Drug-associated hyperpigmentation of the oral mucosa: report of four cases

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Objective. The aim of this study was to describe 4 patients with oral mucosa hyperpigmentation associated with 4 drug classes and to review the relevant literature.

Study Design. Two patients under imatinib and hydroxychloroquine treatment exhibited diffuse palatal hyperpigmentation and 2 patients treated with minocycline and golimumab showed multifocal pigmented macules. In all cases, biopsy was performed.

Results. Microscopically, in all cases, there was no increase in the number of melanocytes in the epithelium, and pigment granules were present in the lamina propria. The pigment granules in minocycline- and golimumab-associated hyperpigmentation were seen in the superficial lamina propria and reacted for silver but not iron, whereas in imatinib- and hydroxychloroquine-associated hyperpigmentation, pigment granules were found in the reticular lamina propria and reacted for both silver and iron. A review of the literature found 38 cases of hyperpigmentation of the oral mucosa attributed to minocycline, 23 to imatinib, 1 to hydroxychloroquine without microscopic documentation, and none to golimumab.

Conclusions. The temporal relationship between pigmentation and onset of drug effect, resolution following drug withdrawal, and exclusion of other causes support the diagnosis of drug-induced hyperpigmentation. Microscopic examination may be contributory to diagnosis, as there are differences among drugs with regard to the distribution of pigment granules and the histochemical reactions of the drugs. (Oral Surg Oral Med Oral Pathol Oral Radiol 2018;125:e54–e66)

Many systemically administered drugs are associated with, among other adverse events, hyperpigmentation of the oral soft tissues, with antibiotics, antimalarials, chemotherapeutics, hormones, and tranquilizers being the best known examples. Drug-associated hyperpigmentation of soft tissues shows nonspecific histologic changes, and various mechanisms may be involved in its pathogenesis. They include deposition of the drug substance in tissues, as seen with heavy metals such as silver, gold, or bismuth, or of pigmented metabolites of the drug that chelate with tissue components (i.e., melanin or iron); increase of the melanin content of the mucosa directly, by initiation of melanin production by melanocytes, or indirectly, through a postinflammatory reaction after a fixed-drug eruption; and accumulation of iron after damage of the vessels and hemorrhage. The mechanisms of other drugs remain unknown.

There is poor evidence for a causal association between a drug and soft tissue hyperpigmentation because most reports are case studies. Because the dosing regimen and the temporal association between medication intake and the occurrence of hyperpigmentation remain unclear, additional cases may be of clinical use.

We describe the clinical, histologic, and histochemical features of 4 white patients with diffuse or multifocal hyperpigmentation of the oral mucosa associated with 4 different classes of drugs (i.e., minocycline, imatinib, hydroxychloroquine, and golimumab) and review the pertinent literature.

CASE REPORTS

Case 1: Minocycline-associated hyperpigmentation

A 55-year-old female was referred by her dentist for diagnosis and management of an area of black pigmentation on the gingiva around the lower left canine. It had first been noticed approximately 5 months earlier, but it had been extending recently. The patient’s medical history was significant for cystic acne complicated by Staphylococcus infection, which was being treated with 200 mg/d minocycline hydrochloride for the last 8 months, and 125 mg/d of terbinafine hydrochloride for onychomycosis diagnosed 2 months ago. There was, in addition, vitamin D deficiency, which was being managed with vitamin D supplementation. Her recent complete blood count (CBC) total was within normal limits. She had been smoking approximately 20 cigarettes per day since she was 25 year-old.

Statement of Clinical Relevance

Diffuse/multifocal oral mucosal pigmentation may present as a drug-associated adverse effect. Correct diagnosis is based on medical history and exclusion of other conditions; microscopic examination is contributory to diagnosis, as there are differences among drugs with regard to pigment granule distribution and histochemical reactions.
Clinical examination showed hyperpigmentation on the facial gingiva distal to the lower right central incisor, involving both marginal and attached gingivae. The pigmentation was of a pale brown color with a dark spot (Figure 1A). Areas of pale brown pigmentation were also seen on the facial attached gingiva of the maxilla, proximal to the upper right first premolar and canine (Figure 1A, black arrows) and distal to the upper left canine (Figure 1B); on the mandible, proximal to the right first premolar to distal to the lateral incisor (Figure 1A, white arrows); and between the left lateral incisor and the canine. The rest of the oral mucosa was normal. No ocular, skin, or nail hyperpigmentation was evident or reported by the patient.

