# Left Atrial Cardiomyopathy with Left Atrial Thrombus despite Sinus Rhythm in a Patient with Severe Ventricular Cardiomyopathy Requiring Cardiac Transplantation

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## INTRODUCTION

Atrial myopathy is increasingly recognized as a clinical entity and describes an abnormal left atrial (LA) substrate with LA dysfunction that can result in and manifest as atrial fibrillation (AF). While LA dysfunction and LA thrombosis are most commonly due to AF, we report a case where the LA dysfunction was so severe that it resulted in LA appendage thrombus, despite sinus rhythm (SR) being maintained.

This report highlights a rare case of an idiopathic atrial and ventricular cardiomyopathy that resulted in ventricular arrythmias and eventual heart failure, but not sustained AF.

## CASE PRESENTATION

A 49-year-old male patient presented to a tertiary hospital in Australia in February 2014 with conscious rapid ventricular tachycardia (VT) that was cardioverted with intravenous amiodarone. Electrocardiogram after cardioversion demonstrated SR with first-degree atrioventricular block. He also experienced transient atrial flutter and AF during the admission. Coronary angiography revealed normal coronary arteries. Transthoracic echocardiogram (TTE) showed normal biventricular size and function with no valvular abnormalities and a mildly dilated left atrium (LA). Electrophysiology study revealed atypical atrial flutter and inducible VT, which was similar in morphology to his VT on presentation. A dual-chamber implantable cardioverter-defibrillator (ICD) was implanted, and he was commenced on sotalol. He was also started on anticoagulation due to a transient ischemic attack after ICD implantation. He continued to experience frequent runs of VT, terminated with antitachycardia pacing by his implanted defibrillator. He had no further atrial arrythmias recorded on his defibrillator after this initial presentation.

The patient underwent electrophysiology study (EPS) and VT ablation on December 3, 2014; this revealed VT from the posterior and posteroseptal aspects of the right ventricular (RV) outflow tract (RVOT). These foci were successfully ablated, and no low-voltage (<1.5 mV) areas were identified on detailed electroanatomic mapping. He remained well, with no sustained VT episodes for the next 4 years. He presented again while on holiday to a remote hospital 4 years later (November 2018) with VT storm (27 VT events resulting in nine direct current shocks). He was treated with amiodarone and referred for another VT ablation.

A TTE performed at the time (November 26, 2018; Video 1) revealed normal left ventricular (LV) size and mild LV dysfunction (LV ejection fraction [LVEF] = 47%) with regional wall abnormalities (mid-apical anteroseptal, inferoseptal, and inferior hypokinesis). There was mild tricuspid regurgitation (TR) and mitral regurgitation. Diastolic function assessment is demonstrated in Figure 1A. The E/A ratio was 1.7, septal e′ was 7 cm/sec, and lateral e′ was 8 cm/sec, with an elevated TR velocity of 3.1 m/sec. These findings were suggestive of grade II diastolic dysfunction. However, E/E′ was 10, suggesting normal LV end-diastolic pressures. Left ventricular global longitudinal strain was reduced at −12%, with patchy reduction in strain (Figure 1B). The LA was severely dilated (LA volume = 57 mL/m$^2$) with severely reduced LA reservoir strain (3.2%) despite being in SR (Figure 1C). An ICD check (December 2018) revealed no episodes of AF and a pacing rate of 10% in the atrium and 1% in the ventricle.

Transesophageal echocardiogram (TEE) prior to VT ablation on November 28, 2018, revealed severe spontaneous echo contrast (SEC) but no thrombus in the LA (Video 2). Three-dimensional electroanatomic mapping was performed during EPS. No low-voltage (<1.5 mV) areas were identified except in the RVOT, and these were in relation to previous ablation sites. Two VT morphologies were mapped to the posterior aspect of the RVOT and lateral aspect of LV outflow tract. These were successfully ablated. No VT was inducible postablation.

Unfortunately, a few months later, he developed further VT episodes, suggesting progression of his cardiomyopathy. In preparation for the VT ablation, TEE was performed on January 18, 2019, which showed severe SEC (sludge) and a more defined echogenic lesion suggestive of LA thrombus (Video 3). In lieu of the VT ablation, the patient had stopped rivaroxaban 2 days prior. He was restarted on rivaroxaban, and the procedure was delayed.

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Keywords: Ventricular tachycardia, Atrial myopathy, Left atrial strain, Cardiomyopathy, Left atrial thrombus

Conflicts of Interest: None.

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2468-6441

https://doi.org/10.1016/j.case.2021.03.007

## VIDEO HIGHLIGHTS

**Video 1:** Transthoracic echocardiogram from November 2019 demonstrating mild LV dysfunction with markedly enlarged LA.
**Video 2:** Transesophageal echocardiogram prior to VT ablation on November 28, 2018, demonstrating severe SEC in the LA.
**Video 3:** Transesophageal echocardiography revealing thrombus within the LA appendage (LAA) along with viscid sludge/prethrombus visible at the mouth of the appendage.
**Video 4:** Transthoracic echocardiogram in March 2019 after recurrence of VT, demonstrating worsening LV systolic function and severely dilated atria.

