Case History

A 78-year-old female was referred to an oral surgery clinic for a bluish brown discoloration in her palate noticed by her dentist for several months. The discoloration was not painful to the patient. The patient's medical history was significant for hypertension, hyperlipidemia, hypothyroidism, and chronic myeloid leukemia. Her current medication list included Gleevec, metoprolol succinate, losartan, Zetia, L-thyroxine, furosemide, potassium chloride oral capsule, and baby aspirin.

Intraoral-examination revealed a diffuse bluish-brown discoloration that involved most of the palatal vault (Figure 1). It extended anteriorly to the rugae and posteriorly to the soft palate. The discoloration showed variation in color and ill-defined borders. Palatal tori were also noted. No other pigmented lesion was found in the oral cavity. Upon questioning, the patient stated that she noticed pigmented lesions on both of her arms a few months prior to her dentist noticing her oral lesion (Figure 2). She did not recall any trauma or injury to either of her arms. The clinical differential diagnoses for the oral lesion included hematoma/ecchymosis, amalgam tattoo, and melanoma. An incisional biopsy was taken.

Histological examination revealed a soft tissue specimen demonstrating increased melanogenesis. The specimen was covered by stratified squamous epithelium showing no cellular atypia. The underlying lamina propria consisted of fibrous connective tissue, with scattered melanophages and melanin incontinence (Figure 3). There was no sign of inflammation.

What is your diagnosis?

See page 642 for the answer and discussion.

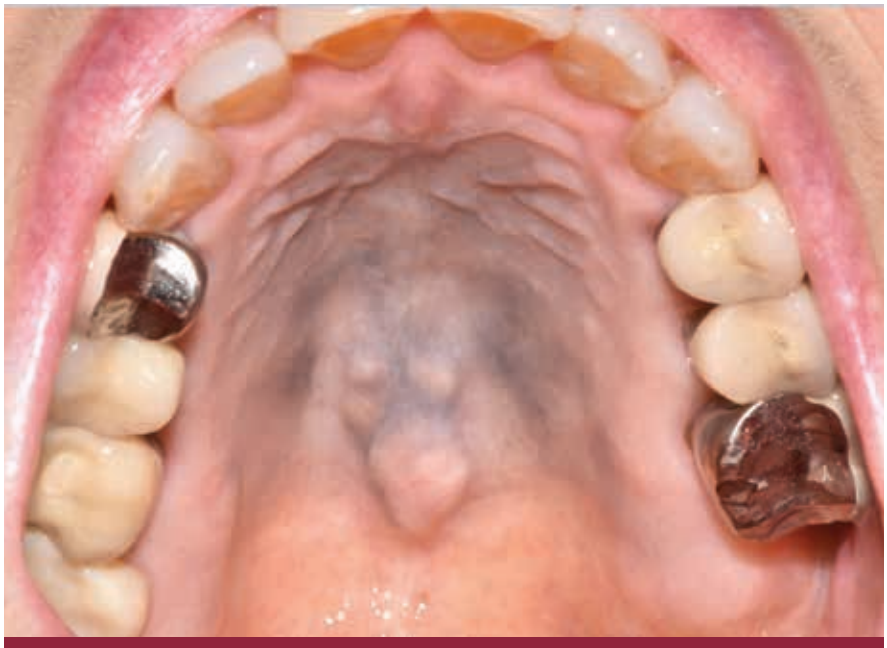

Figure 1. *Clinical examination revealed an asymptomatic diffuse bluish-brown discoloration involving the palatal vault. Palatal tori were also noted.*

