



A SHEEP IN WOLF'S CLOTHING, OR A WOLF IN SHEEP'S CLOTHING? KERATOACHANTOMA

Kurt Postunda Koyun mu veya Koyun Postunda Kurt mu? Keratoakantom

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Abstract

A Keratoacanthoma is a dome-shaped, pink-colored benign skin tumor, around 1–2 cm in height with a central crater filled with keratinous plaque, that is assumed to be caused by the exposure of hair follicles to sunlight. The most prominent discussion on Keratoacanthoma is whether it is malignant or benign, and this discussion is challenging for a clinician and absorbing for a researcher, as it can play a key role in understanding cancer regression. Keratoacanthomas resemble squamous cell carcinomas, both clinically and histologically and in the resulting confusion, Keratoacanthoma can be defined as a sheep in wolf's clothing, but can also be regarded as the wolf in the sheep's clothing, as there is an emerging view that it could be the precursor to squamous cell carcinomas. A total or partial excision of the biopsy material, including subcutaneous fat tissue, or a fusiform partial excision, including the center and both sides along the entire course of the lesion, to represent the whole lesion. In addition, the excised biopsy material should include at least 2 mm of intact skin on both sides.

Keywords: Keratoacanthoma, malignant, benign

Öz

Keratoakantom, ciltten 1-2 cm yükseklikte, kubbe şeklinde, santral bölgede keratinöz plak ile dolu krateri olan pembe renkli benign bir cilt tümörü olarak tanımlanabilir. Genellikle güneş gören alanlarda saç foliküllerinden köken aldığı varsayılmaktadır. Keratoakantom hakkındaki en yaygın tartışma ise malign ve benign arasındaki durumu ile ilgili olup, bu durum bir klinisyen için zorlayıcı, araştırmacı için de ilginç olabilmektedir. Çünkü bu tümör kanser regresyonunun anlaşılmasında anahtar rol oynayabilir. Keratoakantom, hem klinik hem de histopatolojik bulgularda skuamöz hücreli karsinom benzerlik göstermekte ve tanı konulurken karıştırılabilmektedir. Bu karışıklıktan dolayı keratoakantomlar kurt görünümlü koyun olarak tanımlanabilirken, son zamanlarda skuamöz hücreli karsinom öncüsü görüşü artması nedeniyle koyun görünümlü kurt olarak da düşünülebilir. Biyopsi materyalinin, subkütanöz yağ dokusunu içeren, total ya da kısmi eksizyonunu ya da merkezi ve her iki tarafı da dahil olmak üzere Keratoakantom'un tamamı boyunca tüm lezyonu temsil edecek şekilde fusiform kısmi eksizyon yapılmasını önermişlerdir. Buna ilave olarak da her iki yanda sağlam deriden en az 2 mm biyopsi materyalinde kalacak şekilde eksizyon uygulanmalıdır.

Anahtar Kelimeler: Keratoakantom, malign, benign.

INTRODUCTION

A Keratoacanthoma (KA) is a dome-shaped, pink-colored benign skin tumor, around 1–2 cm in height with a central crater filled with keratinous plaque, that is assumed to be caused by the exposure of hair follicles to sunlight ^{1,2}.

KA was first described by Sir Jonathan Hutchinson in 1888, although its epidemiology, histopathological diagnostic criteria, prognosis, and treatment options are still a matter of debate.^{3,4,5}

The various terms used to define KA, such as “molluscum sebaceum”, “pseudo tumor”, “regressing tumor” and “self-healing squamous cell carcinoma” (SCC) are clear evidence of these ongoing debates ^{3,4}.

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The most prominent discussion on KA is whether it is malignant or benign, and this discussion is challenging for a clinician and absorbing for a researcher, as it can play a key role in understanding cancer regression. KAs resemble squamous cell carcinomas, both clinically and histologically,^{6,7} and in the resulting confusion, KA can be defined as a sheep in wolf's clothing, but can also be regarded as the wolf in the sheep's clothing, as there is an emerging view that it could be the precursor to SCC.

