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CASE REPORT

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Fulminant septicemia of *Bacillus cereus* resistant to carbapenem in a patient with biphenotypic acute leukemia

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Abstract We report a case of fulminant septicemia with *Bacillus cereus* resistant to carbapenem. A 33-year-old man was suffering from febrile neutropenia (FN) on day 15 after the start of remission-induction therapy for biphenotypic acute leukemia under gut decontamination with polymyxin B and nystatin. Meropenem, a carbapenem, was administered according to the guideline for FN. Two days later (on day 17), he complained of severe abdominal pain, lost consciousness, went into sudden cardiopulmonary arrest, and died. Autopsy showed multiple spots of hemorrhage and necrosis caused by bacterial plaque in the brain, lungs, and liver. *B. cereus* was isolated from a blood sample obtained in the morning on day 17 and it was after his death that the isolated *B. cereus* was revealed to be resistant to carbapenem. *B. cereus* obtained from blood samples has been reported to be usually sensitive to carbapenem and also to vancomycin, new quinolones, and clindamycin. If *B. cereus* resistant to carbapem increases, our method of gut decontamination with polymyxin B and nystatin may have to be changed to one containing a new quinolone for the prevention of septicemia. Careful watching to determine whether *B. cereus* resistant to carbapem increases may be also important for empiric therapy, because carbapenem is often selected as the initial therapy for FN in patients with severe neutropenia.

Key words *Bacillus cereus* · Carbapenem · Febrile neutropenia

Introduction

Members of the genus *Bacillus* are aerobic Gram-positive spore-forming rods that are ubiquitous in the environment. *Bacillus cereus* isolated from blood samples may be a contaminant or it may be the causative pathogen of opportunistic infections. *B. cereus* may form abscesses in the brain, lungs, liver, and digestive tract in an immunocompromised host, and may induce a rapidly fatal course. This type of opportunistic infection has been reported as fulminant *B. cereus* septicemia.[1–8] In 1993, we reported two patients with acute leukemia with fulminant *B. cereus* septicemia.[9] Here we report a patient with biphenotypic acute leukemia who died of fulminant septicemia with *B cereus* that was resistant to carbapenem. We discuss the drug sensitivity of the isolated bacteria, the gut decontamination regimen during chemotherapy for acute leukemia, and the present guideline for the treatment of febrile neutropenia (FN).[10]

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Case report

A 33-year-old man suffering from biphenotypic acute leukemia was admitted to our center in August 2006. On admission, his leukocyte count was 5400/μl with 13.5% blasts, hemoglobin concentration was 11.2 g/dl, and platelet count was 130 000/μl. Bone marrow examination revealed hyperplastic marrow with an increase in blasts to 87.4%. The blasts were positive for CD22, CD10, CD19, HLA-DR, CD34, KOR-SA, CD13, and CD33, and negative for cytoplasmic MPO by a flow cytometric method, suggesting the leukemia was biphenotypic. Karyotypic analysis revealed 46, XY. At age 6 years he had suffered from rhabdomyosarcoma in the right elbow, and had undergone operation and irradiation. He had a relapse in the right humerus at age 9 years and underwent irradiation and chemotherapy. No further relapse was seen.

He received remission-induction therapy, which consisted of cyclophosphamide 1200 mg/m^2 administered intravenously on day 1; vincristine 2 mg administered intravenously on days 1, 8, 15, and 22; doxorubicin 60 mg/m^2 administered intravenously on days 1 to 3; L-asparaginase 3000 ku/m^2 administered intravenously on days 9, 11, 13,

