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Leuconostoc bacteremia in 3 patients with malignancies.

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Abstract

Leuconostoc is a gram-positive coccus characterized by its resistance to glycopeptide antibiotics. Generally, this bacterium is susceptible to β-lactam antibiotics; however, here we present a leukemia patient who developed *leuconostoc* bacteremia during antimicrobial therapy with carbapenem. The appropriate choice of antibiotics with optimal doses enables *leuconostoc* infection to be overcome even in compromised hosts. We report 3 cases of *leuconostoc* bacteremia, the leukemia case which was successfully treated, along with discussion of two other cases with malignancies.

Introduction

Chemotherapy for patients with malignancies often causes critical infections because of the use of cytotoxic agents and the immunodeficiency associated with the disease itself. In particular, remission induction therapy for hematologic malignancies causes severe neutropenia for 2 weeks or even longer, which can lead to fatal infection. Antimicrobial therapy in such cases is clinically less effective, even with treatment following the IDSA guideline [1].

Generally, microbial substitution develops from inappropriate use of antibiotics. Most bacteria in such cases have attenuated virulence, but patients with infections caused by such bacteria often have a dismal outcome because of their poor general conditions and bacterial resistance to antibiotics.

Leuconostoc is a gram-positive coccus~~, that has multi-drug resistance; in particular, this bacterium is~~ characterized by native resistance for glycopeptides such as vancomycin (VCM) because it lacks binding sites for these agents [2]. Some reports have documented successful treatment of *Leuconostoc* bacteremia, but most of these are old [3,4], and there are very few papers published in the ‘carbapenem era’ relating to this bacterium [5,6]. We report here a case in which *Leuconostoc* bacteremia that developed during chemotherapy for leukemia was successfully treated, along with discussion of

two other cases.

Case report

Case 1. A 52-year-old woman was referred to our institution for hypermenorrhea and pancytopenia. The morphological examination of bone marrow smears showed 58% myeloblasts, resulting in a diagnosis of acute myeloid leukemia (AML). The patient was treated with remission induction chemotherapy for AML, consisting of idarubicin and cytarabine. Since febrile neutropenia developed after chemotherapy, cefepim (CFPM) was given, followed by a combination of meropenem (MEPM), teicoplanin, and micafungin (MCFG) 3 days after CFPM treatment, but moderate fever persisted. Leukocyte counts recovered slowly around 3 weeks after the initial chemotherapy, but the majority of leukocytes were myeloblasts, with no normal granulocytes in the peripheral blood (Figure). Therefore, second remission induction therapy consisting of daunomycin and cytarabine was performed while continuing antimicrobial therapy for persistent fever. The patient's temperature normalized around the 7th day after the second chemotherapy regimen, while on biapenem (BIPM) and MCFG (Figure). However, moderate fever reappeared on day 12. A gram-positive coccus was detected in blood culture samples obtained the same day, and vancomycin (VCM) was added the

next day. On the 14th day, the patient developed cellulitis involving the right thigh, and the blood culture revealed that the gram-positive coccus was a *Leuconostoc* species. According to the drug susceptibility test (Table 1a), the antibiotics were switched to imipenem/cilastatin (IPM/CS), gentamicin (GM), and MCFG. Clindamycin (CLDM) was added from day 16 because her fever pattern was worsening. On day 17, the blood culture taken on day 13 was found to be positive for *Leuconostoc* and *Stenotrophomonas maltophilia* (results of the drug susceptibility were shown in Table 1b); GM was deemed ineffective and was discontinued, and sulfamethoxazole-trimethoprim was started. Her fever then improved, and she was afebrile on day 27, when she achieved remission of leukemia, and her neutrophils exceeded 500/μl. The result of the minimal inhibitory concentration (MIC) tests for the bacteria, obtained at a later date, revealed that the *Leuconostoc* was susceptible to IPM/CS at less than 1 μg/ml and BIPM at less than 4 μg/ml, although the patient was being treated with carbapenem when the bacterial infection developed.

