Subdural empyema due to *Burkholderia cepacia*: an unusual complication after lung transplantation for cystic fibrosis

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INTRODUCTION

Lung disease accounts for most of the morbidity and mortality in cystic fibrosis and for many, lung transplantation becomes the final therapeutic option. With the emergence of *Burkholderia cepacia* as a serious pathogen in cystic fibrosis, an increasing number of patients infected with this organism are being referred for lung transplantation. There has been concern over the prognosis for these patients after transplant[1] and this has become an important issue for transplant centres.

We present a case of a child infected with *B. cepacia* who underwent lung transplantation and suffered an unusual and serious complication in the post-operative period. This case is used to illustrate some discussion points related to cystic fibrosis, *B. cepacia* and lung transplantation.

CASE HISTORY

The patient is a 16-year-old Welsh girl diagnosed with cystic fibrosis when 3 years old. Her diagnosis followed the death of her younger sister, aged 9 months, with newly diagnosed cystic fibrosis. Aged five years, she contracted pulmonary tuberculosis but made a good recovery. Although chronically colonized with *Pseudomonas aeruginosa*, her lung function and general health remained reasonable. Aged 15 years she was infected with *B. cepacia* leading to a rapid deterioration in her health. After assessment[2], she was placed on the active waiting list for lung transplantation, only four months after *B. cepacia* was first isolated from her sputum. At the time, she did not attend school, was wheelchair-bound, and her FEV_1 was 17% predicted for sex and height.

After a wait of 10 months she had a bilateral sequential lung transplant. Since she had no evidence of cor pulmonale, she did not require transplant with a heart-lung bloc. She underwent our routine peri-operative care which has been described[3] and was immunosuppressed with anti-lymphocyte globulin, azathioprine, methylprednisolone and cyclosporin A. Initially she made a good recovery and was ventilated for 48 h only. However on the fifteenth post-operative day she had a 3 min grand mal seizure which ceased spontaneously. For a few hours prior to this she had complained of visual hallucinations and a pain above the right eye. On examination there were no focal neurological signs and blood pressure was normal. At the time her serum magnesium was low (0.63 mmol/L) so this was corrected and it was noted that her cyclosporin levels were within the therapeutic range. Two days later, she again developed visual hallucinations, followed by a 2–3 min left-sided focal fit so she was started on intravenous phenytoin.

Investigations

A computerized tomography (CT) brain scan showed a small subdural empyema over the right cerebral hemisphere and enhancement of the meninges but no evidence of raised intracranial pressure (Figure 1). A lumbar puncture was normal and electroencephalogram (EEG) showed no epileptiform activity but occasional slow components over the right posterior temporo-occipital region.

Treatment

She required a right occipital craniotomy to drain the subdural empyema. There was a localized 'gel-like' collection of pus with 'oily' liquid over the rest of the hemisphere. The pus grew two strains of *B. cepacia* (genotypically identical but phenotypically different). Both strains were identical to those grown from her sputum both pre- and post-transplant.

Progress and follow-up

She made a good recovery and was treated with intravenous antibiotics (chloramphenicol, ceftazidime, vancomycin and metronidazole) for 5 weeks. She went home at 8 weeks post-transplant with a normal follow-up CT brain scan and no neurological sequelae. She developed recurrent chest infections particularly on the left side and left-sided bronchial stenosis was diagnosed at bronchoscopy. At six months she required a bronchoscopically-placed stent to correct this stenosis. A CT lung scan at the time confirmed the clinical suspicion of obliterative bronchiolitis and one year post-transplant her lung function has deteriorated to