A biopsy on the area of the lower right central incisor revealed minocycline-associated hyperpigmentation (see below). Treatment with minocycline and terbinafine hydrochloride was terminated a month later, and although the patient did not quit smoking, the lesion did not recur, no additional lesions appeared, and the hyperpigmented areas faded considerably.

Case 2: Imatinib-associated hyperpigmentation
A 61-year-old male was referred by his hematologist for assessment of palatal pigmentation. The patient was unaware of the presence of the lesion, although he recalled that approximately 6 months earlier, his regular dentist had noticed “black macules” on the palate during

Fig. 1. Multifocal gingival hyperpigmentation in a minocycline-medicated patient. A, Hyperpigmentation of brown color with a dark spot on the facial marginal and attached gingiva distal to the lower right central incisor; areas of pale brown pigmentation proximal to the upper right first premolar and canine (black arrows); and proximal to the lower right first premolar to distal to the lateral incisor (white arrows). B, Pale brown hyperpigmentation on the attached gingiva distal to the upper left canine. C, Microscopic examination showed increased deposition of melanin in the cells of the basal and parabasal layer (black arrows) that (D) were positive for methenamine-silver stain. C, Hematoxylin and eosin stain; D, Grocott (Gomori) methenamine-silver stain (original magnifications C and D, ×400). A high-resolution version of this slide for use with the Virtual Microscope is available as eSlide: VM04566.
routine dental examination, but it did not prompt further investigation. Nineteen years ago, he had undergone bone marrow transplantation for chronic myeloid leukemia (CML), and for the past 11 years, he was being treated with imatinib mesylate 400 mg/d. According to his attending physician, the patient had not received hydroxyurea, prednisone, chloroquine, or minocycline in the last 11 years. The patient’s most recent CBC was significant for mild leukopenia and anemia. He was taking lepirudin daily, and he did not smoke. He could not recall palatal trauma or any kind of symptomatic irritation to this area. No skin or nail pigmentation was evident, and he was unaware of any changes in cutaneous pigmentation.

Clinical examination showed that the hard palate had a homogeneous gray-black discoloration that was symmetric and well defined and did not blanch on pressure (Figure 2A). The rest of the oral mucosa appeared normal.

An incisional biopsy revealed imatinib-associated hyperpigmentation (see below). No modification was made to his medication, and approximately 31 months later, palatal hyperpigmentation was still present, but without any significant change.

Case 3: Hydroxychloroquine-associated hyperpigmentation

A 53-year-old female was referred by her dentist for evaluation of an area of black pigmentation on her palate; the pigmentation was not present on a previous routine examination performed approximately 2 years earlier. The patient was receiving treatment for rheumatoid arthritis with 400 mg/d hydroxychloroquine for approximately 5

Fig. 2. Palate hyperpigmentation in a patient treated with imatinib. A, A symmetric, well-defined, homogeneous gray-black discoloration of the hard palate. B, Numerous brown-yellow granules within the reticular lamina propria, among collagen fibers, which were positive for (C) methenamine-silver stain and (D) iron stain. Normal melanin deposition and normal melanocytes number were seen in the covering epithelium (B, hematoxylin and eosin stain; C, Grocott [Gomori] methenamine-silver stain; D, Perls’ iron stain; original magnifications B-D, ×400). A high-resolution version of this slide for use with the Virtual Microscope is available as eSlide: VM04565.
years and for hypertension with nebivolol hydrochloride 5 mg daily. She recalled using “prednisone for a long period many years ago” and reported that she did not smoke.

Clinical examination showed homogeneous, diffuse, blue-brown pigmentation on the hard palate (Figure 3A) and a small brown macule on the attached gingiva of the lower left canine. The palatal lesion was symmetric and diffuse and did not blanch on pressure. The rest of the oral mucosa was within normal limits. Hyperpigmentation of the skin of the neck and thorax was also present.

An incisional biopsy revealed hydroxychloroquine-associated hyperpigmentation (see below), and because of the increased risk for retinopathy in patients with hydroxychloroquine-induced hyperpigmentation, this patient was referred for ophthalmologic evaluation. Ocular examination results were within normal limits; treatment with hydroxychloroquine was stopped, and the palatal hyperpigmentation faded considerably within the next 30 months.

