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Bordetella bronchiseptica Pneumonia and Bacteremia Following Bone Marrow Transplantation

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***Bordetella bronchiseptica* is a frequent cause of respiratory infections in animals but rarely causes disease in humans. We describe a patient with *B. bronchiseptica* pneumonia and bacteremia that developed following bone marrow transplantation. *B. bronchiseptica* infection persisted despite antimicrobial therapy and may have progressed because of the combined effects of the patient's underlying immunosuppression and the antimicrobial antagonism between doxycycline and ciprofloxacin.**

Bordetella bronchiseptica, a small, pleomorphic, gram-negative coccobacillus, causes atrophic rhinitis in swine, snuffles in rabbits, and kennel cough in dogs (10, 18). Humans, however, are rarely infected with this organism. When infections in humans occur, they are often acquired through animal contact and typically involve immunocompromised patients (18). The spectrum of immunocompromised patients who have developed *B. bronchiseptica* infection includes patients with malignancies such as Hodgkin's disease (17) or chronic lymphocytic leukemia (1), one cardiac transplantation patient (4), one patient with AIDS (7), and debilitated alcoholics (9, 12). Our report of a bone marrow transplantation patient with *B. bronchiseptica* infection expands the spectrum of immunocompromised hosts who have developed infections with *B. bronchiseptica* and illustrates the potential adverse effects of antimicrobial antagonism.

Case report. A 20-year-old white female with acute myelogenous leukemia was admitted to the Fred Hutchinson Cancer Research Center for allogeneic bone marrow transplantation. At the time of admission, physical examination revealed a temperature of 38°C. Initial laboratory studies showed an absolute neutrophil count of 0.2×10^9/liter, hematocrit of 30.0%, and a platelet count of 21×10^9/liter. Following preparative chemotherapy with cyclophosphamide, 60 mg/kg of body weight per day for 2 days, and total body irradiation for 4 days, the patient received the donor marrow on 6 September 1991. Throughout the patient's hospital course she received fluctuating doses of cyclosporin and prednisone as prophylaxis for graft-versus-host disease. Ten days following the bone marrow transplantation, the patient developed orthopnea, cough, and conjunctival injection. A chest radiograph demonstrated no abnormality. At the time, the patient was receiving imipenem and vancomycin.

On day 11 posttransplantation, coarse, "honking" rhonchi were auscultated in the chest, particularly on the left side. One day later, the patient complained of shortness of breath and a productive cough. Gram staining of sputum revealed no polymorphonuclear cells or microorganisms. A chest radiograph demonstrated bilateral pulmonary infiltrates, and a computed tomographic scan of the chest demonstrated consolidation in the left lower lobe with an associated small pleural effusion.

At 15 days posttransplantation, the patient remained neutropenic and underwent bronchoscopic examination by bronchoalveolar lavage (BAL); profuse secretions were noted, particularly in the left lower lobe bronchus. Gram staining of the BAL specimen demonstrated alveolar macrophages and bronchial epithelial cells but no microorganisms. Intravenous ciprofloxacin, 300 mg twice daily, and tobramycin, 90 mg every 8 h, were added to the patient's antimicrobial regimen.

Two days later, the BAL specimen grew more than 20,000 CFU of an off-white or buff-colored gram-negative rod per ml. The organism was positive in tests for oxidase, citrate utilization, and urea hydrolysis. The Gram Negative Identification card (Vitek System Co., St. Louis, Mo.) and the Rapid NFT (API System SA, Montalieu-Vercieu, France) identified the organism as *B. bronchiseptica*. Upon further questioning, the patient revealed that several days prior to admission she had contact with a dog that had a barking cough. Ciprofloxacin was continued and intravenous doxycycline, 100 mg twice daily, was added. Imipenem and tobramycin were discontinued. The patient improved over the next 10 days, and her neutropenia resolved on day 24 posttransplantation. She remained afebrile until posttransplantation day 37, when she developed a temperature of 39°C. A repeat chest computed tomographic scan revealed a cavitary lesion in the left lower lobe.

