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CASE REPORT

ADVANCED

CLINICAL CASE

Dual-Organ Transplantation in a Woman With Right Ventricular Failure Secondary to Arrhythmogenic Right Ventricular Cardiomyopathy

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ABSTRACT

We report a case of a woman with arrhythmogenic right ventricular cardiomyopathy (ARVC) who presented with severe right-sided heart failure and cardiac cirrhosis that mandated heart-liver transplantation. This case highlights an emerging sex-based difference in ARVC where female sex is associated with a higher risk of heart failure than in male patients with ARVC. (**Level of Difficulty: Advanced.**) (J Am Coll Cardiol Case Rep 2020;2:59-63) © 2020 The Authors. Published by Elsevier on behalf of the American College of Cardiology Foundation. This is an open access article under the CC BY-NC-ND license (http://creativecommons.org/licenses/by-nc-nd/4.0/).

HISTORY OF PRESENTATION

A 45-year-old white woman with long-standing arrhythmogenic right ventricular (RV) cardiomyopathy (ARVC) developed progressive fatigue, early satiety, and abdominal bloating that were initially treated with over-the-counter gas relief medication. She was ultimately hospitalized locally and underwent a 3-l paracentesis and an abdominal ultrasound scan that showed cirrhosis and decompensated portal hypertension. This was her first heart failure (HF) presentation, and she was started on oral diuretic agents. After discharge, she was referred to an advanced HF and ARVC center.

LEARNING OBJECTIVES

- Understand differences in phenotypic expression of ARVC in female and male patients.
- Recognize heart failure risk in women with ARVC.
- Recognize signs and sequelae of right-sided heart failure.

PAST MEDICAL HISTORY

ARVC was diagnosed at the age of 18 years, when she experienced recurrent elevations in heart rate that persisted after exercise and ultimately presented in ventricular tachycardia (VT) requiring cardioversion. She was a competitive runner until that time. Over the next 20 years, she had multiple appropriate therapies for ventricular arrhythmias from her

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Informed consent was obtained for this case.

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ABBREVIATIONS AND ACRONYMS

ARVC = arrhythmogenic right ventricular cardiomyopathy

HF = heart failure

MACE = major adverse cardiovascular events

RV = right ventricular

SCD = sudden cardiac death

VT = ventricular tachycardia

implanted cardioverter-defibrillator and several ventricular and atrial ablations. She was seen in our ARVC clinic for arrhythmia management approximately 10 years before her HF presentation, and at that time she met diagnostic criteria for ARVC on the basis of an electrocardiogram (inverted T waves in the right precordial leads and epsilon waves), late potentials on a signal-averaged electrocardiogram, severe RV enlargement and dysfunction on imaging, and sustained VT. Following her multiple ablations and established antiarrhythmic maintenance therapy, she remained free of any sustained arrhythmia for approximately 7 years before her HF presentation. She also had a history of intermittent second-degree atrioventricular block, hypothyroidism, iron deficiency anemia, and rheumatoid arthritis.

DIFFERENTIAL DIAGNOSIS

Her presenting symptoms were attributed to progressive RV failure in the setting of ARVC. However, given atypical features including atrioventricular conduction disease, autoimmune disease, and lack of a pathogenic variant or family history of ARVC, alternate causes of her cardiomyopathy were considered. These included subacute giant cell myocarditis and cardiac sarcoidosis. Possible causes of her cirrhosis included sequelae of chronic infectious or autoimmune hepatitis, cryptogenic cirrhosis, and congestive hepatopathy.

