Case Report

Linezolid-resistant *Enterococcus faecalis* in leukemia patients: Rare cases with review of literature

Naveen Kumar[1], Sonu Kumari Agrawal[2], Aishwarya Govindaswamy[2], Vijeta Bajpai[2], Tej Bahadur[2]

Departments of [1]Oncology and [2]Microbiology, All India Institute of Medical Sciences, New Delhi, India

Abstract

Resistance to linezolid is rare in clinical isolates of Enterococcus faecalis. Here, we report cases of linezolid resistant Enterococcus fecalis in leukemia patients with review of literature.

Keywords: *Enterococcus*, linezolid, resistant

Introduction

Linezolid is bacteriostatic agent and acts against gram positive bacteria. Resistance to linezolid is rare in clinical isolates of Enterococcus faecalis. Here, we report cases of linezolid-resistant *E. fecalis* in leukemia patients with review of literature.

Case 1

A 17-year-old male, a recently diagnosed case of acute myeloid leukemia not started on treatment, presented to the emergency with history of reduced appetite along with vomiting for 5 days. The patient developed high-grade continuous fever 3 days prior to the admission. Respiratory system examination showed crackles in left infra-axillary and infrascapular regions. A provisional diagnosis of pneumonia with septic shock and acute leukemia was made and initial investigations were done. Blood culture was sterile. In view of the septic shock in a case of leukemia, the patient was started on Inj. cefoperazone + sulbactam 1.5 gm TDS along with amikacin 500 mg OD according to the antibiotic sensitivity pattern of the hospital in a case of febrile neutropenia. As the general condition did not improve in the next 48 hours, gram positive coverage in the form of teicoplanin 400 mg was started and amphotericin B was initiated for fungal coverage. Contrast-enhanced computed tomography (CT) of the chest and abdomen was done and revealed tubo-ovarian abscess, as well as bilateral consolidation involving right upper lobe and left lower lobe; the treatment was subsequently continued. Bone marrow aspiration and biopsy was done which showed monocytic undifferentiated acute myeloid leukemia. Immunohistochemistry showed CD7+, CD11c+, CD34+, CD38+, and CD 117. Chemotherapy induction was initiated with hydroxyurea which was later changed to three doses of inj. daunorubicin 78 mg and inj. cytarabine 420 mg for 7 days. The patient's bleeding manifestations subsided, however, after 2 weeks of hospital stay patient developed a swelling on the left medial canthus along with left nasal obstruction. The swelling gradually progressed over the next few days and a provisional diagnosis of fungal sinusitis was made. Patient had persistent fever during the hospital stay, Antifungals were changed to liposomal amphotericin and caspofungin. After 21 days of meropenem, the antibiotic was changed to inj. piperacillin + tazobactam. Nasal swab was sent for pus culture which showed *E. faecalis* resistant to vancomycin and linezolid, which is a rare entity in Indian scenario. Patient succumbed on the same day following an episode of acute respiratory distress that led to invasive ventilation and later had cardiac arrest.

Address for correspondence: Dr. Sonu Kumari Agrawal, Department of Microbiology, All India Institute of Medical Sciences, New Delhi, India.
E-mail: dr.sonu1986@gmail.com

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Case 2

An 11-year-old boy presented with history of fever and nonproductive cough for 3 weeks. The fever was continuous high-grade in nature. On examination, he had pallor, generalized lymphadenopathy, and reduced air entry in the right axillary area. Few crackles were audible in the right infra-axillary region and abdominal examination revealed moderate hepatosplenomegaly. Bone marrow biopsy and flow cytometry was done which concluded the pathology as acute myeloid leukemia. Chest X-ray showed right middle lobe consolidation and the patient was initiated on inj. cefoperazone + sulbactam, amikacin, and teicoplanin. Fever subsided, and induction regimen was started after few days. However, he restarted with fever on the 6th day of induction therapy and was started on inj. meropenem along with liposomal amphotericin B. CT chest showed consolidation in right upper lobe along with consolidation patches in right middle lobe and left upper lobe, and few ground glass opacities in left upper lobe suggesting a mixed bacterial and fungal infection. Blood culture grew *Escherichia Coli*, sensitive to imipenem and colistin. As the fever persisted, colistin and linezolid was added. On day 13 of induction, he developed worsening respiratory distress and was intubated. Later, he went into septic shock and acute kidney injury, requiring inotropic support. The repeat blood culture sent on that day showed linezolid-resistant *E. faecalis*. By the time of reporting of the culture and sensitivity, the patient developed cardiac arrest and could not be revived despite resuscitation.

