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CASE REPORT

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Diltiazem-associated Photodistributed Hyperpigmentation

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Diltiazem is a calcium-channel blocker commonly used for the treatment of hypertension. Common adverse effects include dizziness, headache, and edema. Fewer than 20 cases of diltiazem-associated photodistributed hyperpigmentation have been reported in the literature. Here, we present the case of a 71-year-old woman with new-onset facial hyperpigmentation 6 months after initiating treatment with diltiazem.

CASE REPORT

A 71-year-old woman with Fitzpatrick type V skin presented with a 4-month history of progressive hyperpigmentation of her face. The patient first noted darkening of her nose approximately 6 months after starting diltiazem hydrochloride extended-release tablets at a dose of 100 mg daily. She denied redness, burning, itching, or other associated symptoms. Prior to the onset of the hyperpigmentation, she was not using any lotions or make-up and would wash her face only with warm water. She did not regularly use sunscreen, but denied sunburns and significant sun exposure. Before presentation, the patient had previously treated the hyperpigmentation with a mask she created from vinegar, horseradish, lemon, and honey applied once weekly for several hours; there was no improvement and this treatment was discontinued after approximately 1 month. The patient's past medical history was significant for hypertension, hyperlipidemia, diabetes, and seasonal allergies. Her medications included diltiazem, losartan, hydrochlorothiazide, spironolactone, furosemide, pravastatin, aspirin, metformin, pioglitazone, and fluticasone.

Physical examination was notable for dark brown symmetric patches with a subtle velvety texture distributed over the forehead, eyelids, nose, temples, cheeks, and chin, sparing the upper cutaneous lip and bilateral eyebrows (Figure 1). Skin biopsy from the patient's chin revealed vacuolar interface change with pigment incontinence (Figure 2). CD123 staining was negative.

Diltiazem-associated hyperpigmentation was suspected, and the patient was asked to discontinue diltiazem. Strict protection from sun exposure and avoidance of other photosensitizing medications was recommended. The patient was started on tacrolimus 0.1% ointment nightly and hydroquinone 4% twice daily for 3 months.

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Abbreviations: UV-B, ultraviolet-B.

Keywords: Diltiazem, hyperpigmentation, photodistributed, interface

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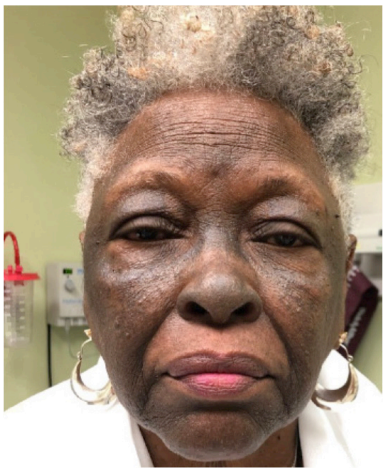

Figure 1. Physical exam on presentation. A 71-year-old woman with dark brown symmetric patches with a subtle velvety texture distributed over the forehead, eyelids, nose, temples, cheeks, and chin, sparing the upper cutaneous lip and bilateral eyebrows.

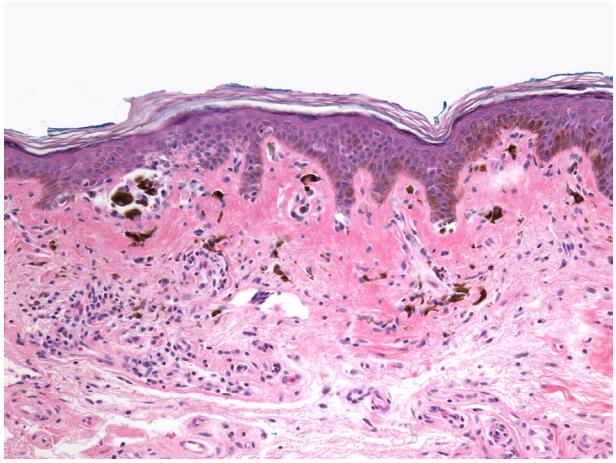

Figure 2. Histopathology. Skin biopsy notable for vacuolar interface change with pigment incontinence.

