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CASE REPORT

Reversible transition from a hypertrophic to a dilated cardiomyopathy

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Abstract

We report the case of a 17-year-old female patient with known hypertrophic cardiomyopathy and a Wolff-Parkinson-White syndrome. She came to our department for further evaluation of a new diagnosed dilated cardiomyopathy characterized by an enlargement of the left ventricle and a fall in ejection fraction. Clinically, she complained about atypical chest pain, arrhythmic episodes with presyncopal events, and dyspnea (NYHA III) during the last 6 months. Non-invasive and invasive examinations including magnetic resonance imaging, electrophysiological examinations, and angiography did not lead to a conclusive diagnosis. Therefore, endomyocardial biopsies (EMBs) were taken to investigate whether a specific myocardial disease caused the impairment of the left ventricular function. EMB analysis resulted in the diagnosis of a virus-negative, active myocarditis. Based on this diagnosis, an immunosuppressive treatment with prednisolone and azathioprine was started, which led to an improvement of cardiac function and symptoms within 3 months after initiating therapy. In conclusion, we show that external stress triggered by myocarditis can induce a reversible transition from a hypertrophic cardiomyopathy to a dilated cardiomyopathy phenotype. This case strongly underlines the need for a thorough and invasive examination of heart failure of unknown causes, including EMB investigations as recommend by the actual ESC position statement.

Keywords Dilated cardiomyopathy; Hypertrophic cardiomyopathy; Transition of cardiomyopathy

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Introduction

Hypertrophic cardiomyopathy (HCM) is the most common cause of sudden death in young patients. The progression of the disease is variable and heterogeneous. Whereas especially patients with a non-obstructive form of HCM are thought to stay stable for a long time; a small distinct subset of patients can develop end stage heart failure, which includes a reduction of systolic function and a transition from a former HCM-phenotype to a dilated phenotype.[1] Several mechanisms underlying this transition are discussed and may include specific genetic backgrounds and micro-ischemia-induced damages. Reverse remodelling is under these rare circumstances. In addition, temporary progression of the disease can be induced because of not primarily cardiac-dependent stress factors. Therefore, the differential diagnosis of the so-called 'end stage' HCM is important not to overlook specific treatment options.

We report here a case from a young HCM patient where cardiac inflammatory but not primarily HCM-dependent processes induced a decompensating dilated cardiomyopathy (DCM)-like phenotype and show that an anti-inflammatory treatment led to a reverse remodelling under these conditions.

Case report

We report about a 17-year-old woman with known HCM without left ventricular (LV) outflow obstruction characterized by a concentric hypertrophy (anterior-septal wall measured 15 mm, posterior 16 mm), preserved LV ejection

fraction (EF), and a Wolff-Parkinson-White (WPW) syndrome for which the patient was already ablated twice in her childhood.

She was submitted to our department for evaluation of a progression of heart failure, indicated by a new diagnosed drop of the LV-EF to 40%, hypokinesia of the apical and inferior wall, an increase in LV diameters (LV end diastolic diameter (LVEDD): 59 mm; mitral valve-septum: 18 mm), increased filling pressures, and a mitral regurgitation grade II. Holter electrocardiogram examinations showed high numbers of ventricular and supraventricular episodes. Clinically, she complained of chest pain, dyspnea already at rest (NYHA III), and paroxysmal palpitations with presyncopal events during the past 6 months. Blood analysis showed increased N-terminal pro-brain natriuretic peptide (NT-pBNP) levels of 5201 pg/mL and slightly increased transaminases (ALT 40 U/L, AST 60 U/L), without changes in TNT, hsCRP, or leukocyte numbers. Over the following 7 days, LV-EF dropped to 20%, indicating a rapid progression of heart failure.

