Cardiomyopathies

Clare R. Bunning and S. Kim Suvarna

1 Introduction

Cardiomyopathies are disorders of the myocardium resulting in structural and functional abnormality, unexplained by coronary artery narrowing or abnormal ventricular loading. They have a variable prevalence and may be misdiagnosed under other cardiac conditions. They most commonly demonstrate an autosomal dominant pattern of inheritance, although other patterns of inheritance such as autosomal recessive, X linked recessive and mitochondrial patterns are seen. Acquired forms of cardiomyopathy are also seen. The most recently proposed classification system is the 2013 WHF-MOGE(S) system which proposes a descriptive genotype phenotype classification system. The parameters are: morphofunctional phenotype (M), organ(s) involvement (O), genetic inheritance pattern (G), aetiological annotation (E) including genetic defect or underlying disease/substrate, and the functional status (S) of the disease [1]. The aim of this system is to address the main attributes of cardiomyopathy in lieu of a future genetic classification system.

This chapter will focus primarily on the main morphofunctional phenotypes of cardiomyopathy. These are dilated cardiomyopathy (DCM), isolated left ventricular non compaction cardiomyopathy (LVNC), hypertrophic cardiomyopathy (HCM), arrhythmogenic right ventricular cardiomyopathy (ARVC) and restrictive cardiomyopathy (RCM). It will address how the pathologist can make an accurate diagnosis by performing a detailed macroscopic and microscopic examination of the heart and appreciate the genetic factors associated with these disorders that apply to surviving family members.

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2 Dilated Cardiomyopathy (DCM)

Dilated cardiomyopathy is the most common pathology creating congestive heart failure in the adult population worldwide. It is best regarded as a pattern of disease which can have a multitude of genetic, acquired or idiopathic aetiologies. It manifests as ventricular dilatation, with contractile dysfunction of the left, or both ventricles (Fig. 1). Clinically, it is associated with progressive congestive heart failure, being diagnosed in life. Genetic causes of DCM involve defects in genes encoding myocyte sarcomere, cytoskeleton, nuclear membrane or mitochondrial proteins [2].

Titin (TTN) is the largest human protein and is required for sarcomere assembly, function and stability. At a genetic level mutations in TTN predominate with truncating mutations in TTN accounting for up to 25% of primary DCM cases [3]. These truncating mutations in TTN are also implicated in peripartum-related cardiomyopathy [4] and may be associated with other acquired forms of DCM. Truncating mutations are present in 1.5% of the population [5]. Some sarcomere encoding genes such as MYH7 and TNNT2 can cause DCM, although these genes may also be mutated in HCM. These are less common causes than TTN mutations and alter different residues to the HCM mutations [5].

DCM may be associated with conduction defects and arrhythmias, particularly with mutations in the LMNA gene. This encodes the nuclear membrane protein lamin A/C, being involved in approximately 6–8% of DCM cases [6]. Fatal cardiac arrhythmia occurs in approximately half of LMNA cardiomyopathy genotypes and can occur before DCM symptoms [7], meaning it will be an autopsy diagnosis. Mutations in the ABCC9 gene encoding a cardiac potassium channel subunit have likewise been associated with DCM and atrial fibrillation [8].

Mutations in cytoskeletal proteins such as cardiac actin, desmin, beta-sarcoglycan, delta-sarcoglycan, dystrophin and vinculin affect force transmission during cell contraction. Desmin associated mutations are implicated in less than 1% of DCM cases [9], but also affect force transmission. They

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Fig. 1 Dilated cardiomyopathy in a case of prior myocarditis. There is generalised ventricular dilatation (bar marker 3 cm). This pattern of chamber enlargement is the standard format seen in many toxic, inflammatory and degenerative disorders as an end point

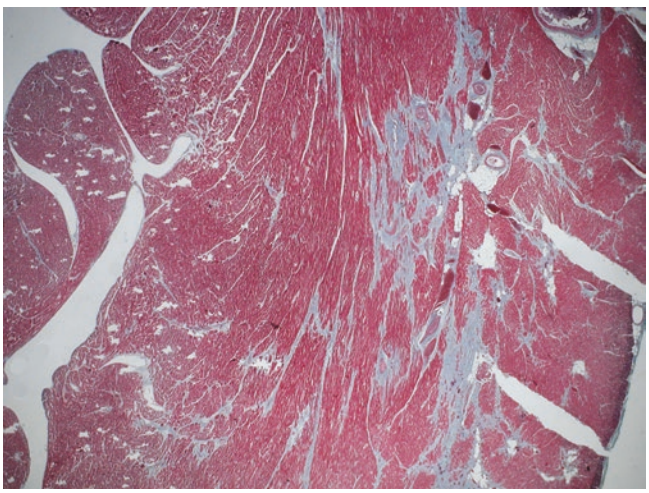


Fig. 2 Left ventricle tissues in a case of Duchenne-type muscular dystrophy. The trichrome highlights the scarred/fibrous element (green) as compared with the viable muscular tissue (red). Clearly electrical depolarisation and cardiac contractility will be degraded by this amount of fibrous tissue replacement

can also cause an accumulation of misfolded proteins resulting in cardiac cell toxicity, especially if mutations of the alpha-beta-crystallin chaperone protein are present [10]. Dystrophin mutations are X linked recessive and associated with dystrophinopathies (Figs. 2 and 3). Similarly mitochondrial TAZ gene mutation related DCM (Barth Syndrome) also shows X linked recessive inheritance [11]. Sarcoglycan mutations exhibit an autosomal recessive or dominant pattern of inheritance and are associated with muscular dystrophy.

One of the more recent developments, as a result of genetic linkage and gene mapping studies, is the identification of heterozygous missense mutation of a spliceosome protein (pre-mRNA splicing is catalysed by a spliceosome ribonucleoprotein complex composed of five SnRNPs and proteins), the ribonucleic acid binding motif protein 20

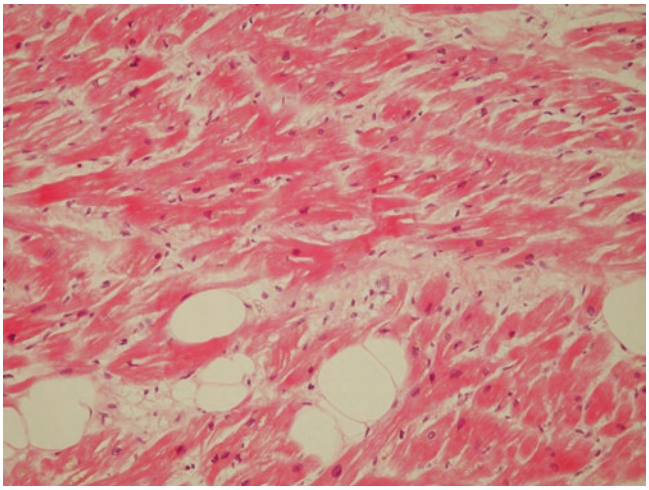


Fig. 3 A case of sudden death in myotonic dystrophy. The macroscopy was minimally dilated, but there was histological diffuse fibrous and fatty tissue replacement seen across the ventricular tissues, more easily discerned on the left side (haematoxylin and eosin stain)

(RBM20) in DCM [12]. This has been found to regulate pre-mRNA splicing of multiple genes, some of which affect TTN [13, 14].

Acquired causes of DCM account for the majority (about two thirds) of congestive cardiac failure cases seen in life, having no overt gene linkage. In such cases, the DCM phenotype may reflect coronary artery disease, valvular disease, hypertension, post-viral myocarditis and in association with Lyme disease, HIV infection or Chagas disease. Likewise, the DCM phenotype can be seen in peripartum/postpartum states [15] and infiltrative diseases of the heart (e.g., sarcoidosis, amyloidosis and haemochromatosis). It can also occur as a consequence of toxins such as alcohol, cocaine and following chemotherapy (in particular, doxorubicin). Finally, it can also occur in the context of other disease processes such as end-stage renal failure, obstructive sleep apnoea, and autoimmune conditions such as systemic lupus erythematosus, celiac disease and various endocrine dysfunction.

Alcoholic cardiomyopathy is perhaps the most common cause of acquired DCM, often underappreciated by clinician and pathologist. The adverse effects of ethanol misuse on the cardiac muscle is believed to be the result of several mechanisms including apoptosis, oxidative stress and free radical generation, impaired mitochondrial function, accelerated protein catabolism and deranged fatty acid metabolism and transport [16].

The macroscopic and microscopic phenotypes of DCM are similar in the vast majority of cases, regardless of the underlying cause (Fig. 3). DCM is characterised by an increase in heart weight along with relative thinning of the left ventricular wall. There is enlargement of both ventricular cavities (Figs. 1 and 4). The normal trabecular pattern is partly flattened outwards/effaced and diffuse endocardial

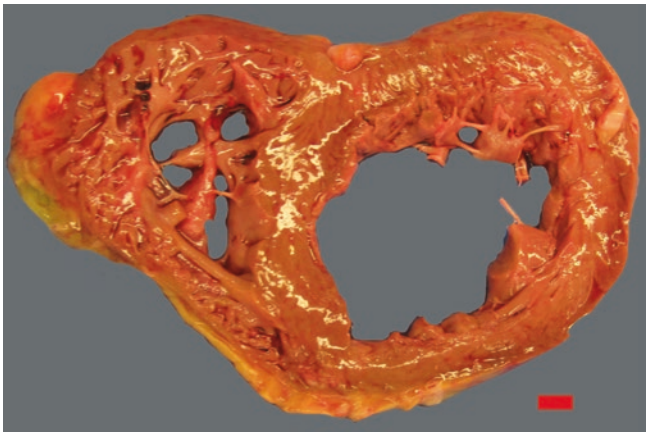


Fig. 4 A mid-ventricular transverse slice of heart tissue in an autopsy case of dilated cardiomyopathy needs to be positioned carefully in order to fully appreciate the degree of ventricular dilatation (bar marker 1 cm)

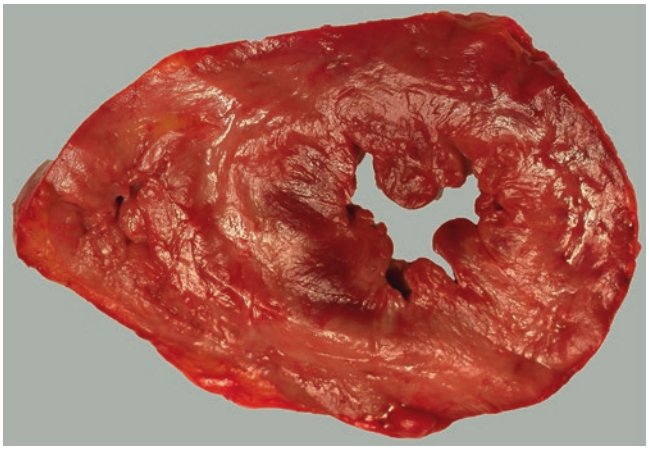


Fig. 6 Photograph of an autopsy transverse slice of the heart at mid-septal level from a patient with familial HCM. There is disproportionate left ventricular hypertrophy affecting the interventricular septum. The right ventricle is also involved by the hypertrophic process

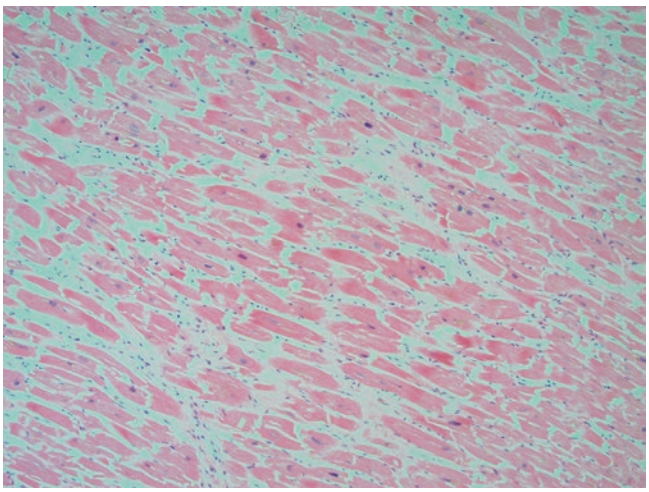


Fig. 5 There is often a diffuse fibrosis involving the myocardium in cases of dilated cardiomyopathy. Such changes should not be confused with fibrosis from ischaemic heart disease or fatty/fibrous tissue replacement in cases of arrhythmogenic cardiomyopathy. The cardiac myocytes may be of variable size, although they are generally enlarged in the long axis

thickening may be seen. Mural thrombus due to non-laminar blood flow is occasionally present, surrounding the ventricular trabeculations and/or within the atrial appendages.

