

Linezolid induced Hairy Tongue: A rare but possible clinical presentation.

¹Joyabrata Sarkar, Final Year Undergraduate Student, Kusum Devi Sunderlal Dugar Jain Dental College & Hospital.

²Dr.Surajit Bose, Assistant Professor, Department of Oral and Maxillofacial Pathology & Microbiology, Kusum Devi Sunderlal Dugar Jain Dental College & Hospital.

³Dr. Jayanta Chattopadhyay, Professor & Head, Department of Oral and Maxillofacial Pathology & Microbiology, Kusum Devi Sunderlal Dugar Jain Dental College & Hospital.

Corresponding Author: Joyabrata Sarkar, Final Year Undergraduate Student, Kusum Devi Sunderlal Dugar Jain Dental College & Hospital.

Citation of this Article: Joyabrata Sarkar, Surajit Bose, Jayanta Chattopadhyay, “Linezolid induced Hairy Tongue: A rare but possible clinical presentation.”, IJDSIR- July - 2021, Vol. – 4, Issue - 4, P. No. 44 – 51.

Copyright: © 2021, Joyabrata Sarkar, et al. This is an open access journal and article distributed under the terms of the creative commons attribution noncommercial License. Which allows others to remix, tweak, and build upon the work non commercially, as long as appropriate credit is given and the new creations are licensed under the identical terms.

Type of Publication: Case Report

Conflicts of Interest: Nil

Abstract

The term Black Hairy Tongue (BHT) is used to describe an abnormal coating on the top (dorsal) surface of the tongue. Various contributing factors are cited in literature for this benign condition of tongue which is characterized by a temporary discolouration & furry appearance of tongue, but the actual etiology is unknown and uncertain. Beside heavy smoking, general debilitation, poor oral hygiene, drugs can be the precipitating factors. Out of the drugs, Linezolid-induced hairy tongue has been rarely clinically presented.

The aim of this paper is to record a rare clinical case of Linezolid-induced Hairy Tongue.

Keywords: Black Hairy Tongue, Linezolid, Benign.

Introduction

According to American Academy of Oral Medicine (AAOM), the term Hairy Tongue is used to describe an abnormal coating on the top (dorsal) surface of tongue.

Black hairy tongue (BHT) is an acquired, benign condition characterized by the appearance of abnormally hypertrophied and elongated filiform papillae on the dorsal surface of the tongue. The name is a misnomer and comes from its classical presentation as a superficial black and hairy carpet-like lingual growth. Hairy tongue may also appear brown, yellow, green, blue, or even unpigmented [1-3]. Amatus Lusitanus was first coined the term Black Hairy Tongue in the year 1557[4]. The exact etiology of BHT is still remaining unknown and unclear. But the contributing factors can be broadly classified into extrinsic (i.e. environmental) and intrinsic (i.e. chromogenic oral micro flora) [2]. Heavy smoking, alcohol consumption, intravenous drug use, excessive coffee consumption, poor oral hygiene, general debilitation, and recent radiation therapy to the head and neck region are important extrinsic risk factors that

predispose some patients to develop BHT [5-8]. Local and systemic medication use has been commonly associated with development of BHT. Antibiotics like such as penicillin, doxycycline, erythromycin, aureomycin, neomycin are often linked with this disorder whereas systemic use of linezolid can be a rare precipitating factor [3, 5, 11-13]. Prolonged exposure to oxidizing mouthwashes containing sodium perborate, sodium peroxide, and hydrogen peroxide has also been proved as precipitating factors in some cases of BHT [9]. Similarly, the pathophysiology of BHT has not been fully decoded till now but is thought to be arising from derangement of desquamation of dorsal surface of tongue, thus prevents normal debridement and results into accumulation of keratinized layers [10]. From the pathological aspect we can say that Hairy Tongue is a clinical presentation of marked keratinisation over the filiform papillae on the dorsum of tongue in histopathology. The prevalence of BHT varies from 0.6% to 11.3% with respect to geographical site of occurrence [4]. In a large case-controlled study conducted by Hau.T., it was found that incidence of BHT in patients on linezolid therapy is 0.2% [14].

