Case report

Brevibacteria tibial osteomyelitis

Yehuda Eidensohn\textsuperscript{a}, Abraham W\textsuperscript{b}, Michael Sirkin\textsuperscript{c}, Lisa L. Dever\textsuperscript{b,⁎}

\textsuperscript{a} Department of Medicine, Rutgers New Jersey Medical School, Newark, NJ, United States
\textsuperscript{b} Division of Infectious Diseases, Department of Medicine, Rutgers New Jersey Medical School, Newark, NJ, United States
\textsuperscript{c} Department of Orthopaedics, Rutgers New Jersey Medical School, Newark, NJ, United States

\textbf{A B S T R A C T}

Brevibacteria are Gram-positive rods found in human skin flora and dairy products. Although generally not considered human pathogens, case reports have implicated \textit{Brevibacterium} species as rare causes of bacteremia, endocarditis, peritonitis, and osteomyelitis. We report a case of \textit{Brevibacterium} tibial osteomyelitis in an immunocompetent individual with implanted hardware and highlight the challenge of identifying the organism and recognizing it as a potential pathogen. © 2021 The Author(s). Published by Elsevier Ltd. This is an open access article under the CC BY-NC-ND license (http://creativecommons.org/licenses/by-nc-nd/4.0/).

\textbf{Introduction}

Brevibacteria are Gram-positive rods that appear as diphtheroid rods in cultures for the first 24 h and then transition to coccoid or coccobacillary morphology [1]. They are found in raw milk and contribute to the taste and scent of cheese. They are normal human skin flora and are thought to contribute to foot odor. We report a case of tibial osteomyelitis associated with implanted hardware in an immunocompetent adult due to this organism.

\textbf{Case presentation}

A 40-year-old man with a history of extensive lower extremity trauma two years prior requiring left leg open reduction and internal fixation presented to the emergency department with left ankle pain and serous drainage for two months. He had been treated previously with oral cephalaxin with no response. He was afebrile and his vital signs were within normal limits. Physical examination was remarkable only for a 0.5 cm open wound over the left medial malleolus. There was no drainage, erythema or swelling noted. Laboratory studies were performed including complete blood count, complete metabolic panel, erythrocyte sedimentation rate (ESR), C-reactive protein (CRP) and procalcitonin. All were within normal limits. Plain radiograph of the left ankle showed a healed fracture of the distal tibia with intact plate and screws. There were no acute changes. He was discharged with wound care instructions.

In outpatient follow-up one week later, he was found to have expansion of the left ankle wound with profuse serous drainage concerning for underlying osteomyelitis. He underwent incision and drainage of the left distal tibia. Surgical exploration revealed a purulent sinus tract from the skin to the implanted plate and screws. All hardware was removed. Four operative cultures were obtained; two from the wound, one from deep ankle tissue, and one from the periostium. Post-operatively, he received empiric intravenous (IV) vancomycin 1250 mg every 8 h, cefepime 2 g every 8 h, and metronidazole 500 mg every 8 h. Routine laboratory studies were normal with the exception of an elevated CRP that trended from 24 to 3 mg/L and ESR that trended from 9 to 17 mm/hour during the course of his hospitalization. Blood and urine cultures were negative. Two wound cultures and one tissue culture grew coryneform Gram-positive rods initially identified as \textit{Corynebacterium} species. Two days later, the isolate was confirmed to be \textit{Brevibacterium} species via biochemical testing (Analytical Profile Index Coryne, bioMerieux, Marcy-l’Etoile, France), but was unable to be identified to the species level.

The patient had decreased pain and improved wound healing following surgery. Due to subtherapeutic vancomycin levels despite aggressive dosing, he was changed to IV daptomycin 10 mg/kg (750 mg) every 24 h. He was discharged home to complete a five-week course of therapy. The susceptibility of the \textit{Brevibacterium} species was not known at the time of discharge. Agar disc diffusion susceptibility testing was not available at the time due to a nationwide shortage of Mueller-Hinton agar during the coronavirus pandemic. The isolate was sent to an external laboratory for susceptibility testing.

http://dx.doi.org/10.1016/j.idcr.2021.e01046
2214-2509© 2021 The Author(s). Published by Elsevier Ltd. This is an open access article under the CC BY-NC-ND license (http://creativecommons.org/licenses/by-nc-nd/4.0/).
Susceptibility results returned two weeks later. The isolate was susceptible to erythromycin (MIC < 0.50 μg/mL), gentamicin (MIC < 1.0 μg/mL), penicillin (MIC 0.12 μg/mL), rifampin (MIC < 1.0 μg/mL), tetracycline (MIC < 1.0 μg/mL), and vancomycin (MIC < 2.0 μg/mL).

