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Community acquired *Burkholderia cepacia* sepsis in a patient with megaloblastic anemia: a case report and review of literature

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ABSTRACT: *Burkholderia cepacia* complex (Bcc) is known to cause respiratory tract infections among patients with cystic fibrosis. *Burkholderia* infection is also seen in patients admitted in ICUs who are immunocompromised and results in lower respiratory tract infection, necrotizing pneumonia or septicemia. It is inherently resistant to many antibiotics like carboxypenicillins, polymyxin and aminoglycosides. In this case report, we present the case of a patient with Vitamin B12 deficiency who acquired Burkholderia infection from the community and presented with features of septic shock and generalized tonic-clonic seizures. Patients with Bcc infection can be treated by co-trimoxazole, meropenem, ceftazidime or piperacillin-tazobactam which can be given as monotherapy or as combination therapy along with other antimicrobial agents.

Keywords: *Burkholderia*, Cystic fibrosis, Cepacia syndrome.

INTRODUCTION

Burkholderia cepacia complex (Bcc) consists of a group of 24 closely related pathogenic bacterial species which are known for causing opportunistic infections among patients with cystic fibrosis and other vulnerable population[1]. They are gram negative, non-lactose fermenting, oxidase positive organisms which are resistant to antimicrobial like polymyxin and aminoglycosides[1,2]. They are distributed widely in the environment and are commonly isolated from water, soil, and moist environments where they can survive for many months. The efflux pump makes it highly resistant to many antibiotics like carboxypenicillins, polymyxin and aminoglycosides. They are known for surviving in nutrient deficient conditions and can metabolize even antimicrobials as carbon sources[3]. *Burkholderia cepacia complex* can contaminate sterile aqueous pharmaceutical products like intravenous (iv) drugs and solutions. It can contaminate non-sterile pharmaceutical products like preoperative skin solutions, hand sanitizers, nasal sprays, mouthwash and personal care products. It is a frequent cause for recall of various non-sterile pharmaceutical products[1]. *Burkholderia complex* is known for causing several nosocomial outbreaks in hospitals particularly affecting patients with cystic fibrosis and other immune-compromised patients. Its ability to survive in the presence of disinfectants, antimicrobials and biocides used in pharmaceutical products has led to several *Burkholderia* outbreaks in hospitals.

Cepacia syndrome is a clinical condition among patients with *Burkholderia cepacia* infection which was initially documented among children with cystic fibrosis. Patients with cepacia syndrome present with features of necrotizing pneumonia and bacteremia which is associated with sudden deterioration in pulmonary function, fever, leukocytosis and raised inflammatory markers[4]. Among patients with cystic fibrosis, *Burk-*

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holderia cepacia can also result in asymptomatic carriage and long-term colonization of the respiratory tract[5,6]. Ceftazidime, meropenem, doxycycline, minocycline, Trimethoprim-sulfamethoxazole and doripenem are effective antibiotics against *Burkholderia* infection. They are resistant to antibiotics like carboxypenicillins, polymyxin and aminoglycosides[7].

Burkholderia outbreaks have been reported in several health care facilities particularly in ICUs, oncology units and renal failure patients. Studies[8-12] have reported several sources of Bcc infection like indwelling venous catheter, contaminated water ampules, ultrasound gel, nebulized medications and lipid emulsion stoppers. Bressler et al[8] have reported that patients requiring dialysis, bronchoscopic procedures, presence of central venous catheter, tracheostomy and recent abdominal surgery were at increased risk of developing *Burkholderia cepacia* bacteremia. Recently, the incidence of *Burkholderia cepacia* infections is increasing due to prolonged and frequent hospital admissions, particularly among the immunocompromised patients in ICU. It can cause bacteremia, urinary tract infections, peritonitis and respiratory tract infections[13,14]. The number of reported cases is probably lower than the actual number of infections in many hospitals due to difficulty in detection of this organism on routine testing and they are falsely reported as *Pseudomonas* species in several cases[15]. Oxidation-fermentation polymyxin bacitracin lactose agar (OFPBL), *Burkholderia cepacia* selective agar (BCSA), and *Pseudomonas cepacia* agar (PCA) are used for selective isolation. It may take 48-72 hours to grow Bcc on these agars[16,17]. Broth microdilution, agar dilution or Etest MIC are recommended for antibiotic susceptibility testing for Bcc. Species-specific *recA*-based PCR test and Matrix Assisted Laser Desorption/Ionization-Time of Flight (MALDI-TOF) mass spectrometry is used for species identification of Bcc[18,19]. Cox et al[20] concluded that combining MALDI-TOF mass spectrometry with phage amplification is a rapid, sensitive, and reproducibly predictable approach for protein-based bacterial identification and determining antibiotic resistance among Bcc.