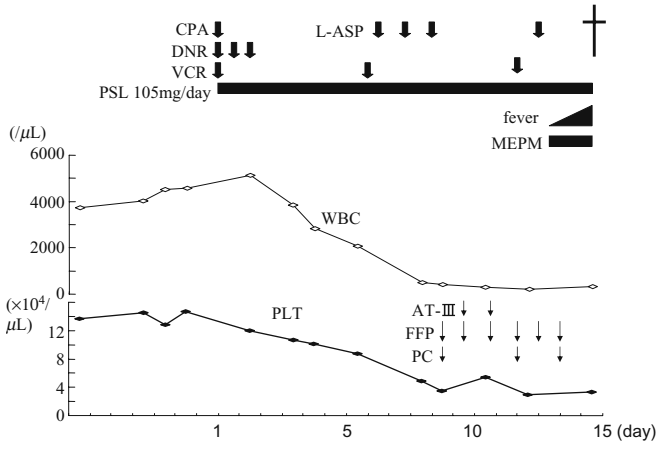

Fig. 1. Patient's clinical course. *CPA*, Cyclophosphamide; *DNR*, doxorubicin; *VCR*, vincristine; *L-ASP*, L-asparaginase; *PSL*, prednisolone; *MEPM*, meropenem; *PLT*, platelets; *AT-III*, antithrombin III; *FFP*, Fresh Frozen Plasma; *PC*, platelet count

16, 18, and 20; and prednisolone 60 mg/m^2 administered orally on days 1 to 21, after a central venous catheter was inserted (Fig. 1). During the chemotherapy, he stayed in an aseptic management room and received polymyxin B and nystatin for gut decontamination. On the night of day 15 after the start of chemotherapy, his temperature rose to 38.1°C, without complaints. He received meropenem, a carbapenem, according to the guideline for febrile neutropenia (FN), but the high temperature continued. In the early morning on day 17, he developed severe abdominal pain which gradually increased. Laboratory tests in the morning had the following results: leukocyte count was 330/μl with 44.7% neutrophils; hemoglobin concentration, 8.0 g/dl; platelet count, 33 000/μl; total bilirubin, 2.3 mg/dl; indirect bilirubin, 1.3 mg/dl; aspartate aminotransferase, 62 IU/l; alanine aminotransferase, 117 IU/l; alkaline phosphatase, 330 IU/l; γ-glutamyl transpeptidase, 108 IU/l; lactate dehydrogenase, 176 IU/l; amylase, 32 IU/l; blood urea nitrogen, 19 mg/dl; creatinine, 0.6 mg/dl; and C-reactive protein, 1.8 mg/dl. His abdominal computed tomography and ultrasound images showed no abnormality. In the evening on day 17, he suddenly lost consciousness. He underwent evaluation via urgent computed tomography of the head. Just after the computed tomography was completed, he went into cardiopulmonary arrest and died in spite of cardiopulmonary resuscitation. The computed tomography scan of the head revealed hemorrhagic infarction in the brainstem (Fig. 2). Autopsy showed multiple lesions of hemorrhage and necrosis caused by bacterial plaque in the brain, lungs, and liver (Fig. 3). *B. cereus* was isolated from a blood sample obtained in the morning on day 17, and it was after the patient's death that the isolated *B. cereus* was revealed to be resistant to carbapenem (imipenem and meropenem). It was sensitive to ofloxacin; a sensitivity test to vancomycin was not performed (Table 1).

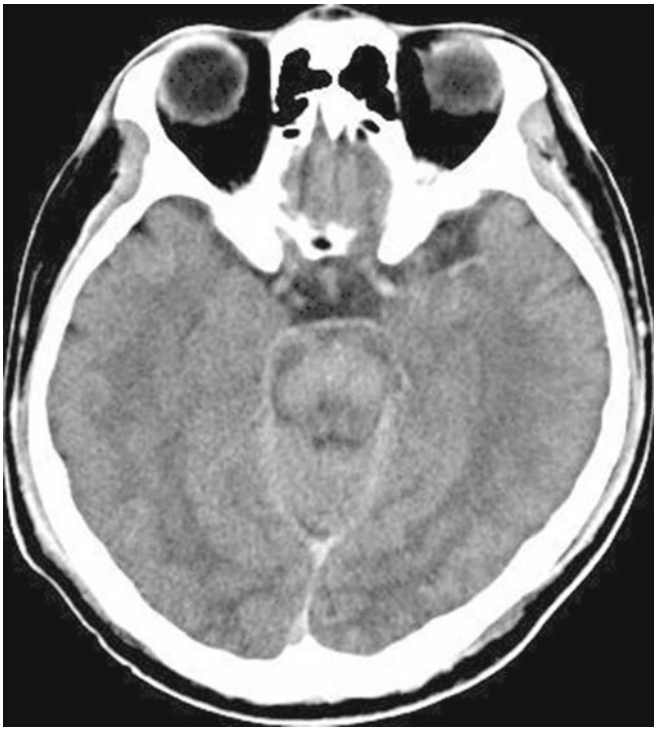

Fig. 2. Computed tomography scan of the head on day 17. The brainstem was swollen and its density was high for the most part and low in a small portion; revealing hemorrhagic infarction in the brainstem

