

RICKETTSIAL, EHRLICHIAL AND BARTONELLA INFECTIONS OF THE MYOCARDIUM AND PERICARDIUM

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1. ABSTRACT

Myocarditis and pericarditis are uncommon complications of human Rickettsial, Ehrlichial and Bartonella infections. Myocardial inflammation usually occurs in the setting of acute disseminated infection. Organisms associated with myocarditis include: *Rickettsia rickettsii*, *R. conorii*, *Orientia tsutsugamushi*, *Coxiella burnetii*, *Anaplasma phagocytophila* (the causative agent of Human Granulocytic Ehrlichiosis) and *Bartonella henselae*. Pericarditis has been described in the setting of *R. conorii* and *Coxiella burnetii* infections. This article reviews the epidemiology, pathologic characteristics, clinical manifestations, diagnosis and treatment of myocarditis and pericarditis caused by these organisms.

2. INTRODUCTION

The *Rickettsiaceae* are generally obligate intracellular, small gram-negative pathogens. They belong to the class *Proteobacteria*. Recent advances in the use of 16S rRNA sequence analysis have led to changes in taxonomy for several of the organisms previously classified with the *Rickettsiae*. The *Rickettsiae* and *Ehrlichiae* are now classified in the alpha-1 subgroup of *Proteobacteria*, *Bartonella* are in the alpha-2 subgroup, and *Coxiella burnetii* is in the gamma subdivision. The genus *Rickettsia* is divided into the Typhus group (Epidemic and Relapsing typhus [*R. prowazekii*], and Murine typhus [*R. typhi*]); the Spotted Fever group (Rocky Mountain Spotted Fever [*R. rickettsia*], Mediterranean Spotted Fever [*R. conorii*], and Rickettsial pox [*R. akari*]); and the Scrub Typhus group (Scrub typhus [*Orientia tsutsugamushi*]). Rickettsiae are transmitted via arthropod vectors including mites, ticks, flies, fleas and lice. In most rickettsial infections humans are incidental hosts, except for Epidemic (*R. prowazekii*) typhus. Rickettsial organisms are widely distributed

around the world (Table 1). The severity of disease following rickettsial infection may vary but is usually associated with mild to significant incapacitation, and may be fatal. The typical clinical syndrome consists of fever, intense headache, myalgias, often associated with rash (Spotted Fever and Typhus groups) and sometimes with eschar (e.g. *R. akari*, *R. conorii* and *O. tsutsugamushi*). The patient may or may not recall an insect or tick bite. Since the symptoms are often non-specific, the diagnosis may be delayed or missed (1). Symptomatic involvement of the heart in rickettsial infection is uncommon. Myocarditis associated with Rocky Mountain Spotted Fever (RMSF), Scrub typhus, Mediterranean Spotted Fever, Q Fever, Ehrlichia, and Bartonella infections have been described, and pericarditis with MSP and Q fever have been reported. Cardiac involvement may occur more often than is recognized due to wide variability in severity and relative lack of specificity of the clinical presentation.

The diagnosis of acute rickettsial infection is based on clinical presentation. Serologic testing (acute and convalescent) is useful for retrospective confirmation. However, routine serology does not allow distinction of the specific causative organism within the Spotted Fever group (2). Culture techniques are not readily available. Rickettsial antigens may be detected in skin biopsies by immunohistochemical staining, however they are not usually found in tissue after 5-7 days of appropriate antibiotic therapy (1). Diagnostic methods using the polymerase chain reaction (PCR) are under investigation but are not widely available.

Myocarditis may occur during acute rickettsial infection due to disseminated endothelial infection of the small vessels or by secondary immune mediated

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Table 1. Rickettsioses and Bartonella Associated with Myocarditis and Pericarditis

| Organism | Disease | Transmission | Geographic Location |
|---------------------------------|---|-----------------------|---|
| <i>Rickettsia rickettsii</i> | Rocky Mountain Spotted Fever | Tick | United States, Central and South America |
| <i>Orientia tsutsugamushi</i> | Scrub Typhus | Chigger | China, Japan, SE Asia, N Australia, Indian sub-continent |
| <i>Rickettsia conorii</i> | Mediterranean Spotted Fever | Tick | Africa, Indian sub-continent, Mediterranean, Eastern Europe |
| <i>Anaplasma phagocytophila</i> | Human Granulocytic Ehrlichiosis | Tick | United States, Europe |
| <i>Coxiella burnetii</i> | Q Fever | Inhalation, Ingestion | Worldwide |
| <i>Bartonella henselae</i> | Cat Scratch Disease Bacillary angiomatosis Peliosis hepatis | Cat scratch | Worldwide |