Ventricular tachycardia ablation was subsequently performed on January 30, 2019. Rivaroxaban was omitted 2 days prior, and he was bridged with intravenous heparin. Transesophageal echocardiogram revealed severe SEC but no thrombus. Three-dimensional electrophysiological mapping demonstrated new endocardial scarring along the basal lateral LV. Three different morphologies of VT were mapped to the basal-lateral, basal-anterior, and basal-septal aspect of LV that were ablated. However, VT was still inducible postablation, indicating the complex nature and extent of the arrhythmogenic substrate.

He had subsequent recurrence of VT in March 2019. Transthoracic echocardiogram at that time (Video 4 and Figure 2) during ventricular pacing revealed worsening LV function, with an LVEF of 32% and similar regional wall abnormalities as reported previously. The LV global longitudinal strain (GLS) was significantly reduced and estimated at −7%, albeit measured during a paced rhythm. Diastolic function was difficult to determine given ventricular pacing, although E/E′ had increased to 17, suggesting increasing LV end-diastolic pressure. There was mild mitral regurgitation and mild-moderate TR with elevated pulmonary pressures (RV systolic pressure = 49 mm Hg). The LA remained severely dilated at an LA volume of 57 mL/m$^2$, and LA strain remained severely reduced at 1.9%. At this point a diagnosis of a severe atrial and ventricular cardiomyopathy was made, and further investigations were performed in order to determine the etiology of his cardiomyopathy. Repeat coronary angiography revealed normal coronary arteries. Right ventricular pressure was elevated (73/14-25) mm Hg on catheterization. Right ventricular biopsy revealed mild myocyte hypertrophy without evidence of amyloid, iron deposition, fat, inflammation, fibrosis, or malignancy. There was no significant lymphadenopathy on computed tomography scan of the neck, chest, abdomen, and pelvis. Fluorodeoxyglucose (FDG) positron emission tomography (PET) scan revealed subtle basal-anterior wall FDG uptake, which corresponded to a region of perfusion defect on myocardial perfusion imaging (Figure 3).

Due to VT storm, the patient had an urgent VT ablation on April 6, 2019, during which eight different morphologies of VT (cycle lengths between 375 and 620 msec) were mapped and ablated from basal anterior, posterior, and lateral left ventricle. He experienced acute pulmonary edema at the end of the procedure. Figure 4 demonstrates the voltage maps, which showed areas of low voltage in the LV base, consistent with scar in these areas. Throughout this period, his defibrillator interrogation continued to show absence of AF.

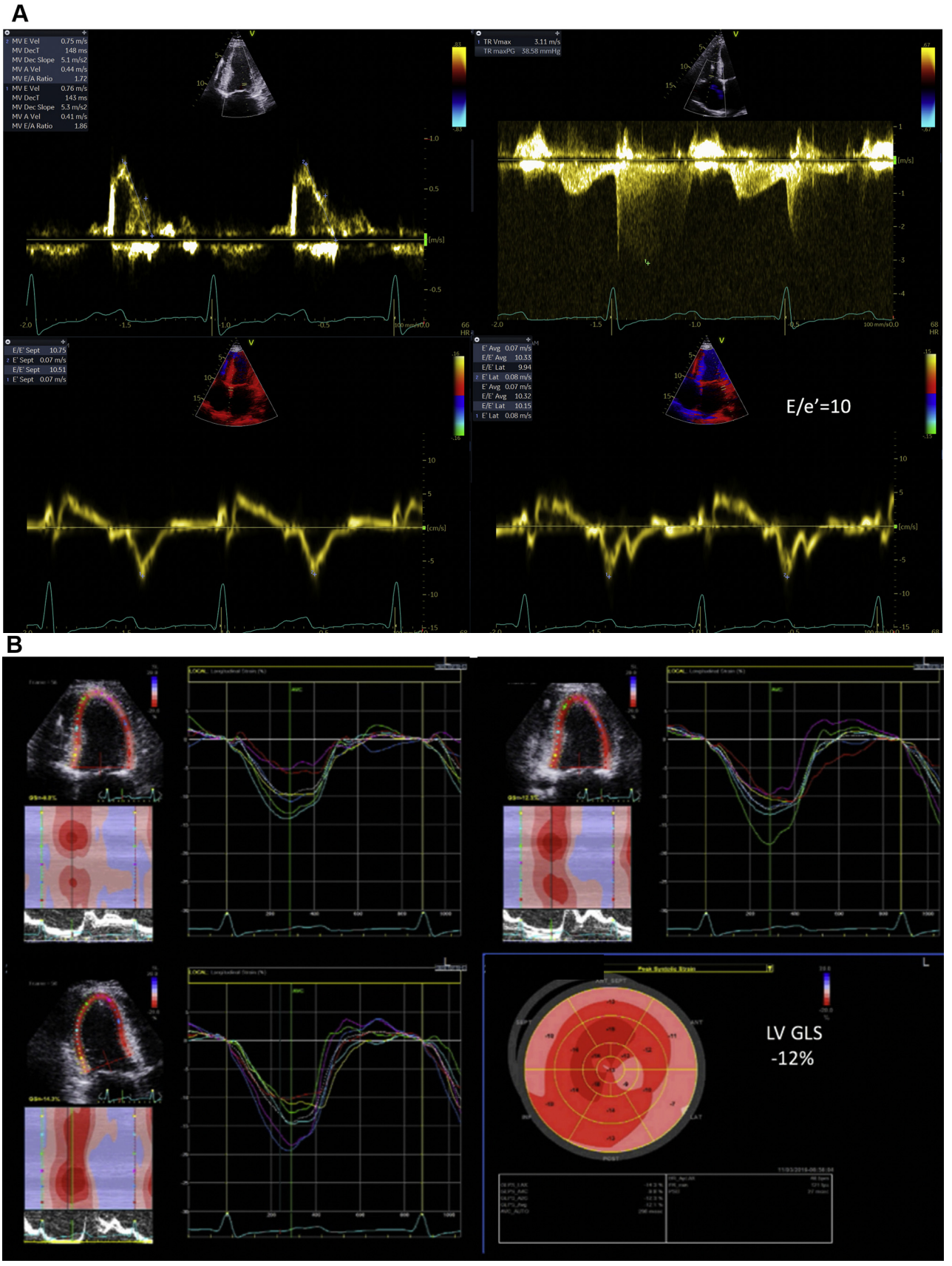
He developed worsening heart failure, and subsequently underwent heart transplantation in May 2019. The patient's native atria were not explanted and were unavailable for histopathological evaluation. The LA appendage was available for macroscopic analysis and had an organizing clot inside it. Figure 5A shows a macroscopic horizontal section of the ventricles showing the LV, RV free wall, and interventricular septum. Areas of pallor rimmed by hemorrhage are visible in the LV subendocardium, which corresponded to areas of ablation. Figure 5B demonstrates histological sections of explanted ventricular myocardium, which shows features of diffuse moderate to severe cardiomyopathy with moderate to severe anisonucleosis, moderate to severe myocytolysis, and moderate multifocal patchy cardiomyopathy-related fibrosis affecting varying levels of the wall. These changes were seen in both ventricles, with no evidence of fiber disarray. The Masson trichome stain (Figure 5B) highlights the areas of patchy interstitial fibrosis. The Congo red stain for amyloid and the Perl's stain for iron were both negative. A sample of normal ventricular myocardium is provided for comparison in Figure 5C.[1]

