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CASE REPORT

Successful Treatment of Ustekinumab-Associated Lichenoid Drug Eruption with Upadacitinib: A Case Report

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Abstract: Ustekinumab is an antibody targeting the common p40 subunit shared by interleukin (IL)-12 and IL-23, demonstrating favorable efficacy in the treatment of psoriasis. Herein, we report the case of a 69-year-old male with psoriasis, managed with ustekinumab, who presented with a new cutaneous eruption. Biopsy findings were consistent with lichenoid drug eruption (LDE). The patient's condition was promptly managed by upadacitinib, a selective Janus kinase (JAK) inhibitor. Physicians need not be overly concerned about this rare adverse reaction. JAK inhibitors may offer new treatment options with an advantage of rapid onset of action for patients experiencing LDE induced by biologic therapies for psoriasis.

Keywords: psoriasis, lichenoid drug eruption, ustekinumab, upadacitinib

Introduction

Ustekinumab is a fully human monoclonal antibody against the common p40 subunit of IL-12 and IL-23, with exact efficacy for moderate-to-severe psoriasis by inhibiting Th1 and Th17/Th22 responses.[1] The most commonly associated adverse effects include nasopharyngitis and headache.[2] As its usage increases, a thorough understanding of adverse events becomes essential for guiding treatment and subsequent management. We report a case of lichenoid drug eruption (LDE) associated with ustekinumab. The patient's condition was successfully managed by upadacitinib, a selective Janus kinase (JAK) inhibitor. A thorough understanding of the potential adverse events associated with biologic therapies enables clinicians to intervene promptly and develop optimal treatment strategies, especially as novel therapies are increasingly adopted in clinical practice. JAK inhibitors work by selectively blocking enzymes involved in immune cell signaling, thereby reducing the inflammatory response. This makes them a valuable tool in managing inflammatory skin conditions like psoriasis, especially when traditional treatments or biologics cause unwanted side effects.

Case Report

The patient, who had a 3-year history of erythematous scaling plaques accompanied with mild pruritus on his scalp, trunk and limbs, was pathologically diagnosed with plaque psoriasis. Due to the lack of response to photo therapy and topical tapinarof, the treatment was switched to subcutaneous ustekinumab (Stelara; Janssen Cilag), administered initially at weeks 0 and 4, and then every 12 weeks thereafter, with a dosage of 45 mg per injection. The patient was otherwise healthy and denied a history of hypertension, diabetes or other chronic diseases. The treatment was discontinued due to stable remission after the fourth dose of ustekinumab. One year later, a recurrence of psoriasis was observed and ustekinumab was restarted without the addition of other medication. However, an intense pruritic rash developed five days after the first injection. Physical examination revealed the presence of multiple, generalized, flat, and polygonal erythematous papules on the chest, abdomen, lumbar, and extremities (Figure 1a and c). Neither Wickham striae or

