Arrhythmogenic Right Ventricular Cardiomyopathy Presenting as Clinical Myocarditis in Women

Paul J. Scheel, III, MD[a], Brittney Murray, MS[a], Crystal Tichnell, MGC, RN[a], Cynthia A. James, PhD[a], Harikrishna Tandri, MBBS, MD[a], Hugh Calkins, MD[a], Stephen P. Chelko, PhD[a,b], and Nisha A. Gilotra, MD[a,*]

Patients with arrhythmogenic right ventricular cardiomyopathy (ARVC) classically initially present with ventricular arrhythmias or, less commonly, heart failure. Myocardial inflammation has been implicated in pathogenesis, but clinical myocarditis in ARVC is less described. We therefore studied clinical myocarditis as an initial ARVC presentation, and hypothesized that these patients have distinct clinical and genetic characteristics. Using the Johns Hopkins ARVC Registry, we identified 12 patients (all female, median age 20) referred between 2014 and 2019 diagnosed with myocarditis at presentation who were subsequently diagnosed with ARVC by Task Force Criteria. Majority presented with chest pain (n = 7, 58%) or ventricular arrhythmia (n = 3, 25%). All patients had troponin elevations and left ventricular (LV) function was reduced in 5 (42%). Magnetic resonance imaging demonstrated LV delayed gadolinium enhancement and/or pericardial enhancement in 10 (83%); only 3 (25%) patients had right ventricular abnormalities. Pathogenic genetic variants were identified in 11 (92%) patients: 10 desmoplakin (*DSP*) and 1 desmoglein-2 (*DSG2*). Thus, nearly 1/3 (10/32, 31%) of overall *DSP* ARVC patients were originally diagnosed with myocarditis. Patients were diagnosed with ARVC 1.8 years (IQR 2.7 years) after presentation and 8 (75%) patients did not meet Task Force Criteria without genetic testing. ARVC diagnosis led to an additional 5 (42%) patients referred for implantable cardiac defibrillator and 17 family member diagnoses. In conclusion, ARVC may initially present as myocarditis and these patients have distinct characteristics including female gender, LV involvement and *DSP* gene variants. Genetic testing is key to ARVC diagnosis and should be considered in select myocarditis patients. **(Am J Cardiol 2021;145:128−134)**

Myocarditis is a nonspecific inflammatory disease of the myocardium with varied presentation and etiology.[1-3] Given limitations of endomyocardial biopsy, the diagnosis is often based on clinical presentation and cardiac magnetic resonance (CMR) imaging.[3-6] There is increasing evidence that underlying genetic abnormalities associated with cardiomyopathy may predispose patients to myocarditis.[7-10] Arrhythmogenic right ventricular cardiomyopathy (ARVC) is classically associated with myocyte loss due to disruption of the cardiac desmosomes, leading to fibrofatty replacement and an arrhythmic presentation.[11-14] Heart failure is also now recognized as an alternative presenting phenotype.[15] Diagnosis of ARVC is based on the 2010 Task Force Criteria (TFC) which incorporates functional (ECG, echocardiography, and CMR imaging) and pathological phenotypes, arrhythmia history, and family history and/or genetics (pathogenic gene variants and family history). Inflammation is increasingly recognized in ARVC pathogenesis.[11-14] We hypothesized that a subset of patients ultimately diagnosed with ARVC initially present with a clinical picture of myocarditis and have specific distinguishing characteristics.

Methods

The Johns Hopkins ARVC Program evaluates patients referred for possible ARVC and their family members. The ARVC Registry prospectively enrolls those affected or at risk for ARVC. The registry includes detailed medical records obtained at time of referral, dating back to the original clinical presentation. The registry data for each patient is updated regularly with information gathered through either direct clinical contact with the ARVC Program or communication with patients supplemented with outside institution records. We prospectively identified patients enrolled in the registry from 2014 to 2019 who (1) met 2010 ARVC TFC by last follow-up, (2) were initially diagnosed with clinical myocarditis, and (3) met the European

[a]Division of Cardiology, Department of Medicine, Johns Hopkins School of Medicine, Baltimore, Maryland; and [b]Department of Biomedical Sciences, Florida State University College of Medicine, Tallahassee, Florida. Manuscript received October 9, 2020; revised manuscript received and accepted December 31, 2020.

