

Oral Surgery, Oral Medicine, Oral Pathology, Oral Radiology, and Endodontology

CLINICOPATHOLOGIC CONFERENCE

Editor: Paul C. Edwards

Pigmentation of the hard palate

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(*Oral Surg Oral Med Oral Pathol Oral Radiol Endod* 2009;107:8-12)

CASE REPORT

A 57-year-old African-American female presented for implant evaluation with slate-black pigmentation of the hard palate (Fig. 1). She was unaware of this condition, and therefore the duration of the condition could not be ascertained. Extraoral examination revealed brown macular lesions on her nose, extensor surfaces of arms, and dorsa of hands (Fig. 2). She reported that these cutaneous lesions had been present for approximately 12 years.

Her medical history was significant only for discoid lupus erythematosus (DLE). She was prescribed quinacrine for DLE, and she did not report the use of other prescription or over-the-counter medications. She reported an allergy to penicillin and denied a history of smoking or of alcohol use.

DIFFERENTIAL DIAGNOSIS

The differential diagnosis for a large flat pigmented area of the palate included the following: physiologic pigmentation, pigmentation associated with systemic disease, medication-related pigmentation, postinflam-



Fig. 1. Black macular pigmentation of the palatal mucosa.

matory pigmentation, oral melanoacanthosis (melanoacanthoma), blue nevus, and malignant mucosal melanoma. Small localized pigmented lesions including oral melanotic macules, melanocytic nevi, amalgam tattoos, and vascular lesions were not seriously considered. A diagnosis of Kaposi sarcoma (KS) was briefly entertained; however, the brown and black coloration of the patient's skin and oral lesions, her lack of known risk factors that would predispose her to KS, and the fact that this condition uncommonly presents in women all helped rule out this diagnosis.

Physiologic (racial) pigmentation is the most common form of intraoral multifocal diffuse pigmentation.¹ It is seen most commonly in individuals with dark complexions and it may involve any mucosal site. The pigmentation is asymptomatic and patients are often unaware of its presence. Classically, the gingiva, tongue, hard palate, buccal mucosa, and/or lips present with light to dark brown macules with irregular and

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Received for publication May 29, 2008; returned for revision Jul 16, 2008; accepted for publication Jul 17, 2008.

1079-2104/\$ - see front matter

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doi:10.1016/j.tripleo.2008.07.022

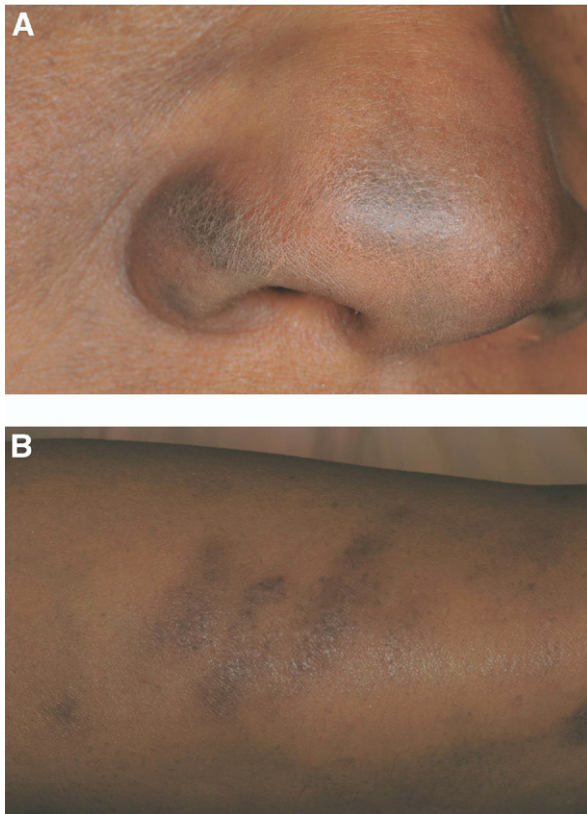


Fig. 2. Light brown macules involving the patient's nose (A) and arm (B).

poorly defined borders. Pigmentation is due to an increase in the production of melanin; the number of melanocytes remains normal. In this case, physiologic pigmentation was an unlikely diagnosis because of the sharply demarcated borders, the localized involvement of the palate, and the slate-black coloration.

