Respiratory Medicine Case Reports 31 (2020) 101159

Contents lists available at ScienceDirect

Respiratory Medicine Case Reports

journal homepage: http://www.elsevier.com/locate/rmcr

Case report

Adverse reaction report and retrospective analysis of black hairy tongue caused by linezolid

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A B S T R A C T

The adverse reaction of Black Hairy Tongue (BHT) caused by linezolid is rare. We reports a case of linezolid-induced BHT, and reviews relevant literatures at home and abroad. It aims to provide a safe and reasonable basis for clinical medication use. A 14-year-old adolescent with pneumonia caused by methicillin-resistant *Staphylococcus aureus* (MRSA) developed a rash and pruritus due to Vancomycin. Instead, the patient was given linezolid 600mg q12h in injection during hospitalization and in tablet after discharge. On the 14th day after injection and the second day after oral administration the patient showed BHT without other abnormal taste symptoms. But all the symptoms could be tolerated and he completed the therapy course of linezolid. Tongue symptoms completely disappeared on the 8th day after drug withdrawal. Based on the Karch and Lasagna evaluation methods and the cause-and-effect evaluation methods of the WHO collaborating center for international adverse drug reaction (ADR) monitoring, it is likely that this patient had a BHT caused by linezolid. The mean time of occurrence of BHT was 14.36 days, and the mean time of symptom disappearance was 23.43 days after drug administration. When linezolid is prescribed to patients, especially those with atopy, the patient's tongue should be closely observed and good oral hygiene is recommended.

1. Background

Linezo1id, the chemical name is (S)–N-[[-3-(3-Fluoro-4-(4-morpholino) phenyl)-2-oxo-5-oxazolidinyl] methyl]-acetamide, getting listed on the American FDA approval in 2000, is the first chemical total synthesis of a new type of well applied to clinical azole alkane ketone antimicrobials, and mainly used to treat infections caused by methicillin-resistant *Staphylococcus aureus* (MRSA) or *vancomycin-resistant enterococcus* (VRE) [1]. The common adverse reactions are diarrhea, headache, nausea, vomiting, etc., while the long-term adverse reactions are myelosuppression, including anemia, leukopenia, pancytopenia and thrombocytopenia with peripheral neuropathy and optic neuropathy, most of which occur in patients who used more than 28 days [2].The adverse reaction of Black Hairy Tongue (BHT) caused by linezolid is very rare.

2. Case report

The 14-year-old male patient, a student, was admitted on December 20, 2019 due to cough and expectoration for half a month. He expectorated large amount of yellow phlegm, had chills and pyrexia up to 38.7 °C, and had no symptoms such as chest distress and pain, gasping, nasal obstruction, or palpitation. Since onset, the patient had been in fair mental state and had average appetite, and his weight didn't change apparently. There were vital signs when he was admitted: body temperature was 36.7 °C, heart rate was 68 bpm, respiratory rate was 18 bpm, blood pressure was 111/70mmHg. The patient had no history of food or drug allergies. His chest CT revealed multiple patchy opacities with cavity lesions in both lungs. His sputum culture showed MRSA grew.

On December 26, 2019, bronchoscopy showed unobstructed trachea and bronchus with congested mucosa. Bronchoalveolar lavage (BAL) was performed in anterior segment of right upper lobe with 100 ml normal saline, and 64 ml light yellow and slightly turbid BAL fluid was collected.

On 21 December 2019, intravenous drip was performed with 1g vancomycin injection (import registration certificate No. H20140174, batch No. D74823) every 12 h. Rashes accompanied with pruritus occurred on the neck after 30 min intravenous drip. After discontinuing the injection and taking loratadine tablets orally, the symptoms were gradually relieved. On December 22, 2019, antibacterial drug was changed to 600 mg linezolid and glucose injection (Tianli, batch No. 191202116, Zhengda Tianqing Pharmaceutical Group Co., Ltd.), which was intravenously dripped every 12 h until 2 January 2020. A total of

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https://doi.org/10.1016/j.rmcr.2020.101159
Received 29 April 2020; Received in revised form 16 June 2020; Accepted 3 July 2020
Available online 7 August 2020

