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Catheter Related Bloodstream Infection by *Brevibacterium casei* in a Patient with B Cell Acute Lymphoid leukemia - A Case Report

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ABSTRACT

Patients with long term indwelling catheters with underlying immunosuppression or comorbid conditions are predisposed to develop catheter related blood stream infections with unusual organisms. *Brevibacterium* spp. are catalase-positive, non spore-forming, non-motile, aerobic, Gram-positive bacteria. *Brevibacterium* spp were not considered a human pathogen, until recently few infections were noted. We report a case of catheter related blood stream infection by *Brevibacterium casei* in 17 year old young adult with B cell acute lymphoid leukemia. Patient was treated successfully with intravenous Vancomycin and Piperacillin-tazobactam along with peripherally inserted central catheter removal.

Keywords: *Brevibacterium casei*, Catheter related blood stream infections, Sepsis, Immunocompromised

INTRODUCTION

Indwelling catheter related blood stream infections (CRBSI) pose a massive challenge, especially in the management of patients who are immunocompromised or receiving cancer chemotherapy. Chemotherapy induces long-term neutropenia, which greatly increases the risk of infection. [1] Although the spectrum of possible pathogens from CRBSIs in clinical settings is rapidly growing and the most common organisms isolated are coagulase-negative *Staphylococci* and *Staphylococcus aureus.* [1] *Brevibacterium* spp. was not considered as human pathogens, until recently few infections were noted in immunocompromised patient. Literature regarding the infection is also sparse, so we found it worthwhile to report this case of CRBSI and sepsis with *Brevibacterium casei* in patient with acute lymphoid leukemia (ALL).

CASE REPORT

A 17 years old male patient with B-cell ALL was admitted with history of high grade fever since one day. He had received bone marrow transplant 6 months before. Combination chemotherapy was given and complete remission was achieved. Patient was on maintenance chemotherapy with CNS prophylaxis. Patient had developed fever with chills 9 days after maintenance therapy. He appeared toxic, with temperature 102.8^0 F, pulse rate 110/min, respiratory rate 26/min and blood pressure 90/60 mm Hg. Systemic examination was unremarkable.

The complete blood cell count (CBC) at the time of fever included a white blood cell count of 1783 mm^3/L with absolute neutrophil count of 387 mm^3/ L, haemoglobin of 7.17 g/dL and a platelet count of 55×10^3 mm^3/ L. C-reactive protein was 9.1 mg/dL. Renal function tests and urine routine examination did not show any significant abnormality. Two sets of blood cultures were taken from the peripheral vein and peripherally inserted central catheter

(PICC) line. The PICC was removed on the day of hospital admission. As his whole blood cell counts revealed pancytopenia; he was then put on antibiotic Piperacillin-tazobactam empirically.

After 24 hours of incubation in automated blood culture system (BD BACTEC ™ FX Instrument, Becton Dickinson, USA), blood culture bottles flagged positive for growth. The differential time to positivity (DTP) between blood taken from PICC and the peripheral vein was 5 hours 20 minutes. The Gram stain smears from blood culture bottles showed Gram positive, slender, slightly curved, rod shaped bacteria. After 24 hours of incubation at 37°C in a CO_2 atmosphere, on sheep blood agar colonies were grayish-white in colour, non-haemolytic, smooth, round and had a distinctive cheese odour (Figure 1). No colony growth was observed on MacConkey agar. On nutrient agar, colonies were small, opaque, convex, with a shiny, smooth surface. After 4–7 days of incubation the colonies became large, 2–4 mm in diameter. (Figure 2) The isolate was catalase positive, oxidase negative and non-motile. On further biochemical testing, glucose was oxidized, urea was not hydrolysed, nitrates were reduced to nitrites, esculin and gelatin hydrolysis was positive. It was presumptively identified as *Brevibacterium* spp. Subsequently, it was identified as *Brevibacterium casei* (*B. casei)* by Matrix-Assisted Laser Desorption/Ionization-Time of Flight Mass Spectrometry (MALDI TOF MS) (bioMérieux, France) with 99. 9 confidence value. Diagnosis of CRBSI caused by *B. casei* was made. Vancomycin was then added to the treatment protocol.

