

## CASE REPORT

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# Noncompaction cardiomyopathy in mother and newborn: Value of genetic testing in conjunction with history and imaging

Most Sirajum Munira, Kenneth Ong, Lekshmi Dharmarajan

## ABSTRACT

**Introduction:** Noncompaction cardiomyopathy (NCCM) is a rare disorder in which affected individuals have variable clinical presentations ranging from being asymptomatic to sudden cardiac arrest. While its typical phenotypic expression often triggers the initial evaluation, the etiology is heterogeneous with genetic, familial, or sporadic traits. Treatment and prognosis depends on factors such as the presence or absence of heart failure, cardiac arrhythmia, thromboembolic events, and type of genetic mutation identified.

**Case Report:** We present a case of familial NCCM in a young woman, presenting as pre-eclampsia and heart failure during pregnancy. Following an echocardiogram in the mother and baby that suggested NCCM, genetic testing revealed an MYH7 mutation in both mother and newborn. The mother improved after management with guideline directed treatment for heart failure, with subsequent improvement of left ventricular function after one year.

**Conclusion:** This case illustrates the value of genetic testing in conjunction with focused history and imaging during the peripartum management of the obstetrical patient and her child.

**Keywords:** Cardiomyopathies, Genetic testing, Non-compaction cardiomyopathy, Peripartum cardiomyopathy

## How to cite this article

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## INTRODUCTION

The prevalence of cardiovascular disease during pregnancy has been increasing. Socioeconomic factors such as improved and nontraditional employment opportunities, educational pursuits, and changing attitudes toward the timing of pregnancy contribute to increased mean maternal age resulting in an increase in cardiovascular risk factors that are normally associated with advancing age [1]. While systemic hypertension and women with congenital heart disease are common among the cardiovascular disorders that occur during pregnancy, cardiomyopathies, although rare, are the source of some of its most serious complications [2].

Noncompaction cardiomyopathy (NCCM) is a heterogeneous disorder that often presents with a familial association. Affected individuals may be asymptomatic but can also develop heart failure, cardiac arrhythmias, thromboembolic events, and cardiac arrest. Recognition of this entity and differentiation from other cardiomyopathies is important due to the genetic impact on the patient and future generations. We describe a woman diagnosed with NCCM after presenting with pre-eclampsia and heart failure during the third trimester. Evaluation and screening of other family members subsequently identified additional relatives diagnosed with or suspected to have NCCM.

Most Sirajum Munira<sup>1</sup>, Kenneth Ong<sup>2</sup>, Lekshmi Dharmarajan<sup>1</sup>

**Affiliations:** <sup>1</sup>Attending Cardiologist, Department of Medicine, Lincoln Medical Center, Bronx, NY, USA; <sup>2</sup>Chief of Cardiology, Department of Medicine, Lincoln Medical Center, Bronx, NY, USA.

**Corresponding Author:** Kenneth Ong, Lincoln Medical Center, 234 East 149th Street, Bronx, NY 10451, USA; Email: kenneth.ong@nychhc.org

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## CASE REPORT

A 24-year-old woman (second gravida with one abortion) with a history of obesity [baseline body mass index (BMI) 44 kg/m<sup>2</sup>] and gestational hypertension was hospitalized for induction of delivery due to pre-eclampsia. She was in her 37th week of gestation. Her blood pressure was initially controlled with nifedipine intravenous (IV) as opposed to labetalol due to a heart rate of 61 bpm. She was also given magnesium sulfate. Although loop diuretics initially improved her shortness of breath, her dyspnea subsequently worsened during induction of labor and was now accompanied by tachycardia and tachypnea. Her blood pressure remained stable but the oxygen saturation had decreased to 84%. There were no signs of eclampsia. As lung auscultation was suboptimal, a chest X-ray was obtained which revealed severe pulmonary congestion. A chest computed tomography (CT) was also performed, showing no evidence of pulmonary embolism. The patient was then intubated and successfully underwent urgent caesarian section under general anesthesia. She had an uneventful recovery in the surgical intensive care unit.

