



# 임상 검체에서 검출된 녹농균에서의 NDM-1 Metallo- $\beta$ -Lactamase: 증례 보고 및 문헌 검토

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## Detection of NDM-1 Metallo- $\beta$ -Lactamase Genes in *Pseudomonas Aeruginosa* from Clinical Surveillance Sample: A Case Report and Literature Review

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*Pseudomonas aeruginosa* is an opportunistic pathogen that can be an important nosocomial pathogen. Herein, we report a case of NDM-1-carrying *P. aeruginosa* isolated from a clinical specimen in Korea. An 82-year-old man was transferred to our hospital because of aspiration pneumonia. Blood tests revealed leukocytosis and elevated C-reactive protein levels. The Xpert Carba-R assay was performed before admission, and the test result was positive for *bla*<sub>NDM</sub>. After admission, cultures using rectal swabs were used for carbapenem-resistant *Enterobacteriaceae* surveillance, and carbapenem-resistant *P. aeruginosa* was grown. Repeat Xpert Carba-R assay and sequencing for *bla*<sub>NDM</sub> detection in *P. aeruginosa* detected *bla*<sub>NDM-1</sub>. Therefore, the patient was treated with meropenem and transferred to a long-term care hospital. Experts working in the clinical microbiology departments should investigate multidrug resistance for other gram-negative bacteria not only for *Enterobacteriaceae*. For effective infection control in hospitals, it is essential to determine the presence of resistance genes in clinical isolates.

**Key Words:** *Pseudomonas aeruginosa*, Beta-lactamase NDM-1, Metallo- $\beta$ -Lactamase

### Introduction

Infections caused by gram-negative organisms are a global concern [1,2]. *Enterobacteriaceae*, *Acinetobacter baumannii*, and *Pseudomonas aeruginosa* are major pathogens that can cause healthcare-associated infections, especially if the organisms are carbapenem resistant [3,4]. *P. aeruginosa* is an opportunistic pathogen that can cause severe infections, such as respiratory tract infec-

tions, sepsis, and urinary tract infections, particularly in immunocompromised patients. Moreover, it is an important nosocomial pathogen [5]. In Korea, there have been several reports of metallo- $\beta$ -lactamase (MBL)-producing *P. aeruginosa*, including those that produce Verona integron-encoded metallo- $\beta$ -lactamase (VIM) and active-on-imipenem (IMP) [6], but reports on New Delhi metallo- $\beta$ -lactamase 1 (NDM-1) are rare. It is important to detect MBL-producing organisms early because these organ-



isms have high mortality rates once they cause infection. Here, we report a case of NDM-1-carrying *P. aeruginosa* isolated from a clinical specimen in Korea.

## Case Report

An 82-year-old man was transferred from a long-term care facility in November after 1 day of dyspnea. He was discharged from our hospital 8 days ago after 8 months of admission. He presented with dyspnea and low blood pressure. Upon arrival, the blood pressure was 103/71 mmHg, and pulse rate was 119 beats/min. Initial laboratory investigations showed a leukocyte count of 11,960 cells/ $\mu$ L with a dominant neutrophil count and normal platelet count of  $37 \times 10^4/\mu$ L. Serum blood urea nitrogen and creatinine levels were elevated to 29.3 and 1.30 mg/dL, respectively, and the estimated glomerular filtration rate was 52.8 mL/min/1.73 m<sup>2</sup>. Moreover, lactic acid and C-reactive protein (CRP) levels were elevated to 8.8 and 17.4 mg/dL, respectively. Chest radiography and computed tomography revealed multifocal peribronchial mixed consolidations in both lungs, suggestive of pneumonia.

The patient was tested for carbapenemase genes before admission according to the infection control guidelines of our hospital. The Xpert Carba-R assay (Cepheid, Sunnyvale, CA, USA), which detects *bla*<sub>KPC</sub>, *bla*<sub>NDM</sub>, *bla*<sub>VIM</sub>, *bla*<sub>OXA-48</sub>, and *bla*<sub>IMP-1</sub> using real-time polymerase chain reaction (PCR), was performed to test the patient's rectal swab. Since the test resulted in *bla*<sub>NDM</sub> positivity, culture for carbapenem-resistant *Enterobacteriaceae* was performed as a follow-up test. After 24 h of incubation, no *Enterobacteriaceae* were found, and only non-fermentative gram-negative organisms were grown on MacConkey agar. *P. aeruginosa* was identified by Vitek MS (bioMérieux, Marcy-l'Étoile, France) and tested for antimicrobial susceptibility by Vitek 2 (bioMérieux, Marcy-l'Étoile, France). This isolate was resistant to carbapenems, cephalosporins, aminoglycosides, and quinolones. The modified Hodge test results were weakly positive. Sequencing for detecting *bla*<sub>NDM</sub> was conducted using the primers and PCR conditions used in a previous study [7]. It yielded a 100.0% match with *bla*<sub>NDM-1</sub> (GenBank accession number

HQ652608.1).