Germline genetic testing was also undertaken. There was no relevant family history apart from a maternal aunt who had died suddenly in her 60s. His two adult children were well with no cardiac symptoms. Targeted panel testing of 114 genes associated with cardiomyopathy and/or arrhythmia revealed a pathogenic variant by American College of Medical Genetics and Genomics criteria.[2] This sequence change creates a premature translational stop signal (p.Trp792*) in the *MYBPC3* gene. It is expected to result in an absent or disrupted protein product. This specific variant has been listed in ClinVar in association with familial hypertrophic cardiomyopathy (HCM; variation ID: 217484), although there is emerging evidence showing that other variants in the same gene are associated with other cardiomyopathy phenotypes, including restrictive cardiomyopathy (RCM).[3,4] He also had two variants of uncertain significance in the *LMNA* and *MYOM1* genes. Both of his adult children underwent predictive genetic testing for the *MYBPC3* variant, and both were negative for the familial variant. Unfortunately, his parents were unavailable for cascade testing.

## DISCUSSION

Our case demonstrates an example of an undifferentiated progressive atrial and ventricular cardiomyopathy, so severe as to require cardiac transplantation. Moreover, it highlights the complexity of diagnostics, including multimodality imaging and electrophysiologic mapping, used in the evaluation and management of the cardiomyopathy. Despite these careful investigations, a documented genetic abnormality, and extensive histological evaluation of the explanted ventricles, the etiology still remains unclear.

This case is unique for a number of reasons. First, the atrial myopathy worsened significantly prior to development of significant LV dysfunction. Table 1 demonstrates the timeline of the TTE findings. The TTE in November 2018 demonstrated only mild LV systolic dysfunction with LVEF estimated at 47% (albeit with reduced GLS of −12%), whereas the LA was severely dilated and LA strain was significantly reduced (LA strain, 3%). This is compared to the "normal" value of LA strain, which has previously been reported as 39%.[5] On


A
MV E Vel 0.75 m/s
MV DecT 148 ms
MV Dec Slope 5.1 m/s2
MV A Vel 0.44 m/s
MV E/A Ratio 1.72
MV E Vel 0.76 m/s
MV DecT 143 ms
MV Dec Slope 5.3 m/s2
MV A Vel 0.41 m/s
MV E/A Ratio 1.86
TR Vmax 3.11 m/s
TR maxPG 38.58 mmHg
E/E' Sept 10.75
E' Sept 0.07 m/s
E/E' Sept 10.51
E' Sept 0.07 m/s
E' Avg 0.07 m/s
E/E' Avg 10.33
E/E' Lat 9.94
E' Lat 0.08 m/s
E' Avg 0.07 m/s
E/E' Avg 10.32
E/E' Lat 10.15
E' Lat 0.08 m/s
E/e'=10
B
LV GLS
-12%