There are no randomized controlled trials regarding the treatment of Bcc infection. Treatment is given according to the antibiotic sensitivity on a case by case basis due to lack of studies regarding Bcc infection. Meropenem, doripenem, ceftazidime, trimethoprim-sulfamethoxazole, doxycycline and minocycline are the most effective drugs based on *in vitro* antibiotic sensitivity data[21]. These drugs can be used as first-line therapy or a combination of these drugs can be used in view of increasing resistance[22,23]. Cochrane systematic review by Horsley et al[24,25] (conducted in 2012 and 2016) and Regan et al[26-28] (conducted in 2014, 2016 and 2019) could not identify any relevant study on eradication of Bcc in patients with cystic fibrosis. A systematic review on treatment options in patients with Bcc infection concluded that co-trimoxazole, meropenem, ceftazidime, or piperacillin-tazobactum can be given either as monotherapy or in combination with other antimicrobial agents[29,30]. The review analyzed 8 cohort studies or trials and 48 case reports. On analyzing the data, it was found that ceftazidime had a favorable outcome in 77.8% (42/54) patients. 33 patients received monotherapy with ceftazidime while 21 patients received combination therapy with ceftazidime. The combination therapy included ceftazidime along with aminoglycoside, piperacillin-tazobactum, aztreonam and co-trimoxazole. Among patients who received carbapenems, 66.7% (11/15) had a favorable outcome. Monotherapy with meropenem was given to 9 patients, while 6 patients received combination therapy with imipenem and ceftazidime. However, due to insufficient data, the clinical benefit of combination therapy over monotherapy for Bcc infection could not be determined[30].

Among patients with cystic fibrosis, exacerbations due to Bcc infections are usually treated with intravenous therapy with a combination of two antimicrobials for 14 -21 days[31,32]. A study[32] comprising 102 patients with cystic fibrosis with acute pulmonary exacerbations due to *Pseudomonas aeruginosa* and/or *B. cepacia complex* concluded that combination of meropenem with tobramycin and ceftazidime with tobramycin improved clinical outcome in these patients with acute pulmonary exacerbations[32]. Bronchodilators and intensive chest physiotherapy are also recommended for patients with cystic fibrosis and acute pulmonary exacerbations[33]. Trimethoprim-sulfamethoxazole, minocycline or doxycycline can be used when oral drugs are preferred.

CASE REPORT

A 23-year-old divorced women of a lower socio-economic background who was working as a receptionist in a private firm presented to the Emergency Department with complaints of fever for 2 days. The patient was apparently well 10 days prior to admission when she started having generalized weakness, decreased appetite and nausea. Her temperature was documented to be around 99°F-100.8°F at that time. Patient took paracetamol (acetaminophen) tablet as she was having myalgia and fever. She did not show in any hospital as her fever subsided after taking paracetamol. However, 2 days prior to presentation patient started having multiple episodes of loose stools and vomiting. She had 3 to 4 episodes of loose stools per day. There was no history of blood in stools or hematemesis. She started having fever ranging from 100°F-102°F. In view of the above symptoms, one day prior to presentation she gave her blood investigations in an outside laboratory. Her hemoglobin was 4.3 g/dl (Normal range: 12.0-15.5 g/dl), total leucocyte count (TLC) was 1.9 x 10^9/L (Normal range: 4.5 to 11.0 × 10^9/L) and platelet count was 59 x10^9/L. However, the patient did not go to any hospital, and she continued taking paracetamol tablets thrice a day for fever. On the day of the presentation, her general condition worsened, the patient became lethargic and drowsy. In view of the worsening of her condition, relatives brought the patient to the Emergency Department of the hospital. On arriving at the emergency department, patient had 1 episode of generalized tonic-clonic seizure.

