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Myriad facades of keratocanthoma: Benignity VS malignancy

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ABSTRACT

Keratoacanthoma (KA) is a self-limiting benign epithelial neoplasm. It occurs predominantly on sun-exposed areas of the body and is believed to arise from hair follicle. It shows a unique behavior in being clinically benign and microscopically malignant. Earlier it was considered as a pseudomalignant lesion but now it is believed to be pseudobenign in nature. The most common concern is related to its nosological position at the border of malignancy and benignity. We hereby report a rare case of keratoacanthomatous type of squamous cell carcinoma in an elderly female showing aggressive nature of the lesion. The various terminologies used for KA in the past have also been tabulated.

1. Introduction

The term "Keratoacanthoma" (KA) was coined by Freudenthal in the year 1936. It was first described way back in 1889 by Hutchinson and was called molluscum sebaceum and self-limiting epithelioma. KA is benign, self-limiting squamo-proliferative lesion. It shows male preponderance and most commonly arises on the sun-exposed parts predominantly face, neck and forearms. Cutaneous lesions arise from hair follicles whereas mucosal lesions originate from ectopic sebaceous glands.[1] It is said to have multifactorial etiopathogenesis and the most accepted factor is the derangement of normal regulatory apoptotic mechanism in the follicles. Other contributory factors could be traumatic, genetic, viral, nutritional and endocrine disturbances. Clinical stages of KA are proliferative, maturative and regressing. Its entire process of maturation and regression completes within 4–6 months whereas some KAs may be devastating and could metastasize like squamous cell carcinoma. Earlier it was thought to be exclusively benign but later Hodak, Jones, and Ackerman presented three cases of KA showing metastatic behavior. Such lesions lead to emergence of a new terminology "Keratoacanthomatous type of squamous cell carcinoma".[2] Originally this term was introduced for classic KAs having squamous cells along with dysplastic features. Such type of nomenclature fueled the dispute whether KA is a transfiguration of SCC or a neoplasm sui generis. Therefore, few authors contemplated KA as a pseudo-benign lesion having potential of malignant transformation.[3] This opinion is not universally accepted and has been discussed in scientific literature extensively. We report a case of KA of lower lip with aggressive behavior, which manifested with the histological features of both KA and squamous cell carcinoma.

1.1. Case report

A 70 year-old female reported to our department with chief complaint of a swelling on her lower lip since 1 year and burning sensation since past 2 weeks (Fig. 1). Swelling was insidious in onset and gradually increased to present size. There was neither history of any medical ailment nor any associated family history. No evidence of trauma was recorded. Patient was well built, nourished and oriented with time, place and person. On examination, the swelling was present on right side of lower lip, oval in shape measuring approximately 3 × 2.5 cm, firm, non-compressible, non-tender and fixed to underlying structures having crateriform surface. Based on the clinical appearance and history, a provisional diagnosis of actinic keratosis was made. Other differential diagnoses included were keratoacanthoma, basal cell carcinoma and crateriform squamous cell carcinoma. Screening of the lesion was done by exfoliative cytology. The PAP stained smear revealed abundant keratin flecks and anucleate squames when observed under light microscope. Afterwards, the tumor was excised completely under local anaesthesia along with normal tissue outline and sent for histopathological examination. Tissue sections showed overlying hyperplastic parakeratinized stratified squamous exo-endophytic epithelium. Extensive areas of parakeratin plugging and craters filled with parakeratin squames were evident (Compatible with features of KA). Underlying connective tissue stroma was edematous and infiltrated extensively by mixed inflammatory cells. Peripheral ends showed normal epithelium in continuity with the lesion (Fig. 2). Certain

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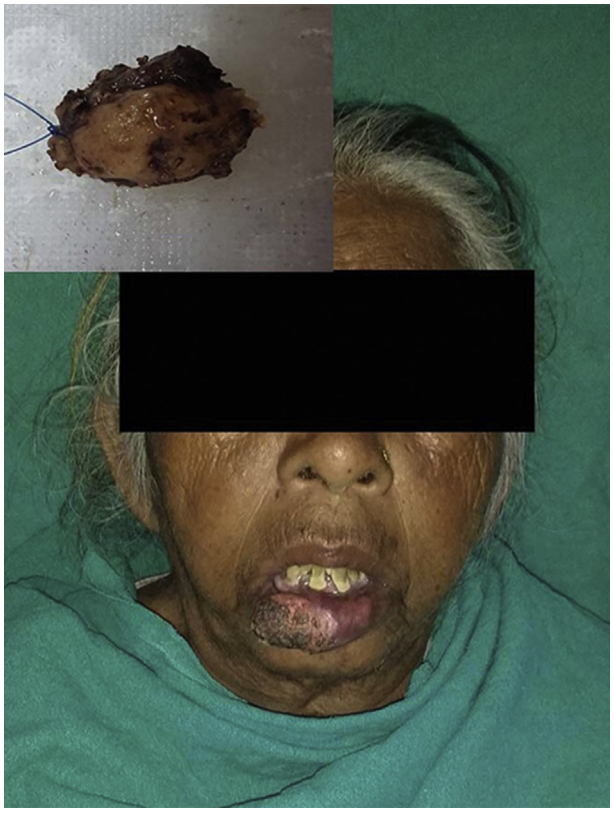

Fig. 1. Extraoral view showing crateriform lesion at right side of lower lip. Inset shows excised mass of the lesion.

