Dilated Cardiomyopathy With Conduction Disease and Arrhythmia

Neal K. Lakdawala, MD; Michael M. Givertz, MD

Case presentation: A 48-year-old woman presents with exertional dyspnea and recurrent syncope. One year earlier, a permanent pacemaker was placed after she complained of fatigue and was found to have high-grade atrioventricular block. Now, she has echocardiographic evidence of moderate to severe left ventricular (LV) systolic dysfunction with regional wall-motion abnormalities. Nuclear imaging is notable for heterogeneous myocardial uptake of technetium Tc99m sestamibi, and coronary angiography reveals widely patent epicardial vessels. Multiple episodes of nonsustained ventricular tachycardia (VT) are documented on continuous ECG monitoring. What are the diagnostic considerations for this patient, and what further evaluations are indicated?

This patient presents with dilated cardiomyopathy (DCM) with electric instability (DCM/E), which we define as conduction disease and arrhythmia out of proportion to the severity of LV systolic dysfunction. Diverse causes can result in DCM/E and fall into general categories of inflammatory, infectious, hereditary, and infiltrative processes. Cardiac presentation associated with these conditions is distinct from more common causes of DCM such as ischemic heart disease, viral myocarditis, valvular dysfunction, pregnancy, or substance abuse. Clinical features that are suggestive of DCM/E include supraventricular arrhythmias or conduction disease that precedes cardiomyopathy, multiple VT morphologies, and features suggestive of ischemic heart disease (Q waves, regional wall-motion abnormalities, perfusion defects, ventricular aneurysm) in the absence of epicardial stenoses. In this Clinician Update, we focus on the diagnostic approach to patients with DCM/E. Emphasis is placed on diagnoses that are relatively common or for which the clinical management would be impacted significantly by recognition of the underlying cause.

Differential Diagnosis of DCM+E

Ischemic heart disease may present with conduction disease and a high burden of arrhythmia, especially in the setting of acute myocardial ischemia/infarction. The exclusion of obstructive coronary artery disease is strongly recommended in patients with DCM+E because atherosclerosis is so prevalent, evidence-based treatment is readily available, and the consequences of missed diagnosis are potentially catastrophic. Tachycardia-mediated cardiomyopathy should be considered in cases in which tachyarrhythmias are frequent or sustained or when LV systolic dysfunction recovers rapidly after rate or rhythm control. A similar presentation may also be seen with high-density ventricular ectopic activity. However, if systolic dysfunction persists after control of ventricular rate or rhythm, then causes of DCM/E (Table 1) should be considered.

Inflammatory Processes

Cardiac Sarcoidosis

Sarcoidosis is an inflammatory disease of unknown origin characterized by noncaseating granuloma formation in multiple organ systems. After an early stage of granulomatous inflammation, sarcoidosis may resolve or progress to end-organ fibrosis. Autopsy series suggest that up to 50% of patients with sarcoidosis have some degree of cardiac involvement, but only a fraction of these had previously recognized...
Table 1. Differential Diagnosis of DCM+E: Clinical Presentation, Diagnostic Features, and Disease-Specific Therapy

