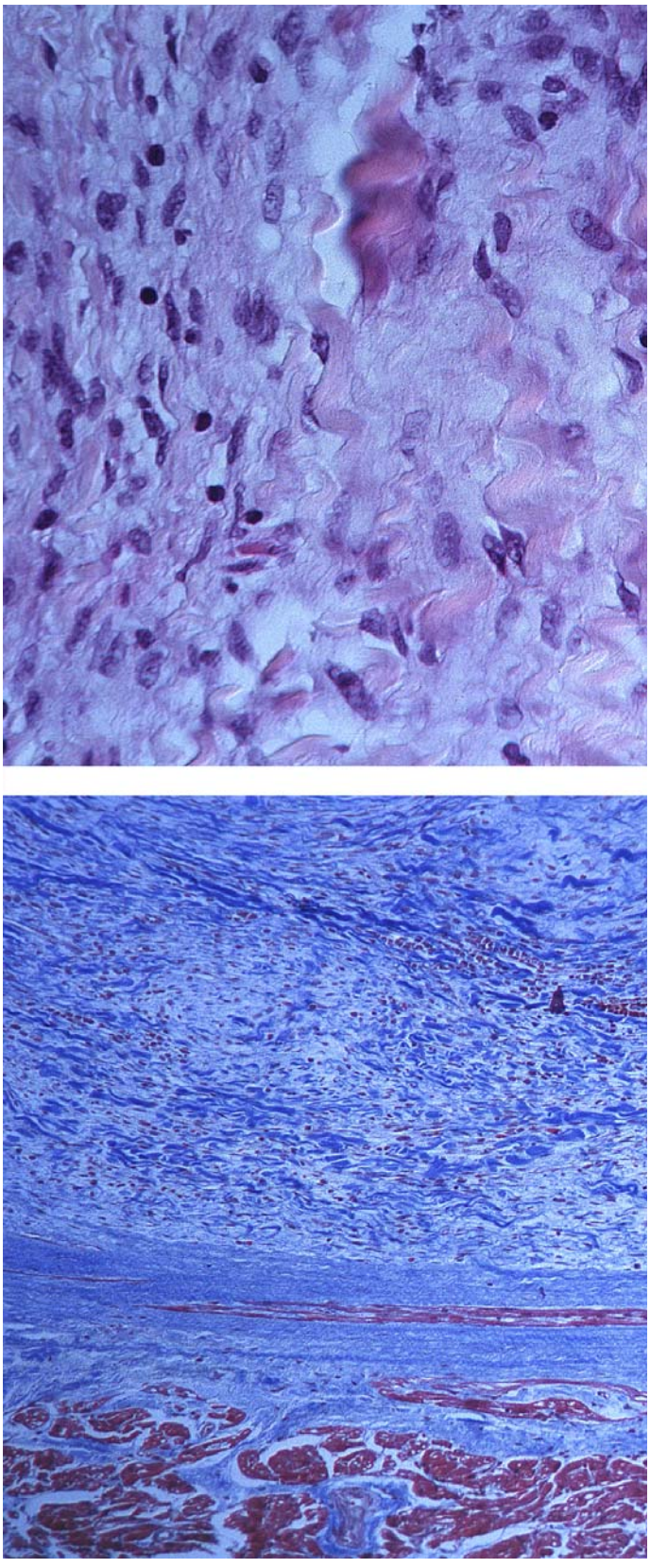

Fig. 66. Cardiac fibromas show abundant coarse bundles of birefringent collagen and a conspicuous fibroplasia with slender and plump fibroblasts in the H&E stained upper panel. The tumor is usually well delimited from the myocardium but interdigitations of the tumor fibrous tissue can reach into the myocardial interstitium . The trichrome stain shows the tumor in blue and the myocardium in red.

## *Lipomatous Hypertrophy of the Interatrial Septum*

### *Clinical*

- May represent acquired processes related to metabolic disturbance
- Often associated with obesity, advanced age, and cardiomegaly
- May cause atrial arrhythmia

### *Macroscopic*

- Massive adipose tissue infiltration of the interatrial septum cephalad and caudal to the fossa ovalis, often associated with increased amount of subepicardial adipose tissue (Fig. 67)

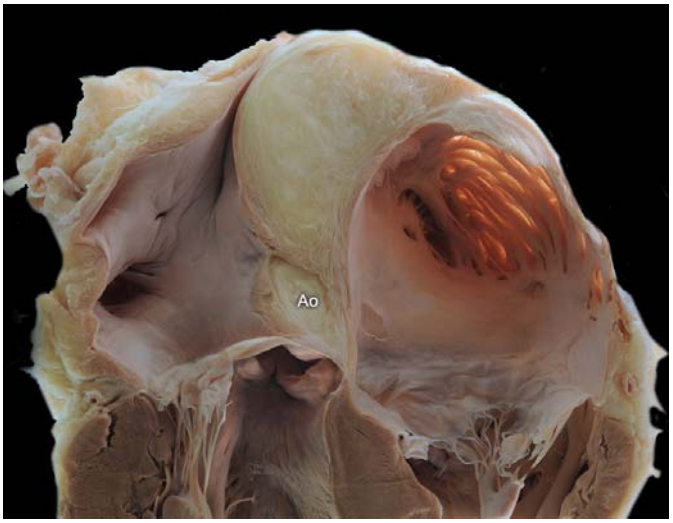


Fig. 67. Lipomatous hypertrophy of the atrial septum is shown in this dorsal view of a coronal section through the atria. The two layers of cardiac muscle flanking the adipose tissue are the corresponding layers of septum primum and secundum, which trap mesenchymal cells when they merge and seal. The aortic root (Ao) and valve are seen just caudal to the lipomatous mass.

### *Microscopic*

- Unencapsulated predominantly adipose tissue with entrapped cardiac myocytes
- Fetal fat present in variable amount

### *Differential Diagnosis*

- Liposarcoma
  - Lipoblasts, plexiform vascular pattern, and mitotic figures
- Lipoma
  - Epicardial or intramyocardial location
  - Mature adipose tissue with fine vascular network and fibrous septa

## *Cystic Tumor of the Atrioventricular Node*

### *Clinical*

- Usually occurs in young adults with female predilection
- May cause complete heart block due to its location
- Believed to be a developmental abnormality
- May be associated with other congenital anomalies (midline developmental defects)

### *Macroscopic*

- Poorly circumscribed nodules located in the inferior interatrial septum in the region ofatrioventricular node
- Multiple cysts may be grossly visible

### *Microscopic*

- Ductules, cysts, and solid nests of epithelial (cuboidal, columnar, transitional, squamous) cells in a dense fibrous stroma
- Positive for cytokeratin, epithelial membrane antigen (EMA), carcinoembryonic antigen (CEA),

and B72.3 favoring an endodermal origin of cells
- Electron microscopy shows desmosomes and microvilli (thus lesion once thought of as a type of mesothelioma)

***Differential Diagnosis***

- Bronchogenic cyst
  - Usually occur on the epicardial surface or in the myocardium
  - Bronchogenic cysts lined by ciliated columnar epithelium, goblet cells may be present, smooth muscle and cartilage noted in the cyst wall
- Teratoma
  - Usually extracardiac but within the pericardial space, attached close to the root of the great vessels; intracardiac teratomas are often located in the ventricular septum
  - Multicystic tumors with solid areas
  - Presence of neural and other ectodermal components
- Blood cysts
  - Congenital cysts located in valves (atrioventricular > semilunar valves) of fetuses and infants that spontaneously regress
  - Blood-filled cysts lined by endothelium

## *Paraganglioma*

***Clinical***

- Young to middle-aged adults
- Patients with functional tumors may have hypertension and elevated urine catecholamine levels
- Most commonly presents as a left or right atrial tumor

***Macroscopic***

- Poorly circumscribed tumors, may be epicardial, myocardial or intraluminal

***Microscopic***

- Similar to extraadrenal paragangliomas
- No histologic features to predict malignant behavior (Fig. 68)

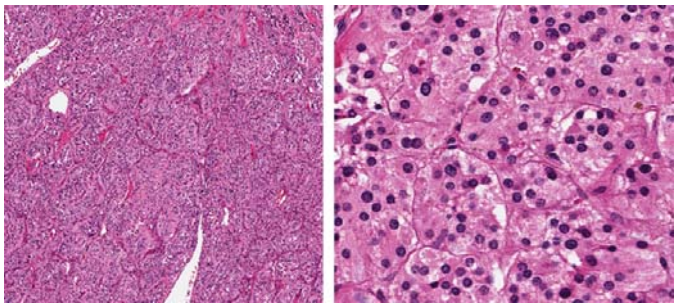

Fig. 68. Paragangliomas show the same organoid pattern as they show in any other location. The cells are polygonal with eosinophilic cytoplasm and central nuclei. They form nests which are surrounded by sustentacular cells. Capillaries are conspicuous. The nests of cells are delimited by a thin reticular stroma.

***Differential diagnosis***

- Metastatic carcinoid tumor
  - Stain positive for cytokeratin

## *Other benign tumors of the heart*

- Granular cell tumor
- Hemangioma
- Lymphangioma
- Lipoma
- Leiomyoma
- Schwannoma
- Teratoma
- Ectopic thyroid
- Ectopic thymus tissue

## MALIGNANT TUMORS

- In general, primary malignant tumors of the heart are very rare.
- The majority are sarcomas, the remainder are primary cardiac lymphomas.
- Metastatic tumors to the heart are much more common, including carcinomas of the lung, breast and thyroid, malignant melanoma, lymphomas and leukemias
- The two most common primary cardiac sarcomas are angiosarcoma and undifferentiated pleomorphic sarcomas
- Symptoms include chest pain, arrhythmias, congestive heart failure or pericardial effusion
- Classification of cardiac sarcomas follows the nomenclature used for soft tissue sarcomas
- Commonly used grading system is that of the Fédération Nationale des Centres de Lutte Contre le Cancer (FNCLCC); histologic grading is based on mitotic activity, presence of necrosis and histologic type
- Presently, there is no uniform, agreed upon staging scheme for primary malignant tumors of the heart
- The TNM scheme may be useful, but regional lymph node metastases in most primary malignant tumors of the heart is rare
- Because complete resection is often not possible in most primary malignant tumors, prognosis is generally poor

## *Angiosarcoma*

### *Clinical*

- Marked predominance of occurrence in the right atrium compared to other malignant cardiac tumors
- Infiltration of the pericardium is common and often associated with hemorrhagic pericardial effusion

### *Macroscopic*

- Large, hemorrhagic, invasive tumor, often with extensive necrosis (Fig. 69)

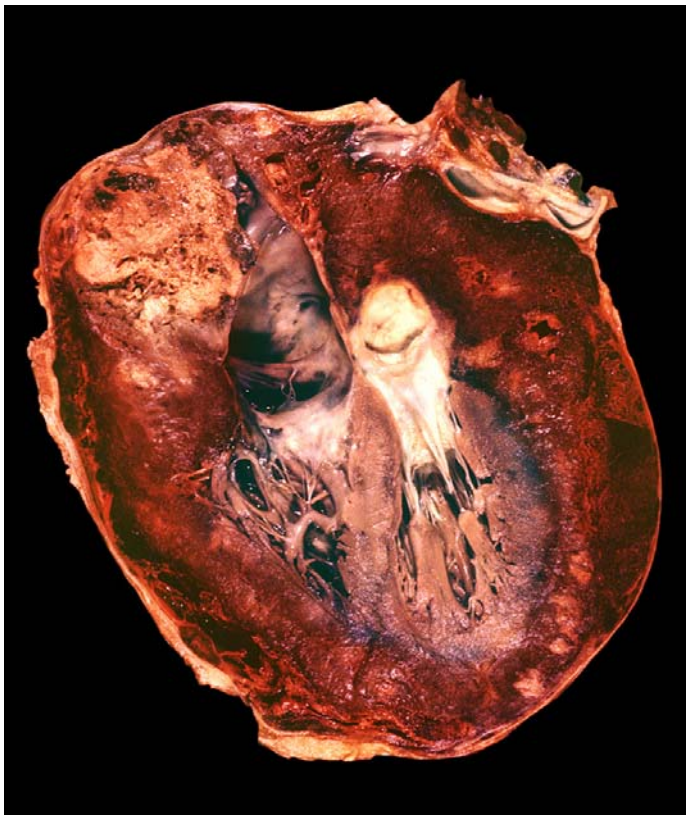

Fig. 69. Angiosarcoma of the pericardium surrounds completely the heart and tends to infiltrate the myocardium. It also surrounds the great vessels, venae cavae and pulmonary veins. These features preclude complete surgical removal of the tumor, which often recurs.

