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Carbapenem-resistant *Klebsiella pneumoniae* in a Febrile Neutropenia Patient With Acute Myelogenous Leukemia After Hematopoietic Stem Cell Transplantation

To the Editor:

Carbapenem-resistant *Klebsiella pneumoniae* (CRKP) in patients with a hematological malignancy has received increasing focus as a therapeutic issue, because such infections are frequently severe and markedly increase the morbidity and mortality rates.[1] Particularly in neutropenic patients after transplantation, *K. pneumoniae* is a common bacterial pathogen, and recently, carbapenemase-producing isolates of *Klebsiella* species, including *K. pneumoniae*, have been reported to cause life-threatening infections that are resistant to carbapenems.[1] We experienced CRKP sepsis in a patient with acute myeloid leukemia (AML) after CRKP and carbapenem-susceptible *K. pneumoniae* (CSKP) were detected in stool.

CASE DESCRIPTION

A 55-year-old man with AML presented with AML-related changes and febrile neutropenia (neutrophils <0.003/μL) at 5 days after hematopoietic stem cell transplantation (SCT). Both CRKP and CSKP were detected in the stool 5 days after SCT (Table 1). Sepsis by CRKP was obtained from the 2 sets of blood cultures 15 days after SCT. Although the patient was treated with tigecycline, he ultimately died 36 days after SCT.

The CRKP specimens were resistant to all of the tested antimicrobials except for tigecylcine and colistin. Carbapenem-susceptible *K. pneumoniae* was resistant to ampicillin, piperacillin, cefcapene, ampicillin/sulbactam, gentamicin, amikacin, minocycline, levofloxacin, ciprofloxacin, sulfamethoxazole-trimethoprim, and fosfomycin. Both CRKP and CSKP were negative for carbapenemases such as *K. pneumoniae* carbapenemase and metallo-β-lactamase and positive for $bla_{\text{SHV-28}}$ and plasmid (HI1B and R). They were found to belong to sequence type (ST) 15 on multilocus sequence typing and exhibited *IntI1*, *aacA*4, *oqxA*, *aac(6')Ib-cr*, and *armA* genes, insertion/deletion causing stop codon in *ompK35* and *ompK36* and mutations in *gyrA* (Y83F and D87A) and *parC* (S80I), as analyzed by a next-generation sequencer (Illumina, Inc, San Diego, CA). Only CRKP was found to be carrying $bla_{\text{DHA-1}}$ and plasmid FIA(HI1).

The isolated CRKP and CSKP specimens were resistant to fluoroquinolone and aminoglycoside, which was found to be due to the following molecular mechanisms: *gyrA* and *parC* mutations, *oqxA, aac(6')Ib-cr*, *aacA4*, *armA,* and *aac(6')Ib-cr*.[2,3] The plasmid-mediated AmpC, such as $bla_{\text{DHA-1}}$ with defects in outer-membrane porins (OmpK35 and OmpK36), plays an important role in carbapenem resistance.[4]

DISCUSSION

The isolates of both CRKP and CSKP shared ST15 and susceptibility to antimicrobial agents with responsible genetic alterations, except for the former carrying $bla_{\text{DHA-1}}$. These findings suggested that CRKP isolated from the blood likely derived from the *K. pneumoniae* strain with ST15 in the stool flora. *K. pneumoniae* with ST15 is known to carry a high risk of acquired antimicrobial resistance. A resistant subclone that acquired carbapenem resistance through the possession of $bla_{\text{DHA-1}}$ might have translocated into the blood and caused septicemia. Preconditioning with a course of systemic administration of piperacillin/tazobactam before SCT in the current case might have increased the selection of the resistant subclone. The emergence of carbapenem-resistant gram-negative bacteria drastically narrowed the number of therapeutic options against them. These bacteria are mostly susceptible to tigecylcine and colistin. However, despite the administration of tigecylcine in the current case, the treatment was not successful, implying the importance of prevention of infection due to such resistant bacteria.

