Diagnosis and Management of Myocarditis During Lyme Disease

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Abstract

Lyme disease is a common yet under-diagnosed condition that presents with cardiac manifestations in approximately 1 out of every 10 patients. Although rare, Lyme myocarditis is one of the most serious complications of Lyme disease and can be fatal if not diagnosed and treated promptly. The presence of a tick bite and/or erythema migrans is a "red flag" that should prompt immediate suspicion of Lyme disease. The diagnostic criteria for Lyme myocarditis are similar to other types of myocarditis, but the particular presence of high-grade or complete AV block should raise suspicion for Lyme disease as an etiology. Endomyocardial biopsies are not usually necessary in these scenarios. Early treatment with appropriate antibiotics can change the course of the disease and may even reverse complete AV block.

Keywords

Lyme disease • Lyme carditis • Lyme myocarditis • Atrioventricular block • Heart block

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1 Introduction

Lyme disease (LD) is an infectious condition caused by bacteria from the Borrelia genus, particularly *Borrelia burgdorferi* and *Borrelia afzelii*. This disease is the most common tick-borne multisystem infection in the Northern Hemisphere, primarily affecting the United States, Canada, and many European countries [1, 2].

Cardiac involvement is typically observed in more than 10% of LD cases. Lyme Carditis (LC) can have a broad spectrum of manifestations, ranging from mild or asymptomatic involvement to severe cases that can result in the death of affected individuals [3]. Therefore, it is essential to consider LD as a potential etiology when diagnosing myocarditis. This is especially important in the early stages, as LC can be cured with targeted antibiotics against Borrelia [3, 4]. The most frequent manifestation of LC is the development of a high-grade atrioventricular block (AVB); however, cases of Lyme myocarditis (LM), including the fulminant form, have also been reported. Hence, in endemic areas, it is crucial to keep this possibility in mind.

2 Clinical Presentation of Myocarditis in Lyme Disease

The term myocarditis implies inflammation of the myocardium, which has many different etiologies, including infectious, post-infectious, drug-induced and autoimmune diseases. Viruses are usually the leading cause of myocarditis worldwide, and the course of the disease tends to be favorable. Bacteria and spirochetes of the Borrelia genus can occasionally cause myocarditis, which are clinically indistinguishable from other etiologies of myocarditis upon presentation.

One of the most challenging aspects of managing patients with myocarditis is diagnosing the disease itself [5, 6]. Many experts have named myocarditis as one of the "chameleons" of cardiology, given its wide spectrum of clinical presentations. The clinical presentation suggestive of acute myocarditis can include:

- ***Chest pain***: Acute chest pain, with pericarditic or pseudo-ischaemic characteristics. Chest pain usually starts within 1–4 weeks after an infection, most commonly of respiratory or gastrointestinal origin. Symptoms tends to be recurrent.
- ***Heart failure***: New (days to 3 months) or worsening dyspnea at rest or with exercise, and/or fatigue, with or without signs of left and/or right heart failure. Less frequently it can be subacute/chronic (>3 months) worsening of this symptoms.
- ***Arrhythmias***: Including palpitations, unexplained arrhythmia symptoms, including dizziness, syncope, and/or aborted sudden cardiac death.
- ***Shock***: Unexplained cardiogenic shock, defined as hypotension and organ malperfusion.

Although it is very difficult to make a diagnosis of Borrelia infection based on clinical findings alone, some information from the history and physical examination are "red flags" that should rise the suspicious of the disease [7]:

- Outdoor activity in endemic areas, specifically during summer months.
- Constitutional symptoms: Fever, malaise, arthralgia, and dyspnea
- Tick bite
- Erythema migrans

The last two signs (tick bites and erythema migrans) are highly suggestive of Lyme disease. Each of these signs confers an intermediate risk for patients, so these findings should launch diagnostic investigations (Fig. 1). The Suspicious Index in Lyme Carditis (SILC) score can be used to evaluate the likelihood that a patient's disease is caused by LC [7]. Althought not specifically validated for LM, it an be useful to assess who should be evaluated in more detail. More information is covered in Chap. 7. However, it is important to note that some patients with confirmed LC may not recall a history of tick-bite, which could result in delayed diagnosis [8]. Therefore, it is crucial to maintain a high level of suspicion for LC, especially in patients presenting with unexplained cardiac symptoms in endemic areas.

The most common manifestation of myocarditis is an acute myocardial infarction-like syndrome or acute heart failure [9]. Less frequent presentations include the new onset of supraventricular/ventricular arrhythmias or sudden cardiac death. Lyme myocarditis can also have protean presentations, but its cardinal signs tends to be the presence of high-grade AV block, and even complete AV block [10]. Finally, although rare in the setting of LM, acute myocarditis can be asymptomatic but patients may develop chronic heart failure.