### *Microscopic*

- Malignant mesenchymal neoplasm showing endothelial differentiation
- Irregular anastomosing vascular channels are lined by atypical endothelial cells; some are poorly differentiated with solid areas of spindled to epithelioid cells (Fig. 70)

- Immunohistochemistry for Factor VIII, CD34, CD31, ERG is positive
- Electron microscopy shows Weibel–Palade bodies

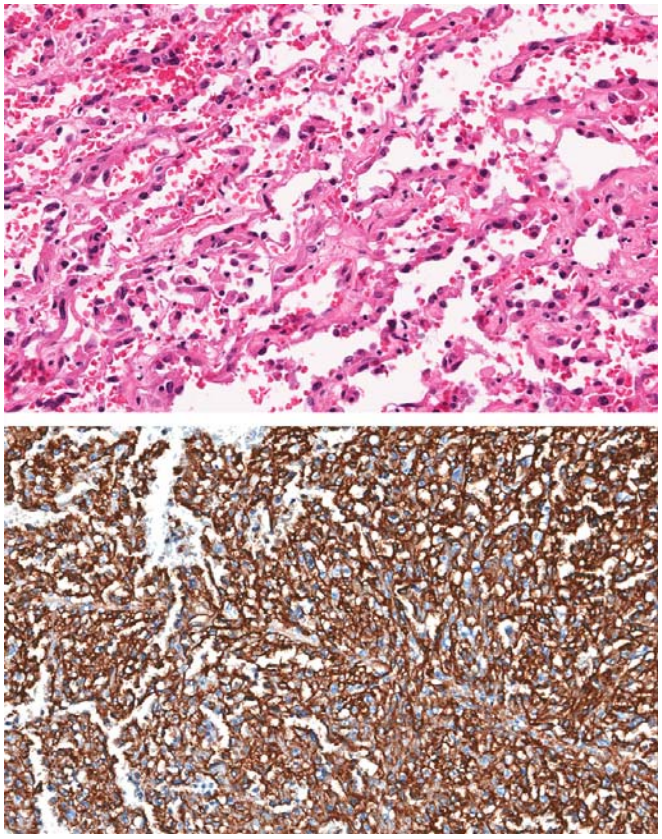

Fig. 70. On microscopic examination Angiosarcoma shows channels and papillary structure lined by malignant epithelial cells. Chords forming sinusoids and anastomosing channels are common (upper panel). The malignant cells are positive for CD32 in this image (lower panel).

### *Differential Diagnosis*

- Hemangioma
  - Lacks mitotic figures or cytologic atypia
  - Papillary endothelial hyperplasia may resemble papillary tufting of endothelial cells in angiosarcoma

## *Undifferentiated sarcomas*

### *Clinical*

- Most commonly located in the left atrium
- Affects middle-aged adults without sex predilection

### *Macroscopic*

- Nodular to polypoid masses that are firm and white, often with hemorrhages

### *Microscopic*

- Spindle to large epithelioid cells arranged haphazardly or in storiform pattern in a fibrous stroma
- Foci of myxoid stroma often present

## *Lymphoma*

### *Clinical*

- Primary cardiac lymphomas are rare
- Secondary involvement by advanced lymphoma or leukemia is much more common

### *Macroscopic*

- Firm, white nodules on the epicardium and pericardium with infiltration of the myocardium

### *Microscopic*

- Usually non-Hodgkin diffuse large B-cell type (Fig. 71)

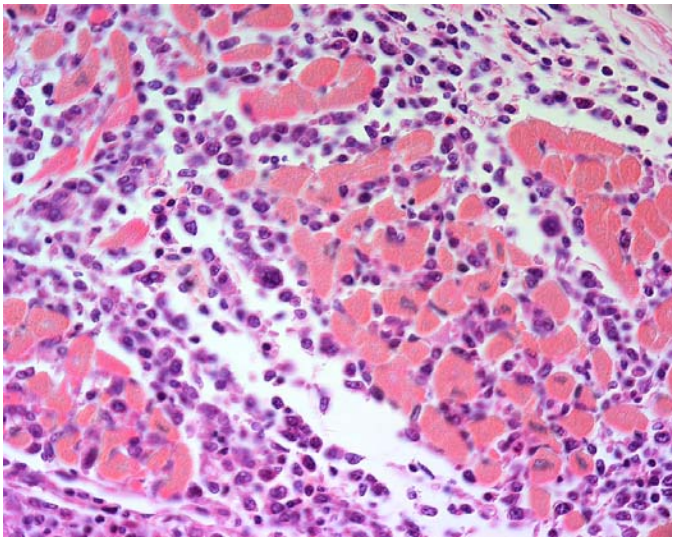

Fig. 27.71. Myocardial infiltration by lymphoma shows conspicuous malignant mononuclear cells in the interstitium between myocytes (endomysium) and between fascicles of myocytes (perimysium).

## *Other Malignant Tumors of the Heart*

- Leiomyosarcoma
- Rhabdomyosarcoma
- Osteosarcoma
- Fibrosarcoma
- Liposarcoma
- Synovial sarcoma
- Malignant peripheral nerve tumor

# II. Pathology of Blood Vessels

## NORMAL VASCULAR STRUCTURE

- Elastic arteries (Fig. 72)
  - As any other artery, they have three layers: adventitia, media and intima.
  - The media is composed of multiple layers of elastic laminae which alternate with bundles of smooth muscle cells, thus forming muscle-lamellar units.
  - The smooth muscle cell bundles are oriented perpendicular to the axis of flow
  - The adventitia is rich in vasa vasorum which perfuse the media
    - Examples
      - Aorta
      - Innominate, subclavian, carotid arteries
      - Iliac arteries
      - Pulmonary arteries

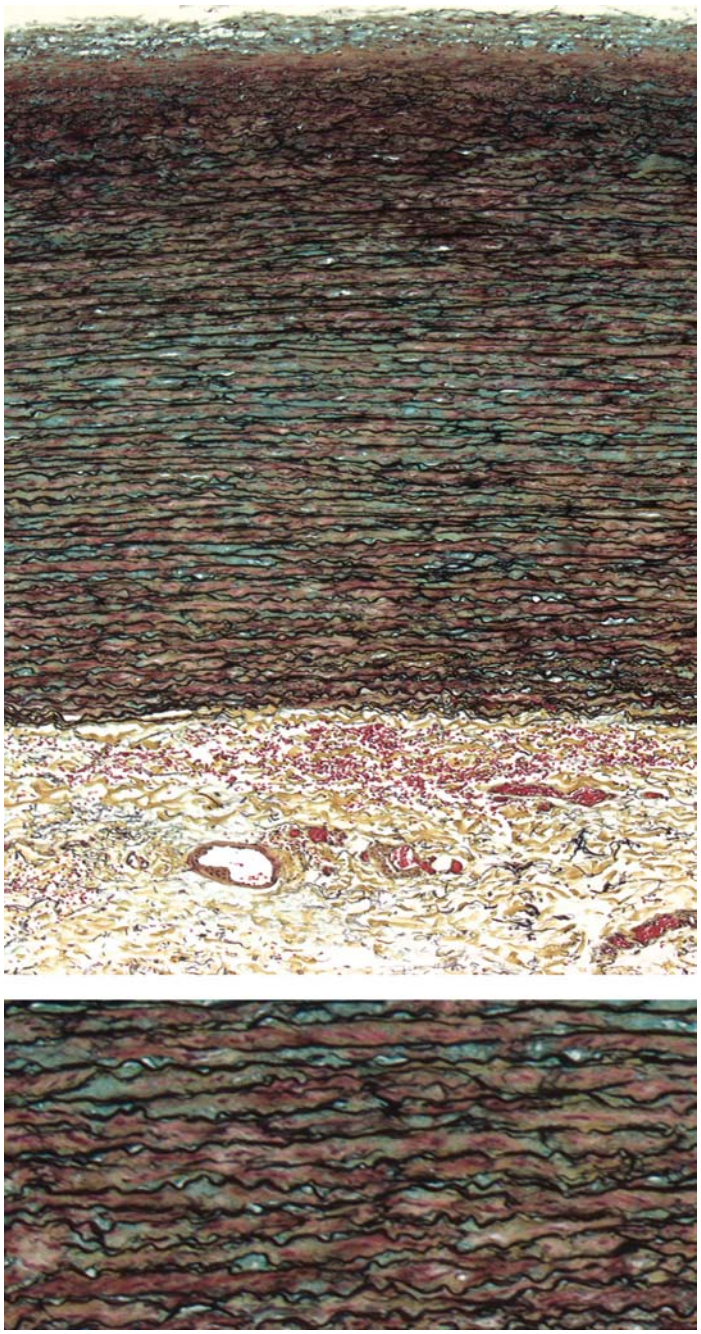

Fig. .72. Elastic type arteries, like any other type of arteries have a tunica intima, a tunica media and a tunica adventitia (upper image). The distinguishing architectural feature of an elastic type artery is that it is composed of lamellar units. The components of the lamellar unit are two elastic lamellae containing a small amount of fibrous tissue and mucopolysaccharide synthetized by smooth muscle cells in the middle of the lamellar unit (lower image). The aorta has approximately 40 lamellar units in the ascending portion which progressively diminish distally, with only about 20 lamellar units in the lower abdominal aorta. The elastic arteries in the body include aorta, carotids, subclavian, iliacs and some branches from these. In addition the pulmonary artery is also an elastic-type artery. Vasa vasorum are prominent in the adventitia and rarely penetrate into the media unless there are pathologic changes in the arterial wall.

Muscular arteries or distributing arteries (Fig. 73)

- Adventitia, media and intima are distinct
- The media shows bundles of smooth muscle cells oriented perpendicular to the axis of flow
- Well-defined internal and external elastic laminae
- Vasa vasorum diminish as a function of the decreasing caliber of the branching arteries
- Diameter 2 - 10 mm
  - Examples
    - Coronary arteries
    - Mesenteric arteries
    - Renal arteries
    - Internal carotid arteries

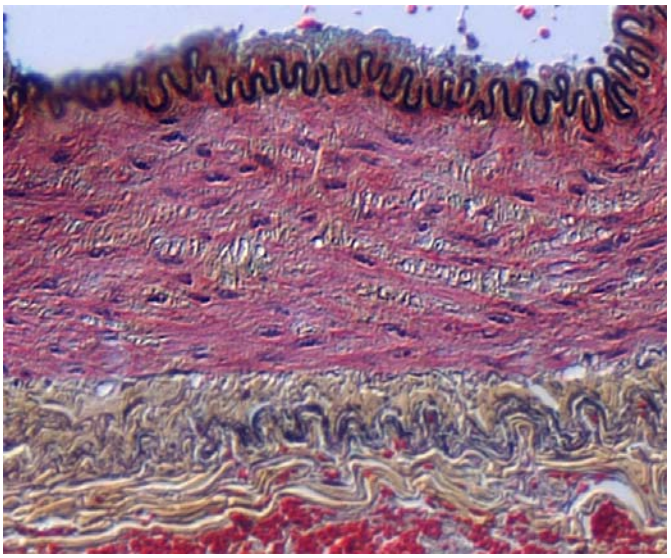

Fig. 73. Muscular type artery showing a tunica intima (top) which consists of a single layer of endothelial cells. Immediately subjacent to it is the internal elastic lamina (black undulating line). The internal and external elastic laminae delimit the tunica media, which is composed of smooth muscle cells arranged in a circular fashion, perpendicular to the axis of the vessel. The tunica adventitia is the yellow fibrous tissue below the external elastic lamina (black).

- Arterioles (Fig. 74)
  - Adventitia, media and intima are present
  - Lack internal elastic lamina
  - Capacitance vessels

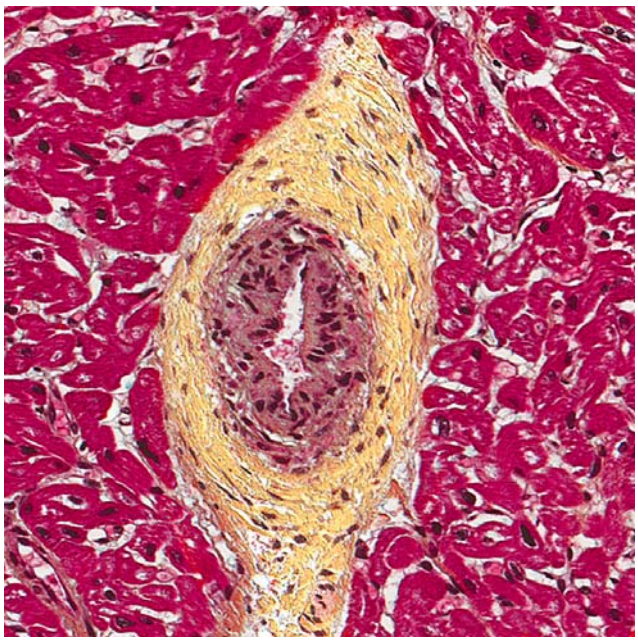

Fig. 74. Arterioles have the same three layers (intima, media and adventitia), but they lack elastic laminae.