After 8 months, the patient was noted to have significant lightening of the hyperpigmented patches (Figure 3).

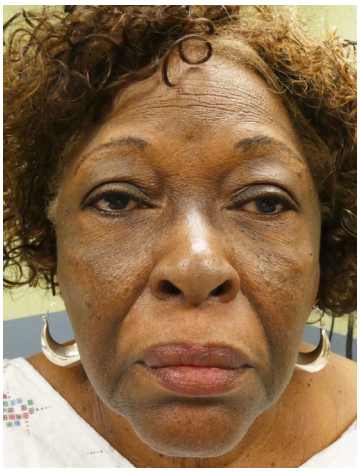

Figure 3. Physical exam at 8-month follow-up. After treatment with tacrolimus 0.1% ointment nightly for 8 months and hydroquinone 4% twice daily for 3 months, the patient was noted to have significant lightening of hyperpigmented patches on the face.

DISCUSSION

Diltiazem is a calcium-channel blocker commonly used for the treatment of hypertension. Common adverse effects include dizziness, headache, and edema. The most common cutaneous reactions include exanthematous and urticarial eruptions, erythema multiforme, Stevens-Johnson syndrome, and acute generalized exanthematous pustulosis [1,2]. Photodistributed hyperpigmentation is a rare adverse effect of diltiazem with fewer than twenty cases reported in the literature and is most frequently associated with the extended-release formulations of diltiazem [3-13]. It can appear months to years after starting the medication and is most commonly found on the face, neck, forearms, and chest. The pattern of hyperpigmentation may be confluent or reticulated. The color ranges from dark slate-blue to gray and dark brown. Interestingly, as in our patient, the pattern of pigmentation may not exactly match a classically photodistributed pattern.

Diltiazem-associated photodistributed hyperpigmentation is more common in patients with Fitzpatrick skin phototype V and VI skin than those with lighter skin types, and more common in women than men [6,13]. The average age at presentation is 65 with most patients presenting in the fifth to seventh decade of life.

The clinical differential includes post-inflammatory hyperpigmentation secondary to phototoxicity/photoallergy or other photodistributed inflammatory disorder and photodistributed hyperpigmentation secondary to other medications. Patients with post-inflammatory hyperpigmentation may report a history of itching, burning, redness, or other eruption prior to onset of hyperpigmentation.

Adult patients in the United States are often on four or more medications [14] and careful consideration of a patient's medication list is essential for the evaluation of a patient with photodistributed hyperpigmentation. Photodistributed hyperpigmentation has been reported in association with several classes of medications including antibiotics such as minocycline, antiarrhythmics such as amiodarone, and psychotropic medications such as chlorpromazine, amitriptyline, chlorpromazine, citalopram, desipramine, imipramine, mirtazapine, phenytoin, sertraline, and thioridazine. Clinical and histopathological findings can be helpful in differentiating between potential offending agents (Table 1) [15,16].

Table 1. Clinical and histopathological findings in drug-associated photodistributed hyperpigmentation by medication class.

Drug	Clinical Findings	Histopathology
Diltiazem	Brown, slate-gray, or gray-blue macules, patches; may be reticulated	Interface change with dermal melanophages
Minocycline	Type III: diffuse “muddy brown” pigmentation	Increased melanin within the basal epidermis and/or dermal melanophages
Amiodarone	Slate-gray or violaceous discoloration, especially of the face	Yellow–brown granules in dermal macrophages, mostly perivascular
Psychotropic medications	Slate-gray or brown macules/patches	Golden-brown granules in the upper dermis

The exact pathogenesis for diltiazem-associated photodistributed hyperpigmentation is not known, but has been proposed to involve absorption of solar radiation by diltiazem leading to free radical formation, binding of reactive intermediates to cellular proteins and DNA, and release of erythrogenic and pigmentary mediators. Supporting this is the finding that the absorption range for diltiazem is 220-300 nm, within UV-B spectrum [13].