DCM shows non-specific microscopic features and some, but not all, may be seen with each case. Classically, the myocytes are sometimes thinned, although many are of normal shape and size. There may be albeit nuclear hypertrophy and some pleomorphism. There may be loss of myofibrils resulting in myocyte pallor. There are varying degrees of either coarse, or diffuse, interstitial fibrosis within the ventricular myocardium depending on disease duration—chronic cases have greater levels of fibrosis (Figs. 3 and 5). A patchy and sparse lymphocytic infiltrate accompanies some cases, but is not specific and should not be automatically taken to suggest resolving myocarditis. Some histiocytes, associated with myocyte loss can be seen in some cases. As the macroscopic and microscopic features are similar irrespective of the aetiology, a detailed scrutiny of the history is required to determine the likely underlying cause. If acquired causes of DCM have been excluded, then it is important to consider the referral of first-degree relatives of potential familial DCM for cardiac screening.

3 Hypertrophic Cardiomyopathy (HCM)

Hypertrophic cardiomyopathy is a common cardiovascular disease with an estimated prevalence ranging from 1 in 200–500 of the population. It has an autosomal dominant pattern of inheritance in most cases [17]. In adults, it *classically* shows non-dilated left ventricular hypertrophy (LVH) (Figs. 6 and 7) with asymmetric left ventricular myocardial thickness of more than 15 mm on imaging studies. At autopsy, it is associated with myocardial and myofibrillar disarray (Fig. 8) and an increase in interstitial fibrosis unexplained by other systemic or cardiac causes of LVH. The adult phenotype is variable, some with concentric ventricular walls or only minimal thickening. It is an important cause of SCD in young adults, and in particular athletes, with sudden death most commonly occurring in asymptomatic adults under 35 years of age [18].

HCM is caused by mutations in the genes encoding sarcomeric proteins. The most frequently encountered mutations are in cardiac myosin binding protein C (MYBPC3), which result in mutated mRNAs and truncated proteins lacking the myosin and/or titin binding sites. These impair sarcomere

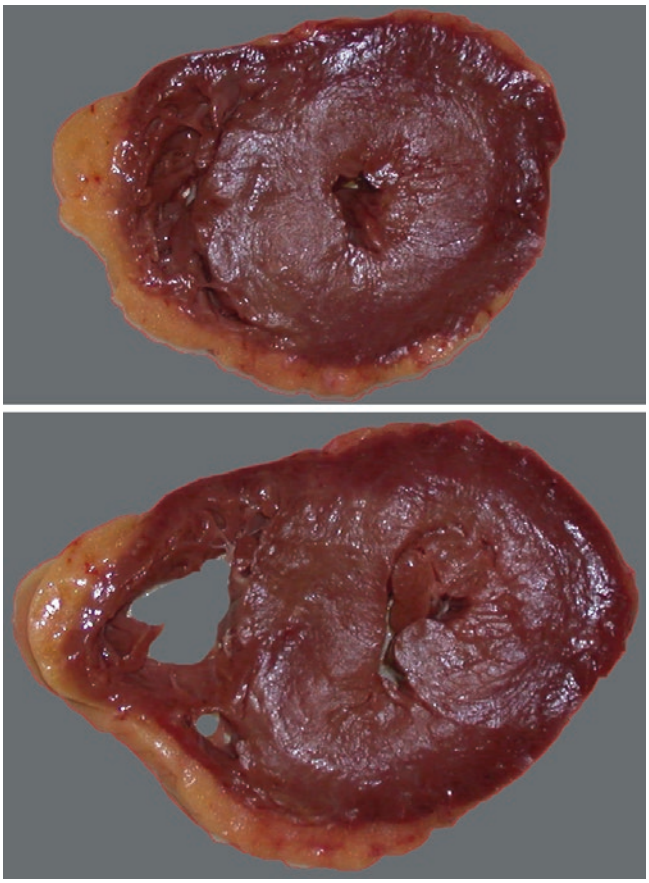


Fig. 7 Two transverse slices at mid- and low level across the ventricles in another case of hypertrophic cardiomyopathy showing the very pronounced left ventricle hypertrophy. The differential diagnosis in such cases would have to include hypertension and various infiltrative disorders

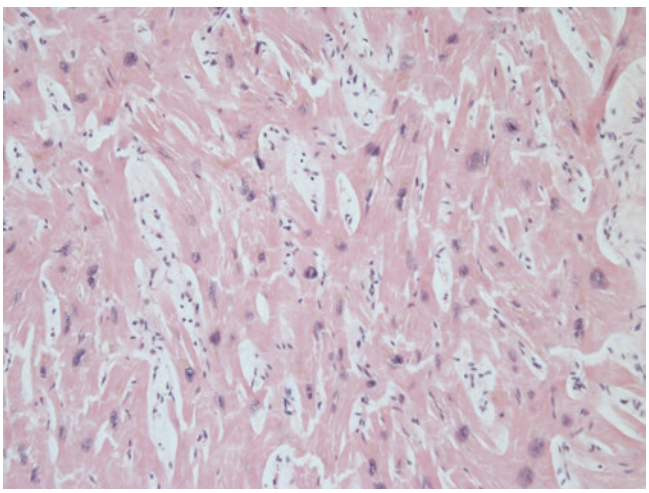


Fig. 8 Haematoxylin and eosin stained section showing florid myocyte disarray and fibrosis in familial HCM. Disarray is characterized by hypertrophic myocytes with enlarged and pleomorphic nuclei aligned at odd angles to one another

structure and function. HCM mutations are also seen with myosin heavy chain 7 (MYH7) which encodes the beta-myosin heavy chain. These mutations account for approximately 50% of cases [19] with MYPBC3 mutations accounting for up to 40% of cases [20]. Genes for thin filaments, sarcomere-associated proteins, and genes encoding plasma membrane proteins such as Junctophilin 2, mitochondrial proteins and Z-discs have also been identified as less common causes of HCM. Sporadic non-familial cases of HCM may also arise as a result of de-novo mutations.

A further cause of HCM has been identified resulting from mutations in the 'four and a half' LIM domain 1 (FHL1) with an X linked pattern of inheritance [21]. LIM domains mediate protein-protein interactions critical to cellular processes. In the heart FHL1 is associated with TTN with FHL1 upregulation seen in cardiac hypertrophy [22].

The clinical spectrum of HCM as shown by genotype-phenotype correlation analyses is highly variable reflecting gene penetrance. Patients with more than one mutation may have a more severe form of the disease presenting with symptoms or SCD at an earlier age. Genes may be affected by mutations at various sites. Furthermore, different mutations in the same gene may be associated with different disease severity and/or prognosis. The same genotype in one individual may be expressed as a different phenotype in another, indicating both genetic and environmental factors contribute to the ultimate phenotype expressed in an individual [5].

Due to this heterogeneity HCM mutations are considered to be pathogenic if there is familial co-segregation of the HCM phenotype previously reported as a cause of HCM. The mutation must be absent from unrelated and ethnic matched controls. Likewise, protein structure and function must be detrimentally altered with amino acid change in a highly conserved protein region [23].

Highly pathogenic mutations, with early manifestation of LVH and an increased risk of SCD, are found with R403Q, R453C, G716R and R719W mutations resulting in malignant defects in MYH7. R92W mutation in the cardiac troponin T has also been associated with an increased risk of SCD [24].

One should be aware that cardiac hypertrophy may occur as a consequence of valvular heart disease, essential hypertension, non-compaction cardiomyopathy, athletic training, haemochromatosis and infiltrative cardiomyopathies (discussed below). It is therefore unwise to reach a diagnosis of HCM simply on macroscopic assessment. One should also be aware of the effects of agonal contraction. In such cases the systolic contraction results, in apparent increased left ventricular wall thickness, this can potentially lead to misdiagnosis of HCM. Cardiac mass correlated with body weight is required to give a more accurate indicator of genuine LVH, instead of measurements of left ventricular wall thickness in

isolation (see chapter "The Normal Adult Heart and Methods of Investigation").

However as stated HCM does not always present with marked ventricular hypertrophy. Indeed, isolated papillary muscle hypertrophy is thought to be another phenotypic variant. Cardiac troponin T mutations associated with SCD are also associated with minimal hypertrophy [18, 25].

HCM is characterised by several different morphological patterns which may be asymmetrical or symmetrical. The most common phenotype is asymmetrical septal hypertrophy with or without subaortic obstruction. Systolic anterior motion (SAM) of the mitral valve is seen on echocardiogram in approximately 30–60% of patients, with HCM thought to be due to septal hypertrophy causing outflow tract obstruction at high flow velocities. Mitral valvular apparatus abnormalities are also common in patients with HCM, which may also be a cause of SAM [26]. Endocardial fibrosis over the septum leads to a sub-aortic mitral impact lesion due to contact of the anterior cusp of the mitral valve with the hypertrophied basal septum (Fig. 9). SAM and this lesion may occur in HCM as well as in hypertrophied hearts due to hypertension, in hyperdynamic states or hypovolaemia [26]. Thus, progression of any HCM diagnosis requires wide-ranging consideration of the macroscopic phenotype in conjunction with histology and other data.

The symmetrical form of HCM is characterised by concentric thickening of the left ventricle. Macroscopically it is indistinguishable from hypertrophy due to essential hypertension, aortic stenosis or indeed athletic training. Adequate histological sampling is therefore essential. In HCM, often the right ventricle may also be involved by the hypertrophic process [27]. Various morphological variants of HCM are seen. These comprise apical HCM, asymmetric posterior left ventricular wall hypertrophy, mid-ventricular obstructive HCM with hypertrophy confined to the middle portion of the left ventricle and involvement of the papillary muscles [26]. A further sub-group of HCM patients with left ventricular apical aneurysms has also been observed [26]. Some HCM sub-types are of relevance since patients with mid-ventricular HCM and asymmetric left ventricular wall hypertrophy are generally severely symptomatic. In end-stage HCM ventricular dilatation occurs due to myocyte loss with extensive replacement-type fibrosis. This may simulate DCM.

The classic microscopic features of HCM are myocyte hypertrophy and disarray (Fig. 8), although many variations are recognised (Figs. 10, 11, and 12). Myocyte disarray occurs due to the loss of the normal parallel arrangement of

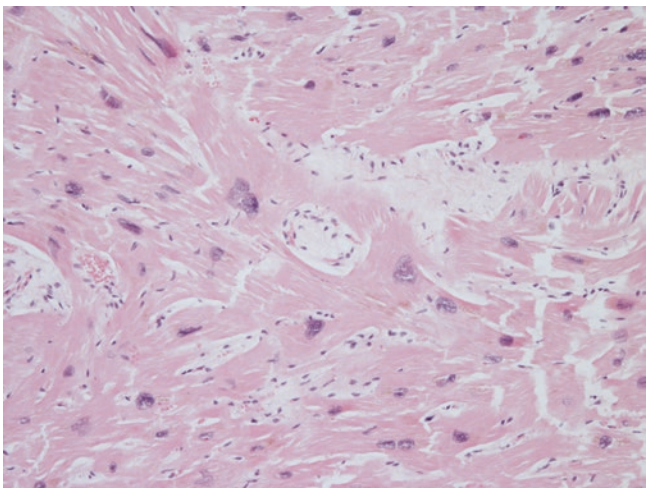


Fig. 10 A case of HCM with marked enlargement of the haphazard myocytes with enlarged nuclei

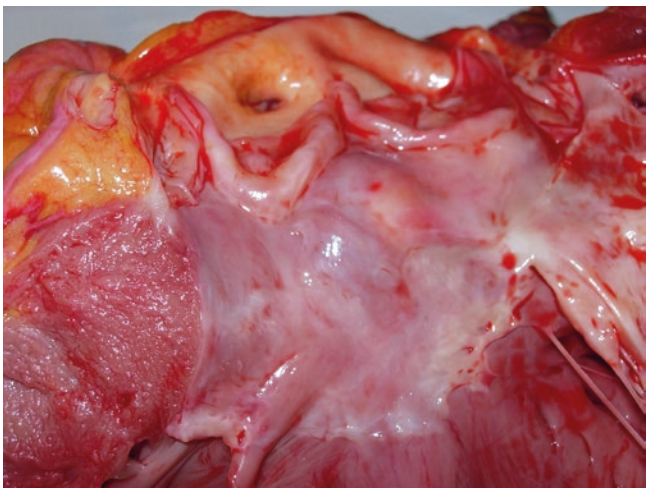


Fig. 9 Photograph of a sub-aortic mitral impact lesion, which resembles a mirror-image of the anterior cusp of the mitral valve in a patient with familial HCM