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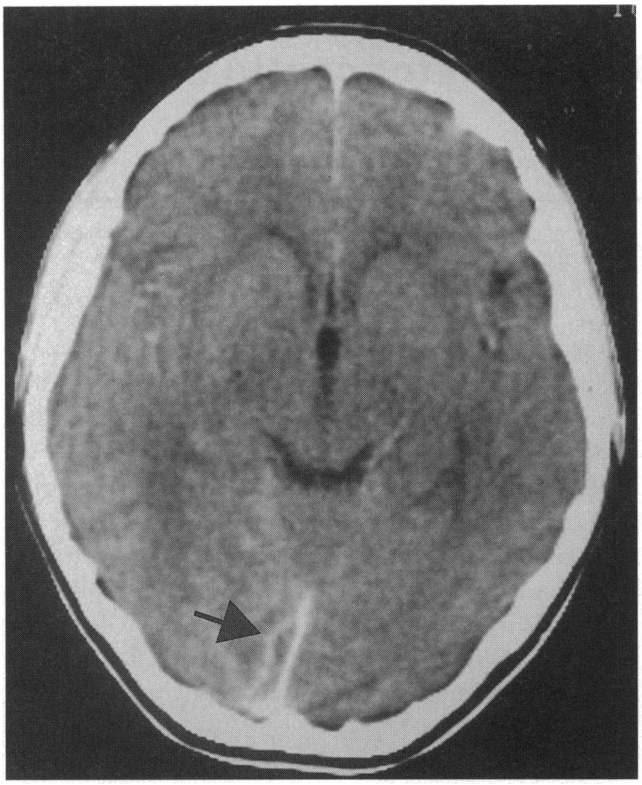


Figure 1 **Computerized tomography brain scan with contrast showing subdural empyema in the right occipital lobe (arrow). The falx is pushed over to the left by the empyema. Meningeal enhancement is noted due to the secondary inflammatory effects but there are no signs of raised intracranial pressure**

the extent that she requires intermittent home oxygen therapy. *B. cepacia* is still being isolated from her sputum.

DISCUSSION

Extra-pulmonary manifestations of *Burkholderia cepacia*

B. cepacia is ubiquitous in the environment and frequently found in soil, water and plants[4]. It is effectively non-pathogenic in healthy individuals but serious infections can occur in patients with altered host defences, such as burns victims or patients with chronic granulomatous disease[5]. It can survive in disinfectant solutions and numerous hospital-aquired outbreaks of colonization and infection have been reported, caused by contaminated solutions, medicines and medical devices[5]. Infection with *B. cepacia* has become an increasing problem for patients with cystic fibrosis and the manifestations of pulmonary infection with *B. cepacia* are well documented[6–8]. Infected patients may remain stable for a while, although many deteriorate gradually over a period of months or years[9]. Some infected patients experience a rapidly fatal deterioration, and this, together with its ease of transmissibility and antibiotic resistance make it a truly feared organism among the cystic fibrosis community.

Extra-pulmonary sites of infection with *B. cepacia* include the endocardium, blood, peritoneum, wounds, urogenital tract, bones and joints[5,10]. Reports of infection in the central nervous system are rare. There have been three reports of neonatal meningitis[11–13], one of which was secondary to contamination of a Holter valve inserted for congenital hydrocephalus. There is also a case reported in which superimposed meningitis with *B. cepacia* led to resolution of primary cryptococcal meningitis[14]. Recently a case has been described in which an adult with cystic fibrosis developed *B. cepacia* brain abscesses secondary to chronic suppurative otitis media[15]. This is the first case we are aware of in which *B. cepacia* has caused a subdural empyema in a patient with cystic fibrosis. It highlights concerns over the effects of this organism in patients who need to be immunosuppressed after organ transplantation.

The source of *Burkholderia cepacia* in this patient

The index case of *B. cepacia* in the Cardiff CF centre which this patient attended developed the infection whilst on holiday in a CF camp in Canada in 1987[16]. The index case cross-infected two other patients during hospital admissions in 1988 and 1990 and both these patients had siblings who subsequently became infected. In 1994, our patient was in the hospital at the same time and socialized with one of these siblings and also developed *B. cepacia* infection. It would seem that social contact is important in the spread of epidemic strains of *B. cepacia* and needs to be controlled[17–19]. However, while segregation may limit the spread of epidemic strains, it will not necessarily prevent new sporadic cases from occurring[20]. Although segregation of infected patients may have detrimental psychosocial consequences, many CF centres are now adopting this policy[4,7,8,16].

