Case Report: Sudden cardiac death due to ventricular myocardial non-compaction [version 2; peer review: 2 approved]

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Abstract
Ventricular non-compaction (VNC) is a rare myocardium disorder, which can be both genetic and sporadic. A poor wall compaction process or an excessive trabeculae formation may be at the genesis of myocardial hypertrabeculation with multiple recesses. It is often complicated by ventricular dysfunction, arrhythmias and cardiac embolism. Herein we report a case of a 20-year-old male patient with no particular past medical history who was followed up at the cardiology department for dyspnea. Echocardiography showed reduced ejection fraction of the left ventricle with potential hypertrabeculation in the right ventricle, confirmed by cardiac MRI. The patient was not put under medication and was later lost to follow-up. He died few months later without a clear cause explaining death. A forensic autopsy was performed that attributed death to acute ventricle arrhythmia secondary to VNC, emphasizing the major role of an early and specific treatment to avoid such a fatal outcome.

Keywords
Isolated Non compaction of the Ventricular Myocardium, Cardiomyopathy, Histology, Sudden Cardiac Death, Autopsy.

Open Peer Review

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2

version 2
(revision)
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version 1
26 Aug 2020

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Any reports and responses or comments on the article can be found at the end of the article.
Introduction

Ventricular non-compaction (VNC) is a complex and heterogeneous cardiomyopathy first described in 1926. It is a rare disease with a reported prevalence of 0.014–0.17%\(^1\). Several terms are used to describe this disease namely: “cardiac hyper and excessive trabecularization”, “spongy myocardium”, “honeycomb myocardium”, or “persisting myocardial sinusoids”, and even “isolated ventricular abnormal trabeculation”. It is characterized by hypertrabeculation with an excessive lace-like network of trabeculae and deep trabecular pockets in the ventricle, creating a perfect environment for thrombi formation. VNC can be detected in all age groups, ranging from the fetal period to adulthood\(^2\). It can occur sporadically or is hereditary secondary to chromosomal abnormalities. It can also be associated with other cardiac diseases, which may be congenital. Additionally, VNC is represented by a large spectrum of symptoms and clinical features ranging from normal variants to pathological phenotypes. Indeed, VNC may remain asymptomatic until a complication occurs. Cardiologists must pay more attention to various clinical manifestations, including heart failure, arrhythmias and cardio embolic events, which can be related to VNC, to initiate an early treatment and avoid potentially fatal complications\(^3\).

Herein, we report a fatal case of VNC in a 20-year-old male, attested by the autopsy, and we discuss different mechanisms involved in the occurrence of death.

Case report

A 20- year-old Caucasian student male, who presented with dyspnea and chest pain in March 2019, was followed up by the cardiology department and classified as stage 2 on the New York Heart Association (NYHA) Functional Classification. The patient had no other relevant personal or family past medical history. The patient had 172 cm tall and weighs 62 Kg; BMI are 21 Kg/m\(^2\). Blood pressure was 120/70 mmHg with a pulse of 80 bpm. Physical examination showed no other abnormalities. ECG showed no significant abnormalities as well as laboratory findings. As part of an etiological assessment of dyspnea, a transthoracic echocardiography showed a dilated left ventricle, reduced left ventricular ejection fraction at 40%, septo-apical myocardial hypokinesia and left ventricular hypertrabeculation. (Figure 1).

A cardiac magnetic resonance imaging (CMRI) was performed and revealed reduced left ventricular ejection fraction (LVEF) at 30%, globular shape of the left ventricle with an overall wall hypokinesia, hypertrabeculation located at the left ventricle, a thickness of 2.8cm of the trabeculated myocardium on the compact myocardium. less contrast enhancement of the trabeculated myocardium compared to normal, and no thrombus in the left ventricle. The ratio of noncompacted myocardium to compacted myocardium was 3.1. (Figure 2). It was concluded that the appearance was most likely left VNC cardiomyopathy with a LVEF at 30% without intra-cardiac thrombus or mitral insufficiency (Figure 2). Twenty-four hour Holter monitoring showed occasional ventricular premature beats (grade 1 of Lown and Wolf classification)

He was discharged with aspirin 100 mg per day, bisoprolol 2.5 mg per day and Ramipril 2.5 mg per day.

