Volume 22 Number 1
February 2016

Case report

Amitriptyline-induced cutaneous hyperpigmentation: case report and review of psychotropic drug-associated mucocutaneous hyperpigmentation

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Dermatology Online Journal 22 (2): 6

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Abstract

Background: Several drugs can be associated with hyperpigmentation of mucosa or skin. They include antibiotic, antimalarial, antineoplastic, and psychotropic medications.

Purpose: To describe a 42-year-old woman with amitriptyline-associated photo-distributed hyperpigmentation and to review psychotropic drug-induced hyperpigmentation of the skin.

Materials and Methods: The features of a woman with amitriptyline-induced hyperpigmentation are presented. Using PubMed, the following terms were searched and relevant citations were assessed and discussed for context: amitriptyline, chlorpromazine, citalopram, desipramine, drug-associated, drug-induced, Fontana Masson, hyperpigmentation, imipramine, melanin, melanophages, mirtazapine, phenytoin, psychotropic, sertraline, thioridazine, tricyclic antidepressant.

Results: Photo-distributed hyperpigmentation on the upper back of a woman developed six and a half years after initiation of amitriptyline therapy. Biopsy of the affected area showed pigment-laden melanophages and intradermal melanin deposition.

Conclusions: Psychotropic drugs associated with cutaneous hyperpigmentation include amitriptyline, chlorpromazine, citalopram, desipramine, imipramine, mirtazapine, phenytoin, sertraline, and thioridazine. The hyperpigmentation may initially appear many years after starting the medication. Pathology typically shows melanophages and melanin in the dermis. Fontana Masson stain confirms the presence of melanin; Perl stain for hemosiderin or iron is negative. Discontinuation of the drug may result in spontaneous improvement. Further studies are needed to better understand the role of Q-switched laser in treating drug-induced hyperpigmentation.

Keywords: amitriptyline, chlorpromazine, citalopram, desipramine, drug-associated, drug-induced, Fontana Masson, hyperpigmentation, imipramine, melanin, melanophages, mirtazapine, phenytoin, psychotropic, sertraline, thioridazine, tricyclic antidepressant

Introduction

Several drugs have been associated with hyperpigmentation of mucosa and skin. In addition to antibiotic, antimalarial, antineoplastic, and anti-arrhythmic medications, they also include psychotropic medications [1]. We describe a woman with amitriptyline-induced photo-distributed hyperpigmentation and review the features of cutaneous hyperpigmentation associated with other psychotropic drugs.

Case synopsis

A 42-year-old woman presented for evaluation of dark areas of one-year duration on her upper back in June 2014. Her past medical history was significant for interstitial cystitis for which she was prescribed amitriptyline. During the past year, the patient and her husband noted that her upper back had become darker and the affected area was increasing in size but otherwise was asymptomatic.

She had no history of photosensitivity and enjoyed sunbathing at the beach. Her current medications included amitriptyline, which she had been taking since December 2006. She was also receiving the following medications: albuterol inhaler, estradiol, fluticasone propionate nasal spray, levothyroxine, progesterone, and venlafaxine.

Cutaneous examination showed a non-pruritic brown-gray discoloration of her upper back (Figure 1). There was a distinct line of sparing, which corresponded to the location of the bra and bikini strap.



Figure 1 a, b and c. Distant (a = left sided view, b = direct view, c = right sided view) views of the upper back of a 42-year-old woman with amitriptyline-induced photo-distributed hyperpigmentation on the upper back.

Biopsies were performed from affected hyperpigmented skin and from normal appearing skin, for comparison. Microscopic analysis of the hyperpigmented skin revealed perivascular melanophages and fine granular melanin pigment within the collagen fibers in the superficial dermis (Figure 2). Normal appearing skin showed neither melanocytes nor melanin deposition in the dermis (Figure 3). The dermal pigment stained positive with Fontana Masson stain (Figure 4) and negative with Perl stain.

