Hepatic abscess due to *Burkholderia (Pseudomonas) cepacia* in cystic fibrosis

**Kristin L Fraser MD, Robert H Hyland MD, Elizabeth Tullis MD**

*The Adult Cystic Fibrosis Programme, The Wellesley Hospital, University of Toronto, Toronto, Ontario*

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**Abcès hépatique causé par Burkholderia (Pseudomonas) cepacia chez un patient atteint de fibrose kystique**

*RÉSUMÉ* : *Burkholderia (Pseudomonas) cepacia* a été cultivé à partir des sécrétions bronchiques de patients atteints de fibrose kystique à une fréquence variable. Dans le centre où pratique l'auteur, la prévalence globale de *B. cepacia* chez les patients de plus de 18 ans est de 51%. Les infections extrapulmonaires sont rares chez les patients non immunodéprimés atteints de fibrose kystique, et *B. cepacia* n'a été mis en cause que dans trois précédents rapports. On décrit deux cas de patients atteints de fibrose kystique qui ont développé des abcès hépatiques causés par *B. cepacia*. Un des patients a deux autres frères chez qui cette complication avait déjà été décrite.

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**Chronic Pulmonary Infection due to Burkholderia (Pseudomonas) cepacia** is documented in 20 to 30% of patients with cystic fibrosis (CF) in some clinics (1). However, extrapulmonary infections with this organism are rare in nonimmunosuppressed patients and have previously been reported in only three cases (2,3). Two brothers from Toronto developed hepatic abscesses and one male from Toronto was treated for recurrent neck abscesses due to this organism. The present report describes two further Toronto patients who were treated for hepatic abscesses due to *B cepacia*.

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Correspondence and reprints: Dr D Elizabeth Tullis, Suite 241, EK Jones Building, 160 Wellesley Street East, Toronto, Ontario M4Y 1J3. Telephone 416-926-5046, fax 416-926-4921
CASE PRESENTATIONS

Case 1

A 28-year-old woman with CF was admitted to hospital with a two-week history of fever, chills, weight loss and dyspnoea. She was diagnosed with CF in infancy based on a positive sweat chloride test, a clinical history of pancreatic insufficiency and a positive family history. Her clinical course was one of slowly progressive pulmonary disease with two infectious exacerbations requiring hospitalization over the preceding 10 years. She was known to have chronic pulmonary infection with *Pseudomonas aeruginosa* and *B. cepacia* since age 17. At age 18 she developed diabetes mellitus. She was malnourished with a weight and height less than the 85th percentile since age 6. Her last recorded body mass index (BMI) was 19.0. Liver function tests had previously been normal. Baseline pulmonary function showed moderately severe disease with forced vital capacity (FVC) 2.16 L (47% predicted) and forced expiratory volume in 1 s (FEV1) 1.44 L (36% predicted).

On admission, she appeared chronically ill with a heart rate of 120 beats/min, respiratory rate of 30 breaths/min and a temperature of 37.8°C. She measured 175 cm in height and weighed 54.6 kg giving a calculated BMI of 17.8. Bilateral, diffuse inspiratory crackles were heard on pulmonary auscultation and abdominal examination revealed new hepatomegaly without splenomegaly. Spirometry revealed FVC 1.13 L (29% predicted) and FEV1 0.81 L (21% predicted). Laboratory studies demonstrated a white blood cell count of 14.9x10³/L (82% polymorphonuclear leukocytes [PMNs]), alkaline phosphatase (ALP) 518 U/L (normal less than 100 U/L), gamma glutamyl transferase (GGT) 130 U/L (normal less than 31 U/L), albumin 24 g/L (normal 35 to 50 g/L) with normal alanine aminotransferase (ALT), aspartate aminotransferase (AST) and lactate dehydrogenase. Chest x-ray was unchanged from previous studies.

Abdominal ultrasound demonstrated mild hepatomegaly and the liver contained at least six poorly defined hypoechoic nodules occupying both right and left lobes, the largest measuring 3.7 cm in maximum diameter. An abdominal computerized tomogram (CT) with contrast confirmed these findings (Figure 1) and purulent fluid was aspirated under CT guidance. Gram stain was remarkable for polymophonuclear cells and Gram-negative bacilli. Subsequent culture grew *B cepacia*, sensitive to cefotaxime, imipenem, piperacillin and resistant to tobramycin, trimethoprim-sulfamethoxazole, gentamycin, ciprofloxacin and ampicillin. Serology was negative for echinococcus and amoebiasis. Previous testing for quantitative immunoglobulins was normal and a human immunodeficiency virus (HIV) test was negative.

