Keratoacanthoma (KA): An update and review

Bartlomiej Kwiek, MD, PhD,[a] and Robert A. Schwartz, MD, MPH[b]
Warsaw, Poland, and Newark, New Jersey

Keratoacanthoma (KA) is a common but underreported tumor of the skin. Two striking features of KA are its clinical behavior with spontaneous regression after rapid growth and its nosological position on the border between benignity and malignancy. We review current knowledge on the clinical, histopathological, and dermoscopic features of KA to ensure a proper diagnosis and describe its variants, including different types of multiple KAs. We highlight current concepts of KA ethiopathogenesis with special emphasis on the genetic background of multiple familial KA, the role of Wnt signaling pathway, and induction of KA by BRAF inhibitors and procedures of esthetic dermatology. Finally, treatment strategies are presented with surgical excision as a first option, followed by other modalities, including intralesional chemotherapy, topical and systemic agents, lasers, cryotherapy, and photodynamic therapy. (J Am Acad Dermatol 2016;74:1220-33.)

Key words: BRAF inhibitor; erlotinib; Ferguson-Smith; Grzybowski; histopathology; keratoacanthoma; multiple keratoacanthoma; multiple self-healing squamous epithelioma; squamous cell carcinoma; treatment.

Keratoacanthoma (KA) is common and somewhat cryptic tumor in human beings. Although it had been described already in 1888 by Sir Jonathan Hutchinson,[1,2] its epidemiology, histopathological diagnostic criteria, prognosis, and treatment guidelines remain controversial.[3] Several names used to label KA, including "molluscum sebaceum," "pseudotumor," "regressing tumor," and "self-healing squamous cell carcinoma" (SCC), reflect some of these controversies.[4,5] The most common concern is related to its position on the border between malignancy and benignity. This imprecision makes it both challenging for a clinician and fascinating for a researcher, as this tumor may hold a key to understanding cancer regression.

Abbreviations used:

GEKA:	generalized eruptive keratoacanthoma
KA:	keratoacanthoma
MSHSE:	multiple self-healing squamous epithelioma
MTS:	Muir-Torre syndrome
SCC:	squamous cell carcinoma

EPIDEMIOLOGY

The true incidence of KA is probably underestimated because of misdiagnosis as a SCC, underreporting KA by physicians, or spontaneous regression before the diagnosis can be made. A 2014 study of Carr and Houghton[6] documented a huge difference in the SCC/KA ratio reported by pathologists from different centers in Great Britain and Ireland. This ratio varied from 2.5:1 to 139:1 and was influenced by each pathologist's approach to the diagnosis of KA.

Sporadic solitary KA has an incidence of 104 and 150/100,000 in Australian and Hawaiian populations, respectively.[7,8] It affects mostly fair-skinned people and was not reported in native Australians. Sun-damaged skin predisposes to KA; its peak incidence has shifted toward the age group 65 to 71 years from 50 to 69 years observed in 1990s.[3,9] Men are more often affected than women.[4,9] Variants of KA, including different multiple KA subtypes and KA centrifugum, are rare.

ETIOLOGY

In contrast to ordinary SCC, KA is assumed to originate from the hair follicle.[3,4] This concept of KA implies it is a benign counterpart of the follicular

From Dermatology and Immunodermatology, Medical University of Warsaw[a]; and Dermatology and Pathology, Rutgers University New Jersey Medical School, and Rutgers University School of Public Affairs and Administration.[b]

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Reprint requests: Bartlomiej Kwiek, MD, PhD, Dermatology and Immunodermatology, Medical University of Warsaw, Koszykowa 82A Street, 02-008 Warsaw, Poland. E-mail: bkwiek@wum.edu.pl.

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SCC rather than to ordinary SCC.[10] KA exhibits markers that are consistent with those found in the follicular isthmus and infundibulum. Its triphasic nature with proliferative (early, growth), stabilization (well-developed stage), and regression phases has led to the concept of a hair cycle mimicking nature with the KA.[11,12] In mice with KAs provoked by chemical carcinogens, KA tumor regression was not dependent upon the immune system, but to Wnt/retinoic acid signaling pathways that could support this hypothesis.[13] The role of the immune system in tumor appearance and resolution is controversial, but has to be considered.[11,14-17]

Other major signaling pathways potentially involved in KA pathogenesis are summarized in Table I.[18-25]

Rare cases of solitary and multiple mucous membrane KA, the latter in course of generalized eruptive KA (GEKA) of Grzybowski type, indicate the possibility of different origins of these tumors and differentiation into upper segment hair follicle–like cells.

