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CASE REPORT

Bacillus cereus bacteraemia and cerebral lesions in two patients with haematological malignancies

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Abstract

The clinical course of *Bacillus cereus* bacteraemia can be severe in the subset of patients that are immunocompromised, such as patients after chemotherapy for haematological malignancy. Haematogenous spread with central nervous system complications such as cerebral abscesses can occur. We report two patients who developed *B. cereus* bacteraemia after induction chemotherapy for acute myeloid leukaemia. Both developed cerebral lesions with neurological symptoms. While the first recovered swiftly after treatment with the appropriate antibiotics, the second was admitted to the ICU because of neurological impairment and respiratory insufficiency. His course was furthermore complicated by persistent fever and a fluctuating level of consciousness. Clinicians must have a high index of suspicion for intracerebral lesions when patients develop neurological symptoms during neutropenic fever after chemotherapy. Early imaging, appropriate antibiotic therapy and early removal of the central venous catheter are pivotal in the management of these patients.

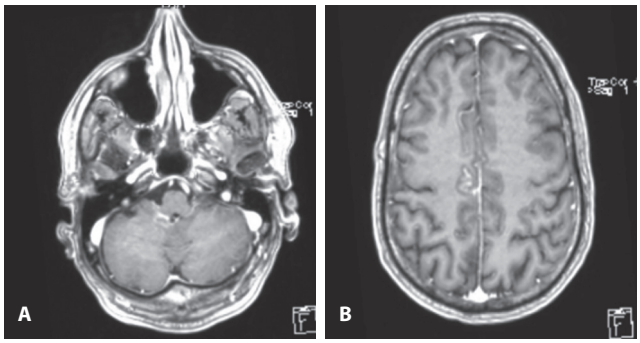
Introduction

Bacillus cereus is a spore-forming, Gram-positive rod that can survive in extreme environmental conditions. In contrast to *B. anthracis*, it has been regarded as an opportunistic pathogen. *B. cereus* can cause significant disease, particularly in immunocompromised patients, in patients with indwelling or implanted devices or after trauma or surgery. Disease classically manifests in three distinct syndromes: food intoxication, localised (soft tissue, musculoskeletal and bone) infection and bacteraemia.[1,2] Bacteraemia is sometimes associated with haematogenous complications such as cerebral abscesses. It is recognised that haematological patients have a higher risk for invasive opportunistic *B. cereus* infection.[3-6] Sources of bacteraemia are the intestinal tract, contaminated wounds and central venous catheters (CVC). Catheter-related infections might be associated with worse outcome and frequent neurological complications. The overall outcome is mostly favourable with long-term antibiotic treatment without the need to surgically drain the cerebral abscesses.[7] Informed consent for publication was obtained from both patients.

Case reports

Case 1

A 53-year-old male with a prior history of musculoskeletal pain presented to his general practitioner with neck pain. He mentioned spontaneous bruising without overt bleeding or melaena. A complete blood count was performed showing anaemia (haemoglobin 7.9 mmol/l), neutropenia (0.02 x 10^9/l) and thrombocytopenia (56 x 10^9/l). Bone marrow aspiration revealed dysplasia in all three haematopoietic lineages with 20% myeloblasts. The diagnosis of acute myeloid leukaemia with myelodysplasia-related changes was made. The patient was admitted to our hospital and after placement of a CVC, induction chemotherapy was started the day after. Sixteen days after the start of chemotherapy and still in the neutropenic phase he developed fever and severe headache and was initially treated with analgesics and ceftazidime (2000 mg, three times a day). Blood cultures subsequently taken from both a peripheral site and his CVC became positive for *Staphylococcus epidermidis* and *B. cereus* two days later. The catheter was removed, the fever subsided but the headache persisted. An MRI scan was performed, showing post contrast enhancing lesions at the right cerebello-medullary junction and in the right parafalcine region *(figure 1)*. Based on these findings brain abscesses were suspected. Treatment with meropenem (2000 mg, three times a day), voriconazole (6 mg/kg, twice a day) and vancomycin (15 mg/kg, three times a day) was started 20 days after admission to cover opportunistic bacteria, invasive fungi and the cultured *B. cereus*, respectively. To rule out invasive fungal infection and atypical organisms further diagnostic tests were done.



