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Teriflunomide-related development of inverse psoriasis and worsening of pre-existing plaque psoriasis

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Abstract

Leflunomide can be used in management of psoriatic disease. Leflunomide's active metabolite, teriflunomide, is used in the treatment of multiple sclerosis and has unexpectedly been rarely reported to induce pustular psoriasis. In this report, we present a patient with multiple sclerosis who developed inverse psoriasis after starting teriflunomide.

Keywords: adverse event, drug-induced, drug reaction, inverse psoriasis, leflunomide, psoriasis vulgaris, teriflunomide

Introduction

Inverse psoriasis presents with psoriasiform plaques in intertriginous or flexural regions of the skin. Although a clinically uncommon variant of, and distinct from classic psoriasis, onset may similarly occur in an idiopathic manner or as an adverse medication reaction. Leflunomide, a dihydrooratate dehydrogenase inhibitor, can be used in management of psoriatic disease. Leflunomide's active metabolite teriflunomide, used in the treatment of multiple sclerosis under the brand name Aubagio, has demonstrated adverse events of worsening existing psoriasis and inducing new onset pustular psoriasis in rare reports [1]. Herein we present a patient with multiple sclerosis and existing psoriasis vulgaris, for whom teriflunomide induced new onset inverse psoriasis, a novel clinical pattern not previously reported.

Case Synopsis

A 49-year-old woman presented to dermatology clinic for evaluation of a worsening rash beneath the breasts and abdomen. She has history of mild plaque psoriasis that was previously well controlled with as-needed topical products. After initiation of teriflunomide two years prior for multiple sclerosis, she had recurrence and worsening of plaque psoriasis to the extensor surfaces and development of new lesions in intertriginous areas. Physical examination demonstrated well demarcated, shiny erythematous plaques to the infrapannus (**Figure 1**) and inframammary areas. Additionally, she had psoriasiform plaques on the elbows and knees. A biopsy from the infrapannus region exhibited regular acanthosis, hypogranulosis, thinning of suprapapillary plates, and focal mounds of neutrophils with numerous eosinophils (**Figure 2**). Periodic acid-Schiff staining was negative for fungal

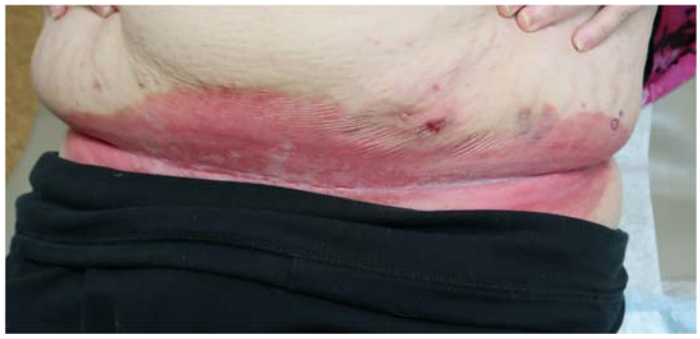

Figure 1. *Well demarcated erythematous shiny plaque to the infrapannus. Marked area to the left lateral abdomen is the site of the punch biopsy.*

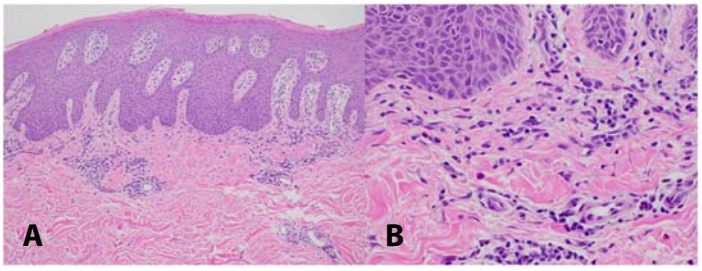

Figure 2. *H&E histopathology of biopsy site from plaque to the infrapannus demonstrating* ***A)*** *regular acanthosis, hypogranulosis, thinning of suprapapillary plaques and focal mounds of neutrophils in the stratum corneum, as well as a mixed perivascular inflammatory infiltrate, 100×.* ***B)*** *Visible dermal lymphohistiocytic infiltrate with eosinophils, 400×.*

organisms. Bacterial and fungal cultures from the inframammary area were negative for infectious organisms. With clinicopathologic correlation, she was diagnosed with drug-induced new-onset inverse psoriasis and exacerbation of plaque psoriasis. Her psoriasis initially improved with infrequent application of alternating halobetasol 0.05% and calcipotriene 0.05% ointments.

Case Discussion

Therapeutic use of teriflunomide is predicated on inhibition of B and T lymphocyte proliferation in treating select autoimmune conditions [1,2]. The presumed mechanism of action involves inhibition of dihydrooratate dehydrogenase, a key enzyme in de novo synthesis of pyrimidines. Teriflunomide is indicated for the treatment of multiple sclerosis. Teriflunomide is the active metabolite of leflunomide, converted rapidly and nearly completely in vivo through the opening of the prodrug isoxazole ring. Clinical use of the prodrug leflunomide has a longer history and broader scope of treating autoimmune disorders, including psoriatic disease [3]. Post-market analysis of teriflunomide found induction of new pustular or nail psoriasis and worsening of preexisting plaque psoriasis [1,4]. In the case presented, we identified association of new-onset inverse psoriasis secondary to teriflunomide, with worsening of pre-existing psoriasis vulgaris.

