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Aaron Tisack

A Fotouhi

Chelsea Fidai
Henry Ford Health, cfidai1@hfhs.org

Ben J. Friedman
Henry Ford Health, bfriedm1@hfhs.org

David M. Ozog
Henry Ford Health, dozog1@hfhs.org

See next page for additional authors

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DR AARON TISACK (Orcid ID : 0000-0002-7693-4729)
DR BEN JACOB FRIEDMAN (Orcid ID : 0000-0002-2266-8197)

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A Clinical and Biologic Review of Keratoacanthoma

A. Tisack,[1] A. Fotouhi,[1] C. Fidai,[2] B. J. Friedman,[2] D. Ozog[2] and J. Veenstra[2]

[1]Wayne State University School of Medicine, Detroit, MI

[2]Department of Dermatology, Henry Ford Health System, Detroit, MI

Corresponding Author: Jesse Veenstra, M.D., Ph.D.

Email: jveenst1@hfhs.org

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ABSTRACT

Keratoacanthoma (KA) is a common skin tumor that remains controversial regarding classification, epidemiology, diagnosis, prognosis, and management. Classically, a KA manifests as a rapidly growing, well-differentiated, squamoid lesion with a predilection for sun-exposed sites in the elderly and a tendency to spontaneously regress. Historically, KAs have been considered a variant of cutaneous squamous cell carcinoma (cSCC) and are often reported as KA-type cSCC. However, the

penchant for regression has led many to categorize KAs as biologically benign tumors with distinct pathophysiological mechanisms than malignant cSCC. The clinical and histopathological similarities between KA and cSCC, particularly the well-differentiated variant of cSCC, have made definitive differentiation difficult or impossible in many cases. The ambiguity between entities has led to the general recommendation for surgical excision of KA to ensure a potentially malignant cSCC is not left untreated. This current standard creates unnecessary surgical morbidity and financial strain for patients, especially the at-risk elderly population. There have been no reports of death from a definitive KA to date, while cSCC has an approximate mortality rate of 1.5%. Reliably distinguishing cSCC from KA would shift management strategies for KAs toward less-invasive treatment modalities, prevent unnecessary surgical morbidity, and likely reduce associated healthcare costs. Herein, we review the pathophysiology and clinical characteristics of KA, and conclude on the balance of current evidence that KA is a benign and distinct lesion from cSCC.

HISTORY

Initially described in 1888, the term 'keratoacanthoma' (KA) was coined in the 1940s to represent the marked acanthosis observed on histopathology.[1] However, 'Keratocarcinoma' was also applied in early literature to denote malignant potential, which stemmed from the many shared clinical and histological features with well-differentiated cutaneous squamous cell carcinoma (cSCC).[2] Thus, grouping KAs with cSCC has been the standard for over a century. A marker to readily delineate them has yet to be identified, making definitive diagnosis and clinical management challenging given the disparate behavior between the two lesions. Consensus between clinicians and pathologists on the diagnosis and treatment paradigm remains largely unresolved.[3]

Many strategies have been proposed to distinguish KA from cSCC with limited success. A variety of histopathologic criteria have been devised, but the abundance of similar morphologic features has made differentiation on histopathological grounds alone dubious.[4] In an attempt to further dichotomize KA and cSCC, an array of immunohistochemical markers have been utilized, including cytokine signatures, cell adhesion markers, cell surface receptors, and regulators of cell cycle/apoptosis.[5–14] Nevertheless, no strategy has reliably been able to predict biologic behavior.

CLINICAL BEHAVIOR OF cSCC AND KA

cSCC Epidemiology

cSCC is the most common type of cancer with metastatic potential and historically has accounted for approximately 20% of all cutaneous malignancies; however, recent studies indicate cSCC is increasing in incidence and may constitute up to 50% of non-melanoma skin cancer.[15–17] Malignant transformation of keratinocytes primarily arises in photo-damaged skin of elderly patients with fair skin.[18] Major risk factors include repeated ultraviolet exposure, radiation, immunosuppression, chronic non-healing wounds, and human papillomavirus (HPV) infection.[19–22] Additionally, the advent of targeted molecular therapies and immune checkpoint inhibitors has led to increased incidence of cSCC stemming from dysregulated cell-regulatory pathways.[23–27]

