

BRIEF ARTICLES

Successful Treatment of Multiple Post-Operative Keratoacanthomas with Topical 5-FluorouracilNelson C. Ugwu, BS¹, Nour Kibbi, MD²¹Department of Dermatology, Yale University School of Medicine, New Haven, CT²Stanford Dermatologic Surgery, Redwood City, CA**ABSTRACT**

Keratoacanthomas (KAs) are fast-growing tumors and can be difficult to distinguish from squamous cell carcinomas (SCCs). Most KAs are sporadic, but KAs may also arise following traumatic procedures. We report the case of a 94-year-old male who developed multiple KAs following surgical excision of an SCC on the right lower extremity. The patient declined additional procedures including biopsy, surgery, or intralesional therapy. He was started on 5% topical FU using a 2 week on, 2 week off regimen for 16 weeks with resolution of disease. No recurrence was noted at 13 months. Topical 5-FU is a conservative, non-invasive treatment for post-traumatic KAs that is particularly suitable in the elderly, in whom the risks and morbidity from surgical or other non-invasive approaches are worth considering.

INTRODUCTION

Keratoacanthoma (KA) is a rapidly growing, low-grade variant of cutaneous squamous cell carcinoma that often arises as a solitary lesion on sun-exposed skin in adults over age 40. Following a rapid growth phase, KAs may spontaneously regress, but predicting which tumors will do so is challenging. For this reason, KAs are often treated with surgery, however, non-surgical modalities have also been employed, including intralesional 5-FU, intralesional methotrexate, or oral retinoids. Response rates with these non-surgical therapies vary, ranging from 83 to 100%.¹

Most KAs arise sporadically, but KAs have also been reported as a reactive phenomenon following traumatic procedures, such as skin surgery,² skin grafting,³ laser resurfacing,⁴ and spontaneous injuries such as piercing or scratch injuries.⁵ Here, we

present the case of a very elderly gentleman with multiple post-operative eruptive KAs treated successfully with topical 5-fluorouracil and review the literature on KAs treated with topical 5-fluorouracil.

CASE PRESENTATION

A 94-year-old healthy man presented with a 3-4 week history of five rapidly enlarging, crateriform nodules with central hemorrhagic crust on the right lower leg (Figure 1A). Some of the lesions were painful to the touch. Approximately 6 weeks prior, the patient had undergone Mohs micrographic surgery (MMS) for a well-differentiated squamous cell carcinoma of the lower extremity that was repaired with a linear closure. The patient had a history of multiple non-melanoma skin cancers treated with MMS. He declined further surgical intervention on the new lesions, including

Figure 1. (A) On the right lower leg were five crateriform friable nodules which developed following excision of a well-differentiated squamous cell carcinoma. (B) Following two months of cyclical topical 5% 5-fluorouracil therapy, there was a notable reduction in nodule size, crusting of the lesions, and a moderate irritant reaction of the lower extremity. (C) The lesions resolved after four months of cyclical therapy.



biopsy and did not wish to undergo any systemic therapy. He had previously tried tazarotene 0.1% cream without improvement. He elected to initiate 5-fluorouracil 5% cream twice daily on an alternating 2 weeks on then 2 weeks off regimen without occlusion. Two months following initiation of therapy, he was noted to have a significant response with reduction in nodule size and a moderate irritant reaction of the lower extremity (Figure 1B). He declined topical corticosteroids for the irritant reaction and used emollients as needed between the 5-fluorouracil treatments. Four months after presentation, the lesions had resolved (Figure 1C), and the patient was

using 5-fluorouracil as needed. The patient was seen in close clinical follow-up until 13 months following initial presentation and was noted to have no recurrence. He had continued to use topical 5-fluorouracil for other keratotic lesions on his upper and lower extremities that failed to regress spontaneously. He died two months later of unrelated causes.

DISCUSSION

This case report highlights the phenomenon of multiple post-operative KAs arising in an elderly man. While biopsy and/or additional

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Table 1. Summary of 43 keratoacanthoma cases treated with topical 5-fluorouracil (5-FU) therapy.

