

CASE REPORT

Left Ventricular Non-Compaction Associated with Atrial Septal Defect — a Rare Cause of Refractory Severe Cardiac Failure

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ABSTRACT

Left ventricular non-compaction (LVNC) is a cardiomyopathy that can either result from arrested or abnormal myocardial morphogenesis during heart development, or can be acquired later in life. Current practice guidelines recommend different strategies for the management of patients with LVNC. Common clinical features of this disease include cardiac failure, thromboembolism, life-threatening arrhythmia or sudden cardiac death, which could indicate a worse prognosis. The disease may occur alone or in association with other congenital cardiac, neuromuscular, mitochondrial or metabolic disorders. The association of left ventricular non-compaction with other structural cardiac congenital diseases (such as atrial or ventricular septal defect, patent ductus arteriosus, obstruction of ventricular outflow tract) is rare. As clinical manifestations of LVNC are non-specific, particular imaging modalities (echocardiography, cardiovascular magnetic resonance imaging or ECG gated computed tomography) should be used in order to establish the diagnosis of LVNC. Antiarrhythmic drugs and implantable cardioverter defibrillators may be considered for the management of ventricular arrhythmias in patients with ventricular non-compaction. We report the presentation, diagnosis and management of a 46 year-old female with refractory severe cardiac failure, repeated syncope due to LVNC and atrial septal defect, requiring medical therapy and an implantable cardioverter defibrillator as a "life bridge" to heart transplantation.

Keywords: isolated left ventricular non-compaction, heart failure, imaging techniques, arrhythmias, implantable cardioverter defibrillator

ARTICLE HISTORY

Received: 15 July, 2015

Accepted: 15 October, 2015

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INTRODUCTION

Left ventricular non-compaction (LVNC) is a cardiomyopathy characterized by changes in myocardial wall, caused by prominent left ventricular trabeculae and deep

intertrabecular recesses [1,2], as well as the thickening of the myocardium into two distinct layers (compacted and not compacted) [3–5]. The first case of LVNC associated with other cardiac abnormalities was described in 1932 by Bellet and Gouley in a paper concerning an autopsy of a

newborn [6]. Since then several articles and reviews have described cases of LVNC associated with other congenital heart diseases [7–10]. The prevalence of this disorder in the general population has not been well established yet, ranging between 0.06 and 0.3% [7], however other recent studies [11] demonstrate an unexpectedly high percentage (23.6%) of patients with heart failure fulfilling current echocardiographic criteria for LVNC.

We report a case of a 46 year-old woman with refractory severe heart failure and repeated syncope due to LVNC associated with an atrial septal defect, requiring medical therapy and an implantable cardioverter defibrillator (ICD) device as a "life bridge" to an orthotopic heart transplant.

CASE PRESENTATION

A 46 year-old Caucasian woman was admitted in the hospital with a 5-year history of progressive exertional dyspnea, orthopnea and atypical chest pain. In the last 2 weeks before admission she experienced 2 episodes of palpitations associated with syncope. Previous personal medical records revealed a 5-year history of LVNC diagnosis, sequelae of a "cryptogenic" stroke (a 3×3.5 cm basal ganglia hypodense lesion on head CT scan) and a gastroesophageal reflux disease. A coronary angiography performed 2 years before the current presentation revealed normal coronary anatomy and flow. The family history was highly suggestive for cardiac disease and

a sudden cardiac death was reported in her first degree relatives (brother deceased at age 20 from SCD, possibly associated with dilated cardiomyopathy, and a sister with LVNC). On examination she presented regular sinus rhythm with a rate of 88 beats/minute and a blood pressure of 90/60 mmHg. Cardiac auscultation revealed a diminished first and second heart sound and mild holosystolic mitral murmur. Coarse crepitations at both lung bases and a moderate hepatomegaly were also identified. Oxygen saturation was 93% in ambient air and 99% on oxygen mask. No changes were observed in full blood count, serum electrolytes, renal and thyroid function. The rest ECG revealed sinus rhythm, mild tachycardia (90 beats/minute), intermediate QRS axis, a QRS complex of 120 milliseconds and biventricular hypertrophy.