The following day, a point-of-care echocardiogram showed severely depressed left ventricular systolic function and increased trabeculation in its apical region. While NCCM was suspected, the differential diagnoses also included peripartum cardiomyopathy and hypertensive heart disease.

The transthoracic echocardiogram performed on the following day revealed highly trabeculated left and right ventricles particularly in the apex and reduced left and right ventricular ejection fractions (Figure 1A and B). The ratio of the thick noncompacted to thin compacted layers at end-systole was  $\geq 2$ . Color-flow Doppler revealed intertrabecular signals consistent with blood flow and suggestive of NCCM [3]. Cardiac magnetic resonance confirmed NCCM, demonstrating a ratio of noncompacted myocardium to compacted myocardium greater than

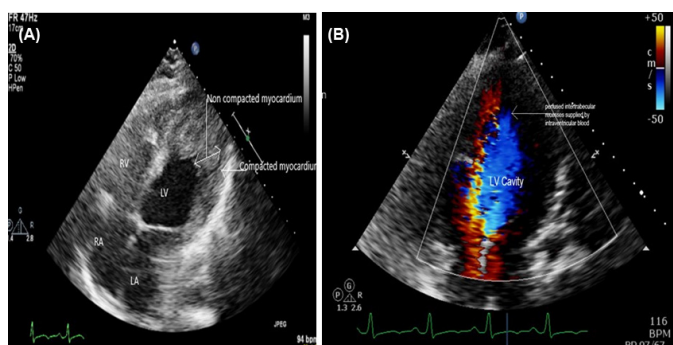


Figure 1: (A) Maternal echocardiogram showing prominent noncompacted myocardium localized to the apex and lateral walls of the left ventricle. The ratio of the noncompacted layer to compacted layer is  $>2$  during end-systole.

Abbreviations: LA = left atrium, LV = left ventricle, RA = right atrium, RV = right ventricle. (B) Color Doppler image revealing flow within the intertrabecular recesses.

2.3 during diastole (Figure 2). Right ventricular (RV) noncompaction was also identified.

The patient's blood pressure improved following Cesarean delivery of a baby boy. She was treated with a beta blocker, angiotensin converting enzyme inhibitor, and warfarin with further clinical improvement. Her left ventricular ejection fraction normalized on repeat echocardiogram at one year. There was persistent noncompaction in the left ventricle.

An echocardiogram of the newborn performed shortly after birth showed left ventricular (LV) noncompaction with normal LV systolic function and a small muscular ventricular septal defect (Figure 3). His electrocardiogram showed sinus rhythm with QTc prolongation. There were no cardiac events during his first year.

Due to the echocardiographic findings in both mother and child as well as a history of sudden death of the index patient's mother in the fifth decade of life, an extended family history was obtained, which revealed a pattern of premature death (Figure 4). Genetic testing identified

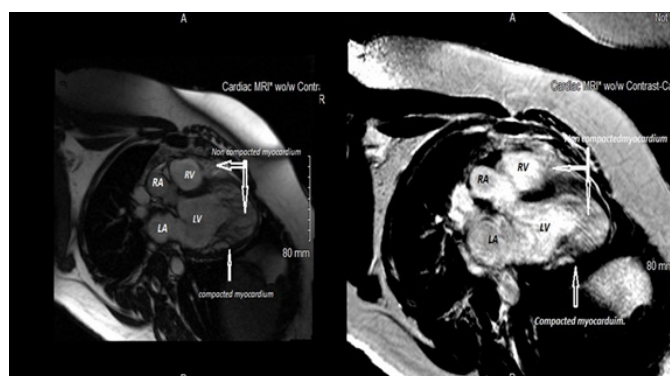


Figure 2: Maternal cardiac magnetic resonance image. Cardiac MRI without and with contrast showing noncompacted (dual arrows) and compacted myocardium (single arrow). The calculated ratio is 2.3 during diastole. RV noncompaction is also demonstrated.

