The Brief Case: *Capnocytophaga sputigena* Bacteremia in a 94-Year-Old Male with Type 2 Diabetes Mellitus, Pancytopenia, and Bronchopneumonia

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**CASE**

A 94-year-old male presented to the emergency department with 3 days of fever and total body weakness. The patient’s past medical history was significant for coronary artery disease, type 2 diabetes mellitus, gastroesophageal reflux disease, Parkinsonism, hypertension, and chronic kidney disease. Physical examination revealed fever (38.7°C), mild elevation in blood pressure (138/62 mm Hg) and a normal room air oxygen saturation of 96%. Lung sounds were distant, and no rales, wheezing, or rhonchi were appreciated. The patient presented with tachycardia (heart rate, 112 beats per minute [bpm]) without murmur, rub, or gallop. The patient’s abdomen was soft and nontender, and no peripheral edema was observed. Neurologic examination showed diffuse, generalized motor weakness and fine resting hand tremor but was otherwise normal. Recent laboratory tests showed pancytopenia (white blood cells, $1.16 \times 10^3$/mm$^3$; platelets, $8 \times 10^3$/mm$^3$) and low hemoglobin (8.5 g/dl). Creatinine was 1.78 mg/dl with a known baseline of 1.7 mg/dl. Chest X-ray (CXR) revealed peribronchial cuffing. The patient denied cough, diarrhea, mouth pain, nausea, or vomiting. No recent pet exposures or animal bites were reported. No mucositis, gingival disease, or mouth tenderness was noted in patient history. However, given the patient’s advanced age, tooth loss, and poor dental care, the existence of damage to the oral mucosa could not be ruled out. The patient’s social history was significant for residing at an assisted living facility where a coronavirus disease 2019 (COVID-19) outbreak had been present. The patient was initially suspected of having COVID-19, but initial and follow-up COVID-19 molecular testing were both negative. Two sets of blood cultures were obtained, and intravenous fluids were administered. Due to the peribronchial cuffing noted on CXR, ceftriaxone and azithromycin were initiated to treat for possible early bronchopneumonia. Within 24 h of admission, the patient developed acute hypotension and subsequently died of circulatory collapse.

Two sets of anaerobic blood culture bottles (Bactec; Becton, Dickinson, Sparks, MD) collected at the time of admission signaled positive on day 4 of incubation. Thin, spindle-shaped, Gram-negative bacilli were observed on Gram stain (Fig. 1A and B). After 24 h, very small, gray, nonhemolytic colonies with spreading edges grew on a Columbia blood agar plate incubated at 35°C with 5% CO$_2$ (Fig. 1C). They reached 2 to 4 mm in diameter after 2 to 4 days and were convex or flat and slightly yellow. The colonies were resistant to vancomycin (5 μg; Hardy Diagnostics, Santa Maria, CA) and penicillin (10 IU; Becton, Dickinson, Sparks, MD) disks (Fig. 1C), and there was no growth on MacConkey plates. The isolate was identified as *Capnocytophaga sputigena* by matrix-
assisted laser desorption ionization–time of flight mass spectrometry (MALDI-TOF MS) (Bruker Daltonik GmbH, Bremen, Germany) using Biotyper software with the 8468 spectrum database. The MALDI score of the isolate was 2.46, which was well above the threshold for a high-confidence species-level identification ($\geq 2.0$), and all database matches were for *C. sputigena*. Additional biochemical testing confirmed that the isolate was negative for catalase, oxidase, or indole production but positive for esculin hydrolysis, consistent with the biochemical characteristics of *C. sputigena*. Antimicrobial susceptibility testing (AST) was performed by adding 50 $\mu$l of a standard bacterial suspension (0.5 McFarland) to 11 ml brain heart infusion broth supplemented with 5% lysed horse blood due to the fastidious nature of the organism. The organism suspension was used to inoculate custom broth microdilution AST panels (Sensititre; Thermo Fisher), followed by incubation at 35°C in 6.6% CO$_2$ for 24 h. MIC values were determined for penicillin ($\geq 4 \mu$g/ml), ceftriaxone ($\geq 4 \mu$g/ml), meropenem ($\leq 0.06 \mu$g/ml), ciprofloxacin ($\leq 0.12 \mu$g/ml), levofloxacin ($\leq 0.06 \mu$g/ml), and azithromycin (0.12 $\mu$g/ml).

