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CASE REPORT

Bacillus cereus septicemia in a patient with acute lymphoblastic leukemia: A case report and review of the literature

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Bacillus cereus is an aerobic Gram-positive, spore-forming, rod-shaped bacterium that is responsible for foodborne illnesses. We report on a 15-year-old girl with B-cell acute lymphoblastic leukemia, who fell into a somnolent state after presenting with a 12-hour history of fever, muscle soreness, myalgia in both calves, sore throat, and vomiting. Fulminant septicemic syndrome caused by *B. cereus* was finally identified. The aim of this work is the introduction of *B. cereus* as a differential diagnosis of sepsis in patients with acute leukemia in induction chemotherapy, to prevent delayed treatment.

Introduction

Bacillus cereus, an aerobic Gram-positive, rod-shaped, spore-forming bacterium, is widely distributed in the environment and is usually considered a contaminant when recovered from cultures. Although it commonly causes foodborne gastroenteritis, which is mostly benign and self-limiting, it occasionally causes severe infections in immunocompromized patients, including septic shock, meningitis, brain abscess, colitis, endocarditis, respiratory infections, and infection-related coagulopathy and hemolysis. Inoue et al reviewed 58 case reports of *B. cereus* sepsis in patients with leukemia and found that only 28 of those patients survived.[1] We present a fatal case of *B. cereus* sepsis in a patient with acute leukemia.

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Case report

A 15-year-old girl presented to hospital with a 7-day history of fever, sore throat, abdominal fullness, yellowish skin color, and general weakness. Based on her physical symptoms, clinicians at the hospital diagnosed tonsillitis and the patient received medicine. Her symptoms, however, did not subside, and the patient was taken to a different hospital. Liver function tests performed at that time revealed elevated levels of aspartate aminotransferase (1356 units/L), alanine aminotransferase (1930 units/L), and anemia (hemoglobin = 8.1 g/dL). She was referred to our hospital 3 days later, where an initial diagnosis of acute hepatitis was made.

After admission, complete blood count showed a hemoglobin level of 6.5 g/dL and a platelet count of 19,000/mm^3. The white blood cell (WBC) count was 17,570/mm^3, with 5% segmented neutrophils, 43% lymphocytes, 9% atypical lymphocytes, and 43% immature cells. After a series of examinations, acute B-cell lymphoblastic leukemia was diagnosed. Based on the TPOG-2002-ALL protocol, the patient was classified as belonging to the very high risk group. The Taiwan Pediatric Oncology Group (TPOG) was formed with the cooperation of all leukemia treatment centers in Taiwan in 1988 and has since initiated national cooperative group studies. A TPOG-2002-ALL VHR induction phase protocol was started 3 days after admission. Prednisolone 40 mg/m^2 was administered. Within 2 days, there was a marked decrease in blast cell count and WBC count, indicating a good response. However, neutropenic fever was noted. In response, cefepime (1 g by intravenous drip, twice daily) was administered as empiric therapy. Urine culture grew *Escherichia coli* ($>10^5$ colonies/mL), which was susceptible to ampicillin, gentamicin, and cefepime.

Four days after induction chemotherapy, the patient experienced a sleepless and restless night, and had a fever of 38—39 °C. Skin rashes over the forehead, a sore throat, and myalgia over both lower limbs, in addition to another fever spike (40.1 °C) and one vomiting incident, were noted the next morning.

Sudden onset of consciousness disturbance, with anisocoric pupils occurred 2 hours later. The Glasgow Coma Scale was 8. Endotracheal intubation was performed. Brain computed tomography showed no intracranial hemorrhage. During the next 2 days, the patient suffered from four episodes of pulseless electrical activity, with a return of spontaneous circulation after resuscitation. Inotropic agents, including dopamine, epinephrine, dobutamine, norepinephrine, empiric antibiotics comprising meropenem (1 g by intravenous drip, 3 times daily), vancomycin (1 g by intravenous drip, 3 times daily), acyclovir (500 mg by intravenous drip, 3 times daily), fluconazole (400 mg by intravenous drip, once daily), and granulocyte colony-stimulating factor, were administered. However, the patient's general condition worsened. There was a rapid onset of epistaxis, gastrointestinal (GI) bleeding, menorrhagia, hematuria, and hypoalbuminemia, in addition to acute renal failure and acute pulmonary edema. The patient died 2 days after onset of the symptoms of septic shock.

