Pathophysiology of Early Disseminated Lyme Carditis

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Abstract

Due to the presence of extra-cellular proteins, the myocardium possesses a very inviting environment for *B. burgdorferi* to adhere. This allows for a mechanism of direct invasion into the myocardial tissue, leading to cardiovascular manifestations such as myocarditis. An exaggerated inflammatory response can be seen through elevated levels of proinflammatory cytokines and deposition of the complement membrane attack complex (MAC) in patients with Lyme carditis. The maladaptive immune response to Borrelia infection is characterized by multifocal collections of T-cells, plasma cells, and macrophages. Infections often result in increased depositions of IgG and IgM in the heart. This chapter will outline the pathophysiology of early disseminated Lyme disease manifesting as Lyme carditis.

Keywords

Early disseminated Lyme carditis • Direct spirochete invasion • Proinflammatory cytokines • Inflammation • Autoimmune response

1 Introduction

Lyme disease is a bacterial infection caused by the spirochete Borrelia burgdorferi, transmitted through the bite of infected hard-bodied ticks in the genus Ixodes [1]. In the early disseminated phase of Lyme disease, the spirochete spreads into

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various organs [2]. When Borrelia invades cardiac myocytes, this causes Lyme carditis [3]. The most common presentation of LC is high degree atrioventricular block (AVB), with less common manifestations including myocarditis, pericarditis, and arrhythmias (see Chap. 6 for details) [3]. Although Lyme carditis is a rare event affecting approximately 10% of patients with Lyme disease, the incidence of Lyme disease is increasing each year [3]. Prompt recognition of this bacterial invasion into the heart is crucial, as rapid treatment of Lyme carditis can reverse high degree AVB and prevent the need for permanent pacemaker implantation [4].

2 Method of Transmission

The stages of Lyme disease are important to differentiate to clearly understand and classify the pathophysiology of each individual phase of the disease. Firstly, spirochetes are transmitted to humans through the saliva of the ticks at the site of the bite [5]. Infection risk increases if the tick remains on the skin for at least 48 h, as this allows the bacteria to travel from the gut of the tick to its salivary glands [6]. After this initial transmission of the pathogen to the human host, Lyme disease progresses into three distinct stages: early localized, early dissemination, and late dissemination [5]. The stages of Lyme disease are described in detail in Chap. 4. In brief, the early localized phase is characterized by the appearance of erythema migrants within 3–32 days of transmission [6]. After this phase, the spirochetes spread through the circulatory and lymphatic systems to several organs throughout the body. This causes dermatological, joint, neurological, and cardiac manifestations [7]. This phase is known as the early dissemination phase and occurs days to weeks after the tick bite. The last stage, the late dissemination phase, occurs after approximately 2–3 years after pathogen transmission [5].

This chapter will focus on the specific manifestation of early disseminated Lyme carditis and the associated pathophysiology.

3 Pathophysiological Mechanisms

The pathophysiological mechanisms implicated in Lyme carditis are complex and under active study. Overarching themes of involvement include direct invasion of myocardial tissue by *B. burgdorferi*, an exaggerated inflammatory response and a maladaptive immune response (Fig. 1).

4 Direct Invasion of Myocardial Tissue by *B. Burgdorferi*

The myocardium possesses a very inviting environment for *B. burgdorferi* due to the presence of several extra-cellular proteins [8–11]. Self-adhesion to these proteins while also evading the host immune response allows for direct invasion of the myocardial tissue [12]. A study by Stanek et al. was able to isolate *B.*