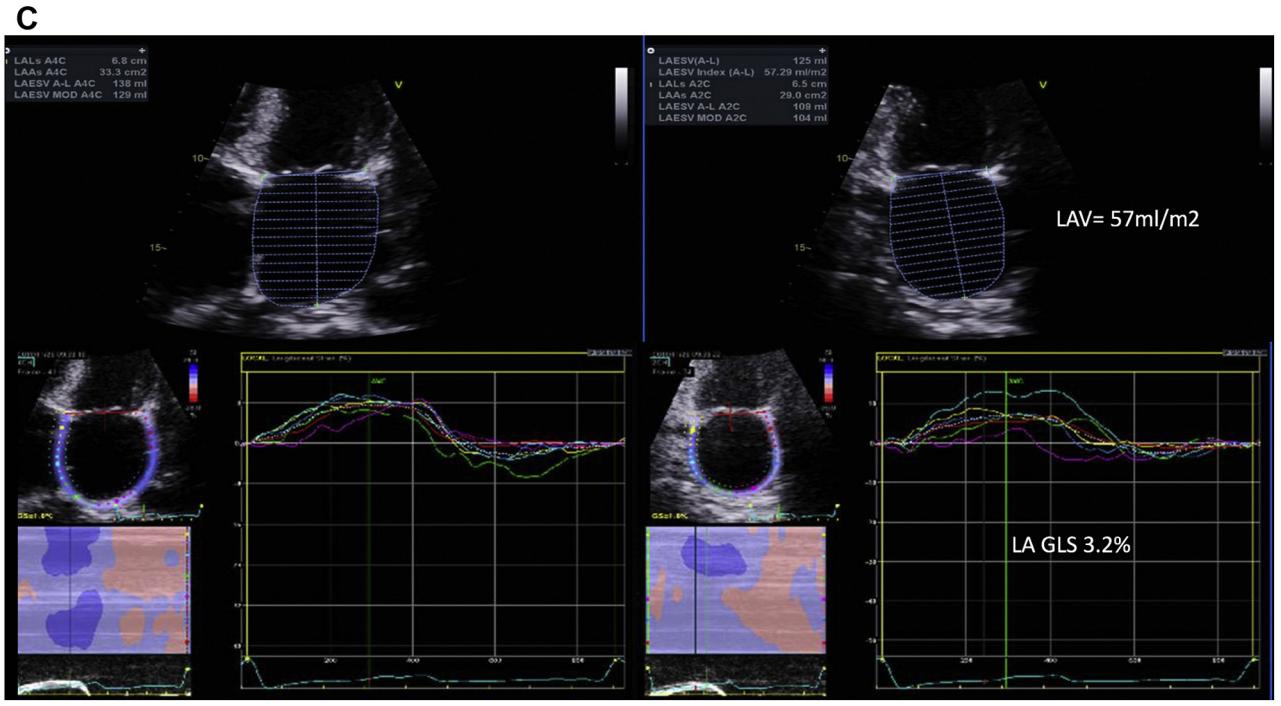



**Figure 1** Transthoracic echocardiogram from November 2018 after second presentation with VT. **(A)** Diastolic function assessment demonstrated likely grade II diastolic dysfunction but normal E/E′ of 10. **(B)** LV strain map showing reduced LV strain (–12%) with patchy reduction in strain pattern. **(C)** Enlarged LA volume and severely reduced LA reservoir strain of 3.2%.

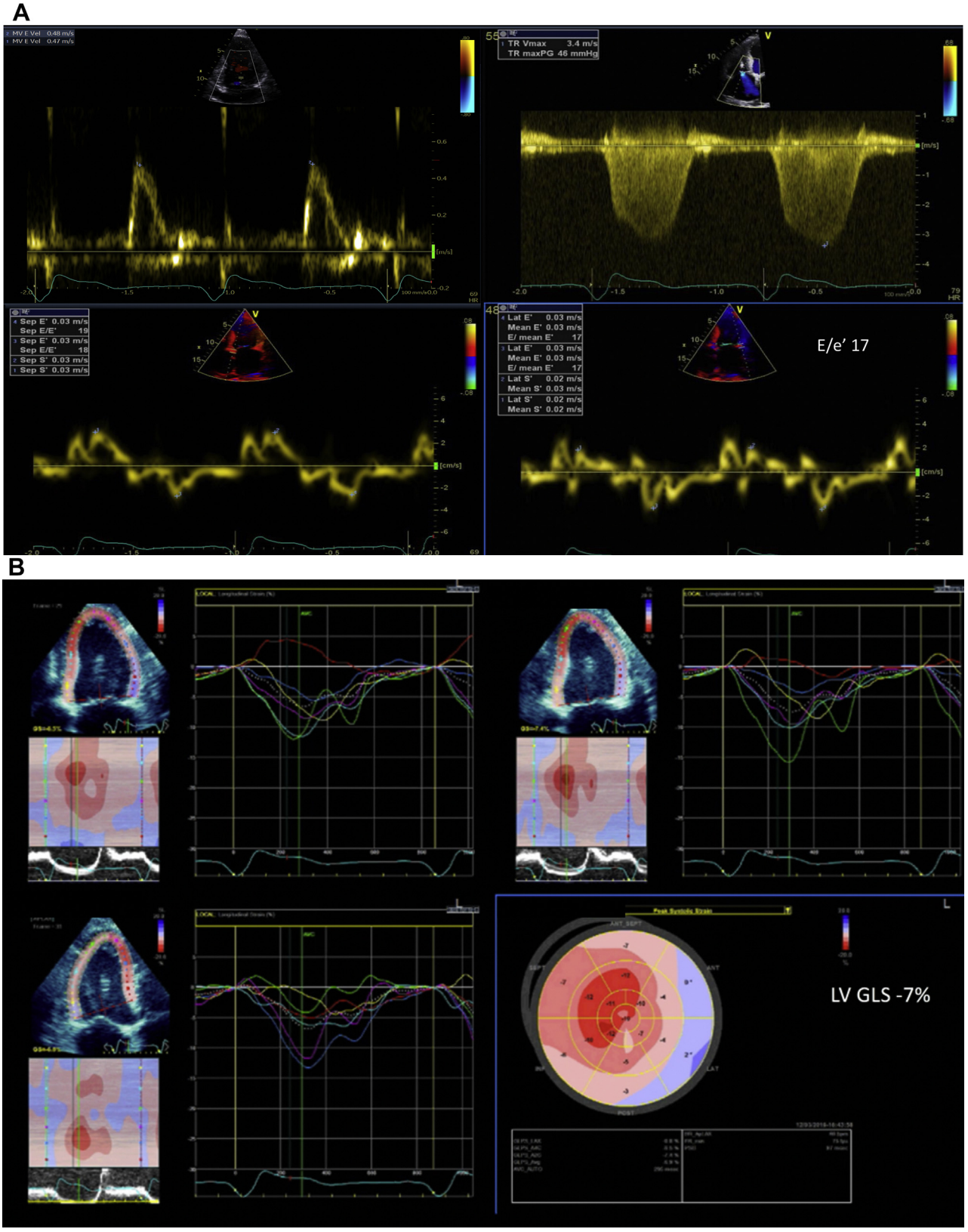
subsequent echocardiogram in March 2019, the patient's LV function deteriorated further (LVEF of 32% with a corresponding LV GLS of −7%), while LA function remained significantly impaired (LA strain, 1.9%).