<table>
<thead>
<tr>
<th>Disease</th>
<th>Rapid Cardiac Deterioration</th>
<th>Extracardiac Features</th>
<th>Laboratory Tests</th>
<th>Sinus Node Dysfunction</th>
<th>Conduction Disease</th>
<th>Arrhythmia</th>
</tr>
</thead>
<tbody>
<tr>
<td>Cardiac sarcoidosis</td>
<td>+/−</td>
<td>+ + Restrictive lung disease, lupus pernio, lymphadenopathy, iritis</td>
<td>None</td>
<td>−</td>
<td>+/−</td>
<td>+/− (PAC)</td>
</tr>
<tr>
<td>Giant cell myocarditis</td>
<td>+ +</td>
<td>+ + Autoimmune diseases: inflammatory bowel disease, optic neuritis; thymoma</td>
<td>None</td>
<td>−</td>
<td>+</td>
<td>−</td>
</tr>
<tr>
<td>Chagas disease</td>
<td>−</td>
<td>+ + Gastrointestinal dysmotility</td>
<td>T cruzi serology</td>
<td>Early: −</td>
<td>Early: + (RBBB, LAFB) Late: + + (CHB)</td>
<td>−</td>
</tr>
<tr>
<td>Arrhythmogenic RV cardiomyopathy</td>
<td>−</td>
<td>+/− Woolly hair, hyperkeratosis</td>
<td>Desmosome mutation</td>
<td>+</td>
<td>+ (RBBB)</td>
<td>−</td>
</tr>
<tr>
<td>Cardiolaminopathy</td>
<td>−</td>
<td>+/− Skeletal myopathy</td>
<td>LMNA mutation</td>
<td>+</td>
<td>Early: + + (1° AVB and 2° AVB) Late: (CHB and IVCD)</td>
<td>−</td>
</tr>
<tr>
<td>LV noncompaction</td>
<td>−</td>
<td>+/− Skeletal myopathy</td>
<td>Sarcomere, LDB3 or TAZ mutation</td>
<td>−</td>
<td>+ (WPW)</td>
<td>−</td>
</tr>
<tr>
<td>End-stage hypertrophic cardiomyopathy</td>
<td>−</td>
<td>−</td>
<td>Sarcomere mutation</td>
<td>−</td>
<td>+ (IVCD, BBB)</td>
<td>+</td>
</tr>
<tr>
<td>Cardiac iron overload</td>
<td>+ +</td>
<td>+ + + Diabetes, bronzed skin, arthralgias, cirrhosis</td>
<td>Iron studies</td>
<td>−</td>
<td>+</td>
<td>+</td>
</tr>
</tbody>
</table>

SVT indicates supraventricular tachycardia; CMR, cardiac magnetic resonance; EMB, endomyocardial biopsy; PAC, premature atrial contraction; LGE, late gadolinium enhancement; RBBB, right bundle-branch block; LAFB, left anterior fascicular block; CHB, complete heart block; PVC, premature ventricular contraction; NA, not available; AVB, atrioventricular block; IVCD, intraventricular conduction delay; AF, atrial fibrillation; WPW, Wolff-Parkinson-White; BBB, bundle-branch block; and LVH, LV hypertrophy. The (+) and (−) are semiquantitative estimates of diagnostic accuracy.

*Infect pattern refers to regional wall-motion abnormalities and/or LV wall thinning.
†Neither is approved by the US Food and Drug Administration, but they can be obtained from the Centers for Disease Control.
‡Not approved by the US Food and Drug Administration, but may be obtained via a Treatment Investigational New Drug (IND) Application.

Cardiac sarcoidosis (CS). Cardiac disease is one of the more common causes of death in sarcoidosis and may be preventable with the use of appropriate therapies. Approximately 5% of patients will have cardiac-predominant disease and present without characteristic pulmonary, dermatologic, or ocular features. CS most commonly affects the myocardium but may also affect the pericardium and endocardium. Myocardial infiltration may be associated with VT, aneurysm formation, or global systolic dysfunction, but the most common clinical feature is conduction disease.

The noncaseating granuloma is the characteristic pathological lesion of sarcoidosis (Figure, A); however, granulomas are not specific to sarcoidosis and can be the result of various infectious and noninfectious causes. Diagnostic criteria for CS have been proposed that rely on pathological demonstration of cardiac granulomas or noninvasive evidence of cardiac involvement in a patient with pathologically proven extracardiac sarcoidosis (online-only Data Supplement Table I). Owing to patchy involvement, often of the LV, a right ventricular (RV) endomyocardial biopsy provides diagnostic evidence of CS in only 25% to 50% of autopsy-confirmed cases. Contempory imaging with fluorodeoxyglucose (18F-FDG) positron emission tomography or cardiac magnetic resonance can identify inflammation (Figure, B and C), has better diagnostic accuracy than older techniques (thallium 201 or gallium 67 scintigraphy), provides complementary information, and can predict adverse events.

Corticosteroids are the mainstay of therapy for sarcoidosis with cardiac involvement. Retrospective observational studies suggest benefit, particularly in the stabilization or improvement of LV function; however, steroids may not reduce the frequency or severity of VT or eliminate conduction disease.
Corticosteroids should be initiated at a high dose (prednisone 40 to 60 mg daily) and tapered off slowly over months if clinical and imaging features remain stable or improve.

