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CASE REPORT

Adverse drug reaction with silodosin: a case report of an unusual skin rash

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Abstract
Silodosin is a selective alpha-1 adrenergic receptor antagonist approved for the treatment of lower urinary tract symptoms associated with benign prostatic hypertrophy. Adverse events include retrograde ejaculation, dizziness, diarrhea, vasodilator symptoms, and postural hypotension. Skin adverse reactions to silodosin such as eruption, purpura, and jaundice are uncommon. This article reports a case of unusual silodosin-related skin rash, Naranjo score 5, which regressed after applying combined intense pulsed light (IPL)/fractional CO_2 laser/chemical treatments and drug interruption.
Level of evidence: Level V, risk/prognostic.

Keywords Post-inflammatory hyperpigmentation · Silodosin · Intense pulsed light · CO_2 laser

Introduction

Benign prostatic hypertrophy (BPH) is a common progressive disease among men with age-dependent incidence. The management of patients with BPH includes pharmacological and surgical options, with the choice of therapy typically depending on the presence and severity of the symptoms. Pharmacological treatments include α1-adrenergic receptor antagonists (or blockers) and 5α-reductase inhibitors [1].

In the early 1990s, Kissei Pharmaceutical Co. Ltd. began the development of α1-adrenergic receptor antagonists that were highly selective for the lower urinary tract without affecting blood pressure. This led to the discovery of silodosin, a novel indoline derivative approved by the US Food and Drug Administration (FDA) in 2008. Phase II/III studies reported several silodosin-related adverse events with a variable incidence. Retrograde ejaculation was the most frequent (28%), followed by dizziness (3.2%), diarrhea (2.6%), orthostatic hypotension (2.6%), headache (2.4%), and nasal congestion (2.1%). Toxic skin eruption, purpura, and jaundice were uncommon [2].

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The authors herein report a case of an unusual skin rash, which occurred after silodosin assumption, introducing a combined approach to help hasten its resolution.

Case report

A 77-year-old Caucasian man presented bilateral mandibular skin rash, which occurred after 6 months of assumption of silodosin (8 mg a day). The skin lesions presented purple/bluish discolored and confluent spots that did not blanch after applying pressure (Fig. 1). There were no associated itch, sting, or any other symptoms and clinical manifestations. The physical examination of the patient was normal. The patient did not assume any other drugs. At first, systemic lupus erythematosus was suspected, but the diagnostic hypothesis was rejected after some investigations, as the patient did not meet any other clinical or immunologic (ANA, anti-DNA, anti-Sm, antiphospholipid Ab, low complement, direct Coombs test) criteria. Histopathological examination revealed chronic inflammation of the epidermis with melanin pigment deposits in the reticular dermis, as for a post-inflammatory hyperpigmentation (PIH).

The drug was discontinued 11 months after the appearance of the skin rash; another alpha1-blocker, doxazosin, was prescribed, with no adverse reactions reported in the following 12 months.

According to the Naranjo questionnaire [3], our patient was evaluated using the questions reported in Table 1, and his final

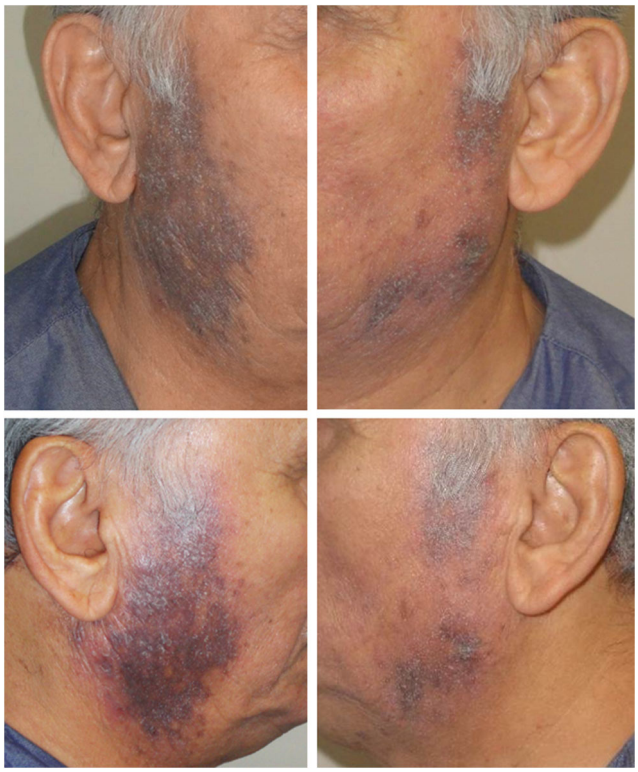

Fig. 1 Pretreatment view of bilateral mandibular skin rash. Skin lesions are purple/bluish and do not blanch with pressure

