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Letter to the Editor

Bacillus Cereus in Hematological Malignancies

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To the editor.

After reading the publication entitled "Infections in Myelodysplastic Syndrome in Relation to Stage and Therapy" (Mediterr J Hematol Infect Dis. 2018; 10(1): e2018039) that was published in your journal, we would like to congratulate the authors for this interesting review article and make some contributions specifically concerning *Bacillus cereus* infections in patients with hematological malignancies.

Bacillus cereus is a spore-building, Gram-positive rod that may cause three distinct syndromes: food intoxication, localized infection, or bacteremia with potential hematogenous complications (e.g., liver and cerebral abscesses).[2,3] Furthermore, patients with hematological diseases are at greater risk for invasive *B. cereus* infections.[2] Herein, we present an interesting case of fulminant *B. cereus* septicemia in a patient with myelodysplastic syndrome (MDS).

A 74-year-old woman was diagnosed with MDS upon assessment of severe pancytopenia. Bone marrow (BM) examination revealed a blast percentage of 12% compatible with MDS with excess blasts 2 (MDS-EB-2) per the 2016 World Health Organization (WHO) classification,[4] whereas the BM cytogenetic analysis was normal (46, XX). She was started on treatment with 5-azacytidine at a dose of 75 mg/m^2/day subcutaneously (IV) for 7 days in 28-day cycles. On day 20 of Cycle 2, while the patient was neutropenic (0.5x10^9/L), she developed a fever of 39^{o}C accompanied by chills, fatigue, and fainting. Her physical examination and initial chest X-ray did not reveal any specific findings. Computed tomography (CT) scan of the brain, conducted to investigate fainting, did not suggest central nervous system (CNS) involvement. Within one hour from the febrile episode, IV piperacillin/tazobactam at a dose of 4,5 g q6h was started along with filgrastim at a dose of 300 mcg daily. The patient reported diarrhea within the next 20 hours, and stool cultures were obtained. By that time, gram-positive, rod-shaped bacteria were isolated from both blood cultures, and vancomycin was added to the regimen. *B. cereus* was identified in the blood but was not isolated from the stool. Her central venous catheter was considered to be the source of her infection. The patient remained febrile for an additional 3 days after *B. cereus* isolation. A transthoracic echocardiogram did not reveal findings compatible with *B. cereus* endocarditis. Two days later, the fever subsided, and clinical improvement was noted within four days, as diarrhea and fatigue ameliorated.

In our case, a 74-year-old patient with MDS was diagnosed with isolated *B. cereus* bacteremia while on cycle 2 of chemotherapy. Studies have shown that immunocompromised patients with isolated *B. cereus* bacteremia usually follow a more benign course compared to organ-involved cases, having a more severe clinical presentation and life-threatening course.[3] In this context, we gathered reported cases of *B. cereus* bacteremia with contemporary manifestations from various organ systems in patients with hematological malignancies (**Supplementary file 1**).

Concerning general patient characteristics, 30 out of 73 patients were female (41%) and 31 were male (42.4%), while sex was not mentioned in 12 cases. Most patients were middle-aged, with the median age of 36 and the interquartile range being 45 years. Concerning risk factors for infection, all patients were neutropenic, and 45 had a diagnosis of acute leukemia (61.6%). Among patients with acute leukemia, 66.6% had acute myeloid leukemia (AML). The percentage of patients with intravascular catheters, an important risk factor since *B. cereus* can adhere to foreign bodies by producing biofilms,[3] was 76.7%. Notably, 56.1% of these patients had concurrent gastrointestinal symptoms, such as abdominal pain and diarrhea. However, CNS involvement was the most common manifestation (80.8% of patients). Other common symptoms included fever in 46.5% and headache in 23.1% of patients. Although the issue of ICU hospitalization was not mentioned in all cases, it was reported in 10.1% of patients. The death occurred in 34.2% of patients, and 92% of these deaths occurred within 30 days of symptom onset. Of note, 76.7% of patients received

vancomycin, and 26.7% of those died, whereas 61.1% of patients who did not receive vancomycin died.

This outcome is in line with the well-studied susceptibility pattern of *B. cereus*, which is characterized by susceptibility to vancomycin but is resistant to penicillins and cephalosporins.[5] The presence of a CVC in most patients, which can be a source of infection similarly to our case, highlights the importance of early central catheter removal within 72 hours from the onset of *B. cereus* bacteremia, as previously recommended.[3] In addition, catheter infection may be associated with a worse outcome with frequent neurologic complications. Regardless of the presence of a central catheter, *B. cereus* infections should be included in the differential diagnosis of neutropenic patients with hematologic malignancies who have recently received chemotherapy and present with neurological symptoms.

