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Shaun S.C. Ho
Hospital for Sick Children University of Toronto

Nancy Nashid
Hospital for Sick Children University of Toronto, nancy.nashid@lhsc.on.ca

Valerie J. Waters
Hospital for Sick Children University of Toronto

John J. LiPuma
University of Michigan Medical School

James E.A. Zlosnik
The University of British Columbia

See next page for additional authors

DR SHAUN SIONG CHUNG HO (Orcid ID : 0000-0002-5690-6560)

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Burkholderia multivorans Septicemia in a Pediatric Liver Transplant Patient

AUTHORS:
Shaun S. C. Ho*, MBBS, Division of Gastroenterology, Hepatology and Nutrition, The Hospital for Sick Children, University of Toronto, Toronto, Ontario, Canada
Nancy Nashid*, MD, Division of Infectious Diseases, The Hospital for Sick Children, University of Toronto, Toronto, Ontario, Canada
Valerie J. Waters, MD, MSc, Division of Infectious Diseases, The Hospital for Sick Children, University of Toronto, Toronto, Ontario, Canada
John J. LiPuma, MD, PhD, Department of Pediatrics and Communicable Disease, University of Michigan Medical School, Ann Arbor, Michigan, United States
James E. A. Zlosnik, PhD, Department of Paediatrics, University of British Columbia, Vancouver, British Columbia, Canada
Anthony Otley, MD, MSc, Division of Gastroenterology & Nutrition, IWK Health Centre, Dalhousie University, Halifax, Nova Scotia, Canada
Gino R. Somers, MD, Division of Pathology, The Hospital for Sick Children, University of Toronto, Toronto, Ontario, Canada
Binita M. Kamath, MBBChir, Division of Gastroenterology, Hepatology and Nutrition, The Hospital for Sick Children, University of Toronto, Toronto, Ontario, Canada
Yvonne C. W. Yau, MD, Division of Microbiology, The Hospital for Sick Children, University of Toronto, Toronto, Ontario, Canada
* SSCH and NN contributed equally to this work

CORRESPONDENCE:
Yvonne C. W. Yau
Division of Microbiology,
Department of Paediatric Laboratory Medicine,
Hospital for Sick Children, 555 University Ave,
Toronto, Ontario, M5G 1X8, Canada.
Email: Yvonne.yau@sickkids.ca

ABBREVIATIONS:
BC - blood culture, Bcc - *Burkholderia cepacia* complex, CF - cystic fibrosis, CGD - chronic granulomatous disease, CVL - central venous line, EBV - Epstein-Barr virus, HLH - hemophagocytic lymphohistiocytosis, MLST - multi-locus sequence type, PTLD - post-transplant lymphoproliferative disorder.

ABSTRACT:
'Cepacia syndrome' caused by *Burkholderia cepacia* complex and often found to be associated in patients with cystic fibrosis, carries a high mortality rate. It is rare for *Burkholderia multivorans*, a species within the *Burkhoderia cepacia* complex to cause 'cepacia syndrome' even among the cystic fibrosis patients. This is the first reported fatal case of 'cepacia syndrome' caused by *Burkholderia multivorans* occurring in a non-cystic fibrosis pediatric liver transplant recipient. We describe the unique characteristics of this pathogen among the non-cystic fibrosis population and the importance of early recognition and treatment.

INTRODUCTION

The *Burkholderia cepacia* complex (Bcc), consisting of 22 species, is a group of aerobic, Gram-negative, non-spore-forming bacilli that are phenotypically similar but genotypically distinct(1). Bcc are well recognized opportunistic pathogens associated with high morbidity and mortality in persons with cystic fibrosis (CF)(2). Bcc infections in non-CF settings have been described in nosocomial outbreaks attributable to contaminated disinfectants, intravenous solutions, and medical devices, and in opportunistic infections in immunocompromised hosts such as patients with chronic granulomatous disease (CGD) or malignancies(2-4). 'Cepacia syndrome', a necrotizing pneumonia characterized by rapid clinical deterioration and septicemia frequently leading to death(5), has mostly been associated with *Burkholderia cenocepacia*, a Bcc species, isolated most commonly in CF patients(2). Cases of cepacia syndrome secondary to *Burkholderia multivorans* have been described infrequently(6-8), but no cases have been reported in the literature outside of the CF population.