CAPSULE SUMMARY

- There remains confusion in establishing the diagnosis of keratoacanthoma (KA), which can lead to misdiagnosis followed by inappropriate treatment.
- This article summarizes recent data on epidemiology, genetic background, pathophysiology, and histopathology of KA. It also updates classification of KA types and reviews current treatment strategies.
- A correct diagnosis of KA based on clinicopathological findings facilitates appropriate treatment and provides a wide spectrum of available therapies.

Genetic background

Predisposing genes for solitary sporadic KA are not known. DNA repair failures associated with the Muir-Torre syndrome (MTS) and xeroderma pigmentosum lead to development of multiple tumors, including KAs.[3,26,27] Disease-specific mutations in transforming growth factor beta receptor 1 have been described in multiple KAs of Ferguson-Smith type; however, further studies indicated this entity as digenic rather than monogenic.[28,29]

Provoking factors

Both natural and artificial ultraviolet exposure is a predominant risk factor for KA.[7,30-34] We have observed development of KA on the x-ray-exposed hand of an interventional radiologist. In fact, roentgen radiation is a well-documented causative factor for KA.[35,36] Other provoking factors are summarized in Table II.[37-43]

CLINICAL MANIFESTATIONS

Solitary KA

The most common variant of KA is the sporadic and solitary one (Fig 1). Usually it is 1 to 2 cm in diameter and 0.5 cm in thickness. However, it can vary from a few millimeters up to more than 20 cm in the KA centrifugum variant, also known as KA centrifugum et marginatum.[44] It cannot be judged at the initial stage how large an individual KA will grow before it will undergo resolution. The first case of KA centrifugum, described by Miedzinski and Kozakiewicz[44] in Gdańsk, Poland, covered the back of hand. Since then several cases reaching 20 cm in diameter have been documented. The large solitary KA usually has a less regular shape that can mimic a coral reef. If a KA is large and not growing further, one can name them "giant" to distinguish that entity from the constantly enlarging KA centrifugum type.

Rarely solitary KA can be localized on mucous membranes, mostly in the oral cavity, but occasionally on conjunctiva or vulva.[45-50] Subungual KAs can be challenging both for diagnosis and management.[7,51-53]

Multiple KAs

Multiple KAs are rare and can be sporadic or familial. Multiple persistent KAs belong to the first group and are often named "multiple keratoacanthoma centrifugum (et marginatum)" to underline their resemblance to constantly growing neoplasms with a coral reef–like appearance (Fig 2).[54-57]

Multiple KAs may rarely be associated with prurigo nodularis, usually on the lower limbs of elderly women with sun-damaged skin.[58]

Multiple familial KAs of Ferguson-Smith type, also known as multiple self-healing squamous epithelioma (MSHSE) (Online Mendelian Inheritance in Man [OMIM] 132800), were first described in Scottish families. Genetically confirmed cases have been described worldwide.[28,59,60] A minor proportion of gene carriers are asymptomatic.

Only around 30 cases of GEKAs of Grzybowski type have been documented (Fig 3).[61-63] They were first described in 1950 in Warsaw by Marian Grzybowski.[63] Differences between GEKA and MSHSE are presented in Table III. The criteria for the GEKA diagnosis were proposed and divided into mandatory and variable (Table IV).[64] Visceral

Table I. Cell cycle regulatory pathways involved in the pathogenesis of keratoacanthoma

Pathway	
Wnt	- Wnt is activated in the growth and inactivated in the regression phase. Retinoic acid reverses Wnt-related KA proliferation, promoting tumor regression. That supports the idea of retinoid treatment of KA.
B-Raf	- KAs can appear in course of melanoma treatment with B-Raf inhibitors.
H-ras	- KA has H-ras mutation more commonly than does an ordinary SCC. - HRAS may be involved in the switch from proliferation into regression phase in the biphasic nature of both KA and Spitz nevus. - KAs can appear within nevus sebaceous. Nevus sebaceous is considered to be a segmental RASopathy. These KAs express mutated HRAS.
Hedgehog pathway	- KA can appear in the course of treatment with vismodegib, which is a hedgehog pathway modifier used for the therapy of basal cell carcinoma.
p27	- Cyclin-dependent kinase inhibitor p27 expression is present during the regression stage only, but not during KA growth.

KA, Keratoacanthoma; *SCC*, squamous cell carcinoma.