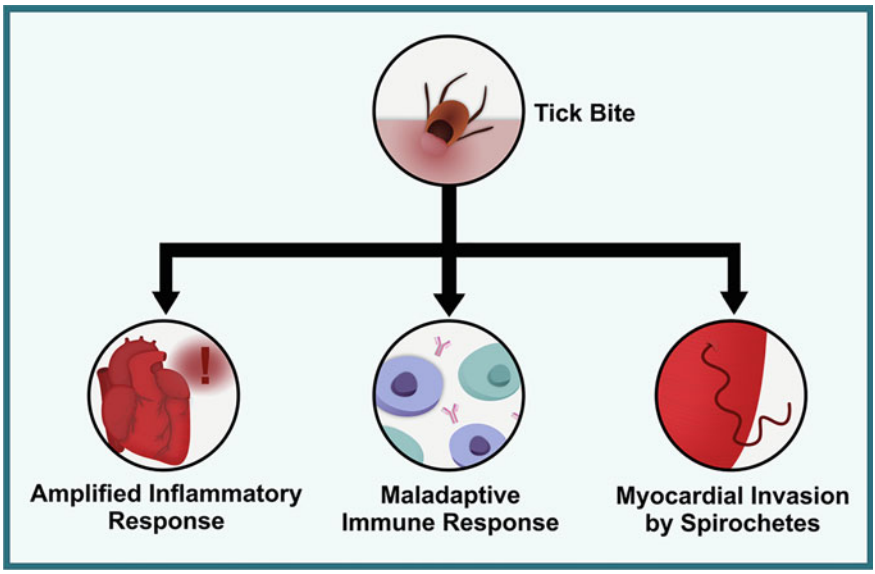

Fig. 1 Three main pathophysiological mechanisms of early disseminated Lyme Carditis include an amplified inflammatory response, maladaptive immune response and myocardial invasion by spirochetes

burgdorferi from a myocardial biopsy of a patient with Lyme carditis [13]. Histological analysis showed a characterization of enlarged, vesicular myonuclear, atrophic and hypertrophic myocardial fibers, and thickening and invasion of vessels in the endomysium by mononuclear cells.

Within the connective tissue, collagen fibers at the base of the heart, basal interventricular septum, perivascular regions, blood vessels and valves and outer and inner membranes exist [14–17]. The spirochete works to invade these structures and cause damage. Although still being investigated, research has shown that *B. burgdorferi* may also be isolated within the extracellular matrix but it does not produce any endotoxins and exotoxins [18, 19].

In early disseminated Lyme disease, myocyte necrosis is of particular concern as the endomyocardial tissue is typically impacted [20]. Moreover, between muscle fibres in the endocardium, inflammatory infiltrates are also present [20]. Amongst patients with longstanding cardiomyopathy induced by early disseminated Lyme carditis, endomyocardial biopsies have shown growth of *B. burgdorferi.* [21] Hypertrophic myocardial fibers and thickening of the walls of small endomysia vessels have also been noted [21].

Myocarditis caused by invasion of the myocardium can be a clinical manifestation alone or also in conjunction with the pericardium [22, 23]. The pathophysiology of Lyme myocarditis reveals itself to be an extensive infiltration of lymphocytes and spirochetes [8, 24]. Cross reactive antibodies react with proteins in the body, causing autoimmune injury [25]. The immunological component

of Lyme carditis shows that initial exposure to bacteria causes an inflammatory response that leads to tissue damage.

5 Proteins Involved in Spirochete Invasion

B. burgdorferi spirochetes adhere to the extracellular matrix during the early disseminated phase of the Lyme disease infection [18]. Decorin, a small cellular or pericellular matrix glycoprotein, plays a key role in this adherence process [26]. Decorin binding is perpetuated by *B. burgdorferi* decorin binding proteins [27–29]. Specifically, decorin binding protein A, a 20-kDa surface protein, allows for the process to occur. For the spirochete to infect the tissues of the heart, decorin binding is essential. Decorin binding protein A allows for cardiac localization. This has been proven using mice models. In mice where decorin proteins have been knocked out, cardiac infection has been completely diminished. Moreover, spirochete colocalize with decorin in the myocardium of these mice models as observed through autopsy tissues. Case series have shown marked cardiac tropism, as compared to other organs such as the brain, liver, kidney, and prostate [30]. This glycoprotein has varied, and differential glycosaminoglycan chains attached to the protein core. Theories suggest that cardiac specific modifications of glycosaminoglycan chains alter and propagate *B. burgdorferi* spirochete adhesion in the myocardium [31, 32].

6 Exaggerated Inflammatory Response

The persistence of Borrelia or bacterial antigen in cardiac tissue causes chronic inflammation, leading to myocarditis, pericarditis, endocarditis and pancarditis [22, 33–37]. The presence of *B. burgdorferi* in the myocardium in the early disseminated phases of the disease subsequently causes processes that lead to an exaggerated inflammatory response.