3 Diagnosis of Lyme Myocarditis

The complexity of LM patients cannot be under-stated as currently there is no clear gold standard for the diagnosis of the disease. The initial clues to suspect this diagnosis are an elevation of cardiac troponin (seen in up to 80% of patients with myocarditis), along with new electrocardiographic (ECG) or echocardiographic abnormalities (Table 1). Although these findings are highly sensitive, they show low specificity for the diagnosis of LM.

Traditionally, endomyocardial biopsy (EMB) was considered the "gold standard" for diagnosing myocarditis. However, the patchy involvement of the myocardium raises the possibility that the zone where the specimens are taken during an EMB is normal. Thus, a normal biopsy does not exclude the diagnosis of LM in the context of high suspicion. In recent years, cardiac magnetic resonance (CMR) has gained a prominent place in the diagnostic workup of this disease,

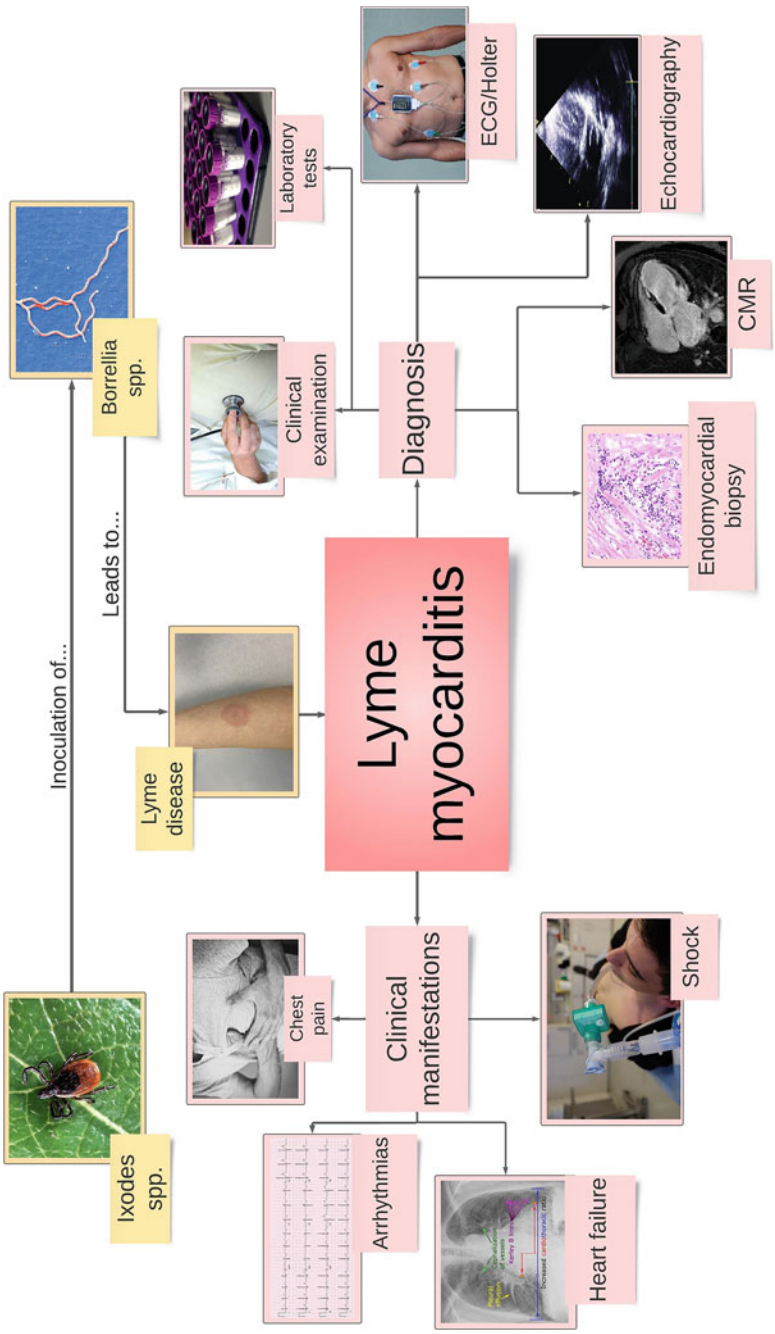

Fig. 1 Signs, symptoms and forms of presentation of myocarditis due to Lyme disease

