Keratoacanthoma: Update on the Debate

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Abstract: Keratoacanthoma (KA) is a cutaneous tumor with a biphasic pattern of growth. A rapidly growing phase is usually followed by involution. KA occurs on sun-damaged skin. There are many listed causative associations, which include some therapeutic agents. Debate continues as to whether KA is a variant of squamous carcinoma (SCC) or a separate entity. Reporting of KA versus SCC is markedly inconsistent. Reasons for inconsistency include overlapping microscopic criteria, variants of KA with more aggressive features, and possibly medicolegal concerns. Genetic studies have shown some differences between the 2 entities. Activation of apoptotic pathways has been demonstrated in KA. Genetic studies have shown a possible role of human polyomavirus 6 in the pathogenesis of at least some KAs. Given that some cases of KA have components that behave as conventional SCCs, KA can be considered as a low-grade variant of SCC with some genetic differences.

Key Words: keratoacanthoma, squamous cell carcinoma

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INTRODUCTION

Keratoacanthoma (KA) is a tumor characterized by having an initial rapid growth phase, often followed by regression, and traditionally has been considered as self-resolving or low-grade squamoproliferative.

There has been much debate as to whether KA is a subtype of squamous carcinoma (SCC) or a separate entity.

BACKGROUND

KA was first described by Jonathan Hutchinson in 1889 as a crateriform ulcer on the face. It was reported as verrucome by Gougerot in 1929 and as kyste sebace atypique by Dupont in 1930.[1] MacCormac and Scarff applied the term molluscum sebaceum in 1936. The term KA was first proposed by Dr Walter Freudenthal and adapted by Dr G. B. Dowling in the 1940s.[2]

KA arises from hair follicles. Microscopically, it is characterized by its exoendophytic, well-defined, and symmetrical architecture, central keratin plugs, overhanging epithelial lips covered with normal epidermis, and minimally infiltrative borders. It consists of lobules of enlarged pale pink cells with ground glass–like cytoplasm, which generally lack nuclear atypia and lobules of large pale eosinophilic cells with a few layers of basophilic cells at the periphery. There may be limited nuclear atypia in the peripheral basophilic cells. In its regressing stage, the lesion consists of shallow-shaped structures formed by thin epithelium and with associated dermal inflammation and fibrosis 3[3] (Fig. 1).

KAs usually arise on sun-exposed skin, most commonly on the head/neck, dorsal hands/forearms,[4] and lower extremities[5,6] (Fig. 2). It also occurs in patients treated with BRAF inhibitors, including vemurafenib, dabrafenib, and encorafenib,[7–9] immunosuppressive drugs, ultraviolet light therapy, and has been associated with industrial exposure to tar,[10] tattoos, aesthetic procedures such as laser surgery, chemical peels, hyaluronic acid with acrylic hydrogel fillers, collagen fillers, and trauma.[11] Multiple KAs have also been described. These may occur sporadically, be familial, or associated with conditions such as xeroderma pigmentosum and Muir–Torre syndrome.[11] Multiple KAs are being seen in melanoma patients receiving BRAF inhibitor therapy without MEK treatment.[12,13]

DISCUSSION

There are no clear microscopic criteria to differentiate KA from SCC,[7,14] which has resulted in a variable rate of tumors being diagnosed as KA versus SCC. Carr and Houghton[14] performed a semiquantitative study, which compared 11,718 cases in 17 departments in the United Kingdom and Ireland over 12 months. In this study, there were 10,720