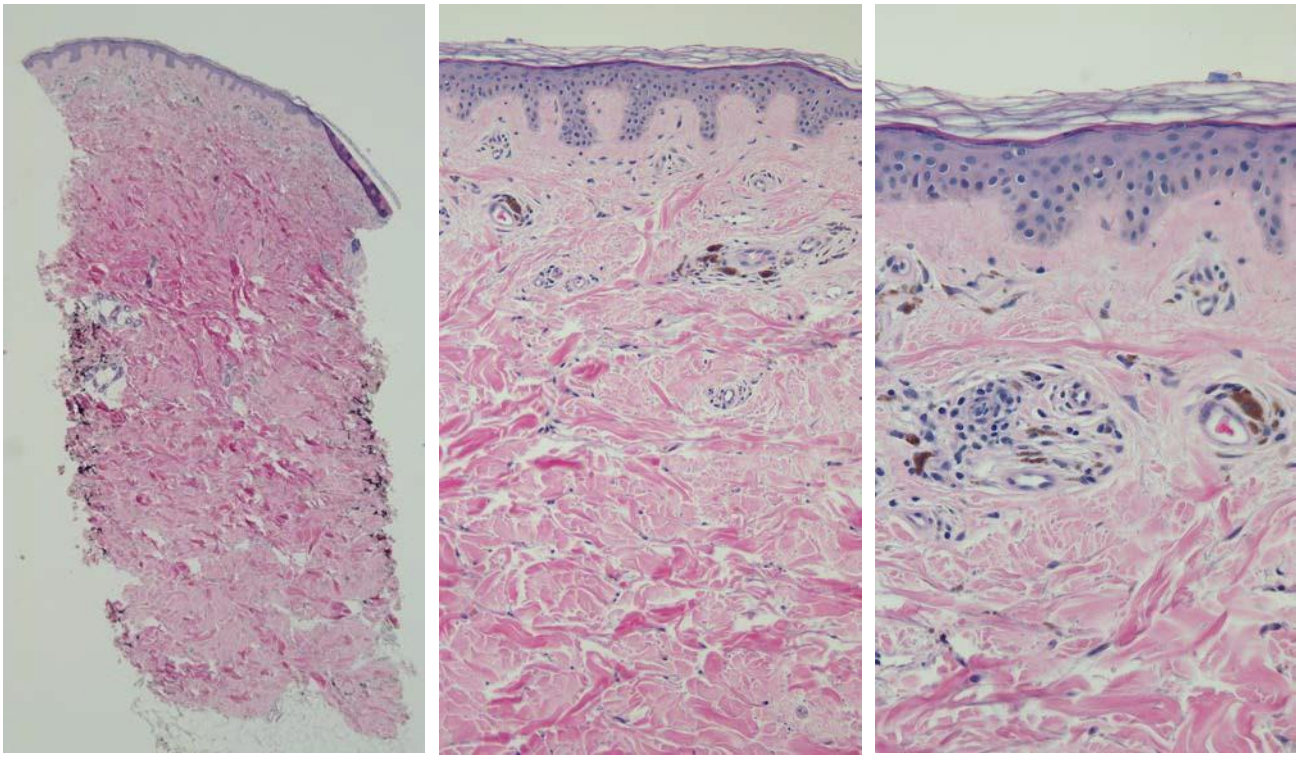


Figure 2. Histology of involved skin in a woman with amitriptyline-induced hyperpigmentation stained with hematoxylin and eosin staining, demonstrating pigment-laden melanophages and melanin deposition in the dermis [Hematoxylin and eosin; 40x].

