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Case Report

Alpelisib induced Hyperglycemia, Rash and Calf Ulcers

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Abstract

Alpelisib together with fulvestrant is approved for use in postmenopausal women with PIK3CA-mutated advanced breast cancer. Yet, adverse reactions to alpelisib may necessitate early discontinuation of this regimen. Important among the latter are alpelisib-induced hyperglycemia and a disseminated maculo-papular rash, typically occurring within the first 2 weeks of treatment. The sequential occurrence of three adverse events under alpelisib treatment is the subject of the present report: hyperglycemia, maculopapullar rash, along with calf ulcers, the latter not mentioned in the literature among alpelisib adverse reactions.

Alpelisib (an α-selective phosphatidylinositol 3-kinase inhibitor) together with fulvestrant is approved for use in postmenopausal women with PIK3CA-mutated advanced breast cancer. Common adverse events of alpelisib are hyperglycemia and a maculo-popular rash, both typically occurring within the first 2 weeks of treatment [1,2]. We describe the sequential occurrence of three adverse events under alpelisib-fulvestrant treatment: the well-recognized hyperglycemia and maculopapullar rash, along with the hitherto not mentioned in the literature stasis dermatitis and calf ulcers.

Keywords: *alpelisib; festoterone; breast cancer; skin ulcer; rash; hyperglycemia*

Case History

A 75-year-old woman was diagnosed with relapse of PIK3CA-mutated breast cancer, with liver and bone metastases. Treatment with festosterone was started 500 mg i.m. once monthly, subsequently combined with alpesilib 300 mg tablets once a day. Two weeks later hyperglycemia was diagnosed and treated with metformin and insulin. Six weeks afterwards a maculo-popular rash developed on the patient's trunk and extremities along with a slight calf edema. Subsequently a large blister appeared on her left calf, ruptured, exposing a large superficial ulcer. Three superficial skin ulcers appeared concurrently on the right calf (Figure 1). The patient's temperature was normal and there were no signs suggestive of an infection. A course of ampicillin-clavulinate prescribed ex juvantibus did not change the clinical picture. Notable in the patient's medical history were arterial hypertension, hypothyroidism and total knee replacement for osteoathrosis. Diagnostic workup in the local teaching hospital showed normal immune globulins and serum complement. A skin biopsy from the rim of the calf ulcer showed a mixed leukocytic infiltrate, no vasculitis. Prednisolone 40 mg/day was started and subsequently tapered. Alpelisib was discontinued whereupon hyperglycemia and the rash subsided. At this point of time the patient was transferred for postacute care. Notable in the patient's history were fairly controlled arterial hypertension and hypothyroidism. Medications included levothyroxine, oxycodone, prednisone 15 mg, and enoxaparin 40 mg. Physical examination revealed an alert, afebrile woman with a regular heart rate of 72 beats/min, blood pressure 138/76 mmHg, respiratory rate was 20 breaths/min, and room air oxygen saturation 92%. There was mild erythema and a grade 2 edema on the dorsal aspect of the feet and calves, reminiscent of stasis dermatitis. Four superficial skin ulcers with irregular borders, 1-4 cm in diameter, had emerged on the volar aspect of the calves. There were neither varicose veins nor venectasia. (Figure 1). At this time the patient was receiving chemotherapy with adriamycin.

