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Case report

First case of New Delhi metallo β-lactamase-1 (NDM-1)-producing *Burkholderia cepacia* complex in Iran

Alireza Rezaei Adariani [a], Sarvenaz Sokhanvari [b], Vajihe Sadat Nikbin [c], Majid Hosseinzadeh [a,d], Zahra Khoram [a], Hamid Solgi [b,a,*]

[a] *Amin Hospital, Isfahan University of Medical Sciences, Isfahan, Iran*
[b] *Isfahan Endocrine and Metabolism Research Center, Isfahan University of Medical Sciences, Isfahan, Iran*
[c] *Department of Bacteriology, Pasteur Institute of Iran, Tehran, Iran*
[d] *Department of Genetics and Molecular Biology, School of Medicine Isfahan University of Medical Sciences, Isfahan, Iran*

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ABSTRACT

The *Burkholderia cepacia* complex (Bcc) is a gram-negative bacillus, which is intrinsically resistant to several used antibiotics, and is now recognized as a group of opportunistic pathogens in Cystic Fibrosis patients. Here, for the first time, we report the case of a patient with New Delhi metallo β-lactamase (NDM)-positive Bcc lower respiratory tract infection in Iran. The patient was a 57-year-old male admitted to our hospital due to breathlessness, with a history of pulmonary thromboembolism and hypertension. On day 14, the patient underwent bronchoscopy and a bronchoalveolar lavage (BAL) specimen was taken. BAL culture grew Bcc. The drug resistance analysis showed positive NDM resistance, with susceptibility to only quinolones, therefore, levofloxacin was prescribed to the patient. He was discharged from the hospital on the 20th day, 4 days after the initiation of levofloxacin therapy, and died at home on the fifth day after discharge. This is the first report of a lung infection caused by an extensively drug-resistant NDM-positive Bcc strain in Iran.

1. Introduction

The *Burkholderia cepacia* complex (Bcc) is opportunistic gram-negative nosocomial pathogen that can cause serious infections in Cystic Fibrosis patients. They are often found in liquid reservoirs and they can survive for long periods in the presence of disinfectants [1]. Infections due to Bcc can be challenging to manage, as Bcc is intrinsically resistant to several antimicrobial agents. Some antibiotics such as trimethoprim-sulfamethoxazole (TMP-SMX), ceftazidime, carbapenem and fluoroquinolones have shown in vitro activities against this bacterium [1–3]. We herein present one such rare case of $bla_{\text{NDM-1}}$ and bla_{TEM} producing *B. cepacia* in a patient who was hospitalized due to respiratory failure.

2. Case presentation

A 57-year-old male patient was admitted to the university hospital on February 7, 2022, with breathlessness, cough and weakness from the day before. The physical examination upon admission revealed the following vital signs: heart rate 115 beats/min, respiratory

* Corresponding author. Isfahan Endocrine and Metabolism Research Center, Isfahan University of Medical Sciences, Isfahan, Iran.
E-mail address: hamid.solgi@gmail.com (H. Solgi).

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rate 22 breathes per minute, blood pressure 95/60 mmHg and temperature 38.5 °C. Oxygen saturation (SpO 2) was 73 % on room air. His laboratory data showed a white blood cell (WBC) count of 11,200 per μl, lymphocyte 15.5%, C-reactive protein (CRP) 92 mg/L, D-dimer 728 mg/L and neutrophils 85%. He had a history of a head injury 20 years ago which resulted in cerebral atrophy, quadriplegia and aphasia. The patient has had a history of pulmonary thromboembolism in the past year which was under treatment. He also had a history of hypertension and several hospitalizations.

3. Diagnosis and treatments

Initially, the patient was diagnosed with pulmonary thromboembolism due to history and was treated with ceftriaxone (1 g IV every 8 hours), heparin and dexamethasone. On day 2, after the patient didn't respond to the treatment a computed tomography (CT) scan of the thorax was performed that was highly suggestive of ground-glass opacity (GGO) and consolidation (Fig. 1a and Fig. 1b). The result of the patient's real-time PCR test was reported negative for Covid-19.

