

Multiple Keratoacanthomas Occurring in Surgical Margins and De Novo Treated With Intralesional Methotrexate

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PRACTICE POINTS

- Keratoacanthomas (KAs) are rapidly growing tumors most prominently found on sun-exposed areas but also may develop in areas of trauma including burns, laser treatment, radiation, and surgical margins from excisional biopsies or skin grafting.
- Intralesional methotrexate is a potential alternative to surgical treatment of KAs as a less invasive and less costly treatment modality with decreased morbidity for multiple KAs.
- Isotopic response refers to the occurrence of a new skin disorder arising at the site of another unrelated and already healed skin disease. Isomorphic response indicates the appearance of typical skin lesions of an existing dermatosis at sites of injuries.

Keratoacanthomas (KAs) are common skin lesions known for their rapid growth and spontaneous regression. Keratoacanthomas also can occur in sites of prior trauma, such as surgical scars. We report a case of multiple KAs occurring in the site of trauma from a prior surgery and de novo as well as the response to treatment with intralesional methotrexate (MTX).

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Keratoacanthomas (KAs) are rapidly growing tumors most prominently found on sun-exposed areas of the skin. The normal

progression of a KA is to show rapid growth followed by spontaneous resolution.¹ Most KAs are solitary; however, there are several variants of multiple KAs including the familial Ferguson-Smith type, Gryzbowski syndrome (generalized eruptive KAs), KA centrifugum marginatum, Muir-Torre syndrome, and xeroderma pigmentosum.²⁻⁴ Keratoacanthomas also may develop in areas of trauma, including burns, laser treatment, radiation, and surgical margins from excisional biopsies or skin grafting.⁵ Treatment of multiple KAs can be difficult due to a potentially large field size and number of lesions.⁶ We present a case of multiple KAs developing both in the surgical margins and de novo that responded dramatically to treatment with intralesional methotrexate (MTX).

Case Report

A 55-year-old man with a history of a surgically treated squamous cell carcinoma (SCC) on the anterior aspect of the right leg developed multiple nodules involving the surgical scar. He previously underwent Mohs micrographic surgery (MMS); within a month after the second surgery the patient

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noticed increased pruritus along with scaly pink changes at the site of the surgical scar.

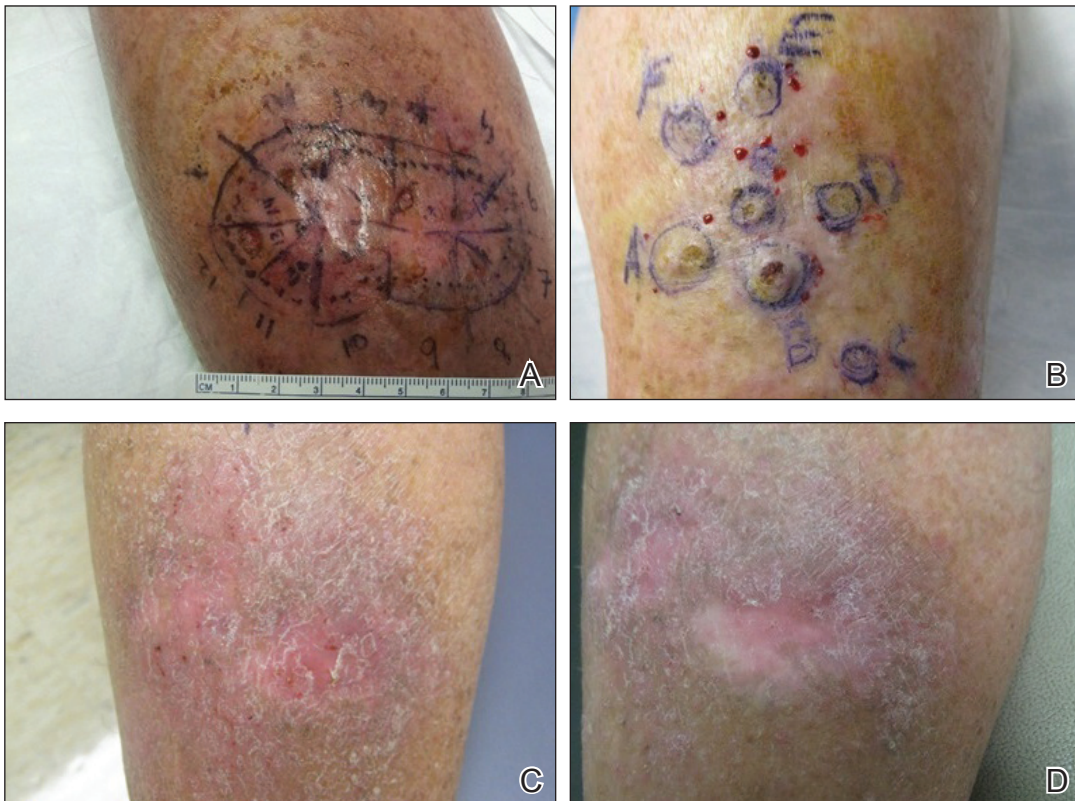
One month prior to presentation, biopsies from the anterior aspect of the right leg demonstrated well-differentiated SCC and he was subsequently treated with MMS; however, examination 1 month after MMS revealed an 11×7-cm indurated plaque with multiple nodules ranging from 1 to 2 cm near the periphery of the plaque with central atrophy and scarring, reminiscent of KA centrifugum marginatum (Figure, A). In a similar fashion, an 8×5-cm plaque composed of 7 nodular areas was noted on the posterior aspect of the right leg (Figure, B). The patient denied any history of trauma to this area. There was no palpable regional lymphadenopathy and the remainder of the skin examination was normal, except for signs of venous stasis in both legs.