INVESTIGATIONS

Initial vital signs included blood pressure of 102/58 mm Hg and heart rate of 85 beats/min. Baseline laboratory test results were as follows: serum creatinine, 1.3 mg/dl; total bilirubin, 0.9 mg/dl; aspartate transaminase, 26 U/l; and alanine transaminase, 19 U/l. An expedited work-up was pursued. Transthoracic echocardiography (**Figures 1A and 1B**, Video 1) showed a severely dilated right ventricle with severe RV global hypokinesis (tricuspid annular plane systolic excursion, 0.7 mm; and systolic excursion velocity of the right ventricle, 4.2 cm/s) with preserved left ventricular function. Right-sided heart catheterization (**Figure 2**) showed low cardiac output with elevated and nearly equalized filling pressures (right atrial pressure, 16 mm Hg; RV end-diastolic pressure, 16 mm Hg; mean pulmonary artery pressure, 16 mm Hg; pulmonary capillary wedge pressure, 12 mm Hg; cardiac output, 2.53 l/min; cardiac index, 1.49 l/min/m^2; RV stroke work index, 0.34 g/m/beat/m^2). Bicycle cardiopulmonary exercise testing with excellent effort demonstrated normalized peak venous oxygen consumption of 9.86 ml/kg/min and a V_E/V_{CO_2} slope of 56, both consistent with severe cardiac limitation and poor transplant-free prognosis. Transjugular liver biopsy revealed stage 3/4 fibrosis, consistent with early cardiac cirrhosis. Results of genetic testing for 67 genes implicated in ARVC and inherited cardiomyopathies were negative for pathogenic or likely pathogenic variants (see the list of tested genes in **Table 1**).

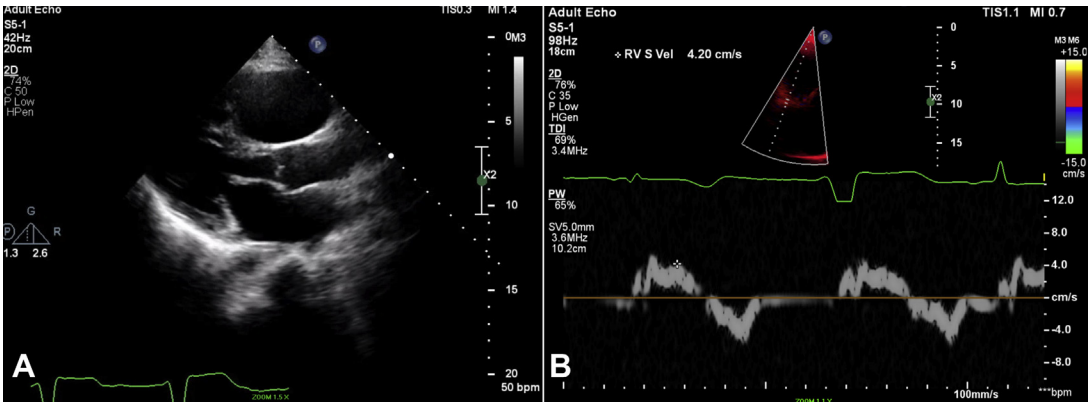
MANAGEMENT

Despite escalating diuretic agent use, her symptoms progressed, and she was admitted to our center with development of peripheral cyanosis on examination and worsening liver enzymes (total bilirubin increasing to 3.0 mg/dl and transaminases doubling). Options for advanced cardiac therapeutics included intravenous inotropes and/or temporary right-sided mechanical circulatory support simultaneous to pursuing heart transplantation. Inotropes were initially avoided, given her predisposition to arrhythmias. Temporary right-sided support options included percutaneous and surgically implanted mechanical pumps (Impella-RP [Abiomed, Danvers, Massachusetts] vs. RV CentriMag [Thoratec, Pleasanton, California] or ProtekDuo [CardiacAssist, Pittsburgh, Pennsylvania], respectively). Percutaneous RV support was chosen to minimize the likelihood of bleeding complications in the setting of hepatic dysfunction that could lead to sensitizing blood product exposure. However, percutaneous RV assist device placement was unsuccessful on multiple attempts because of migration of the device from the left pulmonary artery in retrograde fashion to the massively dilated RV. Despite her arrhythmic history, her condition was temporized with inotropes and sotalol, resulting in improvements in perfusion, renal function, and diuresis. After multidisciplinary evaluation she was waitlisted for combined heart and liver transplantation, which she successfully underwent on hospital day 80. Severe RV failure was grossly apparent on entering her chest at the time of transplantation, and pathological inspection of her native heart revealed severely thinned, fibrofatty RV myocardium consistent with ARVC (**Figures 3A to 3C**, Video 2).