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*Corresponding author: Tel: (443) 287-6720; fax: (443) 873-5019

E-mail address: naggarw2@jhmi.edu (N.A. Gilotra).

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Society of Cardiology diagnostic criteria for clinically suspected myocarditis on presentation. The Johns Hopkins Institutional Review Board approved the study protocol. Written, informed consent was obtained from each patient.

Demographic and clinical data including ARVC TFC, imaging studies, pathology results, and genetic testing results were obtained from the registry. Genetic testing including at a minimum 50 genes was performed in each patient. All patients underwent mutation analysis of the desmosomal genes encoding plakophilin-2 (*PKP2*), desmoplakin (*DSP*), desmoglein-2 (*DSG2*), desmocollin-2 (*DSC2*), and plakoglobin (*JUP*) as well as nondesmosomal gene analysis including transmembrane protein 43 (*TMEM43*) and phospholamban (*PLN*). Medical records were reviewed for the initial diagnostic impression and clinical course. The time of initial presentation was considered the first medical contact for symptoms that led to a diagnosis of myocarditis. Left ventricular ejection fraction (LVEF), left ventricle (LV) diastolic diameter measured in the parasternal long axis, degree of RV dilation and degree of RV dysfunction were obtained from the transthoracic echocardiogram (TTE) report during the index presentation. If TTE results were not available, CMR estimate of these parameters was used if it was performed during the index presentation. Time of ARVC diagnosis was defined as when the patient was evaluated for and met ARVC TFC.[16] Follow-up cardiac function was determined by the most recent TTE or CMR. Patient family history was determined based on patient report, including whether a family member was diagnosed with ARVC. Variants in the ARVC Registry were readjudicated per ACMG criteria[17] with only pathogenic or likely pathogenic variants reported as recently described.[18]

Descriptive statistical analysis was performed as follows: continuous variables were expressed as mean±SD (normally distributed) or median (IQR) (skewed) and categorical variables as numbers (percentages).

Results

Of the 520 patients enrolled in the Johns Hopkins ARVC Registry during the study period, 236 met ARVC TFC. Of those, we identified 12 female Caucasian patients (referred to as Patient 1 − 12) who were originally diagnosed with clinical myocarditis. The presenting characteristics and subsequent diagnostic work-up for each patient is presented in Table 1. The median age at presentation was 20 years (IQR 14.5). The most common presenting symptom was chest pain and all patients had elevated serum troponin levels (Table 1). The only abnormal electrocardiographic characteristics that appeared in multiple patients at presentation were T wave inversion in multiple leads and widened QRS interval. LV dysfunction (LVEF ≤45%) was seen in 5 (42%) patients at presentation. Coronary angiography was performed in 6 (50%) patients and was normal in each. All patients underwent CMR either during their index presentation or at the time of repeat presentation with recurrent symptoms. Late gadolinium enhancement (LGE) abnormalities were observed in most patients and generally occurred in a sub-epicardial distribution and primarily involving the LV. An RV abnormality was noted in 3 (25%) patients and none of these were in isolation of LV abnormalities. The overall diagnostic radiologic impression of 6 (50%) of the CMR reports was myocarditis. Endomyocardial biopsy was performed in 7 (58%) patients. Only 1 biopsy (Patient 4) showed findings consistent with borderline myocarditis based on Dallas criteria.[3] Biopsy in Patient 5 showed fibrofatty replacement and interstitial fibrosis. The only abnormalities seen on the other biopsies included mild hypertrophy and minimal interstitial fibrosis.

