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Case Report

A New Potential Threat for Nosocomial Infections: *Cupriavidus metallidurans* as a Cause of Bacteremia in Children

Nozokomiyal Enfeksiyonlarda Yeni Bir Olası Tehdit: Çocuklarda Bakteriyemi Sebebi Olarak Cupriavidus metallidurans

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ABSTRACT

Hospital infections associated with uncommon pathogens usually originated from environmental sources and are challenging for microbiologists and clinicians because of the difficulties in the differentiation of colonization vs infection. Increasing reports of bacteremia caused by environmental pathogens point out their importance in hospital infections. The increasing number of case reports of bacteremia due to *Cupriavidus* spp., impose to consider these unusual microorganisms which are aerobic Gram-negative rods that live in soil and water. In this report, we present two cases of bacteremia in which *Cupriavidus metallidurans* were isolated from blood cultures and discuss the roles of the isolates in hospital infection.

Keywords: *Cupriavidus metallidurans*, bacteremia, opportunistic premise plumbing pathogens, hospital infection

ÖZ

Enfeksiyon etkeni olarak sık rastlanmayan ancak klinik örneklerde çevresel kökenli mikroorganizmaların soyutlandığı hastane enfeksiyonlarında, saptanan mikroorganizmanın kolonizasyon mu yoksa enfeksiyon etkeni mi olduğu konusundaki ayrımın güçlüğü hem mikrobiyologlar hem de klinisyenler yönünden başa çıkılması zor bir durum yaratır. Bakteriyemi olgularında çevresel kökenli mikroorganizmalara ilişkin artan bildirimler bu etkenlerin hastane enfeksiyonlarındaki önemini ortaya koymaktadır. Giderek daha çok sayıda Bakteriyemi olgusunda *Cupriavidus* türlerinin soyutlanması, su ve toprakta bulunan bu Gram-negatif çomakların hastane enfeksiyonları yönünden dikkate alınması gerektiğini düşündürmektedir. Bu çalışmada iki olguda kan kültürlerinden soyutlanan *Cupriavidus metallidurans* kökenlerinin özellikleri ve hastane enfeksiyonundaki rolleri ele alınmaktadır.

Anahtar kelimeler: *Cupriavidus metallidurans*, bakteremi, yapı tesisat sistemi fırsatçı patojenleri, hastane enfeksiyonu

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INTRODUCTION

Hospital-acquired infections can be related to several factors associated with health care services in which the water system can be an important one of them. Increasing reports of outbreaks associated with hospital water environments impose to consider the unusual microorganisms isolated from the patients and the hospital environment[1]. *Cupriavidus* bacteria that are aerobic Gram-negative rods that live in soil and water. Even though invasive infections are uncommon in healthy people, case reports suggest that they could be significant in immunocompromised patients. Various cases of significant infections caused by different species of the genera have been recorded in the literature to date[2-6]. Besides reporting cases with *Cupriavidus metallidurans* isolated from blood culture samples

in two children, it was also intended to emphasize the importance of the assessment of the environmental bacterial isolates from blood in determining whether the isolate is a contaminant or a real pathogen.

CASE REPORTS

Case 1

The first case was a 3-year-old girl with graft-versus-host disease following her second allogeneic hematopoietic stem cell transplantation for acute lymphoblastic leukemia. She was transferred to the pediatric intensive care unit (PICU) because of septic shock symptoms and intubated due to increasing work of breathing and increased requirement for inotropes. On the third day of the PICU hospitalization, due to persistent hyperlactatemia, compromised renal functions, and decreased urine output, continuous venovenous hemodiafiltration was started. Due to refractory septic shock and respiratory insufficiency, the patient developed acute respiratory distress syndrome and died on the fifth day of his PICU stay. While no growth was found in the urine sample, *C. metallidurans* was isolated in blood culture. While the isolate grew initially under antimicrobial therapy with various antibiotics such as meropenem, amikacin, and voriconazole, no growth was identified in both blood cultures acquired from the venous catheter and recurrent peripheral blood cultures after the catheter was replaced.