EPIDEMIOLOGY

Although KA is rare before the age of 20, it can be observed in all age groups. It has been reported that solitary KA occurs most commonly between the ages of 50 and 70 years, although making an accurate assessment of the number of incidences can be difficult, as SSC is often misdiagnosed, KA is misreported or KA spontaneously regresses before a diagnosis can be made. According to a study by Carr and Houghton in 2014, SCC/KA ratios reported by pathologists from different centers in the United Kingdom and Ireland ranged from 2.5:1 to 139:1, with this significant difference suggested to be a result of the differences in the approach of different pathologists to KA diagnosis^{8,9}.

The ratio of male-female cases is 2:1, and it most commonly occurs in light-skinned people, the harmful effects of sunlight can lead to the development KA, and it is more common and more locally invasive in the immunocompromised. Multiple KA-containing subtypes and KA variants such as KA centrifugum are observed only rarely, and KA and squamous cell carcinoma share many common epidemiological features^{8,9,10}.

ETIOLOGY AND GENETICS

Many factors play a role in the etiology of KA, including ultraviolet (UV) light, chemical carcinogens, immunosuppression, BRAF inhibitors, genetic p53 or H-Ras mutations, viral agents, including the human papilloma virus (HPV), trauma or previous surgery sites.¹⁰⁻¹²

In terms of stimulating factors, both natural and artificial UV light exposure is known to be a dominant risk factor for KA, while chemical carcinogens constitute another significant risk. A study conducted with mice stimulated with chemical carcinogens found that KA tumor regression is not dependent on the immune system, and the Wnt /retinoic acid signal pathways support this hypothesis. The role of immune system in the appearance and regression of tumors is controversial, but nevertheless, must be taken into consideration.¹¹⁻¹⁴

Although the predisposing genes for the appearance of solitary sporadic KA are not exactly known, DNA repair-deficiency disorders such as Muir-Torre syndrome (MTS) and xeroderma pigmentosum are known to play a role in the development of KA, among other tumors. Furthermore, multiple KAs can occur in Ferguson-Smith syndrome, in which mutations are observed in TGF b1. That said, further studies have shown that KA is a monogenic condition rather than being digenic^{15,16}.

Another study identified p53 gene mutations in approximately 40 percent of KAs, indicating that the mutation is closely related to the nuclear accumulation of the p53 protein.^{12,14,15,16}

Rare sporadic pruritic generalized eruptions of KA are known as Gryzbowski's generalized eruptive keratoacanthoma (GEKA). The solitary and multiple mucosal KAs that are rarely observed in the course of GEKA point to a different origin of these tumors, and the possibility of differentiation from the upper segment hair follicle like cells.^{16,17}

CLASSIFICATION

KA is characterized by initial accelerated growth, followed by a variable stable period and spontaneous regression phase, and KAs have been categorized into different subtypes in different studies. These subtypes include solitary KA, subungual KA, mucosal KA, giant keratoacanthoma, KA centrifugum marginatum, Grzybowski's generalized eruptive KA and Ferguson-Smith syndrome, involving multiple KAs^{17,18}.

Solitary KA is the most common sporadic subtype, being often 1–2 cm in diameter and 0.5 cm thick. Solitary KAs rarely occur on mucosal membranes, with the most common location being the oral cavity and rarely involving the conjunctiva and vulva¹⁸⁻¹⁹.

Subungual KAs may pose challenges to both diagnosis and treatment. Fast growth phase causes nail dystrophy and it is followed by the regression phase¹⁹.

However, another subtype known as KA centrifugum marginatum can vary in size, from a few millimeters to 20 cm, and the extent to which this subtype will enlarge cannot be predicted. If a solitary KA is larger than normal and does not show further growth, this is termed “giant” to distinguish it from KA centrifugum marginatum. Giant solitary KAs usually have irregular margins and have been described as having an appearance similar to a coral reef^{19,20}.

Multiple KAs are rare, and may be either sporadic or familial. Multiple sporadic KAs are often referred to as “keratoacanthoma centrifugum marginatum” and multiple familial KAs include the Ferguson-Smith or Grzybowski subtypes and the self-healing Witten-Zak type²¹.

