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CLASSICAL CASE REPORTS
Heart failure

Fulminant Lyme myocarditis without any other signs of Lyme disease in a 37-year-old male patient with microscopic polyangiitis—a case report

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Background Lyme disease is a tick-borne multisystem infection. The most common cardiac manifestation is an acute presentation of Lyme carditis, which often manifests as conduction disorder and rarely as myocarditis.

Case summary We report the case of a 37-year-old male with a history of microscopic polyangiitis receiving immunosuppressive therapy. He was admitted for severe dyspnoea secondary to acute heart failure. Echocardiography and cardiac magnetic resonance imaging indicated a severely reduced left ventricular ejection fraction (LVEF) with global hypokinesia. Coronary heart disease was excluded, and endomyocardial biopsies (EMB) were performed. The left ventricular EMB revealed a rare case of fulminant Lyme carditis with evidence of typical lymphocytic myocarditis. *Borrelia afzelii*-DNA was detected without any relevant atrioventricular blockage or systemic signs of Lyme disease. The patient had no clinically apparent tick-borne infection or self-reported history of a tick bite. Immunological testing revealed a positive ELISA and Immunoblot for anti-Borrelia immunoglobulin G antibodies. After specific intravenous antibiotic therapy and optimized medical therapy for heart failure, the LVEF recovered, and the patient could be discharged in an improved condition. Repeat EMB a few months later revealed a dramatic regression of the cardiac inflammation and absence of Borrelia DNA in the myocardium.

Discussion A severely reduced LVEF can be the primary manifestation of Lyme disease even without typical systemic findings and can have a favourable prognosis with antibiotic treatment. A thorough workup for Lyme carditis is required in patients with unexplained heart failure, particularly with EMB, especially in immunosuppressed patients.

Keywords Lyme carditis • Lyme disease • Microscopic polyangiitis • Myocarditis • Endomyocardial biopsy • Case report

ESC Curriculum 2.2 Echocardiography • 6.2 Heart failure with reduced ejection fraction • 6.5 Cardiomyopathy • 6.1 Symptoms and signs of heart failure • 2.1 Imaging modalities

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Learning points

- Cardiac involvement can be the sole manifestation of Lyme disease.
- This case explicitly underlines the importance and value of left ventricular endomyocardial biopsy, providing (immuno-)histological evidence of typical lymphocytic myocarditis and detection of spirochaete by PCR. Cardiac magnetic resonance imaging and blood ELISA were neither informative nor specific enough (especially in relation to cardiac involvement).
- Lyme carditis can have a favourable prognosis with appropriate antibiotic treatment, even when a severely reduced left ventricular ejection fraction is the main finding and apparent atrioventricular block is missing.

Introduction

Lyme disease (LD) is the most common tick-borne multisystem infection in Europe and the USA.[1] Typical *Borrelia* strains include *Borrelia burgdorferi* and *Borrelia afzelii*. While dermatological, neurological, and ophthalmological manifestations are quite common, cardiac involvement is rare. Cardiac involvement in LD occurs in 0.3–10% of patients.[2,3] The most common cardiac manifestation is an acute presentation of Lyme carditis (LC), which manifests as conduction disorder, pericarditis, and/or myocarditis. The most frequent LC manifestation, however, is a high-degree atrioventricular (AV) block.[4] The isolation of spirochaetes from the myocardium of patients with cardiomyopathy and a positive serology of these patients in several studies showed that *B. burgdorferi* might cause acute and chronic heart muscle disease.[5,6] Because of the limited sensitivity and specificity of laboratory blood tests, these findings should only be interpreted in conjunction with other clinical and diagnostic features. While early stages of LD usually show a good response to antibiotic therapy, later manifestations constitute a therapeutic challenge. This is further complicated due to the absence of definitive, evidence-based guidelines for the diagnosis and management of LC. Concerning the diagnosis of myocarditis in general, the ESC report[7] strongly endorses the concept of endomyocardial biopsies (EMB) as the gold standard for the diagnosis of definite myocarditis and recommends extended criteria for clinically suspected myocarditis to improve its recognition in clinical practice.