Case 2

The second case was a previously healthy 11-year-old boy who had been diagnosed with coronavirus disease-2019 pneumonia. He was admitted to the hospital and given favipiravir and ceftriaxone therapy. *C. metallidurans* was isolated from a blood culture obtained after hospital admission. Because the patient was asymptomatic and the ceftriaxone treatment has not resulted in a recurrence of fever, the medication was not changed and the patient was continued in the same manner. On the fourth day of treatment, there was no growth in repetitive blood culture. On the seventh day of stay, the patient was discharged with full recovery, and isolation of the bacteria was recognized as contamination.

The blood samples were inoculated into the aerobic blood culture bottles and incubated by using an automated blood culture system (BD BACTEC FX, Becton Dickinson Company, USA) Gram-negative rods from the small, greyish colonies that grew on subcultures were identified as *Cupriavidus pauculus* with VITEK-2 compact system (bioMerieux, France) Consequently, both strains were identified as *Cupriavidus metallidurans* by matrix-assisted laser desorption ionization-time of flight mass spectrometry (MALDI-TOF MS) (Bruker Daltonics GmbH, Leipzig, Germany).

Antimicrobial sensitivity testing was initially performed using the VITEK®2 Compact automated ID/AST System (bioMerieux, France), and interpreted using the EUCAST *Pseudomona*s breakpoints. In addition, broth microdilution assays were used to determine the minimal inhibitory concentrations (MICs) of the isolates using Sensititre™ Gram-negative DKMGN Plates (Thermo Fisher Scientific, Cleveland, USA) according to the manufacturer's instructions. Clinical and Laboratory Standards Institute 2021 breakpoints for additional non-enterobacterales[7] were used to interpret the antibiotics' MICs (Table 1).

DISCUSSION

Because of its resistance to heavy metals, ability to mediate the extracellular manufacture of antimicrobial nanoparticles, and vast genetic diversity derived from a large, mobile gene pool and megaplasmids, *C. metallidurans* has sparked attention in various sectors of microbiology. Endogenous megaplasmids are thought to have resistance qualities that help them survive even in harsh environments like space[8,9].

Langevin et al.[6] reported the first report of human infection caused by *C. metallidurans* that resulted in nosocomial septicemia in 2011. In 2015, four examples of the species were recorded in Italy, following the initial report[10]. All published cases of *C. metallidurans* infections had bloodstream infections and were most likely nosocomial in origin, just as in the first case.

In both cases, the bacterial growth was determined in the initial blood cultures. However, in the first case, the patient's clinical picture supported an infection, while in the second case, the clinical picture strongly suggested the contamination. Growth in a blood culture bottle does not always indicate the presence of a real pathogen, and distinguishing a contaminant from a bacteremia-causing agent might be difficult[11]. The earlier case reports' superiority is the isolation of germs from several blood culture bottles, which is improbable in our pediatric cases since blood culture sets including a single bottle were employed.

Although the initial growths were questioned due to the lack of growth in repetitive blood cultures or concomitant cultures from other body sites, the unusual

Table 1. Antimicrobial susceptibility testing of *Cupriavidus metallidurans* isolates

	***C. metallidurans* Strain 1**				***C. metallidurans* Strain 2**			
	VITEK®2		**Sensititre™**		**VITEK®2**		**Sensititre™**	
Antibiotics	**MIC_{50}**	**AST Result**	**MIC_{50}**	**AST Result**	**MIC_{50}**	**AST Result**	**MIC_{50}**	**AST Result**
Amikacin	≥64	R	≥32	R	≥64	R	≥32	R
Amoxicillin/clavulonic acid	N/A	-	4/2	N/A	N/A	-	4/2	N/A
Aztreonam	16	I	>32	R	16	I	>32	R
Cefotaxime	N/A	-	2	S	N/A		2	S
Cefepime	2	I	N/A	-	1	I	N/A	-
Ceftazidime	8	I	16	I	8	I	16	I
Ceftazidime/avibactam	N/A	-	8/4	N/A	N/A	-	8/4	-
Ceftolozane/tazobactam	N/A	-	16/4	N/A	N/A	-	16/4	-
Ciprofloksasin	0,25	I	0,5	S	0,25	I	0,25	S
Colistin	≥16	R	>8	N/A	≥16	R	>8	N/A
Ertapenem	N/A	-	2	N/A	N/A	-	2	N/A
Gentamicin	≥16	R	>8	R	≥16	R	>8	R
Imipenem	≤0,25	I	1	S	≤0,25	I	0.5	S
Levofloksasin	0,5	S	N/A	-	0,5	I	N/A	-
Meropenem	1	S	0.5	S	0,5	S	1	S
Netilmicin	≤32	R	N/A	-	≥32	R	N/A	-
Piperacillin/tazobactam	≤4	I	2/4	S	≤4	I	2/4	S
Tigecyline	N/A	-	1	N/A	-	N/A	0,5	N/A
Tobramycine	≥16	R	>8	R	≥16	R	>8	R
Trimethoprim/sulphamethoxazole	N/A	-	2/38	S	N/A	N/A	2/38	S

