Concurrent Keratoacanthomas and Nonsarcoidal Granulomatous Reactions in New and Preexisting Tattoos

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PRACTICE **POINTS**

- Keratoacanthomas (KAs) are common keratinizing, squamous cell lesions of follicular origin distinguished by their eruptive onset, rapid growth, and spontaneous involution.
- The etiology of KAs remains controversial, but several factors have been correlated with their development, including UV light exposure, chemical carcinogenesis, genetic predisposition, viruses (namely human papillomavirus infection), immunosuppression, scarring disorders, and trauma (including tattoos).
- Because of the unusual histology of KAs and their tendency to spontaneously regress, it is not totally understood where they fall on the benign vs malignant spectrum. Our case adds additional weight to the idea that some KAs are primarily reactive phenomena sharing features of other reactive cutaneous proliferations such as foreign body granulomas.

To the Editor:

Cutaneous reactions to tattoos are common and histologically diverse. As outlined by Jacob,[1] these reactions can be categorized into 4 main groups: inoculative/infective, hypersensitive, neoplastic, and coincidental. A thorough history and physical examination can aid in distinguishing the type of cutaneous reaction, but diagnosis often requires histopathologic clarification. We report the case of a patient who presented with painful indurated nodules within red ink areas of new and preexisting tattoos.

A 48-year-old woman with no prior medical conditions presented with tender pruritic nodules at the site of a new tattoo and within recently retouched tattoos of 5 months' duration. The tattoos were done at an "organic" tattoo parlor 8 months prior to presentation. Simultaneously, the patient also developed induration and pain in 2 older tattoos that had been done 10 years prior and had not been retouched.

Physical examination revealed 2 smooth and serpiginous nodules nested perfectly within the new red tattoo on the left medial ankle (Figure 1A). Examination of the retouched tattoos on the dorsum of the right foot revealed 4 discrete nodules within the red, heart-shaped areas of the tattoos (Figure 2A). Additionally, the red-inked portions of an older tattoo on the left lateral calf that were outlined in red ink also were raised and indurated (Figure 3A), and a tattoo on the right volar wrist, also in red ink, was indurated and tender to palpation. The remainder of the physical examination was normal.

The lesions continued to enlarge and become increasingly painful despite trials of fluticasone propionate cream 0.05%, clobetasol propionate gel 0.05%, a 7-day course of oral levofloxacin, and a 10-day course of oral amoxicillin-clavulanate. Ultimately, a shave biopsy from the new tattoo on the left medial ankle revealed an early keratoacanthoma (KA)(Figure 1B). Subsequent shave biopsies of the retouched tattoos on the dorsal foot and the preexisting tattoo on the calf revealed KAs and a granulomatous reaction, respectively (Figures 2B and 3B).

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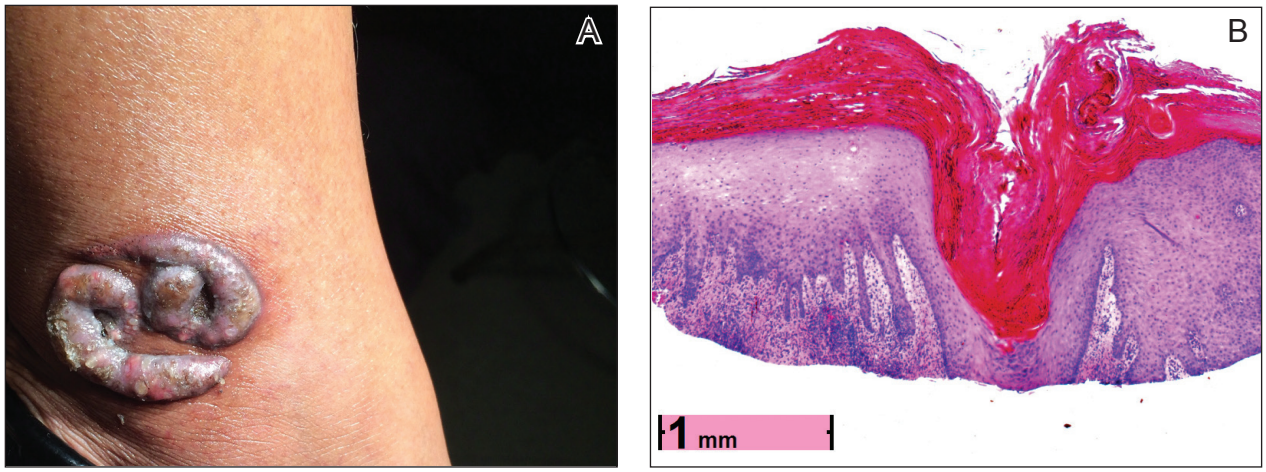

FIGURE 1. A, Discrete, smooth, and serpiginous nodules nested perfectly within the new red tattoo on the left medial ankle, measuring approximately 4×3 cm in diameter. B, A shave biopsy revealed crateriform neoplasm in the dermis composed of aggregates of 2 types of atypical keratinocytes, including ones with abundant eosinophilic cytoplasm and basal ones with large hyperchromatic nuclei, consistent with an early keratoacanthoma (H&E, original magnification ×2.2).

