The Pathology of Cardiomyopathies

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In 1972, Goodwin and Oakley defined cardiomyopathies as myocardial diseases of unknown origin and proposed three morphological types: dilated (DCM), hypertrophic (HCM), and restrictive or obliterative (RCM) [1]. In 1980, the World Health Organization (WHO) and the International Society and Federation of Cardiology (ISFC) introduced the term, specific heart muscle disease, where the cause of myocardial dysfunction was known [2]. This expanded the definition of cardiomyopathies by adding the functional component. Thus, the definition was expanded to diseases of myocardium with myocardial dysfunction.

This definition was used until 2006 when the American Heart Association (AHA) proposed a genetic-based classification [3]. It redefined cardiomyopathy as a heterogeneous group of diseases of myocardium associated with mechanical and/or electrical dysfunction, which usually (but not invariably) exhibit inappropriate ventricular hypertrophy of dilation, due to a variety of causes that frequently are genetic. With this modification, some cardiomyopathies could no longer be classified as idiopathic or heart muscle disease of unknown cause. Their cause has been discovered. In the AHA definition, primary cardiomyopathy referred to sole or predominant cardiac involvement. It did not mean diseases of myocardium associated with myocardial dysfunction as in the WHO/ISFC classification. The term secondary cardiomyopathy was used when dysfunction was part of a systemic process, excluding coronary, hypertensive, valvular, or congenital heart disease.

In 2008, the European Society of Cardiology developed a classification, which included two aspects: a morpho-functional phenotype and an etiologic description [4]. Cardiomyopathy was defined as a myocardial disorder in which the heart muscle is structurally and functionally abnormal. The phenotypes, which are used in day-to-day clinical practice, are: dilated, hypertrophic, restrictive, arrhythmogenic right ventricular cardiomyopathy, and unclassified variety. The accompanying etiologic classification is either familial genetic or nonfamilial nongenetic. The cardiomyopathy was defined as familial when present in more than one member of the family. A genetic cardiomyopathy is sporadic when the causative mutation is de novo—occurring for the first time in a single-family member.

In this chapter we adapt the AHA classification. There are two groups of cardiomyopathies: primary and secondary. These will be discussed separately. Primary cardiomyopathy is discussed in this chapter. This condition is predominantly confined to the myocardium and may include genetic, nongenetic, or acquired diseases.

Genetic

Hypertrophic Cardiomyopathy

The condition hypertrophic cardiomyopathy has been extensively studied. Details of its pathologic and physiologic features have been studied by many investigators [5, 6]. HCM is a complex cardiac condition characterized by variable degrees of left ventricular (LV) hypertrophy. It is not associated with defined causes of LV hypertrophy, such as systemic hypertension, but with mutations in sarcomeric protein genes. It is a common genetic heart disease, occurring as an autosomal dominant condition [7]. The prevalence is reported to be 1:500 individuals in the general population, which yields an estimate of over one million in Europe alone.

The hypertrophy may be either asymmetrical, involving primarily the ventricular septum, or symmetrical, involving both the septum and the free wall. The right ventricle may be involved as well. HCM may obstruct the left ventricular outflow tract. The obstructive form historically has been called hypertrophic obstructive cardiomyopathy (HOCM) and idiopathic subaortic stenosis (IHSS), reflecting the obstruction of the subaortic area by the hypertrophied ventricular septum (Fig. 5.1a). Systolic movement of the anterior leaflet of the mitral valve toward the ventricular septum contributes to the obstruction in many patients. In some of these patients, mitral regurgitation occurs as well, often from coexistent abnormalities of the mitral valve itself. These include mitral valve prolapse and insertion of the papillary muscle directly into the valve leaflets (absent chordae) cusps. The area of the ventricular septum where the mitral valve repeatedly strikes develops a fibrous plaque, often referred to as "SAM" (systolic anterior motion) lesion (Fig. 5.1b). Histologically, there is disarray of myocardial fibers from the normal linear orientation. The fibers run in various directions (Fig. 5.1c). The myocardial cells are significantly hypertrophied, and there is often increased interstitial fibrosis, which affects ventricular compliance and, ultimately, leads to decreased systolic and diastolic function.

Microvascular ischemia and myocardial fibrosis may be present, and intramyocardial arteries are often dysplastic.

Hemodynamically, patients with asymmetrical HCM often exhibit dynamic LV outflow obstruction either at rest or with physiological provocation. Mitral valvular regurgitation related to systolic anterior motion of the anterior leaflet of the mitral valve also may contribute to the outflow tract obstruction. With the onset of ventricular systole, there is normally rapid early ejection of blood into the aorta; then, as the anterior leaflet of the mitral valve contacts the ventricular septum, a marked reduction in outflow takes place until late systole. The degree of obstruction is affected by changes in myocardial contractility, afterload, and preload. An increase in contractility as from inotropic agents, a decrease in preload as from a Valsalva maneuver, or a decrease in afterload from standing increases the gradient between the left ventricle and aorta. The opposite effects in each of these changes results in a decreased gradient.

In both forms of the condition, in addition to the development of systolic dysfunction, the left ventricle becomes stiffer because of myocardial hypertrophy and fibrosis. Ventricular relaxation becomes limited. Adverse effects of systolic and diastolic dysfunction result.

The LV outflow obstruction may cause dyspnea, chest pain, and presyncope. Heart failure is uncommon, except in