Based on the location and morphology of the lesions, the clinical presentation was consistent with multiple KAs. Histologic examination from punch biopsies taken from the plaque's periphery demonstrated well-differentiated SCC (KA type), as well as a lichenoid inflammatory

process, epidermal hyperplasia, and cystic and endophytic squamous proliferation suggestive of hypertrophic lichen planus (HLP).

In consideration of the size and number of the lesions as well as the prolonged wound healing with prior surgery, the patient consented to treatment with intralesional MTX (1 mL of 12.5 mg/mL every 2 weeks) rather than undergoing further surgery. The MTX injection was distributed between the lesions on the anterior and posterior aspects of the lower right leg. At each injection session, the size, thickness, and nodularity of the tumor decreased with markedly less pruritus and symptomatic relief was achieved. After 3 injection sessions, resulting in a total of 3 mL of 12.5 mg/mL of MTX, biopsies were taken from the residual atrophic scar on the anterior aspect of the right leg and the remaining 3 papules on the posterior aspect of the right leg to rule out HLP and invasive SCC. The pathology report commented on the presence of prurigo nodules without any evidence of SCC.

At 3-month follow-up, the patient demonstrated no new lesions or recurrence (Figure, C and D).



Initial presentation after Mohs micrographic surgery of 2 lesions of keratoacanthoma centrifugum marginatum on the anterior (A) and posterior aspects of the right leg (B). At 3-month follow-up, a well-healed surgical site with no evidence of cancer recurrence was noted following treatment with 3 rounds of intralesional methotrexate (C [anterior] and D [posterior]).

The right leg continued to heal with scarring and postinflammatory pigmentary changes. The patient was monitored for recurrence and to determine the diagnosis of HLP.

Comment

We report the development of multiple KAs arising both from within surgical margins and de novo, and resolution with intralesional MTX. Keratoacanthomas, especially various KA types, have been observed to develop due to various types of trauma, including sites of surgical scars, lichen planus, tattoos, thermal burns, radiation, and discoid lupus erythematosus, and within skin grafts and donor sites.⁵⁻¹⁹

Hypertrophic lichen planus is a chronic variant of lichen planus that often is found on the pretibial areas of the lower legs.¹³ Both SCC and reactive KAs have been observed to develop within lesions of HLP.¹⁴ Our pathologist commented on the presence of a lichenoid infiltrate with necrotic keratinocytes and epidermal hyperplasia suspicious for HLP, with a small focus of cystic and endophytic squamous proliferation. The latter lacked notable atypia or an invasive component and could represent an irritated infundibular cyst versus an early evolving KA.

The lichenoid inflammation is suspicious for HLP, which has been associated with eruptive KAs¹³⁻¹⁶ and may have contributed to the development of persistent KAs in our patient, both in sites of surgical scars (the anterior aspect of the leg) and in uninvolved skin (the posterior aspect of the leg). Trauma from the prior surgery may have stimulated a local inflammatory response and, if coupled with a pre-existing underlying chronic inflammatory condition such as HLP, may have triggered the development of new lesions on the posterior leg. Skin pathergy reactions also are caused by an upregulated inflammatory response, which is reduced with immunosuppressive agents such as MTX.¹²

In our patient, there was both an isotopic and isomorphic response. The term *isotopic response* refers to the occurrence of a new skin disorder at the site of another unrelated and already healed skin disease. It was first defined by Wolf and Wolf²⁰ in 1985 and hence is also known as Wolf isotopic response. The isotopic response in our patient occurred in the setting of lichen planus. The isomorphic response indicates the appearance of typical skin lesions of an existing dermatosis at sites of other skin injuries.

Initially, we thought the patient had recurrence of SCC, but with the rapid development of multiple lesions, the diagnosis of multiple KAs was more likely. Kimyai-Asadi et al⁸ demonstrated that surgical trauma can precede the development of KAs, as

they reported a patient who developed a KA at an excision site. Tamir et al⁷ reported the simultaneous appearance of KAs in burn scars and skin graft donor sites 4 months after a 40% total body surface area burn. Hamilton et al¹¹ described surgical trauma from a split-skin graft donor site as a trigger for the onset of a KA.

Multiple treatment alternatives exist for KAs, with the standard of care for large or high-risk KAs being excisional surgery^{21,22}; however, other approaches may need to be considered in certain cases, such as with multiple KAs in which lesions may be large and extensive, thereby yielding poor cosmetic outcomes, or with increased surgical risk.²³ Furthermore, multiple KAs that develop in the setting of surgical scars require special consideration. Topical 5-fluorouracil, various systemic and intralesional agents (eg, retinoids, interferon, bleomycin, MTX), laser therapy, electrodesiccation and curettage, radiotherapy, and photodynamic therapy all have been reported as methods employed for the treatment of KA.²³⁻²⁷ Goldberg et al⁵ reported cases of resolution of eruptive KAs arising in both surgical and nonsurgical sites with a combination of deep shave excision, MMS, curettage and desiccation, and oral isotretinoin.

For our patient, we opted for treatment with intralesional MTX, both due to its effectiveness for solitary KAs and reasonably decreased risk of morbidity compared to surgical excision of regions of the pretibial calves. Treatment with MTX would not have been attempted if there was any clinical doubt that the lesions were not the well-differentiated KA type. Also, we had a low threshold for discontinuing therapy and reverting to MMS treatment if any of the lesions displayed a paradoxical growth post-MTX treatment or failed to respond after 3 treatments. Intralesional MTX is less invasive, relatively inexpensive, and a treatment modality with decreased morbidity for KAs, especially for multiple KAs. It should be considered as a potential alternative to surgery in such cases.²³⁻²⁷

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