DISCUSSION

ARVC is a disease characterized by fibrofatty replacement of the heart muscle that leads to ventricular arrhythmias, ventricular dysfunction, and increased risk of sudden cardiac death (SCD) (1,2). A

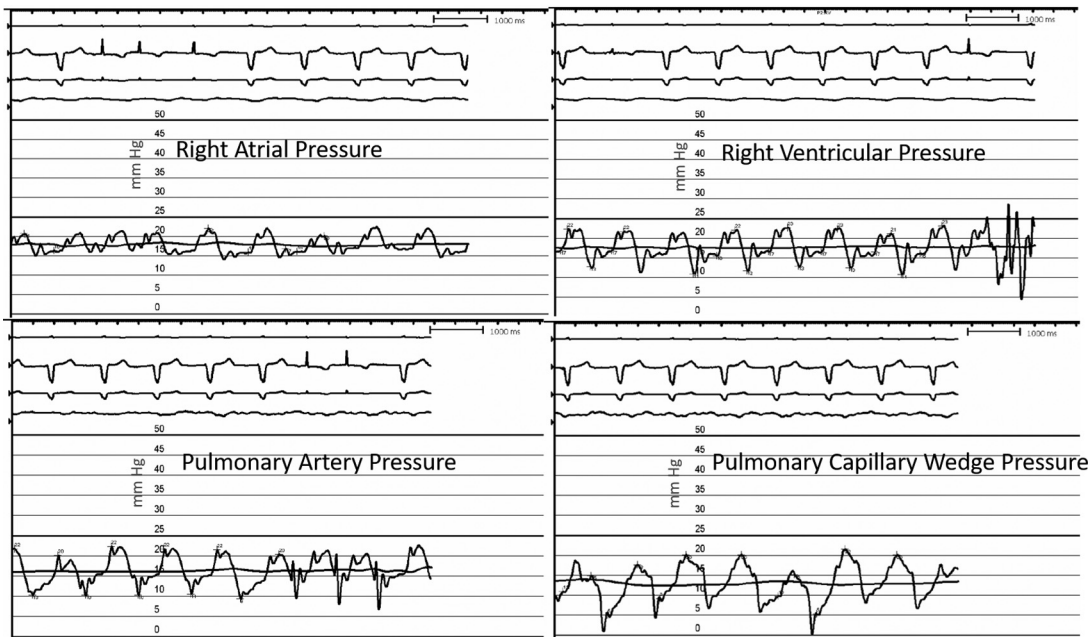
FIGURE 1 A 2-Dimensional Echocardiogram and Echocardiographic Parameters of Right Ventricular Dysfunction



(A) Parasternal long-axis view of a severely dilated and hypokinetic right ventricle. **(B)** Right ventricular systolic excursion velocity (S′; RV S Vel) reflecting right ventricular dysfunction.

pathogenic variant (e.g., mutation) can be identified in nearly two-thirds of individuals with ARVC (3). These variants primarily affect desmosomal genes responsible for "cell-to-cell bridging" and typically have an autosomal dominant inheritance pattern, genetically affecting men and women equally (4,5). However, ARVC is known to have variable penetrance and severity, affecting men and women differently.

FIGURE 2 Invasive Hemodynamics of Severe Right Ventricular Failure



Right-sided heart catheterization showing elevated and nearly equalized filling pressures. The patient had low cardiac output and cardiac index (not shown). The vertical scale shown is in millimeters of mercury (mm Hg). The horizontal axis is in time, with 1,000-ms markers shown.