Table II. Keratoacanthoma provoking factors

Groups of factors	Provoking factors
Immunosuppression/ immunodeficiency	Iatrogenic: Immunosuppressive and immunomodulatory drugs: Classic immunosuppressant (eg, azathioprine, cyclophosphamide, corticosteroids) Leflunomide Biologic drugs (anti−tumor necrosis factor-alfa) Photochemotherapy Noniatrogenic: Inherited immunodeficiencies Acquired immunodeficiencies: Leprosy, leukemia
Electromagnetic radiation	UVA, UVB, UVC, x-rays including megavoltage radiation
Trauma−koebnerization	Iatrogenic: Surgical procedures Chemical peelings Dermabrasion/microdermabrasion Ablative and coagulating lasers (including fractional lasers) Cryotherapy Photodynamic therapy Irritation after topical drugs (imiquimod) Noniatrogenic: Tattoos Traumas
Chemical factors	Tar
Drugs influencing cell cycle	BRAF inhibitors (vemurafenib, dabrafenib) Hedgehog pathway inhibitor (vismodegib)
Foreign bodies	Tattoos Hyaluronic acid with acrylic hydrogel fillers Collagen fillers

UV, Ultraviolet.

malignancies may be associated with this variant; however, they are far more specific for multiple KAs in the setting of MTS.[26]

Multiple familial KA of Witten and Zak type is not well characterized. It shares clinical features of MSHSE and GEKA by having multiple tiny KAs and typical bigger ones coexisting in the same patient. Most cases in the literature can be classified as MSHSE, or as GEKA, or the newly recognized KA associated with prurigo nodularis.[64-67]

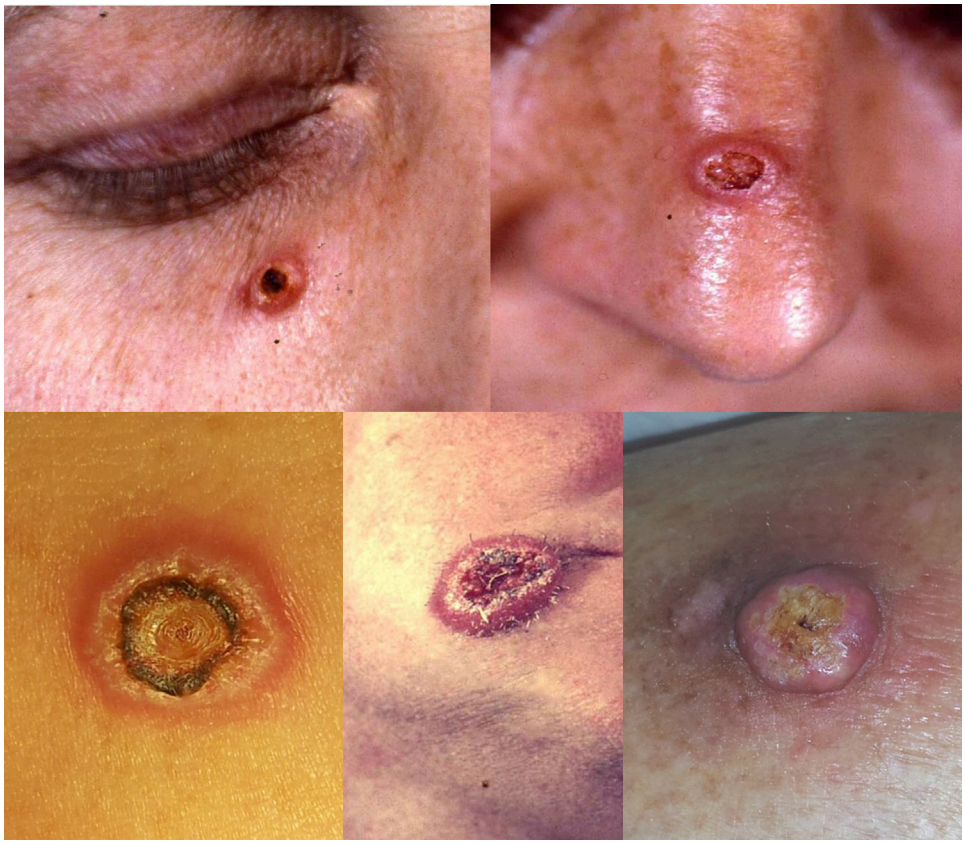

Fig 1. Keratoacanthoma (KA). The solitary and sporadic variant is the most common variant of KA. The lesion starts as a minute papule. The mature KA is a dome- or bud-shaped well-demarcated umbilicated nodule with a hyperkeratotic plug in the center. It is typically localized on sun-exposed areas and evolves in 3 clinical stages: proliferative, mature, and resolving. The process from origin to spontaneous resolution usually occurs within 4 to 6 months and can lead to atrophic hypopigmented scar.