Genetic testing was performed in all patients either because of recurrent presentation for myocarditis without a clear etiology or due to family history. The known family history of cardiovascular disease at index presentation is shown in Table 1. Patient 8 underwent genetic testing and medical evaluation after an ARVC diagnosis in her half-sister (Patient 5) led to ARVC being diagnosed in their father. During her initial evaluation, Patient 8 did not meet TFC for ARVC. Patient 10 had no family history at index presentation but later had multiple family members suffer cardiac arrest and receive cardiomyopathy diagnoses (see Figure 1 for pedigree). All but 1 (n = 11/12, 92%) of the patients had a pathogenic or likely pathogenic (P/LP) variant on genetic testing (Table 1). Ten of these 11 patients (91%) had a variant in the desmoplakin (*DSP*) gene. Of the Registry cohort from 2014-2019, 54 had a P/LP *DSP* mutation, with 32 of these meeting TFC. Therefore, 31% (10/32) of ARVC patients with a P/LP *DSP* mutation had a myocarditis presentation. To compare, there were 109 patients with *PKP2* meeting TFC and none of them had an initial diagnosis of myocarditis.

The TFC met by each patient is shown in Table 1. Due to the presence of the P/LP desmosomal variants, almost all patients (n = 11/12, 92%) met major TFC for family history. Repolarization abnormalities (n = 7/12, 58%) and arrhythmias (n = 8/12, 75%) fulfilling minor criteria were also met by a majority of the patients at the time of ARVC diagnosis. It is notable that most of these patients (n = 8, 75%) required fulfillment of the family history and/or genetics criteria to establish a definite ARVC diagnosis.

The clinical course timeline for each patient is shown in Figure 2. Almost half (n = 5/12, 42%) of the patients had recurrent symptoms necessitating medical care prior to being diagnosed with ARVC. Patient 7 had recurrent syncope but also developed intermittent chest pain and was eventually found to have ventricular arrhythmias leading to recurrent presentations prior to her ARVC diagnosis. Her genetic testing was gene-elusive and she did not meet criteria for ARVC until she ultimately developed RV morphologic changes on close follow-up. The median time from presentation to ARVC diagnosis was 1.8 years (IQR 2.7) with the ranges shown in Figure 2. Patient 8, who was diagnosed 14 days after index presentation, had initially presented to an outside institution, at which time she had already had a negative ARVC evaluation as described above, and therefore was diagnosed with myocarditis. After discharge she was re-evaluated by the Johns Hopkins ARVC Program at the request of her family and ultimately met ARVC TFC criteria. At the time of ARVC diagnosis, 6 (50%) patients had an implantable cardiac defibrillator (ICD). An additional 5 (42%) patients either had an ICD placed or were recommended for an ICD after their

Table 1
Characteristics of patients diagnosed with myocarditis and subsequently meeting 2010 Task Force Criteria for ARVC

Pt	Age	Sx*	Trop peak†	ECG‡	CMR Findings§	LVEF (%)	InitialTreatment	FamHx#	Gene w/ variant	TFC Met¶	Most recent LVEF (%)
1	10	CP	9.4 (T)	TWI (V1)	LV LGE RV LGE	55	NSAID	-	*DSP;* c.3526delG, *p.V1176Ffs*20*	FAMHX, arr, structure	40
2	12	CP, dyspnea	unk	Normal	LV sub-epicardial LGE Segmental IVS LGE	50	-	-	*DSP;* c.5212C>T, p.R1738*	FAMHX, STRUCTURE, arr	55
3	13	CP	200	TWI (V1-V2)	LV sub-epicardial LGE, RV LGE	55	-	-	*DSG2;* c.1163T>G, p.F338C, c.593A>G, p.Y198C (*in trans*)	FAMHX, REPOL, depol, structure	69
4	15	CP	65 (I)	TWI (V1) LAD	LV/IVS LGE Pericardial enhancement	60	NSAID, IVIG	Myocarditis#	*DSP;* c.1420-1G>T, p.IVS11-1G>T	FAMHX, arr, repol	62
5	17	CP	unk	TWI (V3-V6), LAD, Low voltage	LV sub-epicardial LGE	50	NSAID, steroid	-	*DSP;* c.4531C>T, p.Q1511*	FAMHX, arr, repol	40
6	20	CP	276	*TWI (V1, III), iRBBB* *Low voltage*	LV sub-epicardial & Mid-myocardial LGE	35	BB, ACEi	Myocarditis#	*DSP;* c.1691C>T, p.T564I	FAMHX, REPOL, STRUCTURE, arr	50
7	20	Syncope	0.87 (I)	*TWI (II,aVF,III,V1-V5),* *LAFB*	LV/IVS LGE Pericardial enhancement	55	NSAID	SCD# Syncope#	-	ARR, REPOL, STRUCTURE	55
8	22	CP	52	*TWI (V1-V2)*	LV sub-epicardial LGE RV dyskinesis	58	BB	ARVC#	*DSP;* c.4531C>T, p.Q1511*	FAMHX, arr, repol, structure	58
9	25	Syncope, VT	3	*RAD*	No enhancement	35	-	SCD	*DSP;* c.967G>C, p.E323Q, c.692A>G, p.Y231C (*in cis*)	FAMHX, depol, repol	50
10	41	SCD	unk	Inferior T-wave flattening	LV sub-epicardial LGE	15	Steroid	-	*DSP;* c.1352G>A, p.R451H	FAMHX, arr, repol	OHT
11	58	SCD	unk	*LBBB*	No enhancement	20	Steroid	SCD#	*DSP;* c.8438T>C, p.L2813S	FAMHX, arr, repol	55
12	60	Dyspnea, PVCs	0.35 (I)	TWI (V1-V2)	sub-epicardial LV/IVS LGE RV mild dilation	40	BB, ACEi	SCD#	*DSP;* c.8170C>T, p.Q2724*	FAMHX, arr, repol	30