Numerous studies have shown that *B. burgdorferi* can cause the release of proinflammatory cytokines, such as interleukin-1α (IL-1α), IL-1β, IL-6, IL-8, IL-12, tumor necrosis factor alpha (TNF-α), gamma interferon (IFN-γ), IL-17, granulocyte–macrophage colony-stimulating factor (GM-CSF) and IL-18 [38]. These cytokines contribute to the inflammatory response seen in Lyme carditis, which causes tissue inflammation and damage [39]. Although inflammation is important in response to tissue injury and is required for tissue repair from the invasion of spirochetes, uncontrolled inflammation results in even more tissue damage [38].

Another point of interest is BLC (also called BCA-1 or CXCL13) [39]. BLC is a chemokine that is especially selective for B-cells. BLC is characterized as a homing chemokine and has been implicated in the trafficking of lymphocytes and dendritic cells in lymphoid organs [39, 40]. Studies have found that one of the consequences of *B. burgdorferi* infection of the heart is the upregulation of BLC [16, 41–43]. This leads to infiltration of plasma cells and causes uncontrolled

production and deposition of large amounts of IgM. This further exacerbates the immune response.

Another study also found deposition of the membrane attack complex (MAC) in the heart of Chagas cardiomyopathy patients [44, 45]. MACs have not only been found on spirochetes but also on the membranes of cardiac myocytes. Studies propose that MAC deposition may also add to an exaggerated immune response in early disseminated Lyme disease [16].

7 Maladaptive Immune Response

Evidenced by the above paragraphs, the pathophysiology of Lyme carditis involves direct myocardial invasion by the bacteria and inflammatory responses. Subsequent maladaptive immune processes follow, leading to further tissue damage [30].

As established, carditis is a main manifestation of early disseminated Lyme disease. More cardiac T-cells as compared to B-cells is a characterizing feature of host response during the early disseminated stage of the disease [30]. The dermal infiltrate is typically T-cells, especially found in early erythema migrants [46, 47]. B-cell infiltrates with germinal centers and evidence of pseudo clonality are also present in early disseminated Lyme disease. In European patients, it has been noted that high densities of B-cell infiltration are so alarming that the infection often mimics B-cell lymphoma [16, 48].

In mouse models during early infection states, myocardial infiltrates are made up of T-cells and very few B-cells [49]. In a nonhuman primate model of Lyme carditis, cardiac plasma cells, tissue IgG, and IgM deposition, and increased levels of the B-cell chemoattractant chemokine CXCL13 were observed in one study. In a case series, patient who were positive for Lyme IgG serology also had the greatest ratio of cardiac B0cells to T-cells [16].

Moreover, researchers have isolated dendritic cells from healthy patients and exposed them to Borrelia burgdorferi [50]. Results have shown that the bacterial infection causes receptor sites on the surface of dendritic cells, known as HLA-DRs, to mature and become active. In a typical situation, HLA-DRs cells presents antigens to killer T-cells which remove bacterial infections from the body. However, when HLA-DRs interact with Borrelia burgdorferi, they are structurally modified and prevent the dendritic cells from "marking" the bacterial proteins as foreign. This causes dendritic cells to attract T-cells, but they then attack healthy cells instead of infected cells.

Overall, there is a significant role of B- and T-cell proliferation in the early disseminated phase of Lyme carditis. The presence of cardiac T-cells is a defining characteristic of a patient with Borrelia, leading to further tissue damage. There is typically a high density of B-cell infiltration and an increased level of chemoattractant chemokines, causing a maladaptive immune response for the host.

8 Conclusions

The main pathophysiologic mechanisms of Lyme carditis can be broken down into three main points (Fig. 1). Direct spirochetal invasion of cardiac myocytes leads to myocarditis [3]. An exaggerated inflammatory response can be seen through elevated levels of proinflammatory cytokines and deposition of the complement membrane attack complex (MAC) in patients with Lyme carditis [38, 44, 45]. Finally, the maladaptive immune response to Borrelia infection is characterized by multifocal collections of T-cells, plasma cells, and macrophages [30, 49]. Infections often result in increased depositions of IgG and IgM in the heart. Overall, further elucidation needs to be conducted to determine the etiology of relapsing and persisting symptoms [51]. More research should be done to fully appreciate the presence of *B. burgdorferi* in the extracellular matrix, and the subsequent potential production of endotoxins and exotoxins [18, 19].

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