KAs related to predisposing or provoking conditions and factors

Multiple KAs can also appear in the context of rare genetic disorders that predispose to carcinogenesis, such as xeroderma pigmentosum and MTS.[3,26,27] MTS is characterized by appearance of multiple sebaceous adenomas and other sebaceous tumors along with KAs and high risk of visceral tumors. Subungual KAs were found in patients with familial incontinentia pigmenti.[68]

Iatrogenic KA induced by drugs or medical procedures are summarized in Table II.[14,20,25,32-34,36,40-42,69-74] With the rapidly growing number of esthetic and antiaging procedures, the risk of inducing KA on sun-damaged skin by laser procedures (mostly resurfacing, including fractional laser), chemical peels, and fillers has to be considered. Koebnerization can also appear in the course of KA treatment with topical drugs (imiquimod) or surgical procedures, increasing the numbers of treatment failures mimicking tumor regrowth after incomplete removal.

DERMOSCOPY

Dermoscopy of KA shares some features with SCC and cannot be used to clearly differentiate these 2 entities.[75,76] Keratin had the highest sensitivity to differentiate KA and SCC from other amelanotic nodules, and white circles had the highest specificity. Both features together with dot vessels are useful predictors for the diagnosis of KA and SCC. It can help to differentiate other crateriform rapidly growing nodules, including amelanotic melanoma.[77] Typically, dermoscopy of KA appears as concentric circles of central crater, surrounded by an ivory-whitish area and adjacent peripheral vessels and the most outer circle of whitish halo.[77]

HISTOPATHOLOGICAL EXAMINATION

Diagnosis of the KA is based on 3 principles: typical clinical presentation of a crateriform tumor, rapid (weeks to months) growth with a triphasic course, and histopathological examination of a suitable biopsy specimen.[78,79] Histopathology of KA is enhanced

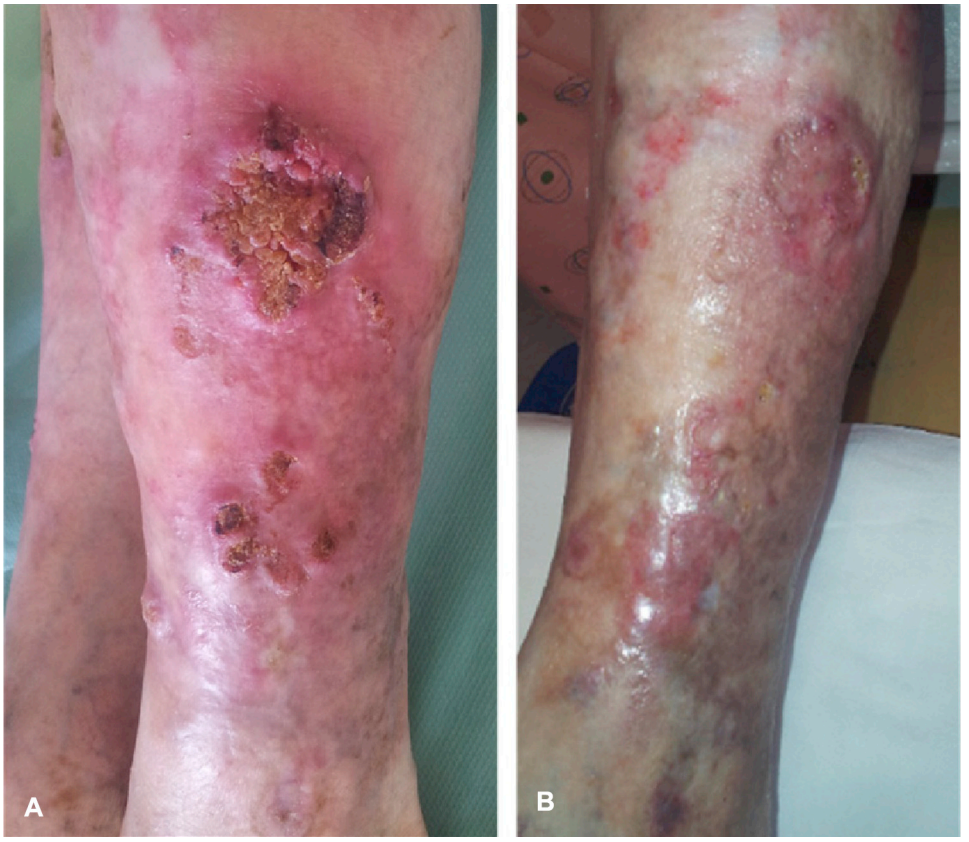

Fig 2. Multiple persistent keratoacanthomas (KA). **A**, This 71-year-old woman had multiple KAs varying in size from 1 to 5 cm without a tendency to undergo spontaneous remission and following the typical pattern of lower leg involvement. Some of the KAs aggregated and some lasted for 15 years, with a chronic course of constant growth with some lesions developing a coral-reef appearance as seen in solitary KA centrifugum marginatum. Linked with moderate itching, it was misdiagnosed as prurigo nodularis until the clear morphology of KA became obvious. **B**, Treatment with acitretin 0.5 mg/kg/d for 4 weeks followed by 20 mg/d (0.3 mg/kg/d) for another 8 weeks resulted in marked improvement.

