CASE REPORT

Delayed-onset psoriasiform eruption secondary to a phosphoinositide 3-kinase inhibitor: A case report and literature review

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INTRODUCTION

Phosphoinositide 3-kinase (PI3K) inhibitors belong to a class of small-molecule inhibitors that target the PI3K/Akt/mammalian target of rapamycin signaling cascade, a central pathway in cellular proliferation, immune regulation, and carcinogenesis.1 Despite being important anticancer therapies, the spectrum of cutaneous toxicity of PI3K inhibitors is poorly characterized. Here we report a case of delayed-onset psoriasiform eruption secondary to duvelisib and present a summary of all the reported cases in the literature.

CASE

A man in his 50s with a 12-year history of recurrent follicular lymphoma presented to his oncologist with a subacute, multifocal, pruritic, painful eruption. The rash started on the abdomen and progressed to the scalp, groin, and extremities. The patient endorsed severe pain on his feet but denied fevers, chills, weight loss, and any other systemic symptoms. Besides oxycodone, the only medications that he was taking were duvelisib, a PI3K inhibitor, and trimethoprim-sulfamethoxazole (TMP-SMX) for pneumocystis pneumonia prophylaxis, both started 14 months prior for the management of recurrent follicular lymphoma. The physical examination was notable for well-demarcated erythematous plaques on the abdomen, axillae, and inguinal folds (Fig 1). There were also scattered, erythematous, scaly papules and plaques on the scalp, upper and lower extremities, palmar and dorsal hands, and buttocks as well as confluent, erythematous, hyperkeratotic plaques with plate-like scales on the planter feet (Figs 1 and 2). Two biopsies of the abdomen and left foot both showed parakeratosis with collections of neutrophils, hypogranulosis, regular epidermal hyperplasia with elongated rete ridges, thin suprapapillary plates, dilated blood vessels in the papillary dermis, and dermal eosinophils (Fig 3). The findings were consistent with a psoriasiform drug reaction.

The patient was first evaluated by his oncologist, and both duvelisib and TMP-SMX were discontinued. He was started on a short prednisone taper; however, this was incompletely adhered to by the patient due to insomnia. He was subsequently seen in our clinic and was started on topical corticosteroids (TCSs), which he used only intermittently. Despite a short trial of TCSs, the patient had significant improvement of the eruption on his scalp.

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and plantar feet at the 1-week follow-up appointment (Fig 2, B). The patient was initially lost to follow-up but returned to the clinic 6 months later with complete resolution and no recurrence of the eruption. The patient never restarted duvelisib.

**DISCUSSION**

Duvelisib is a small-molecule inhibitor of the PI3K/Akt/mammalian target of rapamycin pathway that is responsible for the proliferation of clonal B cells and the recruitment and differentiation of T cells and macrophages in the tumor microenvironment. By targeting PI3K, duvelisib and other drugs of its class disrupt key signaling cascades that potentiate the progression of hematologic malignancies. Due to its role in immune regulation, PI3K blockage can also lead to the loss of immune self-tolerance, potentially promoting the development or progression of cutaneous or systemic inflammatory disorders.

Although PI3K inhibitors are widely used for the treatment of chronic lymphocytic leukemia and follicular lymphoma and are currently under investigation for other solid and hematologic malignancies, their cutaneous adverse profile is poorly characterized, with only a few reported cases of hypersensitivity reactions, ‘maculopapular’ eruptions, erythema multiforme, and toxic epidermal necrolysis. Psoriasiform and other papulosquamous eruptions,
such as pityriasis rubra pilaris (PRP)-like reactions, occurring in association with PI3K inhibitors are also not well described.4-7 The exact mechanism of PI3K inhibitor-induced psoriasiform eruptions remains unknown but is likely related to the intricate effects of the PI3K pathway on both proinflammatory and anti-inflammatory cytokines.4

Our patient presented with a sudden-onset eruption with clinical and histopathologic features consistent with a psoriasiform drug eruption. Despite not having an adequate course of TCSs, his eruption quickly improved following duvelisib discontinuation. The temporal relationship between the duvelisib initiation and the onset of the eruption (14 months in our patient) is consistent with those in reported cases, which ranged from 15 days to 17 months.4,6 Although we cannot definitively rule out TMP-SMX as a causative agent, psoriasiform eruptions are almost never reported with TMP-SMX despite the widespread use of the medication. We were able to find only 1 such case report, which documented an erythrodermic psoriasis flare following TMP-SMX initiation.8 The Naranjo algorithm9 for assessing causality in adverse drug reactions indicates that duvelisib is a “probable” culprit (Supplementary Table I, available via Mendeley at https://doi.org/10.17632/fs839x372j.1), while the Jones algorithm10 suggests only a “possible” relationship in this case due to the simultaneous use and discontinuation of TMP-SMX.