- Veins (Fig. 75)
  - Adventitia, media and intima are present
  - The adventitia is rich in elastic fibers, which are short and interrupted
  - Smooth muscle in the media is less organized than in the media of arteries
  - The internal and external elastic lamellae are less conspicuous and somewhat discontinuous, compared to arterial elastic lamellae

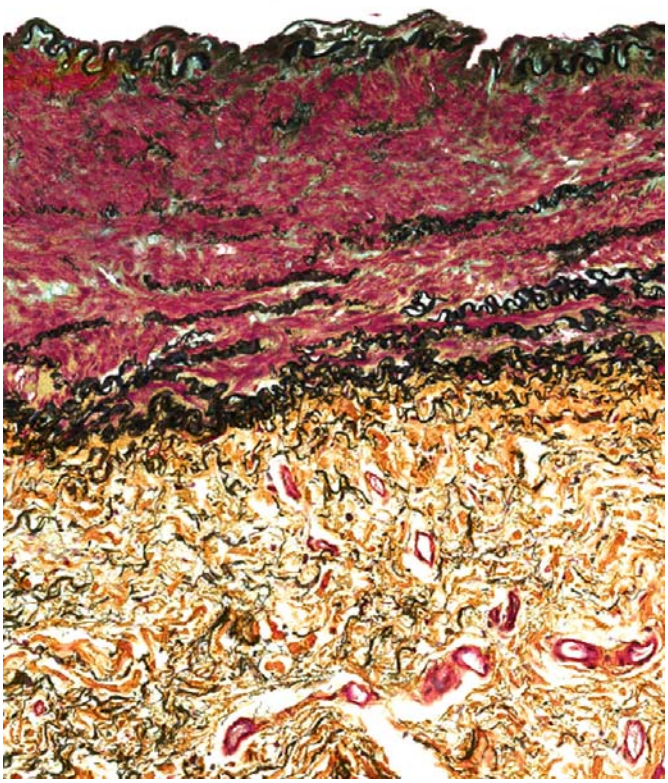

Fig. 75. Veins also have three layers. Unlike arteries they have more elastic lamellae in the media and adventitia (black), which are thinner and somewhat discontinuous, giving an appearance of fragmentation.

# Diseases of the great vessels (elastic-type arteries)

## ATHEROSCLEROSIS

### *Clinical*

- Accounts for more deaths in the West than any other disease
- Morbidity and mortality due to ischemic consequences of narrowed vessels, e.g., myocardial infarction, stroke, gangrene of extremities
- Aortic aneurysms are another important consequence
- Risk factors include genetic predisposition, male gender, advanced age, positive family history, hyperlipidemia, hypertension, diabetes, cigarette smoking, and inflammation

### *Gross*

- Affects elastic and large and small muscular arteries
- Intimal lesions (atheroma) consist of a raised plaque, with a fibrous cap and a lipid core of mostly cholesterol and cholesterol esters
- The fatty streak, seen usually in children and adolescents, thought to be the precursor lesion (Fig. 76)
- Plaques may be predominantly fibrous or atheromatous, calcified or ulcerated (Fig. 76)

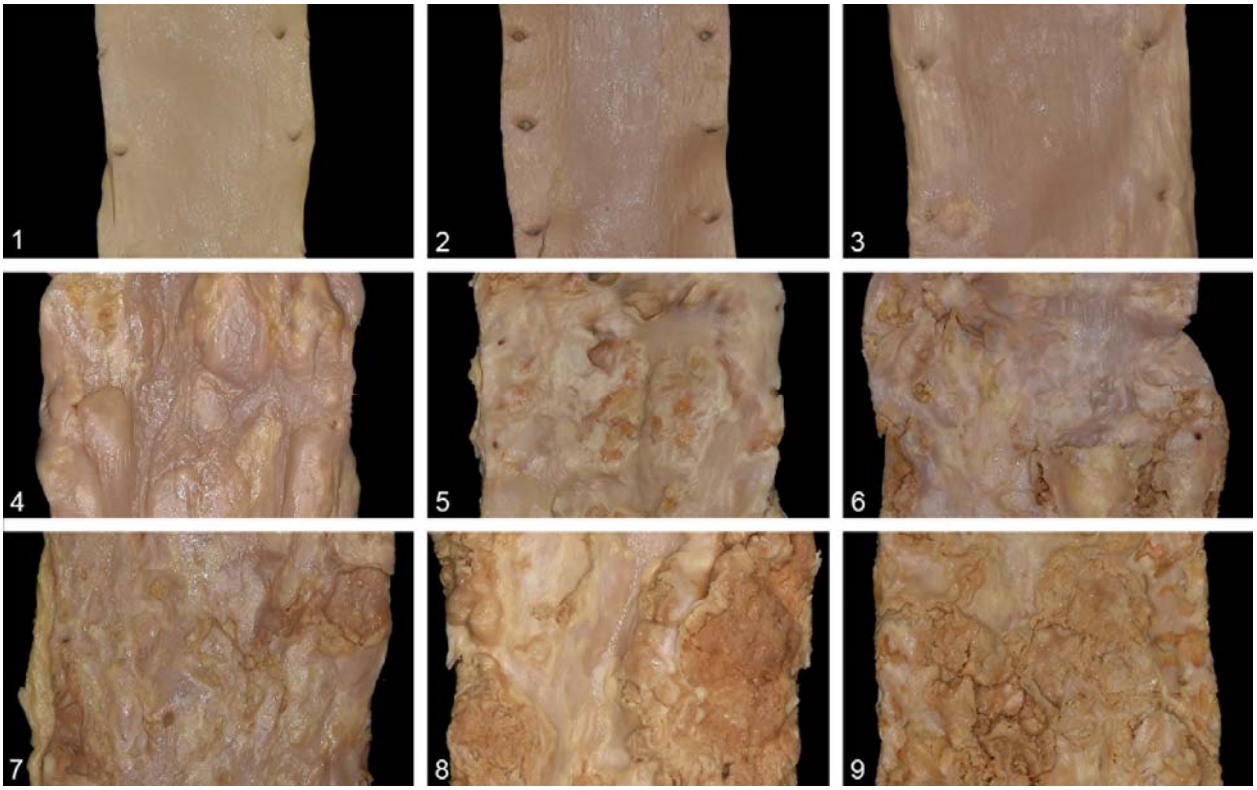


Fig. 76. Atherosclerosis in the aorta is a progressive disease. This panel show the intima of thoracic aortae. 1. Normal aorta without atherosclerosis. 2. Early fatty streaks in the intima run parallel to the axis of the artery. 3. The fatty streaks are more prominent raising above the surface of the intima. 4 – 6. Atheromatous plaque grow in size and coalesce to cover the entire surface of the vessel. Fibrous caps are cover the atheroma in a continuous fashion. However the lesions in image number 6 begin to show defects on the intimal surface. 7. The defects on the surface ulcerate and thrombose. 8-9. Further ulceration and thrombosis form complex plaques.

- In smaller vessels, atherosclerosis results in stenosis (Fig. 77)
- In larger vessels, lesion results in focal destruction and weakening of the wall, with potential to aneurysm formation and thrombosis
- Abdominal aorta is affected more severely than thoracic aorta

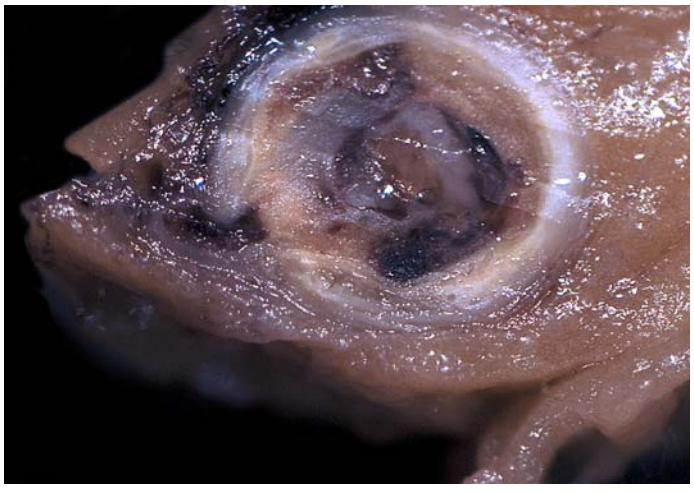

Fig. 77. Coronary artery with marked atherosclerosis, plaque hemorrhage and organizing thrombus which narrow the lumen >95%.

***Microscopic***

- Fibrous cap consists of smooth muscle cells and collagen; inflammatory cells, primarily macrophages and T lymphocytes, are often present beneath the surface and at the shoulder of the cap (Fig. 78)

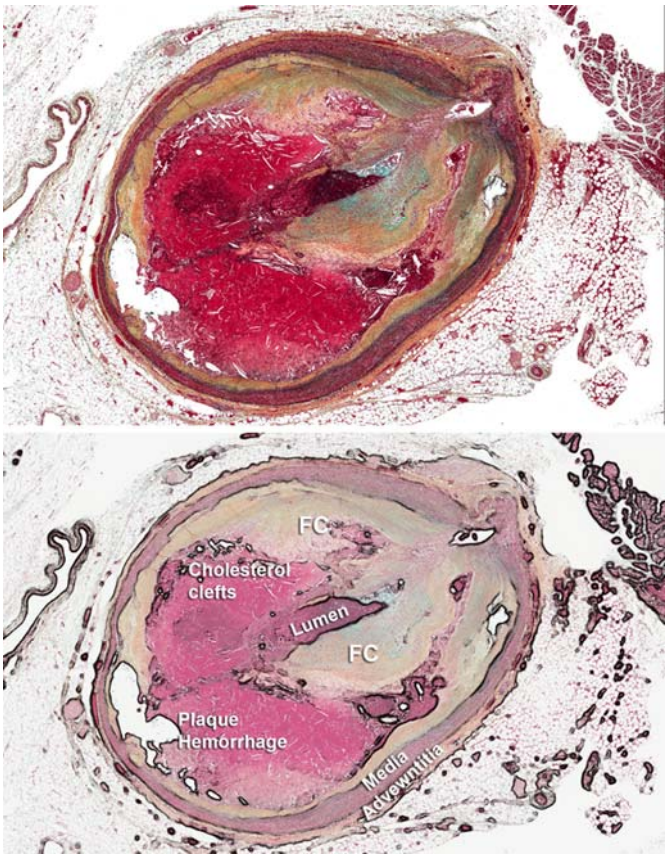


Fig. 78. Atherosclerosis in a coronary artery showing hemorrhage of the atheromatous plaque and rupture of the fibrous cap (FC) that overlies the hemorrhagic plaque. The hemorrhage is communicating with the small residual lumen of the artery, which is now completely occluded by thrombus.

- Core contains lipids with cholesterol clefts, necrotic debris, and foam cells derived from both macrophages and smooth muscle cells (Fig. 79)

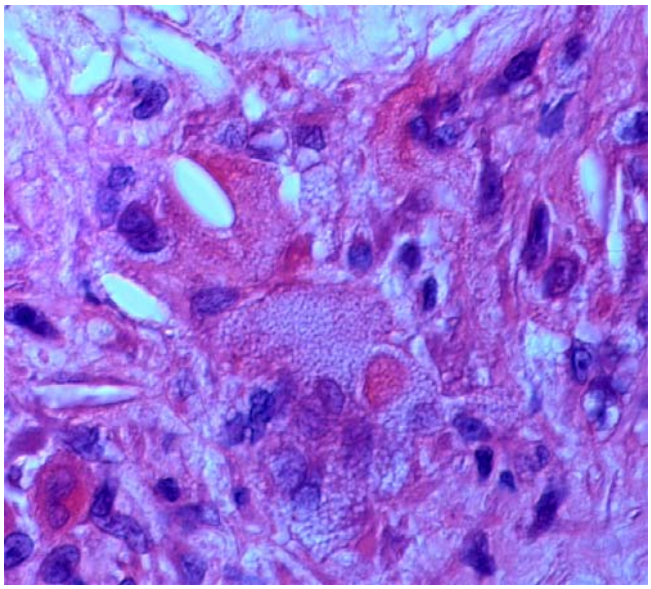

Fig. 79 Foamy macrophages accompanied by fibroblasts are commonly found within the atheroma.