Three weeks following surgery, the patient’s left tibial wound was healing and sutures were removed. After 5 weeks of IV daptomycin he was transitioned to oral amoxicillin 500 mg every 8 h for a planned 4 week-course of therapy. Six weeks post-operatively, his surgical wound was well healed with no tenderness or erythema, and ESR and CRP levels were normal.

**Discussion**

The genus *Brevibacterium* includes many species but only nine have been isolated from humans: *B. linens, B. iodinum, B. epidermidis, B. casei, B. mcbreirleri, B. oitidis, B. paucivorans, B. massiliense* and *B. sanguinis*. *Brevibacterium* species were thought to be apathogenic until 1991, when the first case of sepsis due to *B. epidermidis* central line-associated blood stream infection was reported by McCaughhey [2]. Since that time, at least 18 total case reports have implicated *Brevibacterium* species in human disease (Table 1) [3–21]. *B. casei* is the most frequent species isolated from clinical specimens [1]. The most common infection has been bacteremia (n = 10), with the rest of cases being peritonitis, pericarditis, endocarditis, brain abscess, and osteomyelitis.

Reported patient characteristics vary widely. Five patients were immunocompromised; two had acquired immunodeficiency syndrome (AIDS) and three were receiving chemotherapy for cancer. Others had a history of cancer, or had other systemic diseases including Zollinger-Ellison, aplastic anemia, pulmonary hypertension, heart failure or methylmalonic acidemia. Presence of foreign material or central venous catheters (CVC) were common. Most cases of bacteremia were associated with CVC. The patient with peritonitis was receiving continuous ambulatory peritoneal dialysis, and the patient with endocarditis had prosthetic valves. The cases of *Brevibacterium* brain abscess and osteomyelitis occurred in immunocompetent healthy patients with no apparent predisposition [2,20].

A theme of these case reports is the challenge of recognizing the organism is not a skin contaminant and correctly identifying it. This often requires extensive biochemical testing or sending

| Author/Year | Age | Comorbidities | Foreign Material | Type of Infection | *Brevibacterium* species | Antibiotic Therapy | Identification Technique | Outcome |
|-------------|-----|---------------|------------------|-------------------|------------------------|-------------------|------------------------|---------|
| McCaughhey 1991 [2] | 40 years | Zollinger-Ellison | Central catheter | Bacteremia | *B. epidermidis* | Erythromycin | Reference laboratory | Recovered |
| Neumenster 1993 [3] | 4 weeks | None | None | Osteomyelitis | Not specified | Cefazolin | Fatty acid analysis | Recovered |
| Lina 1994 [4] | 19 years | Acute lymphocytic leukemia | Not reported | Bacteremia | Not specified | Ceftazolin | API Coryne System and biochemical tests | Recovered |
| Reinert 1995 [5] | 25 years | Testicular choriocarcinoma | Central catheter | Bacteremia | *B. casei* | Piperacillin | Recovered |
| Kaukoranta-Tolvanen 1995 [6] | 46 years | Hodgkins lymphoma | Central catheter | Bacteremia | Not specified | Cefalexin | API Coryne System and biochemical tests | Not reported |
| Castaglona 1996 [7] | Not reported | Neuroblastoma | Central catheter | Bacteremia | *B. casei* | Not reported | Reference laboratory | Not reported |
| Antoniou 1997 [8] | 69 years | Not reported | Peritoneal catheter | Peritonitis | *B. iodinum* | Cefuroxime | API Coryne System and biochemical tests | Recovered |
| Brazzola 2000 [9] | 18 years | HIV infection | Implanted central catheter | Bacteremia | *B. casei* | Ciprofloxacin | API Coryne System | Recovered |
| Wauters 2000 [10] | 73 years | Peritoneal dialysis | Peritoneal catheter | Peritonitis | *B. oitidis* | Cefazolin | Fatty acid analysis and rRNA analysis | Recovered |
| Ogunc 2002 [11] | 60 years | Chronic lymphocytic leukemia | Central catheter | Bacteremia | Vancomycin | Reference laboratory* | Recovered |
| Janda 2002 [12] | 34 years | AIDS | Prosthetic heart valve | Endocarditis | *B. casei* | Vancomycin | API Coryne System | Recovered |
| Dass 2002 [13] | No reported | No reported | Central catheter | Bacteremia | Endocarditis | Vancomycin | Not reported | Recovered |
| Cannon 2004 [14] | 78 years | Cancer | None | Pericarditis | *B. casei* | Vancomycin | Not reported | Recovered |
| Vecten 2006 [15] | 4 years | Methylmalonic acidemia | Gastric tube | Bacteremia | *B. massiliense* | Olfloxacin | Not reported | Recovered |
| Ulrich 2006 [16] | 62 years | Pulmonary hypertension | Central catheter | Bacteremia | Not specified | Vancomycin | 16s rRNA analysis | Recovered |
| Kumar 2011 [17] | 31 years | None | None | Brain abscess | *B. casei* | Moxifloxacin | Biochemical testing | Recovered |
| Bal 2015 [18] | 6 years | Acute lymphocytic leukemia | Central catheter | Bacteremia | *B. casei* | Moxifloxacin | Biochemical testing and genetic sequencing MALDI-TOF | Recovered |
| Magi 2018 [19] | 48 years | Breast cancer | Implanted central catheter | Bacteremia | *B. casei* | Teicoplanin | Not reported | Recovered |
| Asai 2019 [20] | 94 years | Heart failure, diabetes mellitus | Central catheter | Bacteremia | *B. paucivorans* | Teicoplanin | MALDI-TOF | Recovered |
| Joshi 2020 [21] | 6 years | Aplastic anemia | Central catheter | Bacteremia | *B. casei* | Teicoplanin | MALDI-TOF | Died from candida sepsis | Recovered |

