

Isolated JUP Plakoglobin Gene Mutation with Left Ventricular Fibrosis in Familial Arrhythmogenic Right Ventricular Cardiomyopathy

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Abstract

Introduction: Arrhythmogenic Right Ventricular Cardiomyopathy (ARVC) is a rare inherited disorder usually affecting the *right* ventricle (RV), characterized by fibro-fatty tissue replacement of the healthy ventricular myocardium. It often predisposes young patients to ventricular tachycardia, heart failure, and / or sudden cardiac death. However, recent studies have suggested predominantly *left* ventricle (LV) involvement with variable and / or atypical manifestations. Cardiac Magnetic Resonance (CMR) imaging has emerged as the non-invasive gold standard for the diagnosis of ARVC. **Case summary:** A 21-year-old athletic male with a family history of unknown ventricular arrhythmias, presented with near syncope, chest pain and exertional palpitations. He had an initial work-up that was grossly unremarkable including, electrocardiography (ECG), echocardiography and CMR imaging. Six months later, he presented again with recurrent symptoms during exercise and his ECG demonstrating a new epsilon wave. He had markedly elevated cardiac biomarkers, (troponin I >100 ng/dl, normal value < 0.04 ng/dl). A subsequent coronary angiogram was performed, which was normal. Holter monitoring further showed subsequent episodes of ventricular tachycardia with a right bundle branch morphology. An endomyocardial biopsy was performed, which was negative. A follow-up CMR demonstrated *the new development* and prominent *left* ventricular epicardial scar in the lateral wall. The patient underwent familial genetic testing, which confirmed the presence of an isolated JUP gene mutation and showed multiple genes consistent with ARVC in his mother. Thus, he manifested a partial transmission of only one abnormal gene for ARVC and exhibited a markedly different expression in his disease without evidence of typical right-sided heart pathology. A third CMR study was performed, which showed partial improvement in myocardial fibrosis after exercise cessation. **Conclusion:** We present a case of a young male with a newly diagnosed isolated JUP gene mutation and a genetically diagnosed family history of ARVC. During his course, he demonstrated the progression of a characteristic epsilon wave on ECG and the presence of *new, atypical, left* ventricular fibrosis on repeat CMR imaging. This case demonstrates a complex interplay between variable genetic penetrance, phenotypical heterogeneity, and lifestyle factors including exercise, in his disease expression and provides insight on the natural course of an isolated JUP mutation. Although rare, clinicians should have a high threshold for the suspicion of ARVC or variants of this disorder even in the absence of classic right sided pathologies and /or an initially normal work-up.

Isolated JUP Plakoglobin Gene Mutation with Left Ventricular Fibrosis in Familial Arrhythmogenic

Right Ventricular Cardiomyopathy

An MRI based Case Report

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The patient underwent familial genetic testing, which confirmed the presence of an isolated JUP gene mutation and showed multiple genes consistent with ARVC in his mother. Thus, he manifested a partial transmission of only one abnormal gene for ARVC and exhibited a markedly different expression in his disease without evidence of typical right-sided heart pathology. A third CMR study was performed, which showed partial improvement in myocardial fibrosis after exercise cessation.

Conclusion:

We present a case of a young male with a newly diagnosed isolated JUP gene mutation and a genetically diagnosed family history of ARVC. During his course, he demonstrated the progression of a characteristic epsilon wave on ECG and the presence of *new, atypical, left* ventricular fibrosis on repeat CMR imaging. This case demonstrates a complex interplay between variable genetic penetrance, phenotypical heterogeneity, and lifestyle factors including exercise, in his disease expression and provides insight on the natural course of an isolated JUP mutation. Although rare, clinicians should have a high threshold for the suspicion of ARVC or variants of this disorder even in the absence of classic right sided pathologies and /or an initially normal work-up.

Author Disclosures and Consent:

The authors have no conflicts of interest or financial disclosures to report. Informed consent was obtained for publication and all images and all patient information has been kept confidential.

Appendix: ACM: *Arrhythmogenic Cardiomyopathy*, AIVR: *Accelerated Idioventricular Rhythm*, ARVC: *Arrhythmogenic R*

Keywords: Case report, Arrhythmogenic Right Ventricular Cardiomyopathy, Arrhythmogenic Cardiomyopathy, Plakoglobin, JUP mutation, Cardiac magnetic resonance

Background:

ARVC is a rare inherited disorder usually affecting the right ventricle, characterized by fibro-fatty tissue substitution of healthy ventricular myocardium. It often predisposes young patients to ventricular tachycardia, heart failure, and sudden cardiac death. However, due to multiple disease variants, it can involve both ventricles or predominantly the left ventricle with atypical manifestations. Recent post-mortem stud-

ies of patients with Arrhythmogenic Cardiomyopathy (ACM) suggest left ventricular involvement in up to 87% of patients.¹ Abnormal ECG findings and ventricular arrhythmias may often precede abnormal imaging or structural findings. To date fifteen genes have been identified to cause ARVC with a subset encoding for desmosomal proteins including *Plakoglobin (JUP)*.² Phenotypic expression is highly variable, but some evidence suggests young athletic males tend to have a more malignant disease course in part due to their level of hormonal and or physical activity, which in turn contributes a greater degree of mechanical cardiac stress.³

We present a case of a 21-year-old male with a genetically proven family history of ARVC who presented to the hospital with near syncope and through extensive workup, had no evidence of ARVC on initial imaging (echo and CMR). Subsequently, he was found to have multiple episodes of ventricular ectopy and tachycardia. During his second hospitalization, work-up demonstrated atypical, predominantly left ventricular dysfunction on echocardiogram with evidence of *new, leftventricular* fibrosis on repeat CMR study. A third CMR scan showed interval improvement in myocardial fibrosis once exercise was limited.

Case Report:

Initial Presentation:

A 21-year-old physically fit male emergency medical technician trainee with recurrent pre-syncope presented to our emergency department for an episode of chest pain with near syncope in March 2021. He was in his usual state of health when he began to experience transient substernal chest pain while rigorously biking in cold weather with associated lightheadedness, diaphoresis, and blurred vision. He reported similar symptoms in the past with palpitations and dyspnea on exertion. He denied any other toxic habits and urine toxicology screen was negative. He notably reported a family history of ventricular tachycardia for which his mother (at age 40) had received an implantable cardiac defibrillator (ICD). He had seen a cardiologist prior where work up for thyroid disease and holter monitoring were unremarkable.

On initial admission, his peak Troponin I was minimal (Table 1). ECG showed normal sinus rhythm without any acute ST/T wave changes (Image 1). Transthoracic echocardiogram revealed normal diastolic filling pattern, right sided pressures, and LV systolic function with an Ejection Fraction (EF) 55-60% and no regional wall motion abnormalities. He had no events on telemetry. An exercise stress test was performed but stopped due to hypotension (BP 70/50), sinus tachycardia (190 bpm) and near syncope at Bruce stage 5 (maximal exercise). There were no significant arrhythmias or evidence of ischemia during exercise and very rare PVCs were noted in recovery. The patient was subsequently discharged with outpatient telemetry monitoring, which revealed infrequent ventricular ectopy/PVCs, with 2 episodes of brief PVC in couplets and triplets.