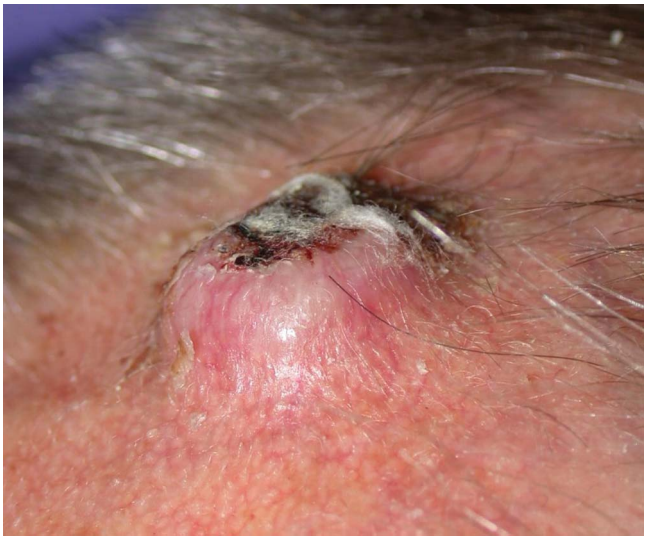

FIGURE 1. Low-power microscopic view of a keratoacanthoma.

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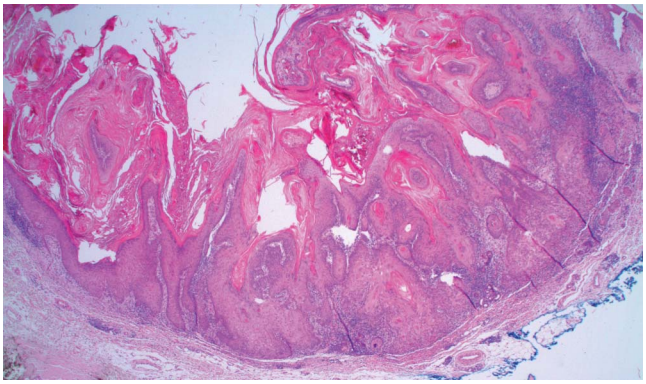

FIGURE 2. Clinical photograph of keratoacanthoma.

diagnoses of SCC and 998 diagnoses of KA. Although the combined average ratio of SCC to KA was 10.7:1, there was considerable variation among departments, with the ratio ranging from 2.5:1 to 139:1 in the centers participating in the study.

Although some variation in the incidence of KA across the centers in the study would be expected, the large disparity between centers at least in part may be related to differences in applying the diagnostic criteria.

Another possible reason is the wide spectrum of clinical behavior and appearance of crateriform tumors. This may explain the wide spectrum of pathological diagnoses, which include KA, KA with SCC components, KA-like SCC, KA with malignant transformation,[4] and crateriform verruca.[15]

There have been case reports of metastasizing keratoacanthomas. Hodak et al[16] reported 3 cases in which the metastases histopathologically resembled the original tumor.

An additional potential reason is that pathologists may be reluctant to diagnose tumors as KA because of the clinical and legal risk of underdiagnosing an aggressive SCC. In the study by Carr and Houghton,[14] histopathologists' comments included that they would be more likely to make a confident diagnosis of KA in a formal excision specimen and when the clinical history of a regressing lesion was provided.

Genetic studies show that some mutations are shared by both KA and SCC. One study showed that the MAP3K8 (TPL2) oncogene may be a driver in the development of both tumors. TPL2 overexpression is also found in other malignancies, including breast and prostate cancer, and lymphoma.[7]

Seong et al, using microarray techniques, studied genetic profiles of KAs and compared these with existing databases of cutaneous SCCs and normal skin. KA demonstrated 1449 genes with different expression to SCC, with 908 genes upregulated and 541 genes downregulated. In KA, the most significantly upregulated genes included *CDR1, S100A, MALAT1, TPM4, CALM1*, and *TMED2*. The most significantly downregulated genes include *LOC441461, TYRP1, CEL, INTS6*, and *WWOX*.[17]

Seong et al also found that there were 2435 genes with different expression to normal skin, with 1085 genes upregulated and 1350 genes downregulated. Most significantly upregulated genes included *MALAT1, S100A8, CDR1, TPM4*, and *CALM1*, and the most significantly downregulated genes included *SCGB2A2*, *DCD*, *THRSP*, *ADIPOQ*, adiponectin, and *ADH1B*. Compared with normal skin, the most significantly enriched molecular and cellular functions in KAs included cellular development, cellular growth and proliferation, cell death/apoptosis, and cell cycle pathways.[17] This is in keeping with previous studies of regressing KAs that have shown strong expression for the proteins bax and bak, which are essential for apoptosis and also decreased expression of the antiaptotic protein BCL-xL and BCL-2. BCL-2 is a proto-oncogene involved in protecting cells from undergoing apoptosis.[17]