Second, there was discordance between the sequence of pump failure versus ventricular arrhythmogenesis versus atrial function. In the ventricles, incessant arrythmias preceded pump failure. In contrast, in the atria the pump failure was not associated with persistent AF. The LA was severely enlarged, and function was severely impaired by strain measurement, despite maintenance of SR. The atrial myopathy, however, was severe enough to result in LA thrombus, despite the patient maintaining SR and being on treatment with rivaroxaban until 2 days prior to EPS.

Restrictive cardiomyopathy is defined as a cardiomyopathy associated primarily with impaired diastolic function, increased LV filling pressures, and enlarged atria, in the absence of LV hypertrophy or dilatation.[6] While most RCMs are secondary to conditions such as amyloidosis or sarcoidosis, idiopathic/primary RCM is much rarer and often has a genetic predisposition, with common genes shared between RCM and HCM.[6,7] This patient had a pathogenic variant in a gene encoding myosin-binding protein C (MYBPC3), which is arrayed transversely in sarcomere A bands and binds myosin heavy chain in thick filaments and titin in elastic filaments.[8] Phosphorylation of this protein appears to modulate contraction and allows fine-tuning of cardiac muscle contraction.[9] The *MYBPC3* gene has been more extensively described in HCM[8] but in recent years has been reported in association with RCM.[3,4] This further highlights the common pathogenetic pathway that underlies these cardiomyopathies whose final phenotype may be modulated by other epigenetic factors.

Although our patient's FDG-PET scan revealed subtle anterobasal wall FDG uptake corresponding to a region of perfusion defect on myocardial perfusion imaging, the histopathology of his explanted heart showed nonspecific findings, with no positive stains suggesting an infiltrative cause. Indeed, RCM histopathology is often nonspecific and can include focal or diffuse perimyocytic fibrosis,[10] as was observed in this patient. Association with myocyte hypertrophy and myofiber disarray is also documented[10] but was not evident in this instance. It is well described that ventricular fibrosis promotes triggered activity and that early after depolarization it can lead to VT.[11] While most RCM presents with heart failure,[10] ventricular arrythmias can be present, but the latter is more commonly described in infiltrative RCM such as sarcoidosis.[12] Although a diagnosis of idiopathic RCM seems fitting in this patient, given some of the characteristics on his echocardiogram and elevated RV pressures on catheterization, it is unusual that the LA enlargement and dysfunction preceded an overt increase in LV filling pressures as demonstrated by a normal E/E′ on the echocardiogram performed in November 2018; Figure 1). However, LV filling pressure were subsequently raised, with worsening LV systolic function. Thus, it is likely that LA alterations, including LA enlargement and dysfunction, may have been driven by the primary cardiomyopathic process, rather than as a consequence of elevated LV filling pressures.

The discordance between the severe LA dysfunction and the absence of atrial arrhythmias highlights the importance of considering LA myopathy as a process even in the absence of overt atrial arrhythmias. While traditional schools of thought have hitherto centered around AF leading to structural and electrophysiological changes in the LA, with consequent perpetuation of AF (the so-called AF begets


A
MV E Vel 0.48 m/s
MV E Vel 0.47 m/s
TR Vmax 3.4 m/s
TR maxPG 46 mmHg
Sep E' 0.03 m/s
Sep E/E' 19
Sep E' 0.03 m/s
Sep E/E' 18
Sep S' 0.03 m/s
Sep S' 0.03 m/s
Lat E' 0.03 m/s
Mean E' 0.03 m/s
E/ mean E' 17
Lat E' 0.03 m/s
Mean E' 0.03 m/s
E/ mean E' 17
Lat S' 0.02 m/s
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E/e' 17
B
LV GLS -7%

