Cepacia-like syndrome caused by *Burkholderia multivorans*

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The variable severity of *Burkholderia cepacia* complex infections in cystic fibrosis (CF) has recently been ascribed to differences in the virulence between genomovars. Specifically, genomovar III isolates have been associated with higher transmission rates and adverse outcomes compared to other *B cepacia* genomovars, and consequently further segregation between genomovar III and non-genomovar III *B cepacia* infected patients is advocated in some centres. The important role of non-genomovar III isolates is presented in the context of a clinical case whereby a patient with long-standing pulmonary infection with *B multivorans* developed bacteremic infection reminiscent of the fatal 'cepacia syndrome'.

Key Words: *Burkholderia*; *Cepacia* syndrome; Cystic fibrosis; Genomovar

Burkholderia cepacia (previously known as *Pseudomonas cepacia*) complex consists of nine species that, based on molecular differences, are divided into genomovars of which only some have received species names (1,2). *B cepacia* complex was first reported as a human pathogen in the 1960s, and until the mid-1980s case reports were sporadic and mainly limited to ill, chronically hospitalized patients (3). In 1984, the clinical impact of *B cepacia* complex in cystic fibrosis (CF) patients was first published (4). As well, nosocomial *B cepacia* complex outbreaks are being reported with increasing frequency from hemodialysis (HD) units (5). Therapy with aminoglycosides, quinolones, and most β -lactams is ineffective and in-vitro susceptibilities often don't correlate with in-vivo activity, complicating successful treatment (6,7). These bacteria can also survive in commonly used antiseptic solutions (8).

In CF, acquisition of *B cepacia* complex results in increased morbidity and mortality (4,9). Consequently, segregating *B cepacia* complex positive and negative patients has become standard of care (9,10). CF patients with *B cepacia* complex are frequently categorized into one of three clinical syndromes: 1) infection/colonization without change in pulmonary status, 2) infection with accelerated pulmonary decline and 3) acute pulmonary deterioration with bacteremia, necrotizing pneumonia, leukocytosis, and death within weeks to months. The

Un syndrome pseudo-cepacia causé par le *Burkholderia multivorans*

La gravité variable des infections complexes à *Burkholderia cepacia* en cas de fibrose kystique a récemment été attribuée à des différences de virulence entre genomovars. Plus précisément, des isolats genomovars III s'associent à un taux de transmission plus élevé et à des issues négatives par rapport aux autres genomovars à *B cepacia*. Par conséquent, une ségrégation accrue entre les patients infectés par le genomovar III et le *B cepacia* non genomovar III est préconisée dans certains centres. Le rôle important des isolats non genomovars III est illustré par le cas clinique d'un patient atteint d'une infection pulmonaire à *B multivorans* de longue date qui a développé une infection bactériémique

latter has been named 'cepacia syndrome' (4). A recent study suggests genomovar III *B cepacia* is responsible for cepacia syndrome (11).

CASE PRESENTATION

A 60-year-old man was diagnosed with CF at age 48 (genotype $\Delta F508$ /unknown) after a chronic history of cough and diabetes with associated nephropathy. Surveillance sputum cultures grew *B cepacia* complex five years after CF was diagnosed. His respiratory status remained stable for the next six years. Pulmonary exacerbations were infrequent (less than two per year) and responded to oral antibiotics. Past medical history was significant for allergic bronchopulmonary aspergillosis requiring steroids, gout and moderate exocrine pancreatic insufficiency.

Within the six months before expiring, he had four hospital admissions for pulmonary exacerbations that failed oral antibiotic treatment and required intravenous broad-spectrum antibiotics. Serial chest imaging demonstrated persistent bronchiectasis, fleeting infiltrates and a left upper lobe consolidation with progressive diffuse opacities developing in multiple lobes. Bronchoscopy only showed thick secretions. Sputum cultures grew *Staphylococcus aureus*, *B cepacia* complex, *Acinetobacter baumannii* complex, *Haemophilus* species and viri-

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dans streptococci. His stable renal function began to decline rapidly during this time, requiring urgent HD after an episode of uremic encephalopathy. A tunneled central venous catheter (CVC) was placed for routine HD. Shortly thereafter he experienced a severe pulmonary exacerbation associated with fever and leukocytosis. Peripheral and CVC blood cultures grew *S aureus* and *B cepacia* complex, the latter only susceptible to trimethoprim-sulfamethoxazole, which was administered along with ceftazidime, piperacillin/tazobactam and vancomycin. The *S aureus* bacteremia cleared promptly with antibiotic treatment. Respiratory failure and *B cepacia* complex bacteremia persisted despite treatment and CVC removal. He died four weeks later.

