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Case report

Burkholderia multivorans: A rare yet emerging cause of bacterial meningitis

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ABSTRACT

Burkholderia multivorans is a member of the *Burkholderia cepacia* complex. Although it is usually associated with infections in patients with cystic fibrosis, chronic granulomatous disease, and immunosuppression, central nervous infections are not commonly reported. Moreover, management of these infections is difficult due to multiple mechanisms of bacterial resistance to antimicrobial agents. We report a 55-year-old-man who developed *Burkholderia multivorans* meningitis after two episodes of central line-associated bloodstream infections. The patient was successfully treated with intravenous trimethoprim/sulfamethoxazole. *Burkholderia multivorans* is an emerging cause of meningitis with limited antibacterial treatment options. However, trimethoprim/sulfamethoxazole remains an effective agent with excellent penetration into the central nervous system. To our knowledge, this is the first case reported of *Burkholderia cepacia* complex meningitis identified to the species level as *Burkholderia multivorans*.

Introduction

Burkholderia multivorans (formally known as *Pseudomonas cepacia* and *Burkholderia cepacia* genomovar II) is an aerobic, glucose non-fermenting, gram-negative bacillus and member of the *Burkholderia cepacia* complex (BCC) [1]. The BCC is a group of opportunistic pathogens that can be found in soil and water [2,3]. There are 17 different and highly virulent species in the complex that are primarily associated with causing infections in patients with cystic fibrosis (CF), chronic granulomatous disease (CGD), and immunosuppression [2,4–7]. Nosocomial infections have also been reported through contaminated anesthetic solutions, water sources, medical devices, disinfectants, and non-sterile medical products [3–5,8–10]. Infections of the central nervous system have been previously described [11–13], but there are no reports, to our knowledge, specifically of *Burkholderia multivorans* meningitis.

Case

A 55-year-old-man presented with two days of fever, chills, nausea, vomiting, and abdominal pain followed by deterioration of his mental status. His medical history included hypertension, seizure disorder, and multiple myeloma (MM) which was treated with chemotherapy and homologous stem cell transplantation (HSCT) three years before admission. Ongoing maintenance chemotherapy was continued with carfilzomib, pomalidomide, and dexamethasone after undergoing HSCT. He also underwent a craniectomy during his childhood to correct an arteriovenous malformation (AVM).

Six months before this admission, he had developed pneumonia and two episodes of *Burkholderia cepacia* central line-associated bloodstream infections (CLABSI) that were treated with intravenous trimethoprim/sulfamethoxazole (TMP/SMX) and had the most recent antibacterial treatment two weeks before presentation. Moreover, he developed a catheter-associated deep venous thrombosis (DVT) of the left upper extremity that was managed with catheter removal and anticoagulation. Of note, his chemotherapy was placed on hold after he developed pneumonia.

Upon examination, he was febrile (38.5 °C), bradycardic (44 bpm), and had epigastric tenderness with palpation. He was confused with a Glasgow coma scale of 13/15 (E3, V4, M6). There was no neurological deficits or meningeal signs. The rest of his examination was not remarkable. An initial head CT showed diffuse ventricular enlargement without transependymal fluid migration, concerning for elevated intracranial pressure. This suspicion, however, was dismissed after neurosurgery evaluation. A lumbar puncture was performed after anti-Xa levels were reported as undetectable. Cerebrospinal fluid (CSF) was colorless and slightly hazy, RBC 30/mm^3, WBC 910/mm^3 with 94% neutrophils, glucose 10 mg/dL, and proteins 162 mg/dL (Table 1). He

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Table 1
Cerebrospinal fluid analysis.

	Reference Range	Day 1	Day 4	Day 7	Day 10	Day 16
Appearance Spun		Colorless	Colorless	Xanthochromia	Slight Xanthochromia	Colorless
Appearance		Slightly hazy	Slightly hazy	Cloudy	Blood Tinged	Clear
RBC	< 5 cells/μL	30	530	14400	1600	10
WBC	< 5 cells/μL	910	260	384	5	95
Neutrophils	%	94	88	69	26	14
Lymphocytes	%	6	7	15	66	78
Monocytes	%	None Seen	5	16	8	8
Glucose	40–75 mg/dL	10	24	38	36	49
Proteins	15–45 mg/dL	162	102	196	121	175

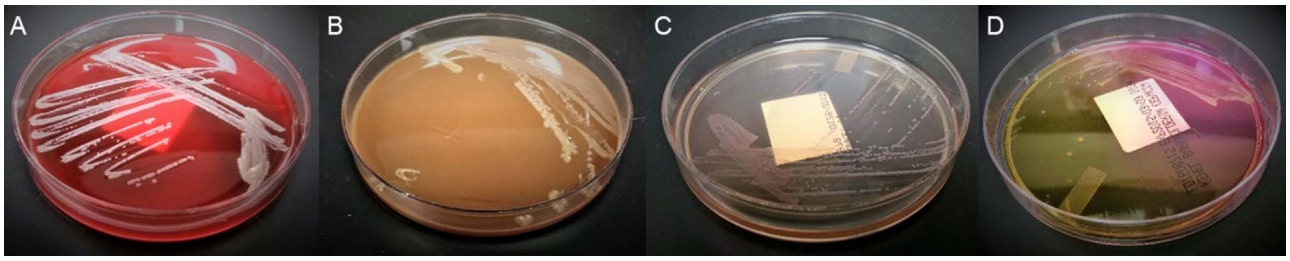

Fig. 1. *Burkholderia multivorans* colonies in Blood (A), Chocolate (B), MacConkey (C), and Burkholderia Cepacia Selective (D) agars.

