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Infectious Pericarditis Due to Bordetella holmesii
in an Adult Patient with Malignant Lymphoma:
First Report of a Case

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\textbf{Abstract}

\textit{Bordetella holmesii} is a fastidious Gram-negative rod first identified in 1995. Though
rare, it is isolated mainly in immunocompromised and asplenic hosts, and is associated with bacteremia, pertussis-like respiratory tract infection and endocarditis. Herein, we describe a unique \textit{B. holmesii} infectious pericarditis patient with malignant lymphoma. (46 words)

Case Description

A 71-year-old male was hospitalized because of fever and dyspnea on effort. He had received 8 cycles of chemotherapy for malignant lymphoma (diffuse large B-cell lymphoma) over the prior year, but complete remission was not achieved. Because of a persistent lesion, we initiated maintenance therapy including rituximab administration which was continued until the present hospitalization. Approximately 2 weeks prior to presentation, he complained of dyspnea on effort and a rising low-grade fever. Follow-up computed tomography suggested pericardial effusion (Fig. 1A) and pleural change was suspected (Fig. 1B). He was thus admitted under a diagnosis of possible pericarditis. Clinical examination findings on presentation were unremarkable other than a temperature of 37.5°C. Initial laboratory investigations revealed elevations of aspartate aminotransferase (AST) and alanine aminotransaminase (ALT) to 30 and 59 IU/l, respectively (normal ranges: 10 to 28 and 5 to 33 IU/l, respectively), an alkaline phosphatase level of 392 IU/l (normal range: 104 to 338 IU/l), a hemoglobin level of 11.1 g/dl (normal range: 12 to 18 g/dl) and a C-reactive protein (CRP) level of 22.99 mg/dl (normal value, less than 0.3 mg/dl). The white blood cell count
was 6,200/µl, i.e. within normal limits. However, the percentage of segmented neutrophils was 86.5 % (normal range: 38 to 58 %). Serum electrolytes and creatinine were within normal limits. Chest radiographs showed slight cardiomegaly, whereas abdominal radiographs revealed no abnormalities. HBs antigen and anti-hepatitis C antibody were negative.

In view of the possibility of pericarditis, he received pericardial drainage therapy and empirical antimicrobial administration (ceftriaxone 2000mg/day) upon admission. The pericardial effusion was bloody and contained neutrophil-rich inflammatory cells but no malignant cells. Gram staining was negative. With empirical antimicrobial therapy, his clinical symptoms disappeared and pericardial effusion did not re-accumulate after drain removal. We ultimately removed more than 1,000ml of pericardial effusion, and culture of approximately 20ml of this effusion was started. Forty-eight hours after starting the culture, gray, smooth, round colonies less than 1mm in diameter, were isolated from blood agar (Eiken Chemical Co., Tokyo, Japan) (Fig. 2). There was no colony growth at 24 h when bacteria were inoculated onto 5% sheep blood agar plates and incubated in 5% CO2 under aerobic conditions, whereas they grew after 5 days on MacConkey agar (Oriental Yeast Co., Tokyo, Japan). Isolates were small gram-negative coccobacilli on microscopic observation and no motility was seen in sulfide-indole-motility medium. Furthermore, isolates were
oxidase test negative and showed neither nitrate reduction nor urease production. We finally identified the strain with 16s ribosomal RNA genotyping, as previously described [7], as being *Bordetella holmesii* and a similarity search was conducted using the BLAST program (DDBJ, Shizuoka, Japan). The results (1,456 bp) showed 100% similarity to the reference strain (GenBank accession no. DQ409136) [similarity to *B. pertussis* (GenBank accession no. BX640420), 99.73%; similarity to *B. parapertussis* (GenBank accession no. BX640434), 99.52%, similarity to *B. bronchiseptica* (GenBank accession no. BX640449), 99.52%]. Furthermore, the isolates were confirmed by PCR detection of *bhoE* [2], a gene not found in *B. pertussis* but present in *B. holmesii*, using primers Bh-bhoE-F (tggggagcaaacaggattag) and Bh-bhoE-R (agagtgccctttcgtagcaa). Agglutination testing (Denka Seiken, Co., Ltd., Tokyo, Japan) for identification of *B. pertussis* was negative. Susceptibility to representative antimicrobial agents was determined by Etest on Mueller-Hinton agar. The present isolate was sensitive to ampicillin (MIC, 1 µg/ml), ceftriaxone (MIC, 1 µg/ml), clarithromycin (MIC, less than 2 µg/ml) and ciprofloxacin (MIC, less than 0.12 µg/ml). The patient’s fever resolved within 2 days of commencing intravenous ceftriaxone, and the pericardial fluid did not reaccumulate after beginning antimicrobial therapy. He felt better, and CRP normalized. Administration of ceftriaxone was continued for 4 weeks, but myelosuppression associated with ceftriaxone administration developed. Ceftriaxone was thus switched to levofloxacin, in
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...response to the ongoing neutropenia. He was given granulocyte-colony stimulating factor, and his neutrophil count normalized. On the 63rd hospital day, he was discharged in good condition.