The patient underwent a CMR scan (initial scan- three months from initial presentation) which was a grossly normal study without evidence of myocardial fibrosis, infiltrative disease, and did not meet criteria for ARVC (Image 3).

Second Presentation:

Six-months after the initial presentation, the patient again presented to the emergency department with severe, sharp, mid-substernal chest pain with associated diaphoresis, and lightheadedness. He remained physically active including frequent exercise. Physical exam including orthostatic vitals was unremarkable. Electrocardiogram showed sinus bradycardia at 40 bpm without ST elevation or depression and a right ventricular conduction delay with an epsilon wave (Image 2), which were new findings compared to prior. Troponins continued to rapidly and markedly increase in addition to elevations of transaminases and inflammatory markers (Table 1). Infectious work-up including covid-19 PCR was negative. Cardiac angiography revealed no coronary artery disease but a very prominent mid LAD myocardial bridge with near complete obliteration at resting HR in 70s. A repeat echocardiogram showed a new reduction in EF to 40-45% and diffuse hypokinesis of the LV (in comparison to six months earlier).

A repeat CMR three months after the previous scan (2ndCMR study) revealed new findings of mildly

reduced LV systolic function with mild-moderate hypokinesia of the mid to apical lateral wall, and prominent epicardial fibrosis and an area of small, focal mid-myocardial fibrosis in a non-ischemic pattern with elevated native T1 and T2 values on mapping, respectively (Image 4). Of note, the study still did not meet any CMR criteria for ARVC. The patient subsequently received an endomyocardial biopsy without any significant histologic changes reported. Genetic testing demonstrated one pathogenic variant in the JUP gene in our patient, along with multiple genetic abnormalities for ARVC in his mother including abnormal JUP, NEBL and ACTN2 genes. Given these genetic results along with his family history, the patient was referred for an ICD implant for primary prevention of sudden cardiac death along with exercise limitation. A follow-up (3rd CMR scan) was performed after 11 months after initial CMR scan, which showed improvement in myocardial fibrosis (Image 5).

Discussion

ARVC is an inherited disorder, either autosomal dominant or rarely autosomal recessive, that is predominantly believed to affect the right ventricle, but a growing number of studies have noted involvement of both or either ventricle.⁴ It is characterized by fibro-fatty tissue substitution of healthy ventricular myocardium, predisposing these patients to ventricular tachycardia, heart failure, and sudden cardiac death. Its prevalence in the general population is estimated at 1 in 5000, but closer to 1 in 2000 in select European countries and constitutes up to 20% of sudden cardiac death cases in individuals under 30 years of age.^{5,6} In addition, phenotypic expression in males differs, in which males have a more malignant disease course and develop life threatening ventricular arrhythmias at an earlier age, possibly due to differences in sex hormones (testosterone) and increased level of physical activity, which may contribute to a greater degree of mechanical cardiac stress.⁷

Due to an expanding phenotypic spectrum of arrhythmogenic cardiomyopathy, from multi-gene variability in expression as well as incomplete penetrance, the diagnosis has been challenging requiring revisions to originally published criteria. The previously established Task Force criteria for diagnosis of arrhythmogenic cardiomyopathy first proposed in 1994, later revised in 2010, continues to evolve to include left-sided variants and CMR findings of late-gadolinium enhancement.⁸ The current criteria incorporate electrical features (12 lead ECG), structural features (seen on echocardiography and imaging), tissue characteristics (via biopsy) and genetic familial evaluation (Figure 1). While most of the Task Force criteria was originally developed from cohorts with predominantly right ventricular involvement, this potentially missed those with left ventricular dominant or biventricular disease. Pathological and imaging studies have reported the prevalence of LV involvement ranging between 17-87% of cases.^{9,10}

While ARVC can involve multiple genes and proteins, its primary genetic defect involves proteins constituting desmosomes – cell adhesion structures – which over time disrupt normal functioning of intercellular junctions, as well as altering transcription to favor adipogenesis/fibrogenesis over normal myocyte differentiation and healthy cardiac development. Loss-of-function mutations in desmosomal proteins such as plakophilin, desmoplakin, or desmoglein have been most commonly described, but up to 13 other genes involved in ARVC have been identified to date. Furthermore, cardiac biopsies have suggested an immunological component of pathogenesis, noting the presence of inflammatory infiltrates with T lymphocytes associated with myocyte necrosis.¹¹ As myocardial scarring develops, ventricular arrhythmias may develop through macro-reentry mechanisms but also due to gap-junction remodeling from the loss of desmosomal integrity and resulting in alteration of sodium current.

Plakoglobin (JUP) gene and Arrhythmogenic Cardiomyopathy (ACM)

The Junction Plakoglobin (JUP) gene encodes for the protein plakoglobin, found in cells of the heart and skin where it is part of adherens junctions and desmosomes which help to hold neighboring cells together. It also plays a role in cell signaling within the *Wnt* pathway involved in the normal development of the heart, skin, and hair.¹² Naxos disease, a cardio-cutaneous syndrome, is an autosomal recessive condition involving a two base-pair deletion of plakoglobin, characterized by effects on the heart (ARVC), skin (palmoplantar keratosis) and hair (woolly hair).¹³ The first case of isolated ARVC without cutaneous manifestations came

from the only known autosomal dominant mutation in JUP which was reported in a proband in Germany in 2007. This mutation came from a three base pair insertion causing an addition of a terminal serine residue in the plakoglobin gene which affects the stability and degradation of plakoglobin.¹⁴ In contrast, a rare but severe phenotype associated with a homozygous JUP mutation with complete loss of plakoglobin can cause diffuse skin erosion, a condition referred to as lethal congenital epidermolysis bullosa (LECEB).¹⁵ Of note, our patient, in contrast, was found to have an isolated (heterozygous) JUP gene mutation, and appears to have manifested much less severe phenotype, particularly without the manifestation of any cutaneous symptoms. Moreover, to date, there has not been any published cases on left sided or biventricular dysfunction or fibrosis in patients with an isolated plakoglobin mutation.