Forty-five days posttransplantation, *B. bronchiseptica* and *Aspergillus fumigatus* were isolated from a sputum specimen. On posttransplantation day 47, the patient underwent resection of the left lower lobe cavitary lesion, and *A. fumigatus* was the only organism isolated. Tissue stains, however, revealed small numbers of gram-negative, coccobacillary organisms. Sputum cultures obtained on posttransplantation days 49 and 50 again demonstrated *B. bronchiseptica*. *B. bronchiseptica* was isolated from blood cultures drawn on 4 consecutive days (beginning on posttransplantation day 53). Echocardiography had been performed on posttransplantation day 30, but it did not demonstrate any valvular lesions. The patient died on posttransplantation day

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57 because of multi-organ system failure. No autopsy was granted.

Microbiologic investigation. Antimicrobial susceptibility testing by the Kirby-Bauer disk method showed the original *B. bronchiseptica* isolate from the BAL specimen to be susceptible to amikacin, cefoperazone, ceftazidime, imipenem, mezlocillin, piperacillin, ticarcillin-clavulanate, ciprofloxacin, trimethoprim-sulfamethoxazole, polymyxin B, and tobramycin. Broth dilution MICs and MBCs were performed on the initial isolate obtained from the BAL specimen and the first isolate obtained from blood. The MICs of ciprofloxacin for the two isolates were 0.25 and 1.0 μg/ml, respectively. The MBCs were 0.5 and >1.0 μg/ml, respectively. The MICs of doxycycline for the two isolates were 0.125 and 4.0 μg/ml, respectively; the MBCs were >4.0 and >32 μg/ml, respectively. Synergy testing by the checkerboard method (13) showed that the combination of ciprofloxacin and doxycycline exhibits antagonism at both the inhibitory and bactericidal levels.

Twenty-five cases of *B. bronchiseptica* infection have previously been described in humans (18). Among these patients, the respiratory tract has most frequently been involved, with a range of clinical manifestations such as sinusitis, tracheobronchitis, whooping cough, and pneumonia being noted (18). Radiographic appearances of lower respiratory tract infections have included diffuse infiltrates (1), interstitial pneumonia (4), and lobar pneumonia (14). Seven cases of bacteremia, including two cases of endocarditis (11, 15) and two cases of concomitant pneumonia (8, 9), have been attributed to *B. bronchiseptica* infections (6, 8, 11, 12, 16). Other clinical manifestations have included peritonitis and meningitis (2, 3).

The optimal therapy for *B. bronchiseptica* infections has not been established. In vitro susceptibility testing may not correlate with in vivo efficacy. Nevertheless, recent in vitro antimicrobial susceptibility testing suggests that aminoglycosides, antipseudomonal penicillins, tetracyclines, and chloramphenicol are the most effective agents (18). Some difficulty in treating *B. bronchiseptica* may occur because *Bordetella* species produce an enzyme, adenylate cyclase, that enters host polymorphonuclear cells and macrophages and disrupts chemotaxis, superoxide production, and bacterial killing (5).

The patient we describe represents the first report of *B. bronchiseptica* infection following bone marrow transplantation. Our patient's history suggested that her infection began as an upper respiratory tract infection acquired through contact with an ill dog. Her infection progressed to pneumonia and bacteremia. The persistence of her infection occurred despite antimicrobial therapy and may have resulted from a combination of the following three factors: the patient's underlying immunosuppression, the ability of *B. bronchiseptica* to inhibit leukocyte function, and antimicrobial antagonism between ciprofloxacin and doxycycline. The contribution of each of these factors is uncertain; but given the patient's persistent immunosuppression and the failure of multiple antibiotics, including imipenem, tobramycin, ciprofloxacin, and doxycycline, it is likely that the immunosuppression played the most important role. The course of infection in the patient described here illustrates the potential seriousness of *B. bronchiseptica* infections in immunosuppressed hosts and suggests that treatment of *B. bronchiseptica* infections with combined antimicrobial therapy may, in certain instances, contribute to a poor clinical outcome. Physicians should be aware of the potential for *B. bronchiseptica* infections in immunosuppressed patients who have contact with sick pets.

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