Based on these findings, we discussed at least four possible differential diagnosis: (1) tachycardia-induced cardiomyopathy (CM), (2) progression of HCM including (micro) angiopathy-induced changes, (3) development of a severe primary mitral valve regurgitation, and (4) another undetected acquired form of CM. In an invasive electrophysiological evaluation, no malignant heart rhythm disturbances were inducible. We found a sufficient working atrioventricular node without any signs of accessory bundles excluding a WPW-syndrome induced tachycardiomyopathy. Transesophageal echocardiography excluded a primary mitral valve regurgitation. For further evaluation of the myocardial structure, we performed cardiac magnetic resonance imaging (MRI). The MRI showed a significant hypertrophic and dilated LV (LV diastolic volume of 286 mL) with a further reduced LV-EF (17%). There was a pronounced signal of late gadolinium enhancement (LGE) sequences of myocardial necrosis (scar) and/or fibrosis to detect, especially in the septum, apical and lateral part of the LV (reticular delayed enhancement) (*Figure 1*). Further on, there were no signals of myocardial inflammatory processes in the T1-weighted and T2-weighted images detected. To investigate whether or not a primarily HCM-dependent progression of the disease or other etiologies were responsible for these findings, we evaluated right ventricular endomyocardial biopsies (EMBs) after exclusion of coronary abnormalities. Histological characterization of the EMBs demonstrated perivascular and interstitial fibrosis and significant hypertrophy of myocytes indicated by diameters up to 31 μm. A HCM-typical disarray was not detected. Similar, no signs of cardiac storage diseases were found using different staining techniques. However, immunohistochemical staining showed an extensive active inflammation response of the myocardium (*Figure 2*): highly increased β2-leukocyte-integrins/infiltrates (LFA-1/CD11a+ and Mac-1/CD11b+) and mixed cellular infiltrates of both lymphocytes and macrophages (CD45RO-positive and HLA-positive cells) (*Table 1*).[2] Molecular biological analyses by nested polymerase chain reaction excluded the presence of known cardiotropic viruses including enterovirus, adenovirus, Epstein-Barr-virus, human herpesvirus 6, and parvovirus B19.[3]

Based on the EMB results, which evidenced a virus-negative active myocarditis, which was most probably the cause of the impairment of cardiac function, we initiated an immunosuppressive therapy with corticosteroid (Prednisolone 1 mg/kg/day) and azathioprine (100 mg/day) under blood count control and liver/kidney function control. After 4 weeks, the dose of prednisolone was tapered off every 4 weeks by 10 mg until a maintenance dose of 10 mg was reached.[2] Within the time frame of 3 months after starting the immunosuppressive treatment, the LV-EF continuously improved up to 52%, and the LVEDD decreased to 56 mm. Also, NT-proBNP levels dropped to 968 pg/mL accompanied by regular levels of transaminases, CRP, and leukocytes. In addition, her clinical symptoms improved.

In summary, we show that external stress triggered by myocarditis can induce a transition from a HCM-phenotype to a dilated CM (DCM)-phenotype. Specific anti-inflammatory treatment strategies after diagnosis by performing EMBs could reverse this transition.

Discussion

Hypertrophic cardiomyopathy generally underlies a genetic disorder: around 40–60% of all causes of HCM account for gene mutations of cardiac sarcomere proteins (e.g. myosin-binding protein C, β-myosin heavy chain, cardiac troponin I and T, myosin light chain 3 and tropomyosin α-1 chain). Especially in infants and adolescents with isolated cardiac hypertrophy, more than 50% of all cases are due to genetic disorders.[4] In addition, mixed genetic disorders causing HCM and rhythm diseases are also known and include the so-called PRKAG2 cardiac syndrome defined by the presence of HCM, ventricular pre-excitation and tachyarrhythmia (WPW-syndrome), and progressive conduction system disease.[5] This genetic disorder, first described in a French-Canadian family by Gollob[6], underlies a mutation in the gene (PRKAG2) encoding for the γ2-subunit of the $\alpha\beta\gamma$-heterotrimer AMP-activating protein kinase.[7–10] However, the presence of a PRKAG2 syndrome in our patient was already excluded years ago. In addition, the evaluation of other well-known mutations able to cause HCM, including the screening for mutations of *MYH7*, *MYBPC3*, *TNNT2*, *TPM1*, *TNNI3*, *MYL3*, *MYL2*, *CSRP3*, *PLN*, *ACTC*, and *TNNC1* did not lead to a definite result in our patient. It is well accepted that in up to 30% of HCM, specific mutations cannot be detected or are still unknown. In addition, up to 20% of patients with