**Case 4: Golimumab-associated hyperpigmentation**
A 67-year-old woman was referred by her rheumatologist for evaluation of numerous macules on the oral mucosa, with a request for assessment to rule out melanoma. The lesions had been observed by the patient 5 days earlier, on self-examination. Her last regular dental

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**Fig. 3.** Palate hyperpigmentation in a rheumatoid arthritis patient under hydroxychloroquine treatment. **A,** A symmetric, diffuse, homogeneous blue-brown hyperpigmentation on the hard palate. **B,** Many fine, brown-yellow granules of approximately the same size in the reticular lamina propria that stained with **C** methenamine-silver stain and **D** iron stain. Note the evident infiltration by erythrocytes in the papillary dermis (**B**, hematoxylin and eosin stain; **C**, Grocott [Gomori] methenamine-silver stain; **D**, Perls’ iron stain; original magnifications **B-D**, ×400). A high-resolution version of this slide for use with the Virtual Microscope is available as eSlide: VM04564.
checkup was done approximately 3 months ago, and her
dentist did not report any abnormal oral finding. She was
being treated for rheumatoid arthritis with 10 mg/d of
leflunomide for approximately 11 years and 50 mg per
month of golimumab for approximately 6 years;
levothyroxine sodium for Hashimoto disease; and
nebivolol hydrochloride for hypertension. Her medical
history was significant for systemic lupus erythemato-
sus, which had been treated for 3 years with
corticosteroids and hydroxychloroquine, but the treat-
ment had stopped 8 years ago. She had been smoking
20 cigarettes per day since she was 31 year-old.

Fig. 4. Multifocal oral mucosal hyperpigmentation in a patient treated with golimumab. Dark to light brown, smooth macules with
well-defined borders (A) on the right and (B) left buccal mucosa, (C) the hard palate, and (D) the upper lip close to the vermilion
border. E, Microscopic examination from a buccal macule in the golimumab-treated patient revealed increased melanin deposit-
ion in the basal and parabasal layers and dark pigmented granules similar to melanin in the superficial lamina propria (black arrows)
that stained positive (F) for methenamine-silver stain (E, hematoxylin and eosin stain; F, Grocott [Gomori] methenamine-silver
stain; original magnifications E and F × 100). A high-resolution version of this slide for use with the Virtual Microscope is avail-
able as eSlide: VM04563.

Clinical examination showed macules on the buccal
mucosa (6 on the right [Figure 4A] and 1 on the left
[Figure 4B]), hard palate (3 [Figure 4C]), and the upper
lip close to the vermilion border (1 [Figure 4D]). The
macules were homogeneous, were of a dark to light brown
color, had smooth and well-defined borders, and mea-
sured 0.3 to 0.5 cm. The mucosal texture was normal,
and there was no blanching or hemorrhage on pressure.
The rest of the oral mucosa was within normal limits.
No pigmentation was reported by the patient or was
evident on her skin or nails. Biopsy was performed on
1 palatal and 1 buccal macule.
Golimumab treatment was continued, but approximately 14 months later, she had to discontinue golimumab because of the development of nephrotic syndrome with heavy proteinuria, for which she is currently under treatment. The patient reported that no additional oral mucosal lesions developed and that the existing ones tended to fade; however, because of her severe medical condition, she did not present for re-examination.

**Microscopic examination**

In all cases, biopsy was performed under local infiltration anesthesia, and 5-μm-thick formalin-fixed and paraffin-embedded tissue sections were stained with hematoxylin and eosin, Grocott (Gomori) methenamine-silver stain, and Perls’ iron stain, by using standard procedures. (Grocott [Gomori] methenamine-silver stains melanin black, and Perls’ iron stains ferric iron blue [Prussian-blue reaction]). The mucosal fragments were covered by stratified squamous epithelium.

In patients with minocycline-associated hyperpigmentation (Figure 1C) and in those with golimumab-associated hyperpigmentation (Figure 4E), there was increased deposition of melanin in the cells of the basal and parabasal layers, as well as in cell processes, but no increase in the number of melanocytes. Fine, dark-pigmented granules similar to melanin were seen in the superficial lamina propria, free among collagen fibers or intracellularly within macrophages. The microscopic features were identical to those of the oral melanotic macule. In the former case, there was, in addition, a focally intense inflammatory infiltration by lymphocytes and plasmacytes. The granules were positive for methenamine-silver stain (Figures 1D and 4F) and negative for iron stain.