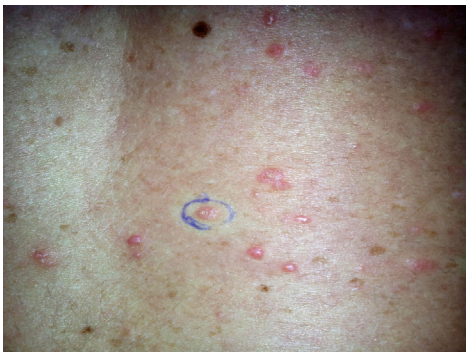

Fig 3. Generalized eruptive keratoacanthoma of Grzybowski. The back of a 51-year-old woman with generalized eruption of hundreds to thousands of small well-demarcated papules, some with keratotic center.

when the clinician is aware of the clinical diagnosis and performs an adequate biopsy.[4,79] As Dabska and Madejczykowa[78] emphasized in 1959, the specimen should be sufficiently representative, including subcutaneous fat, by total or partial excision or by a fusiform partial excision through the entire KA including its center and both sides. This approach allows analysis of not only cellular component, but also its full architecture. Not taking the sample properly may result in a diagnosis of SCC and can lead to overtreatment. Deep shave biopsy of a small KA (during curettage) can be used; however, the deep part of the tumor can be missed.

Cellular characteristics of KA are similar to those of SCC; the architecture is a key feature to establish diagnosis (Fig 4).[3,80] There are several approaches to distinguish these 2, but none of them have proved to be sufficient.[16,81-116] The differences between SCC and KA are summarized in Table V.[117-119]

Some dermatopathologists prefer to use the term of "squamous cell carcinoma, keratoacanthoma type" or "probable keratoacanthoma; squamous

Table III. Comparison of multiple familial keratoacanthomas of Ferguson-Smith and generalized eruptive keratoacanthomas of Grzybowski

	KAs of Ferguson-Smith	GEKA of Grzybowski
Family history	Positive, autosomal dominant inheritance	Negative
Onset	First to seventh decade of life	Fifth to seventh decade of life,
Course	KAs slowly grow and resolve within months, but more new KAs are continuously appearing	Eruptive onset and progressive
Lesions:	- Varies among individuals	- Hundreds to thousands
- No.	- Large papules (around 1 cm on the face and bigger on	- Small, miliary (1-2 mm)
- Size and shape	limbs) with horny plug that can fall out leaving an ulcer	- Dome-shaped follicular papules with or without keratotic center
Distribution	Extremities and face (nose, ears, circumoral) Trunk is rarely affected and palms and soles are not affected	Generalized; sun-exposed areas including upper aspect of trunk and face; intertriginous areas
Scarring	Pitted scars, more disfiguring on the face than on the limbs	Not pronounced
Pruritus	Not present	Prominent

GEKA, Generalized eruptive keratoacanthoma; *KA*, keratoacanthoma.

Table IV. Diagnostic criteria for multiple eruptive keratoacanthomas proposed by Nofal et al[64] and modified by the sixth consistent criteria: lack of family history of multiple keratoacanthomas

Consistent criteria
Onset in adulthood (usually fifth to seventh decade of life)
Generalized eruption of hundreds to thousands of small well-demarcated papules, some with a keratotic center
Progressive course
Severe and persistent pruritus
Histopathology consistent with KA
Lack of family history of multiple KA
Variable criteria
Masked face (“mask of Zorro” sign)*
Mucosal lesions
Crateriform nodules (typical solitary KA)
Ectropion

KA, Keratoacanthoma.
*Included into variable criteria is extensive facial involvement that affects predominantly periorbital region.

cell carcinoma cannot be ruled out.” The study of Carr and Houghton[6] placed emphasis on the importance of clinical description, quality of the specimen obtained with excisional biopsy, and evidence of regression favoring KA diagnosis. The last feature decreases the ratio of SCC/KA diagnosis in those centers with longer wait times for surgery.

A variety of different immunohistochemical staining for several markers has been used to help to distinguish KA from SCC (Table VI).[16,90,93,101,103,106,108,109,112,113,116,120-127] Unfortunately, the huge number of potentially specific markers used is testimony to the fact that there is no really adequate one.