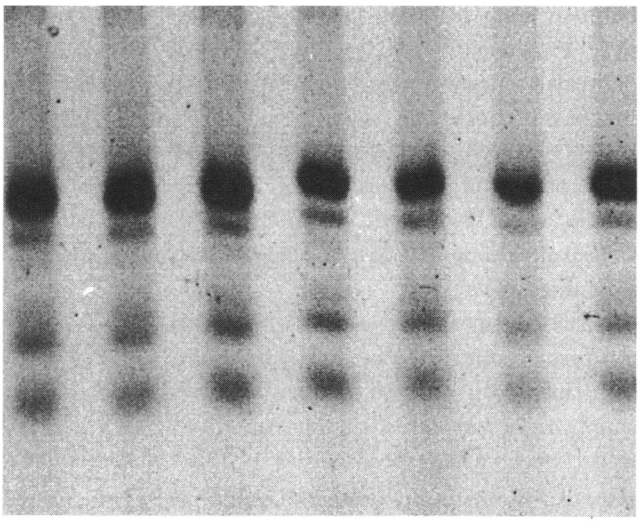
Until recently it has been difficult to understand the epidemiology of *B. cepacia* because of the marked phenotypic variability exhibited by isolated strains[21]. A single sputum sample from a patient may yield colonies of *B. cepacia* which differ in morphology, antibiotic sensitivity and pigment production[21]. However, these colonies may still be derived from the same original strain and share the same genotype. *B. cepacia* can now be characterized by polymerase chain reaction (PCR) ribotyping; this gives information on the organism's genotype and epidemiologically unrelated strains can now be differentiated[22,23].

The molecular epidemiology of the *B. cepacia* strains found in Cardiff have been extensively investigated[23]. Our patient had two strains of *B. cepacia* isolated in her sputum pre-transplant. These had an identical genotype [using PCR in ribotyping after Taq 1 digestion] to each other, and were

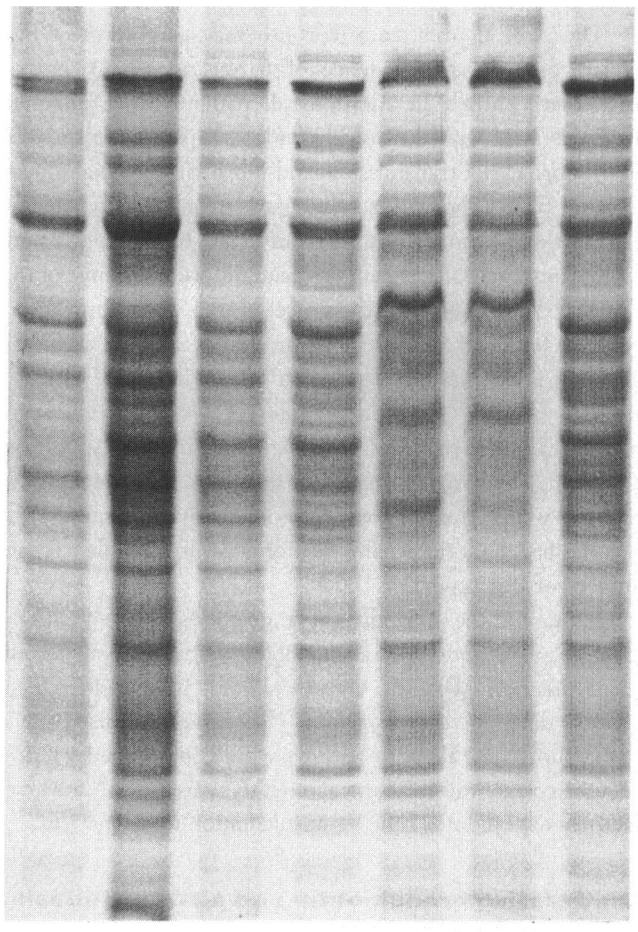
also identical to the other strains isolated in Cardiff, including the index case from 1987 (Figure 2A). However, using polyacrylamide gel electrophoresis, it was shown that her two strains were phenotypically different from each other, and displayed different antibiotic sensitivities (Figure 2B). This phenotypic change was the first seen with this strain since its first isolation. The mechanism for phenotypic variation in genotypically-identical strains is probably one of genomic rearrangement and variable gene expression[21]. Interestingly, this change resulted in greater antibiotic sensitivity, which is the opposite to what one would expect. However, once the more sensitive strain became dominant, it developed a more antibiotic-resistant pattern. Incidentally, the strain found in Cardiff is not the same as the 'epidemic strain' (J2315) described by Govan *et al.*[19] which has been identified in several centres in the UK, although both strains were imported from Canada.

