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CASE REPORT
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Diabetic foot infection caused by bacteria of the *Burkholderia cepacia* complex: report of an unusual case and a scoping literature review

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ABSTRACT

Burkholderia cepacia complex (BCC) is group of widespread gram-negative bacillus organized in over 20 phylogenetically distinct bacterial species. According to previous studies, BCC species pathogens are widely reported in patients with cystic fibrosis (CF), but not in individuals with diabetes mellitus (DM). In this case report, a 42-year-old male patient with DM and a foot infection caused by BCC is presented. The patient was hospitalized after antibiotic treatment failure and improved after two surgical debridement procedures and a high-dose extended infusion (EI) of meropenem. The team of vascular surgeons and the infectious disease specialists worked fervently to solve the case. Finally, a scoping review was conducted to map BCC infections in patients with DM.

KEYWORDS: *Burkholderia cepacia* complex. Diabetic foot infection. Non-cystic fibrosis patients.

INTRODUCTION

The *Burkholderia cepacia* complex (BCC) is a group of universal non-glucose fermenter aerobic gram-negative bacilli organized into at least 20 phylogenetically related bacterial species and can be recognized by the *recA* gene sequences analysis[1]. *Burkholderia cenocepacia* is the most virulent species associated with human diseases, which causes higher mortality rates than any other *Burkholderia* spp. In addition, *B. cenocepacia* causes recurrent respiratory infections in patients with cystic fibrosis (CF), and it is associated with other healthcare-associated disorders[1]. It is essential to highlight that severe infections caused by other species have been reported, like *Burkholderia multivorans* and *Burkholderia dolosa*[1].

The various BCC species are not the most common pathogens causing skin and soft tissue infections (SSTIs)[2], especially in diabetic patients with polymicrobial flora[1]. This case is reported here due to the BCC infection and its rarity in non-cystic fibrosis patients, in addition to its intrinsic resistance to several antimicrobial drugs. A scoping review was also conducted to map the relevant publications on the association between diabetes mellitus (DM) and BCC infections.

CASE REPORT

In October 2018, a 42-year-old male patient with type-2 DM (T2DM) reported he played soccer in a muddy soccer field that contained rubbish and dog feces, where

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and when he likely suffered a plantar puncture injury caused by a piece of glass, which he did not notice right after the game because he suffers from small-fiber DM neuropathy.

Once he realized what had happened, he came to our emergency room (ER) to seek the surgical removal of the glass fragment. Two days after that, the patient came back to the ER with intense pain, erythema and swelling at the plantar site of his left foot. During a consultation, the emergency physician prescribed a seven-day course of amoxicillin/clavulanate 875/125 mg orally (PO), twice daily (q12h) associated with ciprofloxacin 500 mg PO q12h. As no clinical improvement was noted, the patient sought medical care for the third time and was hospitalized for evaluation by the vascular surgery team (VST). The wound was categorized as PEDIS 3 infection severity (PEDIS: P = perfusion, E = extent/size, D = depth/tissue loss, I = infection, S = sensation). The PEDIS 3 grade corresponds to a moderate infection as it extends beyond the subcutaneous tissue or the erythema surpasses a 2-cm rim on the ulcer. No systemic signs of infection were noted.

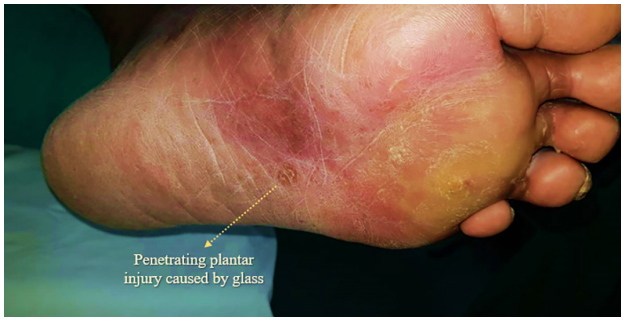

Figure 1 – Clinical aspect of the patient's foot on admission.