**Giant Cell Myocarditis**

Giant cell myocarditis (GCM) is an autoimmune disorder that is rapidly progressive and highly fatal. In patients presenting with GCM, there is an increased prevalence of thymoma and coexistent autoimmune diseases (eg, inflammatory bowel disease), and the diagnosis is made by histology in the appropriate clinical setting. Heart failure develops rapidly (days to weeks) and is accompanied or preceded by VT, often with multiple morphologies. Although LV function is moderate to severely depressed, LV size may be only mildly enlarged, reflective of the rapid course and limited time for remodeling.

Widespread and multifocal inflammatory infiltrates admixed with myonecrosis, multinucleated giant cells, and the absence of the noncaseating granuloma are the characteristic histopathologic features. In contrast to CS, the yield of endomyocardial biopsy is relatively high (>80%) because of the severe and diffuse nature of cardiac involvement. Heart failure in GCM is severe, usually refractory to standard pharmacological therapies, and may require mechanical circulatory support as a bridge to transplantation. Median transplant-free survival (5.5 months in 1 series) is significantly worse than in more typical lymphocytic myocarditis. Recent multicenter studies suggest that potent immunosuppressive therapy, which includes cyclosporine, can achieve disease remission in a minority of patients. GCM may recur after cardiac transplantation but is usually mild and responsive to increased immunosuppression.

**Infectious Processes**

Viral infections are a proposed mechanism for idiopathic DCM, but definitive evidence for causation is lacking, and the associated cardiomyopathy is not notable for an exaggerated burden of conduction disease or arrhythmia. Among the infectious causes of DCM, Chagas disease is most common worldwide. Other less common infectious causes of DCM include African trypanosomiasis, toxoplasmosis, and, rarely, Lyme disease.

**Chagas Disease**

Chagas disease is caused by the protozoal parasite *Trypanosoma cruzi* and is spread by an insect vector, the triatome bug. Infection is largely re-

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**Table 1. Continued**

<table>
<thead>
<tr>
<th>Echocardiography</th>
<th>Nuclear</th>
<th>CMR</th>
<th>EMB</th>
<th>Histopathology</th>
<th>Disease-Specific Treatment</th>
</tr>
</thead>
<tbody>
<tr>
<td>Infarct pattern,* inferobasal aneurysm</td>
<td>+ + Perfusion defect, inflammation</td>
<td>+ + LGE, edema</td>
<td>+ + Patchy noncaseating granulomas, variable inflammation</td>
<td>Corticosteroids, antimalarial drugs, methotrexate, azathioprine</td>
<td></td>
</tr>
<tr>
<td>Nonspecific</td>
<td>+</td>
<td>+</td>
<td>+ + Widespread or multifocal necrosis, mixed inflammatory infiltrate, giant cells without granulomas</td>
<td>Corticosteroids, cyclosporine, muromonab-CD3</td>
<td></td>
</tr>
<tr>
<td>Infarct pattern, apical aneurysm or thrombus</td>
<td>+/− Perfusion defect</td>
<td>+ LGE, apical aneurysm</td>
<td>+/− Early: Intracellular parasites Late: Nonspecific</td>
<td>Benznidazole, nifurtimox†</td>
<td></td>
</tr>
<tr>
<td>RV:&gt;LV dilation/ dysfunction, focal aneurysms of RV free wall, increased RV trabeculation, echo-bright moderator band</td>
<td>−</td>
<td>+ + Fat, LGE, RV dilation, dysfunction and focal aneurysms</td>
<td>+ Fibrofatty replacement of myocytes</td>
<td>NA</td>
<td></td>
</tr>
<tr>
<td>Nonspecific</td>
<td>−</td>
<td>+ LGE</td>
<td>− Nonspecific</td>
<td>NA</td>
<td></td>
</tr>
<tr>
<td>↑ Trabeculation, LV thrombi</td>
<td>−</td>
<td>+ + ↑ Trabeculation, LGE</td>
<td>− Nonspecific</td>
<td>NA</td>
<td></td>
</tr>
<tr>
<td>LVH (may have regressed)</td>
<td>−</td>
<td>+ + LGE</td>
<td>+/− Myocyte disarray</td>
<td>NA</td>
<td></td>
</tr>
<tr>
<td>Nonspecific</td>
<td>−</td>
<td>+ + ↓ ↓ T2*</td>
<td>+ + Iron overload (prussian blue stain)</td>
<td>Deferoxamine, deferiprone‡</td>
<td></td>
</tr>
</tbody>
</table>
stricted to endemic regions of Central and South America; however, because of immigration patterns, increasing numbers of cases are expected in Western Europe and the United States. The acute phase of Chagas disease is usually not recognized and is rarely life-threatening. Ten to 20 years after initial infection, approximately 20% of patients will develop chronic Chagas disease, most prominently affecting the heart and to a lesser extent the gastrointestinal tract. The mechanism of cardiac damage is unknown but is hypothesized to be a robust immune response to a small population of remaining protozoa.