Histopathology is necessary to rule out other diseases that can present as crateriform papules or nodules (Table VII),[53,118,128-140] and can delineate variants of SCC, especially the follicular SCC, which may mimic KA.[139,140]

KA TREATMENT

Solitary KA

Controversies remain about the management of the solitary KA. A wait-and-see strategy for a solitary KA, which assumes spontaneous regression, is questionable unless clear signs of involution are already present.[141] One cannot predict the final size of a KA that can reach several centimeters before it will regress, leaving a potentially disfiguring scar. The potential for transformation into invasive SCC with metastases is extremely low; however, it has to be considered when choosing the treatment.[142-144] Interestingly, there has been no single case of KA reported in the literature that has led to fatal outcome, as reviewed by Savage and Maize[145] in 2014. It has to be mentioned that the authors did not include the patient who died from metastatic SCC described by Hodak et al[144] because of an inadequately proven link between KA and metastases. The diagnosis of KA should correlate clinical and histologic findings, implying a tissue specimen is highly desirable before or concurrent with treatment.

Whenever possible, surgical treatment is a gold standard regimen with full-thickness fusiform excision providing good esthetic outcome and an optimal specimen for the pathologist. Unfortunately, there are no specific margins established for KA, but the same as for noninvasive SCC can be advised (5 mm) to assure 95% chance of complete

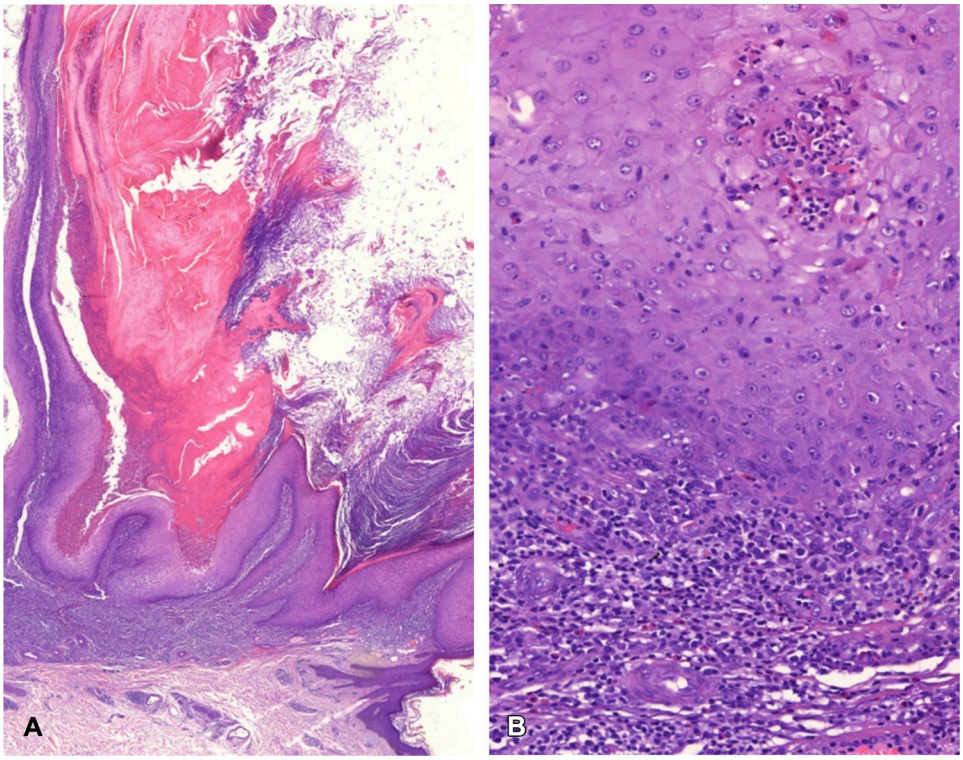

Fig 4. Histopathology of keratoacanthoma (KA). **A**, Epithelial lip at the periphery that extends partially over the central keratin plug and dense lichenoid infiltrate. **B**, Glassy appearance of keratinocytes along with lymphocytic and eosinophilic infiltrate. Intraepithelial microabscess is not always judged as a hallmark of KA.

Table V. Histopathological features used for keratoacanthoma and squamous cell carcinoma differentiation

Histologic feature	KA vs SCC
Symmetry*	KA>>SCC
Epithelial lipping*	KA>FSCC>SCC
Sharp demarcation between tumor and stroma*	KA>SCC
Ulceration*	KA<SCC
Mitoses*	KA<SCC
Pleomorphism/anaplasia*	KA<SCC (SCC randomly scattered; KA gradually increased in deeper parts of tumor)
Ground-glass appearance*	KA>FSCC>SCC
Intraepithelial elastic fibers	KA>SCC
Keratin-filled crater	KA>SCC
Extension beyond sweat glands	KA<SCC
Intraepithelial abscess	KA=SCC or KA>SCC depending on author
Lateral growth predominance	KA=SCC
Dyskeratosis	KA=SCC, KA<FSCC
Parakeratosis	KA=SCC or KA<SCC depending on author
Acantholysis	KA<SCC; FSCC has intraepithelial mucin in association with acantholysis in >50% of cases, which is not seen in KA
Perineural invasion	SCC, aggressive behavior KA, not consistent sign of aggressive behavior

FSCC, Follicular squamous cell carcinoma; *KA*, keratoacanthoma; *SCC*, squamous cell carcinoma.
*None of the 16 histologic features can be used as a clear-cut criterion for the diagnosis or exclusion of keratoacanthoma, but the most valuable ones are marked with asterisks. FSCC can clinically mimic keratoacanthoma in 15% of cases. The most distinctive features of this variant important for differential diagnosis of keratoacanthoma are indicated.