TABLE 1. Antimicrobial Susceptibility of Clinical Isolates of *K. pneumoniae* From Stool and Blood

	MIC, μg/mL*	
Antimicrobials	**CRKP**	**CSKP**
Ampicillin	>16 (R)	>16 (R)
Piperacillin	>64 (R)	>64 (R)
Cefazolin	>16 (R)	≦4 (S)
Cefotiam	>16 (R)	≦8 (S)
Cefotaxime	>2 (R)	≦1 (S)
Ceftazidime	>8 (R)	≦4 (S)
Cefepime	16 (R)	≦2 (S)
Ceftriaxone	>2 (R)	≦1 (S)
Cefaclor	>16 (R)	≦8 (S)
Cefcapene	>1 (R)	>1 (R)
Cefmetazole	>32 (R)	≦8 (S)
Flomoxef	>32 (R)	≦8 (S)
Ampicillin/Sulbactam	>16/8 (R)	16/8 (I)
Piperacillin/Tazobactam	>64 (R)	≦16 (S)
Cefoperazone/Sulbactam	>32/16 (R)	≦16/8 (S)
Aztreonam	>8 (R)	≦4 (S)
Doripenem	4 (R)	≦1 (S)
Imipenem	>8 (R)	≦1 (S)
Meropenem	>8 (R)	≦1 (S)
Gentamicin	>8 (R)	>8 (R)
Amikacin	>32 (R)	>32 (R)
Minocycline	>8 (R)	>8 (R)
Levofloxacin	>4 (R)	>4 (R)
Ciprofloxacin	>2 (R)	>2 (R)
Sulfamethoxazole-Trimethoprim	>2/38 (R)	>2/38 (R)
Fosfomycin	>16 (R)	>16 (R)
Tigecycline	0.25 (S)	0.25 (S)
Colistin	1 (S)	1 (S)

*MICs were determined by a microdilution broth method based on the Clinical and Laboratory Standards Institute (2010) guideline using MicroScan WalkAway (Beckman Coulter, Inc, Brea, CA) for ampicillin, piperacillin, cefazolin, cefotiam, cefotaxime, ceftazidime, cefcapene, ceftriaxone, cefaclor, cefmetazole, flomoxef, ampicillin/sulbactam, piperacillin/tazobactam, cefoperazone, aztreonam, doripenem, imipenem, meropenem, gentamicin), amikacin, minocycline, levofloxacin, ciprofloxacin, sulfamethoxazole-trimethoprim, and fosfomycin, and using E-test (SYSMEX bioMérieux Co, Ltd, Tokyo, Japan) for tigecycline and colistin.

MIC indicates minimum inhibitory concentration; R, resistant; S, susceptible; I, intermediate.

The prophylactic treatment of the enteral tract using polymyxin B, an old class of cationic agents (cyclic polypeptide antibiotics like colistin), was previously recommended for high-risk patients with difficult-to-treat infections undergoing SCT. Nowadays, the premedication with polymyxin B is no longer recommended as the standard protocol.[5] Although new quinolones are recommended as candidate prophylactic antimicrobials, the isolates of both CRKP and CSRP in the current case were resistant to levofloxacin and ciprofloxacin. As the risk of the proliferation of carbapenem-resistant gram-negative bacteria increases, the use of polymyxin B as a prophylactic treatment should be reconsidered, particularly when *K. pneumoniae* with specific STs such as ST15 is detected in surveillance culture.

In conclusion, CRKP carrying $bla_{\text{DHA-1}}$ was isolated after septicemia in a febrile neutropenia patient with AML after SCT, and the treatment with tigecycline was unsuccessful. The prophylactic treatment of the enteral tract with polymyxin B might be considered when an isolate carrying a high risk of antimicrobial resistance is detected in surveillance cultures from a patient with SCT. Further studies on molecular mechanisms against antimicrobial resistance in clinical isolates may provide suggestions regarding the prevention and treatment of serious bacterial infections in leukemia patients with SCT.

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