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Linezolid Induced Black Hairy Tongue an Uncommon Phenomenon: A Case Report with Update of Review of Literature

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Abstract As the use of newer antibiotics like Linezolid is tremendously increasing due to their efficacy and safety against methicilin resistant staphylococcus aureus and Vancomycin resistant entero-cocci, its rarer side effect like black hairy tongue is often overlooked. Case presentation: A 26 year-old-male, reported with asymptomatic black hairy tongue (BHT) on tenth day after taking Linezolid 600mg twice daily for his left foot infection. His tongue examination was consistent with black hairy tongue. He neither exhibited any predisposing factor nor any history of substance abuse or drug except Linezolid and prompt withdrawal of drug led to complete resolution of BHT on seventh day. Re-challenge test revoked similar response on tenth day. WHO-UMC causality scale showed certain adverse drug reaction and on Naranjo's adverse drug reaction probability scale score of 10 indicates definite association. Conclusion: This case report is highlighted due to its rarity, self-limiting and reversible condition. The purpose of the paper is to create awareness amongst medical fraternity about Linezolid induced Adverse Drug Reaction.

Keywords: *Oxazolidinone, Naranjo's algorithm, adverse event, Linezolid, Lingua villosa nigra, DSM-5, HADS*

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1. Introduction

Linezolid is an oxazolidine and its use in the community has been increasing tremendously because it is active against both methicilin-resistant staphylococcus aureus (MRSA) and Vancomycin resistant entero-cocci (VRE) bacteria [1]. In the United States, the frequency of MRSA was 43% among hospitalized patients in intensive care units in 1999. Currently it has exceeded 50% [2].The incidence of black hairy tongue (BHT) in patients receiving Linezolid was 0.2% as reported by Hau T [3]. This condition has been associated with numerous medications and predisposing conditions. The known predisposing factors include smoking or chewing tobacco, excessive coffee/black tea consumption, poor oral hygiene, Trigeminal neuralgia, general debilitating conditions, Xerostomia, using peroxide containing oxidizing mouth washes, substance abuse like cocaine, alcoholics and HIV drugs like steroid, tetracycline, methyl-dopa, lansoprazole, antibiotics included cephalosporin's, penicillin's, clarithromycin and olanzapine [1,4,5]. Clinical presentation of the tongue varies from brown, yellow, green, blue to even un-pigmentation. It is also associated with gagging, dysgeusia, nausea, metallic taste, burning mouth and halitosis [6].

Typically asymptomatic, aesthetic concern commonly led patient to seek medical or dermatological consultation. Clinical diagnosis was relied on visual observations, detailed history and occasionally microscopic evaluation.

This case is reported due to its rarity, which highlights adverse drug reaction (ADR), that was benign and self limiting due to Linezolid and its incidence is going to increase due to drug usage in near future.

2. The Case

A 26 year-old-male presented to the out-patient Department of Dermatology at Government Medical College, Patiala with asymptomatic black hairy tongue on tenth day after taking Linezolid 600mg twice daily for his left-foot infection (calcaneum osteomyelitis). On examination of his oral cavity, yellow to brown discoloration was seen on the posterior aspect of the dorsal surface of tongue sparing tip and the sides [Figure 1]. This hairy coating neither caused any hindrance in swallowing nor any abnormal sensations. He did not have any palpable cervical lymphadenopathy or any skin rash. His other systemic examination was unremarkable. MRI scan (1.5 T) of left ankle showed marrow edema in the calcaneum and fluid collection of the subcutaneous tissue along lateral aspect of left ankle joint [Figure 2]. Patient's complete haemogram was normal. Swabs for bacterial and fungal cultures were negative for micro-organism that grew normal flora. Potassium hydroxide