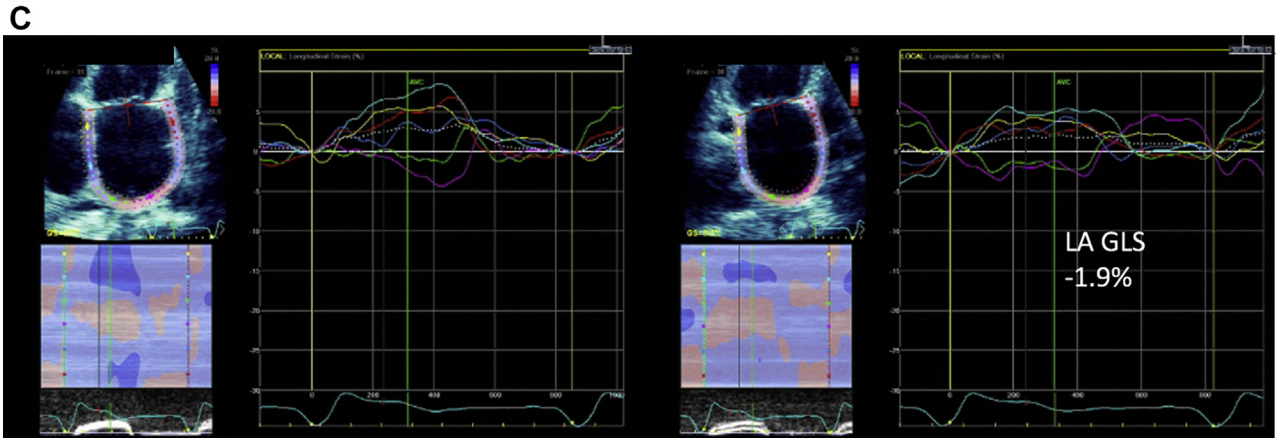


Figure 2 Transthoracic echocardiogram in March 2019 after recurrence of VT, demonstrating worsening diastolic function **(A)**, LV strain **(B)**, and LA strain **(C)**.

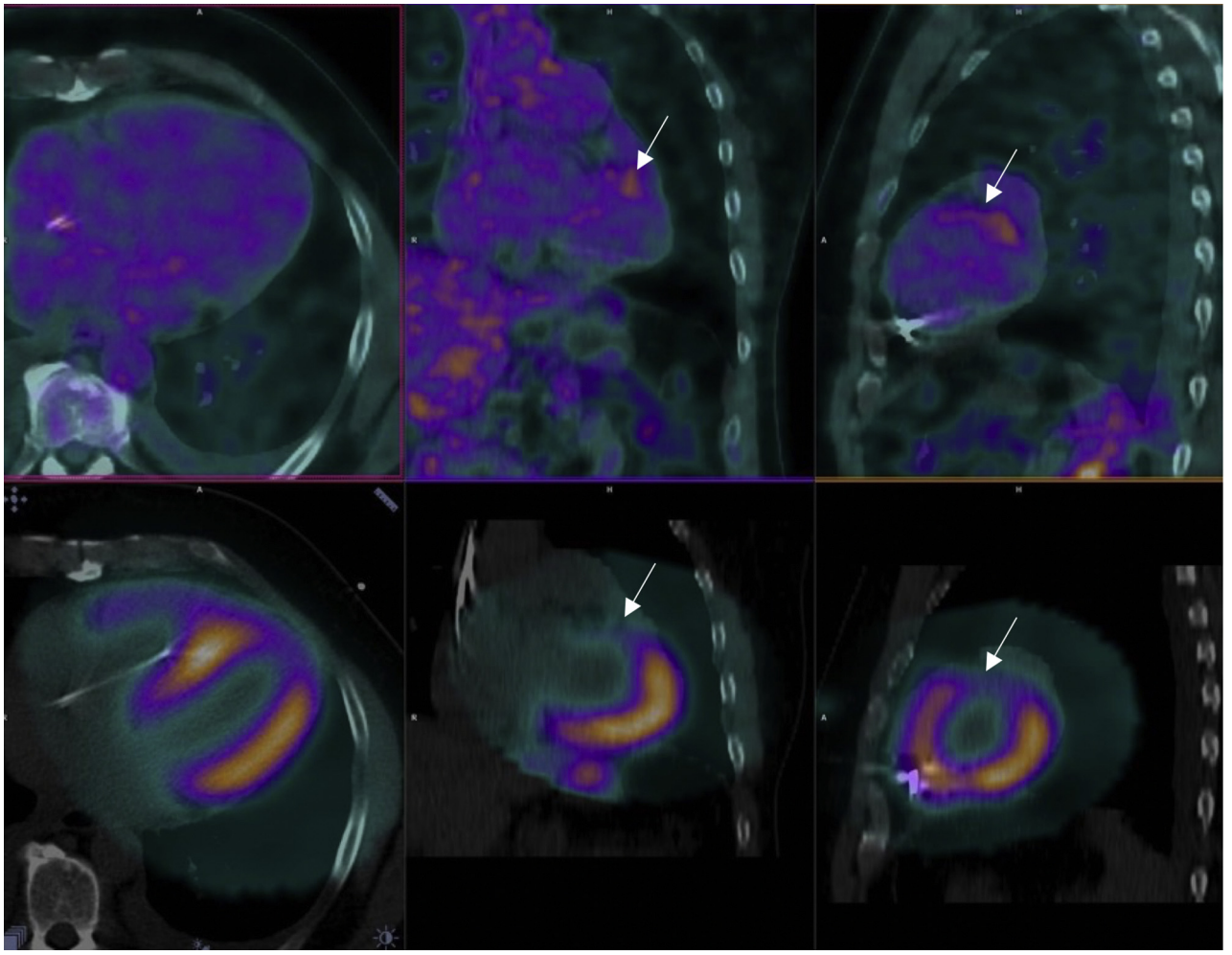

Figure 3 The *top* (FDG-PET) shows subtle anterobasal wall FDG uptake (*white arrows*), corresponding to region of perfusion defect on myocardial perfusion imaging (*bottom*).