The patient's follow-up showed a preserved mental state; systemic blood pressure was 130/80 mm Hg; heart rate was 97/min; temperature was 36.4 °C; respiratory rate was 16/min, and body mass index (BMI) was > 30 kg/m^2. From the findings of laboratory tests on admission, hemoglobin = 12.4 g/dL; white cell count = 10,700/mm^3 (neutrophils, 73.2%; eosinophils, 1.9%; lymphocytes, 20.4%; monocytes, 4.2%); platelets = 304 x 10^3/mm^3; glycemia = 119 mg/dL; creatinine = 0.72 mg/dL, and blood urea nitrogen (BUN) = 10.27 mg/dL. Based on the above mentioned parameters, the VST decided on a surgical approach: they performed a debridement and a decompressive fasciotomy and the main intraoperative finding was the presence of a mild and thick exudate, friable tissue and inflammatory signs restricted to the aponeurosis. Afterward, the VST started with clindamycin 600 mg IV four times a day (q6h) and ciprofloxacin 400 mg IV q12h. However, a new debridement was necessary due to the lack of clinical improvement. Despite the new surgical procedure, the infection remained at the aponeurosis level.

Due to therapeutic failure, an infectious disease team was consulted, and afterwards the VST started with piperacillin/tazobactam 4.5 gm IV q6h in a 4-hour extended infusion (EI). After 48 h, inflammation signs persisted and an additional surgical approach was recommended due to the soft tissue culture result from the first surgical procedure which had isolated and identified bacteria belonging to the *Burkholderia cepacia* complex (VITEK® 2) after plating soft tissue fragments and deep exudate on 5% sheep blood agar in aerobic conditions. These bacteria were susceptible only to meropenem (minimum inhibitory concentration (MIC) = 2, VITEK® 2), according to the Clinical and Laboratory Standards Institute on Antimicrobial Susceptibility Testing published in 2018[3]. Then, we prescribed meropenem at 2 gm IV q6h in a 3-hour EI after considering MIC = 2, BMI > 30 kg/m^2 and the patient's microangiopathy as a major obstacle to achieving the treatment goal with a high probability of target attainment (PTA).

After 24h of meropenem treatment, the clinical improvement was evident. An magnetic resonance imaging of the foot revealed signs of phalangeal osteomyelitis in the third and fourth toes, as well as ulcerations and fistulous pathways of the cutaneous, subcutaneous and deep myoadipose tissues in the plantar region of the forefoot. Thus, we chose a conservative treatment with 14 days of meropenem. At the end of the first-year of follow-up, mild infections occurred but amputation was not required.

DISCUSSION

BCC ranges from relatively mild infections to sepsis, especially in patients with CF or chronic granulomatous disease. Some previous studies argued that BCC is not a common pathogen in diabetic foot infections (DFI)[4,5]. The present case shows the importance of collecting tissue samples for microbiological diagnoses and is unique since it gave us the chance to identify a rare microorganism in DFI, such as BCC, which is aggressive and naturally resistant to several antimicrobials. Our hospital protocol considers the following items to decide on antibiotic therapy and hospitalization: PEDIS severity classification, hospitalization in the last six months, antimicrobial therapy for any reason in the previous three months and previous colonization/infection by a multidrug-resistant microorganism. The protocol does not contemplate uncommon pathogens, except for an ongoing outbreak or endemic scenario. Regarding therapeutics, the choice of treating osteomyelitis for 14 days is graded as a moderate recommendation, according to the IWGDF 2019 update[2]. Despite the clinical improvement using meropenem in

this case, *in vitro* studies showed that the combination of two or three medicines drugs is more effective than the monotherapy[6,7]. Nevertheless, these positive outcomes were from *in vitro* investigations with BCC isolated from CF patients, who are used to double or triple antibiotic combinations instead of single therapy. Therefore, clinical trials on BCC infections are needed to obtain a stronger degree of evidence.