On examination she had tachypnea (respiratory rate of 26 breaths/min), tachycardia (pulse rate of 138/minute) and blood pressure was unrecordable. Patient was in altered sensorium, however there was no focal neurological deficit. There were no other significant findings on examination. She did not have any enlarged lymph nodes or organomegaly. Her blood sugar was 104 mg/dl. She was started on inotropic supports as her blood pressure remained unrecordable despite giving fluid boluses. Her arterial blood gases showed severe metabolic acidosis with high lactate. Her serum lactate was 16 mmol/L (Normal range: 0.6 to 1.4 mmol/L). Computed tomography (CT) of the head was done which was normal. Her chest x-ray was normal. Ultrasound of the abdomen and pelvis was done and did not show any focus of infection. Her investigations revealed pancytopenia. Her haemoglobin level was 3.1 gm/dL (Normal range: 12.0-15.5 g/dl), red blood cell count (RBC) was 0.88 x 10^{12}/L (Normal range: 3.8-5.8 x 10^{12}/L), total leucocyte count (TLC) was 1.9 x 10^9/L (Normal range: 4.5 to 11.0 × 10^9/L), platelets 42 x10^9/L (Normal range: 150 to 400 × 10^9/L). Her absolute neutrophil count was 569 cells/ µL. Hence patient was managed as a case of fever with neutropenia and septic shock. Patient was empirically started on meropenem to cover for gram negative infections and Teicoplanin as an agent against methicillin-resistant *staphylococcus aureus*. The Infectious Diseases Society of America recommends starting an anti-pseudomonal beta-lactam agent (such as cefepime, meropenem, imipenem, or piperacillin-tazobactam) along with an agent active against methicillin-resistant *staphylococcus aureus* in patients presenting with febrile neutropenia and septic shock. Her serum creatinine was 1.9 mg/dl (Normal range 0.7 to 1.3 mg/dL), blood urea was 54 mg/dl (Normal range 5 to 20 mg/dl), lactate dehydrogenase level (LDH) was 3931 (Normal range: 140-280 U/L). Her total bilirubin was 2.3 mg/dl (Normal range: 0.3-1 mg/dl), direct bilirubin was 0.9 mg/dl (Normal range: 0.1-0.3 mg/dl), aspartate aminotransferase (AST) was 143 U/L (Normal range 4-32 U/L) and alanine aminotransferase (ALT) was 35 U/L (Normal range: 4-33 U/L). Her C-reactive protein was 44 mg/dL (Normal range: less than 3.0 mg/L). Direct coombs test (DCT) and indirect coombs test were negative.

The possibility of dengue hemorrhagic fever/malaria/rickettsial infection was also considered in view of pancytopenia. Blood investigations which were sent to rule out other infectious diseases came negative. Her dengue Ns1 antigen, Dengue IgM, Dengue IgG, Scrub typhus serology, leptospira antigen, leptospira serology, film for malarial parasite, malarial antigen, Weil-Felix test and Widal test were negative. Screening for Human immunodeficiency virus (HIV) was negative. Peripheral smear showed macrocytosis. Mean corpuscular volume (MCV) was 115 fL (Normal range: 80-95 fL). Her Vitamin B12 level was 140 pg/ml (Normal range: 300-950 pg/mL). Folic acid level was 2.85 ng/ml (Normal range: 4-19.9 ng/ml). As she was a vegetarian by diet, a possibility of Vitamin B12 and Folic acid deficiency with Megaloblastic anemia was kept. Corrected reticulocyte count was 0.2% (Normal range: 0.5%-1.5%). Her pancytopenia was attributed to Vitamin B12/ Folic acid deficiency and sepsis. Elevated LDH level was attributed to hemolysis secondary to megaloblastic anemia[34,35]. She was transfused packed red blood cells in view of hypotension and low haemoglobin levels. Her procalcitonin level was >100 ng/ml (Normal range: less than 0.25 ng/mL).

Two sets of blood cultures which were sent on admission came positive for *Burkholderia cepacia*. Subculture of the organism was done in blood agar and MacConkey agar. The organism was Gram negative, non-lactose fermenter and oxidase positive. Sugar fermentation test was positive for mannitol, sucrose and sorbitol. Lysine decarboxylase test was positive and the organism was resistant to Polymyxin B. Arginine dihydrolase, gelatin hydrolysis and deoxyribonuclease (DNase) test was negative. Oxidation Fermentation mannitol test was positive. Hence the organism was diagnosed to be *Burkholderia cepacia*. It was sensitive to meropenem, piperacillin-tazobactam, and cefoperazone-sulbactam. It was resistant to amikacin, ampicillin, colistin and polymyxin B. Her urinalysis and urine culture did not show any evidence of urinary tract infection and blood cultures did not show the growth of any other organism.

