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A case with two faces: noncompaction or phospholamban cardiomyopathy? ☆

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ABSTRACT

Noncompaction cardiomyopathy is a well-known clinical entity, whereas phospholamban gene mutation is a relatively recently known mutation with phenotypes as arrhythmogenic cardiomyopathy and dilated cardiomyopathy. We report the case of a 15-year-old girl that presents with rapid progressive heart failure based on a noncompaction cardiomyopathy as confirmed through cardiovascular imaging. As a result of her progressive heart failure 22 months later she received a heart transplant. Genetic testing showed a phospholamban gene mutation. We present cardiovascular images together with macroscopic and microscopic anatomy. This case shows the importance of considering phospholamban gene mutation in a case of severe noncompaction cardiomyopathy.

1. Introduction

Noncompaction cardiomyopathy (NCCM) is a rare cause of cardiomyopathy as hypothesized due to an arrest in myocardial morphogenesis [1]. The diagnosis is based on the pathognomonic morphological features on cardiac imaging, usually with cardiac ultrasound or magnetic resonance imaging, showing morphological abnormalities [1–3]. The clinical presentation can vary from asymptomatic to arrhythmias, severe heart failure, and/or thromboembolic events [4,5]. Phospholamban (PLN) is a protein that inhibits the calciumpump of the sarcoplasmatic reticulum (SR). When this protein is phosphorolyzed it loses its inhibitory effects. Several clinically relevant mutations have been described in the PLN gene [6–9]. PLN gene mutations are a known cause of arrhythmogenic (specifically in the case of the R14del mutation) ventricular cardiomyopathy and dilated cardiomyopathy [6]. However, there are also reports of some specific mutations to be associated with hypertrophic cardiomyopathy [5]. It is known that PLN mutations show higher rates of sudden cardiac death and ventricular tachycardias compared to for example sarcomeric gene mutations [10].

The aim of this case report is to describe the features of a classical phenotypic NCCM in a patient with PLN gene mutation, probably a third mode of clinical manifestation of PLN gene mutation associated cardiomyopathy. Genotype-phenotype correlations are important in recognizing genetic causes and the prognosis of diseases.

1.1. Case report

A 15-year-old girl without previous cardiac history presented to our hospital with symptoms of progressing fatigue. She used to be very active in swimming, judo, and scouting. Since several months before presentation she became more passive and preferred laying on a couch. She eventually became fatigued to a point where she skipped school. Furthermore, since one and half week she complained of nausea with a weight loss of 2 kg and night sweats with a sub febrile temperature in the evening. Her physical exam revealed a height of 170 cm and a weight of 61.8 kg resulting in a BMI of 21. On cardiac auscultation normal heart sounds without murmurs were heard. On pulmonary auscultation normal breath sounds were heard. Further physical examination did not reveal abnormalities. As medication she was using oral anticonception. The electrocardiogram as shown in the figure displays a sinus rhythm of 82 beats per minute with frequent premature ventricular complexes (left bundle branch block like morphology with a superior axis), QRS axis of 90 degrees, PR interval of 180 ms, QRS width of 90 ms and a QTc time of 350 ms, relatively low voltages

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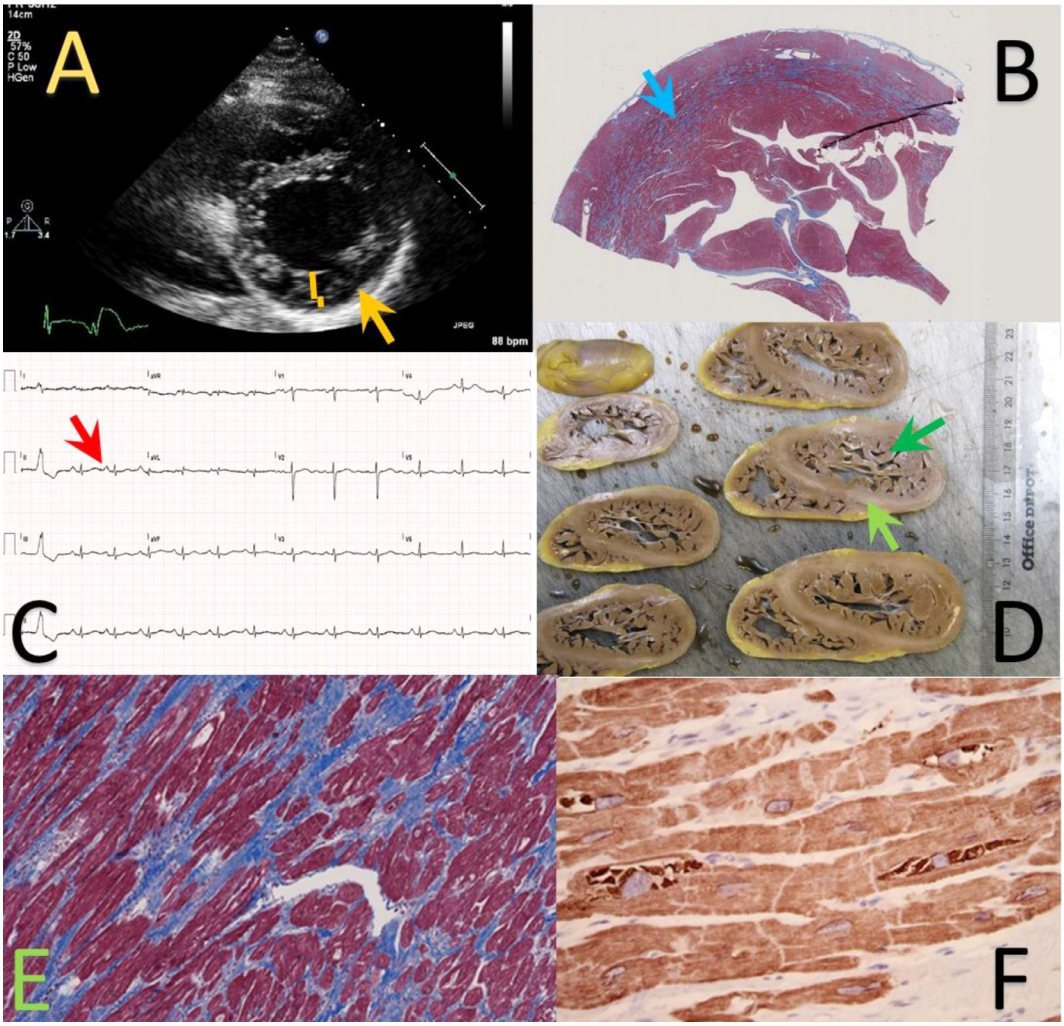