DIAGNOSIS

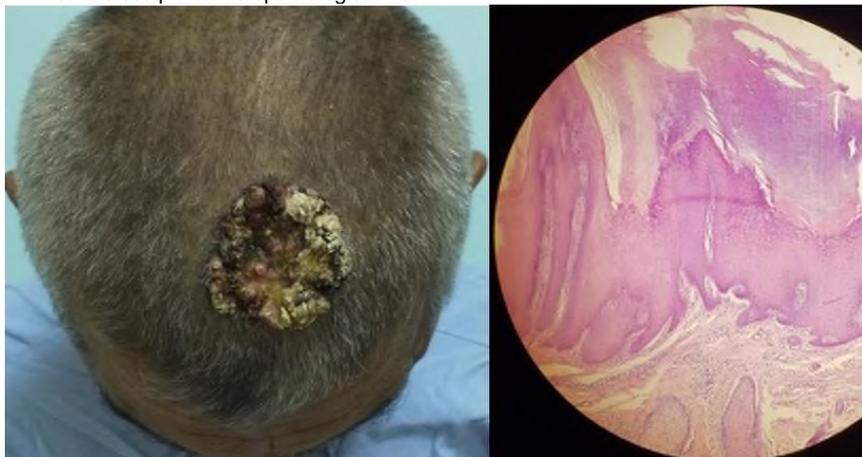
Diagnosis of KA is based on three principles: typical clinical appearance of the crateriform tumor, a three-phase growth pattern (between weeks and months) and a histopathological examination of the biopsy specimen^{20,21,22}.

An attentive medical history and physical examination is the first step in a diagnosis, which needs to be followed up by a biopsy for a histopathological examination.

CLINICAL EVALUATION

Keratoacanthoma is usually characterized by a rapid growth at baseline followed by a variable period of stabilization and spontaneous regression^{4,8,17,18,21,22}

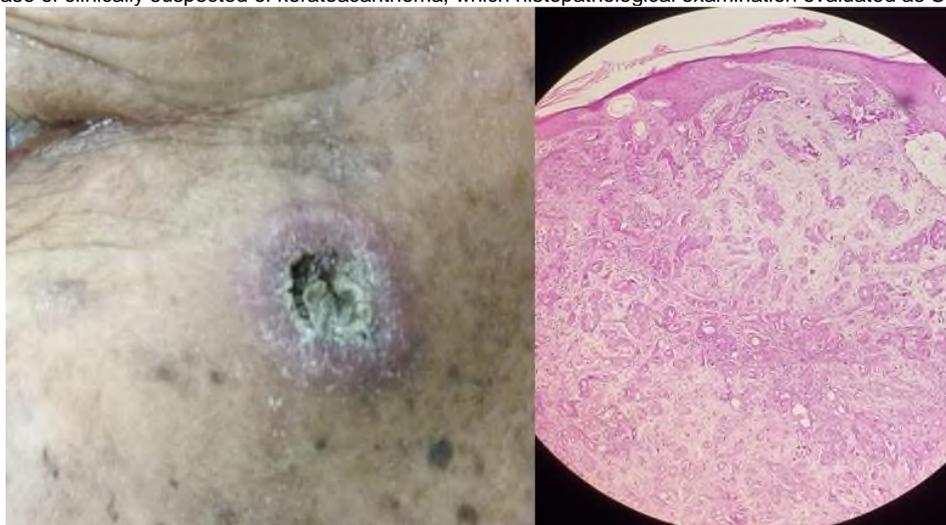
The three phases of KA, including the proliferative (early, growth), stabilization (maturation) and regression (involution) phases, suggest that KA mimics natural hair follicle growth cycle^{1,3,22} (Figure 1).

Figure 1. A case of KA on the scalp and histopathological view

KAs arising from a pilosebaceous unit manifest with an abnormality that causes infundibulum hyperkeratosis. Although considered to be associated with hairy areas and sunlight, such tumors can occur in other areas, such as the mouth, lips, gingiva, hard palate and other mucus membranes ^{3,5,10,18,21,22}.