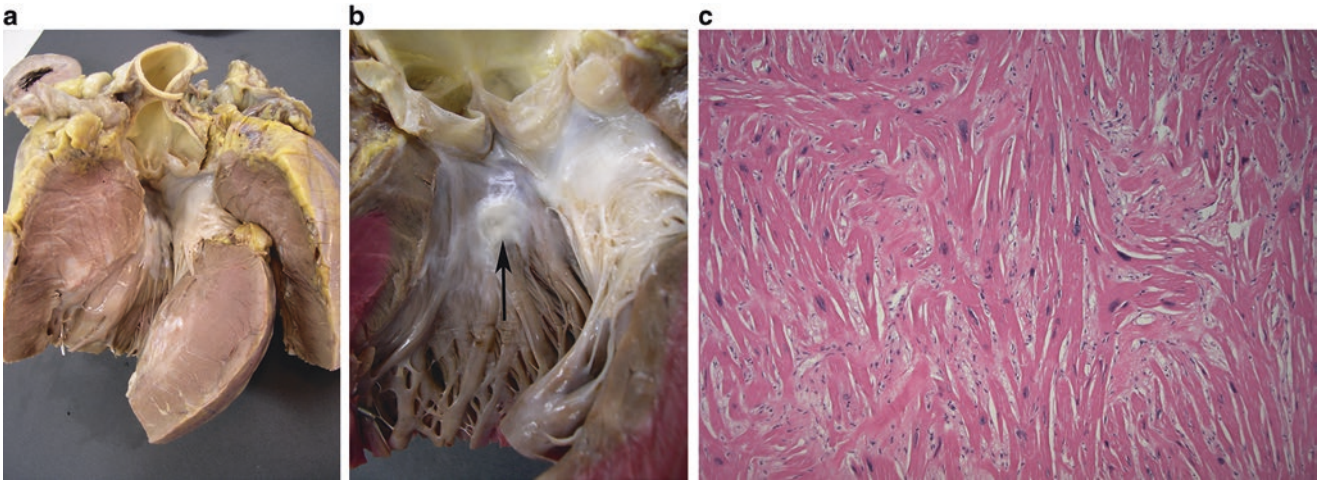

Fig. 5.1 (**a**). Hypertrophic cardiomyopathy. Left ventricular outflow tract view showing marked left ventricular hypertrophy, outflow tract obstruction, and systolic anterior motion lesion. (**b**) Closer view of systolic anterior motion lesion (*arrow*) in left ventricular outflow tract. (**c**) Myocyte disarray, hallmark histologic feature of hypertrophic cardiomyopathy (H&E; 40×)

the subgroup of patients who develop end-stage disease, which manifests itself as extensive myocardial fibrosis, often with markedly dysplastic intramyocardial arteries. Sudden death may be the initial presentation of the disease and represents the target of preventive efforts.

On physical examination, the arterial pulses are sharp from the rapid ejection during the first part of systole. The apex may be displaced leftward and a left ventricular heave palpated. The first and second heart sounds are normal, but the third and fourth heart sounds are present in about half of patients. A systolic ejection murmur is present in most patients, its loudness increases with maneuvers, which accentuate contractility or reduce pre- or afterload (standing, straining on a Valsalva maneuver, nitroglycerine).

Echocardiography enables assessment of the degree and location of ventricular hypertrophy, the degree of obstruction, and its significance. Systolic and diastolic function can be assessed (Fig. 5.2a, b). Mitral regurgitation can be recognized and its severity analyzed. If the ratio of the ventricular septum to free wall exceeds 1.2:1, the diagnosis of HCM is strongly suspected. Also, absolute measurements of the free wall and septum can be made and compared to normal.

Although echocardiography is an excellent technique for assessing patients with HCM, it is occasionally limited by poor acoustical windows, incomplete visualization of the left ventricular wall, and inaccurate evaluation of the left ventricular mass. MRI has the ability to evaluate wall thickness and the distribution of involvement better than echocardiography, especially in the anterolateral wall of the LV (Fig. 5.2c).

In the differential diagnosis, glycogen storage diseases must be considered. Although uncommon, their clinical features and prognosis differ from classic hypertrophic cardiomyopathy. Mutations have been found in LAMP2 and PRKAG2 genes in patients with ventricular hypertrophy. In the LAMP2 variant, myocardial cells have prominent cytoplasm, many vacuoles, and pleomorphic nuclei (Fig. 5.3). Patients present with symptoms similar to hypertrophic cardiomyopathy, but usually at a younger age, and the prognosis is poor. Patients have concentric hypertrophy and pre-excitation electrocardiographically. In the PRKAG2, variant shows ventricular hypertrophy and prolonged survival. Progressive conduction system involvement may require placement of a pacemaker and control of arrhythmias.

Arrhythmogenic Ventricular Cardiomyopathy

Historically, this condition has been called dysplasia, but this is inaccurate, and the term has largely been eliminated [8]. This is a common genetically determined myocardial disorder, which may involve primarily the right ventricle, primarily the left ventricle, or both. It is characterized by fibrofatty replacement of the right ventricular (RV) or left ventricular (LV) myocardium. In the early disease stage, structural changes may be absent or subtle. The changes are initially confined to a localized region of a ventricle. In the right ventricle, the area may be in the inflow tract, outflow tract, or apex. In the left ventricle, the findings are within the subepicardial myocardium (Fig. 5.4a).

Patients are often asymptomatic in the early disease stages but are at risk of sudden death, particularly with exercise. In the electrical phase, individuals present with symptomatic arrhythmias and morphological RV abnormalities, recognized by imaging of the heart (Fig. 5.4b). Later still, with more diffuse involvement, biventricular heart failure develops, resembling dilated cardiomyopathy.

Arrhythmogenic cardiomyopathy (AC) is familial with autosomal dominant inheritance. There are recessive forms, however, including Naxos disease and Carvajal syndrome.

