**Letter to the Editor**

*Bacillus cereus* is a saprophyte that is prevalent in the environment, and is generally considered to be a weak pathogen. Identification of this organism in clinical cultures is assumed to represent contamination; however, it occasionally causes serious infection in immunocompromised patients. This organism produces extracellular toxins including phospholipase C, proteases, hemolysins, and enterotoxins, which damage some vital organs. Patients with acute leukemia are particularly susceptible to bacteremia resulting from *B. cereus*. We report clinical courses of a patient who developed fatal *B. cereus* septicemia following reduced-intensity cord blood transplantation (RI-CBT). A 25-year-old man with chemorefractory T-cell acute lymphoblastic leukemia was referred to our hospital in July 2003. He had received multiple courses of chemotherapy and autologous peripheral blood stem-cell transplantation. Physical examination revealed generalized lymphadenopathy and high-grade fever, but no signs of infection. High-dose methotrexate was initiated at 2 g/m² for 2 days; however, lymphadenopathy recurred with fever, and prophylactic antibiotics including third-generation cephalosporins, ciprofloxacin and carbapenems were administered. He had not undergone rachicentesis. After providing written informed consent, he elected to undergo RI-CBT in August 2003. While surveillance culture was not obtained before transplantation, pretransplant evaluations failed to show any evidence of infections. Acyclovir 600 mg/day, ciprofloxacin 600 mg/day, and fluconazole 100 mg/day were administered orally as prophylaxis for infection. Preparative regimen comprised 25 mg/kg of fludarabine for 6 days, 4 mg/kg of busulfan for 2 days and 4 Gy total body irradiation (TBI). Prophylaxis for graft-versus-host-disease was oral cyclosporin 6 mg/kg/day. During the preparative regimen, neutrophil counts remained <0.1 x 10⁹/L, but his clinical course was uneventful except for persistent low-grade fevers and mild nausea. We speculated that fever and gastrointestinal symptoms could be attributed to residual leukemic cells and regimen-related toxicities. He was transfused two antigen-mismatched cord blood containing 2.2 x 10⁹/kg mononuclear cells. On day 1, he developed high-grade fever. While he remained alert, physical examination revealed nuchal rigidity and hypesthesia in the right lower extremity. Blood pressure decreased to 80 mm Hg. Septic shock with probable meningeval involvement was diagnosed. Blood examination showed normal functions of the liver and kidney. Hydration and intravenous administration of cefepime, vancomycin and tobramycin were initiated. Over the next 10 hours, he showed a substantial deterioration of mental status, and he became obtunded. Focal seizures were followed by generalized seizures and apnea, which required intubation, cardiac resuscitation, and fluid and vasopressor support. Lumbar puncture revealed elevated cerebrospinal fluid (CSF) pressure (27 cm H₂O). CSF was bloody, and examination under microscopy revealed the presence of gram-positive rods (Figure 1). CSF concentrations of protein and glucose were not determined. Meropenem was added on day 3. He had never received intrathecal administration of antibiotics. Computed tomography of the head on day 5 revealed diffuse cerebral edema with multiple cerebral and subarachnoid hemorrhages. His condition deteriorated rapidly, and finally died of multiorgan failure on day 8. No autopsy was permitted. *B. cereus* was later cultured from the blood and CSF, but not from catheter tips or transfused cord blood. Stool culture was not obtained. Antimicrobial susceptibility was tested using a broth microdilution test (Sceptor system, Nippon Becton Dickinson Company, Ltd., Japan). Isolated *B. cereus* was sensitive to tobramycin, vancomycin and meropenem; however, it was resistant against cefepime and ciprofloxacin. As seen in this case, *B. cereus* septicemia has been characterized by fulminant clinical courses. While the cause of rapid deterioration remains unclear, it most likely involves toxins produced by *B. cereus*. In animal models, a crude extract of *B. cereus* toxin, a diarrheal toxin and hemolysin, is lethal when injected intravenously or intraperitoneally. Autopsy studies have shown that tissues damaged by *B. cereus* septicemia show widespread necrosis without inflammatory cell reactions. These findings suggest that the necrotizing toxins secreted by *B. cereus* play a key role. If toxins are involved in the onset of symptoms associated with *B. cereus* septicemia, antibacterial therapy may be ineffective once systemic conditions deteriorate. To improve the prognosis of patients, an early diagnosis is essential. Dysesthesia and gastrointestinal symptoms may be useful early diagnostic markers for *B. cereus* septicemia. *B. cereus* septicemia is often accompanied by central nervous system injury and neuropathologically is associated with necrotizing leptomenigitis and subarachnoid hemorrhage. The present case showed consciousness disorder from the
early stages of illness, and B. cereus was isolated from CSF, confirming the findings in previous cases. Several investigations have reported that central nervous system (CNS) injury caused by B. cereus is due to toxins produced by the bacterium. However, whether CNS injury associated with B. cereus septicemia is caused by bacterial toxins or circulatory failure due to septic shock has not yet been clarified. Several risk factors of B. cereus septicemia have been reported. These included neutropenia and intrathecal chemotherapy. Considering the prolonged neutropenia due to underlying disease and repeated cytotoxic chemotherapy, the present case was at high-risk of B. cereus septicemia. However, it should be noted that it developed immediately after preparative regimen, suggesting a close association between them. Since both flu darabine and TBI are highly immunosuppressive, reduced-intensity preparative regimen using them might increase a risk of B. cereus septicemia in patients with advanced acute leukemia. Identification of infection routes is critical to prevent B. cereus septicemia. The risk of patient-to-patient transmission for B. cereus is generally low. B. cereus is frequently cultured from hospital environments including our hospital, and the intestinal tract of healthy individuals. It is reasonable to assume that most patients experience consistent exposure to the organism. Since gastrointestinal symptoms were present prior to the development of septicemia, B. cereus in the gastrointestinal tract might have entered the circulation through damaged intestinal mucosa. However, damages of the gastrointestinal tract were mild, and B. cereus might have invaded through other infectious ports. An interesting aspect of the present case was that the etiological agent was sensitive to most antibiotics, except fluoroquinolones. This was markedly different from other cases of B. cereus isolated at our and other institutions, where B. cereus is resistant to fluoroquinolones at a rate of <10%. B. cereus produces beta-lactamase, and has become resistant to some antibiotics, including third-generation cephalosporins. In our institution, fluoroquinolones are used to prevent post-transplant bacterial infections. Long-term use of this agent might have resulted in the selection of drug-resistant B. cereus, which raises a potential problem with the prophylactic administration of antibiotics. This case indicates that B. cereus septicemia can be a fatal complication following RI-CBT. The unfocused prophylactic administration of antibiotics might increase the risk of B. cereus septicemia. Considering its rapid and deteriorating clinical courses, an early diagnosis and effective prevention are essential.

Kazuhiko Kobayashi,1 Masahiro Kami,1 Masayuki Ikeda,1 Yukiko Kishi,1 Naoko Murashige,1 Ryuji Tanosaki,1 Shin-ichiro Mori,1 Yoichi Takawake1

Hematopoietic Stem Cell Transplantation Unit, the National Cancer Center Hospital, Tokyo, Japan
Department of Neurology, National Center Hospital for Mental, Nervous and Muscular Disorders, Tokyo, Japan
Department of Hematology and Rheumatology, JR Tokyo General Hospital, Tokyo, Japan

References