mononuclear inflammatory reaction. The clinical findings of myocarditis are nonspecific and indistinguishable from other etiologies and may include: fever, shortness of breath, and orthopnea (3). Physical examination may reveal jugular venous distension, rales, a ventricular gallop, or systolic murmur in the apex (3,4). Electrocardiogram (ECG) is often abnormal: sinus tachycardia, varying atrioventricular and bundle branch block, atrial fibrillation and non-specific T wave abnormalities are most common. Some cases may be identified solely by the finding of an abnormal ECG without associated clinical symptoms. Enlargement of the cardiac silhouette and vascular congestion may be seen on chest radiograph, although pulmonary vasculitis may account for some of the radiologic findings observed in the lung fields (5). Creatinine phosphokinase and lactic dehydrogenase levels may be elevated with myocardial involvement (6,7). Similarly the symptoms and clinical presentation of rickettsial pericarditis are non-specific and include chest pain, dyspnea, fatigue and the presence of a friction rub on heart auscultation. Echocardiography may demonstrate a pericardial effusion and T wave abnormalities may be observed on ECG (8).

Doxycycline is the drug of choice. There is some evidence that its therapeutic effect may not only be limited to its antimicrobial effect but also by the drug's anti-inflammatory properties and possible down regulation of proinflammatory cytokines.

3. SCRUB TYPHUS

Orientia tsutsugamushi is the causative agent of scrub typhus. Scrub typhus is characterized by a febrile illness, headache, maculopapular rash and multi-organ involvement most often pneumonia, meningoencephalitis and myocarditis. Like RMSF, patients can develop DIC as a severe manifestation. Scrub typhus has a wide distribution in the Asian-Pacific region and humans are infected following a chigger (or larval trombiculid mite) bite that can cause an eschar to form.

The incidence of myocarditis associated with scrub typhus is unknown. During World War II, Levine performed meticulous post-mortem examinations in 31 U.S. soldiers who succumbed to scrub typhus and described varying degrees of myocardial inflammation in 25 (81%)

cases (9). The contribution of myocardial disease to the cause of death in these patients was not established as multiple other organs, especially the lungs, were involved. Even though myocarditis due to infection with *O. tsutsugamushi* may occur frequently, it is usually transient with no residual cardiac dysfunction and, therefore, may not be recognized. Furthermore, permanent cardiac damage is not likely based on descriptions of clinical outcomes supported by some histologic observations (3,4). Rare deaths associated with cardiac arrhythmias and congestive heart failure have been described (4). Delayed onset of symptoms of myocarditis for several weeks following acute scrub typhus has been reported (3). This presentation may occur after incomplete treatment or if residual organisms persist in endothelial tissues in the heart (3).

O. tsutsugamushi infects endothelial cells and can lead to apoptosis and both focal and disseminated vasculitis and perivasculitis involving small blood vessels. In scrub typhus myocarditis, nonspecific damage to myocytes, with minimal necrosis, can occur as a result of vascular endothelial damage and an inflammatory response consisting of infiltrating lymphocytes, monocytes, plasma cells associated with hemorrhage and edema induced by adjacent infection (10). Lack of coronary artery involvement has been demonstrated by histopathology and coronary angiography (3,9). Similarly, native heart valves are spared. Focal petechial hemorrhages observed in many organs have been noted in the subendocardium and subepicardium (4,9). The lack of significant myofibril necrosis may explain the absence of chronic cardiac sequelae (4).

Standardized treatment recommendations for scrub typhus myocarditis have not been established, however doxycycline or tetracycline has replaced chloramphenicol as the treatment of choice for *O. tsutsugamushi* infection. Treatment for 14 days may be necessary to prevent relapse.

4. ROCKY MOUNTAIN SPOTTED FEVER

Myocardial tissue is often involved by infection with *R. rickettsiae* as part of widespread vasculitis involving the venules, capillaries, and arterioles, especially in fatal cases (6,11,12). RMSF is associated with high case

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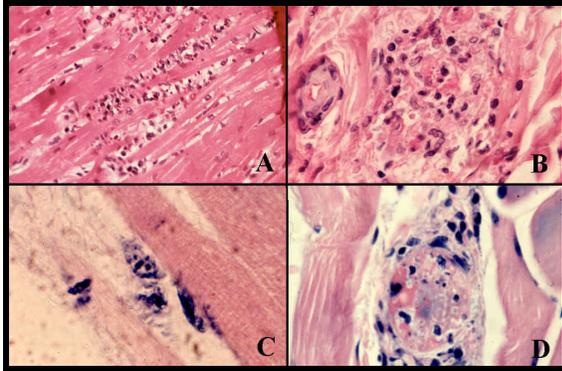