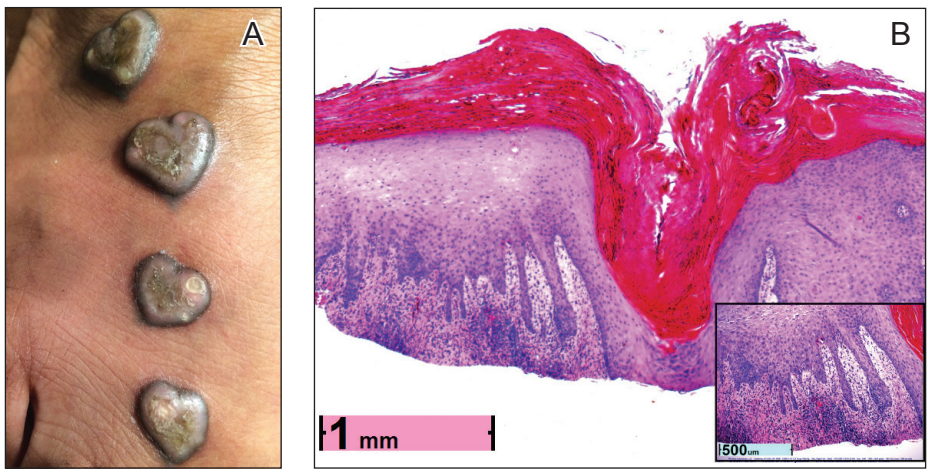

FIGURE 2. A, Four discrete nodules within the red, heart-shaped areas of retouched tattoos on the dorsum of the right foot, measuring 1.0 to 1.5 cm in diameter. B, A shave biopsy revealed contiguous dilated follicular infundibula with atypical keratinocytes that had hyperchromatic nuclei, consistent with a keratoacanthoma, as well as a lymphocytic infiltrate in the dermis above a dense infiltrate of lymphocytes and histiocytes (H&E, original magnification ×2.5 [original magnification ×6.2]).

The left ankle KA was treated with 2 injections of 5-fluorouracil without improvement. The patient ultimately underwent Mohs micrographic surgery of the left ankle KA and underwent total excision with skin graft.

The development of KAs within tattoos is a known but poorly understood phenomenon.[2] Keratoacanthomas are common keratinizing, squamous cell lesions of follicular origin distinguished by their eruptive onset, rapid growth, and spontaneous involution. They typically present as solitary isolated nodules arising in sun-exposed areas of patients of either sex, with a predilection for individuals of Fitzpatrick skin types I and II and in areas of prior trauma or sun damage.[3]

Histologically, the proliferative phase is defined by keratin-filled invagination of the epidermis into the dermis, with areas of hyperkeratosis, acanthosis, and mitotic activity within the strands and nodules. A high degree of nuclear atypia underlines the diagnostic difficulty in distinguishing KAs from squamous cell carcinomas (SCCs). A fully developed KA has less prominent cellular atypia and a characteristic buttressing lip of epithelium extending over the edges of an irregular, keratin-filled crater. In the final involution stage of KAs, granulation tissue and fibrosis predominate and apoptotic cells may be noted.[4]

The etiology of KAs remains controversial, but several factors have been correlated with their development, including UV light exposure, chemical carcinogenesis, genetic predisposition, viruses (namely human papillomavirus infection), immunosuppression, treatment with BRAF inhibitors, and trauma. Keratoacanthoma incidence also has been associated with chronic scarring diseases such as discoid lupus erythematous[5] and lichen planus.[6] Although solitary lesions are more typical, multiple generalized KAs can arise at once, as observed in generalized eruptive KA of Grzybowski, a rare condition, as well