The patient was later lost to follow-up. A few months later, he died without a clear cause explaining the death. A forensic autopsy was performed.

Autopsy findings

The body was that of a man of average build, with an approximate weight of 70kg. There was no specific sign on the external examination particularly, no asymmetry in comparing the circumference of the two calves.

The heart was globose weighing 325g. The coronary arteries were in a normal position without any significant lesion. The axial dissection of the heart found left ventricle hypertrabeculation with parietal thinning measured at 0.5cm and some intra-cavitary

Amendments from Version 1

1. Several data about the patient such as: the patient's race (this is important due to the influence of genetic factors); how long the symptoms have occurred; symptoms other than dyspnea; the patient's occupation; medications that have been taken; physical examination; laboratory findings; and how the patient was diagnosed with heart failure, ECG data, therapy administered were all included in the new version.
2. Histopathological findings are added.
3. Discussion was enriched with other references.
4. The role of autopsy and collaboration between cardiologists and forensics is added in the summary

Any further responses from the reviewers can be found at the end of the article.
adhering thrombi (Figure 3). Left ventricular examination found wall thickening at 1.2cm. Valvular examination was normal. No systemic thrombi were found. The lungs were the site of profuse oedema. The rest of the organs were congestive without any abnormality. Histologically, the endocardial surface was relatively smooth with anastomosing broad trabeculae resulting in irregular, large staghorn like endocardial lined spaces. A fibrous band separating the spongy from the compact portions of the myocardium was also noted. Toxicology test was negative. Based on clinical history and the necropsy findings, death was attributed to acute ventricle arrhythmia secondary to a myocardium non-compaction.

Discussion
The European Society of Cardiology (ESC) categorizes VNC as “unclassified cardiomyopathy” with a structural and functional abnormal heart muscle without any other diseases sufficient to cause the observed myocardial abnormality”. However, The American Heart Association (AHA) categorizes it as “genetic cardiomyopathy”. The etiology and embryogenetic mechanisms leading to VNC are still unknown and several hypotheses are suggested. The most frequent hypothesis is that hypertrabeculation may result from excessive trabeculae formation and/or a defect in the later compaction processes.

VNC, and specifically on the left side, has been found in association with more than 40 mutated genes, which encode for several cell structures. The most common are MYH7, MYBPC3, TTN, at a rate of 71%. Burke et al. reported that the presumed genetic defect resulting in LVNC in the
second month of development may cause a variety of other cardiac abnormalities, including epicardial coronary malformation, histiocytoid cardiomyopathy, ventricular septal defects, and conotruncal diseases…In their pathological study of 14 cases of patients with myocardial non compaction, they found eight patients with associated cardiac anomalies, which did not appear related to the non compaction. They concluded that there was no difference in the gross pattern of trabeculation or microscopic features in the isolated versus the “secondary” forms.

Some cases of VNC associated with congenital hemoglobinopathies have been described in the literature. Kayvanpour E et al. have reported cases of LVNC in association with sickle cell disease. Some other cases reported LVNC in a group of family members, including a pair of identical twins, each of whom suffered from thalassemia.

Although the usual site of hypertrabeculation involvement is the left ventricle, the right ventricle is rarely affected. Right VNC can lead to ventricular tachycardia or right heart failure. In addition, patients with right VNC can be perfectly asymptomatic with only electrocardiographic disorder. In addition, concomitant damage of right VNC is not rare and it can be difficult to distinguish between non-compaction and arrhythmogenic right ventricular cardiomyopathy (ARVD). Diagnosis criteria for ARVD, even if it coexists with typical VNC, may lead to a diagnosis of ARVD rather than VNC. Less frequently, both ventricles can be affected leading to entirely non-compaction cardiomyopathy.

The most common findings in initial ECGs were left bundle branch block, LV hypertrophy, and repolarisation abnormalities. A normal ECG was rare and rather seen in younger patients with less severe structural cardiac abnormalities.

Different imaging-based classification systems have been used to make VNC diagnosis. Cardiac Magnetic Resonance Imaging (CMRI)-based criteria (Petersen criteria) is considered as the gold standard. Not all definitions are anatomically controlled and these criteria are nonspecific. Autopsy performed on individuals with known VNC can be a good way to compare radiological criteria to anatomical findings. Collaboration between forensic medicine and cardiology should be take into consideration with the aim to standardize diagnostic criteria and to avoid over diagnosis in healthy people with a benign prognosis.

