Keratoacanthoma Centrifugum Marginatum: A Diagnostic and Therapeutic Challenge

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GOAL

To recognize and explain keratoacanthoma centrifugum marginatum (KACM)

OBJECTIVES

Upon completion of this activity, dermatologists and general practitioners should be able to:

1. Describe the clinical presentation of KACM.
2. Differentiate KACM from similar presenting lesions.
3. Discuss the therapeutic options for KACM.

CME Test on page 263.

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Drs. Divers, Correale, and Lee report no conflict of interest. The authors report discussion of off-label use for imiquimod, intralesional methotrexate, isotretinoin, and 5-fluorouracil cream. Dr. Fisher reports no conflict of interest.

A keratoacanthoma centrifugum marginatum (KACM) may pose a diagnostic and therapeutic challenge. Clinically and histologically, it may resemble mycobacterial or deep fungal infection or halogenoderma. Therapy can be challenging because the lesion can expand to a great size. We report on a patient with multiple lesions of KACM. The diagnostic difficulty and the therapeutic failure of imiquimod, intralesional methotrexate (MTX), and isotretinoin, as well as the therapeutic success of 5-fluorouracil (5-FU) cream, are discussed.

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Although Belisario first referred to the large annular keratoacanthoma (KA) as *keratoacanthoma centrifugum marginatum* (KACM) in 1965, a variety of names have been applied to this entity,

including *squamous cell pseudoepithelioma*, *aggregated KA*, *coral-reef KA*, *nodulo-vegetating KA*, *KA centrifugum*, and *multinodular KA*.[1,2] KACM is characterized by central regression with concomitant growth and expansion of the periphery but no tendencies toward complete regression in contrast to other types of KAs. A proper diagnosis can be challenging because clinically and histologically the lesions may resemble halogenoderma or infections such as verrucous tuberculosis or deep fungal infection. Therapy can be challenging because the lesions can reach a great size. The present case illustrates this diagnostic and therapeutic conundrum in a patient with multiple KACM.

Case Report

A 78-year-old man being treated for more than 9 years for multiple KAs on his upper and lower extremities presented with an annular plaque with an elevated crusted keratotic border on the right ankle. Over the course of a year, the plaque enlarged to measure 20 cm (Figure 1). Additional annular and arciform plaques ranging from 13 to 16 cm developed on both legs over this period. The patient's medical history included type 2 diabetes mellitus, peripheral vascular disease, hyperlipidemia, coronary artery disease, and benign prostatic hypertrophy. There was no history of internal malignancy or family history of KAs. Chromoblastomycosis, verrucous tuberculosis, and KACM were considered in the differential diagnosis. No fungi or mycobacteria were isolated in any of the several skin biopsies or cultures performed. There were frequent secondary bacterial infections of the lesions, which were treated with appropriate antibiotics.

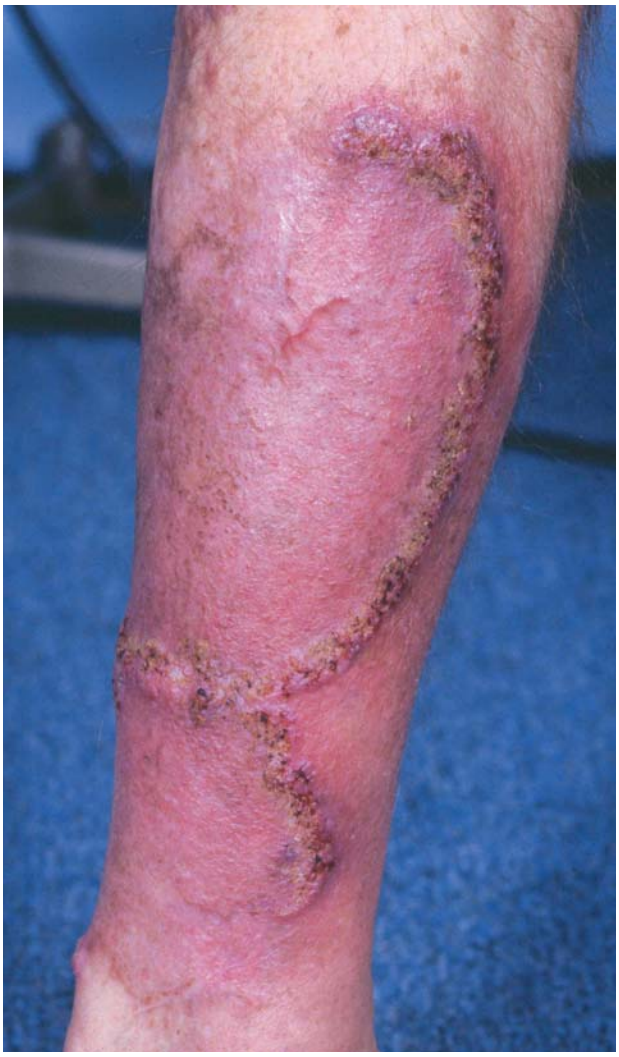

Figure 1. Right calf showing polycyclic annular plaque with crusted elevated border.

