Case reports

Chronic *Burkholderia cepacia* bronchiectasis in a non-cystic fibrosis individual

M J Ledson, M J Gallagher, M J Walshaw

Abstract

Infection with *Burkholderia cepacia* due to social contact is well described in patients with cystic fibrosis. However, social transmission to non-cystic fibrosis individuals or chronic colonisation in non-cystic fibrosis individuals has not been described. A report of *B cepacia* bronchiectasis is presented where a previously healthy mother of two cystic fibrosis children colonised with *B cepacia* became infected by the same epidemic strain. The implications of this for parents, siblings, and partners of individuals with cystic fibrosis are discussed.

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Keywords: *Burkholderia cepacia*; cross infection

Burkholderia cepacia is a well recognised pathogen in patients with cystic fibrosis, immunocompromised patients, and those undergoing mechanical ventilation.[1] Rare cases of acute non-pulmonary *B cepacia* infection have also been described in immunocompetent patients.[2] Transmission is either nosocomial[3] or, in the case of cystic fibrosis, by social contact.[4 5] However, social transmission to or chronic colonisation in non-cystic fibrosis individuals has not been described. We present a case of chronic *B cepacia* bronchiectasis in the mother of two children with cystic fibrosis already colonised with *B cepacia*.

Case report

A 47 year old non-smoking woman with an unremarkable previous medical history presented to her GP with persistent right pleuritic chest pain in September 1995. A chest radiograph showed vague shadowing in the right upper zone and she was treated with analgesia and oral co-amoxiclav. A repeat chest radiograph showed little change and, although her symptoms remained, no immediate further action was taken. Three months later she was referred to her local district general hospital complaining of increasing malaise and more chest pain. A further chest radiograph showed progression of the right upper zone shadowing and a diagnosis of tuberculosis was considered. She was not producing sputum and fibreoptic bronchoscopy was carried out in order to obtain microbiological samples. This revealed an inflamed right upper lobe orifice, washings from which grew a fully sensitive strain of *Haemophilus influenzae*. She had a two week course of co-amoxiclav with no benefit. Direct smear examination of the washings showed no evidence of tuberculosis.

One month later she presented to the local accident and emergency department complaining of progressive malaise, weight loss, and pyrexia and a further chest radiograph showed marked worsening of the right lung shadowing (fig 1). She was transferred to our unit because of the possibility that she was suffering from tuberculosis. On admission she was pyrexial (38.5°C), tachypnoeic, and mildly hypoxaemic (Pao_2 9.6 kPa). She had lost 6 kg in weight over the preceding two months. There were crackles over the right upper lobe. Her white cell count was 15 400 (82% neutrophils, rest of differential count normal). A Mantoux test was negative and she was unable to produce sputum. An HIV test was negative, serum immunoglobulins showed a non-specific polyclonal increase, IgG subclasses showed no isolated deficiencies, autoantibodies were negative, ANCA test was negative, and blood sugar and ACE levels were in the normal range. She was commenced speculatively on quadruple antituberculous chemotherapy and oral steroids and intravenous cefotaxime. However, she continued to deteriorate and a chest CT scan showed extensive consolidation in the right upper and middle lobes, now with peripheral consolidation in the left lung. She underwent rigid bronchoscopic examination and an open right lung biopsy specimen was taken. The surgeon who undertook this noted that the whole of the right lung was very inflamed, typical of an acute infective process. Histological examination of the open lung biopsy specimen merely revealed an acute inflammatory process. Washings taken at rigid bronchoscopy, however, grew only *Burkholderia cepacia* which was intermediately sensitive to ceftazidime and co-trimoxazole but resistant to all other antibiotics tested. Subsequently, sputum culture grew *B cepacia*.

Anti-tuberculous chemotherapy was stopped and she was commenced on high dose intravenous ceftazidime and co-trimoxazole. Following this her pyrexia gradually settled and her appetite and weight increased. All microbiological samples sent for tuberculous culture were ultimately negative. After six weeks in hospital she was discharged home on a reducing course of steroids and oral co-trimoxazole. All subsequent sputum cultures have grown *B cepacia* and a further CT scan in July 1996 showed bronchiectasis in the right middle and upper lobes. She has since required one further

The Regional Adult Cystic Fibrosis Unit, Cardiothoracic Centre
M J Ledson
M J Walshaw

Department of Microbiology
M J Gallagher

Royal Liverpool Hospitals, Liverpool L14 3PE, UK

Correspondence to:
Dr M J Walshaw.