Although the prognosis of cSCC is typically favorable, nodal metastasis rates range from 4-6%, but have been reported as high as 30% for high-risk locations such as the lip and ear.[28,29] The 5-year survival rate for metastatic cSCC may be as low as 34.4%, and approximately 1.5% of all cases are

fatal.[30–32] Both the American Joint Committee on Cancer Staging Manual (AJCC) and the Brigham and Women's Hospital Tumor Classification System (BWH) have been utilized for cSCC staging; the latter of which may predict outcomes more accurately.[33]

KA Epidemiology

The incidence, rate of regression, and persistence of KAs remains poorly characterized. Reports estimate the incidence of KA to range between 100 and 150 cases per 100,000 individuals; however, this is likely grossly underestimated due to misclassification of these lesions as well-differentiated cSCC, underreporting, or spontaneous regression before diagnosis.[34,35] Risk factors for KA development are similar to that of well-differentiated cSCC; uniquely, cutaneous trauma (i.e., surgery, laser resurfacing, radiation) appears to be an additional risk factor for local KA development, suggesting dysregulated inflammatory responses may contribute towards its pathogenesis.[4,34,36–38] Neither the AJCC or BWH incorporate any additional consideration for KA-type cSCC.

KA Diagnosis

Currently, diagnosis of KA is based upon three key facets[38]:

1. Characteristic clinical presentation of a rapidly developing crateriform lesion over the course of weeks to months.
2. Triphasic evolution consisting of proliferation, stabilization, and regression (for untreated lesions).
3. Histopathology of an adequate specimen with intact architecture. Distinguishing a KA from well-differentiated cSCC relies on often subtle architectural and cytological differences.[39]

KA Morphology

Gross. Solitary KAs are the most common type, arising as minute papules that mature into dome- or bud-shaped, sharply circumscribed, umbilicated nodules with a central hyperkeratotic plug.[38] The process from origin to spontaneous resolution usually occurs over 4 to 6 months and may heal with or without prominent scarring. There are several other variants of KAs and associated syndromes (Table

1).[40–68] Each of these is classified as KA due to morphology; however, based on their disparate behaviors they may harbor different genetic drivers.

Imaging. The keratinocytic origin of both KA and cSCC makes discrimination unreliable by dermoscopy.[69] KAs are often characterized by a central, yellow-brown, structureless keratin plug surrounded by elongated hairpin vessels, but this is not specific to KAs.[70,71] One study of 32 cSCCs and 29 KAs found central keratin to be more common in KAs (51.2% vs. 30%)[69], whereas another study of 100 KAs and 410 cSCC found "branching vessels" more frequently in KAs (25% vs. 10.3%).[72] However, the low sensitivity and high variability of these features limits the clinical application of these findings. Reflectance confocal microscopy has also been investigated, but has similar issues as dermoscopy with poor discrimination between KA and cSCC.[73,74]

Micro: Histopathological Architecture and Cytology. Differentiating KAs from well-differentiated cSCC on routine histology can be difficult due to subtle distinguishing features. This is further complicated by the high frequency of biopsy samples that fail to include the complete tumor architecture.[3,5] Inadequate sampling of a KA is more likely to lead to a diagnosis of cSCC and potentially overtreatment. Best exemplifying the dermatopathologist's dilemma is the vast discrepancy in reported ratios of cSCC:KA, ranging from 2.5-139:1, among medical centers across Great Britain and Ireland.[3]

The histopathologic features of KAs are phase-dependent (Figure 1).[75,76] Early lesions consist of an exo-endophytic proliferation of pale squamous cells in lobules, some resembling distorted infundibular structures.[39] These start in contiguity with the adjacent epidermis and then progressively extend into the mid-to-deeper portions of the reticular dermis, with further extension beyond the sweat glands being unusual.[77] In later biopsies, the infundibular structures become more cystic and hyperkeratotic, coalescing to form a central keratin plug.

Well-developed KAs are largely symmetric with most peripheral tumor islands demonstrating little infiltration beyond the confines of the central mass.[78] Typically, there is buttressing of the surrounding normal epidermis around the tumor.[79] The peripheral keratinocytes notably have enlarged, pink, glassy-appearing cytoplasm, a low nuclear-to-cytoplasmic ratio, and minimal nuclear atypia.[39,76,80] A mixed infiltrate of inflammatory cells is common. In some cases, neutrophils and

eosinophils may be prominent, often extending into the epithelial islands forming small microabscesses.[78]