Nonspecific histopathological findings have been described, including hypertrophy of the cardiomyocytes, ischemic necrosis with fibrosis due to insufficient vascular supply of the trabeculations, and disorganization of cardiomyocytes. VNC leads to variable complications that can be misdiagnosed and lead to sudden cardiac death. The most common is conduc- tion defects in approximately 90% of patients followed by myocardium arrhythmia. Thromboembolic events are not very frequent and occur in only 10% of cases, mostly in adults. Three main factors are involved in the occurrence of thromboem- bolic events: the presence of thrombi into ventricular trabeculations, left ventricular systolic dysfunction with reduced ejection fraction, and/or atrial fibrillation. The prognosis of patients with VNC can vary according to structural and haemodynamic complications. Initial cohorts of VNC suggested 35% to 38% mortality over median 5 to 11 years of follow-up. However, patients with LVNC with preserved left ventricular ejection fraction had similar survival rate to the general population.

Currently, there are no guidelines for the management of patients with VNC. Recommendations for treatment include prophylactic anticoagulation therapy and the implantation of a cardiac defibrillator. Treatment for VNC is therefore that of any cardiomyopathy with heart failure. A periodic check with a 24-hour ECG holter is indicated in order to assess the risk of a possible asymptomatic arrhythmia. Finally, first-degree family members of all patients diagnosed with VNC should undergo an echocardiographic screening examination and genetic exploration.

In summary, there are multiple controversies related with VNC comprising etiology and pathogenesis, genetic findings, relation with extra-cardiac diseases, diagnostic criteria, treatment, and prognosis. Cardiologists have to pay attention to various clinical manifestations, including heart failure, arrhythmias and cardio embolic events, which can be related to VNC in order to initiate an early treatment and avoid potentially fatal complications. Collaboration between cardiologists and forensic pathologists is mandatory in cases of VNC related deaths. It is well known that pathological examination of the diseased heart can provide valuable information on the processes that are encountered clinically.

Data availability
All data underlying the results are available as part of the article and no additional source data are required.

Consent
Written informed consent for publication was obtained from the legally authorized representative of the decedent.

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The authors have made significant revisions as suggested. However, they should check again for grammatical errors, e.g:
- "Caucasian student male" should be "male Caucasian student".
- BMI was...
- "...septo-apical myocardial hypokinesia and left ventricular hypertrabeculation" should be "septo-apical myocardial hypokinesia, and left ventricular hypertrabeculation".
- "bisoprolol 2,5 mg per day and Ramipril..." should be "bisoprolol 2,5 mg per day, and Ramipril..."
- "death was attributed" should be "the death was attributed".

It will also be more comprehensive if histological figures are provided.

**Competing Interests:** No competing interests were disclosed.

**Reviewer Expertise:** Molecular cardiology

I confirm that I have read this submission and believe that I have an appropriate level of expertise to confirm that it is of an acceptable scientific standard.
In this case report, Dr. Mannoubi and colleagues reported a case of a man with ventricular non-compaction and sudden cardiac death. This case shows a good collaboration between cardiologists and forensics. However, I have some major and minor comments to improve the quality of the article, especially regarding the completeness of the data:

1. Several data are lacking about the patient, such as: the patient's race (this is important due to the influence of genetic factors); how long the symptoms have occurred; symptoms other than dyspnea; the patient's occupation; medications that have been taken; physical examination; laboratory findings; and how the patient was diagnosed with heart failure. Is there any cardiomegaly? Was the patient in shock at his admission to the hospital? ECG data is also important because ventricular non-compaction is closely related to arrhythmia.

2. Histology is present in the Abstract but no histopathological findings mentioned. The histopathological findings should be added.

3. Data regarding therapy administered to the patient is also not mentioned.

4. How much is the ratio of non-compacted myocardium to compact myocardium at the end of systole/diastole (Petersen criteria)?

5. Completing the patient's data is important for the diagnosis of LVNC, as hypertrabeculation can also be observed in other comorbidities or even athletes. Will these conditions give different results in the autopsy findings? This should also be mentioned in the Discussion.

