ESC European Society of Cardiology

European Heart Journal - Case Reports (2022) **6**(2), 1–6
https://doi.org/10.1093/ehjcr/ytac053

CASE REPORT
Congenital Heart Disease

A novel Troponin I mutation associated with severe restrictive cardiomyopathy—a case report of a 27-year-old woman with fatigue

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Received 6 May 2021; first decision 5 July 2021; accepted 19 January 2022; online publish-ahead-of-print 2 February 2022

Background Restrictive cardiomyopathy is rare and heterogeneous in origin, clinical manifestation, and prognosis. Familial forms have, amongst others, been associated with mutations in the TNNI3 gene. We present a case of familial restrictive cardiomyopathy associated with a novel TNNI3 mutation including longitudinal follow-up.

Case summary A 27-year-old woman was evaluated for fatigue in the context of a family history of sudden cardiac death. Echocardiography was normal except for mild left atrial dilatation. Focused genetic screening, limited to the most common genes associated with cardiomyopathy, was unremarkable in 2006. In biopsy, mild inflammatory cardiomyopathy was diagnosed, and the patient was discharged. Thirteen years later, rapid clinical deterioration occurred in the context of new-onset atrial fibrillation (AF). Echocardiography now showed gross bi-atrial dilatation and evidence of diastolic dysfunction. Based on haemodynamic tracings during angiography, a diagnosis of restrictive cardiomyopathy was made. In 2018, next-generation sequencing revealed the hitherto undescribed Troponin I variant Lys193Glu in a functionally critical domain. Haemodynamic stabilization was achieved by pulmonary vein isolation. Until now, the patient remains symptom free under diuretic treatment.

Discussion Diagnosis of restrictive cardiomyopathy is complicated by often oligosymptomatic early presentation and a diverse clinical picture. Thorough medical and family history and early invasive haemodynamic tracing are indispensable in diagnosis. Therapy-refractory AF should raise suspicion. Reporting of longitudinal follow-up cases is essential to better understand the early symptoms, development, and prognosis of this rare disease. Broad genetic testing in unclear cases has become more available and affordable and should be considered early in the diagnostic workflow.

Keywords Case report • Hereditary heart disease • Restrictive cardiomyopathy • Troponin I mutation • Genetic testing

ESC Curriculum 6.5 Cardiomyopathy • 2.1 Imaging modalities • 5.3 Atrial fibrillation • 6.1 Symptoms and signs of heart failure

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Handling Editor: Belinda Gray
Peer-reviewers: Vincenzo Nuzzi; Sadaf Raza
Compliance Editor: Zhiyu Liu
Supplementary Material Editor: Anthony Paulo Sunjaya

Learning points

- Work-up for cardiomyopathy should be considered in young patients with refractory atrial fibrillation and positive family history.
- Early diagnosis of restrictive cardiomyopathy should include invasive haemodynamics measurement.
- Early extensive mutation screening is advisable in all cardiomyopathy patients with positive family history and has become much more easily available and more affordable.
- Patients with suspicious family history for heart disease and poorly explained abnormal diagnostic findings should receive regular follow-up including echocardiography.

