A Brief Review and Update of the Clinicopathologic Diagnosis of Arrhythmogenic Cardiomyopathy

Stephanie M. McGregor, MD, PhD; Aliya N. Husain, MD

• Arrhythmogenic cardiomyopathy (AC) has traditionally been regarded as a rare disease with variably penetrant autosomal-dominant inheritance. Recent years have revealed that AC is actually a spectrum of disease with prevalence much higher than previously thought. Diagnosis can be quite challenging because of highly variable clinical presentation, even among family members sharing a mutation. Unlike other cardiomyopathies, AC has a concealed phase during which patients have arrhythmias in the absence of structural heart disease but remain at risk of sudden cardiac death. Importantly, it is in the setting of sudden cardiac death that pathologists are most likely to encounter AC. It is critical that these findings not be overlooked, as family members of the deceased may also be affected and could potentially avoid such a dismal outcome. With time, advances in ancillary studies are likely to expand the role for pathologists in AC diagnosis.

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Arrhythmogenic cardiomyopathy (AC) is a primarily autosomal-dominant cardiomyopathy resulting from defects of desmosomal proteins that would normally provide structural integrity to cardiomyocytes.[1] The incidence is frequently cited as 1 in 5000, but it is arguably greater than 1 per 1000 if mild cases and potentially unrecognized disease are considered; such a higher incidence would preclude its designation as a rare disease.[1–3] Although it was originally regarded as a congenital dysplasia, additional insight regarding its pathogenesis has revealed that AC is a true cardiomyopathy that—despite being heritable—is variably penetrant, acquired over time, and progressive in nature. Unfortunately, the diagnosis of AC can be quite difficult, as the clinical presentation is highly variable, biopsy is often negative even in the face of severe disease, and the molecular basis is only understood for approximately half of known cases. Moreover, even when a known molecular defect can be identified, interpretation of this finding is complicated by compound mutations and variable penetrance even among members of the same family who share a mutation.[1,4,5] Given such a complex clinical scenario, there are many aspects regarding this multifaceted approach to diagnosis with which the practicing pathologist must be familiar.

HISTORY

Arrhythmogenic cardiomyopathy has gone by many names over time. The first known report was put forth in 1905 by Osler, in which he described an otherwise healthy man who died during mild exertion and was found to have "parchment-like" thinning of both the right and left ventricular free walls as an isolated finding.[6] A second report of this same patient appeared in 1950, and subsequently multiple reports emerged describing similar presentations, including one from Uhl, describing a congenital anomaly consisting of an aplastic right ventricular free wall with parchmentlike thinning. This latter case was named *Uhl anomaly* or *Uhl disease* after the author, and though originally regarded to be the same as AC, Uhl anomaly appears to reflect a distinct entity, and these terms are no longer accepted as interchangeable.[1–3,6–8] The term *arrhythmogenic right ventricular dysplasia* without the additional designation of *cardiomyopathy* was originally proposed because the disease appeared to be a developmental abnormality, which was supported by its similarity to Uhl anomaly. Over time it has become clear, however, that although the genetic etiology of AC is frequently inherited, the physical defects are not actually present at birth, and *cardiomyopathy* has thus been adopted. An additional issue with naming the condition stems from the fact that the disease process is not actually limited to the right ventricle. Many argue that the term *arrhythmogenic cardiomyopathy* without any mention of the right ventricle is more appropriate, whereas others favor, for historical reasons and clarity, retaining *right ventricular* as a descriptor.[1–3] To date there is no international consensus and multiple names persist in the literature.

CLINICAL FEATURES

Arrhythmogenic cardiomyopathy classically presents in the fourth decade with palpitations, syncope, and even sudden cardiac death. However, less common presentations occur, and people of nearly any age can be affected, though it is exceedingly rare in persons younger than 10 years.[1,3–5] Symptoms occur either at rest or with exertion, and unfortunately sudden cardiac death is not uncommon in this population. An autopsy review of nearly 2000 patients with sudden cardiac death found that more than 10% of

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From the Department of Pathology, University of Chicago Medicine, Chicago, Illinois.

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Reprints: Stephanie M. McGregor, MD, PhD, Department of Pathology, University of Chicago Medicine, 5841 S Maryland Ave, Room P615, Chicago, IL 60637 (e-mail: stephanie.mcgregor@uchospitals.edu).

