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# Amitriptyline-Induced Multifocal Oral Mucosal Dyspigmentation—Bridging Pharmacopsychodermatology in Skin of Color

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## INTRODUCTION

During focused, new-patient dermatology encounters, examination of the oral mucosa is often deferred, leading to missed diagnoses that patients may not be aware of. This is especially valid during an encounter with a non-English-speaking patient as they cannot effectively convey their concerns. This obstacle, in addition to major depression, which is frequently encountered in outpatient dermatology, together confer a challenging patient encounter that may render a poor quality of life for the afflicted patient. Vulnerable ethnic patient populations require special attention, provider cultural competency, and a thorough review of their history with the assistance of a certified foreign language interpreter. Herein, we present the case of a middle-aged Bengali female whose chief complaint of periorificial hypopigmentation led to an oral cavity examination, revealing unique findings.

## CASE REPORT

A 43-year-old South Asian, Bengali-only-speaking female with a past medical history of major depressive disorder and schizophrenia, well-controlled with compliant use of risperidone for 20 years and amitriptyline for 12 years, presented to the dermatology clinic with a chief complaint of periorificial hypopigmentation of six months' duration. She reported using a peroxide-containing toothpaste twice daily and a moisturizing SPF 15 facial cream, and always dressing modestly with long-sleeved clothing and a religious veil. She denied use of tobacco, alcohol, illicit drugs, chewing betel quid, paan, or other exotic plants, or having amalgam dental fillings. On physical examination, a continuous, periorificial, mildly hypopigmented patch surrounding the vermilion border of the upper and lower cutaneous lips was noted in the patient with Fitzpatrick skin type (FST) IV. On examination of the oral cavity, slate-gray pigmented, ill-defined macules and patches were noted on the superior and inferior mucosal lips, buccal mucosae, hard palate, soft palate, and dorsal tongue without secondary changes, which were all unnoticed by the patient (Figures 1 and 2). The main differential diagnoses at this point included black hairy tongue, mucosal melanosis as an ethnic variant of normal physiologic pigmentation, drug-induced dyspigmentation, and, less likely, an underlying endocrinopathy. A biopsy was deemed the best next step in management.

**FIGURE 1.** Ill-defined, slate-gray pigmented macules and patches on the dorsal tongue.

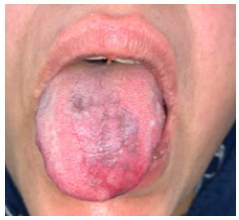


**FIGURE 2.** Ill-defined, slate-gray pigmented macules and patches on the right buccal mucosa, and hard and soft palates.

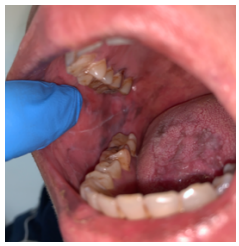


**FIGURE 3.** Fontana-Masson stain highlighting melanin in basal keratinocytes and pigment in the superficial dermis (10x).

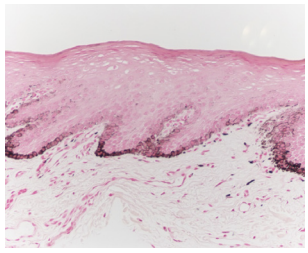
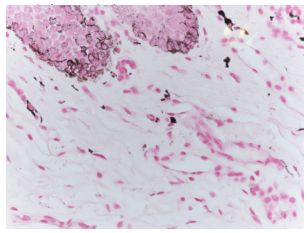


**FIGURE 4.** Fontana-Masson stain highlighting free granules of melanin in the dermis as well as a few melanophages without a melanocytic proliferation (20x).



Upon tangential shave biopsy of the inferior mucosal lip, dermatopathology results were obtained. A hematoxylin and eosin (H&E) stain illustrated squamous mucosal epithelium with prominent melanin in the basal layer. A Fontana-Masson stain highlighted melanin in basal keratinocytes, and free melanin granules, as well as a few melanophages in the superficial dermis without a melanocytic proliferation (Figures 3 and 4). A Perl's stain for iron was negative. With this information, the main differential diagnoses were revisited.