Regressing lesions are characterized by a well-formed crater of keratin with thinning of the surrounding squamous epithelium, fewer overall squamous lobules, and progressive development of underlying dermal fibrosis.[76,78] The main histopathologic features which are thought to exclude a KA and confirm a diagnosis of cSCC are the presence of asymmetry, extension beyond the sweat glands, signs of infiltration and associated desmoplasia, and the presence of more conspicuous nuclear atypia.[39,81] Often only 1 or 2 of these features are present (with the assessment of atypia being subjective), making the diagnosis especially difficult. Both murine models and human KAs have been utilized to characterize each of the phases by histopathology (Figure 1).[40,76,78]

Rare cases of metastasis purported to originate from KAs can be found in the literature; however, these exceptional scenarios can be challenged in a number of ways.[82–84] First, cSCC can probably arise within a KA, and it is that component that would be likely to metastasize.[85] Second, some KAs that have metastasized may have truly been cSCCs with a distinct follicular pattern of differentiation.[86] Third, a number of visceral carcinomas that can metastasize to the skin have the capability to masquerade as KA.[87,88] Depending on the adequacy of the original cutaneous biopsy, these former possibilities may or may not be detectable at the time of the initial diagnosis. The future development of a reliable, distinctive proteomic signature will help differentiate true KA from these other possibilities. Finally, some immunocompromised patients with large KAs have developed metastasis of unclear clinical significance.[84] This scenario undoubtedly calls for additional investigation regarding clinical outcome and whether or not further treatment that would be directed towards cSCC is necessary to prevent further morbidity or mortality. Interestingly, no cases of death from a definite KA have been reported.[82]

Furthermore, there is a significant prognostic difference between perineural invasion in KAs and cSCC; while perineural invasion is a poor prognostic factor in cSCC when involving a nerve in the subcutis > 0.1 mm in caliber, no metastasis or direct death are attributable to the presence of perineural invasion in KA.[89,90] One study of 18 patients with KAs of the head and neck with invasion of nerves (ranging from 0.04 mm-0.22 mm) treated with excision had no recurrences/metastasis after a follow-up period ranging from 3-12 years.[90] Similarly, another study of 4 patients with perioral KAs

exhibiting perineural invasion were treated with excision and had no metastasis after a follow-up period of 7-44 months. Based on a larger study of 3,465 KAs, perineural invasion had a reported incidence of 0.2% while estimates for cSCC range from 2%-14%.[17,51,85,89–92]

KA Treatment

Since the discovery of KA, management has remained controversial. Although a suspected regressing KA could be monitored for several months, it is difficult to predict the maximum size before the lesion regresses or how it will ultimately heal.[93] The current standard treatment of KA is that of a well-differentiated cSCC - surgical excision with clear margins; though this may be excessive given the dubious metastatic propensity of KA.[94] While tumors on the trunk and extremities can often be successfully excised with relatively little surgical morbidity, patients with lesions developing on sensitive areas or those with numerous lesions are more susceptible to increased surgical morbidity and disfigurement, such as ectropion.[36,38] Unfortunately, the skin of the head and neck is one of the most common areas affected due to repeated sun exposure.[95] This problem is amplified in the at-risk elderly population who commonly have facial lesions, frequent comorbidities, and limited physiologic reserve.[95,96] Other successful, less invasive treatment options for KAs are summarized in Table 2.[93,97–106] Based on the current literature, we recommend treating histopathologically definitive KAs conservatively after careful consideration to location, patient risk factors, and associated procedure risks.

TUMOR BIOLOGY

Cell Cycle/Regulation

The triphasic nature of the KA life cycle has drawn parallels to follicular morphogenesis, with anagen, catagen, and telogen cycles. This has led to the hypothesis that KAs have a follicular origin and undergo apoptosis akin to catagen involution of the hair follicle. Expanding upon this, a murine model of chemically induced KAs demonstrated that follicle signaling pathways, namely the Wnt and retinoic acid (RA) pathways, are important regulators of regression observed in KAs.[57] Wnt signaling was selectively active in the KA growth phase relative to the regression phase, and RA-mediated inhibition of Wnt was sufficient to induce KA regression. Furthermore, RA was able to induce

regression of a proportion of cSCC-like non-spontaneously regressing tumors via Wnt downregulation. These findings reinforce the use of retinoids in the treatment of KAs, especially in patients with multiple lesions.[51] It also provides further rationale for the use of retinoids, such as acitretin, as a prophylactic agent for patients at increased risk of keratinocytic carcinomas. Table 3 further expands upon key cell cycle regulators whose role in KA and cSCC has been elucidated in clinical studies.[13,18,49,51,56,107-127]