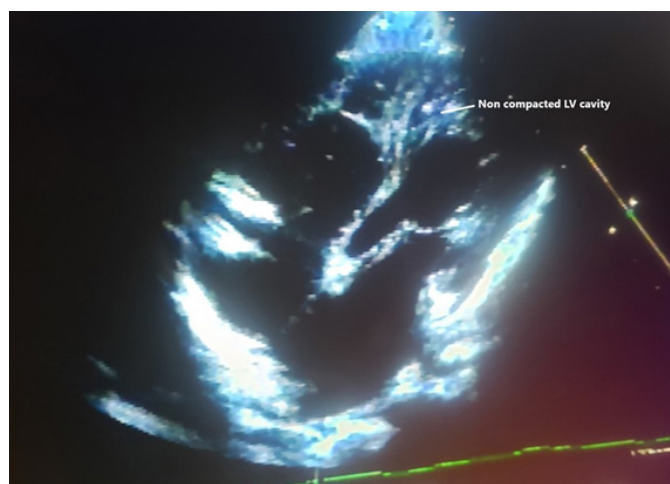


Figure 3: Echocardiogram of child at 2 months reveals left ventricular noncompaction.

the presence of MYH7 mutation in both the mother and newborn. In view of the family history of premature sudden death, a defibrillator was implanted in the patient for primary prevention of sudden cardiac death.

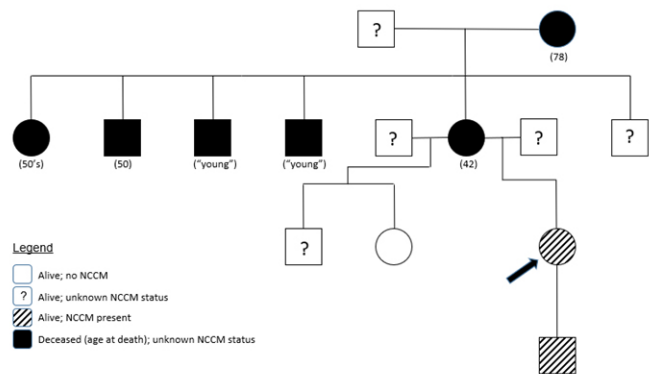


Figure 4: Family tree of the index patient (arrow) and son and survivorship of relatives. Squares=male, circles=female.

## DISCUSSION

The detection of cardiovascular disease during pregnancy has been on the increase, occurring in 1–4% of all pregnant women. Factors contributing to this rise include older maternal age, a higher prevalence of cardiac risk factors in the general population such as diabetes mellitus, hypertension, pre-eclampsia, multifetal pregnancies, and an increasing number of women with congenital heart disease reaching childbearing age [1, 4]. Hypertensive disorders remain the most frequent finding with gestational hypertension dominating this category [5]. Pre-eclampsia is a distinct entity that shares many risk factors with those who develop gestational hypertension and was the presenting syndrome in our patient [6]. Following hypertensive disorders, congenital heart disease is the leading cardiac disorder in western society [2, 4].

Hemodynamic changes and alterations in cardiac physiology during pregnancy may precipitate acute heart failure in a previously stable patient with preexisting cardiac dysfunction. Intravascular blood volume can increase by up to 50% accompanied by an increased stroke volume and heart rate [7]. The net effect is a similar increase in cardiac output. There is marked individual variability in the magnitude of cardiac responses which are partially influenced by maternal age, height, and weight.

Heart failure during pregnancy is associated with considerable morbidity and mortality. Fetal mortality is also substantial and may be as high as 30% [8]. Predictors of heightened risk include moderate or severe LV dysfunction and New York Heart Association functional

class III or IV [9]. The development of peripartum cardiomyopathy (PPCM) also confers a risk of pregnancy-related morbidity and mortality in previously healthy young women [10].