## DISCUSSION

Though these dermatopathology findings may have some overlapping features observed in post-inflammatory pigmentary alterations and mucosal melanosis, the presence of free melanin granules in the superficial dermis not associated with histiocytes, and the lack of a melanocytic proliferation, supported amitriptyline-induced pigmentation, and undermined the other leading differential diagnoses. The multifocal distribution of the non-contiguous oral mucosal dyspigmentation on physical examination and negative social history dismissed black hairy tongue and smoker's melanosis, respectively, as the former, is limited to findings on the anterior two-thirds of the dorsal tongue, and the latter primarily affects the anterior maxillary and mandibular gingivae with infrequent involvement of other oral mucosal sites.[1] Hyperpigmentation secondary to endocrinopathies was excluded due to an otherwise normal endocrine history and prior laboratory results on chart review. Altogether, the clinicopathologic correlation and a thorough review of the patient's medications supported a diagnosis of drug-induced multifocal oral mucosal dyspigmentation associated with amitriptyline.

Major depressive disorder (MDD) is proposed by the World Health Organization (WHO) to be a prominent cause for loss of disability-adjusted life years,[2] and is frequently encountered in a dermatology practice[3] among other psychiatric disorders either as a primary disease process or secondarily as a result of a cutaneous dermatosis. Common tricyclic antidepressants (TCAs) include amitriptyline and imipramine. Whereas amitriptyline induces hyperpigmentation via increased melanin deposition in the basal layer and free melanin granules in the dermis,[4] imipramine causes golden-brown globular dermal deposits.[4] Both drugs stain positive with a Fontana-Masson stain and negative with a Perl's stain,[4] as observed in this case with amitriptyline. Amitriptyline is metabolized by the CYP2C19 hepatic system to its active metabolite nortriptyline, which is also a TCA nearly twice as potent as other TCAs.[5] Amitriptyline and nortriptyline may be stimulated even after one exposure to ultraviolet radiation (UVR) or visible light to activate tyrosinase, thereby increasing melanin[6] and capturing amitriptyline free radicals.[6] The amitriptyline-induced free melanin particles are known to cause a clinically blue or slate-gray hyperpigmentation on sun-exposed skin,[7] which was distinctively absent on this patient's physical exam, making the oral mucosal findings particularly unique.

Selective serotonin reuptake inhibitors (SSRIs) have become the first-line therapy in the outpatient management of MDD, generally replacing TCAs[2] for many decades largely due to their enhanced safety profile. To date, over 13 cases of imipramine-induced and three cases of amitriptyline-induced cutaneous hyperpigmentation have been reported,[4,5,7] with the onset of dyspigmentation often occurring many years after initiation of the TCA.[7] Although amitriptyline[8] and olanzapine[9] have been reported in the literature to cause black hairy tongue, amitriptyline has not yet been reported to cause multifocal oral mucosal dyspigmentation.

Discontinuation of the offending drug does not lead to resolution of the dyspigmentation, but rather prevents further worsening.[4,5,7] In the setting of having achieved stability of the patient's MDD, it was unfavorable to stop amitriptyline, so reassurance was provided and the patient remained unbothered by the oral lesions. Finally, the patient's chief complaint of periorificial hypopigmentation was attributed to her peroxide-containing toothpaste and reassurance was also provided for this finding.

Establishing rapport and trust with vulnerable patient populations, such as skin of color (SOC) minorities or those who do not speak English as their first language, is of critical importance in the dermatology clinic. This was achieved with consistent use of a certified language interpreter and personal cultural competency. The common cultural practice of chewing betel quid or paan among South Asian populations, which can lead to gum disease and cutaneous irritant contact dermatitis[10] with subsequent post-inflammatory hyperpigmentation, served as a significant topic of discussion during the office visit. This culturally relevant knowledge and questioning enriched the patient encounters, allowing the patient to build trust with her provider, and aided in arriving at the best diagnosis. Dermatologists must always strive to provide well-rounded, culturally sensitive, high-quality care to all SOC patients, and especially those with an established, concomitant mental illness.

## DISCLOSURES

The authors have no conflict of interest to declare.

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