**DISCUSSION**

Belonging to the *Flavobacteriaceae* family, members of the genus *Capnocytophaga* are fastidious, facultatively anaerobic, indole-negative, fusiform Gram-negative bacilli, consisting of eight species, i.e., *Capnocytophaga canimorsus*, *Capnocytophaga cynodegmi*, *Capnocytophaga gingivalis*, *Capnocytophaga granulosa*, *Capnocytophaga haemolytica*, *Capnocytophaga leadbetteri*, *Capnocytophaga ochracea*, *Capnocytophaga*
sputigena, and the unnamed genospecies AHN8471 (1). As suggested by its name (the Greek “kapnos” meaning “smoke”), Capnocytophaga is capnophilic (carbon dioxide loving) and displays enhanced growth in high concentrations of carbon dioxide. Capnocytophaga species fail to grow on enteric media and are infrequently isolated from clinical samples. They are nonmotile, but their colonies on blood agar can demonstrate spreading edges with gliding motility (Fig. 1C).

Most bacteria in the genus Capnocytophaga are normal but not prominent members of the oral or nasopharyngeal microbiota of animals or humans and may cause opportunistic infections in humans. Catalase and oxidase can be used to divide Capnocytophaga spp. into zoonotic and human groups. The oxidase- and catalase-positive species C. canimorsus and C. cynodegmi are considered part of oral flora of healthy dogs and cats (2). Human clinical cases of C. canimorsus or C. cynodegmi infection are often associated with dog or cat bites or contact (e.g., licking of wounds). Conversely, the oxidase- and catalase-negative species, such as C. ochracea, C. gingivalis, C. sputigena, C. haemolytica, and C. granulosa, inhabit the oral cavities of humans. Among them, C. ochracea, C. gingivalis, and C. sputigena are considered periodontal pathogens, although they were also isolated from adults without periodontitis (1, 3, 4). Furthermore, the oxidase- and catalase-negative species can also cause extraoral infections in immunocompetent and immunocompromised patients, including septicemia, empyema, endocarditis, endometritis, osteomyelitis, soft tissue infections, peritonitis, ophthalmic lesions, and noma (1, 5).

C. sputigena bacteremia has been reported among immunocompromised patients with hematological malignancy during the neutropenic period, for instance, chronic lymphocytic leukemia, relapsed lymphoma/leukemia after hematopoietic stem cell transplantation (HSCT), or Hodgkin’s lymphoma after bone marrow transplantation (6–10). Most of these infections were found to be accompanied with oral mucositis and ulceration during chemotherapy, which may increase the risk of spreading the organisms from oral cavity to the bloodstream (9). In contrast to C. ochracea, the most frequently isolated species causing bloodstream infections in auto-HSCT patients (9), C. sputigena has been isolated from sputum or pleural fluid in rare cases of community-acquired pneumonia and empyema and from other body sites in patients with mild or unnoted mucositis (5, 6, 9, 11). Lo et al. recently reported C. sputigena pneumonia and bacteremia in an 84-year-old patient with type 2 diabetes mellitus (12). Interestingly, though C. sputigena is not present in the female genital tract, it appears to be a potential risk factor for second-trimester abortion, chorioamnionitis, and neonatal infections (13–15). Organisms introduced into the vaginal area during pregnancy may result in preterm labor as well as septicemia and respiratory failure in newborn children (13, 14).

Identification of Capnocytophaga species using conventional phenotypic methods is challenging and may present some difficulties in disease diagnosis. In positive blood culture samples, the organisms may be difficult to discern from the background due to weak staining (Fig. 1A and B). Colonies of Capnocytophaga spp. on blood agar are very small after 24 h of incubation at 37°C (Fig. 1C) and would need an additional 1 to 3 days to grow to a larger diameter for recognition. Other fastidious Gram-negative bacteria that colonize the human or animal oral cavity, such as the HACEK group (a group of Gram-negative bacilli consisting of Haemophilus spp., Actinobacillus actinomycetemcomitans, Cardiobacterium hominis, Eikenella corrodens, and Kingella spp.), may cause similar endogenous infections as Capnocytophaga species (1). As shown in Table 1, animal contact or exposure history, Gram stain appearance (typical morphology of medium-to-long fusiform cells), colony characteristics, and biochemical testing, to some extent, may be helpful to distinguish some Capnocytophaga spp. (e.g., C. canimorsus) from the HACEK group. Catalase and oxidase are useful to distinguish zoonotic C. canimorsus and C. cynodegmi from other catalase- and oxidase-negative human oral Capnocytophaga spp. However, within the oxidase-negative group, similar biochemical reactions of some species may make their phenotypic differentiation inconclusive. Of note, esculin hydrolysis is a useful biochemical test to confirm C. sputigena, which is positive. Molecular methods,
<table>
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<th>Characteristic</th>
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<th>Capnocytophaga canimorsus</th>
<th>Capnocytophaga cynodegi</th>
<th>Aggregatibacter aphrophilus</th>
<th>Aggregatibacter actinomycetemcomitans</th>
<th>Cardiobacterium hominis</th>
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like 16S rRNA gene PCR and sequencing, are considered useful diagnostic tools for the identification and differentiation of Capnocytophaga species. Commercial MALDI-TOF MS systems can reliably identify C. sputigena, and the Vitek 2 ID-NH card may also be used for genus-level identification (1).