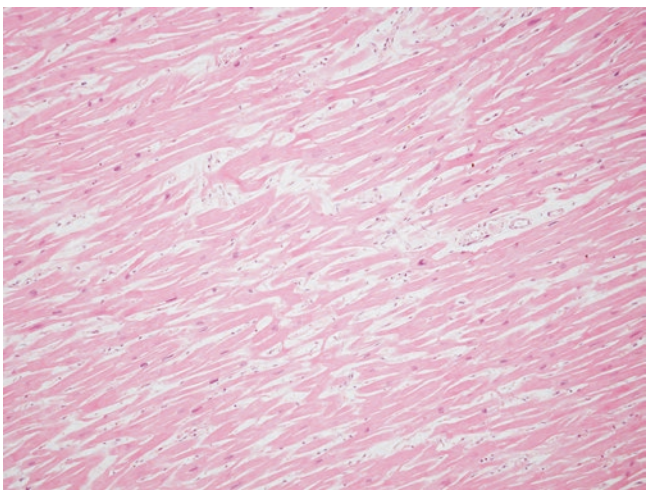


Fig. 11 Some cases of HCM show relatively mild disarray, even if the macroscopic features are characteristic

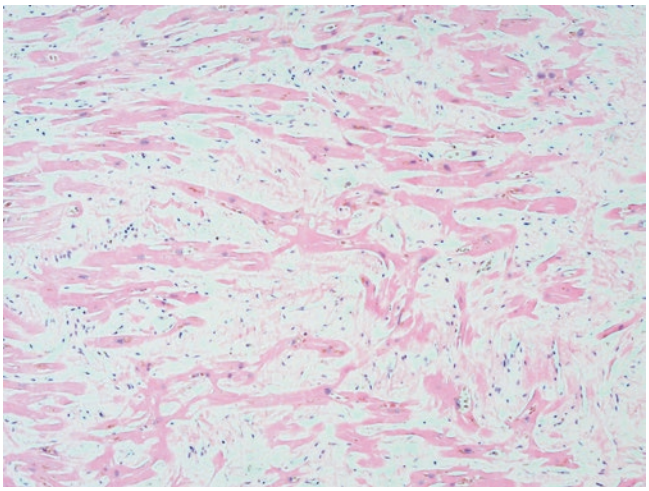


Fig. 12 Late stage HCM often has pronounced interstitial fibrosis. This may be associated with a dilated or restrictive cardiomyopathy

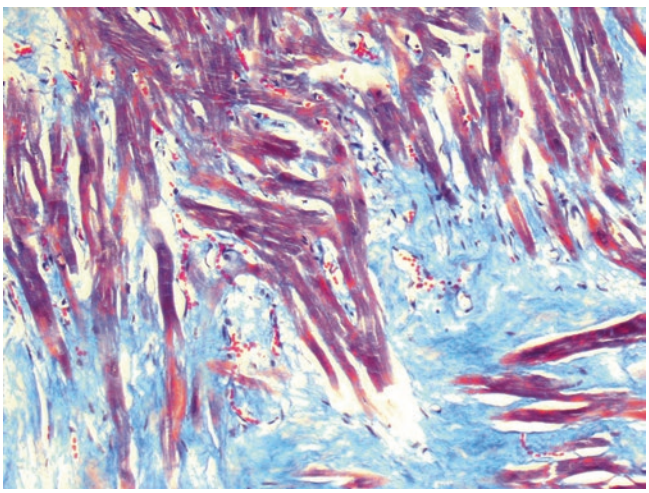


Fig. 13 Masson's trichrome stain confirming the marked increase in interstitial collagen, which is an integral part of the disease process and a hallmark of familial HCM (*Courtesy of Dr. S. Hughes*)

myocytes within the myocardium. The myocytes may assume a cartwheel or herringbone pattern due to abnormal cell-to-cell contacts. There is often disruption of the myofibrillary architecture, with criss-crossing of the myofibrils, which can be best demonstrated by phosphotungstic acid-haematoxylin (PTAH) staining and/or electron microscopy. Coarse or fine interstitial fibrosis, or a combination of these patterns, due to increased amounts of collagen, may be seen depending on the chronicity of the disease. Special stains such as Masson's trichrome (or other stain) can be used to stain collagen and permit assessment of fibrosis (Fig. 13). Fibrosis is a hallmark of HCM and is associated with an increased risk of arrhythmias and progression to heart failure.

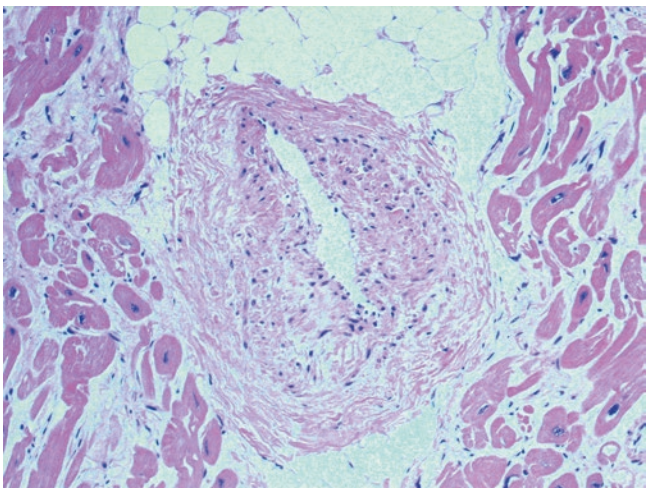


Fig. 14 The small intramural branches of coronary arteries exhibit luminal narrowing and medial hypertrophy (dysplasia) in HCM, contributing to myocardial ischaemia and myocyte loss leading to increased fibrosis (*Courtesy of Dr. S. Hughes*)

Provided an entire circumferential left ventricular slice of myocardium at mid-septal level is sampled in HCM cases (large blocks or standard multiple blocks), disarray will usually be evident in more than 20% of the myocardium in at least two blocks. Overdiagnosis of fibre disarray is possible in normal hearts, where the left and right ventricles interdigitate anteriorly and posteriorly (see chapter "The Normal Adult Heart and Methods of Investigation"). The myocytes are not usually parallel at these points in normal hearts, providing a risk of a misdiagnosis of HCM. Mild degrees of fibre irregularity can also be seen in normal hearts around trabeculations, adjacent to blood vessels, near areas of fibrosis and where large muscle bundles converge.

Abnormal myocardial vasculature is seen with HCM. The small intramural branches of coronary arteries often show 'dysplasia', which is characterized by luminal narrowing and medial hypertrophy (Fig. 14). These vascular changes likely contribute to ischaemia and myocyte loss with replacement fibrosis, although some of the changes may reflect abnormal myocardial contraction around the vessels. The vascular changes may contribute to electrical instability, resulting in arrhythmia and/or SCD. The end-point effect may also explain the DCM phenotype of HCM culminating in congestive heart failure.

In summary HCM is a common genetic disorder and should always be considered in cases of sudden death, particularly in young adults and those with a family history of cardiac disease. Accurate diagnosis is essential to identify those families who will need cardiac screening, mutation analysis, and genetic counseling. However, if recognised and treated, HCM may have a good prognosis, with patients being asymptomatic with a near normal life expectancy.

4 Arrhythmogenic Right Ventricular Cardiomyopathy/Arrhythmogenic Cardiomyopathy

Arrhythmogenic cardiomyopathy (AC) is a form of cardiomyopathy which characteristically affects the right ventricle (Arrhythmogenic right ventricle cardiomyopathy, ARVC), although left ventricle formats (Arrhythmogenic left ventricle cardiomyopathy, ALVC) are also known. AC has an estimated prevalence of 1 in 1000 to 1 in 10,000 and a predominantly autosomal dominant pattern of inheritance [28]. It is an important cause of SCD in young people and athletes.

ARVC is characterised by progressive myocardial loss and fibro-adipose replacement primarily affecting the right ventricle (Figs. 15, 16, and 17), although some co-involvement of the left ventricle is also often present. ALVC (where the disease is mainly left ventricular biased) has also been described with similar fatty tissue replacement and fibrous tissue replacement of the myocardium [29]. In AC, the fibrous and fatty changes tend to be centripetal, spreading from the epicardium inwards (Figs. 18 and 19). They may be seen macroscopically and histologically. There are at least 12 subtypes of ARVC (Fig. 20) with different genetic mutations in desmosomal and non-desmosomal proteins attributed to the different subtypes [30].

In life, the diagnosis of ARVC is based on the revised 2010 task force criteria that includes ventricular functional and structural changes, ECG abnormalities, arrhythmias, familial and genetic factors [31]. There is, however, currently no single diagnostic test for AC.

The pathogenesis of AC is associated predominantly with mutations in desmosomal proteins, structures which provide cell:cell adhesion and mediators of intra- and intercellular signalling pathways (Fig. 20). These are localised to the intercalated disc in cardiac myocytes (see chapter "The Normal Adult Heart and Methods of Investigation"). The most common mutation observed affects plakophilin 2 (ARVC Type 9), a linker between desmoplakin and the cadherin tails [32, 33]. The incidence of this mutation within individuals with ARVC is between 10% and 45%. These individuals present earlier than other subtypes and arrhythmia free survival is low [32, 34].

Mutations in desmoplakin, desmoglein 2, desmocollin 2 and plakoglobin are desmosomal mutations seen in other ARVC subtypes, with desmoplakin being the second most common mutation found [32]. Desmoplakin (ARVC Type 8) mutations are associated with earlier left ventricular involvement. Recessive mutations cause Carvajal syndrome. Desmoglein 2

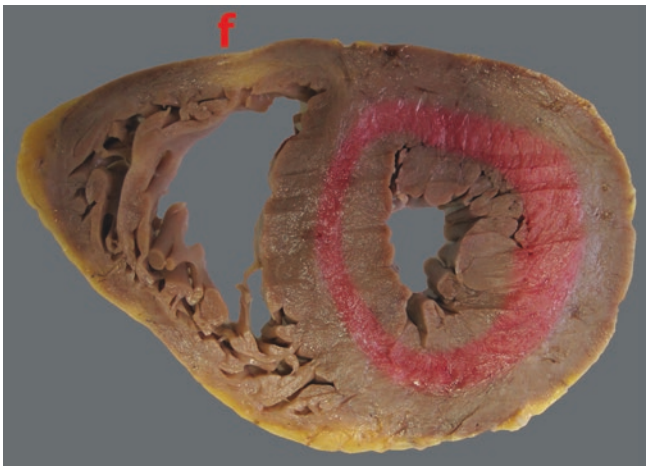


Fig. 16 Arrhythmogenic cardiomyopathy can show very focal fatty tissue replacement and one needs to be alert to patchy replacement of ventricular tissue both in the right, as well as the left, ventricle parenchyma. In this case, focal right ventricle fatty tissue replacement is indicated by the "f"

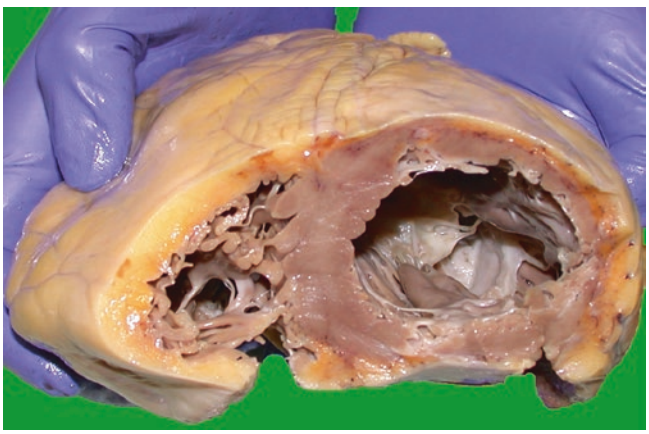


Fig. 15 A case of arrhythmogenic cardiomyopathy, biased to the right side (ARVC). This shows florid fatty change on the right ventricle cut surface. Some minor changes may be present on the left side, but this would need histology to confirm the disorder

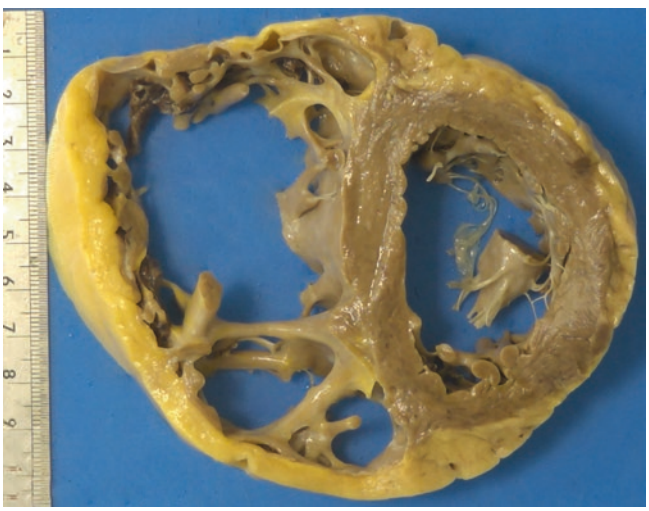


Fig. 17 The characteristic ARVC dilated right ventricle with a pronounced fatty wall is seen (*Courtesy of Dr. C. Howitt*)

