

Suppurative mediastinitis secondary to *Burkholderia cepacia* in a patient with cystic fibrosis

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Burkholderia cepacia is an important opportunistic pathogen among patients with cystic fibrosis (CF); it is associated with deterioration of lung function, poor outcome following lung transplantation and increased mortality. Fever, an elevated white blood cell count, weight loss and an often fatal deterioration in pulmonary function characterize a particular clinical course, termed 'Cepacia syndrome'. The present case report describes a 40-year-old man with CF who developed Cepacia syndrome complicated by suppurative mediastinitis, from which *B cepacia* was isolated. Despite optimal medical and surgical therapy, this patient succumbed to his illness. Those caring for patients with CF should be aware of this potentially catastrophic complication of *B cepacia* infection, especially in the setting of Cepacia syndrome.

Key Words: *Burkholderia cepacia*; *Cepacia syndrome*; Cystic fibrosis; Mediastinitis

Cystic fibrosis (CF) is the most common fatal genetic disorder among Caucasian people. *Burkholderia cepacia* is an important opportunistic pathogen among CF patients. *B cepacia* is a diverse group of bacteria with heterogeneous outcomes in CF patients. *B cepacia* infection has been associated with deterioration of lung function, poor outcome following lung transplantation and increased mortality in this patient population (1-5). In CF patients, *B cepacia* typically proceeds along one of three clinical pathways: colonization; infection with an acceleration in the rate of decreasing pulmonary function; or acute deterioration associated with necrotizing bronchopneumonia, sepsis and, frequently, acute respiratory failure and death (1-3). The latter clinical presentation is often referred to as 'Cepacia syndrome'.

Cepacia syndrome, as originally described by Isles et al (3), is characterized by sustained fever, an elevated white blood cell count (WBC), weight loss and often fatal deterioration in pulmonary function. *B cepacia* bacteremia and radiographic changes consistent with bronchopneumonia are also recognized as a part of this relatively uncommon acute clinical presentation (6-8).

We present the case of a 40-year-old man with CF who developed Cepacia syndrome complicated by suppurative mediastinitis, from which *B cepacia* was isolated.

Une médiastinite suppurée secondaire à une infection à *Burkholderia cepacia* chez un patient atteint de fibrose kystique

L'infection à *Burkholderia cepacia* est un pathogène opportuniste important chez les patients atteints de fibrose kystique (FK). Il s'associe à une détérioration de la fonction pulmonaire, à une issue médiocre après la transplantation pulmonaire et à une mortalité accrue. De la fièvre, une leucocytémie élevée, une perte de poids et souvent une détérioration fatale de la fonction pulmonaire caractérisent une évolution clinique particulière, dite « syndrome de *cepacia* ». Le présent rapport de cas expose la situation d'un homme de 40 ans atteint de FK qui a développé un syndrome de *cepacia* compliqué par une médiastinite suppurée, dans laquelle l'infection à *B cepacia* a été isolée. Malgré une thérapie médicale et chirurgicale optimale, le patient a succombé à sa maladie. Les personnes qui soignent des patients atteints de FK devraient connaître cette complication au potentiel catastrophique de l'infection à *B cepacia*, surtout en présence d'un syndrome de *cepacia*.

CASE PRESENTATION

A 40-year-old man with known CF presented to the emergency department (ED) complaining of productive cough, shortness of breath and pleuritic chest pain that was made worse by lying supine. The patient also had fever, chills and night sweats for approximately two weeks. One month before presenting to the ED, the patient was seen by his family doctor for what was thought to be a mild pulmonary exacerbation; he was subsequently treated with oral telithromycin. The patient completed a 14-day course but, due to persistent respiratory symptoms, was restarted on a second course of the same antibiotic by his family doctor.

