



Bacteremia due to a VIM-1 Producing *Klebsiella Pneumoniae* Isolate from an Acute Lymphoblastic Leukemia Patient in Antalya

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Abstract

A *Klebsiella pneumoniae* clinical isolate resistant to imipenem was recovered from blood culture of a 4 years old child with the diagnosis of acute precursor B cell lymphoblastic leukemia. PCR assays of *Klebsiella pneumoniae* isolate were positive with bla_{CTX-M} and bla_{VIM-1} genes. Sequence analysis of the 160 bp amplicon matched with bla_{VIM-1}. Patient was discharged on the 15th day of ciprofloxacin therapy with remission. We report here the first VIM-1 positive *Klebsiella pneumoniae* isolate case from Akdeniz University Hospital. Urgent and rapid precautions must be preferred including antibiotic policy and infection control practices when the first case with different resistance pattern is detected.

Key Words: K. Pneumoniae; Metallo-B-Lactamases; VIM 1.

Antalya'da Akut Lenfoblastik Lösemili Hastada VIM-1 Üreten *Klebsiella Pneumoniae*'ye Bağlı Gelişen Bakteremi

Özet

Akut Prekürsör B Hücreli Lenfoblastik Lösemi tanısıyla izlenen 4 yaşındaki bir çocuğun kan kültürü örneğinden imipenem dirençli *Klebsiella pneumoniae* izole edildi. İzolatın PCR analizi sonuçları VIM ve CTX- M enzimleri açısından pozitif olarak saptandı. Yapılan DNA sekans analizi sonucunda 160bp'lik bölge bla_{VIM-1} ile uyumlu olarak bulundu. Hasta siprofloksasin tedavisinin 15. gününde remisyonla taburcu edildi. Bu olguda Akdeniz Üniversitesi Hastanesi'nde ilk kez saptanan VIM 1 pozitif *Klebsiella pneumoniae* izolatı sunulmuştur. Farklı direnç paternine sahip bir vaka görüldüğünde, hızlı bir şekilde antibiyotik politikalarını da içeren enfeksiyon kontrol önlemleri alınmalıdır.

Anahtar Kelimeler: K. Pneumoniae; Metallo-B-Laktamaz; VIM 1.

INTRODUCTION

Carbapenems are the most effective agents against Gram negative bacteria and they are mostly used as the preferred treatment method for ESBL (Extended-spectrum β - lactamase) producing isolates (1,2).

Resistance to carbapenems is rare but there are increasing reports of Enterobacteriaceae. Infections caused by carbapenem resistant bacteria have limited treatment options and these have been associated with high mortality rates. The emergence of carbapenem resistant enterobacteriaceae due to acquired metallo- β -lactamases (MBL) is an international health problem (2-4). IMP and VIM enzymes are the most prevalent types in acquired MBL and they have appeared globally. VIM producing *Klebsiella pneumoniae* isolates have been established in Europe, mostly in Greece and Italy (5,6). In Turkey, VIM producing *Klebsiella pneumoniae* isolates are usually sporadic cases and no outbreak has been reported yet. We present here the first case of VIM-1 positive *Klebsiella pneumoniae* isolated from a 4 years

old boy with acute lymphoblastic leukemia in Akdeniz University Hospital.

CASE REPORT

In May 2007, a 4 years old child was admitted with acute febrile attack and arthralgia to the tertiary hospital of Akdeniz University. Physical examination revealed **hepatomegaly and splenomegaly**. Abnormal laboratory findings included hemoglobin of 7.6 g/dl, a white blood cell count of **18300/mm³** and a platelet count of 149000/mm³; bone marrow aspiration was consistent with ALL and immunophenotypic studies revealed B precursor ALL.

A chemotherapy was initiated in accordance with BFM-2000 protocol with 5-drug induction including prednisolone, vincristine, daunorubicin, L-asparaginase, and methotrexate. After the 22nd day of the initial chemotherapy, the patient underwent the first episode of febrile neutropenia. The patient's urine examination, X-ray of chest, and abdominal ultrasonography did not reveal abnormal findings. The patient was treated with a

course of broad spectrum antibiotics consisting cefepime and non lipid amphotericin B deoxycholate on the fifth day of the febrile attack. The blood, urine, and sputum cultures were also negative; the fever resolved on the 33rd day along with the remission of the bone marrow. Hepatomegaly and splenomegaly regressed, too.

On the 39th day, the patient underwent a second cycle of chemotherapy. One week after the chemotherapy, the patient's fever and neutropenia emerged again upon which a piperacillin tazobactam therapy was initiated. One week later, the patient remained febrile neutropenia. Suspecting an invasive pulmonary aspergillosis, non lipid amphotericin B deoxycholate was added to the therapy. But the patient's febrile attack did not regress; the high-resolution computed tomography revealed diffused ground glass opacity in the bilateral lung fields. The Aspergillus galactomannan antigen was negative in plasma sample at this time. The cultures of separate blood samples were obtained from central venous catheter and percutaneously, they yielded ESBL producing *Klebsiella pneumoniae*, which was susceptible to ciprofloxacin and levofloxacin and intermediate to amikacin and resistant to all cephalosporines and carbapenems (Table 1).

