Mucosal Pigmentation Caused by Imatinib: Report of Three Cases

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Abstract Imatinib mesylate (STI-571, Gleevec®), a tyrosine kinase inhibitor, is a first-line medication for treating chronic myeloid leukemia (CML). Clinical studies revealed very good hematological responses without significant side effects. However, imatinib may lead to mucosal pigmentation. Three patients, two males aged 64 and 53 and one female aged 29 presented with a painless, diffuse, grey-blue pigmentation of the mucosa of the hard palate. Both male patients had a history of CML and had been on imatinib for 4 and 10 years, respectively. The female patient had been on imatinib for 4 years for pelvic fibromatosis. Histopathologically, deposition of fine, dark-brown, spherical granules was noted within the connective tissue. There was no inflammation or hemorrhage, and no melanosis or melanocytic hyperplasia in the epithelium. The granules stained positively for both Fontana-Masson and Prussian blue stains. Imatinib-induced pigmentation is similar to that caused by other medications such as minocycline and anti-malarial medications, namely the deposition of a drug metabolite containing melanin and iron.

Keywords Imatinib mesylate · Gleevec® · STI-571 · Oral mucosal pigmentation · Chronic myeloid leukemia

Introduction

Oral mucosal pigmentation is a common clinical finding presenting as focal or diffuse lesions, which may be caused by exogenous material (such as amalgam) or endogenous pigmentation (such as melanin or hemosiderin). The differential diagnosis of *focal* melanotic pigmentation includes oral/labial melanotic macule, post-inflammatory hypermelanosis, melanoacanthosis, and nevo-melanocytic lesions. Causes of *diffuse* melanotic pigmentation include physiologic pigmentation, post-inflammatory hypermelanosis, pigmentation associated with systemic diseases, and medication-related pigmentation.

Imatinib mesylate (Gleevec®, Novartis, Basel, Switzerland) is a tyrosine kinase inhibitor that impairs the constitutively active tyrosine kinase BCR-ABL, and is therefore,

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a first-line medication for treating CML [1–3]. In five recently published articles, patients on imatinib were noted to develop cutaneous pigmentation [4, 5], diffuse hyperpigmentation on the hard palate mucosa [5–7] or melanonychia [8].

Herein, we report three cases of oral mucosal pigmentation involving the hard palate mucosa in patients on imatinib therapy and discuss the potential mechanism for such pigmentation.

Case Report

Case 1

A 64-year-old Caucasian male presented with a painless, diffuse, grey-blue pigmentation on the hard palate mucosa that the patient was unaware of until a routine dental examination (Fig. 1a). There were no other areas of pigmentation on the oral mucosa, skin, or fingernails. His medical history was significant for CML only, and he had been treated with imatinib 400 mg daily for 4 years. Other medications included ibuprofen and multi-vitamins. He had never taken hydroxyurea, minocycline, or anti-malarial agents, and was a nonsmoker. An incisional biopsy was performed.

Case 2

A 53-year-old Caucasian male presented with a painless, diffuse, grey-blue pigmentation on the hard palate mucosa of unknown duration (Fig. 1b). There were no other pigmented lesions on the oral mucosa, skin, or fingernails. His medical history was significant for CML, hypertension, hyperlipidemia, diabetes mellitus, and allergic rhinitis. His medications included imatinib (400 mg/day for 10 years), fosinopril sodium, amlodipine besylate, metoprolol succinate, simvastatin, gemfibrozil, fenofibrate, cetirizine, aspirin, and vitamin D. The patient had been on hydroxyurea for 8 weeks after he was diagnosed with CML but this was discontinued 10 years ago. He had never taken minocycline or anti-malarial medications and was a non-smoker. An incisional biopsy was performed.

Case 3

A 29-year-old Caucasian female presented with a sudden onset of an asymptomatic, diffuse blue-black pigmentation of the hard palate noted on routine dental examination (Fig. 1c). No other pigmented lesions were noted on the skin or fingernails. Her medical history was significant for pelvic fibromatosis involving the right ureter for which she had undergone a left nephrectomy 4 years earlier. She also

Fig. 1 Diffuse, grey-blue macular pigmentation on of the hard palatal mucosa in **a** Case 1, **b** Case 2, **c** Case 3

was prescribed imatinib as adjuvant therapy after surgery (400 mg/day for 4 years). Following surgery, she developed deep vein thrombosis and iron deficiency anemia and her medication list included warfarin, oxycontin, cyclizine, and iron replacement therapy. She had never taken hydroxyurea, minocycline, or anti-malarial agents and was a non-smoker. An incisional biopsy was performed.

