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Fatal myocarditis due to *Clostridium novyi* type B in a previously healthy woman: Case report and literature review

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Abstract

Clostridium novyi is a Gram-positive anaerobe, which is commonly a pathogen of domestic and wild animals. Disease in humans typically presents as myonecrosis. *C. novyi* has not previously been reported as a cause of myocarditis. We report a fatal case with infection of the myocardium by *C. novyi* type B.

Introduction

Species in the genus *Clostridium* are anaerobic, spore-forming Gram-positive rods (excepting *C. piliforme*, which is Gram-negative). Some are ubiquitous in the environment and many are commonly encountered as flora of the human gastrointestinal tract, female genital tract and urethra. Spore survival in the environment has been documented to more than 100 y, but is likely much longer (J.G. Songer, unpublished data).

Clostridium novyi is a common pathogen of domestic animals and also causes disease in humans. The species is divided into 4 types on the basis of toxin production [1]. These potent exotoxins usually mediate clostridial pathogenesis. The α -toxin is produced by types A and B, and β -toxin by types B and D. The lethal α -toxin has cardiotoxic effects [2]. β -toxin is a phospholipase/sphingomyelinase which is similar to the α -toxin of *C. perfringens* [3].

The most common human pathogen is type A, which is an important cause of gas gangrene [1]. It was also responsible for the widespread outbreak of severe inflammatory illness in heroin users in the

United Kingdom and Ireland in early 2000 [2]. Type B is an occasional cause of gas gangrene [1]. Type D (also called *C. haemolyticum*) infection of humans has not been reported; type C is non-toxicogenic, and, therefore, avirulent.

We report here an apparently unique case of clostridial myocarditis. The case featured acute onset in a patient without apparent risk factors for clostridial infection. The strain was *C. novyi* type B, which has not previously been reported as a cause of myocarditis. Type A cases have been associated with a myeloid/granulocytic reaction in the myocardium [2], but this is the first case in which *C. novyi* has been demonstrated in the heart.

Case report

A 23-y-old female presented to our emergency department with a 2-d history of chest pain and dyspnea. She complained of chills without fever and a 1-week history of upper respiratory infection symptoms. Before illness onset, she suffered a trivial wound to her hand.

The patient reported a diagnosis of systemic lupus erythematosus. The diagnosis was based on a positive antinuclear antibody titer 5 y earlier, for which she had never been prescribed any medication. Otherwise, her medical and surgical history was not significant. She reported occasional tobacco use, but denied any alcohol or illicit drug use.

The patient was well nourished but ill-appearing. Her triage vital signs were: temperature 38.3°C, heart rate 71 beats/min, respiratory rate 20 breaths/min, and blood pressure 92/49 mm Hg. Otherwise, her physical examination was unremarkable.

Her white blood cell count was 7900/ μ l with 68% neutrophils and 13% band neutrophils. The patient had essentially normal electrolytes, except for a bicarbonate of 15 mmol/l. Her creatinine kinase level was 1698 U/l with a MB fraction of 92.7 μ g/l and a relative index of 5.5%. Troponin T was 2.71 μ g/l. C-reactive protein level was 4 mg/l and erythrocyte sedimentation rate was 80 mm/h. Urine screen for illicit drugs was negative. Electrocardiography demonstrated ventricular bigeminy with a ventricular rate of 134 beats/min, a right bundle branch block, and diffuse ST segment depression. Chest radiography revealed no acute disease.

A bedside echocardiogram showed global left ventricular hypokinesis with an ejection fraction of 20%. Emergent cardiac catheterization was performed, which revealed normal coronary arteries, diffusely diminished left ventricular contractility, and a dyskinetic high lateral ventricular wall. A Swan-Ganz catheter and intra-aortic balloon pump were inserted. Despite appropriate intensive care management, the patient experienced cardiac arrest, and died 15 h after emergency department presentation.

As per her family's wishes, a post mortem examination limited to her heart was performed. Sections were fixed in buffered formalin, embedded in paraffin, and sectioned. Hematoxylin-and-eosin and Gram-stained sections, examined microscopically, revealed Gram-positive bacilli, predominantly lymphocytic inflammatory infiltrates, and widespread areas of myocardial necrosis (Figure 1). Evidence of gas formation or abscess was not seen. Epicardium and valves were normal. No fresh tissue was obtained for bacteriologic culture. However, polymerase chain reaction (PCR) amplification of the 16s rDNA followed by DNA sequencing revealed that the infectious organism was *C. novyi* (BT Cookson, University of Washington, Seattle, WA).

