Capnocytophaga bacteremia in a girl with relapsed acute lymphoblastic leukemia

Taha Khattab; Sami Felimban; Basheer Ahmed; Abdullah Zayed; Abimbola Osoba; David Baker

Capnocytophaga is a gram-negative bacillus, formerly classified as an anaerobe, that can cause serious life-threatening systemic infections in immunocompromised patients, particularly in granulocytopenic patients with oropharyngeal ulcerations. Severe infections due to this organism, such as bacteremia, meningitis and endocarditis have also been described in immunocompetent patients.[1-5]

We report the case of an 11-year-old girl who developed *Capnocytophaga* septicemia whilst granulocytopenic during re-induction for relapsed acute lymphoblastic leukemia (ALL). To our knowledge, this is the first reported case of this infection in Saudi Arabia.

Departments of Paediatrics & Microbiology, King Khalid National Guard Hospital, Jeddah, Saudi Arabia.

Correspondence to:
Dr. T. Khattab
Department of Paediatrics,
King Khalid National Guard Hospital,
P. O. Box 9515,
Jeddah. 21423
Saudi Arabia
E-mail : khattabt@hotmail.com

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Case

An 11-year-old Saudi girl diagnosed with ALL was admitted to hospital with febrile neutropenia associated with cough. She was on week 50 of maintenance therapy for standard risk ALL (CCG1991). She was given empiric first line intravenous (IV) antibiotic therapy (ceftazidime, amikacin and vancomycin). At 7 days she continued to be neutropenic with frequent spikes of temperature. Abdominal examination showed increasing hepatosplenomegaly. Viral hepatitis screen was negative. By day 10 of admission she was found to have blast cells in the peripheral blood. Bone marrow aspiration confirmed relapsed leukemia and the cerebrospinal fluid (CSF) was negative for blast cells. The patient was reinduced using the BFM-REZ 96 relapse protocol (dexamethasone, vincristine, methotrexate, L-asparaginase and intrathecal triple chemotherapy). Fluconazole was added later due to suspected oral candidiasis, but systemic antibiotics were ceased after 10 days due to negative cultures in association with absence of fever for 2 days and an absolute neutrophil count (ANC) of 300/mL. On day 15 the patient was discharged against medical advice despite having mild mucositis, occasional vomiting and poor oral intake. Within 48 hours (on day 17) she was readmitted with a temperature 38°C, extensive oropharyngeal mucositis, moderate dehydration and tachycardia but normal blood pressure. The CBC on admission showed Hb 10.9 g/L, WBC 0.3X109/L, an ANC of 100 and platelets 26X109/L. Empiric IV ceftazidime, amikacin, vancomycin and fluconazole were commenced with fluid resuscitation. Empiric IV metronidazole was added one day later because of increasing ulcerative stomatitis and persistent fever. High-dose cotrimoxazole for presumptive *Pneumocystis carenii* pneumonitis (PCP) was also added later on the same day, due to an increasing respiratory rate in association with a fall in oxygen saturation (arterial oxygen $Pa0_2$ of 7.5 Kp) and a chest x-ray demonstrating interstitial infiltrates. Two days from the second admission (day 19), a rounded necrotic lesion developed on the dorsum of the right hand which was clinically suspicious of *Pseudomonas* or fungal infection. Consequently, liposomal amphotericin B (Abelcet) was commenced and intravenous fluconazole was discontinued. On day 20 the right hand lesion became bullous and its scrapping grew *Aspergillous spp.* Over the next few days, the respiratory distress resolved and several oral swabs and scrapings failed to reveal evidence of *Candida* or Herpes simplex virus. However, blood cultures performed on readmission (day 17) subsequently grew a gram-negative filamentous organism, identified as *Capnocytophaga spp.* sensitive to ceftazidime and metronidazole, 5 days later (day 22). Appropriate intravenous antimicrobial therapy was continued (ceftazidime, amikacin, metronidazole and Abelcet) for 12 days until her neutrophils regenerated. On day 29 from first admission the patient was discharged home in a stable condition.

Microbiological Investigations

The organism was initially isolated from an anaerobic blood culture bottle and subsequently subcultured on sheep blood agar under anaerobic conditions. The organism was non-haemolytic and the colonies had a yellowish pigment, with finger-like projections (gliding motility). The organism grew on chocolate agar but not on MacConkey

agar. On gram stain microscopy, it was shown to be a gram-negative bacillus with fusiform morphology. It had moderate biochemical activity but was oxidase, catalase and indole negative. Identification was confirmed by the API system (bioMerieux SA, 69280 Marcy, L'Etoile, France.). Susceptibility testing by the Kirby-Bauer technique showed the organism to be resistant to gentamicin, amikacin, cotrimoxazole and penicillin but susceptible to ceftazidime, ceftriaxone, cefuroxime, ciprofloxacin, metronidazole and imipenem. The identity of the organism was confirmed by OmniLabs Pathological Services, Harley Street, London.

Discussion

Capnocytophaga ("eater of carbon dioxide") species, previously known as *Bacteriodes ochraceus*, are indigenous to the oral cavity and are one of the etiologic agents in juvenile periodontal disease in immunocompetent individuals.[1] Immunocompromised patients with granulocytopenia are susceptible to septicemia with *Capnocytophaga*, usually in association with dental infections, stomatitis, or intraoral ulcerations.[1-5] Some studies have suggested that *Capnocytophaga septicemia* is more common in children than in adults.[1]

The case presented here shows typical clinical features of *Capnocytophaga* infection, highlighted by extensive oropharyngeal ulceration in an immunocompromised febrile neutropenic patient not responding to empiric first-line antibiotic therapy. Smears from the oral lesions were negative for *Candida* and Herpes simplex virus. First-line antimicrobial agents used in this patient included ceftazidime, amikacin, and vancomycin, the latter due to a high incidence of gram-positive organisms in the blood cultures of our patient population who present with fever and neutropenia. In addition, fluconazole, cotrimoxazole, metronidazole and lipid complex amphotericin B were subsequently added on clinical grounds. Clinical response occurred when metronidazole was added to the ceftazidime, as the organism was susceptible in vitro to both ceftazidime and metronidazole but resistant to cotrimoxazole.

The pathogenesis of *Capnocytophaga* is unclear, as it does not appear to produce any endotoxins. However, Shurin et al[7] have demonstrated a dialyzable material from clinical isolates that inhibits granulocyte motility. The combination of leukocyte immobility and the organism's gliding motility appear to predispose these organisms to blood stream invasion from sites of infection in the oral cavity.[6,7] Considerable interest has been focused recently on *Capnocytophaga* because it has been shown to be a predominant cultivable organism in the advancing front of periodontal lesions in individuals with juvenile onset diabetes, and in individuals with defects in neutrophil adherence or chemotaxis, or both.[8] The organism has been recognized increasingly as a cause of bacteremia in immunocompromised granulocytopenic patients, and more recently it has been reported in immunocompetent patients as a cause of sepsis and local infections.[8]

There have been some reports that blood isolates of *Capnocytophaga* demonstrate enhanced serum resistance when compared with isolates from the human subgingival plaque. A mutation leading to a change in liposaccharide structure of the cell wall has been thought to be responsible for this increased serum resistance and pathogenicity of these blood isolates.[1]

Clinicians should consider *Capnocytophaga bacteremia* in the differential diagnosis of febrile neutropenia in immunocompromised patients in the setting of persistent fever and oropharyngeal mucositis or ulceration. The diagnosis can be rapidly confirmed if the microbiologist is alerted to this clinical suspicion and appropriate laboratory studies are undertaken. Clinical response can then be expected with appropriate antimicrobial therapy.

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