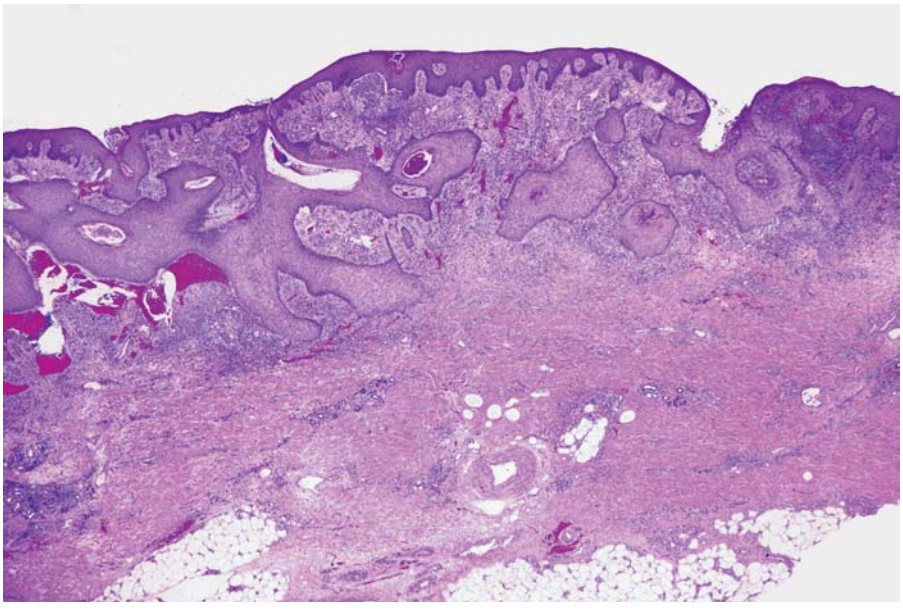

Figure 2. Jagged outlined aggregations of pale-staining keratinocytes emanating from the epidermis (H&E, original magnification ×20).

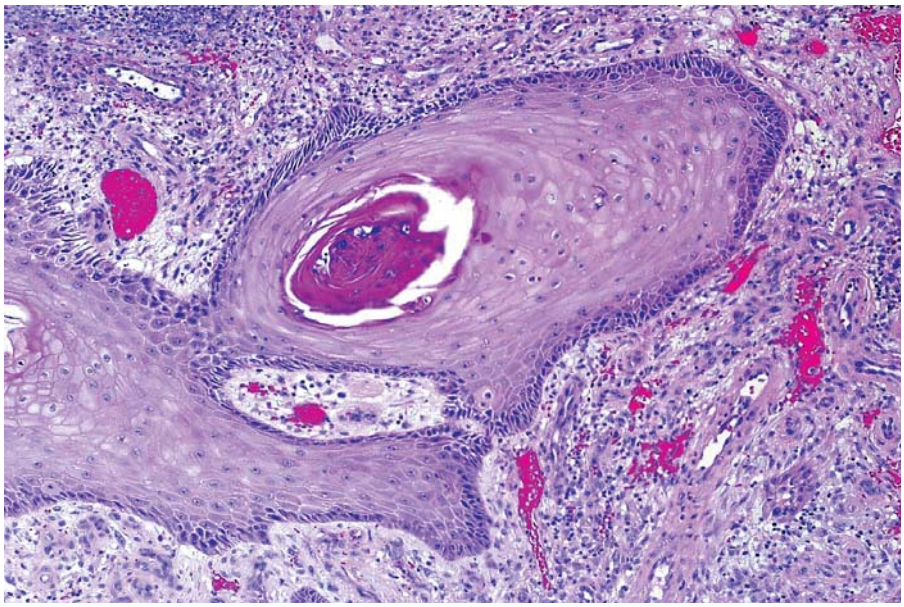

Figure 3. Jagged outlined aggregation lined by atypical keratinocytes with hyperchromatic nuclei with horn pearl and larger pale-staining keratinocytes centrally (H&E, original magnification ×100).