Species-specific primers were prepared and used in PCR reactions to provide further taxonomic information. Template was extracted from paraffin-embedded tissue. Primers targeting the *C. novyi* type B flagellin gene yielded an appropriate sized product

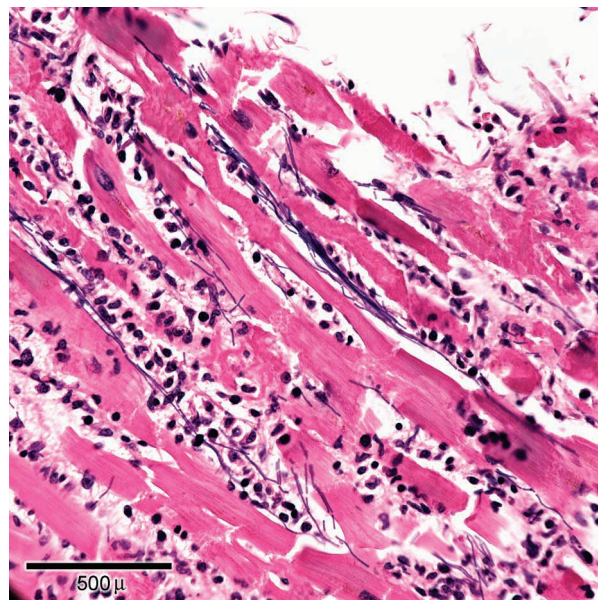


Figure 1. Hematoxylin-and-eosin stained sections demonstrate chaining rod-shaped bacteria with myocyte necrosis and lymphocytic infiltrate (40 \times magnification).

and no amplification was seen with primers for *C. novyi* types A or D, *C. chauvoei*, or *C. septicum* (primer sequences and detailed protocol available from the authors).

Discussion

In addition to our patient, there are 16 cases of clostridial myocardial infections reported in the English medical literature covering the 1950s to December 2005 [4–11]. Clostridial pericarditis and endocarditis were not considered. The mean age was 49 y (range 15–70 y), and 65% of the cases were male. Almost all of the myocardial infections could be classified as myonecrosis (lacking significant inflammatory response) or myocardial abscess (typically associated with a robust inflammatory reaction). The histology in our case and in 1 other [10] demonstrated myocarditis, which is defined clinically as inflammation of the myocardium. Interestingly, the inflammatory reaction in our patient was predominantly lymphocytic, whereas in all other cases the response was almost exclusively neutrophilic. Evidence of gas formation was variably seen. Gas was not evident in our patient's myocardium, which is not atypical for *C. novyi* infections [12].

Clostridial species previously associated with myocardial infections in humans are *C. perfringens*, *C. septicum*, and *C. fallax* [4–11]. It has been suggested that *C. tetani* may cause a 'toxic myocarditis' but this organism has not been demonstrated in the myocardium [13]. *C. perfringens* is the most commonly reported cause of clostridial myocardial

infections (11/17 reported cases), while *C. septicum*, *C. fallax*, and now *C. novyi* type B, have been described in 1 patient each. In 12 patients, the source of the infection was likely endogenous, while 3 other patients had clostridial wound infections or frank gas gangrene. In this case and 1 other [5], the source was not established.

Diagnostic findings support our contention that our patient had a true cardiac *C. novyi* infection. Overgrowth of clostridia can occur after death, but the autopsy was carried out less than 24 h post mortem. Moreover, autopsy findings are consistent with her clinical course. Myocyte necrosis and the diffuse inflammatory response observed in cardiac tissue are consistent with such an infection.

The source of the infecting organism is unclear. Given lack of signs in other parts of the body, it seems unlikely that the heart was seeded with vegetative cells from another active focus of infection. Clinically significant bacteremia is usually from an underlying bowel source but there is no historical or physical evidence suggesting an intra-abdominal source in our patient [14]. Even though illicit drug use may allow entry by clostridia, our patient denied its use, had none of the typical stigmata observed in injection drug abusers, and her toxicologic screen was negative. The portal of entry may have been her hand wound, although cellulitis and abscess were absent at her emergency department presentation. Entry of spores via minor wounds, resulting in deposition in normal tissue, may be followed by lengthy latent periods [3]. Local cardiac muscle ischemia may have been induced by some unknown factor, allowing germination of dormant spores and subsequent myocarditis. A complete postmortem examination might have provided more clear information.