Chest X-ray identified cardiomegaly, a cardiothoracic ratio of 0.6 and small bilateral pulmonary congestion.

Transthoracic echocardiography showed a small atrial septal defect (3 mm diameter) and a mild circumferential pericardial collection (both unknown from the previous examinations). The left ventricle was enlarged, with a diameter of 74 mm and an end-diastolic volume of 125 ml. The diameters of the left ventricular (LV) walls were 13 mm at the level of the interventricular septum and 24 mm at the level of the posterior wall. A global left ventricular hypokinesia was identified, with a left ventricular ejection fraction of 15%. The aspect of the LV was typical for non-compaction, with a 22/14 ratio between non-compactant/compactant myocardium, with extensive prominent tra-

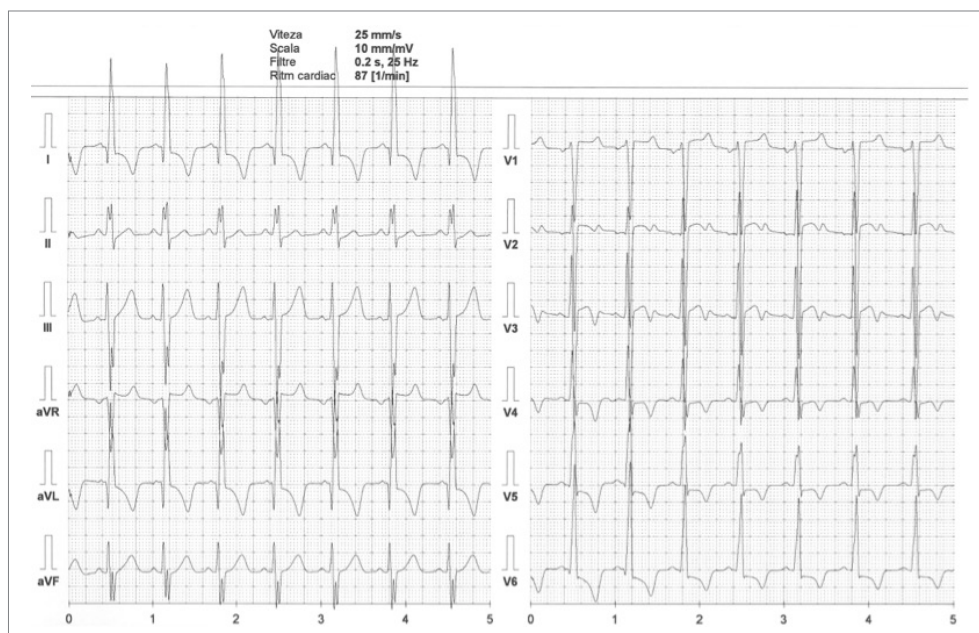


FIGURE 1. Patient's rest surface ECG



FIGURE 2. Transthoracic echocardiography, short axis view; presence of trabeculations (arrows) and left ventricular recesses; LV – left ventricle; RV – right ventricle; RA – right atrium. The ratio between non-compacted and compacted myocardium is 22/14.

beculations and deep intertrabecular recesses in the whole left ventricular lateral wall, apex and two thirds apical of the interventricular septum. Mild mitral and tricuspid regurgitation were also identified, with a pulmonary systolic pressure OF 31 mmHg. The size of the right ventricle was preserved (29 mm in diameter), and no signs of intra or interventricular asynchronism were described.

Two subsequent 24-hour simultaneous ABPM + Holter ECG recordings (Custo Screen 300, Custo-med GmbH, Ottobrunn, Germany) were highly suggestive for ventricular arrhythmias (frequent premature ventricular contractions and two episodes of non-sustained ventricular tachycardia NVST).