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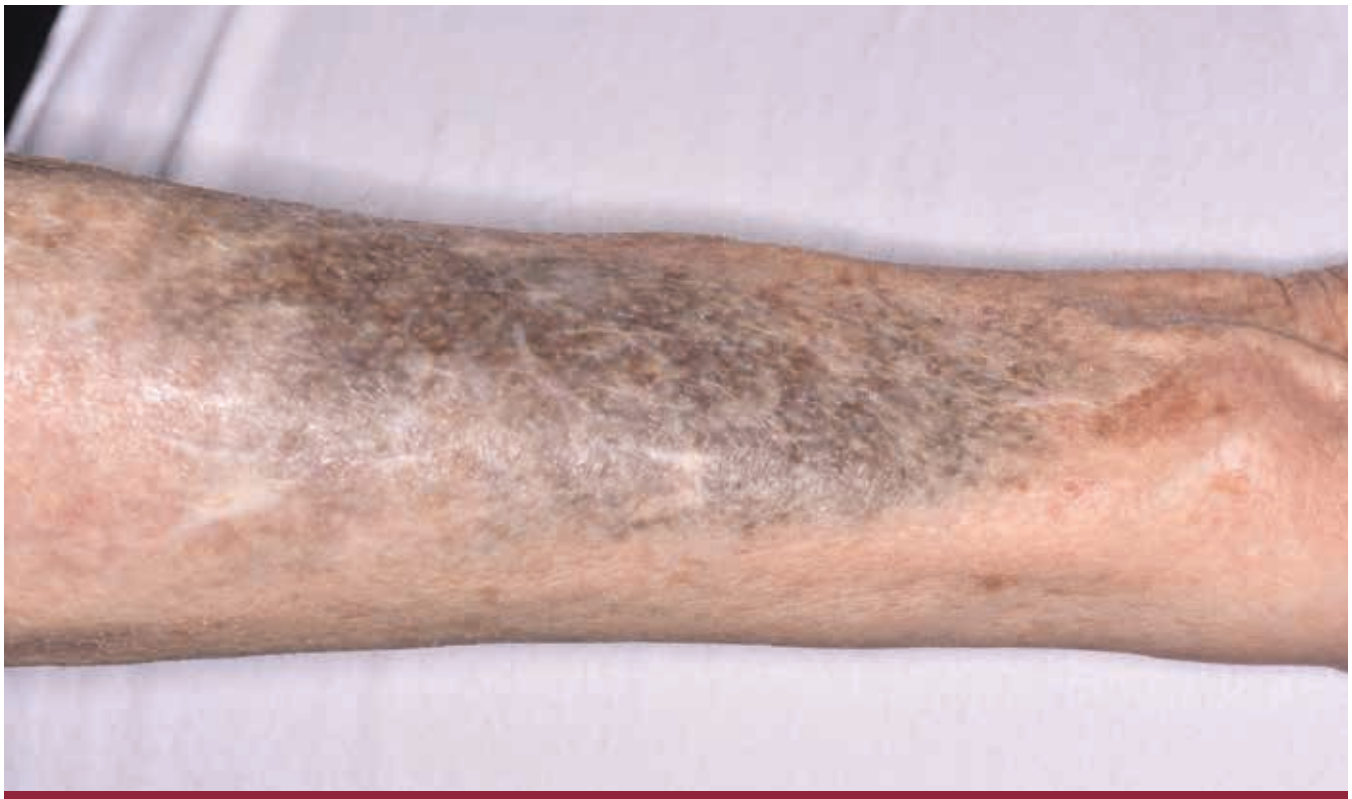

Figure 2. *A large diffuse bluish-brown lesion was also noted on patient's arm a few months prior to her dentist noticing her oral lesion.*