Immunosuppression and myocardial infarction may predispose to clostridial myocardial infections. 13 of 17 patients with such infections were on chemotherapy and/or steroids or had poorly-controlled diabetes mellitus [7–11]. Germination of latent spores is usually associated with an event that causes ischemia in surrounding tissue, such as an old or acute myocardial infarct. Korns [4] described an unusual case of a patient where frank suppuration with *C. perfringens* occurred within an acute myocardial infarct in the left posterior ventricular wall, leading to rupture. Rarity of myocardial infection by clostridia may be a consequence of its excellent blood supply.

Two patients in addition to our own had no significant comorbidities. Schulz [5] presented a 58-y-old-male with a remote history of surgically-resected laryngeal cancer. He suffered from clostridial sepsis complicated by infection of the heart and

papillary muscle rupture. The source of infection was not established. The second case was a previously healthy 16-y-old boy who died of *C. fallax* sepsis after a 1-week history of a 'gastrointestinal disorder' [6]. He did not initially seek medical treatment, and the infection may have originated in the gastrointestinal tract. The organism was demonstrated in the left ventricular myocardium.

Supportive therapy for myocardial infections includes intravenous inotropic therapy, ventricular assist device or intra-aortic balloon pump, and extracorporeal membrane oxygenation. Clostridial soft tissue myonecrosis is treated with aggressive surgical debridement, antibiotics, and possibly hyperbaric oxygen therapy, none of which are likely to be life-saving in clostridial myocarditis or myonecrosis of the heart. It is not known if surgical resection or evacuation in combination with intensive antibiotic therapy may be curative in patients with clostridial myocardial abscesses. In fact, none of the 17 reported patients with confirmed clostridial infection of the myocardium survived. To the best of our knowledge, the presence of *Clostridium* spp. in an endomyocardial biopsy has not been reported.

In summary, clostridial infection of the myocardium is extremely rare, and we have reported such a case involving *C. novyi* type B. In all reported cases, including ours, the outcome was fatal.

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Fatal *Salmonella enteritidis* septicaemia in a rheumatoid arthritis patient treated with a TNF- α antagonist

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Abstract

We report a patient with a rare presentation of extra-intestinal salmonellosis after infliximab therapy for rheumatoid arthritis. We discuss the increasing incidence of primary infections and reactivation of intracellular microorganisms after treatment with TNF- α blockade, with emphasis on salmonellosis.

Introduction

TNF- α is a pro-inflammatory cytokine that plays an important role in the pathogenesis of many inflammatory conditions, such as rheumatoid arthritis (RA) and Crohn's disease. TNF- α is also an important cytokine in the defence against intracellular microorganisms. It is essential for the formation and maintenance of granulomas, being key components of host defences against intracellular pathogens.

The use of TNF antagonists has resulted in significant clinical benefits to large number of patients with RA [1], but it has also resulted in an increase of infections, especially infections of intracellular pathogens such as *Mycobacterium tuberculosis*, *Histoplasma capsulatum*, *Listeria monocytogenes*, *Pneumocystis jiroveci* and *Aspergillus fumigatus* [2]. Considering the role of TNF- α , blockage leads to an impaired cellular immune response and inadequate granuloma maintenance, causing atypical presentation of primary infections with intracellular microorganisms or reactivation

of latent granulomatous infections as a result of disintegration of granulomas [3,4].

In this case report we present a patient with disseminated salmonellosis. The case illustrates the consequences of blockage of TNF- α for the development of a severe and fatal infection by *Salmonella enteritidis*. To our knowledge, such a case has not yet been published until now.

Case report

A 74-y-old male was diagnosed in 1998 with erosive, rheumatoid factor positive rheumatoid arthritis, with at that time symptoms of active polyarthritis and pleuritis. He was a smoker and also had a history of a transient ischaemic attack, hypertension and hypercholesterolaemia. He was treated with prednisone and escalating doses of methotrexate without sufficient effect. After 2 infusions with infliximab (3 mg/kg) over 2 weeks, he was readmitted at our hospital, 4 weeks after the last infusion, with shortness of breath and high fever (39°C). No gastrointestinal

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