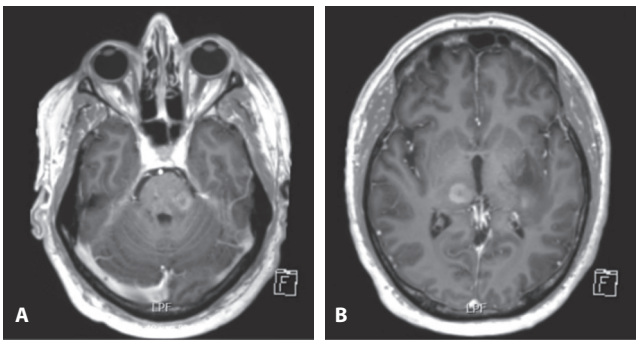
Figures 1. T1-weighted MRI images after intravenous contrast and multiplanar reconstruction showing post contrast enhancing lesions at the right cerebello-medullary junction (a) and right parafalcine region (b)

PCR analysis and culture of cerebrospinal fluid taken on day 20 remained negative; thoracic CT could rule out invasive aspergillosis and nocardiosis. All blood cultures taken after day 20 remained negative throughout. It was decided to treat the patient conservatively because of his multiple lesions and the greater risk of wound infections during the neutropenic phase. The antimicrobial therapy was de-escalated to meropenem (2000 mg, three times a day) and it was decided to switch to ciprofloxacin (750 mg, twice a day) as soon as bone marrow repopulation took place. The patient returned home on day 35 after admission. A follow-up MRI showed the parafalcine lesion had decreased in size and the cerebellar lesion had disappeared. The total duration of antibiotic treatment was eight weeks. No neurological complications or positive cultures for *B. cereus* were observed during a second round of chemotherapy and subsequent allogeneic stem cell transplantation.

Case 2

A 57-year-old male patient with a prior history of cerebral palsy and right-sided Erb's palsy presented to his general practitioner with dyspnoea on exertion and an increased bleeding tendency. A complete blood count was performed and showed anaemia (haemoglobin 5.2 mmol/l), neutropenia (0.00 x 10^9/l) and thrombocytopenia (64 x 10^9/l). Bone marrow aspiration revealed 95% monomorphic blasts with morphology suggestive of acute myeloid leukaemia with maturation. The patient was admitted to our hospital and induction chemotherapy was started on day 2. Three days after the start of therapy he developed neutropenic fever and ceftazidime (2000 mg, three times a day) was empirically started along with corticosteroids.

An indwelling central venous catheter was removed and later replaced because of positive blood cultures for coagulase negative staphylococci. Because of increasing fever and isolation of *Pseudomonas aeruginosa* from rectal swabs, therapy was escalated to meropenem (1000 mg, three times a day) on day 13. Blood cultures taken from the CVC as well as from peripheral blood grew *B. cereus*, initially reported sensitive to meropenem. The indwelling catheter was removed once again. Shortly thereafter, the patient was found on the ground alongside his bed. He had a reduced level of consciousness with verbal perseveration and agitation and was admitted to the ICU. Because the fall took place while the patient was severely thrombopenic, a CT scan of the brain was performed and ruled out intracranial haemorrhage. However, it showed three supratentorial lesions suspect for abscesses, chloroma or distal metastasis of another tumour. The cultured *B. cereus* was reported resistant to meropenem, and high-dose ciprofloxacin (400 mg, three times a day) was started. Flow cytometry on cerebrospinal fluid did not detect leukaemic blastocytes. Although it was obtained only 24 hours after starting effective antibiotic therapy the cerebrospinal fluid culture taken on day 18 remained negative. As in case 1, the patient was treated conservatively because there were multiple lesions and because of the greater risk of wound infections during the neutropenic phase. The patient was sedated and intubated and an MRI scan was performed 15 days after starting initial antimicrobial therapy *(figure 2)*. It showed ring enhancing lesions in the right thalamus, the right frontoparietal cortex and the left pons. Several complications occurred during his ICU stay. He was extubated



Figures 2. T1-weighted MRI images after intravenous contrast and multiplanar reconstruction showing ring enhancing lesions in the left pons (a) and right thalamus (b)

and reintubated several times because of his fluctuating level of consciousness, delirium, suspected obstructive sleep apnoea syndrome and morbid obesity. Because of persisting fever he was empirically treated for a suspected ventilator-associated pneumonia with additional piperacillin-tazobactam (4500 mg, three times a day) for five days, trimethoprim-sulfamethoxazole (1920 mg, three times a day) for four days and voriconazole (400 mg twice a day) for seven days. His fever never subsided but microbiological analysis of a bronchoalveolar lavage sample remained negative for *Pneumocystis jirovecii, Aspergillus* or any other microorganism. As a diagnosis of exclusion, this persistent fever was attributed to the immune reconstitution inflammatory syndrome. Forty-five days after induction chemotherapy, bone marrow testing showed complete remission. The total duration of antibiotic treatment was eight weeks. The patient could leave the ICU approximately one month after admission. A follow-up MRI was performed and showed a reduction in size of the

known intracerebral lesions and the surrounding perilesional oedema. Since then neurological recovery has been almost complete.