Rectal, throat, and urine samples were analyzed to determine the causative agent. The results of all tests performed (urine culture, blood culture, PCR for enterovirus, influenza, and adenovirus) revealed Gram-positive bacilli in three sets of blood cultures. The isolates were subjected to 16S ribosomal RNA gene sequencing using the broad-range bacterial specific primer pair Bact 5F (GAA GAG TTT GAT CMT GGC TC) and Bact 809R (GCG TGG ACT ACC AGG GTA TC), which is highly conserved throughout the phylogenetic tree and is found in all prokaryotic organisms.[2,3] The product was compared with known sequences in the National Center for Biotechnology Information (NCBI) blast database and the result confirmed the presence of *B. cereus*. Therefore, *B. cereus*-induced fulminant septicemic syndrome was diagnosed.

Discussion

The incidence of *B. cereus* septicemia accounts for approximately 2% of all cases of bacteremia or fungemia.[4] There have been several reports of *B. cereus* septicemia in patients receiving cancer chemotherapy, especially in patients with hematologic malignancies.[5—15] All had severe neutropenia and high fever. The clinical course was fulminant, and death was rapid. In our patient, who had acute lymphoblastic leukemia, and who was severely neutropenic and iatrogenically immunosuppressed due to chemotherapy, fatal septicemic shock, and coma caused by *B. cereus* developed rapidly. The clinical course in our patient was compatible with that reported by Musa et al, which was marked by two phases: a mild febrile illness lasting 6—14 hours, accompanied by subtle symptoms of autonomic sympathetic nervous system overactivity, and a second short fulminant phase, marked by high fever (40—41 °C) accompanied by major central nervous system (CNS) disturbances, resulting in deep coma and brain stem dysfunction.[16]

Inoue et al reported on 12 cases and analyzed a total of 58 previously reported cases of *B. cereus* septicemia in patients with hematologic malignancies.[1] They found that acute leukemia, a neutrophil count of near 0/μL, or the presence of CNS symptoms during febrile episodes, were associated with a fatal prognosis. Their findings are compatible with the clinical presentation of our patient.

In our patient, all three sets of blood cultures showed Gram-positive bacilli, and the laboratory staff considered it as a contaminant. However, the three sets of blood cultures were sampled from different sites and at different times using sterile procedures. Therefore, it is unlikely that the samples were contaminated. *B. cereus* was definitively diagnosed after a full PCR workup. According to a previous study, the presence of *B. cereus* in blood cultures should not be regarded as contamination in patients receiving intensive chemotherapy for leukemia.[1,4,17]

Our patient was treated with meropenem and vancomycin after she manifested symptoms of septic shock. According to a previous study, all of the isolated *B. cereus* strains were sensitive to imipenem, vancomycin, levofloxacin, and gentamicin, and the authors strongly recommend immediate initiation of treatment with meropenem and vancomycin in such situations. However, they also experienced cases of fatal *B. cereus* sepsis, in which appropriate antibiotic treatments were not effective.[1]

