Prosthetic-Joint-Associated *Bordetella holmesii* Infection

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***Bordetella holmesii* is a globally distributed pathogen that is increasingly recognized as a cause of both pertussis-like respiratory infections and invasive disease. In this study, we describe a case of an immunocompetent man who developed *B holmesii* infection of his femoral prosthesis—the fifth *B holmesii* orthopedic infection reported in literature to date. This article highlights the potentially underrecognized role of *B holmesii* in orthopedic infections by reviewing these previously reported cases in the context of the current literature.**

Keywords. *Bordetella holmesii*; prosthetic joint infection; septic arthritis.

CASE REPORT

A 20-year-old male college student presented with a 3-day history of worsening left groin and anterior thigh pain. He denied fever and he recalled no recent history of a pertussis-like illness or sick contacts. His medical history was significant for stage IIA osteosarcoma of the distal left femur diagnosed 5 years earlier. At that time, he was treated with resection of the tumor (a limb-sparing resection using a bipolar hip replacement and proximal femoral prosthesis) and subsequent chemotherapy (cisplatin, doxorubicin, and methotrexate). His last administration of chemotherapy was 4.5 years before this presentation, and he had no evidence of recurrent or residual disease. He had no family history or personal history to suggest functional or anatomic asplenia or other immune deficiency. A blood smear performed at the time of his cancer diagnosis did not identify the presence of Howell-Jolly bodies, and a postchemotherapy assessment of immune function, including antibody titers to prior vaccinations (tetanus, polio, measles, and mumps) and a lymphocyte stimulation assay, was normal.

On physical exam, he was afebrile and his other vital signs were normal. His left thigh appeared slightly larger than the right, had limited left hip flexion (with pain beyond 75°), pain with internal and external rotation, and was tender to palpation over the left greater trochanter. The white blood cell count (WBC) was 15 200 cells/mm^3 (77% neutrophils, 12% lymphocytes), erythrocyte sedimentation rate (ESR) was 64 mm/h, and C-reactive protein (CRP) was 30 mg/dL.

A computed tomography (CT) scan of his left hip and femur revealed a 4 × 3 cm rim-enhancing fluid collection along the proximal length of the femoral prosthesis (Figure 1). There was no radiographic evidence of osteomyelitis. A CT-guided percutaneous needle aspirate yielded cloudy fluid, analysis of which revealed 33 950 WBC (82% neutrophils). No organisms were seen on a Gram stain. Small gray colonies were visible on a chocolate agar plate after 96 hours of incubation, whereas blood and MacConkey agar plates remained without growth. The Gram stain of a colony revealed small Gram-negative coccobacilli (Figure 2). Automated biochemical analysis with MicroScan (Dade-Microscan, Sacramento, CA) identified *Acinetobacter lwoffii*. However, the small size of the organisms on Gram stain and the finding that it was catalase negative made *A lwoffii* unlikely.

The isolate was sent to a reference laboratory for 16S rRNA sequencing (MicroSEQ ID; Applied Biosystems), which revealed 100% homology to *B holmesii* and 99% homology to *Bordetella bronchiseptica* in both SmartGene and MicroSeq databases. However, *B bronchiseptica* was ruled out because the isolate was urease, oxidase, nitrate, and motility test negative [1].

The patient underwent a hip joint and wound debridement and 1-stage exchange of the femoral prosthesis (with femoral prosthesis and bipolar hemiarthroplasty) and vancomycin bead implantation. Intraoperatively, 20 mL of murky fluid and fibrinous material in the hip and around prosthesis was noted. The hip socket had significant loss of cartilage and some erosion of the acetabulum. Four of 8 cultures obtained from the fluid collection surrounding the proximal prosthesis during surgery also grew *B holmesii*. No surgical biopsy was

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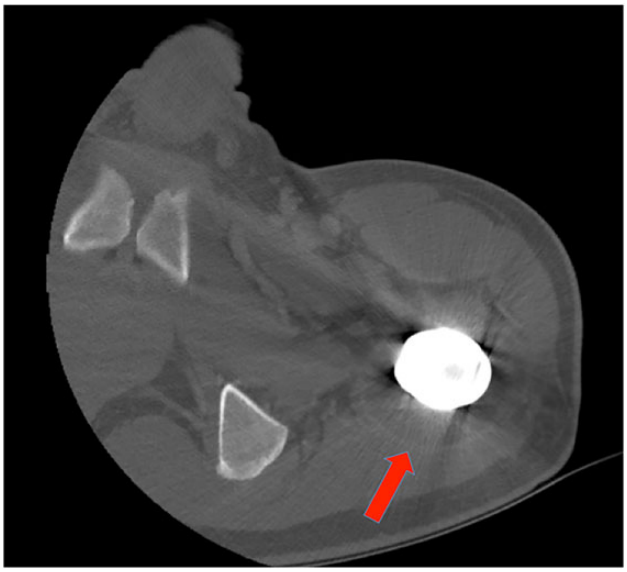