KA shows rapid growth in the proliferative phase that lasts from 6 to 8 weeks, the maturation phase lasts for a few weeks or months, and the crater form appearance is stably maintained. Involution phase is the final phase, during which the lesion becomes an atrophic scar. The duration of these phases can vary ^{4,18,19,22}.

Although clinical appearance is important in establishing a diagnosis, the similarities of KA and SCC at a clinical and cellular level complicates the distinguishing of these lesions ^{5,10,18,22}(Figure 2).

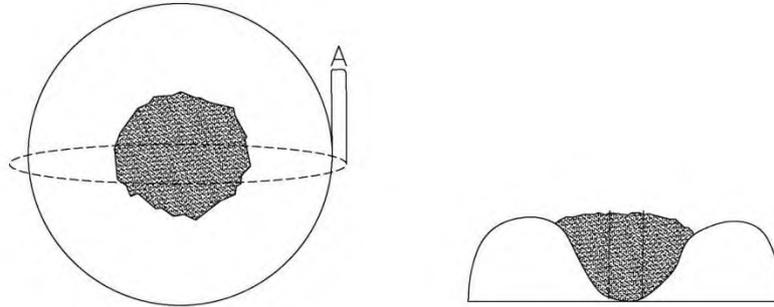
Figure 2. A case of clinically suspected of keratoacanthoma, which histopathological examination evaluated as SCC

BIOPSY

The best diagnostic test is excisional biopsy for small lesion, as a shave biopsy may not reveal the depth of the lesion, which would allow KA to be distinguished from SCC ^{21,22}. A fusiform incisional biopsy is the best choice for the suspicious lesions including keratin plug.

In 1959, Dabska and Madejczykowa suggested a total or partial excision of the biopsy material, including subcutaneous fat tissue, or a fusiform partial excision, including the center and both sides along the entire course of the lesion, to represent the whole lesion ^{15,17,18,20,21,22}. In addition, the excised biopsy material should include at least 2 mm of intact skin on both sides (Figure3).

Figure 3. Fusiform biopsy for KA. A: It represents at least 2 mm margin of intact skin which will be excised.



Patients with a subungual KA may require a radiographic examination to reveal the osteolysis in the affected finger ^{3,7,8,21,22}.

This approach allows not only an analysis of the cellular component, but also of the entire architecture of KA. Improper sampling may lead to an SCC diagnosis and subsequently to more comprehensive treatment ^{5,11,12,22}.

HISTOPATHOLOGY

Although KA is considered to be a benign lesion, its histopathological features resemble those of SCC ^{22,23}.

The histopathological features that are specific to KA include: (i) being an exophytic tumor; (ii) symmetrical outer margins; (iii) multilobular lesion with central keratin; and (iv) overhanging epithelial lips with a normal overlying epidermis ^{3,24}.

In addition, three findings can be explained by: (i) the presence of the characteristic components of KA, invaded infundibular structures (laminated keratinization) and pale pink cell lobules with a glassy ample cytoplasm, often devoid of nuclear atypia; (ii) a few layers of basophilic cells on the periphery of large, pale eosinophilic cell lobules; (iii) nuclear atypia or mitotic figures surrounded by peripheral areas of basophilic cells; and (iv) minimally infiltrated margins ^{24,25}.

The histopathological features in the proliferative phase of KA may make the histopathological diagnosis of KA difficult, as a well-differentiated infundibulocystic SCC described by Kossard et al.²⁶ was suggested to be KA in the proliferative phase. In order to diagnose KA accurately in the early/proliferative phase, the absence of nuclear atypia must be demonstrated in the proliferative cells of the invaginated epidermal or infundibular structures ²⁶. Immunohistochemical studies of KA in this phase using cytokeratin CK1, CK10, CK15, CK16 and CK17, Misago et al ²⁷ postulated that follicles show an infundibular differentiation ²⁷.