Table VI. Spectrum of selected histochemical and cytogenetic markers that were proposed to be of value in keratoacanthoma/squamous cell carcinoma differentiation

Group of markers	Marker	KA/SCC
Inflammatory infiltrate		
Plasmacytoid dendritic cells	BDCA2	KA>SCC
Regulatory T cells	$CD3^{+}FoxP3^{+}$	KA<SCC
Macrophages	CD163	KA<SCC
IL-27—producing cells	IL-27	KA>SCC
Apoptosis/cell death		
	Bcl-2	KA<SCC
	Bcl-x	KA<SCC
	AIF	KA<SCC
	TUNEL	KA>SCC
	Le^{y}	KA>SCC
	Cyclin A and B	KA>SCC
	$P2X_7$	KA>SCC
Proliferation		
	NUCKS	KA<SCC
	PCNA	Different patterns
	IMP3	KA<SCC
Differentiation		
	Keratins	Outer root sheath beneath infundibulum pattern of KA and epidermis pattern of SCC
	Filaggrin	KA>SCC
Signaling		
	p53	KA<SCC
	p50	KA>SCC
Adhesion and migration		
	VCAM (CD106)	Expression associated with triphasic nature of KA and maturation status of SCC
	ICAM (CD54)	
	Syndecan-1	KA>invasive SCC
	Desmoglein 1 and 2	Different pattern
	E-cadherin	KA>SCC
	Cortactin	KA>SCC
	Lectins	KA>SCC
Genetic		
	Microsatellite instability and loss of heterogenicity	KA in the setting of Muir-Torre syndrome
Other		
	Oncostatin M on: - Tumor cells - Macrophages - COX2	KA>SCC KA<SCC KA<SCC

AIF, Apoptosis inducing factor; *Bcl-2*, B-cell chronic lymphocytic leukemia/lymphoma-2; *Bcl-x*, B-cell chronic lymphocytic leukemia/lymphoma-2 related genes; *BDCA*, blood dendritic cell antigen; *COX-2*, cyclooxygenase 2; *FoxP3*, fork-head box P3; *ICAM*, intercellular adhesion molecule; *IMP3*, insulin-like growth factor II mRNA binding protein 3; *IL*, interleukin; *KA*, keratoacanthoma; *Le^{y}*, Lewis- y; *NUCS*, nuclear ubiquitous casein and cyclin-dependent kinases substrate; *$P2X_7$*, ionotropic P2 receptor family 7; *PCNA*, proliferating cell nuclear antigen; *SCC*, squamous cell carcinoma; *TUNEL*, terminal uridine nick-end labeling; *VCAM*, vascular cell adhesion molecule.

removal.[146-148] Negative margins are of predictive value for complete removal. Positive margins usually do not indicate tumor recurrence.[149] Mohs micrographic technique is desirable for large KA (including KA centrifugum) and/or those in cosmetically sensitive areas.[150] Deep curettage of an entire KA can be an alternative approach for small ones, but has to be followed by histologic evaluation. Paradoxically, curettage is probably increasing the ratio of SCC:KA in pathology reports, as dermatopathologists tend to overdiagnose SCC when they do not have a full-thickness specimen.[6]

We often use intralesional chemotherapy after obtaining a properly performed incisional skin

Table VII. Differential diagnosis of keratoacanthoma

Crateriform lesions with SCC features	KA-like SCC
	KA with malignant transformation
	Follicular (infundibular) SCC (crateriform)
	Crateriform SCC arisen from actinic keratosis
	Crateriform Bowen disease
	Verrucous carcinoma
	Onycholemmal carcinoma (for subungual KA)
Other tumors	Exophytic pilomatricoma
	Cutaneous metastatic disease
	Amelanotic melanoma
	Primary cutaneous CD30 anaplastic large-cell lymphoma
Infectious diseases	Cryptococcosis
	Chromoblastomycosis
	Sporotrichosis
	North American blastomycosis
	Tuberculosis verrucosa cutis
	Giant molluscum contagiosum
Inflammatory diseases	Prurigo nodularis
	Hypertrophic discoid lupus erythematosus
	Hypertrophic lichen planus
	Halogenoderma

KA, Keratoacanthoma; *SCC*, squamous cell carcinoma.

