ESC European Society of Cardiology

European Heart Journal - Case Reports (2020) **4**, 1–7
doi:10.1093/ehjcr/ytaa124

CASE REPORT
Arrhythmias/electrophysiology

An unusual case of severe myocarditis in a genetic cardiomyopathy: a case report

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Received 19 November 2019; first decision 10 December 2019; accepted 23 April 2020; online publish-ahead-of-print 9 June 2020

Background Myocarditis is an inflammatory disease of the myocardium caused by infectious pathogens, immune-mediated conditions, or toxic agents. This report explores a rare case of severe myocarditis occurring in an inherited cardiomyopathy.

Case summary A 24-year-old female patient presented with progressing dyspnoea and chest discomfort. Echocardiography and cardiac magnetic resonance imaging revealed dilated cardiomyopathy (DCM) with severe biventricular dysfunction [left ventricle ejection fraction (LV-EF) 10%]. Myocardial inflammation was suspected due to extensive subendocardial to transmural late gadolinium enhancement. Endomyocardial biopsy (EMB) showed severe chronic lymphocytic myocarditis. As inflammatory DCM was assumed, immunosuppressive therapy with prednisolone was initiated in addition to standard heart failure therapy. Endomyocardial biopsy after 3 months showed resolving inflammation. However, a marked architectural disarray observed in all biopsies raised the suspicion of an inherited cardiomyopathy. Genetic testing revealed a *de novo* mutation with effect on splicing of lysosome-associated membrane protein 2, as found in Danon disease. Periodic acid–Schiff (PAS) staining confirmed a glycogen storage disorder. Immunosuppressive therapy was intensified due to reactivation of myocardial inflammation and led to improvement of LV-EF and to significant symptom relief over a 16-month follow-up period.

Discussion This is the first report of Danon disease initially presenting as a severe myocarditis. It illustrates the clinical value of EMB for diagnosis and immunosuppressive therapy monitoring in chronic myocarditis. Increasing evidence suggests that myocardial inflammation may modify disease progression and prognosis in inherited cardiomyopathies. The causal role of cardiac protein mutations in the pathophysiology of myocarditis remains to be determined.

Keywords Lymphocytic myocarditis • Dilated cardiomyopathy • Inherited cardiomyopathies • Endomyocardial biopsy • Danon disease • Case report

Learning points

- Consider genetic cardiomyopathy in young patients presenting with severe myocarditis and dilated or hypertrophic cardiomyopathy.
- Endomyocardial biopsy is essential in establishing the aetiology of myocardial inflammation and for guiding immunosuppressive therapy in virus-negative chronic myocarditis.
- Immunosuppressive therapy may modify the progression of myocardial dysfunction in inherited cardiomyopathies presenting as myocarditis.

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Handling Editor: Flavio D'Ascenzi

Peer-reviewers: Alberto Aimo, Monika Arzanauskaite, and Mark Abela

Compliance Editor: Amir Aziz

Supplementary Material Editor: Vishal Shahil Mehta

Introduction

Myocarditis is an inflammatory disease of the heart muscle caused by infectious agents, systemic diseases, drugs, or toxins.[1] The clinical manifestation is very heterogeneous and ranges from mild symptoms to cardiogenic shock and sudden cardiac death. The incidence of myocarditis is difficult to determine due to great aetiological and clinical variability. Furthermore, the diagnostic gold standard, endomyocardial biopsy (EMB), is infrequently employed.[2] In nearly 30% of cases, myocarditis progresses to inflammatory dilated cardiomyopathy (DCM).[3] This report explores a rare case of severe myocarditis occurring in an inherited cardiomyopathy.