Case 2. A 73-year-old man presented with high fever and brown urine. On physical examination, he had jaundice of his bulbar conjunctiva and hepatosplenomegaly. On admission, he presented with pancytopenia, high C-reactive protein levels, and hepatic

dysfunction. Computed tomography showed multiple neck lymphadenopathy ~~in his neck~~ and hepatosplenomegaly. Atypical lymphocytes were increased on bone marrow smears, leading to the diagnosis of non-Hodgkin's lymphoma. The patient was treated with CHOP therapy, consisting of cyclophosphamide, doxorubicin hydrochloride, vincristine, and prednisolone. However, the effect of the chemotherapy was transient; persistent fever and hepatosplenomegaly improved after the first dose of CHOP, but these symptoms flared up around 15 days after ~~the~~ therapy. There were no symptoms suggesting focal infection, which led to the diagnosis of tumor fever. However, the patient was given 1.5 g/day of MEPM and fluconazole (FLCZ) when the second course of CHOP therapy was started on the 18th day, because he was an immunocompromised host with no granulocytes. Since his fever and hepatosplenomegaly improved immediately, the antibiotics were stopped on day 6 after the 2nd CHOP therapy. Because a high fever reappeared on day 10, the antimicrobial and antifungal therapies (panipenem/betamipron at 2 g/day, GM, and FLCZ) were restarted. Since the blood culture was positive for *α-Streptococcus* on day 10, these drugs were continued based on the drug susceptibility test results (Table 1a). VCM was added on day 14 for high fever, but the patient developed acute respiratory distress syndrome (ARDS) and died on day 15. On autopsy, the patient had systemic lymphadenopathy, hepatosplenomegaly

with nodular lesions consisting of T-cell lineage non-Hodgkin's lymphoma, and severe pulmonary edema. Involvement of *Leuconostoc* species in the development of ARDS was unclear, and intracardiac blood culture was not performed. Since the attending physician noticed the contradictory result for the susceptibility test for *α-Streptococcus* indicating resistance to VCM, the blood culture test was re-evaluated, and the gram-positive coccus was found to be a *Leuconostoc* species.

Case 3. A 65-year old man, who was being seen regularly at a clinic for alcoholic liver cirrhosis, was referred to our institution for investigation of a space occupying lesion (SOL) of the liver. The SOL was diagnosed as hepatocellular carcinoma by angiography and magnetic resonance imaging, but the patient was not a candidate for aggressive treatment because of hepatic failure. Low-grade fever developed during the admission, and he was treated with piperacillin (PIPC) for 10 days. Since there were no signs of focal infection, the major reason for the fever was considered to be the patient's compromised status due to end-stage hepatic failure. His antibiotics were switched to IPM/CS, 1 g/day, because a moderate fever developed on the 11th day after PIPC administration, and the temperature decreased ~~came down~~. On the 8th day after withdrawal of IPM/CS, the moderate fever reappeared, and 1 g/day of IPM/CS was

restarted. Since coagulase-negative *Staphylococcus* (CNS) and *Clostridium* species were detected in the blood culture samples taken on the day when the fever flared up, the central venous catheter was removed. The fever disappeared temporarily, and the blood culture became negative for CNS. However, a high fever developed on the 9th day after the restart of IPM/CS. *α-Streptococcus*, susceptible to IPM/CS on susceptibility testing (Table 1a), was detected in the blood culture sample collected on the same day when the fever flared up. However, the patient's blood pressure decreased, and the patient died on the 5th day after the IPM/CS was restarted. The blood culture test was re-evaluated because resistance of the bacterium to VCM was incidentally discovered as a result of internal transcribed spacer-PCR, leading to the final conclusion that it was a *Leuconostoc* species.