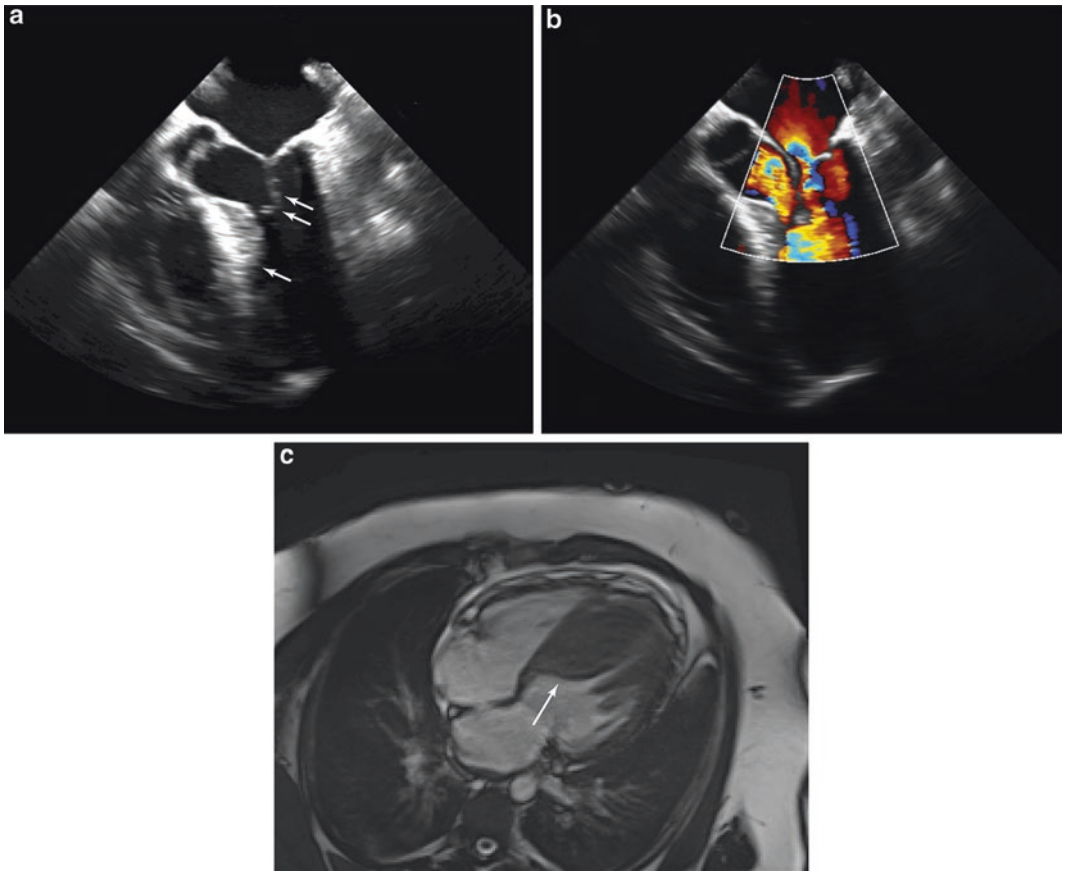

Fig. 5.2 (**a**) Hypertrophic cardiomyopathy. Transesophageal echocardiogram. Four-chamber view. Markedly thickened interventricular septum (IVS) (arrow). The anterior leaflet of mitral valve displaced toward the IVS (SAM) narrows the LV outflow tract (arrows). (**b**) Color Doppler shows posteriorly directed jet of mitral regurgitation. (**c**) Cardiac MRI. Axial view. Marked thickness of IVS (*arrow*). In contrast, thickness of posterior wall (PWLV) is normal

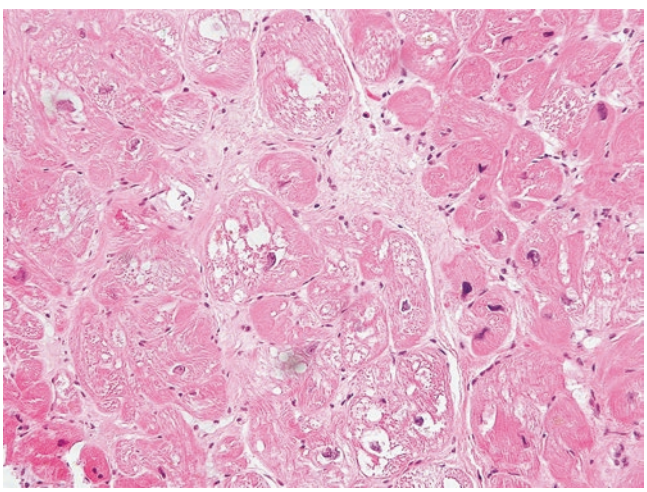

Fig. 5.3 Markedly hypertrophic myocytes with numerous cytoplasmic vacuoles, characteristic of glycogen storage disease, which may mimic hypertrophic cardiomyopathy clinically (H&E; 40×)

Left Dominant Arrhythmogenic Cardiomyopathy (LDAC)

As the study of ARVC progressed, it became evident that the spectrum was broader than originally thought. Recently, forms of predominant involvement of the left ventricle have been reported [9]. These patients tend to have inverted T waves in the lateral and inferior EKG leads and ventricular arrhythmias of left ventricular origin. The frequency and severity of arrhythmias are greater than the extent of left ventricular dysfunction. There is an enlargement of the left ventricle with reduced systolic function. Dyskinesis may coexist. Pathologically, this form of the condition is characterized by subepicardial fibrofatty replacement of the myocardium and compact myocardium of the septum. These changes are often circumferential but may be confined to the free walls only. The posterior wall is the most frequently involved wall. Myocyte degeneration is present in myocytes entrapped within the areas of fibrosis, and foci of myocarditis are often present (Fig. 5.5).

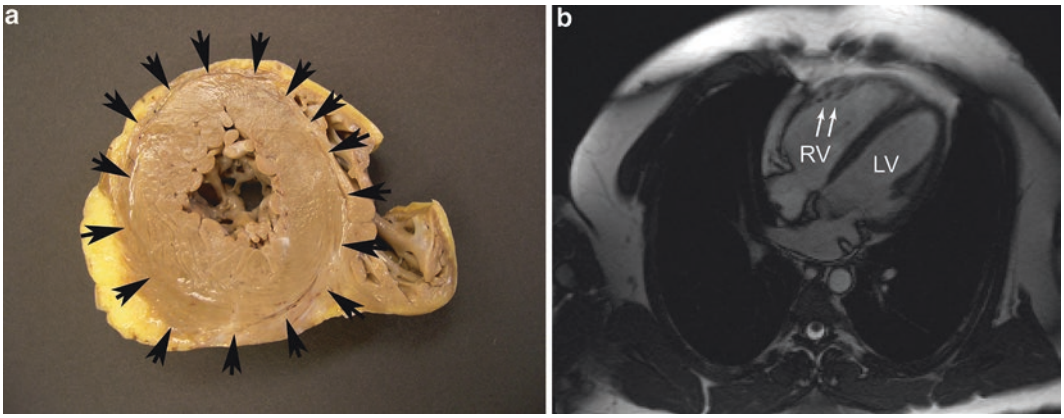

Fig. 5.4 (**a**) Arrhythmogenic cardiomyopathy/ventricular cross-sectional slice containing circumferential subepicardial fibrofatty replacement of the left ventricular free walls and compact myocardium of the septum, characteristic gross finding of arrhythmogenic cardiomyopathy, left ventricular dominant form (*arrows* point to subepicardial and septal fibrofatty replacement). (**b**) Arrhythmogenic cardiomyopathy. Cardiac MRI. Axial views. Right ventricular (RV) enlargement. Fatty replacement (*arrows*) of cardiac muscle in RV wall

