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CASE REPORT

'Hot phase' non-dilated left ventricular cardiomyopathy with atypical onset and recurrence: a case report

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Abstract

Non-dilated left ventricular cardiomyopathy (NDLVC) is a newly categorized cardiomyopathy phenotype includingseveral aetiologies with a linking characteristic represented by the normal left ventricular volume. Inflammatory heart disease (InHD) is a heterogeneous process with variegate clinical manifestations, sometimes in overlap with NDLVC. A 26-year-old woman was admitted forcomplete heart block (CHB) and persistently raised troponin. Echocardiography and coronary angiography were normal. Extensive oedema and late gadolinium enhancement was found at cardiac magnetic resonance. Endomyocardial biopsy showed no signs of active myocarditis. Steroid therapy was started with restoration of atrioventricular conduction but subsequently the patient experienced a mild recurrence with a new troponin relapse. Genetic test was negative for mutations related with the clinical scenario. In this case of NDLVC with InHD the precise diagnostic work-up, including genetic test, was crucial for diagnostic, prognostic andtherapeutic purposes. Multimodality approach is crucial to detect and treat possible recurrences.

Keywords Cardiac magnetic resonance; Cardiomyopathy; Multimodality imaging; Endomyocardial biopsy

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Introduction

Non-dilated left ventricular cardiomyopathy (NDLVC) is a newly categorized cardiomyopathy phenotype including several aetiologies with a linking characteristic represented by the normal left ventricular volume.[1] The differential diagnosis includes other forms of cardiomyopathy, such as sarcoidosis, lymphocytic myocarditis, giant cells myocarditis, infective myocarditis and transient LV impairment. Inflammatory heart diseases (InHD) are heterogeneous conditions requiring an integrated work-up, almost always in overlap with NDLVC. InHD diagnostic criteria changed considerably over the last decades, mainly due to striking improvements in cardiac magnetic resonance (CMR) and high-sensitivity troponin.[2] The course of InHD is often benign with spontaneous recovery but the most severe forms might have an unfortunate progression if untreated.[3] In some cases, 'hot phase' recurrences were reported, frequently with specific genetic aetiologies.[4] In this clinical setting, genetics and histology constitute informative tests leading to the correct diagnosis and accurate clinical management.[5]

Case Report

A 26-year-old woman presented with worsening fatigue, exertional dyspnoea and bradycardia. Body temperature was 36.8°C and she denied tick bite or flu-like symptoms (*Table S1*). The patient was bradycardic but no signs of heart

failure or low cardiac output were detected as well as any signs of local inflammation. The ECG revealed a complete heart block (CHB), 36 b.p.m., with infra-Hisian escape rhythm and large fragmented QRS (*Figure 1*).

The patient had no chronic diseases. Two maternal uncles had pattern 1 Brugada without indication of implantable defibrillator and her paternal aunt had Sjogren's syndrome.

Echocardiography showed normal biventricular volumes, wall thickness and kinetics; ejection fraction was 57% (Global left ventricular strain −23.7%), without pericardial effusion or valvulopathies. Laboratory assessment (*Figure S1A*) showed a high and increasing troponinI (TnI) (20 813->32 632 ng/L, normal value <18 ng/L). Inflammatory biomarkers (C-reactive protein 0.70 mg/L; white blood cells $4.86*10^3/\mu L$; procalcitonin 0.03 μg/L) and bacterial and viral serology were negative. Furthermore, autoimmunity screening was negative (specifically anti-ENA antibodies and anti-RO/SSA included) and plasmatic angiotensin-converting enzyme (ACE) was 15 U/L (extensive laboratory tests in Supplementary *Table S2*, *Table S3*). Continuous ECG monitoring showed CHB with 36–45 b.p.m. during the first days (isoprenaline infusion was started at 0.015 γ/kg/min). No tachyarrhythmias were recorded, except sporadic isolated ventricular extrasystoles. Coronary angiogram ruled out coronary artery disease. CMR showed a mild thickening of the basal interventricular septum and diffuse transmural oedema especially at the septal and anterior wall segments. Subepicardial late gadolinium enhancement (LGE) was reported on the anterior and anterolateral walls (*Figure 2*).