Her clinical condition gradually improved and her inotropic supports were gradually tapered and stopped on the 4th day of hospital stay. She was started on vitamin B 12 injections and folic acid supplements and meropenem was given for a total of 14 days. Her TLC and platelets gradually improved, and the patient was discharged as her clinical condition became better. On follow-up after 1 month, the patient was asymptomatic and her haemoglobin, TLC, platelets and reticulocyte count were found to be normal. Her peripheral smear, creatinine, Liver function test, LDH, C-reactive protein and procalcitonin levels were normal. Patient was on regular follow-up for 6 months following discharge and she remained asymptomatic. Her hematologic and biochemical parameters were within normal range on follow-up.

DISCUSSION

On reviewing the literature, most cases of Bcc sepsis have been reported in patients who are admitted in hospital with cystic fibrosis, underlying pulmonary disease, patients with HIV or immunocompromised patients and in most cases, it is a hospital acquired infection. Patients requiring hemodialysis, intensive care admission, indwelling catheters and mechanical ventilation are at increased risk of Bcc infection[28]. Cases among patients without cystic fibrosis have been reported in ICUs due to contaminated intravenous (iv) cannulas, medications or solutions which are being used in the hospital. These patients present with symptoms of respiratory tract infection or necrotizing pneumonia along with features of bacteremia[4].

Uncommon presentations like endophthalmitis post-ocular surgery or eye trauma, spontaneous bacterial peritonitis in patients with liver cirrhosis, skin, and soft tissue infections among children with chronic

granulomatous disease and vaginitis in a patient with smoldering myeloma has been reported in literature[36-38]. Marioni et al[39] reported a case of cervical necrotizing fasciitis by Bcc in an immuno-competent patient which was treated by surgical debridement and 2 weeks of IV cefepime according to antibiotic sensitivity. Spontaneous bacterial peritonitis with Bcc has been reported in literature probably due to the higher degree of neutrophil dysfunction among patients with alcoholic cirrhosis. Successful treatment using combinations of meropenem with ciprofloxacin and tobramycin has been reported, and doripenem has therapeutic potential against spontaneous bacterial peritonitis due to Bcc[40]. Gautam et al[41] reported *Burkholderia cenocepacia* sepsis in a patient with mitral stenosis which was treated using Ceftazidime 2 grams twice daily. Case report of a patient with smoldering myeloma and *Burkholderia cenocepacia* vaginitis was treated with piperacillin-tazobactum for 4 weeks following which her symptoms resolved and repeat vaginal swab cultures were negative[38]. In a study by Mann et al[42], *Burkholderia* bacteremia has been reported among patients with solid tumors and hematological malignancies. To our knowledge, this is the first reported case of Bcc sepsis in a patient with underlying megaloblastic anemia. Patients with megaloblastic anemia are susceptible to various infections due to impaired leucocyte function which results in impaired intracellular killing of ingested bacteria by neutrophils and macrophages[43-45].

In our patient, there has been no history of previous hospital admissions, IV cannula or catheter insertion prior to presentation. As the initial blood culture sent from the Emergency Department was positive for *Burkholderia cepacia*, she acquired this infection from the community. Unlike most of the reported cases of *Burkholderia* infection, our patient did not have any respiratory symptoms and she presented with features of septic shock and generalized tonic clonic seizures. However, regarding the source of infection, we did not get any history regarding usage of contaminated pharmaceutical products, solutions, or contaminated water in our patient.

CONCLUSIONS

Bcc is known for causing hospital acquired infections in immune compromised patients and patients with Cystic fibrosis. As reported in this case, patients can acquire Bcc infection from the community and they can present without any respiratory symptoms. Bcc infection and cepacia syndrome should be considered in patients who are at increased risk of developing these infections. Identification of the organism and antibiotic according to the culture sensitivity report is important as this organism is inherently resistant to many antibiotics.

Conflict of Interests:
The authors declare that they have no conflicts of interest.

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The patient signed the informed consent.

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