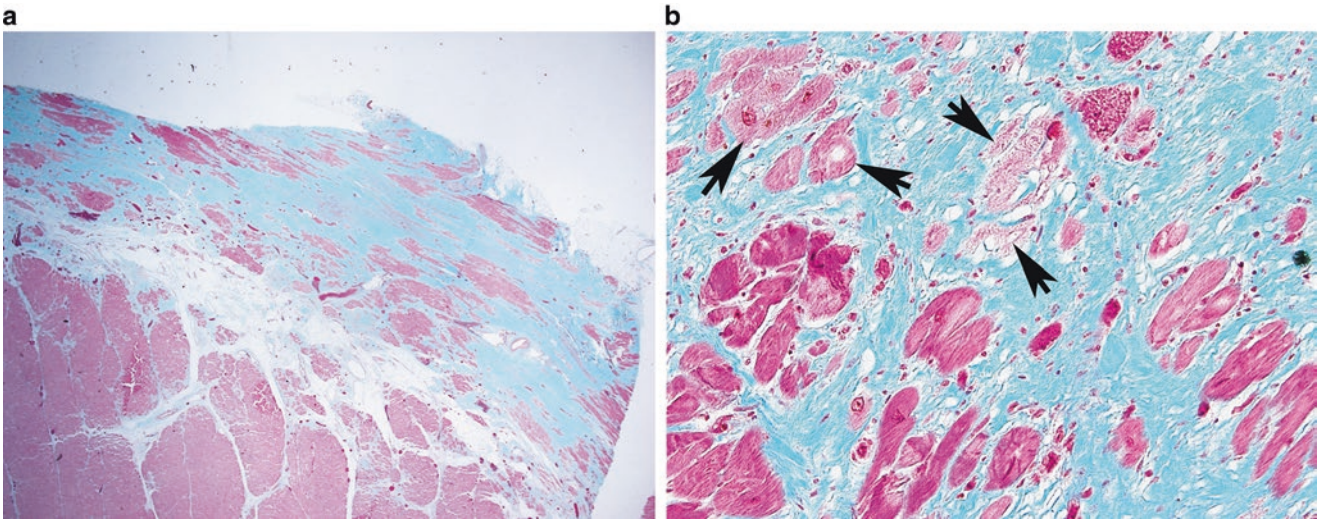

Fig. 5.5 (**a**) Fibrofatty replacement of the subepicardial myocardium of the free wall of the left ventricle in a band-like distribution, hallmark histologic finding of arrhythmogenic cardiomyopathy, left ventricular dominant form (Masson's trichrome; 1.25×). (**b**) Photomicrograph demonstrating degeneration of entrapped myocytes within the areas of fibrofatty replacement (at *arrows*), a histologic requirement of arrhythmogenic cardiomyopathy (Mason trichrome; 40×)

LV Noncompaction (LVNC)

LVNC, previously termed "spongy myocardium," is a rare cardiomyopathy that can be diagnosed at any age. It probably results from arrest of the compaction process during development. During cardiac development, the myocardium is trabeculated and gradually becomes denser and compacted. If this process does not occur, a spongiform cardiomyopathy results.

LVNC is characterized by a thin, compacted subepicardial layer and an extensive noncompacted subendocardial layer. The subendocardium has prominent trabeculations and deep recesses that communicate with the cavity of the LV, particularly at the apex and mid-portion of the ventricle (Fig. 5.6a, b). It does not communicate with the coronary circulation. The compacted section may be thinned. A ratio of noncompacted to compacted myocardium of 2:1 at the end of systole has been considered a criterion for diagnosis. The trabeculae have the same appearance as the noncompacted myocardium and move synchronously with ventricular contraction. A second form characterized by hypertrabeculation also is recognized.

Since it was relatively recently described, we do not know the exact occurrence of LVNC, but it may be present in 1:500 individuals. It may be isolated or coexist with cardiac abnormalities. The proportion coexisting with other abnormalities of the heart may be exaggerated, since it is identified by echocardiography or other imaging techniques which many

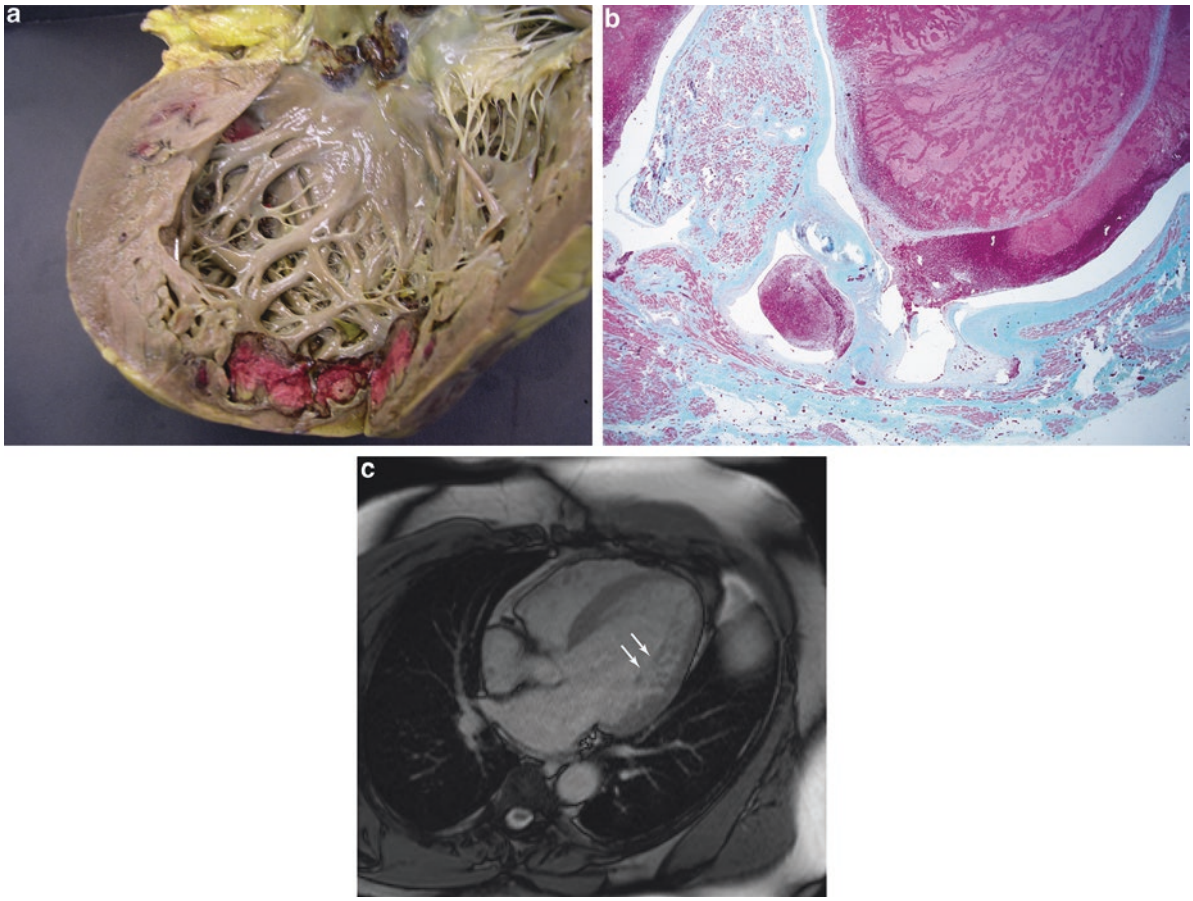

Fig. 5.6 (**a**) Noncompaction. Left ventricular apex with poorly formed compact myocardium, large trabeculae, and apical mural thrombus. (**b**) Photomicrograph from (**a**) demonstrating the large trabeculae and intratrabecular recesses with mural thrombus. There is marked myocardial fibrosis (Mason trichrome; 1.25×). (**c**) Left ventricular noncompaction. Cardiac MRI. Axial view. Noncompacted areas (*arrows*) show prominent trabeculation and deep intertrabecular recesses

cardiac patients undergo. The prevalence lies between 0.014 and 1.3 % in the general population as observed on echocardiographic examinations.

