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Doxorubicin induced tongue hyperpigmentation

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ABSTRACT

Oral hyperpigmentation is an infrequent phenomenon reported in the literature as a side effect that may be seen with the administration of certain chemotherapy agents such as doxorubicin. Given the under reported nature of mucosal hyperpigmentation, treating providers are frequently unaware of this benign presentation and thus may pursue unnecessary testing. The exact pathophysiology and mechanism of action of this phenomenon is poorly understood; however, it is hypothesized that some chemotherapy drugs may trigger increased melanin deposition. With regard to management, clinical monitoring for eventual resolution status post chemotherapy without additional therapy is sufficient. Increased familiarity with this uncommon side effect will prevent invasive testing and undue stress to the patient. We present a case of tongue hyperpigmentation that occurred during administration of doxorubicin and cyclophosphamide in the neoadjuvant setting for management of stage IIIA(cT2,cN1,M0) hormone receptor positive breast cancer, which resolved without intervention after completion of chemotherapy course.

Introduction

Treatment with cytotoxic chemotherapy agents can result in a variety of systemic side effects. More frequently, typical oral mucosal side effects associated with systemic chemotherapies include candidiasis, mucositis, and taste alterations. While the episodes of oral mucosal hyperpigmentation specifically associated with doxorubicin has been documented since 1976, the incidences of tongue hyperpigmentation and management has varied greatly in literature (Rao et al., 1976). According to Acharya et al. (2017), in a study of 52 of women receiving doxorubicin and cyclophosphamide, 50% reported oral mucosal hyperpigmentation (Acharya et al., 2017). However, literature has reported, less frequent occurrences of hyperpigmentation of the oral mucosa, nails, and skin with doxorubucin (Carvalho et al., 2009). While mucosal hyperpigmentation may be an underreported finding, it is imperative for treating oncology providers to be familiar with doxorubicin's spectrum of side effects to guide appropriate clinical management.

Case report

A 39-year-old premenopausal, African American female with a non-significant past medical history presented to the medical oncology for evaluation of clinical stage IIIA (cT2, cN1, M0) invasive breast cancer. The invasive ductal carcinoma was nuclear grade 3, Ki-67 45%, estrogen receptor positive (H-score 270), progesterone receptor negative (H-score 0), HER-2/neu negative (2+ on IHC, FISH 1.57, Copy Number 2.63). Staging scans with computerized axial tomography (CT) of the chest, abdomen and pelvis as well as bone scan were negative for distant metastatic disease. Due to the extent of her nodal involvement, she was recommended to have neoadjuvant chemotherapy with dose dense administration of doxorubicin (60 mg/^{2}) and cyclophosphamide (600 mg/m^2) was initiated and given every 2 weeks for 4 cycles with growth factor support with Pegfilgrastim and subsequent plan for paclitaxel (100 mg/m2) to be given weekly x 12 cycles.

After the second cycle of dose dense doxorubicin and cyclophosphamide, she developed painless black macules on her tongue (Fig. 1). No other oral lesions, mucosal changes, melanonychia, nail changes or hyperpigmented cutaneous findings on body were identified. The patient is a nonsmoker. She denied taking tetracycline based antibiotics, bismuth containing products, or oxidizing mouth rinses. She denied prior experience of oral and skin hyperpigmentation, as well as new symptoms aside from her spontaneous resolving fatigue that was likely from chemotherapy. Complete blood count with differential (CBC w/diff), complete metabolic panel (CMP) were all within normal limits with the exception of mild leukocytosis that was expected secondary to Pegfilgrastim.

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Fig. 1. Initial tongue hyperpigmentation documented after 2 cycles of dose-dense neoadjuvant doxorubicin/cyclophosphamide.

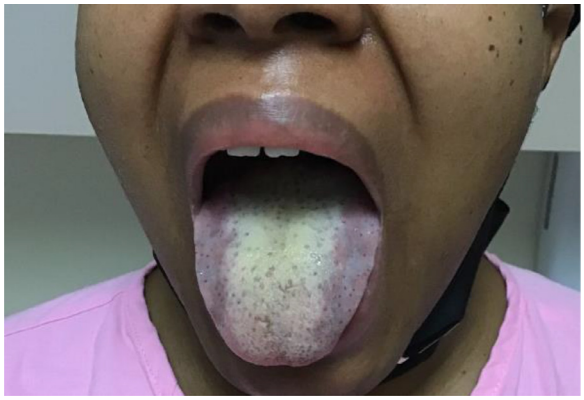


Fig. 2. Resolving tongue hyperpigmentation 16 weeks after initial onset.

