Oral pigmentation in the hard palate associated with imatinib mesylate therapy: a report of three cases

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Imatinib mesylate is a tyrosine kinase inhibitor which targets Bcr-Abl-protein, c-Kit, and platelet-derived growth factor receptor. The drug was originally developed for treatment of chronic myeloid leukemia but is also regarded as first-line treatment of patients with metastatic gastrointestinal stromal tumours (GIST). Dermatologic side effects are common, with superficial edema and rash as the most frequent. In addition, imatinib mesylate treatment is often associated with hypopigmentation. Intraoral side effects are very rare. The present paper demonstrates 1 patient with GIST and 2 patients with chronic myeloid leukemia treated with imatinib mesylate for 5-6 years. All 3 patients presented with diffuse solitary bluish-brown pigmentation in the hard palate. The lesions persisted at follow-ups. There were no other pigmentations in the oral mucosa. The histopathologic examination showed depositions of melanin pigment in the lamina propria. The possible relationship between the observed melanotic maculae and imatinib mesylate treatment is discussed. (Oral Surg Oral Med Oral Pathol Oral Radiol Endod 2011;111:e12-e16)

Oral pigmentation related to excessive melanin production are common clinical findings. In Sweden, such lesions are found in ~10% of the population.1 The etiology behind them is varied, representing a broad spectrum from physiologic pigmentations to manifestations of systemic diseases.2 Some physiologic pigmentation is related to ethnicity and predominantly found in dark-skinned populations. These pigmentations are usually bilateral and found in gingival and buccal mucosa.3,4 Systemic diseases such as Peutz-Jehgers syndrome, Addison’s disease, and some other rare diseases, such as polyostotic fibrous dysplasia, Nelson syndrome, and hyperthyroidism, are associated with oral melanotic pigmentation.3,4 Deposition of melanin in the connective tissue may also be found after long-standing inflammation in conditions such as oral lichen planus, pemphigus, and pemphigoid.5,6

Furthermore, tobacco and a number of drugs, i.e., antimalarials, tetracyclines, chemotherapeutic drugs (bleomycin, cyclophosphamide, 5-fluorouracil, doxorubicin), phenothiazines, amiodarone, quinidine, and clofazamine, may cause oral pigmentation.2,3,7-10 Furthermore, hyperpigmentation has been associated with antiretroviral drugs such as azidothymidine.11,12

Imatinib mesylate (Glivec; Novartis Pharma, Basel, Switzerland) is a tyrosine kinase inhibitor that targets Bcr-Abl-protein, c-Kit, and platelet-derived growth factor receptor. The drug was originally developed for treatment of chronic myeloid leukemia but is also regarded as first-line treatment of patients with metastatic gastrointestinal stromal tumors (GIST).13

Imatinib mesylate treatment is associated with various side effects, such as nausea, diarrhea, periorbital edema, and myelosuppression. Dermatologic side effects are not unusual, with superficial edema and rash as the most common. Other side effects are erythroderma, pruritic maculopapular exanthema, graft-versus-host–like disease, small vessel vasculitis, and lichenoid eruptions.13-17

In contrast, intraoral side effects seem to be rare, with a few case reports of lichenoid reactions18-21 and dental hyperpigmentation.22 Recently, a case report described a patient with a diffuse hyperpigmentation of the hard palate presumably related to imatinib mesylate therapy.23 The purpose of the present paper was to describe another 3 patients with similar solitary melanotic maculae in the palatal mucosa and to discuss a possible relationship to imatinib mesylate treatment.

CASE 1

A 66-year-old woman was referred in December 2008 to the Clinic of Oral and Maxillofacial Surgery, Central Hospi-
tal, Karlstad, for evaluation of a pigmented lesion in the hard palate. The lesion was discovered at a routine examination by the patient's regular dentist, and the patient was not aware of the lesion and consequently free from subjective symptoms. Her case history revealed that she was diagnosed with leiomyoblastoma in 1993 and that since then she had received surgical treatment to her abdomen on ≥10 occasions. She had been on continuous treatment with imatinib (Glivec; Novartis) since 2003, and at the time of examination the dose was 400 mg daily. The patient used no other medication. She was a nonsmoker.