Table 1. Diagnostic Criteria for Arrhythmogenic Cardiomyopathy (AC)

Category	Major Criteria	Minor Criteria
Global or regional dysfunction and structural alterations	By 2D echocardiography: • Regional RV akinesia, dyskinesia or aneurysm • *and* 1 of the following (end diastole): - PLAX RVOT ≥32 mm (corrected for body size [PLAX/BSA] ≥19 mm/m^2) - PSAX RVOT ≥36 mm (corrected for body size [PSAX/BSA] ≥21 mm/m^2) - *or* fractional area change ≤33%	By 2D echocardiography • Regional RV akinesia or dyskinesia • *and* 1 of the following (end diastole): - PLAX RVOT ≥29 mm but <32 mm (corrected for body size [PLAX/BSA] ≥16 but <19 mm/m^2) - PSAX RVOT ≥32 mm and <36 mm (corrected for body size [PSAX/BSA] ≥18 but <21 mm/m^2) - *or* fractional area change >33% but ≤40%
	By MRI: • Regional RV akinesia or dyskinesia or dyssynchronous RV contraction • *and* 1 of the following: - Ratio of RV end-diastolic volume to BSA ≥110 mL/m^2 (male) or ≥100 mL/m^2 (female) - *or* RV ejection fraction ≤40%	By MRI: • Regional RV akinesia or dyskinesia or dyssynchronous RV contraction • *and* 1 of the following: - Ratio of RV end-diastolic volume to BSA ≥100 but <110 mL/m2 (male) or ≥90 but <100 mL/m2 (female) - *or* RV ejection fraction >40% and ≤45%
	By RV angiography • Regional RV akinesia, dyskinesia or aneurysm	
Tissue characterization of wall	• Residual myocytes <60% by morphometric analysis (or <50% if estimated), with fibrous replacement of the RV free wall myocardium in ≥1 sample, with or without fatty replacement of tissue on endomyocardial biopsy	• Residual myocytes 60–75% by morphometric analysis (or 50–65% if estimated), with fibrous replacement of the RV free wall myocardium in ≥1 sample, with or without fatty replacement of tissue on endomyocardial biopsy
Repolarization abnormalities	• Inverted T waves in right precordial leads (V_1, V_2, and V_3) or beyond in individuals >14 years of age (in the absence of complete right bundle-branch block QRS >120 ms)	• Inverted T waves in leads V_1 or V_2 or beyond in individuals >14 years of age (in the absence of complete right bundle-branch block) • Inverted T waves in leads V_1, V_2, V_3, and V_4 or beyond in individuals >14 years of age in the presence of complete right bundle-branch block
Depolarization/conduction abnormalities	• Epsilon wave (reproducible low-amplitude signals between end of QRS complex to onset of the T wave) in the right precordial leads (V_1 to V_3)	• Late potentials by SAECG in ≥1 of 3 parameters in the absence of a QRS duration of >100 ms on the standard ECG • Filtered QRS duration (fQRS) of ≥114 ms • Duration of terminal QRS <40 uV (low-amplitude signal duration) or ≥38 ms • Root-mean-square voltage of terminal 40 ms <20 uV • Terminal activation duration of QRS >55 ms measured from the nadir of the S wave to the end of the QRS, including R prime, in V_1, V_2, or V_3, in the absence of complete right bundle-branch block
Arrhythmias	• Nonsustained or sustained ventricular tachycardia of left bundle-branch morphology with superior axis (negative or indeterminate QRS in leads II, III, and aVF and positive in lead aVL)	• Nonsustained or sustained ventricular tachycardia of RV outflow configuration, left bundle-branch block morphology with inferior axis (positive QRS in leads II, III, and aVF and negative in lead aVL) or of unknown axis • >500 ventricular extrasystoles per 24 hours (Holter)
Family history	• AC confirmed in a first-degree relative who meets current task force criteria • AC confirmed pathologically at autopsy or surgery in a first-degree relative • Identification of a pathogenic mutation categorized as associated or probably associated with AC in the patient under evaluation	• History of AC in a first-degree in whom it is not possible or practical to determine whether the family member meets current task force criteria • Premature sudden death (<35 years of age) due to suspected AC in a first-degree relative • AC confirmed pathologically or by current task force criteria in a second-degree relative

Abbreviations: AC, arrhythmogenic cardiomyopathy; BSA, body surface area; ECG, electrocardiogram; MRI, magnetic resonance imaging; PLAX, parasternal long-axis view; PSAX, parasternal short-axis view; RV, right ventricle; RVOT, right ventricle outflow tract; SAECG, signal-averaged electrocardiography.

