Imipramine-Induced Hyperpigmentation

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PRACTICE **POINTS**

- Imipramine is a tricyclic medication used for the treatment of depression and mood disorders.
- A rare side effect of treatment with imipramine is a blue-gray discoloration of the skin.
- Thorough medication review is important in patients who present with skin discoloration.

Imipramine is a tricyclic medication that has been used for the treatment of depression and other mood disorders. Although rare, a slate gray discoloration of sun-exposed skin may occur in patients taking this medication. We present the case of a 63-year-old woman who had been taking imipramine for depression for more than 20 years when she developed a bluish gray discoloration on the face and neck that was diagnosed as imipramine-induced hyperpigmentation based on histopathology and clinical history. A number of other drugs that may cause hyperpigmentation also are reviewed as well as their histopathologic staining characteristics.

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Imipramine is a tricyclic medication uncommonly used to treat depression, anxiety, and other psychiatric illnesses. Although relatively rare, it has been associated with hyperpigmentation of the skin including slate gray discoloration of sun-exposed areas.

We present the case of a 63-year-old woman who had been taking imipramine for more than 20 years when she developed bluish gray discoloration on the face and neck. Histopathology of biopsy specimens showed numerous perivascular and interstitial brown globules in the dermis that were composed of melanin only, as evidenced by positive Fontana-Masson staining and negative Perls Prussian blue staining. A diagnosis of imipramine-induced hyperpigmentation was made based on histopathology and clinical history.

In addition to the case presentation, we provide a review of drugs that commonly cause hyperpigmentation as well as their associated histopathologic staining characteristics.

Case Report

A 63-year-old woman presented with blue-gray discoloration on the face and neck. She first noted the discoloration on the left side of the forehead 3 years prior; it then spread to the right side of the forehead, cheeks, and neck. She denied pruritus, pain, redness, and scaling of the involved areas; any recent changes in medications; or the use of any topical products on the affected areas. Her medical history was remarkable for hypertension, which was inconsistently controlled with lisinopril and hydrochlorothiazide, and depression, which had been managed with oral imipramine.

Physical examination disclosed blue-gray hyperpigmented patches with irregular borders on the bilateral forehead, temples, and periorbital skin (Figure 1). Reticulated brown patches were noted on the bilateral cheeks, and the neck displayed diffuse muddy brown patches with sparing of the submental areas.

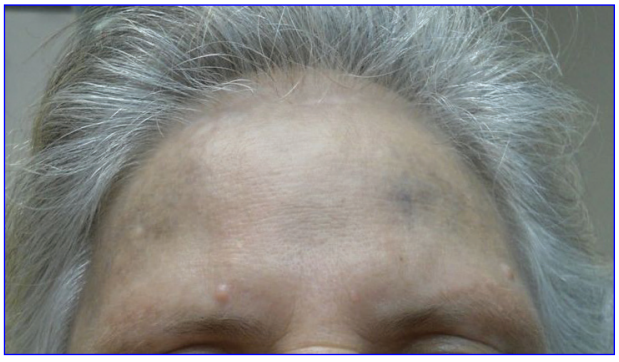

FIGURE 1. Blue-gray hyperpigmented patches with irregular borders on the bilateral forehead.

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Punch biopsies obtained from the lateral forehead showed an unremarkable epidermis with deposition of numerous golden brown granules in the upper and mid dermis and in perivascular macrophages (Figure 2). The pigmented granules showed positive staining with Fontana-Masson (Figure 3), and a Perls Prussian blue stain for hemosiderin was negative. Based on the clinical history, a diagnosis of imipramine-induced hyperpigmentation was made.

The patient revealed that she had taken imipramine for more than 20 years for depression as prescribed by her mental health professional. She had tried several other antidepressants but none were as effective as imipramine. Therefore, she was not willing to discontinue it despite the likelihood that the hyperpigmentation would persist and could worsen with continued use of the medication. Diligent photoprotection was advised. Additionally, she started taking lisinopril some time after the appearance of the hyperpigmentation presented and had not taken hydrochlorothiazide consistently for several years. Although these drugs are known to cause various cutaneous reactions, it was not considered likely in this case.

Comment

Drug-induced hyperpigmentation accounts for 10% to 20% of all cases of acquired hyperpigmentation.[1] Common causative drugs include amiodarone, antimalarials, minocycline, and rarely psychotropics including phenothiazines and tricyclic antidepressants such as imipramine.[1-4] Although amiodarone-induced hyperpigmentation is associated with lipofuscin in addition to melanin, most other medications, including imipramine, induce cutaneous effects through deposition of melanin and/or hemosiderin. A review of the histopathologic staining characteristics in pigment anomalies caused by these drugs is summarized in the Table.