Case Report

A 54 year old Indian man was presented to a General Surgeon with hydrocoel and ulcerative scrotum. Surgeon prescribed with:

1. Linezolid 600mg twice daily after meals for 5 days. (To reduce the secondary infection)
2. Trypsin-Chymotrypsin 1,00,000 AU Twice daily after meals for 5 days (for reducing the swelling & redness.)
3. Mupirocin 2% w/w ointment for topical application (for reducing the secondary infection and proper healing of the ulcer.)

At Day 5, He visited a dental surgeon and complained of blackish discolouration on the dorsum of the tongue with no complain of associated pain, burning sensation, paraesthesia or anesthesia of tongue. He said the discolouration started to appear after 2-3 days of starting the medications for the hydrocele. It is a constant type of discolouration and increases in the darkness of the patch. He has no history of any deleterious habits like chewing tobacco or smoking and no history of any other comorbidities and not taking any other medications on daily basis other than the above medications. And doesn't have any history of drug allergy.

On Clinical Examination, the extra-oral findings are under normal limits with respect to age, sex and other parameters. Intra-orally, dorsum of tongue reveals a brownish-black midline discolouration on the anterior 2/3 rd portion of tongue, hypertrophy of papillae with no other significant findings. The patient was suspected of suffering from Black-Hairy Tongue.



Image 1: Intra-oral presentation of Patient on 5th day of Linezolid Therapy.

The Patient was not willing to go for biopsy or histopathological examination. On Naranjo Probability Scale of Adverse drug reactions, the score for linezolid

induce BHT in this case is 5, which signifies the adverse reaction is probable in this case [15].

The patient was asked to discontinue the drug Linezolid and the General Surgeon advised alternate medication and advised to maintain proper oral hygiene by rinsing the mouth with normal saline twice or thrice daily. After 12 days, Patient came for follow-up and the discoloration started to disappear and there was marked improvement and on 20th day of follow-up, it was totally disappeared and not relapsed again. From the Clinical Course and Naranjo's Probability Scale, it was diagnosed as Linezolid-induced black hairy tongue.



Image 2: Intra-oral picture of patient on 12th day Follow-up after discontinuation of drug.



Image 3: Intra-oral picture of patient on 20th day Follow-up showing full resolution of the lesion.

Discussion

The patient was on three medications, out of which chymotrypsin-trypsin and mupirocin has no systemic effect. Mupirocin was advised to use topically on scrotal area so can't cause BHT. And there was no case reported in previous literature about chymotrypsin-trypsin induced BHT. Though it is rare but reported cases are there about Linezolid induced BHT. And the lesion resolved after Linezolid is discontinued in this patient and no other specific treatment is advised in this case. Other known causative factors of BHT like Smoking, Poor Oral Hygiene, Xerostomia, Using Peroxide Containing Mouth Wash, Drugs like steroids, olanzepine, and methyl dopa are ruled out by proper history taking and clinical examination.

Linezolid is the first purely synthetic antibiotic of oxazolidinone group. Its mechanism of action is to inhibit bacterial protein synthesis by binding to the A-site of 50S ribosomal subunit near the interface with 30S subunit, where the amino acid moiety of aminoacyl tRNA normally binds. The initiation complex formation for bacterial protein synthesis is thus prevented [16]. The antimicrobial activity of Linezolid is confined within Gram positive bacteria as it is effluxed out by Gram negative bacteria. So, it can be used for the treatment of infections caused by Multi-Drug resistance Gram-positive bacteria such as in case of Vancomycin Resistant Enterococcus faecium, endocarditis, bacteraemia by MRSA, nosocomial and acquired pneumonia by Staphylococcus aureus (including MRSA) and penicillin sensitive streptococcus pneumonia, complicated skin infections by MRSA and penicillin resistant streptococcus pyogenes. It is also sometimes active against gram positive bacilli infections like Corynebacterium diphtheriae, Bacillus anthracis, Bacteroides fragilis, Clostridia [16, 17]. It is also approved for pediatric use

and diabetic foot [18, 19]. The standard approved regimen for linezolid is 400mg or 600mg 12 hourly for 10 to 28 days duration depending upon severity, in oral or intravenous route as per indication [17].