Figure 1. Computed tomography scan of the proximal left thigh demonstrating a 4 × 3 cm rim-enhancing collection surrounding a femoral prosthesis. Culture of this fluid grew *Bordetella holmesii*.

performed. However, pathologic examination of the sampled fibrinous material showed acute and chronic inflammation. Broth microdilution susceptibility testing for the *B holmesii* isolate demonstrated the following: amikacin (≤8 μg/mL), cefepime (≤2 μg/mL), ceftazidime (≤4 μg/mL), ciprofloxacin (≤1 μg/mL), levofloxacin (≤1 μg/mL), gentamicin (≤1 μg/mL), tobramycin (≤1 μg/mL), and trimethoprim/sulfamethoxazole (≤0.5 μg/mL). He was initially treated with ceftriaxone and oral doxycycline for 1 week. After the organism was identified as *B holmesii*, the patient was switched to oral levofloxacin for a total antibiotic course of 6 weeks. His ESR and CRP had normalized by the end of antibiotic therapy. One year later, he was healthy and showed no signs of recurrent infection.

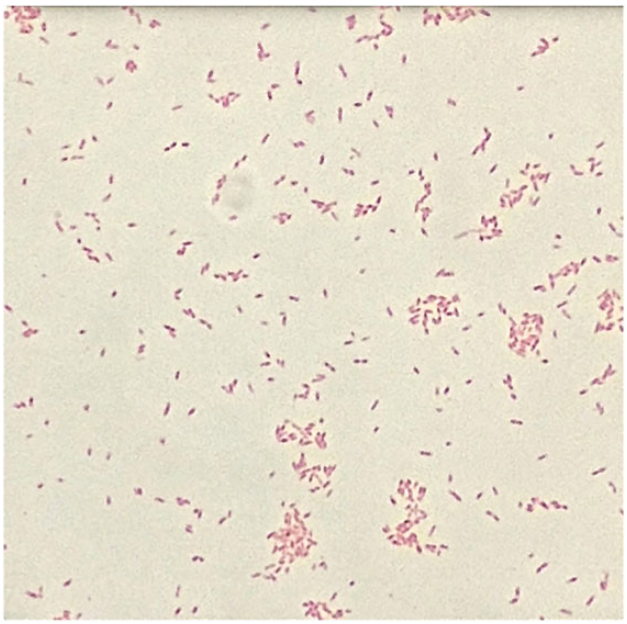

Figure 2. Small, Gram-negative coccobacilli identified as *Bordetella holmesii*.

DISCUSSION

Bordetella holmesii is unique among human *Bordetella* species for causing invasive infections such as bacteremia and endocarditis [2]. However, septic arthritis is uncommon, with our case representing only the fifth report of such infection and only the second associated with a prosthesis (Table 1) [1, 3, 4]. Many questions remain regarding the epidemiology and management of *B holmesii* infections, as raised by this case.

A notable feature of *B holmesii* is its propensity to cause nonrespiratory infections among individuals with underlying medical predispositions [2]. Asplenia or splenic dysfunction is the most commonly reported risk factor for *B holmesii* bacteremia [5]. However, the reasons that underlie it—such as whether *B holmesii* is encapsulated—remain unknown. Among the 4 previously reported cases of *B holmesii* septic arthritis, 2 occurred in apparently healthy individuals, whereas the other 2 occurred in individuals with asplenia—1 patient who had undergone splenectomy for treatment of chronic hemolytic anemia whereas the other patient had a history of sickle cell disease, both resulting in functional asplenia (Table 1). Our patient had a normal-sized spleen on prior imaging and no known splenic dysfunction or other immune abnormalities. A previous blood smear had not demonstrated Howell-Jolly bodies, although the presence of this finding has been shown to be an insensitive marker of splenic function [6]. Counting the percentage of pitted erythrocytes is a similarly noninvasive but more sensitive method of screening for splenic dysfunction, but it requires an interference phase microscope and trained personnel.