Discussion

B. cereus isolated from blood samples has been reported to be resistant to penicillins and cephems and usually susceptible to carbapenems, new quinolones, vancomycin, and clindamycin.[11,12] We have reported here fulminant septicemia with *B. cereus* resistant to carbapenem in a patient with biphenotypic acute leukemia. To our knowledge, this is the first report of fulminant septicemia with *B. cereus* resistant to carbapenem.

In 1993, we reported two cases of fulminant septicemia with *B. cereus* which occurred during remission-induction chemotherapy for acute leukemia under the same gut decontamination regimen with polymixin B and nystatin as in the present patient.[9] We had thought that the reason we lost these two patients was because, at that time, carbapenems, new quinolones, and vancomycin were not available. Since then we have had no case of *B. cereus* fulminant septicemia even though we have been using the same gut decontamination with polymyxin B plus nystatin in remission-induction chemotherapy in acute leukemia. We treated the FN in the present patient with carbapenem according to the guideline for FN,[10] which recommends the use of a third- or fourth-generation cephem or carbapenem with or without aminoglycoside as the initial therapy. Soon after the patient's death the *B. cereus* isolated from the blood sample was revealed to be resistant to carbapenem. The reason that we lost the present patient was thought to

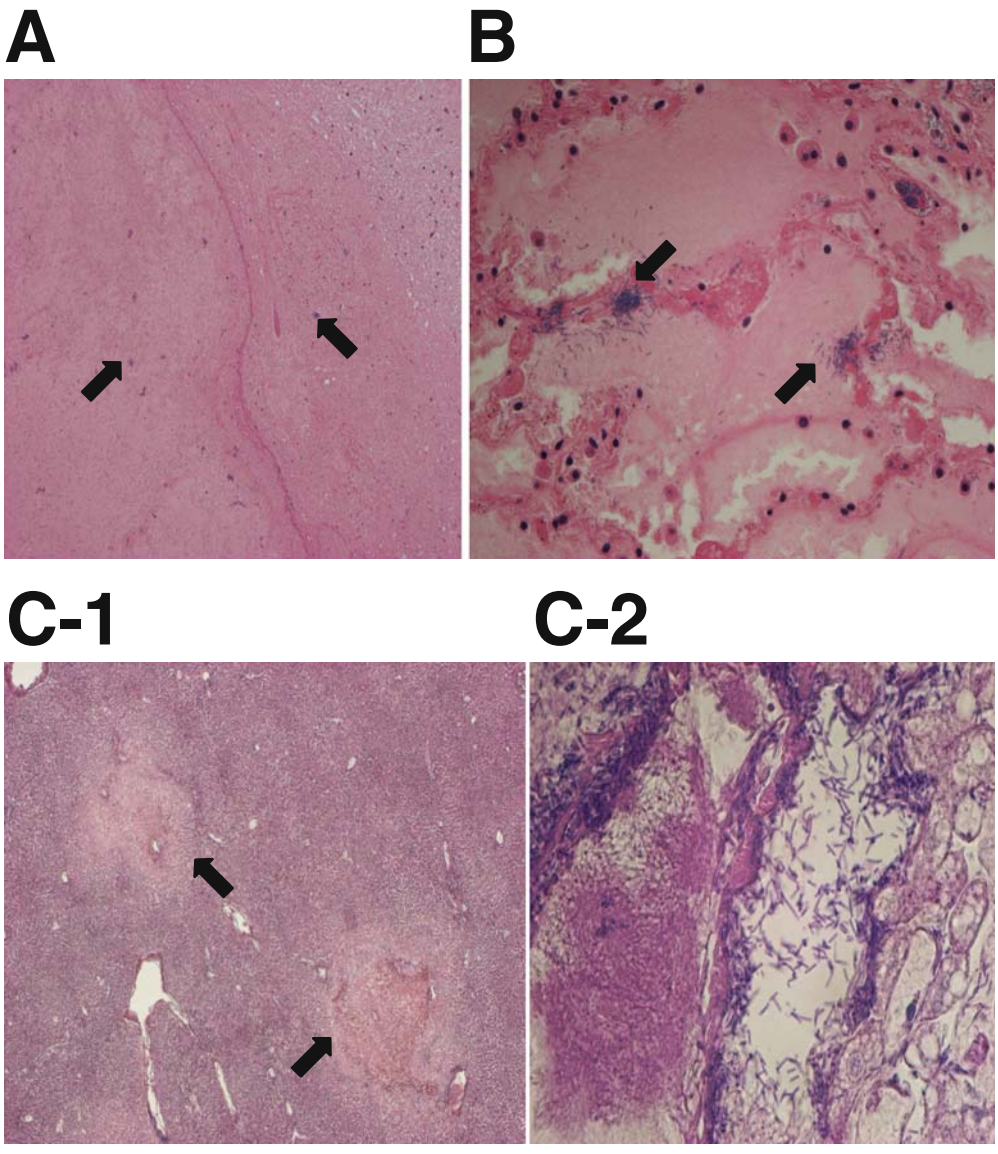

Fig. 3. **A** The brain stem tissue showed multiple bacterial plaques (*arrows*) with a background of hemorrhage; **B** the lung tissue showed many bacterial clots in vessels and the bacteria had invaded the alveoli (*arrows*); **C-1, 2** the liver tissue showed multiple focal and necrotic lesions (*arrows*). On the magnified image, there were many rods. **A** ×250; **B** ×80; **C-1** ×14; **C-2** ×560

be that *B. cereus* isolated from blood was resistant to carbapenem and the clinical course was very rapid.