A temporary pacemaker was placed to maintain an adequate heart rate (HR) during the acute phase. Considered the high-risk scenario, the patient was transferred to the hub centre and underwent EMB (performed 2 days after CMR) with five tissue samples (*Figure 3*). Histologic analysis showed mild oedema with a discrete amount of fibrosis. No granulomas or relevant lymphocytic infiltration were reported (<14 mononuclear leukocytes/mm^2 and <7 T-lymphocytes/mm^2). Immunohistochemical analysis was negative for lymphocytic infiltrate. The analysis of the viral genome persistence in cardiomyocytes was negative.

Considering the CHB with substantial oedema found using CMR (and partially at EMB), together with the increasing TnI, the inflammation was deemed crucial in the pathophysiological process and immunosuppressive therapy with intravenous prednisone 1 mg/kg/day was started. After 24 h, CHB regressed with persistent grade 1 atrio-ventricular block (AVB) (*Figure 4*). CMR at 12 days showed a significant reduction both in the oedema and LGE. Before discharge, a loop recorder was implanted and a 6 months corticosteroid tapering programme was started.

At the scheduled 1 month follow-up no arrhythmias were recorded, and TnIwas 344 ng/L. CMR scheduled at 78 days reported a further improvement with residual oedema only at the basal segment of inferior wall, at the septum and inferolateral wall with a subendocardial LGE unchanged compared with the previous CMR. Furthermore, hypokinesia of the anterolateral and inferior segments was reported. At 7 months after the first event, 34 days after steroids suspension, she complained of palpitations, without arrhythmias at loop recorder interrogation. TnI was persistently elevated (160 -> 88 -> 40 -> 54 ng/L) (*Figure S1*) while echocardiography was normal. The patient underwent a 30 W × 3 min protocol on a bicycle ergometer with continuous ECG monitoring, without O_2 consumption evaluation, with frequent ventricular extrasystoles and bigeminal ventricular rhythm (maximum HR 120 b.p.m.), followed by symptomatic 20 min grade 2 AVB Mobitz 1. In the suspect of InHD active recurrence, with tachy and bradi-arrhythmic expression, she was

Figure 1 ECG. Total heart block with infra-Hisianescape rhythm.

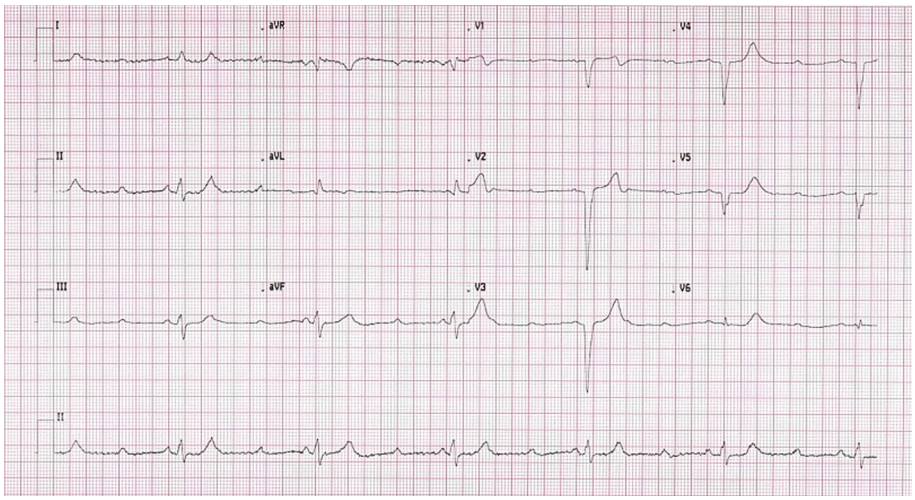

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Figure 2 Cardiac magnetic resonance. (A) T2-weighted STIR sequence. Diffuse oedema. Transmural pattern at the basal segments of the septum, the anterior wall, and the remaining medio-apical segments. (B) Post-contrast single-shot magnitude-only inversion recovery sequence. LGE on the entireanterior wall and on the mid-ventricular segments of the antero-lateral and infero-lateral wall with subepicardial distribution. The arrows indicate diffuse oedema in anterior wall, infero-septum and antero-lateral wall in *Figure 2A*, while in *Figure 2B*, they indicate late gadolinium enhancement in anterior wall and antero-lateral wall, with non-ischaemic pattern. Left ventricular end diastolic volume was 126 mL (76 mL/m^2) and end-systolic volume was 55 mL (33 mL/m^2), while right ventricular end diastolic volume was 121 mL (73 mL/m^2) and end systolic volume was 52 mL (31 mL/m^2).