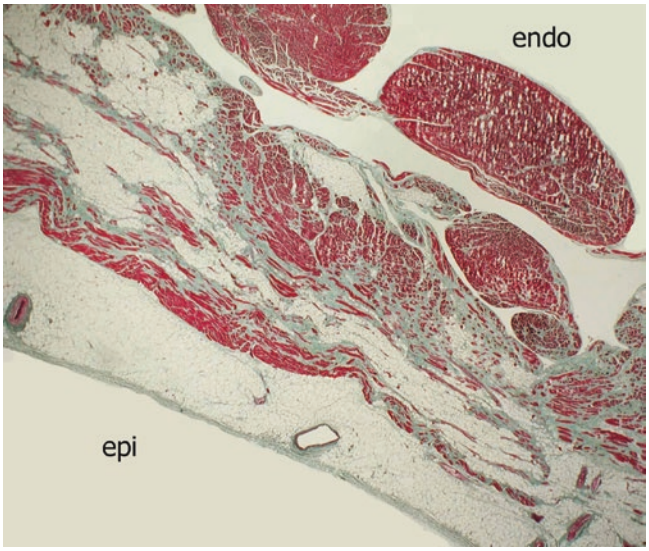


Fig. 18 Masson trichrome histology demonstrating the right ventricle fibrous and fatty tissue replacement that has swept inwards from the epicardial (epi) aspect to the endocardial (endo) aspect of the ventricle chamber

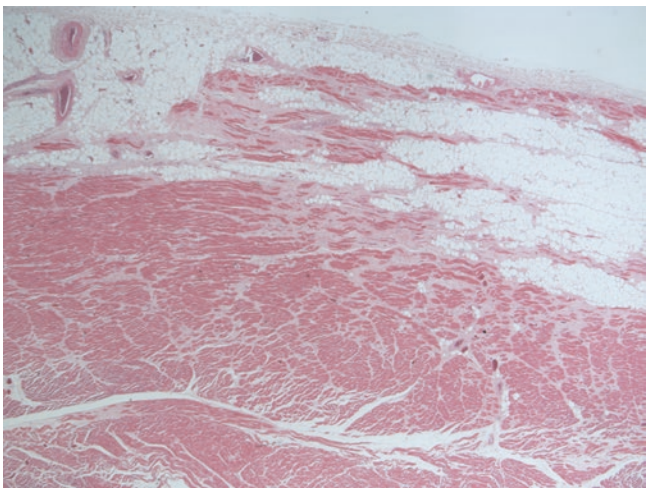


Fig. 19 This photomicrograph shows myocardial substitution and replacement by fibro-adipose tissue involving the outer third of the posterior wall of the left ventricle in a patient with AC with predominant left ventricular involvement. The fibroadipose replacement is advancing from the epicardium (top of image) towards the endocardium

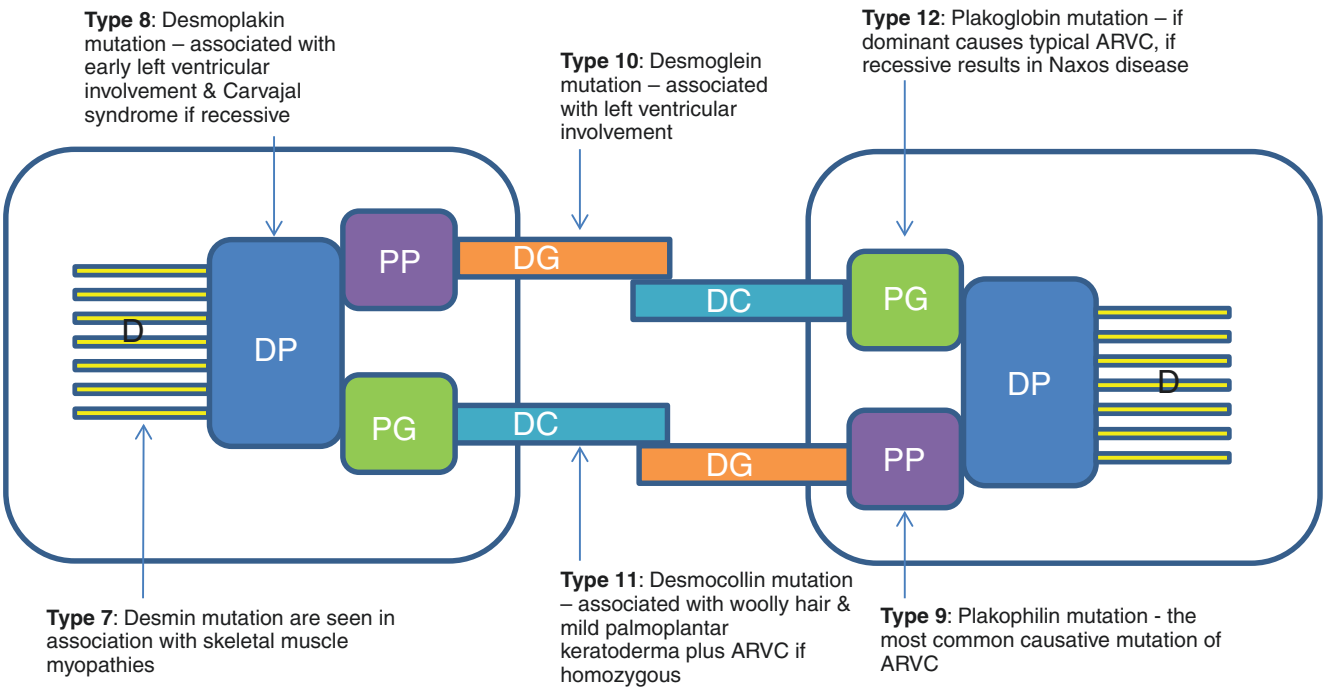
(ARVC Type 10) mutations are mainly associated with left ventricular involvement. Desmocollin 2 (ARVC Type 11) mutations are associated with woolly hair and mild palmoplantar keratoderma, in addition to ARVC if homozygous. Plakoglobin (ARVC Type 12) mutations, if recessive, cause Naxos disease and, if dominant, more typical ARVC [34].

Mutations in non-desmosomal genes are also attributed to rarer subtypes of ARVC. These mutations include genes which encode proteins such as phospholamban. This regulates calcium movement within cardiac myocytes and transmembrane protein 43 (ARVC Type 5, a highly lethal subtype) [35]. Transmembrane protein 43 may have a role in maintaining nuclear envelope structure and also has a response element for an adipogenic transcription factor. Mutations in the cardiac ryanodine receptor gene (ARVC Type 2), which encodes a sarcoplasmic reticulum calcium release channel protein, are associated with catecholaminergic polymorphic ventricular tachycardias without overt cardiac structural abnormality. However, areas of fibro-fatty replacement of the sub-epicardial layer of the right ventricle may be seen on histology in this subtype [36]. Transforming growth factor beta-3 mutations (ARVC Type 1) are believed to increase myocardial fibrosis and modulate the expression of desmosomal genes [37]. Desmin mutations (ARVC Type 7) are seen in association with skeletal muscle myopathies. Titin mutations (ARVC type 4) and lamin A/C mutations are also associated with an AC phenotype.

It is thought that the common pathway of pathology involves repeated mechanical stress causing myocyte detachment/damage and apoptosis. It has to be appreciated that mechanical integrity of the intercalated discs is also lost as a consequence of mutations. There may be accompanying inflammation and induction of adipogenic and fibrogenic genes in the stromal cells. Repair by fibrous and adipose tissue replacement occurs as a response to myocyte damage (Fig. 21). There is the loss of normal cell:cell depolarisation and interspaced fat and fibrous tissue resulting in a risk for re-entry ventricular arrhythmias.

A broad spectrum of structural and functional abnormalities has been described in AC depending upon the stage of the disease. In some cases, the features may be marked and blatant (Fig. 15) or difficult to appreciate even if you know the histology is characteristic (Fig. 22). The condition starts as a primary concealed phase, with little structural or functional change, although there is still a risk of SCD from arrhythmias—especially during/immediately after extreme exertion. The secondary overt arrhythmic phase with structural and functional cardiac changes and arrhythmias. The tertiary phase shows global right ventricular dysfunction and dilatation, with a quaternary phase showing left ventricular involvement often with bi-ventricular cardiac failure.

The changes of early ARVC are often localised, with a predilection for the apical, subtricuspid, and pulmonary outflow regions of the right ventricle: the so-called ‘triangle of dysplasia’ which manifests as segmental aneurysms or wall thinning [38–40]. As the disease progresses, right ventricular dilation and involvement of the left ventricle can occur (Fig. 16). Left ventricular wall involvement usually begins as subepicardial posterior wall fibrosis, which becomes diffuse



DG=Desmoglein, DC=Desmocollin, PP=Plakophilin, PG=Plakoglobin, DP=Desmoplakin, D=Desmin

ARVC Subtype	Mutation
Type 1	Transforming growth factor beta 3 mutation
Type 2	Cardiac ryanodine receptor gene mutation
Type3	Unknown
Type 4	Titin mutation
Type 5	Transmembrane protein 43
Type 6	Unknown

Fig. 20 A diagrammatic representation of the genes and proteins involved in arrhythmogenic cardiomyopathy

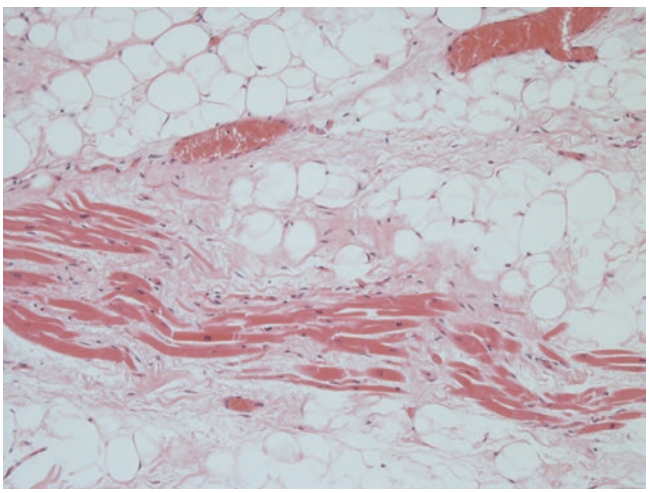


Fig. 21 High magnification histology of AC showing the fat and fibrous tissue replacement of ventricular tissues

Fig. 22 Multiple slices of the right ventricular wall are seen in a case of AC. The degree of fatty tissue replacement may be subtle and overlooked unless one takes appropriate histology samples

resulting in end-stage AC. One should be aware that this can simulate DCM in appearance [40–44].

Microscopically classical ARVC is characterized by fibrous and adipose tissue infiltration of the right ventricle starting in the outer epicardial layer and progressing towards the endocardium (Figs. 17, 18, and 19). As described the left ventricle can also be variably involved with fibrosis being the diagnostic hallmark [45, 46].

A variant characterised by subepicardial and mediomural fibrous and adipose tissue replacement confined to the left ventricle has been identified as a cause of SCD in the young [42, 43, 47, 48]. Despite extensive disease involvement of the left ventricle, SCD was the initial presenting symptom. A subepicardial distribution pattern of fibrous and adipose tissue replacement at autopsy should alert the pathologist to the possibility of ARVC with predominant or exclusive left ventricular involvement. Left ventricular subepicardial myocardial lesions are rare in other cardiac diseases [49], but frequent in ARVC.

Alternate conditions for the pathologist when considering a diagnosis of ARVC are Brugada syndrome, 'athletes' heart and the normal adipose tissue replacement of the right ventricle with advancing age (especially in women and/or obese individuals). Myocardial fibrosis is also a consequence of other cardiac pathology, such as hypertensive heart disease, myocardial ischaemia, toxins, some illicit drugs (amphetamines and cocaine) and post-viral myocarditis. Such non-AC fibrosis contrastingly favours the subendocardial zone, with sparing of the epicardial region of the heart with hypertensive heart disease and myocardial ischaemia. In such cases the fibrosis is patchy and randomly distributed throughout the entire ventricular wall of both ventricles. This pattern of fibrosis is also seen with post-viral myocarditis.