Now it is possible to use new quinolones for gut decontamination, and they might be effective for the prophylaxis of *B. cereus* septicemia. The reason that we do not use new quinolones for gut decontamination during remission-induction chemotherapy for acute leukemia is that the new quinolones are absorbable, and the widespread use of these agents may encourage the growth of organisms resistant to new quinolones. Indeed, Kobayashi et al.[6] reported a patient suffering from fulminant septicemia with *B. cereus* resistant to a new quinolone during the administration of a new quinolone for gut decontamination.

At our center, since 1990, *B. cereus* has been isolated from blood samples in 22 patients (3.2% of all isolated pathogens) during chemotherapy for hematological malignancy. No isolate, excluding that from the present patient, was resistant to carbapenems or new quinolones. In 7 of the 22 cases, sensitivity tests to vancomycin were also performed. No isolate was resistant to vancomycin. The present patient had never received carbapenem before this septicemia. We do not know how the *B. cereus* isolated from the present patient acquired resistance to carbapenem. The widespread use of carbapenems might have caused the resistance of *B. cereus* to carbapenem.

We have been using a new quinolone plus nystatin for gut decontamination only after allogeneic stem cell transplantation. *Bacillus* species have been isolated from blood samples in only 2 of the 227 patients who have received allogeneic stem cell transplantation at our center. The *Bacillus* species isolated from 1 patient were considered to be contaminants. The other patient, a 45-year-old man, had received two units of cord blood transplantation for acute myeloid leukemia, and a new quinolone and nystatin for gut decontamination. He developed sepsis due to methicillin-resistant *Staphylococcus epidermidis* on day 3 post-transplant. His fever was alleviated after the administration of vancomycin. He became unable to take the new

Table 1. Microbial sensitivity tests in specimens from the present patient, in one patient who recovered after two units of cord blood transplantation, and in our two previously reported patients in 1993