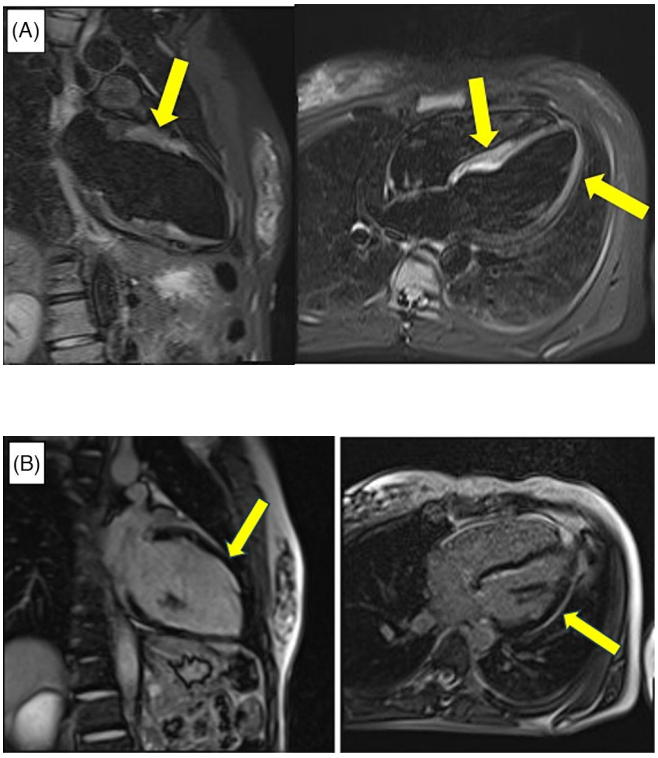


Figure 3 Histological analysis. (A) Azan-Mallory (10×): mild oedema and a discrete amount of fibrosis. (B) Haematoxylin–eosin (10×): no relevant lymphocytic infiltration. (C) Haematoxylin–eosin (20×): no myocardial fraying or granulomas. Immunohistochemical analysis of endomyocardial biopsy, negative for acute inflammation. Spotty leukocyte common antigen (D), no CD 4, spotty CD8 (E), mild presence of CD16 and polyfocal CD163 (F). The inflammation was graded comparing these samples to other normal patients previously analysed at our institution. The arrows indicate in (A) the fibrotic tissue in blue-stained areas, whereas in (B) and (C), they indicate diffuse oedema.

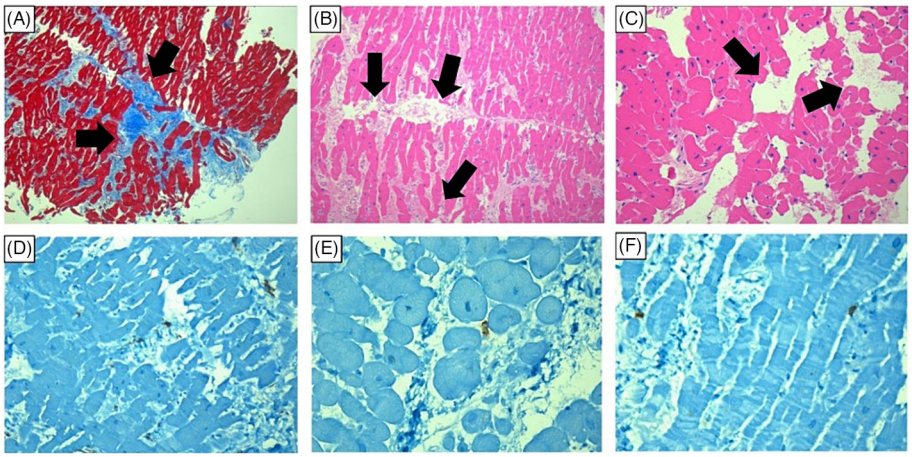


Figure 4 ECG. Normal spontaneous atrio-ventricular conduction, narrow QRS with mild right intra-ventricular delay (QRS 120 ms) and atrio-ventricular block grade I.