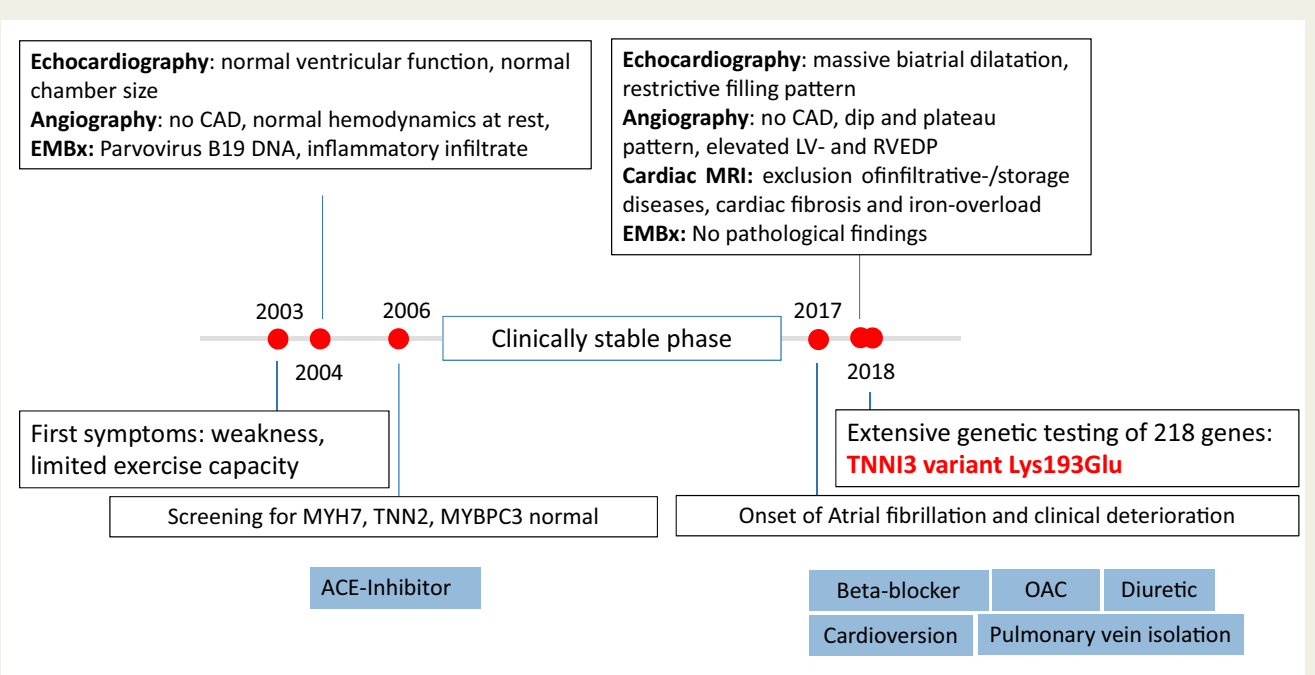
Introduction

The European Society of Cardiology differentiates five major classes of cardiomyopathies: dilated, hypertrophic, arrhythmogenic right ventricular, and restrictive cardiomyopathy as well as unclassified [left ventricular (LV) non-compaction and Takotsubo cardiomyopathy].[1] Restrictive cardiomyopathies (RCM) are a pathogenetically and clinically heterogenous group characterized by myocardial stiffening and resulting abnormality of diastolic filling with only small increases in volume.[2] The diverse underlying causes may be idiopathic, genetic, or secondary to systemic disorders and can be assigned to infiltrative (e.g. amyloidosis), storage (e.g. haemochromatosis), non-infiltrative (familial, idiopathic), and endomyocardial (e.g. endomyocardial fibrosis) forms.[2,3] Mutations in sarcomeric and cytoskeletal genes, amongst them the troponin complex subunits T (*TNNT2* Troponin T)[4] and I (*TNNI3* Troponin I),[5] have been associated with hereditary RCM.

Endomyocardial biopsies (EMB) are not commonly indicated in heart failure work-up but remain the golden standard to reveal the pathological basis of unexplained heart failure when non-invasive diagnostics cannot sufficiently inform on therapeutic decisions. A joint AHA/ACC/ESC-scientific statement on EMBs defines specific clinical circumstances in which the benefit of an EMB outweighs its risk, including a Class IIa recommendation for 'heart failure associated with unexplained restrictive cardiomyopathy'.[6]

Timeline

Timeline showing symptoms, echocardiographic, angiographic, endomyocardial biopsy, and molecular genetic findings and therapy.



Case presentation

In 2003, a 27-year-old woman was referred to our hospital due to limited exercise capacity and progressive fatigue. She reported on flu-like symptoms 3-month before the first presentation and no full recovery since then. She had no history of palpitations or syncope, no chest pain, and the physical examination was without pathological findings. Particularly, she had no peripheral oedema, no heart murmur, and a normal respiratory examination. She had no history of malignancy, radiation, or diabetes, and denied alcohol abuse or intake of cardiotoxic drugs. Her only long-term medication at the first presentation was an oral contraceptive.

Family history (*Figure 1*) up to the time of the first presentation revealed sudden cardiac death (SCD) in one grandmother, two aunts (22 and 60), and one cousin (26). The aunt deceased at age 60 had been diagnosed with cardiomyopathy with atrial amyloid deposition with severe diastolic heart failure. The past medical history of the other deceased family members was not known. The patient's mother had a history of recurrent, therapy-resistant atrial fibrillation (AF), as well as a restrictive filling pattern with preserved systolic function in echocardiography. She had received an implantable cardioverter-defibrillator for recurrent syncopes due to ventricular tachycardia. One remaining cousin had been diagnosed with hypertrophic cardiomyopathy.