Timeline

Month 0	Initial presentation with chest discomfort, severe dyspnoea [New York Heart Association (NYHA) III–IV]
Electrocardiogram (ECG)	Atrial fibrillation (AF), wide QRS complexes (170 ms) with left and right bundle branch block pattern, ventricular extrasystoles
Laboratory blood test results	Troponin T high-sensitive (hs) 0.213 ng/mL (normal range: <0.014 ng/mL), NT-proBNP 4440 ng/L (normal range: <170 ng/L); creatine kinase (CK) (<170 U/L), creatine kinase myocardial band (CK-MB) (<24 U/L), and C-reactive protein (CRP) (<5 mg/L) within normal ranges
Transthoracic echocardiogram (TTE)	Severely dilated left ventricle (LV) (interventricular septal wall thickness in diastole 11 mm, LV end-diastolic diameter 64 mm, LV end-systolic diameter 57 mm), LV-ejection fraction (EF) 20%, functional mitral regurgitation III–IV°/IV°
Transoesophageal echocardiogram (TOE)	Left atrial appendage (LAA) thrombus (15 mm × 6 mm)
→ Initiation of heart failure therapy and direct acting oral anticoagulant (DOAC) (apixaban)	
Month 3	
Holter ECG	Paroxysmal AF, sick sinus syndrome, intermittent complete atrioventricular block with junctional escape rhythm, ventricular extrasystoles, and non-sustained ventricular tachycardias
TTE and TOE	LV-EF 25%. Resolved LAA thrombus
Cardiac magnetic resonance	Extensive transmural and subendocardial late gadolinium enhancement (LGE) in the LV (EF 10%), together with mid-myocardial LGE in the inferior septum and in the right ventricle (EF 15%), consistent with dilated cardiomyopathy and myocardial inflammation
Endomyocardial biopsy (EMB) (first)	Severe chronic lymphocytic myocarditis with diffuse infiltration of $CD3^+$ T-lymphocytes (42 T cells/mm^2). Severe architectural disarray with diffuse interstitial fibrosis and marked cardiomyocyte hypertrophy. Negative polymerase chain reaction for cardiotropic pathogens
→ Internal cardioverter-defibrillator (ICD)-Cardiac resyncronisation therapy (CRT)-implantation	
→ Initiation of oral immunosuppressive therapy with prednisolone 1 mg/kg/day for 1 week. The dose was then tapered off every week by 5 mg/day until reaching the maintenance dose of 5 mg/day	
Month 5	Improved clinical state (NYHA II)
EMB (second)	Slightly resolving inflammatory reaction (21 T cells/mm^2 lymphocytes). Marked architectural disarray, suggestive of a genetic cardiomyopathy
Genetic testing	Heterozygous missense variant (c.928G>A) with effect on splicing of lysosome-associated membrane protein 2 Diagnosis of Danon disease
TTE	Improved EF (LV-EF 32%)
CRT-ICD-control	30% Mode-switch-episodes due to AF, no sustained ventricular tachycardias, no ICD discharges
Month 8–9	
→ Discontinuation of immunosuppressive therapy (prednisolone 2.5 mg/day)	
Month 10	Acute clinical deterioration (NYHA III–IV)
Laboratory blood test results	Troponin T (hs) 0.132 ng/mL (normal range: <0.014 ng/mL), NT-proBNP 4170 ng/L (normal range: <170 ng/L); CK, CK-MB, and CRP within normal ranges
TTE	LV-EF 25%
CRT-ICD	Increasing mode-switch-episodes
EMB (third)	Increased inflammatory activity (56 T cells/mm^2)
→ Restarting of immunosuppressive therapy: initial prednisolone pulse therapy with 250 mg i.v. for 3 days, subsequently 1 mg/kg/day prednisolone for 4 weeks, followed by the above-mentioned tapering regimen + treatment intensification with tacrolimus (1 mg 2×/day), and mycophenolate mofetil (500 mg 2×/day)	
Month 16	Compensated clinical state (NYHA II)
TTE	LV-EF 25%, mitral regurgitation II–III°/IV°
CRT-ICD-control	100 Mode-switch episodes due to paroxysmal AF, no sustained ventricular tachycardias
→ Continuation of immunosuppressive therapy: prednisolone 7.5 mg/day (maintenance dose), tacrolimus 1 mg 2×/day, and mycophenolate mofetil 500 mg 2×/day	