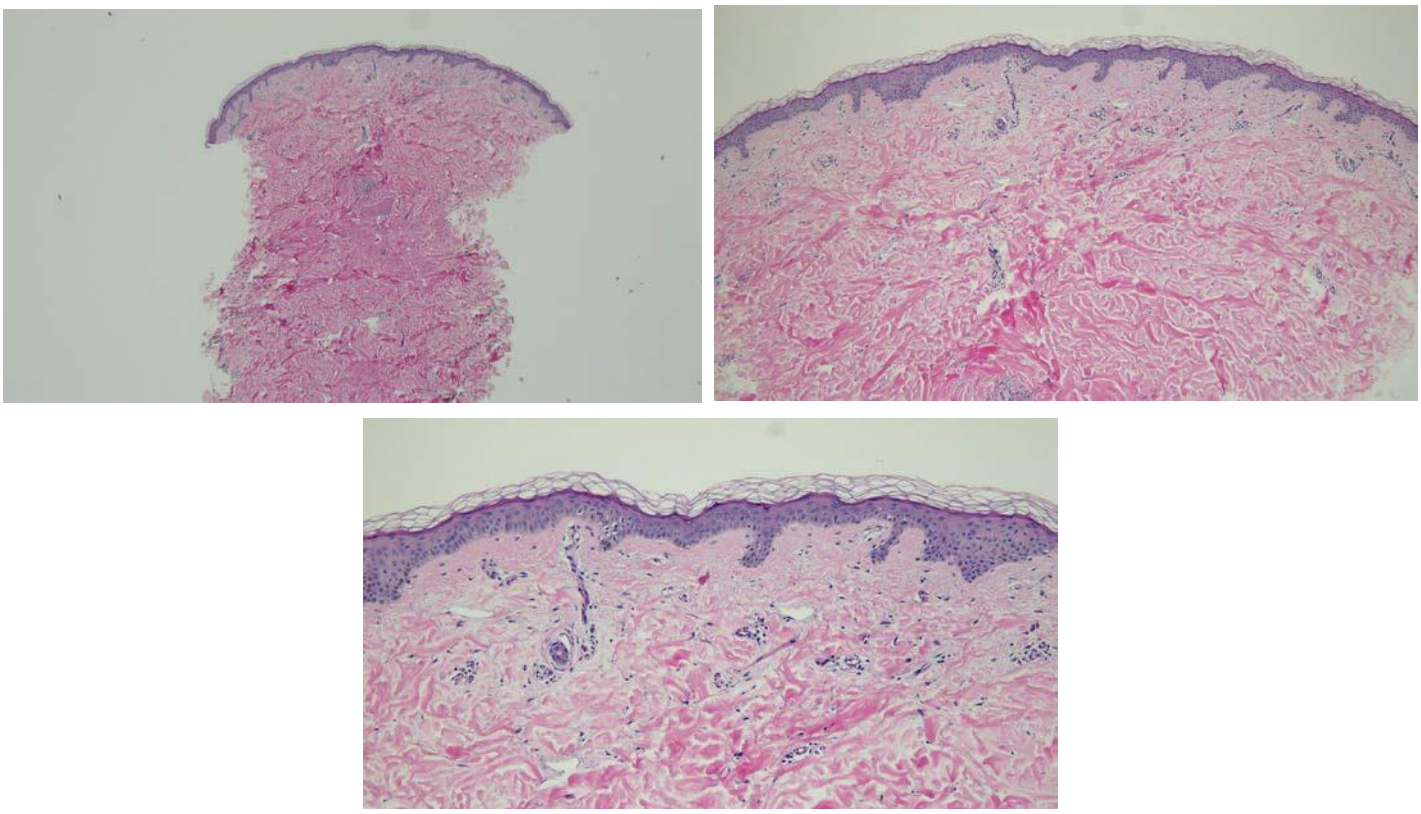


Figure 3. Histology of normal appearing skin in a woman with amitriptyline-induced hyperpigmentation shows neither melanophages nor melanin in the dermis [Hematoxylin and eosin staining, 40x].