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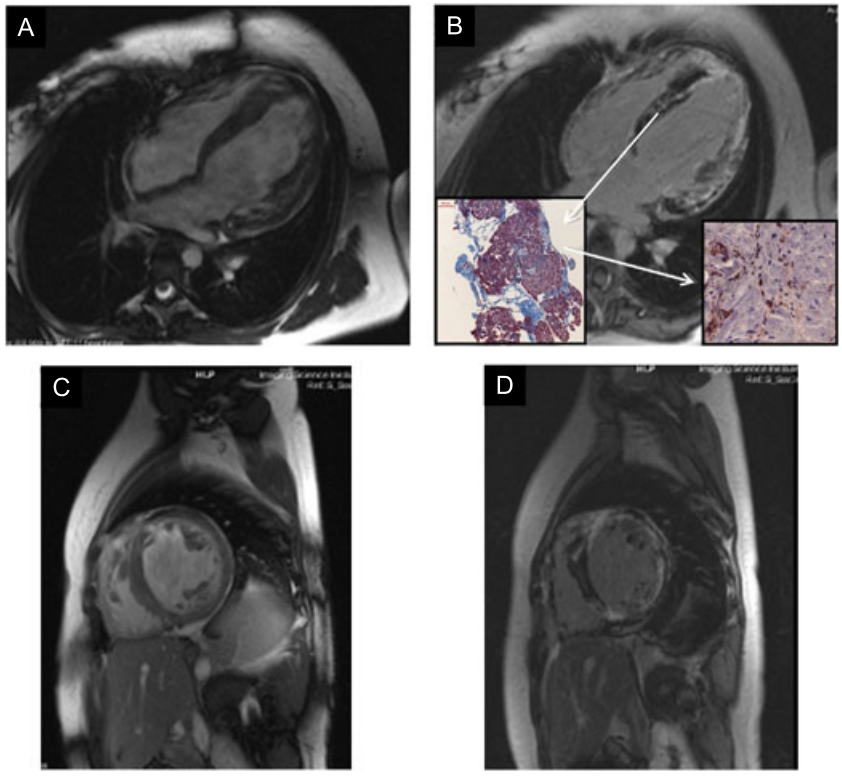
Figure 1 Magnetic resonance images of the heart and histological/immunohistochemical staining for fibrosis and inflammation. Representative pictures showing A) Four chamber view and C) short-axis view of T1-weighted magnetic resonance imaging scan. B) Four chamber view of a pronounced positive late gadolinium enhancement-magnetic resonance imaging scan. Left corner: representative Azan-Mallory staining image for fibrosis (original magnification ×100), right corner: representative LFA-1/CD11a+−staining image for cellular infiltration (original magnification ×200) from the septum of the right ventricle and D) short axis view of B.



the phenotype of a significant LV hypertrophy do not belong to the classical form of HCM and comprise other genetic and non-genetic causes including storage diseases.[11,12]

Forms of HCM can develop a DCM-phenotype under stress conditions, but this is not very common and mostly seen in severe forms of HCM with LV obstructions. Additional external stress includes emotional stress, toxic substances like alcohol or chemotherapeutics, pregnancy, ischemia, tachycardia-induced heart rhythm disturbances, and inflammation. Matsumori *et al*. reported that viral myocardial infection can belong to these risk factors, too.[13] The myocardial virus itself as well as inflammatory responses can lead to a deterioration of the HCM leading together with an increased intraventricular pressure to a LV dilatation.[14] This mechanism has been described in patients with HCM and myocarditis most likely belonging to the worsening of cardiac function and to the induction of electrical imbalances.[15]

Based on the EMB findings, we concluded that our patient suffered from a virus-negative active myocarditis. Thus, immunohistochemical analyses evidenced a significant, partly confluent lymphocyte infiltration, and increased expression of adhesion molecules. It also showed a marked infiltrate of macrophages and other inflammatory cells, but no increased specific cytotoxic T lymphocytes (perforin positive) were found. In opposite to the EMBs, the cardiac MRI did not show specific signs for cardiac inflammatory processes. The MRI resulted in the detection of fibrosis (LGE), which could belong to the HCM phenotype or to an additional inflammatory-induced damage. Fibrosis could be detected in EMBs taken from the LGE-areas of the septum, too (*Figure 1B*). However, only the further staining for inflammatory cells of these EMBs led to the definite diagnosis of a severe virus-negative active myocarditis (*Figure 2*). These results are in agreement with the findings of others showing that cardiac MRI sensitivity (76%), specificity (54%), and accuracy (68%) has important limitations for detection of inflammatory processes and might not be sufficient to diagnose myocarditis in all cases.[16] A negative MRI-result does not automatically exclude a myocarditis and need further evaluation by EMB, as concluded by the ESC working group on myocardial and pericardial diseases.[17]

The EMB-based diagnosis of a severe virus-negative active myocarditis led us immediately to start with an immunosuppressive treatment including prednisolone and azathioprine for 6 months as recommended by Caforio *et al*.[17] In accordance

Figure 2 Immunohistological staining of inflammatory cells of right ventricular septal biopsies. Representative images depicting A) Mac-1/CD11b+=infiltrates (original magnification ×200); B) LFA-1/CD11a+=infiltrates (original magnification ×200); C) CD45RO cellular infiltrates (original magnification ×200); and D) HLA cellular infiltrates (original magnification ×100) present in the endomyocardial biopsy.