The patient had pale complexion without pigmentation. The palatal mucosa showed a bluish-brown U-shaped pigmentation (Fig. 1, a). There were no other pigmentation or mucosal lesions. An incisional biopsy was taken in the hard palate and fixed in 4% buffered formaldehyde.

At a control visit 5 months later, the lesion was unchanged.

CASE 2
A 66-year-old woman was referred in May 2010 from the Department of Hematology to the Department of Oral and Maxillofacial Surgery, Lund Academic Hospital, for evaluation of a pigmentation in the hard palate (Fig. 1, b). The patient had chronic myeloid leukemia and since 2005 was treated with imatinib mesylate (Glivec) 400 mg daily. She also used erythropoietin (NeoRecormon), cyanocobalamin (Behepan), iron (Duroferon), and esomeprazole (Nexium). She had no other general diseases. She was a nonsmoker. The lesion had initially been observed by her regular dentist 6 months earlier. The lesion was asymptomatic, and there were no other pigmentation or other lesions in the oral mucosa. A biopsy was taken from the pigmented lesion in the palatal mucosa and fixed in 4% buffered formaldehyde.

A control visit in October 2010 showed that the lesion was clinically unchanged but also that the area where the punch biopsy was taken now had normal pigmentation.

CASE 3
A 64-year-old woman was in December 2008 seen at the Clinic of Oral and Maxillofacial Surgery/Hospital Dentistry–Oral Medicine, Ryhov Hospital, Jönköping, because of pain from an extraction wound involving a mandibular premolar. The case history revealed that she suffered from chronic myeloid leukemia. Her doctor reported that blood tests currently revealed normal values. She also had tachycardia and joint pain. She used furosemide (Lasix Retard), allopurinol, calcium carbonate with cholecalciferol (Calcichew), and simvastatin (Zocord). Her leukemia was treated with imatinib mesylate (Glivec) 400 mg daily since May 2003. She was a nonsmoker.

The patient had a pale complexion. Intraorally, the patient displayed a bluish-brown pigmented lesion which was symmetrically distributed on both sides of the hard palate (Fig. 1, c). There were no other oral mucosal lesions. She had no subjective symptoms. The patient refused a biopsy.

A follow-up with the patient's regular caregiver in October 2010 confirmed that the pigmented lesion still persisted.

HISTOPATHOLOGICAL FINDINGS
The histopathologic examination of both case 1 and case 2 revealed noninflamed palatal mucosa covered by normal epithelium. Numerous pigment-laden cells with
roundish or spindled shape were found in the lamina propria. A few pigmented cells were found also in the submucosal tissue but no pigment was observed within the epithelium (Fig. 2, a and b). The pigment was shown to be melanin; it was bleachable with 0.25% potassium permanganate (Fig. 2, c), whereas Berlin blue staining for hemosiderin was negative.

**DISCUSSION**

The patients in this report demonstrated solitary pigmented lesions in the hard palate, and the histopathologic examination revealed melanin pigment in the lamina propria, consistent with melanotic maculae. The oral melanotic macula is a frequent lesion in the population,1 with the palate being the most common location. The lesions are caused by increased melanin production by melanocytes, and the deposited melanin is found within the basal cell layer of the epithelium, the lamina propria, or both.3,8

The etiology of the presently observed pigmentations can be debated. First, it was impossible to establish how long the lesions had been present, because all 3 patients were free of symptoms and the lesions were found at visits to other caregivers. However, 1 patient who had used imatinib mesylate for 5-6 years (case 1) was seen by her regular dentist 1 year before and the lesion was not present at that time.

Before addressing the possible relationship between the observed melanotic macules and imatinib mesylate treatment, some other etiologic factors must be considered. All 3 patients were caucasian and 2 of them (cases 1 and 3) had notably pale complexions. There was no reason to suspect ethnic hyperpigmentation. None of the patients had any of the systemic diseases usually associated with melanoplakia development or used other drugs associated with excessive melanin pigmentation. All 3 were nonsmokers. Notably, in all of these conditions, melanin is primarily found in the basal cell layers of the epithelium, in contrast to the present cases where melanin was almost exclusively found in the lamina propria.