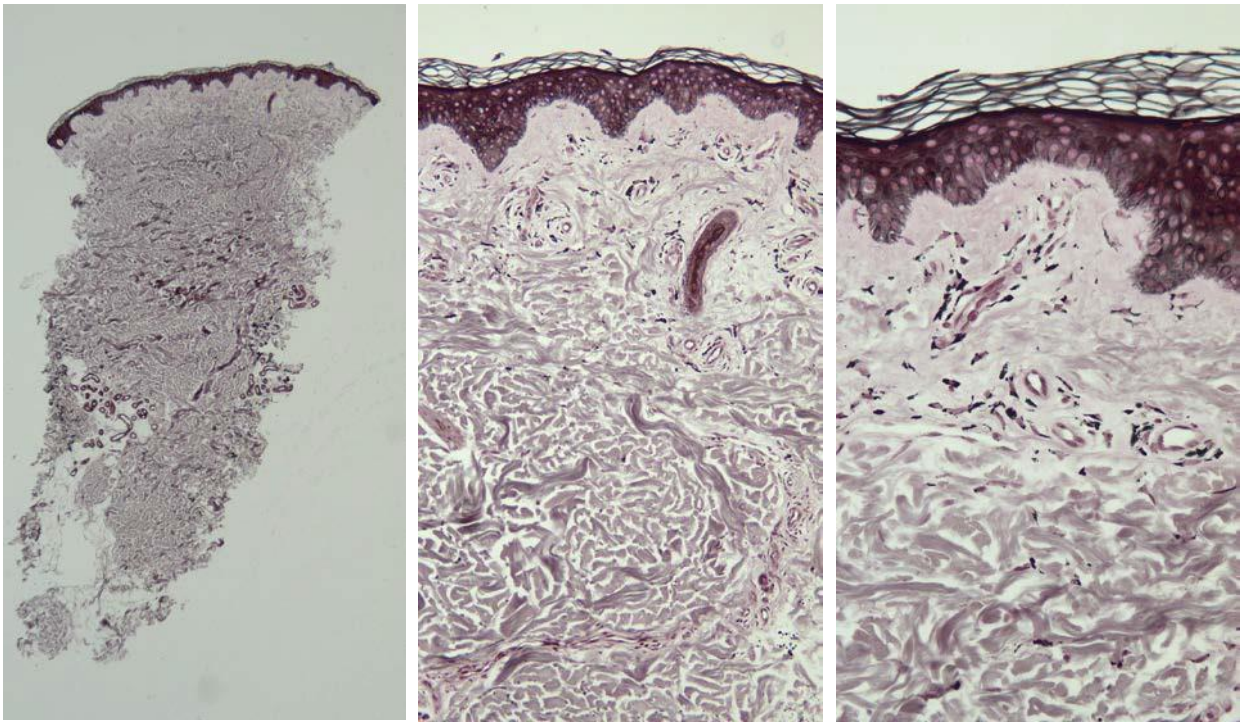


Figure 4. Fontana Masson stain demonstrates deposits of brown granules (melanin) in the dermis of affected skin in a woman with amitriptyline-induced hyperpigmentation [Fontana Masson, 40x].

Laboratory studies showed normal complete blood count, serum chemistries, thyroid studies, liver panel, and iron panel, as well as negative hepatitis A, B, and C serologies. Anti-nuclear antibody was positive at 1:160 in a homogenous and speckled pattern. However, other rheumatologic serologies, including Sjogren syndrome A (SSA) and Sjogren syndrome B (SSB) antibodies, were negative.

Correlation of the clinical presentation, pathology findings, and laboratory studies established the diagnosis of amitriptyline-induced photo-distributed hyperpigmentation. None of her other medications have previously been associated with photosensitivity or hyperpigmentation in sun-exposed areas. The patient elected to continue amitriptyline so that her interstitial cystitis would continue to remain in remission. She started wearing clothing that covered her upper back and discontinued sunbathing at the beach.

Discussion

Hyperpigmentation of the mucous membranes and the skin can be associated with systemic diseases (Addison's disease, hemochromatosis, hyperthyroidism, and Wilson's disease), exposure to heavy metals (gold, iron, and silver) [2, 3], and ingestion of drugs (antibiotic, antimalarial, antineoplastic, anti-arrhythmic, and psychotropic medications) (Table 1) [1, 4-21]. Psychotropic drugs associated with cutaneous hyperpigmentation include amitriptyline, chlorpromazine, citalopram, desipramine, imipramine, mirtazapine, phenytoin, sertraline, and thioridazine (Table 2) [1, 5, 7, 14, 22-32]. Amitriptyline-induced hyperpigmentation has been previously (Table 3) [33, 34], albeit seldom, described in the literature.

Table 1. Drug-induced mucocutaneous hyperpigmentation [a, b].

Drug class	Examples	Onset	Description	Distribution	Pathology	Resolution and Notes	References
Antibiotic	Doxycycline Methacycline Minocycline Tetracycline	Months to years	A. Blue-gray macules and patches. B. Diffuse "muddy brown". C. Hyperpigmentation.	A. Lower legs and sites of inflammation or scaring. B. Sun-exposed areas. C. Sclera, conjunctiva,	Granules with iron containing compounds in dermal macrophages. Increased melanin in the basal cell layer (A) of the	Resolves after discontinuation.	1, 5-9