(KOH) prepared direct cytology for yeast or fungal elements were negative. Human immune deficiency virus (HIV) serology was non-reactive. Patient did not give consent for biopsy of his lesion. He neither has any predisposing factor nor any history of substance abuse or drug intake except Linezolid. Prompt withdrawal of Linezolid drug led to complete resolution of the discoloration on seventh day [Figure 3]. Patient self medicated himself with Linezolid drug, at the same dose, frequency and duration as his ankle swelling worsened after stoppage of medication. Due to this re-challenge test, he again developed yellow-brownish pigmentation (discoloration) of the tongue on day fifth and tenth day, respectively [Figure 4]. WHO-UMC causality scale showed that this phenomenon was certainly due to adverse reaction [7] and Naranjo's adverse drug reaction probability scale [8] score of 10 indicates definite association. Its recurrence on day tenth of re-challenge test asserts with certainty the relationship of Linezolid induced BHT. The diagnosis for co-morbid psychopathology was assessed by semi-structured clinical interview on Diagnostic and Statistical Manual of Mental Disorder -5 (DSM-5) [9]. The severity for general anxiety was assessed on Hospital Anxiety and Depression Scale-Anxiety (HADS-A) [10] and the clinical outcomes on Clinical Global Impression- Severity Scale (CGI-S) [11] scores were 9 and 4 respectively, indicating mild anxiety. These symptoms of anxiety were due to perceived adverse events of the drug on tongue. It can be a normative stress reaction in most of the cases when people hear or realize bad things happening to them. It can neither be attributed to drug nor to the premorbid anxious personality State or Trait of the patient because of low level scores i.e., 27 and 35, as assessed on State and Trait Anxiety Inventory (STAI) [12]. After 4 weeks, HADS-A and CGI-S scores were 6, 2 respectively, indicating much improvement.

Figure 1. Black hairy tongue after receiving Linezolid for ten days

Figure 2. MRI finding of left ankle showing marrow oedema in the calcaneum and subcutaneous tissue

Figure 3. Complete resolution of black hairy tongue after withdrawal of drug

Figure 4. Reappearance of black hairy tongue after restart of Linezolid drug

3. Discussion

A systemic review of literature and articles on Linezolid induced Black hairy tongue in English was conducted by searching in PubMed, SCOPUS, EMBASE, EBSCO, Index Copernicus, Medline, Ulrichs, Hinari, Google scholar and Cochrane Library. Additionally, grey literature (referring to documents produced in print and electronic formats protected by intellectual property rights was searched. Free text search terms were "Linezolid induced Black hairy tongue", "yellow discoloration of tongue", "yellowish-brown discoloration of tongue due to Linezolid", "Linezolid induced side effects of tongue", "Adverse drug reaction due to Linezolid", "Side-effects of Linezolid". The following terms were also included as MeSH terms combined with the Boolean term "All Fields AND negative [All Fields]; AND diagnosis [Subheading] OR diagnosis [All Fields] OR symptoms [All Field] OR diagnosis MeSH terms OR symptoms [All Field] AND "Linezolid," "Black hairy tongue" etc., and others words vide-supra [Mesh Terms] to support firmer conclusion." Dates of publication were limited from January 2000 to June 2016 using Cochrane library. The total of 108 articles was screened (76 records +32 additional records) and assessed for study eligibility [Figure 5]. After narrowing down the search with words BHT, Linezolid and excluding 94 articles from the study, only 14 case reports were included that fulfill the conditions vide infra for the final analysis of review of literature [Table 1] [Figure 5].