In patients with imatinib-associated hyperpigmentation (Figure 2B) and in those with hydroxychloroquine-associated hyperpigmentation (Figure 3B), there was no increased deposition of melanin in the basal cell layer and no increase in the number of melanocytes, but in the latter, erythrocytes were evident in the superficial lamina propria. Many fine, brown-yellow granules of approximately the same size were seen within the reticular lamina propria, among collagen fibers or intracellularly within macrophages. They were not consistent with melanin because there was no increased deposition of melanin in the basal cell layer or with hemosiderin. However, they stained with methenamine-silver stain (Figures 2C and 3C) and iron stain (Figures 2D and 3D), probably representing deposition of the drug or drug products that are chelated to iron or express chemical groups of melanin or ferric iron that react with the respective histochemical stains. Figure 5 presents the main microscopic and histochemical features of drug-associated hyperpigmentation of the oral mucosa by class of medication. It should be noted that the information about hydroxychloroquine- and golimumab-associated hyperpigmentation was based only on our cases, as microscopic and histochemical

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![Diagram of drug-associated hyperpigmentation](image_url)

**Fig. 5.** Main microscopic and histochemical features of drug-associated hyperpigmentation of the oral mucosa by class of medication, according to our cases and literature review. The information considering hydroxychloroquine- and golimumab-associated hyperpigmentation was based only on our cases because their microscopic and histochemical characteristics have not been previously described.
characteristics of these types of hyperpigmentation have not been previously described.

**DISCUSSION**

Diagnosis of drug-associated hyperpigmentation is based on the temporal relationship between hyperpigmentation and initiation of drug administration, resolution following drug withdrawal, aggravation upon re-exposure, and exclusion of other etiologies with similar clinical or histologic features. The “diverse and extensive” differential diagnosis of multifocal or diffuse mucosal hyperpigmentation has been thoroughly discussed in previous publications and includes racial/normal pigmentation; smoking-related pigmentation; post-traumatic or postinflammatory hyperpigmentation; pigmentation associated with systemic diseases such as Addison disease and hemochromatosis; syndromes such as Peutz-Jegher syndrome, McCune-Albright syndrome, and neurofibromatosis; and deposition of exogenous pigmented material.

Localization of lesions on the gingiva in the case of the patient treated with minocycline could be consistent with normal (racial) pigmentation or smokers’ melanosis. However, acute onset of lesions and exclusive marginal gingival distribution conflicts with such a diagnosis. These conditions could also be included in the differential diagnosis of golimumab-associated pigmentation, but in that case, gingival involvement and early onset would be expected. Although the patients in two of the cases presented here did not quit smoking, no additional lesions appeared, and the hyperpigmented areas either faded considerably or tended to fade. In the case of golimumab, the microscopic features were consistent with oral melanotic macules that are typically solitary, whereas lack of striate melanonychia conflicted with a diagnosis of Laugier-Hunziker syndrome. A traumatic event or inflammation preceding the development of the lesions could not be substantiated—that is, patients with palatal lesions did not wear a denture that could cause erythematous can-

**Minocycline-associated hyperpigmentation**

Minocycline is a semi-synthetic tetracycline used as a broad-spectrum antibiotic in the treatment of various systemic infections; an anti-inflammatory drug in the management of dermatologic diseases, in particular acne vulgaris; and an immunosuppressive drug in immune-mediated diseases, such as rheumatoid arthritis. Hyperpigmentation is an uncommon, but well-documented adverse effect of minocycline treatment. It may affect various organs, in particular skin and nails, subcutaneous fat, bones (“black bone disease”) and cartilage, ocular mucosa, thyroid gland, viscera, and body fluids. Hyperpigmentation of skin, nails or bones was seen in 15% of 333 case reports of adverse events of minocycline treatment over a nearly 40-year period. Although pigmentation is considered dose dependent, the total dose or duration of medication does not affect the intensity of skin hyperpigmentation that may be associated with other factors, such as exposure to sunlight, concurrent treatment with other drugs, and genetic predisposition.