Recognition rests on suspecting the disease in an individual who has lived in an endemic region, and the presence of coexistent gastrointestinal dysmotility is an important clue. Chronic infection is diagnosed by serological evidence of *T. cruzi* infection and demonstration of typical cardiac or gastrointestinal involvement.

Cardiac involvement in chronic Chagas disease develops gradually, usually over many years, with electrical abnormalities preceding changes in LV morphology and function. Minor ECG abnormalities in the early phase (right bundle-branch and/or left anterior fascicular block, premature ventricular contractions) are associated with a slightly increased risk of sudden cardiac death (SCD) due to VT. Morphological changes in the LV do not develop until the intermediate phase of disease. Apical aneurysms, regional ventricular thinning, and wall-motion abnormalities may predispose to thrombus formation and lead to thromboembolic events. Marked ECG abnormalities usually accompany LV remodeling and include sinus bradycardia, atrial fibrillation, high-grade atrioventricular block, low QRS voltage, and pathological Q waves. Death in this phase may result from VT or bradyarrhythmias. End-stage disease is characterized by severe global LV dysfunction and refractory heart failure.

Traditionally, therapy for Chagas cardiomyopathy has been supportive, including pacer/implantable cardioverter defibrillator (ICD) and cardiac transplantation where available. However, emerging data suggest that antiprotozoal therapy may alter the cardiac course of disease.

**Genetic Cardiomyopathies**

Genetic causes of DCM+E share several management strategies in common. Clinical evaluation of family members is critical once the proband has been diagnosed, because other relatives may have clinically silent cardiomyopathy and...
may benefit from therapy. Moreover, genetic testing may help clarify the diagnosis and identify at-risk family members who carry the pathogenic mutation but are currently unaffected.17

Arrhythmogenic RV Cardiomyopathy
Arrhythmogenic RV cardiomyopathy (ARVC) is a rare genetic disease that results in fibrofatty replacement of the myocardium. Sporadic and familial cases have been described, with mutations in desmosomal genes identified in 50% of cases.18 Although first recognized as a disease of the RV, various degrees of LV involvement may precede or obscure RV involvement.19 Accordingly, the diagnosis of ARVC should remain in consideration when patients present with DCM+E, even in the absence of substantial RV involvement.

Diagnosis rests on fulfilling the recently updated consensus criteria (online-only Data Supplement Table II) that classify major and minor abnormalities in RV structure and function (eg, dilation, aneurysm, and akinesia), histopathology (fibrofatty replacement), ventricular depolarization (eg, epsilon waves; Figure, D), ventricular repolarization (eg, precordial T-wave inversions), ventricular arrhythmia (eg, left bundle-branch VT), and family history. Combinations of 2 major, 1 major and 2 minor, or 4 minor criteria are required for definitive diagnosis.20 The previous diagnostic criteria were criticized for being qualitative, insensitive in the context of family evaluations,21 and nonspecific when applied to patients with alternative diagnoses but similar presentations.22 The revised criteria are more quantitative, thereby eliminating ambiguity; however, they were derived entirely from a comparison between previously diagnosed ARVC patients and healthy control subjects. Therefore, the specificity of the revised criteria when applied to patients with other forms of DCM+E remains unproven.