- Dystrophic calcification often present; osseous metaplasia with bone and bone marrow elements common in femoral artery plaques (Fig. 80)

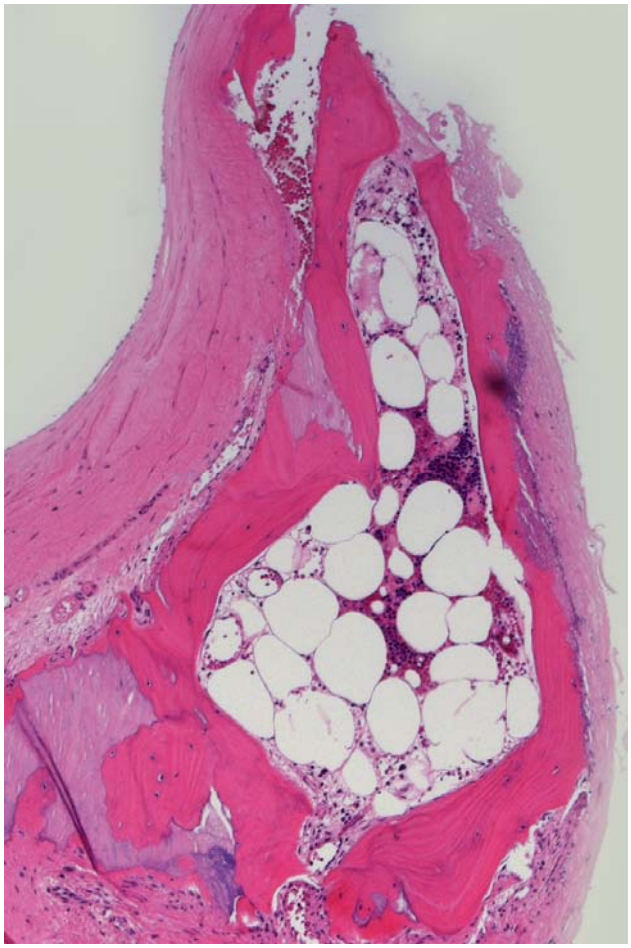

Fig. 80. Dystrophic calcification of the atheromatous plaque is common. In this example the calcification is seen toward the bottom of the image. In some instances there is also dystrophic ossification with bony trabeculae showing osteocytes. Bone marrow is present within the ossified trabecula.

- Plaque rupture leads to luminal thrombosis, thrombus gets incorporated into the plaque and contribute to plaque growth
- Hemorrhage from small vessels at the periphery of the plaque (plaque hemorrhage) also contribute to plaque expansion (Fig. 81)

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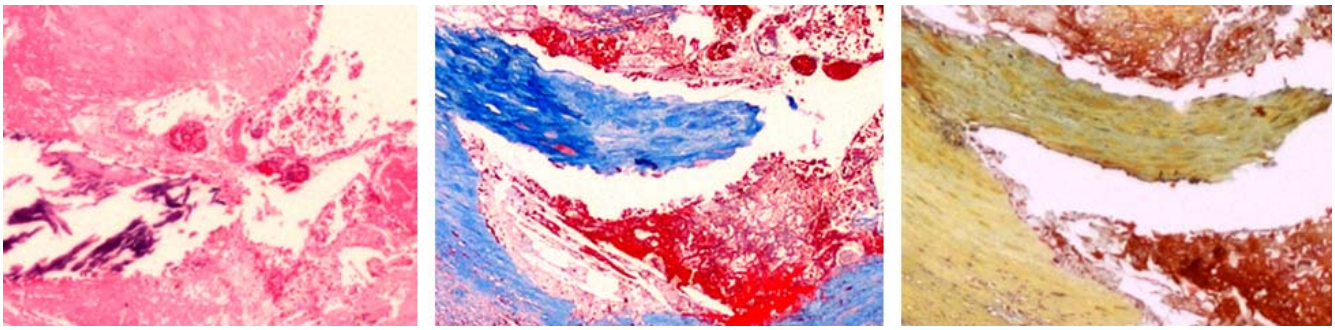

Fig. 81. Detailed view of a calcified plaque in which the fibrous cap is ruptured. Note the cholesterol crystals in the center (Trichrome stain) below the hemorrhage. The Movat stain (right) shows no evidence of elastic lamina, thus confirming that this fibrous tissue is actually the fibrous cap of the atheromatous plaque.

## Cystic Medial Degeneration of Aorta

### *Clinical*

- Cause unknown
- Can be seen as an age-related change, more commonly in idiopathic aortic aneurysms and genetic syndromes such as Marfan syndrome
- Also referred to as cystic medial necrosis; despite its name, it is not associated with smooth muscle necrosis, connective tissue necrobiosis or cyst formation

### *Microscopic*

- Fragmentation and/or loss of elastic fibers (seen best with elastic stain) with "cystic" spaces containing mucopolysaccharide
- It may appear myxoid on H&E section (Fig. 82)

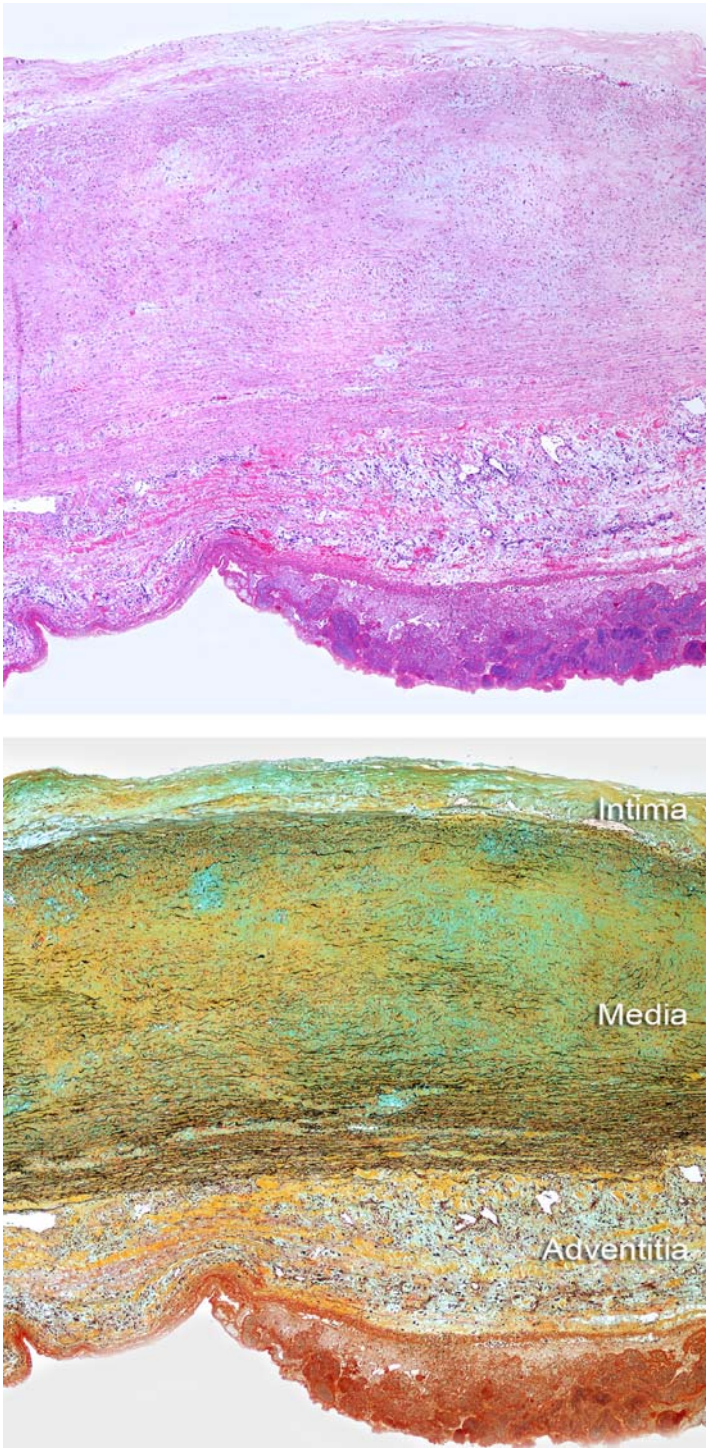


Fig. 82. Cystic medial degeneration of the aorta. This is not a necrotizing process of smooth muscle cells. Instead it is a degenerative process the affects the elastic lamellae of the aorta. It is an interruption of the parallel array of elastic laminae (black lines, compare to Fig. 27.72). This interruption creates areas devoid of elastic lamellae, thus giving an impression that a "cyst" in the parallel pattern of lamellae has formed. The Movat stain (lower image) show these areas clearly. They show fibrous tissue (yellow) and can show large pools of mucopolysaccharide/proteoglycan material. This change is non-specific and can be seen in aneurysms with a clear genetic basis as well as in atherosclerosis.

## DISSECTION

- Blood from the lumen enters into the arterial wall through an intimal defect, splits the media and then can propagate in both antegrade and retrograde fashion
- Mistakenly called a dissecting "aneurysm," when it is really a hematoma

### *Clinical*

- Typically presents with sudden severe chest and/or back pain
- May also present with hypotension, shock, loss of arterial pulse, cardiac tamponade, and ischemic effects of encroachment upon true vascular lumen
- Occurs three times more frequently in men
- Most common in the sixth and seventh decades of life
- Clinically are classified as Stanford type A (dissections involving the ascending aorta) and type B (dissections limited to the descending aorta)
- Ascending aortic dissections carries a higher mortality due to risk of rupture in the pericardial sac or thoracic cavity
- Risk factors for dissection include: hypertension, pre-existing aortic aneurysm, connective tissue disorders (Marfan, Ehlers-Danlos), bicuspid aortic valve, crack cocaine, iatrogenic (arterial cannulation, coronary artery bypass grafting)

### *Macroscopic*

- Most often affects the thoracic aorta with extension to its major branches (Fig. 83)
- Occurs in dilated and non-dilated aorta

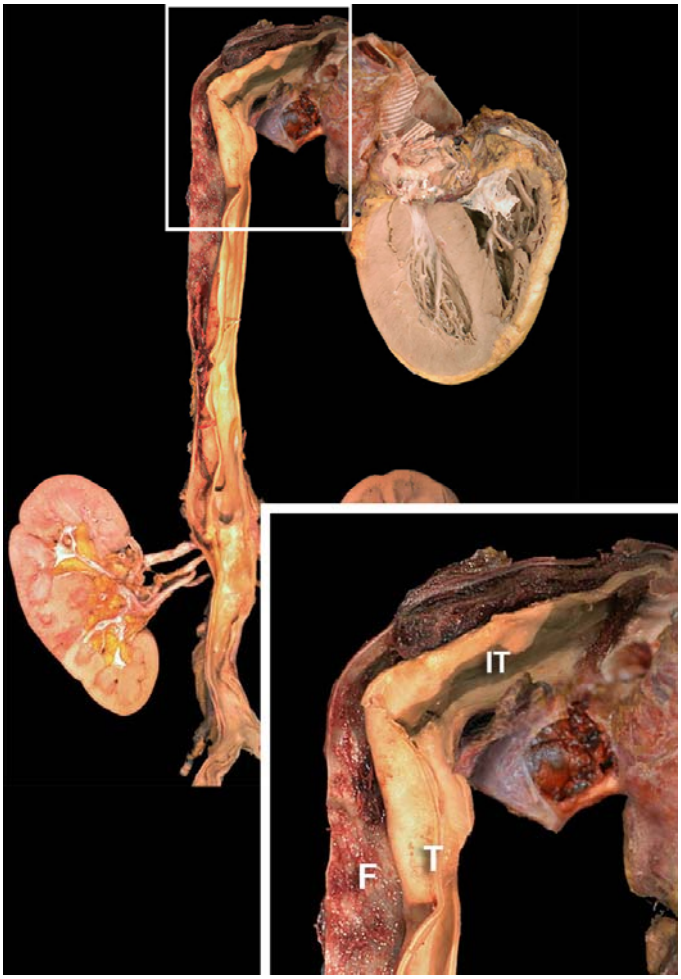


Fig. 83. Gross specimen showing a a posterior view of an aortic dissection. A type "A" dissection occurred in the past and was repaired by replacing the ascending aorta with a Dacron graft. Another dissection (Type B) extending from just beyond the left subclavian. The inset shows the new intimal tear (IT) the true lumen (T) and the false lumen (F) of the dissected aorta.