Case presentation

A 24-year-old female patient presented with progressing shortness of breath, chest discomfort, and generalized weakness over the past 4 months. Upon admission, she presented with orthopnoea, elevated high-sensitive troponin T (0.213 ng/mL), and NT-proBNP (4440 ng/L) but normal CK and CK-MB levels. Physical examination revealed an irregular pulse (64 b.p.m.), a holosystolic murmur over the mitral valve, coarse crackles on the lungs, and hypotension (80/55 mmHg). The initial electrocardiogram showed atrial fibrillation (AF) with severe conduction abnormalities and ventricular extrasystoles (*Figure 1*). Echocardiography revealed a dilated left ventricle (LV) and right ventricle (RV) (*Figure 2A and B*) with severely reduced biventricular function consistent with a DCM. Functional mitral valve insufficiency III/IV° (*Figure 2C and D*) and a thrombus in the left atrial appendage were also identified. Medical heart failure therapy and oral anticoagulation were initiated and the patient referred to our centre for further evaluation. Cardiac magnetic resonance (CMR) imaging revealed extensive subendocardial to transmural late gadolinium enhancement (LGE) of the LV [left ventricle ejection fraction (LV-EF) 10%] as well as mid-myocardial LGE of the inferior septum and of the RV (*Figure 3* and Supplementary material online, *Video S1*). Since post-inflammatory DCM was suspected, right ventricular EMB was performed prior to internal cardioverter-defibrillator (ICD)-CRT-system implantation. Endomyocardial biopsy revealed a severe chronic lymphocytic myocarditis with diffuse infiltration of $CD3^+$ T-lymphocytes (42 T cells/mm^2) (*Figure 4A*). Additionally, the myocardium presented with a severe architectural disarray including diffuse interstitial fibrosis and marked cardiomyocyte hypertrophy (*Figure 4B*). Acute or persistent infection with cardiotropic pathogens was excluded in all biopsies by polymerase chain reaction (PCR).

Immunosuppressive therapy with prednisolone (1 mg/kg/day, followed by a tapering regimen as specified in the timeline) was initiated. The patient presented 3 months later for a control EMB, which revealed a slightly resolving inflammatory reaction (21 T cells/mm^2 lymphocytes). However, recurrent marked architectural disarray (*Figure 4G and H*) raised the suspicion that chronic myocarditis occurred on a pre-existent genetic (hypertrophic) cardiomyopathy. Genetic testing revealed a heterozygous missense variant (c.928G>A) with effect on splicing of lysosome-associated membrane protein 2 (LAMP-2), as previously described in Danon disease.[4] Additionally, PAS staining revealed a significantly enhanced storage of glycogen in cardiomyocytes of all biopsies investigated, as exemplarily shown in the first and second biopsies (*Figure 4E and G* without and *Figure 4F and H* with diastase digestion). Family history indicated a *de novo* mutation, since the two elder brothers and the parents of the patient are clinically healthy. An improvement of LV-EF (32%) and significant symptom relief (New York Heart Association II) were noted with no significant changes in NT-proBNP levels. Six months later, the patient presented with progressing dyspnoea and acute