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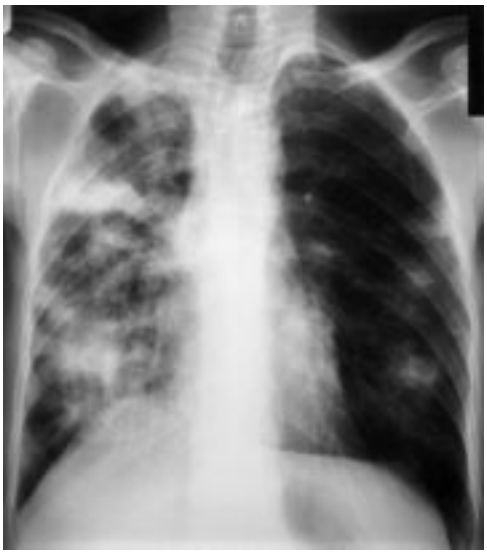

Figure 1 Chest radiograph showing patchy consolidation in the right upper and middle lobes and peripheral consolidation in the left lung.

hospital admission for an exacerbation of *B cepacia* infection and this organism continues to be the only one in her limited daily sputum sample. Although she remains well, simple spirometric tests are now only 70% predicted.

This patient has had nine children, two of whom suffer from cystic fibrosis. She has been intimately involved in the care of these children, preparing and administering their nebulised antibiotics and bronchodilators and helping them with their physiotherapy. Both children became colonised by *B cepacia* in 1991. Microbiological screening of the rest of the family has failed to reveal any other members colonised by this organism. Genetic testing revealed both children to be DF508/621+1(G>T) and the mother to be heterozygous for DF508. Extensive DNA screening tests have failed to reveal a further cystic fibrosis gene for the mother, and her sweat chloride level is only 8 mmol/l (low normal range).

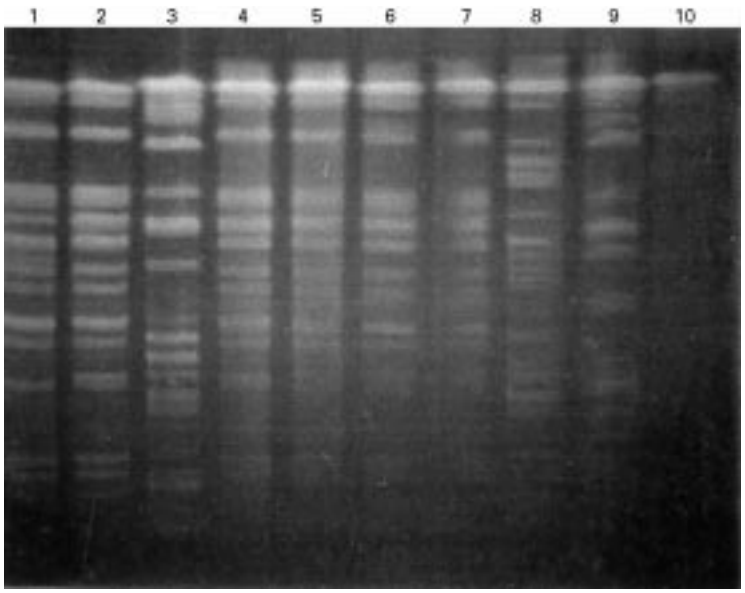

Figure 2 Pulse field gel electrophoresis of several Burkholderia cepacia strains obtained from 10 patients. Those of the siblings (lane 4 and 5) and mother (lane 6) are identical.

Pulse field gel electrophoresis of genomic cepacia DNA has been shown to give different patterns for organisms from different sources[6] and this method has become accepted as the gold standard for epidemiological typing of *B cepacia*.[7] It was therefore chosen to identify the relationship of the patient's strain to those of her children with cystic fibrosis. The patterns derived from the three strains were identical, proving them to be from the same source (fig 2). Polymerase chain reaction (PCR) for the cable pilus also established that all three strains possessed the gene for the pilus and were therefore related to the "epidemic" strain (data not shown).

Discussion

In patients with cystic fibrosis the transmission of *B cepacia* depends on many factors. High numbers of *B cepacia* ($>10^8$ cfu/ml) are present in the saliva of colonised patients and it has been shown that indirect spread via contaminated fomites is possible.[3] Whilst airborne dissemination may present a small risk of acquisition,[8] the highest risk occurs in the direct exchange of respiratory secretions associated with kissing and the intimate social contact which occurs between family members.[9] Different *B cepacia* strains differ greatly in their rates of transmission. In the UK a very transmissible strain of *B cepacia* has been identified which is identical to a strain from Ontario, Canada.[10] This strain, labelled ET 12 or UK "epidemic strain", has a unique form of pilus designated "cable pilus" due to its length (2 μm) and intertwining properties. Up to 40% of patients in UK cystic fibrosis centres are colonised by *B cepacia*, 38% of which is due to the "epidemic strain", involving 50% of cystic fibrosis centres.[11] Transient colonisation can occur with some strains of *B cepacia*, but individuals who acquire the epidemic strain invariably remain chronically colonised.