ARVC shows substantial clinical heterogeneity. Presenting symptoms include palpitations, syncope, heart failure, and SCD.23 Sudden death due to VT is more common when certain high-risk features are present, including syncope, extensive RV dilation/hypokinesia, any LV involvement, and family history of SCD. Death due to progressive heart failure is less common and is thought to affect ≈10% of patients.24

Cardiolaminopathy
Mutations in LMNA, which encodes the nuclear envelope protein lamin A/C, are a well-described cause of autosomal-dominant familial DCM+EL25 Different mutations in the same gene are associated with diverse clinical phenotypes, including progeria, lipoatrophy, and limb-girdle muscular dystrophy. The pathophysiological basis of cardiolaminopathy remains undefined but likely differs from other nonmyopathic disease caused by LMNA mutations.

Mutations in LMNA associated with DCM+E are highly penetrant, with nearly 100% of mutation carriers demonstrating some evidence of cardiac involvement by 65 years of age.26 Initial manifestations are first-degree atrioventricular block with frequent premature atrial contractions, which rarely present before adulthood. Gradually, the severity of atrioventricular block progresses to complete heart block, and frequent premature atrial contractions transition to atrial fibrillation. Cardiomyopathy usually follows the development of conduction disease by several years, and the risk of VT and SCD appears highest when systolic dysfunction is present. Nevertheless, clinical manifestations vary significantly, even within individual families. A minority of cardiolaminopathy patients will have overt or subclinical skeletal myopathy. Genetic testing for LMNA mutations is widely available and can assist in the identification of at-risk family members.

LV Noncompaction
Isolated LV noncompaction is a rare disorder, defined by hypertrabeculation of the LV, that has been linked to mutations in sarcomere genes, tafaz-

zim, and Cypher/ZASP and may be associated with neuromuscular disease.27 Diagnosis relies on detection and quantification of LV hypertrabeculation with demonstration of flow in communication with the LV cavity. The current imaging criteria, however, lack sufficient sensitivity and specificity.28 Initial descriptions of LV noncompaction highlighted the high risk of SCD, heart failure, and thromboembolism, and ventricular preexcitation has also been described. Recent studies suggest that prognosis is less ominous, especially for patients diagnosed incidentally or identified through family screening.29 Because of the concern for thromboembolism, long-term anticoagulation should be considered.

End-Stage Hypertrophic Cardiomyopathy
Five to 10% of patients with hypertrophic cardiomyopathy will develop end-stage or “burned-out” morphology, characterized by LV dilation, wall thinning, and hypokinesia. In some patients, the initial presentation of hypertrophic cardiomyopathy may be with end-stage morphology and indistinguishable from DCM until autopsy or explantation demonstrates myocyte disarray. Compared with patients with primary DCM and advanced heart failure, patients with end-stage hypertrophic cardiomyopathy often have lesser degrees of LV dilation or systolic dysfunction, which may be a clue to the underlying diagnosis. End-stage hypertrophic cardiomyopathy is associated with a high risk of atrial and ventricular arrhythmias and death due to progressive heart failure or VT.30 Other important diagnostic clues are increased ventricular wall thickness and a family history of hypertrophic cardiomyopathy. Demonstration of a sarcomere gene mutation may help with diagnosis; however, distinct mutations in several sarcomere genes can also cause primary DCM.

Other Genetic Cardiomyopathies
Other inherited causes of DCM+E have been reported, usually in the context of severe skeletal myopathy.
Implicated genes include DMD (dystrophin), SCN5A (voltage-gated sodium channel), DES (desmin), DMPK (myotonin protein kinase), and EMD (emerin).31