Given the patient's clinical presentation, history, and recent treatment with doxorubicin the there was a low suspicion that her tongue hyperpigmentation was due to malignancy. Additionally, the absence of additional mucosal, cutaneous, melanonychia, tobacco abuse, consumption of hyperpigmenting medications such as minocycline, bismuth, or antipsychotics and lack of concerning systemic symptoms supported the decision not to pursue further clinical investigation. Upon literature review it was confirmed that doxorubicin is known to cause of mucosal hyperpigmentation especially in darker pigmented patients.

Ultimately the patient perceived the tongue hyperpigmentation as a cometic nuisance to the patient. Although the patient never questioned the necessity of treatment with doxorubicin, she was concerned that the hyperpigmentation would be permeant. With patient reassurance that the tongue hyperpigmentation was a self-limiting, benign side effect and close surveillance, she agreed to continue treatment with doxorubicin. The patient was advised to continue good oral hygiene by brush her teeth with soft toothbrush twice a day and to avoid known hyperpigmenting drugs such as Bismuth, minocycline, and oxidizing mouthwashes as this could enhance her tongue hyperpigmentation and prolong resolution.

The patient's tongue hyperpigmentation persisted throughout the four cycles of doxorubicin and cyclophosphamide. Once the course of doxorubicin and cyclophosphamide was completed, the hyperpigmentation gradually resolved without intervention (Fig. 2). Ultimately, her tongue returned to its normal pigmentation over several months (Fig. 3).

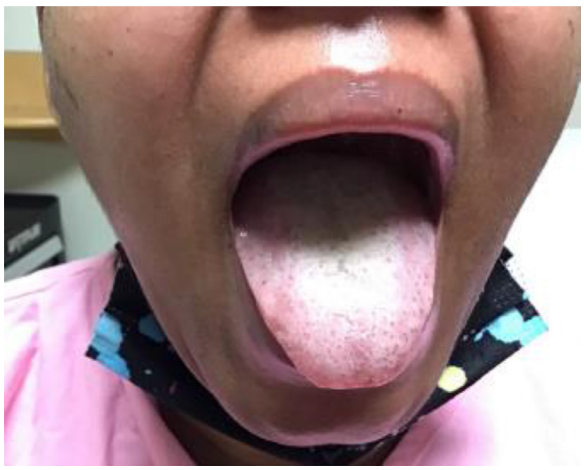


Fig. 3. Resolution of tongue hyperpigmentation, 24 weeks after onset.

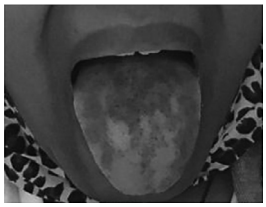
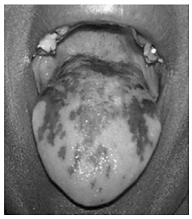
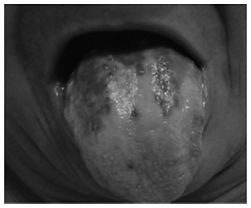
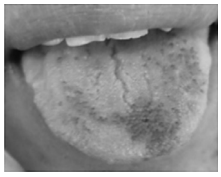
Discussion and conclusion

While chemotherapy associated hyperpigmentation is documented in the literature, oral hyperpigmentation is an infrequent and benign side effect of certain chemotherapeutic agents. Given the absences of additional mucosal changes, systemic cutaneous abnormalities, or prior episodes of tongue discoloration, it was suspected that the tongue hyperpigmentation in our patient was likely caused from doxorubicin. As a provider, the tongue hyperpigmentation was viewed a clinical nuisance, that still required thoughtful clinical decision making to ensure a new malignancy was not present, followed by exclusion of alternative cause of the hyperpigmentation. Initially, this side effect was mildly distressing to the patient from a cosmetic standpoint; however, it did not alter the course of her treatment regimen and she was able to successfully complete neoadjuvant chemotherapy without any additional interventions.