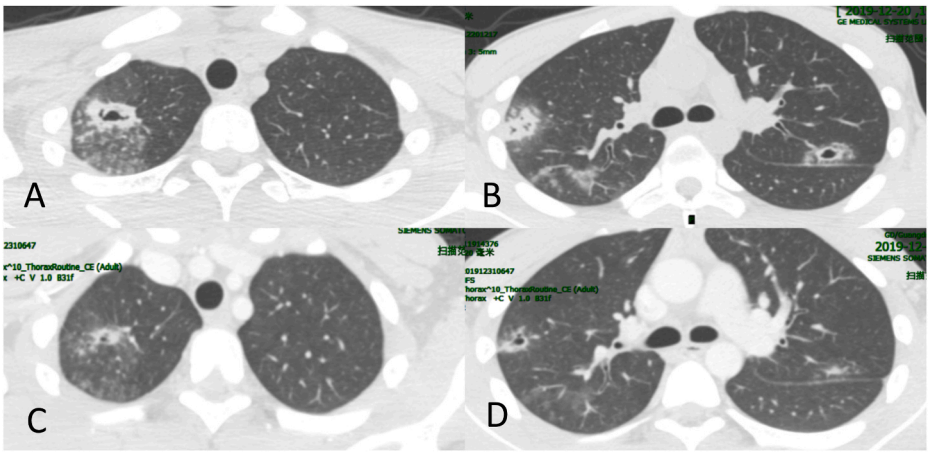

Fig. 1. Chest CT scan A and B on Dec 20, 2019 showed multiple lesions with thick wall cavities. Scan C and D on Dec 31, 2019 showed significant absorption of the lesions.

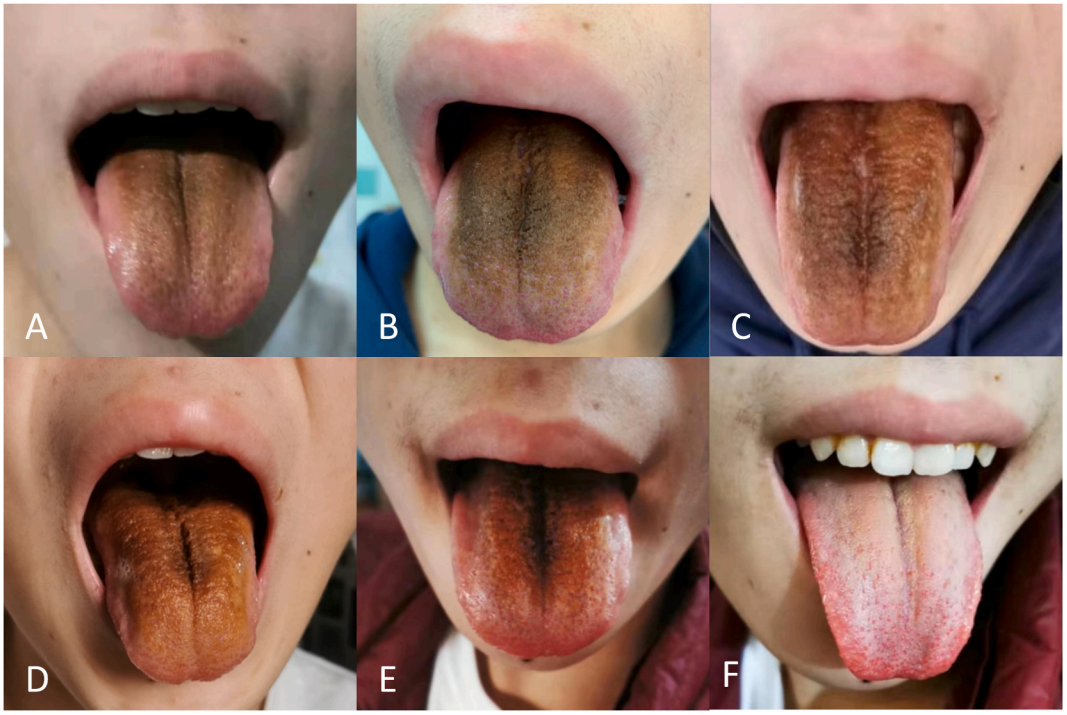

Fig. 2. Serial changes of the coating on the patient's tongue. Figure A, January 5, 2020; Figure B, January 15, 2020; Figure C, January 21, 2020, discontinuation of oral Linezolid; Figure D, January 23, 2020; Figure E, January 27, 2020; Figure F, January 29, 2020, normal as premorbid.

13.6 g linezolid was used and no adverse drug reactions were noticed. Additionally, 5 mL terbutaline plus 3 mL acetylcysteine inhalation solution were used for nebulization three times a day. Chest CT scan on December 31, 2019 showed significant absorption compared with that on December 20, 2019. On January 3, 2020, linezolid tablets (H20193189, batch No. 2019001, Chongqing Huabang Pharmaceutical Co., Ltd.) were taken orally after discharge. The color of tongue coating changed on the second day after oral administration. With the duration of orally taking medicine, the tongue coating of the patient showed an aggravated blackening trend. The color of the tongue coating changed according to different food consumption, such as changing to green after eating spinach. No discoloration occurred in the oral mucosa, maxillary mucosa, teeth or gingiva.(see Figs. 1 and 2)

After retrieval of Linezolid & tongue in PubMed, thirteen articles dated from January 2018 to December 2019 were found (two of which have no full text), all of which were case reports. Eleven articles were analyzed, and a total of 14 patients at the age of 5–80 had tongue discoloration or BHT on day 14.36 after taking the drug on average, and the symptoms disappeared on day 23.43 after drug withdrawal on average. The results were shown in Table 1.