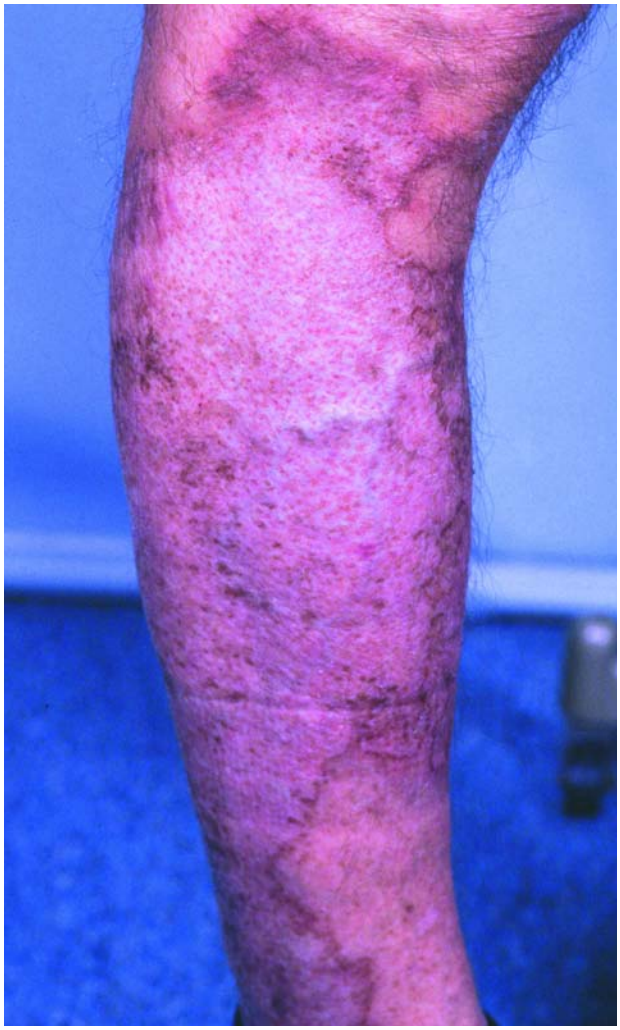

Figure 4. Right calf after 11 months of treatment with 5-fluorouracil cream.

A wedge biopsy of the large annular plaque was performed. The area of regression showed fibrosis with an overlying flattened epidermis. The peripheral expanding area showed aggregations of large epithelial cells with abundant pink cytoplasm emanating from the epidermis (Figure 2), while the trailing clearing areas showed fibrosis. Some of the aggregations had jagged outlines that were lined by atypical epithelial cells (Figure 3). Within the aggregations, there were varying degrees of keratinization with presence of parakeratotic cornified cells and neutrophils centrally (Figure 3). Although the histopathologic changes were compatible for KACM, the differential diagnosis included halogenoderma and infectious etiology such as deep fungal or mycobacterial infection. The clinical and histopathologic findings, the lack of halogen exposure, the history of multiple KAs, and the absence of organisms in tissue biopsy and culture results led to the diagnosis of multiple KACM.

Once the frequent secondary bacterial infections were under control, the patient was treated with several therapeutic agents including imiquimod cream, intralesional methotrexate (MTX), and 5-fluorouracil (5-FU) cream. Because the lesions were multiple and large, surgery was not performed. As chemoprophylaxis, isotretinoin was initiated at 40 mg/d and then increased to 60 mg/d after 4 months. The total duration of isotretinoin therapy was 13 months. Along with the usual mucocutaneous side effects, the patient experienced back pain and mild mood alteration after the dose was increased. His complete blood count, liver function tests, and serum triglyceride levels all

remained within reference range throughout the duration of therapy.

At the time of initiation of isotretinoin, MTX was injected into 2 different areas of the peripheral border of the largest lesion 3 weeks apart. The doses totaled 68 mg and 60 mg at each site, respectively. In addition, imiquimod under occlusion was applied every night to several of the lesions for the next 7 months. None of the lesions treated with either intralesional MTX or imiquimod resolved. Subsequent to the failure of imiquimod and MTX, 5-FU cream was applied to all of the annular lesions while the patient was still receiving isotretinoin therapy. Clinical response to 5-FU was apparent after 2 months. A complete clinical resolution, however, occurred over a period of 11 months (Figure 4). Isotretinoin was discontinued 5 months prior to the completion of the course of 5-FU cream.

While receiving isotretinoin therapy, the patient developed several more solitary KAs, and the annular lesions enlarged to varying sizes. The solitary KAs were managed either surgically or with liquid nitrogen, depending on the size. The new annular lesions were promptly eradicated with 5-FU cream.