Left-dominant Arrhythmogenic cardiomyopathy (LDAC)

Left-dominant Arrhythmogenic cardiomyopathy (LDAC) differs from ARVC in more ways than only predominantly involving the LV. Ventricular arrhythmias of typical ARVC are characterized by LBBB morphology, whereas over 75% of LDAC demonstrated RBBB morphology. Additionally, findings of lateral and/or inferior T wave inversion found in LDAC differ in pattern seen with ARVC which involves anterior T-wave inversion and epsilon waves of the right precordial leads.¹⁶ Epsilon waves are low-amplitude positive signals following a QRS complex that arise from prolonged depolarization in the affected part of the myocardium (as shown in our patient, Image 2). On echocardiography, 30% of LDAC patients have LV dilation and/or impairment with preserved RV volume and function. In the classic pattern of ARVC, isolated RV dysfunction precedes LV involvement throughout the disease course. In addition, there is general sparing of the septum in late stage ARVC with LV involvement.¹⁷ It is noteworthy that our patient manifested ventricular ectopy with RBBB pattern (a typical characteristic of left ventricular involvement), despite developing an epsilon wave, (which is similarly seen in typical ARVC) along with other features of left sided involvement such as a reduction in left ventricular function and the interval development of left ventricular fibrosis seen on CMR.

CMR in diagnosis of Arrhythmogenic cardiomyopathy

As the diagnostic criteria evolved and studies over the decades have uncovered more about the various phenotypic expression of ARVC, CMR imaging has emerged as the noninvasive gold standard for ARVC workup. It provides a useful tool to evaluate morphology, function, and tissue characteristics. It can highlight myocardial fibrosis, fatty replacement or identify wall motion abnormalities with high accuracy. The most recent 2020 International diagnostic criteria of arrhythmogenic cardiomyopathy relies on CMR to characterize the phenotype and aid with the exclusion of other diagnoses. The new criterion adds the minor criterion for the diagnosis of biventricular or left dominant variants with the demonstration of LV systolic dysfunction.^{18,19}

Late gadolinium enhancement (LGE) of the myocardium is often used to assess myocardial fibrosis but has a limited role in the current diagnostic criteria of ARVC. LGE is nonspecific and the differential diagnosis can include sarcoidosis, myocarditis, amyloidosis, or dilated cardiomyopathy.²⁰ Furthermore, LGE is less useful in classic ARVC where the thin RV wall makes the technique less useful, in comparison to LDAC where LGE has been reported in up to 61% of cases presenting in a circumferential, mid-myocardial pattern extending to the right side of the septum.²¹ Of note the circumferential or mid-myocardial fibrosis pattern is seen in only left dominant/biventricular ARVC. Autopsy studies of ARVC patients have demonstrated fibro-fatty infiltration predominantly on the epicardial surface leading to the understanding that the disease starts in the epicardium with progression toward the endocardium. LV systolic dysfunction can become more severe in advanced stages as there is progression of transmural involvement. Our patient's second CMR study reflected early yet significant changes with normal cavitory size/wall thickness but mild-moderate hypokinesis of the mid to apical lateral wall. Furthermore, he had predominately epicardial fibrosis in a relatively circumferential pattern of the lateral wall with mid myocardial fibrosis involving the septal walls.

Role of Testosterone and Physical Activity in ARVC Pathogenesis

Testosterone, the hormone generally found in higher amounts in males, has been shown to have pro-arrhythmic effects, accelerate ARVC pathogenesis including myocardial apoptosis and lipogenesis, indepen-

dent of age, BMI, ventricular function and desmosome mutation status.²² Other concomitant factors that may have accelerated his phenotypical expression, particularly with left sided involvement, include (male) gender and the degree of physical activity including strenuous exercise. The patient's rigorous exercise capacity (evident by his exercise treadmill study reaching Bruce Stage 5) and recent physical training for becoming a firefighter/EMT (which is generally 18 weeks in duration), we feel, are likely to have progressed his disease process in the short time with recurrent hospitalizations. High intensity exercise is of particular importance in ARVC as it increases wall stress, increases sympathetic stimulation, predisposes to greater incidence of fatal ventricular arrhythmia, and is correlated with reduced LV (and RV) function.²³ Those with ARVC are encouraged to avoid competitive sports, especially endurance or high intensity sports due to the arrhythmic risk and accelerated disease progression.^{24,25} Endurance training studies of plakoglobin deficient mice (similar to the protein deficiency produced by the JUP gene mutation in our patient), have demonstrated alterations in *right* ventricular dilation/dysfunction and electrophysiological function (increased spontaneous ventricular ectopy).²⁶ To the best of our knowledge, we could not find similar documented reports demonstrating structural *left* ventricular changes within such a short time period with this isolated gene mutation. Ultimately, our recommendation for exercise cessation may also help explain his improvement in scar/fibrotic burden seen in his third CMR scan.

Conclusion:

We present a case of a young male with a family history of ventricular arrhythmias, who had two separate hospitalizations for pre-syncope with the manifestations of ARVC including the development of an epsilon wave on ECG along with atypical, left sided myocardial dysfunction and the development of left ventricular fibrosis on repeat CMR scan. He was found to have an isolated JUP mutation with other family members having multiple abnormal genes for ARVC. The timing and manifestations of these findings over two separate hospitalizations have been seldom reported, particularly with only any isolated JUP mutation. Since its discovery, ARVC has undergone an evolution in diagnostic criterion due to its variability in presentation and manifestations, as well as the discovery of a broad spectrum and interplay of genes. Clinicians should recognize the disease heterogeneity, as demonstrated in our case, particularly where the initial cardiac work-up including his initial CMR study and endomyocardial biopsy was unremarkable. Finally, this case provides insight into the potential complex interplay in genotype and lifestyle factors in the expression of an isolated JUP mutation, and its involvement in various arrhythmogenic cardiomyopathies.

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Images:

Image 1: ECG 1 findings from 3/2021, below:

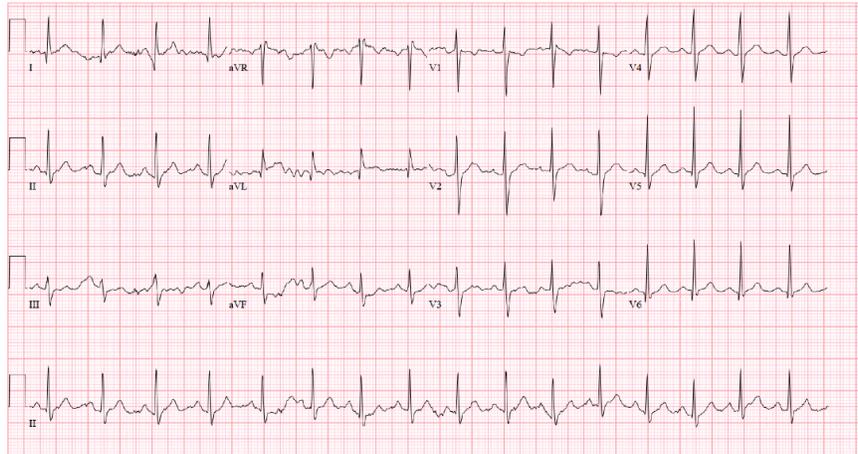


Image 2: ECG 2 from second hospitalization, (6 months from prior) with intraventricular conduction delay changes, RBBB morphology, QRS widening and possible Epsilon wave (red arrow). Prolonged S-wave upstroke in V3 with QRS widening (green arrow)

