Varenicline-induced drug eruption: case and review of the literature

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Abstract

Cutaneous side-effects of varenicline, a selective partial agonist of the α4β2 nicotinic acetylcholine receptor used to treat smoking addiction, are relatively rare and mainly consist of acute generalized exanthematous pustulosis. We describe an atypical clinical presentation of a varenicline-induced drug eruption, which occurred one day after drug initiation. We report this case since we believe no drug reaction to varenicline has had this clinical presentation or rapidity of onset. Clinicians should be aware of this potential adverse cutaneous reaction in patients taking varenicline for smoking cessation.

Keywords: drug eruptions, smoking cessation, varenicline

Introduction

Cutaneous side-effects of varenicline, used to support smoking cessation, are relatively rare [1]. We found only eight cases documented in PubMed, predominantly of five cases of acute generalized exanthematous pustulosis (AGEP), [1–4], two cases of maculopapular eruptions, and one case of symmetrical drug-related intertriginous and flexural exanthema (SDRIFE), [5–7]. All occurred at least two days after varenicline introduction [1-8].

Case Synopsis

A 68-year-old male smoker was referred to our dermatology emergency unit with a 4-day history of a disseminated maculopapular eruption. The patient started treatment with varenicline for smoking cessation one day before this eruption appeared and stopped immediately after its start, having taken only two pills. The patient had never been treated with varenicline. He denied fever, recent infectious process, or use of other new medication. Physical examination revealed disseminated confluent erythematous macules and papules on the trunk and proximal parts of the extremities, as well as edematous facial involvement. There were also more pronounced erythematous patches, symmetrically distributed over the anterior neck, buttocks, and axillary and inguinal regions. Targetoid lesions were present on the trunk (**Figure 1**), but no pustular/vesiculobullous lesions, mucous membranes involvement, or Nikolsky sign were exhibited.

Laboratory tests, chest X-ray, and electrocardiogram were normal. Skin biopsy of a target lesion showed irregular acanthosis of the epidermis with foci of spongiosis and a superficial dermis perivascular lymphocytic infiltrate with interstitial eosinophils (**Figure 2**). Thus, we established the diagnosis of maculopapular drug eruption associated with varenicline. The patient was treated successfully with antihistamines and betamethasone cream 0.5mg/g, with complete clinical resolution one week after. Patch testing was performed three weeks later, with a 0.5mg and 1mg varenicline tablet, diluted to 30% in petrolatum on the disease-free back skin with IQ Chambers™ (Chemotechnique Diagnostics, Vellinge, Sweden), but was negative at 48h and 72h. The

