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Case Report

Catheter-related bloodstream infection by *Microbacterium paraoxydans* in a pediatric patient with B-cell precursor acute lymphocytic leukemia: A case report and review of literature on *Microbacterium* bacteremia☆

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ABSTRACT

Microbacterium species are coryneform gram-positive rods that are widely distributed in the environment and have been recently recognized as rare pathogens in humans. However, information about the epidemiologic and clinical characteristics of *Microbacterium* species is scarce. We herein reported an 11-year-old girl with acute leukemia who was found to have catheter-related bloodstream infection in her neutropenic phase. Gram-positive bacilli repeatedly grew on the blood cultures and were later confirmed by 16S rRNA analysis as *Microbacterium paraoxydans*. A literature review found available clinical courses in 21 cases (7 pediatric cases) of *Microbacterium* spp. bacteremia. Our case and those in literature suggested that *Microbacterium* spp. bacteremia often occurs in patients with indwelling central venous catheters; the literature review further suggested that removal of central venous catheters is required in most cases and that 16S rRNA sequence was useful in identifying in detail the species of *Microbacterium*.

1. Introduction

Microbacterium species are gram-positive rods that were formerly designated as CDC coryneform groups A-4 and A-5 [1]. The phenotypically and phylogenetically closely related genera Microbacterium and Aureobacterium have been united in a redefined genus Microbacterium [2]. Although *Microbacterium* species are mainly distributed in the environment, such as in soil and sewage, they are occasionally detected from human clinical specimens [1]. To date, endophthalmitis, peritoneal dialysis-related infection, and catheter-related bloodstream infection (CRBSI) have been reported [3–8]. However, information on the epidemiologic and clinical characteristics of *Microbacterium* spp. bacteremia is scarce. We herein reported the case of an 11-year-old girl with acute leukemia and who was found to have CRBSI, which was later confirmed to be from *Microbacterium paraoxydans* by 16SrRNA analysis. We also reviewed the previous reports on bacteremia due to *Microbacterium* spp.

2. Case report

An 11-year-old girl who was diagnosed a year ago with B-cell precursor cell acute lymphocytic leukemia (BCP-ALL) was admitted to the hospital for delayed intensification therapy. A tunneled Hickman catheter with dual lumen was inserted a year ago, and she had been undergoing chemotherapy according to the Japan Pediatric Leukemia/Lymphoma Study Group ALL B12 intermediate risk protocol for children with BCP-ALL. The first remission was accomplished after the induction therapy.

After admission, delayed intensification therapy with dexamethasone, vincristine, pirarubicin hydrochloride, L-asparaginase, cyclophosphamide, cytarabine, mercaptopurine, and triple intrathecal therapy was started. On hospital day 17, she developed

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Table 1
Summary of 21 cases with *Microbacterium* spp. bacteremia.

