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CASE REPORT

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Capnocytophaga sputigena bloodstream infection in hematopoietic stem cell transplantations: two cases report and review of the literature

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ABSTRACT

Capnocytophaga is a group of facultative anaerobic gram-negative bacteria present in the oral cavity of humans, dogs and cats, as part of their normal oral flora. Here, we described two cases of bloodstream infections (BSI) caused by *Capnocytophaga* in neutropenic autologous hematopoietic stem cell transplantation (auto-HSCT) patients with mucositis (Grade I and Grade III) identified by Maldi-Tof. They were successfully treated with β-lactam (meropenem and piperacillin-tazobactam). The species *C. sputigena* was confirmed by 16S rRNA gene sequencing in one patient. The review of literature showed that *C. ochraceae* was the most frequent species causing BSI in auto-HSCT patients and that the patients usually presented mucositis and were neutropenic at the onset of the infection.

KEYWORDS: *Capnocytophaga*. Bloodstream infection. Hematopoietic stem cell transplantation.

INTRODUCTION

Capnocytophaga is a group of facultative anaerobic gram-negative bacteria, belonging to the *Flavobacteriaceae* family. These organisms are present in the oral cavity of humans, dogs and cats, as part of their normal oral flora[1,2]. Up to now, there are nine *Capnocytophaga* species reported in human oral microbiota: *C. gingivalis, C. granulosa, C. haemolytica, C. leadbetteri, C. ochracea, C. sputigena, C. genospecies* AHN8471; while *C. canimorsusand C. cynodegmi* are described in the oral microbiota of dogs and cats[3]. All the species have been reported as pathogens in humans.

Capnocytophaga spp. has been described as cause of bloodstream infections (BSI), both in immunocompetent and immunocompromised hosts. Although mucositis is very frequent during chemotherapy, up to now, few cases of BSI caused by *Capnocytophaga* have been reported in hematopoietic stem cell transplantation (HSCT) patients[4-9].

We described here two cases of *Capnocytophaga* BSI in autologous HSCT (auto-HSCT) patients at the Bone Marrow Transplantation Unit of Hospital das Clinicas of University of Sao Paulo observed in 2018, and we also reviewed the main aspects concerning this infection in the literature.

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CASE REPORT

Case 1

A 23-year-old man who had been diagnosed with Hodgkin's Lymphoma in 2015 with an IIA initial stage and refractoriness to multiple chemotherapy regimens was admitted to the bone marrow transplantation ward. The patient was submitted to an autologous stem cell transplantation (auto-HSCT) after a conditioning with CBV (cyclophosphamide-carmustine-etoposide).

The patient had a history of obesity grade III, with a body mass index (the weight in kilograms divided by the square of the height in meters) of 53.76 on the admission's day, systemic arterial hypertension and onychomycosis in both feet. He lived with his parents and two younger brothers and had two dogs that were kept outdoors.

The patient was colonized by *K. pneumonia* carbapenem-resistant and VRE, he had mobilized peripheral blood progenitor cells (PBPCs) during the chemotherapy with gemcitabine plus vinorelbine in March 2018 with 1,800 mcg of GCSF and collected 5.8 x 10^6 CD34+ cell per kg/body weight by a long-term hemodialysis catheter (permcath) that was preserved for the PBPCs infusion. During this hospitalization, he used prophylaxis against infections with a single dose of ivermectin, cotrimoxazole until D-1, fluconazole in the neutropenic period and acyclovir. On day +1 the patient complained of mouth pain due to grade I oral mucositis, even if he had been on laser prophylaxis daily. On day +2 he presented with low-grade axillar fever (37.8 ºC) and chills, so that blood and urine cultures were taken and he was started on meropenem (2 g de 8/8 h). As the patient continued to present with daily fever and the C-reactive protein increased to 173 mg/L on day +4, blood culture taken through a peripheral vein yielded a gram-negative rod on D+5 and the medical team decided to introduce amikacin and vancomycin,

On day +7, the laboratory identified *Capnocytophaga* spp. in blood cultures from the peripheral vein using Maldi-Tof (BioMérieux, France, Crapone, France) and the catheter was removed on the same day. As the neutrophils grafting happened on day +9 and the skin infection got better, gram-positive coverage was discontinued and the patient finished a 10 day-treatment with meropenem.