**Infiltrative Processes**

**Cardiac Iron Overload**

Inherited disorders of iron metabolism (eg, hemochromatosis) or hemoglobin biosynthesis (eg, β-thalassemia) can result in primary or secondary iron overload involving the heart. Typically, extracardiac involvement is obvious and predominant, but the unifying diagnosis may be missed if iron overload is not recognized. If left untreated, cardiac iron overload may lead to DCM+E. Indeed, cardiac failure is the primary cause of death in β-thalassemia major, a disease with a worldwide incidence of 60 000 new cases annually.32 Effective iron chelation strategies have shown promise in preventing progressive cardiomyopathy but depend on timely recognition of cardiac involvement. Echocardiographic features are nonspecific, and Doppler assessment of diastolic function has not proved valuable in the recognition of preclinical cardiac iron overload.33 Delayed T2* recognized by cardiac magnetic resonance is a sensitive marker of cardiac iron deposition and can predict future cardiac events.32 Histopathological examination and cardiac magnetic resonance imaging are diagnostic and usually are performed in the context of biochemical evidence of increased iron stores. Chelation therapy is generally ineffective for patients with DCM+E and refractory heart failure.

**Diagnostic Approach**

Several of the above diseases have diagnostic criteria established by consensus (online-only Data Supplement tables). Previously published case series have identified patients with 1 diagnosis (eg, CS) who met diagnostic criteria for another (eg, ARVC).22 Thus, a broad differential diagnosis and a comprehensive evaluation (with special attention to the time course of illness, ECG, and laboratory abnormalities) are recommended, as well as imaging (Table 1). Genetic testing and endomyocardial biopsy are most likely to provide a definitive diagnosis.

The time from onset of symptoms to the development of severe heart failure may help narrow the differential diagnosis. A precipitous decline in LV systolic function and the rapid development of heart failure are well described in cardiac iron overload and in GCM. A slower time course is typical for Chagas disease and genetic cardiomyopathies. The recognition of affected family members is suggestive of a genetic cardiovascular disease, especially when multiple family members are involved and an autosomal-dominant pattern of inheritance is present. However, the reduced penetrance of some genetic cardiomyopathies (especially ARVC) and the clustering of nongenetic diseases within families (eg, sarcoidosis) are confounding factors.

Conventional laboratory investigation is unlikely to identify the underlying disease process, with key exceptions being cardiac iron overload and Chagas disease. Accordingly, serum iron, ferritin, and iron binding capacity should be measured in all patients presenting with DCM+E, and T cruzi titers can be measured in patients from endemic regions. ECG abnormalities are prevalent in all conditions, but few are sufficiently distinctive to identify the cause. One exception is epsilon waves, which represent a major criterion for the diagnosis of ARVC (Figure, D).

Contemporary imaging techniques offer enhanced diagnostic accuracy via improved characterization of morphology and the ability to image adipose tissue, inflammation, fibrosis, and iron. Distinguishing echocardiographic features are uncommon, except for the presence of RV dysfunction greater than LV dysfunction that is suggestive of ARVC and the inferoposterior and apical aneurysms seen in sarcoidosis and Chagas disease, respectively. As shown in panel C of the Figure, cardiac magnetic resonance can identify fibrosis (late gadolinium enhancement) and inflammation (T2-weighted images). It can also identify increased adipose tissue (T1-weighted) and iron (T2*) and offers better characterization of RV morphology than echocardiography. Increased intramyocardial fat is suggestive of ARVC, whereas excess iron would be diagnostic of cardiac siderosis. A noncoronary pattern of fibrosis may distinguish nonscarring from ischemic cardiomyopathy but is nonspecific and unlikely to distinguish among the diverse causes of DCM+E. Myocardial inflammation can be imaged by positron emission tomography with radiolabeled glucose (18F-FDG), which is taken up by inflammatory cells (Figure, B). Because hibernating myocardium is associated with similar findings, the exclusion of critical coronary disease is required. Demonstration of inflammation is supportive of CS or GCM but is nondiagnostic.

Endomyocardial biopsy can establish a definitive diagnosis in patients presenting with DCM+E secondary to GCM, CS, and iron overload, but the diagnostic yield varies by condition. In GCM and cardiac iron overload, the yield is >80%, and in CS, the yield is lower than 50% (even with 4 or more specimens). Advanced imaging techniques, including cardiac voltage mapping, can improve the yield of endomyocardial biopsy in CS by directing the biopsy toward affected regions of the myocardium, including the LV.34 The American Heart Association/American College of Cardiology consensus statement on the use of endomyocardial biopsy supports its application in patients presenting with acute or chronic DCM+E.11

**Therapeutic Considerations**

Evidence-based medical and device therapies for heart failure have not been studied specifically in DCM+E but are recommended. Disease-specific therapies are available for CS and GCM (immunosuppression) and cardiac iron overload (chelation), which emphasizes the importance of
making a definitive diagnosis (Table 1). Cardiac transplantation has been used successfully in DCM+E; however, the recurrence of inflammatory (CS and GCM) and infectious (Chagas) disease in the allograft has been described. Mechanical circulatory support can be used, but the increased burden of VT, especially in GCM, requires biventricular assistance as a bridge to transplantation.