Table 1 Diagnostic criteria of acute Lyme myocarditis*

Laboratory Testing for Myocarditis • Elevated troponins (myocardiocytolysis markers) is the more sensitive determination during the acute phase • Other useful tests that can be considered (depending on suspicion and availability): - Natriuritic peptides (BNP, NT-proBNP) - White blood cell count to exclude eosinophilia - C-reactive protein (CRP) and others acute phase reactants (e.g. erythrocyte sedimentation rate) - Skeletal muscle enzymes, liver and renal function, thyroid function tests and iron status - In punctual situations: PCR testing of common cardiotrophic viruses, circulating IgM or IgG antibodies for specific pathogens
Laboratory Testing for Lyme disease The standard workout is a 2-tiered approach€: 1. First step: IgM and IgG antibody screening test with the ELISA method (Enzyme-linked immunosorbent assay) *If the results are positive or borderline;* 2. Second step: confirmation with Western blot assay
ECG or Holter Monitor for Lyme carditis There may be numerous alterations, isolated or in combination including; ST deviation, T wave change (T wave inversion or flattening), new bundle branch block, ventricular tachycardia or fibrillation and asystole, 1st to 3rd degree atrioventricular block, sinus arrest, supraventricular tachycardia (including atrial fibrillation), reduced R wave height, intraventricular conduction delay (widened QRS complex), abnormal Q waves, low voltage, frequent premature beats. LC most commonly presents with significant bradycardia secondary to varying degrees of AV block. Progression to high-grade AV block can be very rapid, even occuring within a few hours LM can share many similar electrocardiographic manifestations as other types of myocarditis
Echocardiography Regional wall motion and/or global systolic or diastolic function abnormalities affecting left ventricle, right ventricle or both. The affected ventricles have varying degrees of dilatation, wall thickness and presence of endocavitary thrombi Individuals may also present with pericardial effusions
Other Cardiac Imaging - The most useful test is CMR which allows for tissue characterization, with or without contrast administration. Aside from the findings that can be detected by echocardiography, CMR can show**: • Edema • Hyperemia or capillary leak (early gadolinium enhancement) • Necrosis or scar (late gadolinium enhancement) - Coronary angiography, or in selected cases Cardiac CT, can be used to rule out significant coronary stenosis - Cardiac PET can be considered in patients who cannot undergo CMR or with specific aetiologist (e.g.: cardiac sarcoidosis)

(continued)

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Endomyocardial Biopsy (EMB) EMB is gold standard for the diagnosis of myocarditis, although it is usually reserved for life-threatening cases, when the etiological diagnosis cannot be determined using other tests At least three to five samples from the right or from the left ventricle should be taken to increase the diagnostic accuracy
Absence of Coronary artery disease (epicardial vessel coronary stenosis $\geq 50\%$), and other pre-existing cardiovascular disease or extra-cardiac causes that could explain the syndrome (e.g.: valve disease, congenital heart disease, hyperthyroidism, etc.)

CMR = Cardiac Magnetic Resonance; PET = positron emission tomography; CT = computed tomography; ECG = Electrocardiogram
* adapted from reference [5]
** adapted from reference [11]
€ To review the false positive and false positive results of the test, see Chap. 11

given its high sensitivity with a fair specificity [11, 12]. With the advent of the parametric maps (T1 mapping, T2 mapping, T2*, and extracellular volume), CMR has ascended to a place of privilege, as these tools allow for a more quantitative (not only qualitative) assessment. Additionally, CMR does not require the administration of gadolinium, which is a limitation in patients with renal failure [13]. Unfortunately, CMR cannot be considered the gold standard for the diagnosis of myocarditis, for different reasons [14]:

- Although there are abnormalities highly suggestive of myocarditis, they are not all found in all affected individuals and the timeline can be different for each patient. Moreover, the usefulness of CMR is greater during the first days of onset of the disease, but the diagnostic yield decreases after 15 days from the onset of the symptoms.
- It is an expensive study, and it has low accessibility in certain socio-demographic contexts (e.g., rural areas or in low- and middle-incomes countries).
- Some patients cannot be studied with CMR, especially those who are more critical illness (e.g., those with hemodynamic instability or cardiogenic shock, temporary pacemaker requirement, and those with non-MRI compatible prosthetic material).

- Performing CMR is difficult in some contexts, such as atrial fibrillation (especially with high ventricular rates), heart failure, or other comorbidities that limit the performance of apnea, and claustrophobia.
- Finally, CMR accuracy varies with the operator and the center's experience in evaluating suspected myocarditis.