The patient was treated for six weeks with parenteral cefotaxime and tobramycin at high doses adjusted according to blood levels. After three weeks, the liver function tests had improved (ALP 366 U/L, GGT 98 U/L) and ultrasound examination revealed complete resolution of the abscesses; however, a concomitant CT scan revealed multiple remaining hypodense lesions within the liver, although reduced in size (Figure 2). Intravenous therapy was continued for a total of six weeks, followed by oral ofloxacin for six weeks more. Follow-up imaging with CT at three and eight months revealed complete resolution of the lesions although ALP remained elevated at 220 U/L. Her nutritional status improved to a BMI of 20.5. Three years later there was no evidence of recurrence.

Case 2

A 33-year-old male diagnosed with CF in infancy was chronically infected with *B. cepacia* and *P aeruginosa*. He had moderate lung disease requiring admission to hospital approximately once yearly for pulmonary exacerbations. Baseline pulmonary function tests showed FVC 2.47 L (52% predicted) and FEV1 1.43 L (50% predicted). His usual weight was 65.3 kg and he measured 173 cm, representing a BMI of 21.8. His family history was significant for CF in a twin brother who died in 1991 and a younger brother who
died in 1993. Both brothers had been treated for hepatic abscesses felt to be due to *B. cepacia* (see Discussion).

In May 1995, he was admitted to another hospital complaining of several months of fever, chills, cough, sputum, left upper quadrant and epigastric pleuritic pain. An abdominal CT scan revealed a hepatic lesion and percutaneous drainage. An abdominal CT scan revealed a hepatic lesion and percutaneous drainage. Shortly thereafter the patient developed diffuse abdominal pain with peritoneal signs and underwent laparotomy, peritoneal lavage and biopsy.

Parenteral nutrition and antibiotics were administered in an intensive care unit for six days. While culture results were awaited, piperacillin, tobramycin and metronidazole were given. After 10 days of improvement, the antibiotics were discontinued. Four days later the fever recurred accompanied by abdominal pain. The abdominal incision was partly dehiscence, draining purulent fluid. Intraoperative cultures returned growing *B. cepacia*. Antibiotics were restarted and the patient was transferred to the authors’ centre three weeks following his initial admission.

At the time of admission he appeared chronically ill. He weighed 60.0 kg and was febrile. There was some epigastric tenderness and the percutaneous drain was in place. Air entry was decreased bilaterally in the chest. Laboratory results revealed leukocytosis (white blood cell count 12.2 x 10^9/L) with 10.4 x 10^9/L PMNs. ALP was 501 U/L (normal less than 100 U/L), and AST and ALT were mildly elevated at 43 U/L (normal less than 40 U/L) and 73 U/L (normal less than 45 U/L), respectively. Bilirubin was normal and albumin was 30 g/L (normal greater than 35 g/L). The chest radiograph was unchanged from previous studies.

The patient was treated empirically for *B. cepacia* infection of liver, lungs and abdominal wound with piperacillin, imipenem and tobramycin. Ciprofloxacin and ceftazidime could not be used due to previous severe allergic reactions. A CT scan showed multiple small hepatic fluid collections not significantly changed compared with the CT from the other hospital performed one week previously. A slight increase in the size of one small collection anterior to the stomach was noted but this area could not be reached percutaneously.

Unfortunately, the patient developed a severe urticarial rash after five days of treatment. This was felt most likely to be due to a beta-lactam agent so the tobramycin was continued alone. Four days later aztreonam became available and was added to the regimen.

Over the next week, abdominal pain and fever subsided. Liver enzyme tests improved (AST 42 U/L, ALT 61 U/L, ALP 389 U/L) and a repeat CT scan showed resolution of fluid between the stomach and liver and one persistent low density focus in the left lobe of the liver. The patient was discharged home on parenteral tobramycin and aztreonam.

After one month ALP remained elevated at 416 U/L but the CT scan was compatible with complete resolution of abscess cavities. Serum immunoglobulin (Ig) G and IgA were significantly elevated. Serum complement levels and an HIV test were normal. The patient returned to his previous weight. Intravenous antibiotics were discontinued after six weeks of therapy.