The risk of sudden death in DCM+E is a major challenge. Antiarrhythmic drugs do not effectively prevent SCD. Furthermore, limiting ICDs to patients who meet traditional indications for implantation (eg, LVEF <35%, resuscitated arrest) will likely exclude patients with DCM+E who might benefit from prophylactic ICD placement. Consensus guidelines recognize the increased risk of SCD in DCM+E and recommend broader indications for ICD placement. Large prospective studies do not exist to validate these criteria. However, emerging data support the expansion of ICD placement in several scenarios: whenever a pacemaker would be placed, if there is LV damage or systolic dysfunction, or in the presence of unexplained syncope, VT, or family history of SCD (Table 2).

Clinical Follow-Up

The patient underwent endomyocardial biopsy and was found to have noncaseating granuloma and myocarditis consistent with CS. Extensive clinical and radiographic evaluation did not reveal evidence of pulmonary, dermatologic, or ocular involvement, and a gallium scan did not suggest active cardiac disease. Corticosteroids were administered, but the burden of VT and severity of LV systolic dysfunction remained relatively unchanged. An ICD was placed, and the patient subsequently received multiple appropriate shocks for VT. Six years after presentation, she is well compensated and has been maintained on prednisone, mexilutine, sotalol, enalapril, spironolactone, digoxin, and furosemide.

Summary

Patients with DCM presenting with a disproportionately high burden of arrhythmia or conduction disease (DCM+E) have unique diagnostic considerations, including inflammatory, infectious, genetic, and infiltrative processes. Correct recognition of the underlying cause may have important therapeutic and prognostic implications. Although established diagnostic criteria are available for several of the specific disorders, definitive diagnosis may not be possible without supportive histopathology or genetic testing. Patients with DCM+E are at high risk of sudden death, and consideration should be given to ICD implantation, even in the absence of traditional indications.

Disclosures

None.

References


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SUPPLEMENTAL TABLES

Supplemental Table 1. Guidelines for Diagnosis of Cardiac Sarcoidosis from the Japanese Ministry of Health and Welfare

<table>
<thead>
<tr>
<th>Category</th>
<th>Criteria</th>
</tr>
</thead>
<tbody>
<tr>
<td>Histologic diagnosis</td>
<td>Cardiac sarcoidosis is diagnosed when histologic analysis of operative or endomyocardial biopsy specimens demonstrates epithelioid granuloma without caseating granuloma</td>
</tr>
<tr>
<td>Clinical diagnosis</td>
<td>Histologic diagnosis of extracardiac sarcoidosis plus ECG abnormalities (RBBB, left-axis deviation, atrio-ventricular block, VT, premature ventricular contraction, or abnormal Q or ST-T changes), and at least one of the following:</td>
</tr>
<tr>
<td></td>
<td>1. Abnormal wall motion, regional wall thinning, or thickening, or dilatation of LV on ultrasound</td>
</tr>
<tr>
<td></td>
<td>2. Perfusion defect on $^{201}$Tl myocardial scintigram or abnormal accumulation on $^{67}$Ga-citrate or $^{99m}$Tc-pyrophosphatemyocardial scintigram</td>
</tr>
<tr>
<td></td>
<td>3. Abnormal intracardiac pressure, low cardiac output, or abnormal wall motion or depressed LV ejection fraction</td>
</tr>
<tr>
<td></td>
<td>4. Interstitial fibrosis or cellular infiltration over moderate grade in endomyocardial biopsy even if findings are nonspecific</td>
</tr>
</tbody>
</table>