When heart failure is the presentation late in the course of pregnancy, NCCM cannot be readily differentiated from PPCM without imaging studies. Nevertheless, distinctive features of both have been identified (Table 1).

Noncompaction cardiomyopathy is diagnosed less frequently than PPCM, at approximately one-tenth the rate overall [11, 12]. It is transmitted in an autosomal dominant fashion and etiologically unrelated to pregnancy [13, 14]. The diagnosis is often suspected or established on echocardiography when performed in the evaluation of heart failure. The most widely used criteria as proposed by Oechslin are based on four characteristics: (a) absence of other cardiac anomalies; (b) identification of two myocardial layers—a compacted thin epicardial band and a thicker noncompacted endocardial layer with an end-systolic ratio of noncompacted to compacted layers of >2; (c) localization of noncompaction to the mid-lateral, apical, and mid-inferior regions of the left ventricle, and; (d) color Doppler flow in the intertrabecular recesses [15]. Alternative imaging studies such as cardiac magnetic resonance or cardiac computed tomography are also useful for diagnosis and may be considered if the echocardiographic study is indeterminate [16, 17].

Table 1: Noncompaction cardiomyopathy versus peripartum cardiomyopathy

	Noncompaction	Peripartum
Incidence	1 per 7,000 live births	1 per 20,000 to 1 per 100 live births
Genetics	Autosomal dominant with variable penetrance	Idiopathic and familial genetic predisposition
Onset	Childhood and adults	Late term during pregnancy or within five months following delivery
Diagnosis	Multiple echocardiographic and MRI criteria published	Generally a diagnosis of exclusion in the appropriate timeline with left ventricular ejection fraction <45%
Clinical presentation	Clinical heart failure and arrhythmia with equally frequency	Signs and symptoms of heart failure
Prognosis	High rate of progression to stroke, ICD shocks, cardiac transplantation. 4.3% annual mortality rate	Improvement expected in majority of patients

Due to the familial association in patients with LV noncompaction, obtaining a detailed family history, phenotype evaluation of the index case and at-risk family members, and genetic testing is a standard part of the evaluation process [18]. The benefit of genetic mapping followed by appropriate interventions offers potential to improve morbidity, mortality, and quality of life [17]. Distinguishing hereditary and sporadic subtypes allows more precise prognostic information and individualization of management strategies.

Based on a core test panel of 45 cardiomyopathy genes plus the family history, patients with NCCM can be classified into three groups. Group 1—genetic: family history positive, mutation positive. Group 2—probably genetic: family history positive, mutation negative. Group 3—sporadic: family history negative, mutation negative [19]. Genetic mutations are more common in children with NCCM compared to adults using the same genetic panel screen. Mutations are commonly found in the MYH7, MYBPC3, and TTN genes. HCN4 and RYR2 genotypes are also frequently reported [3]. Less common are mutations in ACTC1, ACTN2, MYL2, TNNC1, TNNT2, and TPM1 [20]. The MYH7 mutation is associated with lowest risk of major adverse cardiac events and is the only sarcomere gene associated with congenital heart disease. Isolated NCCM has been associated with familial, autosomal dominant, X-linked (Barth syndrome), autosomal recessive, maternal mitochondrial, and genetic mutations commonly found in other cardiomyopathies [21, 22].

The characteristic findings of hypertrabeculation stemming from failure of the myocardial compaction process that occurs between 12 and 18 weeks of gestation persist after birth although sporadic acquired forms have been reported in adults [23]. Whether NCCM is a distinct entity or one of many cardiomyopathies with similar morphology is the subject of ongoing debate. Interestingly the pathologic anomaly is not always associated with abnormal LV function. This has led to discrepant classifications from various organizations. The American Heart Association labels NCCM as a genetic cardiomyopathy whereas it is designated as unclassified by the European Society of Cardiology and the World Health Organization International Classification of Diseases [24, 25].