Timeline

Time point	Diagnostic findings and treatments
Admission	Decompensation with New York Heart Association IV, severely reduced left ventricular ejection fraction (LVEF) (10%), existing immunosuppressive medications for MPA suspended
From Day 1/2	Optimal medical heart failure therapy commenced along with heart rate control. Transoesophageal echocardiography (TOE) showed possible left atrial appendage (LAA) thrombus—IV heparin commenced.
Day 5	Exclusion of CHD and performed endomyocardial biopsies (EMB)
Days 13–14	Electrical cardioversion after exclusion of cardiac thrombus (Re-TOE) and stable sinus rhythm (with amiodarone administration)
From Day 14	Diagnosis of fulminant carditis with detection of *Borrelia afzelii* in the LV EMB, antibiotic therapy IV with ceftriaxone (14 days) and subsequently with doxycycline oral
Days 19–26	Moderate LVEF recovering (25–30%) and clinical recompensation
After 4 weeks	Discharged with life vest (without antiarrhythmic medication)
After 3 months	Nearly normal LVEF (50%) in outpatient clinic
After 9 months	Follow-up with control EMB (dramatic regression of lymphocytic myocardial inflammation) and patient clinically asymptomatic and fit and well
After 12 months	Patient remains clinically asymptomatic, normalized LVEF, immunosuppressive therapy with Rituximab was re-started

Case presentation

A 37-year-old male Caucasian patient had a history of microscopic polyangiitis (MPA) for 5 years. He had no history of cardiac involvement secondary to MPA. He had received various immunosuppressive therapies, including Rituximab (RTX) and cyclophosphamide as remission induction/relapse therapy, followed by multiple immunosuppressive drugs including azathioprine and mycophenolate mofetil. Maintenance therapy with RTX had been started 3 years before his current admission. Since then, he had been stable without any major relapses with RTX (500 mg every six months) and low-dose prednisolone therapy (1 mg per day).

His medical history included arterial hypertension (without evidence of secondary causes), hypothyroidism, hyperuricaemia (treated with angiotensin-converting enzyme inhibitor, L-thyroxine, allopurinol), and severe obesity (body mass index 42 kg/m^2). Initially, he presented to the emergency department of a different hospital

with general fatigue, palpitations, and shortness of breath for 1 week. Then, after a newly diagnosed severely reduced left ventricular ejection fraction (LVEF), he was transferred to our hospital. Echocardiography, performed 1 year before, as a baseline due to his MPA and use of immunosuppressive agents such as cyclophosphamide, had shown a normal LVEF.

On admission, he was severely dyspnoeic (New York Heart Association IV), afebrile, and tachycardic (heart rate of 123/min) with blood pressure of 95/55 mmHg (without inotropic support). Clinical examination indicated normal heart and lung sounds and no relevant oedema. Chest X-ray revealed moderate cardiomegaly and marginal costophrenic angle effusions. The electrocardiogram (ECG) showed atrial fibrillation with T-wave inversion in the inferior, anterior, and lateral leads. Blood gas analysis indicated O_2 saturation of 95% and pO_2 pressure of 62 mmHg (8.3 kPa; without O_2 insufflation). Laboratory analysis showed slightly elevated C-reactive protein (CRP) levels at 9 mg/L (NR < 5 mg/L) without leucocytosis. NT-proBNP was markedly elevated at 1884 ng/L (NR < 125 ng/L) and normal creatinine of 1.0 mg/dL (NR 0.7–1.2 mg/dL). The initial echocardiography revealed a dilated LV (left ventricular end diastolic diameter 62 mm) with a severely reduced LVEF of 10% with global hypokinesia, and a normal left atrium (35 mm) in PLAX view. Transoesophageal echocardiography (TOE) on Day 2, revealed a left atrial thrombus and the considered electrical cardioversion was not performed. A cardiac magnetic resonance imaging (MRI) was performed on Day 4. It showed visually normal dimension of the left and right ventricle (LV and RV) with global LV hypokinesia, acute oedema of the LV and RV, no late gadolinium enhancement, no myocardial scars, and confirmed a severely reduced LVEF (in which image quality was reduced due to severe obesity and arrhythmia). Coronary angiography excluded coronary heart disease. Endomyocardial biopsies were obtained from the LV revealed acute lymphocytic myocarditis, as illustrated in *Figure 1*. As illustrated by haematoxylin–eosin (HE) stain, necrosis of many myocytes is detected in association with numerous CD3+ T cells and CD68+MHCII+ macrophages as visualized by immunohistochemistry. Nested PCR revealed the presence of Borrelia DNA in the EMB (*Figure 2*, see arrows for the presence of Borrelia DNA of the patient's EMB and corresponding positive control). Direct sequencing of the Borrelia product revealed the presence of *B. afzelii*. Subsequently, antibody testing performed showed positive IgG on Enzyme-linked Immunosorbent Assay (ELISA) and Immunoblotting. The patient had no clinical signs of a tick-borne infection, nor did he remember a tick bite.