Discussion

These two cases illustrate the suspected ability of *B. cereus* to invade the central nervous system (CNS) and produce cerebral lesions in patients with haematological malignancies after chemotherapy. In small case series, the incidence of immunocompromised patients with *B. cereus* bacteraemia developing meningitis or abscess formation was 33% to 50%.[5-8] In hospitals, *B. cereus* spores can contaminate the environment, such as wards and operating rooms, and subsequently colonise the skin, catheters and the intestinal tract of patients. Haematological patients are a classic risk group for *B. cereus* bacteraemia due to a compromised mucosal barrier and lack of immune response after high-dose chemotherapy.[9] There is a clear association between mucositis and neutropenic enterocolitis and *B. cereus* bacteraemia.[7,9,10] Intravascular catheters are another important risk factor for *B. cereus* bacteraemia in haematological patients due to a break in the skin barrier and the ability of *B. cereus* to produce biofilms and adhere to foreign bodies.[1,11] Besides our two cases, several other case reports and case series highlight the specific ability of *B. cereus* to invade the CNS and produce cerebral abscesses.[7,10,12] The pathogenesis of CNS invasion is unknown but the clear association with bacteraemia points to a haematogenous route of infection. An interesting observation is that CNS involvement seems to be more common in haematological patients with catheter-related infections while among patients with an uncomplicated course the digestive tract is the most common source of bacteraemia.[7] One possible explanation is there are longer periods of bacteraemia due to biofilm formation in catheter-related infections, hence easier intracerebral dissemination. A paediatric study identified cephalosporin and corticosteroid exposure, neutropenia and intrathecal therapy as risk factors for CNS involvement of *B. cereus*[5] while other authors have described an association with intestinal mucositis.[6] Due to broad-spectrum β-lactamase production, *B. cereus* is usually resistant to β-lactams except for carbapenems.[13] However, resistance to carbapenems as was found in case 2 has been described in the literature.[14,15] According to an in vitro antimicrobial susceptibility study, 14% of *B. cereus* isolates tested resistant against meropenem, whereas none of the tested *B. cereus* isolates were resistant to ciprofloxacin, vancomycin or linezolid.[16] First-line antibiotic treatment of patients with febrile neutropenia consists of broad-spectrum β-lactams with antipseudomonal coverage such as ceftazidime or piperacillin-tazobactam. As *B. cereus* is intrinsically resistant to these agents, bacteraemia with *B. cereus* might occur because of selective antibiotic pressure. Positive cultures with *B. cereus* are also frequently regarded as contamination. This may cause appropriate therapy to be started later in the disease process and may predispose these patients to longer periods of bacteraemia and subsequently to easier intracerebral dissemination. The mortality rate reported in *B. cereus* brain abscesses case series is variable, from 10% [7] to case series with mortality rates as high as 42%. [17] Prolonged use of systemic antibiotics is necessary for 6-8 weeks with a high risk of relapse and significant morbidity with abbreviated therapy. No data are available for recommendation of specific dosing regimens or duration of therapy. In most case series, surgical excision of the abscesses was precluded by the number and location of the multiple abscesses although brain and abscess biopsy was critical in establishing the microbiological diagnosis.[17,18] Neurosurgical intervention, such as stereotactic aspiration, could be performed for the purposes of identification of the causative pathogen or decompression in selected patients with larger abscesses when antimicrobial agents alone are prone to failure.[19] In patients with haematological malignancies after chemotherapy, conservative therapy is often preferred to surgery because of the greater risk of wound infections and compromised wound healing during the neutropenic phase. Guidelines recommend removing a CVC within 72 hours after onset of *B. cereus* bacteraemia[20] and studies have indicated that the risk of recurrence is higher if the CVC is retained.[21,22]

Conclusion

When patients with haematological malignancies develop neurological symptoms during neutropenic fever after intensive chemotherapy, clinicians must have a high index of suspicion for intracerebral lesions. Especially *B. cereus* bacteraemia in immunocompromised patients is known to have a complicated course with cerebral abscesses. Early imaging, appropriate antibiotic treatment and removal of the CVC are pivotal in the management of these patients.

Disclosures

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