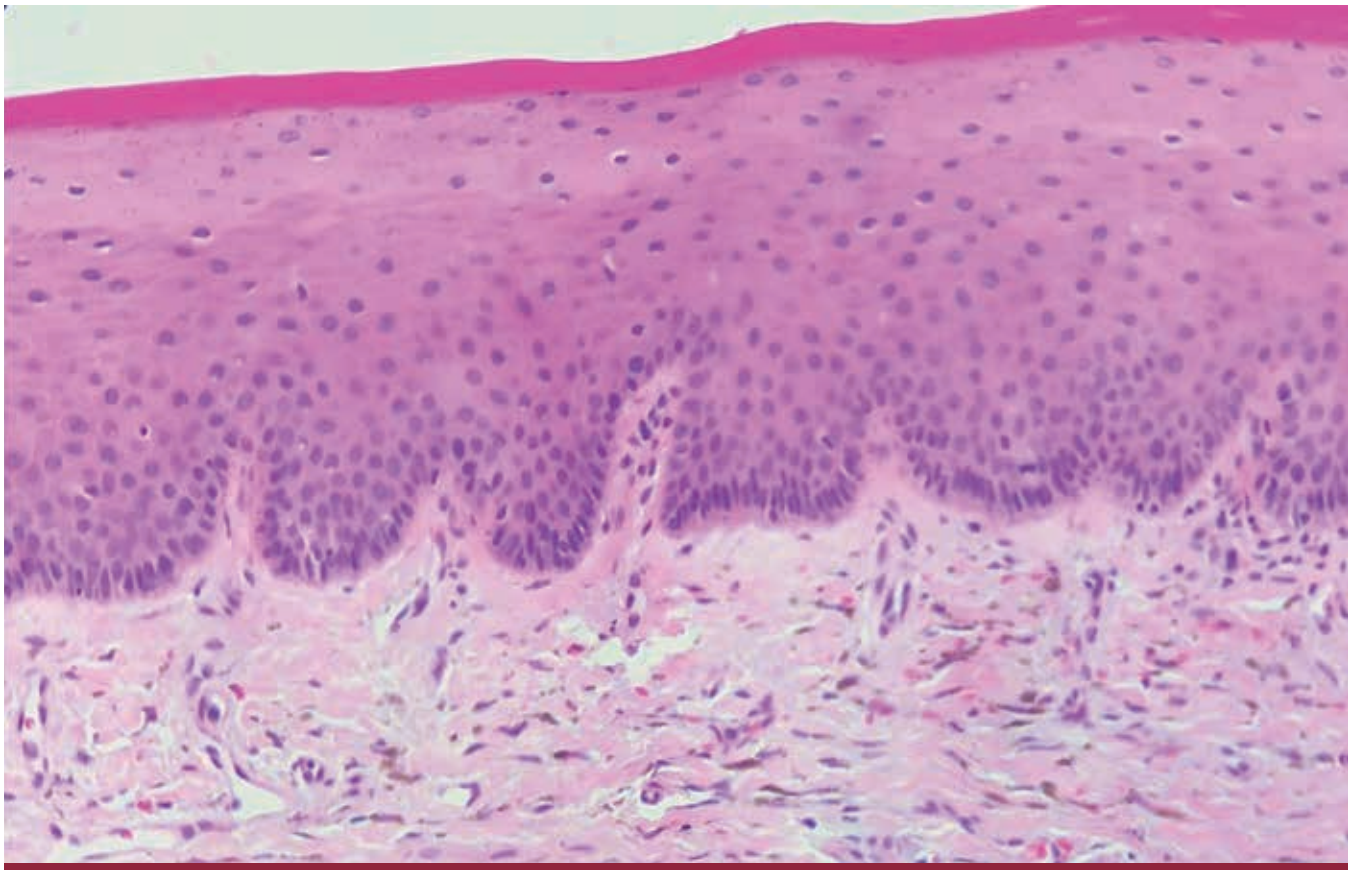

Figure 3. *Histopathology of the biopsy showed a wedge of mucosa with melanophages and melanin incontinence interspersed in the lamina propria (H&E stain, original magnification 400x).*

Melanin incontinence, consistent with imatinib mesylate-associated oral hyperpigmentation

Discussion

Imatinib mesylate (Gleevec®) is a tyrosine kinase inhibitor that is the first-line treatment for patients with newly diagnosed, Philadelphia chromosome-positive, chronic myeloid leukemia. It is also used to treat patients with metastatic malignant gastrointestinal stromal tumors or other malignancies.[1] Imatinib mesylate has been reported to cause either hypopigmentation in skin, or hyperpigmentation in skin and mucosa.[2] The hyperpigmentation can appear on skin, nails, oral cavity, or conjunctiva of the eyes.[3] The duration between the start of therapy and the appearance of hyperpigmentation varies, ranging from a few months to more than 10 years.[4]

To the best of our knowledge, 23 cases of oral imatinib mesylate-associated hyperpigmentation (IAH) have been found in the literature to date.[1,4-21] The most common intra-oral site for IAH is the hard palate.[4] Sometimes, it can be the only manifestation of this drug side effect without skin involvement.[6,14,17-21] Clinically oral IAH is characterized by diffuse gray or bluish-brown discoloration with ill-defined borders. The size of the discoloration is often larger than 6mm. Histologically, oral IAH is characterized by melanin with or without hemosiderin deposited in lamina propria. It is interesting that all reported oral IAH cases, including our case, showed melanin deposition localized in the lamina propria without deposition in surface epithelium.[1,4-21] The mechanism responsible for hyper- or hypo-pigmentation observed in patients using imatinib is not clear. Diagnosis is often based on clinical presentation and history, although biopsy may help to exclude other possibilities (see below). Once the diagnosis is established, no treatment is required.