MIC: Minimal inhibitory concentration, AST: Antimicrobial susceptibility testing, R: Resistance, S: Sensitive, I: Intermediate, N/A: Not applicable

growth of *Cupriavidus* species from blood cultures in our facility and isolation from the blood cultures of first patient with hospitalization history led us to believe these strains could be responsible for bacteremia. During the febrile episode, blood cultures were collected in both patients, and the first case had possible risk factors such as a central venous catheter and hospitalization in PICU. Because of the absence of risk factors for nosocomial infection such as prolonged hospital stay or invasive medical procedures and having no growth in repetitive blood cultures, the strain isolated from the second case was evaluated as a contaminant.

As it was stated that environmental microorganisms can be associated with hospital infections[12], the isolation of the rare environmental bacteria in the same period from two children's blood samples promoted us to consider that the isolates might be potential nosocomial agents colonized or contaminated from environmental sources. However, the isolation of *C. metallidurans* was limited in two cases and the second case had no evidence of nosocomial infection.

Environmental pathogens associated with water in healthcare settings which are also called as opportunistic premise plumbing pathogens (OPPPs) inhabit and grow in water systems. Nosocomial transmission of these pathogens may become with direct contact or indirectly by use of contaminated water for personal or medical purposes. Besides being highly tolerant to chlorine and chloramine, *C. metallidurans* can also maintain and spread antibiotic resistance in potable water systems. Contamination of water systems might be originated either from retrograde seeding of water from contaminated outlets or low-level seeding of the microorganisms from the incoming supplying system[4,13,14].

Despite routine water supply monitoring as part of hospital infection control surveillance, no pathogen was found in water analysis performed at the public health laboratory. This could be due to the lack of the OPPPs' intended analysis. Routine water analysis is most likely to detect only a few pathogens, and no specific analysis for OPPPs has been performed. *Cupriavidus* spp., isolation

from clinical specimens should trigger a warning, and particular testing for uncommon waterborne infections should be performed[15].

Following these occurrences, no other indication of hospital infection linked to the *Cupriavidus* genus was found in our facility. Unfortunately, sequencing for phylogenetic analysis was not possible, but MALDI-TOF MS analysis, which has been shown to be superior in terms of diagnostic accuracy and reproducibility, was used to rule out phenotypic tests misidentification[16].

The discovery of a matching database in MALDI-TOF MS and an identical antimicrobial susceptibility profile led to the hypothesis that the two strains originated from the same source, raising awareness of nosocomial infections caused by OPPPs such as *Cupriavidus* spp. However, while evaluating isolations due to rare microorganisms such as *C. metallidurans,* not only the isolated organism, but also the other factors such as the patients findings, co-morbidities and risk factors should be taken to account to differentiate the colonization and infection.

Furthermore, OPPPs should be considered as potential threats for nosocomial infections, and surveillance of these pathogens in hospital water systems must be implemented in the hospital infection control procedures.

Ethics

Informed Consent: Informed consent is not required.

Author Contributions

Surgical and Medical Practices: U.K., M.G., Ö.A.Ö., A.A.K., G.G.Ö., Concept: F.Y.A, Design: F.Y.A, H.A., Data Collection or Processing: F.Y.A, U.K., A.A.K., Analysis or Interpretation: F.Y.A, H.A., Literature Search: F.Y.A, U.K., Writing: F.Y.A, H.A.

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