Case	Age	Gender	Underlying condition	Focus of the infection	Use of CV catheter	Removal of CV catheter	Neutrophil count (/μL)	Species	Antimicrobial therapy	Method for identification	Outcome	Reference
1	67	M	Congestive heart failure	Endocarditis	No	N/A	N/A (WBC 10,730)	CDC group A4	AMP + GEN→AMP (total 6 weeks)	Biochemical analysis	Recovered	[9]
2	11	M	Acute myelomonocytic leukemia	CRBSI	Yes	Yes	328	CDC group A5	TIM + TOB (2 days) →TIM + TOB +VAN (2 days) →CTX (3 days)	Biochemical analysis	Recovered	[10]
3	64	M	Myelodysplastic syndrome	CRBSI	Yes	Yes	2106	CDC group A4	TIM + GEN + CIP (2days) →TIM + GEN + VAN (unknown duration) →CRO (18 days)	Biochemical analysis	Recovered	[12]
4	39	M	Acute myeloid leukemia Porphyria cutanea tarda	Cellulitis of the left index finger or CRBSI	Yes	Yes	Neutropenic (<500)	*Aureobacterium* sp.	VAN + ATM +AMK (5 days)→VAN +ATM + AMK +ERY (2days) → VAN + AMK + IMP +RIF (5days)	Biochemical analysis Peptide glycan analysis	Died	[13]
5	75	M	N/A	Systemic infection (Focus not confirmed)	No	–	N/A	*Aureobacterium* sp.	IPM + PEN G + CIP (5days)	16S rRNA gene analysis	Died	[14]
6	73	F	Familial tubular interstitial nephropathy Hemodialysis	Transient bacteremia (Focus not confirmed)	No	–	N/A	*Aureobacterium* sp.	TEC + NET (1 day) →AMX (7 days)	Biochemical analysis The cellular fatty acid profile	Recovered	[15]
7	68	M	Multiple myeloma Post BMT	Febrile Neutropenia	Yes	No	Neutropenia	*Aureobacterium liquefaciens*	CAZ + GEN (3days) → CAZ + IPM (3days) → CAZ + IPM +VAN (8 days)	16S rRNA gene analysis	Recovered	[16]
8	50	F	Non-Hodgkin's lymphoma	N/A	Yes	Yes	50	*Microbacterium species* CDC group A5	VAN + TOB + CAZ (unknown duration)	conventional biochemical tests	Recovered	[17]
9	31	F	Pheochromocytoma	N/A	Yes	N/A	6127	*Microbacterium species* CDC group A5	N/A	conventional biochemical tests	Recovered	[17]
10	64	M	Pancreatic adenocarcinoma	N/A	Yes	N/A	3975	*Microbacterium species* CDC group A5	N/A	conventional biochemical tests	Recovered	[17]
11	49	F	Non-small-cell lung carcinoma	Possible CNS infection	Yes	N/A	5200	*Microbacterium species* CDC group A5	TOB + NAF (3days)	conventional biochemical tests	Died	[17]
12	48	F	Acute myeloid leukemia	N/A	Yes	N/A	14	*Microbacterium species* CDC group A5	N/A	conventional biochemical tests	Recovered	[17]
13	77	F	Non-Hodgkin's lymphoma	N/A	Yes	N/A	28	*Microbacterium species* CDC group A5	N/A	conventional biochemical tests	Recovered	[17]
14	39	F	Chronic myeloid leukemia	CRBSI	Yes	Yes	2700	Microbacterium sp.	VAN (unknown duration)	16S rRNA gene analysis	Recovered	[7]
15	5	F	Acute myeloid leukemia	N/A	Yes	Yes	3600	Microbacterium sp.	PEN G→oral PEN (unknown duration)	16S rRNA gene analysis	Recovered	[7]
16	5	M	Acute lymphoblastic leukemia	CRBSI	Yes	Yes	N/A	*Microbacterium paraoxydans*	AMP(unknown duration)	16S rRNA gene analysis	Recovered	[18]

(*continued on next page*)

Table 1 (*continued*)

Case	Age	Gender	Underlying condition	Focus of the infection	Use of CV catheter	Removal of CV catheter	Neutrophil count (/μL)	Species	Antimicrobial therapy	Method for identification	Outcome	Reference
17	13	F	Non-Hodgkin's lymphoma	N/A	Yes	No	4880	Unknown	VAN (10 days) + CAZ (2days)	Amplification and sequencing of 16S rRNA or the β-subunit of the DNA-dependent RNA polymerase genes	Recovered	[20]
18	13	M	Acute myeloid leukemia	N/A	Yes	Yes	6800	Unknown	VAN (10 days) + CRO (1 day)	Amplification and sequencing of 16S rRNA or the β-subunit of the DNA-dependent RNA polymerase genes	Recovered	[20]
19	15	F	Congenital gut enteropathy	CRBSI	Yes	Yes	N/A (WBC 5500)	*Microbacterium paraoxydans*	TEC (7 days)	16S rRNA gene analysis	Recovered	[8]
20	28	M	Sickle cell anemia	Focus not identified	No	–	N/A	*Microbacterium binotii*	TZP (once) → VAN (2 weeks)	16S rRNA gene analysis	Recovered	[23]
21	11	F	Acute lymphoblastic leukemia	CRBSI	Yes	Yes	273	*Microbacterium paraoxydans*	TZP + TEC (16 days)	16S rRNA gene analysis	Recovered	Present case

Abbreviation: AMP: Ampicillin, GEN: Gentamicin, TIM: Ticarcillin-clavulanic acid, TOB: Tobramycin, VAN: Vancomycin, CTX: Cefotaxime, CIP: Ciprofloxacin, CRO: Ceftriaxone, ATM: Aztreonam, ERY: Erythromycin, IMP: Imipenem, RIF: Rifampin, PEN G: Penicillin G, NET: Netilmicin, AMX: Amoxicillin, CAZ: Ceftazidime, NAF: Nafcillin, PEN: Penicillin, TEC: Teicoplanin, TZP: Piperacillin-tazobactam.

febrile neutropenia. Tazobactam/piperacillin at 360 mg/kg/day was started after collecting two sets of blood cultures from the two different lumens of the central venous catheter (CVC) (Table 1). On hospital day 18, there was resolution of fever, and the blood test performed showed WBC 500/μL, neut 19.6%, and CRP 1.42 mg/dL. On hospital day 19, the two sets of blood cultures performed on hospital day 17 revealed gram-positive bacillus.