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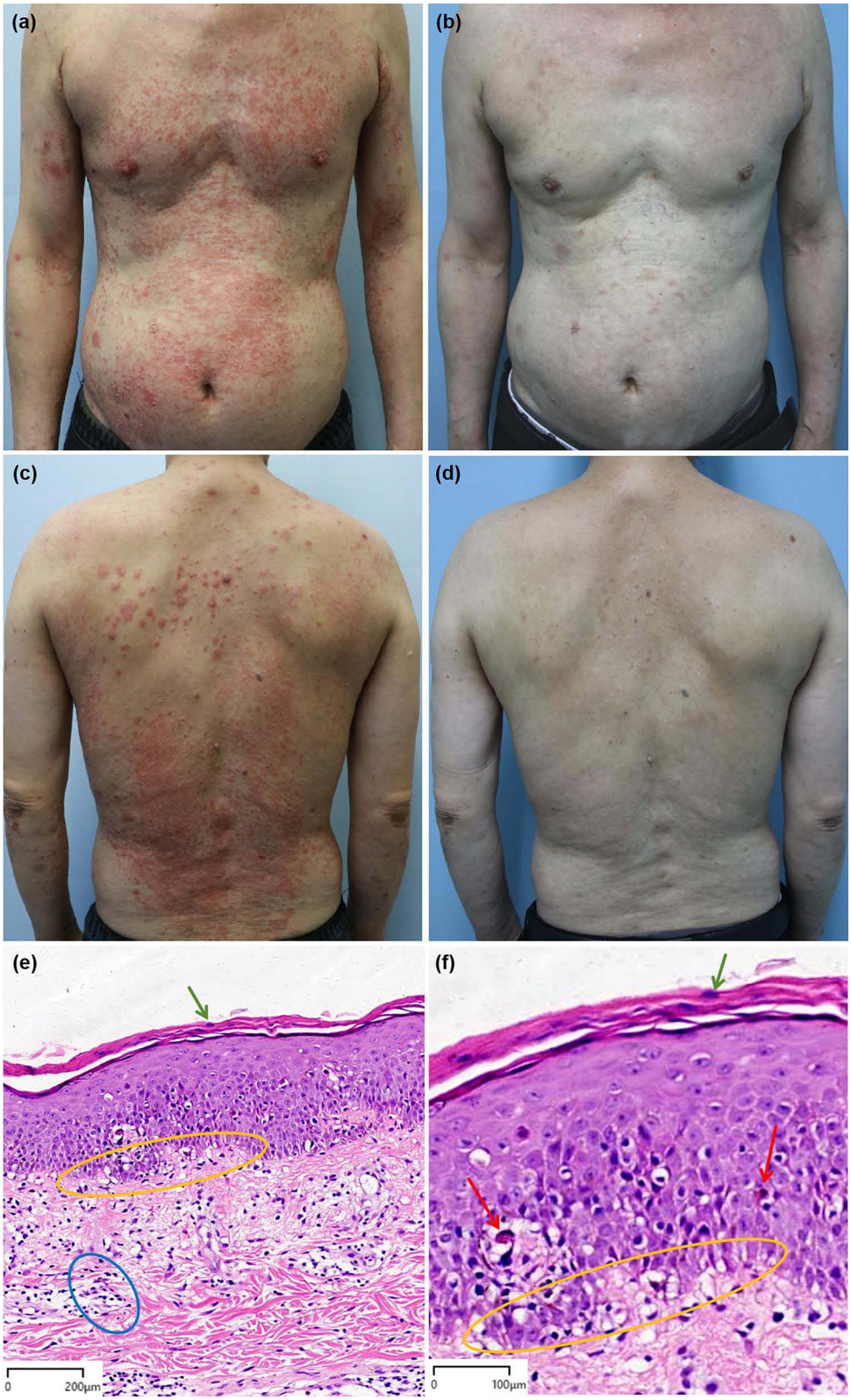

Figure 1 (**a**) Multiple polygonal erythematous papules on the chest and abdomen of the patient. (**b**) The rashes on the chest and abdomen regressed after discontinuation of ustekinumab and oral upadacitinib for 1 month. (**c**) Multiple polygonal erythematous papules and psoriasiform plaques on the back. (**d**) The psoriasiform plaques and erythematous papules on the back were almost resolved. (**e** and **f**) Histological images illustrate mild parakeratosis (green arrow), acanthosis, scattered eosinophils infiltrating the epidermis (red arrow), liquefaction of basal cells (yellow circle), and perivascular lymphocytic infiltrate in the superficial dermis (blue circle) (e, H&E, ×200; f, H&E, ×100).

mucosal involvement were observed. Scattered psoriasiform plaques were seen on the scalp and back (Figure 1c). Histological images illustrate mild parakeratosis, acanthosis, scattered eosinophils infiltrating the epidermis, liquefaction of basal cells, and perivascular lymphocytic infiltrate in the superficial dermis (Figure 1e and f). According to the patient's recollection, in the past two years, ustekinumab is the only systemic drug to which he has had a first-time exposure. In the past 12 weeks, there has been no history of infection or the use of other systemic medications. Based on the clinical course, a diagnosis of LDE was established, and ustekinumab was suspected to be the most likely causative agent. The rashes and pruritus gradually worsened over the course of two weeks. The patient expected quick symptomatic relief. With patient consent, oral administration of upadacitinib was initiated at a daily dosage of 15 mg. All subsequent ustekinumab treatment was cancelled. One month later, both the psoriasis and LDE rashes nearly completely resolved (Figure 1b and d). The patient continued the prescribed dose of upadacitinib without developing any new rashes. Three months later, the patient independently discontinued the medication. Telephone follow-up revealed that one month after discontinuation, the patient intermittently developed scattered scaly plaques on the back and scalp, accompanied by minimal pruritus. The condition gradually improved with the application of topical corticosteroid ointment. To date, there has been no severe psoriasis relapse, and no LDE rashes have occurred.