The 16S rRNA gene sequencing was performed through the MicroSeq 500 system (AppliedBiosystems, Foster City, CA, USA) with PCR and sequencing kits designed with universal primers to cover all the bacteria, as the biochemical methods did not identify the *Capnocytophaga* species. Sequences were analyzed by using an ABI PRISM 3730 Series DNA Analyzer (Applied Biosystems, Foster city, CA, USA) and showed 100% identity with the GenBank sequence MH078434.1 (*C. sputigena)*.

Case 2

A 50-year-old male who had been diagnosed with Peripheral T-cells NOS Lymphoma in 2017 was admitted to the bone marrow transplantation ward to receive an auto-HSCT.

He lived with his family and had a dog that lived in the same house. He was colonized with VRE five months prior to this ward admission. During this hospitalization, he was submitted to CBV (cyclophosphamide-carmustine-etoposide) conditioning, used prophylaxis against infections with a single dose of ivermectin, cotrimoxazole until D-1, fluconazole in the neutropenic period and acyclovir.

On day D+2 his leukocyte count came down to less than 500. On day D+4 he experienced grade III mucositis, even receiving laser prophylaxis daily. The C-reactive protein increased to 321 mg/L on day +7 and he presented with fever (38.1 ºC) without chills. He was started on linezolid and piperacillin tazobactam, as he was diagnosed with severe mucositis and febrile neutropenia.

As the patient's condition improved, he remained for 48 hours without fever and the neutrophils grafting happened on day +11, so that the medical team decided to discontinue the antibiotic. On day +10 the blood culture from the catheter yielded a gram-negative rod and on D+14 the laboratory identified *Capnocytophaga* spp. using Maldi Tof (BioMérieux, France, Crapone, France). The blood cultures from the peripheral veins resulted negative and the catheter was removed.

The most important clinical and microbiological characteristics of our case report and the review of cases of *Capnocytophaga* spp. BSI in HSCT patients described in the literature are shown in Table 1.

DISCUSSION

We described two cases of BSI caused by *Capnocytophaga* in neutropenic auto-HSCT patients with mucositis, that were successfully treated with β-lactam (meropenem and piperacillin-tazobactam). The CVC was removed in both patients and the species *C. sputigena* was confirmed by sequencing in one patient.

Although *C. sputigena* is part of the human oropharyngeal microbiota, it has been reporting causing infections in neutropenic patients with mucositis[10-11]. *Capnocytophaga sputigena* BSI has been described as well in non-neutropenic patients[12]. A recent report described a patient with diabetes mellitus and gastric cancer that

Table 1 - Clinical and microbiological characteristics of BSI by *Capnocytophaga* spp in HSCT patients described in the literature and in these two cases report.

Articles	Isolated species	Site of infection	Underlying disease	Type of HSCT	Mucositis	Day of sepsis onset after HSCT	Risk fator for BSI	Treatment	Identification of bacteria	Outcome
Ugai *et al.*[4]	*C. canimorsus*	Blood stream infection	acute myeloid leukemia	mismatched unrelated donor	No	7 years earlier HSCT	Chronic GVHD, but no IST; marked splenic atrophy on CT history of licked wound by a dog 2 days before admission	meropenem and vancomycin followed by ceftriaxone	No data avaliable	Discharged
García-Cía *et al.*[5]	*C. sputigena* plus Escherichia coli	Blood stream infection	Hodgkin's lymphoma	Autologous HSCT	Yes	D+2	Neutropenia	amoxicillin/ clavulanate followed by cefepime and amikacin	No data avaliable	Discharged
Bonatti *et al.*[6]	*C. ochraceae*	Blood stream infection	chronic myelogenous leukemia	No data available	Yes	D+9	Neutropenia	Cefandamole, amikazin vancomycin followed by Imipenem–cilastatin, PenG	RAPID-ANA II System (Innovative Diagnostic Systems, Inc., Norcross, GA, USA); Restriction fragment length polymorphism (RFLP)	Discharged
Bonatti *et al.*[6]	*C. ochraceae*	Blood stream infection	chronic myelogenous leukemia	No data available	Yes	D+9	Neutropenia	Cefamandole, tobramycin, vancomycin followed by Piperacillin–tazobactam	RAPID-ANA II System (Innovative Diagnostic Systems, Inc., Norcross, GA, USA); Restriction fragment length polymorphism (RFLP)	Discharged
Bonatti *et al.*[6]	*C. ochraceae*	Blood stream infection	acute myeloid leukemia	No data available	Yes	D+6	Neutropenia	Cefamandole, amikacin vancomycin followed by Imipenem–cilastatin	RAPID-ANA II System (Innovative Diagnostic Systems, Inc., Norcross, GA, USA); Restriction fragment length polymorphism (RFLP)	Discharged
Bonatti *et al.*[6]	*Capnocytophaga* sp	Blood stream infection	chronic myelogenous leukemia	No data available	Yes	D+8	Neutropenia	Cefamandole followed by Imipenem–cilastatin	RAPID-ANA II System (Innovative Diagnostic Systems, Inc., Norcross, GA, USA)	Discharged
Geisler *et al.*[7]	*C. gingivalis*	Pneumonia	Acute myelogenous leukemia	Autologous HSCT	Yes	No data avaliable	Neutropenia	Gentamicin and levofloxacin followed by linezolid and metronidazole	Morphology and the following biochemical reactions	Discharged
Bilgrami *et al.*[8]	*Capnocytophaga* sp	Blood stream infection	Hodgkin's disease	Autologous HSCT	Yes	D+3	Neutropenia	Ceftazidime and clindamycin followed by ampicillin	API AN-Ident System (Analytic Products, Plainview, NY)	Discharged
Baquero *et al.*[9]	*C. ochraceae*	Blood stream infection	acute myeloid leukemia	Autologous HSCT	Yes	D+2	Neutropenia	Ceftazidime amikacin followed by piperacillin and subsequently clindamycin	Morphology and the following biochemical reactions	Discharged
This report	*Capnocytophaga* sp	Blood stream infection	Hodgkin's lymphoma	Autologous HSCT	Yes	D+5	Neutropenia	Meropenem	MALDI-TOF	Discharged
This report	*Capnocytophaga* sp	Blood stream infection	Peripheral T-cells NOS Lymphoma	Autologous HSCT	Yes	D+10	Neutropenia	Piperacillin tazobactam	MALDI-TOF 16sRNA sequencing	Discharged