There are at least 3 well-described clinicopathologic types of minocycline-associated skin hyperpigmentation that may present alone or in combination. Types I and II present mostly with a blue color, mixed with gray or brown. Type I is localized to sites of skin inflammation, trauma, or scarring and is not influenced by duration of therapy or cumulative dose, whereas type II is diffuse and affects normal-appearing skin, in particular the skin of the extremities. Type III is also diffuse, has a mostly brown color, and affects normal-appearing sun-exposed skin. Types II and III are usually associated with long-term high-dose minocycline treatment. Type IV, which is less common, presents as circumscribed hyperpigmentation of blue to gray color, particularly within acne scars on the back.

The microscopic features of minocycline-associated skin hyperpigmentation are described mostly in case reports, which are occasionally contradictory with regard to the presence of melanin. Typically, type I and II lesions demonstrate pigment granules in the dermis, aligned between collagen fibers or accumulated in macrophages distributed around vessels or adnexa that react with Fontana-Masson silver staining and Perls’ iron staining, but the staining reaction is not considered confirmatory for the presence of melanin in all cases. The study by Argenyi et al. reported that no
melanosomes are seen on electron microscopic examination, whereas X-ray energy spectroscopic examination showed that they contain iron, sulfur, chlorine, and calcium. On the basis of those findings, it is thought that the lesions represent oxidized minocycline (type I) or minocycline products (type II) chelated with iron because the normally yellow minocycline becomes black after oxidation. In type III lesions, iron is absent, and there is increased melanin deposition in basal keratinocytes and adjacent dermal melanophages, possibly as a result of minocycline-induced melanin production or formation of minocycline–melanin complexes.

Type IV resembles type I histopathologically, but granules react with Fontana-Masson silver staining but not with Perl’s iron staining. Intraoral minocycline-associated hyperpigmentation is common in alveolar bone and predominantly in the middle third of the crown or roots of erupted teeth, causing darkening of the overlying mucosa as the black color appears through the translucent non-pigmented mucosa. Hyperpigmentation of the oral soft tissues in mucosal sites not directly associated with alveolar bone or teeth, such as the tongue, lips, and buccal mucosa, as well as the gingiva and hard palate, is very rare and no case was seen among 331 patients who were treated for acne with at least 100 mg/d of minocycline for a minimum of 6 months. In contrast, approximately 10% of the patients showed blue pigmentation of alveolar bone. Treister et al. reviewed 33 cases of minocycline-induced oral hyperpigmentation and added 2 new cases. They noticed, however, that most of the reviewed cases could represent staining of the underlying alveolar or palatal bone because in cases where a mucosal flap was elevated, the bone was pigmented, whereas when a biopsy was performed, it showed no mucosal deposition of staining material. Our literature review from 2000 to 2016 revealed 3 additional cases with gingival involvement, which, in contrast to our case, was associated with hyperpigmentation of other intraoral or extraoral sites. Our patient had been treated with a daily dose of 200 mg minocycline for less than 1 year. In other cases, hyperpigmentation was associated with daily doses of 100 mg or 200 mg and appeared even after 2 weeks of treatment.

There is limited information on the microscopic features of minocycline-associated hyperpigmentation of oral soft tissue. In a review of 33 cases of intraoral minocycline pigmentation reported up to 2004, all involved alveolar bone, and in 6 cases where biopsy was performed on the gingival hyperpigmentation, no pigment was seen in the mucosa. In 2 cases of palatal pigmentation, the granules stained for iron but were not considered morphologically consistent with hemosiderin, whereas they did not bleach with hydrogen peroxide, thus excluding the presence of melanin. In contrast, in a case of gingival pigmentation, the distribution of the granules in the basal and parabasal layers of the epithelium, as well as within the macrophages in connective tissue, was consistent with melanin. The clinical and microscopic features of the latter case are comparable with those of our case, where, in addition, the pigmented granules were positive with methenamine silver staining, but negative for iron. Although the patients were smokers in both cases, making smokers’ melanosis a possible diagnosis, we found that pigmentation was confined to the marginal gingiva and did not extend to the attached gingiva. Induction of melanin production by minocycline or its metabolites and formation of minocycline-melanin complexes that resist degradation cannot be excluded, but an effect of exposure to sunlight because of the location of the lesions seems unlikely. Previous reports have classified oral lesions as consistent with type I or II cutaneous hyperpigmentation, but this classification was developed for skin lesions, so more cases should be studied for clinical utility in oral lesions to become evident.

