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Successful Management of Ustekinumab-Induced Pustular Psoriasis without Therapy Discontinuation

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SUMMARY We present a 34-year-old female patient with methotrexate unresponsive longstanding plaque psoriasis who developed pustular psoriasis ten weeks after initiation of ustekinumab therapy. Given the lack of other side effects and the rapid initial response of the underlying plaque psoriasis, we opted against discontinuing ustekinumab therapy. Topical corticosteroids were added for the management of pustular lesions on initial presentation. Given the treatment-resistant nature of our patient's underlying plaque psoriasis, we chose dose-intense regimen (every 8 weeks). After successful remission of the pustular lesions, topical corticosteroids were discontinued. Following nearly complete clearance of the underlying plaque psoriasis, maintenance ustekinumab therapy at the recommended 12-week intervals was initiated starting week 28. No recurrence of pustular psoriasis was noted during the 18-month follow-up. Our experience shows that pustular lesions associated with ustekinumab can be successfully managed with topical corticosteroids without discontinuing ustekinumab therapy and compromising therapeutic benefit seen in the underlying condition.

KEY WORDS: ustekinumab, adverse events, pustular psoriasis, plaque psoriasis

INTRODUCTION

Traditional treatments for psoriasis have relied upon systemic therapy with methotrexate, cyclosporin, oral retinoids and phototherapy. Activation of an abnormal immune response, which leads to keratinocyte hyperproliferation and epidermal thickening, is believed to be at the root of psoriasis (1). Interleukin (IL)-12 and IL-23 mRNA has been found to be overexpressed in psoriatic skin lesions, and gene polymorphisms within the genes that encode for IL-12, IL-23 or their associated receptor complex components are linked to an increased risk of psoriasis (2-4). Ustekinumab is a monoclonal antibody directed against the common p40 subunit of IL-12 and IL-23, so, it attenuates the immune cell activation properties of both IL-12 and IL-23. IL-12 promotes the differentiation of naive CD4+ T lymphocytes to T helper-1 (Th1) cells, and IL-23 supports the development of Th17 cells (5,6). Both Th1 and Th17 cells accumulate in psoriatic lesions, where they release an array of cytokines such as tumor necrosis factor (TNF)-α, interferon-γ (IFNγ), IL-17 and IL-22, that result in epidermal hyperproliferation and development of psoriatic plaques (7,8).

While numerous cases of pustular psoriasis induced by anti-TNF-α therapies have been published, there are only two cases of pustular psoriasis flares

potentially induced by ustekinumab in the literature (9,10). Unlike these two cases, which developed within days of the initial dose, we present here a methotrexate-resistant plaque psoriasis patient that developed pustular lesions 10 weeks after initial ustekinumab therapy. Furthermore, while in the other two cases ustekinumab therapy was discontinued on pustule presentation, we present an alternative approach of successfully managing pustular lesions with topical corticosteroids without discontinuing ustekinumab therapy and potentially compromising the clinical benefit of managing the primary plaque psoriasis.

CASE REPORT

A 34-year-old woman with longstanding severe plaque psoriasis since the age of 10 was admitted to the University Department in Skopje because of her deteriorating condition (PASI 57.0) while on methotrexate. Since the initial diagnosis, the patient had received topical corticosteroids, psoralen plus ultraviolet A irradiation (PUVA), and acitretin. Ustekinumab therapy was administered at weeks 0 and 4 at a dose of 45 mg, rapidly reducing disease severity to PASI 17.7 by week 4. However, painful erythemosquamous eruptions with pustules on the trunk and limbs developed by week 10, and the overall PASI score rose to 27.8 (Fig. 1). Our patient had not previously experienced flares with a pustular component. No laboratory abnormalities at any of the visits or other patient-reported adverse events were noted. Bacterial and fungal cultures of the pustules were negative. Histopathologic examination of a pustular lesion showed epidermal psoriasiform hyperplasia with parakeratosis, and the presence of both subcorneal and spongiform pustules, consistent with pustular psoriasis. Topical corticosteroids were added on for the local treatment of pustular lesions on their initial presentation at week 10. Given the good response of primary psoriasis and the lack of other adverse events, we chose not to discontinue ustekinumab therapy. Moreover, since dose intensification of ustekinumab therapy resulted in improved efficacy in the PHOENIX-2 pivotal trial (11), we opted for dose-intense therapy every 8 weeks instead of the recommended every 12-week regimen, to further control the underlying plaque psoriasis in this highly therapy refractory patient. By week 12, the pustular psoriatic lesions almost completely cleared, the overall PASI score decreased to 15.2, and ustekinumab was started every 8 weeks. By week 20, topical corticosteroid therapy was discontinued and the overall PASI score dropped to 7.6. At week 28, the overall PASI score further dropped to 3.9 and ustekinumab dosing was adjusted to every 12 weeks going forward. No recurrence of pustular lesions over the 18-month follow-up was noted.