- An intimal tear is always present, commonly a few centimeters above the sinotubular junction
- Dissection may extend into and compromise coronary, carotid, renal, mesenteric, and/or iliac arteries (Fig. 84)

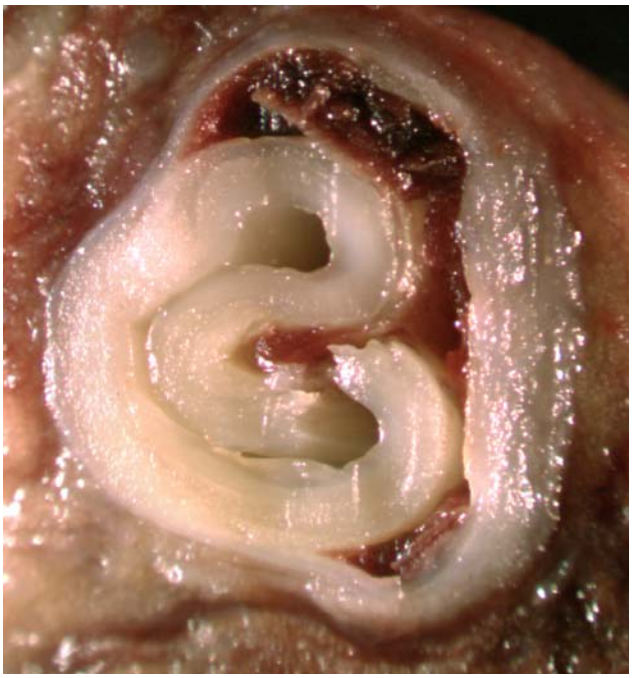

Fig. 84. Coronary artery dissection. Left main coronary artery showing collapse of the true lumen and hemorrhage between the media and the adventitia, which is the result of a retrograde dissection of the ascending aorta. This interrupts flow to the entire left circulation of the heart.

- Dissection may penetrate back into the original aortic lumen, creating a "double-barrel" aorta
- Rupture with adventitial tear may give rise to hemopericardium, hemomediastinum, hemothorax, and retroperitoneal hemorrhage
- Origin of arteries arising from the aorta may be sheared off and organ perfusion is supplied from the false lumen instead

***Microscopic***

- Dissection usually between the middle and outer third of the media
- Histopathology of aorta variable and nonspecific (Fig. 85)

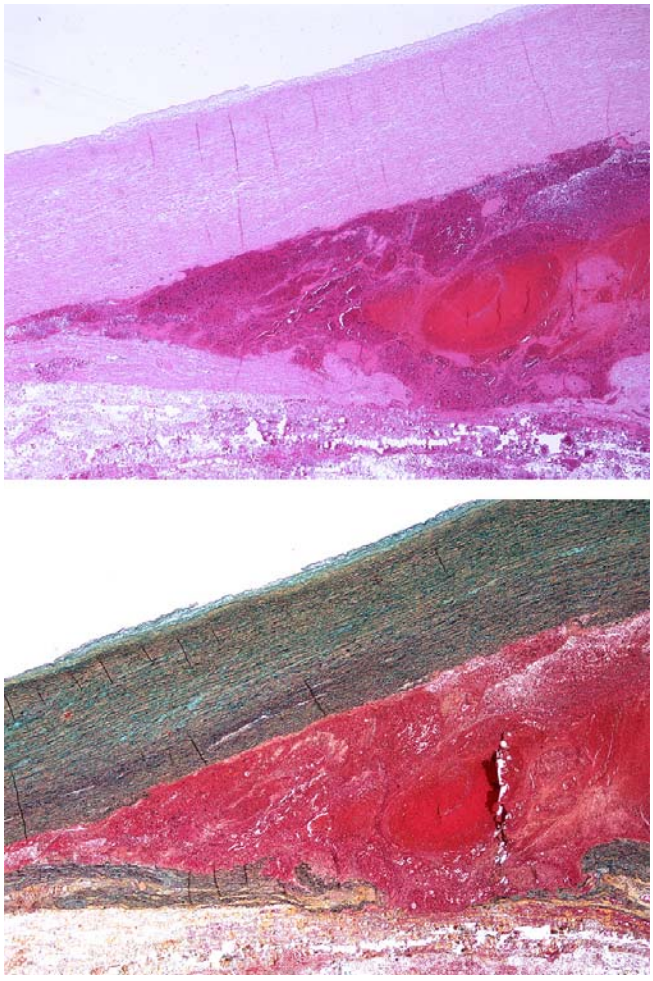

Fig. 85. Acute aortic dissection. The media of the aorta shows a dissection plane filled with blood which is extravasating into the adventitia.

## ANEURYSMS

- Abnormal dilation of part of an artery
- Caused by an acquired or congenital weakness of the media
- Described according to shape as saccular or fusiform
- May predispose to dissection or rupture
- True aneurysms contain all three layers of the vascular wall, however the media in large aneurysms may become very attenuated
- False aneurysms (pseudoaneurysms) are contained extravascular hematoma due to a disruption in the vascular wall and surrounded by periarterial connective tissue

## *Thoracic Aortic Aneurysm*

### *Clinical*

- Usually asymptomatic and diagnosis made as incidental discovery on imaging studies
- Can present with aortic insufficiency or acute complication of rupture and dissection
- Non-atherosclerotic non-inflammatory in majority of ascending aortic aneurysms; other causes are inflammatory diseases/vasculitis and rarely atherosclerosis
- Genetic predisposition to ascending aortic aneurysm formation in patients with bicuspid aortic valve, Marfan, Loeys-Dietz and Turner syndromes

### *Macroscopic*

- Smooth intima except in inflammatory conditions where the intima appears wrinkled and opalescent white due to intimal proliferation
- Notable lack of atherosclerosis or calcifications

### *Microscopic*

- Histology is variable and can be a combination of any of the following
  - cystic medial degeneration
  - decreased number of smooth muscle cells
  - disarray of elastic fibers and smooth muscle cells (Fig. 86)
  - interstitial fibrosis

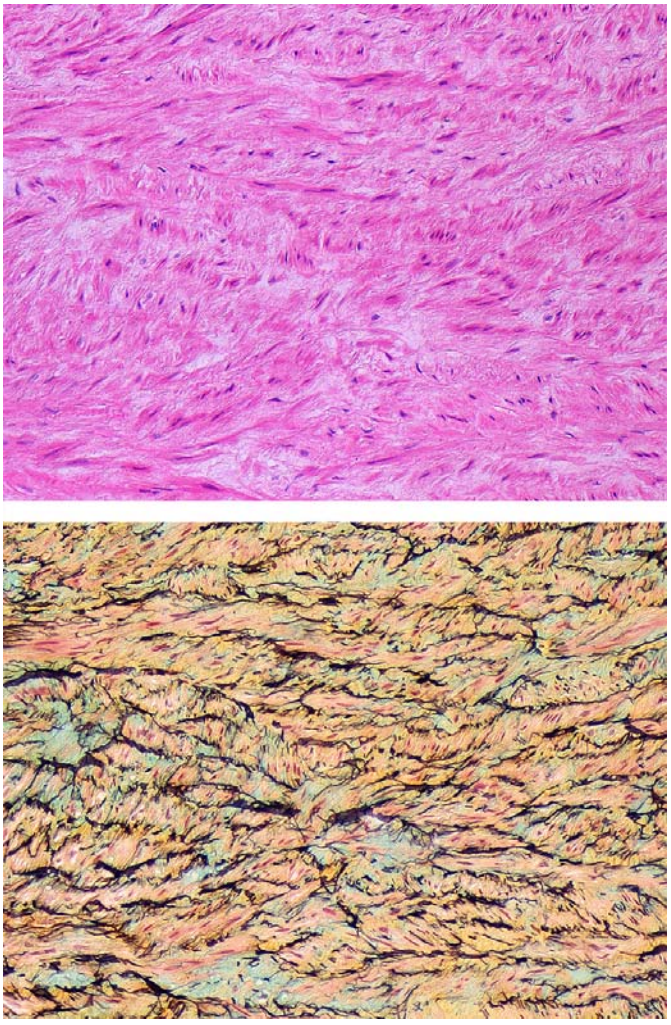

Fig. 86. Aortic wall with marked disarray of the smooth muscle bundles. Despite correct orientation of the sample, the circular array of smooth muscle cells is lost. The Movat stain also shows a rather disarrayed organization of the elastic lamellae, which are no longer parallel.

## *Atherosclerotic Aneurysm of the Abdominal Aorta*

### *Clinical*

- Mostly occurs in patients older than 50 years
- May present as palpable abdominal mass and/or radiographic finding
- Atherosclerotic aneurysm of thoracic aorta is much less common
- Most patients are men, and half of them are hypertensive
- Risk of rupture is greater with increasing size of aneurysms (>6 cm)
- Impingement on adjacent structures may lead to fistula formation (eg., aorto-duodenal fistula)

### *Macroscopic*

- Mostly occur between renal artery ostia and iliac aortic bifurcation
- May be saccular or fusiform (Fig. 87)

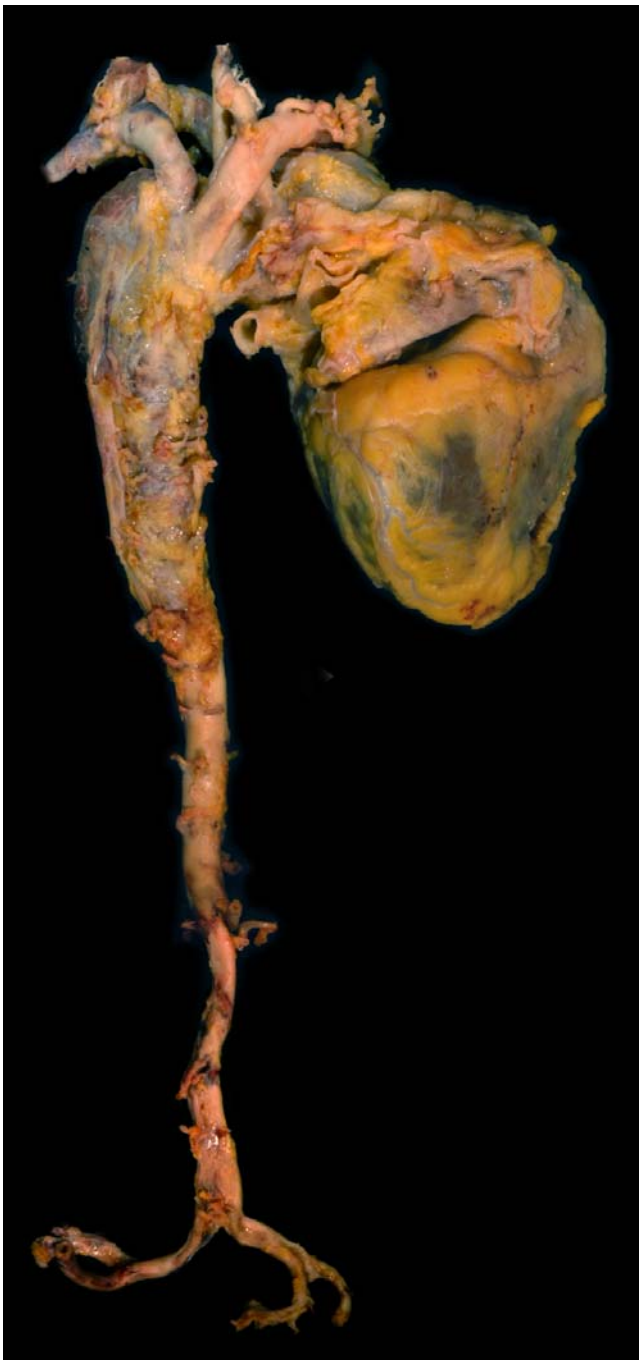

Fig. 87. Posterior view of the thoracic aorta with a fusiform aneurysm starting in the aortic arch.