Fig. 1. A. Parasternal short axis image of the left ventricle showing hypertrabecularization (orange arrow) and a dilated left ventricular diameter; the ratio between compacted and noncompacted myocardium has been shown with orange lines. B. Microscopic image of the left ventricle with trichrome counterstain showing fibrosis in which fibrosis is depicted as blue areas (blue arrow). C. ECG with low voltage in the frontal leads and an enlarged P wav are noted (red arrow). D. Macroscopic image of the left ventricle with hypertrabecularization (dark green arrow) and midwall fibrosis (light green arrow). E. Higher power view of the myocardium in the area of the light blue arrow from D, with anisonucleosis and extensive interstitial fibrosis. F. Immunohistochemical PLN stain, showing extensive perinuclear aggregates.

in the frontal leads with a maximum of 0.8 mV, borderline criteria for right and left atrial dilatation, normal R wave progression, normal repolarization. Her cardiac ultrasound showed a severe dilatation of the left atrium (44 mm in parasternal long axis view), a normal left ventricular end diastolic diameter (53 mm) and an increased left ventricular end systolic diameter (44 mm), irregular left ventricular endomyocardium suspicious of NCCM (Fig. 1), and severely diminished left ventricular function, moderate mitral valve regurgitation, and moderate tricuspid valve regurgitation. Directly after the emergency room visit patient was admitted to our hospital for further diagnostics and treatment.

Her chest X-ray showed an enlarged heart without further pathology. An MRI showed hypertrabecularization of the left ventricle with a ratio above 5 matching with NCCM, and generalized hypokinesia of the left ventricle. The end-diastolic volume of the left ventricle was 268 ml, the ejection fraction 23%. The end-diastolic volume of the right ventricle was 176 ml, the ejection fraction 33%. No delayed gadolinium enhancement was seen.

Laboratory testing for infectious, hematopoietic, immunologic, metabolic, neurological and genetic causes for cardiomyopathy was performed. These showed a mutation in the PLN gene: c.25C>T, p.Arg9Cys. Furthermore, there was a heterozygous variant of unclear significance in the titin gene. The following genes were tested without abnormalities: MYL2, TNNC1, ACTC1, MYL3, PLN, TAZ, CALR3, MYBPC3, MYH7, TNNT2, TNNI3, CSRP3, TPM1, TCAP, LMNA. ABCC9, ACTN2, ANKRD1, CASQ2, CAV3, CRYAB, DES, EMD, FHL1, FKTN, GLA, ILK, JPH2, LAMA4, LAMP2, LDB3, MYOZ2, MYPN, NEXN, NRG1, PDLIM3, PRKAG2, RBM20, SCN5A, SGCD, TBX20, TMPO, TTR and VCL

Lab results were the following: natrium 141 mmol/l, potassium 4.6 mmol/l, Chloride 104 mmol/l, calcium 2.32 mmol/l, phosphate1.10 mmol/l, magnesium 0.850 mmol/l, ASAT 20U/l, ALAT 18 U/l, LDH 157 U/l, ureum 7.1 mmol/l, creatinine 81 mmol/l, glucose 4.2 mmol/l, CRP <1 mg/l, BSE 6 mm/h, hemoglobin 8.7 mmol/l, hematocrit 0.41 l/l, MCV 84fL, RDW 12.5%, thrombocytes 161*10E9/l, leukocytes 6.6*10E9/l. Additionally, extensive viral, bacterial, and parasitical diseases including tuberculosis, toxoplasmosis and syphilis were negative.