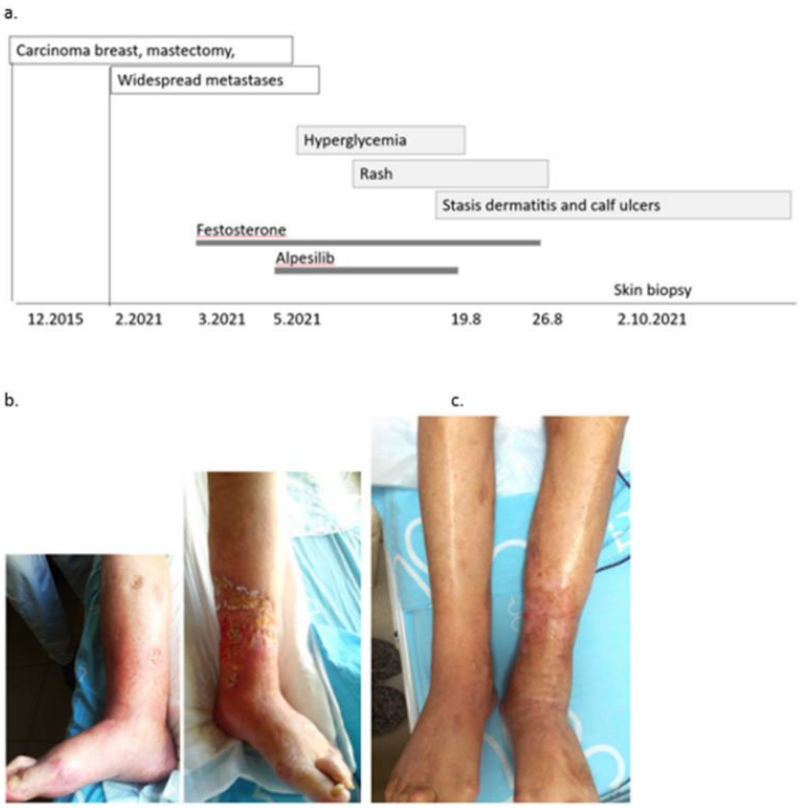

Figure 1: a. Outline of the patient's medical history, **b.** stasis dermatitis and skin ulcers on admission in postacute care, **c.** three months later skin ulcers were healed

Discussion

Alpelisib (α-selective phosphatidylinositol 3-kinase inhibitor) together with fulvestrant is used for treatment of postmenopausal women with PIK3CA-mutated advanced breast cancer. Alpelisid treatment is often associated with adverse events, the most common among them being hyperglycemia and a maculo-popular rash on the trunk and extremities, both usually observed within the first 2 weeks of therapy [1,2]. In the proposito, alpelisib was the trigger of hyperglycemia and rash, and later of stasis dermatitis and skin ulcers.

Stasis dermatitis manifest as erythema, hyperpigmentation, scaling, erosions, and may complicate with skin ulcers. It occurs as a complication of lymph stasis secondary to venous insufficiency or due to a variety of other causes, also comprising medications [3-5]. The edematous fluid is rich in plasma proteins and inflammatory cells. There is increased local production of cytokines and growth factors, altered immunoreactivity, collagen deposition, and increased activity of matrix metalloproteinases (especially MMP-2). Unrestrained metalloproteinase activity may contribute to the breakdown of extracellular matrix, promoting development of ulcers and impaired healing [3,4]. Under alpelisib treatment, inhibition of PI3Kα signaling may cause intrinsic structural changes to the epidermis and dermis [1] and could be a trigger of inflammation and skin breakdown. Skin ulcers in the proposito differ from "venous" ulcers, ischemic ulcers, neutrophilic dermatoses, infection-induced, and neoplastic skin ulcers [6] and there was no evidence for either in this patient. According to the Naranjo scale for estimating the probability of adverse drug reactions [7], a "possible' causal determinism can be implemented between alpelisib treatment and stasis dermatitis. Absence of an alternative etiology of stasis dermatitis and skin ulcers provides collaborative evidence. Also, the subsequent course was instructive: three months after discontinuation of alpelisib the skin ulcers were healed. During another 6 months there was no recurrence of skin ulcers. Among cutaneous adverse drug reactions, skin ulcers caused by medications used in oncology are increasingly recognized [8,9]. In the proposito, alpelisib was probably the trigger of first-time stasis dermatitis and skin ulcers, an underrecognized adverse reaction to this drug. If the causality is genuine, similar cases reports may multiply, expanding our knowledge and understanding.

Conflict of Interest

The author declares not to have conflict of interest.

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