Laboratory measurements revealed elevated N-terminal prohormone of brain natriuretic peptide of 896 ng/L (normal 1–75 years: <125 ng/L). All other laboratory measurements were within the normal range, including D-Dimers and parameters of infection. Electrocardiography (ECG) was unremarkable. Echocardiography showed normal systolic function, normal biventricular chamber- and right atrial size, and normal wall thickness. The left atrium (LA) was moderately dilated (46 mm). Coronary artery disease was excluded in angiography. Haemodynamic tracing showed normal filling pressures at rest, but pathologically high pulmonary artery pressures at exertion [56/26/36 mmHg (P_{sys}, P_{diast}, P_{mean})].[7] Screening for the three most frequent genes causing hereditary cardiomyopathy (MYH7, TNNT2, MYBPC3) was unremarkable.

Endomyocardial biopsy showed low-level inflammatory cell infiltration, ICAM-1 overexpression, and parvovirus B19 (B19V) DNA was detected in one out of the three biopsy specimens. The patient was diagnosed with clinically mild inflammatory cardiomyopathy accompanying a recent upper respiratory tract infection and discharged with the recommendation for regular ambulatory clinical and echocardiographic follow-up at her city of residence to ensure early detection of possible progression.

Only after a symptom-free interval of 13 years, however, in 2017, the patient was readmitted to our centre due to rapid clinical deterioration. She now suffered from dyspnoea New York Heart

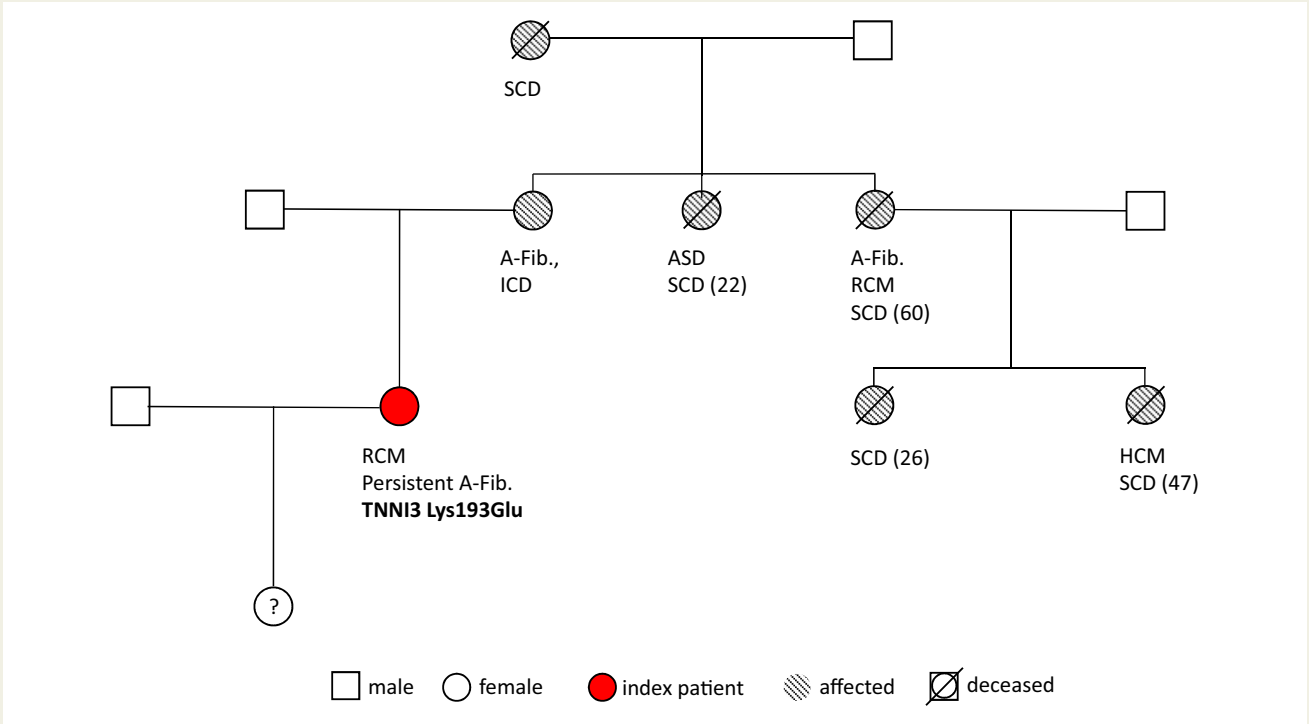


Figure 1 Family tree showing the index patient (red) and known relatives. A-Fib., atrial fibrillation; ASD, atrial septal defect; HCM, hypertrophic cardiomyopathy; ICD, implantable cardioverter-defibrillator; RCM, restrictive cardiomyopathy; SCD, sudden cardiac death.