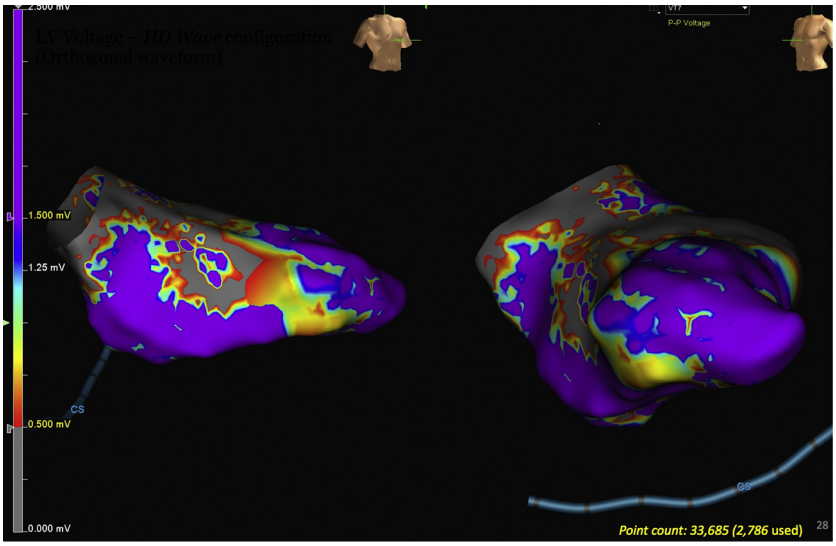


**Figure 4** Electrophysiological bipolar voltage maps in the right anterior oblique (*left*) and left anterior oblique (*right*) projections demonstrating areas of scar (areas that are not purple) predominantly in the LV base.

AF concept),[13] the relationship is probably more complex. Various animal models have demonstrated that an atrial myopathy is characterized by atrial fibrosis on histology,[14] and it is thought that this substrate in itself provides a nidus for thrombus formation consequent to LA dysfunction. The hypothesis that an atrial myopathy can exist without associated AF is supported by the lack of temporal relationship between patients with stroke and AF, as demonstrated in previous studies.[15] Moreover, LA dilatation and LA dysfunction on imaging have been associated with poorer prognosis in a number of conditions.[16] As such, noninvasive echocardiographic markers such as LA size and novel markers of LA function (e.g., LA strain) may provide quantitative information that may help identify an underlying atrial myopathy and potentially guide management for prevention of thromboembolic disease.

While it is possible that the alterations in LA enlargement and function may have been partly attributable to LV diastolic dysfunction, LA changes usually occur consequent to chronically elevated LV filling pressures. Hence, it is interesting that the traditional noninvasive marker of LV filling pressure was not elevated (E/e′ = 10) at initial presentation, despite the severe alterations in LA size and function. One limitation of the diastolic function assessment on echocardiography is that it is altered by loading conditions and is difficult to assess with AF or paced rhythm. However, E/E′ is often regarded as a robust marker of LV filling pressures, even in the absence of SR, and is less affected by loading.[17]

Our case additionally demonstrates the potential clinical utility of adopting newer markers such as LA strain in the diastolic dysfunction assessment.[18] Furthermore, it is possible that the primary pathogenesis of the LA myopathy may be related to the cardiomyopathic disease process itself, which resulted in extensive LV scarring as demonstrated on electrophysiological voltage mapping of the LV, which was subsequently confirmed by histology.

## CONCLUSION

Our case demonstrates a rare, possibly genetic cardiomyopathy that is potentially a variant of RCM, presenting with incessant VT and a coexistent atrial myopathy. The severe LA myopathy, characterized by LA enlargement and reduced LA strain on TTE, was present, despite the absence of sustained atrial arrythmias. Moreover, even with SR, LA appendage thrombus formation occurred consequent to LA dysfunction. This case highlights the importance of recognizing a coexistent LA myopathy with an RCM, as this may have potential prognostic and management implications, including prevention of thromboembolism.

## SUPPLEMENTARY DATA

Supplementary data related to this article can be found at https://doi.org/10.1016/j.case.2021.03.007.