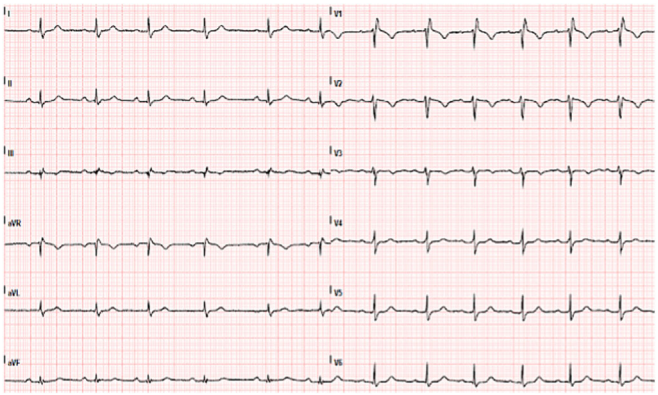
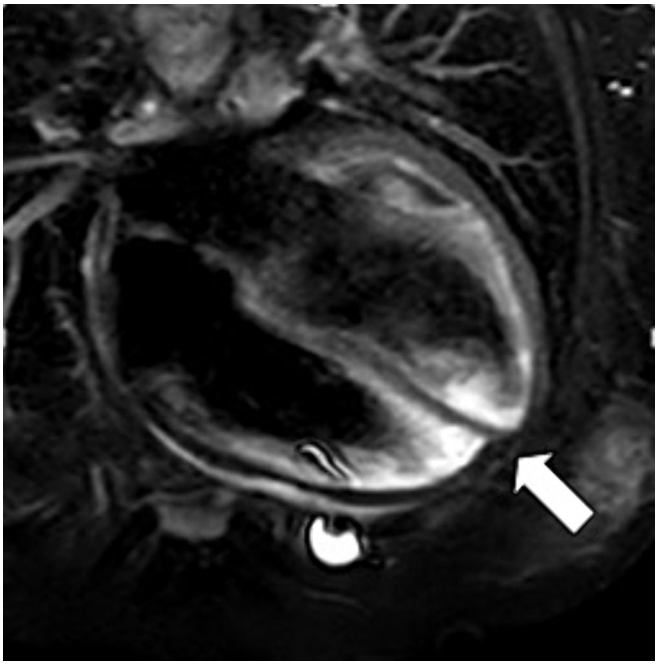


Figure 5 Cardiac magnetic resonance. T2-weighted STIR sequence. Diffuse oedema, transmural pattern at the apex. The arrow indicates apical oedema.



admitted to the cardiology ward. TnI was raised (601 ng/L after stress test >2117 ng/L on day 2 -> 727 ng/L on day 3), with negative inflammatory markers and no other causes that can justify such an alteration (i.e. myocardial ischaemia, anaemia, pathological blood pressure and heart rate raises). Positron emission tomography (PET) was negative, excluding ongoing high metabolism processes like sarcoidosis. CMR documented re-increased oedema and transmural LGE at the apex further supporting a disease recurrence (*Figure 5*). Next-generation sequencing genetic test revealed a double mutation for a potassium channel, one likely pathogenetic for long-QT syndrome and a variant of uncertain significance, both not related to the clinical scenario. Corticosteroid therapy was restarted in line with the first episode with an initial dose of 1 mg/kg/die with slow tapering in 6 months (*Table S4*), and the patient was discharged with a diagnosis of NDLVC with 'hot phase'.

Discussion

We report an uncommon case of NDLVC with InHD episodes in a young woman with an atypical bradyarrhythmic inflam-