Table I. MIC results of *K. pneumoniae* isolate.

Antibiotics	Phoenix MIC results	E test MIC results
Cefotaxime	>32	96
Cefepime	>16	32
Imipenem	>8	24
Piperacilin tazobactam	>64/4	128
Meropenem	>8	8
Amikacin	32	32
Ciprofloxacin	<=0,5	0,25

Multidrug resistant *K. pneumoniae* was evaluated from the urine culture at the same time. The piperacilin tazobactam therapy was discontinued and central venous catheter was removed. Eventually we lowered the therapy to the pediatric dosage of ciprofloxacin. The patient's fever resolved within 72 hours from the administration of ciprofloxacin. The cultures of the catheter tip were sterile while repeated blood cultures were negative. The patient was treated with ciprofloxacin for 14 days and discharged with remission.

Initially, the identification and antimicrobial susceptibility of *K. pneumoniae* were evaluated using Phoenix system (BD, U.K). The MIC's were determined by E test according to CLSI recommendations and the manufacturer's instructions (AB Biodisk, Solna, Sweeden). The E test results of antibiotics are shown in Table 1. Clavulanate and cefotaxime/ceftazidime disk diffusion showed synergy. The PCR was performed on ABI 2700 thermocycler (AB Applied Biosystems, USA) and PCR assays were positive with bla_{CTX-M} gene and negative for bla_{TEM}, SHV, PER and OXA. The isolate was screened for MBL production by E test method with IMP and IMP+EDTA. The MIC of IMP with and without EDTA was measured. The MIC of IMP without EDTA was 16 µg/ml and with

EDTA it was 1 µg/ml. The PCR of bla_{IMP}, SIM, GIM and SPM were performed and the isolate was only positive for bla_{VIM}. Both strands of PCR products were sequenced with an Applied Biosystems (ABI 3100, USA) and the analysis of the 160bp amplicon matched with bla_{VIM1} (7).

DISCUSSION

K. pneumoniae is primarily an opportunistic pathogen which causes life threatening infections in immunocompromised patients. Gastrointestinal tract and hands of health care staff are the major reservoirs for *K. pneumoniae*. The most important problem is their ability to spread rapidly within hospital environment (6, 7). According to EARSS (European Antimicrobial Resistance Surveillance System) rates of ESBL producing *Klebsiella* isolates in Turkey is 44% (8). Among ESBL producing *Klebsiella* isolates, CTX-M is the most prevalent enzyme; it is widely disseminated and the therapy options include wide spectrum effective agents like carbapenems (9, 10). But, mostly, ESBL producing *Klebsiella* isolates have been increasingly reported with carbapenemase production in the last decade. Until now, three main classes of carbapenemases have been identified: Ambler class A beta-lactamase (KPC), class B (metallo-enzymes), and class D (OXA-48 type). *Klebsiella pneumoniae* carbapenemases (KPC) was first reported in the United States in late 1990s, and since then it is worldwide. Carbapenemases of the oxacillinase-48 type (OXA-48) have been identified mostly in the Mediterranean and southern European countries. OXA-48 was the most prevalent enzyme reported from Turkey. Carbapenemase NDM-1 (New Delhi metallo-beta-lactamase-1) is one of the most recently reported metallo-enzymes. It has spread widely in the Indian sub-continent and then around the world. VIM and IMP type enzymes are the most prevalent genes in the east of Europe (7,9,10). As far as we know, VIM type enzymes were first reported in Ankara and İstanbul but no other reports have been identified from the south of Turkey (11,12). This is the first report from the southern Turkey, and for that matter, from our hospital. No other resistant *K. pneumoniae* isolates were recovered from the patients in our hospital during this period.

MBL producing isolates are a great clinical problem in haematology patients as well because antibiotic options available are extremely limited. Infections caused by MBL producing *K. pneumoniae* have poorer outcomes with high mortalities (13,14). The dissemination of VIM positive *K. pneumoniae* isolates is associated with ineffective infection control practices. Strict hygiene practices and careful use of antibiotics are critical to prevent spreading of VIM positive *K. pneumoniae* isolates. Reduction in antibiotic consumption is clearly important to minimize the antimicrobial resistance in Gram negative bacilli (6,15).

It must be kept in mind that travelling persons are known to be a major factor in spreading of multidrug resistance organisms. To prevent carbapenemases spread into Northern and Western European countries is vital due to the fact that these enzymes are not endemic

(4,5). Our case had no travel history to another part of Turkey or Europe where metallo-beta-lactamases are endemic. No other patient was transferred to our hospital either.

In conclusion, urgent and rapid precautions must be taken in such cases including antibiotic policy and infection control practices when the first case is detected.

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Received/Başvuru: 04.11.2013, Accepted/Kabul: 18.02.2014

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For citing/Atıf için

Ozen NS, Ogunc D, Ongut G, Seyman D, Daglar D, Baysan Ozhak B, Colak D, Hazar V, Naas T. Bacteremia due to A VIM-1 producing *klebsiella pneumoniae* isolate from an acute lymphoblastic leukemia patient in Antalya. *J Turgut Ozal Med Cent* 2014;21:291-3 DOI: 10.7247/itomc.2014.1470.