Eruptive keratoacanthomas secondary to topical 5-fluorouracil application

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Key words: actinic keratosis; drug reaction; eruptive; 5-fluorouracil; keratoacanthoma; skin neoplasm.

INTRODUCTION

Keratoacanthoma (KA) is a common tumor that has been described as part of numerous syndromes as well as sporadic growths that can arise spontaneously or after trauma. While UV exposure is a predominant risk factor for KA, koebnerization or trauma-induced KAs have been reported after surgical procedures, laser therapy, and cryotherapy.[1] 5-fluorouracil (5-FU) cream is frequently used to treat actinic field damage in patients. We describe a case of 5-FU cream-induced formation of numerous KAs.

CASE REPORT

A man in his 60s with a history of eruptive and reactive KAs and squamous cell carcinoma after trauma presented with a 2-week history of painful, pruritic, and enlarging nodules on his left arm during the use of 5% 5-FU cream to treat multiple actinic keratoses on both forearms. He began to develop the lesions 2 weeks into a 4-week course, which he completed. Of note, he had a history of both spontaneous KAs and KA-like squamous cell carcinomas as well as trauma-induced (after excision and injury) lesions on his upper and lower extremities for the preceding 5 years. Physical examination revealed multiple, tender, hyperkeratotic, and erythematous crateriform nodules with central ulceration on the left forearm at the sites of 5-FU application for actinic keratoses (Fig 1). Biopsy findings were consistent with KA. While he did have a history of eruptive KAs (between 10 and 15 lesions), he had never developed so many large, painful lesions over such a short period of time. There are multiple reports of eruptive KA being associated with internal malignancy. Given this abrupt eruption and significant smoking history (>30 pack years), a low-dose chest computed tomography scan was obtained and was unremarkable. The patient was also up to date with his age-appropriate malignancy screening. Review of systems was non-contributory. Of note, he had used 5-FU cream on his face before and did not have a similar reaction.

Abbreviations used:

KA: keratoacanthoma
5-FU: 5-fluorouracil

Because of the clinical and histopathologic features, the patient was diagnosed with eruptive KAs secondary to topical 5-FU application for the treatment of actinic keratoses. He was treated with acitretin 10 mg daily in addition to serial shave excisions followed by intralesional 5-FU, which was well tolerated and led to a decrease in pruritus. One month after initiating therapy, there was a decrease in the size and number of lesions, resulting in an overall improvement in skin disease (Fig 2).

DISCUSSION

KAs are cutaneous lesions that typically present as crateriform nodules that may regress spontaneously. Solitary lesions are most common, but when there are multiple, these have been associated with rare genetic or sporadic syndromes such as xeroderma pigmentosum, Muir-Torre syndrome, Ferguson-Smith syndrome, and Grzybowski syndrome, also known as generalized eruptive KA of Grzybowski.[1,2]

Eruptive and reactive KAs have been reported to occur in the context of several provoking factors such as immunosuppressive medications,

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Funding sources: None.
IRB approval status: Not applicable.

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JAAD Case Reports 2021;16:19-21.
2352-5126

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https://doi.org/10.1016/j.jdcr.2021.08.001

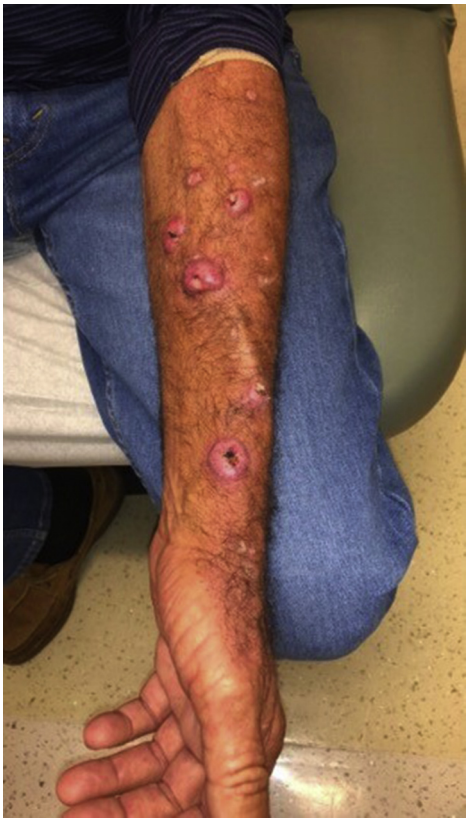

Fig 1. Eruptive keratoacanthomas: multiple hyperkeratotic and erythematous crateriform nodules with central ulceration on the left forearm at the sites of 5-fluorouracil application.