Figure 1. The following figures are taken from a case of fatal Rocky Mountain Spotted fever. **A.** Myocardial sections showing interstitial infiltrates. **B.** Myocardial section showing vasculitis. **C.** Giemsa stain showing intracellular organisms. **D.** Skeletal muscle section showing vasculitis.

fatality rates (4 – 8%) that may reflect a delay in diagnosis (13). As with scrub typhus, inflammation in the myocardium consists of lymphocytic infiltration (Figure 1).

In an effort to determine the contribution of cardiac involvement to the morbidity of RMSF, Walker, et al (11) conducted a blinded review of the microscopic slides and specimens obtained from paraffin blocks from nine cases of fatal RMSF compared to nine age, sex and heart weight matched controls who died of other causes. All nine cases of fatal RMSF demonstrated lymphocytic infiltrates, of varying severity and distribution, between the myofibrils that was greater than seen in controls. Although the heart weights were increased suggesting the presence of edema, there was no gross evidence of ventricular failure or dilatation and death was attributed to central nervous system involvement in most cases. Immunofluorescent staining of cardiac tissue for *R. rickettsia* was positive in 8 of 9 cases; the one negative case had been treated with chloramphenicol for five days. Organisms were located between myocardial fibers, consistent with infection of the endothelium of small blood vessels. No rickettsial organisms were seen inside the myocardial fibers. Little or no necrosis of myocardial fibers is generally seen. These findings suggest that while the heart is involved as part of disseminated *R. rickettsia* infection its contribution to mortality may not be significant. Cardiac conduction abnormalities including atrioventricular and bundle branch blocks have been described in cases of RMSF; however, their impact on morbidity and mortality remains unclear.

Myocarditis in RMSF may go unrecognized. Paddock, et al studied nine patients who died of suspected RMSF with negative or absent serology in whom diagnosis was established postmortem by use of immunohistochemical staining of tissue (1). Four of eight patients with myocardial tissues available had evidence of localized myocarditis. RMSF is usually diagnosed by finding an immunofluorescence antibody titer to rickettsial antigens of $\geq 1:64$, which is generally not achieved until the second week of illness (1). Therefore, a high index of

suspicion is needed for early identification of cases on clinical grounds.

Although neurologic sequelae following RMSF are not uncommon, residual cardiac dysfunction is rarely seen. Echocardiogram during acute infection may demonstrate left ventricular enlargement and dysfunction relative to the disease severity. These abnormalities, described early in the disease course, often before any clinical symptoms of myocarditis are manifested, generally resolve during convalescence (14,15).

Treatment of RMSF is generally with tetracycline, doxycycline or chloramphenicol for 7 days, intravenously if the patient is intolerant of oral therapy. Some of the newer quinolones and rifampicin have *in vitro* activity but lack sufficient clinical efficacy data to be recommended at this time (16).

5. MEDITERRANEAN SPOTTED FEVER

Rickettsia conorii, the etiologic agent of Mediterranean Spotted Fever, has been implicated as a cause of myocarditis and pericarditis. Mediterranean Spotted Fever is generally a mild disease consisting of fever, maculopapular rash and eschar at the site of the tick bite. More fulminant cases have been described in patients with chronic disease states such as hepatic insufficiency, congestive heart failure and diabetes mellitus. Nine cases of pericarditis have been described in the literature (17-19). Signs of pericarditis may develop two or more weeks into the illness and generally respond well to antibiotic therapy (the drug of choice is doxycycline). Pericardial involvement, as with myocarditis, is thought to arise from widespread infection of endothelial cells of venules and capillaries leading to rickettsial-induced vasculitis. The treatment of choice for Mediterranean Spotted Fever is tetracycline or doxycycline for 7 to 10 days, chloramphenicol and ciprofloxacin have also been used successfully (16).

6. EHRLICHIOSIS

The ehrlichial agent associated with Human Granulocytic Ehrlichiosis, *Anaplasma phagocytophila*, was implicated in a case of fatal myocarditis (20). The pathogenetic mechanism is incompletely understood. Immunohistochemical staining demonstrated the HGE agent in the cytoplasm of inflammatory cells in autopsy specimens of perivascular myocardial tissue. However, it is uncertain whether HGE directly induces myocardial damage or if it induces transient immunosuppression and concomitant inflammatory cell dysfunction that causes nonspecific damage to myocytes. Tetracycline or doxycycline is recommended to treat HGE.