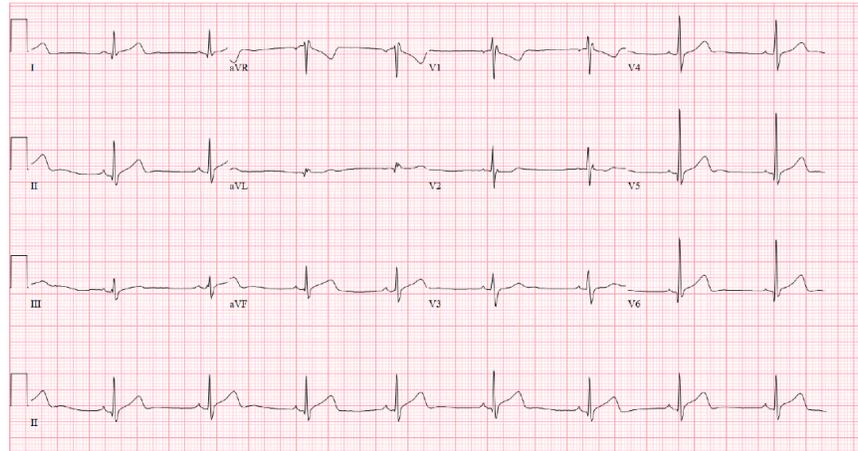
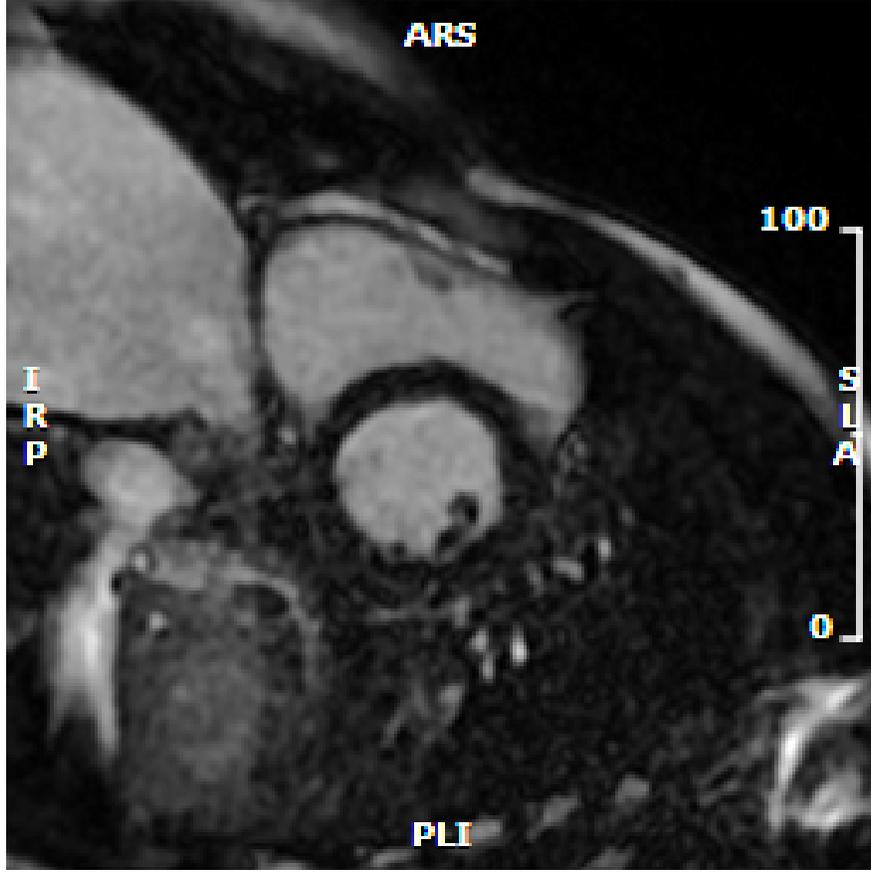
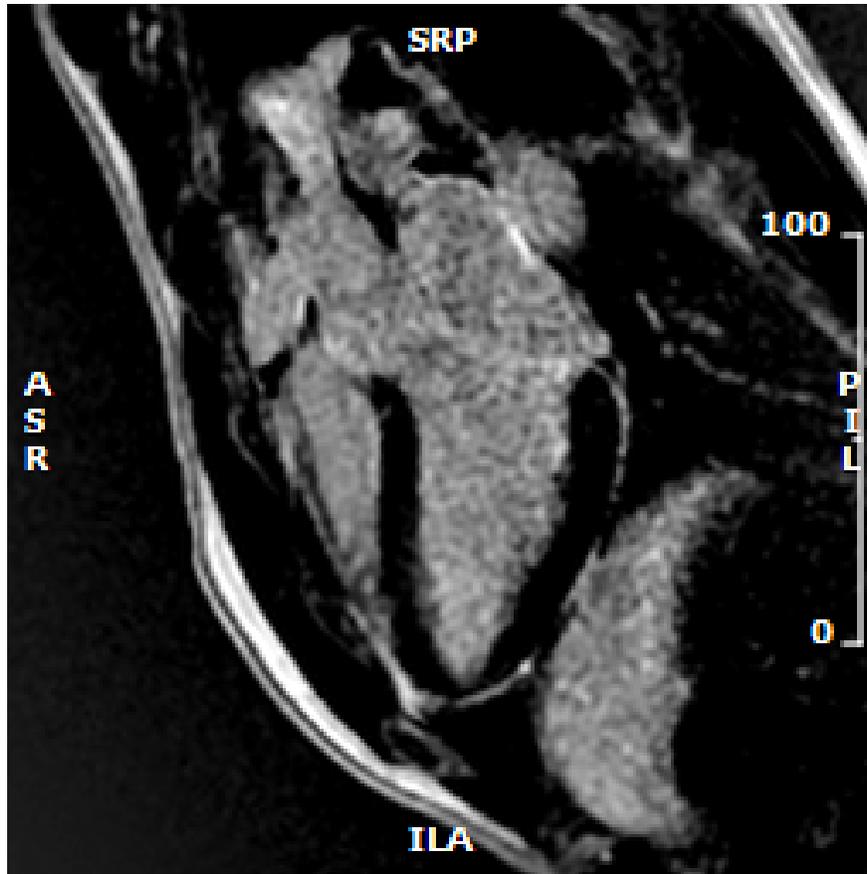


Image 3 (Initial CMR scan):