Antimicrobial susceptibility testing was done and interpreted as per Clinical and Laboratory Standards Institute (CLSI) M45 recommendations for *Corynebacterium* spp.[2] The isolate was found to be susceptible to Vancomycin (MIC 0.25 μg/mL), Meropenem (MIC 0.5 μg/mL), Cefepime (MIC 1 μg/mL) and Gentamicin (MIC 2 μg/mL). Resistance was noted for Penicillin (MIC $\geq$ 8 μg/mL) Cefotaxime (MIC $\geq$ 4 μg/mL), Clindamycin (MIC $\geq$ 4 μg/mL) Ciprofloxacin (MIC $\geq$ 4 μg/mL) and intermediate susceptibility was observed for Erythromycin (MIC 1 μg/mL). Fever subsided after 24 hours of antibiotic therapy. Two follow-up blood cultures were collected in the subsequent weeks which were negative for any bacterial growth. The patient recovered 10 days after starting therapy. Bacteraemia due to the *B. casei* had not recurred for more than six months.

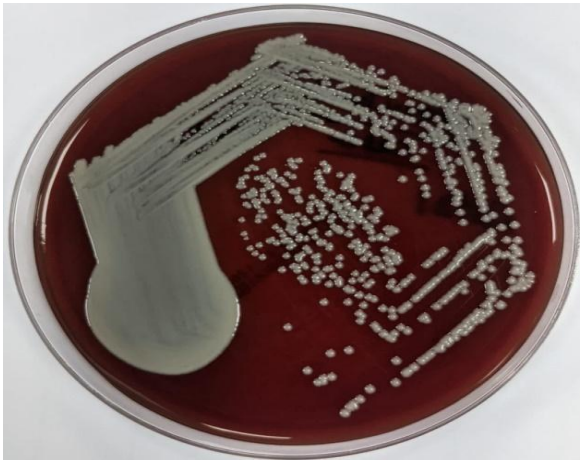

Figure 1: Grayish-white, non-haemolytic, smooth colonies *B. casei* on a sheep blood agar

Figure 2: Opaque, convex, shiny, smooth colonies *B. casei* on a nutrient agar

DISCUSSION

The genus *Brevibacterium* was established in 1953 by Breed and is characterized by non-sporing, non-motile, catalase-positive, Gram-positive rods. [3] In nature, *Brevibacterium* contributes notably

to the aroma and colour (orange pigment) of surface-ripened cheese. The organism can also be found in raw milk and human skin. [4] Presently, the genus *Brevibacterium* consists of 45 different species, of which only nine, namely, *B. linens*, *B. casei*, *B. epidermidis*, *B. iodinum*, *B. mcbrellneri*, *B. otitidis*, *B. paucivorans*, *B. sanguinis* and the recently described *B. massiliense* have been isolated from clinical samples. Not only *B. casei* is by far the most frequently isolated *Brevibacterium* species from otherwise sterile human sites but also opportunistic infections by *B. casei* mostly in nosocomial settings, are on the rise. [4] Reports of *Brevibacterium* causing a variety of infections like bacteraemia with sepsis, brain abscess, peritonitis and endocarditis have been documented.[1, 5-9] Most patients had presented with specific underlying conditions such as malignant tumours, renal failure or an immunocompromised status. [1, 7-9] However, Kumar VA et al [4] and Ulrich S et al [10] had reported *B. casei* infection in immunocompetent patients. Long term medical catheters are often required for treatment in patients with underlying diseases such as malignant tumours, renal failure or an immunocompromised status. These indwelling catheters increase the risk of acquiring CRBSIs. Catheter related infections are reported in 7-33% cases, secondary to either chronic colonization of the intravascular portion of the catheter from the exit site or external portions of the catheter. [11] In general, management of CRBSI includes systemic antibiotic therapy, choice and duration of therapy depending upon clinical symptoms and underlying disease along with catheter removal or replacement. In cases reported in literature, Vancomycin, Ceftazidime, Ciprofloxacin and Piperacillin-tazobactam were preferred treatment options. (Table 1) No relapsed infections had been noted in patients with CRBSI due to *B. casei* in whom catheter removal was performed as an empiric therapy. [7-10] However, there is no consensus about the management of uncomplicated CRBSI. Antibiotic-lock has been proposed for cases of catheter-related bacteraemia caused by *Staphylococcus aureus*, coagulase-negative Staphylococci and Gram-negative bacilli. [12]