Table 2
Burkholderia multivorans susceptibility profile.

Antibiotic	CSF				Blood			
	Etest®		VITEK® 2		Etest®		VITEK® 2	
	MIC (μg/mL)	Interpretation	MIC (μg/mL)	Interpretation	MIC (μg/mL)	Interpretation	MIC (μg/mL)	Interpretation
Amikacin	256	R	> 64	R	256	R	> 64	R
Cefepime	256	R	> 64	R	256	R	> 64	R
Ceftazidime	256	R	> 64	R	256	R	> 64	R
Ciprofloxacin	32	R	> 4	R	32	R	> 4	R
Colistin	256	R			256	R		
Gentamicin	256	R	> 16	R	256	R	> 16	R
Levofloxacin	32	R	> 8	R	32	R	> 8	R
Meropenem	32	R	> 16	R	32	R	> 16	R
Minocycline	8	I			8	I		
Piperacillin	256	R	> 128	R	256	R	> 128	R
Piperacillin/Tazobactam	256	R	> 128/4	R	256	R	> 128/4	R
Trimethoprim/Sulfamethoxazole	0.75	S	1/16	S	0.75	S	1/16	S

received empiric intravenous vancomycin, ampicillin, cefepime and TMP/SMX since CSF features were compatible with bacterial meningitis. Within the next 48 h, a gram-negative rod, later identified as *Burkholderia multivorans*, grew in both CSF and blood cultures (Fig. 1). The VITEK® MS, VITEK® 2, and Etest® (bioMérieux, Marcy-l'Étoile, France) were used for microbial identification and antibacterial susceptibility, respectively (Table 2). The bacterial identification and susceptibility were confirmed at the state reference laboratory.

The patient's therapy was streamlined to TMP/SMX alone as it was the only agent exhibiting antibacterial activity with a minimal inhibitory concentration of 0.75 mμ/ml by Etest® and 1/16 mμ/ml by VITEK® 2. A transesophageal echocardiogram performed did not show evidence of endocarditis. Repeated CSF and blood cultures proved clearance of *Burkholderia multivorans*, demonstrating the effectiveness of TMP/SMX treatment. He completed a total of 21 days of intravenous TMP/SMX therapy after obtaining negative CSF cultures.

Discussion

This case illustrates *Burkholderia multivorans* as a rare but emerging cause of bacterial meningitis and the complexity of its management due to the bacterium's multiple mechanisms of antimicrobial resistance. With this in mind, our case provides a unique account because *Burkholderia multivorans* has never been reported as a specific cause of bacterial meningitis. Although reports of BCC meningitis exist [11–13], isolates were never identified to the species level as seen with our patient. The identification of the BCC species is usually difficult due to the phenotypic and genotypic similarities among them and other *Burkholderia* species outside of the BCC [3]. In our patient, *Burkholderia multivorans* was initially identified using the VITEK® MS system in our facility and confirmed at the state reference laboratory.

Multiple risk factors including MM-associated immunosuppression, maintenance chemotherapy, extensive healthcare exposure, and prolonged use of a central venous catheter ultimately led to our patient's likely acquisition of this *Burkholderia multivorans* infection. Patients with MM have abnormalities in both cellular and humoral immunity that increase the risk of infection. Those defects include hypogammaglobulinemia, low number and anomalous function of dendritic and T cells, abnormal Th1/Th2 $CD4^+$ ratio, disruption of T cell diversity, and dysfunction of natural killer cells [14,15]. MM treatment also increases the risk for infections, cytopenias, and thrombotic events [16–19]. These complications are underscored in this case by the

patient developing pneumonia, DVT, CLABSI, and meningitis after receiving maintenance chemotherapy with carfilzomib, pomalidomide, and dexamethasone. The patient spent several weeks in different healthcare facilities, increasing the exposure risk to nosocomial pathogens. The prolonged use of a central venous catheter was likely the port of entry for *Burkholderia multivorans* and consequently led to the patient's CLABSI and meningitis.

BCC management is challenging due to its ability to evade the action of multiple antimicrobials through intrinsic and acquired resistance mechanisms [2,5]. Those mechanisms include the production of β-lactamases, carbapenemases, and antibacterial drug efflux pumps as well as the ability to decrease the number of membrane porins, modify bacterial lipopolysaccharide structure, and mutate antimicrobial binding targets [2]. Although these resistance mechanisms have limited our antimicrobial armamentarium against BCC infections, certain isolates can show susceptibility to beta-lactams including ceftazidime, meropenem, and piperacillin. These medications are considered alternatives to TMP/SMX, the primary regimen for therapy and prophylaxis of BCC infections. Moreover, beta-lactams can be used as a treatment option when patients have an intolerance, allergy, or resistance to TMP/SMX [5].

In this case, only TMP/SMX showed activity against the isolate which confirms the resilience of *Burkholderia multivorans* to therapy and supports TMP/SMX as an effective option to treat *Burkholderia multivorans* infections including meningitis [11,20]. Due to its lipophilic properties, TMP/SMX efficiently penetrates into the CSF in both the absence and the presence of meningeal inflammation [21].

Conclusion

Burkholderia multivorans is a rare yet emerging cause of meningitis as demonstrated in our case. Although *Burkholderia multivorans* is commonly isolated in patients with CF and CGD, nosocomial infections are increasing in number. Its complex antimicrobial susceptibility profile in conjunction with its ability to evade multiple antimicrobials makes its management quite complicated. TMP/SMX remains useful in the management of meningitis since it provides excellent penetration into the CSF and retains activity against *Burkholderia multivorans*.

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