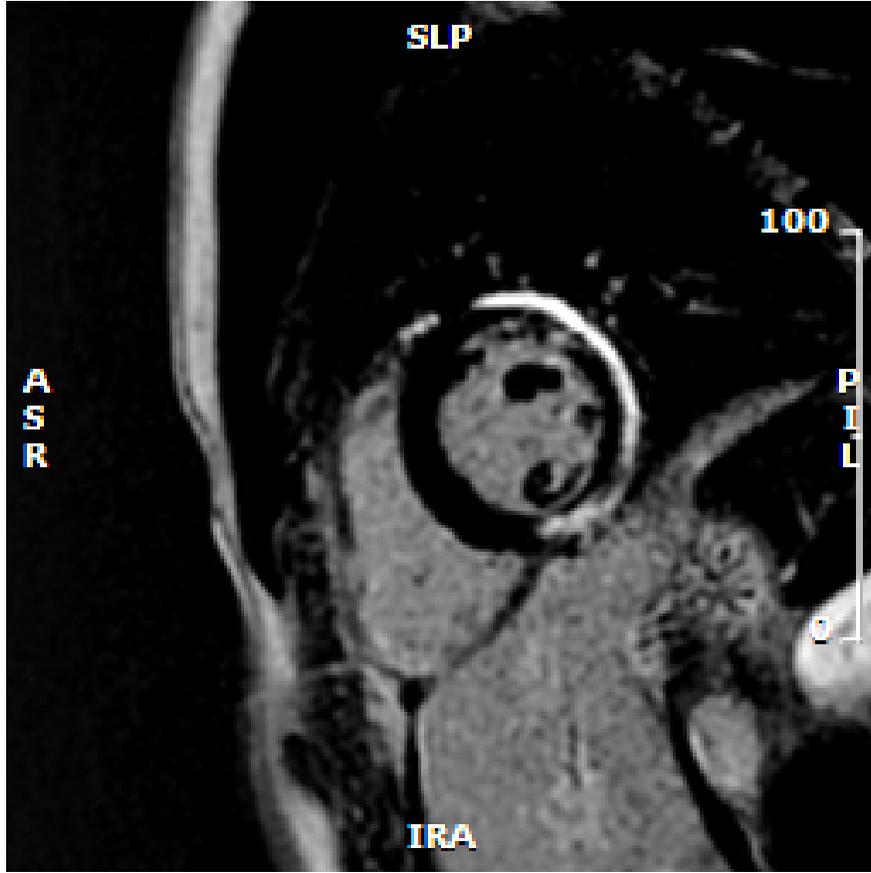
ab

Above, CMR, short axis gradient echo (a) and PSIR (b) , short axis and 3 chamber view post contrast WITHOUT any delayed gadolinium enhancement. T1 maps were also normal (not shown).

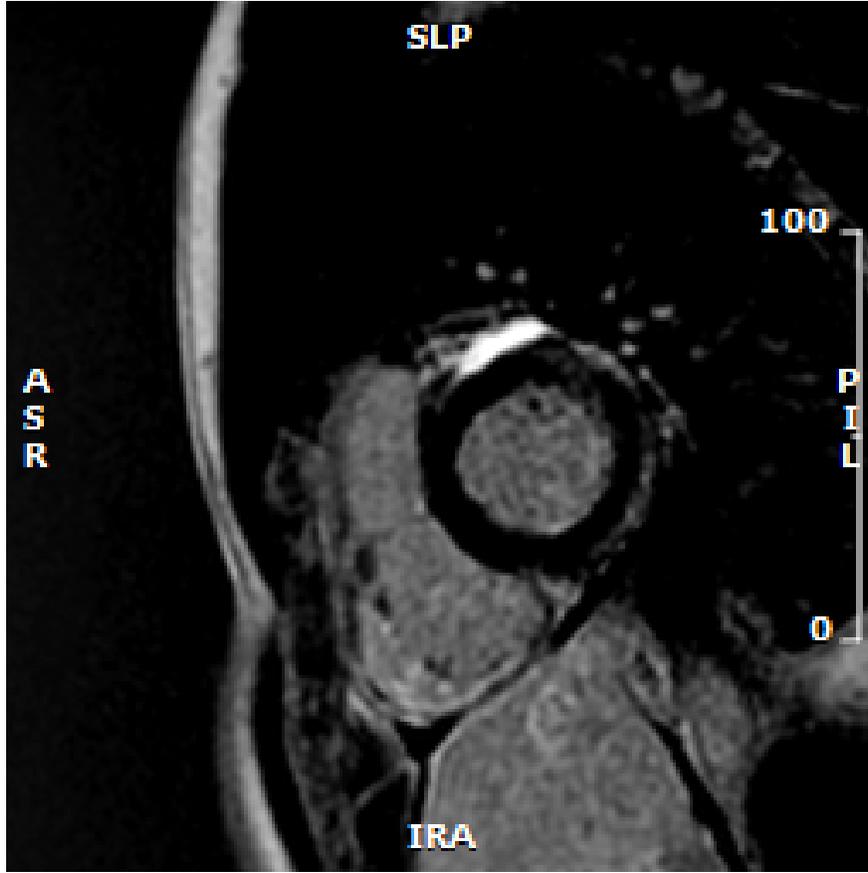
Image 4, Follow-up CMR scan- 3 months after 1st study:

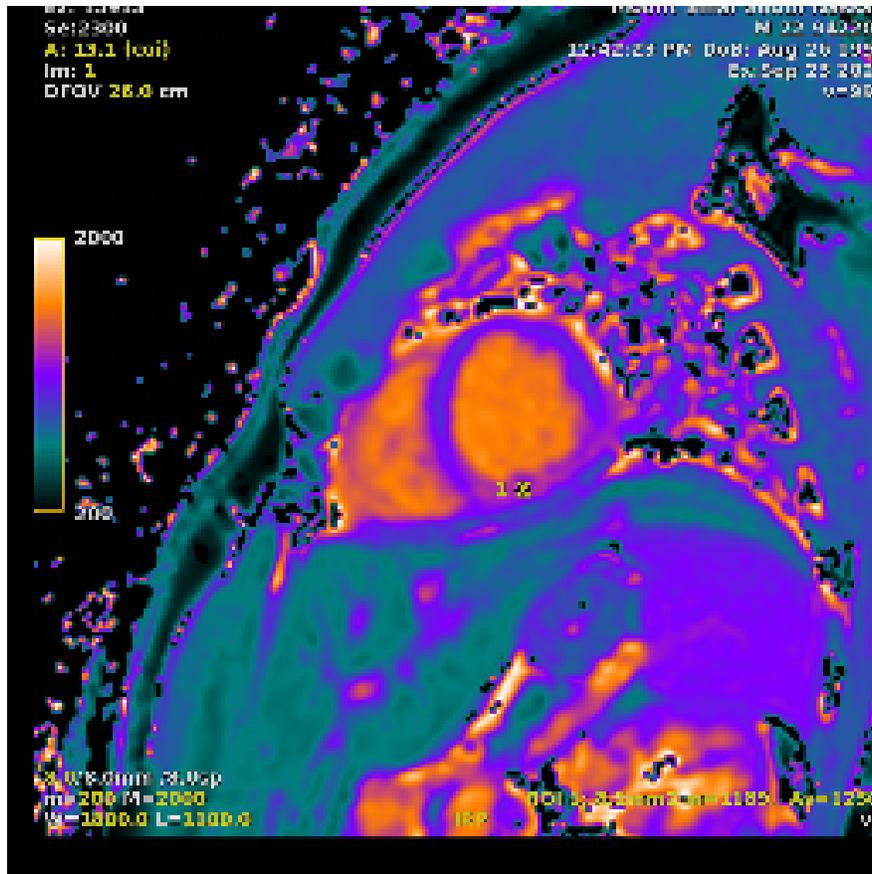






- a
- b
- c



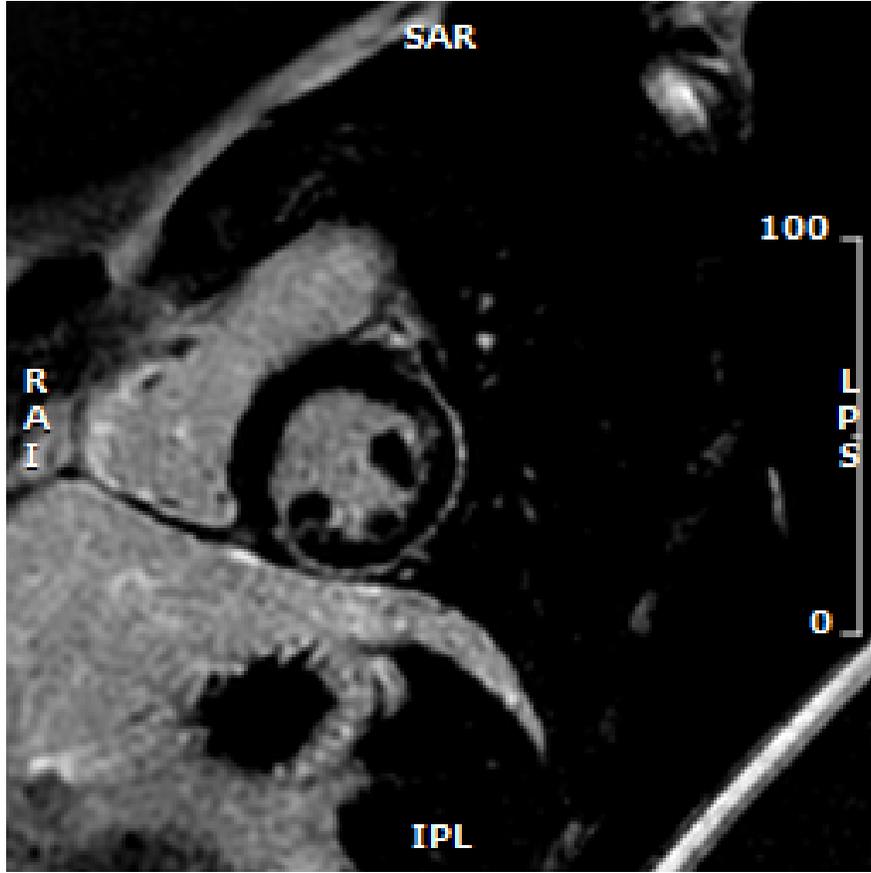


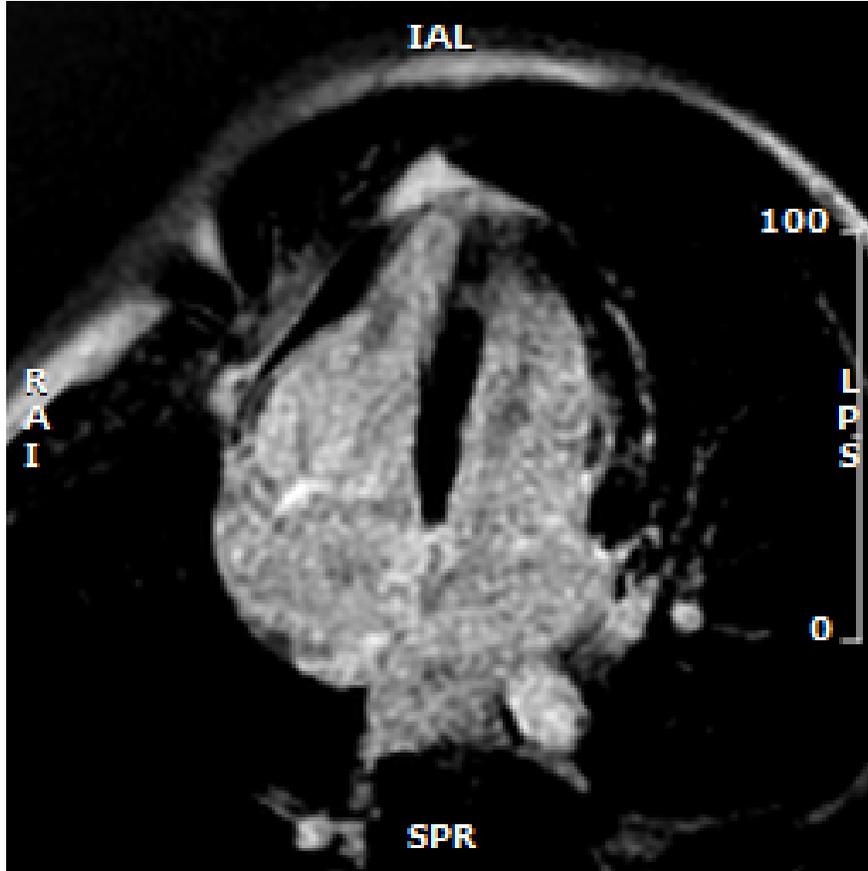
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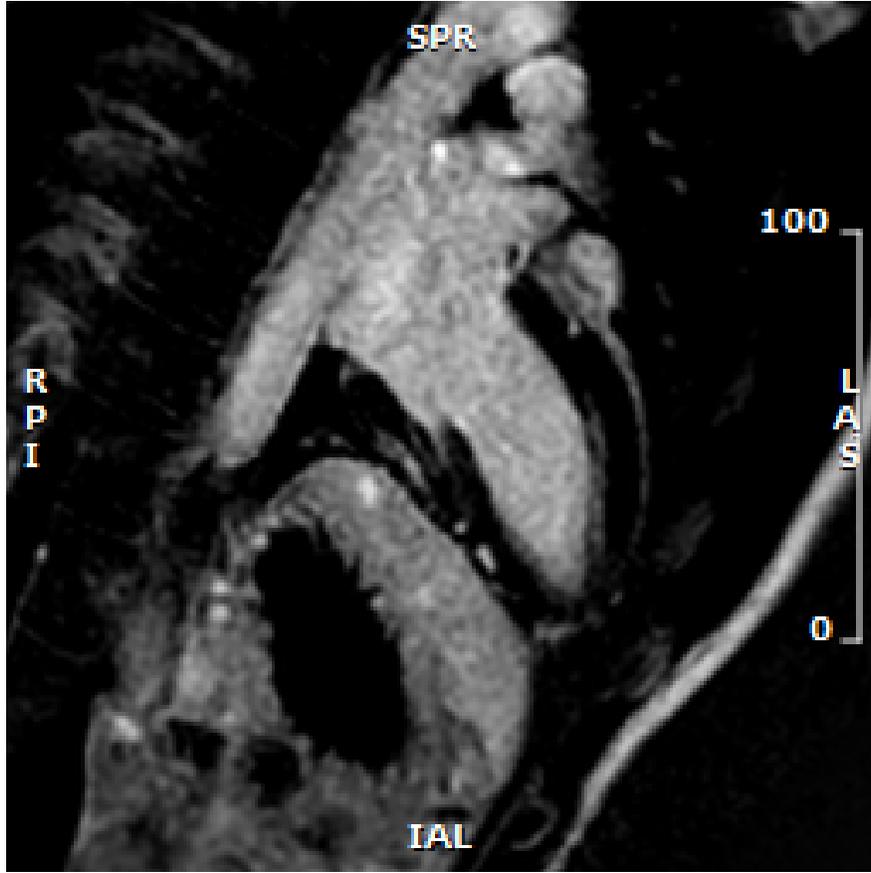
e