On hospital day 20, repeat blood cultures from the CVC again yielded gram-positive bacillus, for which teicoplanin was started at 800 mg/day on the first day and at 400 mg/day on subsequent days. Additional blood cultures were collected in two sets from the two different lumens of the CVC and in one set from a peripheral vein. On hospital day 22, the same gram-positive bacilli grew in all three blood cultures. CRBSI was confirmed based on the fact that the blood culture taken from the CVC became positive at more than 2 hours earlier from the one taken from the peripheral vein.

Because the conventional biochemical test could not confirm the organism, MALDI-TOF-MS was used and identified *Microbacterium* sp., with a matching score of 2.154; however the details of the species were not identified. We performed antimicrobial drug susceptibility testing using the broth microdilution method (MICroFAST 7J; Beckman Coulter, Tokyo, Japan). Using the E-test (ETEST; bioMérieux, Tokyo, Japan), the MIC of the VCM was determined to be 4 μg/mL. This MIC result was interpreted according to the Clinical and Laboratory Standards Institute (CLSI) method M45Ed3 (Table 2).

The patient remained afebrile, but her blood cultures performed on hospital days 26, 29, and 33 were persistently positive. The serum trough level of teicoplanin measured on hospital day 29 was 27.8 μg/mL. No signs of infection, such as redness, tenderness, or discharge, were observed surrounding the exit site or along the subcutaneous tunnel of the CVC. Physical examination and abdominal ultrasound revealed no sign of metastatic infection. Moreover, a transthoracic echocardiogram showed no sign of endocarditis. The CVC was removed on hospital day 37. Thereafter, on hospital day 40, both culture of the catheter and blood culture from a peripheral vein were negative. The subsequent blood cultures were also negative. Tazobactam/piperacillin and teicoplanin were continued for 16 days until the neutropenia resolved. The patient was discharged on hospital day 71 after initiating maintenance therapy (Fig. 1); no signs of recurrence were observed during the follow-up period of 1 year.

We performed 16S rRNA gene sequencing to identify the organism. The consensus sequence had the highest similarity (1433/1437 bp 99.41% match in GenBank, Accession No. KY425786.1, and 1437/1439 bp 99.86% match in EzBioCloud, Accession No. BCRH01000180) with the *16S rRNA* gene of *M. paraoxydans*.

3. Discussion

Bacteremia due to *Microbacterium* spp. has rarely been reported. In most reported cases, the patients were immunocompromised and had indwelling CVC. In a search for English abstracts from the

Table 2
The results of susceptibility testing.

Antibiotics	MIC	Susceptibility
Penicillin	1	I
Cefepime	≥4	R
Cefotaxime	≥8	R
Meropenem	≥4	R
Vancomycin	≥2	R
Vancomycin (E-test)	4	R
Erythromycin	≥4	R

MIC: Minimum Inhibitory Concentration I: Intermediate, R: Resistant.

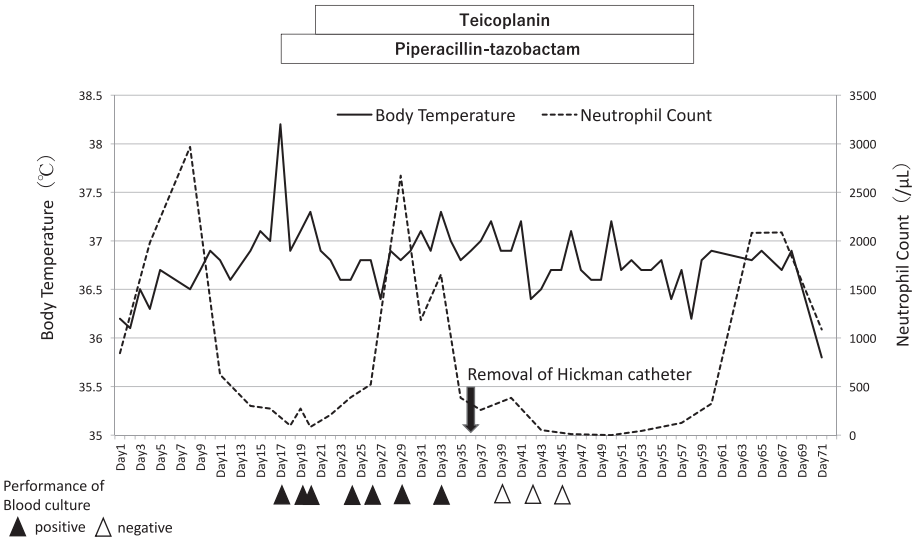

Fig. 1. Clinical course.

