5-FU Treatment Protocol for Keratoacanthoma Arising in Surgical Incisions

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Abstract
Keratoacanthoma is a cutaneous lesion that erupts in photodamaged skin. Trauma from surgical excisions is thought to induce keratoacanthomas through the Koebner phenomenon. This creates a therapeutic challenge in patients with keratoacanthomas in or around surgical sites due to the risk of further keratoacanthoma formation. The authors propose a simple recipe using intralosomal 5-fluorouracil as an alternative treatment in these problematic cases.

Introduction
Keratoacanthoma (KA) is an epidermal tumor characterized by rapid growth over several weeks followed by spontaneous regression.1 These lesions are considered a variant of squamous cell carcinoma (SCC) and thought to be of follicular origin.2,3 Classically, they affect middle-aged, fair-skinned individuals, presenting in sun-exposed areas, commonly the anterior lower legs and forearms. The link between KA and UV light is well established, with lesions presenting in areas of the skin with sun damage and increased incidence of KA in the summer and fall.4,5 Keratoacanthomas have also been associated with immunosuppression, electromagnetic radiation, chemicals such as tar, drugs influencing cell cycle such as BRAF inhibitors, foreign bodies such as tattoos, human papillomavirus, and trauma.6,7

Local trauma has been identified as a causative factor for the development of lesions in a wide range of dermatological conditions. Heinrich Koebner, in 1877, described emergence of psoriatic lesions following trauma to the unaffected, healthy areas of the skin of psoriatic patients.7 Since then, researchers have extensively studied Koebner response in psoriatic patients, providing insight into this phenomenon. In addition to psoriasis, two other main conditions associated with Koebner phenomenon are vitiligo and lichen planus.8 Since the time this phenomenon was first described in psoriasis, development of many other diseases following cutaneous trauma has been described in the literature, necessitating proper classification of koebnerization. In 1990, Boyd and Neldner proposed a four-group classification of Koebner phenomenon.9 The first group, the true Koebner response, includes psoriasis, lichen planus, and vitiligo and indicates the phenomenon is reproducible by a variety of insults and is not attributed to infectious agents or allergens. The second group, the pseudo-Koebner phenomenon, specifies a phenomenon that develops due to seeding of infectious agents, such as verrucae and molluscum contagiosum, to surrounding tissues. The third group, the occasional lesions after trauma, includes conditions such as Darier’s disease, erythema multiforme, and Hailey–Hailey disease in cases that meet some criteria for the Koebner response. The last group, the questionable trauma-induced response, includes a wide range of conditions described in case reports, such as dermatitis herpetiformis, pityriasis rubra pilaris, sarcoidosis, and keratoacanthoma.9

Typically, koebnerization develops within 10 days to 20 days of the inciting trauma, but it may occur rapidly, within three days, or up to two years afterward.10 It has been reported that Koebner phenomenon does not have regional predilection and has been reproduced on the trunk, extremities, and even areas spared by psoriasis, such as the face.11 Although the pathogenesis of Koebner response remains unknown, research studies have proposed several theories, including immunological, vascular, dermal, and growth-factor-involved.12 Eddy et al. performed biopsy experiments revealing vascular changes in the form of meandering capillary loops in areas that would subsequently present lesions. These findings led authors to conclude that microvascularity is altered prior to koebnerization induced by trauma.12 Furthermore, it has been reported that vasoconstrictive drugs such as epinephrine and lidocaine decrease the incidence of Koebner phenomenon.12 Reinertson suggested that vascular trauma alone is not sufficient to induce psoriatic lesions after the trauma.13 In his study, unaffected skin of 20 psoriasis patients was injured in three ways: 1) suction until confluent petechiae were formed; 2) scarification with production of superficial bleeding; and 3) removal of layers of stratum corneum to approximately the level of the stratum granulosum or upper stratum Malpighii. In all cases, Koebner phenomenon failed to occur in sites of petechiae; however, seven patients with scarification and eight patients in the third group developed the response. This led him to conclude that vascular trauma without epidermal damage did not induce Koebner response.13

Several reports in the published literature describe KA lesions arising from a surgical scar or developing in the previously unaffected areas surrounding excision sites. For example, Kimyai-Asadi et al. reported a case of KA arising from a scar after surgical excision of SCC in situ. Importantly, KAs developed despite clear histological margins, demonstrating that surgical trauma preceded the development of KA.14 Goldberg et al. reported six cases of KAs that developed in and around healing and healed surgical sites after treatment of skin cancer with Mohs micrographic surgery.15 Similarly to previous report, cases reported by Goldberg revealed clear histological margins following surgery for SCC, lentigo maligna and basal cell carcinoma. Multiple KAs developed in some cases, indicating that new lesions are newly formed and likely due to traumatic insult. Clark et al. reported a case of a patient who developed eruptive keratoacanthomatous atypical squamous proliferations in split-thickness skin graft donor and recipient sites after SCC excision.16 The authors described a case of a patient who required second skin graft, which was harvested from contralateral lower extremity, because patient underwent multiple excisions for multiple KAs. Furthermore, patient’s donor site on the contralateral extremity also developed multiple KAs, demonstrating that surgical excisions were the likely cause of koebnerization.16 The cases presented in this article reveal KAs developed in or around surgical sites are likely the result of the Koebner phenomenon. Surgical excision is the treatment of choice for de-novo developed solitary KA. In addition other methods are used such as topical steroids under occlusion, cryotherapy, lasers and even photodynamic therapy.1 When a patient presents with multiple KAs, oral retinoid can be used either as monotherapy or in combination with surgery.15 However, in the setting of koebnerization as seen in our cases and those described above, surgery may not only lead to recurrence of KA due to repetitive injury to the tissue, but may also cause significant disfigurement. Therefore, recurrent KAs arising as a result of koebnerization present a therapeutic challenge.