Symptoms of LVNC vary. Many patients are asymptomatic. Symptomatic patients can have congestive heart failure, life-threatening ventricular arrhythmias, and embolic events [10]. There may be both systolic and diastolic dysfunction contributing to the failure. In children, Wolff-Parkinson-White syndrome and ventricular tachycardia occur more commonly, while atrial fibrillation and ventricular arrhythmias are found in adults. Embolization is secondary to mural thrombi in the trabeculations, ventricular dysfunction, or atrial fibrillation. Sudden death is uncommon in this disease.

Both familial and nonfamilial forms have been reported [4]. In familial forms, inheritance may be autosomal dominant, X-linked, or mitochondrial. A number of genes may be associated with LVNC. Family members of a patient with this condition should be screened to identify individuals who may be asymptomatic. The increased incidence of neuromuscular diseases in patients with LVNC suggests careful clinical evaluation of the muscular and neurological systems.

In making this diagnosis, it is critical to have images of the cardiac apex. These are obtained best by magnetic resonance imaging (Fig. 5.6c).

Molecular Cardiomyopathies

Ion Channelopathies

Ion channelopathies are probably more common than HCM. They are inherited disorders causing arrhythmias [11]. They are associated with mutations of the genes encoding ionic channel proteins, which modulate cell membrane transit of sodium, potassium, and calcium ions. Several specific conditions have been identified which can be identified by their electrocardiographic features. They are associated with cardiac dysrhythmias, syncope, and sudden death. They may be transmitted in autosomal dominant or recessive patterns; however, autosomal dominant is more common.

The most common of these is the long QT syndrome in which the QT interval is prolonged. It is associated with a

polymorphic ventricular tachycardia and a considerable risk of syncope and sudden death. Many mutations are associated with this condition. It can coexist with deafness and is termed the Jervell and Lange-Nielsen syndrome [12], or, without deafness, called Romano-Ward syndrome [13]. The former is an autosomal recessive trait and the latter an autosomal dominant trait. Several individual genes controlling primarily potassium channels have been identified and, if found, these are useful in making the diagnosis.

Another channelopathy is the Brugada syndrome [14]. It has a characteristic electrocardiographic pattern showing complete right bundle branch block and ST segment elevation in the anterior precordial leads. It is associated with sudden death. The Brugada syndrome is found in Southeastern Asian men and, in that culture, has been given various names associated with beliefs about the causation.

In the Short QT syndrome [15], the QT interval is less than 330 msec. The T waves are tall and peaked as in hyperkalemia. Ventricular tachycardia or fibrillation can lead to sudden death.

Catecholaminergic Polymorphic Ventricular Tachycardia (CPVT)

CPVT is a rare arrhythmogenic disorder with two defined genetic patterns, one being autosomal dominant and the other autosomal recessive. The mutation involves calcium channels or proteins related to calcium channels.

Patients have no structural cardiac anomaly and a normal electrocardiogram. Patients manifest bidirectional and polymorphic ventricular tachycardia induced by exercise or other adrenergic stress. Often the symptoms present by age 20 years as a fainting spell which may be associated with a seizure. This may be considered as a primary neurologic condition, so the diagnosis of CPVT is delayed. Holter monitoring or exercise stress tests show monomorphic or polymorphic premature ventricular beats or bidirectional or polymorphic VT. Atrial premature beats, atrial tachycardia, and atrial fibrillation commonly coexist [16]. A careful family history revealing exercise-induced syncope or sudden death is very helpful in pursuing a diagnosis of CPVT.

Mixed (Genetic and Nongenetic)

Dilated Cardiomyopathy

Dilated cardiomyopathy is a condition of reduced ventricular function that is unrelated to causes such as myocardial infarction or systemic hypertension. The coronary arteries are not significantly narrowed by atherosclerosis. The heterogeneous group of conditions that causes DCM is characterized by marked LV dilatation with mild hypertrophy of the ventricular wall (Fig. 5.7a). While both ventricles may be involved, it is mainly the LV function that is affected with reduced contractility, leading to progressive congestive heart failure. With the dilatation, mitral regurgitation develops as the papillary muscles are displaced outward. A secondary complication is the development of mural thrombi in the cardiac apex or atria if atrial fibrillation develops. Systemic or pulmonary embolization is a complication of these thrombi.

Histologically, the findings range considerably. In most instances, varying degrees of fibrosis and myocardial degeneration are observed. Foci of myocytolysis may be present. Diffuse interstitial fibrosis may be found. Lymphocytes may be present in interstitial areas and found in perivascular locations. The nonspecific nature of the histologic changes precludes making a diagnosis of dilated cardiomyopathy on the basis of biopsy alone.

The patient presents with symptoms and signs of progressive reduction in systolic function of the left ventricle. Initially, there is fatigue on exertion which progresses to reduced exercise tolerance. As the LVED pressure becomes elevated, dyspnea and orthopnea develop. These symptoms may be associated with rales and signs of right heart failure with hepatomegaly and neck vein distension. With dilatation of the atria, atrial fibrillation occurs. Conduction abnormalities may result from myocardial fibrosis.

The diagnosis is made by echocardiography, which shows abnormalities before the patient has symptoms of the DCM. The findings are diffuse and show enlarged, poorly contracting ventricles (Fig. 5.7b). Ventricular dimensions are increased, and the ejection fraction is reduced. On echo Doppler, evidence of atrioventricular regurgitation from the ventricular dilatation may be found (Fig. 5.7c). Coronary arteriograms in these patients will reveal normal features (Fig. 5.7d, e). Thrombi may be identified in the cardiac apex or atria.

DCM occurs most often in the third and fourth decades of life but can occur at any age, including infancy. Dilated cardiomyopathy is largely irreversible. It is a common cause of heart failure and the most frequent cause of heart transplantation (Elliot et al., [4]).

This form of cardiomyopathy occurs from a variety of origins. About one-third are reported as familial [17]. The predominant mode of inheritance is autosomal dominant, as an X-linked autosomal recessive trait has been identified. Mitochondrial inheritance occurs less frequently. Peripartum cardiomyopathy, alcoholic cardiomyopathy, and chemotherapy-related cardiomyopathy are three distinct clinical situations where it occurs, but they lack specific histologic features. Dilated cardiomyopathy with or without lymphocytic infiltrates has been described in some patients with immune deficiency syndrome. Many types of infectious disease, particularly viral, but also bacterial and fungal, also can involve the heart and may result in dilated cardiomyopathy. In addition, patients with various muscular dystrophies develop DCM as their skeletal muscle disease progresses. The symptoms may be muted by the patient's reduced ability to exercise because of the skeletal myopathy.