* symptom(s) at index presentation
† values reported as number (I or T, if known), if exact troponin is not known then it is reported as 'unk'
‡ earliest electrocardiogram (ECG) result, italicized represents ECGs at index presentation, rhythm was normal sinus for all ECGs
§ Cardiac magnetic resonance imaging (CMR) either from index presentation or representation with recurrent symptoms
# indicates family history occurred in a first degree relative (parent, sibling or child)
¶ criteria in upper case represent major criteria and lower case represents minor criteria

ACEi = angiotensin converting enzyme inhibitor; arr = arrhythmia criteria; ARVC = arrhythmogenic right ventricular cardiomyopathy; BB = beta-blocker; CP = chest pain; depol = depolarization criteria; famHx = family history criteria; iRBBB = incomplete right bundle branch block; IVIG = intravenous immunoglobulin; IVS = intraventricular septum; LAD = left axis deviation; LAFB = left anterior fascicular block; LBBB = left bundle branch block; LGE = late gadolinium enhancement; LV = left ventricle; NSAID = nonsteroidal anti-inflammatory drug; OHT = orthotopic heart transplant; Pt = patient; PVCs = premature ventricular contractions; repol = repolarization criteria; RV = right ventricle; SCD = sudden cardiac death; structure = structural criteria; Sx = symptom; TWI = T-wave inversion; unk = unknown; VT = ventricular tachycardia.