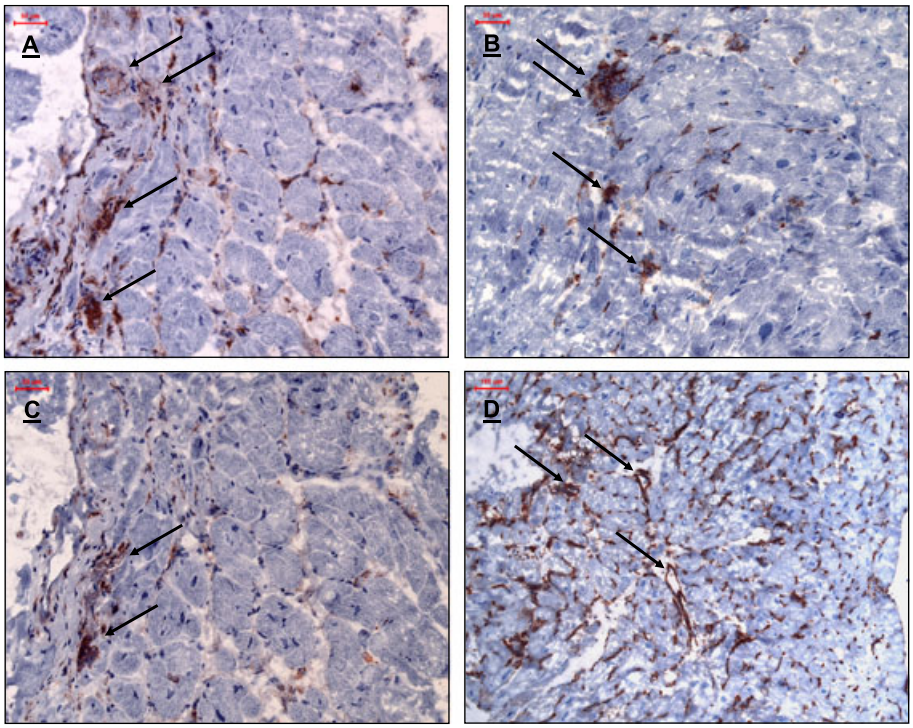


Table 1 Quantification of active inflammation in endomyocardial biopsies

	HLA and CAM-Expression [AF (%)]			Infiltration of immunocompetent cells [cells/mm^2]			
	HLA class-1	ICAM-1	VCAM-1	CD3	LFA-1	CD45RO	Mac-1
Results	10.9	2.1	0.11	15	101	131	330
Reference	5.5	1.2	0.1	7	9	7	35

to the TIMIC study,[18] we evidenced an improvement in LV-EF and a reduction in LVEDD already 3 months after immunosuppressive treatment, correlating with a clinical improvement in NYHA classification (from class III to I).

In conclusion, this case shows that myocardial inflammation can contribute to a transition of a hypertrophic to a dilated phenotype, which can be reversible after induction of a specific anti-inflammatory therapy.

References

1. Harris KM, Spirito P, Maron MS, Zenovich AG, Formisano F, Lesser JR, Mackey-Bojack S, Manning WJ, Udelson JE, Maron BJ. Prevalence, clinical profile, and significance of left ventricular remodeling in the end-stage phase of hypertrophic cardiomyopathy. *Circulation* 2006; **114**: 216–225.
2. Noutsias M, Pauschinger M, Schultheiss HP, Kühl U. Phenotypic characterization of infiltrates in dilated cardiomyopathy—diagnostic significance of T-lymphocytes and macrophages in inflammatory cardiomyopathy. *Med Sci Monit* 2002; **8**: CR478–CR487.
3. Kühl U, Pauschinger M, Noutsias M, Seeberg B, Bock T, Lassner D, Poller W, Kandolf R, Schultheiss HP. High prevalence of viral genomes and multiple viral infections in the myocardium of adults with "idiopathic" left ventricular dysfunction. *Circulation* 2005; **111**: 887–893.
4. Morita H, Rehm HL, Menesses A, McDonough B, Roberts AE, Kucherlapati R, Towbin JA, Seidman JG, Seidman CE. Shared genetic causes of cardiac hypertrophy in children and adults. *N Engl J Med* 2008; **358**: 1899–1908.
5. Cherry JM, Green MS. Familial cardiomyopathy: a new autosomal dominant form (abstract). *Clin Invest Med* 1986; **9**: B31.
6. Gollob MH. Glycogen storage disease as a unifying mechanism of disease in the PRKAG2 cardiac syndrome. *Biochem Soc Trans* 2003; **31**(Pt 1): 228–231.
7. Wolf CM, Arad M, Ahmad F, Sanbe A, Bernstein SA, Toka O, Konno T, Morley G, Robbins J, Seidman JG, Seidman