Histopathology

The histopathologic features of all three cases were identical. The oral mucosa showed deposition of fine, brown, spherical bodies measuring 2–4 μm located within the lamina propria (Fig. 2a), either within melanophages or lying in linear array in between collagen fibers. Some of the particles were within cytoplasmic processes of dendritic mononuclear cells. Melanocytic hyperplasia or increased melanin pigmentation was absent within the epithelium (Fig. 2b–c). There were no signs of inflammation or hemorrhage. The Fontana-Masson stain was positive for melanin (Fig. 3a) and the Prussian blue stain was positive for iron (Fig. 3b). Based on the clinical data and the histopathologic findings, the diagnosis was imatinib-related mucosal pigmentation (Table 1).

Discussion

These patients developed diffuse, blue-grey pigmentation on the oral mucosa of the hard palate after long-term use of imatinib (4, 4 and 10 years of exposure, respectively). Histopathologically, the pigmentation represented fine, spherical brown granules exclusively within the lamina propria and showed positive staining with Prussian blue and Fontana-Masson stains indicating the presence of iron and melanin, respectively. There was no melanocytic hyperplasia or melanosis of the basal cells in the epithelium. The appearance of pigment granules with this staining pattern is characteristic of medication-induced pigmentation, similar to that seen with minocycline or anti-malarial drugs.

Medication-associated pigmentation of the oral cavity is caused by: (a) pigmented breakdown products of the drug itself; (b) drug metabolites chelated with iron; or (c) drugs that are able to induce melanin formation. Clofazamine, a potent anti-inflammatory drug for treating leprosy, has red metabolites which may lead to mucosal pigmentation [9]. Antimalarials, such as chloroquine, hydroxychloroquine, amodiaquine, and quinacrine, possess anti-inflammatory or immunosuppressive functions [10, 11] and cause pigmentation via the complex interaction of drug metabolites, iron, and/or melanin [12, 13]. Conjugated estrogen has also been reported to cause oral pigmentation by lowering the plasma concentration of cortisol and stimulating adrenocorticotrophic hormone (ACTH) production [14, 15]. ACTH and α -melanocyte-stimulating hormone (α -MSH) are both the post-translational processing derivatives of pro-opiomelanocortin (POMC) products, with α -MSH being the first 13 amino acids of ACTH; as such, elevated levels of ACTH automatically increase the expression of α -MSH, thus resulting in hypermelanosis. Oral pigmentation from

Fig. 2 Case 1: **a** Oral mucosa containing pigment within the lamina propria (H&E, $\times 40$). **b** Fine spherical brown particles are exclusively within the lamina propria without melanocytic hyperplasia or melanosis of basal cells (H&E, $\times 200$). **c** Fine spherical brown particles lie between collagen bundles or within melanophages (H&E, $\times 400$)

anti-malarial medications, minocyclines, and imatinib always involves the mucosa of the hard palate and it is unclear why this mucosa and not others is particularly susceptible. The corollary to this is that oral pigmentation,

Fig. 3 Case 1: **a** Pigmented particles showing positive reaction with Fontana-Masson stain (Fontana-Masson stain, $\times 100$). **b** Pigmented particles contain iron (Prussian blue stain, $\times 100$)

associated with other medications, that occurs on non-palate sites more susceptible to trauma are more likely to be post-inflammatory hypermelanosis.

Imatinib is a specific protein kinase inhibitor approved by the Food and Drug Administration in 2001 for the treatment of CML. It blocks the activity of the mutated BCR-ABL tyrosine kinase of CML. In addition, imatinib blocks the binding of ligands to c-kit receptors on melanocytes, reducing the activity of melanocytes and leading to hypopigmentation [16]. However, imatinib may also lead to hyperpigmentation of the skin or mucosa and it likely does this through a drug metabolite chelated to iron and melanin, in a similar mechanism to minocycline and anti-malarial drugs [12, 13, 17]. In one study of 118 patients with CML on imatinib, 41% of cases exhibited hypopigmentation of the skin, and only 4% of the cases showed hyperpigmentation [4]. There are other case reports showing the association between imatinib therapy and pigmentation of the hard palatal mucosa [5–7], nails [8], and skin [5]. Of the 8 total case reports of well-documented imatinib-associated pigmentation, all involved the mucosa of the hard palate. All except two patients had a history of CML (one patient had gastrointestinal stromal tumor and the other pelvic fibromatosis), and all of them were on long-term imatinib (median 5 years, range 3–10 years). The median age was 64 years (range 29–70 years).