Whilst undergoing the various investigations mentioned above, the patient was concurrently being treated for heart failure which medical therapy (with angiotensin receptor neprilysin inhibitor, aldosterone antagonist, diuretic), and a rate control therapy with a beta-blocker and digitoxin. After anticoagulation (using therapeutic doses of heparin IV) for 11 days, the thrombus had resolved (indicated by repeated TOE), and electrical cardioversion was performed to achieve sinus rhythm reliably, and now on the 12 lead ECG there was no AV block and a normal PQ interval was present. Amiodarone was added (in the context of the cardioversion with 1 g per day for 5 days), which led to a stable sinus rhythm. Subsequently, antiarrhythmic therapy with digitoxin and amiodarone was stopped to avoid AV block. Later, heart rate control was achieved with ivabradine (10 mg per day) to decrease the risk for AV block, a typical complication of Lyme carditis. The LVEF continued to be severely reduced in the short term (as indicated by recurrent echocardiography). Once we received the results from the EMB, antibiotic therapy with intravenous ceftriaxone (2 g per day) was commenced for 14 days, followed by oral doxycycline (200 mg per day) and in addition to heart failure therapy, the LVEF recovered to 25%. Thus, the patient could be discharged with a life vest (an antiarrhythmic medication was avoided due to the risk of AV block) in a clinically improved condition.

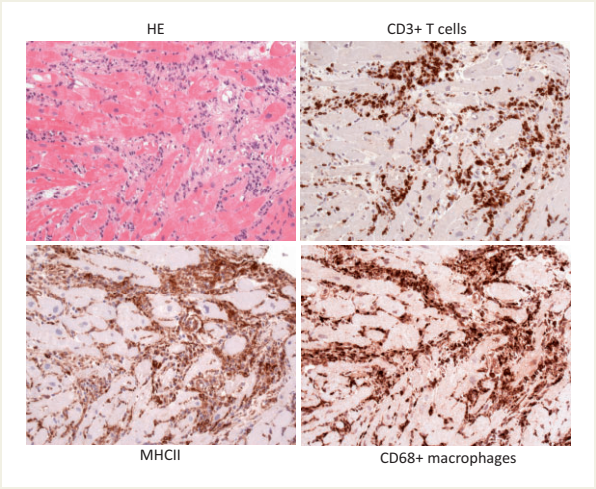

Figure 1 As illustrated by haematoxylin–eosin stain, necrosis of many myocytes is detected in association with numerous CD3+ T cells and CD68+MHCII+ macrophages as visualized by immunohistochemistry. Nested PCR revealed the presence of Borrelia DNA in the endomyocardial biopsy.