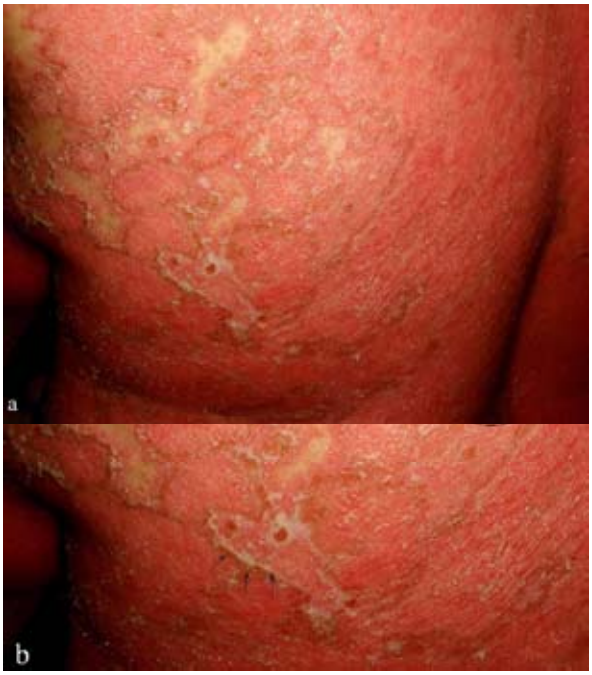

Figure 1. (a) Multiple annular erythematous and desquamating plaques studded with pustules; b) close-up of erythematous plaques with numerous pustules (arrows).

DISCUSSION

Only two cases of pustular psoriasis flares potentially induced by ustekinumab have been published to date, both developing within days of the first dose, one of which observed in a patient with prior history of pustular psoriasis flares before receiving ustekinumab. Importantly, while ustekinumab therapy was discontinued in both cases, we opted for topical corticosteroids to manage pustular lesions without discontinuing ustekinumab therapy. We chose not to discontinue ustekinumab therapy in order not to compromise the favorable results with the underlying methotrexate-resistant plaque psoriasis, particularly given the lack of other adverse events. We believe that in cases of ustekinumab-associated pustular psoriasis, ustekinumab therapy should be continued in cases with significant clinical benefit in the underlying therapy-resistant plaque psoriasis. Furthermore, we recommend using topical corticosteroids to successfully manage the pustular lesions in such cases.

Given the scant literature on pustular psoriasis after initiating ustekinumab therapy, there is little scientific data on the molecular causes of this paradoxical reaction. On the other hand, there is significantly more clinical experience with pustular psoriasis after

initiating anti-TNF-α therapies, potentially due to the greater use of this class of biologics. Importantly, however, we were not able to find reports on pustular psoriasis following therapy with other immunomodulatory biological therapies, such as abatacept (CTLA-4 inhibitor), anakinra (IL-1R antagonist), basiliximab/daclizumab (anti-IL-2Rα mAb), canakinumab (anti-IL1β mAb), efalizumab (anti-CD11a mAb) or tocilizumab (anti-IL-6R mAb). Therefore, TNF-α inhibitors and ustekinumab could drive a similar molecular phenomenon resulting in pustular lesions, which is not affected by other immunomodulatory therapies. While one such mechanism has been put forth (9), we believe that due to the infrequent occurrence of these side effects, it will be difficult to gather robust scientific evidence to elucidate the underlying molecular mechanism of this phenomenon.

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