The genus *Bordetella* belongs to the *Alcaligenaceae* family which is currently comprised of eight known species. Among representative species, *B. pertussis* is the causative agent of whooping cough (pertussis), and *B. parapertussis* and *B. bronchiseptica* have also been implicated in respiratory tract infections in humans. The present species, *B. holmesii*, was also recently reported to have been detected in patients with pertussis-like respiratory syndrome [6, 15]. The other species, *B. avium*, *B. hinzii* and *B. petrii*, are rarely detected in respiratory samples from patients with chronic respiratory infectious diseases including cystic fibrosis [4, 15, 18]. Moreover, *B. trematum* has also reportedly been detected in ear and wound infections [1, 19]. Immunocompromised status is considered to be strongly associated with the establishment of infection due to these rare *Bordetella* species.

*B. holmesii* was first described in 1995 as a cause of sepsis in 15 patients [20], including at least three asplenic children, but no specific clinical findings were described. The first detailed clinical case report was published later that year. A 12-year-old male with a
history of splenectomy for idiopathic thrombocytopenic purpura was diagnosed with sepsis due to *B. holmesii*. However, he complained only of low-grade fever, no other symptoms, and his physical state was essentially normal [8]. Since then, *B. holmesii* has been reported as a causative microorganism of bacteremia, endocarditis and community-acquired pneumonia. In these previous reports, it is noteworthy that most patients were in immunocompromised states, mainly the asplenic condition [2, 5, 10, 11, 12, 14, 16]. Shepard and colleagues reported 26 patients with *B. holmesii* bacteremia and 85 % were in an anatomical or functional asplenic state [14]. Moreover, the clinical courses were usually uneventful and relatively mild. Most patients recovered without complications.

The present case is the first description, to our knowledge, of infectious pericarditis due to *B. holmesii*. Bacterial pericarditis accounts for approximately 5% of all pericarditis cases [9, 13, 17] and occurs via direct infection during trauma, thoracic surgery, or catheter drainage, by spread from an intrathoracic, myocardial, or subdiaphragmatic focus, and by hematogenous dissemination. The frequent causative organisms are *Staphylococcus* spp. and *Streptococcus* spp, which often cause rheumatic pancarditis, *Haemophilus* spp, and *Mycobacterium tuberculosis*. *M. tuberculosis* is considered to be the most common microorganism causing bacterial pericarditis, because the pericardium can be reached via hematogenous spread or extension from adjacent organs, particularly the lungs or pleural
space [13]. In the present case, chest CT showed slight changes of the pleura and adjacent lung parenchyma (Fig. 1B, 1C). However, we were not able to obtain pleura or lung samples from the indicated regions, and can only speculate that \textit{B. holmesii} had migrated to the pericardium from the lung or pleural space.

We advocate that \textit{B. holmesii} be considered among the possible causative microbes of infectious pericarditis. A recent report [15] showed \textit{B. holmesii} to be strongly associated with pertussis-like respiratory syndrome caused by \textit{B. pertussis} and \textit{B. parapertussis}.

Furthermore, \textit{B. holmesii} was identified as a causative microbe of bacterial pneumonia [3]. Hence, we consider \textit{B. holmesii} to be not only a cause of sepsis or septicemia in immunocompromised or asplenic individuals but also a common cause of infectious respiratory system diseases associated with involvement of adjacent organs or tissues including the pericardium. Future development of a rapid and specific technique to detect \textit{B. holmesii} might have a major diagnostic impact.

In conclusion, \textit{B. holmesii} is a rare but important cause of pericarditis. In view of the possibility of this microbe causing respiratory system disease, awareness of \textit{B. holmesii} is warranted.

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Figure legends

FIG. 1. Computed tomography (CT) of the chest on admission shows massive pericardial effusion (FIG. 1A, white solid line) and slight pleural and lung changes adjacent to the pericardium (FIG. 1B, black dashed line). High density lesions are seen in the pleura and lung parenchyma adjacent to the pericardium while chest CT scan of a normal control individual (TN) without pericarditis shows no such changes (FIG. 1C).

Fig. 2. Isolation of colonies from pericardial effusion and microscopic view of isolates (the upper right panel, original magnification X1,000). Colonies grew slowly and at least 48 h were required before they became observable. All colonies are less than 1mm in diameter.
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and appear as brown or green areas in the medium. Isolates were found to be short gram-negative coccobacilli by microscopic study.
Figure 2