A systemic disease associated with diffuse pigmentation is one of the few diagnoses that might explain not only this patient's palatal pigmentation but also her cutaneous lesions. A characteristic feature of primary adrenocortical insufficiency (Addison disease) is a diffuse darkening or bronzing of the skin and mucous membranes. Intraorally, discrete macules or diffuse pigmentation may be noted on the tongue, gingiva, buccal mucosa, or hard palate. Adrenocorticotropic hormone (ACTH) and alpha-melanocyte-stimulating hormone (alpha-MSH) are both melanocortin peptides derived from a precursor protein named pro-opiomelanocortin; alpha-MSH represents the 13-amino acid peptide sequence of the N-terminus of ACTH²; therefore, elevations in ACTH lead to increased MSH activity. Similar findings may be noted in association with oral contra-

Table I. Medications associated with hyperpigmentation

Medication	Proposed source of pigmentation
Minocycline	Hyperproduction of melanin, complex with iron, or stained bone ^{10,11}
Antimalarials	Hyperproduction of melanin ¹²
Clofazamine	Chelated metabolites of medication ¹³
Tranquilizers	Medication/metabolites and/or accumulation of melanin ¹⁴
Hormones	Hyperproduction of melanin ^{3,15}
Heavy metals	Granules of the metal distributed throughout blood vessels ¹⁶
Amiodorone	Increased production of lipofuscin ¹⁷

ceptives and hormone replacement therapy: These medications lower the concentration of cortisol in the plasma and thereby stimulate an increase in ACTH and alpha-MSH.³ Other systemic conditions associated with diffuse oral or cutaneous hypermelaninosis include neurofibromatosis, Albright syndrome, and Peutz-Jeghers syndrome.⁴⁻⁶

Cutaneous café au lait macules have been reported in patients with conditions including neurofibromatosis and Albright syndrome. The pathogenesis of the macules seen in the former condition remains unknown. It has been suggested that because the condition affects tissues derived from the neural crest, including melanocytes, a relative increase in the number of melanocytes causes the pigmentation.⁷ Patients with Albright syndrome may occasionally demonstrate café au lait macules of the oral mucosa in addition to the skin. The proposed mechanism involves a GS-alpha mutation that, in turn, activates the tyrosinase gene in melanocytes and leads to café au lait spots.⁸ The lentiginos of Peutz-Jeghers syndrome are believed to develop secondarily to mutations of the LKB1 gene that increase Wnt signaling, which is in turn associated with melanocyte stimulation.⁹

Diffuse and/or multifocal pigmentation of the oral mucosa and/or skin secondary to systemic drug administration is a well recognized phenomenon. Numerous medications have been associated with hyperpigmentation (Table I), the pathogenesis of which differs for each drug. The primary mechanisms that account for drug-induced pigmentation include increased deposition of melanin induced by the medication; a pigmented metabolite of the medication; chelation of hemosiderin to the medication; and synthesis of lipofuscin or other pigments.

Postinflammatory pigmentation of the oral mucosa may be associated with smoking (smoker's melanosis) or chronic inflammatory diseases, including lichenoid

processes. Brown or black macules and patches appear on the affected tissues and are seen more often in dark-skinned individuals. Hyperpigmentation may result from stimulation of melanocytes by inflammatory cytokines or reactive oxygen species.¹⁸ These pigmented areas are asymptomatic. Pigmentation secondary to smoker's melanosis is usually limited to the gingiva. Involvement of the palate is rare. Although this patient had a history of DLE, she did not demonstrate the white reticulated and erythematous inflammatory lesions often seen in this condition. It was therefore deemed unlikely that her extensive area of pigmentation was postinflammatory secondary to lesions of DLE.

Oral melanoacanthosis is a benign asymptomatic lesion of the oral mucosa believed to be reactive in origin.¹⁹ The lesions are dark brown-black in color and may reach up to several centimeters in size. Although this condition shows a predilection for African-American women, it is rarely reported covering the entire the hard palate. The most common location is the buccal mucosa.²⁰

A blue nevus is an uncommon acquired melanocytic macule of the skin or oral mucosa. It appears blue or blue-black in color and is typically smaller than 6 mm in size.²¹ Although blue nevi have a predilection for the palate, this diagnosis was ruled out based on the absence of blue coloration and the lesion's large size.

Malignant mucosal melanoma must be included in any discussion of pigmented lesions of the oral mucosa, owing to the dismal prognosis associated with this entity. It presents most commonly on the palate or maxillary gingiva,²² generally as an asymptomatic ill defined brown or black macule, papule, or nodule, generally with uneven pigmentation. Although the condition is rare, it is associated with a worse prognosis than cutaneous melanoma. The symmetry, well defined borders, and even pigmentation of the present patient's palatal pigmentation made this diagnosis less likely.

