Orange-Yellow Tongue and Palate: A Case Report

Authored by Stephen A. Harden, DDS; Aamir Sheikh, DDS, MA; and Ronald S. Brown, DDS, MS

Upon successful completion of this CE activity 1 CE credit hour may be awarded
LEARNING OBJECTIVES
After participating in this CE activity, the individual will learn:
• Drugs, conditions, and diseases known to cause oral mucosal pigmentation.
• Characteristics of carotenemia, xanthoderma, dermal pigmentation, and carotene and vitamin A analogue toxicity issues.

ABOUT THE AUTHORS
Dr. Harden is assistant professor, department of restorative dentistry, Howard University College of Dentistry, Washington, DC. He can be reached at sharden@howard.edu.

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Dr. Sheikh is assistant professor, department of oral diagnostic services, Howard University College of Dentistry, Washington, DC. He can be reached at asheikh@howard.edu.

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Dr. Brown is professor, department of oral diagnostic services, Howard University College of Dentistry, and clinical associate professor, department of otolaryngology, Georgetown University Medical Center, Washington, DC. He can be reached at rbrown@howard.edu.

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INTRODUCTION
A number of drug therapies have a previously reported association with drug-induced pigmentation of the oral mucosa. These drugs include antimalarials such as quinacrine, chloroquine, hydroxychloroquine, quinidine, zidovudine, tetracycline, minocycline, chlorpromazine, oral contraceptives, clofazimine, ketoconazole, amiodarone, busulfan, doxorubicin, bleomycin, cyclophosphamide, and 5-fluorouracil.1,2 Quinine antimalarial drugs are associated with blue-gray or blue-black coloring which is usually located only within the palate. The reason for the palatal location of the discoloration is currently not understood. Minocycline is known to cause pigmentation of the alveolar bone, and the clinical appearance demonstrates a gray discoloration of the oral mucosa. Minocycline has also been reported to cause discoloration of the tongue. Furthermore, documentation of oral mucosa discoloration includes diffuse, bilateral, and focal presentations. These include physiologic pigmentation, Peutz-Jeghers syndrome, Addison’s disease, heavy metal pigmentation, Kaposi’s sarcoma, postinflammatory pigmentation, smoker’s melanosis, and such focal presentations as hemangioma, varix, thrombus, hematoroma, amalgam tattoo, blue nevus, melanotic macule, pigmented nevus, melanoma, black hairy tongue, and vitiligo.1,3,4

Carotenemia, an increased level of serum carotene, is known to cause discoloration of the skin, xanthoderma, and particularly the palms of the hands and the soles of the feet. Boere and Hoskam5 reported a case in which the individual was noted for a striking yellow discoloration of the palms of the hands and the plantar area of the feet. Furthermore, high-performance liquid chromatography reported a value of serum beta-carotene at 1.16 micromol when the normal values are between 0.07 and 0.88. Takita et al6 reported a case of carotenemia secondary to beta-carotene supplementation. Their patient, a 66-year-old female, consumed 5.72 mg of beta-carotene daily for 3 months. The patient’s palms and soles were noted for orange-yellow coloration. Stack et al7 also reported a case with yellow-orange coloration of the palms and soles. Their patient, a 29-year-old male from Liberia, had a history of regularly consuming red-palm oil which is rich in beta-carotene. Arya et al8 reported that carotenemia is a
relatively common pediatric condition of yellowing of the skin and elevated serum beta-carotene values and is associated with metabolic disorders due to immature liver function. All of the patients reported above were negative for scleral icterus and positive for elevated serum bilirubin values.

This article presents a case report that represents the first reported case of oral mucosal discoloration (of the dorsal tongue and palate) secondary to carotemia due to a topical retinoid pharmacotherapeutic.

CASE REPORT
A 59-year-old female was referred by her otolaryngologist to an oral medicine clinician with a chief complaint of “orange tongue.” The patient noted that other areas of the mouth were also orange, such as the palate. The otolaryngologist previously performed a fungal culture procedure of the area and the report was negative for fungal infective organisms. The physician also suggested that the patient use a tongue scraper, and prescribed magic mouthrinse. Magic mouthrinse is comprised of nystatin, diphenhydramine, lidocaine, and sometimes triamcinolone. Neither the tongue scraping nor the mouthrinse improved the condition. The patient had been using one toothpaste with an antitartar (triclosan) agent and had recently switched to another toothpaste also containing an antitartar agent.

The medical history noted that the patient had been using such skin cream medications as Tretinoin cream 0.05%. The patient did not smoke cigarettes and drank alcohol only rarely. She was taking simvastatin for cholesterol lowering. She was taking such over-the-counter medications and supplements as fish oil, aspirin (81 mg), and calcium. She sometimes used such sleep aids as zaleplon and zolpidem. The patient reported a previous drug allergy reaction to ciprofloxacin, but noted no other known drug allergies.