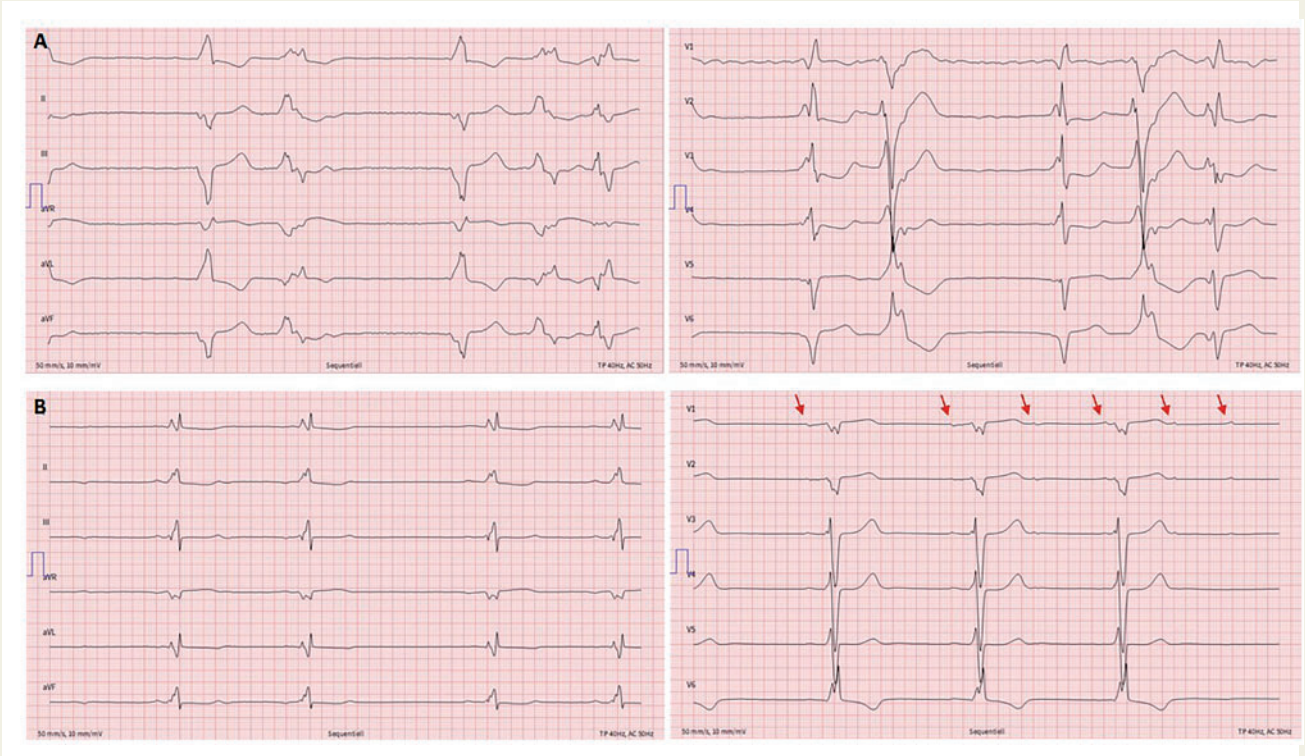

Figure 1 Twelve-lead electrocardiogram at initial presentation. (*A*) Atrial fibrillation with wide QRS complexes (170 ms) presenting both right and left bundle branch block pattern (64 b.p.m.), indicative of severe conduction abnormalities and ventricular extrasystoles. (*B*) Electrocardiogram after spontaneous conversion to sinus rhythm. The partial atrioventricular dissociation (P-waves indicated by arrows) and deformed QRS complexes are suggestive of complete heart block with junctional escape rhythm (47 b.p.m.).