developed an infection by *C. sputigena*[12]. It is a rare opportunistic pathogen that causes infection in HSCT patients. Here we described the first case of BSI caused by *C. sputigena* in an auto-HSCT patient. So far, *C. ochraceae* has been reported as the most frequent species causing BSI in this population of patients, mainly during neutropenia and in patients with mucosistis[9].

The two *Capnocytophaga*'s infections reported in this article illustrated the hazardous potential of this bacteria to cause BSI coinciding with the onset of mucositis, which represents the main portal of entry for this organism, particularly the *C. sputigena,* during the conditioning regimen for auto-HSCT. Moreover, our report highlights the importance of a good oral hygiene and the multidisciplinary team care procedures such as the laser prophylaxis in the peri-transplantation period. Interestingly, both patients had previous contact with dogs and presented mucositis as well. Thus, the species identification is essential to establish that the source of infection and in our patients it was probably the mucositis. Regrettably, we could identify the species by

16SRNA sequencing as *C. sputigena* in only one patient. This is a limitation of our report as the species identification is key to implementinfection control measures and patients care as the species can hypothesize the source of infection such as the animal contact[10].

Since there is no Clinical & Laboratory Standards Institute (CLSI) nor European Committee on Antimicrobial Susceptibility Testing (EUCAST) recommendation for susceptibility break points for this genus; the spectrum of antibiotics and the duration of treatment is based on clinical reports[13]. Antimicrobial susceptibility of *Capnocytophaga* spp. using different methods have shown that clindamycin, linezolid, tetracycline, chloramphenicol, imipenem and β-lactamase inhibitor combinations displayed *in vitro* activities against this bacterium. In contrast, most strains are reported as resistant to polymyxin, fusidic acid, fosfomycin and trimethoprim[13]. A recent study, however, demonstrated that a high proportion of *Capnocytophaga* sputigena isolates were β-lactamase-positive and that β-lactam-resistant isolates, resistant to amoxacillin, amoxacillin plus clavulanic acid and third generation cephalosporins, harboured the β-lactamase genes bla_{CfxA} or bla_{CSP-1}[14]. CSP-1 is a novel extended-spectrum β-lactamase produced by a clinical isolate of *C. sputigena*[15]. Thus, it is important to highlight that *C. sputigena* carrying β-lactamase genes can be resistant to amoxacillin, amoxacillin plus clavulanic acid and third generation cephalosporins.

CONCLUSION

Capnocytophaga sputigena BSI can occur in auto-HSCT neutropenic patients with mucositis mainly during neutropenia and can be successfully treated with meropenem or piperacillin tazobactam. This report highlights the importance of *Capnocytophaga* species identification to guide the HSCT patients' care as well as preventive measures during the peri-transplantation period.

CONFLICT OF INTERESTS

On behalf of all authors, the corresponding author states that there is no conflict of interest.

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