It is hypothesized that prominent enrichment of the clathrin-mediated endocytosis may be because of granzyme-mediated apoptosis.[17] Clathrin-mediated endocytosis is a key process in vesicular trafficking that transports a wide range of cargo molecules from the cell surface to the interior.[18] Cytotoxic T cells have been shown to play an important role in the regression of KA,[17] through the release of granzyme-B. Regressing KAs express p27, an inhibitor of a variety of cycling-dependent kinases, and Le (Y), an antigen related to apoptosis.[19]

Ni et al[20] studied genetic differences between KA- and SCC-appearing components of a single lesion. They noted moderately differentiated to well-differentiated SCC arising from the center of a typical actinic KA. The KA and SCC components were separated by macrodissection, and 4 genes were studied, *MAPK1, CASP14, BAG1*, and *MMP14*. In the KA, *MAPK1* and *CASP14* were upregulated and *BAG1* and *MMP14* were downregulated in comparison with the SCC component. MAPK1 plays a role in cellular proliferation, and CASP14 is involved in keratinocyte death during terminal differentiation and transition into corneocytes, consistent with the behavior of KA. *BAG1* may have a role as an oncogenic driver, and *MMP14* plays a role in cancer invasion and metastasis, consistent with the biological behavior of SCC.

Studies have also shown a possible role of human polyomavirus 6 (HPyV6) in the pathogenesis of at least a proportion of KAs. Beckervordersandforth et al showed a higher rate of detection of HPyV6 in KA than in SCC, basal cell carcinoma (BCC), or trichoblastoma. Polymerasec chain reaction was performed on 299 tumors, including 59 KAs, 86 SCCs, 109 BCCs, and 45 trichoblastomas, and fluorescence in situ hybridization was performed on some of these. HPyV6 was detected in 42.3% of KAs, whereas the detection rate in the other tumors was within the range of detection in normal skin.[21]

Schrama et al[22] reported on one patient who developed multiple KAs while receiving treatment with vemurafenib for BRAF V600E-positive melanoma. The patient had a high load of HPyV6 in multiple KAs, although clinically uninvolved skin was not tested. The authors concluded that the high viral load in multiple lesions suggested active viral replication.[21] The addition of a MEK inhibitor to BRAF treatment in managing melanoma is associated with a substantial reduction of subsequent KA versus events.[23]

CONCLUSIONS

KA is a tumor that microscopically resembles well-differentiated SCC and may have components of less well-

differentiated carcinoma. However, in its pure form, KA differs in biological behavior from SCC. Genetically, there is some overlap; however, there are also distinct differences.

The long-debated question as to whether KA and SCC should be considered as separate entities or as variants of the same entity remains unanswered, and the clinicopathological diagnosis currently resides with personal points of view.

It is our opinion that KA is a squamoproliferative lesion, which arises from the follicular infundibulum, and given that in some cases, it has components that behave as conventional SCCs, it should be considered as a variant of SCC with some genetic differences. This viewpoint is also recognized in the current WHO Classification of Skin Tumors (2018).[24] From the clinician's perspective, KA can be considered as within the less aggressive spectrum of well-differentiated SCC.

The possible role of HPyV6 in at least some cases adds to the number of cutaneous tumors, which are associated with viruses, which also include conventional squamous carcinoma (human papilloma virus) and some cases of Merkel cell carcinoma (Merkel cell polyomavirus).[25]

Regarding the treatment of solitary KAs, particularly in view the findings of Carr and Houghton,[14] complete removal of the lesion is recommended. Surgical treatment with full-thickness excision is often recommended.[26] There are limited studies of the effectiveness of curettage, with follow-up periods too short to assess effectiveness. In the largest study, 111 KAs treated with curettage and electrodissection with follow-up of at least 12 months showed 4 recurrences (3.6%).[27] In cases of multiple KAs, other modalities may be considered, such as systemic acitretin or other retinoids, either as monotherapy or combined with surgery and/or intralesional methotrexate.[26]

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