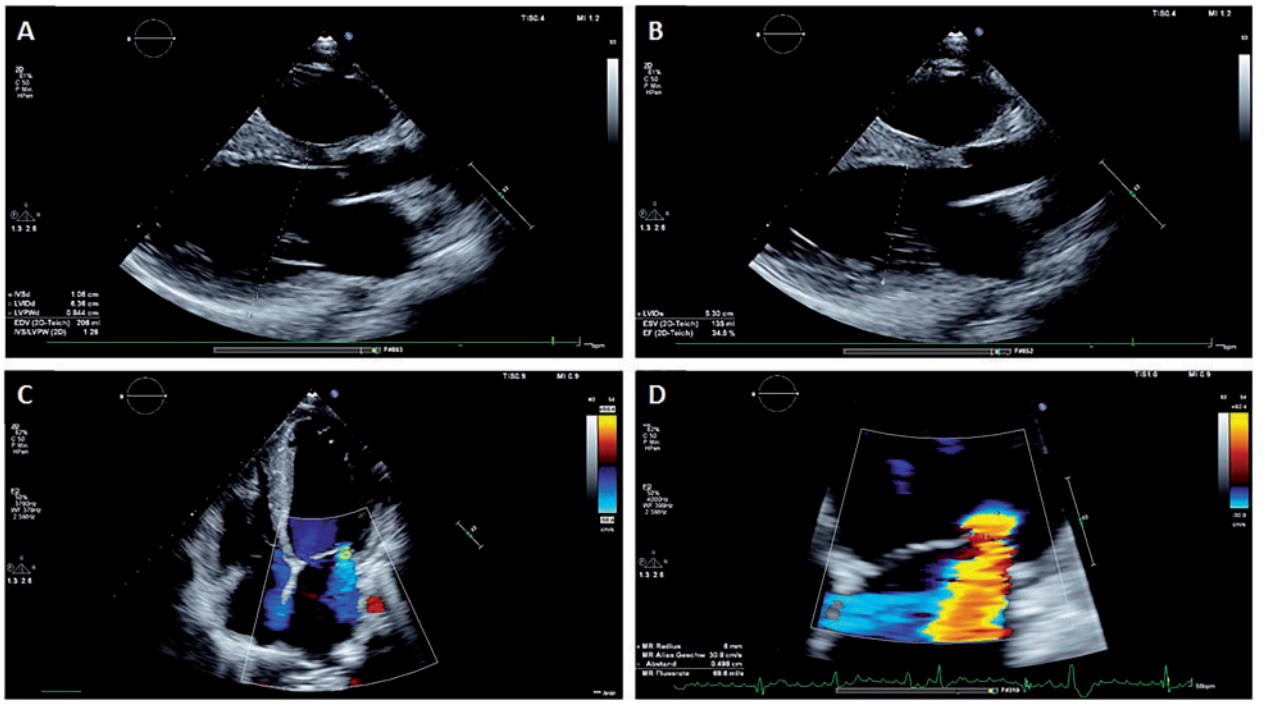

Figure 2 Representative transthoracic echocardiogram images. Severely dilated left ventricle shown in parasternal long axis (PLAX) end-diastolic (*A*) and end-systolic (*B*) view. Interventricular septal wall thickness in diastole 11 mm, left ventricular end-diastolic diameter 64 mm, left ventricular end-systolic diameter 57 mm, and posterior wall thickness in end-diastole 8 mm. Severe functional mitral regurgitation (four-chamber view) with broad regurgitation jet as seen in colour Doppler (*C*), quantified using the proximal isovelocity surface area method (*D*).

decompensated heart failure after discontinuing immunosuppressive therapy. Echocardiography revealed a reduced LV-EF of 25% and increasing mode-switch episodes of the ICD-CRT due to paroxysmal AF, but no sustained ventricular tachycardias. Endomyocardial biopsy revealed an increased inflammatory activity (56 T cells/mm^2) (*Figure 4C*), enhanced interstitial fibrosis, and again, myofiber disarray (*Figure 4D*). Immunosuppressive therapy with prednisolone was re-initiated and intensified by tacrolimus (1 mg 2×/day) and mycophenolate mofetil (500 mg 2×/day), as specified in the timeline section. During the 16-month follow-up, the patient was clinically stable and tolerating immunosuppressive therapy. Consequently, no changes in medication regime were instituted at the time.