Patients with CML are sometimes treated initially with hydroxyurea, which has been reported to cause mucocutaneous hyperpigmentation and melanonychia [18–20]. According to one study involving 29 patients using hydroxyurea, 17 cases (58.6%) showed hyperpigmentation of any site with the most common site being the fingernail; only one case (3.4%) developed pigmentation on the tongue [18]. In addition, hydroxyurea causes mucocutaneous ulceration in approximately 2–3% of patients [18, 20]. The most probable cause appears to be due to an increase in melanin production secondary to direct local activation of melanocytes [19, 21, 22], which is different from

Table 1 Previous and current reported cases of imatinib-related pigmentation involving the hard palatal mucosa

Authors	Presentation	Gender	Age	Significant medical history
Resende et al. [5]	Blue pigmentation on the hard palatal mucosa	Male	38	CML with imatinib treatment for over 5 years
Lewis [6]	Asymptomatic diffuse gray pigmentation on the hard palatal mucosa	Male	70	CML with imatinib treatment for 3 years
Mattsson et al. [7]	Dark-brown pigmentation on the hard palatal mucosa	Female	66	Gastrointestinal stromal tumor with imatinib treatment for 5 years
	Dark-brown pigmentation on the hard palatal mucosa	Female	66	CML with imatinib treatment for 5 years
	Dark-brown pigmentation on the hard palatal mucosa	Female	64	CML with imatinib treatment for 5 years
Li et al.	Painless, diffuse, grey-blue pigmentation on the hard palatal mucosa	Male	64	CML with imatinib treatment for 4 years
	Painless, diffuse, grey-blue pigmentation on the hard palatal mucosa	Male	53	CML with imatinib treatment for 10 years
	Painless, diffuse blue-black pigmentation of hard palate	Female	29	Pelvic fibromatosis with imatinib treatment for 4 years

medication-associated pigmentation as discussed above. Furthermore, the location of hydroxyurea-associated melanosis occurs on sites other than the palate and it is possible that these represent post-inflammatory hypermelanosis after mucositis caused by the hydroxyurea; the associated nail changes are consistent with post-inflammatory hypermelanosis. Unfortunately, there are no histopathologic studies to confirm the nature of the pigmentation.

The diagnosis of imatinib-related pigmentation depends on a thorough medical history and characteristic clinical features. The hyperpigmented lesions are benign, and no treatment is required. Fortunately, the oral lesions occur on the hard palatal mucosa and are not of cosmetic concern.

The clinical differential diagnosis of diffuse pigmentation also includes physiologic pigmentation, post-inflammatory hypermelanosis, and pigmentation associated with systemic diseases. Physiologic pigmentation is the most common form of diffuse intraoral pigmentation, usually presenting as multi-focal or diffuse, symmetric, light to dark brown macules on the gingiva and mucosa of the hard palate [23]. It often occurs in dark-complexioned individuals. Diffuse post-inflammatory hyperpigmentation is a macular hypermelanosis associated with damage to the epithelium, such as in lichenoid processes where the basal cell layer is degenerated. Pigmentation associated with systemic disease, such as Albright syndrome, Peutz-Jegher syndrome, Addison disease, and neurofibromatosis, occurs as *Café au lait* macules or diffuse pigmentation involving mucosa and skin [24]. *Gsx* gene mutation and cAMP-mediated tyrosine kinase activation in melanocytes may play important roles in the formation of pigmented lesions in Albright syndrome [25]. In Peutz-Jegher syndrome, it is suggested that the pigmented lesions develop secondary to the mutation of the *LKB1* gene, which activates the Wnt/ β -catenin pathway and contributes to the stimulation of melanocytes [26], thereby causing the excess production of melanin. Addison disease represents primary adrenocortical insufficiency, stimulating the expression of ACTH and α -MSH similar to the estrogen-induced pigmentation mentioned previously. The pathophysiologic mechanism of pigmentation in neurofibromatosis remains uncertain [24]. In all these conditions, there is an increase in melanin pigment within the basal cell layer with incontinent melanin and melanophages in the lamina propria to varying degrees, without concomitant deposition of iron unless there has been hemorrhage.

In summary, we present three cases of oral mucosal pigmentation related to imatinib therapy. The excessive melanin deposition is most likely due to drug metabolites that chelate with iron and melanin. No treatment is required for this condition. The underlying etiologic mechanism should be further elucidated.

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