During hospitalization, his antibiotic treatment plan was adjusted several times. On day 2, ceftriaxone was changed to levofloxacin (750 mg IV every 24 hours) and on the third day of hospitalization, clindamycin (600 mg IV every 8 hours) and cefepime (1 g IV every 8 hours) were added to levofloxacin (750 mg IV every 24 hours). On day 5, levofloxacin was changed to amikacin (15 mg/kg/day divided IV every 12 hours), with the continuation of clindamycin and cefepime. This regimen of three antibiotics (amikacin + clindamycin + cefepime) continued for 12 days for the patient. On day 14, according to the results of the CT scan, the patient underwent bronchoscopy by a lung specialist and a bronchoalveolar lavage (BAL) sample was sent for microbial culture. 48 hours after culture obtainment, Gram-negative rods ($\geq 10^5$ CFU/mL) were recovered and using morphologically, oxidase test and API 20 NE strips (BioMérieux, Marcy l'Étoile, France) determined to the species level as Bcc, at which time based on antibiogram all antibiotics (amikacin + clindamycin + cefepime) were discontinued and levofloxacin was prescribed again. He was discharged after receiving four days of levofloxacin on the 20th day of hospitalization. After the patient was discharged from the hospital, the specialist prescribed levofloxacin 750 mg oral once daily for 10 days after discharge. The patient died at home after five days due to respiratory problems.

4. Microbiological methods

Antimicrobial susceptibility testing (AST) was performed using the Kirby Bauer disk diffusion method. Antibiotics recommended for testing against Bcc by the Clinical and Laboratory Standards Institute (CLSI) were evaluated [4]. This strain was resistant to all tested antibiotics such as meropenem, ceftazidime, minocycline, chloramphenicol and trimethoprim-sulfamethoxazole and was sensitive only to levofloxacin. According to the antibiotic resistance pattern, this isolate was classified as extensively drug-resistant (XDR). Furthermore, the minimum inhibitory concentration (MIC) of meropenem was determined by the E-test method, according to the manufacturer's instructions (Liofilchem, Italy). Common β-lactam resistance genes including extended-spectrum β-lactamase ($bla_{\text{CTX-M}}$, bla_{TEM}, bla_{SHV}) and carbapenemases (bla_{KPC}, bla_{VIM}, bla_{IMP}, bla_{NDM} and $bla_{\text{OXA-48}}$) were identified by PCR using primers as previously described [5]. PCR assay showed that this strain (meropenem MIC ≥32 μg/ml) was positive for $bla_{\text{NDM-1}}$ and bla_{TEM}, and negative for bla_{KPC}, $bla_{\text{OXA-48}}$, bla_{VIM}, $bla_{\text{CTX-M15}}$ and bla_{SHV}.

5. Discussion

Here, we report the first case of lung infection due to carbapenem-resistant Bcc strain. This resistance was mediated by $bla_{\text{NDM-1}}$ gene. Bcc is a common respiratory pathogen in patients with chronic lung diseases such as cystic fibrosis. Due to the intrinsic resistance of Bcc to several commonly used antibiotics such as colistin, ampicillin-sulbactam and fosfomycin, the presence of $bla_{\text{NDM-1}}$, in combination with extended-spectrum β-lactamases in this organism causes serious concerns in the treatment of patients due to the limitation in the therapeutic options [2]. In this study, the strain isolated from the patient's BAL sample was only sensitive to levofloxacin and ciprofloxacin. Therefore, due to the intrinsic resistance of the Bcc to colistin, the specialist used levofloxacin as the only

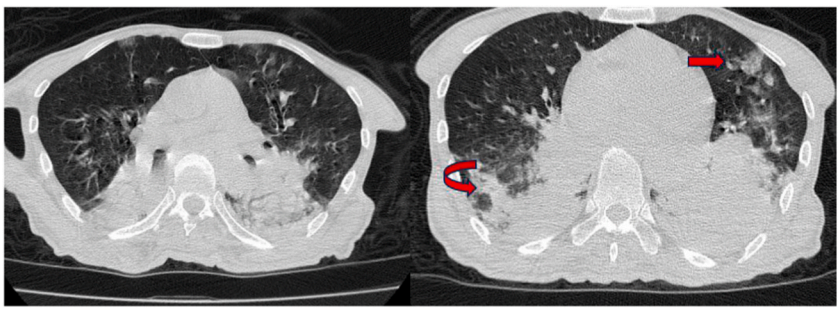

Fig. 1a. CT scan findings on the second day of the patient's hospitalization. CT image showing sub pleural patchy ground-glass opacity (GGO) and consolidation in both lower lobes (prominently left side). Diffuse alveolar infiltration is present in any brunched pathology in both upper lobes (arrow).