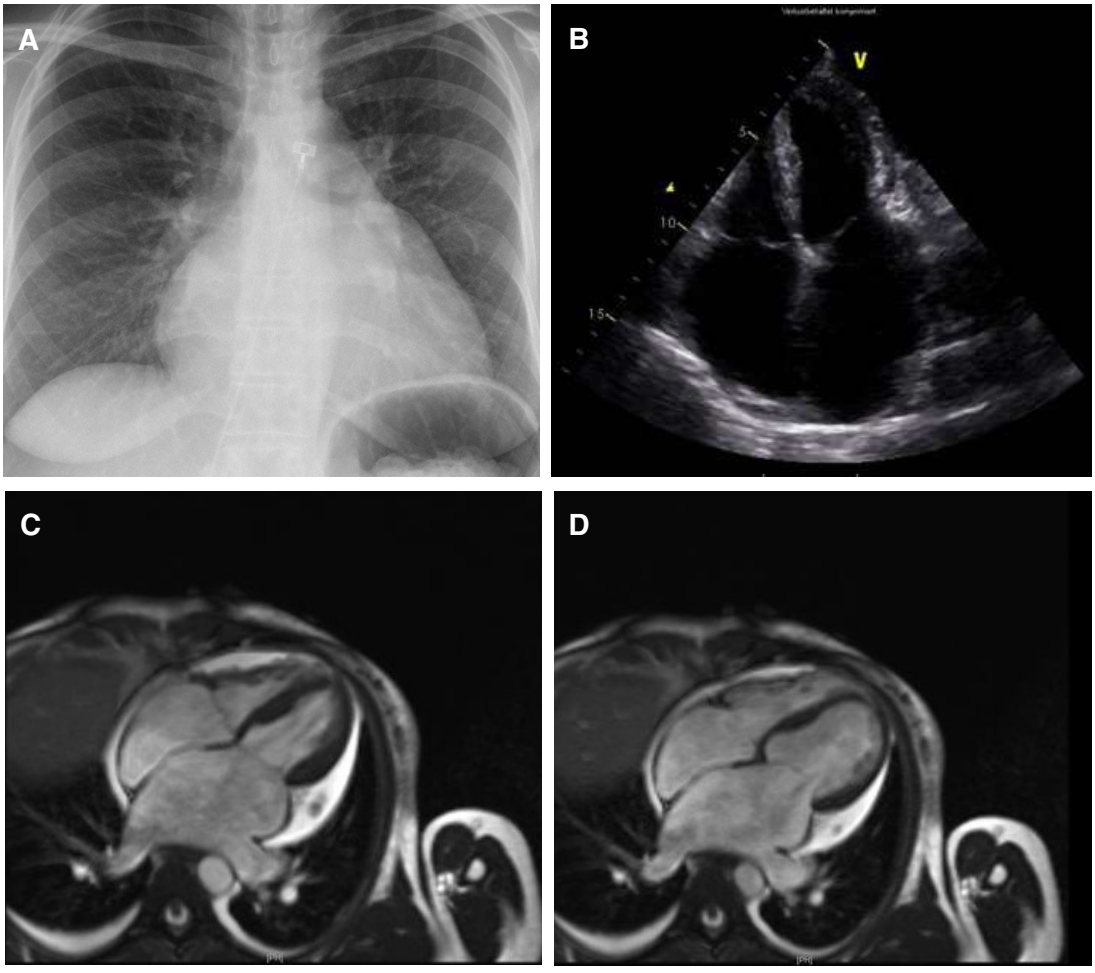


Figure 2 (*A*) X-ray, (*B*) echocardiographic and (*C, D*) magnetic resonance imaging showing gross atrial dilatation.

Association III and palpitations. Electrocardiography showed AF and no Q-, ST-, or T-wave abnormalities. N-terminal prohormone of brain natriuretic peptide was now elevated to 5079 ng/L. All other laboratory measurements were within the normal range.

Echocardiography still showed near-normal systolic function and normal biventricular chamber size but a marked bi-atrial dilatation (LA Vol. 141 mL, right atrium Vol. 64 mL, *Figure 2*), evidence of compromised diastolic function with a restrictive filling pattern and a small circular pericardial effusion (8 mm max.). Strain rate imaging was unremarkable. There was no pericardial thickening or calcification.

