Capnocytophaga ochracea-related Bacterium Bacteremia in a Hypertrophic Cardiomyopathy Patient without Neutropenia

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Abstract

Gram-negative fusiform rods were detected in a blood culture obtained from a 63-year-old man who had been hospitalized for a long duration for severe heart failure. Although the organism could not be identified using a conventional method, it was finally identified as a bacterium of the *Capnocytophaga ochracea* group based on the results of biochemical testing, 16S rRNA sequencing and a matrix-assisted laser desorption ionization time-of-flight mass spectrometry analysis. Although neutropenic patients with poor oral hygiene are exclusively vulnerable to *Capnocytophaga* bacteremia, this case was unique because such predisposing conditions were not noted. A multi-centered investigation is warranted for a better understanding of this clinically rare, but potentially pathogenic organism.

Key words: bacteremia, *Capnocytophaga*, genetic identification, neutropenia, oral hygiene

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Introduction

Capnocytophaga, a genus of anaerobic, fusiform Gram-negative bacterial rod, was first identified in 1979 (1). Since then, six organisms that have been isolated from the oral cavities of humans (*C. ochracea*, *C. sputigena*, *C. gingivalis*, *C. haemolytica*, *C. granulosa*, and *C. leadbetteri*) (2) and two organisms that have been isolated from the oral cavities of animals (*C. canimorsus* and *C. cynodegmi*) have been reported (3). The human-derived pathogens reside in the oral cavity and commonly cause dental infections (4, 5). However, disruption of the oral mucosal barriers due to oral ulcers or periodontitis can predispose patients to bloodstream infections by these pathogens (6-8). In particular, patients with neutropenia are vulnerable to systemic infections with high mortality rates (9-12). Due to its similarity, an accurate

identification of human-derived pathogens is quite difficult, and therefore, the clinical characteristics of each *Capnocytophaga* species remain unknown. We herein report a case of *Capnocytophaga ochracea*-related bacterium bacteremia that occurred in an elderly man with severe heart failure who did not have any known predisposing factors.

Case Report

A 63-year-old man who was in the dilated phase of hypertrophic cardiomyopathy was transferred to our hospital because of symptoms of heart failure. His past medical history included atrial fibrillation, implantation of a cardioverter defibrillator due to sustained ventricular tachycardia, and amiodarone-induced interstitial pneumonia. After hospitalization, the patient underwent intensive treatment for the first seven days at a cardiac care unit; subsequently, he

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Figure 1. Morphological appearance of the pathogen. Gram staining using samples directly extracted from the blood culture bottle revealed Gram-negative fusiform or filamentous rods with tapered points (A). The colonies show gliding motility on a blood agar plate (B).

was moved to a general ward. Seventy-seven days after admission, he suddenly developed a high fever with systemic inflammation (C-reactive protein, 5.15 mg/dL). Prior to this, neutropenia had not been noted and the patient had been strictly managed under hospitalization. Medical procedures leading to bacteremia, such as odontectomy or gastrointestinal endoscopy, were not performed after admission. Treatments that affect the oral hygiene, including tracheal intubation or tracheostomy, were also not performed. A physical examination did not indicate any possible infectious foci. Results of systemic computed tomography were also unremarkable, and his spleen was normal in size. Serum C-reactive protein and procalcitonin levels were elevated, with peak levels of 9.64 mg/dL and 4.26 ng/mL, respectively, and the patient went into shock. A catecholamine treatment was initiated, and combination therapy with vancomycin and meropenem was empirically administered.

An anaerobic blood culture bottle incubated at 37°C in the BacT/ALERT system (bioMérieux, Marcy l'Etoile, France) was positive for Gram-negative fusiform rods after three days (Fig. 1A). *Capnocytophaga* species was morphologically suspected, however, a conventional method failed to identify the pathogen. The patient's condition improved shortly after initiating antibiotic treatment. The patient consulted a dentist who did not note any abnormal findings in his oral cavity. The minimum inhibitory concentrations of the isolate were as follows: ampicillin, 0.5 µg/mL; amoxicillin/clavulanate, <0.12 µg/mL; clarithromycin, <2 µg/mL; tetracycline, 0.5 µg/mL; ciprofloxacin, >2 µg/mL; sulfamethoxazole/trimethoprim, 4 µg/mL; chloramphenicol, 4 µg/mL; and meropenem <0.12 µg/mL. Thus, combination therapy was downgraded to monotherapy with sulbactam/ampicillin. However, the antibiotic was further switched to ceftriaxone due to drug-induced renal impairment. His fever and serum inflammatory reactions subsequently disappeared. Antibiotic therapy was administered for a total of three weeks. Since then, there have been no symptoms or findings suggestive of a recurrence. The clinical course of the patient is shown in Fig. 2.