FIGURE 4. Cardiac MRI ECG gated at the end of diastole; visualization of ventricular trabeculae



FIGURE 3. Transthoracic colour Doppler echocardiography, 4 chambers view, revealing mild mitral regurgitation. LV – left ventricle, LA – left atrium, RA – right atrium, ASD – atrial septal defect, MR – mitral regurgitation

The patient was treated medically with Carvedilol, Ramipril, Furosemide, Spironolactone, Ivabradine, oral anticoagulation with Acenocumarol (in adjusted doses for INR between 2.5–3). Administration of 40 mg Pantoprazol per day, orally, 30 minutes before breakfast was also re-commended for the treatment of the gastroesophageal reflux disease and for the protection of gastric mucosa.

The patient underwent a cardiac MRI (1.5T Magnetom® Symphony MRI system, Siemens Medical Solutions, Germany), and MRI images were interpreted by an experienced cardiologist and post-processed with specialized software for ejection fraction calculation. This imaging technique revealed the non-compacted left myocardium (apical and medial segments and anterior, lateral and inferior wall). MRI results confirmed the presence of extensive areas of prominent trabeculation and inter-trabecular recesses of the left ventricle, with a myocardium NC/C ratio of 8.5, global hypokinesia and a severe depressed LVEF of 14%. Late gadolinium enhancement images (Gadolinium, 0.15 mmol/kg) revealed signs suggestive of myocardial fibrosis in the lateral wall of LV.

Microbiological and immunological studies performed in order to select the patient for cardiac transplantation (VDRL, Elisa for HIV infection, HBV and HCV antibody test, tests for detection CMV, HSV, Toxoplasma gondii, Chlamydia pneumoniae) were negative.

The diagnosis of LVNC and ASD, combined with NSVT and previous cerebral embolism, was established based on the appearance of the left ventricular myocardium, presence of other associated cardiac anomalies on echocardiography, cardiac MRI, Holter ECG examinations and previous cerebral CT scans. Despite optimization of medi-

TABLE 1. Genes associated with LVNC

| Location | Phenotype | Phenotype mapping key | Phenotype MIM number | Gene/Locus | Gene/Locus MIM number |
|----------|---|-----------------------|----------------------|--|-----------------------|
| 1p36.32 | Left ventricular non-compaction 8 | 3 | 615373 | PRDM16, MEL1, LVNC8, CMD1LL | 605557 |
| 1p36.32 | Cardiomyopathy, dilated, 1LL | 3 | 615373 | PRDM16, MEL1, LVNC8, CMD1LL | 605557 |
| 1q32.1 | Left ventricular non-compaction 6 | 3 | 601494 | TNNT2, CMH2, CMD1D, RCM3, LVNC6 | 191045 |
| 1q32.1 | Cardiomyopathy, dilated, 1D | 3 | 601494 | TNNT2, CMH2, CMD1D, RCM3, LVNC6 | 191045 |
| 10q23.2 | Left ventricular non-compaction 3 | 3 | 601493 | LDB3, ZASP, CYPHER, KIAA01613, MFM4, CMD1C, CMH24, LVNC3 | 605906 |
| 10q23.2 | Cardiomyopathy, hypertrophic, 24 | 3 | 601493 | LDB3, ZASP, CYPHER, KIAA01613, MFM4, CMD1C, CMH24, LVNC3 | 605906 |
| 10q23.2 | Cardiomyopathy, dilated, 1C, with or without LVNC | 3 | 601493 | LDB3, ZASP, CYPHER, KIAA01613, MFM4, CMD1C, CMH24, LVNC3 | 605906 |
| 11p15 | Left ventricular non-compaction 2 | 2 | 609470 | LVNC2 | 609470 |
| 11p11.2 | Left ventricular non-compaction 10 | 3 | 615396 | MYBPC3, CMH4, CMD1MM, LVNC10 | 600958 |
| 11p11.2 | Cardiomyopathy, dilated, 1MM | 3 | 615396 | MYBPC3, CMH4, CMD1MM, LVNC10 | 600958 |
| 14q11.2 | Left ventricular non-compaction 5 | 3 | 613426 | MYH7, CMH1, MPD1, CMD1S, SPMM, SPMD | 160760 |
| 14q11.2 | Cardiomyopathy, dilated, 1S | 3 | 613426 | MYH7, CMH1, MPD1, CMD1S, SPMM, SPMD | 160760 |
| 15q14 | Cardiomyopathy, dilated, 1R | 3 | 613424 | ACTC1, CMD1R, CMH11, ASD5, LVNC4 | 102540 |
| 15q14 | Left ventricular non-compaction 4 | 3 | 613424 | ACTC1, CMD1R, CMH11, ASD5, LVNC4 | 102540 |
| 15q22.2 | Left ventricular non-compaction 9 | 3 | 611878 | TPM1, CMH3, CMD1Y, LVNC9 | 191010 |
| 15q22.2 | Cardiomyopathy, dilated, 1Y | 3 | 611878 | TPM1, CMH3, CMD1Y, LVNC9 | 191010 |
| 18q11.2 | Left ventricular non-compaction 7 | 3 | 615092 | MIB1, MIB, DIP1, KIAA1323, LVNC7 | 608677 |
| 18q12.1 | Left ventricular non-compaction 1, with or without congenital heart defects | 3 | 604169 | DTNA, D18S892E, DRP3, LVNC1 | 601239 |