				oral mucosa.	epidermis and dermis (B).		
Antimalarial	Chloroquine Hydroxychloroquine Quinidine Quinine	Months to years	Bluish-black to slate-gray pigmentation.	Face, extremities, oral mucosa, nails.	Intracellular and extracellular golden yellow to dark brown pigment granules in the deep dermis; hemosiderin around capillaries.	Resolves after discontinuation.	1, 5, 7, 10-11
Antineoplastic	Alkylating agents: Busulfan Cyclophosphamide Melphalan	Days to months	Bus: Brownish bronze or "dusky" pigmentation. Cyc: Brown to black hyperpigmentation. Mel: Hyperpigmentation with longitudinal pigmented bands.	Bus: Face, forearms, chest, abdomen. Cyc: Widespread or localized to palms, soles or nails. Mel: Nail bed.	Bus: Melanin in the basilar layer of the epidermis and within dermal macrophages. Variable	Bus: May persist or fade when drug is stopped. Cyc: Fades 6-12 months after discontinuation. Mel: Resolves after discontinuation.	1, 5, 7, 12-14
	Antimetabolites: 5-fluorouracil Methothrexate	Days to months	5-fu: Blue-black hyperpigmentation or melanosis. Mtx: Brownish skin pigmentation.	5-fu: Nail plate; veins where drug has been infused. Mtx: Scalp hair.	Variable	Fades, at least partially, when inducing agent is stopped but may persist for a long time when the treatment is discontinued.	1, 5, 7, 14
	Antibiotics: Bleomycin Dactinomycin Daunorubicin Doxorubicin	Days to months	Bleo: Band like or "flagellate" hyperpigmentation. Dact: Diffuse melanosis. Daun: Brown-black transverse bands. Doxo: Brown-black hyperpigmentation.	Bleo: Trunk and proximal extremities. Daun: Fingernails and toenails. Doxo: Interphalangeal and palmar creases, dorsa of hands, palms, soles, face, nails.	Bleo: Basal vacuolization, mild spongiosis, mixed inflammatory infiltrate with eosinophils in the superficial dermis. Doxo: Increased melanin and melanocytes. Variable		1, 5, 7, 14-19
	Other: Ametantrone Cisplatin Hydroxyurea Procarbazine	Days to Months	Ame: Diffuse gray-blue color. Hydr: Hyperpigmentation.	Ame: Generalized. Hydr: Tongue.	Increased melanin in the basal layer. Variable	Resolves after discontinuation.	1, 5, 7, 14, 20
Anti-arrhythmic	Amiodarone	Months	A. Slate-gray discoloration. B. Blue-red coloration.	A. Sun-exposed areas, especially the face. B. Hands and feet.	A. Yellow-brown lipofuscin granules within dermal macrophages with amiodarone or its breakdown products; lipids	Reversible after discontinuation but may persist for up to 1 year.	1, 5, 7, 21

					within the lysosomes of macrophages.		

[a] Abbreviations: Cyc, cyclophosphamide; Bus, busulfan; Mel, melphalan; 5-fu, 5-fluorouracil; Mtx, methotrexate; Bleo, bleomycin; Dact, dactinomycin; Daun, daunorubicin; Doxo, doxorubicin; Ame, ametantrone; Hydr, hydroxyurea.
[b] For psychotropic drugs, refer to Table 2.

Psychotropic drug-associated hyperpigmentation often presents in a photo-distributed manner similar to our patient whose lesions affected sun-exposed areas and spared skin that was covered or sun protected. Similar distributions of lesions are noted in other patients with imipramine or desipramine-induced hyperpigmentation (Table 2) [5, 7, 28-32]. Previously reported causes of amitriptyline-induced hyperpigmentation show a different distribution, most likely due to the concurrent administration of minocycline (Table 3) [33, 34].

Table 2. Psychotropic drugs associated with mucocutaneous hyperpigmentation of mucosa and skin [a].