Inappropriate antibiotic treatment is predictive of higher mortality rates in patients with bacteremia compared to appropriate therapy.[6] It is, therefore, crucial to select the right antimicrobial agents for empirical treatment according to the antimicrobial susceptibility of the pathogen. In the presence of CNS disease, abscess drainage in large and accessible abscesses should also be encouraged.[7] Most *B. cereus* isolates produce beta-lactamases and are resistant to penicillins and cephalosporins. Therefore, vancomycin should be included in empirical treatment regimens.[8] Alternative agents having *in vitro* activity against Bacillus spp include aminoglycosides, carbapenems, and fluoroquinolones.[9] However, reports of carbapenem resistance have recently been reported, and carbapenems are no longer considered appropriate as an empiric treatment.[10]

In conclusion, *B. cereus* should always be taken into consideration as a potential threat for patients with hematological malignancies, and a low threshold for prompt diagnosis and treatment should be placed.

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Supplementary file.

Supplementary file 1. Included studies of neutropenic patients with hematological malignancies and invasive *B.cereus* infection.

Gender/ Age (years)	Underlying disease	Disease manifestations-complications	Isolation site	Antibiotics used	Further treatment actions	Outcome	Neutrophil count at disease onset	Central catheter	Reference
CNS manifestation-predominant									
F/54	AML	Bacteremia and meningitis with fever, chills and nausea during consolidation chemotherapy	Blood, CSF	Meropenem, linezolid and vancomycin	ICU hospitalization	Recovery	<100/μL	NM	[1]
M/64	AML	Bacteremia and meningitis with fever, nausea, vomiting and diarrhea on day 9 of chemotherapy	Blood, brain liver and stomach autopsy	Piperacillin, gentamicin, cefoperazone, cefotaxime, ampicillin		Death within 30 hours from the onset of septicemia	<300/ μL	Present	[2]
M/63	AML	Brain abscess with fever and eventual coma post-chemotherapy	Postmortem brain biopsy	Gentamicin, oxacillin, carbanicillin		Death on the 6th day of fever	400/μL	NM	[3]
M/19	AML	Meningitis with fever after high dose cytostatic treatment of therapy-resistant AML	CSF culture	Gentamicin, Penicillin G		Death 12 days after antibiotic course initiation	<100/μL	Present	[4]
F/67	MDS/AML	Meningoencephalitis with fever, headache and vomiting, while receiving intensive chemotherapy	Positive blood cultures and postmortem brain, stomach and colon examination	Gentamicin, lincomycin, piperacillin		Death 5 days after symptom onset	100/ μL	NM	[5]
M/3	ALL	Brain abscess with fever and lethargy after induction chemotherapy	Brain biopsy	Gentamicin, Vancomycin, rifampin, chloramphenicol	Chemotherapy continuation	Recovery	<20/ μL	NM	[6]
M/26	AML	Meningoencephalitis/ Subarachnoid hemorrhage with vomiting and visual disturbances, while receiving induction chemotherapy	Blood cultures and brain autopsy	Ceftazidime	Platelet and red blood cell transfusion	Death within 12 hours of neurologic symptom onset	<20/ μL	NM	[7]
M/64	AML	Meningoencephalitis/ subarachnoid hemorrhage with fever, vomiting and diarrhea post chemotherapy	Brain, stomach and liver autopsy	Gentamicin, piperacillin, cefoperazone, cefotaxime, ampicillin	Total blood transfusion	Death 10 hours after neurologic symptom onset	<300/ μL	NM	[8]
F/20	ALL	Cerebral infarction with fever, vomiting, diarrhea, abdominal pain, speech and sensory disturbances the week after intrathecal chemotherapy	CSF, spleen, lung, liver cultures	Vancomycin		Death shortly after diagnosis	0 μL	Present	[9]
F/13	ALL	Meningoencephalitis/hydrocephalus with fever and abdominal pain the week after intrathecal chemotherapy	CSF and stool cultures	Vancomycin		Recovery	0 μL	Present	[9]