BRAF inhibitor therapy for melanoma has elucidated the role of RAS in both cSCC and KA development.[128,129] Recent studies demonstrate an increased frequency of gain-of-function RAS mutations (35%-60%) in BRAF inhibitor-induced cSCC versus sporadic cSCC (12%-20%).[130] BRAF inhibitor-induced KAs and cSCCs appear almost exclusively on sun-exposed skin, suggesting that BRAF inhibition in keratinocytes expressing wild-type BRAF acts as a 'second hit' in sun-damaged skin. It has been postulated that in ultraviolet-damaged keratinocytes harboring RAS mutations, BRAF inhibition leads to activation of the mitogen-activated protein kinase pathway, precipitating tumorigenesis.[129] Use of the BRAF inhibitor vemurafenib led to the development of cSCC in 16% of patients and KA in 10%.[129,131] Multi-kinase inhibitors, such as sorafenib, have similarly triggered growth of KAs and cSCCs; however, the mechanism has yet to be fully characterized.[132]

Apoptosis

KA possesses the ability to regress due to an upregulation of the apoptosis pathway when compared to normal skin.[111] Alternatively, cSCC express fewer pro-apoptotic factors with concurrent expression of anti-apoptotic factors supporting dysregulated growth (Figure 2).[133–135]

Genetics

KA and cSCC have distinct genetic signatures; transcript levels of more than 1,400 genes were found to be greater than fivefold differentially expressed between KA and SCC indicating disparate tumorigenesis pathways.[136] Further, comparative genomic hybridization of 132 KAs and 37 cSCCs showed significant differences in chromosome aberration between the groups.[121,137] Li *et al.* used comparative genomic hybridization to detect gross DNA copy number aberrations, which allowed for the discrimination of KA and cSCC in 85% of cases, as defined by a histopathological criteria.[138,139] A

higher degree of chromosomal instability was demonstrated in SCCs relative to KAs, with recurrent aberrations on chromosomes 7, 8 and 10.[138] Aberrations were less frequently found in KAs and when found involved chromosomes 19, 20, and X.[137] Additionally, loss of heterozygosity appears to be high in SCC and low in KA.[137,140,141]

Several genetic syndromes predispose individuals to KA development: Muir-Torre syndrome, Ferguson-Smith disease, and generalized eruptive KAs of Grzybowski (Table 1).[41,52–55,58,60,64] Generalized eruptive KAs of Grzybowski is considered a serious condition because the eruptions are diffuse, persistent, and recurrent.[53] The KAs associated with Muir-Torre syndrome demonstrate sebaceous differentiation and a loss of DNA mismatch repair genes products.[59,60] However, microsatellite instability and loss of heterozygosity that are present in Muir-Torre syndrome do not appear to play a role in general KA development.[4] Despite similar clinical presentations, the inter-disease relationship of genetic drivers, and between the broader category of solitary KA, remains unclear.

TUMOR MICROENVIRONMENT

Divergent immune reactivity further differentiates KA and cSCC (Figure 2). Both have a tendency to harbor elevated populations of immunosuppressive cells, with KAs having a higher proportion of activated lymphocytes.[5,7,121] This includes greater infiltration of $CD4^+$ T cells with an increased percentage expressing interleukin-2 receptor (CD25), a marker of activation.[7] However, this may be confounded by the population of $CD4^+$ regulatory T cells that express high levels of CD25 constitutively. Nonetheless, a greater number of interleukin-27 producing cells, which favors T helper type 1 differentiation and activation, in the KA tumor microenvironment is suggestive of an inflammatory milieu favoring antitumor response as compared to cSCC.[121] Moreover, recent multimodal analysis of human cSCC found greater populations of regulatory T cells, exhausted T cells, and tolerogenic dendritic cells relative to normal skin.[142] However, a similar multiomics approach has not yet directly compared cSCC and KA.

