Mucocutaneous drug reaction after treatment with Phosphatidylinositol-3-kinase inhibitor

Tory Starzyk, MA,[a] Rebecca Olsen, MS,[b] David Baltazar, DO,[c] Bridget Sledge, DO,[c] and Yebabe Mengesha, MD[c]
Lebanon, Oregon, and Mesa and Scottsdale, Arizona

Key words: alpelisib; drug reaction; immune checkpoint inhibitor; mucocutaneous; PI3K inhibitor.

INTRODUCTION

Phosphatidylinositol-3-kinase (PI3K) inhibitors are a new class of targeted oncology medications that regulate the mammalian target of rapamycin pathway of cellular growth and metabolism. This drug class was previously reported to induce immune-mediated adverse reactions, including cutaneous eruptions.[1] In 2019, alpelisib (an α-specific PI3K inhibitor) and fulvestrant (a selective estrogen receptor degrader) were approved by the Food and Drug Administration as a combination treatment for hormone receptor-positive and human epidermal growth factor receptor-2 (HER2)/neu-negative breast cancer. Exanthematous drug eruptions have been reported with alpelisib, most frequently when used in combination with endocrine therapies such as fulvestrant.[2-4] The current literature depicts these drug reactions as a morbilliform rash without description of morphology.[2,4] The case reported here describes a woman with a history of recurrent metastatic breast cancer who presented with a morbilliform drug eruption after initiation of alpelisib therapy.

Abbreviations used:

HER2: Human Epidermal growth factor Receptor 2
PI3K: Phosphatidylinositol-3-Kinase

CASE REPORT

A 77-year-old woman with a medical history of recurrent metastatic infiltrating ductal breast carcinoma (Estrogen receptor-positive, HER2-negative, and progesterone receptor-positive) presented at the hospital with a generalized erythematous rash of a duration of 10 days. The patient was on palbociclib-fulvestrant combination therapy for 2 years but recently switched to alpelisib-fulvestrant due to a newly diagnosed patient PIK3CA mutation. Within 24 hours of the initial 300-mg dose of alpelisib, the patient experienced generalized pruritus and reported her symptoms to her oncologist. This resulted in a reduction of the alpelisib dosage to 200 mg and introduction of 25-mg diphenhydramine. Initially, symptoms improved; however, erythematous papules appeared on her trunk the following week. The patient was removed from alpelisib treatment, but the pruritus continued, and the patient developed fatigue leading to presentation to the emergency room.

On initial presentation, physical examination revealed generalized pink-to-red, erythematous papules coalescing into plaques on the trunk, extremities, and scalp (Fig 1). Oral examination revealed no mucosal involvement. A drug reaction was suspected, and the patient was started on topical clobetasol (0.05%, twice a day). A 4-mm punch biopsy of a plaque on the patient's upper portion of the left chest revealed an attenuation of the rete ridge pattern, underlying a superficial perivascular and interstitial mixed inflammatory infiltrate, and vacuolar interface damage along the base of the epidermis (Fig 2). Moderate numbers of intraepidermal eosinophilic infiltrates were also observed (Fig 3). Histologic observations were consistent with a drug reaction.

During the first 24 hours after presentation, the patient reported worsening pruritus and a burning sensation. The erythematous plaques on the trunk

From the Western University of Health Sciences, Lebanon[a]; A.T. Still University School of Osteopathic Medicine in Arizona, Mesa[b]; and HonorHealth Dermatology Residency, Scottsdale.[c]
Funding sources: None.
IRB approval status: Not applicable.
Correspondence to: David Baltazar, DO, HonorHealth Dermatology Residency, 20401 N 73rd St, Suite #230, Scottsdale, AZ 85255. E-mail: dbaltazar@honorhealth.com.

JAAD Case Reports 2022;19:25-7.
2352-5126

https://doi.org/10.1016/j.jdcr.2021.10.033

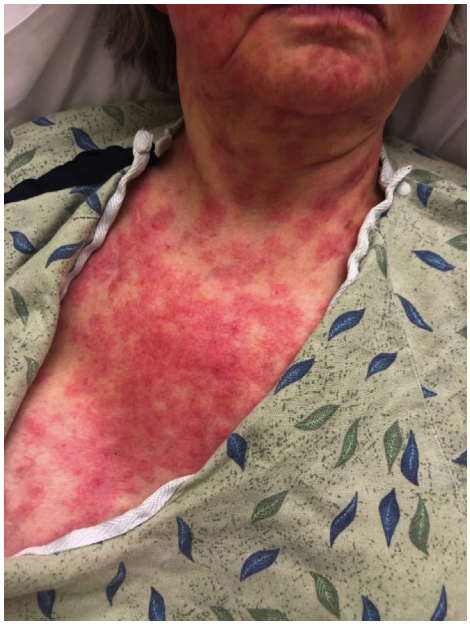

Fig 1. Initial presentation of the patient, with erythematous papules coalescing into plaques on the chest, neck, and face.