Discussion

Leuconostoc is a nonpathogenic resident of the intestinal tract and is detected in immunocompromised hosts, such as organ transplant recipients and patients with malignancy receiving intensive chemotherapy. The primary characteristic of this bacterium is its resistance to glycopeptides and the poor clinical effectiveness of β-lactam antibiotics, even though drug susceptibility testing shows that it is

‘susceptible’ to β-lactam antibiotics, as the MIC is relatively high. In our experience, shown in Table 1, the MIC was as poor as previously reported [6]. The recommended treatment for *Leuconostoc* species is penicillin, ampicillin, CLDM, minocycline, erythromycin, tobramycin, or GM [7]. The results of susceptibility testing may vary; as indicated in Table 1a, poor susceptibility against penicillin G and ampicillin was observed in case 2. The laboratory data must be carefully followed when such difficult cases are encountered. Daptomycin, a novel lipopeptide antibiotic showing a good MIC for *Leuconostoc* but which is not authorized in Japan, must be considered a first-line drug for the treatment of *Leuconostoc* infection [8].

Cases of *Leuconostoc* bacteremia, for which the MIC for carbapenem antibiotics has been previously reported, are listed in Table 2. Cancers, burn injuries, and short bowel syndrome in pediatric patients are common underlying diseases. Important risk factors for the development of *Leuconostoc* bacteremia include invasive mechanical ventilation and complications such as antecedent infection or surgery. All but one patient developed *Leuconostoc* bacteremia during antimicrobial therapy, suggesting that the bacteria is replaced as microbial substitution. The range of MIC for carbapenem varied from 0.01 μg/ml to 8.00 μg/ml, indicating that the attending physician should choose antibiotics based on the results of antimicrobial susceptibility

testing.

The common characteristics of our three cases were their immunocompromised status and the development of *Leuconostoc* infection during carbapenem use (or it was stopped just before in case 2). With the increase in the number of cancer patients, the opportunity to choose carbapenem antibiotics following the IDSA guideline has increased. Most *Leuconostoc* species should be susceptible to carbapenem antibiotics, but some *Leuconostoc* strains are resistant or have a relatively high MIC (Table 2) to the agent [5,9]. Moreover, our experience supports the previous reports that the MIC level against *Leuconostoc* might differ slightly for carbapenems. Furthermore, it is important to note that two of the three cases were initially misdiagnosed as *α-Streptococcus*. The major reason for the error could be the rarity of *Leuconostoc* [4,10]; clinical laboratory technicians might miss it even when the results of microbial sensitivity testing are incompatible for *α-Streptococcus*. Provision of detailed clinical information from the bedside to the laboratory could avoid such errors.

Leuconostoc has attenuated virulence, but it appears to be a critical pathogen in immunocompromised patients. Generally, *Leuconostoc* have a susceptibility to the carbapenem antibiotics, however, the effect of the antibiotics are sometimes insufficient as in the present cases. ~~Avoiding inappropriate use of broad-spectrum antibiotics, such~~

~~as carbapenem, might lead to prevention of *Leuconostoc* infection.~~ When *Leuconostoc* infection occurs, appropriate choice of antibiotics with optimal doses using in combination and with careful observation can result in successful treatment even in compromised hosts. Collecting and analyzing information, such as the fever pattern, the results of repeated blood culture tests, susceptibility testing of the detected bacteria, and close liaison between laboratory and bedside are needed.

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Figure legend

Figure. Clinical course of case 1. Arrow shows the collection of blood cultures. *: Positive for leuconostoc, $^{+}$: positive for *Stenotrophomonas maltophilia* in the blood culture samples.

Abbreviations: BIPM, biapenem; CLDM, clindamycin; IPM/CS, imipenem/cilastatin; MEPM, melopenem; MCFG, micafungin; S-T, sulfamethoxazole-trimethoprim; VCM, vancomycin.

Table 2. Clinical and microbiological characteristics of patients reported with *Leuconostoc* bacteremia, including MIC to carbapenem.