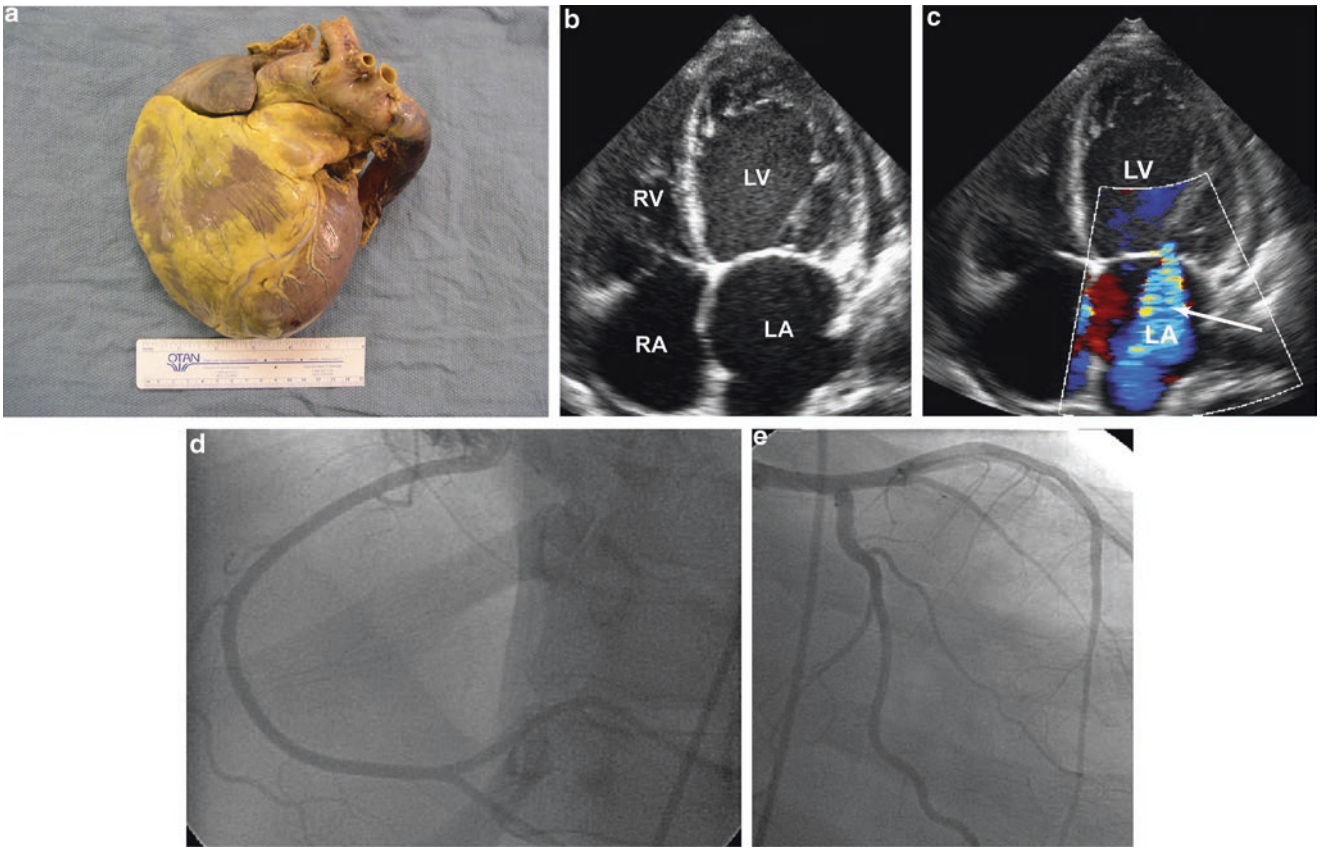

Fig. 5.7 (**a**) Dilated cardiomyopathy with marked four-chamber enlargement and globular shape of the heart. (**b**) Dilated cardiomyopathy. Echocardiogram. Apical four-chamber view. Diffuse dilatation left ventricle (LV), left atrium (LA), and right atrium (RA). (**c**) Color Doppler from (**b**) demonstrates moderate to severe mitral regurgitation (arrow). (**d**) Normal left coronary arteriogram from patient in (**b**). (**e**) Right coronary arteriograms from same patient in (**b**); normal features are present

Primary Restrictive Nonhypertrophied Cardiomyopathy

Primary restrictive nonhypertrophied cardiomyopathy is the least common type of cardiomyopathy. It is associated with biatrial enlargement, a normal- or small-sized LV and RV, and normal atrioventricular valves and ventricular wall thickness [18]. The histologic appearance is often normal, but may show hypertrophied myocytes and interstitial fibrosis. Some cases result from autosomal dominant inheritance, but most appear sporadic.

The functional effect is limited ventricular filling. It appears as if the compliance of this chamber is reduced, so filling is impaired. Systolic function is normal or near normal. With reduced ventricular compliance, the pressure in the corresponding atrium is elevated. The left atrium enlarges, often significantly. Pulmonary venous pressure increases, leading to pulmonary edema. Pulmonary hypertension is associated because of reflex pulmonary vasoconstriction. With the elevated pressures in the right ventricle and atrium, systemic venous pressure increases as well.

The patient's primary symptoms and signs are those of pulmonary venous obstruction and right heart failure. Respiratory symptoms are prominent with dyspnea, fatigue, and reduced exercise tolerance. Sudden death may occur [19]. No murmur is present on physical examination, but the pulmonary component of the second heart sound is accentuated. Gallop rhythm may be found. The liver is enlarged and the jugular venous pulses increased.

Echocardiograms show greatly increased atrial size in the presence of normal atrioventricular valves. Ventricular sizes are normal, but ventricular function may decrease with time. Ventricular diastolic function is decreased as indicated by an elevated E/A ratio and measurement of atrial-pulmonary vein reversal parameters.