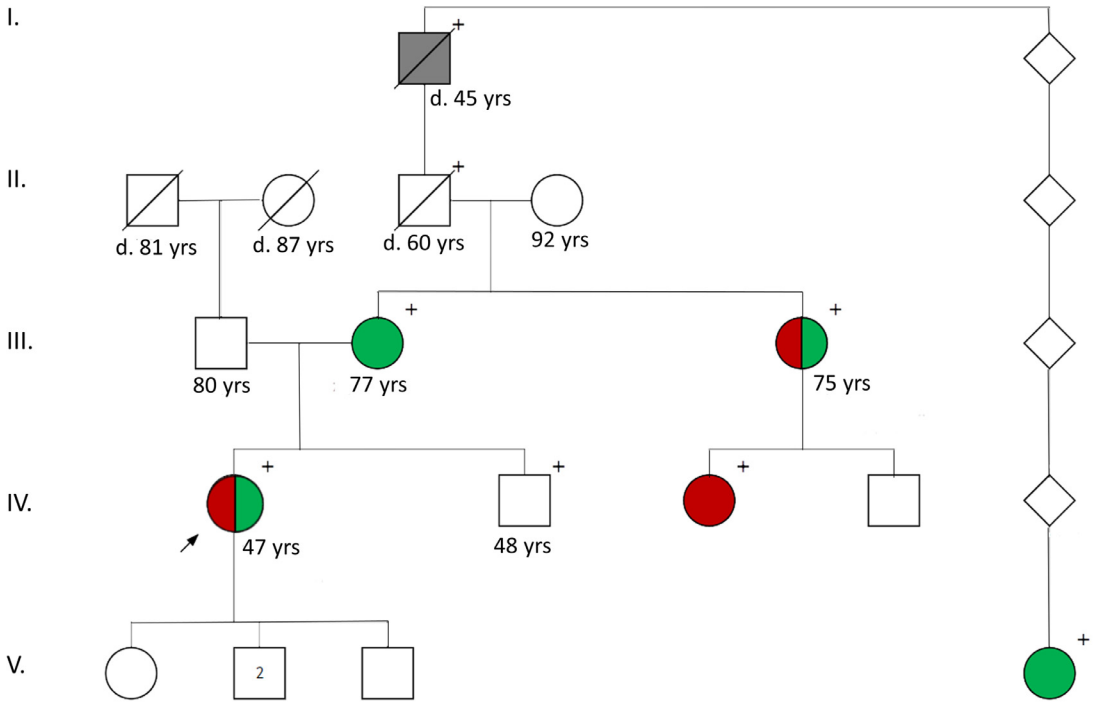

Figure 1. Pedigree demonstrating subsequent symptomatic and asymptomatic ARVC diagnoses in family members of a patient presenting with myocarditis who was then diagnosed with ARVC.

Proband (arrow) is patient 10. Ages represent age at presentation of the proband. She presented with SCD and was diagnosed with myocarditis. She initially had no family history and family screening was not recommended. Subsequently, her first cousin had resuscitated SCD, but sustained anoxic brain injury. A few months later, the proband's maternal aunt also had SCD, and was resuscitated successfully; evaluation showed cardiomyopathy. Proband was then referred for evaluation and found to have a *DSP* variant. Variant was identified in her aunt and cousin leading to ARVC diagnosis and management. Patient's asymptomatic mother was then evaluated (obligate carrier of the variant) and had evidence of cardiomyopathy and scar on MRI; she met criteria for ARVC. A distant cousin also presented with chest pain and was independently diagnosed with myocarditis. She had delayed enhancement on CMR and troponin elevations associated with recurrent chest pain. The same *DSP* variant was identified but she has not yet met diagnostic criteria for ARVC. +=DSP variant carrier, ARVC = arrhythmogenic right ventricular cardiomyopathy; CMR = cardiac magnetic resonance imaging; green = nonischemic cardiomyopathy with MRI scarring; grey = unexplained sudden death; red = sudden cardiac death (SCD).