	Present patient MIC	Patient who recovered after two units of cord blood transplantation MIC	Our previously reported patients in 1993	
			Case 1 MIC	Case 2 MIC
PCG	>4 R	>4		
ABPC	>8 R	8	4	8
MPIPC	>8 R		16	32
PIPC				4
CEZ	>16 R	>16		
CCL	>16 R	8	4	8
CTM	>16 R	>16		
CTX	>16 R	>16		
CMZ			4	8
CZON			8	16
FMOX			4	4
LMOX				1
IPM/CS	>16 R	0.06	0.25	1
MEPM	R[a]			
EM	0.5 S	0.5	0.5	2
CLDM	1 S	0.5	1	1
MINO	0.13 S	0.5	0.25	0.5
OFLX	0.5 S	0.13	0.25	1
VCM		2		
TEIC		0.5		

MIC, Minimum inhibitory concentration; R, resistant; S, sensitive; PCG, penicillin G; ABPC, ampicillin; MPIPC, oxacillin; PIPC, piperacillin; CEZ, cefazolin; CCL, cefaclor; CTM, cefotiam; CTX, cefotaxime; CMZ, cefmetazole; CZON, cefuzonam; FMOX, flomoxef; LMOX, latamoxef; IPM/CS, imipenem; MEPM, meropenem; EM, erythromycin; CLDM, clindamycin; MINO, minocycline; OFLX, ofloxacin; VCM, vancomycin; TEIC, teicoplanin

[a] Disk diffusion method

quinolone because of stomatitis from day 12. On the evening of day 17, his temperature rose to 38.0°C without complaints. On the evening of day 18, Grampositive rods were isolated from a blood sample, so we changed the antibiotics to pazofloxacin and clindamycin, speculating that the Gram-positive rods were *B. cereus*, even though he was receiving vancomycin, and he recovered. On day 19, the rods were confirmed as *B. cereus*, sensitive to imipenem, ofloxacin, clindamycin (Table 1), and also vancomycin. In this patient, *B. cereus* was isolated from a blood sample taken during the period when he was not able to take a new quinolone for gut decontamination (because of stomatitis), but yet during the intravenous administration of vancomycin. The administration of vancomycin may explain why the condition did not become fulminant, and the rapid change of antibiotics to pazofloxacin and clindamycin may explain his recovery from *B. cereus* septicemia. This case is suggestive that the use of a new quinolone for gut decontamination may be very effective for preventing *B. cereus* septicemia.

The clinical courses of the cases of fulminant *B. cereus* septicemia reported in the past 10 years, those of the two cases in our previous report in 1993, and that of the present case are summarized in Table 2. The majority of patients were rather young in age. Many cases were fatal even though the isolated *B. cereus* was sensitive to the antibiotics used for the initial therapy. The timing of the administration of antibiotics might have been too late. The common initial symptoms included fever, acute abdominal pain, diarrhea, vomiting, restlessness, seizure, nuchal rigidity, joint pain, and hepatic symptoms. In the present patient, fever, acute abdominal pain, and deterioration in liver function were also seen. We always need to take *B. cereus* septicemia into consideration in patients having similar symptoms, and to consider the rapid administration of vancomycin, or a new quinolone (if a new quinolone has not been used for prophylaxis), as well as carbapenem.

The rapid clinical course and resistance to carbapenem in the present patient made his treatment difficult. If *B. cereus* resistant to carbapenem increases, our method of gut decontamination with polymyxin B and nystatin may have to be changed to one containing a new quinolone for the prevention of septicemia. Careful watching to determine whether *B. cereus* resistant to carbapenem increases may also be important for empiric therapy, because carbapenem is recommended as one of the initial therapies in the present guideline for FN and is often selected as the initial therapy for FN in patients with severe neutropenia after chemotherapy for acute leukemia.

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Table 2. Reports of cases of fulminant *Bacillus cereus* septicemia in the past 10 years, the present case, and our previous report of two cases in 1993[9]