During pregnancy, ventricular remodeling occurs independent of genetic factors due to changes in metabolic and hemodynamic demands [26]. These changes may become more profound in patients with underlying cardiac abnormalities resulting in reduced cardiac reserve compared to patients with normal hearts. Left ventricular ejection fraction, fractional shortening, and the echocardiographic E/E' ratio are significantly attenuated in women with structural heart disease [27]. Our patient with NCCM developed symptoms of heart failure during the third trimester of pregnancy. Of note, although she had a previously compensated clinical cardiac status, she was unable to adapt to the pressure and volume increases associated with pregnancy.

There is no specific treatment for NCCM. In general, the guidelines for management of patients with heart failure and reduced ejection fraction apply to this entity. Higher rates of stroke or systemic embolism have been reported among patients with systolic dysfunction or atrial fibrillation. Oral anticoagulation as primary prophylaxis should be considered in these patients. Use of the CHADS<sub>2</sub> (congestive heart failure, hypertension, age  $\geq$ 75 years, diabetes mellitus, stroke) score may be a useful decision-making tool regarding oral anticoagulation in those without atrial fibrillation or systolic dysfunction [28].

## CONCLUSION

In summary, not all heart failure that develops during pregnancy is due to underlying hypertension, pre-eclampsia, or peripartum cardiomyopathy. Echocardiography along with a focused history offers clues that can lead to a diagnosis of NCCM which can then be confirmed with subsequent genetic testing.

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### Author Contributions

Most Sirajum Munira – Conception of the work, Design of the work, Acquisition of data, Analysis of data, Interpretation of data, Drafting the work, Revising the work critically for important intellectual content, Final approval of the version to be published, Agree to be accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved

Kenneth Ong – Conception of the work, Design of the work, Acquisition of data, Analysis of data, Interpretation of data, Drafting the work, Revising the work critically for important intellectual content, Final approval of the version to be published, Agree to be accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved

Lekshmi Dharmarajan – Conception of the work, Design of the work, Acquisition of data, Analysis of data, Interpretation of data, Drafting the work, Revising the work critically for important intellectual content, Final approval of the version to be published, Agree to be accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved

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The corresponding author is the guarantor of submission.

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Written informed consent was obtained from the patient for publication of this article.

### Conflict of Interest

Authors declare no conflict of interest.

### Data Availability

All relevant data are within the paper and its Supporting Information files.

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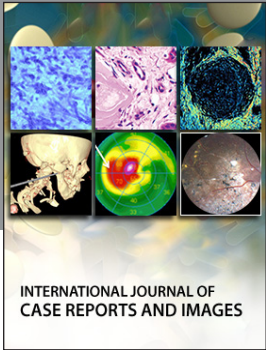
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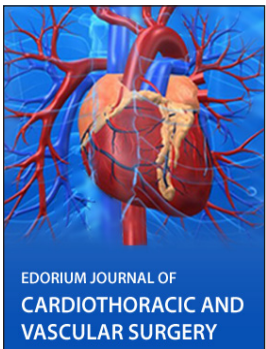
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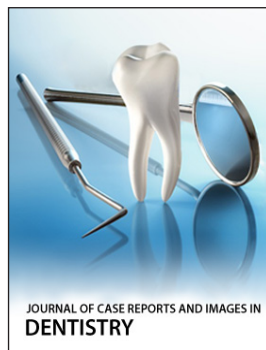
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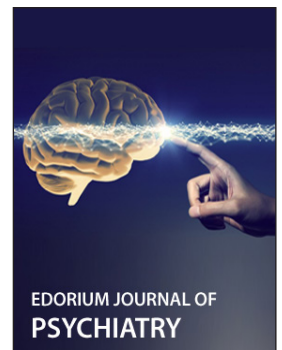
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