The course of minocycline-induced pigmentation of the oral mucosa is unknown, and it is suggested that it may persist even years after withdrawal of the offending drug. Q-switched ruby laser, alexandrite, or neodymium:YAG laser have been successfully applied in the management of this condition.

Imatinib-associated hyperpigmentation
Imatinib mesylate is a tyrosine kinase inhibitor that targets the adenosine triphosphate (ATP) binding site of BCR-ABL tyrosine kinase, as well as the tyrosine kinases of platelet-derived growth factor receptor-β, c-kit, and ABL. It is used in the management of Philadelphia chromosome-positive CML and gastrointestinal stromal tumors. Cutaneous hypopigmentation was seen in 40.9% of 118 patients with CML treated with imatinib and was attributed to inhibition by imatinib of c-kit, which, along with its ligand stem-cell factor (SCF), has a major role in melanogenesis, melanocyte homeostasis, and ultraviolet B–induced pigmentation. In contrast, cutaneous hyperpigmentation is a rare adverse event seen in only 3.6% of 118 patients with CML receiving imatinib, which is dose related and reversible with discontinuation of the drug.

Pathogenetic hypotheses include stimulation of melanogenesis, resulting from activation rather than inhibition of the c-kit receptor by imatinib or because of a lichenoid reaction that regresses, or apoptosis of melanocytes and melanin incontinence, which is caused by increased concentration of imatinib (>12 mol/L). However, accumulation of the drug in macrophages and generation through its processing of chemical groups that react with histochemical stains, such as melanin or lipofuscin, or chelation of the drug’s metabolites
with iron and melanin, seem more reasonable explanations.

Pancholi and Taneja reviewed 16 cases of palatal pigmentation in patients receiving imatinib in 1 case in combination with hydroxyurea, and added 3 more cases; an additional 4 cases have been reported since that review. More cases may have been recognized but have not been described; 2 cases of gingival pigmentation and 1 case of teeth pigmentation have not been documented fully. Sixteen patients with imatinib-associated palatal pigmentation had CML, leiomysoblastoma, and acute lymphoblastic leukemia. In our case where the patient was receiving imatinib 400 mg/d for 11 years, the drug dose was most commonly associated with palatal pigmentation, the lesions were present for at least 6 months before diagnosis. The exact time of onset of pigmentation was uncertain in most cases because the palatal location and lack of symptoms made their identification incidental, but long-term exposure to drug (5-6 years, range 3 months to 10 years) is suggested. In 1 patient, hyperpigmentation was seen after just 3 months of treatment with imatinib 800 mg/d, and the hyperpigmentation could be probably attributed to increased drug concentration in plasma. Our patient did not show any other sign of oral or cutaneous pigmentation. Skin pigmentation coexisted in 2 cases, and was absent in 6 cases and not recorded in 6 cases. One patient with acute lymphoblastic leukemia had also café-au-lait spots on the skin, but those spots were attributed to the synchronous occurrence of neurofibromatosis type I, and another patient with CML had melanonychia of the toenails.

In the case presented here, the clinical and microscopic features were consistent with those in previous reports of imatinib-associated palatal hyperpigmentation. Our patient was not treated for CML with other drugs that may cause hyperpigmentation, in particular hydroxyurea or chloroquine, or with minocycline. Besides, oral melanosis associated with hydroxyurea occurs on sites other than the palate and may represent postinflammatory pigmentation as a result of hydroxyurea-induced mucositis. Hemosiderin deposition—that is, after palatal trauma—could be expected in a patient with CML who has a predisposition for hemorrhage because of the disease or another medication, but in our patient, neither CBC nor the microscopically verified absence of hemorrhage was suggestive of such a condition. We agree with Mattsson et al. that although “it is unwise to categorically state that imatinib mesylate is responsible, … we do suggest that the drug is very strongly implicated.”

The microscopic features in previous reports of palatal melanosis are contradictory: In 4 patients, the pigment granules were positive for melanin and negative for iron, as is also described in skin hyperpigmentation; in another 4 cases, the pigment granules were positive for both melanin and iron; and in 1 case, only the presence of iron was recorded. In our case, the pigment granules reacted for both melanin and ferric iron, although there was no increased deposition of melanin in the basal cell layer or any hemorrhage. Those findings are more consistent with the presentation by the drug byproducts of chemical groups that react like melanin or lipofuscin, but the predilection for this phenomenon to occur in the palate cannot be explained.