Discontinuation of diltiazem is essential for the treatment of diltiazem-associated photodistributed hyperpigmentation. Hyperpigmentation due to other calcium channel blockers such as nifedipine and verapamil has not been reported. There has been reported improvement with hydrocortisone 2.5% cream, topical tacrolimus, and topical bleaching agents including hydroquinone 4% cream [3,6]. Patients should be counseled on photoprotection and should avoid other photosensitizing medications.

Hyperpigmentation can have an enormous psychosocial impact on patients, and diltiazem-associated photodistributed hyperpigmentation may be under-diagnosed, delaying treatment. Additional studies are necessary to further elucidate the underlying pathomechanism of this condition and identify optimal treatment strategies.

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REFERENCES

1. Ingen-Housz-Oro S, Hotz C, Valeyrie-Allanore L, Sbidian E, Hemery F, Chosidow O, et al. Acute generalized exanthematous pustulosis: A retrospective audit of practice between 1994 and 2011 at a single centre. Br J Dermatol. 2015;172(5):1455-7.
2. Knowles S, Gupta AK, Shear NH. The spectrum of cutaneous reactions associated with diltiazem: Three cases and a review of the literature. J Am Acad Dermatol. 1998;38(2 Pt 1):201-6.
3. Scherschun L, Lee MW, Lim HW. Diltiazem-associated photodistributed hyperpigmentation: A review of 4 cases. Arch Dermatol. 2001;137(2):179-82.
4. Campbell M, Ahluwalia J, Watson AC. Diltiazem-associated hyperpigmentation. J Gen Intern Med. 2013;28(12):1676.
5. Jaka A, Lopez-Pestana A, Tuneu A, Lobo C, Lopez-Nunez M, Ormaechea N. Letter: Photodistributed reticulated hyperpigmentation related to diltiazem. Dermatol Online J. 2011;17(7):14.
6. Kubo Y, Fukumoto D, Ishigami T, Hida Y, Arase S. Diltiazem-associated photodistributed hyperpigmentation: Report of two japanese cases and published work review. J Dermatol. 2010;37(9):807-11.
7. Desai N, Alexis AF, DeLeo VA. Facial hyperpigmentation caused by diltiazem hydrochloride. Cutis. 2010;86(2):82-4.
8. Hanson M, Petronic-Rosic V. Reticulated phototoxic eruption in a patient on long-term diltiazem therapy. J Drugs Dermatol. 2008;7(8):792-3.
9. Berendzen SM, Carey JD, Smith EB. Diltiazem-associated photodistributed hyperpigmentation in an elderly hispanic female. Int J Dermatol. 2006;45(12):1450-2.
10. Kuykendall-Ivy T, Collier SL, Johnson SM. Diltiazem-induced hyperpigmentation. Cutis. 2004;73(4):239-40.
11. Boyer M, Katta R, Markus R. Diltiazem-induced photodistributed hyperpigmentation. Dermatol Online J. 2003;9(5):10.
12. Chawla A, Goyal S. Diltiazem-induced hyperpigmentation in an african american woman. J Am Acad Dermatol. 2002;46(3):468-9.
13. Saladi RN, Cohen SR, Phelps RG, Persaud AN, Rudikoff D. Diltiazem induces severe photodistributed hyperpigmentation: Case series, histoimmunopathology, management, and review of the literature. Arch Dermatol. 2006;142(2):206-10.
14. Charlesworth CJ, Smit E, Lee DS, Alramadhan F, Odden MC. Polypharmacy among adults aged 65 years and older in the united states: 1988-2010. J Gerontol A Biol Sci Med Sci. 2015;70(8):989-95.
15. Eichenfield DZ, Cohen PR. Amitriptyline-induced cutaneous hyperpigmentation: Case report and review of psychotropic drug-associated mucocutaneous hyperpigmentation. Dermatol Online J. 2016;22(2).
16. Bolognia J. Dermatology. Fourth edition / ed2018. 2 volumes (xxvii, ,674, I-70 pages).