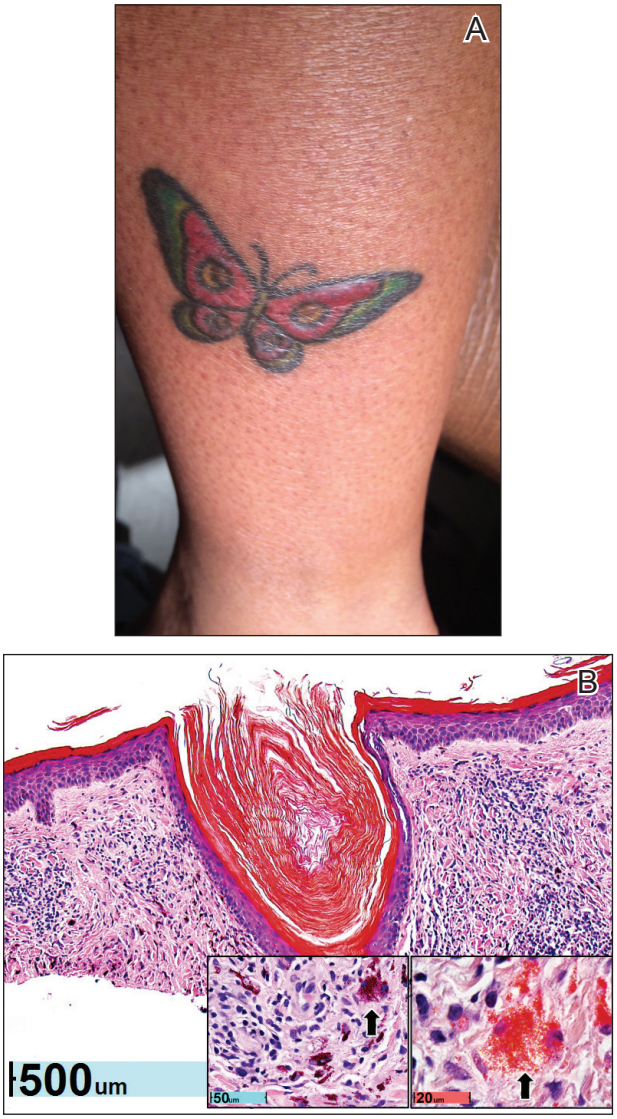

FIGURE 3. A, Raised and indurated borders within the red ink areas of a 10-year-old tattoo on the left lateral calf that had not been recently retouched. B, A shave biopsy revealed an infiltrate of histiocytes with granulomas (H&E, original magnification ×7.3). Multinucleated cells with granular red foreign matter were seen within some histiocytes, consistent with a granulomatous foreign body reaction (arrow)(left inset, original magnification ×86). No neoplasm was noted. Polarized light examination revealed granular refractile foreign matter in the tissue, which glowed a fluorescent coral color (arrow)(right inset, original magnification ×122).

as in the multiple self-healing epitheliomas seen in Ferguson-Smith disease.

Because of the unusual histology of KAs and their tendency to spontaneously regress, it is not totally understood where they fall on the benign vs malignant spectrum. Some contest that KAs are benign and self-limited reactive proliferations, whereas others propose they are malignant variants of SCC.[3,4,7,8] This debate is compounded by the difficulty in distinguishing KAs from SCC when specimen sampling is inadequate and given documentation that SCCs can develop within KAs over time.[7] There also is some concern regarding the remote possibility of aggressive infiltration and even metastasis. One systematic review by Savage and Maize[8] attempted to clarify the biologic behavior and malignant potential of KAs. Their review of 445 cases of KA with reported follow-up led to the conclusion that KAs exhibit a benign natural course with no reliable reports of death or metastasis. This finding was in stark contrast to 429 cases of SCC, of which 61 cases (14.2%) resulted in metastasis despite treatment.[8]

Our patient's presentation was unique compared to others already reported in the literature because of the simultaneous development of nonsarcoidal granulomatous dermatitis within the older and nonretouched tattoos. Nonsarcoidal granulomatous dermatitis, which encompasses inflammatory skin diseases with histiocytes, is a reactive cutaneous proliferation that also has been reported to occur within tattoos.[9,10] Granulomatous tattoo reactions can be further subdivided as foreign body type or sarcoidal type. Foreign body reactions are distinguished by the presence of pigment-containing multinucleated giant cells (as seen in our patient), whereas the sarcoidal type contains compact nodules of epithelioid histiocytes with few lymphocytes.[4]

The concurrent development of 2 clinically and histologically distinct entities suggests that a similar overlapping pathogenesis underlies each. One hypothesis is that the introduction of exogenous dyes may have instigated an inflammatory foreign body reaction, with the red ink acting as the unifying offender. The formation of granulomas in the preexisting tattoos is likely explained by an exaggerated immune response in the form of a type IV delayed hypersensitivity reaction triggered by reintroduction of the antigen—the red ink—in a presensitized host. Secondly, the parallel development of KAs within the new and retouched tattoos could be a result of the traumatic direct inoculation of the foreign material to which the body was presensitized and subsequent attempt by the skin to degrade and remove it.[11]

This case provides an example of the development of multiple KAs via a reactive process. Many other similar cases have been described in the literature, including case reports of KAs arising in areas of trauma such as thermal burns, vaccination sites, scars, skin grafts, arthropod bites, and tattoos.[2-4,8] Together, the trauma and immune response may lead to localized inflammation and/or cellular hyperplasia, ultimately predisposing the individual to the development of dermoepidermal proliferation. Moreover, the exaggerated keratinocyte proliferation in KAs in response to trauma is reminiscent of the Köbner phenomenon. Other lesions that demonstrate köbnerization also have been reported to occur within new tattoos, including psoriasis, lichen planus, molluscum contagiosum, and verruca vulgaris.[1,3]

Although KAs are not always a consequence of trauma among humans, trauma-induced KA has been proven as a reliable phenomenon among animal models; an older study showed consistent KA development after animal skin was traumatized from the application of chemical carcinogens.[12] Keratoacanthomas within areas of trauma seem to develop rapidly—within a week to a year after trauma—while the development of trauma-related nonmelanoma skin cancers appears to take longer, approximately 1 to 50 years later.[13]

More research is needed to clarify the pathophysiology of KAs and its precise relationship to trauma and immunology, but our case adds additional weight to the idea that some KAs are primarily reactive phenomena, sharing features of other reactive cutaneous proliferations such as foreign body granulomas.

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