CE, Berul CI. Reversibility of PRKAG2 glycogen-storage cardiomyopathy and electrophysiological manifestations. *Circulation* 2008; **117**: 144–154.
8. Akman HO, Sampayo JN, Ross FA, Scott JW, Wilson G, Benson L, Bruno C, Shanske S, Hardie DG, Dimauro S. Fatal infantile cardiac glycogenosis with phosphorylase kinase deficiency and a mutation in the gamma2-subunit of AMP-activated protein kinase. *Pediatr Res* 2007; **62**: 499–504.
9. Burwinkel B, Scott JW, Buhrer C, van Landeghem FK, Cox GF, Wilson CM, Hardie DG, Kilimann MW. Fatal congenital heart glycogenosis caused by a recurrent activating R531Q mutation in the gamma2-subunit of AMP-activated protein kinase (PRKAG2), not by phosphorylase kinase deficiency. *Am J Hum Genet* 2005; **76**: 1034–1049.
10. Hendrickx J, Lee P, Keating J, Carton D, Sardharwalla IB, Tuchman M, Baussan C, Willems PJ. Complete genomic structure and mutational spectrum of PHKA2 in patients with X-linked liver glycogenosis type I and II. *Am J Hum Genet* 1999; **64**: 1541–1549.
11. Elliott PM, Anastasakis A, Borger MA, Borggrefe M, Cecchi F, Charron P, Hagege AA, Lafont A, Limongelli G, Mahrholdt H, McKenna WJ, Mogensen J, Nihoyannopoulos P, Nistri S, Pieper PG, Pieske B, Rapezzi C, Rutten FH, Tillmanns C, Watkins H, Authors/Task Force members. 2014 ESC guidelines on diagnosis and management of hypertrophic cardiomyopathy: the task force for the element of hypertrophic cardiomyopathy of the European Society of Cardiology (ESC). *Eur Heart J* 2014; **35**: 2733–2779.
12. Arad M, Maron BJ, Gorham JM, Johnson WH Jr, Saul JP, Perez-Atayde AR, Spirito P, Wright GB, Kanter RJ, Seidman CE, Seidman JG. Glycogen storage diseases presenting as hypertrophic cardiomyopathy. *N Engl J Med* 2005; **352**: 362–372.
13. Matsumori A, Matoba Y, Nishio R, Shioi T, Ono K, Sasayama S. Detection of hepatitis C virus RNA from the heart of patients with hypertrophic cardiomyopathy. *Biochem Biophys Res Commun* 1996; **222**: 678–682.
14. Frustaci A, Verardo R, Caldarulo M, Acconcia MC, Russo MA, Chimenti C. Myocarditis in hypertrophic cardiomyopathy patients presenting acute clinical deterioration. *Eur Heart J* 2007; **28**: 733–740.
15. Chimenti C, Calabrese F, Thiene G, Pieroni M, Maseri A, Frustaci A. Inflammatory left ventricular microaneurysms as a cause of apparently idiopathic ventricular tachyarrhythmias. *Circulation* 2001; **104**: 168–173.
16. Lurz P, Eitel I, Adam J, Steiner J, Grothoff M, Desch S, Fuernau G, de Waha S, Sareban M, Luecke C, Klingel K, Kandolf R, Schuler G, Gutberlet M, Thiele H. Diagnostic performance of CMR imaging compared with EMB in patients with suspected myocarditis. *JACC Cardiovasc Imaging* 2012; **5**: 513–524.
17. Caforio AL, Pankuweit S, Arbustini E, Basso C, Gimeno-Blanes J, Felix SB, Fu M, Heliö T, Heymans S, Jahns R, Klingel K, Linhart A, Maisch B, McKenna W, Mogensen J, Pinto YM, Ristic A, Schultheiss HP, Seggewiss H, Tavazzi L, Thiene G, Yilmaz A, Charron P, Elliott PM, European Society of Cardiology Working Group on Myocardial and Pericardial Diseases. Current state of knowledge on aetiology, diagnosis, management, and therapy of myocarditis: a position statement of the European Society of Cardiology Working Group on Myocardial and Pericardial Diseases. *Eur Heart J* 2013; **34**: 2636–2648 2648a-2648d.
18. Frustaci A, Russo MA, Chimenti C. Randomized study on the efficacy of immunosuppressive therapy in patients with virus-negative inflammatory cardiomyopathy: the TIMIC study. *Eur Heart J* 2009; **30**: 1995–2002.