Discussion

Linezolid, an oxazolidinone antimicrobial agent is used in the treatment of community-acquired pneumonia, skin and soft-tissue infections, and other infections caused by gram positive bacteria including VRE and methicillin-resistant *Staphylococci*.[1,2] Vancomycin was considered as the drug of choice for cases of methicillin-resistant *Staphylococcus aureus* and enterococci since its discovery. However, widespread use led to emerging resistance towards vancomycin by the end of 1980s.[3] Linezolid acts by inhibiting protein synthesis through binding to the peptidyl transferase center of the 50S ribosomal subunit.[4] Clinical enterococcal resistance to linezolid defined by the presence of the *G2576T* mutation was reported in 2008 by Scheetz *et al.* from Chicago.[5] As reported by Rahim *et al.*, polymerase chain reaction amplification of the domain V region of the 23S ribosomal RNA gene demonstrated the presence of the *G2576U* mutation previously reported to be associated with linezolid resistance,[6] which underlines the fact that G2576U mutation has been well demonstrated in linezolid-resistant enterococci. A study in 4461 isolates of enterococci from Germany by Klare *et al.* between 2008 and 2014 elucidated the mechanism of resistance to linezolid.[7]

In the Indian scenario, case reports of linezolid-resistant *Staphylococcus* has been reported from Andhra Pradesh[8] and Kashmir.[9] The first case report of linezolid resistance in *E. faecium* was reported from India in 2014 by Kumar *et al.* from Kolkata,[10,11] which was isolated from the blood culture of a hypoglycemic encephalopathy; the organism was quite surprisingly sensitive to vancomycin. The minimum inhibitory concentration as determined by that case was 1024 μg/mL. Molecular analysis for the possible mutations was done by Rai *et al.* in a case reported from New Delhi,[12] and the sequencing did not indicate presence of any mutation in the two linezolid-resistant and vancomycin-resistant enterococci isolates. Cases of linezolid-resistant *Enterococcus* are shown in Table 1.

Table 1: Showing cases of linezolid-resistant *Enterococcus faecalis*

Year	Reported by	Place/Country	References
2001	Gonzalez *et al.*	Mayo Clinic, USA	Lancet. 2001;357:1179(5)
2003	Rahim *et al.*	New York, USA	Clin Infect Dis. 2003 Jun1;36 (11):E146-8. Epub 2003 May 20(7)
2014	Ingo Klare *et al.*	Germany	Journal of Global Antimicrobial resistance, June 2015
2014	Kumar *et al.*	Kolkata, India	Avicenna J Med. 2014 Jan; 4(1):13-6(11)
2015	Rai *et al.*	India	Indian Journal of Medical Microbiology. 2015 Volume : 33 Issue : 1 Page : 21-24
2008	Scheetz *et al.*	USA	Antimicrob. Agents Chemother. 2008 Jun; 52(6):2256-9.(6)
2002	Auckland *et al.*	UK	Journal of Antimicrobial Chemotherapy (2002) 50, 743-746(13)
2014	Almeida *et al.*	Brazil	Antimicrob. Agents Chemother. May 2014 vol. 58 no. 5 2993-2994(14)
2013	Mutschler *et al.*	Cologne, Germany	International Journal of Infectious Diseases Volume 17, Issue 6, June 2013, Pages e466-e467(15)

Declaration of patient consent

The authors certify that they have obtained all appropriate patient consent forms. In the form the patient(s) has/have given his/her/their consent for his/her/their images and other clinical information to be reported in the journal. The patients understand that their names and initials will not be published and due efforts will be made to conceal their identity, but anonymity cannot be guaranteed.

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Conflicts of interest

There are no conflicts of interest.

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