Table 2. Genes Implicated in Arrhythmogenic Cardiomyopathy				
	Gene Name	Protein Name	Mode of Inheritance	Notes
Desmosomal	*JUP*	Plakoglobin	AD or AR	AR: Naxos syndrome
	DSP	Desmoplakin	AD or AR	AR: Carvajal disease
	PKP2	Plakophilin-2	AD or AR	
	DSG2	Desmoglein-2	AD or AR	
Non-desmosomal	*TMEM43*	Transmembrane protein 43	AD	Highly penetrant and fatal
	TGFB3	Transforming growth factor β	AD	Unclear link
	RYR2	Ryanodine receptor	AD	Associated with catecholaminergic polymorphic ventricular tachycardia; further study is necessary to determine if phenocopy of AC
	DES	Desmin	AD	Possible overlap syndrome with dilated cardiomyopathy
	TTN	Titin	AD	Possible overlap syndrome with dilated cardiomyopathy

Abbreviations: AC, arrhythmogenic cardiomyopathy; AD, autosomal dominant; AR, autosomal recessive.

patients had findings of AC.[4,6,9] Despite such a tragic outcome for many, effective therapeutic options are available for the majority of these patients, making accurate and early diagnosis essential. As the spectrum of presentation is broad, AC is currently diagnosed using a task force–developed model that incorporates criteria of various modalities including family history, clinical imaging, electrocardiography, endomyocardial biopsy, and molecular genetic testing.[2,6–8,10] A positive diagnosis can be reached when patients have either (1) 2 major criteria, (2) 1 major and 2 minor criteria, or (3) 4 minor criteria. A borderline diagnosis is established by (1) 1 major and 1 minor criterion or (2) 3 minor criteria, and a possible diagnosis is rendered by 1 major and 2 minor criteria. The 2010 revised task force criteria are delineated in Table 1.

The spectrum of disease spans essentially normal life, a need for cardiac transplantation, and, as mentioned previously, sudden cardiac death. The natural history has been divided as follows: (1) concealed phase, in which there are no apparent clinical manifestations but the patient is at risk of sudden cardiac death; (2) overt electrical disorder, in which the patient has symptomatic arrhythmias; (3) right ventricular failure; and (4) biventricular pump failure, which resembles dilated cardiomyopathy of various causes.[1–8] Arrhythmogenic cardiomyopathy is the only primary cardiomyopathy with a concealed phase, which is reminiscent of the ion channelopathies and means that AC shares features of both conventional cardiomyopathies and inherited arrhythmias.[4,6,9,11] Although delineating these phases implies a standard progression, patients will not necessarily follow the progression in sequence; many patients may not progress at all, and the left ventricle may be involved even from the outset.[12] As many as 80% of cases have left ventricular involvement, which may be more severe than that of the right ventricle, particularly in cases discovered as a result of screening family members of a proband.[12]

INHERITANCE

Approximately half of AC cases are considered to be familial, most frequently in an autosomal-dominant fashion with variable penetrance. However, autosomal-recessive patterns have also been reported, and it is through autosomal-recessive syndromes with fully penetrant externally visible phenotypes (eg, the dermatologic manifestations of Naxos and Carvajal syndromes) that the initial genetic discoveries of the causative genes of AC actually occurred.[13] Breakthroughs in this setting informed the field that dysfunctional desmosomes may be the root of the disease and led to the discovery of many desmosomal genes implicated in AC (Table 2). Subsequently nondesmosomal genes were reported as well, though many of these have not yet been explored in detail and may reflect a spectrum of disease between AC and conventional dilated cardiomyopathy.