During her admission to the medium care on telemetry several episodes of frequent premature ventricular complexes (PVC's) and non-sustained VT's were seen. Her treatment consisted of salt and fluid restriction, and the start of an ACE inhibitor (enalapril twice daily 5 mg), betablockade (metoprolol slow release once daily 25 mg), Aldosterone antagonist (spironolactone once daily 25 mg), di-

uretics (furosemide twice daily 20 mg) and the start of oral anticoagulation (acenocoumarol according to the INR). The INR's were usually between 2.0 and 3.0 as targeted.

Five months after her initial presentation she showed progressive worsening of her heart failure to NYHA class III with frequent PVC's and non-sustained VT's for which amiodarone was started and an ICD implantation was indicated. At that time screening for eventual heart transplantation was initiated. Three months after implantation of the ICD the system had to be removed because of a staphylococcus aureus infection with re-implantation a month later.

Twenty-two months after initial presentation patient received a heart transplant. Upon gross examination of the explanted heart by a cardiovascular pathologist the heart had a weight of 330 g with a left ventricular thickness varying from 0.7 cm (lateral) to 1.0 cm (posterior and septum) and 1.1 cm (anterior). Right ventricular thickness varied from 0.1 to 0.2 cm. No valvular abnormalities were seen. An abnormal configuration of the entire left ventricle was observed, with lack of papillary muscle formation and hypertrabeculation over more than 2/3 of the wall thickness as measured from the endocardial side. Microscopically, there was evidence of myocardial hypertrophy with anisonucleosis, interstitial fibrosis, as well as noncompaction with slit-like invaginations with a "staghorn" aspect. Microscopically, the RV was not abnormal, with an absence of fatty replacement and fibrosis, specifically. Immunohistochemical staining for PLN of the LV myocardium demonstrated extensive perinuclear aggregates of the protein. The pathology findings are show in Fig. 1.

2. Discussion

To the best of our knowledge this is the first extensive description of a patient that shows a classical phenotype of NCCM with an underlying pathogenic mutation in the PLN gene.

Noncompaction cardiomyopathy is primary cardiomyopathy, mostly presenting with the triad of heart failure, arrhythmia's and thrombo-embolic events albeit many patients could be asymptomatic. In about half of the cases, there is familial and/or genetics etiology with different gene mutations [11]. So far no common final effect on the myocardium has been described to explain the vastly different underlying gene mutation in NCCM [5]. It is assumed that different effects of these mutations result in the same final effect with a phenotype of immature, noncompacted myocardium. The identification of yet a new gene mutation causing NCCM may give further insights in these mechanics or help unravel a final common pathway.

PLN cardiomyopathy is known to have a clinical appearance of arrhythmogenic ventricular cardiomyopathy, dilated cardiomyopathy and hypertrophic cardiomyopathy [12]. This case report adds NCCM as a separate phenotype in PLN cardiomyopathy. Therefore, in patients with NCCM with pronounced arrhythmic features and specific ECG changes (microvoltages and prominent T's in the arm leads), it becomes paramount to test for PLN mutations in addition.

The overwhelming majority of PLN mutations in the Netherlands are R14del mutations believed to be caused by a founder mutation between 575 and 825 years old in the northern part of the country [13]. More than 1000 R14del mutation carriers have been identified and are prevalent all over the country, but heavily skewed to the northern provinces. In total, there are an estimated 2000 mutation carriers in the Netherlands in a population of around 17 million. This makes it the most prevalent mutation in relation to cardiomyopathies. Interestingly our patient has a less common mutation in the Netherlands.

PLN plays a role in the homeostasis of intracellular calcium. A dysfunctional PLN protein could disrupt this homeostasis during the development of the heart. Unfortunately, there is yet no translational research that directly identifies the role of PLN in trabecularization. Even though, there are some reports that could offer pieces of the puzzle how PLN could lead to NCCM. PLN has been found early in the development of the rat heart [14]. So the regulatory role of PLN on calcium handling could have effects early in the development of the heart. Calcium dependent receptors are involved in trabecularization and compaction of the heart [15]. Other routes that change the calcium handling of the myocyte have also been associated with NCCM, for example, NCCM has been described for mutations in the ryanodine receptor RYR2 [16]. This receptor is involved in calcium handling of the sarcoplasmatic reticulum as well. It is conceivable that an abnormal calcium homeostasis in PLN patients interferes in the physiological process of trabecularization and compaction.

In comparison FKBP-12 deficient mice had altered calcium channels and an altered calcium flux [17]. They showed developmental changes to the myocardium that were very similar to NCCM. PLN mutations also change the calcium flux in the cell. Via this route it may very well be possible to induce a similar phenotype in PLN mutations.

The addition of a new clinical pattern in PLN mutations has consequences for daily clinical practice. This finding is of high relevance when deciding when to screen for underlying familiar cardiomyopathies and even more what genes to screen. On an individual basis it offers a better estimate in which patients are probably at risk for ventricular arrhythmias.

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