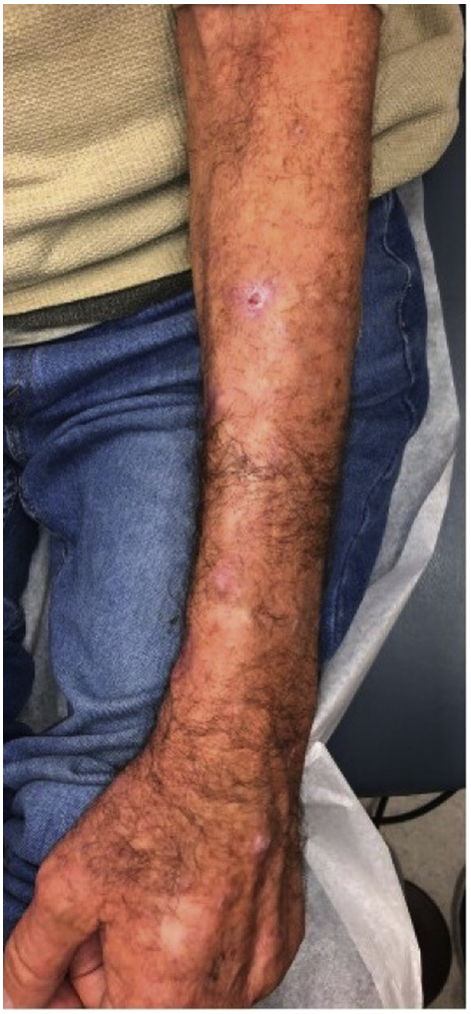

Fig 2. Eruptive keratoacanthomas: Sustained improvement of cutaneous lesions at 3 months following the initial eruption.

electromagnetic radiation (UV-A, UV-B, and UV-C), trauma (surgical procedures, chemical peels, ablative lasers, photodynamic therapy, and topical medications such as imiquimod), BRAF inhibitors, vismodegib, pembrolizumab, and foreign bodies (tattoos and fillers).[2,3] The most likely provoking factor explaining the development of our patient's reactive KAs is trauma due to the exuberant inflammatory response caused by topical 5-FU application. A single report of a similar response to topical imiquimod has been reported where a patient used the cream twice weekly for 3 months. After several weeks of application, numerous KAs developed at treatment sites on the dorsal aspects of her hands and legs. All of the lesions were excised and did not recur.[4]

An association between internal malignancy and KAs has been reported in a few different settings. First, it has been well-described in Muir-Torre syndrome (sebaceous tumors, KAs, and internal malignancy), where patients are at increased risk for developing solid organ tumors involving predominantly the gastrointestinal and genitourinary tract.[5] Eruptive KAs have also been reported as cutaneous metastases from lung cancer.[6] Finally, there are numerous reports of eruptive KAs being associated with different types of internal neoplasms including ovarian cancer, colon cancer, and lymphoma.[7-10] Given our patient's abrupt onset of more than a dozen lesions in addition to his significant smoking history, we worked with his primary care provider to perform an age-appropriate malignancy screening, which was unrevealing.

Treatment of multiple KAs often includes systemic acitretin or other retinoids, which may be combined with IL 5-FU for improved outcomes. Alternatively, topical 5-FU can also be used to treat KAs.[1] To our knowledge, no other cases of eruptive KAs secondary to topical 5-FU application for the treatment of actinic keratoses have been documented in the literature. Dermatologists should be aware of the

potential for this paradoxical reaction occurring in patients with a history of eruptive and reactive KAs being treated with topical 5-FU.

Conflicts of interest

None disclosed.

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