score was 5, meaning that the adverse reaction can be probably ascribed to the drug.

The patient started our combined treatment 1 month after silodosin discontinuation as hyperpigmentation did not clear, and it was refractory to topical agents. We performed two treatment sessions, 2 months apart, with intense pulsed light (IPL), (Synchro HP, DEKA M.E.L.A., Calenzano, Italy), at 500 nm wavelength, single pulse, at 8 J/cm^2. Topical application of gentamicin sulfate cream 0.1% twice a day and zinc oxide cream was recommended on the first few days after treatments and patient was advised to avoid direct sun exposure for 3 weeks after treatment. Then the patient underwent three fractional CO_2 (SmartXide Punto, DEKA M.E.L.A., Calenzano, Italy) laser treatments, 3 months interval, with these parameters: H-pulse, a DOT spacing of 500 μm at 9 W. Following each fractional CO_2 laser session the patient applied for 4 weeks a cream containing kojic acid in 4% concentration, formulated with glycolic acid (10%) and hydroquinone (1%), to increase efficacy [4].

A good cosmetic result was achieved with a complete resolution of the eruption that remained at an improved state 1 year after final treatment (Fig. 2).

Discussion

Post-inflammatory hyperpigmentation (PIH) is an acquired hypermelanosis occurring after cutaneous inflammation that may arise in all skin types, but more frequently affects darker skin types (Fitzpatrick types IV through VI). These pigmentary changes may alter the quality of life of the patients, as they often occur in exposed areas such as the face, the neck, or the décolleté, and when their treatment tends to be difficult and long [5].

A wide range of etiologies exists for PIH: infections such as dermatophytoses or viral exanthems, allergic reactions from insect bites, or a contact dermatitis, cutaneous injuries from irritants, burns, or cosmetic procedures, skin inflammatory (papulosquamous) diseases like atopic dermatitis, lichen planus, psoriasis, or lupus erythematosus as well as hypersensitivity reactions to medications [6].

PIH results from the overproduction of melanin or an irregular dispersion of pigment after cutaneous inflammation. The epidermal inflammatory response, through mediators such as prostaglandins and leukotrienes, stimulates epidermal melanocytes to increase the synthesis of melanin and transfer the

Table 1 Naranjo questionnaire for adverse drug reaction (ADR)

Question	Answer	Score
Are there previous conclusive reports on this reaction?	No	0
Did the adverse events appear after the suspected drug was given?	Yes	2
Did the adverse reaction improve when the drug was discontinued or a specific antagonist was given?	Yes	1
Did the adverse reaction appear when the drug was readministered?	Not done	0
Are there alternative causes that could have caused the reaction?	No	2
Did the reaction reappear when a placebo was given?	Not done	0
Was the drug detected in any body fluid in toxic concentrations?	Not done	0
Was the reaction more severe when the dose was increased or less severe when the dose was decreased?	Not done	0
Did the patient have a similar reaction to the same or similar drugs in any previous exposure?	No	0
Did any objective evidence confirm the adverse event?	No	0

The final score indicates: ≥ 9, definite ADR; 5–8, probable ADR; 1–4, possible ADR; 0, doubtful ADR