Table 1: Characteristics, treatment and outcomes of CRBSI by *B. casei*

Study (Year)	Age (Years) Gender	Underlying Conditions	Clinical Presentation	Device	Empiric Therapy	Treatment After Relapse
Ochi F et al [1] (2021)	8, F	AML, FN	CRBSI	PICC	MERO +VAN+device removal	No relapse
Bal ZS et al [7] (2015)	6, M	ALL, FN	CRBSI	Hickman Catheter	PIP/ TAZ+VAN	No relapse
Magi B et al [8] (2018)	48, F	Breast cancer	CRBSI	Port a cath	CIP + TEIC + device removal, LZD	No relapse
Janda W et al [9] (2003)	34, M	AIDS	CRBSI + Sepsis	Hickman Catheter	CAZ +VAN + device removal	No Relapse
Ulrich S et al [10] (2006)	62, F	PH	CRBSI + Sepsis	CVC	MFLX +VAN + device removal	No relapse
Beukinga I et al [13] (2004)	43, F	Chron's Disease	CRBSI	Port a cath	VAN	AMC , MERO, VAN + device removal
Beukinga I et al [13] (2004)	31, M	HD	CRBSI	Hickman Catheter	VAN	VAN+ antibiotic lock
Present Study	21, M	B ALL	CRBSI	PICC	PIP/ TAZ +VAN	No relapse

AIDS - acquired immunodeficiency syndrome; ALL - acute lymphoblastic leukaemia; AMC- Amoxycilin/ Clavulanic acid AML - acute myeloid leukaemia; CAZ - ceftazidime; CIP - ciprofloxacin; CRBSI – catheter related blood stream infection; CVC - central venous catheter; F - female; M -male; MERO - meropenem; MFLX, - moxifloxacin; FN- febrile neutropenia; NHL- Non Hodgkin's lymphoma; PICC - peripherally inserted central catheter; PH - pulmonary hypertension; PIP/ TAZ – piperacillin- tazobactam; VAN - vancomycin.

Our patient had presented with B cell ALL with long term indwelling PICC. He had developed CRBSI with DTP of more than five hours between PICC and peripheral vein blood culture. Species level identification was done by MALDI TOF MS (bioMérieux, France). MALDI-TOF MS relies on measuring microbial proteins that are typically well conserved within a species. Thus, it provides a more reliable means of discriminating one species from another with a high degree of confidence.

[14] The turnaround time with which MALDI-TOF MS can identify microorganisms helps to quickly guide treatment decisions, which is especially critical when the infecting pathogen is unexpected like in our case. This helps in reduction in the length of hospitalization as well. Although exact virulence factors and pathogenesis of *B. casei* infection are not known, neutropenia related to chemotherapy with abrogated immune responses likely contributed to infection, with likely portal of entry being the compromised mucosal integrity secondary to PICC. We could not establish the exact source of infection as cultures of intravenous fluids and chemotherapeutic drugs infused to patients were sterile. There is no standardised treatment for *B. casei*. Additionally, *B. casei* isolates are known to exhibit varying degrees of susceptibility to a variety of antimicrobial agents. [1] Through extrapolation of the CLSI M45 criteria for MIC breakpoints for *Corynebacterium* spp., our isolate was found susceptible glycopeptides, carbapenems, fourth generation cephalosporins and aminoglycosides. Patient was treated with combination therapy of Piperacillin-tazobactam and Vancomycin to which he responded well. Recurrence of bacteraemia caused by the same strain of *B. casei* had been demonstrated up to 5 months following initial adequate therapy.[13] Based on this, it is suggested that catheter removal should be the preferred treatment for associated *B. casei* bloodstream infection. [13] In our patient, PICC was removed on day of hospital admission, which helped along with antibiotic therapy to achieve infection source control and to reduce bio burden.

CONCLUSION

B casei is able to cause infection in patients with profound immunosuppression. Malignancies with prolonged neutropenia and long term indwelling catheters act as an independent risk factors for bacteraemia with *B casei.* Identification may be difficult by conventional methods only; combination of conventional and automated methods can give correct species level identification. It is of utmost importance to perform antimicrobial susceptibility testing due to its varying degrees of susceptibility to various antimicrobial agents. Multicentre studies should be done to establish clinical breakpoints for *B casei.*

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