In the ED, a physical examination showed that the patient had a respiratory rate of 24 breaths/min, oxygen saturation of 96% by pulse oximetry on room air and a temperature of 37.5°C. The patient had a relatively normal body habitus (body mass index of 22.9 kg/m²). Chest auscultation revealed diffuse, bilateral coarse inspiratory crackles. A laboratory examination showed a WBC of 8.7×10⁹/L; a chest radiograph showed chronic changes consistent with diffuse bronchiectasis related to CF and right paratracheal soft tissue density (Figure 1). The patient was admitted to hospital and started on intravenous antibiotics, including tobramycin, piperacillin/tazobactam,

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Figure 1) Posteroanterior chest radiograph at the time of admission to hospital showing chronic changes consistent with diffuse bronchiectasis related to cystic fibrosis and right paratracheal soft tissue density

and meropenem. Antibiotic choices were based on the most recent sputum culture and sensitivity results.

The patient was diagnosed with CF at five years of age. As an adult, he suffered from progressive chronic obstructive lung disease, pancreatic insufficiency, chronic sinusitis and recurrent pulmonary exacerbations. He was regularly followed by the adult CF clinic at the authors' institution. Over the past few years, he typically experienced four to five pulmonary exacerbations per year that required in-hospital treatment for two to three weeks. He had not been febrile with any prior acute respiratory illness. He was known to be colonized with multidrug-resistant *B cepacia* since as early as 1994, which was routinely cultured from sputum when clinically stable and during pulmonary exacerbations.

On admission, spirometry showed the patient had a forced expiratory volume in 1 s (FEV_1) of 1.25 L (33% predicted), a forced vital capacity (FVC) of 2.39 L (52% predicted) and an FEV_1/FVC ratio of 52%. The most recent pulmonary function tests, performed while he was clinically stable six months earlier, revealed an FEV_1 of 1.45 L (38% predicted), an FVC of 2.99 L (65% predicted) and an FVC/FEV_1 ratio of 48%. He had shown a gradual deterioration of pulmonary function over the previous years; at 32 years of age, he had an FEV_1 of 2.21 L (55% predicted), an FVC of 3.50 L (73% predicted) and an FVC/FEV_1 ratio of 63%.

A sputum culture taken on the day of admission to hospital had a heavy growth of *B cepacia* that was sensitive only to meropenem in the antibiotic panel tested. The patient remained clinically stable, but showed no improvements one week after his admission, at which time his temperature spiked to 39.2°C. Repeat blood cultures and chest radiographs were

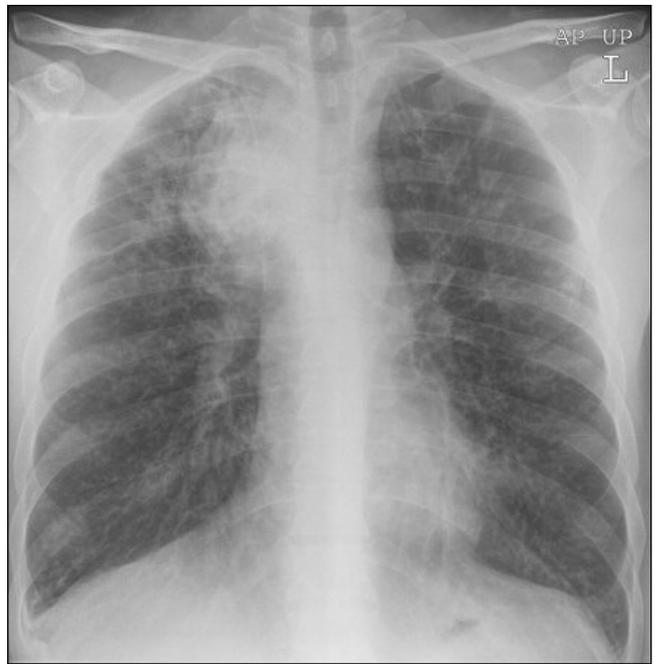


Figure 2) Posteroanterior chest radiograph showing marked enlargement of soft tissue density in the right paratracheal region and adjacent airspace opacities in the right upper lobe. Peripherally inserted central catheter line in place in the superior vena cava

obtained. Blood cultures grew *B cepacia* that was sensitive to meropenem and had intermediate sensitivity to ceftazidime. The infectious disease consultant recommended discontinuing piperacillin/tazobactam and adding ceftazidime to the antibiotic regimen.