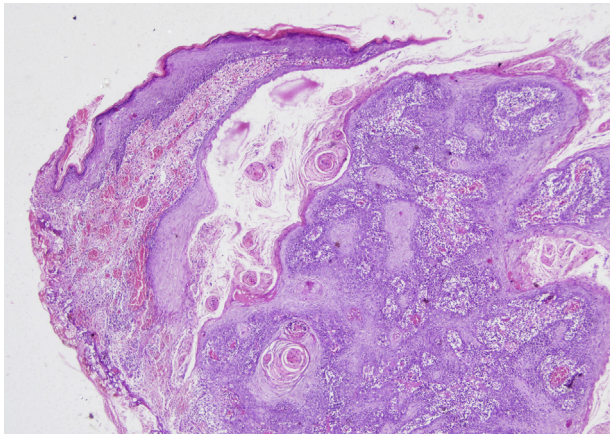

Fig. 2. Photomicrograph showing extensive areas of parakeratin plugging and craters filled with parakeratin. At one end, normal epithelium in continuity with the lesion is also evident. (H&E;10X).

features of squamous cell carcinoma like dysplastic epithelial islands, atypical mitotic figures and pleomorphism were also evident juxtaepithelially in the connective tissue (Fig. 3). The architectural presentation like KA and dysplasia resembling conventional squamous cell carcinoma led us to give a final diagnosis of keratoacanthomatous type of squamous cell carcinoma and patient was kept on regular follow up for any signs or symptoms of recurrence. A few terminologies about KA used in the past are enumerated in Table 1.

2. Discussion

Diagnosis of KA is based on combined clinico-pathological findings, which facilitates appropriate treatment. There remains bewilderment

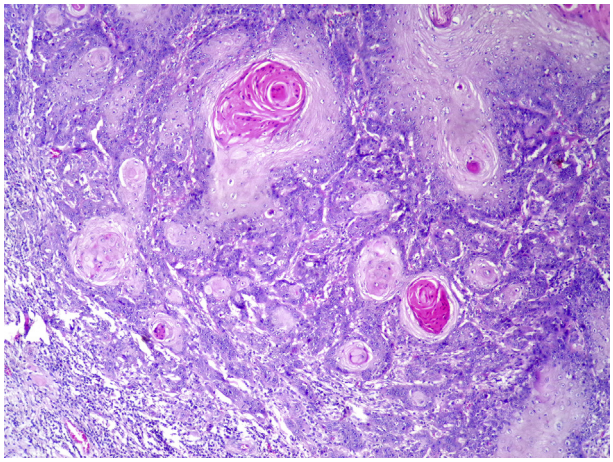

Fig. 3. Photomicrograph depicting dysplastic features in epithelial islands juxtaepithelially in the underlying connective tissue stroma. (H&E; 40X).

whether KA should be considered benign or a type of squamous cell carcinoma and thus dealt accordingly. This controversy can lead to misdiagnosis and hence inappropriate treatment. Therefore, distinguishing these two entities is crucial for the pathologists. Most common disquiet is related to its position on the border between benignity and malignancy.[1] This concern directed many authors to describe the diagnostic dilemma of its nature. Rook and Whimster in 1950 made an effort to distinguish between these two entities. They highlighted four histopathological features of KA namely (a) It arises in normal skin having no signs of precancerous change. (b) The epithelial hyperplasia mainly affects the appendages. There is little hyperplasia of the surface epidermis and no signs of spontaneous ulceration. (c) The atypical cells in KA are minimal. (d) There is no truly invasive growth in KA. They suggested KA as a reactive hyperplastic lesion, which can act as a co-carcinogen with actinic rays to produce squamous carcinoma.[4] After that, Moragas et al., in 1958 attempted to differentiate these two entities. They highlighted that the vertical section had to be done through the exact center of the excised lesion in order to make definitive diagnosis of KA and other factor was correlation between pathological constitution of tumor and age of the lesion. They concluded that the striking feature observed in KA was its tendency of complete keratinization in uppermost central area of tumor and center of isolated cords whereas features found in squamous cell carcinoma were marked anaplasia with pleomorphism, disorderly cellular arrangement, lack of sharp outline between proliferating epithelium and dermis and cells of epithelial growth invading adjacent dermis.[5] Many attempts were further made by several authors for precisely distinguishing KA and squamous cell carcinoma. King and Barr found intraepithelial elastic fibers and glycogen content as the important diagnostic aids in differentiating KA from squamous cell carcinoma. They established that intraepithelial elastic fibers were more common in de novo squamous cell carcinoma than in KA whereas intracytoplasmic glycogen was more abundant in KA than in squamous cell carcinoma.[6] Kern and McCray carried out a study in which histopathological features were considered and they evaluated two hundred diagnosed cases of KA and squamous cell carcinoma. Histopathological features reviewed were invaginating keratin filled craters, collarette presence, epidermal proliferations at sides and bottom, anaplasia or marked pleomorphism and associated actinic keratosis. They concluded that only skin KAs could be classified by using these criteria. Jordan et al. established immunohistochemically that elastic fibers were demonstrated significantly in KA than in squamous cell carcinoma.[7]