Hypermelatonin is not an indication for discontinuation of imatinib in patients with CML, and lesions tend to remain stable, even after 2 years.

Hydroxychloroquine-associated hyperpigmentation

A common adverse effect of antimalarial drugs that are used in the management of rheumatologic or dermatologic diseases because of their anti-inflammatory and immune-modulating properties is hyperpigmentation of the skin. It may occur with all classes of antimalarial drugs, but it is more common with chloroquine and quinacrine and rare with hydroxychloroquine. In a retrospective study, it was seen in 67 of 194 patients (35%) treated with chloroquine, but only 2 of 15 patients (13%) treated with hydroxychloroquine. The median duration of treatment before the development of cutaneous hyperpigmentation is 6.1 years (3 months to 22 years) and the median cumulative dose of the drug 720 g. It is dose-dependent, may decrease over several months after the drug is discontinued, and can persist for many years and even improve despite continuation of therapy. It manifests as well-defined, brown, blue-gray or dark purple pigmentation and is commonly associated with toxic ocular effects, in particular retinopathy that leads to vision loss.

Microscopic examination shows yellow- to brown-colored pigment granules in macrophages and fibroblasts and among collagen fibers; the pigment granules react for iron and some of them for melanin. In 2 cases of hydroxychloroquine-associated skin pigmentation, only melanin was identified, and in another 5 cases, melanin and ferric iron were observed. It is suggested that the pigment represents either hydroxychloroquine chelated to melanin or iron, or melanin whose production is stimulated by hydroxychloroquine, directly or indirectly through an increase in the androgen levels caused by the drug.

Antimalarial drug–induced oral hyperpigmentation is uncommon and is reported to occur on the hard palate, gingiva, lips, and buccal mucosa. In a retrospective study, pigmentation of the buccal mucosa or the hard palate was seen in 10 patients (5%) using chloroquine, but none in hydroxychloroquine, and there are rare case reports of hyperpigmentation in patients with systemic lupus erythematosus treated with
hydroxychloroquine, involving skin and the palate, or only the gingiva. A case of pigmentation of the lower gingiva in a patient with Sjögren’s syndrome treated with hydroxychloroquine is more consistent with racial pigmentation or smoker’s melanosis. The clinical, microscopic, and histochemical features in patients receiving hydroxychloroquine are similar to those of patients taking chloroquine phosphate, suggesting that the drug may be implicated in this phenomenon. There is no other report on the microscopic findings of hyperpigmentation associated with the drug in the oral mucosa. In our case, the pigment granules reacted for both melanin and ferric iron, as is described in some skin lesions. These findings are also quite similar to those in our case of imatinib-associated hyperpigmentation, with the exception of the presence of hemorrhage that could act as a source of iron. However, the reaction for melanin and the absence of granules consistent with hemosiderin can be explained only by the assumption that products of the drug that is locally processed by macrophages express chemical groups that react like melanin or lipofuscin.

Resolution may be seen months to years after drug withdrawal. Thirty months after the palate biopsy, our patient was lost to follow-up, so further information is not available.

**Golimumab-associated hyperpigmentation**

Golimumab is a fully human monoclonal antibody that blocks tumor necrosis factor (TNF)-α signaling. It acts as a decoy receptor that binds both soluble and membrane-bound TNF-α and prohibits it from binding and acting through its true receptors TNFR1 and TNFR2. Because TNF-α is a polypeptide hormone that plays a crucial role in many rheumatologic, gastrointestinal, and dermatologic diseases, its inhibitors are used in the treatment of respective diseases, in particular psoriasis, psoriatic arthritis, rheumatoid arthritis, ankylosing spondylitis, and Crohn’s disease.

TNF-α inhibitors are associated with an increased risk for the development of skin melanoma in patients with rheumatoid arthritis or inflammatory bowel disease, although there is no increased risk for cancer overall. This observation was originally made in patients taking infliximab and later confirmed for 3 other TNF-α inhibitors that are currently in use, namely, golimumab, etanercept, and adalimumab, but not for cetolizumab. Studies have shown that patients with rheumatoid arthritis treated with TNF-α inhibitors have an increased risk of developing invasive melanoma or a second primary melanoma, relative to patients treated with nonbiologic drugs, whereas there is an increased risk of recurrent melanomas in patients with rheumatoid arthritis who have a history of melanoma before starting treatment with TNF-α inhibitors. In contrast, nonbiologic disease-modifying antirheumatic drugs, such as methotrexate, that are typically used in rheumatoid arthritis are not a strong risk factor for melanoma.