We present the first report of a case of cepacia syndrome caused by *B. multivorans* in a pediatric liver transplant recipient and briefly review the literature on Bcc infection in the non-CF setting.

CASE REPORT

A 23-month old Caucasian male, post-liver transplant was transferred from a tertiary children's hospital to our transplant center with persistent fever of unknown cause. His past medical history included biliary atresia and Kasai surgery at 58 days of age. He had normal newborn screening and sweat test. His clinical course was complicated by ascending cholangitis, worsening jaundice and recurrent ascites with progression to end-stage liver disease requiring a living-related liver transplant from his father at 6 months of age. Donor and recipient were both positive for Epstein-Barr virus (EBV) IgG, while both donor and recipient serostatus for cytomegalovirus was negative. He was placed on standard immunosuppression with steroid and tacrolimus post-transplant. He was weaned off steroids three months post-transplant. At 12 months of age, he developed intestinal polymorphous post-transplant lymphoproliferative disorder (PTLD). Serum EBV quantitative PCR became undetectable after four doses of rituximab, and tacrolimus was restarted targeting a serum level between 3-4ug/L. He

remained well apart from a single episode of perianal abscess, treated with a 3-week course of amoxicillin/clavulanic acid.

The current illness began with fever presenting to his local community hospital. He was subsequently transferred to his local academic hospital for ongoing recurrent fever after receiving 4 days of cefotaxime. At the local academic hospital, he was empirically treated with intravenous piperacillin/tazobactam and tobramycin before his blood culture (BC) became positive for Bcc, at which time his therapy was switched to ceftazidime and ciprofloxacin, to which the Bcc isolate was susceptible (See Figure 2). A central venous line (CVL) was inserted due to difficult intravenous access after the BC became negative, and his antibiotics were continued for another 2 weeks. Other investigations, including cerebrospinal fluid and urine culture, chest x-ray, head CT scan, and an abdominal ultrasound were all unremarkable. He had a single recurrence of fever, which was attributable to a possible viral infection on the last day of antimicrobial therapy and he was given piperacillin/tazobactam and tobramycin for an additional 48 hours until repeat BC was negative. His CVL was removed prior to discharge. Given repeatedly negative BCs and a recent serum EBV viral load of $5.6x10^3$ copies per mL, PTLD was suspected as a potential etiology of the recurrent fever within 5 days of discharge. Tacrolimus levels were measured between 2-3ug/L before discontinuation. Endoscopic assessment with luminal biopsies, however, showed no evidence of EBV encoded RNA by in situ hybridization. Another CVL was inserted. A chest x-ray taken at his initial hospital admission was reported as unremarkable. However, a repeat chest x-ray prior to transfer showed small patchy opacities in both lungs fields.

At our institution, he remained febrile. Physical examination was unremarkable except for mildly enlarged tonsils. There was no lymphadenopathy or palpable abdominal masses, and his chest was clear. Within 24 hours, however, he quickly deteriorated, developing septic shock and required oxygen supplementation. Meropenem and vancomycin were commenced to broaden coverage in the context of an immunocompromised patient who failed empiric therapy with pipercillin/tazobactam, ceftazidime and ciprofloxacin. Repeat chest x-ray showed worsening diffuse, ill-defined nodular densities in both lungs suggesting the possibility of disseminated fungal

infection (Figure 1A) and amphotericin B was added. The CVL was removed after both peripheral and CVL BCs simultaneously became positive for Bcc, which was later identified to be *B. multivorans*. Despite broadening antimicrobials to include ciprofloxacin and sulfamethoxazole/trimethoprim, his condition worsened and he died from disseminated intravascular coagulation, multi-organ failure and secondary hemophagocytic lymphohistiocytosis (HLH).