- May contain mural thrombi (Fig. 88)

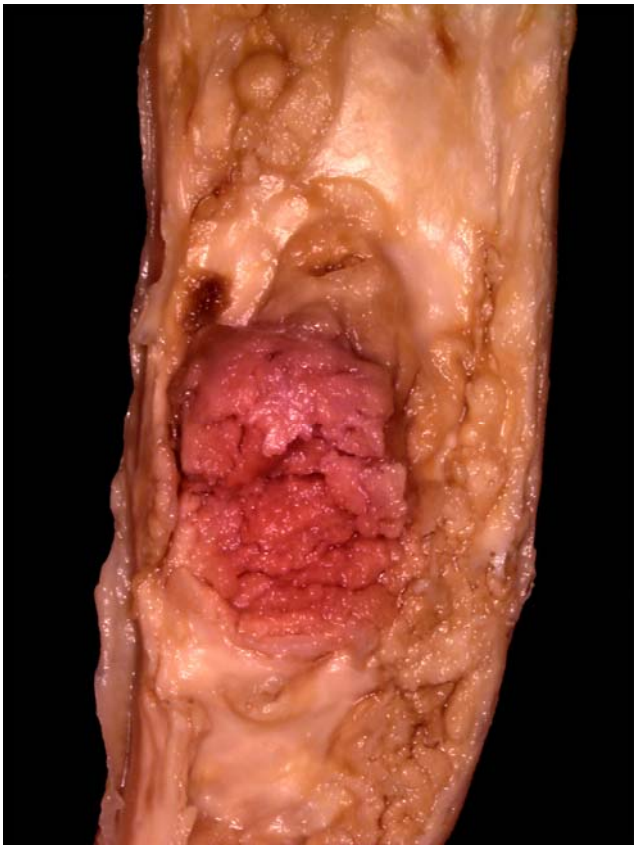

Fig. 88 Luminal view of an aorta with severe atherosclerosis with complicated ulcerated plaques forming a saccular aneurysm, which, in turn, is filled with thrombus.

***Microscopic***

- Atherosclerosis with destruction of media and wall thinning
- Chronic inflammation may be found in the intima, media and adventitia
- Giant cells around cholesterol clefts may be present
- Those accompanied by excessive inflammation in the adventitia (lymphocytes and plasma cells) are sometimes referred to as

inflammatory atherosclerotic aneurysms

## *Syphilitic Aneurysms*

### *Clinical*

- Associated with the tertiary stage of syphilis, luetic aneurysms are very rarely seen in the current era

### *Macroscopic*

- Ascending aortic aneurysm with "tree-barking" of the intima due to intimal hyperplasia and scarring of the media

### *Microscopic*

- Endarteritis/periarteritis of vasa vasorum with plasma cells, lymphocytes, and macrophages
- Necrosis and scarring of media with loss of smooth muscle cells and elastic lamellae

## VASCULITIDES

- For practical purposes, the vasculitides can be classified on the basis of the size of the vessel(s) involved and will be presented accordingly in the following sections
- Specific cause can be identified in only a minority of cases
- Can be divided into infectious and noninfectious groups, with the latter much more extensive
- There is a correlation between the type of antineutrophil cytoplasmic autoantibodies (ANCA) and the specific vasculitis syndrome
- cANCA (antiproteinase 3) is more often seen in
  − Active Wegener disease
- pANCA (antimyeloperoxidase) is more often seen in
  − Microscopic polyangiitis
  − Primary glomerular disease (idiopathic crescentic glomerulonephritis)
  − Churg-Strauss syndrome

## *Takayasu Arteritis*

### *Clinical*

- Onset of disease usually before the age of 50
- Predominantly affects women
- More prevalent in Asia than in the US and Europe
- Disease manifestation is variable and includes decreased/absent pulses in upper extremities, renovascular hypertension

### *Macroscopic*

- Involvement of aorta, aortic arch branches, pulmonary arteries, and occasionally coronary arteries (Fig. 89)

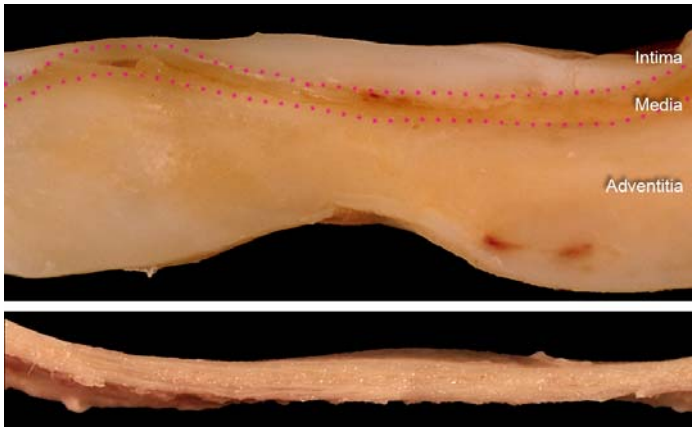


Fig. 89. On gross exam the arteries with Takayasu's disease show marked thickening of the vessel wall because this entity is commonly a pan-arteritis affecting the adventitia, media and intima of the vessel. The inflammatory infiltrates and the extracellular matrix response to the inflammatory insult produce thickening of the adventitia and intima and to some extent thinning of the medial. For comparison a normal thoracic aorta is shown, where the intima and adventitia are thin and most of the wall thickness represents the media.

- May involve only a portion (thoracic more often affected than abdominal) or the entire aorta
- Stenosing lesions more common than aneurysms
- Aorta is thickened, sometimes with superimposed thrombosis

***Microscopic***

- Chronic granulomatous inflammation predominantly affecting the media and adventitia
- Inflammatory cells are composed of lymphocytes, plasma cells and macrophages, giant cells are commonly present (Fig. 90)
- Intima shows reactive hyperplasia
- In chronic lesions, media shows destruction and fragmentation of elastic lamellae and adventitia often markedly fibrotic

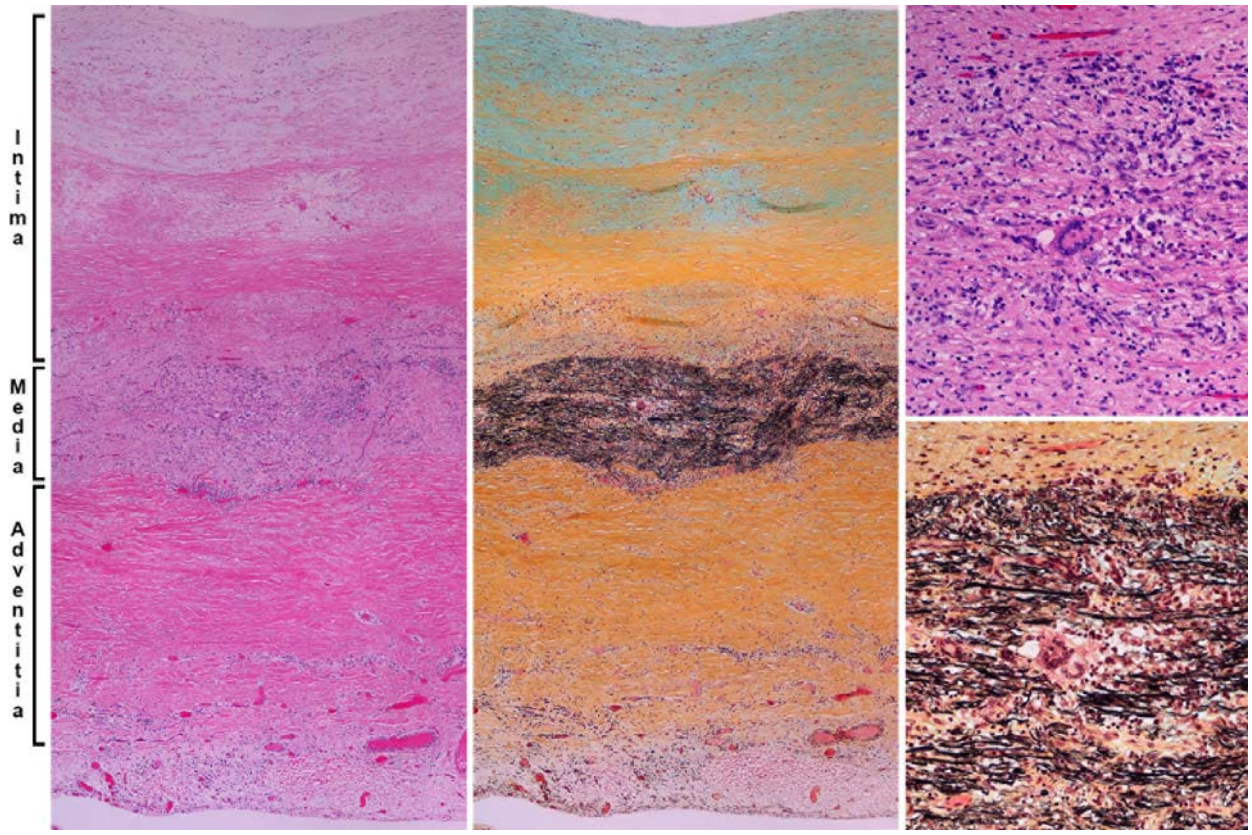


Fig. 90 Takayasu arteritis. The H&E stain shows very thick adventitia and intima layers with a somewhat thinned media. There is inflammatory infiltrate visible in the media and adventitia. The media shows collapse and partial destruction of the elastic lamellae. The intima shows an exuberant "neointima" with dense fibrous tissue as well as proteoglycan-rich connective tissue. The insets on the right panels show higher magnification with mononuclear inflammation and giant cells both on the H&E and the Movat stain.

## *Giant Cell Arteritis (GCA)*

### *Clinical*

- Onset of disease usually after the age of 50
- Female predominance
- May be but not always associated with temporal arteritis
- Clinical manifestations include temporal headache, visual disturbances, jaw or tongue claudication, scalp tenderness, polymyalgia rheumatica
- Aortic aneurysms are late complications of the disease
- Temporal artery biopsy may be performed when GCA is associated with cranial arteritis and visual loss is a serious complication of the disease

### *Macroscopic*

- Preferentially involves the thoracic aorta
- Aortic wall may be thickened with "tree-barking" of the intima and superimposed atherosclerosis (Fig. 91)

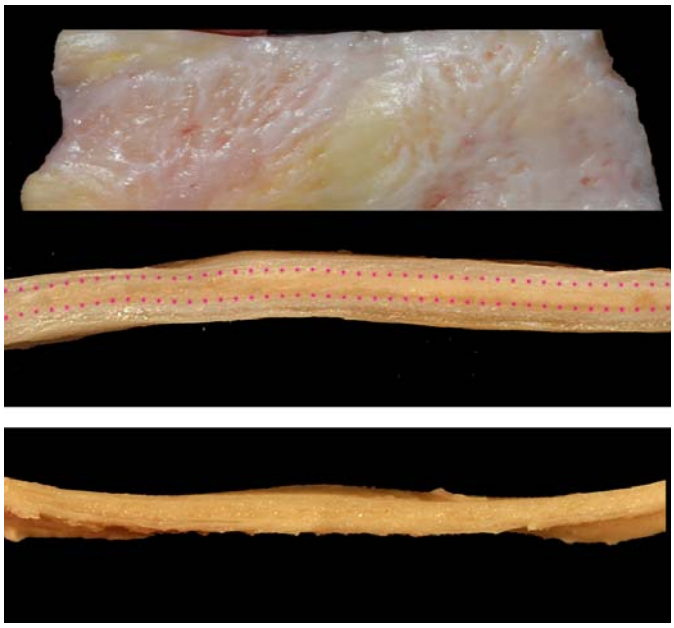

Fig. 91. Giant cell aortitis, in comparison to Takayasu's disease (Fig. 27.88) shows a rather white intima with some "tree barking" alternating with yellowish areas (see microscopic image in Fig. 27.93). On cross section the relative thickness of the intima media and adventitia is similar in the three layers. The aorta with giant cell arteritis is only slightly thicker than the normal aorta shown in the bottom part.

***Microscopic***

- Areas of medial necrosis bordered by mononuclear cells and giant cells
- Proliferation of vasa vasorum with surrounding mononuclear inflammatory cells (lymphocytes, plasma cells, macrophages) (Fig. 92)

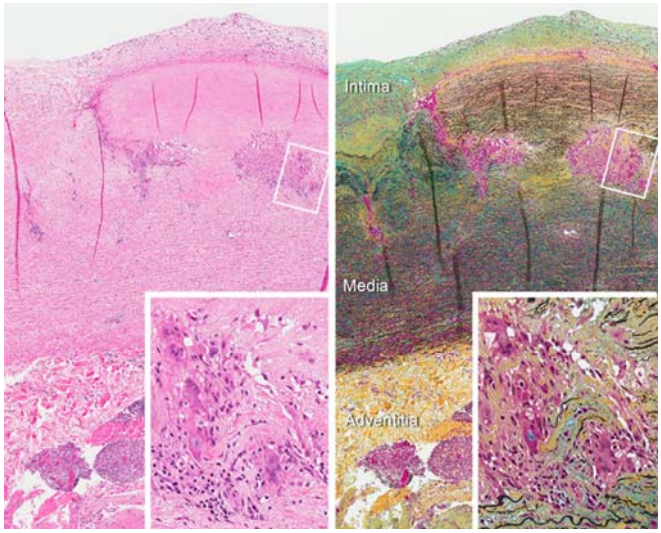


Fig. 92. Microscopic examination shows a proliferative intima. The media shows large areas of laminar necrosis (i.e. necrosis of the smooth muscle, without disappearance of the elastic lamellae, which instead collapse. Proliferation of vasa vasorum from the adventitia into the middle third of the media is common. The inflammatory infiltrates (mononuclear cells and giant cells) are commonly found in the vicinity of these vasa vasorum (insets H&E and Movat).