ECG, electrocardiographic; LV, left ventricle; RBBB, right bundle branch block; VT, ventricular tachycardia
### Supplemental Table 2. 2010 Revised Task Force criteria for the diagnosis of arrhythmogenic right ventricular cardiomyopathy

<table>
<thead>
<tr>
<th>Diagnostic Criteria*</th>
<th>Major Criteria</th>
<th>Minor Criteria</th>
</tr>
</thead>
</table>
| Global and/or regional dysfunction and structural alterations | • By 2D echo: Regional RV akinesia, dyskinesia or aneurysm *and* 1 of the following:  
1. End-diastolic PLAX RVOT ≥32 mm (or† ≥ 19 mm/m²)  
2. End-diastolic PSAX RVOT ≥36 mm (or† ≥ 21 mm/m²)  
3. Fractional area change ≤33%  
• By MRI: Regional RV akinesia or dyskinesia or dyssynchronous RV contraction *and* 1 of the following:  
1. Ratio or RV end-diastolic volume to BSA ≥110 mL/m² (male) or ≥100 mL/m² (female)  
2. RVEF ≤40%  
• By RV angiography: regional RV akinesia, dyskinesia, or aneurysm | • By 2D echo: Regional RV akinesia, or dyskinesia *and* 1 of the following:  
1. End-diastolic PLAX RVOT 29 to 31 mm (or† 16 to 18 mm/m²)  
2. PSAX RVOT 32-35 mm (or† 18 to 20 mm/m²)  
3. Fractional area change 34-40%  
• By MRI: Regional RV akinesia or dyskinesia or dyssynchronous RV contraction *and* 1 of the following:  
1. Ratio or RV end-diastolic volume to BSA 100 to 109 mL/m² (male) or 90 to 99 mL/m² (female)  
2. RV ejection fraction 41 to 45% |
| 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 to 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 V₁-V₃ or beyond in individuals >14 years (in absence of complete RBBB) | • Inverted T waves in V₁ and V₂ in individuals >14 years (in absence of complete RBBB), or in V₄, V₅, or V₆.  
• Inverted T waves in V₁–V₄ in individuals >14 years in the presence of complete RBBB. |
| Depolarization/conduction abnormalities | Epsilon waves (reproducible low-amplitude signals between end of QRS complex to onset of the T wave) in right precordial leads (V_1-V_3) | Late potentials (signal averaged ECG) in ≥1 of 3 parameters in the absence of QRS duration of ≥110 ms on the standard ECG  
- Filtered QRS duration ≥114 ms  
- Duration of terminal QRS <40 μV (low amplitude signal duration) ≥38 ms  
- Root-mean-square voltage of terminal 40 ms ≤20 μV  
- Terminal activation duration of QRS ≥55 ms measured from the nadir of the S wave to the end of the QRS, including R’, in V_1, V_2, or V_3, in the absence of complete heart block. |
| Arrhythmias | Nonsustained or sustained ventricular tachycardia of LBBB 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 LBBB morphology with inferior axis (positive QRS in leads II, III, and aVF and negative in lead aVL) or of unknown axis  
- > 500 PVCs per 24 hours (Holter) |
| Family history |  
- ARVC confirmed in a first-degree relative who meets current Task Force criteria  
- ARVC confirmed pathologically at autopsy or at surgery in a first-degree relative  
- Identification of a pathogenic mutation categorized as associated or probably associated with ARVC in the patient under evaluation |  
- History of ARVC in a first-degree relative in whom it is not practical or possible to determine whether the family member meets current Task Force criteria  
- Premature SCD (<35 yr) due to suspected ARVC in a first degree family member  
- ARVC confirmed pathologically at autopsy or at surgery in a second-degree relative |
ARVC, arrhythmogenic right ventricular cardiomyopathy; ECG, electrocardiogram; LBBB, left bundle branch block; PVCs, premature ventricular contractions; RV, right ventricle; RVEF, right ventricular ejection fraction; SCD, sudden cardiac death. *The presence of either two major criteria, one major and two minor criteria, or 4 minor criteria are considered definitively diagnostic; 1 major and 1 minor or 3 minor are considered borderline diagnostic and 1 manor or 2 minor are considered possibly diagnostic. † = corrected for body surface area.