Drug class	Examples	Onset	Description	Distribution	Pathology	Resolution and Notes	References
Anticonvulsant	Mirtazapine	Months	Darkening of skin.	Face, extensor part of forearm, posterior aspect of the neck.	NR	Improvement over months after discontinuation.	22
	Phenothiazines: Chlorpromazine [b] Thioridazine	Months to years	Tan, blue, or slate-gray pigmentation.	Sun-exposed areas, nail beds, exposed parts of the eye. Mucous membranes are spared.	Perivascular golden-brown pigment granules in the dermis that stain positively for melanin. Melanophages in the dermis. Electron-dense inclusion bodies in various dermal cells and lying free in the extracellular matrix.	Resolution within months after discontinuation.	1, 5, 7, 23-24
	Phenytoin	Months to years	Gray pigmentation.	Face, dorsum of fingers	Increased epidermal melanization.	Resolution with discontinuation.	1, 7, 14, 25
Anti-depressant Subtype: SSRI	Citalopram	Months	Brownish-black pigmentation.	Face, neck, and forearms; sun-exposed areas.	Pigmentary incontinence with melanophages.	Partial regression with discontinuation.	26
	Sertraline	Months	Gray-brown hyperpigmentation.	Forehead	NR	NR	27
Subtype: Tricyclic anti-depressant [c]	Desipramine Imipramine	Months to years	Slate-gray discoloration.	Sun-exposed areas.	Golden yellow granules in the papillary dermis around but not within endothelial cells. Melanophages in the dermis. Electron-dense inclusion bodies in histiocytes, phagocytes, fibroblasts, and dermal dendrocytes.	Resolution with discontinuation of medication.	1, 5, 7, 28-32

[a] Abbreviations: SSRI, selective serotonin receptor inhibitor; NR, not recorded.

[b] Greatest potential for inducing pigmentation.
[c] For amitriptyline-induced hyperpigmentation, see Table 3.

Table 3. Medication-associated hyperpigmentation in patients receiving amitriptyline.

Examples	Age, Race, Sex	Onset	Description	Distribution	Pathology	Resolution and Notes	References
Case 1	23, NR, Female	NR	Darkly pigmented macules.	Areas of acne scarring.	Iron-containing aggregates, hemosiderin positive, in the mid and upper dermis. Dermal macrophages with iron positive material.	Concurrently taking perphenazine and minocycline.	33
Case 2	30, Caucasian, Female	Months	Darkly pigmented perifollicular bluish discoloration.	Lower extremities, below the knees.	Brownish-black granules in the superficial dermis, especially around small blood vessels and skin appendages.	Concurrently taking minocycline.	34
Case 3	42, Caucasian, Female	Years	Non-pruritic brown-gray discoloration with a distinct line or sparing.	Upper back.	Perivascular melanophages and fine granular melanin staining the collagen fibers in the superficial dermis. Dermal pigment was Fontana Masson positive.	Enjoyed sunbathing at the beach.	CR

[a] Abbreviations: NR, not recorded; CR, current case.

In patients with imipramine-associated hyperpigmentation, skin changes occurred after they had been on the drug for several months to years. Our patient had been receiving amitriptyline for at least eight years; hyperpigmentation was initially noted six and a half years after she began the medication. Although her skin lesions were photo-distributed, photosensitivity related to the medication was not noted, similar to other psychotropic medications (Table 1) [5, 7, 22, 26-27, 33-34]. In addition, although our patient tested positive for anti-nuclear antibodies, other tested lupus erythematosus serologies were negative.

The areas affected by amitriptyline-associated macular hyperpigmentation had progressively expanded in size and there was neither scaling nor hyperkeratosis. Pathology of not only amitriptyline-induced hyperpigmentation but also hyperpigmentation associated with other psychotropic drugs (such as chlorpromazine, desipramine, imipramine, and thioridazine) showed similar features: specifically, melanophages and melanin in the dermis. The latter was positive for Fontana Masson stain, and negative for Perl stain (thereby excluding hemosiderin or iron) [23, 28-29, 32, 35-36].

The clinical differential diagnosis of our patient's cutaneous hyperpigmentation also includes other dermatoses (Table 4) [37-41]. Several of these conditions can present with hyperpigmentation in sun-exposed areas. However, clinical history, biopsy of the affected area, or both can enable these conditions to be differentiated from amitriptyline-associated photo-distributed hyperpigmentation (Table 4) [37-41]. Many of the conditions show melanophages in the upper dermis, but granular melanin pigment within the collagen fibers in the superficial dermis – in the absence of amyloid deposits in the papillary dermis - is only observed with psychotropic drug (phenothiazines and tricyclic anti-depressants)-associated photo-distributed hyperpigmentation.