Postmortem examination revealed necrotic abscesses in both lungs (Figure 1B-1D) and most organs, including liver, lymph nodes, bone marrow, brain, spleen, kidneys and adrenal glands. Lung tissue culture grew *B. multivorans*. Hemophagocytosis was seen in the liver confirming the clinical suspicion of secondary HLH. A large, recent intracerebral hemorrhage of the left cerebral hemisphere was also observed, which was negative for bacteria and fungal elements on Gram and Gormori methenamine silver stain. There was no pathological evidence to suggest the presence of PTLD, liver allograft rejection, CGD, or CF.

Further molecular typing of the *B. multivorans* isolate revealed that it was most closely related to a multi-locus sequence type (MLST)(9), ST355, which had only been previously identified from the blood culture of a patient with CGD in the United States(10). Our patient's isolate differed by random amplified polymorphic DNA analysis(11) and was just one base pair different in one of the 7 MLST alleles tested compared to the isolate from the CGD patient. Repetitive extragenic palindromic PCR using BOX A1R primer(12), however, found these two isolates to be identical.

DISCUSSION

To our knowledge, this is the first report of *B. multivorans* infection presenting as 'cepacia syndrome' in a non-CF liver transplant patient. Increased awareness of the severity of this condition amongst transplant physicians may lead to more rapid diagnosis with close monitoring and frequent follow-up, and longer duration of antibiotic therapy.

We performed a literature review of cases of Bcc infections in non-CF and non-outbreak settings by searching the Medline database since 1996 using the terms "*Burkholderia*" and "non-cystic fibrosis". A total of 17 cases were identified (Table 1); most were case

reports(3, 13-19) and one was a prospective observational study(4). Species identification was only available for 3 patients; two involved *B. cenocepacia* and one with *B. multivorans*(16, 19). Four cases (Patient 2, 3, 8 and 12 in Table 1) fit the clinical presentation of 'cepacia syndrome' as characterized by rapid respiratory decline with bacteremia and necrotizing pneumonia. Two of these patients had underlying CGD. All were fatal except one (Patient 8).

The incidence of *B. multivorans* infection has been increasing in CF patients, but it is a rarely seen infection in the non-CF population(10). In one New Zealand study, *B. multivorans* accounted for 79.5% of Bcc infections in CF patients, but only 28% in the non-CF group(20). *Burkholderia lata* and *Burkholderia stabilis,* with low level of diversity based on MLST, accounted for 44% of the non-CF Bcc infections in the study(20). In contrast to *B. cenocepacia* where patient-to-patient transmission has been well described in CF in the past, initial *B. multivorans* infection in CF patients is thought to be acquired from the environment(21). Among the non-CF group, it is thought that person-to-person spread is unlikely, as the infected patients were separated temporally and geographically with no epidemiological links(10, 20). Infection control precautions should be no different for immunosuppressed patients.

In our case, although the patient had a liver transplantation that may have contributed to the development of this infection, he was only on minimal immunosuppression at the time of infection. His rapid clinical deterioration is uncharacteristic for *B. multivorans* infections in a non-CF setting. The underlying reason for the severity of his illness and source of infection remain unclear. The incidence of Bcc infection in transplant patients is unknown. Recognition of chest x-ray changes (Figure 1A), in the setting of recent Bcc bacteremia, should alert transplant physicians to possible cepacia syndrome. Despite the recognition of the clinical significance of Bcc infections in both immunocompromised and CF patients, there is a lack of evidenced based antibiotic treatment for this infection(22, 23). Because of the potential for emergence of resistance while on monotherapy and data from synergy studies, some would consider treatment with multiple intravenous antibiotics initially, follow by two to three drug combination when susceptibility of the Bcc is available. Although the exact duration of

therapy is not clear, the possibility of cepacia syndrome may suggest the need for a longer duration of antibiotics with close monitoring.