Age	Sex	Underlying disease	Complications	Microbiological diagnosis	Prior therapy	MIC (μg/ml) to carbapenem	Treatment	Outcome	Reference
72 years	M	AMI	none	*Leuconostoc sp.*	VCM	IPM; 0.01	catheter removal	dead (3 days, unknown	4
7 months	M	Malabsorption, monosaccharide intolerance	MRSE bacteremia	*Leuconostoc citreum*	VCM	IPM; 0.01	ABPC, catheter removal	improved	4
34 years	F	AML	(HSCT), graft-versus-host disease	*Leuconostoc sp.*	TEIC	IPM; 8.00	ABPC, GM	improved	6
68 years	M	Esophageal cancer	none	*Leuconostoc mesenteroides*	FMOX, TOB	IPM; 4.00	IPM/CS	dead (10 days)	11
63 years	M	Pancreatic cancer	Acute obstructive suppurative cholangitis	*Leuconostoc lactis*	LMOX	IPM; 2.00	LMOX, γ-globulin, drainage	improved	11
1 year	F	Short bowel syndrome	Central venous catheter infection (MRSE)	*Leuconostoc sp.*	CAZ, VCM	IPM; 1.00	ABPC, catheter removal	improved	12
31 years	M	Burn injury	none	*Leuconostoc cremoris*	IPM/CS, AMK	IPM; S*	ABPC, catheter removal	improved	13
52 years	M	Liver abscess	none	*Leuconostoc lactis*	CPFX, NTL, metronidazole	IPM; S*	IPM/CS, NTL, drainage	improved	14
55 years	M	Polytrauma	(Artificial ventilation)	*Leuconostoc lactis*	NA	IPM; 1.50	PIPC/TAZ, CPFX	unknown (transferred)	15
25 years	F	NHL	(Chemotherapy), febrile	*Leuconostoc pseudomesenteroides*	NA	IPM; 1.00	AMPC/CVA, GM, CPFX, ABP(	unknown (discharged)	15
4 years	M	Bronchopneumonia	none	*Leuconostoc mesenteroides ssp. Mesenteroides*	NA	IPM; 4.00	AMK, CXM	improved	15
49 years	M	Burn injury	(Artificial ventilation)	*Leuconostoc mesenteroides ssp. Mesenteroides*	NA	IPM; 6.00	CPFX, MEPM, ABPC, CL	unknown (discharged)	15
18 years	M	Burn injury	Tracheotomy, nephrectomy (artificial ventilation)	*Leuconostoc citreum*	NA	IPM; 0.75	ABPC/SBT	unknown (transferred)	15
6 months	F	Short bowel syndrome	Ileus	*Leuconostoc lactis*	NA	IPM; 1.50	AMPC/CVA	unknown (discharged)	15
26 days	F	ELBWI	Respiratory distress syndrome, hyperbilirubinemia, intraventricular hemorrhage	*Leuconostoc sp.*	CTX, VCM	MEPM; 3.00	ABPC, GM, catheter removal	improved	16
Present report									
52 years	M	AML	(Chemotherapy), febrile neutropeni	*Leuconostoc sp.*	CFPM, MEPM,	IPM; 1.00, BIPM; 4.00	IPM/CS, GM, VCM, CLDM, ST	improved	Case 1
73 years	M	NHL	(Chemotherapy), febrile neutropeni	*Leuconostoc sp.*	MEPM, FLCZ	IPM; S	PAPM/BP, GM, VCM, FLCZ	dead (5 days)	Case 2
65 years	M	Hepatic failure	none	*Leuconostoc sp.*	PIPC, IPM/CS	IPM; S	IPM/CS, catheter removal	dead (5 days)	Case 3

*: Described only the results of drug susceptibility testing.

Abbreviations: ABPC; ampicillin, AMI; acute myocardial infarction, AMK; amikacin, AML; acute myeloid leukemia, AMPC; amoxicillin, BIPM; biapenem, CL; colistin, CLDM; clindamycin, CPFX; ciprofloxacin, CS; cilastatin, CTX; cefotaxime, CTZ; ceftezole, CVA; clavulanic acid, CXM; cefuroxime, ELBWI; extremely low birth weight infant, FLCZ; fluconazole, FMOX; flomoxef, GM; gentamicin, HSCT; hematopoietic stem cell transplantation, IPM; imipenem, LMOX; latamoxef, MCFG; micafungin, MEPM; meropenem, MIC; minimum inhibitory concentration, MRSE; methicillin-resistant*Staphylococcus epidermidis* , NA; information not available, NHL; Non-Hodgkin's lymphoma, NTL; netilmicin, PIPC; piperacillin, S; susceptible, SBT; sulbactam, ST; sulfamethoxazole-trimethoprim, TAZ; tazobactam, TEIC; teicoplanin, TOB; tobramycin, VCM; vancomycin.