**DISCUSSION**

*B. cepacia* is recognized as an important pathogen in CF patients with prevalence rates in some clinics of 20 to 30% (1). In 1993, the prevalence of *B. cepacia* in the Toronto CF clinics was 126/502 (25%). This organism was grown in 20/295 (7%) children under the age of 18 years and 106/207 (51%) of those 18 years and older. The clinical course of CF patients colonized by *B. cepacia* is variable. Three distinct patterns have been described: chronic asymptomatic carriage; progressive deterioration over many months, with recurrent hospital admissions; and rapid, usually fatal deterioration characterized by fever, elevated white blood cell count, elevated erythrocyte sedimentation rate, weight loss and deterioration in pulmonary function, a pattern known as the ‘cepacia syndrome’ (4). Bacteremia is rare but has been reported in cases of acute deterioration (5).

The prognosis is generally worse for patients who are colonized than for those who are culture-negative (1). A review of the published literature and of the Toronto data base identified four patients with extrathoracic infections due to *B. cepacia*. Three cases have been reported in adults from the CF clinics in Toronto. Two brothers were siblings of our second case. They were chronically infected with *B. cepacia* and both developed hepatic abscesses, although aspiration failed to reveal a responsible pathogen. They were treated with intravenous antibiotics for four weeks, and ultrasound follow-up revealed complete resolution of abscess cavities (2). However, one patient suffered recurrent abscess formation and, on the second occasion, *B. cepacia* was isolated from the aspirate. This suggested to the authors that the cause of liver abscess in both brothers was metastatic infection with *B. cepacia* from the lower respiratory tract with recurrence due to incomplete treatment (6). The mechanism of abscess formation in our patients was likely the same.

Recurrent neck abscesses due to *B. cepacia* have been described in a 19-year-old Toronto patient with CF (3). He was known to have severe lung disease, pancreatic insufficiency and diabetes mellitus but was well nourished with a weight for height percentile of 110%. The isolate was only sensitive to ceftazidime. Surgical drainage and intravenous ceftazidime were repeatedly administered but infection recurred. Quantitative serum immunoglobulins, complement screen, nitroblue tetrazolium assay, neutrophil chemotaxis, ingestion, killing of *Staphylococcus aureus* in vitro and lymphocyte markers were normal. Recombinant interferon-gamma therapy resulted in a relatively prolonged response to treatment.

Extrapulmonary infections due to *B. cepacia* including empyema, empyema necessitatis, mediastinitis, pericarditis and malignant otitis externa with osteomyelitis of the temporal bone (7,8) have also been reported. However, these have occurred in immunosuppressed post-lung transplantation patients, a group in whom excess morbidity and mortality is attributed to *B. cepacia* (9).

The reasons for the broad spectrum of disease caused by this organism are not well understood. Alterations in host defences and variations in bacterial virulence are the most attractive hypotheses.
The immune system in patients with CF has been extensively studied and no consistent defect has been found in humoral, cellular, chemotactic, phagocytic or complement mechanisms (10,11). In fact, patients with CF and chronic infection with P aeruginosa or B cepacia commonly have elevated immunoglobulins. High IgG levels and the presence of circulating immune complexes are associated with progressive, more severe pulmonary disease (12).

Extrathoracic infections can be explained by the immunocompromised status of lung transplant recipients. However, in our two patients as well as the other three Toronto cases of extrapulmonary infections with B cepacia, no defect in immunoglobulins or complement could be demonstrated. More sophisticated tests of immune function were not readily available at our institution. Although the young woman in our first case was chronically malnourished, our second patient had a normal baseline BMI and the patient with recurrent neck abscesses was well nourished.

B cepacia is a ubiquitous environmental organism and it is believed that patients become infected by person to person transmission. The high prevalence of chronic infection with B cepacia in Toronto suggests the presence of a highly transmissible strain, and the clustering of extrapulmonary infections in the Toronto clinic may suggest involvement of a particularly virulent strain of B cepacia. The epidemiology of this organism is being investigated through the application of genotyping using pulse field gel electrophoresis. However, the marked predisposition of one family to the development of hepatic abscesses is more consistent with a familial defect in host response rather than a function of bacterial virulence.

Three of four reported cases of hepatic abscess due to B cepacia have occurred within the same family and the fourth has also been from Toronto. Clinicians need to be aware of the rare but definite capability of this organism to cause extrapulmonary infection in nonimmunocompromised patients with chronic infection. Further insight into the virulence factors and host immune response could facilitate the clinicians’ approach to prevention and treatment of this complication.

REFERENCES