In the maturation phase (stabilization), KA presents with the following findings: (i) characteristic crateriform appearance (multilobular, enlarged infundibular structures, exoendophytic lesion with a large keratotic plug in the center); (ii) overhanging epithelial lips with a normal overlying epidermis; and (iii) neoplastic lobules characterized by a proliferation of glassy, large, pale cells with an eosinophilic cytoplasm showing compact keratinization in most specimens. At this stage, KA is shown to differentiate towards follicular isthmus ^{28,29}.

DIFFERENTIAL DIAGNOSIS

Differential diagnoses of KA include SCC, amelanotic melanoma, molluscum contagiosum, prurigo nodularis, metastatic skin lesion, Merkel cell carcinoma, nodular basal cell carcinoma, ulcerative basal cell carcinoma, nodular Kaposi sarcoma, hypertrophic lichen planus, deep fungal infection, atypical mycobacterial infection, foreign body reaction and verruca vulgaris ^{30,31}.

TREATMENT/MANAGEMENT

Although KA is considered to be a benign lesion, treatment is recommended due to its relationship with SCC. Excision with a surgical margin of 3- 4 mm from the healthy skin is one of the treatment options, while small lesions on the extremities that are smaller than 2 cm can be treated with electrodesiccation and curettage. Tissue-preserving surgery may be required in lesions located on areas that pose cosmetic problems and in aggressive tumors that are larger than 2 cm, and Mohs micrographic surgery may be considered ^{1,18,19,32}.

Nonsurgical treatment options include the topical application of %5imiquimod cream, % 5 5-fluorouracil (5-FU) cream, intralesional methotrexate, intralesional bleomycin, and intralesional 5-FU and oral isotretinoin. These treatments, however, have been limited to case reports and retrospective reviews. Most data suggest the use of intralesional 5-FU and methotrexate, administered at a dose of 40–75 mg for 3–8 weeks, from which a % 98 response rate has been achieved. There is a lower number of reported cases that were treated with intralesional methotrexate injection, and although regression has been reported in % 83–100 of patients, it has been suggested that the study was of spontaneously regressing lesions. These series are based on clinical observations and do not rely on histopathological examinations ^{32,33} (Table 1).

Table 1. Keratoacantoma treatment options

Surgery Treatment	Medical Treatment
Total Excision	Topical Treatment
Electrodesiccation or	%5 imiquimod
Curettage	%5 5 FU
Mohs Micrographic Surgery	Intralesional Treatment
	Methotrexate
	Bleomycin
	5-FU
	Systemic Treatment
	Methotrexate
	5-FU
	Systemic Retinoids
	Acitretin
	Systemic Corticosteroids
	Erlotinip

Solitary KA

There is an ongoing debate over the treatment of solitary KA. A wait-and-see strategy may be used for solitary KA with the assumption of spontaneous regression, although it is difficult to predict to what extent a KA will enlarge before entering the regression phase, and it may leave a scar with the potential to cause a cosmetic problem ^{3,33,34}.

KA has a low potential of differentiation into metastatic invasive SCC. In a literature review conducted by Savage and Maize ³⁵ in 2014, no single case of KA that resulted in mortality was reported, although their study could not identify a clear relationship between KA and the tendency for metastasis, and similarly, Hodak et al.³⁶ reported no deaths related to metastatic SCC among patients with KA.

As there is no recommended surgical margin for the excision of KA, the 5 mm margin used for noninvasive SCC is advised, considering that this excision will remove % 95 of the lesion ^{37,38}.

Negative surgical margins indicate the complete removal of the lesion, whereas positive margins do not necessarily indicate a risk of tumor recurrence ³⁷.

Mohs micrographic surgery is preferred in large KAs (containing KA centrifugum) and/or in areas that are prone to cosmetic problems. A deep curettage of the entire KA can be an alternative approach to small lesions, but this must be followed up by a histological evaluation. Increased SCC/KA ratios in pathology reports can be expected considering the fact that the sample obtained from the lesion with curettage will not be of full thickness, along with the tendency of dermatopathologists to recognize SCC ^{3,5,36,37,38}.