Clinically, palpation for lymphadenopathy was negative. The parotid and submandibular salivary glands demonstrated limited function. The filiform papillae of the dorsal tongue and the midline portion of the soft palate had an orange-yellow tinge (Figure 1). The remaining oral tissues appeared to be within normal limits. The skin color and the eye coloration also appeared to be within normal limits.

As the patient was using a vitamin A/carotene analogue, the most likely (tentative/working) diagnosis was carotenemia, which is defined as an increased body burden of beta-carotene and carotenosis/carotenoderma/xanthoderma, which is orange-yellow coloration secondary to carotenemia. The differential diagnosis for orange or yellow discoloration of the oral mucosa includes jaundice, fungal infection, and malakoplakia. As a trial therapy, the clinician advised the patient to discontinue the antiwrinkle cream, which contained a vitamin A analogue. In one month, the color of the tongue faded from orange-yellow back to a healthy pink. This was reported by the patient and confirmed with photographs taken by the patient's husband (at a later date) (Figure 2).

DISCUSSION
Carotenemia and secondary xanthoderma (discoloration of the epidermis) can be caused by a diet with excessive amounts of carotene-rich foods such as carrots, and by
supplements and medications which contain carotene or retinoids. Carotenoids are fat soluble and are deposited in the intercellular lipids of the stratum corneum. Quinine antimalarial drugs are associated with discoloration of the palate. Possibly, the stratum corneum of the palate is an anatomical location with an affinity for lipid-based pharmacotherapeutics. Therefore, the route of drug administration (oral versus topical) may have strongly influenced the location of the epithelial discoloration. Lascari reported that it is important for clinicians to be aware of the differences between jaundice and carotenemia. Ingestion of excessive amounts of carrots and also several other yellow as well as green vegetables is the usual cause of carotenemia. Furthermore, there is the potential of parents to unknowingly contribute to carotenemia by providing commercial infant food combinations to newborns. However, carotenemia is a typically a benign condition as poisoning due to vitamin A is slow and usually reversible.

Serum carotene levels were not ordered for the presented case because the condition improved with the elimination of the topical medication.

Boere and Hoskam reported that their patient's condition was due to beta-carotene in the diet and was possibly influenced by the patient's type 2 diabetic condition. According to Hoe rer et al., there is an association between carotenemia and diabetes, although in the case reported the patient did not have a diabetic history. Possibly, the case reported demonstrated the change in normal coloration due to the proximity of the topical application of the antiwrinkle carotene-containing cream to the oral tissues. The other noted cases of carotenemia/xanthoderma were all secondary to ingestion of particular vitamin A inclusive foods or vitamin A supplements, rather than topical application.

The negative culture assays by the otolaryngologist tended to rule out a diagnosis of fungal infection. Bor et al. reported a case of an Aspergillus flavus infection in a child secondary to acute lymphoblastic leukemia. The child had a yellow-white lesion of the lateral tongue which was successfully treated with amphotericin B. Kitami et al. reported a case of a 72-year-old male with a history of steroid and antibiotic utilization with a curdlike substance on the surface of the tongue and lower lip. The diagnosis of oral sycosis candidiasis was made with KOH-positive microscopic examination. Furthermore, the biopsy sample was cultured and revealed Candida albicans and Candida parapsilosis. The patient was successfully treated with amphotericin B syrup along with oral itraconazole and 2% miconazole gel. Rippon et al. reported a golden orange dorsal tongue lesion in a 54-year-old woman being treated for lymphocytic leukemia. The clinicians performed a biopsy and culture and determined the infective organism was Ramichloridium schulzeri (an uncommonly encountered soil saprophyte). The clinicians treated the patient with nystatin, sulfamethoxazole, trimethoprim sulfate, and eventually amphotericin B therapy. However, the patient died secondary to her leukemia condition compounded by neutropenia, and disseminated A flavus infection.

The relative good health of the patient in the presented case, and the negative culture attained by the referring otolaryngologist, tended to rule out an oral fungal infection as the etiology in the present case.

Jaundice (icterus) is the yellowing skin color secondary to increased bilirubin levels within the serum, known as hyperbilirubinemia. When the yellowish tinge becomes visible, the concentration of bilirubin in plasma exceeds 1.5 mg/dL, which is 3 times the normal value of 0.5 mg/dL. Typically, the skin in fair-skinned individuals takes on a yellowish tinge, and in jaundiced patients the sclera of the eyes have a yellowish appearance. The condition of
jaundice is secondary to obstruction of the biliary tract or such disease states as hepatitis and cancer of the liver.

In the case reported, neither the patient's skin nor eyes appeared to be yellow. Furthermore, there was no history of liver disease or any history consistent with liver disease. Therefore, blood studies to evaluate the patient's bilirubin serum level were not undertaken.