Bacterial identification

The bacterial colonies characteristically showed gliding motility on a blood agar plate after incubation for 72 hours under 5% carbon dioxide (Fig. 1B). The isolate was oxidase- and catalase-negative, suggesting human-derived *Capnocytophaga*. The isolate could not be identified by ID-test HN-20 rapid (Nissui Pharmaceutical, Tokyo, Japan), thus 16S rRNA was analyzed. The targeted gene was amplified by PCR using universal primers 8UA (5'-AGA GTT TGA TCM TGG CTC AG-3') and 1485B (5'-TAC GGT TAC CTT GTT ACG AC-3'). The sequence data (1,479 base pairs) were analyzed using basic local alignment search tool (BLAST) sequence homology search programs (GenBank, EzTaxon-e, and BIBI), and the organism was presumed to be either *C. ochracea* or *C. sputigena* with an accuracy of 98.0% and 96.5%, respectively. The result of a bootstrap analysis with 1,000 replications indicated the isolate to be *C. ochracea*, although the bootstrap value was relatively low (Fig. 3). The biochemical characteristics of the isolate were subsequently examined using api 50 CH (BioMérieux, Marcy l'Etoile, France), and the results were negative for acid production from xylose, mannitol, trehalose, ribose, arabinose, sorbitol and melibiose. Additionally, the organism was found to hydrolyze glycogen and starch, as well as ferment glucose, maltose, fructose, sucrose, lactose, mannose, raffinose, galactose, inulin, amygdalin and cellobiose. The results of this biochemical testing were suggestive of *C. ochracea*, as the organism is known to metabolize glycogen, starch, lactose and galactose, while *C. sputigena* does not. Additionally, a matrix-assisted laser desorption ionization time-of-flight mass spectrometry (MALDI-TOF MS) analysis revealed the isolate to be *C. ochracea* with a score value of 2.375 (Bruker Biotyper, Bruker Daltonics). These results indicated that the isolate was *C. ochracea*; however, we finally determined the isolate as a bacterium in the *C. ochracea* group due to insufficient similarity in the 16S rRNA sequence (98.0%). The nucleotide sequences of 16S rRNA were deposited in DDBJ under the accession number

Figure 2. The clinical course of the case. After hospitalization, the patient underwent intensive treatment for one week at a cardiac care unit; subsequently, he was moved to a general ward and inotrope agents were gradually tapered. However, eleven weeks after admission, he suddenly developed a high fever with shock due to the *Capnocytophaga* bacteremia. Prior to this event, neutropenia had not been noted. His condition improved with antibiotics treatment for a total of three weeks. After inotrope agents were tapered, he was discharged. CRP: C-reactive protein, BNP: brain natriuretic peptide, WBC: white blood cells, VCM: vancomycin, MEPM: meropenem, S/A: sulbactam/ampicillin, CTRX: ceftriaxone

Figure 3. Phylogenetic tree of 16S rRNA nucleotide sequences.

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Discussion

Clinically, *C. canimorsus* is the most well-known *Capnocytophaga* species that is present in the oral cavity of dogs and cats and causes fatal infections in humans who experience animal bites (13, 14). Patients who have undergone splenectomy are at a particularly high risk for extrinsic infections, and the administration of prophylactic antibiotics

after exposure is recommended in such people (15). A recent review article reported the mortality rate of *C. canimorsus* infection to be 26% (15).

On the other hand, human-derived pathogens of the genus *Capnocytophaga* cause intrinsic infections in patients with neutropenia by invading the oral mucosa. Martino et al. reported that 93% (26/28 cases) of the cases occurred in patients with malignancies who were in a chemotherapy-induced neutropenic state (12). The complication of oral mucositis was considered to be highly responsible for the

infection and an importance of oral hygiene in neutropenic patients has been emphasized (12). Patients with heart failure are generally immunocompromised (16) and prone to dry mouth (17), possibly leading to deteriorated oral hygiene. However, our case was unique in that there were no such underlying conditions, indicating that *Capnocytophaga* can infect any patients without these predisposing factors. Although human-derived *Capnocytophaga* pathogens usually induce uncomplicated bacteremia, infections that involve organs, including endocarditis (18), post-partum endometritis (19), cerebral abscess (20) and purpura fulminans (21) have also been described. A growing number of immunocompromised patients are managed in medical facilities, and a better understanding of this rare, but potentially pathogenic organism is required.

For better comprehension of the epidemiology and pathogenicity of the pathogens, an accurate identification of the causative bacterium is essential. Human- and animal-derived species show different features with respect to their biochemical activity and colony morphology. For instance, only animal-derived species show positive results in oxidase and catalase testing, while human-derived species possess the characteristic gliding motility. However, an accurate identification of the *Capnocytophaga* species is challenging without genetic identification tests. Unfortunately, in most of the previously reported cases of *Capnocytophaga* infection, molecular analyses were not performed. To the best of our knowledge, apart from our case, 16S rRNA analyses were performed in only a few cases (20). Thus, a multi-centered prospective investigation including genetic identification tests is warranted to reveal the current characteristics of *Capnocytophaga* infection. In the present case, in addition to the genetic examination, we performed biochemical testing and MALDI-TOF MS analysis for the confirmation of bacterial identification.

A reliable method for *in vitro* antimicrobial susceptibility testing for *Capnocytophaga* is currently unavailable. However, most *Capnocytophaga* spp. are typically susceptible to various antibiotics including penicillin, cephalosporin, macrolides, clindamycin, metronidazole, and fluoroquinolone. Although evidence of beta-lactamase-producing *Capnocytophaga* spp. was scarce in the 1990s (22), an increasing number of studies have reported resistant isolates (7, 12, 23, 24), including isolates resistant to fluoroquinolone (12) and macrolide/clindamycin (24). Multidrug-resistant *Capnocytophaga* strains have also been isolated from clinical specimens (20, 25). Physicians should confirm the results of drug susceptibility tests when treating patients, especially those with severe conditions.

In conclusion, we reported a case of *C. ochracea*-related bacterium bacteremia in a long-term hospitalized patient with hypertrophic cardiomyopathy. The current characteristics of human *Capnocytophaga* infection remain unclear, and a multi-centered investigation with reliable bacterial identification is thus warranted to better understand this rare, but potentially pathogenic organism.

The authors state that they have no Conflict of Interest (COI).

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