biopsy specimen, following the regimen originated by Klein et al.[151] It is the second-line option of KA treatment, but evidence of efficacy is limited.[152] Methotrexate and 5-fluorouracil are preferred as intralesional drugs, with bleomycin or interferons being another option. Methotrexate usually requires 2 or more injections to obtain remission.[153,154] Intralesional chemotherapy can precede surgery to reduce the size of tumor of about 50% to 80% before the excision. Two-step regimen provides a better cosmetic and functional outcome than intralesional treatment alone.[155] Other therapeutic modalities, including those preferred for KA centrifugum, are summarized in Table VIII.[74,151,156-166]

Multiple KAs

Systemic acitretin or other retinoids are a first-line option for variants of multiple KA, as monotherapy or combined with surgery or other second-line procedures as for solitary tumor.[167,168] The dosage varies from 0.5 to 1.0 mg/kg of acitretin at the beginning of treatment and can be tapered as needed. A marked response is usually evident; however, total long-lasting clearance is hardly ever achieved (Fig 2, *B*). Smaller doses of 10 to 20 mg/d of acitretin or repeated courses of treatment are often necessary to sustain clinical response. Resistant KAs may occur, especially in GEKA of Grzybowski,[169] and require other approaches.

Reports on the use of systemic cytostatic agents, such as systemic methotrexate and 5-fluorouracil, are anecdotal. In contrast to intralesional methotrexate, the efficacy of systemic methotrexate is less predictable. Cyclophosphamide was shown to be effective in retinoid- and methotrexate-resistant cases of multiple KAs with pulses of 1 g per month given to reduce cumulative dose and the risk of long-term toxicity.[169] Erlotinib, an epidermal growth factor receptor inhibitor, is a new promising approach for resistant KAs; however, experience with it is still limited.[170] Intralesional corticosteroids are occasionally used in GEKA of Grzybowski type with good response either as monotherapy or with systemic retinoids. The latter combined treatment is a good option in KA arising in the setting of prurigo nodularis.[58,171] The addition of cyclosporine to systemic treatment in these cases may also be considered.[58]

KAs in patients treated with BRAF inhibitor

Solitary KAs related to BRAF inhibitor therapy were successfully treated with total surgical excision and photodynamic therapy. Multiple KAs can be also handled with systemic retinoids combined with intralesional 5-fluorouracil.[128,172] The appearance of KAs in this setting should not influence melanoma treatment.

Follow-up

Patients should be monitored after KA removal. The recurrence rate ranges from 1% to 8%. In addition, a new KA can appear at the site of treatment within 1 week and 8 months because of koebnerization sometimes evident after surgery, cryotherapy, imiquimod, and photodynamic therapy.[173] Patients should be advised to avoid provoking factors, including intense and prolonged ultraviolet light exposure, and to perform self-evaluation in all predisposed areas. Patients with the history of KA should be informed about the higher risk of new KA appearance after traumatizing medical or cosmetic procedures performed on photo-damaged skin.

Conclusion

Rare cases of KA that evolved into SCC or that behaved as malignant tumors have changed the clinical perspective of KA during the last 30 years.[142-144,174] The management of KA has evolved toward that used for well-differentiated SCC.[175] This approach is suitable as long as it does not compromise functional and esthetic outcome more than should be expected during the natural

Table VIII. Alternative to surgery and intralesional chemotherapeutics treatments for solitary keratoacanthoma

Treatment modality	
Ablative lasers	Both modalities are suitable for small KAs when surgery is not available or possible and should be preceded with histopathological examination
Cryotherapy	
Radiotherapy	Postsurgery when aggressive course is predicted or other options are contraindicated
Photodynamic therapy	Several sessions are required to obtain remission Cases of aggravation or induction of KA by this regimen have been described
Topical treatments: - 5-Fluorouracil - Imiquimod - Podophyllin	Can be used as monotherapy or sequential after ablative laser or other destructive techniques For imiquimod, 4-11 wk of application on a daily basis or every 2-3 d is necessary to obtain complete remission
Systemic erlotinib	Epidermal growth factor receptor inhibitor can be used for KA centrifugum when an aggressive course is evident and surgery or combined intralesional treatment and surgery are not possible or are ineffective
Systemic retinoids	In KA centrifugum when other options are not available or contraindicated

KA, Keratoacanthoma.

course of the KA. KA should be regarded as a separate entity with a distinct clinical appearance and course. Many studies addressing the problem of clear histopathological differentiation between SCC and KA support the concept of the peculiarity and importance of KA as a precise diagnosis. In KA, diagnosis should be based on clinical and pathological correlation. A correct diagnosis of KA discourages overtreatment, and provides a wider spectrum of treatment approaches than those recommended for various types of SCC.

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