Given the difficulties associated with this diagnosis and the recent incorporation of molecular genetic testing into the task force criteria, it is tempting to celebrate the possibility of early discovery in family members of probands. However, at the current time diagnosis based on molecular studies alone is difficult.[13] Individuals with a desmosomal mutation have a 30% to 50% likelihood of developing AC, though the presence of more than one mutation in a family member of a proband is associated with an increased risk of penetrant disease.[14] Multiple factors are thought to account for the variable penetrance. First, modifier genes are at least partially responsible, as patients with vastly different clinical presentations share the same core group of mutations.[15,16] Arrhythmogenic cardiomyopathy–associated mutations have been identified in up to 16% of healthy controls, and more than 10% of patients with criteria-established AC have more than one known mutation.[15,17] Among healthy patients with AC-associated mutations, most result in subtle protein changes. If only deleterious mutations are considered, the prevalence is only 0.5% in a control population, but greater than zero nonetheless. Patients with more than one mutation may have compound heterozygosity in a single gene or digenic mutation in more than one desmosomal gene.[4,14,18] Complicating matters further, approximately half of patients fulfilling diagnostic criteria do not have a defined AC-associated mutation.[1] Combined, these obstacles make it essentially impossible at the current time to provide family members with reliable predictions based on genetic screening, and there is undoubtedly a need for continued study in this area.

ETIOLOGY AND PATHOGENESIS

As mentioned previously, multiple studies have implicated mutations in desmosomal genes as the root cause of AC. The most widely recognized function of desmosomes is to form anchors between cells and intermediate filaments or between cells, but they are also important in signal transduction, and in particular in Wnt/β-catenin signaling. Two main schools of thought exist based on these different aspects of desmosomal function: the degeneration-inflammation model and the

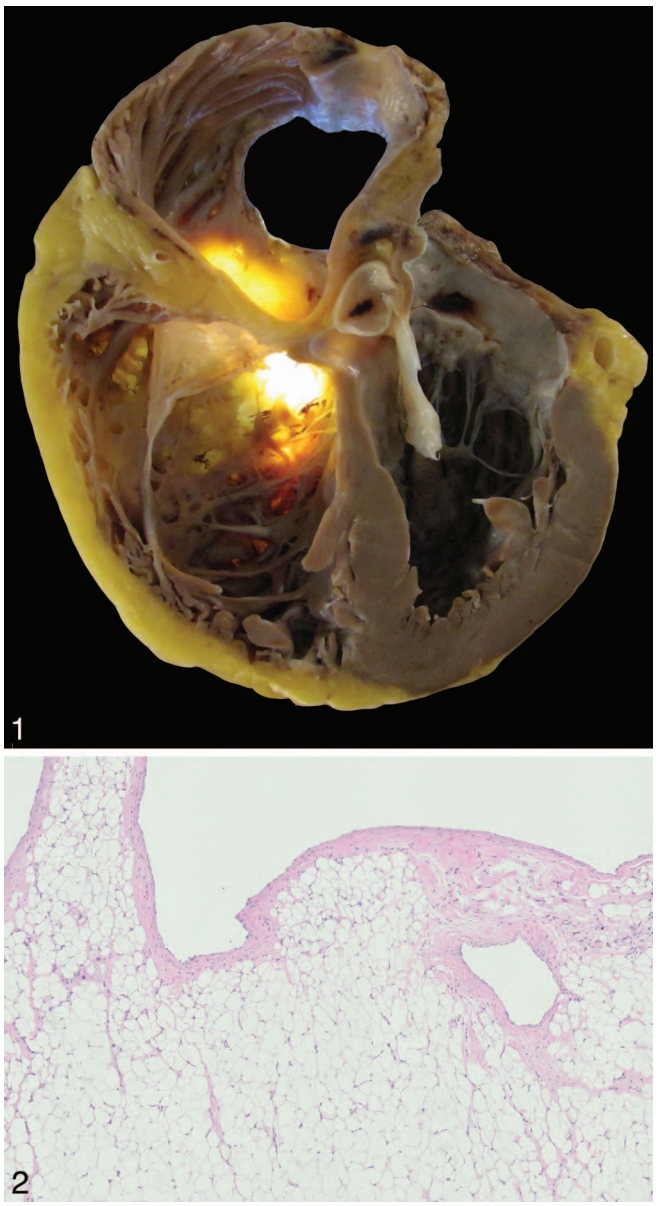

Figure 1. *Transillumination of explanted heart with full-thickness fibrofatty replacement of myocardium. A 4-chamber cut reveals dilatation of the right ventricle (10 cm) and essentially no normal myocardium (<0.1 cm in thickness). In this classic case the left ventricle is relatively normal.*