Table 1. linezolid induced bht reported cases in literature

Author with reference	Clinical indication for Linezolid use	Concomitantly use medications	Naranjo's score	Time duration	Resolving time	Treatment given
Matson and Miller* 2003 [22]	MRSA Toes cellulitis in Immuno-compromised, [HIV] girl	ART [Stavudine, lamivudine, lopinavir-ritonavir, TMP-SMX and fluconazole]	6	2 weeks	1 month	Reversible with manual dental cleaning
Amir KA *et al* 2006 [23]	Kidney transplant	Immunosuppressive, Steroids, antibiotic, anti-virals	7	2 weeks	6 months	Withdrawal of drug
Refaat *et al* 2008 [24]	T cell rich B cell Lymphoma patient	Intravenous Vancomycin	6	2 days	3 days	Discontinuation of drug
Ma JS 2009 [25]	MRSA bacteriema and polyarithits	Intravenous Vancomycin	6	2 weeks	3-4 weeks	No discontinuation of drug done
Jover-Diaz F** *et al* 2010 [1]	Empiric therapy for spondylodiscitis following laminectomy	Intravenous Vancomycin and Rifampin	6	2 weeks	7 days	Discontinuation of drug
Bozkurt I *et al* 2012[26]	Disseminated nocardia infection in a SLE patient with multiple brain abscess	Steroids, Cefota-suppressive (AZP), antibiotics (TMP-SMX)	6	10 days	7 days	Brushing and good oral hygiene
Marina and Kasmani ***2012[27]	Elderly renal transplant recipient with MRSA enterococcal UTI	Immuno-suppressives (CsA, MPA), steroid, Vancomycin	NR	10 days	3 months	Discontinuation of the drug
Khasawneh *et al* 2013[28]	Empirical therapy for MRSA pneumonia	Ertrapenem, hydrocodone and acetaminophen, albuterol and ipratropium bromide MDI	6	2 weeks	4 weeks	Baking soda containing toothpaste
Aijazi and Abdulla 2014[29]	T_2DM, CKD, IHD, Post procedural hypothyroidism, left foot osteomyelitis	Antibiotics	NR	2 weeks	3-4 weeks	Baking soda containing toothpaste, Brushing and good oral hygiene
Petropoulou T* *et al* 2013[30]	5 year child with severe pneumonia with left lung abscess	Intravenous Clindamycin , Cefotaxime, Cefotaxime Meropenem	NR	2-3 weeks	1 month in case of tongue and 2 months in teeth discoloration	Withdrawal of drug along with dental cleaning
	Severe skin infection of left foot	Piperacillin-tazobactum or meropenem			1 month in case of teeth discoloration	
	Subperiosteal abscess of Left (orbital cellulitis)	Intravenous Clindamycin , Cefotaxime, Piperacillin-tazobactum			1 month in case of tongue and 2 months in teeth discoloration	
Balaji G *et al* 2014 [20]	Post surgical infection of left side of radial neck fracture	None	5	2 weeks	11 days	Normal saline
Joana Almeida Santos **et al* 2015 [31]	Subperiosteal abscess of Left (orbital cellulitis)	Intravenous Clindamycin, Cefotaxime, Piperacillin-tazobactum	NR	4 weeks	4 weeks	Withdrawal of drug along with dental cleaning
Mancano MA 2015 [32]	Postsurgical infection after surgery for left radial neck fracture	None	Probable	14 days	11 days	Normal saline
Present case [2016]	left foot infection (calcaneum osteomyelitis)	No other medication given	10	10 days	7 days	Withdrawal of drug and Normal saline

BHT= Black Hairy Tongue, NR = Not reported, AZP = Azathioprine, CsA = cyclosporin, MPA = Mycophenolic acid, TMP-SMX= Trimethoprim-sulfamethoxazole
*Tongue and tooth discoloration
** Oral mucosa and tongue
*** Tongue and lip.

Black hairy tongue (BHT) is an acquired, rare, benign, self-limiting condition characterized by elongation and hypertrophy of filiform papillae of the tongue with brown or black discoloration on the posterior dorsum of tongue [13]. This rarer side-effect is reported in 1.1% of 548 patients in comparator-controlled trials [14]. The exact mechanism for BHT is unknown but the theory propagated delineates to defective desquamation of dorsal surface of the tongue. This defective desquamation prevents normal debridement leading to accumulation of keratinized layers or delayed shedding of the cornified layer [15] that results in excessive growth and thickening of the filiform papillae and then secondarily collection of debris, bacteria, fungi or other foreign materials, which contribute to its discoloration. This collection can include residue from tobacco, tea, coffee and other foods, as well as porphyrin producing chromogenic organisms in the oral flora that lends its characteristic hue [16]. Another theory put forth by Prinz in 1925 regarding main source of pigmentation was that of a local reaction between decomposed food products and iron (secondary to blood within the mouth) [17]. Interference of the melanin at local level could be another factor to be taken in consideration.

Drug intake and appearance of BHT is essential in establishing causative relationship as there is no objective criteria for diagnosing this condition [15]. Cultures may be considered to rule out superimposed bacterial and fungal infections associated with BHT [18]. Tissue biopsy is supportive but not usually required if the lesions appear

characteristic for BHT [19]. Scanning electron microscopic studies have shown lengthening of filiform papillae due to accumulated keratinized layer [16]. Differential diagnosis includes "pseudo-hairy tongue", oral hairy leukoplakia, pigmented fungiform papillae of the tongue and acanthosis nigricans [6].