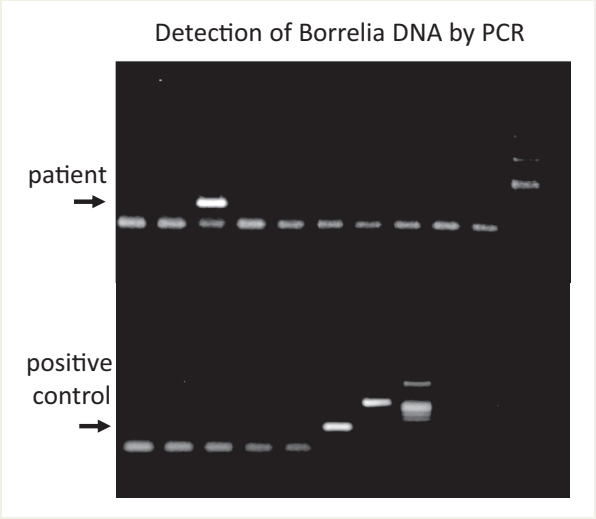

Figure 2 See arrows for the presence of Borrelia DNA of the patient's endomyocardial biopsy and corresponding positive control.

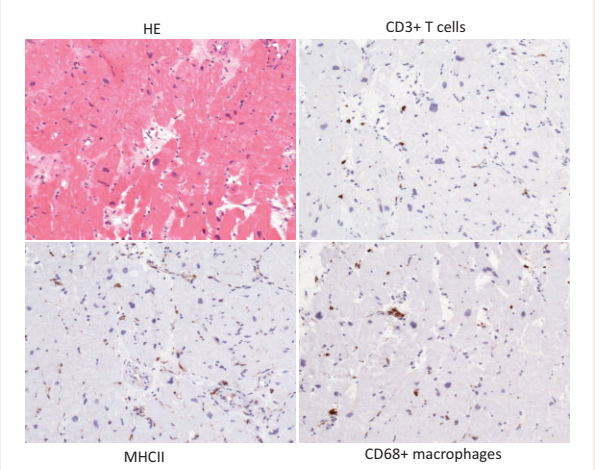

Figure 3 Nine months later, another endomyocardial biopsy revealed no myocyte necrosis anymore or severe fibrosis in haematoxylin–eosin stains. Furthermore, a dramatic regression of lymphocytic inflammation was noted. Only a few CD3+ T cells and some CD68+MHCII+ macrophages were identified in the myocardium.

Three months later, the LVEF recovered nearly completely (50%), no relevant arrhythmia was detected by the life vest. Nine months later, another EMB (*Figure 3*) revealed no myocyte necrosis anymore or severe fibrosis in HE stains. Furthermore, a dramatic regression of lymphocytic inflammation was noted. Only a few CD3+ T cells and some CD68+MHCII+ macrophages were identified in the myocardium (*Figure 3*). *Borrelia afzelii* DNA nested polymerase chain reaction (PCR) was negative in the follow-up EMB. After 1 year of follow-up, the patient remains clinically asymptomatic, immunosuppressive therapy with RTX was re-started, and his LVEF normalized to >55%.

Discussion

Cardiac involvement can be the sole manifestation of Lyme disease.

Lyme carditis must be considered in patients with the typical clinical manifestations of LD, which occur in different phases. The first clinical sign is most often an erythema migrans. Following localized manifestations, patients may develop generalized symptoms as the spirochaetes continue to spread, and cardiac manifestations may arise. However, the presented case and additional reports suggest that many patients do not recall a tick bite, and the typical rash is present in only 40% of patients with LC.[2] The most common objective manifestation of LC is an AV conduction block, and a high-degree AV block occurs in about 80–90% of cases of LC.[1] In our case, the electrophysiological presentation was tachycardic atrial fibrillation without any relevant AV block or with systemic signs or symptoms of LD. Cases of endocarditis with valvular involvement, pericarditis, and/or myocarditis attributed to LD have been published, but these manifestations are reported less commonly than conduction abnormalities.[3,5] The majority of patients with perimyocarditis could present with T wave inversion or ST-segment depression.[3] Our patient demonstrated non-specific T-wave inversions in the inferior-anterior and lateral leads. The severely reduced LVEF with symptoms of heart failure was the predominant diagnostic finding, and the definite diagnosis of myocarditis in LD could only be made with the EMB. However, it cannot be excluded that the patient's previous immunosuppressive treatment could have masked other LD manifestations.