F/15	ALL	Meningoencephalitis with headache and abdominal pain the week after intrathecal chemotherapy	CSF and stool cultures	Vancomycin		Death shortly after diagnosis	0 µL	Present	[9]
M/4	ALL	Neurologic symptoms the week after intrathecal chemotherapy	Hickman line culture	Vancomycin		Recovery	Neutropenic, count NM	Present	[8]
F/10	ALL	Bacteremia and CNS involvement with seizures and altered sensorium	Stool	Vancomycin		Recovery	Neutropenic, count NM	Present	[8]
M/7	MDS	Neurologic symptoms the week after intrathecal chemotherapy instillation	NM	Vancomycin		Recovery	Neutropenic, count NM	Present	[8]
M/17	NHL	Neurologic symptoms the week after intrathecal chemotherapy instillation	NM	Vancomycin		Recovery	Neutropenic, count NM	Present	[9]
M/19	HD	Meningoencephalitis with fever, confusion, epilepsy and hemiparesis after allogenic stem cell transplant	Right ear swab, positive PCR in the CSF and blood	Ampicillin, amikacin, ciprofloxacine, teicoplanin, clindamycin	G-CSF, ICU hospitalization	Recovery	<100/ µL	Present	[10]
F/32	AML	Abdominal pain and diarrhea on day 12 and right occipital lobe abscess with fever, headache, photophobia, blurred vision, left lower extremity pain on day 18 day of induction chemotherapy	Brain biopsy	Vancomycin	Abscess drainage	Recovery	0/ µL	Present	[11]
F/58	AML	Meningitis, brain abscess, ventriculitis and diffuse infarcts with fever, progressing to confusion, slurred speech and seizure on day 16 of induction chemotherapy	Brain and ascending colon autopsy	Vancomycin		Death 28 hours after the onset of neurologic symptoms	0/ µL	Present	[11]
F/54	AML	Meningitis, brain abscess and infarcts with fever with progression to altered mental status and seizure on day 14 of induction chemotherapy	Blood cultures and brain biopsy and autopsy	Daptomycin, levofloxacin and vancomycin		Coma 4 hours and death 42 hours after the onset of neurologic symptoms	0/ µL	Present	[11]
F/50	AML	Meningitis with fever, headache, photophobia and nuchal rigidity with progression to altered mental status and agitation on day 17 of induction chemotherapy	Blood cultures and brain autopsy	Vancomycin		Death 36 hours after onset of neurologic symptoms	0-2/ µL	Present	[11]
F/52	AML	Meningitis with altered mental status and agitation on day 8 of induction chemotherapy	Blood cultures and brain, colon and liver autopsy	Vancomycin		Death 14 hours after onset of neurologic symptoms	0/ µL	Present	[11]
M/25	T- ALL	Septic shock and meningitis with fever, meningism signs, altered mental status, seizures post RT-CBT	CSF, blood	Cefepime, vancomycin, tobramycin and meropenem		Death on day 8 of symptoms after progressive deterioration	0/µL before transfusion	Present	[12]
22 patients (10 M and 12 F/ 33 – 89) *	8 with AML, 3 with ALL, 7 with lymphoma and 4 with myeloma	Bacteremia in 17 patients and brain abscess in 5 patients, with vomiting, diarrhea abdominal pain and septic shock within 2 weeks of either chemotherapy or corticosteroid therapy	Blood	Amikacin, meropenem, ciprofloxacin, vancomycin and linezolid		Death in 2 patients with bacteremia, recovery in 15. Death in 1 patient with brain abscess, recovery in 4	All patients with brain abscess and 6 patients with bacteremia were neutropenic with <500/µL	Present in all patients	[13]

F/67	ALL	Bacteremia multiple brain and liver abscesses with high fever, diarrhea, vomiting, severe headache and nausea after chemotherapy	Positive blood cultures	Minocycline, vancomycin, levofloxacin, chloramphenicol	G-CSF, as well as brain abscess drainage	Recovery after approximately 2 months	200/μL	NM	[14]
M/5	B-cell ALL	Bacteremia and brain abscess with fever, without neurologic symptoms 18 days after initiation of induction chemotherapy	Positive blood cultures	Meropenem	Continued chemotherapy	Recovery after 6 weeks of antibiotic therapy	Neutropenic, count NM	NM	[15]
M/15	ALL	Meningitis	CSF cultures	Vancomycin		Recovery	1900/μL	Not present	[16]
M/3	ALL	Bacteremia-fulminant sepsis	Blood cultures	Ceftazidime, amikacin		Death before the organism was isolated	500/μL	Not present	[16]
10 patients*	5 with AML, 2 with ALL, 3 with MDS	Bacteremia in all patients and brain abscess and/or meningoencephalitis in 3 patients, most with fever, abdominal pain, vomiting, diarrhea, confusion and headache during induction chemotherapy	Positive blood culture, sterile CSF cultures	Vancomycin and carbapenems	ICU hospitalization in 4 patients	Recovery	Neutropenic, count NM	Present in all patients	[17]
M/60	MDS	Brain abscess and necrotizing fasciitis with fever, leg swelling, disorientation	Blood	Gentamicin, panipenem, clindamycin, ciprofloxacin	G-CSF	Recovery	0/μL	NM	[18]
Respiratory manifestation-predominant									
NM	Acute leukemia	Pneumonia within 2 weeks of chemotherapy	Positive blood cultures	Piperacillin and amikacin		Recovery	<100/μL	Present	[19]
NM	Acute leukemia	Pneumonia complicated by severe respiratory distress within 2 weeks of chemotherapy	Positive blood cultures	Piperacillin and amikacin		Recovery	<100/μL	Present	[19]
F/11	ALL	Pneumonia and lung abscess with fever, fatigue and nonproductive cough, progressing to delirium and hemoptysis 7 days post-chemotherapy	Blood cultures, sputum staining, lung autopsy	Oxacillin, ampicillin, kanamycin, carbapenicillin and gentamicin		Death on the 9th day of symptom onset		NM	[3]
M/63	AML	Pneumonia with fever, non-productive cough and hemoptysis 4 days post-chemotherapy	Positive blood cultures and sputum staining, lung brain, heart autopsy	Oxacillin, gentamicin, carbenicillin and amphotericin B		Death on the 6th day of symptom onset	Neutropenic, count NM	NM	[3]
M/60	AML	Carbapenem-resistant *B.cereus* pneumonia with fever during induction chemotherapy	blood and sputum	Cefepime and then switch to panipenem/betamipro n		Death on the 29th day of hospitalization	4/μL	Present	[20]
F/37	ALL	Pneumonia with fever, dry cough and left-sided chest pain on day 20 of hospitalization for salvage chemotherapy	Blood and BAL	Cefepime, amikacin, vancomycin, amphotericin B	G-CSF	Death on day 35 of symptom onset	<100/ μL	NM	[21]
Gastrointestinal manifestation-predominant									