Report	Primary disease (age; years)	Gastrointestinal decontamination	Associated condition	Primary symptoms	Outcome (from the onset)	Initial therapy sensitivity	Sensitivity to other antibiotics
Yoshida et al.[9] 1993	AML(43)	Polymyxin B, nystatin	Intracranial hemorrhage	Fever, diarrhea, epigastralgia	Death (3 days)	Cefclidin N	Refer to Table1
	AML (15)	Polymyxin B, nystatin	Meningoencephalitis, subarachnoid hemorrhage	Fever, diarrhea, epigastralgia	Death (2 days)	Cefuzonam R Carmonam N	Refer to Table1
Akiyama et al.[1] 1997	ALL (64)	Polymyxin B, amphotericin B	Leptomeningitis, subarachnoid hemorrhage, bacterial infiltration (liver, stomach)	Fever, vomiting, diarrhea	Death (30 h)	Gentamicin S Piperacillin S Cefoperazone R	
Musa et al.[2] 1999	AML (30)	Ceftazidime, amikacin[a]	Unremarkable	Fever, restlessness, epigastric tenderness, felt unwell, anxious	Death (8 h)	Ceftazidime R Amikacin S	Vancomycin S Imipenem S Ciprofloxacin S
	AML (43)	Ceftazidime[a]	Subarachnoid hemorrhage	Fever, vomiting, diarrhea, sleepless, restlessness	Death (60 h)	Ceftazidime R Amikacin S	Vancomycin S Imipenem S
	ALL (14)	Ceftazidime[a]	Unremarkable	Fever, unduly anxious and restless	Unknown	Ceftazidime R Amikacin S	Vancomycin S Imipenem S Ciprofloxacin R
de Almeida et al.[3] 2003	AA (16)	Unknown	Meningitis	Fever, nuchal rigidity, altered level of consciousness, tonic-clonic generalized seizures	Death (2 days: brain death)	Ceftazidime R Imipenem S	Amikacin S Vancomycin S
Frankard et al.[4] 2004	ALL (37)	Fluconazole	Pneumonia	Fever, dry cough, chest pain, hypotension	Eradicated but relapse and died (62 days)	Cefepime N Amikacin N	Vancomycin S Clindamycin S Ciprofloxacin S Erythromycin S Penicillin G R
Haase et al.[5] 2005	HD (19)	Unknown	Meningitis	Confusion, seizure, complete flaccid hemiparesis on the left side	Eradicated	Teicoplanin S Ampicillin Amikacin S Ciprofloxacin S Clindamycin S	Gentamicin S Vancomycin S Meropenem S
Kobayashi et al.[6] 2005	ALL (25)	Ciprofloxacin, fluconazole	Meningoencephalitis, subarachnoid hemorrhage	Fever, nuchal rigidity, hypesthesia in the right lower extremity, hypotension	Death (8 days)	Cefepime R Vancomycin S Tobramycin S	Tobramycin S Vancomycin S Meropenem S Cefepime R Ciprofloxacin R

Table 2. *Continued*

Report	Primary disease (age; years)	Gastrointestinal decontamination	Associated condition	Primary symptoms	Outcome (from the onset)	Initial therapy sensitivity	Sensitivity to other antibiotics
Ozkocaman et al.[7] 2006	AML (22)	–	Unremarkable	Fever, gastrointestinal and hepatic symptoms	Death (unknown)	Vancomycin S Imipenem S Amikacin N	Aztreonam S Cefepime S Imipenem S Meropenem S Ciprofloxacin S Levofloxacin S Ofloxacin S Tetracycline S Vancomycin S Clindamycin R Penicillin R Other β-lactam agents R
	AML (19)	–	Unremarkable	Fever	Eradicated	Same as above	Same as above
	AML (3)	–	Pneumonia	Fever, respiratory symptoms	Eradicated	Same as above	Same as above
Kuwabara et al.[8] 2006	AML (54)	Unknown	Brain abscess	Fever, vomiting, headache, generalized joint pain	Eradicated	Meropenem S Minocycline N	Vancomycin S
Present case 2008	AML (45)	–	–	Fever	Eradicated	Pazofloxacin S Clindamycin S	Refer to Table1
Present case 2008	BAL (33)	Polymyxin B, nystatin	Hemorrhage and abscess in the brain, lungs, and liver	Fever, abdominal pain, deterioration in liver function	Death (3 days)	Meropenem R	Refer to Table1

AML, Acute myelogenous leukemia; ALL, acute lymphocytic leukemia; AA, aplastic anemia; HD, Hodgkin's disease; BAL, biphenotypic acute leukemia; S, sensitive; R, resistant; N, unknown

[a]The patients had received antibiotics administered intravenously for prophylactic purposes

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