Figure 2. *Scant rim of remaining endomyocardium in severe disease. The section is taken from the explanted heart shown grossly in Figure 1 (hematoxylin-eosin, original magnification ×20).*

transdifferentiation model.[1] Damage as a result of mechanical force due to disrupted architecture underlies the degeneration-inflammation model, in which dysfunctional desmosomes are unable to withstand mechanical stresses such as stretching of the myocardium and resisting high central pressures. As a result, there is detachment of cells with subsequent necrosis, inflammation, and fibrofatty replacement.[19] In contrast, the transdifferentiation model is based on the premise that desmosomes mediate essential cell signaling via the Wnt/β-catenin pathway. Wnt signaling is an essential pathway that is negatively regulated in part by plakoglobin (also known as γ-catenin) through competition with β-catenin in the nucleus. When desmosomes are dysfunctional, excessive plakoglobin translocates to the nucleus and therefore down-regulates normal Wnt signaling, in turn causing a shift in gene expression from cardiogenic to adipogenic.[20] It is possible that both mechanisms contribute to the pathogenesis, and the need for mechanical stress for disease manifestation could at least partially explain the markedly variable penetrance.

GROSS AND HISTOLOGIC FINDINGS

Arrhythmogenic cardiomyopathy was originally recognized because of striking right ventricular findings, including cases with marked parchmentlike aneurysmal dilatation of the right ventricle and others that retain their structure but have essentially the entire myocardium replaced by fibroadipose tissue.[2] Such cases with full-thickness fibrofatty replacement readily transilluminate (Figure 1). Although this is the classic presentation, explanted hearts and autopsy studies have demonstrated that the left ventricle is frequently involved, and in rare cases even the interventricular septum may have pathologic findings of AC. In contrast to ischemic heart disease, the disease process begins in the subepicardium and progresses toward the endocardium.[21] Even in advanced disease there is usually a rim of remaining endomyocardium, but in extreme cases the fibrofatty change may extend even into the trabeculae carneae (Figure 2). Although most cases have striking gross findings, the disease can be patchy or even so subtle that it is only recognized histologically.[9,10] A mononuclear infiltrate may be present.[9,19] Trichrome stains may be helpful in elucidating subtle fibrosis (Figure 3, A and B) and electron microscopy can reveal remodeling of intercalated discs.[9,19,22] There is currently no established role for immunohistochemistry in the diagnosis of AC.

The essential diagnostic pathologic finding is fibrofatty replacement of the myocardium, with emphasis on the fibrous component. Isolated adipose tissue infiltration is insufficient for diagnosis, as it can be a normal finding in the right ventricle. Autopsy studies have demonstrated that more than 50% of patients have fatty infiltration of the right ventricle, particularly in the settings of old age, morbid obesity, alcohol use, and inherited myopathy.[9,22,23] In these settings the fatty infiltrate is more likely to have a marbled appearance and will not be accompanied by other features such as myocyte necrosis and inflammation; if prominent, these latter features may be sufficient to diagnose AC in the presence of fatty replacement without fibrosis. An example of fatty infiltration in an obese patient is shown in Figure 4.

A ROLE FOR BIOPSY?

Given the severe abnormalities seen in explanted hearts and the resulting pathophysiology prior to transplant, it may seem surprising that false negatives are frequently encountered on endomyocardial biopsies, but several reasons related to sampling easily explain it: (1) the disease process begins in the subepicardial myocardium and progresses inward, so that in early disease the tissue sampled through an endomyocardial approach may not be affected; (2) endomyocardial biopsies are routinely taken from the interventricular septum, which is typically spared; and (3) the disease process is frequently patchy.[23,24] In additional to sampling issues, fibrofatty replacement of the myocardium is a nonspecific finding, so that even if the disease process is sampled, the biopsy may be nondiagnostic. Nonetheless,