Above, CMR, gradient echo, PSIR 3-chamber view with prominent epicardial fibrosis of the infero-lateral wall (a), 2 chamber view showing epicardial fibrosis of the basal anterior wall and inferior walls (b) , short axis view showing circumferential epicardial enhancement of the anterior, lateral and inferior walls (c), short axis-view with prominent patchy epicardial anterior wall enhancement (d); T1 map with elevated native values of the infero wall (1250 ms), (e)

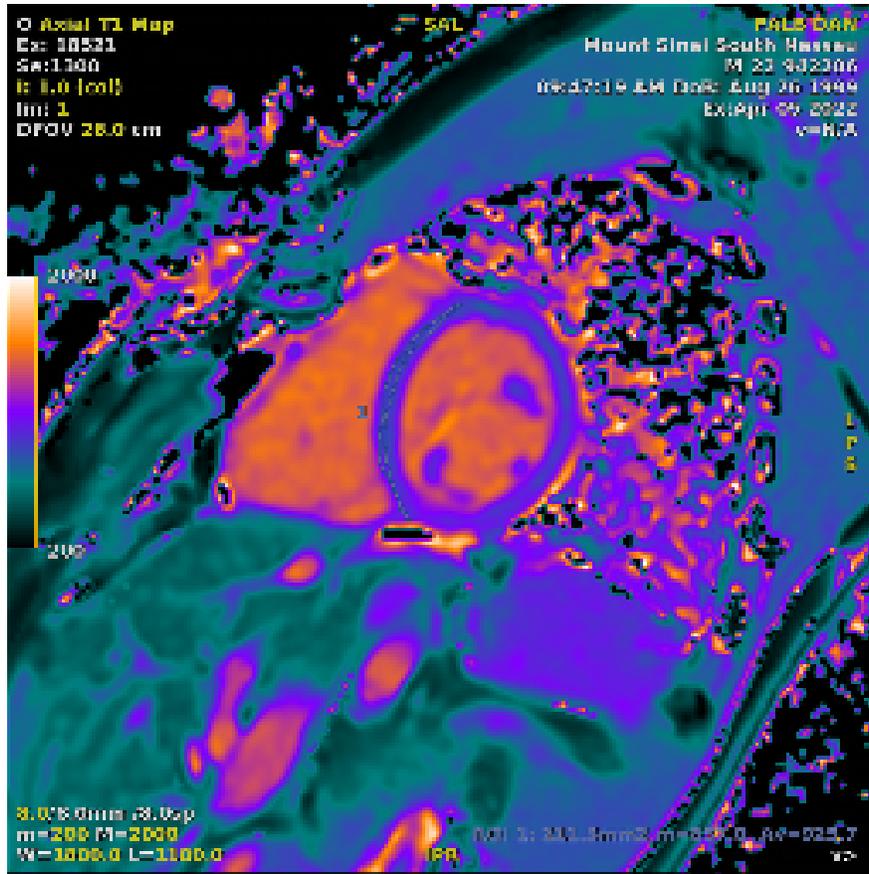
Image 5, (third CMR study, 11 months after the first scan):

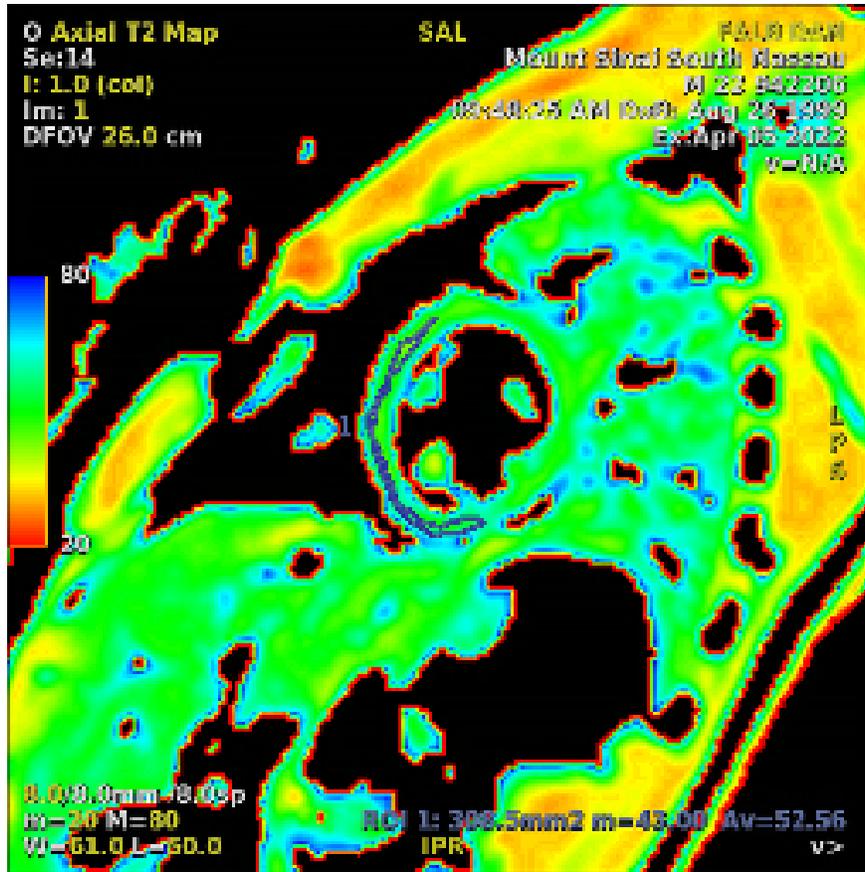






- a
- b
- c





d

e

CMR, above, gradient echo, PSIR short axis (a), 4-chamber (b), 2-chamber (c), with improved myocardial fibrosis (arrows) T1 and T2 maps now normal values (images d, e).

