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Case report

First case report of infection caused by *Cupriavidus gilardii* in a non-immunocompromised Chinese patient

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ABSTRACT

Cupriavidus gilardii was first identified as an aerobic, gram-negative, glucose-nonfermenting rod. *C. gilardii* has been characterized as an organism with low pathogenicity that causes opportunistic infections and few case reports of infection caused by this organism previously. We encountered the first case of bloodstream infection caused in China by *C. gilardii* in a 87-year old man without obvious immunodeficiency. The isolate were identified as *C. gilardii* by 16S rRNA sequencing. The infected patient was treated according to the laboratory's antibiogram of this strain. Similar to the case report in Japan, this is the second report of an infection caused by this organism without obvious immunodeficiency, suggesting that *C. gilardii* exerts its pathogenicity both in immunodeficient and immunocompetent hosts.

Introduction

The genus *Cupriavidus* are Gram-negative β-proteobacteria that have been found from environmental and human clinical sources [1]. The genus *Cupriavidus* currently is comprised of 11 species derived from diverse ecological niches, especially in soils contaminated with heavy metals [2]. Therefore, several bacteria including *Cupriavidus metallidurans* CH34 (*C. metallidurans* CH34) [3], *Cupriavidus necator* N-1 (*C. necator* N-1) [4], *Cupriavidus pinatubonensis* JMP134(*C. pinatubonensis* JMP134) [5], *Cupriavidus taiwanensis(C. taiwanensis)* [6], and *Cupriavidus gilardii* CR3 (*C. gilardii* CR3) [7] are heavy metal tolerant. *Cupriavidus gilardii* (*C. gilardii*), named after a prominent American microbiologist, G. L. Gilardii, is an aerobic, Gram-negative, peritrichously flagellated (motile), glucose-nonfermenting bacillus. The taxonomic history for this species continues to be rather complex, and consequently the species has been known by various names, including *Ralstonia gilardii*, *Wautersia gilardii*, and *C. gilardii* [8–10]. This species was first identified in 1999 by Coenye et al. [8]. While similar to *Alcaligenes faecalis*, it was found to be distinct enough to be separated into its own diagnostic entity, *Ralstonia gilardii* [8]. Later, in 2001, De Baere et al. [11] revealed that the *Ralstonia* genus could be divided into two distinct groups based on phenotype and genotype. That same year, however, the entire genus was entirely reclassified to the genus *Cupriavidus* due to the fact that *Wautersia eutropha* was genetically identical to a previously identified organism, *Cupriavidus necator* [10]. Consequently, *Wautersia gilardii* was given its current name, *C. gilardii*.

Case presentation

A 87-year old man who had several chronic diseases, including chronic obstructive pulmonary disease and hypertension implanted 10 years previously. He was admitted to a community hospital and hypertension with progressive decline on alertness over two years. He did not have an obvious immunodeficiency. After the patient was transferred to our hospital, blood routine examination and analyzing the infectious index were performed on hospital day (HD) 2. Laboratory evaluation at the time of admission was significant for a total white blood cell count of 3520/uL with a differential of 64.2% neutrophils, procalcitonin (PCT) and C-reactive protein (CRP) was 0.05 ng/ml and 10.76 mg/L that were within normal limits. During hospitalization period, the patient developed, chills, palpitation, short of breath and breathing difficulties through HD4. Blood parameters revealed the following values: white blood cells 10560/uL (neutrophils 73.3%), PCT 2.72 ng/ml and CRP 26.30 mg/L, the high PCT and CRP level which suggested a significant infection. Emergency blood surveillance culture was positive and identified as *Cupriavidus pauculus* via VITEK Compact 2 and VITEK MS. But the 16S rDNA sequence analysis of a fragment of 1344 bp obtained by a PCR method showed a homology of 100% with

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Table 1
Antimicrobial agent susceptibilities of *C. gilardii.*

Antimicrobial agents	Specification	Result	Breakpoints (mm)	Interpretation
MEM	10 μg	6 mm	S: ≥19; I: 16–18; R: ≤15	R
AK	30 μg	6 mm	S: ≥17; I: 15–16; R: ≤14	R
CRO	30 μg	34 mm	–	–
FEP	30 μg	42 mm	S: ≥18; I: 15–17; R: ≤14	S
OFX	5 μg	32 mm	S: ≥16; I:13–15; R: ≤12	S
TZP	30 μg	36 mm	S: ≥21; I: 15–20; R: ≤14	S
SCF	150 μg	52 mm	–	–
RD	5 μg	6 mm	–	R
AMP	10 μg	6 mm	–	R
LEV	5 μg	33 mm	S: ≥17; I: 14–16; R: ≤13	S
CIP	5 μg	34 mm	S: ≥21; I: 16–20; R: ≤15	S
ATM	30 μg	23 mm	S: ≥22; I: 16–21; R: ≤15	S
CTX	30 μg	42 mm	–	–
SAM	20 μg	43 mm	–	–
IPM	10 μg	22 mm	S: ≥19; I: 16–18; R: ≤15	S
PRL	100 μg	21 mm	S: ≥21; I: 15–20; R: ≤14	S
CAZ	30 ug	26 mm	S: ≥18; I: 15–17; R: ≤14	S
SXT	25 μg	22 mm	–	–

MEM Meropenem, AK Amikacin, CRO Ceftriaxone, FEP Cefepime, OFX Ofloxacin, TZP Piperacillin/Tazobactam, SCF Cefoperazone/sulbactam, RD Rifampicin, AMP Ampicillin, LEV Levofloxacin, CIP Ciprofloxacin, ATM Aztreonam, CTX Cefotaxime, SAM Ampicillin/Sulbactam, IPM Imipenem, PRL Piperacillin, CAZ Ceftazidime, SXT Trimethoprim/sulfamethoxazole.