Discussion

Danon disease is a rare X-linked cardioskeletal myopathy caused by primary deficiency of LAMP-2,[5] which leads to glycogen accumulation in skeletal muscle and myocardium. The disease is characterized by the triad of skeletal myopathy, cardiomyopathy, and mental retardation in males (mean age of onset 12.1 ± 6.5 years). Females develop symptoms at a later age (28.1 ± 15 years) and typically present with cardiomyopathy, while mild cognitive impairment and muscle weakness are only observed in ca. 50% of cases.[6] Our patient did not present any other extra-cardiac symptoms. The echocardiographic finding of DCM and the histological findings of hypertrophic cardiomyocytes with extensive fibrosis are in line with clinical manifestation of Danon disease, as DCM is more common in females (71%), while males typically present with hypertrophic cardiomyopathy (HCM) (84%).[7] However, cases of mixed DCM and HCM have been described in Danon and are thought to reflect disease progression. LAMP-2 mutations were previously reported in 4% of patients initially diagnosed with HCM in a paediatric population.[8] Prognosis is generally poor in Danon disease and is determined by heart failure. Male patients usually succumb to sudden cardiac death or require cardiac transplant in the second or third decade, while mean ages of cardiac transplant and death in females are 33.7 and 34.6 years, respectively.[6]

To the best of our knowledge, this is the first report on Danon disease primarily presenting as a severe myocarditis. This case points out that a genetic cardiomyopathy should be considered in young patients with myocardial inflammation and dilated or hypertrophic cardiomyopathy and underlines the importance of EMB in myocarditis. According to current ESC guidelines, histological and immunohistochemical analysis is considered the gold standard for the diagnosis of definite myocarditis, as it identifies the aetiology of myocardial inflammation and is a prerequisite for safe immunosuppressive or antiviral therapy. Cardiac magnetic resonance represents the most accurate non-invasive tool to detect active myocardial inflammation. Sensitivity and specificity are highest in patients with histologically confirmed acute myocarditis, while diagnostic accuracy is decreased in chronic myocarditis.[1,3] Additionally, CMR allows assessment of