Both KA and well-differentiated cSCC can express elevated levels of the immune checkpoint molecule programmed cell death-1 (PD-1) and its ligand PD-L1. In a study examining tumor membrane staining for PD-L1, 33.3% of KAs and 26.9% of cSCC were positive, whereas actinic

keratosis and Bowen's disease were negative.[143] Additionally, tumor-infiltrating lymphocytes expressing PD-L1 were found in 33.3% of KAs and 34.6% of cSCCs. Thus, both KA and cSCC may have a variably immunosuppressive environment relative to precursor lesions. Tumor associated macrophages have been found to secrete elevated levels of matrix metalloproteinase 9, which plays a key role in remodeling extracellular matrix and has been widely implicated in carcinogenesis and metastasis.[144–146] Significantly increased matrix metalloproteinase 9 expressing tumor associated macrophages have been observed in cSCC vs. KA (266.7 ± 23.7 vs. 105.7 ± 25) reflecting their difference in malignant potential.[121]

Despite similarities in PD-L1 expression, KA and cSCC behave disparately in response to PD-1 checkpoint blockade; PD-1 inhibition is an efficacious treatment for advanced cSCC whereas the same therapy may precipitate eruptive KAs.[27] The lesions preferentially appear on sun-exposed skin similar to inhibitors of BRAF, TGF-beta, and JAK.[27,117,131,147] A recent report of 3 patients suggest that PD-1 inhibition leads to formation of KAs via upregulation of an inflammatory pathway and represents reactive hyperplasia, not neoplasia as observed in sporadic KAs; however, the mechanism has yet to be defined. Anti-inflammatory treatments, including hydroxychloroquine and topical steroids, led to resolution of both the underlying dermatitis and KAs in these patients.[148]

Prolonged immunosuppression greatly increases the risk of developing cSCC, but the risk is not as clear with KA.[17] T cell immune surveillance against commensal beta HPV suppresses cSCC in immunocompetent individuals, which is substantially blunted in immunosuppressed patients. Importantly, it was found that the increased risk of cSCC in immunosuppressed patients was caused by dampened immunosurveillance rather than the oncogenic effect of unchecked HPV.[149] In KA, HPV DNA has been identified in about half of cases and is more common among those from immunosuppressed individuals but has yet to be identified as a driver of tumorigenesis in KAs.[150–152]

DISCUSSION

Current research has led to improved understanding of KA and cSCC but has yet to elucidate a reliable set of criteria to discriminate between them. However, several morphological, biological, molecular, and immunological characteristics have begun to separate KA from the cSCC spectrum, suggesting a separate, but related, benign entity (Figure 2). Recent investigation of the Wnt and RA

pathways has led to new insights into the development paradigm of KAs, which has helped better distinguish them from cSCC. This, in conjuction with the differential immune reactivity and response to immune checkpoint inhibitors, suggests discordance in the pathways that lead to cSCC and KA development.

Identifying reliable markers to differentiate malignant cSCC from benign and reactive squamoproliferative lesions, such as KA, is crucial to avoid overtreatment and provide a wider degree of flexibility in treatment than those recommended strictly for cSCC. Definitive removal of cSCC is necessary due to the malignant potential these tumors possess, however, that does not appear to be the case with KAs, where noninvasive treatment options can be highly successful.[97,100] Additionally, new insights generated from Wnt pathway blockade suggest retinoids offer a viable treatment approach.[57] Clearly, KAs possess different molecular drivers, immune infiltrates, and phases of evolution, which may be targeted with a unique therapeutic approach.

Further investigation is needed to reliably discriminate KA from cSCC to better inform patient prognosis, guide clinical management, and optimize outcomes. Whole genome or total RNA sequencing looking beyond coding elements has yet to be performed. While multimodal single-cell analysis of cSCC has recently been undertaken, further single-cell studies of KA in direct comparison to cSCC are required to fully characterize unique cell populations, cellular interactions, and insights into the activation/behavioral status within the tumor microenvironement. This will enable the development of clinically applicable biomarkers for improved tumor characterization to better guide management strategies, encourage the use of less invasive treatments, and decrease surgical morbidity.

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FIGURE LEGENDS

Figure 1. Keratoacanthoma Evolution: Histopathological Features.

Figure 2. Comparison of KA and cSCC. Features of keratoacanthoma, left, and well-differentiated cutaneous squamous cell carcinoma, right. Gross images as well as low- and high-power histopathology exemplify the similar but varied presentation of these entities. Prominent nuclear changes, intracellular factors, and tumor microenvironment features of both lesions are listed. Cutaneous squamous cell carcinoma has greater expression of the anti-apoptic factors Bcl-2, Bcl-xL, and Bcl-X and pro-apoptotic factors AIF and M30.[14,133,135,153,154] Keratoacanthoma demonstrates greater expression of pro-apoptotic factors P2X7 and Bak.[120,134,135] Overall, pro-apoptotic markers have been found to be more prominent in KAs relative to cSCC. cSCC tended to exhibit a proliferative phenotype with concurrent expression of anti-apoptotic markers supporting dysregulated growth.[133] Created with BioRender.com. Abbreviations: cSCC, cutaneous squamous cell carcinoma; KA, keratoacanthoma.