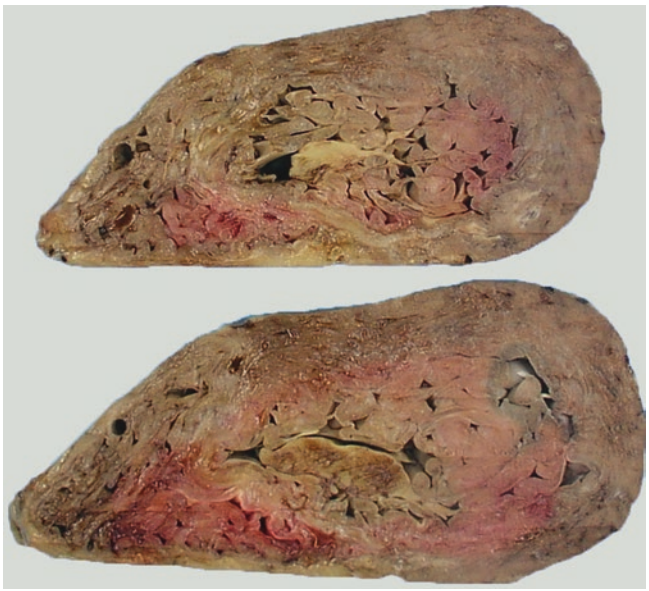


Fig. 23 Photograph of left ventricular myocardium from the autopsy of a patient with LVNC. The non-compacted endocardial layer is composed of a complex meshwork of elongated and thinned trabeculations with deep intertrabecular recesses imparting a sponge-like appearance to the left ventricular wall

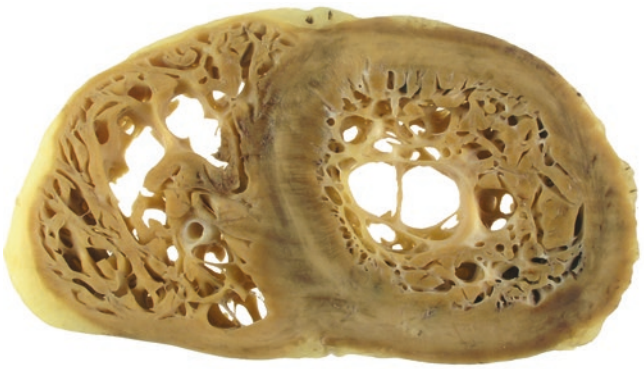


Fig. 24 Another case of LVNC showing the classic spongy left ventricle wall (*Courtesy of Dr. A. Warfield*)

5 Isolated Left Ventricular Non-compaction (LVNC)

Isolated left ventricular non-compaction (LVNC) is a rare congenital myocardial disorder with a poor prognosis that can present in either childhood or adulthood. It may present with systolic and diastolic dysfunction, arrhythmia or thromboembolic complications [50]. It occurs due to the persistence of the non-compacted endocardial layer, characteristic of the early fetal period before myocardial compaction is complete within the left ventricle [51]. Diagnosis is generally made via echocardiography or magnetic resonance imaging (MRI) (Figs. 23 and 24).

LVNC shows both an X linked and autosomal dominant pattern of inheritance. Mutations in several genes have been associated with isolated LVNC, with these reflecting alterations to the Z band alternatively spliced PDZ-motif protein (ZASP) (a protein involved with sarcomere stability), alpha-dystrobrevin (DTNA; a component of the dystrophin associated protein complex which localises to the sarcolemma), tafazzin (TAZ-G4.5; an enzyme involved in the metabolism of cardiolipin) and genes encoding alpha-cardiac actin, troponin T and beta-myosin with sarcomere protein mutations, being more common in adults [52]. Mutations in hyperpolarization-activated cyclic nucleotide channel 4 (HCN4) have also been linked with bradycardia and LVNC [53].

Isolated LVNC was detected in 9.2% of children with cardiomyopathy, being the third most common type [54]. In the paediatric population it can be present with other cardiac abnormalities, neuromuscular diseases and mitochondriopa-

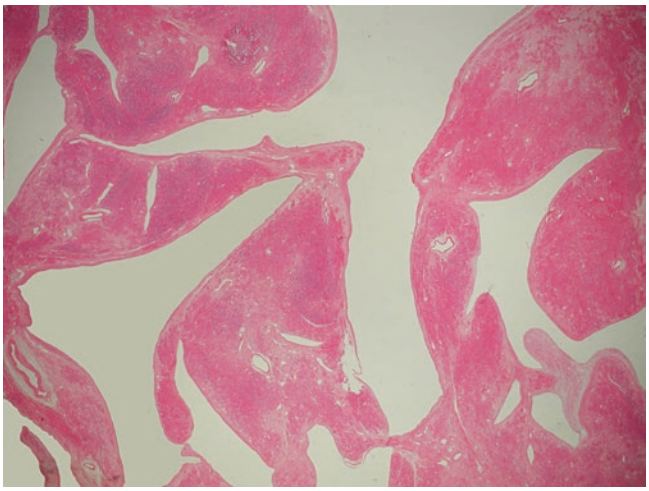


Fig. 25 Low power haematoxylin and eosin stained photograph of LVNC showing that the non-compacted layer is composed of 'finger-like' projections

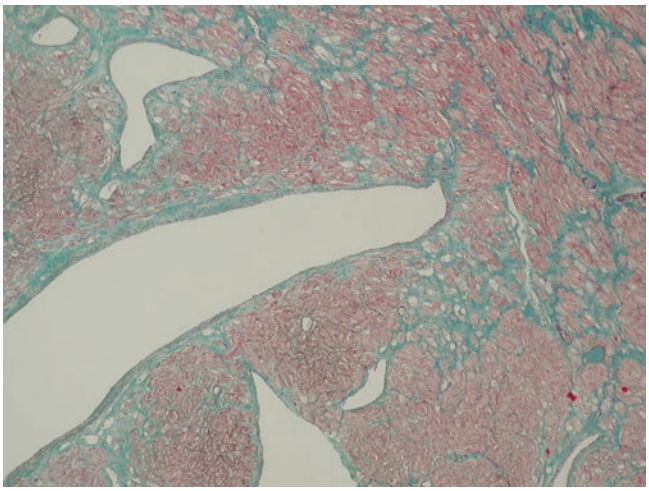


Fig. 26 A Masson's trichrome stain confirms the prominent endocardial and subendocardial fibrosis, which is a feature of this disease due to abnormal myocardial microperfusion

thy [55]. By contrast, its prevalence in the adult population is estimated between 0.01% and 0.26% [56, 57].

LVNC may be encountered as an incidental finding at autopsy, but is more commonly seen in the setting of heart failure. In adults, it can present as SCD without preceding cardiac or family history. Macroscopically, a sponge-like appearance to the wall of the left ventricle is seen (once called 'spongy left ventricular myocardium') (Figs. 23 and 24). This complex pattern of trabeculation is seen in association with deep intertrabecular recesses. It is often associated with overlying mural thrombus due to stasis. The diagnosis of LVNC should be confined to the assessment of trabeculations in the left ventricle, where the compaction during development is normally greatest. The right ventricle is less compacted and could simulate pathological non-compaction. Histologically, LVNC is characterized by prominent and thinned trabeculations, manifest as finger-like processes. Subendocardial fibrosis is usually evident, due to the impaired coronary microcirculation associated with this disease (Figs. 25 and 26).

6 Restrictive Cardiomyopathy (RCM)

Restrictive cardiomyopathy (RCM) encompasses a broad group of cardiomyopathy disorders, characterised by impaired filling of the ventricles due to stiffness and non-compliance (inelasticity) of the heart as a result of infiltrative processes or fibrosis (myocardial or endomyocardial). The contractile function and myocardial thickness may appear normal.

RCM has both primary and secondary disorders, with primary causes being less common. Examples include tropical endomyocardial fibrosis (TEMF), Loeffler's endomyocarditis and idiopathic RCM. The secondary causes of RCM include a multitude of infiltrative and non-infiltrative cardiac pathologies, often as a component of a multisystem disease process, with the best example being amyloid (see below).

TEMF is found in tropical regions, encompassing areas of Africa, Asia and South America and is rarely encountered in the industrial world. It affects children and adolescents resulting in heart failure and death. It is characterised by fibrous tissue deposition within the endomyocardium. It is believed that a multitude of factors conspire in a susceptible individual to result in TEMF, with these including dietary, environmental, infectious and genetic factors [58].

There is often an initial active phase with acute inflammation of the heart resulting in myocardial oedema, an eosinophilic infiltrate, subendocardial myofibre necrosis and vasculitis. Mural thrombi may develop in the ventricular apices with a risk of thromboembolic events [58]. RCM develops in the chronic phase with atrial dilatation and ventricular restriction, due to fibrosis which usually ceases just below the ventricular outflow tract. Microscopically endocardial thickening is seen with hyalinised collagen deposition. Lymphocytes may be present along the endocardial myocardial interface. Eosinophil infiltration is not seen in the chronic phase. Marked ascites is often the consequence of the progressive cardiac failure.

Loeffler's endomyocarditis is an infrequently encountered form of RCM (Fig. 27). This condition is found in conjunction with hypereosinophilic disease states, such as Churg-Strauss, eosinophilic leukaemia, parasitic infection, drug reactions and myeloproliferative disorders. Microscopically the initial stages of the disease show an acute inflammatory predominantly eosinophilic myocarditis, principally involving the endocardium and myocardium. Endocardial thrombus (Fig. 28), associated with underlying

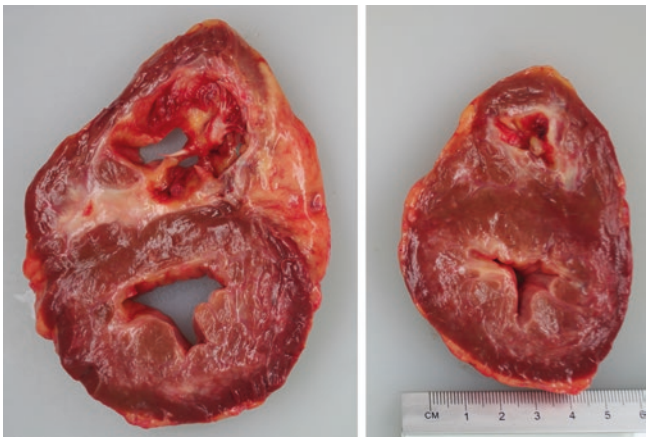


Fig. 27 Photograph of a transverse slice of the heart at mid-septal level from a patient with hypereosinophilic syndrome and Loeffler's endomyocarditis. A shaggy coat of thrombus is seen coating the right ventricle and there is fibrosis and white endocardial thickening of the left ventricle

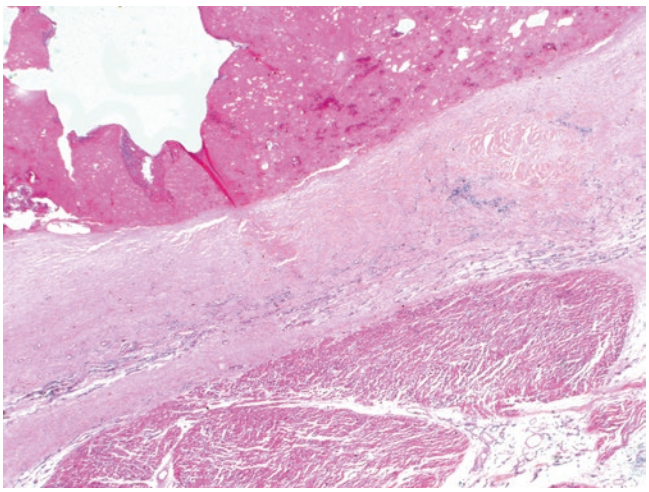


Fig. 28 Haematoxylin and eosin stained photomicrograph showing that in the acute phase the endocardial thickening is due to granulation tissue covered by more recently formed thrombus (top) imparting a layered appearance

granulation tissue, may also be seen. Extensive fibrosis of the endocardium is later seen, ultimately causing a restrictive syndrome.

Studies into the genetics of idiopathic RCM show that it is primarily a genetic disease. A disease causing mutation was found in more than 50% of cases of individuals involved in the studies [59, 60]. The mutations were found in sarcomeric and cytoskeletal proteins, ion channel genes and mitochondrial proteins including genes such as MYH7, DES, MYBPC3, TNNT and TTN [59, 60].

The more commonly encountered RCMs reflect secondary diseases mainly including infiltrative pathologies. The best example is amyloid. Other less common causes are storage disorders where intracellular deposits are characteristic. These include haemochromatosis, some glycogen storage disorders and lysosomal disorders which will be discussed later.

Rare non-infiltrative secondary causes of RCM include iatrogenic causes such as radiotherapy, chemotherapy, changes following heart transplantation and rarely carcinoid heart disease.

7 Amyloid Heart Disease

Cardiac amyloidosis occurs as part of a multisystem or localised disorder resulting from the deposition of extracellular insoluble fibrils of amyloid beta-pleated sheet protein in the interstitium of the myocardium and/or walls of blood vessels. There are several forms of amyloidosis that can involve the heart. These include senile cardiac amyloidosis, immunoglobulin in origin (AL amyloidosis), familial transthyretin related amyloidosis (TTR amyloidosis) or secondary to chronic infection as part of the acute phase serum amyloid A (amyloid AA).