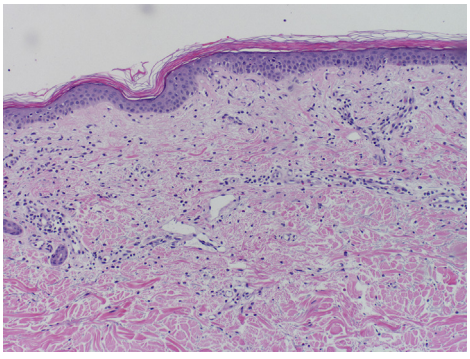

Fig 2. Medium-power view of the punch biopsy, showing attenuation of the rete ridge pattern with vacuolar interface damage along the base of the epidermis; a superficial perivascular and an interstitial mixed inflammatory infiltrate were noted.

became more numerous, and the papules coalesced into larger plaques with violaceous centers (Fig 4). Additional lesions were noted in the vulva. Although no oral lesions were observed on initial examination, the patient reported onset of pruritus and burning in her mouth. Methylprednisolone (20 mg, twice a day) was initiated, and within 12 hours, the onset of new lesions ceased, and the patient reported moderate relief from pruritus and burning sensations. At 48 hours, the erythema and violaceous color decreased in intensity and size. Due to continued improvement, the patient was discharged after 2 days with instructions to continue prednisone

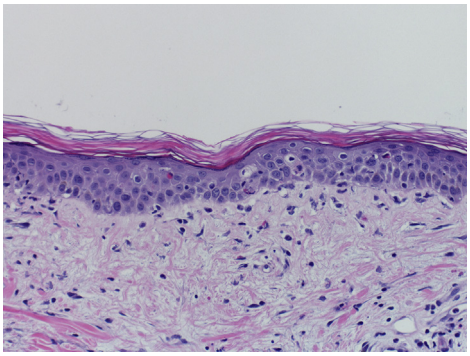

Fig 3. High-power view of the punch biopsy, showing intraepidermal eosinophils.

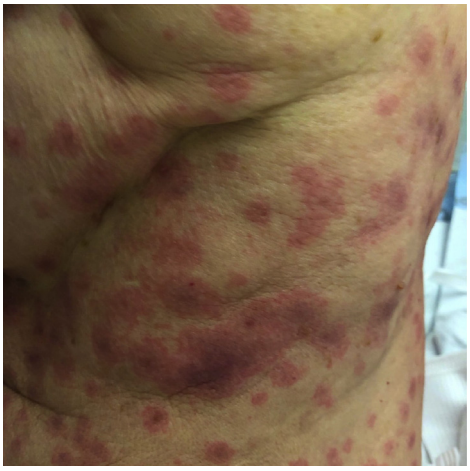

Fig 4. 24 hours after the initial presentation, violaceous centers evolving in the center of the erythematous plaques were noted.

(40 mg, daily) with a taper. One week later, the patient reported significant improvement, and at 4 weeks, she demonstrated resolution of the cutaneous rash. On examination at approximately 8 weeks after the onset of the rash, the patient and her oncology team were considering reintroduction of alpelisib therapy.

DISCUSSION

Alpelisib is a new targeted therapy anticipated to be increasingly utilized in combination with fulvestrant for treatment of PIK3CA-mutated advanced or metastatic breast cancer (mutations present in approximately 40% of patients with estrogen receptor-positive and HER2-negative breast carcinomas).[3] Due to the utility of alpelisib therapy, it is anticipated that potential adverse effects will be of medical importance.

The potential for targeted therapies, such as epidermal growth factor receptor, HER2, and mitogen-activated protein kinase inhibitors, to

induce dermatologic adverse events, most commonly as acneiform rashes, is well documented.[5] This lesion contrasts with the papular and plaque morphology presentation in the current case. Although rash is reported in approximately 50% of patients receiving alpelisib for breast cancer, few detailed reports describing the lesion exist in the literature.[4]

In the current case, the patient was treated with palbociclib and fulvestrant for 2 years before she was switched to alpelisib. The patient did not demonstrate any adverse effects before discontinuing palbociclib but became symptomatic within 24 hours of initiating alpelisib. Rashes associated with alpelisib have a median onset of 13 days.[6] The acute temporality of rash onset supports the notion that alpelisib is the most likely cause of the observed exanthem.