Pneumonia was treated with meropenem for 8 days. On the eighth day of hospitalization, laboratory tests showed that leukocyte and creatinine levels normalized to 7930 cells/ $\mu$ L and 1.0 mg/dL, respectively, and the serum CRP level decreased to 1.0 mg/dL. The patient was discharged from our hospital to a long-term care facility.

## Discussion

Since the first discovery of NDM-1-producing *P. aeruginosa* from Serbia in 2011 [8], it has been isolated mostly in Asia, Europe, and Africa [9-28] (Table 1). ST235 was the only sequence type identified in all previously isolated NDM-1-producing *P. aeruginosa* strains. A significant number of NDM-1-producing *Pseudomonas* species have been isolated in West Asian countries, which are known as NDM-1 endemic regions. One study in India investigated 290 clinically isolated carbapenem-

**Table 1.** Microbiological and Epidemiological features of NDM-1-producing *Pseudomonas* species reported in the previous publications and this study

	Countries	Reported year	Number of isolates	Reference
Europe	Serbia	2011	1	[8]
	France	2012	1	[27]
	France	2013	1	[18]
	Italy	2013	1	[19]
	Slovakia	2015	1	[20]
	Albania	2020	2	[15]
Africa	Uganda	2016	1/25	[26]
Western Asia	Iran	2020	29/236	[12]
Asia	Iraq	2011	1	[28]
	Iraq	2014	2/36	[11]
	Iraq	2018	4	[10]
	Turkey	2020	11	[13]
	Egypt	2014	1	[14]
	South Asia	India	2016	16/290
India		2020	1	[12]
India		2013	4/200	[21]
Nepal		2017	2/11	[23]
Myanmar		2019	20	[22]
Myanmar		2019	7/152	[25]
East Asia	Japan	2019	1	[24]
	China	2020	14/149	[34]
	South Korea	2021	16/183	[30]

resistant *P. aeruginosa* (CRPA), and 16 (6.6%) were NDM-1 positive [17]. In Iran, one study in 2020 reported that 12.3% (29/236) of CRPA were found to be positive for *bla*<sub>NDM-1</sub>, which highlights the importance of *bla*<sub>NDM-1</sub> screening in endemic areas, including Iran [12].

Korean studies on MBL-producing *P. aeruginosa* reported that VIM and IMP were the main MBL types contained in CRPA [6,9,29]. In 2015, one study reported that 17% (17/100) and 4% (4/100) of CRPA carried *bla*<sub>IMP-6</sub> and *bla*<sub>VIM-2</sub>, respectively [9]. In 2019, among 345 carbapenem-resistant *Pseudomonas* species isolated from clinical specimens, 28 carried *bla*<sub>VIM-2</sub> and 23 carried *bla*<sub>IMP-6</sub>, and there were no *bla*<sub>NDM-1</sub>-positive isolates [6]. Furthermore, Hong et al. analyzed 183 CRPA isolates and found that 8.74% (16/184) harbored the *bla*<sub>NDM-1</sub> gene and exhibited high-level resistance to many antibiotics [30].

The current Korean antimicrobial resistance surveillance system covers the mandatory reporting of carbapenem-resistant *Enterobacteriaceae* [31]. The remaining gram-negative organisms, such as *A. baumannii* and *P. aeruginosa*, are not included in the mandatory reporting list; therefore, it is difficult to accurately track and manage infections caused by these organisms with antimicrobial resistance genes. However, it should be considered that *bla*<sub>NDM</sub> can be transferred to different species within hospitals through horizontal spread, including plasmid-mediated spread [16,32]. This indicates that *bla*<sub>NDM</sub> in *P. aeruginosa* can be transferred to *Enterobacteriaceae* that can spread in the absence of infection control practice. The World Health Organization listed CRPA on the “critical” groups among priority pathogens for antibiotics [33]. We have to monitor and manage gram-negative organisms more actively, not only *Enterobacteriaceae* but also *A. baumannii* and *P. aeruginosa*, which are highly ranked antibiotic-resistant bacteria [33]. Although NDM-producing organisms are mainly endemic in Middle Eastern countries, NDM-1-producing *Pseudomonas* species were first reported in China in 2020 [34]. Similar to the East Asian region, it is necessary to strengthen the surveillance of carbapenemase genes, including *bla*<sub>NDM</sub>, in Korea.

Experts working in clinical microbiology departments should monitor multidrug resistance in other gram-negative bacteria, not only in *Enterobacteriaceae*. Although the risks and benefits should be considered, it is necessary to pay attention when CRPA is isolated, and it will also be necessary to consider periodic monitoring, even if not all samples.

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Not applicable.

## Disclosure of conflict of interest

All authors declare that they have no conflicts of interest.

## Ethics approval and consent to participate

The study was approved by the Institutional Review Board of Inje University Ilsan Paik Hospital (IRB number: ISPAIK 2021-05-025), and the requirement for written informed consent was waived.

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