Inverse psoriasis presents as erythematous plaques most commonly affecting the inguinal folds, followed by axillae, inframammary folds, perianal area, umbilicus, and retroauricular areas [5]. Although clinical features comprise the mainstay of diagnosis, histopathologic specimens demonstrate hypogranulosis, parakeratosis, thinning of the suprapapillary plate, dilated tortuous papillary dermal vessels, and predominantly perivascular lymphohistiocytic inflammation [6]. Although infiltrating eosinophils may be more likely to be found in inverse psoriasis (with a mean of 2.6 eosinophils per high power field) compared to psoriasis vulgaris [6], the presence of numerous eosinophils together with clinicotemporal correlation can indicate a drug etiology. In our case, the correlation of new-onset inverse psoriasis with worsening psoriasis vulgaris after teriflunomide further supports a medication etiology.

Identifying drug association with inverse psoriasis includes concurrence of symptoms with adherence to the drug. However, a lack of understanding regarding drug-induced psoriasis, potential delays in onset, or persistent flares after discontinuing the drug may complicate concurrency [7]. In our patient, worsening of previous mild plaque psoriasis concurrent to the onset of inverse psoriasis symptoms supported a potential drug association. Furthermore, the absence of known inverse psoriasis history or other triggering factors suggested drug-induced etiology. Development of inverse psoriasis in a patient with a history of palmoplantar psoriasis after starting ustekinumab has similarly been reported [8]. Overall, analysis of our patient's history, clinical presentation, and histopathology best correlates with teriflunomide-induced inverse psoriasis.

The differential diagnosis of intertriginous rash includes erythrasma, dermatophyte, and candidal infections. These diagnoses can lead to erythematous plaques, with variable pustules, with associated pain, pruritus, or discomfort. In our case, negative fungal, bacterial cultures and special stains do not support an infectious etiology. In addition, the patient responded rapidly to topical corticosteroids, further supporting an inflammatory etiology. Intertrigo is also on the differential diagnosis; however, clinically does not present with

the sharply demarcated plaques seen in inverse psoriasis and shows absence of psoriasiform histopathologic findings. Finally, the differential diagnosis of drug eruptions presenting in intertriginous areas also includes symmetric drug-related intertriginous and flexural exanthem (SDRIFE), which presents with sharply demarcated, V-shaped symmetric erythema involving the skin folds. On histopathology, SDRIFE shows variable interface and spongiotic dermatitis rather than psoriasiform findings [9,10].

Current research has an incomplete understanding of drug-induced psoriasis and suspected mechanisms vary, including direct immune provocation, indirect hypersensitivity, allergic, irritant, or phototoxic reaction [7]. Reports of teriflunomide-induced pustular psoriasis postulate an aberrant feedback response to the blockade of lymphocyte proliferation, causing reactivation of inflammatory pathways more specifically involved in psoriasis [4]. Given the similar etiologies of psoriasis variants and their strong inter-associations, aberrant feedback could contribute to inverse psoriasis induction as well. Regardless of the mechanism, the unexpected nature of teriflunomide-induced psoriasis remains poorly understood, as its prodrug leflunomide is used for the treatment of psoriatic disease.

Conclusion

We present a novel case of teriflunomide induced new onset inverse psoriasis which has not been previously reported. Exacerbation or induction of psoriasis by teriflunomide has previously reported with plaque, pustular, or nail psoriasis in rare reports. Our case expands the clinicopathologic spectrum of teriflunomide induced psoriasis. Furthermore, as the package information for teriflunomide (brand name Aubagio) currently does not include inverse psoriasis as a potential adverse effect, it is important for dermatologists to be aware of this variant of psoriasis induced by teriflunomide.

Potential conflicts of interest

The authors declare no relevant conflicts of interest.

References

1. AUBAGIO® (teriflunomide) tablets, for oral use. Package Insert. https://products.sanofi.us/Aubagio/aubagio.html#section-8.2. Accessed on September 2, 2023.
2. Wu Q, Wang Q, Yang J, et al. Teriflunomide modulates both innate and adaptive immune capacities in multiple sclerosis. *Mult Scler Relat Disord*. 2023;75:104719. [PMID: 37172367].
3. Nash P, Thaci D, Behrens F, Falk F, Kaltwasser JP. Leflunomide improves psoriasis in patients with psoriatic arthritis: an in-depth analysis of data from the TOPAS study. *Dermatology*. 2006;212:238-249. [PMID: 16549920].
4. Dereure O, Camu W. Teriflunomide-induced psoriasiform changes of fingernails: a new example of paradoxical side effect? *Int J Dermatol*. 2017;56:1479-1481. [PMID: 28884799].
5. Micali G, Verzi AE, Giuffrida G, Panebianco E, Musumeci ML, Lacarrubba F. Inverse psoriasis: from diagnosis to current treatment options. *Clin Cosmet Investig Dermatol*. 2019;49:246-251. [PMID: 32099435].
6. Knabel M, Mudaliar K. Histopathologic features of inverse psoriasis. *J Cutan Pathol*. 2022;49:246-251. [PMID: 34611907].
7. Balak DM, Hajdarbegovic E. Drug-induced psoriasis: clinical perspectives. *Psoriasis (Auckl)*. 2017;7:87-94. [PMID: 29387611].
8. Darwin E, Deshpande A, Lev-Tov H. Development of drug-induced inverse psoriasis in a patient with Crohn's disease. *ACG Case Rep J*. 2018;5:e47. [PMID: 29951562].
9. Schuler AM, Smith EH, Chaudet KM, et al. Symmetric drug-related intertriginous and flexural exanthema: Clinicopathologic study of 19 cases and review of literature. *J Cutan Pathol*. 2021;48:1471-1479. [PMID: 34159622].
10. Kandala H, Gonzalez-Mosquera LF, Barua P, Podrumar A. Zoledronic acid-associated symmetrical drug-related intertriginous and flexural exanthema (SDRIFE). *Dermatol Online J*. 2021;14:e245326. [PMID: 26437156].