The oral bioavailability of linezolid is 100%. Its absorption is not delayed or enhanced by food intake. It is metabolized in liver and excreted in urine as free drug. It has plasma-half life of 4-6 hours. Adverse effects of long term usage include reversible thrombocytopenia, neutropenia, and optic neuropathy. Minor adverse effects are diarrhea, pseudo-membranous colitis, headache, taste alteration, oral candidiasis [16, 17].

If there is an imbalance between desquamation of keratinized layer and its formation then it results into excessive growth and broadening of filiform papillae which leads to formation of crypts in between them and

micro-organisms and food debris are collected. Poor Oral hygiene accelerates this process. The exact pathophysiology of drug-induced Black Hairy Tongue is not known. No specific step is taken for the initial treatment of BHT. Only the suspected drug is advised to discontinue and to maintain a good oral hygiene [20]. Generally, in most of the cases, the lesion subsides after this therapy. If no improvement is seen after following these advices, many literature is there to treat with 40% urea, salicylic acid or to go for surgical excision in persistent cases [5,21].

After going through a meticulous searching with the words Linezolid, BHT, excluding 98 articles of study only 16 case reports were included that fulfill the conditions vide infra for the final analysis of review of 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 polyarthritits	Intravenous Vancomycin	6	2 weeks	3-4 weeks	No discontinuation of drug done
Jover-Diaz F et al 2010 [26]	Empiric therapy for spondylodiscitis following laminectomy	Intravenous Vancomycin and Rifampin	6	2 weeks	7 days	Discontinuation of drug

Bozkurt I <i>et al</i> 2012 [27]	Disseminated nocardia infection in a SLE patient with multiple brain abscess	Steroids, Cefotaxime, suppressive (AZP), antibiotics (TMP-SMX)	6	10 days	7 days	Brushing and good oral hygiene
Marina and Kasmani 2012 [28]	Elderly renal transplant recipient with MRSA enterococcal UTI	Immuno-suppressives (CsA, MPA), steroid, Vancomycin	NR	10 days	3 months	Discontinuation of the drug
Khasawneh <i>et al</i> 2013 [29]	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 [30]	T ₂ DM, 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 <i>et al</i> 2013 [31]	5 year child with severe pneumonia with left lung abscess	Intravenous Clindamycin , 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-tazobactam or meropenem			1 month in case of teeth discoloration	
	Subperiosteal abscess of Left (orbital cellulitis)	Intravenous Clindamycin , Cefotaxime, Piperacillin-tazobactam			1 month in case of tongue and 2 months in teeth discoloration	
Balaji G <i>et al</i> 2014 [20]	Post surgical infection of left side of radial	None	5	2 weeks	11 days	Normal saline

	neck fracture					
Joana Almeida Santos <i>et al</i> 2015 [32]	Subperiosteal abscess of Left (orbital cellulitis)	Intravenous Clindamycin, Cefotaxime, Piperacillin-tazobactam	NR	4 weeks	4 weeks	Withdrawal of drug along with dental cleaning
Mancano MA 2015 [33]	Postsurgical infection after surgery for left radial neck fracture	None	Probable	14 days	11 days	Normal saline
Rakesh et al 2016 [34]	left foot infection (calcaneum osteomyelitis)	No other medication given	10	10 days	7 days	Withdrawal of drug and Normal saline
Jain AK et al 2017 [35]	Drug resistant Pulmonary TB (2 Cases)	No other medications are given	NR	2-3 Weeks	14 days	
Angoori et al 2019 [36]	Septic Arthritis	No other medications given	Possible	2 weeks	2 weeks	

Conclusion

Black Hairy Tongue (BHT) induced by Linezolid is an uncommon condition which is rarely reported. This is completely a benign condition. In the patients under Linezolid therapy, Linezolid-induced Black Hairy Tongue should be diagnosed after excluding the other precipitating factors of BHT. Patients prescribed with Linezolid should also advised by the physician to maintain a good oral hygiene to prevent the development of BHT. The exact etiopathogenesis of BHT is not known, more study and research should be incorporated in this topic to reveal the unknown pathways.