Clinically, a differential diagnosis was pigmentation associated with bleeding and subsequent degeneration of hemoglobin, and palatal hyperpigmentation has also in fact been described in association with hemochromatosis.2,24 However, none of the patients had laboratory findings indicating hemochromatosis, and the histopathologic examination showed absence of hemosiderin, ruling this possibility out. Furthermore, there was no history of trauma.

Consequently, it is difficult to associate the observed lesions with any of the conditions mentioned above. Instead, the common aspects of the 3 cases were the location and clinical appearance of the pigmented le-

![Fig. 2. Histologic section from case 2. a, Noninflamed palatal mucosa covered by normal epithelium. Numerous pigment-laden cells were found in the lamina propria (arrows). b, Higher magnification of the histologic section in a, displaying several pigment-laden cells in the lamina propria. c, A histologic section from the same area as in b. The melanin pigment is almost completely removed with potassium permanganate. Only a few residual granules are detected (arrow). Hematoxylin-eosin and potassium permanganate C. Objective magnification: a ×20, b ×60, c ×40.](image-url)
cells, and melanocytes. Signaling through c-Kit is essential for the development of these cells. c-Kit is normally activated by binding of its ligand, the stem cell factor initiating a process which finally activates various transcription factors in different cell types. Such activation regulates apoptosis, cell differentiation, proliferation, chemotaxis, and cell adhesion. Gain-of-function mutations in the KIT oncogene, which encodes c-Kit, are intimately associated with GIST development and ~80%-85% of GISTs harbor activating mutations of the c-Kit tyrosine kinase. Chronic myeloid leukemia is associated with similar mutations.

c-Kit affects melanocytes in several ways, including migration, proliferation, and differentiation. Inhibition of c-Kit by various substances has been shown to have an antipigmentary effect and imatinib mesylate therapy also has been associated with hypopigmentation of the skin. A study by Arora et al. found hypopigmentation in 41% of patients with chronic myeloid leukemia treated with imatinib mesylate. It appears to be reversible when therapy is discontinued or when the dose is reduced.

Therefore, the presently observed hyperpigmentation is in contrast to what is to be expected from the inhibitory effect from imatinib mesylate on c-Kit receptors on melanocytes. However, imatinib mesylate has been associated with hyperpigmentation of fingernails and skin as well as repigmentation of skin, although such cases are rare. It is not known how imatinib mesylate can induce both loss of pigment and darkening of skin in different patients. There are families with germline mutations in KIT who present with hyperpigmentation, and it has been suggested that imatinib mesylate may exacerbate a genetic predisposition to cutaneous hyperpigmentation related to a mutated KIT gene, or a variant of the kinase which is activated rather than inhibited by imatinib mesylate.

The location and clinical appearances were similar among the 3 cases, as was the histopathologic appearance from the 2 cases where biopsies could be obtained. The clinical appearance of a diffuse pigmentation in the palate related to drugs is, however, not unique and may be found in patients treated with quinacrine or minocycline. Interestingly, 1 case of solitary hyperpigmentation of the palate and with similar histopathologic appearance in relation to imatinib mesylate therapy was recently described. To the best of our knowledge, this is the only previously reported case of this relationship.

In conclusion, it seems that the development of melanotic maculae represents a reaction pattern in the oral mucosa which may be induced by several etiologic factors. Clinically, the lesions are benign and require no treatment. Neither GIST nor chronic myeloid leukemia are disease entities associated with hyperpigmentation of the oral mucosa. The similarity of the present cases therefore makes it reasonable to assume that they were related to the use of imatinib mesylate. Why the palatal mucosa was the only affected location is unclear, as is the precise mechanism behind the excessive melanin pigmentation.

Because imatinib mesylate is a common treatment for GIST and some hematologic malignancies, and the number of reported cases of hyperpigmentation is so small, it is tempting to speculate that imatinib mesylate has a direct influence on melanocytes, but individual genetic or other predisposing factors are necessary for the development of melanotic maculae.

REFERENCES


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