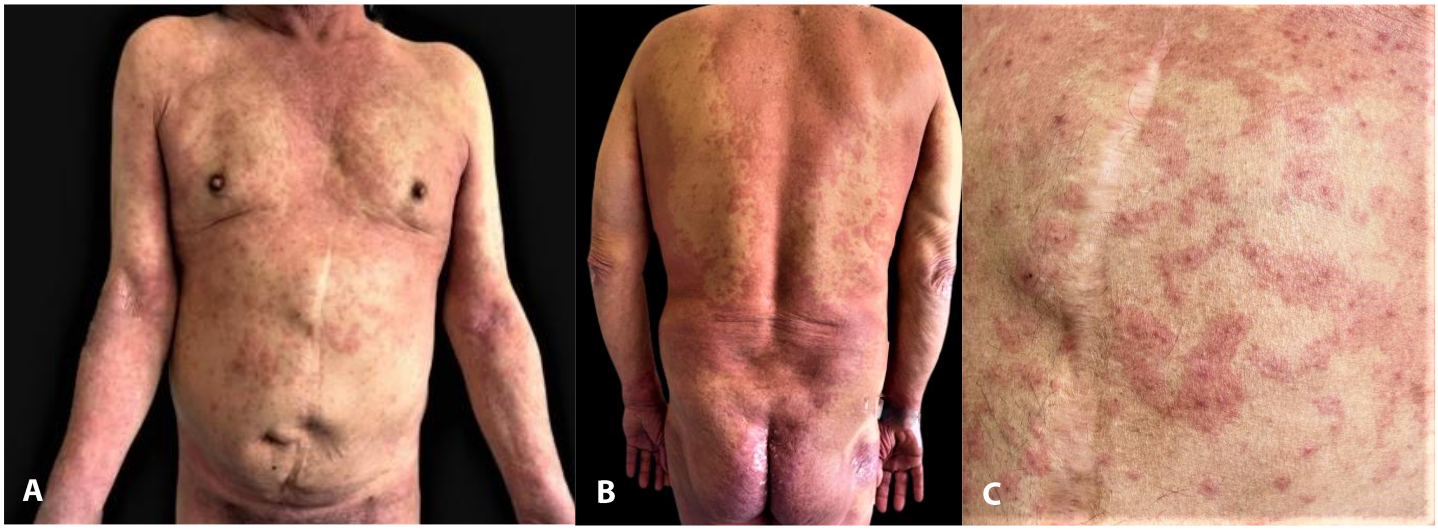

Figure 1. ***A-C)*** *Varenicline-induced drug eruption, clinical image: disseminated confluent erythematous macules and papules* ***A, B)*** *on the trunk and proximal parts of the extremities, with more pronounced erythematous patches, symmetrically distributed over the anterior neck, buttocks, and axillary and inguinal regions.* ***C)*** *Targetoid lesions on the trunk.*

patient refused to perform a lymphocyte activation assay and oral provocation test. He was followed up for six months, with no symptom recurrence.

Case Discussion

Varenicline is a selective partial agonist of the α4β2 nicotinic acetylcholine receptor, used to treat smoking addiction [4,6]. Its main adverse events include headache, nausea, abdominal pain, increased risk for suicide, and myocardial infarction [8]. Adverse mucocutaneous drug reactions to varenicline are rare, mainly consisting of AGEP [1-8]. Besides these, multiforme exudative erythema, Stevens-Johnson syndrome, and angioedema are listed on the product specification sheet [4]. The published characteristics of patients with drug reactions to varenicline are summarized in **Table 1** [1-8].

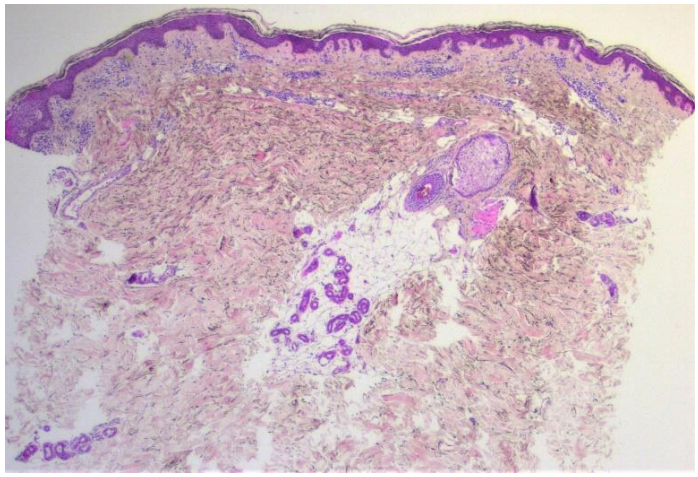

Figure 2. *Varenicline-induced drug eruption, histopathological features: irregular acanthosis of the epidermis with foci of spongiosis and a superficial dermis perivascular lymphocytic infiltrate with interstitial eosinophils. H&E, 25×.*

Regarding our patient, the eruption onset after starting varenicline, clinical and histopathological findings, and the rapid resolution of the lesions following the withdrawal of the drug and corticosteroid therapy confirmed the diagnosis of varenicline-induced drug eruption. Naranjo probability score was seven, suggesting a probable causal relationship between varenicline and the eruption [5]. Epicutaneous tests were negative but do not exclude the diagnosis since their sensitivity in these cases is usually low.