Reportedly, a generalized morbilliform rash frequently occurs when alpelisib is combined with endocrine therapies (ie, fulvestrant).[2,3] In a randomized phase 3 trial, adverse cutaneous drug reactions appeared in 9.9% of patients treated with alpelisib-fulvestrant as compared with only 0.3% in the placebo-fulvestrant treatment group.[7] This data supports the hypothesis that cutaneous eruptions are a common adverse effect of alpelisib. In the current case, generalized exanthematous eruptions occurred after introduction of alpelisib, suggesting that this PI3K inhibitor initiated the development of immune-mediated cutaneous rashes.

In the randomized phase III SOLAR-1 (Study Assessing the Efficacy and Safety of Alpelisib Plus Fulvestrant in Men and Postmenopausal Women With Advanced Breast Cancer Which Progressed on or After Aromatase Inhibitor Treatment) study of alpelisib-fulvestrant in patients with hormone receptor-positive breast cancer, drug-induced rashes were graded, and treatment was based on the body surface area distribution of lesions.[8] Our patient had >30% body surface are involvement, with active skin toxicity corresponding to a grade 3 rash. Treatment of the current patient was in accordance with recommendations, including interruption of alpelisib therapy, initiation of topical corticosteroid (clobetasol), and oral antihistamine treatment.

Antihistamines may be used prophylactically with introduction of alpelisib. If given before the onset of a rash, antihistamines may decrease rash severity.[4] Systemic low-dose corticosteroid use may be considered for more extensive dermatologic lesions. In the current case, diphenhydramine was given post-development of pruritus but prior to the onset of erythematous papules. However, the patient did not improve after antihistamine treatment and developed mucosal lesions. Therefore, systemic steroid treatment was initiated.

Following therapy for adverse rash development, patients frequently restart alpelisib at a reduced dose.[4] For our patient with a grade 3 rash, alpelisib may be resumed at the same dose once the rash resolves. In general, patients can be rechallenged with alpelisib but should be monitored by their oncologist.

Conflicts of interest

None disclosed.

REFERENCES

1. Curigliano G, Shah RR. Safety and tolerability of phosphatidylinositol-3-kinase (PI3K) inhibitors in oncology. *Drug Saf*. 2019; 42(2):247-262. https://doi.org/10.1007/s40264-018-0778-4
2. Juric D, Janku F, Rodón J, et al. Alpelisib plus fulvestrant in PIK3CA-altered and PIK3CA-wild-type estrogen receptor-positive advanced breast cancer: a phase 1b clinical trial. *JAMA Oncol*. 2019;5(2):e184475. https://doi.org/10.1001/jamaoncol.2018.4475
3. André F, Ciruelos E, Rubovszky G, et al. Alpelisib for *PIK3CA*--mutated, hormone receptor-positive advanced breast cancer. *N Engl J Med*. 2019;380(20):1929-1940. https://doi.org/10.1056/NEJMoa1813904
4. Wang DG, Barrios DM, Blinder VS, et al. Dermatologic adverse events related to the PI3Kα inhibitor alpelisib (BYL719) in patients with breast cancer. *Breast Cancer Res Treat*. 2020; 183(1):227-237. https://doi.org/10.1007/s10549-020-05726-y
5. Lacouture M, Sibaud V. Toxic side effects of targeted therapies and immunotherapies affecting the skin, oral mucosa, hair, and nails. *Am J Clin Dermatol*. 2018;19(Suppl 1):31-39. https://doi.org/10.1007/s40257-018-0384-3
6. Khan NAJ, Alsharedi M. Bullous skin rash: a rare case of palbociclib-induced dermatological toxicity. *Cureus*. 2020; 12(9):e10229. https://doi.org/10.7759/cureus.10229
7. Rugo HS, André F, Yamashita T, et al. Time course and management of key adverse events during the randomized phase III SOLAR-1 study of PI3K inhibitor alpelisib plus fulvestrant in patients with HR-positive advanced breast cancer. *Ann Oncol*. 2020;31(8):1001-1010. https://doi.org/10.1016/j.annonc.2020.05.001
8. Dunn LA, Riaz N, Fury MG, et al. A phase 1b study of cetuximab and BYL719 (alpelisib) concurrent with intensity modulated radiation therapy in stage iii-ivb head and neck squamous cell carcinoma. *Int J Radiat Oncol Biol Phys*. 2020;106(3):564-570. https://doi.org/10.1016/j.ijrobp.2019.09.050