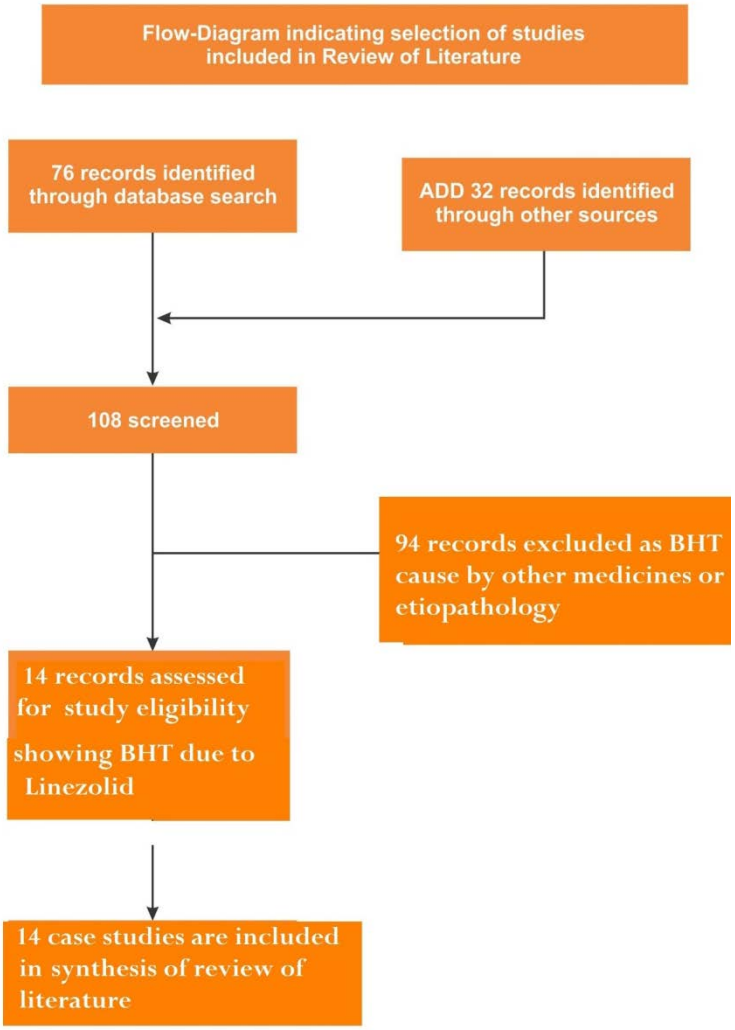

Figure 5. Flow chart showing selection of case studies

Presently, no definite therapy has been advocated for BHT but various treatments used vary from topical agents (hydrogen peroxide solution, topical triamcinolone acetonide etc.,) to oral retinoids, Yogurt and probiotic supplement [6]. Once BHT is diagnosed, discontinuation of the offending agent alongside practicing good oral hygiene usually resolves the problem [4]. Withdrawal of the drug with good oral hygiene along with baking soda was recommended as treatment by most of the authors while Balaji *et al* 20l4 [20] and Mancano MA 2015 [32] reported resolution of BHT with normal saline. Resistant BHT may require carbon dioxide lasers [6]. Cure has been also reported with application of 40% urea, gentian violet, thymol, Salicylic acid, vitamin B complex and surgical excision [4]. Other authors have suggested topical podophyllin and tretinoin but they are associated with problematic side effects [21].

We observed 14 case reports till date from our search. Although it is seen in adults (seven cases) [1,20,23,24,26,27,28,29,31] and pediatric (seven cases) have been reported in the literature due to their affinity towards dental structures [22,25,30], Table 1. Male prevalence was a common observation in the aforementioned case reports. Three authors [23,25,27] did not observe hair like filiform papillae changes on clinical examination and others used yellowish brown tongue discoloration as a parameter [1,25,31,33] suggesting BHT as a misnomer, while Mancano MA [32] had taken both the aspect in his case report.