Haemodynamic re-evaluation in angiography at rest now showed elevated LV end-diastolic pressure (18 mmHg) with a considerable difference to the right ventricular end-diastolic pressure (12 mmHg), pulmonary hypertension, and a restrictive diastolic filling pattern with a dip-plateau configuration in ventricular diastolic tracings. To exclude constrictive pericarditis as a differential cause for this haemodynamic pattern, LV-filling pressure gradients were measured during respiration phases and showed no discordance of intracavitary and intrathoracic pressures.

A working diagnosis of restrictive cardiomyopathy (RCM) was made. To identify the specific RCM-subtype, cardiac magnet resonance imaging (*Figure 2C,D*) and endomyocardial biopsy were undertaken. Neither identified an infiltrative- or storage disease, cardiac fibrosis or iron-overload as possible causative pathology. There was no residual inflammation. No (auto)antibodies were found.

Given the highly suspicious family history, genetic analysis by high-sensitive next-generation sequencing covering 218 genes clinically relevant to arrhythmias and cardiomyopathies was applied. A plausible candidate variant was located in one copy of the patient's TNNI3 gene (NP_000354.4: p.Lys193Glu/NC_000019.9: g.55663258T>C, *Figure 3*). This variant is unknown and is to date unpublished. It is absent in the general population and located in a highly conserved, functionally critical region of the gene (*Figure 3*). The evolutionarily conserved C-terminal peptide of troponin I is an independently configured regulatory structure acting as a myofilament Ca^{2+} desensitizer[8–10] and is important for the inhibitory activity of the protein. Other variants affecting this domain have frequently been associated with SCD.[11] In a prior study of mutations in this region, 9 out of 50 cases presented with RCM and half had diastolic dysfunction.[11]

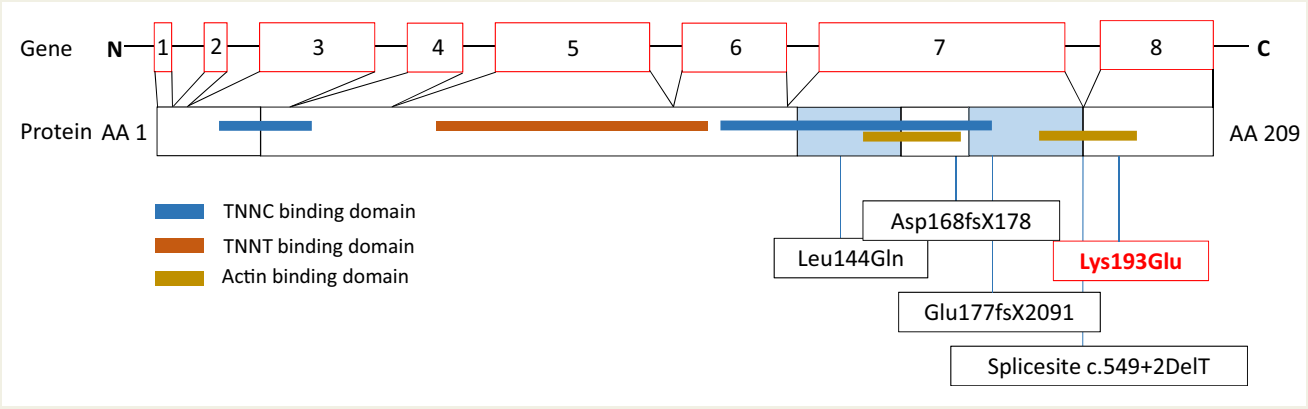


Figure 3 Distribution of the TNNI-sequence variants associated with restrictive cardiomyopathies reported in the literature. The novel variant described in this case report indicated in red, coding genes indicated by boxes, protein binding sites in different colours. Modified from reference 6.

Although the new variant we describe has not been functionally evaluated directly, it thus seems a very likely pathogenic driver.