matory onset and subsequent recurrence. The precise diagnostic work-up was crucial for the diagnosis, the prognostic stratification, and the choice of the optimal management, as the combination of clinical manifestations, histological analysis and CMR findings led to specific therapeutic approaches in our case. Clinical cardiologist, imager and pathologist allowed for a timely and correct diagnosis, as highlighted by the recent European guidelines on cardiomyopathies.[1] The presence of a non-ischaemic scar in the left ventricle (LV), without LV dilation, even in the absence of systolic dysfunction categorized the patient as an NDLVC. The first issue faced is the clinical manifestation that in patients with NDLVC and InHD could be very variegated in terms of symptoms, timing of presentation and severity.[6] Bradyarrhythmias are rare in InHD, with a prevalence below 2%, but they imply a very high risk of adverse in-hospital outcomes. In a previous report, it was shown that the incidence of cardiogenic shock, respiratory failure and renal failure were higher in these patients.[7] However, the risk of recurrences and the associations with LV wall abnormalities are unknown. The second issue faced was to determine if the patient had an acute or chronic InHD. According to recent consensuses, this patient showed characteristics of both the entities.[2] The features supporting the acute onset were (a) short symptoms duration; (b) increasing cardiac biomarkers (*Figure S1A*); (c) signs of oedema. On the other hand, a non-acute onset was suggested by the unmet Dallas criteria, that consider the inflammatory infiltrate and associated myocyte necrosis, alongside the negative immunohistochemical analysis. However, the negative result of EMB may be related to the sensitivity of the method that can be largely below 100% (40% in the oldest series) when associated with immunohistochemical analysis.[8] Therefore acute myocarditis cannot be ruled out, even if several samples were taken near the atrio-ventricular junction, where the inflammation was more represented, and analysed by an expert cardiac pathologist, raising the sensitivity of the method. The third challenge was the indication of EMB and immunosuppressive therapy. The CHB classified the InHD as a high-risk scenario and, according to current recommendations, EMB was indicated. Indeed, EMB could reveal specific aetiologies with potential targeted effective therapies.[2] Moreover, the absence of viral infection further supported the immunosuppression.[4] Immunosuppressive therapy in InHD demonstrated a positive benefit in a randomized clinical trial, both in terms of short-term functional outcomes and long-term survival free from adverse events.[9,10] Sarcoidosis, that in some cases might present with similar features, was excluded by PET other than EMB. The immunosuppression schedule considered (only prednisone) was in accordance with previous small experiences on young patients with InHD and bradyarrhythmic onset.[11] Finally, the recurrence of cardiac manifestations, which occurred with arrhythmias, new troponin release and oedema found using CMR confirms the pathophysiological role of inflammation and requires great attention. We believe that considering the signs of fibrosis at EMB, the recurrent troponin release and the dynamic imaging findings, the patient suffers from an NDLVC with relapsing 'hot phase'. However, genetic analysis did not find known genetic mutations that could explain the disease (e.g. desmoplakin),[4] and the patient never reported chest pain, as usually occurs in cases of 'hot phases' cardiomyopathies. Moreover, in a case series of what used to be called 'arrhythmogenic cardiomyopathy', conduction delay was present in 13% of patients, but the degree of AVB was unknown.[12] Considering the cases of InHD with 'hot phase' in patients with specific genetic mutations, we can speculate that unknown mutations or the complex interplay between different genes (e.g. polygenic risk score) with auto-immune system could lead to this specific clinical picture. Further studies are needed to obtain comprehensive knowledge in this field. Moreover, sub-clinical inflammation might play a key role in this case, despite it is not identifiable with current tests. Previous cohort studies reported the possibility of negative inflammatory biomarkers InHD, often associated with a more severe presentation compared with positive biomarkers patients. In possible support of this hypothesis, cardiac manifestations regressed following the initiation of corticosteroid therapy and the recurrence happened as soon as the therapy was suspended. Genetic testing and counselling are therefore recommended in settings of challenging InHD, to support the diagnostic hypothesis and to improve the follow-up and recurrence surveillance of these patients.[13] The last challenging decision regarded the implantation of a permanent pacemaker, which is not currently indicated in patients with potentially reversible causes of CHB, like InHD.[14] Among possible alternatives, the presence of anti-Ro/SSA antibodies was evaluated and excluded.[15] Nevertheless, an accurate follow-up is mandatory. Indeed, a second line of immunosuppressive treatment with methotrexate or interleukin-1 inhibitors should be discussed with the cardio-immunologist in selected cases.

Conclusions

NDLVC is a clear entity but as a whole heterogeneous group of cardiomyopathies, it might present several variegated features. InHD can be found often in overlap with NDLVC and in some cases present with atypical manifestations like CHB. An extensive diagnostic flow chart has crucial therapeutic and prognostic implications. The relationship between inflammation and genetic background is poorly understood yet, but it should be systematically and deeply investigated. Immunosuppressive therapy may favour the resolution of InHD-related CHB, however long-term surveillance is needed to study possible further 'hot-phases'. In this context, in the lack of specific guidelines, a comprehensive approach including CMR, genetic testing, PET and EMB in selected cases is probably the most appropriate.

Learning objectives

1 To identify patients with NDLVC and InHD with atypical onset.
2 To understand the practical management of high risk InHD.
3 To detect and investigate the recurrences of InHD with 'hot phases'.

Conflict of interest

The authors have nothing to disclose.

Supporting information

Additional supporting information may be found online in the Supporting Information section at the end of the article.

Figure S1. Troponin trends. A) In-hospital troponin trend with 20813 ng/L at admission and a maximal level of 32632 ng/L.
Figure S1. B) Troponin trend at follow-up. The dotted line shows the upper limit of normal. The red star marks the recurrence.
Table S1: *Timeline.*
Table S2: Laboratory exams.
Table S3: Main laboratory test results.
Table S4: Steroid tapering schedule.

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