Fulminant Septicemic Syndrome of *Bacillus cereus* in a Leukemic Patient


We report a rapidly fatal *Bacillus cereus* septicemia in a leukemic patient receiving remission-induction therapy. Symptoms resembling food poisoning and fever preceded coma accompanied by neurologic abnormalities. Autopsy revealed necrotizing leptomeningitis with subarachnoid hemorrhage and coagulation necrosis of the liver with bacterial infiltration. These clinicopathologic findings were closely similar to those of reported cases. Because of a rapidly fatal clinical course, suspicion of this syndrome early in the course is important to determine an appropriate treatment. Therefore, we propose that this type of septicemia should be termed as fulminant septicemic syndrome of *Bacillus cereus*.

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*Key words:* subarachnoid hemorrhage, coagulation necrosis

**Introduction**

*Bacillus cereus* (*B. cereus*) is a gram-positive, spore-forming, and rod-shaped bacterium widely distributed in the environment. Since this microorganism was considered a saprophyte, it was often dismissed as a contaminant when recovered from clinical specimens. However, *B. cereus* is now recognized as a potential pathogen causing food poisoning and such serious infections as pneumonia, meningitis, and septicemia. It produces a variety of extracellular toxins including phospholipase C, proteases, hemolysins, and enterotoxins (1, 2). Here, we report a leukemic patient who died of *B. cereus* septicemia 30 hours after onset during remission-induction therapy. Autopsy demonstrated necrotizing leptomeningitis accompanied by massive subarachnoid hemorrhage. Fatal intracranial hemorrhage in *B. cereus* septicemia has been only sporadically reported as a rare complication (3–5). Thus, this rapidly fatal complication has not been systemically characterized. The present patient’s septicemia had important clinical and pathologic features in common with previously reported *B. cereus* septicemias. Due to the rapidly fatal clinical course and resistance to β-lactam antibiotics, a high index of suspicion for this type of septicemia early in the course is important in managing severely immunocompromised patients.

**Case Report**

A 64-year-old man was admitted to the University of Tokyo Hospital to receive cytotoxic chemotherapy for acute myeloblastic leukemia (Fig. 1). On admission, he was afebrile and asymptomatic. Pallor and an elevated blood pressure of 178/104 mmHg were the only abnormal physical findings. The leukocyte count was 1,400/μl with 1% myeloblasts, 22% mature neutrophils, 2% monocytes, and 75% lymphocytes; the hemoglobin concentration was 9.5 g/dl; the platelet count was 40,000/μl. Bone marrow examination revealed a hypoplastic marrow showing an increase in myeloblasts to 34% of all nucleated cells and dysplasia of erythroid, myeloid, and megakaryocytic lineages. The patient was diagnosed with acute myeloblastic leukemia with trilineage dysplasia. BHAC-DMP combination therapy (enocitabine, daunorubicin, 6-mercaptopurine, and prednisolone) was initiated as remission-induction therapy after a central venous catheter had been inserted. At the same time, intestinal decontamination with polymyxin B and amphotericin B was started. In the early morning hours of chemotherapy day 9, his temperature rose to 40.2°C. Chills were the patient’s only symptom. Gentamicin (120 mg/day), piperacillin (4 g/day), and sulbactam/cefoperazone (4 g/day) were administered empirically after blood cultures were drawn. The blood count showed severe leukocytopenia (300/μl) with...
Agranulocytosis. Fourteen hours after onset, the patient complained of nausea, vomiting, and diarrhea, without neurologic symptoms. In the next 6 hours, he became comatose, and demonstrated marked hyperventilation at the rate of 30/min, decerebrate rigidity, and neurologic abnormalities such as conjugate deviation of the eyes to the right, anisocoria (right-left), and sluggish light reflex. Babinski’s sign, increased deep tendon reflex, and nuchal rigidity were not present. Although no significant abnormality was detected on computed tomograms of the brain, meningoencephalitis or cerebrovascular accident were suspected at first. Cefotaxime (2 g), ampicillin (6 g), and glycerol were started. However, signs of brain herniation continued to progress until he died 30 hours from the onset of septicemia. Only B. cereus was recovered from the blood culture, and was sensitive to gentamicin and piperacillin. Twelve hours after the onset, the prothrombin time and activated partial thromboplastin time were within normal range, and fibrinogen was mildly increased. No bleeding tendency was apparent throughout the course.

Autopsy revealed systemic infection of gram-positive rods mainly colonizing the brain, liver, and stomach. Examination of the brain disclosed necrotizing leptomeningitis accompanied by massive subarachnoid hemorrhage. No aneurysm was found. Microscopic examination demonstrated necrosis of the leptomeninges with numerous bacteria in the subarachnoid space (Fig. 2). The necrotic lesions were diffusely distributed over the whole brain and spinal cord. In the liver, scattered foci of coagulation necrosis without inflammatory reaction were present, and the bacterial colonies were mainly found in the sinusoids of the necrotic areas (Fig. 3). In the stomach, several bacterial colonies were accompanied by mucosal necrosis without apparent inflammatory reaction (Fig. 4). Focal organizing pneumonia was detected in the right lower lobe, but no bacterial colonies were found. The bone marrow was markedly hypoplastic and showed no leukemic cell infiltration. Consequently, the cause of death was concluded to be leptomeningitis associated with subarachnoid hemorrhage due to B. cereus septicemia. The details of neuropathologic findings were described in a separate manuscript in submission (N. Motoi et al).