This case explicitly underlines the importance and value of left ventricular EMB, providing (immuno-)histological evidence of typical lymphocytic myocarditis and detection of spirochaete by PCR. Cardiac MRI and blood ELISA were neither informative nor specific enough, especially concerning cardiac involvement.

The ESC report[7] already 2013 states that EMB 'confirms the diagnosis of myocarditis and identifies the underlying aetiology and the type of inflammation which imply different treatments and prognosis'. However, it is also pointed out that EMB is used infrequently. The pathophysiology of LC involves the direct myocardial invasion by spirochaetes and subsequent immunologic processes leading to an exaggerated inflammatory response. Unlike the neutrophil-predominant inflammation of Lyme arthritis, the transmural inflammation in LC is mainly composed of macrophages and lymphocytes, which is similar to viral myocarditis. The discrepancy between the only sporadically identified spirochaetes and the extent of lymphocytic infiltration indicates the importance of an immunologic component in the aetiology of LC.[6,8] Borrelia could not be identified directly by immunohistochemistry most of the time. In most reports of LC, bacteria are absent in tissue samples, and other diagnostic methods, such as PCR, could be used to identify bacterial DNA of the spirochaete and the specific strain, as performed in our case.[5] In fact, *B. afzelii* could be identified, a widely spread borrelia strain in Germany and Europe.[9] Whereas in less severe cases or earlier stages of infection, the pathology and localization of cardiac infiltrates are not obvious, in our case, a severe, acute lymphocytic myocarditis could be visualized by immunohistochemistry.

In general (in case series), it seems that the LV biopsy is somewhat more sensitive to recognized pathologies in the heart compared to the RV biopsy. In this case, the LV function was greatly reduced while the RV function was normal. In this context, the hypothesis can be set up or represented that the LV biopsy seems to be somewhat more meaningful with regard to the histological diagnosis. Larger case series showed that the diagnostic yield of LV biopsies is higher than RV tissue samples. The same finding was noted in a recent retrospective series of 136 patients in which the sensitivity of LV biopsies was three-fold higher than that of RV biopsies.[10]

Lyme carditis can have a favourable prognosis with appropriate antibiotic treatment, even when a severely reduced LVEF is the main finding, and apparent AV block is missing.

Generally, with appropriate antibiotic treatment, LC as a manifestation of LD has an overall good prognosis. In some cases, AV blocks persist, but these instances are extremely rare.[4] Nevertheless, deaths secondary to severe myocarditis have been reported.[11,12] To prevent such an outcome and unnecessary implantation of permanent pacemakers, a straightforward approach to the diagnosis and treatment appears to be required. Although LC may resolve spontaneously, antibiotic therapy shortens the disease duration, prevents further cardiovascular complications, and avoids sequelae.[1] For patients with suspected LC, empiric intravenous (IV) antibiotics should be

administered immediately pending the diagnostic evaluation for a definitive diagnosis of LD. Patients with confirmed LD should be treated with IV antibiotics (ceftriaxone is considered first-line therapy), followed by oral antibiotics (e.g. doxycycline) for 14–21 days.[1,13] Among patients with severe heart failure, earlier ceftriaxone treatment may be associated with complete recovery and/or improved LVEF.[14] The role of additional glucocorticoid therapy remains unclear. Glucocorticoids have been reported to be associated with substantial clinical improvement, cessation of life-threatening arrhythmias, marked decline in CRP, and restoration of near-normal LVEF.[14]

In conclusion, our rare case of LC demonstrates that a severely reduced LVEF secondary to severe myocarditis can be the first manifestation of LD even in the absence of typical cutaneous or systemic findings. Therefore, EMB (particularly of the LV) with subsequent immunohistological analysis and PCR for detecting cardiotropic agents, including borrelia strains, is a very important step in the diagnostic process, especially in immunosuppressed patients, as in the present case.

Lead author biography

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Supplementary material

Supplementary material is available at *European Heart Journal - Case Reports* online.

Slide sets: A fully edited slide set detailing this case and suitable for local presentation is available online as Supplementary data.

Consent: The authors confirm that consent for submission and publication of this case report has been obtained from the patient in accordance with COPE guidance.

Conflict of interest: None declared.

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