7. Q FEVER

Coxiella burnetti, another obligate intracellular pathogen, causes acute or chronic Q fever. The organism proliferates in the phagolysosome of the host cell. Humans usually acquire the disease following inhalation of

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organisms aerosolized from infected animals or infected tissue, such as placenta (21). Cardiac disease usually manifests as endocarditis. Fournier et. al (22) described 8 cases of acute Q fever-induced myocarditis culled from a review of 1276 patients with the acute form of *C. burnetti* infection. Myocarditis (or perimyocarditis) complicating Q fever can occur at any age and compared to other cases of acute Q fever have a more severe form of disease. In the French series of 1276 cases, twelve patients died of which two resulted from cardiac complications of myocarditis. Acute Q fever myocarditis is usually diagnosed in the appropriate clinical setting and/or by abnormal ECG (particularly T-wave changes) and by positive serologic tests for phase II *C. burnetti* antibodies (a single titer of IgM \geq 1:50 and/or IgG \geq 1:200, or by a series of titers that become increasingly positive) (23). Doxycycline, usually for 3 weeks, is the treatment of choice; in addition, patients may require therapy to mitigate the clinical complications of myocarditis. Cross-reacting antibodies may be responsible for autoimmune-mediated damage of the myocardium following *C. burnetti* infection (24). Direct damage to myocardial cells has also been implicated as *C. burnetti* has been cultured from tissue obtained from an endomyocardial biopsy (22). However, the exact mechanism of Q fever associated myocarditis is not completely understood. Animal models suggest that high inoculum of *C. burnetti* are more likely to cause myocarditis.

C. burnetti pericarditis (with or without myocarditis) has also been described (8). Although most cases of Q fever pericarditis occur, similar to myocarditis, in the acute form of the disease, it has been described in the chronic form with elevated phase I antibodies. Levy et. al (8) reported 15 cases of Q fever pericarditis and described 3 patients who presented in cardiac tamponade with large pericardial effusions and one patient who had recurrent pericarditis in the setting of chronic infection. Cases of chronic infection may require a more prolonged course of combination antimicrobial therapy that would include doxycycline as one of the agents.

8. BARTONELLA INFECTIONS

Infection with *Bartonella henselae*, the etiologic agent of cat scratch disease, bacillary angiomatosis and peliosis hepatis, has been implicated in a case of chronic lymphocytic myocarditis. Meininger et al (25) described the case of a 32-year-old male who presented with a clinical picture consistent with cat scratch disease manifested by the acute onset of fever, malaise and unilateral tender inguinal lymphadenopathy shortly after having obtained a kitten. After several days he developed symptoms consistent with congestive heart failure, including dyspnea on exertion, orthopnea and fatigue. Echocardiography revealed bilateral ventricular enlargement and reduced ejection fraction establishing the diagnosis of cardiomyopathy. Myocardial biopsy with immunohistochemical staining revealed a T-lymphocyte predominant inflammatory reaction with necrosis and fibrosis in the myocardium. A lymph node biopsy demonstrated granulomatous inflammation, which was

positive by PCR for *B. henselae* DNA. The myocardial tissue was negative by immunologic staining for *B. henselae* antigens. The patient continued to have symptoms of severe congestive heart failure including syncope despite antibiotic treatment, ciprofloxacin for 2 weeks, and immunosuppressive therapy and eventually underwent a heart transplant. Pathologic examination of the heart demonstrated persistent myocardial inflammation. The authors speculate that the etiology of myocarditis in this case was not due to direct infection by *B. henselae* of the myocardium or secondary to perivasculitis, but was instead immunologically mediated by cross reaction of the inflammatory response generated against the organism toward myocardial tissues.

Several antimicrobials have activity *in vitro* against *B. henselae*, however, the drugs of choice for treatment are erythromycin and doxycycline. The optimal treatment, including duration and need for initial parenteral therapy, of *B. henselae* associated myocarditis has not been established. However, based on recommendations for bacteremia and endocarditis, initial parenteral therapy and a minimum of 4 weeks of treatment would be appropriate for myocarditis (26). It is important to monitor heart function after completion of antimicrobial therapy in view of the possibility for continued cardiac inflammation and subsequent fibrosis.

9. CONCLUSIONS

The organisms described here are important emerging human infections that do not commonly cause diseases of the myocardium. Nevertheless, it is important to recognize the cardiovascular complications of these infections because early institution of therapy may be life saving.

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