Acquired

Myocarditis (Inflammatory Cardiomyopathy)

Myocarditis is an inflammatory disease of the myocardium with cardiac dysfunction. It is most commonly of viral origin. At least half of patients recover, perhaps a quarter of patients progress to cardiac failure, and an

Table 5.1 Causes of myocarditis

Infectious agents
1. Viral: group B coxsackievirus, influence A and B virus, adenovirus, parvovirus B19, HIV, cytomegalic virus, enterovirus, hepatitis C virus, Epstein-Barr virus
2. Bacterial: diphtheria, mycoplasma pneumonia, meningococcal, psittacosis, streptococcus staphylococcus, tick-borne bacterium
3. Rickettsia: typhus, Rocky Mountain spotted fever, fungal (*Aspergillus fumigatus*)
4. Parasitic (*Trypanosoma cruzi* in Chagas disease, *Toxoplasma gondii*)
5. Fungi: *Candida*, *Aspergillus*, *Histoplasma*
Toxins and drugs
Cocaine, interleukin, as well cases with giant cell myocarditis and endocardial fibroelastosis
Other diseases
These include lupus, connective tissue disorders, and rare inflammatory conditions, such as Wegener's granulomatosis

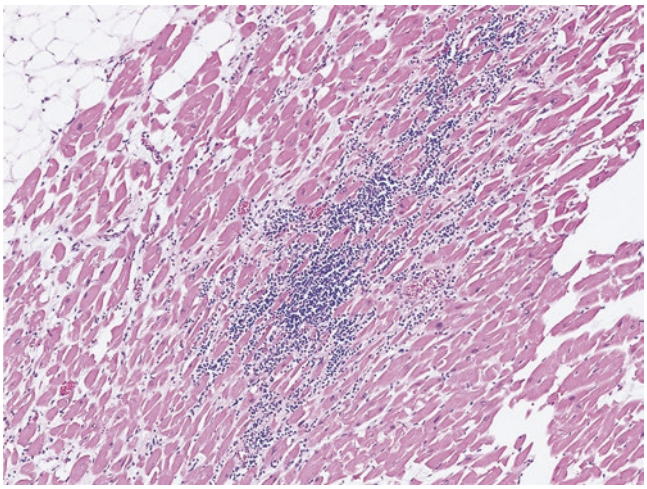

Fig. 5.8 Prominent lymphocytic infiltrate with definite myocyte injury, classic histologic findings in lymphocytic myocarditis (H&E; 10×)

unknown percentage die suddenly. The gross appearance of the heart is often unremarkable, even in the presence of diffuse histologic changes. It may be diffusely dilated in acute myocarditis. The natural history of myocarditis is frequently characterized by the evolution to a dilated cardiomyopathy.

Clinical features vary considerably from being asymptomatic to unexplained congestive heart failure. In patients with myocardial involvement by an infectious disease, the only manifestation is isolated ST segment changes. Other patients may have a period of tachycardia and easy fatigability, which gradually resolves. With more severe cardiac involvement, congestive cardiac failure develops rapidly and presents a major problem in management. LV dilatation and/or segmental wall motion abnormalities are observed on an echocardiogram. Another serious clinical issue relates to the conduction system. A variety of arrhythmias and conduction abnormalities develop which can be associated with syncope and, occasionally, sudden death. Usually, the electrocardiographic changes are temporary and resolve with time. LV dilatation and/or segmental wall motion abnormalities are observed on an echocardiogram.

Life-threatening arrhythmias may occur in both the acute and healed stages of the disease. The wide spectrum of clinical forms ranging from subclinical to severe depends on various factors, such as the infectious agents, genetics, age, and gender of the patient and underlying immunocompetence.

Different infectious agents and a variety of toxins and drugs have been implicated as causes of myocarditis [20] (Table 5.1). Toxins such as anthracyclines and cocaine can diffusely damage myocardium and result in the histologic features of myocarditis. Viral myocarditis can trigger an autoimmune reaction that causes damage to the myocardium and skeletal muscles.

Early and definitive diagnosis of myocarditis still depends on detection of inflammatory infiltrates in endomyocardial biopsy specimens (Fig. 5.8). Immunohistochemistry has not been useful in identifying cell populations or the causative agent.

Stress (Takotsubo) Cardiomyopathy

Stress or "takotsubo" cardiomyopathy has been described as a stress-induced cardiomyopathy or as an apical ballooning syndrome. It is an acquired condition that disproportionately affects women [21]. It occurs abruptly after a profound psychological stress, an acute medical illness, or major neurologic event and results in myocardial injury. Patients usually present with chest pain and electrocardiographic abnormalities of ST segment elevation as with an acute myocardial infarction. About a quarter of patients have mild to moderate congestive cardiac failure on presentation. Sudden death is uncommon but may occur. Moderate troponin elevation is found. Echocardiographic and other left ventricular imaging techniques show preserved basilar function but akinesis or hypokinesis of the cardiac apex.

The name takotsubo refers to the characteristic image of the apex, which resembles a Japanese fishing pot designed to capture octopus. The apex has a narrow neck and a fat, round body. Wall motion abnormality and significant reduction of global LV function are evident (Fig. 5.9).

Many patients have an excellent prognosis with full recovery of LV function, but the long-term consequences are

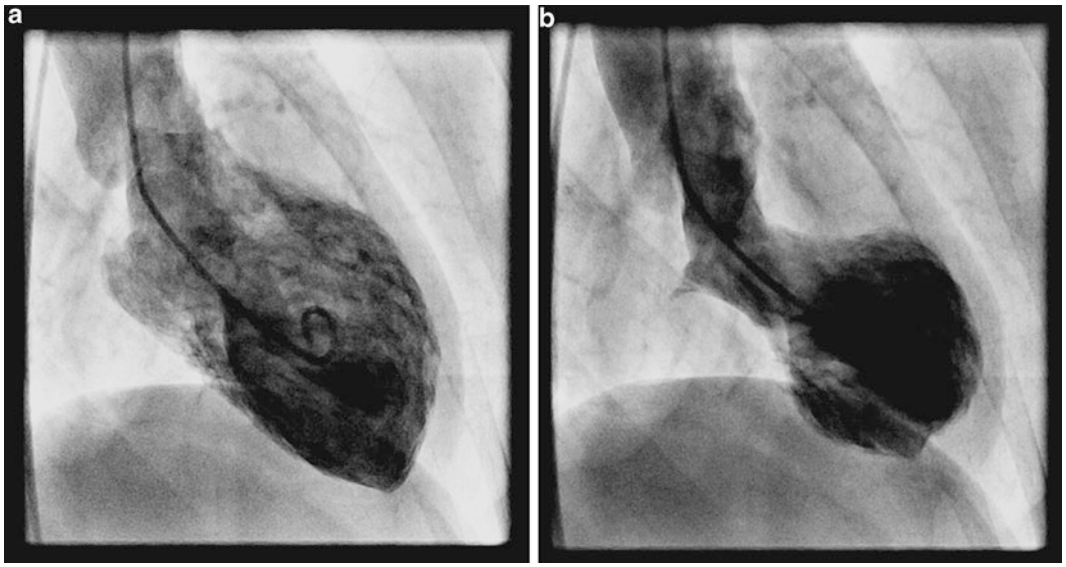

Fig. 5.9 Stress cardiomyopathy. Left ventriculogram. RAO view in 30° projection. (**a**) Diastole. (**b**) Systole. Large anterior wall motion abnormality

unknown. In those with congestive cardiac failure, there may be significant myocardial fibrosis. Mechanisms for the injury to the myocardium include effects of excess catecholamines, coronary spasm, and microvascular dysfunction induced by the extreme distress. The most widely accepted mechanism is excess plasma catecholamines, increased epinephrine release from the adrenal medulla, and increased sympathetic tone. Multiple focal areas of myocardial ischemia are often found scattered throughout the myocardium. Evidence of cell injury and death may be present.