With the aim of simplifying the diagnosis of myocarditis, the European Society of Cardiology published a Position Statement for the diagnosis and management of the disease [5]. For LM, the criteria for diagnosis using cardiac magnetic resonance imaging (CMR) are similar to those for other causes of myocarditis (Table 2). However, caution is required when performing CMR in patients with temporary pacemakers. Thus, when Lyme myocarditis is suspected, the diagnosis is usually based on electrocardiographic and echocardiographic findings, followed by confirmation using serological tests (Table 1). In severe cases requiring pacemaker, it may be prudent to delay CMR imaging for a few days or weeks while the patient receives antibiotic treatment, to reduce the risk of complications. Thus, it is important to realize that the diagnostic accuracy of CMR is greater within four weeks from the onset of symptoms.

As CMR has been increasingly used in the diagnosis of myocarditis, EMB has been relegated to specific cases [5, 6, 15]. While it is important to consider EMB in every patient with suspected acute myocarditis, its use is restricted to situations where:

- There is severe or progressive disease with no response to initial treatment;
- Life-threatening ventricular arrhythmias or high-grade AV block are present with no expected short-term improvement; or
- Specific etiologies are suspected that could benefit from targeted treatment.

Due to the high sensitivity and specificity of diagnostic tests for LD, alongside its excellent response to specific antibiotic treatment, the need for an EMB is exceptional in the course of the disease.

Table 2 The 2018 Lake Louise Criteria for Diagnosing Myocarditis by CMR

Main criteria	***Myocardial edema***: visualized with T2-mapping or T2
	Non-ischemic myocardial injury: detected with late gadolinium enhancement, abnormal T1 mapping or extracellular volume
Supportive criteria	***Pericarditis***: pericardial effusion or abnormal pericardial signal (late gadolinium enhancement, T2 or T1)
	Ventricular dysfunction: regional or global wall motion abnormality affecting the left and/or right ventricle
Lyme myocarditis	Diagnostic criteria are identical; however, in patients requiring ***temporary pacemakers***, it is generally recommended to ***defer the cardiac MRI*** until the patient is stable

In addition to specific investigations for LC, all patients should undergo transthoracic echocardiography to assess the degree of left ventricular dysfunction associated with the infection as well as for the presence of pericardial or valvular involvement. Patients with evidence of significant left ventricular dysfunction will require ongoing medical treatment as directed by heart failure guidelines. Patients may also require long-term follow-up with echocardiography to ensure resolution of left ventricular dysfunction at least three months after initiating therapy.

4 Management of Myocarditis During Lyme Disease

Most cases of myocarditis during LC tend to be mild. However, a small subset of these patients experience a fulminant form, even in childhood [16, 17]. In these scenarios, prompt and accurate treatment can change the evolution of the patients. The approach to patients with myocarditis in the context of LC is essentially the same as any other myocarditis, but with the addition of antibiotic treatment.

Most patients with myocarditis of any etiology with elevation of cardiac enzymes (troponins) require hospitalization for at least 48 h. Typically, myocarditis naturally resolves within 2–4 weeks in up to 50% of cases. About 12.5%-25% of patients may acutely deteriorate or progress to severe heart failure, with a high risk of death of needing heart transplantation. With proper antibiotic treatment, LM has a better prognosis than the general statistics of myocarditis patients. One of the most powerful predictors of worse outcomes in myocarditis is ventricular dysfunction at presentation, of one or both ventricles. The medical treatment can be classified according to the presentation of the patients:

- ***Antibiotics***: are the cornerstone in the management of all cases of LC, including myocarditis. For LM, a combination of intravenous and oral treatment is needed, and the length of the treatment varies according to the severity of the disease (Table 3).
- ***Arrhythmias***: LM has a higher risk of temporary pacemaker implantation compared to other causes of myocarditis. As the inflammation within the conduction system tends to be transient and resolve over days with appropriate treatment, and most of patients with LM are quite young, it is important to be cautious when implanting a permanent pacemaker. In some cases, a definitive pacemaker can be removed after close monitoring (see Chap. 13) [18].
- ***Hemodynamically stable patients*** require initial monitoring in hospital for at least a few days, because the risk of worsening or evolving to haemodynamic instability is higher at the onset of the disease. If ventricular dysfunction or heart failure is present, the patient should receive the standard of care for this condition: diuretics according to congestion state, angiotensin-converting enzyme inhibitor (ACE-I) or angiotensin receptor blockade (ARB), beta-adrenergic blockers (with special caution in the context of LC given the high risk of AVB) and mineralocorticoid-receptor antagonists (spironolactone or eplerenone). New treatments for heart failure, such as angiotensin receptor-neprilysin inhibitor

(Sacubitril/Valsartan) or Sodium-glucose co-transporter 2 (SGLT-2), are also recommended in the context of ventricular dysfunction. However, it is important to note that the use of these drugs are not supported by clinical trials in this scenario.