3. Discussion

BHT, also known as Black tongue disease, is characterized by abnormal growth of filamentous nipples on tongue coating, leading to tongue base turning brown to black [3]. According to our knowledge, this is the first case of BHT induced by linezolid in mainland China. The patient had no symptoms in general, but some patients may experience itching, swelling or burning of the tongue, nausea, halitosis or different tongue appearances [4,5]. The exact mechanism by which drugs cause black hairy tongue remains unclear. It may be associated with poor oral hygiene, smoking, drinking coffee or other colored beverages. Other

Table 1
Review of Black hairy tongue related to linezolid.

	country	age (year)	administration	duration (year or day)	time to appear (day)	time to disappear (day)
2018 [12]	Italy	80	po	null	14	14
2017 [13]	India	25	po	2years	10–15	15
		30	po	2years	15	10
2015 [11]	USA	10	po	14days	14	11
2014 [14]	UAE	62	po	null	14	21
2014 [4]	India	10	po	14days	14	7
2013 [10]	Greece	5	ivdrip	21days	21	30
		8	ivdrip	12 days	7	30
		14	ivdrip	21days	21	30
2013 [15]	India	7	po	14days	14	14
2013 [5]	USA	56	po	10 days	14	28
2012 [16]	Turkey	40	po	null	10	7
2012 [17]	USA	78	po	14days	14	90
2009 [18]	Taiwan	8	po	21days	14	21
					$\bar{x}$ = 14.36 (7 21)	$\bar{x}$ = 23.43 (7–90)

related factors include drugs that cause dry mouth, such as anticholinergics, antihypertensives and antidepressants, and antibiotics, such as tetracycline and penicillin [6]. BHT may be related to the presence of color-producing organisms (such as Candida albicans) or the attachment of drugs that cause discoloration. This may be due to the proliferation of filamentous papillary bacteria on the tongue, which can stain porphyrin-producing chromogenic bacteria or yeasts black. For severe BHT that needs treatment, bacterial or mold detection and drug use could be an important reference [7].

Glossophytia induced by linezolid is a rare condition, and no specific indicator has been available to identify it, and the incidence of black tongue in a large, controlled clinical study of 1498 patients was 0.2% [8]. The incidence of tongue discoloration caused by linezolid in patients diagnosed with uncomplex skin and soft tissue infections was 1.3% [9].

The patient was an adolescent male, who did not smoke, drink alcohol or drink coffee. During the treatment, he was treated with linezolid injection, nebutaline inhalation and acetylcysteine. After discharge, he only took linezolid tablets orally and did not use other drugs. According to the Karch and Lasagna evaluation methods and the WHO-UMC system for case causality assessment, the BHT symptom in this case was assessed as possibly related to linezolid.

Through the analysis of existing literature reports, Petropoulou T et al. reported that 3 patients appeared after intravenous medication, including 2 patients after 21 days, and the occurrence time of BHT was longer than that in other literatures of oral administration [10]. As the patient developed the symptom on the 14th day of intravenous injection and the 2nd day of oral administration, it was assumed that the symptom was related to both intravenous and oral administrations [11]. Direct contact of medication with the teeth and tongue was assumed to be the main cause of BHT associated with oral administration, and the affinity of linezolid to the tongue and teeth was assumed to be the main cause of BHT associated with intravenous administration. Due to personal reasons, the patient's tongue was not examined for etiology.

The patient was treated with vancomycin and had an adverse reaction of rash and pruritus. It could be assumed that the patient had allergic constitution, indicating that close observation is desirable for these patients. Figures in the literature reports revealed that the symptom initially affected the tongue base in most cases. In the course of medication, the situation of the tongue should be observed. In this paper, the symptoms of the patient completely disappeared on the 8th day after the drug was stopped, and the BHT caused by linezolid was self-limited. If the patient could not tolerate the drug, it was recommended to stop the drug. If the drug could not be stopped, it was recommended that the patient rinse the mouth with normal saline or hydrogen peroxide, and clean the tongue with soft toothbrush. In the event of serious symptom, conducting an etiological examination was recommended to detect whether there is bacterial or fungal infection. Antibiotics administration should be considered according to the positive results.

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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