MEDLINE database using the keywords CDC coryneform group A-4 and A-5, Aureobacterium, and Microbacterium, only 48 cases of bacteremia due to *Microbacterium* spp. were found [1,7–23]. Of these, 21 cases (7 pediatric cases) were reported with clinical courses [7–10,12–20,23] (Table 1). Among these 21 cases, there was indwelling CVC in 16 cases, hematologic malignancy in 12 cases, and neutropenia in 5 cases. Similar to the previously reported cases, the present case had the typical profile of neutropenia due to the treatment for the hematologic malignancy and the presence of indwelling CVC.

In most cases, the CVC was removed during the treatment, and only few cases had successful treatment without removal of the CVC. Among the 17 cases with indwelling CVCs, the management of the CVC was mentioned in 12 cases. Of these, the CVC was removed in 10 cases. In the present case, the antimicrobial treatment was continued without removal of the CVC, but the persistent bacteremia eventually made the physician decide to remove it. The bacteremia was cleared immediately after the removal of the CVC. Completion of antimicrobial treatment was successful in only two cases. In the first case (case 7), there was recurrence of bacteremia 6 days after the completion of antimicrobial treatment, and the CVC was eventually removed. In the second pediatric case (case 17), the patient was not neutropenic and was successfully treated with vancomycin and ceftazidime.

Our case and literature review showed that 16S rRNA sequence was useful for a detailed identification of *Microbacterium* species. The details of the species and the clinical course were described in 6 of 22 cases, including the present case. 16S rRNA sequencing was used for all six cases. In the present case, MALDI-TOF-MS was initially used to identify the details of the species; however, the identification was limited to the confirmation as *Microbacterium* spp. This was probably because *M. paraoxydans* was not registered to the database, and it was only subsequently confirmed using 16sRNA sequencing. Bacteremia by *Microbacterium* spp. may be underestimated because a detailed identification of gram-positive bacilli is not always performed when the conventional biochemical method does not confirm the organism.

Glycopeptides, such as vancomycin and teicoplanin, are often used for the treatment of *Microbacterium* spp. bacteremia. The selected antimicrobial was mentioned in 18 of 22 cases, including the present case. Either vancomycin or teicoplanin was used in 13 cases. The CLSI M45Ed3 provides the breakpoint for vancomycin (i.e., susceptible if MIC is $\leq$ 2) but not for teicoplanin. One study from Germany has reported that most of the *Microbacterium* spp. was susceptible to vancomycin [21]; however, another study from Canada has shown that 26% of *Microbacterium* isolates were resistant to vancomycin [24]. The susceptibility of *Microbacterium* isolates to other antimicrobials varied, with only linezolid showing 100% susceptibility in the both studies [21,24]. In the present case, *M. paraoxydans* was judged to be resistant to vancomycin. Instead, tazobactam/piperacillin was used with teicoplanin, because the patient was neutropenic; this combination regimen seemed to be effective, at least after the removal of the Hickman catheter. Although the trough level of teicoplanin was confirmed to be within the therapeutic range, the assessment of its effectiveness in the present case was difficult because no susceptibility test was performed. Tazobactam/piperacillin might have contributed to this favorable response, because the *M. paraoxydans* isolate showed intermediate susceptibility to penicillin.

The mortality of bacteremia by *Microbacterium* spp. was reported to be about 14%. The outcome was favorable when the focus of infection was CRBSI. On the other hand, fatal outcome was observed in three cases (case 4, case 5, and case 11) that had necrotizing soft tissue infection, disseminated infection, and central nervous system infection. In pediatric cases, the outcomes were favorable, and no fatal case was reported.

4. Conclusions

We encountered a pediatric case with neutropenia and CRBSI due to *M. paraoxydans* identified using 16S rRNA sequencing. Based on available literature, *Microbacterium* spp. bacteremia often occurred in patients with indwelling CVC, and removal of the CVC during the treatment was required in most cases.

Conflicts of interest

None.

Ethical approval

Written informed consent was obtained from the patient's parents for the publication of this case report.

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