Abbreviations: MALDI-TOF: Matrix assisted laser desorption ionization time of flight. API Coryne system is licensed by Bio-Merieux.

* Isolate was misidentified by API Coryne system.

* This identification is questioned by Funke et al. [1].
isolates to a reference laboratory for identification. Simple mass spectrometry is not adequate for identification. Earlier identification techniques such as the API Coryne System (bioMérieux, USA), were reported having discrepancies or errors in identification [10,18]. Other adjunctive tests include 16s rRNA analysis, fatty acid analysis with gas chromatography, and degradation of casein, tyrosine, and xanthine. Matrix-assisted laser desorption/ionization-time of flight (MALDI-TOF) using spectra of bacterial peptides is the most reliable newer modality of identification, but is not yet widely available in microbiology laboratories.

Antimicrobial susceptibility testing is also a challenge. Techniques most commonly reported are Etest and agar disc diffusion, with only a few successful instances of automated microdilution testing. Even when a MIC value is obtained, no standard breakpoints exist for Brevibacterium. The most commonly used breakpoints were proposed by Funke in 1996 [22]. More recent reports used the Clinical and Laboratory Standards Institute's recently established breakpoints for Corynebacterium [23]. Isolates are universally sensitive to the glycophosphates with occasional beta-lactam resistance. These are consistent with early work by Funke, and are why the most common empiric therapy has been vancomycin or teicoplanin [22]. We chose to use daptomycin in our patient due to the inability to achieve therapeutic levels of vancomycin despite every 8-h dosing.

Conclusion

Brevibacterium can cause serious infections even in immunocompetent individuals, especially in the presence of CVC or implanted hardware. The presence of implanted hardware was likely a predisposing factor in our patient. Our case highlights the need for greater awareness of the potential pathogenicity of Brevibacterium species, especially in patients with implanted material, and the possibility of misidentification as apathogenic coryneform bacteria.

Funding

None.

Consent

The patient provided verbal and written consent for publication.

Ethical approval

N/A.

Author contribution

Yehuda Eidensohn: Care of patient, writing and editing of manuscript.
Abraham Wei: Care of the patient, editing of manuscript.
Michael Sirkin: Care of patient and review of manuscript.
Lisa L. Dever: Care of patient, writing, editing, submitting and revising manuscript.

Declaration of Competing Interest

The authors report no declarations of interest.