The chest radiographs showed marked enlargement of soft tissue density in the right paratracheal region and development of airspace changes in the right upper lobe (Figure 2). An enhanced computed tomography (CT) scan of the thorax showed compression of the superior vena cava and bowing of the trachea by a large paratracheal mass measuring 4.5 cm × 5 cm, with heterogeneous fluid-like attenuation (Figure 3). Consistent with CF, extensive changes were also observed in both lungs (predominantly in the upper lobes), including cystic changes, diffuse cylindrical bronchiectasis and areas of tree-in-bud involvement with mucoid impaction in the periphery of both lungs (Figure 4). A presumptive diagnosis of suppurative mediastinitis was made and thoracic surgery services were consulted.

Twelve days after admission, primarily for diagnostic purposes, the patient underwent a bronchoscopy with a bronchoalveolar lavage and cervical mediastinoscopy under general anesthesia. Thoracic surgeons drained a large, pus-filled mediastinal cavity. Specimens taken from the mediastinum and the bronchoalveolar lavage fluid both had a heavy growth of *B cepacia*, which was sensitive to meropenem and ceftazidime. Pathological examination of the surgical specimen showed fibrotic connective tissue with a prominent mixed inflammatory cellular infiltrate. No evidence of granulomas or malignancy was found. Special stains for mycobacteria and fungal microorganisms were negative.

The patient quickly recovered from the surgery and defervesced over the next week (Figure 5). However, 11 days after the cervical mediastinoscopy, his maximum daily temperature rose again to 39.5°C. The patient complained of chills, rigors,

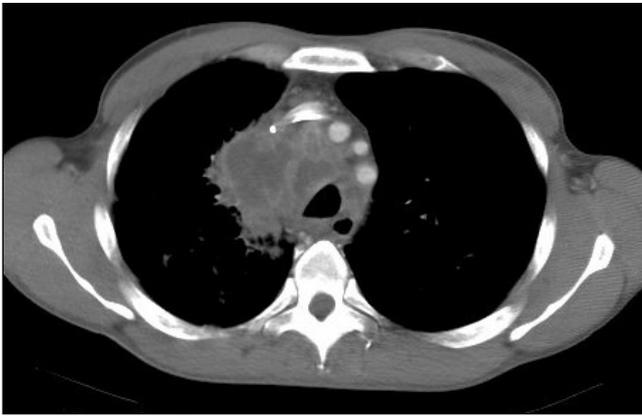


Figure 3) Mediastinal windows of a 7 mm, enhanced axial computed tomography scan section of the thorax showing compression of the superior vena cava and trachea by a large mass, measuring 4.5 cm × 5 cm, with heterogeneous fluid-like attenuation



Figure 4) Lung parenchymal windows of a 7 mm, enhanced axial computed tomography scan section of the thorax showing extensive changes in both upper lobes, including cystic changes and diffuse cylindrical bronchiectasis with mucoid impaction in the periphery

increased pleuritic chest pain and neck stiffness. A repeat enhanced CT scan of the thorax revealed extension of the mediastinal mass lesion with no new pulmonary changes. After discussion among thoracic surgery, respirology and infectious disease services, the patient elected to undergo a right thoracotomy for surgical drainage of a presumed mediastinal abscess. This procedure was performed 26 days after admission to hospital.

