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Brown-gray hyperpigmentation in a photosensitive distribution after levofloxacin exposure

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Abstract

Photosensitive drug reactions resulting in hyperpigmentation occur when there is an accumulation in the skin of melanin, heavy metals, or the drug itself. Herein we describe an immunocompromised orthotopic liver transplant patient with levofloxacin-induced hyperpigmentation with iron deposition. To identify the causal agent, consideration was given to medications the patient had taken long-term, as well as medications introduced more recently before the event. Levofloxacin and posaconzole emerged as the most likely culprit drugs, neither of which have a strong history in the literature of being associated with photosensitive hyperpigmentation. Levofloxacin was determined to be the culprit drug when the hyperpigmentation gradually resolved several weeks after discontinuation of levofloxacin, with continuation of posaconazole and all other long-term medications. This case highlights the challenges in identifying the causal agent in photosensitive drug reactions when patients are taking multiple medications. Key clinical data can be very helpful in making an assessment.

Keywords: drug reaction, photosensitivity, hyperpigmentation

Introduction

Photosensitive drug reactions occur when an exogenous chemical substance interacts with UV or visible radiation to produce cutaneous disease [1]. Over 300 drugs have been associated with photosensitivity [2]. Antimicrobials, antipsychotics, and antiarrhythmics are medication classes containing the most common culprits. Hyperpigmentation reactions, which are a specific kind of photosensitivity, have been associated with a smaller number of agents; tetracyclines, amiodarone, heavy metals, antimalarials, and phenothiazines are the most frequently reported [3]. Depending on the medication, different histopathological patterns may emerge in the hyperpigmented skin. One pattern exhibits iron deposited in macrophages, which occurs in relation to drug-induced damage to dermal vessels resulting in leakage and lysis of red blood cells [3]. In addition to histopathological findings, it is critical to consider the timing of exposure, characteristics of the reaction, and timing of resolution in identifying the causal agent. Even with this data, the diagnosis can be challenging.

Case Synopsis

A 58-year-old man with a history of orthotopic liver transplant in 2014 presented with new onset hyperpigmented brown-gray patches over his upper extremities, neck, and shins (**Figure 1**). Immunosuppressive medications as well as the other long-term medications the patient had taken for over one year were oral tacrolimus, prednisone, mycophenolate mofetil, albuterol, budesonide, carvedilol, doxazosin, propranolol, furosemide, spironolactone, hydralazine, and fexofenadine.

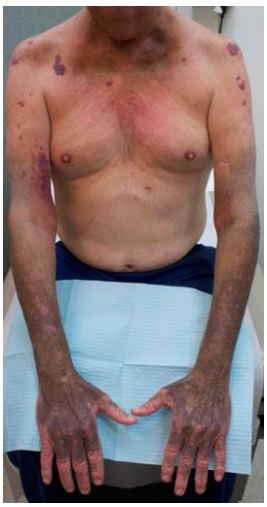

Figure 1. *Clinical image on initial presentation showing hyperpigmented brown-gray macules and patches distributed across the bilateral upper extremities and neck.*

Other than hydrocodone/acetaminophen, the patient had no documented drug allergies.

For two months prior to presentation the patient had been undergoing treatment for cutaneous *Fonsecaea sp*. phaeohyphomycosis of the left index finger. His antifungal regimen consisted of 300mg/day of posaconazole. Additionally, eleven days prior to presentation the patient had completed a ten-day course of levofloxacin for *Klebsiella pneumoniae* identified on bronchoalveolar lavage.

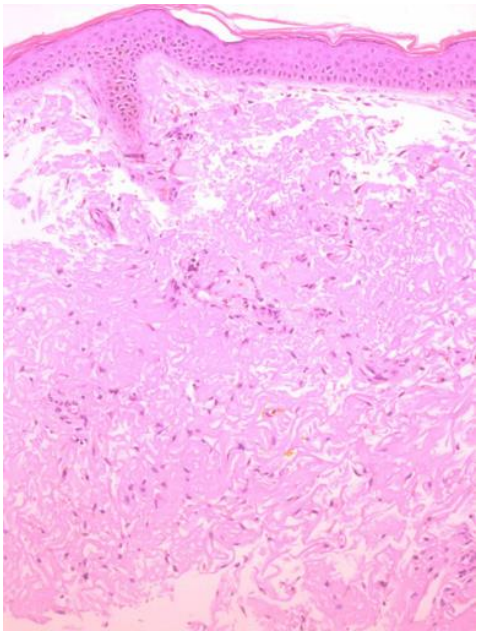

Figure 2. *H&E stain of left arm punch biopsy showing pigmented macrophages in dermis, 100×.*

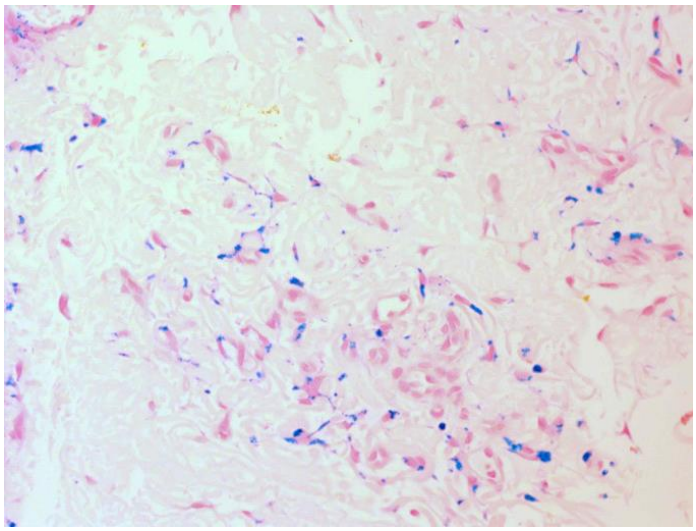

Figure 3. *Histopathology of left arm punch biopsy with iron staining, 100×.*

A punch biopsy of the hyperpigmented patch from the left arm was taken for histopathological exam and staining for iron and melanin. Histopathological exam of the biopsy revealed numerous pigmented macrophages in the dermis (**Figure 2**). This pigment tested positive for iron and negative for melanin with Fontana-Masson (**Figure 3**).