The mechanism underlying the development of melanoma in patients treated with TNF-α inhibitors is not known. Direct association with the ensuing immunosuppression because of the disease or the inhibitory role of TNF in tumor surveillance is supported by the association between organ transplantation or HIV and the risk for melanoma. There is, in addition, the possibility of increased detection of melanoma in this group of patients as a result of better medical monitoring. Another explanation is that TNF-α inhibitors may increase skin photosensitivity or directly influence melanocytes, an effect that is under investigation because it may prove useful in the management of vitiligo. In particular, melanocytes both produce TNF-α and express TNFR1 and TNFR2 receptors in response to stress, and TNFR1 may mediate apoptosis through a caspase-3-dependent pathway in a variety of cells, including melanocytes.

In neonatal human melanocytes, TNF-α inhibits proliferation and melanogenesis by decreasing tyrosinase activity in a dose-dependent manner, and it may promote melanocyte apoptosis. At the same time, however, TNF-α may stimulate the secretion of melanogenic factors, such as stem cell factor, hepatocyte growth factor, basic fibroblastic growth factor, and endothelins, as is seen in postinflammatory or post-trauma n pigmentations. Therefore, it may be hypothesized that TNF-α inhibitors directly promote melanocyte survival and melanogenesis, but this may be an oversimplification because the interplay of TNF-α with other cytokines that affect melanocytes is a complex process. In our case, a temporal relationship with golimumab administration could not be established with certainty because the lesions were asymptomatic. In addition, as a result of the development of nephrotic syndrome, the patient could not present for re-examination, although she thought that withdrawal from the drug had a positive effect on the pigmented lesions. Increased melanin deposition without increased number of melanocytes, observed on microscopic examination, is consistent with the effect of TNF-α on melanocytes. The patient was also treated with hydroxychloroquine plus corticosteroids, but that treatment had been terminated 8 years before the patient observed the dark macules, and in the meantime, no pigmentation was seen during a number of routine dental examinations. Although there are no reports of soft tissue pigmentation caused by golimumab, exclusion of other diseases and the possibility that the drug may stimulate melanogenesis implicate it in the development of hyperpigmentation.
CONCLUSIONS
Correct diagnosis of drug-associated pigmentation is crucial for patient management and to avoid confusion with other systemic diseases and conditions, but it also protects the patient from unnecessary anxiety, testing, and other adverse effects. The last is particularly true for chloroquine, where cutaneous and mucosal hyperpigmentation may be a marker for retinopathy that is irreversible and may lead to blindness. 

Hard palate pigmentation without involvement of the soft palate is a strong indication of a drug-induced adverse effect. Biopsy is indicated for lesions developing on mucosal sites, such as the hard palate, where melanoma usually develops and in patients taking drugs, such as golimumab, in which case there is an increased risk for the development of melanoma.

In conclusion, drug-associated hyperpigmentation of the oral mucosa is microscopically characterized by a normal number of melanocytes in the epithelium and the presence of pigment granules within the lamina propria, among collagen fibers, and within macrophages. An increased deposition of melanin in the basal cell layer and the presence of granules in the superficial lamina propria are strongly indicative of minocycline- and golimumab-associated pigmentation. In the former, the histochemical findings considering the reaction of the granules for silver or iron are conflicting, but in the latter, the granules react for silver but not for iron. In contrast, lack of deposition of melanin in the basal cell layer and the presence of granules in the reticular lamina propria point to imatinib- and hydroxychloroquine-associated hyperpigmentation. In the former, the granules react for silver and variably for iron, whereas in the latter, they react for both silver and iron, and there is hemorrhage. It should be noted that our report of the microscopic and histochemical characteristics of hydroxychloroquine- and golimumab-associated hyperpigmentation is the first in the literature, so our findings should be further verified.

The excellent technical assistance of Mrs. Maria Manou, MTL, MSc, and Mr. Eugene Danas, MTL, MSc, is acknowledged.

REFERENCES


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