Under general anesthesia, the right pleural space was entered via a standard posterolateral incision at the fourth intercostal space. Turbid pleural fluid suggested that the mediastinal abscess may have already ruptured into the pleural space. A mass lesion was apparent involving the anterior and apical segments of the right upper lobe. The lung was densely adherent medially. After careful dissection at the level of the superior mediastinum, free pus was suctioned from an inflammatory mediastinal mass. Microbiological and pathological tissue samples were obtained. The chest was irrigated with saline. Three chest tubes were placed – one in the mediastinal cavity through the anterior chest wall and two in the right pleural space along the diaphragm. Finally, a bronchoscopy was performed for pulmonary toilet and to collect further microbiological samples.

The patient remained sedated, intubated and mechanically ventilated, and was transferred to the intensive care unit. During the seven days he spent in the intensive care unit, he remained febrile despite attempts to actively cool him. The antibiotic regimen was altered to ceftazidime, meropenem and colistin based on results of multiple combination bactericidal testing on isolates from blood and the mediastinum. The patient transiently improved and was extubated on postoperative day (POD) 3; however, he was reintubated on POD 6 due to increasing respiratory distress, fatigue and chest discomfort that impaired performance of chest physiotherapy. On POD 7, he required vasopressor support for low blood pressure. A repeat CT scan of the thorax showed persistence of the mediastinal mass and worsening pulmonary opacities. It became increasingly apparent that the patient would not recover from this acute illness; following a family meeting, life-supporting therapies were withdrawn and the patient died shortly thereafter.

DISCUSSION

In the 1940s, an unknown pathogen was presumed to be causing soft rot among vegetation, predominantly onions ('onion rot'). When this pathogen was isolated in 1947 by Burkholder, it was

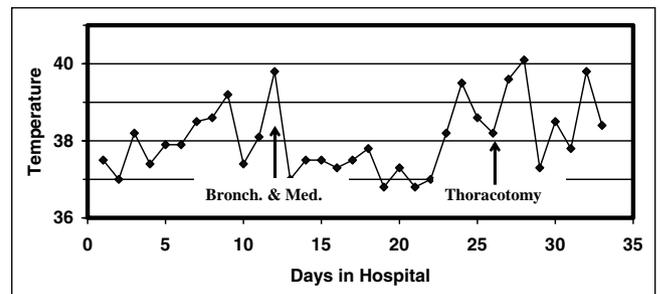


Figure 5) Maximum daily temperature (°C) during hospitalization. Bronchoscopy and cervical mediastinoscopy (Bronch & Med) was performed on day 12, and thoracotomy was performed on day 26

named cepacia, meaning 'of or like onion'. It was known as *Pseudomonas cepacia* or *Pseudomonas multivorans* until 1992, when it was reclassified as the heterogeneous group of bacteria known as *Burkholderia cepacia* (5,9).

B cepacia is a diverse class of bacteria comprised of several species that make up the *B cepacia* complex. There are currently nine phylogenetically distinguishable species or genomovars (10). Not all of the genomovars are phenotypically distinguishable; for example, genomovars I and III cannot be distinguished, nor can genomovar VI and *Burkholderia multivorans*. Genomovar III is the predominant species that infects individuals with CF in Canada, accounting for 80% of cases; *B multivorans* is responsible for approximately 9% (11). However, in Canada, *B multivorans* has rarely been isolated outside of British Columbia. The prevalence of *B cepacia* is highest in Ontario and eastern Canada, with approximately 25% of CF patients in eastern Canada being infected (11). Unfortunately, the genomovar identity of our patient's strain of *B cepacia* is unknown. Given the predominance of genomovar III in eastern Canada, and the linkage between genomovar III and Cepacia syndrome, it is highly likely that genomovar III was the culprit organism in the present case.

Hypersecretion of mucus and luminal mucostasis associated with CF appears to predispose these individuals to colonization with *B cepacia* (12). Two genetic elements of *B cepacia* have been identified as virulence factors. The *cblA* gene encodes for the cable pilus of the bacterial structure that binds to tracheobronchial mucin, and a second appendage, the mesh

pili, may facilitate adherence to cells and possibly interfere with clearance of secretions (12,13). A second genetic marker, the *B cepacia* epidemic strain marker, is a negative transcriptional regulator that encodes for a protein of unknown function (10,11). These genes are found predominantly in genomovar III and, specifically, in a highly transmissible epidemic strain of apparent enhanced virulence, the Edinburgh/Toronto 12 (ET12) strain, which has been linked to *Cepacia* syndrome (9-11).