The mode by which our patient or any of the other cases reviewed herein contracted *B holmesii* is also unresolved. Respiratory droplet transmission is the most likely origin given the organism's biologic similarities to *B pertussis* and its ability to cause a similar respiratory syndrome [7]. Our patient did not report having a preceding or concurrent respiratory illness, although the latter finding is present in only a minority of cases of invasive disease, and neither finding has been shown to carry any predictive value in invasive *B holmesii* infection [5, 8].

Diagnosis of *B holmesii* remains a challenge to the clinician and the conventional microbiology laboratory. In is worth noting that no organisms were seen on synovial fluid Gram stains in our case nor in any of the 3 previously reported cases of *B holmesii* septic arthritis. Moreover, this organism grows poorly in routine culture media and is not uncommonly misidentified by automated

Table 1. Reported Cases of *Bordetella holmesii* Orthopedic Infections

Age	Sex	Medical Hx	Infection	Site Aspirate	Surgery	Antibiotic	Outcome	Ref.
20 y	M	Osteosarcoma 4 y prior	R femoral prosthesis	33 950 WBC/mm^3 (82% neutrophils) Gram stain neg.	1-Stage exchange procedure	Ceftriaxone + doxycycline for 1 wk followed by levofloxacin for 4 wks	Cure	Current
54 y	F	Bilateral knee arthroplasty	R knee prosthesis	26 060 WBC/mm^3 (94% neutrophils) Gram stain neg.	2-Stage exchange procedure	Ceftriaxone followed by ciprofloxacin for 2 mo	Cure	[3]
15 y	M	None	R native knee	54 000 WBC/mm^3 Gram stain neg.	Washout	Ceftriaxone for 2 wks followed by levofloxacin for 7 wks	Cure	[3]
15 y	M	Chronic hemolytic anemia, splenectomy	L knee	100 000 WBC/mm^3 (80% neutrophils) Gram stain neg.	Washout	Cefotaxime + rifampicin for 1 d followed by routine oral penicillin prophylaxis for asplenia	Cure	[4]
15 y	M	Sickle cell anemia	Native knee	n/a	n/a	n/a	n/a	[1]

Abbreviations: Hx, history; L, left; n/a, not available; neg., negative; R, right; Ref., references; WBC, white blood cell count.

microbial identification systems. Misidentification as *A lwoffii*, as occurred in our case, has been reported as a recurring phenomenon in such systems [9]. Such a result should alert clinicians to the possibility of *B holmesii* so that molecular methods of identification may be pursued when possible, particularly when epidemiologic and microbiologic features are conflicting. More importantly, the presence of small, slowly growing Gram-negative coccobacilli should also alert laboratories to the potential for bioterrorism agents such as *Francisella tularensis*, *Yersinia pestis*, and *Brucella* spp [10]. In the future, novel commercial diagnostics such as matrix-assisted laser desorption and ionization time-of-flight mass spectrometry are likely to assume the routine role of diagnosing *B holmesii* [2, 3]. At this time, however, many laboratories (including the one involved in our case) rely on 16S rDNA sequencing for this purpose [2].

At the time of this writing, there are no standardized treatments or antimicrobial susceptibility breakpoints for *B holmesii*. The organism in our case was inhibited by the minimum concentrations of antibiotics tested, although no supporting clinical data currently exists to corroborate this finding. Resistance has been reported for broad-spectrum β-lactams including the cephalosporins [2]. Macrolides are recommended as monotherapy for *B pertussis* infection, but they are not routinely used for bone and joint infections. Despite this lack of guidance, no treatment failures were identified among 3 of the previously reported individuals with *B holmesii* orthopedic infections, all of whom were initially treated with third-generation cephalosporins with 2 transitioning to oral fluoroquinolones [3, 4]. In another reported case, a 15-year-old boy with asplenia who developed septic arthritis of the knee was reportedly cured after only undergoing a washout and 24 hours of treatment with broad-spectrum antibiotics before resuming routine oral penicillin prophylaxis [4].

CONCLUSIONS

With the increasing use of molecular diagnostics, our collective experience with difficult-to-culture organisms such as *B holmesii* will undoubtedly grow. In the interim, *B holmesii* should be considered in cases of clinical septic arthritis or prosthetic joint infection with negative cultures or when small, fastidious Gram-negative coccobacilli are identified on Gram stain. In so doing, *B holmesii* may yet emerge as a more common cause of native or prosthetic joint infection than currently reported, and it may have been the etiology in at least some cases previously labeled "culture-negative infective arthritis" [3].

Acknowledgments

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Potential conflicts of interest. All authors: No reported conflicts.

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