TABLE 1 Genes Tested for Sequence Changes and Exonic Deletions or Duplications*

ABCC9, ACTC1, ACTN2, AGL, ANK2, BAG3, CACNA1C, CACNB2, CALM1, CALM2, CALM3, CASQ2, CAV3, CRYAB, CSRP3, DES, DMD, DOLK, DSC2, DSG2, DSP, EMD, EYA4, FHL1, FKRP, FKTN, FLNC, GAA, GLA, GPD1L, HCN4, JUP, KCNA5, KCNE1, KCNE2, KCNH2, KCNJ2, KCNQ1, LAMP2, LMNA, MYBPC3, MYH7, MYL2, MYL3, MYL4, NKX2-5, PKP2, PLN, PRKAG2, RAF1, RBM20, RYR2, SCN5A, SGCD, SLC22A5, TAZ, TCAP, TGFB3, TMEM43, TNNC1, TNNI3, TNNT2, TPM1, TRDN, TTN, TTR, VCL

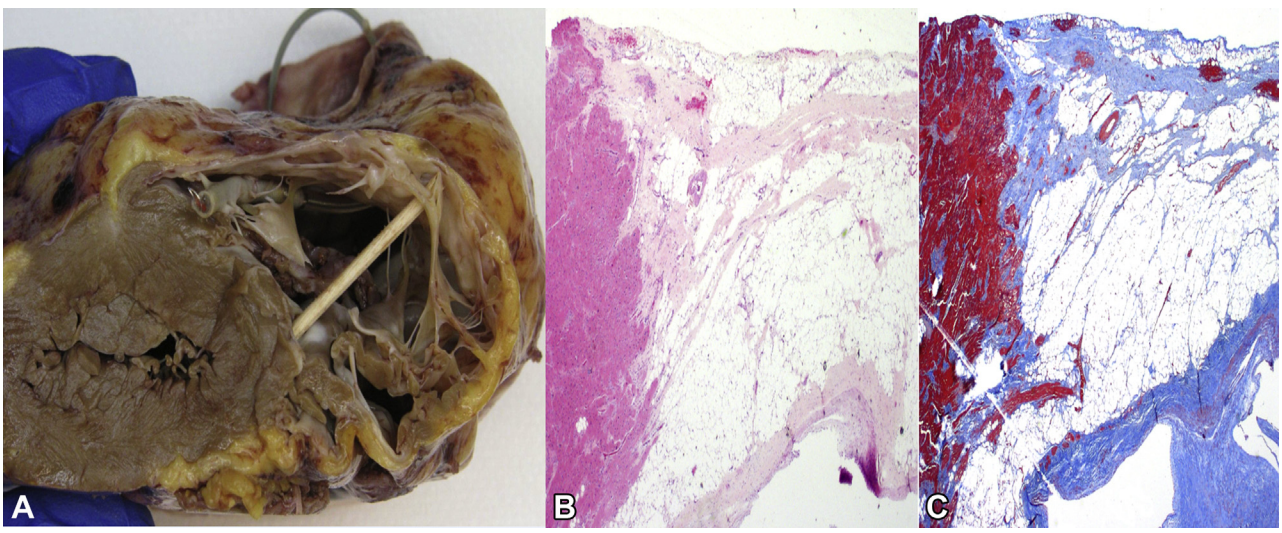
*No pathogenic sequence variants or deletions or duplications were identified.

Thus, understanding the variability in clinical course and differential risk profiles across the sexes is particularly relevant.

Several studies have reported that male patients are more phenotypically affected. Male patients present at a younger age, are disproportionately the family proband, and have worse arrhythmic outcomes, including SCD (2). Women are reportedly affected by milder forms of disease with less severe arrhythmic burden (1). A comprehensive study of gene-positive ARVC patients and family members from U.S. and Dutch cohorts with 45% female representation found significantly lower composite arrhythmic outcomes in women compared with men (29% vs. 53%; $p < 0.001$) (2). HF occurrence, however, was equivalent across the sexes (2). A recent study of sporadic cases of ARVC suggested a remarkably higher risk of end-stage HF, cardiac transplantation, and HF-related death in women (22% vs. 5%; $p = 0.002$) compared with men (6). An additional study found that female sex was associated with increased odds of HF (odds ratio: 2.2; $p = 0.01$) (7). These studies illustrate that HF risk is at least equivalent, but likely significantly higher, in affected women compared with men.