To further characterize the clinical features of this type of eruption, we also summarized all reported cases of PI3K inhibitor-induced psoriasiform (7 cases, including our patient) and PRP-like (3 cases) eruptions in Table I. We included PRP-like cases because PRP was in the clinical differential diagnosis for our patient and shares similar management strategies. Both psoriasiform and PRP-like reactions represent class side effects of PI3K inhibitors rather than being limited to a specific agent. The median time to onset was 11 months (range 15 days to 17 months) for the psoriasis group and 6 weeks (range 4 days to 5 months) for the PRP-like group. In 1 case series of PI3K-induced psoriasiform eruptions, the patient who developed the rash most quickly (15 days after therapy initiation) was the only one with a history of psoriasis.5 In addition to the classic cutaneous findings, other features, including palmoplantar, intertriginous, and nail involvement, non-scarring alopecia (2 PRP cases), and bilateral ectropion (1 PRP case), were described. Similarly to our patient, all reported cases saw dramatic improvement, even resolution, after the discontinuation or dose reduction of the offending drugs. Two patients with psoriasiform eruptions improved with TCSs alone, without therapy interruption. Acitretin was an effective treatment for both psoriasiform (1 case) and PRP-like eruptions (2 cases). Other treatments that were used included prednisone (all PRP cases and our patient), antihistamines, topical tazarotene, topical tacrolimus, ketoconazole shampoo, and emollients.

Finally, this case demonstrates the pivotal role that dermatologists play in managing the cutaneous side effects of oncologic therapies. The effective management of skin toxicity helps to minimize patient discomfort and interruptions in oncologic care.

**Conflicts of interest**

Dr Lo Sicco is an investigator for Regen Lab and Pfizer and a recipient of an educational grant from Pfizer. Dr Milam received honorarium from the National Eczema Association for assistance with creation of educational material. Dr Tran, Author Karim, Drs Tattersall and Brinster have no conflicts of interest to declare.
Table I. Clinical characteristics of all reported cases of psoriasiform and PRP-like eruptions in patients treated with PI3K inhibitors

| Psoriasiform drug eruption | PRP-like reaction |
|----------------------------|-------------------|
| n                          | 7                 | 3                 |
| Age, mean                  | 67.7              | 61.3              |
| Men (%)                    | 71%               | 67%               |
| PI3K isoform targeted      | p110δ (5)         | p110δ (2)         |
| Diagnosis                  | Chronic/small lymphocytic lymphoma (3) | Chronic/small lymphocytic lymphoma (2) |
|                            | Follicular lymphoma (2) | Anaplastic oligodendroglioma |
|                            | Marginal zone lymphoma |                |
|                            | Mantle cell lymphoma |                |
| Concurrent therapies       | None (2)          | None (2)          |
|                            | Ibrutinib         | Ofatumumab & TMP-SMX |
|                            | Rituximab         |                   |
|                            | Fludarabine, cyclophosphamide, & rituximab |           |
| Time to onset, median (range) | 11 months (15 days-17 months) | 6 weeks (4 days-5 months) |
| Special sites of involvement | Scalp (5) | Scalp (2) |
|                            | Palmoplantar (3) | Palmoplantar (3) |
|                            | Intertinginous (4) | Alopecia (2) |
|                            | Nail              | Ectropion         |
| Treatment                  | Topical corticosteroids (7) | Topical corticosteroids (3) |
|                            | Prednison (nonadherent) | Prednison (3) |
|                            | Acitretin         | Acitretin (2)     |
|                            | Antihistamine     | Antihistamine     |
|                            | Topical tacrolimus | Tazarotene        |
|                            | Topical tazarotene |                   |
|                            | Ketoconazole shampoo |               |
| PI3K inhibitor status      | No dose reduction or discontinuation (2) | Discontinued due to unrelated side effects (2) |
|                            | Held, restarted at lower dose (2) |                   |
|                            | Held, restarted at same dose |                   |
|                            | Held, not restarted (2) | Discontinue |

The numbers in parentheses represent the number of cases.

mTOR, Mammalian target of rapamycin; PI3K, phosphoinositide 3-kinase; PRP, pityriasis rubra pilaris; TMP-SMX, trimethoprim-sulfamethoxazole.

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