References

1. Pegum JS. Urea in the treatment of black hairy tongue. *Br J Dermatol.* 1971;84:602.
2. Pouloupoulos AK, Antoniadis DZ, Epivatianos A, Grivea IN, Syrogiannopoulos GA. Black hairy tongue

in a 2-month-old infant. *J Paediatr Child Health.* 2008;44:377–379.

3. Prinz H. Black tongue. *Br Dent J.* 1925;46:1265–1274.
4. Gurvits GE, Tan A. Black hairy tongue syndrome. *World J Gastroenterol* 2014;20(31):10845-50.
5. Thompson DF, Kessler TL. Drug-induced black hairy tongue. *Pharmacotherapy.* 2010;30:585–593.
6. Avcu N, Kanli A. The prevalence of tongue lesions in 5150 Turkish dental outpatients. *Oral Dis.* 2003;9:188–195.
7. Nisa L, Giger R. Black hairy tongue. *Am J Med.* 2011;124:816–817.
8. Taybos G. Oral changes associated with tobacco use. *Am J Med Sci.* 2003;326:179–182.
9. Sarti GM, Haddy RI, Schaffer D, Kihm J. Black hairy tongue. *Am Fam Physician.* 1990;41:1751–1755.

10. Manabe M, Lim HW, Winzer M, Loomis CA. Architectural organization of filiform papillae in normal and black hairy tongue epithelium: dissection of differentiation pathways in a complex human epithelium according to their patterns of keratin expression. *Arch Dermatol.* 1999;**135**:177–181.
11. Pigatto PD, Spadari F, Meroni L, Guzzi G. Black hairy tongue associated with long-term oral erythromycin use. *J Eur Acad Dermatol Venereol.* 2008;**22**:1269–1270.
12. Refaat M, Hyle E, Malhotra R, Seidman D, Dey B. Linezolid-induced lingua villosa nigra. *Am J Med.* 2008;**121**:e1.
13. Jover-Diaz F, Cuadrado-Pastor JM, Talents-Bolos A, Martin-Gonzalez C. Black tongue associated with linezolid. *Am J Ther.* 2010;**17**:e115–e117.
14. Hau T. Efficacy and safety of linezolid in the treatment of skin and soft tissue infections. *Eur J Clin Microbiol Infect Dis.* 2002;**21**:491–8.
15. Naranjo CA et al. A method for estimating the probability of adverse drug reactions. *Clin Pharmacol Ther* 1981; 30: 239245.
16. Seyed Mohammad Reza Hashemian, Tayebeh Farhadi, Mojdeh Ganjparvar. Linezolid: a review of its properties, function, and use in critical care. *Drug Des Devel Ther.* 2018; 12: 1759–1767.
17. Paul W. Ament, Namirah Jamshed, John P. Horne. Linezolid: Its Role in the Treatment of Gram Positive, Drug-Resistant Bacterial Infections. *Am Fam Physician.* 2002 Feb 15;65(4):663-671.
18. Saiman L, Goldfarb J, Kaplan SA, Wible K, Edge-Padbury B, Naberhuis-Stehouwer S, Bruss JB. Safety and tolerability of linezolid in children. *Pediatr Infect Dis J.* 2003 Sep;22(9 Suppl):S193-200.
19. Majcher-Peszynska J, Haase G, Sass M, Mundkowski R, Pietsch A, Klammt S, Schareck W, Drewelow B. Pharmacokinetics and penetration of linezolid into inflamed soft tissue in diabetic foot infections. *Eur J Clin Pharmacol.* 2008 Nov;64(11):1093-100.