Senile cardiac amyloidosis (also known as wild type ATTR amyloidosis) is a common incidental autopsy finding in the elderly (usually in those aged 75 or more years), being an under-diagnosed condition. The disorder is caused by the deposition of wild type transthyretin within the heart and is thought to affect 10–25% of patients with heart failure, albeit with preserved ejection fraction [61]. There is often substantial left ventricular wall thickening at diagnosis. Carpel tunnel syndrome is commonly associated, preceding the cardiac symptoms by 10–15 years [62]. Another form of age-related amyloidosis is isolated atrial amyloidosis resulting from overproduction of atrial natriuretic factor (see chapter "The Normal Adult Heart and Methods of Investigation"). Amyloid deposits are limited to the atria with left atrial predominance and there is an association with atrial fibrillation [63].

AL amyloidosis (monoclonal immunoglobulin light chain amyloidosis) is the most common generalised type of amyloidosis to affect the heart. It is associated with plasma cell dyscrasias, such as B cell lymphoma, Waldenstrom's macroglobulinaemia and multiple myeloma. AL amyloid fibrils are composed of monoclonal immunoglobulin kappa or lambda light chain fragments. Extracardiac involvement can also be seen, although the heart is the main organ affected.

Familial transthyretin related amyloidosis (FTTR) is caused by the deposition of mutant TTR. In the majority of cases this is caused by a single point mutation in the TTR gene, resulting in a single amino acid substitution [62]. It is associated with an autosomal dominant pattern of inheritance, but different phenotypes are seen depending on the TTR mutation involved.

Macroscopically cardiac amyloidosis with ventricular involvement may appear as normal to thickening of the ven-

tricular wall with a hypertrophic appearance which could be confused with HCM. The heart has a firm rubbery feel with a reportedly 'waxy' appearance to the cut surface of the myocardium. Limited amyloid in the heart may be seen in the right atrium, sometimes termed isolated atrial amyloidosis. Rarely this is seen as small translucent nodules coating the atrial surface which may appear brown after formalin fixation.

Microscopically, amyloid is seen as interstitial infiltrates of homogeneous eosinophilic material surrounding individual myocytes forming a honeycomb pattern and/or nodules of amyloid due to coalescence of amyloid following myocyte death (Figs. 29 and 30). Nodular amyloid deposits may also be seen within the media and adventitia of the intramural coronary vessels, these may cause luminal narrowing [64, 65]. Amyloid deposition can occur in all layers of the heart. The pattern of deposition can be nodular, pericellular or mixed type with or without vascular involvement [66] (Figs. 30 and 31). This is visible with a standard H&E stain. Amyloid material can be highlighted by a Sirius or Congo red stain (Fig. 30). The amyloid deposits classically appear red/orange when viewed by light microscopy (see chapter "The Heart at Autopsy, Including Radiological Autopsy of the Heart") and display apple-green birefringence when viewed under polarized light.

Electron microscopy and immunohistochemistry can occasionally be used for further diagnostic confirmation and analysis of the amyloid fibril sub-type. Electron microscopy reveals the presence of linear non-branching fibrils with a diameter of 7.5–10 nm externally coating myocytes (Figs. 31 and 32). Immunohistochemistry can be used to identify the major protein component of the amyloid fibril, which may be pertinent to familial cases.

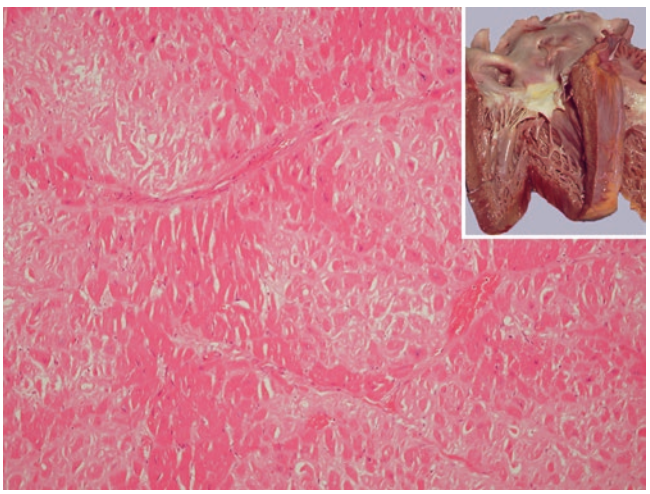


Fig. 29 The myocardium is heavily infiltrated by eosinophil matrix around cells and throughout the interstitium. The inset macroscopic view of cardiac amyloidosis shows a semi-rigid structure that is self-supporting, even in the fresh post-mortem state. This macroscopic quality often provides a clue to the ultimate histology

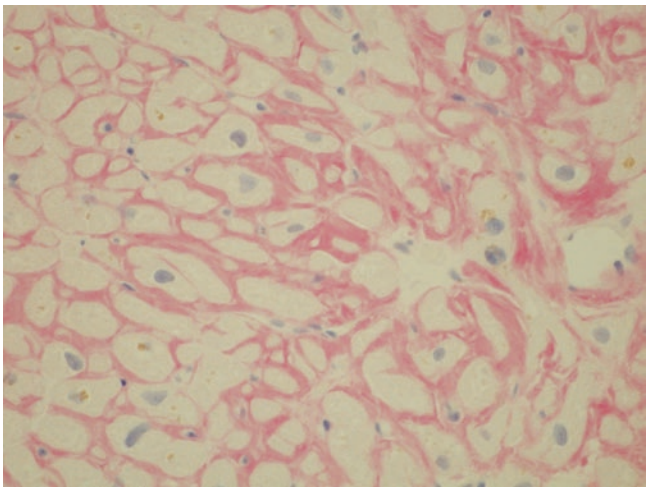


Fig. 30 Sirius red histochemistry highlights the case of amyloid deposition around individual myocytes

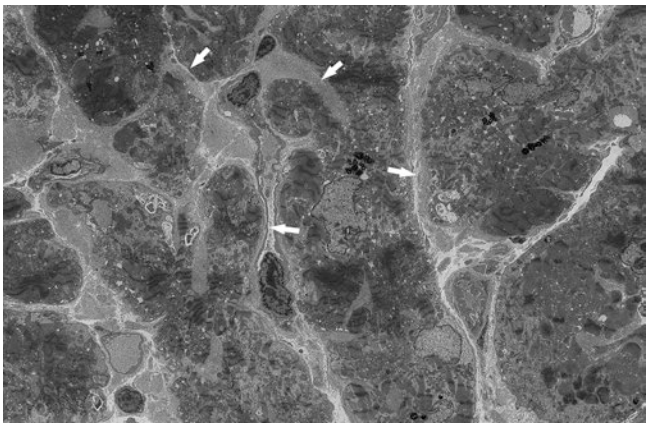


Fig. 31 Ultrastructural view of cardiac myocytes, externally coated by amyloid fibrils (marked by arrows)

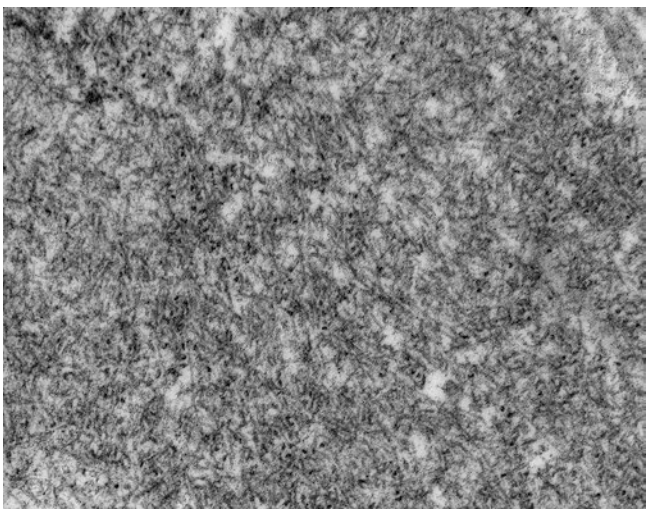


Fig. 32 Electron micrograph of amyloid fibrils which typically have a diameter of 7.5–10 nm

8 Cardiomyopathy Associated with Storage Disorders

This is a diverse group of cardiomyopathies. Glycogen storage disease and lysosomal storage disorders are hereditary conditions characterised by various disorders of carbohydrate and glycolipid metabolism resulting in an intracellular accumulation of substances. Some conditions are rapidly fatal from multiple organ system dysfunction soon after birth, but others present solely with cardiomyopathy later. Some storage disorders will produce a very restrictive pattern.

9 Anderson-Fabry Disease

Anderson-Fabry (often abbreviated to Fabry) disease is a lysosomal storage disorder with an X linked recessive pattern of inheritance, resulting in deficient/absent lysosomal alpha-galactosidase A activity [67]. This results in the accumulation of glycophospholipid in multiple organs leading to angiokeratoma, renal failure, cardiomyopathy, arrhythmias and peripheral and nervous system disorders. Macroscopically the most common appearance of cardiac Fabry's disease is concentric ventricular hypertrophy (Fig. 33), although it may mimic HCM [68]. On histological examination prominent myocyte sarcoplasmic vacuolation is seen (Fig. 34), although in some cases this may not be present. Electron microscopy shows classic concentric lamellar bodies of alternating dense and pale material ('myelinoid' bodies) within the myocyte sarcoplasm [69] (Figs. 35 and 36).

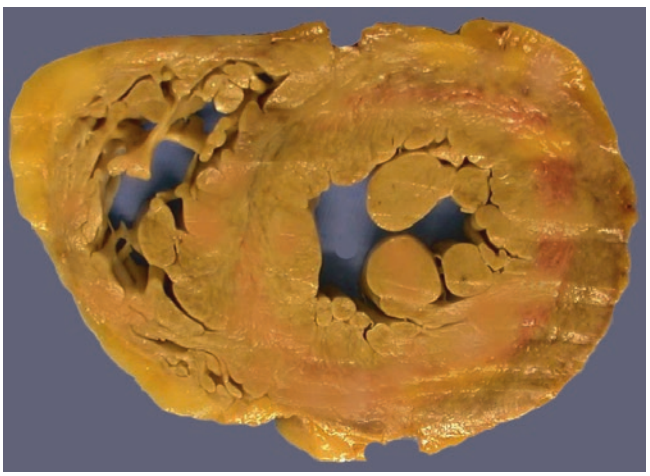


Fig. 33 Macroscopic photograph of the cardiac variant of Anderson-Fabry disease with asymmetrical ventricular hypertrophy. This can mimic HCM and needs histology and other tests to confirm the diagnosis

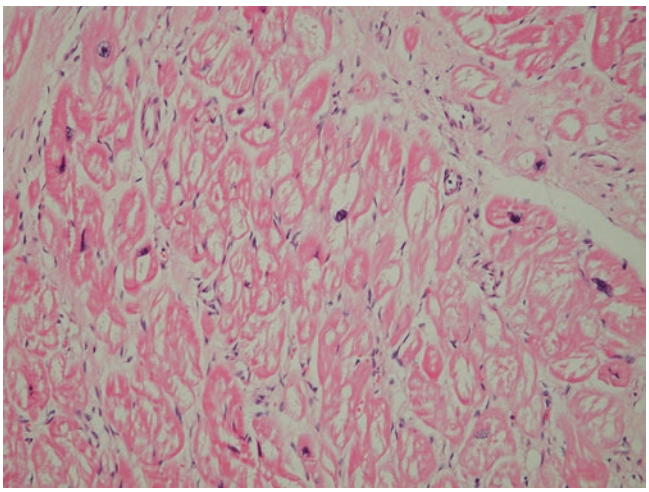


Fig. 34 Haematoxylin and eosin stained photomicrograph showing cytoplasmic vacuolization which is characteristic of Anderson-Fabry disease

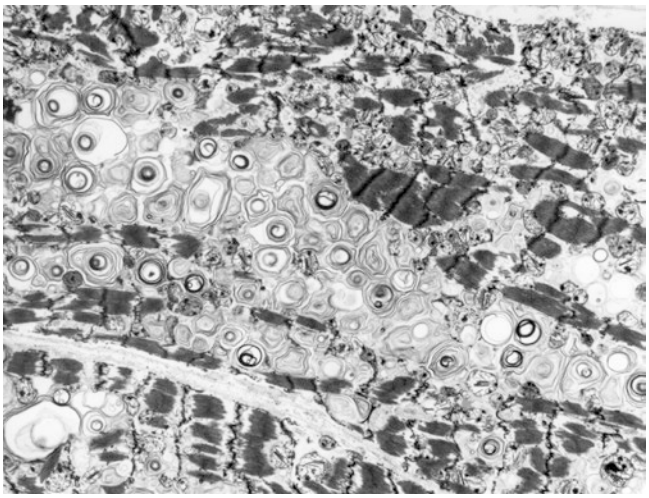


Fig. 35 Electron micrograph of 'myelinoid' figures within the myocyte sarcoplasm in a case of Anderson-Fabry disease

10 Danon Disease

This cardiomyopathy is a rare X linked lysosomal/glycogen storage disorder resulting in cardiomyopathy of hypertrophic type together with skeletal myopathy. The causative mutation occurs in the lysosomal associated membrane protein 2 gene (LAMP2). This results in decreased/complete absence of LAMP 2 protein depending on the mutation present and impairment of lysosomal transport and degradation of cellular material. The result of this is an accumulation of autophagic material and glycogen in cardiac and skeletal muscle cells [70]. On histology/electron microscopy of skeletal muscle/cardiac biopsy intracytoplasmic vacuoles are seen within the myocytes (Figs. 37 and 38).