Discussion

Reported cases of B. cereus septicemia in leukemic patients are summarized in Table 1. The present case shares clinical and pathologic features with the previous cases reported by Funada et al (3), Yoshida et al (4), and Marley et al (5). The leukocyte counts of these patients were markedly decreased. The patients initially presented with fever and gastrointestinal symptoms resembling those of food poisoning such as nausea, vomiting, epigastric pain, and diarrhea. These symptoms appeared prior to any neurologic abnormalities. Thus, they are not considered as the results from meningitis or subarachnoid hemorrhage. The patients all died after rapid downhill courses ranging from twelve hours to five days. Necrotizing leptomeningitis with subarachnoid hemorrhage and coagulation necrosis of the liver were pathologic characteristics in these cases. In some cases, B. cereus directly involved the gastrointestinal tract, while other cases showed no remarkable gastrointestinal changes despite symptoms resembling food poisoning. The latter situation indicates that the microbes in the blood stream produced toxins causing these gastrointestinal symptoms. A crude extract of B. cereus toxin has been reported to be lethal for mice when injected intravenously or intraperitoneally (6). The intraperitoneal injections also gave rise to coagulation necrosis on the serosal surface of various organs. The lethal and necrotizing effects are believed to be caused by two toxins: a diarrheal toxin and a hemolysin (cereolysin) (2, 7). In the present case, the necrotic lesions of the leptomeninges were diffusely distributed over the whole brain and spinal cord. No emboli were found in sections of the brain and liver as well as in the lung and kidney.
Fulminant *Bacillus cereus* Septicemia

![Image of cerebrospinal fluid with labels for subarachnoid space, pia mater, and cerebral cortex]

**Figure 2.** a) Necrotizing leptomeningitis (HE stain, original magnification, ×33). b) High power view of the inset area in a) (HE stain, original magnification, ×132).

**Figure 3.** a) Coagulation necrosis of the liver (HE stain, original magnification, ×25). Numerous bacilli have infiltrated into hepatic sinusoids (arrowheads). In the right lower corner, essentially normal hepatic tissue is seen. b) A number of bacilli are found in the sinusoid (HE stain, original magnification, ×250).

In which systemic microembolism generally occurs. These findings were considered incompatible with subarachnoid hemorrhage due to aneurysmal rupture or microembolism caused by disseminated intravascular coagulation syndrome or bacterial overgrowth. The bacterial colonies infiltrating into hepatic sinusoids were surrounded by necrotic tissue without inflammatory reaction. And the necrotizing gastritis was considered to result from direct infiltration of the bacilli into the gastric mucosa. Therefore, these findings suggest that the main cause of the necrosis was bacterial toxins, though ischemic damage due to bacterial overgrowth in vessels may also have been involved.
In contrast, in other reported cases, septicemia was less severe. Half of the patients recovered, and the remainder died six days or later from onset. In all of these cases, abdominal symptoms were absent, and necrotic changes were unremarkable. Five of six cases were complicated by pneumonia. Thus, the septicemia of B. cereus in leukemic patients can be categorized into two types based on clinical and pathologic features. Although the severity of infections is generally determined by a balance between the immunity of the host and the virulence of the microbe, previous investigations have demonstrated that the severity of B. cereus infection significantly correlates with the ability to synthesize toxins (7). B. cereus septicemia characterized by gastrointestinal symptoms and tissue necrosis is most likely caused by strains producing both of the above toxins.

When an agranulocytic patient with leukemia becomes febrile, antibiotics targeting gram-negative rods are empirically administered. However, β-lactam antibiotics are effective only rarely against B. cereus, since it produces β-lactamase. The organism is susceptible to imipenem, ciprofloxacin, gentamicin, vancomycin, tetracycline, chloramphenicol, clindamycin, and erythromycin (2). In addition, an ordinary dose of sensitive antibiotics has proven ineffective in some cases including the present case. Thus, the antibiotics doses must exceed the usual amount.

In the present case, B. cereus was identified in the stomach, considered to be the portal of entry, though the central venous catheter could not be completely excluded as the route of infection. In Western case reports, outbreaks of the B. cereus food poisoning are closely associated with fried or boiled rice. B. cereus is present in raw rice, and its heat-resistant spores survive boiling (1, 2). Autoclaving boiled rice is required for complete decontamination of B. cereus and its spores. Food poisoning caused by B. cereus represents only 1 to 2% of total outbreaks in Japan. In Asian countries where people eat boiled rice daily, it is necessary to pay attention to the B. cereus infections particularly in severely immunocompromised patients.