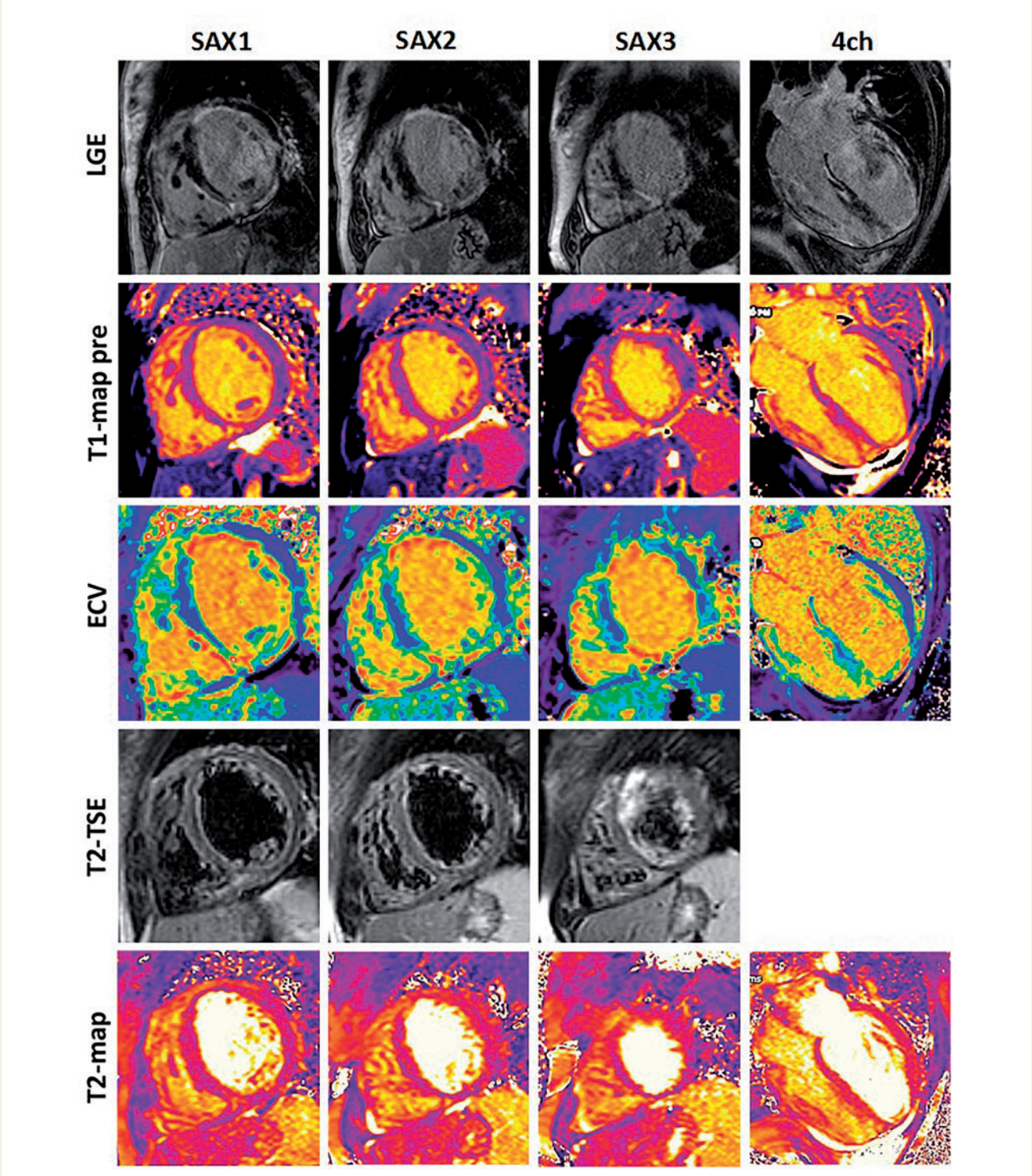

Figure 3 Representative cardiac magnetic resonance images in short-axis view and four-chamber view. Dilated left ventricle with markedly reduced global ejection fraction (10%) and akinesia of the thin basal anteroseptal and apical inferior wall. Both areas show transmural late enhancement. In addition, subendocardial and subepicardial enhancement can be observed in the anterolateral and inferolateral wall, respectively. The inferior septum presents predominantly mid-myocardial enhancement. Furthermore, a marked increase in extracellular volume is observed in these areas (up to 60%). T2-TSE shows an increased signal intensity in the mid-cavity septum (three-fold increase compared to the pectoral muscle). The T2-relaxation time (54 ms) determined in T2-mapping is in the normal range. 4ch, four-chamber view; ECV, extracellular volume; LGE, late gadolinium enhancement; SAX, short-axis view.