6. As the death of the patient was attributed to acute ventricle arrhythmia secondary to a myocardium non-compaction, the prognosis and mortality of the patients with LVNC should also be explained, like the mortality/survival rate.

7. “Some cases of VNC associated with congenital hemoglobinopathies have been described in the literature.” Please put citations and more explanations regarding this.

8. In the Discussion, please explain ECG findings that should be found in VNC.

9. “VNC leads to variable complications that can be misdiagnosed and at the origin of sudden cardiac death. The most common is conduction defects in approximately 90% of patients..."
followed by myocardium arrhythmia. Thromboembolic events are not very frequent and occur in only 10% of cases, mostly in adults. Three main factors are involved in the occurrence of thromboembolic events: the presence of thrombi into ventricular trabeculations, left ventricular systolic dysfunction with reduced ejection fraction, and/or atrial fibrillation.”. Please put references to these statements.

10. The role of autopsy and collaboration between cardiologists and forensics should be added in the summary.

11. There are many grammatical errors, for example:
   - “Ventricular non-compaction (VNC) is a rare myocardium disorder…” should be “myocardial disorder”.
   - “…a transthoracic echocardiography was requested showing”. The word “requested” is unneeded.
   - “…and patient was put under treatment” should be “and the patient”.
   - “A cardiac magnetic resonance imaging (CMRI) was requested”, “requested” should be changed to “performed”.
   - “Left ventricle examination” should be “left ventricular”.
   - “Toxicology was negative” should be "toxicology examination" or "toxicology test".
   - “The European Society of Cardiology (ESC) categorize VNC” should be "categorizes".
   - “However, The American Heart Association (AHA) categorize” should be "categorizes".
   - “The most frequent on” should be “the most frequent hypothesis”.
   - “…at the origin of sudden cardiac death” should be “lead to sudden cardiac death”.
   - “…in order to initiate an early treatment and avoiding” should be "avoid".

Is the background of the case's history and progression described in sufficient detail?
Partly

Are enough details provided of any physical examination and diagnostic tests, treatment given and outcomes?
No

Is sufficient discussion included of the importance of the findings and their relevance to future understanding of disease processes, diagnosis or treatment?
Partly

Is the case presented with sufficient detail to be useful for other practitioners?
Partly

**Competing Interests:** No competing interests were disclosed.

**Reviewer Expertise:** Molecular cardiology

I confirm that I have read this submission and believe that I have an appropriate level of expertise to confirm that it is of an acceptable scientific standard, however I have significant reservations, as outlined above.

Author Response 07 Jul 2021

med amin mesrati, Taher Sfar Hospital, Mahdia, Tunisia

Dear Reviewer,

First, we thank you for the interest and the time that you have gave to the article. This manuscript was revised according to your relevant comments. We realize that the quality of the article is now improved.

We hope that these changes make our work acceptable for indexing.

Best regards,

**Competing Interests:** none

Reviewer Report 09 September 2020

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Mokhles lajmi

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This is a case report about a young male deceased from ventricular arrhythmia due to left ventricular non compaction (VNC) syndrome, a rare but quite controversial pathology. In fact, this condition can express itself in various ways (ranging from completely asymptomatic patients to severe heart failure or arrhythmias) misleading the diagnosis, and imagery criteria are lacking specificity.

We thank the authors for this quality case report.

Q1:
The case description had all the necessary information to fully understand the case.

Q2:
- Clinical findings (autopsy findings in this case) are accurate and concise.

Q3:
- I congratulate the author's for their interesting and insightful point of view regarding the potential importance of collaboration between forensics and cardiology to further improve the diagnosis accuracy. In fact diagnosis of VNC is very controversial and misleading, and imaging criteria are perplexing, thus dealing with VNC from a cardiology-only point of view is narrow minded, forensics could be a huge asset to correlate imagery to anatomy.
- We know that some degree of non compaction of the left ventricle is not uncommon in the anterior apical region and trabeculations of the left ventricle can be increased in physiological conditions such as pregnancy and exercise training, would this be a diagnostical challenge for forensics? Can this mislead the autopsy findings? Is there any differential diagnosis in VNC?

Q4:
- Author's succeeded in explaining a relatively complex pathology, in a way that it's understandable for non cardiologists/forensics.