References

[1] Funke G, von Graevenitz A, Claridge JE, Bernard KA. Clinical microbiology of coryneform bacteria. Clin Microbiol Rev 1997;10(1):125–39, doi:http://dx.doi.org/10.1128/CMR.10.1.125-139.1997.
[2] McCaughey C, Danami NN. Central venous line infection caused by Brevibacterium epidermidis. J Inf 1991;23:211–2.
[3] Neugebauer B, Mandel T, Gruner E, Piffler GE. Brevibacterium species as a cause of osteomyelitis in a neonate. Infecion 1993;21(3):177–8, doi:http://dx.doi.org/10.1007/BF00710543.
[4] Lina B, Carlotti A, Lesaint V, Devaux Y, Freney J, Fleurette J. Persistent bacteremia due to Brevibacterium species in an immunocompromised patient. Clin Infect Dis 1994;18:487–8, doi:http://dx.doi.org/10.1093/clinids/18.3.487.
[5] Reinert RR, Schnitzler N, Haase G, Luttmicken R, Fabry U, Schaaf KP, et al. Recurrent bacteremia due to Brevibacterium casei in an immunocompromised patient. Eur J Clin Microbiol Infect Dis 1995;14:1082–5, doi:http://dx.doi.org/10.1007/BF01590493.
[6] Kaukoranta-Tolvanen SS, Sivonen A, Kostiila AA, Hormila P, Vaara M. Bacteremia caused by Brevibacterium species in an immunocompromised patient. Eur J Clin Microbiol Infect Dis 1995;14:801–4, doi:http://dx.doi.org/10.1007/BF01690997.
[7] Castagnola E, Conte M, Venzano P, Garaventa A, Viscoli C, Pescoto L, et al. Brovoc catheter-related bacteremias due to unusual pathogens in children with cancer: case reports with literature review. J Infect 1997;34:215–8, doi:http://dx.doi.org/10.1016/S0163-4453(97)90419-2.
[8] Antonsou S, Dimitriadis A, Polydorou F, Malaka E. Brevibacterium iodum peritonitis associated with acute urticaria in a CAPD patient. Perit Dial Int 1997;17:614–5.
[9] Brazzola P, Zbinden R, Rudin C, Schaad UB, Heininger U. Brevibacterium casei sepsis in an 18-year-old female with AIDS. J Clin Microbiol 2000;38:3313–4, doi:http://dx.doi.org/10.1128/JCM.38.9.3513-3514.2000.
[10] Wauters G, Van Bosterhaut B, Avesani V, Cuvelier R, Charlier J, Janssens M, et al. Peritonitis due to Brevibacterium ottiditis in a patient undergoing continuous ambulatory peritoneal dialysis. J Clin Microbiol 2000;38:4292–3, doi:http://dx.doi.org/10.1128/JCM.38.11.4292-4293.2000.
[11] Ogunc D, Gultekin M, Colak D, Timurajaooglu A, Ongut G, Mutlu G, et al. Bacteremia caused by Brevibacterium species in a patient with chronic lymphocytic leukemia. Haematologica 2002;32:151–3, doi:10.1182/haematol.2002.32.3.151.
[12] Janda WM, Tipirneni P, Novak RM. Brevibacterium casei bacteremia and line sepsis in a patient with AIDS. J Infect 2003;46:61–4, doi:http://dx.doi.org/10.1053/jinfec.2002.1076.
[13] Dass KN, Smith MA, Gill VJ, Glodstein SA, Lucey DR. Brevibacterium endocarditis: a first report. Clin Infect Dis 2002;35:e20–21, doi:http://dx.doi.org/10.1086/340984.
[14] Cannon JP, Spandoni SL, Pesh-Iman S, Johnson S. Percutaneous infection caused by Brevibacterium casei. Clin Microbiol Infect 2005;11(2):164–5, doi:http://dx.doi.org/10.1111/j.1469-0691.2004.01050.x.
[15] Vecten M, Gourier F, Cano A, Raoult D. Brevibacterium massiliense bacteremia. IDCases 2016;7:25–6, doi:http://dx.doi.org/10.1053/j.idc.2016.11.010.
[16] Ulrich S, Zbinden R, Pagano M, Fischler M, Speich R. Central venous catheter infection with Brevibacterium sp. in an immunocompetent woman: case report and review of the literature. Infection 2006;34(2):103–6, doi:http://dx.doi.org/10.1007/s00395-004-0819-9.
[17] Kumar VA, Augustine D, Panikar D, Nandakumar A, Dinesh KR, Karim S, et al. Brevibacterium casei as a cause of brain abscess in an immunocompetent patient. J Clin Microbiol 2011;49(12):4374–6, doi:http://dx.doi.org/10.1128/JCM.01086-11.
[18] Bal ZS, Sen S, Karapinar DY, Aytmenir S, Vardar F. The first reported catheter-related Brevibacterium casei bloodstream infection in a child with acute leukemia and review of the literature. Braz J Infect Dis 2015;19(2):213–5, doi:http://dx.doi.org/10.1016/j.bjid.2014.09.011.
[19] Magi M, Migliorini L, Sansoni A, Cusi MG. Brevibacterium casei bacteraemia in a port-a-cath carrier patient: a case report. Infez Med 2018;26(3):263–5.
[20] Asai N, Suematsu H, Yamada A, Watanabe H, Nishiyama N, Sakunashi D, et al. Brevibacterium paucivorans bacteremia: case report and review of the literature. BMC Infect Dis 2019;19(1):344, doi:10.1186/s12879-019-3962-y.
[21] Joshi S, Misra R, Kirolikar S, Mushrif S. Catheter-related Brevibacterium casei bloodstream infection in a child with aplastic anaemia. Indian J Med Microbiol 2020;38(2):226–8, doi:http://dx.doi.org/10.4103/jmm.jmm_20_292.
[22] Funke G, Piñer V, von Graevenitz A. Antimicrobial susceptibility patterns of some recently established coryneform bacteria. Antimicrob Agents Chemother 1996;40(2):2874–8, doi:http://dx.doi.org/10.1128/AAC.40.12.2874.
[23] Clinical and Laboratory Standards Institute. Methods for antimicrobial dilution and disk susceptibility testing for infrequently isolated or fastidious bacteria; CLSI guideline M45. 3rd ed. 2015 Wayne, PA:ce:biography/sec>