Table 1. KA Variants and Syndromes

Type of KA	**C**linical **Features**	**Genetic Defect**
Solitary KA	Most common, sporadic, 5-15 mm solitary lesions[38]	Multiple (i.e., *Wnt* and *TP63* upregulation)[49,56,57]
KA Centrifugum et Marginatum	Solitary or multiple annular plaques progressively expanding peripherally with elevated, rolled margins and central resolution rapidly reaching 3 cm in diameter, but may be as large as 30 cm[45,46,48,50,65]	HPV 6 and 11 have been associated[47]
Giant KA	Greater than 2-3 cm,can be >20 cm in diameter associated with slover, but prolonged, growth and frequently involving the nose and eyelids[42,43,66,67]	HPV 6 and 11 have been associated[44,68]
Generalized Eruptive KAs of Grzybowski	Thousands of papules resembling milia or xanthomas with frequent mucous membrane involvement and severe pruritus most frequently affecting patients in their 50s-70s; resolve slowly over months with scarring and ectropion; associated with visceral malignancies[41,53–55]	HPV 16 and 39 have been associated[41,51]
Multiple self-healing squamous epithelioma (also known as Ferguson-Smith disease)	Multiple spontaneously regressing KAs in sun-exposed sites beginning in the third decade of life; regress over weeks to months; Overlapping features of Grzybowski and of Witten and Zak[52,58]	Autosomal dominantly inherited loss-of-function mutations in *TGFBR1* [52]
Multiple Familial KA of Witten and Zak	Multiple KAs in childhood, heal spontaneously; Overlapping features of Ferguson-Smith and Grzybowski[61,63]	Likely autosomal dominant inheritance of an unknown gene[63]

Muir-Torre syndrome	Characterized by sebaceous neoplasms, KAs, as well as several internal malignancies[60,64]	Defective mismatch repair genes (*MLH1*, *MSH2*, *MSH6*) leading to microsatellite instability[59,60]

HPV, human papillomavirus; KA, keratoacanthoma.

Table 2. Evidence for Treatment Modalities of Keratocanthoma

Treatment	Sample Size (n)	Clearance Rate (%)	Recurrence Rate (%)	Follow-Up	Study	Evidence Quality*
Excision	84	100	0	6-8 weeks	Moss et al.[101]	B
Electrodessication and Curettage	111	100%	3.8%	≥2 years	Nedwich[102]	B
Cryosurgery, Electrodessication, and Curettage	90	97.8%	0%	2 years	Panagiotopoulos et al.[103]	B
Intralesional Methotrexate	73	88%	0%	6-8 weeks	Moss et al.[101]	B
	69	95.7%	NR	NR	Smith et al.[99]	B
	60	92%	NR	NR	Seger et al.[104]	A
	38	92%	0%	1 month-7.6 years (average 1.8 years)	Annest et al.[105]	B
Intralesional 5-Fluoruracil	53	96%	NR	6-8 weeks	Seger et al.[104]	A
Intralesional Bleomycin	6	100%	0%	1-3 months	Sayama et al.[106]	C
MAL Photodynamic Therapy	4	100%	0%	4 years	Farias et al.[98]	C
Topical 5-Fluoruracil	41	98%	NR	6-8 weeks	Seger et al.[104]	A
Topical Imiquimod	24	100%	NR	6-8 weeks	Seger et al.[104]	B
	4	100%	0%	6 months-4 years (avg. 19 months)	Jeon et al.[97]	C
Watchful Waiting	18	78%	0%	9 months- 8 years	Griffiths[93]	B

Decreasing Invasiveness

*Evidence was evaluated using grading criteria as discussed by Robinson et al.[155]

MAL, methylaminolevulinic acid; NR, not reported.