The mean time duration for development of black hairy tongue after the start of Linezolid was two weeks ranging between two days to four weeks, which is concomitant with the observation of Khasawneh *et al* 2013 (range was between 2 days to two weeks) [28]. Our case findings were similar to those observed by Bozkurt *et al* 2012 [26] except that no concomitant medications were used.

The mean time duration for resolution of discoloration after discontinuation of Linezolid was of seven days (range from three days to six months), which was consistent with the finding of Khasawneh *et al* 2013 [28]. Ken Kobayashi *et al* 2010 [33] in his study demonstrated yellowish-brown to black hair like elongation of filiform papillae with whitish lingual papillae in two of his Japanese patients clearly proving it to be useful in diagnosis as an objective criteria. Teeth discoloration was observed more in children [22,25,30] and in adults where oral mucosa [1] and lips [27] were involved in addition to tongue.

Naranjo's adverse drug reaction probability scale scoring was used for predicating a probable association in most of the previous case reports [1,20,23,24,25,26,28,32]. None of the authors have used WHO-UMC scale with a re-challenge test in their case reports.

All authors had consensus regarding withdrawal of Linezolid except in the case report of Ma JS 2009 where patient tolerated the drug well in spite of BHT [25]. Khasawneh *et al* 2013 and Aijazi *et al* 2013 [28,29] advocated baking soda tooth paste while Balaji *et al* 2014 [20] and Mancano MA [32] recommended normal saline which was consistent with treatment given in the present case. Matson and Miller 2003 [22] concluded that drug to drug interaction possibility cannot be ruled out where multiple drugs were co-administered along with Linezolid.

In the present case, the appearance of BHT after the intake of Linezolid drug was based on clinical diagnosis, visual observation and microscopic evaluation. Its complete resolution after withdrawal of Linezolid establishes a causative relationship, which was further strengthened by the re-challenge test. WHO-UMC causality scale showed certain adverse reaction and Naranjo's adverse drug reaction probability scale (NADRPS) scoring for drug related adverse event that was 10 out of a maximum score of 12 (i.e. definite) and based on the following proposed diagnostic criteria for Linezolid induced BHT the score was 10/12.

At present, there is no specific histological criterion that has been incorporated for early diagnosis of this condition. In order to make the diagnosis of Linezolid induced black hairy tongue, it is suggested that three major and four minor criteria must be met with a cut off score of ≥7. We propose the following criteria for diagnosis of Linezolid induced black hairy tongue.

Major Criteria	**Score**
• Linezolid induced BHT establishing causal relationship	1
• Site involved posterior part of tongue with characteristic discoloration involving oral mucosa and/or teeth	1
• Prompt withdrawal improves the condition	1
• Re-challenge test	1
• Negative fungal and bacterial swabs	1
Minor criteria	
• Negative Cytology for extraneous material, yeast, bacterial and fungal bodies	1
• Cytological scrape showing hair like projections	1
• Dermoscopic findings demonstrating yellowish-brown to black hair-like elongation of filiform papillae with whitish lingual papillae clearly.	1
• Naranjo's adverse drug reaction probability scale scoring	1
• Histological appearance of marked elongation and hyperparakeratosis of filiform and numerous bacteria on the epithelia surface	1
• Lack of predisposing factors	1
• No specific treatment required	1
TOTAL SCORE	**12**

Based upon the above proposed criteria our total score for the index case was 10/12 that definitely establishes the diagnosis for Linezolid induced BHT. Further, studies are required for validation of the scale.

4. Conclusion

This case report is highlighted due to its rarity and to create awareness amongst the medical fraternity as their services are frequently sought for ameliorating this adverse reaction with utmost professional competence, diligence and prompt human care.

Limitation of Case Study

Lack of dermoscopic and electron microscopic findings.

Implication of This Case Study

The implication of this review will be that Linezolid drug can be continued in situations where it is the only drug for gram positive MRSA especially and in Vancomycin resistant entero-cocci as it acts not only on protein binding sites but also on the alternate binding sites of these organisms. Further, validation of the proposed scale by us and other authors in their studies is required.

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Conflict of Interest

None Declared.

Patients Consent

Written informed consent was obtained from the patient for publication of this case report and accompanying images.

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