Discussion

Lichen planus (LP), characterized by interface dermatitis, is a T cell-mediated autoimmune inflammatory disease.[3] LDE has been described as a clinical variant of lichen planus, triggered by various drug culprits.[3,4] LDE may arise several days to 3 years after the exposure to the perpetrating medication.[3,4] The latent period may vary depending on the offending drug, the dosage of the drug, and host factors.[3,4] Besides, compared to idiopathic lichen planus, LDE has an acute onset and tend to be show more pronounced eczematous morphology.[3,4]

To date, this is the first report of LDE associated with the IL-12/IL-23 inhibitor ustekinumab. LDE has been reported after treatment with tumor necrosis factor (TNF)-α inhibitors and IL-17A inhibitors, such as adalimumab and ixekizumab.[5,6] Similar to our patient, the primary manifestations were multiple, flat and polygonal erythematous papules with a widespread distribution, accompanied by pruritus, without mucosal involvement or Wickham striae. Furthermore, histopathological examination revealed features comparable to those observed in our patient, including basal cell liquefaction, parakeratosis, acanthosis, and superficial dermal lymphocytic infiltration, with a few eosinophils present. It is speculated that TNF-α or IL-17A inhibitors could evoke lichenoid eruptions by activating interferon (IFN), especially IFN-α and IFN-γ, which subsequently induce activation of resident T cells and myeloid dendritic cells, leading to an inflammatory response.[5,6] Ustekinumab reduces the differentiation toward Th17 cell lineage and IL-17 levels through inhibiting IL-23 level.[1] Furthermore, by inhibiting IL-12, ustekinumab may indirectly suppress TNF-α production through the IL-12/IFN-γ/TNF-α axis.[1] The mechanism underlying LDE caused by ustekinumab remains unclear, and we hypothesize that it may be similar to that proposed for TNF-α and IL-17A inhibitors–associated LDE: instigating interferon activation.

The patient's LDE continued to spread. In light of the presence of psoriasis, systemic glucocorticoid therapy appears to be inadvisable. We innovatively utilized a JAK inhibitor to concurrently treat both LDE and psoriasis, yielding promising outcomes. Rapid improvement of rashes and pruritus was observed. Due to the interference with the IFN-γ/CXCL10/CXCR3 axis, JAK inhibitors may be good targets for LP treatment.[7] Case reports have described the efficacy of JAK inhibitors in the treatment of LP variants including lichen planopilaris, nail LP, and erosive LP.[7] Additionally, the activate of intracellular signaling mediated by JAKs can involve in the occurrence of psoriasis by promoting production of IL-17 and IL-22.[8] By downregulating the JAK/STAT pathway, upadacitinib can exert a therapeutic effect on both LDE and psoriasis.

Due to the potential long latency period of LDE,[3,4] which can extend over several years, as well as the possibility of recall bias regarding the patient's medication history, ustekinumab is considered the most likely drug associated with the patient's LDE, though not definitively. Physicians need not be overly concerned about this adverse effect, as if LDE is indeed induced by ustekinumab, it would represent a very rare occurrence that is treatable JAK inhibitors may offer new treatment options with an advantage of rapid onset of action for patients experiencing LDE induced by the administration of biologics for psoriasis. This finding offers a new perspective for future mechanistic research, especially to explore the potential mechanism of action of JAK inhibitors on skin adverse reactions associated with certain drugs. Furthermore, it could provide valuable insights for optimizing clinical treatment strategies and developing relevant guidelines.

Ethics Statement

The Guangzhou Dermatology Hospital approved to publish the case details.

Patient Consent Statement

The patient's written informed consent has been obtained to have the case details and any accompanying images published.

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Author Contributions

All authors made a significant contribution to the work reported, whether that is in the conception, study design, execution, acquisition of data, analysis and interpretation, or in all these areas; took part in drafting, revising or critically reviewing the article; gave final approval of the version to be published; have agreed on the journal to which the article has been submitted; and agree to be accountable for all aspects of the work.

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Disclosure

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

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