This is the first case report of *B. multivorans* presenting as 'cepacia syndrome' in a non-CF pediatric liver transplant recipient. Early recognition and appropriate treatment is crucial.

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DISCLOSURE

The authors of this manuscript have no conflicts of interest to disclose as described by the *American Journal of Trnasplantation.*

FIGURE LEGEND

Figure 1: Imaging, autopsy and histology findings of 'cepacia syndrome'.

A. Chest x-ray showed diffusely ill-defined density nodules in bilateral lungs and small right pleural effusion.
B. Autopsy revealed diffuse multiple foci of necrotic abscesses (red arrow) within both lungs.
C. Image shows histiocytes at the periphery and karyorrhectic debris toward the center of the abscess.
D. Immunohistochemical staining for CD68 (Dako, Carpinteria,CA) confirming marked numbers of histiocytes at the periphery of the lung abscess.

Figure 2: Clinical events with key investigation findings and treatment course (including Bcc susceptibility results).

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TABLE:

Table 1: Review of the literature of Bcc infections in non-CF population.

Authors	Patient no.	Age(y), Sex	Underlying Medical Conditions	Bcc Species	Bcc Bacteremia	Necrotizing Pneumonia	Acute Respiratory Decline	Sepsis	Outcome
Lacy et al.	1	3.5, M	CGD	unknown	Y	unclear (pleural effusion)	Y	Y	died
	2	0.6, M	CGD	unknown	Y	Y	Y	Y	died
Belchis et al	3	44, M	Pulmonary histoplasmosis, chronic bronchitis, recurrent childhood infections	unknown	Y	Y	Y	Y	died
	4	40, F	*Salmonella paratyphi* B pneumonia, maxillary sinusitis, asthma	unknown	N	Y	Y	unclear	died
	5	43, F	Lupus-like syndrome; migraines; hypothyroidism	unknown	N	Y	Y	unclear	died
Sirinavain et al.	6	1.4, M	CGD	unknown	N	Y	Y	Y	recovered
Whitehouse et al.	7	40, F	Mannose binding lectin deficiency	*B. multivorans*	N	Y	N	N	recovered
Hisano et al.	8	29, F	CGD	unknown	Y	Y	Y	Y	recovered

Satpute et al.	9	2, M	healthy	*B. cenocepacia*	Y	N	N	Y	recovered
	10	9, M	immunocompromised	*B. cenocepacia*	Y	N	N	Y	recovered
Suresh et al.	11	63, M	healthy	unknown	N	Y	N	unclear	recovered
Hauser et al.	12	64, M	HT, Type 2-DM	unknown	Y	Y	Y	Y	died
Martino et al.	13	*	malignancies	unknown	Y	Y	unknown	Y	died
	14	*	malignancies	unknown	Y	Y	unknown	Y	recovered
	15	*	malignancies	unknown	Y	N	unknown	N	recovered
	16	*	malignancies	unknown	Y	N	unknown	N	recovered
	17	*	malignancies	unknown	Y	N	unknown	N	recovered

* Prospective trial, specific age and sex of patients not available

y, year; M, male; F, female; HT, hypertension; Type-2 DM, Type-2 Diabetes Mellitus; CGD, Chronic Granulomatous Disease; N, No; Y, Yes;

FIGURE:

Figure 1: Imaging, autopsy and histology findings of 'cepacia syndrome'. (A) Chest x-ray showed diffusely ill-defined density nodules in bilateral lungs and small right pleural effusion. (B) Autopsy revealed diffuse multiple foci of necrotic abscesses (red arrow) within both lungs. (C-D) Photomicrographs of lung abscess. (C) Image shows histiocytes at the periphery and karyorrhectic debris toward the center of the abscess. [H&E, original magnification x 100] (D) Immunohistochemical staining for CD68 (Dako, Carpinteria,CA) confirming marked numbers of histiocytes at the periphery of the lung abscess. [immunohistochemistry for CD68, original magnification x 100]