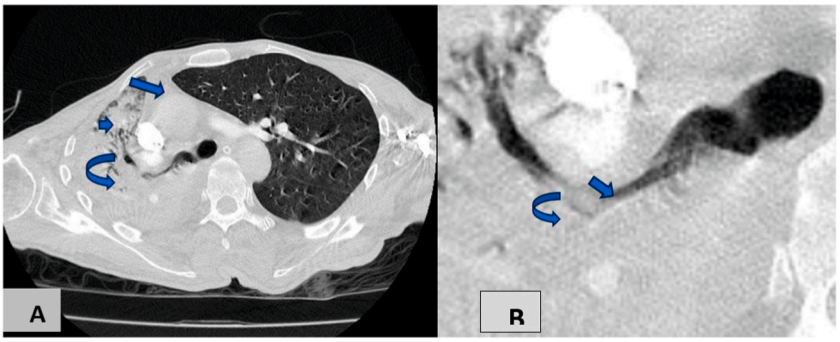

Fig. 1b. CT scan findings on the 14th day of the patient's hospitalization. (Chest CT scan with PTE protocol). (**A**) CT image showing hyperinflated left lung with a mediastinal shift towards the right (arrow) and consolidation in right lower lobe and right middle lobe (curved arrows). CT image showing patchy areas of GGO and consolidation in parts of the right upper lobe (small arrows). (**B**) The right main bronchi are narrower than normal and the lower lobe bronchus is blocked.

available choice based on the antibiotic resistance pattern to treat the patient. In a review study, Gautam et al. showed that, it is not possible to comment on the superiority of combination therapy over monotherapy and combination therapy isn't the recommended modality [6].

It seems that according to the patient's condition and previous hospitalization history, at first patient was colonized with Bcc and after that develops a lower respiratory tract infection. Due to the improvement of the patient's blood inflammatory indicators (WBC count of 6700 per μl, neutrophils 51% and CRP 16 mg/dl) and also after a four-day treatment period with levofloxacin, the patient was discharged after 20 days of hospitalization. The patient, without any request for microbial culture such as blood culture, was discharged with levofloxacin (750 mg oral once daily for 10 days), and unfortunately, we were unable to find out whether or not the patient had continued antibiotic therapy. Therefore, we suggest that patients who are infected with multi-drug resistance strains should be followed up for antibiotic use and infection upon discharge. It is also suggested that in such patients, before discharge, specialists send microbiological cultures to obtain reassurance from the antibiotic treatment process.

There are very limited reports of infections caused by NDM-1-producing Bcc [2]. This study revealed that Bcc isolate co-harbor bla_{TEM} and $bla_{\text{NDM-1}}$ genes. This may be due to its presence on highly mobile genetic elements that facilitates its spread among bacteria. This is in agreement with the findings of Mhlongoa et al. [2], who reported that bla_{TEM} and $bla_{\text{NDM-1}}$ genes were detected in one Bcc isolate. In a study conducted by Ogbolu et al. [7], evaluated the production of beta-lactamases in Bcc isolates, they found that these bacteria 50% were ESBLs producers, 100% harbored bla_{TEM} gene and 50% carried bla_{SHV} and $bla_{\text{CTX-M-15}}$ while no isolate was carried carbapenemase genes. Ferreira et al. [8], in Brazil revealed that two out of 17 *B. cepacia* were harbored bla_{TEM}, $bla_{\text{CTX-M}}$, bla_{SHV}, bla_{OXA} and considered as ESBL producers.

6. Conclusions

To our knowledge, this is the first report of a respiratory infection caused by a carbapenem-resistant, $bla_{\text{NDM-1}}$ and bla_{TEM} producer Bcc that was XDR. For the treatment of this patient, levofloxacin was the only choice to prescribe because the specialist had no other choice and at that time, other antibiotics such as tigecycline and β-lactam/novel β-lactamase inhibitors were not available in the hospital. It is suggested that, when the patient is infected with an XDR strain, infection clearance should be monitored by blood culture before discharge.

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Ethics approval and consent to participate

All ethical issues have been considered to protect the patient's rights.

Consent for publication

Informed consent was obtained from the patient's guardian for the publication of all images, clinical data and other data included in the manuscript.

Data availability statement

The data that support the findings of this study are available from the corresponding author, [H.S], upon reasonable request.

CRediT authorship contribution statement

Alireza Rezaei Adariani: Writing – review & editing, Writing – original draft, Software, Methodology, Data curation. **Sarvenaz Sokhanvari:** Writing – review & editing, Writing – original draft, Methodology, Data curation. **Vajihe Sadat Nikbin:** Writing – original draft, Methodology, Data curation. **Majid Hosseinzadeh:** Writing – review & editing, Investigation, Data curation. **Zahra Khoram:** Writing – original draft, Methodology. **Hamid Solgi:** Writing – review & editing, Writing – original draft, Visualization, Validation, Supervision, Software, Resources, Project administration, Methodology, Investigation, Funding acquisition, Formal analysis, Data curation, Conceptualization.

Declaration of competing interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

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