Case Report
Patients and Treatment Protocol
For the current study, the authors treated four cases of KA in four patients, 60 years to 81 years of age, in or around post-surgical sites with intralesional 5-fluorouracil (5-FU) instead of traditional surgical excision. In each case, the previously excised lesion had clear histological margins. All patients had morphologically typical, solitary KAs (Figures 1-4 [p. 49]). Each had a pretreatment biopsy, which was histologically consistent with a KA (Figures 5, 6 [p. 49]). The KAs ranged from 0.2 cm to 0.5 cm in size. The base of each KA was infiltrated with 50 mg/ml of intralesional 5-FU using a 30-gauge needle. The total initial dose in ml was proportional to the width of the KA at the time of treatment. Using the first patient in Table 1 as an example, the KA was 0.2 cm in size at the time of treatment and was injected with 0.2 ml of 5-FU. If any portion of the lesion remained at two-week follow up, the KA was injected again using the same proportional ml-to-width infiltration. All lesions cleared after receiving between one and three treatments over a two- to six-week period. The summary of the patients and the findings can be seen in Table 1.

Discussion
Intralesional chemotherapy is the second-line option for the treatment of KA, but evidence of efficacy is limited due to a paucity of large, well-designed trials and established treatment protocols. Methotrexate and 5-FU are the preferred intralesional drugs, while intralesional
bleomycin, interferons, or corticosteroids have been used in some cases. Use of topical 5-fluorouracil for treatment of KA has also been reported. Intralesional 5-FU has been reported to have a 98% cure rate in KAs. However, reports in the published literature vary broadly in choice of 5-FU concentration and dose, frequency of treatment and duration of treatment. In this study, the authors attempted to establish a treatment protocol using intralesional 5-fluorouracil for management of recurrent KAs arising in the setting of surgical excision. 5-FU is a structural thymidine analog that acts as an antimetabolite, causing decreased DNA synthesis, a decline in cell proliferation, and death of rapidly proliferating malignant cells.

It is intuitive to assume that this mechanism is responsible for halting proliferation of rapidly growing KAs. We propose that one of 5-FU's adverse effects also contributes to the resolution of KA lesions. Cardiotoxicity, which usually presents as angina-like chest pain, occurs in cancer patients treated with 5-FU. To explore the pathophysiology of 5-FU-related cardiotoxicity, Südhoff et al. investigated the influence of intravenous chemotherapy (CTX) on the diameter of the brachial artery using high-resolution ultrasound. The investigators treated patients with malignant tumors, with 30 subjects receiving 5-FU and 30 subjects receiving non-5-FU CTX. The study revealed that half of the patients treated with 5-FU experienced a contraction of the brachial artery, while none of the patients treated with non-5-FU CTX experienced contractions. The same study also revealed that when patients received glycerol trinitrate prior to 5-FU bolus application, no contraction of the brachial artery was observed. Vasoconstriction induced by 5-FU may play an important role in stopping KA-producing koebnerization and KA regression. As mentioned earlier, vasoconstrictive drugs such as epinephrine decrease the incidence of Koebner phenomenon. Furthermore, Miller et al. showed that external pressure during the first 24 hours after trauma can prevent koebnerization. This led authors to conclude that applied pressure leads to vasoconstrictive obliteration of the vessels.

Using a 50 mg/ml preparation of 5-FU led to complete resolution of the recurrent KAs in our patients. It could be hypothesized that 5-FU's therapeutic success is owed to its dual roles as a cytotoxic anti-tumor agent and local vasoconstrictor.

It is also intriguing that while excisions in our patients led to recurrent KA-producing koebnerization, patients did not experience local KA recurrence following 5-FU injections, though needle injections lead to local trauma. This raises the possibility that the KAs observed in our patients were unrelated to koebnerization and would have developed in the absence of trauma. While trauma appears to be a necessary step for Koebner response, the question is whether the amount of trauma plays a role in inducing the response. Reports in the literature indicate that dermal injections of hyaluronidase, chymotrypsin, or methacholine failed to induce koebnerization in individuals prone to Koebner response. Furthermore, Eddy et al. demonstrated that a 2-mm incision through the epidermis produced a smaller lesion than an 8-mm incision. The investigators also revealed that the overall trauma was directly associated with how fast koebnerization occurred. Similarly, Lipschutz discovered that the degree of Koebner reactivity was associated with the depth of trauma, with patients producing no response when trauma was limited to scraping of the stratum corneum and some response when trauma involved the Malpighian layer. The findings described in our patients as well as those described above suggest that not every type of trauma leads to Koebner phenomenon.

**Conclusion**

Intralesional 5-fluorouracil is an effective, easily administered, and well-tolerated treatment modality for keratoacanthoma, producing excellent results while minimizing occurrence of new KAs in the setting of koebnerization. It is important to keep this therapeutic protocol in mind when treating KA lesions.

| Table 1. Keratoacanthoma treatment: data on injections of intralesional 50 mg/ml 5-fluorouracil |
|---|---|---|---|---|---|---|
| Case | Age/Sex | KA Diameter | Volume | Location | Injections | Wks. to Clear |
| 1 | 60/M | 0.2 cm | 0.2 ml | Left forearm | 1 | 2 |
| 2 | 71/F | 0.4 cm | 0.4 ml | Right forearm | 3 | 6 |
| 3 | 81/M | 0.5 cm | 0.5 ml | Left shin | 3 | 6 |
| 4 | 64/M | 0.3 cm | 0.3 ml | Right shin | 2 | 4 |

**5-FU TREATMENT PROTOCOL FOR KERATOACANTHOMA ARISING IN SURGICAL INCISIONS**
References