She also had the same two strains isolated in her sputum after the transplant and these strains were also isolated from the pus drained from the subdural empyema. This suggests self re-infection, most likely from the organisms that remained in her upper airways and paranasal sinuses, which has been reported in other patients after transplantation[24]. She had also remained isolated in the transplant suite so transmission from another patient was not possible and strain-typing rules out a new environmentally-acquired strain. How the *B. cepacia* reached the subdural space is not clear. It is possible it was blood-borne as haematogenous spread of chronic pyogenic lung infections (including lung abscesses and bronchiectasis) are described[25]. Overall, however, intracranial suppurative conditions are uncommon in children with cystic fibrosis, and tend to occur in older patients[26]. In our case, blood cultures were always negative but a transient bacteraemia or septic emboli cannot be ruled out. A contributory factor may also have been the level of immunosuppression in the patient at the time.

Direct infection from the paranasal sinuses remains a possibility as chronic sinusitis is common in cystic fibrosis, and *B. cepacia* may well reside in the sinuses after transplant[1,27]. Intracranial spread from the sinuses occurs by either direct extension through areas of associated osteomyelitis or through retrograde thrombophlebitis of



(a)



(b)

Figure 2(a) **Polymerase chain reaction ribotyping (after Taq 1 digestion) showing that all seven isolates have the same genotype. The *B. cepacia* strains isolated after transplant were the same as those in the lungs prior to transplant. (*b*) Polyacrylamide gel electrophoresis confirming that the isolates before and after transplant were identical but that the two strains had different phenotypes. *Key*: 1=index case for Cardiff cystic fibrosis strain; 2=isolate from strain thought to have infected this patient; 3=initial isolate from this patient; 4 & 5= two strains isolated from sputum prior to transplant; 6 & 7=two strains isolated from sputum and subdural pus after transplant**

emissary veins that connect the extracranial and dural venous circulations[25]. Because of potential sinus problems, procedures such as lavage or prophylactic surgical drainage of the sinuses have been performed prior to transplantation[27,28]. Although said to be helpful, there is no conclusive evidence as to the efficacy[27,28]. This strategy is more popular in the US than the UK and is not an approach taken at our centre.

Burkholderia cepacia and lung transplantation

As more patients with cystic fibrosis become infected with *B. cepacia*, experience with transplantation in these patients is increasing. An initial report from Toronto gave very poor results with a median survival of only 28 days after lung transplantation[1]. The majority of their mortality was due to *B. cepacia* pneumonia and sepsis, whilst other complications included lung empyema, lung abscess, suppurative pericarditis and sinusitis, all due to this organism[1]. Other centres have reported two cases of empyema necessitatis (the extension of pus from the empyema cavity into cutaneous soft tissues) and a case of osteomyelitis of the temporal bone secondary to malignant necrotizing otitis externa, all due to *B. cepacia*[29,30].

The poor figures from Toronto may partly reflect the high pre-transplant incidence of *B. cepacia* (43%) in this particular centre[1]. In addition, all patients were infected with the same epidemic strain and perhaps that strain was both more easily transmissible and more virulent than those isolated from other centres[31]. Figures from a centre in the US also show no excess mortality due to *B. cepacia* and furthermore all their patients had different strains of *B. cepacia*[24,31]. Reported experience in the UK from three centres found that there was no difference in actuarial survival post-transplant between those infected with *B. cepacia* (n=14) and those infected with *Pseudomonas aeruginosa* (n=73)[32]. At Great Ormond Street Hospital for Children, our own transplant experience is limited to 3 patients with *B. cepacia*; one died of adenovirus pneumonia, one has had no serious complications, whilst the other is the subject of this report.