Three months later the patient returned to clinic where it was noted that the hyperpigmentation was resolving (**Figure 4**). At that point he had been off posaconazole for two weeks and off levofloxacin for three months. Because of recurrence of phaeohyphomycosis identified during that visit, the patient was restarted on posaconazole. At his next

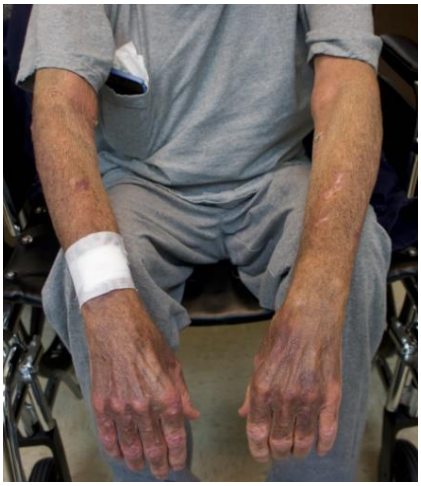

Figure 4. *Clinical image at three-month follow-up showing partial fading of hyperpigmented macules and patches on hands, with more pronounced fading on forearms.*

follow-up four weeks later, the hyperpigmentation showed continued resolution.

Case Discussion

One of the most important factors to consider in identifying the causal agent in a drug-induced photosensitivity event is the timing of drug exposure in relation to symptom onset. In the present case, the timing of presentation correlated with two potential culprit drugs, posaconazole and levofloxacin. Posaconazole is a triazole antifungal that has never been reported in the literature as causing photosensitivity [4]. Itraconazole, which is structurally similar to posaconazole, has been associated with photosensitivity, but not specifically with hyperpigmentation [5]. Voriconazole, also a triazole, has frequently been associated with photosensitivity as well as increased risk of squamous cell carcinoma, though is structurally and metabolically different from posaconazole [6].

Several medications in the fluoroquinolone class of antibiotics have been associated with photosensitivity reactions [7]. Among these, lomefloxacin and sparfloxacin have the greatest potential for phototoxicity. However, lomefloxacin is infrequently used and sparfloxacin is no longer available in the U.S. Commonly prescribed fluoroquinolones such as ciprofloxacin and oflaxacin have less phototoxic potential [7]. Levofloxacin has very low phototoxic potential, with less than 0.01% of healthy subjects exhibiting photosensitivity [8]. Though the potential is low, such reactions have occurred (**Table 1**). One case was reported in the literature in which a woman developed blue-black hyperpigmentation of her extremities one month after starting levofloxacin for an infected prosthesis [9]. A similar case was reported in a 71-year-old man, with onset of hyperpigmentation occurring two months into levofloxacin therapy [10]. As in the present case, the pigment tested positive for iron on Perls stain, but unlike our case was also positive for melanin on staining with Fontana-Masson.

In this case, gradual resolution of hyperpigmentation after withdrawal of the drug was the most revealing factor in confirming the causal agent. The patient had a noticeable decrease in pigmentation three months after stopping levofloxacin. Even after stopping and later restarting posaconazole, the hyperpigmentation continued to fade. This resolution points away from posaconazole as the cause and furthermore provides evidence that the reaction did not result from one of the medications the patient had been taking long term, such as furosemide or tacrolimus. Ultimately, the timing of drug exposure in relation to the onset and initial resolution of hyperpigmentation, low likelihood of alternative causes, and previous report of similar hyperpigmentation led us to conclude that the photosensitivity reaction seen in our patient was related to levofloxacin.

Conclusion

This case highlights the challenges in identifying causal agents in photosensitivity reactions, particularly in patients taking multiple medications and in immunocompromised hosts. Timing, characteristic skin and histopathological findings, and response to medication withdrawal are all important factors to consider when identifying a cause.

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Table 1. *Reported cases of levofloxacin photo-induced hyperpigmentation.*

Reference (last name of first author, year)	Patient description	Levofloxacin dose	Duration of levofloxacin exposure prior to pigmentation	Distribution of pigmentation	Histopathological staining pattern	Time until complete resolution
López-Pestaña, 2007 [9]	68-year-old female. Undergoing treatment for infected knee prosthesis.	500mg/day	1 month	Anterior lower legs, thighs, forearms.	Iron (Perls stain) positive	8 months
Lorente, 2013 [10]	71-year-old male with hypertension, diabetes mellitus, and renal failure. Undergoing treatment for presumed infection following hip surgery.	Not reported	2 months	Dorsal hands, extensor aspect of forearms, shins, and neck.	Iron (Perls stain) positive Melanin (Fontana-Masson stain) positive	12 months
Present case	58-year-old male s/p orthotopic liver transplant. Undergoing treatment for *Klebsiella* pneumonia.	750mg/day	11 days	Dorsal hands, forearms, neck, shins.	Iron (Perl stain) positive Melanin (Fontana-Masson stain) negative	Ongoing (initial fading at 3 months)