The present patient’s septicemia thus shared common clinical and pathologic features with reported B. cereus septicemias with subarachnoid hemorrhage. In particular, initial symptoms like food poisoning are an important clue to suspicion of this rapidly fatal septicemia. We advocate that this type of septicemia should be termed as fulminant septicemic syndrome of B. cereus, though the number of reported cases is small at present.
<table>
<thead>
<tr>
<th>Reporter &amp; Base Year (Ref)</th>
<th>Associated conditions</th>
<th>Primary symptom</th>
<th>Outcome</th>
<th>Time to death</th>
<th>Therapy</th>
<th>WBC count</th>
</tr>
</thead>
<tbody>
<tr>
<td>Cootrod et al (1971) (8)</td>
<td>CLL (52) lung abscess</td>
<td>chest pain, fever (39.5°C)</td>
<td>death</td>
<td>10 days</td>
<td>penicillin G (R) methicillin (R) gentamicin (S) isoniazid (N)</td>
<td>0*</td>
</tr>
<tr>
<td>Ihde et al (1973) (9)</td>
<td>AML (63) pneumonia, brain abscess</td>
<td>cough, fever (40.6°C)</td>
<td>death</td>
<td>6 days</td>
<td>gentamicin (S) oxacillin (R) carbenicillin (R)</td>
<td>400</td>
</tr>
<tr>
<td>Feldman &amp; Pearson (1974) (10)</td>
<td>ALL (17) hemorrhagic pneumonia</td>
<td>chest pain, fever (37.7°C)</td>
<td>death</td>
<td>8 days</td>
<td>gentamicin (S) carbenicillin (R) cephalotin (R)</td>
<td>900</td>
</tr>
<tr>
<td>Leff et al (1977) (11)</td>
<td>ALL (29) pneumonia</td>
<td>cough, hemoptysis, fever (40°C)</td>
<td>recovery</td>
<td></td>
<td>gentamicin (S) penicillin G (R) carbenicillin (R) cephalotin (R)</td>
<td>700</td>
</tr>
<tr>
<td>Trager et al (1979) (12)</td>
<td>AUL (59) pneumonia, groin abscess</td>
<td>cough, chest pain</td>
<td>recovery</td>
<td></td>
<td>gentamicin (S) chloramphenicol (S) carbenicillin (R)</td>
<td>320*</td>
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<tr>
<td>Colpin et al (1981) (14)</td>
<td>AML (19) meningitis</td>
<td>fever</td>
<td>death</td>
<td>48 hours</td>
<td>gentamicin (S) penicillin G (R)</td>
<td>1000</td>
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<td>Miki et al (1985) (13)</td>
<td>AML (55) unremarkable</td>
<td>fever (38°C)</td>
<td>recovery</td>
<td></td>
<td>cefoperazone (S) minocycline (S) cefazolin (N)</td>
<td>100</td>
</tr>
<tr>
<td>Funada et al (1988) (3)</td>
<td>AML (67) meningocerephalitis, subarachnoid hemorrhage, bacterial infiltration: liver, coagulation necrosis, stomach &amp; colon, ulcerations</td>
<td>nausea, vomiting, diarrhea, fever (39.2°C)</td>
<td>death</td>
<td>5 days</td>
<td>gentamicin (S) lincomycin (S) piperacillin (R)</td>
<td>700</td>
</tr>
<tr>
<td>Tomiyama et al (1989) (15)</td>
<td>AML (50) rhabdomyolysis, kidney: acute tubular necrosis, bacterial infiltration: liver, lung, spleen</td>
<td>muscle pain, fever (39.3°C)</td>
<td>death</td>
<td>1 day</td>
<td>piperacillin (N) ceftizoxime (N) tobramycin (N)</td>
<td>500*</td>
</tr>
<tr>
<td>Yoshida et al (1993) (4)</td>
<td>AML (43) intracranial hemorrhage</td>
<td>diarrhea, epigastralgia, fever (38.1°C)</td>
<td>death</td>
<td>3 days</td>
<td>cefcladin (N)</td>
<td>0*</td>
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<tr>
<td>Marley et al (1995) (5)</td>
<td>AML (26) meningocerephalitis, subarachnoid hemorrhage</td>
<td>diarrhea, epigastralgia, fever (39.5°C)</td>
<td>death</td>
<td>2 days</td>
<td>cefzoxanam (R) carumonam (N)</td>
<td>40</td>
</tr>
<tr>
<td>Present case AML (64)</td>
<td>leptomeningitis, subarachnoid hemorrhage bacterial infiltration: liver, coagulation necrosis; stomach, necrosis</td>
<td>nausea, vomiting, diarrhea, fever (40.2°C)</td>
<td>death</td>
<td>30 hours</td>
<td>piperacillin (S) gentamicin (S) cefoperazone (R) cefotaxime (R) ampicillin (R)</td>
<td>300</td>
</tr>
</tbody>
</table>

ALL: acute lymphoblastic leukemia, AML: acute myeloblastic leukemia, AUL: acute undifferentiated leukemia, CLL: chronic lymphocytic leukemia, Ref. the reference number, WBC: white blood cell. Time to death represents the time from initial symptoms to death N: unknown, R: resistant, S: sensitive, *absolute count of granulocytes. This finding was described in a personal communication.
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References