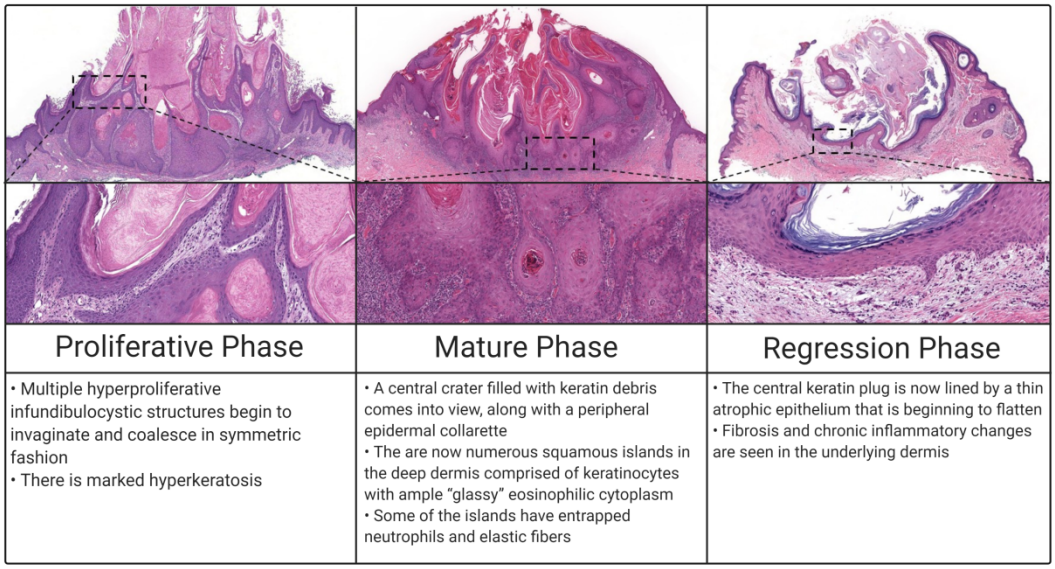
Table 3. Cell Cycle Regulators

Cell Cycle Regulator	Role	KA vs SCC	Subjects Examined	Clinical Relevance
TP53	Critical tumor suppressor gene involved in the activation of apoptosis. Mutated in close to all skin carcinomas due to UV radiation[18,122]	cSCC frequently harbor UV radiation–induced *TP53* mutations while KAs have infrequent p53 aberrations and, when present, correlate with age of the lesion and associated atypia[122–125]	30 squamoid lesions	Frequently mutated in cSCC.[122] Squamoid lesions without *TP53* mutations are more likely to exhibit histopathologic features similar to those of KA[126]
NOTCH	Direct target of p53; plays key role in epidermal keratinocyte differentiation	Loss of function mutations in *NOTCH1* and *NOTCH2* in 75% of cSCC[107,108]	20 cSCCs	Study by Mascitti *et al.* looking at a patient with eruptive KAs of Gryzbowsi found no genetic alterations in *NOTCH1*, *NOTCH 2*, or *TP53*[51]
Zmiz1, also known as retinoic acid-induced protein 17[109]	Encoded protein regulates activity of various transcription factors, including Smad3/4 and p53	Premature truncation of the protein led to the formation of KAs in the mouse model[76]	33 *Zmiz1* mutated mice vs. 42 control mice	Rogers *et al.* found that skin tumors induced by *Zmiz1* expression were consistent with diagnosis of KA rather than cSCC[110]
TPL2	Upstream regulator of MAPK, NF-	NF-κB activity promotes	105 cSCCs, 64 KAs,	TPL2 is a driver in cSCC and KA

	kB, and p38[111,112]	development of KA in mice; Lee *et al.* found that TPL2 is required for KA-like cSCC maintenance and that it is overexpressed in cSCC and KA compared with normal skin[111]	and 8 samples of normal skin	development and could be a possible drug target for treatment of cSCC/KA[111]
TGF-β	Widespread effects on tissue regeneration, homeostasis, and immune cell regulation	Loss-of-function mutations in *TGFBR1* are causative in cases of Ferguson-Smith disease, also known as multiple self-healing squamous epithelioma[113]	Genetic information from 143 members of 22 families with multiple self-healing squamous epithelioma	Recipients of fresolimumab, a TGF-β inhibitor, may develop unanticipated cutaneous toxicities, primarily KAs, as an adverse effect[117]
SOX2	Stem cell transcription factor	Drives cSCC formation and is absent in normal human epidermis; *SOX2* deletion in cSCC induces tumor regression and decreases the tumor's ability to propagate[118]	39 cSCCs and 8 samples of normal skin	*SOX2* is expressed in postnatal dermal papillae of hair follicles; KA could be of follicular origin[119]