Table 4. Clinical differential diagnoses of photo-distributed hyperpigmentation.

Dermatosis or Condition	Clinical Presentation	Histopathology	References
Ashy dermatoses [a]	Bluish-gray macules and patches in the face, arms, neck, or trunk.	Superficial perivascular dermatitis with a mild perivascular lymphocytic infiltrate in the papillary dermis. Vacuolar alteration of the basal layer with infiltrate of lymphocytes and histiocytes. Melanophages in the papillary dermis.	37-38
Macular amyloidosis	Hyperpigmented patches of grayish-brown macules with a rippled pattern, often on the	Mild epidermal thinning with deposition of amyloid material (demonstrating apple green birefringence after staining with Congo red stain) at the dermoepidermal junction. Focal disruption of the basal cell layer with pigmental incontinence and melanophages in	39

	upper back. [b]	the papillary dermis is seen in some patients.	
Notalgia paresthetica	Unilateral pruritus medial or inferior to the scapula. May present as a hyperpigmented patch.	Signs of post-inflammatory hyperpigmentation, mild hyperkeratosis, and mild inflammatory infiltrate of the papillary dermis with dermal melanophages.	40
Post-inflammatory hyperpigmentation	Increased pigmentation after a cutaneous inflammatory process particularly in individuals with darker skin types.	Melanin deposits both in free form and within melanophages located in the upper dermis and around blood vessels.	41
Psychotropic drug associated hyperpigmentation [c]	Tan, blue, or slate-gray pigmentation in sun-exposed areas.	Golden yellow granules in the papillary dermis that stain positively for melanin with Fontana Masson stain. There are also melanophages in the dermis.	1, 5, 7, 23-24, 28-32

[a] Some clinicians consider ashy dermatoses to be part of a spectrum of diseases that also include both lichen planus pigmentosum and erythema dyschromicum perstans.
[b] Distribution not classically associated with sun-exposed sites.
[c] This includes: amitriptyline, chlorpromazine, desipramine, imipramine, and thioridazine.

The pathogenesis of drug-induced hyperpigmentation may result from one or more of four basic mechanisms: (1) an accumulation of melanin - either free in the dermis or within dermal macrophages - may be propagated by drug-induced inflammation and worsened by sun exposure, (2) an accumulation of medication without melanin that is worsened by sun exposure, (3) increased production of lipofuscin secondary to the medication, and (4) deposition of iron secondary to drug-induced damage of dermal vessels [5, 42]. Other investigators have speculated that drugs such as imipramine may disrupt normal melanogenesis, leading to the deposition of an abnormal drug metabolite-melanin complex [31]. In addition, some researchers have hypothesized that chlorpromazine not only forms photo-adducts with DNA, thereby causing DNA strand breaks, but also promotes the production of reactive oxygen species that result in the development of abnormal pigmentation [24].

Psychotropic drug-induced hyperpigmentation is asymptomatic; however, treatment is often sought for cosmetic reasons. Discontinuation of the medication may result in fading and subsequent improvement. Yet, many patients require continuation of the medication for their psychiatric disease. Our patient needed to continue her medication for her interstitial cystitis to remain asymptomatic.

There are individual reports of improvement in patients with imipramine-induced pigmentation who have been treated with Q-switched alexandrite and ruby lasers [35]. Others have reported paradoxical darkening of imipramine-induced pigmentation after treatment with a Q-switched neodymium-doped yttrium aluminum garnet laser followed by treatment with a Q-switched ruby laser [29]. Therefore, additional investigations may be needed to further elucidate the use of laser therapy in the treatment of drug-induced pigmentation.

Conclusion

Psychotropic drug-induced hyperpigmentation is not only found in patients with amitriptyline but also in chlorpromazine, citalopram, desipramine, imipramine, mirtazapine, phenytoin, sertraline, and thioridazine. It presents as a progressive, photo-distributed darkening of the skin. Pathology of affected area shows melanophages and melanin in the dermis; the latter stains positive with Fontana Masson stain and negative with Perl stain. Discontinuation of medication may result in spontaneous remission. Laser therapy may provide a therapeutic intervention for the hyperpigmentation, but darkening of the treated area has occurred in some of the patients in whom this modality was used.

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