Imipramine-induced hyperpigmentation presents as slate gray discrete macules and patches on sun-exposed skin that may appear anywhere from 2 to 22 years after initiating the medication.[1-4] Affected areas include the malar cheeks, temples, periorbital areas, hands, forearms, and seldom the iris and sclera.[2-4] Although the blue to slate gray coloring is classic, other colors have been described including brown, golden brown, and purple.[2]

Histopathology of imipramine-induced hyperpigmentation shows golden brown, round to oval granules in the superficial dermis and within dermal macrophages.[1,3] Generally, Fontana-Masson staining is positive for melanin and Perls Prussian blue staining is negative for iron.[1,2,4]

Imipramine-induced hyperpigmentation likely results from photoexcitation of imipramine or one of its metabolites. These compounds activate tyrosinase, increasing melanogenesis and leading to formation of melanin-imipramine or melanin-metabolite complexes.[1-3] Complexes are deposited in the dermis and basal layer or are engulfed by dermal macrophages and darkened on sun exposure due to their high melanin content.[1] Other possible mechanisms of hyperpigmentation include nonspecific inflammation caused by the drug in the skin, hemosiderin deposition from

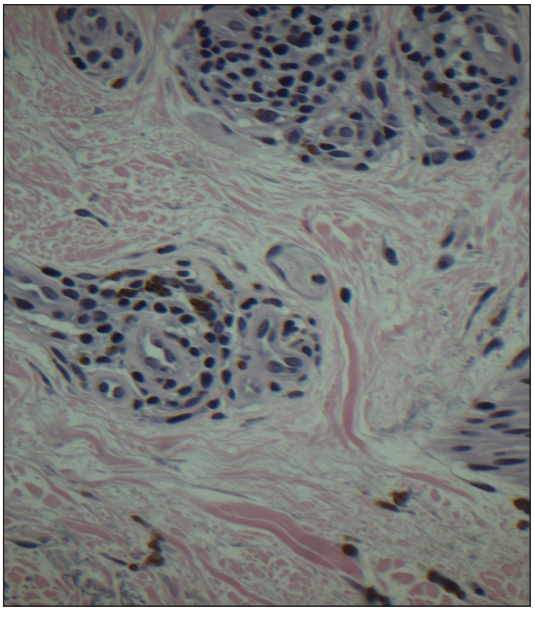

FIGURE 2. Brown globules of pigment in perivascular dermal melanophages (H&E, original magnification ×40).

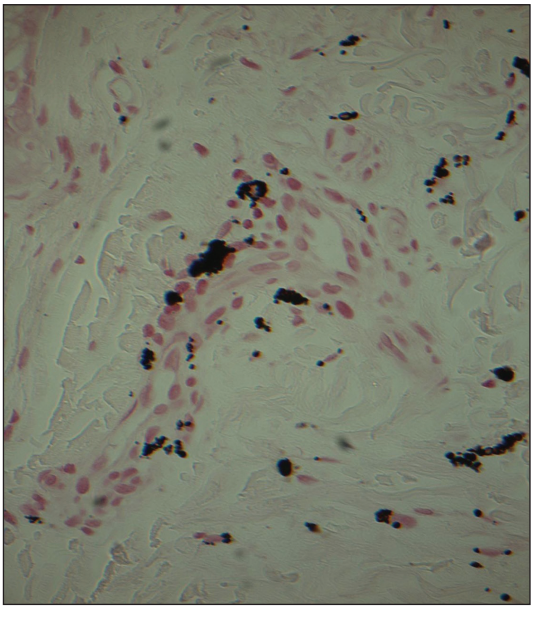

FIGURE 3. Positive staining of globules indicated melanin composition (Fontana-Masson, original magnification ×40).

Histopathologic Staining Characteristics of Drugs Commonly Implicated in Hyperpigmentation

Medication	Staining Characteristics	Deposition Location
Amiodarone	Fontana-Masson, +; Perls Prussian blue, −; PAS, +; prolonged Ziehl-Neelsen, +; Sudan black B, +	In dermal histiocytes
Antimalarials	Variable, may stain + with Fontana-Masson, Perls Prussian blue, or both	In macrophages, free in the dermis
Minocycline	Types I and IV: Fontana-Masson, −; Perls Prussian blue, +; type II: Fontana-Masson, +; Perls Prussian blue, +; type III: Fontana-Masson, +; Perls Prussian blue, −	Types I and IV: perivascular macrophages, free in the dermis; type II: addition of eccrine ducts, adnexa; type III: basal layer keratinocytes
Phenothiazines	Fontana-Masson, +; Perls Prussian blue, −	Perivascular in superficial dermal capillaries, in dermal macrophages
Tricyclic antidepressants	Fontana-Masson, +; Perls Prussian blue, −	In dermal macrophages, along the basement membrane

Abbreviations: +, positive; −, negative; PAS, periodic acid–Schiff.

vessel damage and subsequent erythrocyte extravasation, or deposition of newly formed pigments related to the drug.[1]

Most patients report satisfactory resolution of imipramine-induced discoloration within 1 year of stopping imipramine or switching to a different antidepressant.[1,4] Patients who are unwilling to discontinue imipramine may achieve resolution with alexandrite or Q-switched ruby laser therapy.[1,4] Strict sun protective measures are necessary, both to prevent new deposition of melanin and to prevent darkening of existing pigment.

Despite the advent of new psychotropic medications, imipramine remains the antidepressant of choice for many patients. Although rare, it is important to be able to recognize imipramine-induced hyperpigmentation and to encourage patient-psychiatrist communication to determine an antidepressant regimen that avoids unnecessary cutaneous side effects.

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