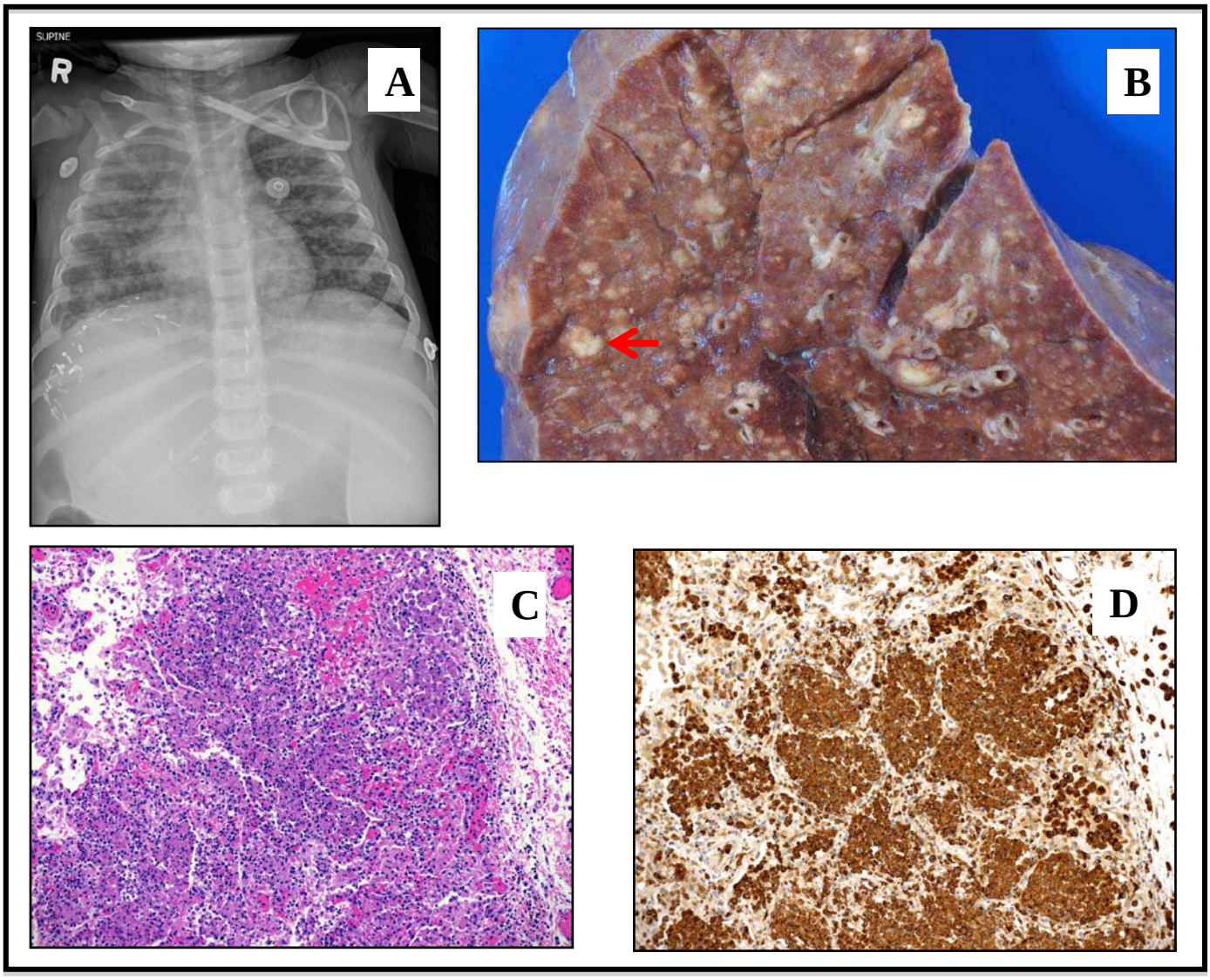
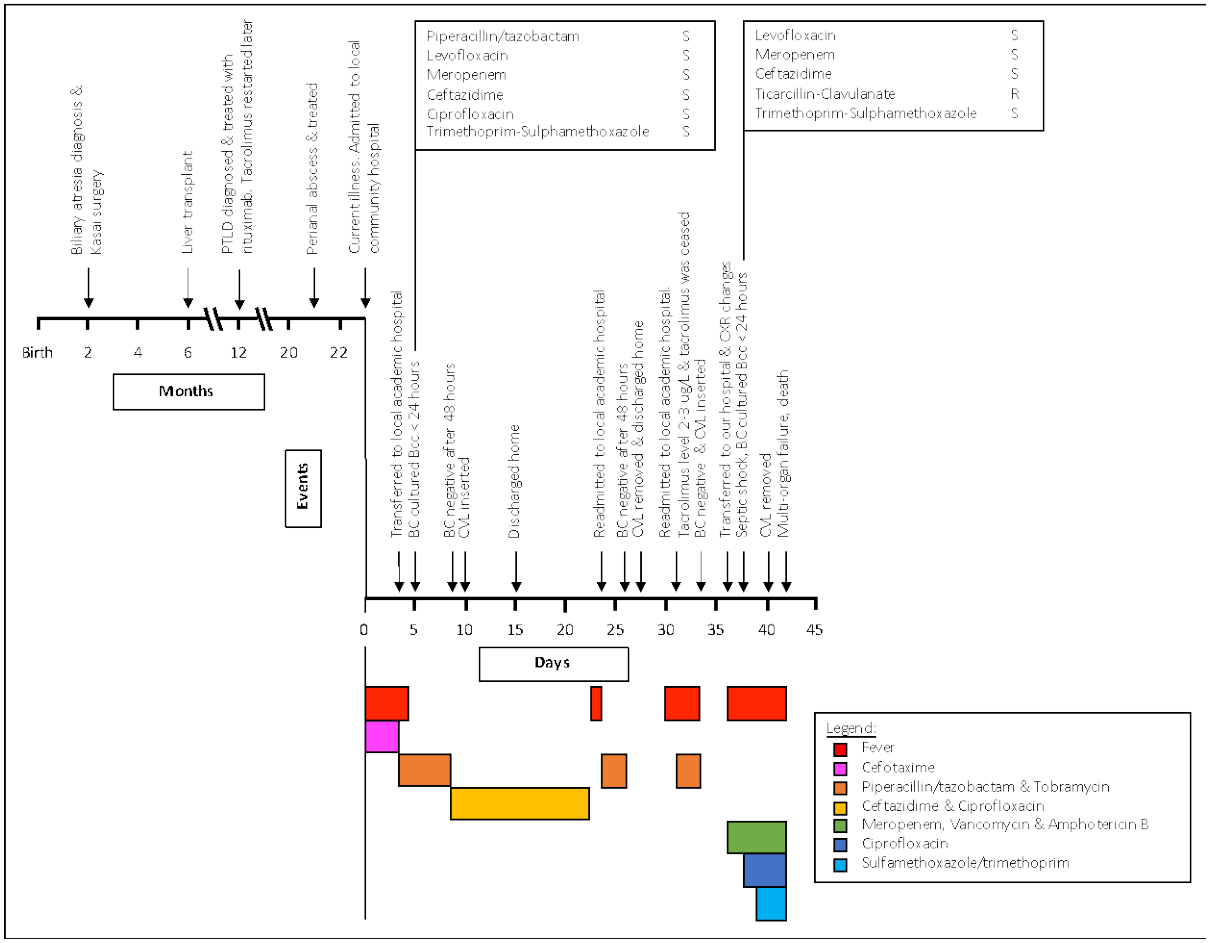


FIGURE:

Figure 2: Clinical events with key investigation findings and treatment course (including Bcc susceptibility results).



PTLD, Post-transplant Lymphoproliferative Disorder; S, Sensitive; R, Resistant; BC, Blood Culture; CVL, Central Venous Line; Bcc, *Burkholderia cepacia* complex; CXR, Chest X-ray.