Because of the case's rarity, a systematic search was conducted using the Preferred Reporting Items for Systematic Reviews and Metanalyses checklist to address preceding relevant data regarding the relationship between DM and BCC infections in non-CF patients[8]. The systematic research was not recorded in the International Prospective Register of Systematic Reviews (PROSPERO) since scope reviews do not meet the registration requirements of the platform[9]. A search was conducted in PubMed and Scopus using search key words relevant to *Burkholderia cepacia* complex and DM. This study applied the MeSH terms in PubMed and Doc Title, Abstract and Keyword (TITLE-ABS-KEY) in Scopus (Supplementary Figures S1 and S2) and included all types of articles and case reports. The relevant titles and abstracts were added, except for papers those that addressed infections in individuals with CF. Full texts were included in observational studies about the presence of DM as an underlying condition or cases of infections caused by BCC in diabetic patients. In addition, references cited in qualified studies were visually checked. Two investigators independently screened the records for eligibility based on titles and abstracts and assessed the full text of each study to extract meaningful data. Opinions from a third review author were sought to resolve disagreements.

Out of 138 records identified (Supplementary Figures S1 and S2), seven fulfilled the described inclusion criteria, three were observational investigations and four were case reports (Table 1). The most recent evidence is a retrospective cohort study that establishes DM as a risk factor for mortality, but in a univariate analysis[10]. One retrospective study concerning the risk factors for mortality in DFI found BCC as a pathogen in two cases of SSTIs (2/401, 0.5%)[11]; other publications refer to two case reports of BCC's SSTI and eye infections – observational study and case report[12-16] (Table 1). Thus, only two cases of DFI caused by BCC were identified in our systematic search. The pyomyositis case report clarified that the right thigh and right shoulder were the primary sites[13].

Regarding BCC's potential to infect non-CF patients, a plausible hypothesis was that a lineage was infecting organs other than the lung since we did not determine the BCC species and its virulence factors[17]. Although BCC has had a low virulence history, the findings of molecular epidemiology reveal that highly transmissible strains emerge unsystematically. BCC can produce rapid mutation and adaptation, and a complex genome is split into chromosomes[18]. In addition, virulence elements may not be allocated equally among *B. cenocepacia*[19]. In a cohort of patients with BCC bacteremia, non-CF patients has a higher 14-day mortality risk compared with those with CF. This investigation showed a strong correlation between bacteremia produced by two strains of *B. cenocepacia* (genomovar III) and mortality[19]. Undoubtedly, the most complicated factor in infections caused by BCC is its intrinsic resistance to several antimicrobials. Primary cellular resistance tools, membrane impermeability, and drug

Table 1 - Relevant studies concerning BCC infection in DM patients without CF.

Article	Study design	BCC infection in a patient with DM
Ku *et al*.[10]	Retrospective cohort study Clinical characteristics and laboratory parameters of 27 patients with positive blood cultures to BCC. Outcome: overall 28-day mortality	Based on a univariate analysis, DM was a risk factor for mortality
Sen and Demirdal[11]	Retrospective cohort study Objective: Risk factors for mortality in DFI	BCC was a pathogen in two cases of SSTI (2/401, 0.5%)
Fadini *et al.*[12]	Case report	Deep neck abscess (SSTI)
Saran *et al*.[13]	Case report	Spread pyomyositis (SSTI)
Pathengay *et al*.[14]	Case report	Recurrent endophthalmitis caused by BCC
Ibrahim and Yap[16]	Case report	BCC keratitis in an elderly patient
Muda *et al*.[15]	Retrospective observational study Objectives: clinical presentation, systemic risk factors, source of the infectious microorganism, treatment outcomesand prognostic indicators of endogenous endophthalmitis	Endophthalmitis (1/120, 0.83%)

CF = cystic fibrosis; DM = diabetes mellitus.

extrusion through efflux pumps provide extensive defense against distinct antimicrobials classes. Nevertheless, BCC strains remain partly susceptible to ticarcillin, ceftazidime, quinolones, minocycline, tobramycin, meropenem, and trimethoprim/sulfamethoxazole[20].

In conclusion, there are insufficient data to define the risks of BCC infection in diabetic patients and patients with DFI. Hence, a detailed anamnesis and an initial therapeutic failure are fundamental clues when considering BCC treatment.

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CONFLICT OF INTERESTS

The authors report no conflict of interests.

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