METHODS/RESULTS

B cepacia complex isolates from both blood and sputum were typed using recA primers as previously described (12). Earlier sputum isolates had been tested at the Burkholderia cepacia Research Laboratory and Repository at the University of Michigan (J LiPuma, personal communication). Every isolate was *B multivorans* (genomovar II).

DISCUSSION

Our patient had sputum cultures persistently growing *B multivorans* for five years and subsequently developed a cepacia-like syndrome after CVC placement. *B multivorans* bacteremia is not unheard of in the CF community. An outbreak of highly transmissible *B multivorans* isolates was seen in a CF centre in Glasgow and fatal "cepacia syndrome" caused by *B multivorans* has been observed in a patient in Manchester, England (J Govan, A Jones, personal communication).

Nevertheless, a Canadian group recently reported molecular epidemiological evidence that genomovar III isolates are more highly transmissible and are associated with increased morbidity and mortality compared with non-genomovar III isolates (11). Furthermore, they describe several patients where *B multivorans* was replaced with a genomovar III strain. The opposite did not occur in their population. Based on these findings, they recommend further segregation between *B cepacia* complex positive patients based on genomovar status. Another observation by this group was that *B multivorans* infection was predominantly in younger patients. In contrast, our patient was older and experienced a fatal clinical course once *B multivorans* bacteremia occurred. Clearly our patient suffered from other chronic comorbidities predisposing him to serious infection; however, the temporal association between CVC placement and subsequent persistent *B multivorans* bacteremia with progression to a cepacia-like syndrome support the important role of *B multivorans* in this syndrome.

Clinical studies exist whereby the relationship between CVC and *B cepacia* complex bacteremia has been studied. In a recent report of an outbreak of CVC-related *B cepacia* complex bacteremia in nine non-CF patients undergoing HD, the source was a disinfectant solution (5). Antibiotic therapy based on in vitro susceptibility testing did not result in clinical improvement or resolution of bacteremia until the CVCs were removed. Another longitudinal, retrospective analysis in non-CF patients with *B cepacia* complex bacteremia identified prolonged intensive care unit stay associated with CVC placement as the most common predisposing condition. All patients with CVC removal cleared the infection, but mortality was 20% if the CVC was not removed (13). Additional

studies confirm that indwelling CVC was the most significant risk factor for acquisition of *B cepacia* complex bacteremia and for a poor prognosis if not removed (6). Unfortunately, none of these studies identified isolates by genomovar or included CF patients.

Persistent *B multivorans* bacteremia in our patient was surprising given that: 1) CF patients with *B cepacia* complex bacteremia and associated respiratory failure are usually infected with genomovar III and 2) CVC-associated *B cepacia* complex bacteremia, even when polymicrobial, should respond favourably after CVC removal. Nevertheless *B multivorans* bacteremia, refractory pulmonary failure, fever and death occurred despite CVC removal.

CONCLUSION

It appears that the clinical features of cepacia syndrome are not restricted to a single genomovar, because we and others have identified CF patients with severe and fatal *B multivorans* infections. This is in distinct contrast to the Canadian findings that *B multivorans* is not highly pathogenic.

As more CF patients survive into adulthood and acquire *B cepacia* complex infection, clinicians will be challenged with age-related comorbidities in a population with a chronic disease that was once limited to childhood. *B cepacia* complex-infected CF patients, even with a strain thought to be "less virulent", can have a clinical course reminiscent of cepacia syndrome, and perhaps are at most risk after a foreign intravascular body is placed. We advocate that caregivers make every effort to avoid CVC placement or minimize duration and choose alternatives (ie, peritoneal dialysis, arterial-venous fistula) in managing renal failure, if possible, in this patient population.

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