DIAGNOSIS

An incisional punch biopsy was performed under local anesthesia. Hematoxylin and eosin-stained sections revealed pigment granules measuring approximately 1-2 microns within the lamina propria and within macrophages. The granules demonstrated a round regular configuration and were often disposed in single file between collagen fibers (Fig. 3). There was no melanin pigment noted within the basal cells, no significant inflammation, and no evidence of fresh hemorrhage. Fontana-Masson stains indicated that the pigment in the connective tissue and the macrophages was

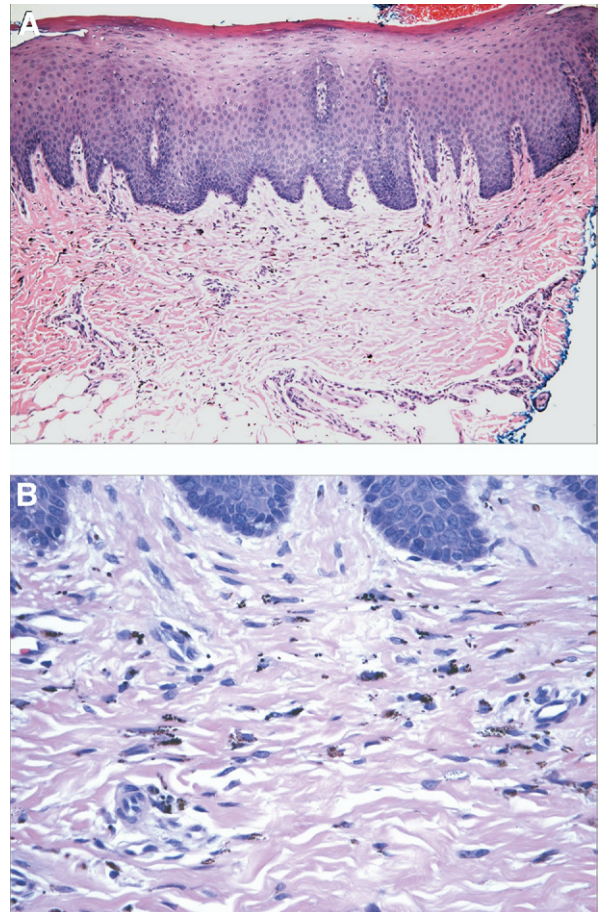


Fig. 3. **A**, Parakeratinized stratified squamous epithelium was noted overlying connective tissue containing pigmented granular particles (hematoxylin and eosin, magnification $\times 100$). **B**, Small regular round particles of pigment were noted within the connective tissue and within macrophages (hematoxylin and eosin, magnification $\times 400$).

primarily due to accumulation of melanin particles (Fig. 4). A small amount of hemosiderin was present within the tissue, as evidenced by focally positive stains for iron.

These findings and history were consistent with a diagnosis of quinacrine-induced oral pigmentation. Because this palatal lesion was a benign condition and did not pose a cosmetic concern, no further treatment was indicated.

DISCUSSION

In 1945, Lippard and Kauer described slate-colored pigmentation of the palate and subungual areas in 156 soldiers stationed in the South Pacific, all of whom had been treated with quinacrine hydrochloride.²³ Hyperpigmentation of the oral mucosa secondary to antimalarial drug administration has since

Fig. 4. Histochemical stains confirmed the presence of melanin within the connective tissue (Fontana Masson stain, magnification $\times 200$).

been reported by many others, typically restricted to the hard palate.²⁴ Classic presentation includes a sharp line of demarcation between the hard and soft palates, as was seen in the present case.²⁵ Quinacrine has also been associated with discoloration of the skin; of note, our patient reported that the onset of her cutaneous lesions was subsequent to initiation of quinacrine therapy.

Among the numerous antimalarial medications implicated in discoloration of the oral tissues are chloroquine, hydroxychloroquine, quinacrine, and amodiaquine.²⁴ These agents all demonstrate antiinflammatory properties in addition to their antimalarial effects. As such, they are commonly used to treat not only malaria but also immune-mediated conditions, including rheumatoid arthritis, lupus erythematosus, and other collagen vascular disorders.

Although early studies suggested that antimalarial-associated pigmentation was related to deposition of hemosiderin,²³ increased production of melanin is currently believed to be the responsible mechanism.¹² Positive staining of the granules with the Fontana Masson stain is consistent with this explanation. Antimalarial drugs have been found to stimulate melanocytes either directly and/or by elevating levels of androgens, which in turn stimulate melanocytes. It is unclear why the pigmentation preferentially involves the palatal mucosa. Because these medications often are used to treat inflammatory conditions, hemorrhage from inflammation may have led previous investigators to believe hemosiderin to be the source of the pigmentation.

Oral mucosal pigmentation secondary to quinacrine administration is a benign condition; no intervention is

required once this diagnosis is rendered. The pigmentation can be expected to resolve within months of discontinuation of the drug, although the discoloration in this particular case was not in an esthetic area and was of little concern to the patient.

In summary, we present an example of quinacrine-induced oral pigmentation. The characteristic finding of slate-black pigmentation of the hard palate extending to, but without involving, the soft palate should immediately alert the clinician to the possibility of a medication-related condition. A thorough medical history is essential in arriving at the correct diagnosis.

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