Perhaps the difference in ARVC phenotypic expression is attributable to higher rates of male participation in competitive sports, which may increase myocardial demand and exacerbate the deleterious effects of a desmosomal mutation on myocardium (1,4). Additional theories for lower penetrance in women involve possible hormonal protection (1). A recent study of sex hormones in 54 ARVC-affected patients found that testosterone levels were significantly higher in men with major adverse cardiovascular events (MACE) versus those without MACE (8). MACE was defined as SCD, survived SCD, ventricular fibrillation, sustained VT, or arrhythmic syncope. In contrast, women with ARVC and MACE had significantly lower estradiol levels than those with favorable outcomes (8). A corollary in vitro ARVC model showed worsened effects with testosterone and improved effects with estradiol on cardiomyocyte apoptosis and lipogenesis (8). The

FIGURE 3 Gross Pathology and Histopathology of Arrhythmogenic Right Ventricular Cardiomyopathy



(A) Native explanted heart shows marked fibrofatty replacement and thinning of right ventricular myocardium. **(B)** Hematoxylin and eosin stain showing fibrofatty replacement of right ventricular myocardium at 2× magnification. **(C)** Masson trichrome stain showing increased fibrosis of right ventricular myocardium at 2× magnification.

mechanisms behind increased HF risk in women with ARVC are not well understood and merit further investigation.

A retrospective study of the Johns Hopkins ARVC registry examined factors contributing to ARVC progression and need for heart transplantation. HF, rather than arrhythmia, was the most common reason for transplantation, and over one-half of patients had left ventricular dysfunction in addition to RV failure at the time of transplantation (9). Patients had a prolonged, rather than a fulminant, course, with a diagnosis of ARVC and HF on average 17.6 ± 13.3 years and 7.2 ± 6.4 years, respectively, before transplantation. Certain pathogenic variants have been more frequently reported in those with HF or undergoing cardiac transplantation, specifically phospholamban (*PLN*), desmoplakin (*DSP*), and multiple pathogenic variants (2). This finding has implications because there are also sex-based differences in genotypes, with females with *PLN* pathogenic variants having higher penetrance and worse outcomes (10). Notably, our patient was gene elusive.

HF as a manifestation of ARVC is increasingly recognized as patients are living longer with arrhythmias, given improved diagnosis and implantable cardioverter-defibrillator therapy (7). Of critical importance is the recognition of RV-predominant HF symptoms that commonly manifest as fatigue or gastrointestinal symptoms, often delaying diagnosis and treatment of RV failure. In this case, progressive RV failure led to severe sequelae of congestive hepatopathy and cardiac cirrhosis necessitating dual heart-liver transplantation, thereby highlighting the importance of early recognition of RV failure. It is imperative to maintain a high index of suspicion for insidious RV failure in this progressive disease.

FOLLOW-UP

The patient's transplant surgery and post-operative course were without complications. She was weaned from inotropic support with normal invasive hemodynamics and discharged home. She has had close follow-up and surveillance without any evidence of cardiac or hepatic allograft dysfunction.

CONCLUSIONS

ARVC is often characterized as an arrhythmia-predominant, genetic mutation-positive condition primarily and most severely affecting men. However, women with ARVC have a significant HF risk that should be considered. Differences in ARVC phenotypic expression may be affected by sex hormones and exercise and warrant further study. In addition to SCD risk and exercise restrictions in ARVC, providers and patients should be aware of the early and insidious symptoms of RV failure.

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KEY WORDS cardiac transplant, cardiomyopathy, right ventricle

APPENDIX For supplemental videos, please see the online version of this paper.