Mirtazapine-induced hyperpigmentation with type II histopathologic findings

Kumar Sukhdeo, MD, PhD,[a] Garrett H. Yoon, BSc,[b] Lisa Rothman, MD,[a] Shane A. Meehan, MD,[a] Melissa K. Levin, MD,[a] and Randie H. Kim, MD, PhD[a]
New York, New York

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INTRODUCTION

Drug-induced hyperpigmentation (DIH) is a common side effect of several medication classes, including atypical psychoactive agents.[1] Mirtazapine is an antidepressant with antiadrenergic and antiserotonergic activity. Indications for mirtazapine use include major depressive disorder and other mood disorders, anxiety, and insomnia. Typical potential adverse effects of mirtazapine include drowsiness, weight gain, xerostomia, and increased appetite.[2] However, reports of hyperpigmentation are extraordinarily rare.[3]

Abbreviation used:

DIH: drug-induced hyperpigmentation

CASE REPORT

A 63-year-old white man with a history of insomnia, advanced congestive heart failure, peripheral vascular disease, coronary artery disease, and orthostatic hypotension presented to the dermatology clinic with photodistributed and asymptomatic hyperpigmented patches (Fig 1). The lesions began approximately 2 years prior, 4 to 6 months after the initiation of mirtazapine. His other medications included aspirin, warfarin, tamsulosin, alendronate, metoprolol, rosuvastatin, pantoprazole, zinc sulfate, gabapentin, and spironolactone, all of which were started after the formation of the hyperpigmented patches.

Physical examination of the dorsal hands, forearms, and upper arms found large, irregular dark brown patches on the dorsal hands, forearms, and upper arms. Islands of sparing were identified within multiple patches. No other areas of the body were affected including mucosal surfaces and other photoexposed regions of skin such as the face, neck, and upper chest. The differential diagnosis included DIH, pellagra, photodermatoses, pigmented contact dermatitis, postinflammatory hyperpigmentation, erythema dyschromicum perstans, and acquired brachial cutaneous dyschromatosis.

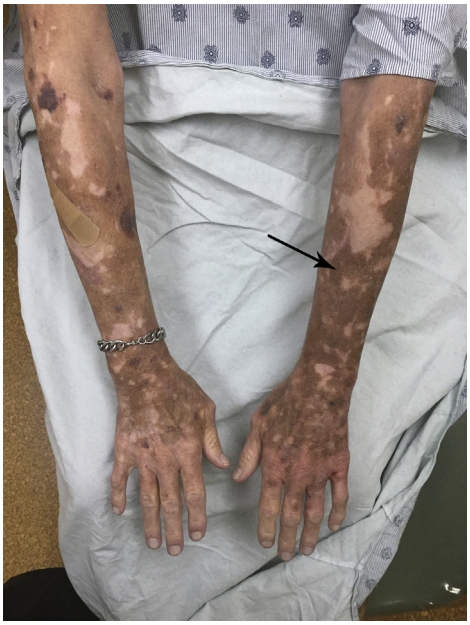

Fig 1. DIH. Clinical images of patient's presentation. Dorsal hands and forearms show large hyperpigmented brown-tan patches with islands of sparing.

From the Ronald O. Perelman Department of Dermatology, NYU Langone Health[a] and NYU School of Medicine.[b]

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Correspondence to: Randie H. Kim, MD, PhD, NYU Langone Health, The Ronald O. Perelman Department of Dermatology, 240 East 38th Street, 11th Floor, New York, NY 10016. E-mail: Randie.Kim@nyulangone.org.

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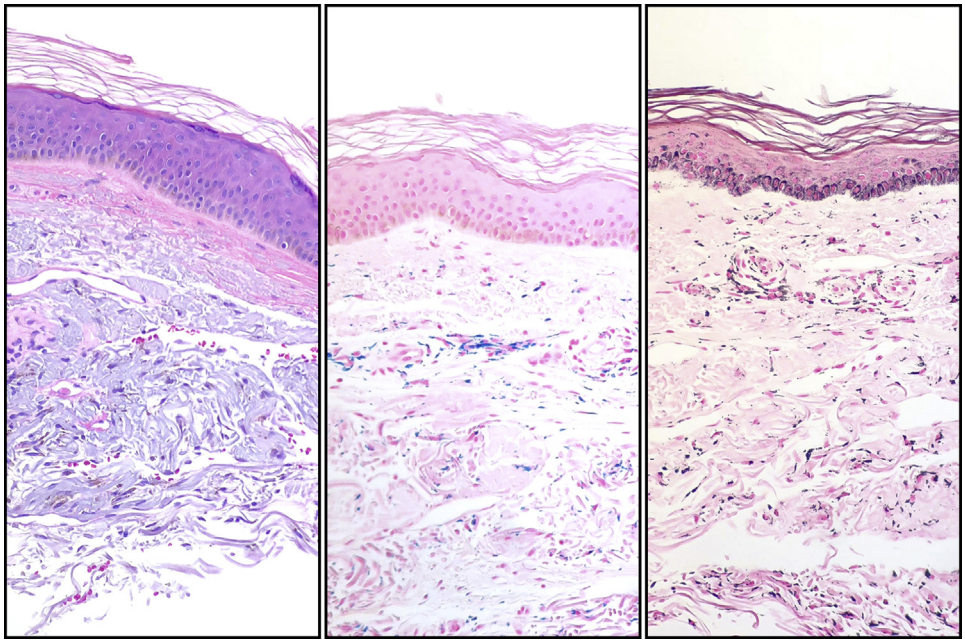