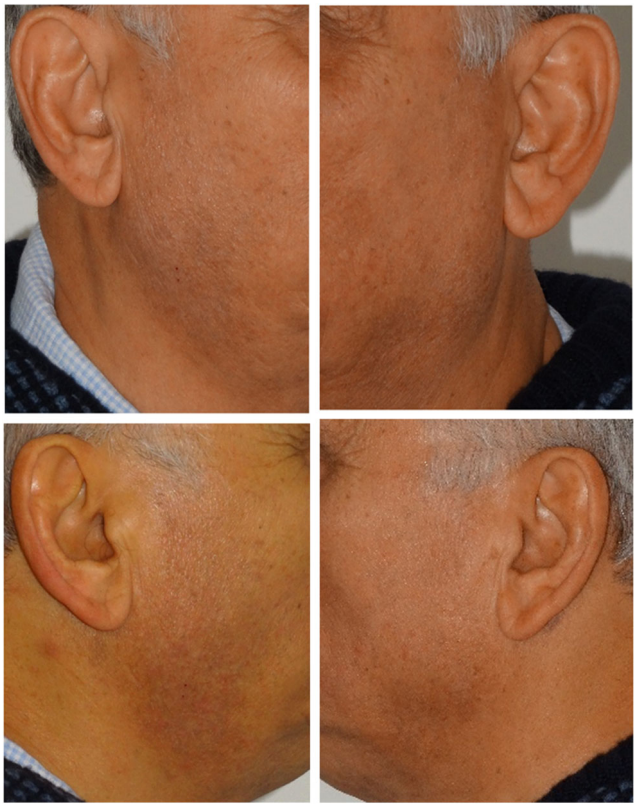

Fig. 2 Post-treatment view with a complete resolution of the eruption

melanin granules to keratinocytes, resulting in epidermal melanosis. On the contrary, dermal melanosis, characterized by a gray or bluish color, occurs when inflammatory processes disrupt the basal cell layer and the melanin pigment is trapped by the macrophages in the papillary or reticular dermis [7].

Treatments include topical depigmenting agents, chemical peels, and laser and light therapy. Topical therapy is typically effective for epidermal hyperpigmentation but usually less effective for dermis localization.

Due to the wide absorption spectrum of melanin (250–1200 nm), many lights and lasers are helpful in recalcitrant hyperpigmentation, but caution has to be paid to prevent worsening of PIH. Typically, short wavelength lasers are for epidermal melanin while longer wavelengths penetrate deeper with selective absorption by dermal targets.

Traditional CO_2 resurfacing and intense pulsed light (IPL) must be used very carefully as their long pulse duration may induce hyperpigmentation as well. They should not be considered in darker skinned individuals and cooling devices should be recommended for safety. In case of high melanin density, laser energy intended for deeper dermal targets could be absorbed within the pigmented epidermis, leading to complications such as dyschromias, blistering, and scars [8].

Nd:Yag Q-switched laser with shorter pulse duration but long wavelength may also be absorbed in the superficial layers leading to complication, so to date pico laser is the most appropriate to treat deep marks [9]. Many papers already published a successful use of fractional CO_2 laser in these kinds of problems [10–15]. Our case first reports a post-inflammatory hyperpigmentation related to silodosin assumption, showing that recalcitrant PIH should benefit from a combined approach and that pico laser is not the only possibility.

Fractional CO_2 treatment in fact is less aggressive on the tissue as the photocoagulation effect is limited to a few points and the heat is scattered. Spacing enough the columns within the spot decreases the thermal effect reducing collateral effects such as erythema, edema, or crusts. Finally, thanks to the very low CO_2 emission time and the high-peak power (H-Pulse), a sort of "cold" ablation inhibits the immediate inflammatory response allowing the chemical agent to penetrate easily.

Conclusions

Silodosin cutaneous adverse reactions are rare but may occur. Early treatment of post-inflammatory hyperpigmentation is advisable and should be started to help hasten its resolution. Fractional CO_2 lasers combined with chemical agents should be definitively considered an adjunctive tool in the treatment of deep hyperpigmentation.

Compliance with ethical standards

Conflict of interest and funding Stefania Tenna, Marco Morelli Coppola, Beniamino Brunetti and Paolo Persichetti declare that they have no conflict of interest. They do not have any commercial associations that might pose or create a conflict of interest with the information presented in this article. No intramural or extramural funding supported any aspect of this work.

Ethical approval All authors have contributed equally to the scientific work.

The study has been performed in accordance with the ethical standards as laid down in the 1964 Declaration of Helsinki and its later amendments or comparable ethical standards.

Informed consent Informed consent was obtained from the patient to use photographs for scientific purposes.

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