Comment

Some of the largest lesions of KACM (measuring ≥20 cm) have been reported to occur on the lower extremities.[3-6] The lesions enlarged over a period of 10 months to several years with no tendency to regress completely, similar to our patient. All of these reported large lesions of the legs were successfully treated surgically. The diagnostic difficulty was not addressed in these previously reported cases; in our case, however, the initial lack of the characteristic exophytic rolled and shiny peripheral border and the frequent secondary bacterial infections contributed to the difficulty in accurate diagnosis. Initially, an infectious etiology such as chromoblastomycosis and verrucous tuberculosis was suspected. Histopathologically, the distinguishing exoendophytic architecture present at the periphery of KACM was not present; instead, the pathologic changes were confined to the superficial dermis, which consisted of jagged outlined epithelial aggregations that were difficult to distinguish from pseudoepitheliomatous hyperplasia secondary to deep fungal or mycobacterial infection or halogenoderma. The history, clinicopathologic correlation, and negative culture results eventually led to the diagnosis of KACM.

A variety of treatment modalities have been employed successfully for KAs, including surgical excision, intralesional MTX, intralesional and topical 5-FU, intralesional bleomycin, and isotretinoin.[2] Isotretinoin has been advocated as both a prophylactic and therapeutic agent for skin cancers, especially in the setting of multiple lesions.[7-9] A relatively high dose (1–3 mg/kg) is required, even for prophylactic outcome. A low dose, in the range of 5 to 10 mg/d, is neither prophylactic nor therapeutic.[10,11] The side effects, which include elevated triglyceride levels, mucocutaneous reactions, and hyperostotic axial skeletal changes, limit the use of isotretinoin. The efficacy of retinoids in the prophylaxis and treatment of KA and KACM also has been reported by several authors.[12-15] The dosage of isotretinoin ranged from 1 to 3 mg/kg per day with a response observed as early as within one week to several months. In our case, despite adequate duration and relative high doses of isotretinoin, there was no prophylactic or therapeutic effect as evidenced by the patient's continual development of nodular KAs without any of the existing KAs regressing while he was receiving isotretinoin therapy. The patient experienced the usual mucocutaneous side effects. His backache and the changes in his mood were suspected to be the side effects of isotretinoin, as well.

Intralesional MTX for the treatment of KAs has been reported to be effective with a regimen of 1 to 3 injections not exceeding a total dose of 100 mg, resulting in resolution of the KAs in 2 to 4 weeks.[16-18] In our patient, although the 2 sites were injected with adequate amounts of MTX, the treatment was unsuccessful. In retrospect, intralesional therapy was unreasonable because of the large amounts of MTX that would have been required. The 2 treated sites accounted for less than 10% of the surface area of the lesions.

The rationale for imiquimod therapy in our patient was 2-fold. First, imiquimod is an immune response modifier emerging as an effective therapy for superficial carcinomas of the skin.[19-22] Most therapies available for superficial skin carcinomas also have been applied to KAs. Second, because human papillomavirus has been found to be present in KA, though not consistently,[23-26] we were hopeful that imiquimod would have a therapeutic effect for KACM similar to that for condyloma. Despite daily application of the cream for 7 months to some of the lesions, far beyond the 6 to 12 weeks' duration recommended for basal cell carcinomas,[19,27] imiquimod had no effect.

Both topical and intralesional 5-FU, a thymine analog, have been reported to be effective therapies for solitary and multiple KAs, though there is no reported case of KACM treated with either

topical or intralesional 5-FU. A dramatic resolution has been observed as early as one week after treatment using topical 5-FU, but the usual duration of therapy was 3 to 4 weeks.[28-30] In contrast to these reports, encouraging signs of resolution were present in our patient after 2 months of therapy, and complete resolution occurred over a period of many months, not weeks. Despite the apparent efficacy of 5-FU, we cannot exclude the possibility that the regression of the lesions was the natural course of the neoplasm, especially when KAs are known to regress without any therapeutic intervention. The evidence supporting topical 5-FU being efficacious is that there was prompt resolution when the cream was applied to the new lesions.

The nature of KA and KACM, whether or not the neoplasm is a squamous cell carcinoma (SCC), has been controversial. A few authors assert that a KA is an SCC.[5,31,32] We consider KA and its variants, including KACM, as one type of SCC encountered in the skin. A few well-documented cases of metastases of KAs to the lymph nodes have been reported.[31,33] At the molecular level, KA has been shown to overexpress p53,[34] a tumor suppressor gene that has been associated with a variety of malignant neoplasms. In contrast to other types of SCC, a complete regression, believed to be an immune-mediated process by some,[35,36] is a unique characteristic of KA. The exact mechanism by which a KA regresses, however, remains largely a mystery. LeBoit[37] has hinted that solving this mystery may have far-reaching applications. We agree.

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