In addition to adherence to respiratory epithelium, *B cepacia* produces both elastase and collagenase, which facilitates invasion of respiratory epithelium (10,13). *B cepacia* has been found in the epithelium of terminal and respiratory bronchioles (12). Presumably, the production of these proteolytic enzymes is responsible for the transcellular movement of *B cepacia*, which eventually may result in bacteremia.

Besides CF, *B cepacia* has been isolated in patients with chronic granulomatous disease (CGD) (5,10,14,15). In CGD, oxidative phagocytosis is disabled; *B cepacia* appears to be highly resistant to nonoxidative phagocytosis, leaving CGD patients particularly susceptible to *B cepacia* infections. It has been postulated that an imbalance between oxidative and nonoxidative phagocytosis in CF may contribute to patients' susceptibility to *B cepacia* colonization and infection (10).

The virulence of *B cepacia* also relates to endotoxin and antimicrobial resistance. Endotoxin and its induction of tumour necrosis factor- α have been shown to play a role in the pathogenesis of *B cepacia* infections (9). The cell envelope of *B cepacia* has a unique lipopolysaccharide structure that renders it resistant to aminoglycosides, and it produces a Bush group 4 beta-lactamase that is not inhibited by clavulanic acid (10,13). It is often susceptible to carbapenems, cephalosporins, quinolones and trimethoprim-sulfamethoxazole. Multidrug-resistant *B cepacia* was consistently recovered from our patient, and this fact likely contributed to the poor clinical response to medical management.

Cepacia syndrome has avoided definitive definition but, in the past 50 years, the term has come to represent an acute deterioration secondary to *B cepacia*. It is typically characterized

by sustained fever, an elevated WBC, necrotizing bronchopneumonia with rapid deterioration of pulmonary function, and septicemia (6,9,16). *Cepacia* syndrome is currently viewed as untreatable, despite the use of aggressive antibiotic regimens (9). Some CF centres have advocated the additional use of immunomodulatory agents, but evidence is lacking for this approach (9). Our patient developed radiographic evidence of bronchopneumonia late in his course, when the mediastinal infection was discovered. To our knowledge, no case of suppurative mediastinitis secondary to *B cepacia* infection has previously been described. Chaparro et al (17) described two CF patients colonized with *B cepacia* who died after lung transplantation; subsequent autopsies revealed localized lung abscesses. As early as 1984, Isles et al (3) described lung microabscess formation in autopsies of CF patients who had died of *B cepacia* infections. In 2000, Belchis et al (15) also described confluent areas of microabscess in patients without CF who had developed *B cepacia* pneumonia (15).

In our patient, the mediastinal infection was likely an extension of the infectious process originating in the pulmonary parenchyma. Treatment of mediastinitis typically involves appropriate antimicrobial coverage and drainage with a tube thorostomy or percutaneous drainage (18). The location of our patient's abscess made a percutaneous approach to drainage less favourable. The patient responded poorly to the antimicrobial therapy. A thoracic surgeon performed a thorough debridement of necrotic and infected tissue. Unfortunately, given the intimate relationship of the infected inflammatory material to vital mediastinal structures, it was impossible to remove all necrotic tissue. Ultimately, the patient died of acute respiratory failure and hemodynamic collapse, likely due to *Cepacia* syndrome complicated by suppurative mediastinitis.

The present report describes a patient colonized with *B cepacia* who developed *Cepacia* syndrome and suppurative mediastinitis. Despite optimal medical and surgical therapy, this patient succumbed to his illness. Those caring for CF patients should be aware of the potential for this catastrophic complication of *B cepacia* infection, especially in the setting of *Cepacia* syndrome.

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