Case Report

ORAL MUCOSA PIGMENTATION RELATED TO IMATINIB MESYLATE: A CASE REPORT

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ABSTRACT

Imatinib Mesylate (IM), a tyrosine kinase inhibitor, is a first-line medication for treating chronic myeloid leukemia and gastrointestinal stromal tumors. Clinical studies revealed excellent hematological responses without significant side effects. Dermatologic side effects are ordinary, with rash and superficial edema the most recurring. Moreover, IM treatment is often associated with hypopigmentation. Intraoral side effects are very infrequent. However, IM may lead to mucosal pigmentation. This paper reports a patient with chronic myeloid leukemia treated with IM for seven years, referred with diffuse solitary bluish-brown pigmentations in the hard palate.

KEYWORDS: *pigmentation, oral cavity, leukemia, skin*

INTRODUCTION

Oral pigmentations linked to excessive melanin production are characteristic clinical findings, and their etiology varies, denoting a broad spectrum from physiologic pigmentations to manifestations of systemic diseases (1). Some physiologic pigmentation is connected to ethnicity and is mainly found in dark-skinned populations (2). They are often bilateral and found in buccal and gingival mucosa. (3). Systemic diseases such as Addison's disease, Peutz-Jehgers syndrome, and other rare diseases, such as Nelson syndrome, polyostotic fibrous dysplasia, and hyperthyroidism, are associated with oral melanotic pigmentation (4). Deposit of melanin in the connective tissue may even be found after long-standing inflammation in conditions such as pemphigus, oral lichen planus, and pemphigoid (5).

Likewise, tobacco and several drugs, i.e., antimalarials, tetracyclines, chemotherapeutic drugs (doxorubicin, bleomycin, 5-fluorouracil, cyclophosphamide), phenothiazines, quinidine, amiodarone, and clofazimine, may cause oral pigmentation (6). Imatinib mesylate (IM - STI-571, Gleevec®; Novartis Pharma, Basel, Switzerland) is a tyrosine kinase inhibitor that targets Bcr-Abl-protein, c-Kit, and platelet-derived growth factor receptors (7). The drug was initially conceived for the therapy of chronic myeloid leukemia (CML) but is also considered the first-line treatment for patients with metastatic gastrointestinal stromal tumors (GIST) (8). IM treatment correlates with side effects, such as diarrhea, nausea, periorbital edema, and myelosuppression (7). Dermatologic side effects are not uncommon, with rash and superficial edema as the most common; additional side effects are pruritic maculopapular exanthema, erythroderma, small vessel vasculitis, graft-versus-host-disease, and lichenoid eruptions (9). In difference, intraoral side effects appear rare,

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with occasional dental hyperpigmentation and lichenoid reactions (10, 11). The present paper aimed to depict a patient with similar solitary melanotic maculae in the palatal mucosa.

CASE REPORT

A 46-year-old woman was referred in March 2021 to the Unit of Oral Pathology and Medicine at the University of Campania "Luigi Vanvitelli" to evaluate a pigmented lesion in the hard palate. She was a nonsmoker, and the lesion was discovered at a routine examination by the patient's regular dentist. The patient had chronic myeloid leukemia (CML) and, since 2015, was treated with IM 400 mg daily. The patient used no other medication. The palatal mucosa showed a bluish-brown U-shaped pigmentation symmetrically distributed on both sides of the hard palate (Fig. 1). The lesion was asymptomatic, and there were no other pigmentations or lesions in the oral mucosa. The patient refused a biopsy. A follow-up in June 2021 confirmed that the pigmented lesion persisted and was clinically unchanged.

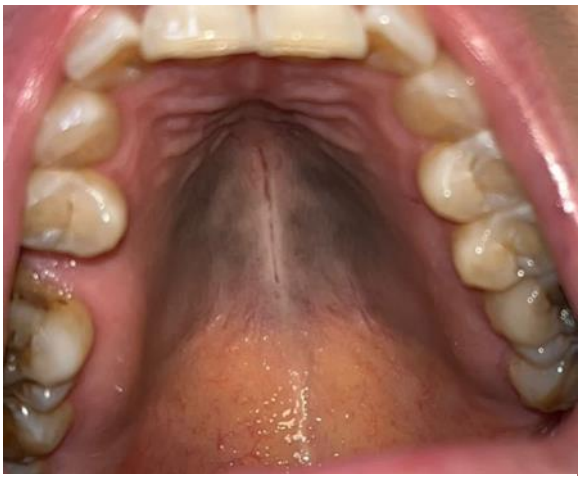

Fig. 1. *Clinical presentation of the palatal mucosa.*

DISCUSSION

Solitary pigmented lesions in the hard palate associated with IM treatment have been previously described in the literature (12-14). The histopathologic examination in the literature indicated melanin pigment in the lamina propria, consistent with melanotic maculae—noninflamed palatal mucosa covered by normal epithelium (13). Multiple pigment-laden cells with roundish or spindled shapes were found in the lamina propria. A few pigmented cells were also seen in the submucosal tissue (14).

The oral melanotic macula is a recurring lesion in the population, with the palate being the most typical site (15). The lesions are generated by grown melanin production by melanocytes, and the deposited melanin is located within the basal cell layer of the epithelium, the lamina propria, or both (16). Some additional etiologic factors must be evaluated before handling the probable relationship between the observed melanotic macules and IM therapy (5). The patient had no systemic conditions usually associated with melanosis development or used other drugs associated with excessive melanin pigmentation; furthermore, she was a nonsmoker. From a clinical point of view, a differential diagnosis was pigmentation associated with bleeding and following degeneration of hemoglobin, and palatal hyperpigmentation has also been reported in association with hemochromatosis (17). Regardless, there was no history of trauma, and the patient had no laboratory findings indicating hemochromatosis.

IM has been associated with hyperpigmentation of fingernails and skin and hypopigmentation of skin, although such cases are rare (18). It is not understood how IM can cause both losses of pigment and darkening of the skin in various patients (13, 19, 20). IM is a specific protein kinase inhibitor approved by the Food and Drug Administration in 2001 for treating CML (21). It blocks the activity of the mutated BCR-ABL tyrosine kinase of CML; IM also blocks the binding of ligands to c-kit receptors on melanocytes, lowering the activity of melanocytes and leading to hypopigmentation (22). Nonetheless, IM may even lead to hyperpigmentation of the skin or mucosa. It likely does this through a drug metabolite chelated to iron and melanin, in a similar mechanism to minocycline and anti-malarial drugs (23). The diagnosis of IM-related pigmentation hangs on a thorough medical history and distinctive clinical features (24). Fortunately, the hyperpigmented lesions are benign, and no treatment is required (25).

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