Fig 2. DIH. A punch biopsy from a pigmented area on the dorsal left arm found numerous dendritic pigmented histiocytes that reacted for both melanin on Fontana-Masson stain and iron by Perls stain. (**Left**, Hematoxylin-eosin stain; **Center**, Perls stain. **Right**, Fontana-Masson stain. Original magnifications ×200.)

A punch biopsy from the left dorsal forearm found numerous dendritic pigmented histiocytes that reacted for both Fontana-Masson stain and Perls stain (Fig 2), confirming the presence of both melanin and iron within the histiocytes. The patient's hyperpigmentation was subsequently given a diagnosis as consistent with DIH.

DISCUSSION

The manifestation of DIH is not well understood but accounts for approximately 10% to 20% of all cases of acquired hyperpigmentation.[1] Several manifestations of DIH exist depending on the underlying agent that can result in the accumulation and deposition of melanin, metabolites, medications, pigments, or iron into the dermis. Overall, there are 4 main mechanisms for DIH: (1) the accumulation of melanin in the dermis or within dermal macrophages, (2) the accumulation of the medication itself or a metabolite of the compound in granules scattered within the matrix or in dermal macrophages, (3) the synthesis of pigments such as lipofuscin stimulated by the drug's effect, and (4) iron deposition from damage of dermal vessels with leakage of erythrocytes and their subsequent lysis.[1] In most mechanisms, sun exposure is an influencing factor by inducing melanin synthesis with the formation of drug-melanin complexes or by conversion of the drug into a metabolite taken up by dermal macrophages.[4]

DIH is classified into 3 different clinical types, particularly in the context of minocycline. Type I presents with blue-black pigmentation within preexisting scars. Type II presents with a blue-grey pigmentation on shins and forearms. Type III presents with a diffuse muddy-brown discoloration in areas of sun exposure. These clinical pictures correspond to distinct histologic patterns: In type I, Perls-positive pigment is found within macrophages as well as free in the dermis. In type II, the pigment reacts for both Perls and Fontana-Masson stains and may be found concentrated around vessels and adnexae, whereas in type III, the pigment stains positive for Fontana-Masson only and is found in basal keratinocytes and dermal macrophages.[5] In the case of minocycline, the melanin in types II and III hyperpigmentation are believed to be caused by drug-melanin complexes forming in the macrophages of the papillary dermis. With regard to the deposits of iron seen in types I and II, one proposed mechanism is the chelation between iron and medication. Furthermore, metals or iron-containing complexes may promote the production of melanin by increasing tyrosinase activity,[6] demonstrating a connection between iron deposition and melanin deposition.

Regarding other psychotropic medications, hyperpigmentation clinically consistent with that of type III has been reported with other antidepressant drugs including citalopram and tricyclic antidepressants such as imipramine and desipramine.[7-9] In these cases, pigmentation has been reported to be photodistributed, with corresponding melanin deposition on histopathologic examination. Pigmentation occurs usually slowly over time, taking often months or years to develop after the initial treatment. The process is usually reversible and fades gradually after discontinuation of the offending agent.[1] It is hypothesized that abnormal drug metabolite-melanin complex formation or the activation of tyrosine leads to increased melanin production from long-term photoactivation. For instance, transmission electron miscopy studies have found that phenothiazine drugs, which are structurally related to tricyclic antidepressants such as imipramine, bind directly to melanin within melanocytes.[10]

Mirtazapine-induced hyperpigmentation is exceptionally rare and only reported in 1 prior case report with the development of hyperpigmentation in photoexposed sites. No histologic correlation was performed in that case, and the patient's hyperpigmentation improved with the discontinuation of mirtazapine.[3]

Here we present histologic correlation of DIH secondary to mirtazapine. Perls and Fontana-Masson stains highlight prominent amounts of melanin and hemosiderin, respectively, within dermal macrophages (Fig 2), a histologic pattern consistent with type II hyperpigmentation. Clinically, the patient's hyperpigmentation was limited to the forearms without involvement of other photoexposed areas, which also supports type II hyperpigmentation.[5] At follow-up, no improvement in hyperpigmentation was noted despite the discontinuation of the drug for 6 months. Given that the patient was exposed to the medication for a couple of years with conspicuous amounts of pigment deposits seen on histologic examination, longer periods off therapy may be required before clinical improvement.

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