- ***Hemodynamically unstable patients*** should receive the same interventions that any patient would receive in this context, including intravenous vasopressors or inotropic agents, mechanical ventilation, or ventricular assist devices/extracorporeal membrane oxygenation (ECMO), as a bridge to recovery or heart transplant.
- ***Other recommendations***: to date, there is no evidence to use intravenous immunoglobulin or immunosuppressive therapy in Lyme myocarditis.

Based on general recommendations for myocarditis, physical activity should be restricted (in athletes and non athletes people) up to 6 months after the onset of symptoms (Fig. 2).

5 Long Term Follow up

There is a possibility that patients who have suffered from LC may develop dilated cardiomyopathy later on, especially if they are not adequately treated [19, 20]. Although the general consensus in the management of patients with myocarditis is to allow for periodic long-term follow-up after an episode of myocarditis [5, 6], its usefulness in patients with LC is uncertain [3]. In any case, this should be addressed on an individual patient basis by the treating team. Research in this area is ongoing (see Chaps. 14 and 15).

Table 3 Antibiotic treatment for Lyme myocarditis in Adults*

Antibiotic	Dose	Duration	
		Hospitalization	Mild presentation
Intravenous			
Ceftriaxone	2 g, once daily	10–14 days (or up to 28 days)	––
Oral			
Doxycycline	100 mg, twice a day	After intravenous treatment,	14–21 days
Amoxicillin	500 mg, three times a day		
Cefuroxime	500 mg, twice a day		

* adapted from reference [3]

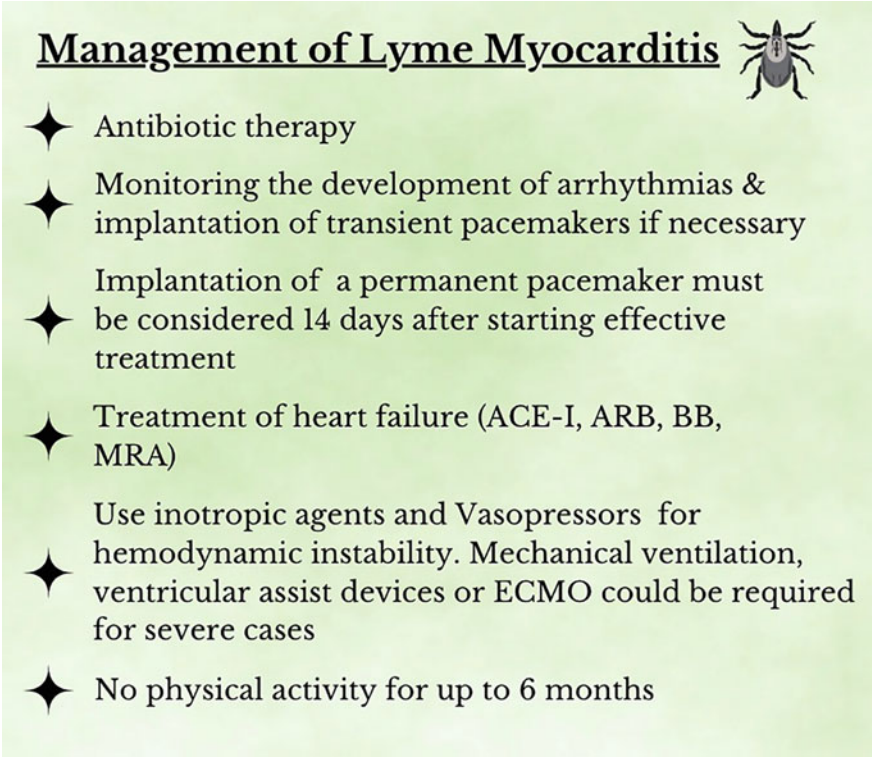

Fig. 2 Main messages in the management of Lyme myocarditis

6 Conclusions

Myocarditis due to LD is a rare but potentially life-threatening condition. A high index of suspicion is needed to diagnose this condition in a timely manner, particularly in endemic zones and amongst travelers who have visited endemic zones in recent weeks. The diagnostic workup for suspected LM should be similar to that of other scenarios of suspected myocarditis. Serological tests have a central role to confirm the disease. Proper and timely antibiotic treatment can change the natural history of LM.

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