There are no AST guidelines or interpretive breakpoints for Capnocytophaga spp. from the Clinical and Laboratory Standards Institute (CLSI) or European Committee on Antimicrobial Susceptibility Testing (EUCAST), making it challenging to perform or interpret AST results for C. sputigena. Despite this, breakpoints established for other organisms, such as anaerobes or HACEK organisms, have been used in previous studies (6, 16), resulting in Capnocytophaga spp. being considered susceptible to clindamycin, linezolid, tetracyclines, carbapenems, and beta-lactam combination agents but resistant to polymyxins. MICs are variable for aminoglycosides, cephalosporins, macrolides, and fluoroquinolones, suggesting that AST should be performed if considering these agents (17). Multidrug-resistant C. sputigena strains have been isolated from patients with bacteremia or lung abscess; a bloodstream isolate with high MICs to β-lactams (e.g., penicillins and first-, second-, and third-generation cephalosporins), ciprofloxacin, and trimethoprim was described (8), and an isolate from a lung abscess following bronchoscopy was considered resistant using EUCAST HACEK breakpoints to all tested drugs except imipenem, including penicillins, first-, third-, and fourth-generation cephalosporins, levofloxacin, azithromycin, clindamycin, and minocycline (18). Clinical treatment failure was observed on initial therapy with garenoxacin, ampicillin-sulbactam, clindamycin, and cefepime, and improvement was seen only after switching to carbapenem therapy (18). Of note, β-lactam antibiotic MICs vary among Capnocytophaga spp. Up to ~80% of Capnocytophaga species isolates may carry β-lactamases, including the extended-spectrum β-lactamases (ESBL) CfxA and CSP-1 in C. sputigena (19, 20). Such isolates are generally considered resistant to amoxicillin and most cephalosporins (19, 20). In a study on 48 Capnocytophaga isolates from periodontitis patients (21), C. sputigena was the predominant species (64%) producing β-lactamases, followed by C. ochracea isolates (11%). Interestingly, blαCSP-1 was identified only in a subgroup of these C. sputigena isolates (21). Another ESBL, TEM-17, has been described in C. ochracea, and whole-genome sequencing revealed a novel class D beta-lactamase (blaOXA-347, related to blaOXA-48) with broad-substrate specificity, including amoxicillin-clavulanate and imipenem, from animal-associated Capnocytophaga species (22, 23).

Macrolide and clindamycin resistance due to erm(C) and erm(F) genes has been described (21), and gyrA mutations are associated with fluoroquinolone resistance (7, 16, 20, 22).

In summary, we present a case on C. sputigena bacteremia in a patient with diabetes and pancytopenia. Our case illustrates the importance of accurate identification for this underappreciated but important Gram-negative organism. Notably, microbiologists and clinicians should recognize that C. sputigena strains can exhibit high MICs to β-lactam antibiotics and fluoroquinolones, necessitating antimicrobial susceptibility testing.

SELF-ASSESSMENT QUESTIONS

1. Which body site is the habitat of Capnocytophaga sputigena in mammals?
   a. Oral cavity of dogs
   b. Oral cavity of humans
   c. Female genital tract of dogs
   d. Female genital tract of humans

2. Which of the following biochemical testing results can differentiate Capnocytophaga sputigena from C. canimorsus?
   a. Catalase positive and oxidase positive
   b. Catalase negative and oxidase negative
   c. Catalase positive and oxidase negative
   d. Catalase negative and oxidase positive
3. Which of the following resistance mechanisms may be found in multidrug-resistant *Capnocytophaga sp*?  
   a. CSP-1  
   b. VanC  
   c. KPC  
   d. NDM

REFERENCES