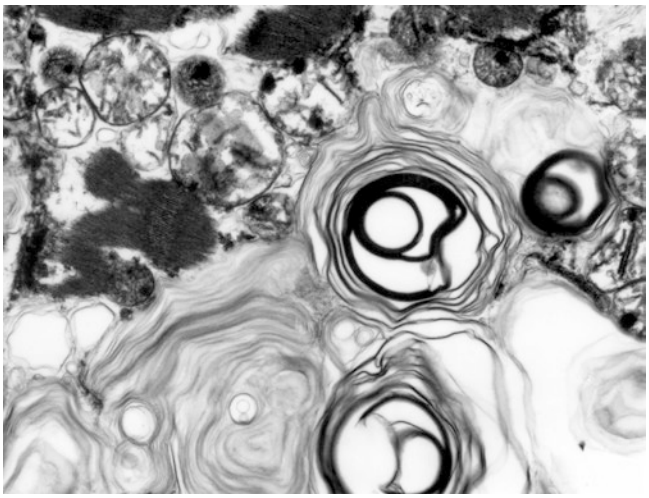


Fig. 36 High magnification of the ultrastructure of the Fabry's cardiac myocyte showing detail of the myelinoid bodies

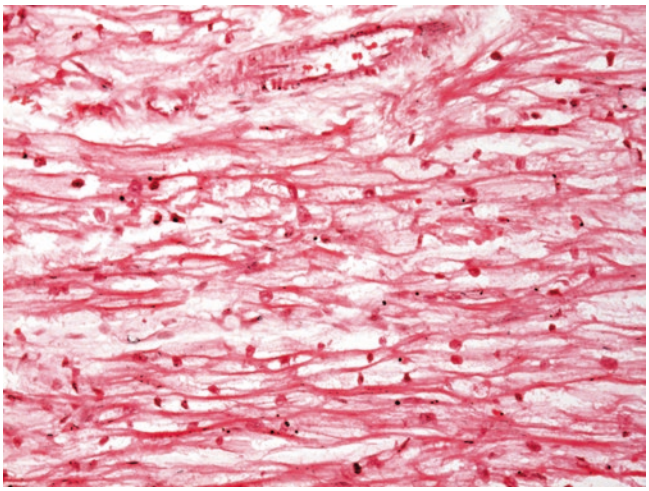


Fig. 39 Haematoxylin and eosin stained section in an autopsy case of infantile Glycogen Storage Disorder (type II) (*Courtesy of Dr. M. Ashworth*)

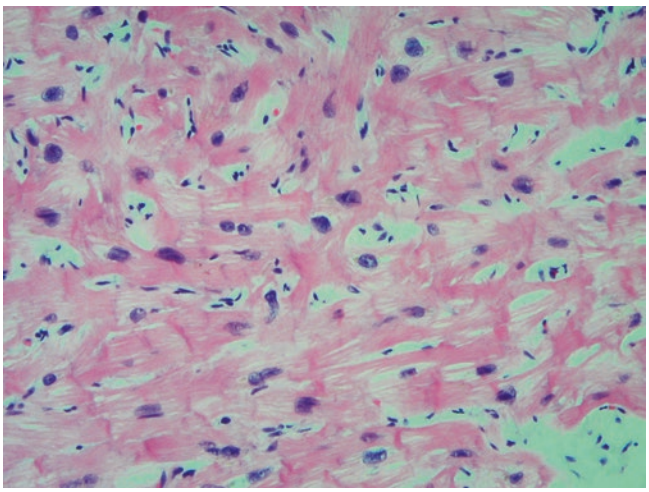


Fig. 37 The histology of Danon disease (re-processed from a previous paraffin embedded piece of tissue), showing mild disarray and minor cytoplasmic vacuolar change

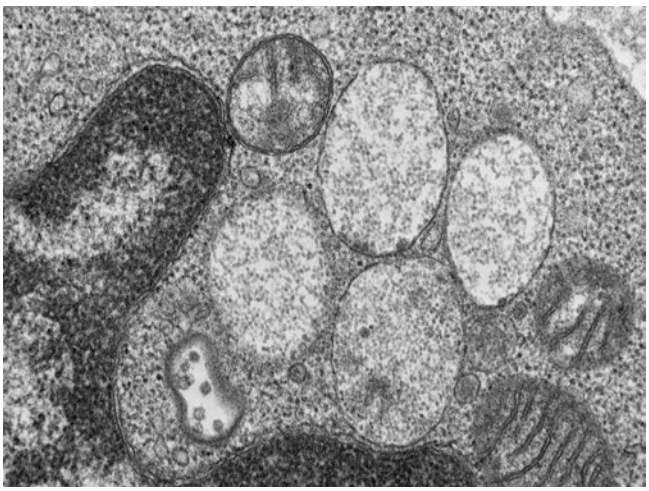


Fig. 40 Buffy coat lymphocyte from a 60 year old woman with enzymatically proven adult-onset Pompe disease showing membrane bound glycogen (*Courtesy of Dr. M. Ashworth*)

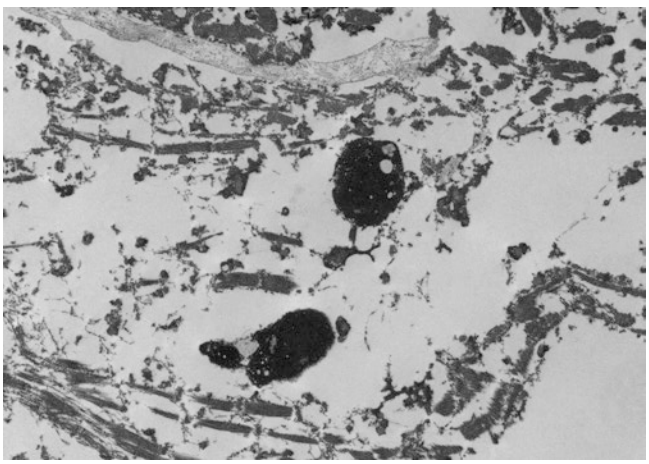


Fig. 38 The ultrastructure of Danon disease shows the autophagocytic vacuole containing cell debris, but little glycogen

11 Pompe Disease

Pompe disease is an autosomal recessive disorder resulting in alpha-glucosidase deficiency and the accumulation of glycogen in the heart, skeletal muscle, liver and nervous system [71]. There is often asymmetric left ventricular hypertrophy, which may have a very similar macroscopic appearance to HCM. The use of a periodic-acid Schiff (PAS) stain highlights the PAS positive glycogen within vacuoles (Figs. 39 and 40).

12 Haemochromatosis

This genetic condition reflects an inherited autosomal recessive iron storage disorder. There is also the similar process of haemosiderosis as a consequence of iron overload—follow-

ing multiple blood transfusions, increased iron absorption or exogenous iron treatment.

Haemochromatosis manifests as iron deposition within multiple organs and tissues such as the liver, pancreas, joints and heart. Cardiac involvement is initially characterised by diastolic dysfunction (RCM) with arrhythmias, and in later stages by dilated cardiomyopathy due to pressure effects on the left ventricle. Iron deposition occurs from the epicardial surface to the endocardial surface, resulting in myocyte damage and death as a consequence of free radical generation. A Perls (Prussian blue) stain is best to assess the amount and distribution of iron (Figs. 41 and 42). In normal hearts no stainable iron should be seen [72].

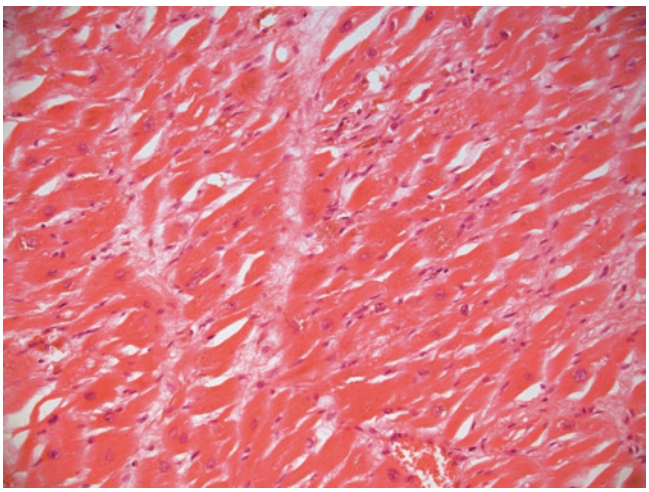


Fig. 41 Haemochromatosis seen on haematoxylin & eosin histology. There is subtle brown pigmentation in the myocytes (*Courtesy of Dr. D. Rassl*)

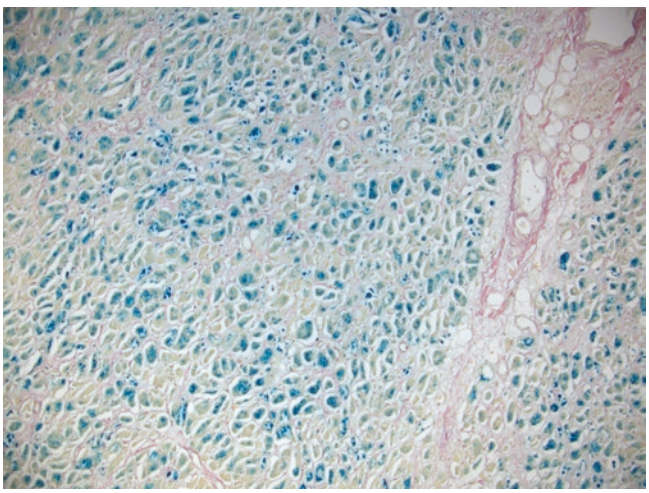


Fig. 42 Haemochromatosis reveals its iron overload with Perl's histochemistry staining of myocytes (*Courtesy of Dr. D. Rassl*)

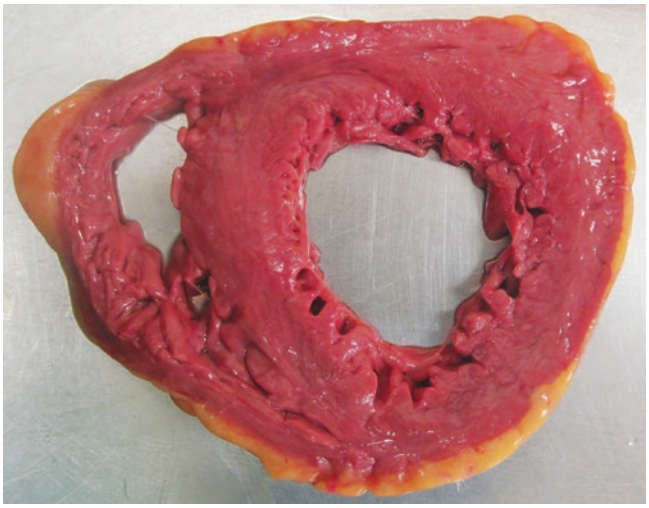


Fig. 43 The dilated and hypertrophic heart (602 g) in a case of a significantly obese individual (BMI 38.9) is seen with both ventricular wall thickening and some chamber dilatation. Other factors such as obstructive sleep apnoea and obesity-hypoventilation syndrome often may aggravate any cardiac dysfunction alongside diabetic vasculopathy and other metabolic consequences of obesity

13 Obesity-Related Cardiomyopathy

This condition is becoming more likely to be encountered by the pathologist with the rising general body mass index (BMI) of the population. It is believed to arise as a result of increased total blood volume and decreased systemic vascular resistance, resulting in a high cardiac output state maintained by an increased stroke volume. The persistence of this high cardiac output state results in adaptive cardiac structural changes such as left ventricular dilatation or concentric or eccentric left ventricular hypertrophy [73, 74] (Fig. 43). The mass of hearts in the morbidly obese is difficult to evaluate, with the heart mass not being directly proportional to the body mass. However, hearts of more that 500–550 g, are recognised to be prone increasingly to failure and/or sudden death.