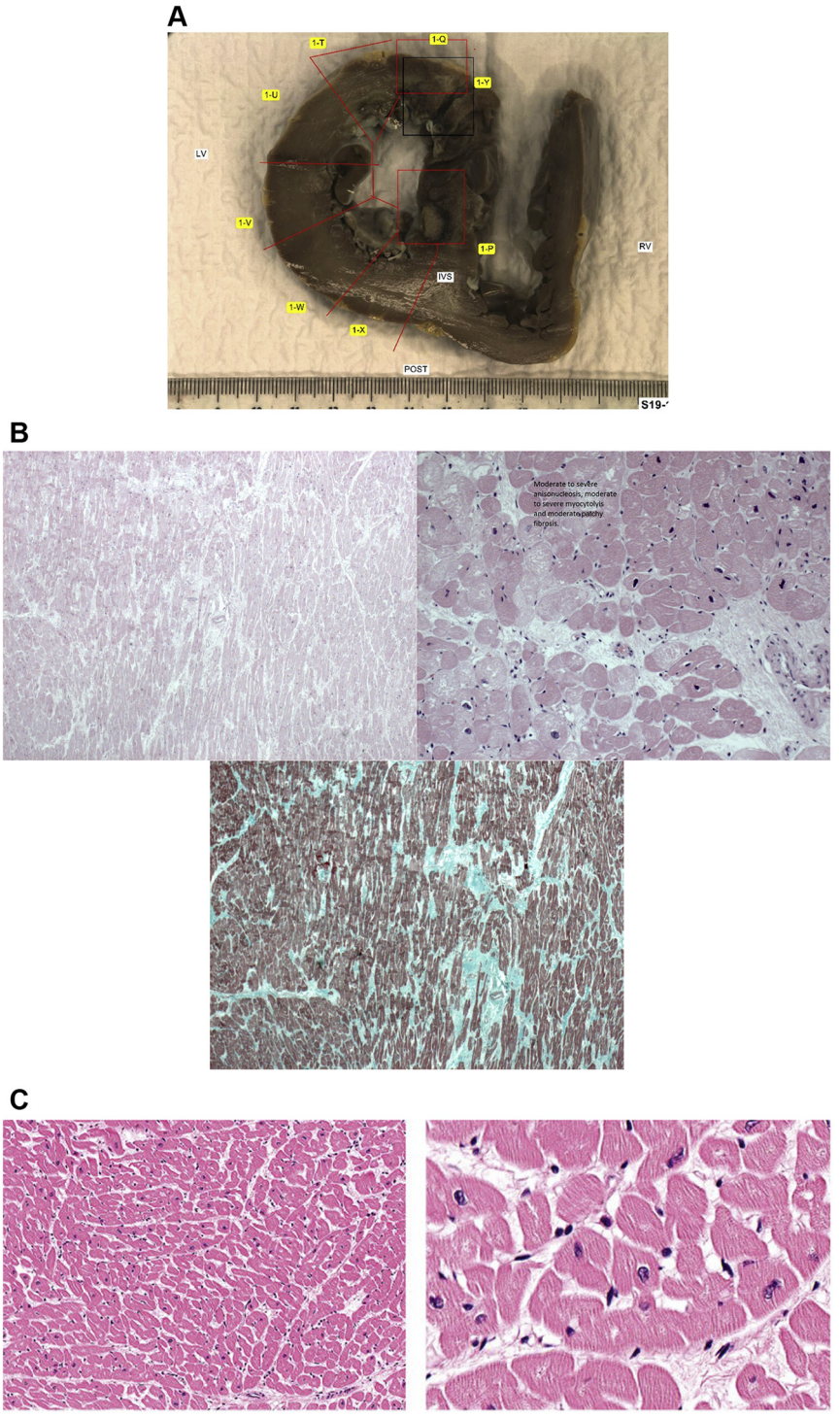


Figure 5 **(A)** Macroscopic horizontal section of the ventricles showing the left ventricle (LV), right ventricle (RV) free wall, and interventricular septum (IVS). The boxes show areas of pallor rimmed by hemorrhage in the LV subendocardium corresponding to areas of ablation. **(B)** Sections of myocardium from this patient in low-power (*left*) and high-power views (*right*) and Masson trichrome stain (*bottom*). The histology demonstrates features of diffuse moderate to severe cardiomyopathy with moderate to severe anisonucleosis (morphological manifestation of nuclear injury characterized by variation in the size of the cell nuclei), moderate to severe myocytolysis (also referred to as "vacuolar degeneration" and "colliquative myocytolysis" of the heart and characterized by the gradual vacuolization of muscle fibers, resulting in a nucleus within a sarcolemmal tube that otherwise appears empty), and only patchy moderate multifocal fibrosis, the latter best highlighted on the Masson trichrome stain. **(C)** Normal histology of LV cardiac muscle in longitudinal (*left*) and cross-sectional (*right*) views. The cardiomyocytes are rectangular on longitudinal sections with scattered acute angle branching and central nuclei and are arranged in vaguely regular bands. On transverse section they have a more rounded appearance, and frequently in this plane of section the nuclei may not be visualized. Reused with permission from Buetow *et al.*[1]

**Table 1** Table summarizing the timeline of the major TTE findings for this case

| TTE measurements | February 2014 | November 2018 | March 2019 |
|---|---|---|---|
| LV size | Normal | Normal | Normal |
| LVEF biplane, % | 65 | 47 | 32 |
| LV wall thickness | Normal | Mildly increased | Mildly increased |
| LA size | 26 $cm^2$ area* | 57 $mL/m^2$ volume | 57 $mL/m^2$ volume |
| E/E′ | NA | 10 | 17 |
| TR velocity, m/sec | 3.2 | 3.11 | 3.4 |
| LV strain, % | NA | −12 | −7 |
| LA strain, % | NA | 3.2 | 1.9 |

NA = not available.
*For the 2014 echocardiogram, E/E′, LA volume, and strain measurements could not be obtained as it was a limited study.

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