p27	Inhibits cyclin-dependent kinases	Expressed in regressing KAs, but not in expanding KAs[13]	5 expanding and 15 regressing KAs	Could be considered as a target to involute proliferating or stable KAs
P63	Supports proliferation by suppressing expression of cyclin-dependent kinase inhibitor 1 and members of the NOTCH pathway[56]	Diffuse expression in cSCC while in KA expression is confined to basaloid cells[56,127]	16 KAs and 17 cSCCs	Expressed in a unique pattern in skin and other types of stratified epithelia making it a possible target for future inhibitor therapies[49]
Ki-67	Functions in the cell cycle, with roles such as maintaining integrity of mitotic chromosomes	Expression in cSCC>KA[114]	35 KAs and 36 cSCCs	cSCC with widespread expression of Ki-67 denotes a greater potential for growth compared to KA[114]
HIPK2	Regulates cell cycle and apoptosis, also directs transcription by inducing p53-mediated apoptosis	KA>cSCC[115]	43 KAs and 90 cSCCs	As a tumor suppressor and apoptosis mediator, *HIPK2* may be a future target for activating involution of KAs[115]
p50	Induces proinflammatory cytokines	KA>cSCC[116]	20 KAs and 20 cSCCs	Greater expression of p50 likely contributes to the more active immune response surrounding KAs[116,121]
Cortactin	Strengthens cadherin-dependent cell–cell junctions	KA>cSCC[116]	20 KAs and 20 cSCCs	Greater cortactin expression in KA likely represents lower metastatic potential due to stronger intercellular connections[120]

cSCC, cutaneous squamous cell carcinoma; KA, keratoacanthoma; MAPK, mitogen-activated protein kinase; NF-κB, nuclear factor kappa-B; TGF-β, transforming growth factor beta; TP63, tumor protein 63; TPL2, tumor progression locus



Proliferative Phase	Mature Phase	Regression Phase
• Multiple hyperproliferative infundibulocystic structures begin to invaginate and coalesce in symmetric fashion • There is marked hyperkeratosis	• A central crater filled with keratin debris comes into view, along with a peripheral epidermal collarette • The are now numerous squamous islands in the deep dermis comprised of keratinocytes with ample "glassy" eosinophilic cytoplasm • Some of the islands have entrapped neutrophils and elastic fibers	• The central keratin plug is now lined by a thin atrophic epithelium that is beginning to flatten • Fibrosis and chronic inflammatory changes are seen in the underlying dermis

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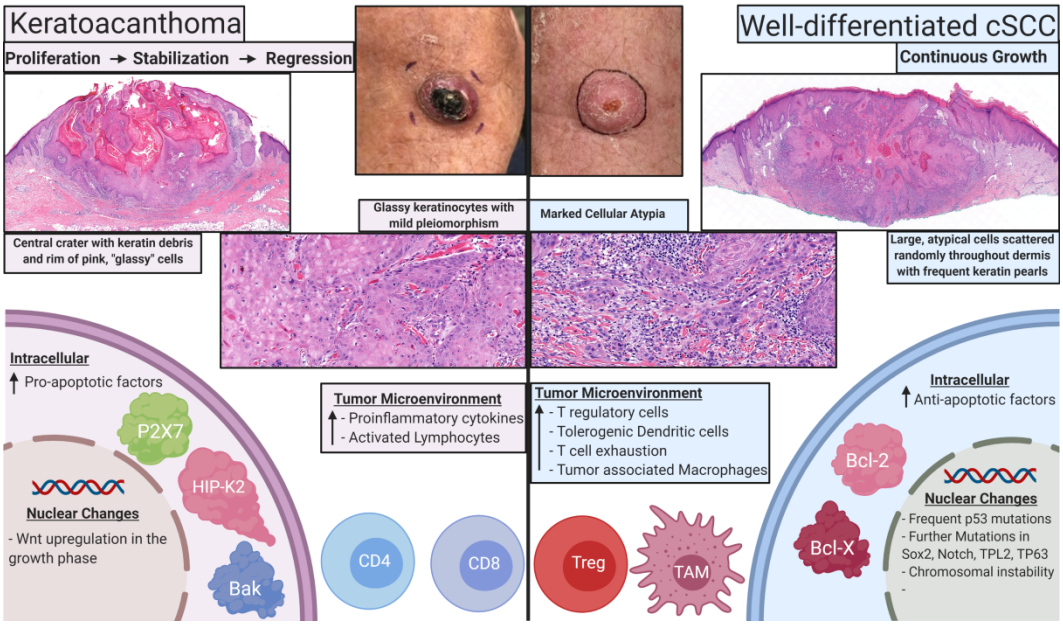

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