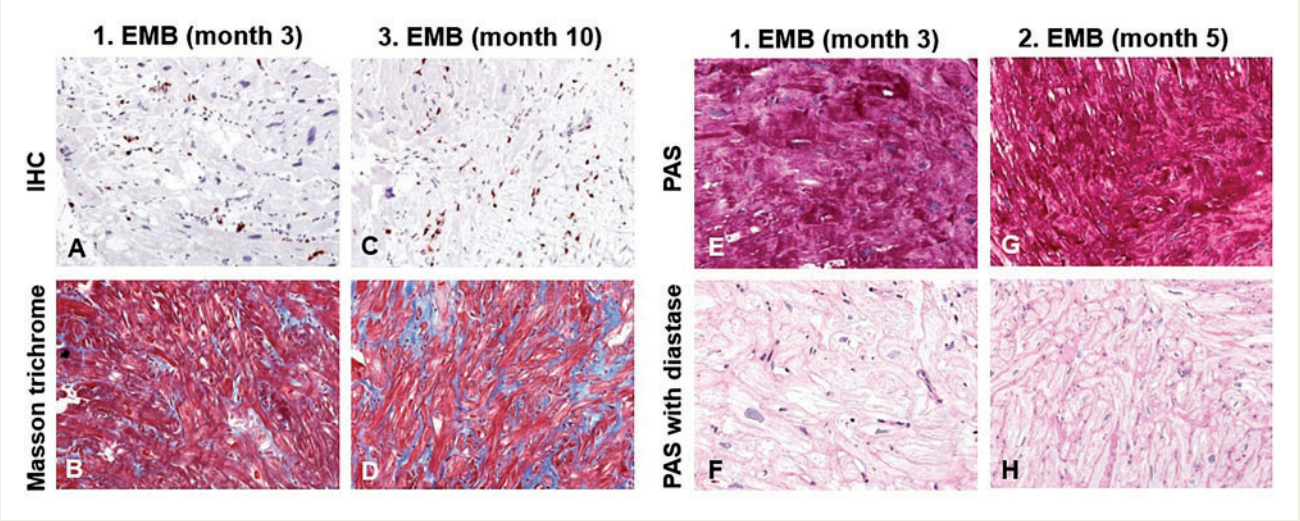

Figure 4 Histological findings in endomyocardial biopsies. Immunohistochemical staining detects numerous CD3+ T cells (*A* and *C*). Masson trichrome stain reveals myofiber disarray, loss of myofibrils, and fibrosis (*B* and D). PAS staining illustrates glycogen deposits within cardiomyocytes without (*E* and *G*) and with (*F* and *H*) diastase digestion. Magnification *A*–*D*, *G* and *H* ×200, *E* and *F* ×400. EMB, endomyocardial biopsy; IHC, immunohistochemistry; PAS, periodic acid-Schiff.

myocardial fibrosis using LGE analysis and represents a Class IC indication for diagnosis of non-ischaemic cardiomyopathies, such as storage disorders.[9] Late gadolinium enhancement patterns described in the current case correspond with previous CMR findings in Danon disease[10] and should prompt investigation for this glycogen storage disorder in an appropriate clinical setting. Nuclear imaging, another non-invasive diagnostic tool, is not routinely recommended in the diagnosis of myocarditis due to its low specificity.[1]

Immunosuppression was shown to improve the LV-EF in histologically proven virus-negative lymphocytic myocarditis[11,12] and should be considered in this group of patients with heart failure refractory to standard medical therapy.[1,3] Due to repetitive negative PCR results, an immunosuppressive therapy was initiated in the present case which led to a slight improvement of LV function and to significant symptom relief. Endomyocardial biopsy thus proved to be an essential tool to guide specific treatment and monitor therapy response. However, complete resolution of myocardial inflammation could so far not be achieved in our patient.

There is increasing evidence that inherited cardiomyopathies are associated with myocardial inflammation, as previously described in arrhythmogenic cardiomyopathy, Fabry disease, and Duchenne muscular dystrophy.[13–15] Whether mutations in cardiac proteins render cardiomyocytes vulnerable to inflammation remains to be determined. This case suggests that chronic myocarditis and subsequent immunosuppressive therapy may modify the progression of myocardial dysfunction in Danon disease. However, both Danon disease and severe chronic myocarditis may progress to end-stage DCM requiring cardiac transplantation. A team of cardiologists, pathologists, radiologists, geneticists, and immunologists are required for correct diagnosis and best supportive care in such rare and complex cases.

Lead author biography

Miruna-Andreea Popa obtained her MD degree from Heidelberg University, Germany in 2017. She currently works in the Department of Electrophysiology at the German Heart Center in Munich and takes research interest in catheter ablation strategies in persistent atrial fibrillation.

Supplementary material

Supplementary material is available at *European Heart Journal - Case Reports* online.

Acknowledgements

We would like to thank Jonathan Champagne for his assistance in language editing of this manuscript.

Slide sets: A fully edited slide set detailing this case and suitable for local presentation is available online as Supplementary data.

Consent: The author/s confirm that written consent for submission and publication of this case report including image(s) and associated text has been obtained from the patient in line with COPE guidance.

Conflict of interest: none declared.

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