To the best of our knowledge, *B. cereus* sepsis has only been diagnosed in a limited number of pediatric patients undergoing chemotherapy for hematological malignancy.[1,7,14,16,18–22] Based on the information available on the 15 previously reported cases as well as our case, we evaluated the risk factors for mortality among patients with sepsis due to that bacterial species. The results are presented in Table 1. The variables that we analyzed included age, sex, underlying diseases, chemotherapy treatment process, presence of GI symptoms, CNS lesions, use of corticosteroids, vancomycin, and absolute neutrophil count (ANC). The 16 pediatric patients (8 boys, 8 girls) ranged in age from 3 years to 17 years. Of the 16 patients, 11 had acute lymphoblastic leukemia, two had acute myeloid leukemia, one had acute leukemia, one had myelodysplastic syndrome, and one had non-Hodgkin lymphoma. GI symptoms were present in 10 patients and nine patients had CNS lesions. In analysis of both the use of corticosteroids and vancomycin, no data were available for six patients. Of the 10 patients with available data, nine received corticosteroids and four received vancomycin. In the WBC count analysis, no data were available for eight patients. All of the eight patients with available WBC count had severe neutropenia (ANC $<$ 100 cells/μL) and five of them had an ANC of 0. In addition, six of the 16 patients died. Some differences in age, chemotherapy treatment process, presence of CNS lesions, and use of corticosteroids were noted between patients who survived and those who died. However, there were no significant differences in abnormalities between the two groups. In addition, there was no significant difference in the use of vancomycin between the two groups. Interestingly, however, all isolates of *B. cereus* were susceptible to vancomycin and imipenem/meropenem and resistant to penicillins and cephalosporins. In addition, most isolates were susceptible to amikacin, gentamicin, chloramphenicol, and erythromycin.[1,16,18,19,22]

Table 1 Comparison of mortality rate of children with *Bacillus cereus* sepsis

Characteristic	Death (n = 6)	Recovery (n = 10)	p*
Age			
<10 y	1/6 (16.7)	4/10 (40)	0.59
>10 y	5/6 (83.3)	6/10 (60)	
Sex			
Male	3/6 (50)	5/10 (50)	0.99
Female	3/6 (50)	5/10 (50)	
Disease			
ALL	4/6 (66.7)	7/10 (70)	0.99
AML	1/6 (33.3)	1/10 (10)	
Chemotherapy treatment process			
Induction	4/6 (66.7)	3/10 (30)	0.12
Non-induction	0/6 (0)	5/10 (50)	
Reinduction	2/6 (33.3)	2/10 (20)	
GI symptom			
Positive	4/6 (66.7)	6/10 (60)	0.99
Negative	2/6 (33.3)	4/10 (40)	
CNS lesion			
Positive	4/6 (66.7)	4/10 (40)	0.61
Negative	2/6 (33.3)	6/10 (60)	
Corticosteroid[a]			
Use	3/4 (75)	6/6 (100)	0.40
Non-use	1/4 (25)	0/6 (0)	
VCM[b]			
Use	2/5 (40)	2/5 (40)	0.99
Non-use	3/5 (60)	3/5 (60)	
WBC (ANC) (cells/mm^3)[c]			
ANC < 100	5/5 (100)	3/3 (100)	0.99

[a] In the corticosteroid use analysis, no data were available for six patients.
[b] In the VCM use analysis, no data were available for six patients.
[c] In the WBC (ANC) count analysis, no data were available for eight patients.
Data are number (%) of patients.
*Based on Fisher's exact test.
ALL = acute lymphoblastic leukemia; AML = acute myeloid leukemia; ANC = absolute neutrophil count; VCM = vancomycin; WBC = white blood cell.

The descriptions of the patient in this article should alert clinicians to the potentially serious nature of *B. cereus* infection in immunocompromized patients. Appropriate antibiotics should be given as soon as *B. cereus* is detected in any blood culture sample obtained from a patient with hematological disease, especially in patients receiving intensive chemotherapy.

In conclusion, *B. cereus* isolated from blood from immunocompromized hosts should not be indiscriminately regarded as a contaminant. Appropriate antibiotics should be given as soon as *B. cereus* is detected in any blood culture sample obtained from patients undergoing intensive chemotherapy for hematological disease. Based on our findings, *B. cereus* should be included in the differential diagnosis of sepsis in patients with acute leukemia who are undergoing induction chemotherapy.

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