MIM number refers to a numerical assignment for genes and functional segments of deoxyribonucleic acid, as well as to inherited diseases. X-linked recessive indicates that both matching genes must be abnormal to cause the disease.

ACTC1 – actin, alpha, cardiac muscle; DTNA – dystrobrevin alpha; LDB3 – Lim domain-binding 3; LVNC – left ventricular noncompaction; MIB1 – homolog of *Drosophila* mindbomb; MYBPC3 – myosin-binding protein C, cardiac; MYH7 – myosin heavy chain 7, cardiac muscle, beta; PRDM16 – PR domain-containing protein 16; TAZ – tafazzin; TNNT2 – troponin T2; TPM1 – tropomyosin 1.

Phenotype Mapping Key: 2 – the disorder was placed on the map by statistical methods. 3 – the molecular basis of the disorder is known [adapted after 14,20].

cal therapy several symptoms (especially palpitations) persisted and the patient continued to be symptomatic. Considering LVNC with decreased LVEF, a family history of SCD and non-sustained VT episodes on Holter recordings, the patient was considered a class I indication (evidence level B) for implantation of a cardiac defibrillator, according to the recent guidelines for the management of patients with VA and the prevention of SCD [12]. A single-chamber implantable cardio-defibrillator (Ellipse™ VR, St. Jude Medical Inc., St. Paul, MN, USA) was implanted and six days after the implantation, the patient was discharged and referred for cardiac transplantation.

At a regular follow-up at 1 month and 6 months respectively, the patient was in good condition, with a stable hemodynamic status, in NYHA II functional class. The transthoracic echocardiogram and ECG monitoring showed an unchanged LV function (EF: 15%), without pericardial effusion or any runs of SVT/NSVT episodes, and the patient remained on the waiting list for heart transplantation.

DISCUSSION

We presented the case of LVNC in a middle-aged female patient with concomitant ASD, former cerebral thromboembolism, ventricular arrhythmias and refractory heart failure, with a remarkable family history of sudden cardiac death associated with cardiomyopathies. This case is particular as it presented a progressively worsening clinical evolution (reduced EF, myocardial fibrosis on MRI, cerebral thromboembolism) and a poor prognosis in the absence of orthotopic heart transplantation.

Left ventricular non-compaction is a cardiomyopathy defined by the presence of prominent left ventricular trabeculae, deep intertrabecular recesses and thin compacted layers [13,14].

It can be classified as a primary genetically-determined cardiomyopathy [1] or, according to European Society of Cardiology statements, an unclassified cardiomyopathy [2].