A review of the literature (Table 1) demonstrates that combination chemotherapy with doxorubicin has been associated with tongue hyperpigmentation in darker skinned individuals and ethnicities that are prone to skin hyperpigmentation at baseline. The exact pathophysiology and mechanism of action of this phenomenon is poorly understood; however, it is hypothesized that some chemotherapy agents may trigger increased melanin deposition via post inflammatory processes or alterations within the melanocyte itself (Agrawal and Kothiwal, 2018). Tongue hyperpigmentation may occur in any patient; however, darker complexed individuals may be at higher risk due to varying levels of melanocyte-stimulating hormone between individuals (Casamiquela and Cohen, 2013). This condition may be misdiagnosed as racial pigmentation or melanoma, the latter of which would require more extensive workup (Krutchik and Buzdar, 1979).

Other differentials to consider include pigmented fungiform papillae which typically presents in childhood and the tongue hyperpigmentation remains unchanged; however, the patient denied any prior instance of mucosal hyperpigmentation (Stringer and Zitella, 2014). Similarly, medications such minocycline, anti-viral, psychotropic and heavy metal drugs like bismuth containing medications are known to potentially cause oral hyperpigmentation (Sreeja et al., 2015). Addison's disease can presents with oral mucosal hyperpigmentation however is more commonly associated with cutaneous hyperpigmentation of the body and hands (Sreeja et al., 2015). Systemic symptoms of Addison's disease include profound fatigue, weight loss, nausea, emesis, joint pain, and abdominal discomfort (Stringer and Zitella, 2014). Infectious etiologies such as Human Immunodeficiency Virus (HIV) and Tuberculosis can also present with oral hyperpigmentation, however this is rare and would be expected to present concomitant with clinical signs such as fever,

Table 1
Case reports on Doxorubicin-induced tongue hyperpigmentation in breast cancer.

Authors	Image and patient demographics	Regimen	Onset	Resolution
Our case	 39yo African American female	AC	After C2	24 weeks
Blaya and Saba (2011)	 42yo dark-skinned female	AC	After C2	12 weeks
Alfreijat, (2013)	 68yo dark-skinned female	AC	Few weeks into treatment	Few months
Iman and Essam (2021)	 46yo Saudi female	AC	After C2	26 weeks
Ranawaka (2009)	30yo Sri Lankan female 41yo Sri Lankan female 36yo Sri Lankan female	AC	15 days after C1 10 days after C1 18 days after C1	18 – 26 weeks
Krtchik and Buzdar (1979)	41yo Black female	AC + 5F	Shortly after 1st cycle	After discontinuation of Doxorubicin
Acharya et al. (2017)	26 Indian females (mean age 47yo)	AC	Within 6- 12 weeks of starting treatment	unknown

*Abbreviations: A: Adriamycin/Doxorubicin, C: Cyclophosphamide, 5F: 5-flurouracil, C1: Cycle 1, C2: Cycle 2.

cough, lymphadenopathy, weight loss or other systemic manifestations that would necessitate additional workup and treatment (Sreeja et al., 2015). It is important for clinicians to take a full history at time of presentation and perform thorough physical examinations both at diagnosis and throughout treatment course to effectively triage patients with regard to next steps.

In conclusion, tongue hyperpigmentation is an infrequent side effect that may be seen with single agent and combination chemotherapies. While the pathophysiology of this phenomenon is poorly understood, it is appreciated to be a benign clinical finding that does resolves with removal of the offending agent – or rather upon completion of therapy course – with no additional need for treatment or invasive interventions. It is imperative for clinicians to be familiar with the spectrum of side effects associated with each antineoplastic agent to guide appropriate management and importantly to allow reassurance of the patient to avoid undue distress.

Consent

The corresponding author confirms that informed patient consent was obtained for the publication of this case. The patient provided written consent to allow publication of case details and images, although all identifying information was removed from the text and images were cropped to emphasize tongue pathology only.

Declaration of Competing Interest

The authors declare no conflicts of interest and this research did not receive any specific grant from funding agencies in the public, commercial, or not-for-profit sectors.

CRediT authorship contribution statement

Karlyn L. Rupert: Writing – original draft, Writing – review & editing. **Rabiah Ahmad:** Writing – original draft, Writing – review & editing. **Adam M. Brufsky:** Writing – review & editing. **Azadeh Nasrazadani:** Writing – review & editing.

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