Several cases of jaundice have been reported in which the patient has a coated tongue secondary to candidiasis, but the tongue or the palate is not involved in yellowing associated with jaundice.15-17

Malakoplakia is a relatively uncommon chronic inflammatory reaction of unknown cause. Rarely, this condition may involve the tongue as a tongue mass with possible discoloring. The most common lesion location sites for this condition are primarily the genitourinary tract and secondarily the gastrointestinal tract and retroperitoneum. Other less common sites include the tongue, lungs, bones, larynx, palatine tonsil, and parotid salivary gland. The prevalent etiological hypothesis is that a reaction occurs secondary to an infectious agent within a patient with an immunologic deficiency. The diagnosis is confirmed with a biopsy and histopathologic evaluation determining the presence of foamy histocytes with distinctive basophilic inclusions which are known as Michaelis-Gutmann bodies, which are due to partially ingested bacteria. Treatment combines antibiotic therapy such as quinolones and trimetoprim-sulphameethoxazol with the surgical removal of the lesion.18

The clinical findings in the presented case were not consistent with a diagnosis of malakoplakia.

Primary carotenoderma is that developing from increased oral ingestion of carotenoids, whereas secondary carotenoderma is caused from underlying disease states (or metabolic dysfunction) that increase serum carotenoids with normal oral intake of these compounds. Primary and secondary carotenoderma can coexist in the same patient. Although extensive amounts of vitamin A can manifest as an overdose with potential lethality, typically carotenemia is a benign condition. Carotenoderma is deliberately caused by beta-carotenoid treatment of certain photosensitive dermatitis diseases such as erythropoietic protoporphyria, where beta carotene is prescribed in quantities which discolor the skin. These high doses of beta-carotene are benign, although the orange appearance is displeasing to some. In a recent meta-analysis of these therapies, however, the efficacy of the treatment is questionable.19

The patient in the presented case was informed that the most probable cause of the oral orange-yellow coloration was the antiwrinkle skin cream containing beta-carotene. Furthermore, the patient was informed that the efficacy of the skin cream formulation was controversial20 and that beta-carotene supplements are associated with a number of negative health consequences, including an increased incidence of cancer and an increased mortality rate.21-23 The patient agreed to discontinue the use of the skin cream, and her discoloration condition resolved within one month. As noted above, Lascari10 reported that the absence of yellow pigment in the sclera and oral cavities distinguishes carotenemia from jaundice. However, the usual causes of carotenemia/xanthoderma are through the digestive system port of entry, while in this unusual case, the carotene was applied topically to the facial skin, which would tend to account for the oral location of the discoloration. Furthermore, this case may serve to alert healthcare providers to the possibility of discoloration secondary to the administration of topical medications.

**CONCLUSION**

A unique case has been presented in which an orange-yellow oral discoloration was attributed to the use of a carotene-containing skin cream which was applied to the facial skin. This case serves to alert clinicians that the administration of certain topical medications may cause discoloration of the skin and/or oral mucosa.
REFERENCES


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1. Blue-gray and blue-black oral mucosal discoloration is associated with _______.
   a. Oral contraceptives.
   b. Zidovudine.
   c. Antimalarial drugs.
   d. Cyclophosphamide.

2. Which of the antibiotics below is associated with pigmentation of the alveolar bone and a gray discoloration of the oral mucosa?
   a. Penicillin.
   b. Clindamycin.
   c. Erythromycin.
   d. Minocycline.

3. An example of physiologic oral pigmentation secondary to a disease or condition would be _______.
   a. Pneumonia.
   b. Peutz-Jeghers syndrome.
   c. Papillon-Lefèvre syndrome.
   d. Osteogenesis Imperfecta.

4. Taking high doses of carotene and/or vitamin A analogues may result in _______.
   a. Carotenemia.
   b. Vitalago.
   c. Pigmented nevus.
   d. Melanotic macule.

5. Xanthoderma is associated with orange-yellow pigmentation of the _______.
   a. Face.
   b. Palms and soles.
   c. Trunk.
   d. Eyes.

6. Jaundice is known for yellowing of the skin and eyes and is associated with increased serum _______.
   a. Albumin.
   b. Glucose.
   c. Bilirubin.
   d. Melanin.

7. Malakoplakia is diagnosed with a biopsy and the significant histopathological finding of partially ingested bacteria is known as _______.
   a. Acid fast staining.
   b. Michaelis-Gutmann bodies.
   c. Lipshutz bodies.
   d. Donovan bodies.

8. Which of the statements below is the most correct?
   a. Beta-carotene has no known toxicity.
   b. Beta-carotene is extremely toxic.
   c. Beta-carotene has demonstrated success in the treatment of oral cancer.
   d. Increased beta-carotene supplementation is associated with decreased lifespan and increased cancer.
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