20. Govindan Balaji, B. Maharani, Velappan Ravichandran, Thiyagarajan Parthasarathi. Linezolid Induced Black Hairy Tongue. *Indian J Pharmacol.* 2014 Nov-Dec; 46(6): 653–654.
21. Langtry JA, Carr MM, Steele MC, Ive FA. Topical tretinoin: A new treatment for black hairy tongue (lingua villosa nigra) *Clin Exp Dermatol.* 1992;17:163–4.
22. Matson KL, Miller SE. Tooth discoloration after treatment with linezolid. *Pharmacotherapy.* 2003 May;23(5):682-5.
23. Amir KA, Bobba RK, Clarke B et al (2006) Tongue discoloration in an elderly kidney transplant recipient: treatment-related adverse event? *Am J Geriatr Pharmacother* 4(3):260–263.
24. Refaat M, Hyle E, Malhotra R, Seidman D, Dey B. Linezolid-induced lingua villosa nigra. *Am J Med.* 2008;121(6):e1.
25. Ma JS. Teeth and tongue discoloration during linezolid therapy. *Pediatr Infect Dis J.* 2009 Apr;28(4):345-6.
26. Jover-Diaz F, Cuadrado-Pastor JM, Talents-Bolos A, Martin-Gonzalez C. Black tongue associated with linezolid. *Am J Ther.* 2010 Jul-Aug;17(4):e115-7.
27. Bozkurt, I., Yontar, I., Doganay, M, Black hairy tongue: a rare side effect of Linezolid, *Our Dermatol Online.* 2012;3(2).136-137.
28. Marina VP, Kasmani R. An uncommon side-effect of linezolid. *Int Urol Nephrol.* 2012 Jun;44(3):995-6.
29. Faisal Abdullah Khasawneh, Dereje Fikremariam Moti, Joseph Anthony Zorek. Linezolid-induced black hairy tongue: a case report. *J Med Case Rep.* 2013; 7: 46.

30. Aijazi I, Abdulla FM. Linezolid induced black hairy tongue: a rare side effect. *J Ayub Med Coll Abbottabad*. 2014 Jul-Sep;26(3):401-3.
31. Petropoulou T, et al. Teeth and tongue discoloration after linezolid treatment in children. *Pediatric Infectious Disease Journal*. Nov 2013; 32: 1284-1285, No. 11.
32. Joana S, Luis V, Cartarina G. Reversible Teeth Discoloration in Children: A Linezolid Therapy Side Effect. *Clinical Pediatrics*. Dec 2014;54(08).
33. Mancano, M., A, High-Dose Loperamide Abuse Inducing Life-Threatening Cardiac Arrhythmias; Topiramate-Induced Diarrhea in a Breastfed Infant; Danazol-Induced Stevens-Johnson Syndrome; Asenapine-Induced Myasthenic Syndrome; Black Hairy Tongue Due to Linezolid; Adalimumab-Induced Priapism, *Hosp Pharm*. 2015 May; 50(5):351-5.
34. Rakesh Tilak Raj, Rajnish Raj, Jitender Nagpal, Raj Kumar. Linezolid Induced Black Hairy Tongue an Uncommon Phenomenon: A Case Report with Update of Review of Literature. *American Journal of Medical Sciences and Medicine*. 2016;4(4), 71-76.
35. Jain AK, Puri MM, Sarin R. Black brown discoloration and hairy tongue - A rare linezolid side effect. *Indian J Tuberc*. 2017 Jan;64(1):44-46.
36. Rao AG, Aparna K, Reddy VS, Farheen SS, Hakkani R, Parimala D, Tejal M, Gupta S. Linezolid-induced black pigmentation of tongue and perioral region. *Indian J Paediatr Dermatol* 2019;20:189-90