C.gilardii strain AU6442 from the GenBank (accession number AY860231) via NCBI BLAST (https://blast.ncbi.nlm.nih.gov/Blast.cgi). Antimicrobial susceptibility testing was performed according to the Clinical and Laboratory Standards Institute (CLSI) standards, performance standards for antimicrobial susceptibility testing, 27th informational supplement. M100-S27. The susceptibility to the antimicrobial agents were determined by disk diffusion using Mueller-Hinton agar (MHA) in ambient air, incubation 16–18 h in 35 °C ± 2 °C and measured the diameter of the zones of completed inhibition, including the diameter of the disk. The breakpoints (susceptible, intermediate, or resistant) was determined according to *Pseudomonas aeruginosa* M100-S27 provided by CLSI. The susceptibility of the bacterium to various antimicrobial agents is shown in Table 1. The strain was resistant to meropenem, amikacin, rifampin and ampicillin, while susceptible to cefepime, ofloxacin, piperacillin/tazobactam, levofloxacin, ciprofloxacin, aztreonam, imipenem, piperacillin, ceftazidime. From the zone diameter, *C. gilardii* also highly possible susceptible to cefoperazone/sulbactam , ceftriaxone , cefotaxime, ampicillin/sulbactam, trimethoprim/sulfamethoxazole. According to the antibiogram of this strain, the antimicrobial agent piperacillin/tazobactam was added, the patient's body temperature decreased gradually and the patient improved. Meanwhile, infection correlation indexes became normal limits, white blood cells 5340/uL (neutrophils 64.2%), PCT 0.06 ng/ml and CRP 4.15 mg/L.

Discussion

Cupriavidus gilardii (*C. gilardii*) is a Gram-negative, aerobic and glucose-nonfermenting bacillus that was first identified by Coenye et al. in 1999 [8]. The taxonomic history for this species is complex. The organism has been known by various names, including *Ralstonia gilardii*, *Wautersia gilardii*, and *C. gilardii* [10,15]. *C. gilardii* has been characterized as an organism with low pathogenicity that causes opportunistic infections as three cases of infection caused by this organism were immunodeficient. One additional case caused by *C. gilardii* was described by Wauters et al. in 2001. The organism was the cause of catheter-related sepsis in a 7-year-old girl with acute lymphoblastic leukemia [15]. A bloodstream isolate from the patient was identified as *Ralstonia gilardii*, which was found to be susceptible to ceftazidime, cefuroxime, ceftriaxone, ofloxacin, imipenem, cotrimoxazole. After combination with antimicrobials, her sepsis resolved completely [15]. A fatal case caused by *C. gilardii* was described by Karafin et al. in 2010 [12]. *C. gilardii* was recovered from the throat, stool, and blood of a 12-year old female with severe idiopathic aplastic anemia. It seems that the patient's underlying immunosuppression and the organism developed new antimicrobial resistances gave rise to fatal outcome. In addition, Tena et al. reported an infection caused by *C. gilardii* in 2014 [14]. The patient with a muscular abscess on the right thigh caused by *C. gilardii* in an immunocompromised patient, who had suffered a septic shock associated with an extensive cellulitis caused by *Streptococcus pyogenes*. The patient was successfully treated with intravenous Ciprofloxacin and surgical drainage. Therefore, *C. gilardii* should be considered as a cause of human infection, especially in immunocompromised patients. Recently, one case of pacemaker-associated bloodstream infection caused by *C. gilardii* in a 90-year old woman without obvious immunodeficiency [13]. The patient was treated with different antimicrobial agents at different points in time based in part on the blood culture results and in part on the patient's response to therapy. Because of the acquisition of antimicrobial resistance during treatment, the antimicrobial agent was changed during the course of treatment. Meanwhile, the patient of our case was elderly (87 years old) that is similar to a case of pacemaker-associated bloodstream infection caused by *C. gilardii* in a 90-year old woman without obvious immunodeficiency [13]. The bacterial strain was verified as *C. gilardii* strain AU6442 according to sequencing analysis of the 16S rRNA gene using DNA extracted from the isolates. The patient was succesfully treated with piperacillin/tazobactam after the known antibiogram of this strain. Although he had no obvious immunodeficiency, his elderly age might have affected the expression of pathogenicity of *C. gilardii*.

Conclusion

The pathogenicity of *C. gilardii* is unknown, the frequency with which it has caused human disease and rare colonizer of human tissues has been masked by the difficulty in accurate species identification, genetics and phenotypic behavior. *C. gilardii* previously reported have been found have intrinsic antimicrobial resistance and the ability to acquire resistance to other antimicrobial agents were observed in different isolates from the present patient as well as previous reports. Our case report represents the fifth identified infection caused by *C. gilardii*. This is the second report of an infection of *C. gilardii* in an older patient without obvious immunodeficiency. Our isolate, *C. gilardii* was multidrug resistant, including meropenem, amikacin, rifampicin and ampicillin and susceptible to cefepime, ofloxacin, piperacillin/tazobactam, levofloxacin, ciprofloxacin, aztreonam, imipenem, piperacillin, ceftazidime. This patient was successfully treated with Piperacillin/

tazobactam when the antibiogram was available. Although the true pathogenicity of *C. gilardii* is unclear, the present case and another case report of infection in a 90-year old female patient represent the identified infection caused by *C. gilardii* in patients without immunodeficiency. The possibility that this organism may represent an emerging pathogen in both patients with or without immunodeficiency and its ability to acquire new resistances as it colonizes its human host. Understanding the nature and pathogenicity of *C. gilardii*, a large number of further cases caused by this organism is urgent needed.

Conflict of interest

The authors declare no conflicts of interests.

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