- Reactive intimal hyperplasia (Fig. 93)
- Adventitia with mild inflammation and mild fibrotic thickening
- Histopathology sometimes indistinguishable between systemic (aortic involvement in GCA) and isolated aortitis

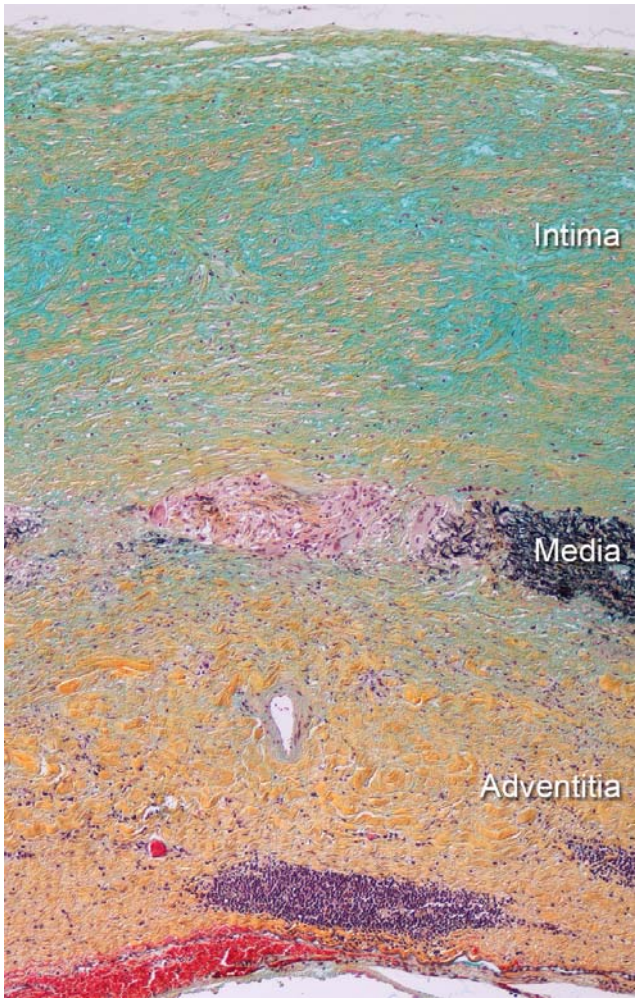


Fig. 27.93. The intima in giant cell aortitis shows exuberant proteoglycan-rich extracellular matrix. In this example the destruction of the media has produced distinct collapse of the elastic lamellae of the media or complete disappearance of the elastic lamellae as the process heals. The adventitia is slightly thickened by dense fibrous tissue, but no giant cells or granulomata are present, in contrast to Takayasu's disease.

Temporal arteritis

- Granulomatous inflammation in the media consisting of macrophages and lymphocytes (Fig. 94)
- Giant cells are present in most cases, but not a prerequisite for the diagnosis of temporal arteritis

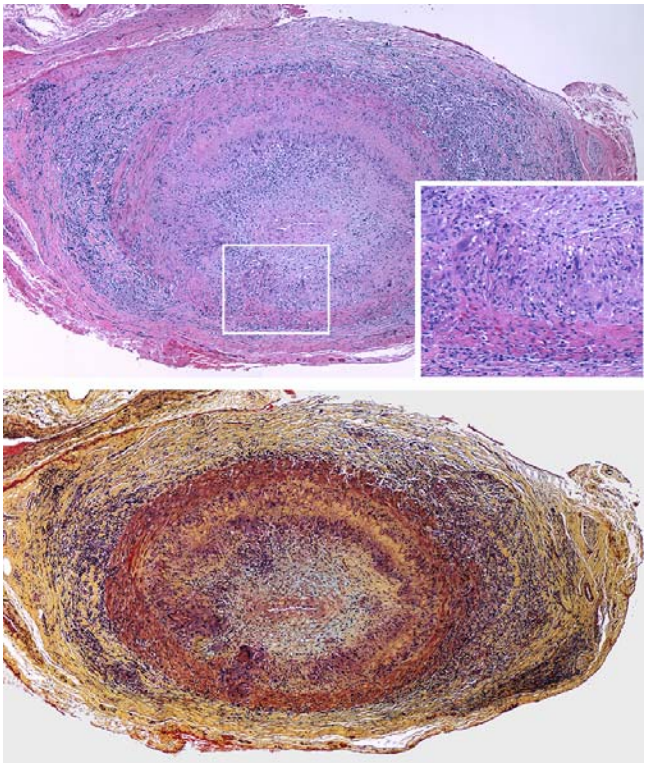

Fig. 94. Temporal arteritis in its classic form is a panarteritis in which the inflammatory infiltrate affects the adventitia, the media and the intima. These images show dense inflammatory infiltrates in the adventitia, and intima with a somewhat less prominent infiltrate of the media. The inset shows the giant cells at the interface between the media and the intima. Note the absence of fibrinoid necrosis. The Movat stain shows that the internal elastic lamina is destroyed. In addition it demonstrates a reactive intimal proliferation rich in proteoglycans which narrows the lumen almost completely.

- Disruption of the internal elastic lamina associated with the inflammatio

## *Other rare causes of large-vessel vasculitis*

- Behcet's disease
- Rheumatoid arthritis
- Ankylosing spondylitis
- Cogan's syndrome
- Relapsing polychondritis
- IgG4-related disorders (Fig. 95)

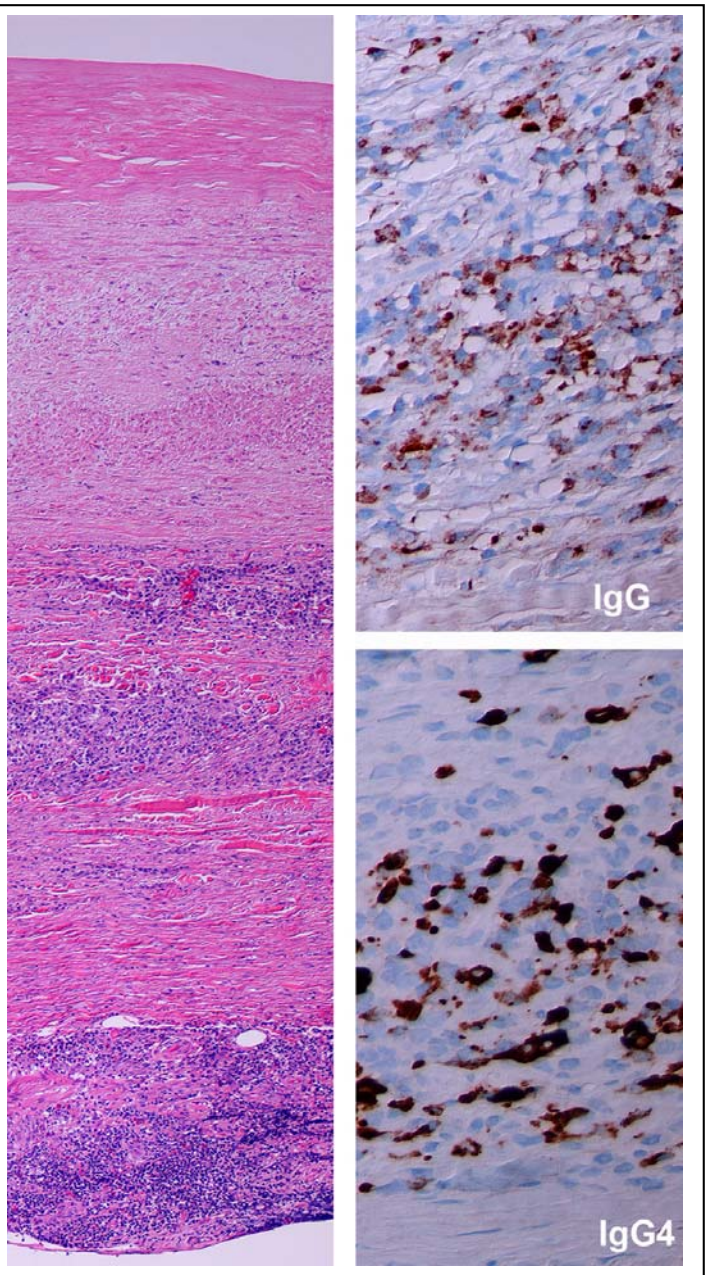


Fig. 27.95. Arteritis of the aorta showing prominent plasma cell populations in the inflammatory infiltrate should be evaluated for immunoglobulin subtypes produced by the plasma cells. If greater than 50% of all the plasma cells stain with IgG4 antibody, the diagnosis of IgG4 related disease can be rendered. The panels on the right show that a little over 50% of the plasma cells expressing immunoglobulin also express IgG4.

# Diseases of medium size vessels (muscular-type arteries)

## ARTERIOSCLEROSIS

- Means literally “hardening of arteries”
- Encompasses several entities that affect large, medium and small arteries including atherosclerosis, arteriolosclerosis, and Mönckeberg medial calcific sclerosis

## MÖNCKEBERG MEDIAL CALCIFIC SCLEROSIS

### *Clinical*

- Minor clinical significance, as this lesion rarely, if at all, produces vascular narrowing
- Occurs typically in individuals older than 50
- May be seen radiographically
- May coexist in same vessel with atherosclerosis
- The cause is unknown

### *Macroscopic*

- Usually affects media of medium-sized and small muscular arteries such as femoral, tibial, radial, and ulnar arteries
- Also seen frequently in arteries of thyroid gland and uterine corpus

### *Microscopic*

- Annular calcifications in media of medium to small muscular arteries
- Internal elastic lamina also calcified

## FIBROMUSCULAR DYSPLASIA

### *Clinical*

- Non-atherosclerotic, non-inflammatory vascular disease that causes stenosis, aneurysms, and dissections
- Female predominance, usually middle-aged
- May be found in virtually any artery of the body but most commonly affects renal, extracranial carotid, and vertebral arteries; involvement of multiple vessels common
- Symptoms are related to renal hypertension, stroke, organ ischemia and infarction; asymptomatic patients discovered on physical exam because of a bruit or on imaging studies

### *Macroscopic*

- Alternating areas of dilatation and stenosis give rise to the characteristic string of beads on radiography (Fig. 96)
- Arterial wall thickening and consequent lumen narrowing

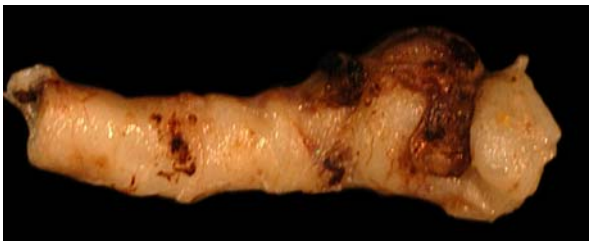

Fig. 96. On gross examination specimens with Fibromuscular dysplasia show a nodular contour. This renal artery shows bulging of its contour on gross exam. The areas of bulging correspond to areas where the media is virtually absent (Fig. 27.97).

***Microscopic***

- Fibrous tissue or fibrous and smooth muscle hyperplasia, which can be affect the intima, media (the most common location), or adventitia (Fig. 97)

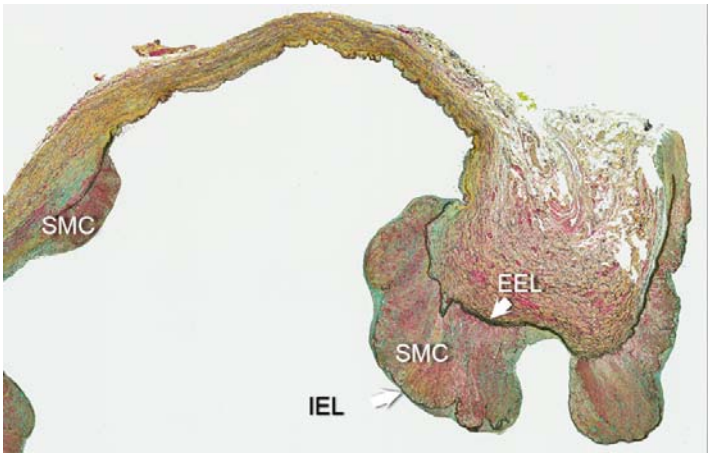


Fig. 97. On microscopic examination the renal artery shows an exuberant disarray of the smooth muscle bundles (SMC) of the media. There are not organized in the usual circular orientation which is perpendicular to direction of blood flow in the lumen. In other areas the media is completely absent. The internal elastic lamina (IEE) can be seen as a black lamina overlying the disarrayed smooth muscle and then it fuses with the external elastic lamina (EEL) in the areas where smooth muscle is absent.