Tables:

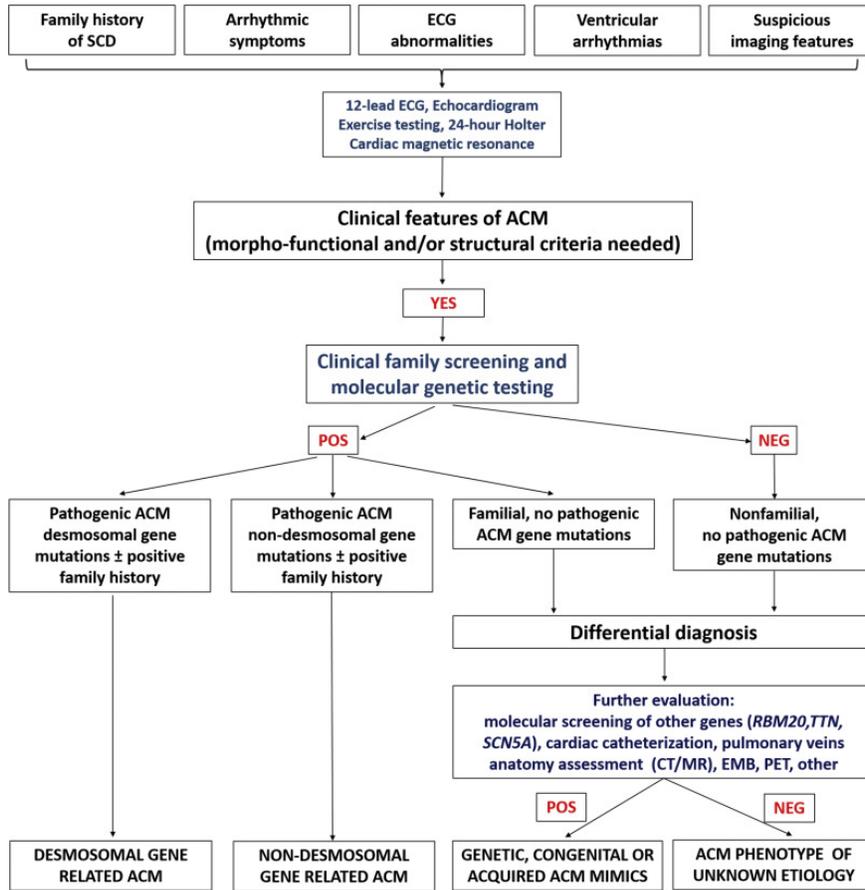
TABLE 1 Hospital course: Key findings from multiple admissions

	Hospital Course 1 (3/2021)	Hospital Course 2 (9/2021)
Peak Troponin	1.207 ng/ml	128.44 ng/ml
Peak CK with CK-MB	100 U/L	3194 U/L
BNP	16 pg/ml	13.9 pg/ml
TSH / FT4	1.2 ng/dL / 6.62 IU/mL	n/a
CRP	1.62mg/L	7.16mg/L
LFTs	AST 15 U/L, ALT 13 U/L	AST 251 U/L, ALT 50 U/L
Na / K / Cr / CO2 / Ca	Within normal limits	Within normal limits
ECG findings	NSR, Normal ECG PR 146, QTc 409	Sinus bradycardia with 'incomplete RBBB'/Epsilon wave PR 142, QTc 392ms

	Hospital Course 1 (3/2021)	Hospital Course 2 (9/2021)
Echo	EF 55-60%. Normal LV size /systolic function without regional wall motion abnormalities.	EF 40-45% with hypokinetic LV without wall motion abnormalities.
Cardiac MRI	6/21: LV has normal systolic function, (EF=55%) and normal cavitory size. There is normal wall thickness. There are no wall motion abnormalities. There is no evidence of myocardial fibrosis, infiltrative disease or arrhythmogenic right ventricular dysplasia.	9/2021: mildly reduced LV systolic function (EF=49%) with normal cavitory size/wall thickness but mild-mod hyperkinesis of the mid to apical lateral wall. There was prominent epicardial fibrosis of the basal anterior and entire lateral inferolateral, inferior, and anterolateral and lateral walls. There is small focal mid-myocardial fibrosis of the basal anterolateral wall and mid to apical infero-septal walls. There is sparring of the sub-endocardium with all scar patterns representing a non-ischemic pattern. There are elevated T1 and T2 values on mapping suggesting inflammatory or edematous component which is overlapping at areas of scar.
Normal Values:	<i>Troponin: < 0.031ng/mL CK: 30-200 U/L BNP: <101.0 pg/mL TSH: 0.8 – 1.5 ng/dL</i>	<i>FT4: 0.4 – 4.2 IU/mL CRP: <5.1 mg/L AST: <36 U/L ALT: <46 U/L</i>
Appendix: ALT: Alanine Aminotransferase, AST: aspartate aminotransferase, BNP: Brain Natriuretic Peptide, Ca: Calcium, CK: Creatine Kinase, CK-MB: Creatine kinase-MB, CO2: Bicarbonate, Cr: Creatinine, CRP: C Reactive Protein, ECG: Electrocardiogram, EF: Ejection Fraction, FT4: Free Thyroxine, K: potassium, LV: Left ventricle, Na: Sodium, NSR: Normal sinus rhythm, RBBB: Right bundle branch block, TSH: Thyroid Stimulating Hormone	Appendix: ALT: Alanine Aminotransferase, AST: aspartate aminotransferase, BNP: Brain Natriuretic Peptide, Ca: Calcium, CK: Creatine Kinase, CK-MB: Creatine kinase-MB, CO2: Bicarbonate, Cr: Creatinine, CRP: C Reactive Protein, ECG: Electrocardiogram, EF: Ejection Fraction, FT4: Free Thyroxine, K: potassium, LV: Left ventricle, Na: Sodium, NSR: Normal sinus rhythm, RBBB: Right bundle branch block, TSH: Thyroid Stimulating Hormone	Appendix: ALT: Alanine Aminotransferase, AST: aspartate aminotransferase, BNP: Brain Natriuretic Peptide, Ca: Calcium, CK: Creatine Kinase, CK-MB: Creatine kinase-MB, CO2: Bicarbonate, Cr: Creatinine, CRP: C Reactive Protein, ECG: Electrocardiogram, EF: Ejection Fraction, FT4: Free Thyroxine, K: potassium, LV: Left ventricle, Na: Sodium, NSR: Normal sinus rhythm, RBBB: Right bundle branch block, TSH: Thyroid Stimulating Hormone

Figures:

Figure 1: Diagnosis of arrhythmogenic cardiomyopathy (Int J Cardiol. 2020 Nov 15;319:106-114.)¹⁹



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