In contrast to these findings, Hodak et al. emphasized that KA is squamous cell carcinoma from onset. It has all the histopathological features of squamous cell carcinoma like nuclear pleomorphism, mitotic figures and dyskeratosis. Briefly, they suggested that KA is squamous

Table 1
Historical aspect of terminologies used for Keratoacanthoma.

Sr. No.	Author/Year	Various terminologies for KA in the past
1	A. Rook and I. Whimster (1950)	Epithelial hyperplasia due to infection
2	H.E. Bowman and H. Pinkus (1955)	Histologically malignant but clinically benign
3	D. G. Davies (1969)	Pre-cancerous lesion
4	R. J. Reed (1972)	Metabolically incomplete SCC
5	J. Kwittken (1975)	Self-healing primary SCC of skin
6	P. I. Schnur and P. Bozzo (1978)	Benign, self-healing lesion.
7	A.Rook and I. Whimster (1979)	Benign, reactive and non-neoplastic
8	R. A. Schwartz (1979)	Abortive SCC
9	H. Pinkus and H.H. Mehregan (1980)	Most common precancerous lesion
10	Kwitten et al. (1980)	Keratocarcinoma
11	G. H. Sanders & T. A. Miller (1982)	Premalignant or malignant
12	M.A. Goldenhersh & T. G. Olsen (1984)	A spectrum of SCC
13	A.H. Mehregan and K. Hashimoto (1991)	Pseudocarcinoma
14	A.F. Straka and J. M. Grant-Kels (1991)	Pseudomalignancy
15	A.B. Ackerman (1991)	Type of SCC
16	Hodak, Jones, & Ackerman et al. (1993)	Expression of squamous cell carcinoma
17	Beham et al. (1998)	Clinical variant of well differentiated SCC
18	Savage JA (2014)	Benign epidermal growths that can be classified as a benign counterpart of SCC

cell carcinoma.[2] A further attempt was made by Cribier, Asch and Grosshans to differentiate KA from squamous cell carcinoma histopathologically. They classified 292 excised tumors on basis of histopathological criteria. Out of these histopathological criteria some tumors showed only sharp outline between stroma and proliferation and presence of lateral lip favoring KA whereas others presented with ulceration, pleomorphism and mitoses supported squamous cell carcinoma.[8] Another effort was made by Misago et al. who defined histopathological criteria for a typical KA to be an exo-endophytic lesion with central keratin horn, overhanging epithelial lips and neoplastic lobules. Using these features, they classified 30 KAs and 762 squamous cell carcinoma cases. Among 30 KAs, only 27 were true whereas among squamous cell carcinoma group, 11 cases were squamous cell carcinoma having crateriform architecture.[9]

Henceforth many efforts have been taken to distinguish these two entities using molecular techniques. One such research established loss of heterozygosity to be a differentiating feature between these two entities. Pyne et al. recognized the vascular features like large diameter and branching vessels of the two entities. Some of the advanced studies have also shown the importance of cell proliferation markers, apoptosis, cell adhesion and telomerase activity in squamous cell carcinoma as well as KA. Recent study by Ra SH et al. compared molecular pathways and expression of genes and suggested that KA can regress in some cases due to up regulation of apoptosis pathway.[10]

The never-ending debate, discussion and reported case series in literature, KAs have not been decided either as benign or a malignant entity. Based upon extensive literature review and present case report, we can look forward it to be a type of squamous cell carcinoma having low-grade malignancy.

3. Conclusion

It is difficult to distinguish these two entities despite the histologic features and advanced techniques. A condensed tale is that the correct diagnosis of KA could be achieved by correlating the clinico-pathological findings. In most of the circumstances, architectural criteria favor KA and cytological criteria supports squamous cell carcinoma. If both the criteria are present we can acknowledge those tumors as keratoacanthomatous type of squamous cell carcinoma having malignant potential and they should be excised aggressively. Regular follow up should be done for any recurrence or metastasis.

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