## Berry Aneurysm of Cerebral Arteries

***Clinical***

- Associated with autosomal dominant (adult) polycystic kidney disease
- Clinically undetected aneurysms are found in as many as 25% of persons older than 55 years
- May present with focal neurologic deficits, headache, fatal subarachnoid hemorrhage from a rupture

***Macroscopic***

- More than 90% are seen at various branch points in the circle of Willis
- Multiple aneurysms are seen in approximately 20%
- Most commonly seen at the junctions of anterior communicating with anterior cerebral arteries, trifurcation of middle cerebral arteries, and junction of internal carotid artery with posterior communicating artery

***Microscopic***

- A discontinuity (thought to be congenital) of internal elastic lamina at branch points
- Gradual attenuation and disappearance of the media at the neck of the aneurysm
- The wall of the sac is made up of thickened intima with a thin adventitial coat
- Mural thrombus may be present

## Infectious (Mycotic) Aneurysms

***Clinical***

- Infection of the arterial wall as a complication of septicemia, and/or embolization of infectious material from endocarditis
- May occur in the aorta, cerebral, mesenteric, splenic arteries, and elsewhere
- May also occur next to a nidus of tuberculosis or bacterial abscess
- Complications are rupture and hemorrhage

***Microscopic***

- Infectious destruction of vessel wall, with pattern of inflammation depending on the type of organisms, which can be bacterial, mycobacterial, or fungal (Fig. 98)

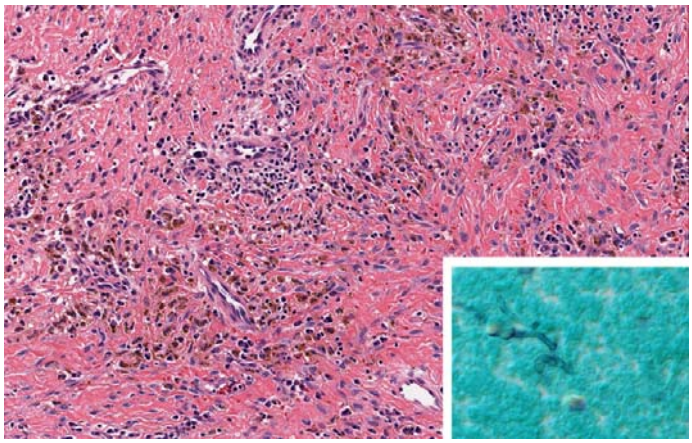

Fig. 98. The wall of this mycotic aneurysm shows dense reactive fibrous tissue and chronic inflammation as well as hemosiderin laden macrophages. The GMS stain show very fain fungal hyphae.

## NONINFECTIOUS VASCULITIS (MEDIUM-SIZED VESSELS)

### *Kawasaki Disease (Mucocutaneous Lymph Node Syndrome)*

#### *Clinical*

- Occurs usually in infants and children less than 5 years old
- Acute phase presents with fever, exanthema, conjunctival injection, reddened "strawberry" tongue, erythema of lips and oropharynx, and cervical lymphadenopathy
- Sudden death from coronary involvement with aneurysm and thrombosis/stenosis
- Leading cause of acquired coronary artery disease in children in industrialized countries

#### *Macroscopic*

- Necrotizing polyarteritis often complicated by formation of arterial aneurysms
- Predilection for the coronary arteries, but may also involve iliac, femoral, renal and mesenteric arteries
- Coronary artery aneurysms may thrombose and result in myocardial infarction

#### *Microscopic*

- Infiltration of arteries by macrophages and T lymphocytes
- Progressive destruction of the internal elastic lamina and media with aneurysm formation as the lesion progresses
- Edema of the wall with little or no fibrinoid necrosis

## *Polyarteritis Nodosa (PAN)*

### *Clinical*

- Segmental necrotizing vasculitis of small- to medium-sized arteries
- Incidence highest in the fourth and fifth decades
- Associated with hepatitis B infection
- Fever, weight loss, arthralgias, myalgias, mononeuritis multiplex, skin lesions (nodules, ulcerations, livedo reticularis), testicular pain
- May cause organ ischemia and infarctions of the gastrointestinal tract, kidneys, liver
- Not associated with antineutrophil cytoplasmic antibodies
- Treated with steroids and cyclophosphamide

### *Macroscopic*

- Visible/palpable nodular arterial thickenings, typically at branch points
- Involves predominantly renal and visceral muscular arteries and arterioles
- Pulmonary arteries and renal glomeruli are spared

### *Microscopic*

- Transmural fibrinoid necrosis and infiltration by neutrophils and mononuclear cells (Fig. 99)
- Coexistent healing/healed lesions and segments of normal vessel (skip lesions)
- Medial destruction with interruption of elastic laminae may result in microaneurysms
- Spares arterioles, capillaries and veins

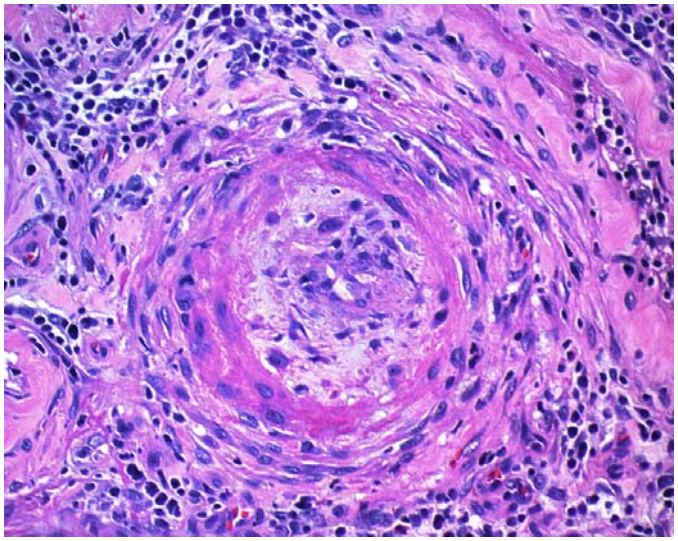

Fig. 99. This artery shows fibrinoid necrosis at the interface of the intima and the media in addition to the mononuclear cell infiltrates which involve the three layers of the vessel.

### *Differential Diagnosis*

- Isolated or localized vasculitis
  - diagnosis of exclusion
  - disease limited to a single organ as defined by clinical criteria and after long-term surveillance
  - histologic features very similar to PAN with necrotizing arteritis
  - often an incidental finding in surgical specimens such as gallbladder, gastrointestinal tract, appendix, testis, breast, uterus and cervix

## *Thromboangiitis Obliterans (Buerger Disease)*

### *Clinical*

- Predominant in young men less than 40 years old
- Associated strongly with the use of tobacco
- Usually present with ischemia of distal extremities manifesting as

claudication, pain, cyanosis, ulcerations and gangrene or migratory superficial thrombophlebitis
- Commonly involves the legs, feet, arms or hands; very rarely involves mesenteric, cerebral, coronary, and other vessels

***Macroscopic***

- Segmental stenosis of small- to medium-sized arteries and veins of extremities

***Microscopic***

- Early stage shows neutrophilic inflammation of medium-sized and small arteries and veins
- Arterial/venous thrombosis with inflammation, sometimes with neutrophilic microabscesses and multinucleated giant cells in thrombus itself
- Later stages characterized by organization of the thrombus and inflammation becomes predominantly mononuclear
- Fibrinoid necrosis not observed

# Diseases of Small Vessels

## Hyaline Arteriosclerosis

***Clinical***

- Most severe and extensive in hypertensive subjects, but also seen in normotensive elderly persons and diabetics
- Vascular narrowing leads to ischemic end-organ damage
- Most notable in kidneys (nephrosclerosis)

***Microscopic***

- Hyaline (pink, glassy) thickening of arterial and arteriolar walls, with concomitant lumen narrowing

## Hyperplastic Arteriolosclerosis

***Clinical***

- Seen in severe and malignant hypertension

***Microscopic***

- "Onion-skinning" of arteriolar walls by concentric layers of smooth muscle cells that thicken and narrow the vessel
- Basement membrane reduplicated
- Fibrinoid necrosis of vascular wall may be observed in malignant hypertension

## Infectious Vasculitis

- Vasculitis associated with infections may be due to direct invasion by microorganisms or septic emboli in normal or atherosclerotic vessels
- Causes are bacterial, fungal, rickettsial (Rocky Mountain spotted fever), and viral (herpes, CMV)
- Histology shows neutrophilic infiltrates in small vessels

## Noninfectious Vasculitis (Small Vessels)

- Involves small arteries, arterioles, capillaries and venules
- May have concurrent involvement of medium-sized vessels, but the small vessel component determines disease expression

- Muscular and large arteries spared

## *Churg–Strauss Syndrome (Eosinophilic Granulomatosis with Polyangiitis)*

### *Clinical*

- Triad of asthma, blood eosinophilia, systemic, and/or isolated organ involvement)
- Ear, nose and throat manifestations include allergic rhinitis, sinusitis, nasal polyposis and late-onset asthma
- Cardiac, gastrointestinal and central nervous system involvement less frequent but implies a poorer prognosis
- Kidney involvement infrequent
- p-ANCA (antimyeloperoxidase) found in up to 40% of patients

### *Microscopic*

- Vasculitis with eosinophil-rich infiltrate and fibrinoid necrosis
- Extravascular necrotizing granuloma may be present
- Both arteries and veins are involved

## *Microscopic Polyangiitis*

### *Clinical*

- Depends on the severity of end-organ involvement
- Hemoptysis, hematuria/proteinuria (necrotizing glomerulonephritis), bowel pain/enterorrhagia, muscle pain and weakness, and/or palpable skin purpura may be seen
- Strongly associated with presence of p-ANCA (antimyeloperoxidase)
- Immune reaction against an antigenic challenge (drugs, microorganisms, etc.) can be postulated in many cases

### *Microscopic*

- Vasculitis with fibrinoid necrosis of media and/or leukocytoclastic vasculitis (infiltration of polymorphonuclear neutrophils into vascular wall with neutrophil disintegration) of arterioles, capillaries, and venules
- Lesions of the same histologic age
- Usually without demonstrable immune complex deposition
- Skin-limited form called cutaneous leukocytoclastic vasculitis may be seen
- Glomerular lesions include focal and segmental necrotizing glomerulonephritis and crescentic glomerulonephritis
- Pulmonary lesions show capillaritis with alveolar hemorrhage

### *Differential Diagnosis*

- Anti-glomerular basement disease
  - May present with similar renal and/or pulmonary involvement
  - Absence of vasculitis outside the kidneys and lungs
  - Presence of anti-glomerular basement antibodies in serum
  - Linear deposits of IgG along glomeruli and alveolar capillaries

## *Wegener Granulomatosis (Granulomatosis with polyangiitis)*

### *Clinical*

- Peaks in fifth decade, with pneumonitis, upper airway inflammation and ulceration, and renal dysfunction (80%)

- Head and neck symptoms include sinusitis, rhinitis, proptosis, septal perforation or subglottic stenosis
- cANCA detected in up to 90% of patients who exhibit active disease
- Most patients die if untreated
- Responds well to immunosuppressive and cytotoxic medication

***Microscopic***

- Necrotizing vasculitis of small- to medium-sized arteries and veins, with tissue necrosis, small and poorly formed granulomas, and neutrophilic microabscesses
- Vasculitis may have granulomatous or nongranulomatous inflammation
- Pulmonary involvement leads to cavity formation and characteristic geographic necrosis
- Renal involvement may manifest as focal segmental necrotizing and/or crescentic glomerulonephritis
- Vascular and/or glomerular immune complexes may be seen in a minority of patients

***Differential Diagnosis***

- Henoch-Schonlein purpura (IgA vasculitis)
  - affects children and manifests as palpable purpura, arthralgias/arthritis, abdominal pain and bloody diarrhea
  - serum IgA elevated
  - glomerular and dermal vascular staining with IgA

- Vasculitis may be associated with connective tissue disease (e.g., SLE and rheumatoid arthritis), malignancy (angiocentric lymphoma, lymphomatoid granulomatosis, drug-induced, sarcoidosis, and cryoglobulinemia.

## III. Suggested Reading


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