To date, there is no specific causal treatment for RCM. Guidelines recommend symptomatic treatment including management of heart failure symptoms and, if possible, treatment of the underlying cause.[1] From 2004, the patient had received an angiotensin-converting-enzyme inhibitor (Ramipril, 5 mg once daily, to date) prescribed by her home physician. At the first manifestation of AF, oral anticoagulation with an anti-Xa inhibitor (Rivaroxaban, 20 mg once daily, 2017–18) was initiated. A beta-blocker treatment with Bisoprolol (1.25 mg once daily) was not tolerated due to symptomatic bradycardia. To avoid future decompensation after several relapses of haemodynamically unfavourable persistent AF, radiofrequency pulmonary vein isolation was conducted in 2018. Significant fluid congestion became clinically apparent in 2018. To reduce volume overload, the patient received low-dose diuretic medication (Torasemid, 5 mg, to date). As cardiac output in RCM-patients relies on high filling pressures, this was especially carefully monitored to avoid excessive diuresis. After restoration of a stable sinus rhythm and under careful diuretic treatment, the patient's haemodynamic situation and clinical state ameliorated significantly. As of now, she is symptom free. In late 2018, the patient suffered an ischaemic stroke under oral anticoagulation with a factor Xa inhibitor (Rivaroxaban, 20 mg once daily). Atrial fibrillation was never detected in electrocardiogram after ablation, but as the patient reports short episodes of palpitations, it was interpreted as likely cardio-embolic due to recurrent AF. Fortunately, she was discharged free from any neurological deficit. Oral anticoagulation was changed to a factor IIa inhibitor (Dabigatran, 150 mg twice daily, to date).

Discussion

Hereditary forms of cardiomyopathies are often precipitated by mutations in proteins of the sarcomere. Several gene mutations have been recognized as a cause of RCM and TNNI3 seems to be the most prevalent disease gene in RCM (*Figure 3*).[2,3,5,8,11–14]

To date, there is no specific causal treatment for RCM. Guidelines recommend symptomatic treatment including management of heart failure symptoms and, if possible, treatment of the underlying cause.[1] In most reported cases and case series, the prognosis of RCM is extremely poor.[15,16] In adults with RCM with confirmed genetic background, the 5-year survival rate was 56%.[15] We present a case of a female RCM patient who is a heterozygous carrier of a hitherto undescribed very likely pathogenic TNNI3 mutation and a strikingly favourable course of disease until now.

Importantly, we include longitudinal follow-up (see *Timeline*) of the natural disease-course of this case of hereditary RCM over 15 years. Such studies are essential to better understand the early symptoms, development, and prognosis of this rare disease and thus be able to provide early evidence-based counselling to members of affected families. Initially, the patient was relatively asymptomatic with her most striking symptom being limited exercise capacity. Later on, the clinical picture was dominated by AF. We would thus like to underline the importance of thorough family medical history in the diagnostic work-up of unclear cardiomyopathy, as well as of recurrent, therapy-resistant AF, especially in young individuals. During diagnostic work-up of cardiomyopathies, early invasive haemodynamic tracing is advisable. In the case presented here, revelation of the underlying genetic problem was delayed by more than 10 years by the limited availability of large-scale genetic testing. Over the recent years, extensive mutation screening has become much more affordable and available. In cardiomyopathy patients with suspicious family history, early broad genetic testing seems indispensable.

Regarding the mild myocardial inflammation seen in the first EMB in 2004, the lack of residual inflammation in 2018 argues against—but does not rule out—a hypothesis that inflammation is an integral part of the long-term pathogenic process elicited by the new mutation. On the other hand, low-level myocardial inflammation is rather frequently observed in genetic cardiomyopathies, and may then be considered as an unspecific secondary phenomenon due to innate immune activation triggered by the primarily structural genetic defect. It seems advisable, however, to not *a priori* interpret inflammation as 'myocarditis' of viral or autoimmune origin. If cardiac-inherited diseases and family history taking suggests a genetic background, the primordial problem may in fact be a genetic defect resulting in inflammation as an epiphenomenon. Inflammation does in fact occur in a

spectrum of mutations ranging from desmoplakin[17,18] to ion channels[19] and may independently increase SCD risk in mutation carriers.[20]

Lead author biography

Teresa Gerhardt, born 1992 in Munich, is a resident cardiologist and clinician scientist currently working at Charite Berlin. Her main research interest concerns immune mechanisms in atherosclerosis and different pathomechanisms of acute coronary syndrome.

Supplementary material

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

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

Consent: The authors confirm that written consent for submission and publication of this case report including images and associated text has been obtained from the patient in line with COPE guidance.

Funding: T.G. is participant in the BIH-Charité Junior Clinician Scientist Program funded by the Charité –Universitätsmedizin Berlin and the Berlin Institute of Health. T.G. received funding by the DZHK (German Centre for Cardiovascular Research) and the DGK (German Society of Cardiology).

Conflict of interest: None declared.

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