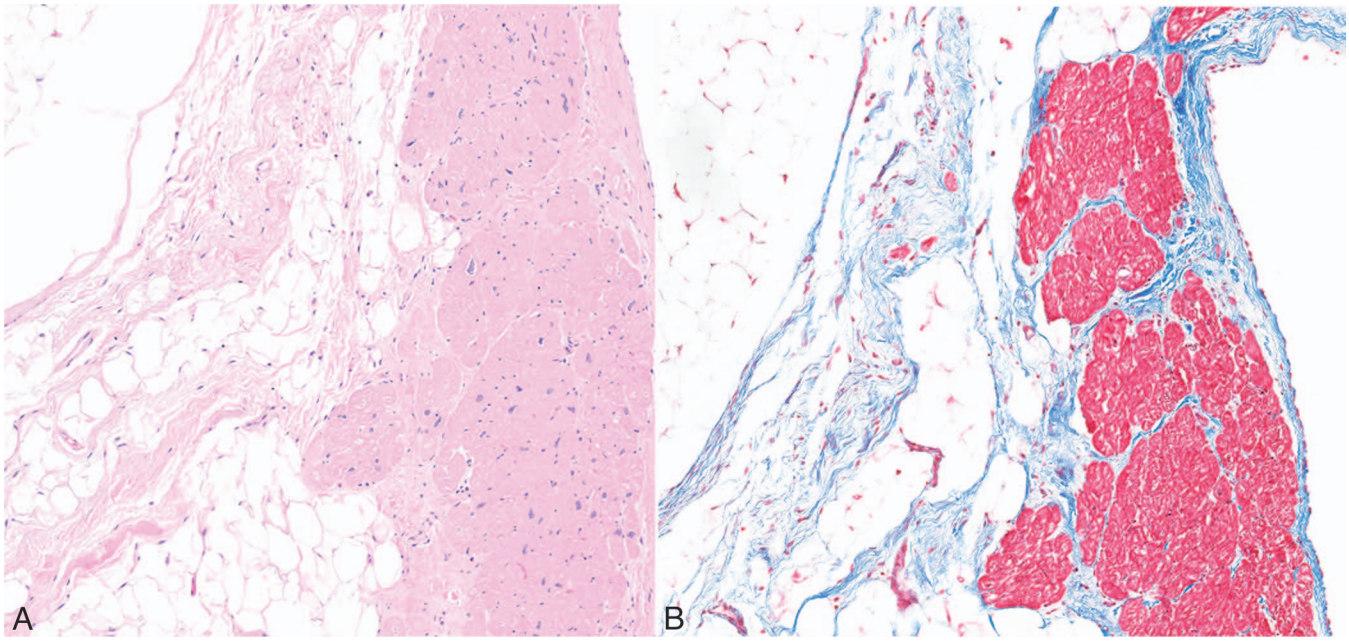

Figure 3. *Subtle fibrous component. The section is taken from the right ventricular outflow tract. Fibrosis is subtle on hematoxylin-eosin (A) but easily appreciated by trichrome staining (B) (original magnification ×20).*

when definitive diagnosis is possible it greatly impacts patient management and is therefore useful in a subset of patients, particularly in those with acute-onset disease.[24,25]

Various approaches have been proposed to improve the utility of biopsy. An attempt to establish specific criteria using simulated biopsies of explanted hearts has demonstrated that the amount of residual myocardium may be the most reliable indicator of AC, but diagnostic yield in this study was highly dependent on location, as would be expected given the nature of the disease.[1,25] Informative biopsies were taken from the so-called "triangle of dysplasia," which consists of the apex, infundibulum, and posteroinferior wall; biopsies of the septum and left ventricle were not helpful. Biopsying the right ventricular free wall instead of the septum could therefore presumably increase the likelihood of obtaining diagnostic biopsies, but there are increased risks with this approach, such as tamponade.[1,26] Using electroanatomic voltage mapping to guide sampling in areas of the right ventricular free wall that demonstrate abnormalities consistent with AC also may improve diagnostic yield of endomyocardial biopsies, but additional studies are necessary to determine if the added risk associated with this procedure outweighs the benefits.[26–29] Reduced plakoglobin in desmosomes has been reported and proposed as a possible clinical test and is particularly appealing as it may highlight a defect in otherwise apparently normal tissue. However, although reported sensitivities are fairly high, ranging from 85% to 91%, specificity is low, with reports ranging from 57% to 82%.[1,10,27–29] Additional studies are necessary to determine the clinical utility of these approaches in the evaluation for AC.