Because of the morbidity and mortality associated with *B. cepacia*, and its potential transmissibility, it has been suggested that infection with *B. cepacia* should be considered a contraindication to transplant[1,27,33]. However, this view is not supported by all[24,31,32] and we would only consider it as a relative contraindication, meaning if this was the only adverse factor we would not refuse transplantation to the patient.

Obliterative bronchiolitis and airway stenosis after transplantation

Obliterative bronchiolitis (OB) is an inflammatory disorder of the small airways resulting in obstruction and destruction of the bronchioles. This leads to bronchiectasis, recurrent infections and an inevitable decline in lung function. The precise aetiology and pathology of OB are obscure but it may be the non-specific response of a transplanted lung to a variety of insults (immunological, infective, ischaemic, mechanical)[34]. Once past the immediate peri-operative period, OB is the major cause of morbidity and mortality in transplanted patients. Its onset is almost inevitable and actuarial freedom from OB in those surviving to three years is only 37%[35]. Treatment is palliative and the only definitive treatment is re-transplantation, but results for this are poor, with only a 41% one-year survival[36].

Unfortunately this patient developed OB within 6 months of transplant. Early onset OB (that is, within the first year) tends to be more aggressive and has a rapidly deteriorating course, ending with respiratory failure and death[35]. The later onset form is usually apparent 2–3 years post-transplant and results in a slower deterioration in lung function[35]. Early onset OB is associated with a higher incidence of episodes of acute pulmonary rejection in the first six months[35] and persistent severe rejection is also associated with OB[37]. A strong association with early episodes of pulmonary infection has not been shown[35,37] but may be a factor in certain cases. Currently there is little evidence to say that patients with *B. cepacia* are particularly prone to develop OB although an association has been reported in some cases[34]. In time, if enough patients with *B. cepacia* are transplanted and survive the early period, if there is a true association between *B. cepacia* and OB, it will become apparent. Certainly, a transplanted lung that has developed OB is more prone to becoming infected[31].

This patient also developed a bronchial stenosis within the first 6 months. Early onset OB has been shown to be associated with tracheal stenosis[35]; airway stenosis may simply represent diffuse airway pathology with a generalized bronchomalacia predisposing to OB[36]. The combination of the two conditions has a poor prognosis in our experience[3]. Tracheal stenosis is commoner in children[39] and may be related to their less well developed coronary–bronchial collateral circulation[40] resulting in poorer anastomotic healing. In this regard, a smaller calibre airway is more prone to developing a stenosis, particularly after interruption of the coronary–bronchial circulation, hence a heart–lung bloc is preferred in the young as this obviates the need for a bronchial anastomosis. Finally, chronic local infection may also be an important factor and *B. cepacia* may have contributed in this case.

Conclusions

This patient developed *B. cepacia* infection which caused such a severe deterioration in her respiratory function that

she required lung transplantation. In the post-operative period, her transplanted lungs became re-infected with the same organisms and she suffered the previously unreported complication of a subdural empyema due to *B. cepacia*. She suffered further complications of a bronchial stenosis and obliterative bronchiolitis.

With a three-year post transplant survival of only 43% for children with cystic fibrosis[41], lung transplantation should still be considered as a palliative procedure. Although some children do remarkably well with a greatly improved quality of life, for many it is simply the start of a whole new set of health problems[42]. Eradicating obliterative bronchiolitis will be necessary before survival figures can improve dramatically, but even then the problem of donor organ scarcity will remain. Xenotransplantation as a serious option is probably a long way off but living related donors may offer new hopes, albeit with ethical concerns. In the meanwhile, *B. cepacia* is pushing more patients with cystic fibrosis towards the need for lung transplantation.

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