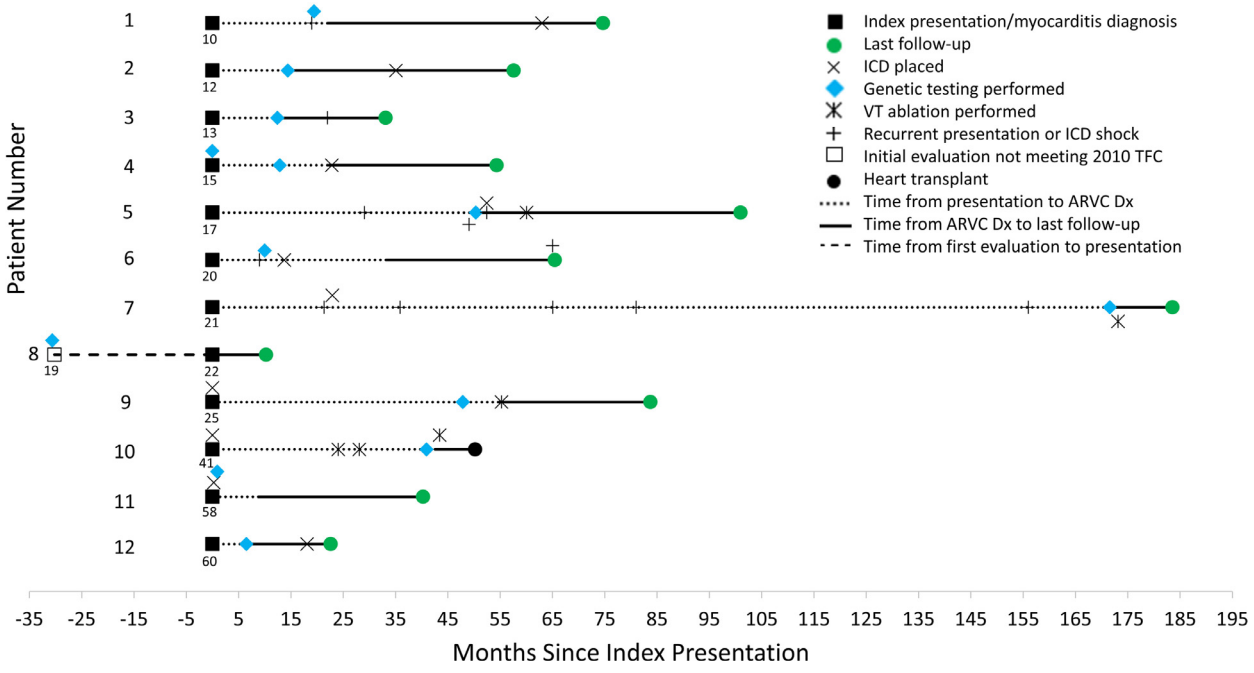

Figure 2. Clinical course timeline for patients presenting with clinical myocarditis eventually diagnosed with ARVC. Numbers below symbols represent the age in years the event occurred. Events that occurred in close proximity are displayed vertically. ARVC = arrhythmogenic right ventricular cardiomyopathy; Dx = diagnosis; ICD = implantable cardiac defibrillator; TFC = Task Force Criteria; VT = ventricular tachycardia.

diagnosis. Patient 8 was recommended to receive an ICD but declined. Patient 3 is followed closely and does not meet current ARVC guidelines for ICD.[19] Four (33%) patients have undergone at least 1 ablation for ventricular tachycardia; these were the only patients to have recurrent ventricular arrhythmias requiring therapy. In total, screening in the study cohort identified at least 17 family members with subsequent ARVC diagnosis. Besides patient 8, who was diagnosed after her half-sister (patient 5), all other family members were diagnosed with ARVC prior to clinical presentation given known family history and genetic testing demonstrating the same mutation as the proband.

Discussion

We describe a cohort of patients initially presenting with clinical myocarditis who were subsequently diagnosed with ARVC. Our findings highlight the unique demographic, clinical and genetic characteristics of a myocarditis presentation of ARVC. In our cohort, patients commonly presented with a classic myocarditis syndrome (chest pain, troponin elevation), there was a female predominance, myocarditis primarily involved the LV, and most patients had a *DSP* genetic variant. Genetic testing results were key to diagnosing ARVC in our cohort, suggesting a role for genetic testing in a subset of patients with myocarditis. A diagnosis of ARVC resulted in changes in management and diagnosis for both patients and family members. Importantly, these findings suggest that ARVC, which is considered a rare disease, may be underreported due to under recognition of less typical presentations including myocarditis.

The presentation, troponin elevation, and CMR findings of our cohort were typical of clinical myocarditis[3] except an etiology was not initially identified. Although viral infection is often implicated in myocarditis of otherwise unknown etiology, genetic risk factors for myocarditis are increasingly recognized. Brown et al identified a cardiac pathogenic or likely pathogenic variant in 7 of 8 pediatric patients presenting with presumed myocarditis.[8] Belkaya et al demonstrated enrichment of rare biallelic nonsynonymous or splice-site variants in genes associated with inherited cardiomyopathies in a pediatric acute myocarditis cohort compared with healthy subjects (12% vs 0.9%).[1] Genetic variants specific for ARVC have also been identified in patients with myocarditis-like presentations. Lopez-Ayala et al identified 7 out of 195 variant carriers who presented with acute myocarditis.[9] Similar to our findings, 5 of 7 had a variant in *DSP*. More recently Smith et al describe the heterogenous characteristics of patients with *DSP* variant cardiomyopathy including 16/105 (15%) who had "acute myocardial injury episodes" akin to clinical myocarditis.[20] *DSP* variants are relatively uncommon, and are identified in approximately 2% to 12% of the ARVC population.[12,21,22,23] Our results, combined with prior work, suggest that pathogenic *DSP* variants may play a unique role in myocarditis in ARVC. The significance of *DSP* enrichment in our cohort should also be taken in the context of its established association with left-dominant disease in ARVC.[20−22] Referral bias affects our ability to accurately assess the true prevalence or genetic variant distribution of this phenotype. The number of gene-elusive ARVC patients may be underreported as may those who died suddenly of ventricular arrhythmias.