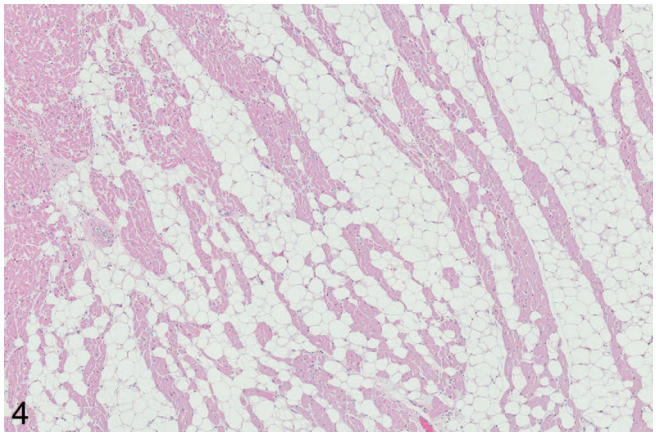

Figure 4. *Fatty infiltration in an obese patient. The section demonstrates marbling of fatty tissue within the right ventricle of an obese 68-year-old woman at autopsy (body mass index = 47.9). The finding of adipose tissue in the absence of a fibrous component is not diagnostic of arrhythmogenic cardiomyopathy (hematoxylin-eosin, original magnification ×20).*

DIFFERENTIAL DIAGNOSIS

The differential diagnosis for AC includes a variety of conditions, including conventional dilated cardiomyopathy, right-sided sarcoidosis, myocarditis, and idiopathic arrhythmias such as right ventricular outflow tract ventricular tachycardia.[1,10] Distinction from conventional dilated cardiomyopathy may be achieved if there is discordance between the degree of arrhythmia and that of ventricular dysfunction, as these features should be similar in conventional dilated cardiomyopathy but not in AC, even in the left-dominant variant. Right-sided sarcoidosis can be quite challenging, as these patients are likely to meet clinical criteria for AC. The major clinical feature to distinguish between AC and sarcoidosis is that sarcoidosis frequently involves the interventricular septum, resulting in high-grade atrioventricular conduction abnormalities that are unusual in AC. If present, noncaseating granulomas are of course helpful in making the diagnosis of sarcoidosis, and sarcoidosis is more likely than AC to run a rapid course. Regarding the distinction from myocarditis, it is currently unclear what role inflammation plays in AC, and serologic studies are essential

in this context. Ideally molecular abnormalities can be demonstrated, which makes the distinction of AC from these various entities much less problematic.

TREATMENT AND PROGNOSIS

Following a diagnosis of AC the pressing question becomes whether or not to pursue placement of an implantable cardioverter defibrillator (ICD).[1,13] An ICD is likely to protect from arrhythmia and prevent sudden cardiac death, but ICDs are also associated with complications that are not to be taken lightly. Several risk factors are associated with higher need for an ICD, such as sustained ventricular tachycardia and/or ventricular fibrillation at presentation. However, patients without such episodes may prefer to be managed medically and monitored on an annual basis with electrocardiogram, echocardiogram, and 24-hour Holter monitoring, with the option of pursuing an ICD only if deemed necessary with time. Strenuous activity is generally to be avoided in these patients, even in the setting of an ICD, as it is associated with an increased risk of sudden cardiac death and possibly also with accelerated disease progression.

First-degree relatives of patients with AC should be screened for the disease beginning at puberty.[13] Such screening should include cardiac magnetic resonance imaging, electrocardiogram, stress testing, and Holter monitoring. Importantly, given the high prevalence of digenic mutations and disease modifiers, even when relatives are found not to harbor a known mutation they should be screened. The possibility of prenatal diagnosis has been raised, but it must be approached with the same caution as with living family members.

CONCLUSIONS

Arrhythmogenic cardiomyopathy is a diagnostically challenging condition that appears to be much more prevalent than previously appreciated, raising the possibility that more and more pathologists even in community settings will be exposed to cases that were previously regarded as rare. The most likely setting for a community pathologist to encounter this condition is at autopsy, in which case it is essential that it be recognized so that the decedent's family members can be screened appropriately. As recognition increases and molecular techniques are more readily adopted for screening family members, it is likely that more and more pathologists will be exposed to it at the biopsy level as well. Currently, the role of biopsy in AC is primarily adjunctive, as false negatives are inherently common. Nonetheless, the prospect of useful ancillary studies is appealing and additional studies will hopefully improve on current strategies. With time there will undoubtedly be ongoing discoveries regarding the molecular basis of the disease, which will likely broaden the role of molecular pathologists as well in making the definitive diagnosis of AC and potentially in prognostication.

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