5: The author's should consider the following points:
- In accordance with CARE guidelines for case reports, "case report" should appear in keywords, with no more than 5 keywords
- As mentioned in the introduction, ventricular non compaction was first described in 1926. I think it would be interesting to add that it was done by Mr Grant and cite the reference: Grant RT. An unusual anomaly of the coronary vessels in the malformed heart of a child. Heart 1926; 13: 273–83.1
- Regarding the prevalence of this disease, although it was deemed rare by many investigators, the distribution of this disease in the global population is very difficult to evaluate, and numbers diverge hugely in the literature. One referenced source in a Lancet paper even stated that it “seems to be the third most commonly diagnosed cardiomyopathy”.2 Thus I advise to not mention a particular prevalence and just state that it is rare and that its prevalence is uncertain.
- Figure 2: it would be more accurate to mention: non compacted left trabeculations.
- Discussion section: Some cases of VNC associated with congenital hemoglobinopathies have been described in the literature. Author's should add a reference relating to this fact.3, 4
- VNC abbreviation is used in abstract. Abstracts should not contain abbreviations unless it is necessary.
6/ We noted some spelling errors:
   - Autopsy findings, line 5; change "found wall thickening at 1.2cm" to "found a wall thickening of 1.2cm".
   - Autopsy findings, line 7; "abnormalities" instead of "abnormality".
   - Discussion, line 12; "disorders" instead of "disorder".
   - Discussion, line 12; "complications of right VNC are not rare" instead of "concomitant damage".
   - Discussion, line 19; "taken" instead of "take".

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Is the background of the case's history and progression described in sufficient detail?
Yes

Are enough details provided of any physical examination and diagnostic tests, treatment given and outcomes?
Yes

Is sufficient discussion included of the importance of the findings and their relevance to future understanding of disease processes, diagnosis or treatment?
Yes

Is the case presented with sufficient detail to be useful for other practitioners?
Yes

Competing Interests: No competing interests were disclosed.

Reviewer Expertise: cardiovascular surgery

I confirm that I have read this submission and believe that I have an appropriate level of expertise to confirm that it is of an acceptable scientific standard.
Q1: The case description had all the necessary information to fully understand the case.  
No comments

Q2: Clinical findings (autopsy findings in this case) are accurate and concise.  
No comments

Q3: I congratulate the author's for their interesting and insightful point of view regarding the potential importance of collaboration between forensics and cardiology to further improve the diagnosis accuracy. In fact diagnosis of VNC is very controversial and misleading, and imaging criteria are perplexing, thus dealing with VNC from a cardiology-only point of view is narrow minded, forensics could be a huge asset to correlate imagery to anatomy. 
We know that some degree of non compaction of the left ventricle is not uncommon in the anterior apical region and trabeculations of the left ventricle can be increased in physiological conditions such as pregnancy and exercise training, would this be a diagnostical challenge for forensics? Can this mislead the autopsy findings? Is there any differential diagnosis in VNC? 
R: After excluding dilated and hypertrophic cardiomyopathy, forensic doctor should consider other diagnoses that can present with similar features. Thus, it is essential to distinguish left ventricular non-compaction from acquired changes seen in pulmonary atresia, mycotic invasion of the heart... and literature disclosed many other differential diagnoses. In our context, the MRI helped us to retain VNC as final diagnosis.

Q4: Author's succeeded in explaining a relatively complex pathology, in a way that it's understandable for non cardiologists/forensics.  
No comments

5: The author's should consider the following points:  
In accordance with CARE guidelines for case reports, "case report" should appear in keywords, with no more than 5 keywords  
R: it is considered

As mentioned in the introduction, ventricular non compaction was first described in 1926. I think it would be interesting to add that it was done by Mr Grant and cite the reference: Grant RT. An unusual anomaly of the coronary vessels in the malformed heart of a child. Heart 1926; 13: 273–83.1  
R: it is considered

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R: it is considered
Figure 2: it would be more accurate to mention: non compacted left trabeculations. 
R: It is considered

Discussion section: Some cases of VNC associated with congenital hemoglobinopathies have been described in the literature. Author's should add a reference relating to this fact.

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Discussion, line 12: "complications of right VNC are not rare " instead of "concomitant damage".

Discussion, line 19: "taken" instead of "take".
R: considered

Competing Interests: none

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