M/22	AML	Rapidly deteriorating pancolitis and typhlitis with fever, right upper and lower quadrant pain with bright red blood in the stool after induction chemotherapy	Blood and stool	Imipenem, oral vancomycin, metronidazole and ciprofloxacin	Bowel rest and ICU hospitalization	Death on the 34th day of hospitalization	Neutropenic, count NM	NM	[22]
F/74	AML	Typhlitis with diarrhea unresponsive to loperamide, right upper quadrant abdominal pain after initiation chemotherapy	Stool	Clindamycin		Recovery	<500/μL	Present	[23]
F/70	ALL	Phlegmonous gastritis with fatigue, nausea and watery diarrhea on day 11 of chemotherapy	Gastric biopsy culture	Biapenem and meropenem	IVIG, G-CSF, hydrocortisone, blood transfusion	Recovery	98/μL	Present	[24]
Cardiovascular manifestation-predominant									
M/38	ALL	Bacteremia and anterior thigh ulcer initially. Sepsis, mitral valve endocarditis and brain abscesses a day after chemotherapy	Ulcer and blood isolates, heart and brain autopsy	Penicillin, vancomycin and gatifloxacin		Death 4 days after chemotherapy	Neutropenic, count NM	NM	[25]
Ophthalmic manifestation-predominant									
M/79	Lymphoma	Endophthalmitis with acute left eye pain with vision loss during scheduled admission for chemotherapy	Blood and eye specimen culture	Vancomycin and gentamicin	Eye evisceration	Recovery	NM	Present	[26]
Multiple organ involvement									
M/NM	AML	Fulminant sepsis with chills, arthralgias, headache, nausea, abdominal and lumbar pain 2 weeks after chemotherapy	Postmortem blood culture	Piperacillin/tazobactam, meropenem, vancomycin	IV norepinephrine	Death within a day of admission	30/μL	NM	[21]
F/20	ALL	Fulminant sepsis with nausea, vomiting, abdominal pain and diarrhea on day 28 of induction chemotherapy	Postmortem blood, heart, liver, lung, spleen, CSF	Ceftazidime, tobramycin, vancomycin	Dopamine and epinephrine, blood transfusion	Death 4 hours after sepsis onset	0/μL	Present	[27]
F/10	ALL	Fulminant sepsis with abdominal pain, lethargy on day 12 of chemotherapy	Positive blood and stool cultures	Cefotaxime, vancomycin, tobramycin, meropenem	Dopamine and epinephrine, blood transfusion	Recovery	0/μL	Present	[27]

Abbreviations: F, Female; M, Male; ICU, Intensive Care Unit; NM, Not mentioned; AML, Acute Myeloid Leukemia; ALL, Acute Lymphoblastic Leukemia; HD, Hodgkin's lymphoma; CSF, Cerebrospinal fluid; BMT, Bone Marrow Transplant; RT-CBT, Reduced-Intensity Cord Blood Transplantation; NHL, Non-Hodgkin's lymphoma; BAL, Bronchoalveolar lavage.
*No individualized data on each patient

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