Our patient simultaneously developed targetoid lesions on the abdomen (suggestive of erythema multiforme), maculopapular lesions on the limbs (suggestive of morbilliform exanthema), and more pronounced confluent erythematous patches, symmetrically distributed over the anterior neck, buttocks, and axillary and inguinal regions, resembling SDRIFE. Although these adverse skin reactions described in the literature occurred after an average of six days, our patient's skin reaction occurred after a single tablet. Clinical resolution was observed six days after initiating topical corticosteroid therapy, as in the first case shown in

Table 1, with no need for systemic corticosteroids and with more rapid resolution than in the other cases [1-8].

Conclusion

We report this case since we believe no drug reaction to varenicline has had this clinical presentation or rapidity of eruption onset to the best of our knowledge. Clinicians should be aware of this potential adverse cutaneous reaction in patients taking varenicline for smoking cessation.

Potential conflicts of interest

The authors declare no conflicts of interest.

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Table 1. *Characteristic features of patients with drug reactions to varenicline described in PubMed.*

Patient [Reference]	Sex, age (years)	The onset of reaction after the first pill	Clinical features (diagnosis)	Histological features	Treatment
1 [1]	F, 41	5 days	Edematous facial involvement; Maculopapular and vesiculopustular lesions on the trunk and extremities; Palmoplantar pseudo-dyshidrosis (AGEP).	Subcorneal pustule with spongiosis, edema of the papillary dermis, and a superficial dermal infiltrate of numerous neutrophils and some eosinophil polymorphonuclear cells.	Emollients and topical corticosteroids. Clinical resolution within 8 days.
2 [3]	F, 61	7 days	Disseminated erythematous and vesiculopustular lesions on the trunk and extremities (AGEP).	Spongiform neutrophilic pustules in the epidermis along with a mixed lymphocytic and neutrophilic infiltrate in the dermis, associated with capillaritis.	Systemic (prednisolone) + topical corticosteroid (clobetasol 0.05% ointment). Clinical resolution within 10 days.
3 [4]	M, 53	8 days	Erythematous papules and plaques with grouped, small, non-follicular pustules on the face, trunk, and proximal parts of the extremities (AGEP).	Acanthosis and spongiform subcorneal pustules formed by neutrophils, without relation to hair follicles, and superficial dermal mixed inflammatory infiltrate.	Systemic corticosteroid (prednisolone). Clinical resolution within 21 days.
4 [2]	F, 26	10 days	Pustular eruption with scattered papules and vesicles on the trunk (AGEP).	None	Systemic corticosteroid (prednisolone). Clinical resolution within 21 days.
5 [2]	F, 45	5 days	Pustular eruption on an erythematous base on the trunk and extremities (AGEP).	Intraepidermal neutrophilic pustule and an inflammatory infiltrate of neutrophils and sparse eosinophils in the papillary dermis.	Systemic corticosteroid (prednisolone). Clinical resolution within 21 days.
6 [5]	M, 50	2 days	Erythematous macules and patches symmetrically distributed on the neck, inguinal region, and buttocks (SDRIFE).	Basket-weave hyperkeratosis, mild acanthosis, perivascular lymphocytes, and eosinophil infiltration.	Topical corticosteroid (furoate 0.1% cream). Clinical resolution within 14 days.
7 [7]	F, 71	8 days	Confluent maculopapular lesions symmetrically distributed on the trunk and extremities (maculopapular drug-eruption).	None	Systemic corticosteroids. Clinical resolution within 8 days.
8 [6]	F, 25	13 days	Erythematous papules coalescing into annular plaques symmetrically distributed over the trunk, neck, hands, and feet (maculopapular drug-eruption).	Spongiosis and subtle focal vacuolar interface dermatitis.	Systemic corticosteroids. Clinical resolution within 14 days.

9 [Present case]	M, 68	1 day	Confluent erythematous macules and papules on the trunk and extremities; Erythematous patches symmetrically distributed over the anterior neck, buttocks, axillary and inguinal region; Target lesions on the trunk.	Irregular acanthosis of the epidermis with foci of spongiosis and a superficial dermis perivascular lymphocytic infiltrate with interstitial eosinophils	Topical corticosteroid (betamethasone cream 0.5mg/g). Clinical resolution within 6 days.

AGEP, acute generalized exanthematous pustulosis; F, Female; M, Male; SDRIFE, symmetrical drug-related intertriginous and flexural exanthema.