Peripartum (Postpartum) Cardiomyopathy

Peripartum cardiomyopathy occurs late in pregnancy or in the first 5 months following delivery. The woman develops symptoms of cardiac failure, and echocardiographic findings show increased LV size and decreased systolic function.

The pathophysiology is unclear. One consideration is a disturbed oxidative stress, which cleaves prolactin into a potent antiangiogenic, proapoptotic, and proinflammatory substance [22]. This theory could lead to discovery of disease-specific biomarkers and novel targets for therapy.

The development of peripartum cardiomyopathy appears to begin with an unknown trigger that initiates an inflammatory process. This process leads to myocardial injury and development of cardiomyopathy. This form of cardiomyopathy occurs most frequently in obese, multiparous women 30 years old or older and in women with preeclampsia. About half of the women recover within 6 months; others may have progressive clinical deterioration leading to heart failure or death or require transplantation.

Amyloid Cardiomyopathy

Amyloid cardiomyopathy is a primary cardiomyopathy as part of a systemic disease or rarely with isolated cardiac involvement. It is a restrictive disease and affects diastolic function. It may be present only in the heart or as one of a number of organs affected by amyloid. It exists as several forms: primary cryptogenic, with multiple myeloma, with non-Hodgkin lymphoma, as a reaction to a chronic disease, or in a senile form. Identifying an underlying disease is useful in directing management. Amyloid is one of the most common causes of cardiomyopathy found on cardiac biopsy.

Amyloidosis results from abnormal protein metabolism so that abnormal amyloid is deposited within the interstitium and blood vessel walls (Fig. 5.10). The principal cardiac change is an increase in wall thickness, be it ventricular septum, free walls, or papillary muscles. As in restrictive physiology, atrial enlargement is present. Deposits may be found on the endocardial surface or in the conducting system. The cardiac involvement produces angina, heart failure, and arrhythmias.

There may be evidence of other organ involvement, such as enlarged lymph nodes, tongue, and liver.

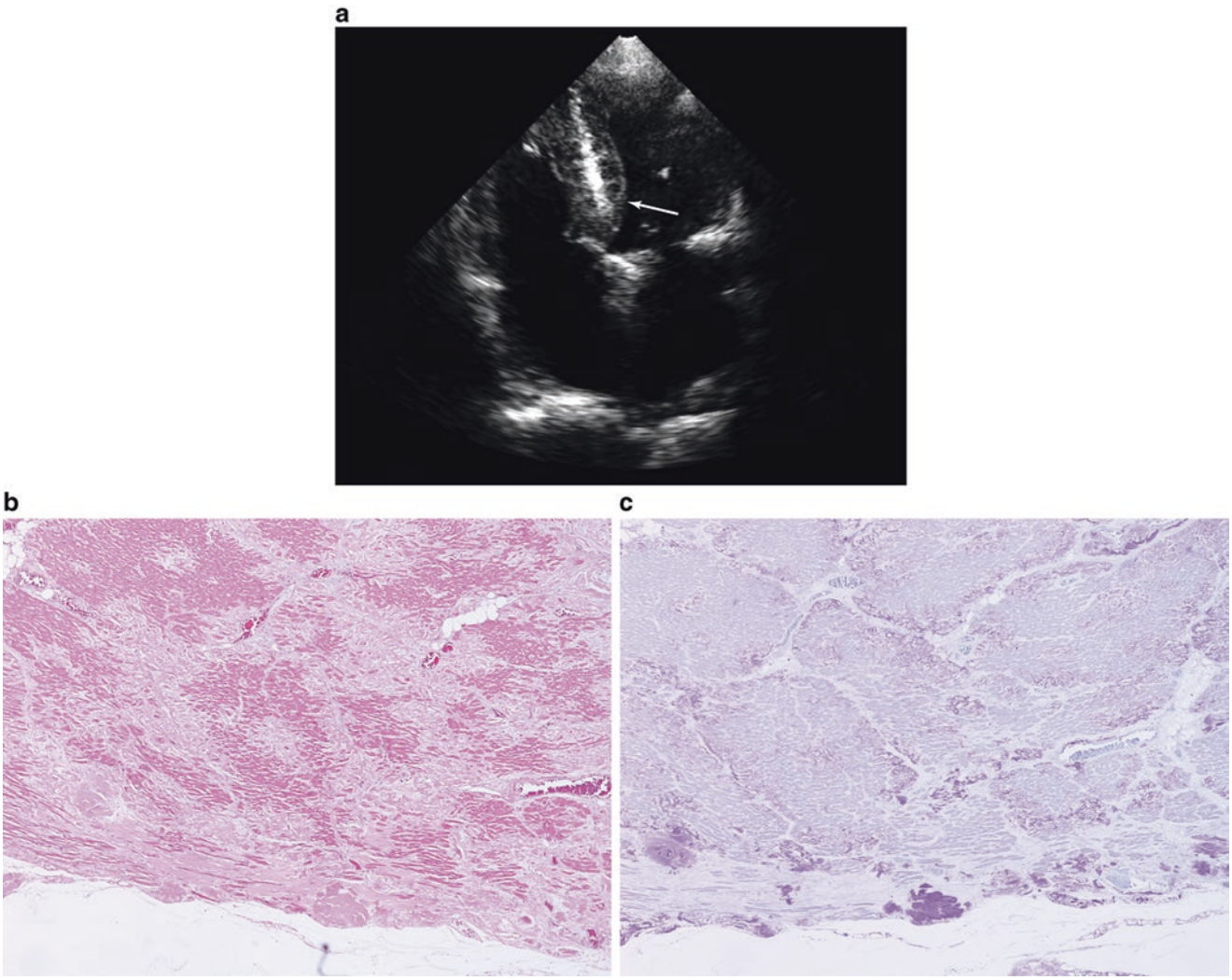

Fig. 5.10 Cardiac amyloidosis. (**a**) Echocardiogram. Apical four-chamber view. Thickening of the interventricular septum (arrow) with "granular" appearance. (**b**) Pale-staining eosinophilic material within the interstitium is amyloid (H&E; 1.25×). (**c**) Crystal violet stain highlights the amyloid material, which stains dark purple (1.25×)

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