The clinical presentation of myocarditis in ARVC may have an underlying pathophysiologic basis. The presence of inflammatory infiltrate in autopsy and pathology samples in patients with ARVC is commonly observed.[14,24-26] Experimental models of ARVC have demonstrated desmosomal disruption leading to altered cytokine and chemokine secretion stimulating inflammatory cell recruitment.[27−29] Additionally, autoantibodies, which have been implicated in other forms of myocarditis,[3] have recently been identified in ARVC. Chatterjee et al demonstrated that anti-DSG2 antibodies in ARVC cause gap junction dysfunction in vitro and the level of antibody correlated with PVC burden.[30] More recently, Caforio et al demonstrated the presence of anti-heart and anti-intercalated disk autoantibodies in a disproportionate number of ARVC patients compared with both patients who had other cardiac pathologies and healthy controls.[31] Traditionally antibody mediated autoimmunity disproportionately affects women[32] and this could provide a pathologic basis for the uniquely all female cohort observed in this study. However, we cannot rule out the fact that there may also be gender differences in patterns of seeking medical care, symptom reporting, or an inherent clinical bias.

Timely diagnosis of ARVC has significant implications for patient management including lifelong exercise restriction, SCD risk stratification and/or prevention and cascade screening of family members. The consequences of delay in diagnosis are demonstrated by the pedigree of patient 10 in Figure 1. Early diagnosis of ARVC in our patient cohort may have been challenging for a number of reasons. First, the current TFC are RV-centric. Structural criteria were met by only half (6/12, 50%) of our cohort and even fewer had these changes at presentation. Major arrhythmia or electrographic TFC are fairly specific for right sided abnormalities classically seen in ARVC and were not commonly seen in our cohort. The minor criterion more commonly fulfilled in our cohort are less specific and can be seen in other forms of cardiomyopathy including myocarditis. To address these challenges, it will be important for future diagnostic criteria to incorporate LV characteristics that help differentiate ARVC and/or arrhythmogenic cardiomyopathy from other cardiomyopathies.[19,33,34] The lack of traditional findings puts increased emphasis on family history and genetic testing to make an accurate diagnosis. Based on our findings at a large inherited cardiomyopathy referral center, we recommend consideration of genetic testing in young patients presenting with clinical myocarditis without a clear etiology, especially in those with recurrent symptoms and family history of sudden death or non-ischemic cardiovascular disease.

In conclusion, myocarditis is a distinct presenting phenotype of ARVC. These patients present with biomarker and imaging evidence of LV inflammation with symptoms of chest pain or ventricular arrhythmias. Diagnosis of ARVC in this clinical phenotype is challenged by the predominant LV involvement, making it harder to meet more RV-centric ARVC TFC. Pathogenic variant detection through genetic testing represented an important step in the diagnosis of

ARVC in this cohort and may be considered in select patients who are diagnosed with myocarditis. Accurate diagnosis carries implications not only for patient management but also for family members.

Credit Author Statement

Paul Scheel: conceptualization, methodology, formal analysis, data curation, writing − original draft, writing − review & editing, visualization. **Brittney Murray:** conceptualization, investigation, methodology, resources, writing − original draft, writing − review & editing. **Crystal Tichnell:** supervision, project administration, writing − review & editing. **Cynthia James:** conceptualization, metholdogy, formal analysis, investigation, writing − review & editing. **Harikrishna Tandri:** supervision, project administration, writing − review & editing. **Hugh Calkins**: conceptualization, methodology, supervision, writing − review & editing. **Stephen Chelko:** conceptualization, methodology, supervision, writing − original draft, writing − review & editing. **Nisha Gilotra:** conceptualization, methodology, formal analysis, supervision, writing − original draft, writing − review & editing.

Declaration of Interests

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this study.

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