Many categories of medications are known to be associated with oral hyperpigmentation as one of the side effects. Some common examples are listed in Table 1. Drug-associated hyperpigmentation is mostly through increased deposition of melanin, pigmented metabolites of medications, or production of lipofuscin/other pigments.[22-26] These pigmented lesions sometimes may show characteristic clinical features or locations. For example, tetracycline and minocycline associated pigmented lesion is characterized by blue-gray discoloration that can be in teeth, bone or soft tissue, and can present as a characteristic linear blue-gray band at the mucogingival junction.[22-24] Anti-malarial drugs or imatinib mesylate associated hyperpigmentation typically presents as diffuse blue-gray discoloration with irregular borders on the palate.[1,4-21,25-27]

The differential diagnoses for this diffuse discoloration in our case include melanotic macule, amalgam tattoo, melanoacanthoma and mucosal melanoma. Melanotic macule is the most common hyperpigmented lesion in the oral cavity and is characterized clinically as a well-defined brown (less frequently blue-black) homogenously pigmented lesion that is less than 7mm in size.[22] Sometimes, it can present as multiple lesions. It is seen more frequently in females, and is often found on lower lip vermilion border, although it also can be seen in the oral cavity. The size of the lesion and the ill-defined borders in our case would argue against the diagnosis of melanotic macule.

Amalgam tattoo typically presents as a well-defined, slate gray lesion that is caused by deposition of silver salts from amalgam into the tissue, where they have an affinity for fibrous connective tissue.[22,28] Correlation with a patient's history of amalgam restorations

in close proximity is useful to confirm a clinical diagnosis of amalgam tattoo. The lesion tends to slightly lighten over time, with the borders becoming more diffuse due to spreading of the silver salts and remodeling of the collagen fibers. The metals in amalgam tattoo sometimes may show up as radiopacities on radiographs; however, absence of these radiopacities does not rule out the possibility of amalgam tattoo, as the particles may be dispersed.[22,28] The ill-defined border and the location (close to midline palate) of the lesion in our case argue against the diagnosis of amalgam tattoo. A biopsy also can assist the differentiation from drug-induced hyperpigmentation.

Oral melanoacanthoma typically presents as an ill-defined, dark-brown to black pigmented lesion. This occurs in most frequently people with dark skin, and it shows a female predilection.[22] It is most commonly seen in the buccal mucosa, and often rapidly increases in size. In contrast to melanoacanthoma in skin, oral melanoacanthoma is believed to be a reactive process, often to physical injuries, and it typically resolves once the source of trauma is eliminated.[22] The race of the patient, and no history of trauma in the area made our case unlikely to be melanoacanthoma.

Mucosal melanoma is a malignancy which is most commonly seen in hard palate and gingiva.[22,29] A pigmented lesion that shows clinical features of ABCDE (asymmetry, irregular borders, color variations, a diameter greater than 6 mm, and evolution with time) is concerning for melanoma. Melanoma may appear as a flat pigmented lesion (macule and plaque phases) in the early stage, and appears as ulcerated or indurated pigmented mass in the late stage.[29] Although our case showed clinical features of asymmetry, irregular border, heterogeneous color, and a size larger than 6mm, a biopsy combined with the patient history of imatinib mesylate assisted to reach the final diagnosis.

In summary, Imatinib mesylate is a relatively new targeted therapy for cancer treatment, and we present a case of oral hyperpigmentation associated with this new medication to increase clinical awareness.

Table 1. Medications that have been reported to be associated with oral hyperpigmentation

Category	Medication
Antibiotic	Tetracycline[23], Minocycline[24]
Anti-fungal	Ketoconazole[30], Clotrimazole[30]
Anti-viral For HIV infection For hepatitis B and C:	 zidovudine (AZT)[31] peginterferon alfa and ribavirin combination therapy[32]
Anti-arrhythmic	Amiodarone[33]
Anti-psychotics	Phenothiazine[34]
Anti-epileptic	retigabine[35]
Antimalarial	chloroquine diphosphate[25], quinacrine hydroxychloroquine[26], and amodiaquine[26] and other quinine derivatives[26]
Chemotherapeutic drugs	imatinib mesylate[1,4-21,27,] Bleomycin[36,37,] cyclophosphamide[26,] 5-fluoruoracil[38], doxorubicin[26,] busulfan[26]
Laxatives	Phenolphthalein[22,26]
Leprosy	Clofazimine[24,34]
Hormone related drugs/oral contraceptives	Estrogen[39], Premarin[39]
Tranquilizers	Chlorpromazine[26,37]

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