In the treatment protocol devised by Klein et al.³⁹, a proper incisional skin biopsy was made, followed by intralesional chemotherapy. Chemotherapy is the second line of therapy in the treatment of KA, although its precise efficacy has not been demonstrated. Methotrexate, 5-fluorouracil, bleomycin and interferon are options for intralesional injection therapy. It has been demonstrated intralesional chemotherapy prior to surgery reduce tumor sizes by % 50–80, and so it is suggested that a two-stage therapy for large KAs would ensure better cosmetic and functional outcomes ^{38,39}.

Multiple KAs

Systemic acitretin and other retinoids are the first-choice monotherapy, or in combination with surgery in multiple KA variants, or combined with other second line procedures in solitary tumors. Acitretin doses vary between 0.5 and 1.0 mg/kg at the beginning of the therapy, and patients may be switched to long-term maintenance therapies, if required. Smaller doses of 10–20 mg/d or repeated treatment methods can be continued to sustain clinical response ^{38,39}.

There are anecdotal reports regarding the use of such systemic cytostatic agents as systemic methotrexate and 5-fluorouracil. In contrast to intralesional methotrexate, less is known about systemic methotrexate ^{35,40}. Intralesional 5-FU and systemic retinoids can be used combination for the treatment methotrexate-resistant cases of multiple KA, and this combination is also a good option for the treatment of KAs occurring in the grounds of prurigo nodularis, and cyclosporine, in addition to

systemic therapy, can be considered in these patients ⁴⁰. Erlotinib, a growth factor receptor inhibitor, is a new and promising option in resistant cases of KA, little is known about this agent ^{32,33,40}. In rare cases, systemic corticosteroids, either alone or in combination with systemic retinoids, have been shown to produce favorable outcomes in Grzybowski's GEKA ⁴⁰. In lesions such as KA or molluscum sebaceum that show spontaneous regression, the majority studies have advocated total excision of the lesion, considering that the lesion is indeed an invasive SCC, and transforms into this lesion afterwards. In a series of 1,000 cases, spontaneous regression was observed in only 20 percent of the lesions, as demonstrated in serial photography in less than 2 percent of all KAs (15 lesions) ^{34,35,40} (Table 2).

Table 2. Keratoacantoma Treatment Protocol

Surgical Treatment	Excision with a surgical margin of 3- 4 mm from the healthy skin is one of the treatment options
Electrodesiccation or curettage	It may be preferred for lesions smaller than 2 cm. Because the lesion is not completely removed, a false diagnosis can be made.
Mohs micrographic surgery	Can be preferred in aggressive occasions greater than 2 cm and in cosmetically sensitive areas
Topical application %5 imiquimod %5 FU	
Intralesional treatment Methotrexate Bleomycin 5-FU	Administered at a dose of 40–75 mg for 3–8 weeks
Systemic Treatment Acitretin and otherretinoids Methotrexate 5-FU	First-choice monotherapy, or in combination with surgery in multiple KA variants, or combined with other second line procedures in solitary tumors. Acitretin doses vary between 0.5 and 1.0 mg/kg at the beginning of the therapy
Intralesional 5-fluorouracil and systemic retinoids	The treatment of KAs occurring in the grounds of prurigo nodularis and multiple KA
Systemic Erlotinib	A growth factor receptor inhibitor, is a new and promising option in resistant cases of KA, little is known about this agent.
Systemic corticosteroids, either alone or in combination with systemic retinoids	Grzybowski's GEKA

PROGNOSIS

KA has a good prognosis after surgical excision. In general, patients require follow-up for primary skin cancers, as KA is generally observed in patients that are exposed to sunlight. These lesions have low potential of metastasis, although previous studies have shown the presence of a perineural invasion ^{5,8,23,40}.

The rate of recurrence varies between 1 and 8 percent. New KAs may present at the treatment site within 1 week to 8 months due to the koebnerization that occurs after surgery, cryotherapy, imiquimod and photodynamic therapy. Accordingly, patients should be advised to avoid predisposing factors, including intensive and prolonged periods of exposure to ultraviolet light, and they should self-examine predisposed body sites. Patients with a history of KA should be aware of the potential to develop new KAs due to trauma associated with medical and cosmetic procedures on photo damaged skin ^{34,34,40}.

Resources

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