In non-cystic fibrosis patients *B cepacia* pneumonia is characteristically a hospital acquired infection in the intubated or immunocompromised. There are rare case reports of community acquired *B cepacia* pneumonia occurring in previously healthy individuals[12] but there are no reported cases of chronic respiratory colonisation.

This patient appears to have developed chronic respiratory colonisation with the epidemic strain of *B cepacia* following an acute infection with the organism acquired from one of her two affected offspring. Whilst it is still possible that she is a "forme fruste" of cystic fibrosis, we have been unable to detect a second gene despite extensive first and second level screening (ruling out 99% of cystic fibrosis genes) and she has a negative sweat test. Furthermore, she has had nine children and reached the age of 47 years without exhibiting any other symptoms. We are not aware of any other such cases, either where *B cepacia* has been transmitted from cystic fibrosis patients to immunocompetent adult individuals or where chronic colonisation and lung damage with the organism has been the end result.

Thisis a potentially worrying development for the parents, siblings, and partners of individuals with cystic fibrosis who are necessarily intimately exposed to the microbiological pathogens carried by cystic fibrosis patients.

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Cross infection between cystic fibrosis patients colonised with *Burkholderia cepacia*

M J Ledson, M J Gallagher, J E Corkill, C A Hart, M J Walshaw

Abstract

Whilst patient to patient spread of the respiratory pathogen *Burkholderia cepacia* is well recognised between patients with cystic fibrosis, prompting a strict segregation policy, cross colonisation between cystic fibrosis patients already infected with *B cepacia* has not been described and surveys show a very low incidence of patients with more than one strain. Five adult cystic fibrosis patients with *B cepacia* are presented who became cross colonised with a second *B cepacia* (UK epidemic) strain, four of whom then died, three from the cepacia syndrome. These cases show that, amongst segregated patients, cross colonisation with different *B cepacia* strains is possible, and even in these patients the acquisition of the UK epidemic strain may have a fatal outcome. In future it may be necessary to segregate cystic fibrosis patients colonised with the UK epidemic strain from all other patients with cystic fibrosis.

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Regional Adult Cystic Fibrosis Unit, The Cardiothoracic Centre
M J Ledson
M J Walshaw

Department of Medical Microbiology
M J Gallagher
J E Corkill
C A Hart

Royal Liverpool University Hospitals, Liverpool L14 3PE, UK

Correspondence to:
Dr M J Walshaw.

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Respiratory colonisation of patients with cystic fibrosis with *Burkholderia cepacia* can cause an accelerated fall in pulmonary function and 20% of cases develop fatal acute fulminant pneumonia (the cepacia syndrome).[1] The spread of *B cepacia* between individuals with cystic fibrosis due to social contact is well recognised[2 3] and, because of this, a strict segregation policy between *B cepacia* colonised (BC+) and non-colonised (BC–) patients is advocated in all cystic fibrosis units.[4]

In the UK a very transmissible strain of *B cepacia* has been identified and labelled electrophoretic type 12 (ET 12)[5] or "UK epidemic" strain, and is present in over 50% of clinics in the UK.[6] Furthermore, patients who are already colonised with *B cepacia* are usually allowed to mix freely with each other, raising the possibility that cross colonisation with this strain may occur. Despite this, there have been no studies to determine whether cross colonisation with *B cepacia* occurs in this patient group, and surveys in Britain and Ireland have shown a very low incidence of patients colonised with more than one *B cepacia* strain.[6]

A number of adult cystic fibrosis patients have been transferred to our clinic from the local paediatric centre who were already colonised with the UK epidemic *B cepacia* strain, and five other patients colonised with non-epidemic *B cepacia* have been transferred mainly from peripheral paediatric clinics. In keeping with the national policy, we segregated these BC+ patients from those who were BC–, but all BC+ patients were allowed to mix socially, attend the same outpatient clinics, and were admitted to the same wards for inpatient treatment. All five of the non-epidemic BC+ patients subsequently became cross colonised with the UK epidemic *B cepacia* strain. Furthermore, four of these rapidly succumbed, three from the "cepacia syndrome". We present the methods used to type the *B cepacia* strains in our clinic and also the case histories of these five patients.

B cepacia typing method

The separate *B cepacia* strains were differentiated by pulsed field gel electrophoresis (PGFE)