14 Alcoholic Cardiomyopathy

This entity has been previously discussed in the DCM section however it is fairly commonly encountered and is therefore worthy of further discussion. Alcohol is a direct cardiac toxin as well as adversely affecting other organs, notably the liver. Alcoholic cardiomyopathy is the result of chronic effects and can present with a hypertrophic, dilated or mixed morphology.

15 Peripartum and Postpartum (PPCM) Cardiomyopathy

This is a rare form of cardiomyopathy occurring towards the end of pregnancy or several months postpartum. It is an idiopathic condition presenting with left ventricular systolic dysfunction and heart failure, sharing many similarities with DCM (Fig. 44).

There are multiple hypotheses as to the aetiology of PPCM. These include a possible genetic predisposition to the condition, an inflammatory background, an angiogenic imbalance during pregnancy, oxidative stress and the pro-apoptotic properties of prolactin during pregnancy [75]. PPCM is more common in older women and women who have had multiple previous pregnancies, as well as those with cardiovascular risk factors such as obesity, smokers and hypertensive patients [76].

16 Sarcoid Heart Disease

Sarcoid is a systemic granulomatous disorder of unknown aetiology. Along with other tissues, especially the respiratory tract, the myocardium can be affected by the granulomas. In addition, the heart may be affected by sarcoid-associated fibrotic lungs resulting in pulmonary hypertension.

Cardiac sarcoidosis occurs clinically in 5–10% of patients with known sarcoid [77]. Indeed, clinically silent cardiac sarcoid has been observed in approximately 20% of Caucasians and black Americans, and potentially up to 70–80% of Japanese patients at autopsy [78, 79]. Cardiac involvement is an unfavourable prognostic factor, with cardiac sarcoid being associated with atrial and ventricular arrhythmogenic activity. Atrioventricular block is the most commonly encountered disorder [80, 81]. Ventricular tachyarrhythmias and fibrillation can also be seen. These arrhythmias are thought to reflect conduction block/re-entrant loops as a direct result of sarcoid granulomas and scar tissue.

Macroscopically, the heart may appear normal, although on section patchy infiltrates may be seen on the myocardial wall (Fig. 45). The left ventricle and interventricular septum are the most commonly involved sites. On histology, the classical appearance is of 'naked' non-caseating granulomas comprising epithelioid histiocytes, with some multinucleated giant cells surrounded by a scanty lymphocytic infiltrate (Figs. 46 and 47). The Langhans type giant cells may have occasional Schaumann and asteroid bodies, but triangulation

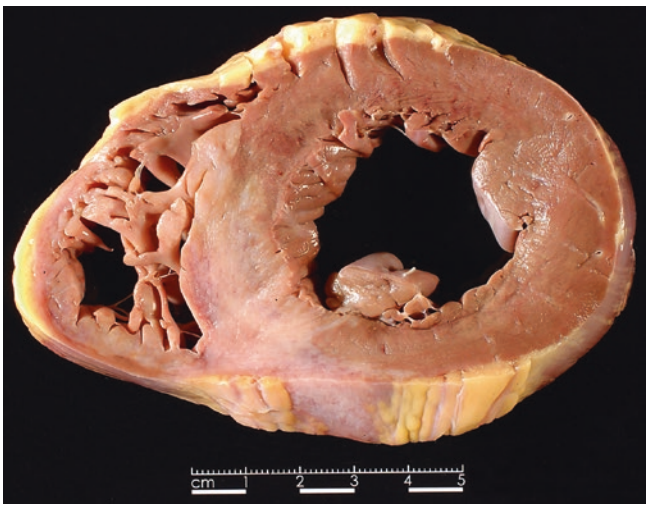


Fig. 45 Macroscopic view in a case of sarcoidosis. The chambers are mildly dilated and there is also some wall thickening. Focal scarring is seen mainly in the septum and left ventricle wall towards the base of the image (*Courtesy of Dr. P. Gallagher)*

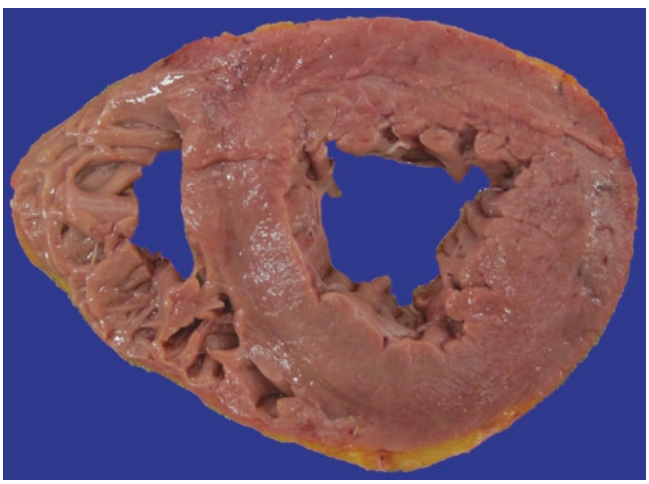


Fig. 44 A case of postpartum cardiomyopathy is seen with some cardiac hypertrophy (often seen in pregnancy). There may be DCM features, although these are not seen in this case

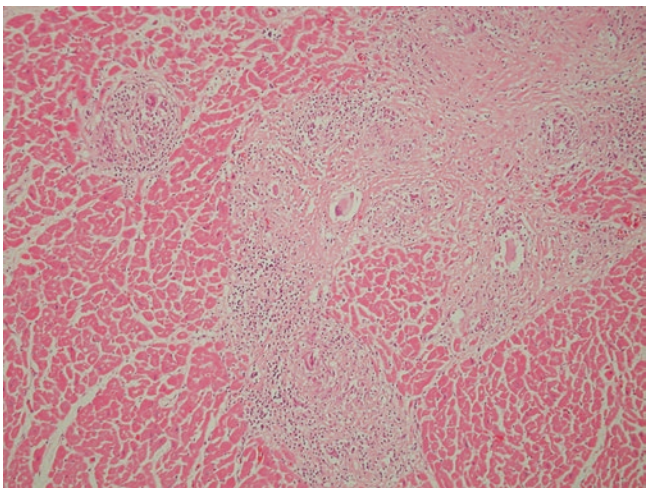


Fig. 46 Histological view of left ventricle tissues affected focally by non-caseating granulomatous inflammation, in a known case of sarcoidosis (*Courtesy of Dr. P. Gallagher*)

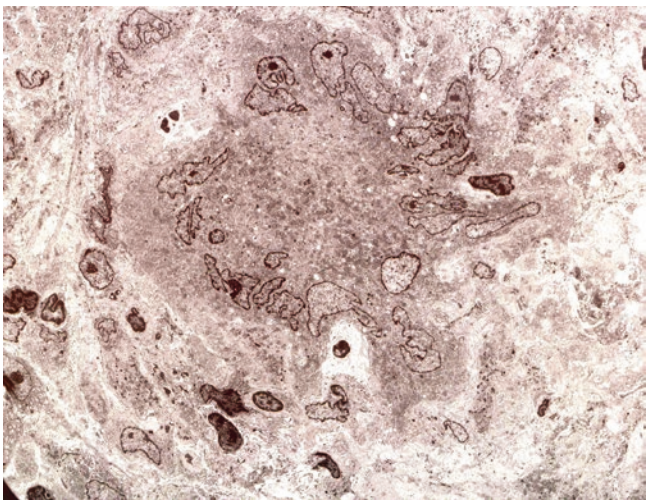


Fig. 47 Electron microscopy in a case of a dilated mixed pattern cardiomyopathy clinically identified a sarcoid granuloma, in a case of unexpected sarcoidosis. The Langhans giant cell has a peripheral rim of nuclei

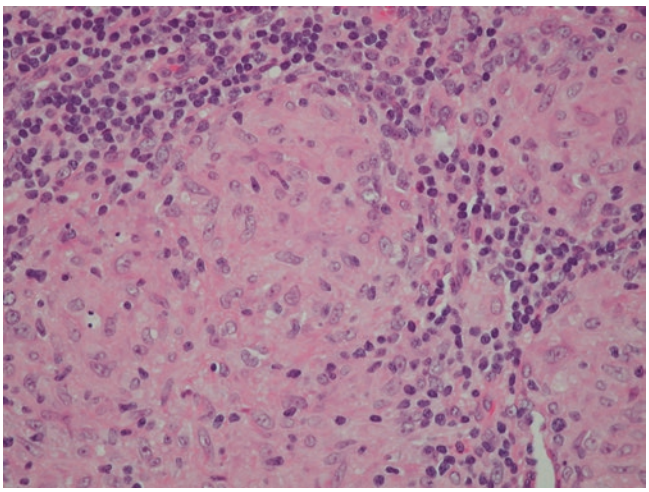


Fig. 48 Mediastinal node tissue with non-caseating granulomatous features, supporting the diagnosis of sarcoid

against mediastinal nodal granulomas may assist (Fig. 48). The granulomas become burnt-out with time and undergo fibrosis. The granulomas may be seen on endomyocardial biopsy, but sensitivity for non-caseating granuloma identification at endomyocardial biopsy is low at less than 20% [82].

17 Channelopathies

These gene-defect lesions may often present as sudden deaths, but are generally considered within the cardiomyopathy families. They generally appear as normal hearts in autopsy studies and require reservation of spleen tissue for genetic studies. These are considered in detail in chapter "Sudden Cardiac Death".

18 Conclusion

There are many forms of cardiomyopathy that should be known to the pathologist, with a multitude of aetiologies and presentations as described in, but not limited to, this chapter (Table 1). Research into these disease processes is continuing to identify numerous gene mutations, associated with the various presentations and forms of cardiomyopathy. This is driving increasing knowledge and new vectors for screening and treatment. Ongoing interest in this dynamic group of pathologies is recommended.

Table 1 Classification of main cardiomyopathies ***(modified from European Heart Journal https://doi.org/10.1093/eurheartj/ehm342)***

DCM
Genetic
• Unknown gene
• Sarcomeric protein mutations (see also HCM)
• Z-band (Muscle LIM protein, TCAP)
• Cytoskeleton genes (dystrophin, desmin, metavinculin, epicardin, sarcoglycan complex, etc.)
• Nuclear membrane (lamin A/C, emerin)
• Intercalated disc protein (see also AC)
• Mitochondrial disorders
Acquired
• Myocarditis (infective/toxic/immune)
• Kawasaki disease
• Eosinophilic syndrome (Churg-Strauss, etc.)
• Viral persistence
• Drugs
• Pregnancy-related (PPCM)
• Nutritional (thiamine, selenium, hypocalcaemia, etc.)
• Alcohol
HCM
Genetic
• Unknown gene
• Sarcomeric gene mutations (beta-myosin heavy chain, cardiac myosin binding protein C, cardiac troponin I, troponin T, alpha-tropomyosin, cardiac actin, alpha myosin heavy chain, titin, troponin C, muscle LIM protein, etc.)
• Glycogen storage disease (Pompe, PRKAG2, Danon, etc.)
• Lysosomal storage disease (Anderson-Fabry, Hurler's syndrome, etc.)
• Disorders of fatty acid metabolism
• Carnitine deficiency
• Mitochondrial cytopathies
• Phosphorylase B kinase deficiency
• Syndromic HCM (Noonan's, LEOPARD, Friedreich's ataxia, Beckwith-Wiedemann, Swyer syndromes)
• Other (familial amyloid, phospholamban promoter)
Acquired
• Obesity cardiomyopathy
• Offspring of diabetic mothers

Table 1 (continued)

• Athletes
• Amyloid
AC
Genetic
• Familial, unknown gene
• Intercalated disc protein mutations (Plakoglobin, Desmoplakin, Plakophilin 2, Desmoglein 2, Desmocollin 2)
• Cardiac ryanodine receptor (RyR2) mutations
• Transforming growth factor beta
Acquired
• None formally recognised
RCM
Genetic
• Unknown gene
• Sarcomeric gene mutations (troponin I, myosin light chain)
• Familial amyloid (TTR = RCM and neuropathy)
• Apolipoprotein (RCM and nephropathy)
• Desminopathy
• Anderson-Fabry
• Glycogen storage disease
• Haemochromatosis
Acquired
• Amyloid
• Scleroderma
• Endomyocardial fibrosis (ergotamine, serotonin, busulphan, etc.)
• Carcinoid heart disease
• Radiation
• Drug toxicity (anthracycline)
Unclassified
Genetic, unknown gene
• Left ventricular non-compaction
• Barth syndrome
• Lamin A/C
• alpha-dystrobrevin
• ZASP
Acquired
• Takotsubo cardiomyopathy

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