Authors	Number of patients	Mean Age (range)	Sex	Tumor location	Number of tumors	Sporadic/Triggering event	Treatment regimen	Adjuvant treatment	Patients achieving CR	Overall follow-up	Additional treatments for patients with incomplete responses
Grupper 1970 ⁸	15	59.9 (38-80)	9M, 6F	head (13) and upper extremity (2)	solitary lesions	9 sporadic, 6 after initial total excision	5% 5FU ointment 1-2 times daily for 1-2 weeks then 2% 5-FU ointment or 2% 5-FU gel under occlusion for 1-4 weeks	None	12/15 at 3-5 weeks	2-18 months. No recurrence	2/3 patients underwent surgery at 3 weeks (1 PR, 1 no response to 5-FU). 1/3 continued 5-topical FU
Goette et al 1982 ⁹	14	66 (44-80)	6M, 8F	head (2), neck (2), upper extremity (5), lower extremity (3), chest (1), shoulder (1)	solitary lesions	sporadic	20% 5FU ointment, 2-3 times daily for 2-4 weeks, (-) or (+) occlusion	None	14/14 at 1-7 weeks	1-7 weeks	none
Gray et al 1999 ¹²	2	74 (68-80)	2M	head (2), neck (2), forearm and hand (5), lower leg (3), chest (1), shoulder (1)	solitary lesions	sporadic	5% 5FU cream daily without occlusion for 4-8 weeks	none	1/2 at 8 weeks	8 weeks	1 patient underwent biopsy with electrodesiccation at 4 weeks after PR
Thompson et al 2014 ¹¹	10	74.4 (52-92)	9F, 1M	lower extremity (5) and head (5)	solitary lesions	sporadic	short-contact (1 hr) topical 5% 5-fluorouracil cream twice daily until resolution	none	9/10 at 4-6 weeks	4-6 weeks	1 patient underwent Mohs surgery after 1 week of 5-FU
Silva et al 2019 ⁷	1	64	F	lower extremity	1	photodynamic therapy for porokeratosis of Mibelli	0.5% 5FU + 10% salicylic acid	acitretin 0.6-1 mg/kg/day prior to 5-FU	1/1 at 8 weeks	12 months. No recurrence	none
Ugwu et al 2020	1	94	M	right lower extremity	5	Surgery for SCC on the right lower extremity	5% 5-FU cream daily for 2 weeks followed by 2 weeks without treatment for 4 months	none	1/1 at 16 weeks	13 months. No recurrence	none

CR – complete response; PR – partial response; M – male; F – female; 1 hr – 1 hour; SCC – squamous cell carcinoma

surgery were among the treatment options discussed with the patient, these approaches carried significant risk. For one, further surgical intervention (biopsy or excision) may have also incited more lesions. Secondly, excision of multiple lesions would have resulted in large wounds on the lower extremity, which may have been further complicated by edema, delayed wound healing, and infection of the lower extremity. Alternative non-surgical treatments also carried significant limitations. Intralesional 5-fluorouracil is painful to administer and requires repeated injections and office visits. Topical 5-fluorouracil with zinc oxide wraps, also known as "chemo wraps," are tedious to apply properly, require repeated applications in the office, and result in significant discomfort⁶. Oral retinoids, which have been used alone or in combination of topical agents, carry significant risks, such as hypertriglyceridemia, bony pain, and transaminitis, require repeated laboratory monitoring, and can result in significant xerosis, all of which are significant risks in an elderly patient^{2,7}. Topical 5-fluorouracil is an ideal medication: since the diseased area is visible to the patient, the medication can easily be applied and adverse events, namely irritant dermatitis, can be readily monitored. We utilized a cyclical application (2 weeks on, 2 weeks off) schedule to allow a period of recovery in between treatment intervals.

To the best of our knowledge, this is the first case outlining the successful treatment of multiple, post-operative KAs with topical 5-fluorouracil. There are 43 published cases of KAs treated with topical 5-fluorouracil (Table 1)⁷⁻¹². The average age among the cohort was 68.8 years with a female to male ratio of 1.3. The most common tumor locations in patients were the head (51.1%), lower extremities (23.3%) and upper extremities (16.2%). The majority of reported lesions

were solitary (98%). Only 11.6% of patients developed KAs following a surgical procedure. The most commonly used 5-fluorouracil formulations were the 5% ointment (35%), 20% ointment (33%) and 5% cream (30%). One patient received acitretin for 1 month prior to initiating 5-fluorouracil treatment. The overall response rate was 95.3% (41/43 patients) with 90.7% (39/43) achieving complete response between 2 and 8 weeks of therapy. Lesions with partial or no response to 5-fluorouracil were treated with surgical excision (2) or shave biopsy with electrodesiccation and curettage (1). One patient opted for Mohs surgery after one week of 5-fluorouracil therapy. Over the follow-up period which ranged from 2 to 18 months, there were no reported recurrences.

This case highlights the successful and cyclical use of topical 5-fluorouracil in the treatment of post-operative eruptive KAs. This conservative, non-invasive treatment is particularly suited for the very elderly and for post-traumatic KAs. Patient selection is critical, and close follow-up is recommended to refine the treatment schedule and interval between treatment courses. Further systematic study into this phenomenon is needed to better outline treatment parameters and resolve the question of whether, under certain circumstances, eruptive KAs may regress spontaneously.

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