In the current practice familial (inherited) and non-familial (sporadic) cases of LVNC are described. The case

TABLE 2. Suggested algorithm for the management of left ventricular non-compaction [adapted after 14,20]

| DIAGNOSIS | MONITORING | TREATMENT |
|---|--|--|
| <ul style="list-style-type: none"> • Echocardiographic diagnosis in probands • Cardiac magnetic resonance imaging (CMR) • Family history and echocardiographic screening of relatives • Genetic testing <ul style="list-style-type: none"> – in probands: clinically guided in case of suspected syndromes/diseases with typical aspect of LVNC and/or testing for genes known to be associated with LVNC – in relatives: cascade testing in relatives, after identification of mutation in the proband and/or segregation studies in the family | <p>Clinical monitoring in probands</p> <ul style="list-style-type: none"> • Physical examination • Resting electrocardiogram • Transthoracic echocardiography • CK-MM (creatine kinase-MM isoform) (at initial evaluation only) <p>In first degree relatives</p> <ul style="list-style-type: none"> • Clinical screening is indicated every 3 years beginning in childhood • If a mutation is identified clinical screening is recommended yearly in childhood and every 1–3 years in adults | <ul style="list-style-type: none"> • According to patient's clinical aspects and corresponding guidelines • Oral anticoagulation • Cardioverter defibrillator (ICD) implantation • Cardiac resynchronization therapy (CRT) |

presented here is a familial one, as demonstrated by positive family history; most of the cases described in the literature are associated with mutations in the same genes that cause other cardiomyopathies such as hypertrophic, restrictive or dilated cardiomyopathy [14–16].

Recently published data offer multiple hypotheses of etiologic bases of LVNC: it can be encountered as an isolated disease, in association with other genetic diseases and congenital defects, isolated or acquired in different conditions; some reports indicate a permanent or transient aspect of LVNC [14,17–19].

Human genetic studies (with inherent limitations) suggest that several genes are associated with LVNC [14].

Embryologic morphogenetic hypotheses suggest two possibilities: arrested or abnormal myocardial morphogenesis occurring during heart development and usually affecting the left ventricle [21] or a form of LVNC resulting from inhibition of the regression of embryonic structures [9,14].

In the management of LVNC the following aspects should be carefully carried out: diagnosis, monitoring and treatment [14]. Table 2 presents the clinical management of LVNC.

Echocardiography is the first-line imaging tool in all settings of cases with suspected LVNC. Some echocardiographic criteria have been suggested as indicators of the disease, together with family history and genetic studies [13,22–24], however none of them can be considered as “gold standard” for LVNC diagnosis. For a positive diagnosis of LVNC, a non-compacted/compacted ratio >2.0 in end-systole must be identified [23].

Cardiac magnetic resonance (CMR) is particularly useful for differential diagnosis of LVNC from normal variants of trabeculations [25]. The cut-off value of 2.3 for the non-

compacted/compacted myocardium ratio has been widely accepted for diagnosis of LVNC [26]. In our patient the non-compacted/compacted ratio was 8.5, therefore one important criterion for diagnosis was fulfilled. Additional MRI findings (subendocardial perfusion defects, delayed enhancement of the subendocardial layer) can provide more relevant data for the diagnosis of LVNC [27,28].

Differential diagnosis includes other dilated cardiomyopathies, endocardial fibroelastosis, presence of thrombus in the apex of the left ventricle, apical hypertrophic cardiomyopathy, or hypertrabeculation with normal compacted LV layer [14].

Today there are no specific guidelines for the management of LVNC. Patients are managed according to their specific clinical aspect and corresponding data derived from scientific research. Complications of LVNC are variable and include cardiac failure, thromboembolism, life-threatening arrhythmias and sudden cardiac death [29].

Implantable cardioverter defibrillators (ICD) may be considered for primary and secondary prevention of sudden cardiac death in patients with this cardiomyopathy. However, only limited data exist describing the clinical outcome of patients with LVNC and implanted ICDs, and no predictors for appropriate ICD therapy are available [30–33].

In patients with LVNC, reduced ejection fraction ($<35\%$) and signs of ventricular dyssynchronism, cardiac resynchronization therapy could be considered in order to improve NYHA functional class [34,35].

Patients with LVNC who have end-stage heart failure are candidates for heart transplantation, and successful orthotopic heart transplantation in LVNC patients with end-stage heart failure has been reported [9,36].

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