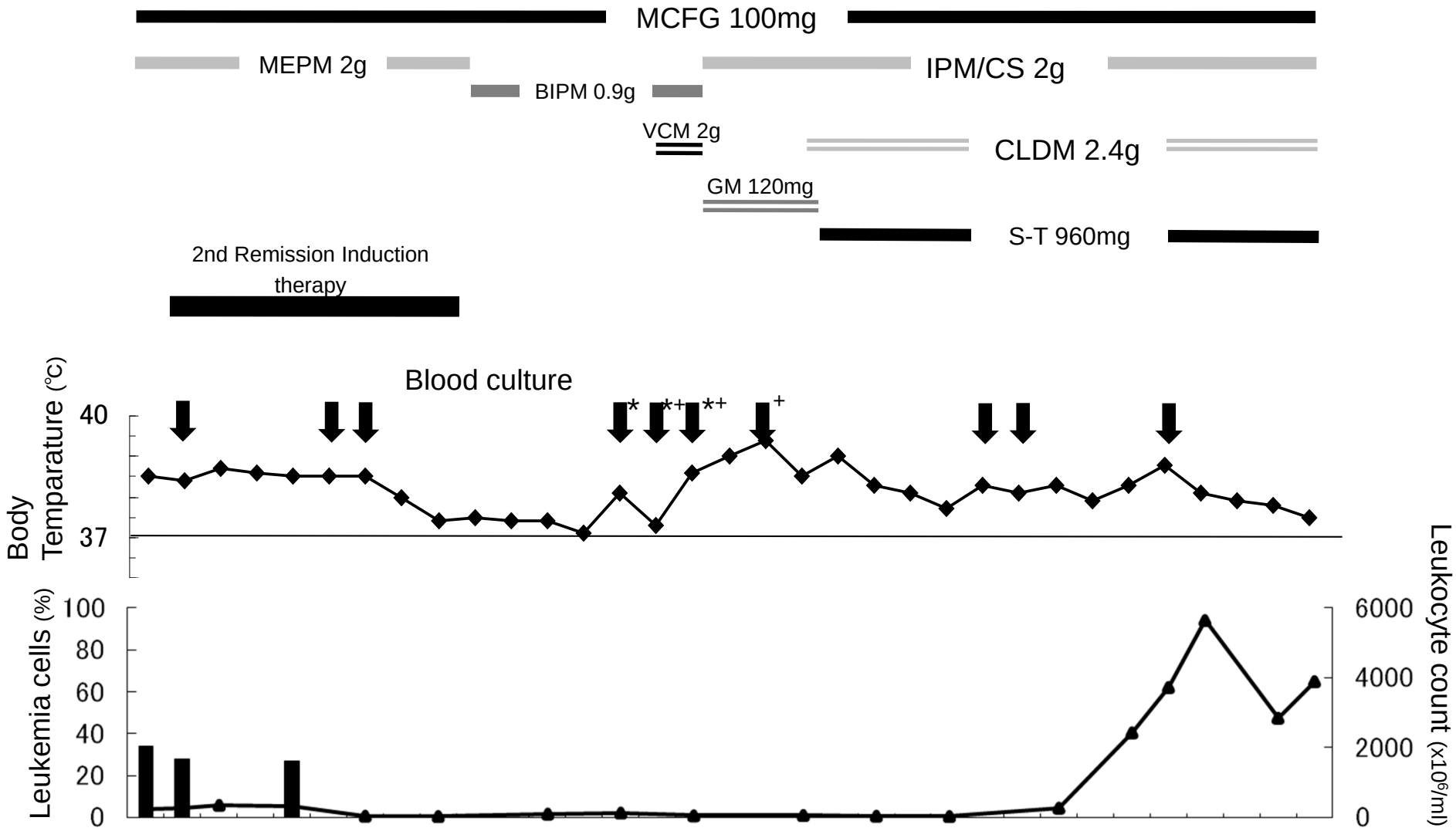

Figure. Clinical course of case 1.