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Keratoacanthoma Revisited: Clinicopathological Features and Malignant Transformation in 115 Patients

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ABSTRACT

Objective: To evaluate the demographic, clinical, and histopathological characteristics of patients diagnosed with keratoacanthoma (KA) and to identify features that may aid in distinguishing benign KA from KA with malignant transformation.

Methods: This retrospective study included 115 patients with histopathologically confirmed KA who underwent total excision. Demographic, clinical, and histopathological data were reviewed and analyzed. Statistical comparisons were performed to identify parameters differentiating benign KA from KA with malignant transformation.

Results: The mean age of the patients was 65.1 ± 14.8 years, with a male-to-female ratio of 1.3:1. Solitary KA was the most common clinical presentation ($n=114$, 99.1%), with lesions predominantly located in the head and neck region ($n=88$, 76.5%). Histopathological evaluation revealed features of malignant transformation in 36.5% ($n=42$) of cases. Maximum tumor diameter and depth of invasion were significantly greater in cases exhibiting malignant transformation ($p=0.012$ and $p<0.001$, respectively).

Conclusion: Our findings suggest that histopathological parameters, rather than clinical and sociodemographic characteristics, are more strongly associated with malignant transformation in KA.

Keywords: Keratoacanthoma, histopathology, malignant transformation

INTRODUCTION

Keratoacanthoma (KA) is classified among non-melanoma skin cancer (NMSC) and most commonly arises in the head and neck region (1). It is generally regarded as a low-grade cutaneous tumor arising from the hair follicle (2). Its precise incidence remains uncertain due to frequent misdiagnosis as cutaneous squamous cell carcinoma (cSCC); however, available data suggest an estimated annual incidence of approximately 150 cases per 100,000 individuals (3).

The diagnosis of KA is based on three key components: (i) a characteristic clinical presentation of a rapidly developing crateriform lesion over weeks to months (Figure 1A and B); (ii) a distinctive three-stage clinical course in untreated cases, comprising proliferation, stabilization, and regression phases; and (iii) histopathological confirmation (4). Although histopathological findings vary depending on the stage, the stabilization phase typically demonstrates a crateriform architecture with epidermal

"lipping" (overhanging epidermal edges) at the lesion margins (Figure 2) (5).

According to the current World Health Organization classification, KA cannot be reliably distinguished histologically from well-differentiated invasive cSCC and is therefore considered a variant of cSCC (6). KA and cSCC share overlapping clinical and histopathological features, which may substantially complicate the diagnostic process (1).

This study aimed to analyze the demographic, clinical, and histopathological characteristics of patients diagnosed with KA to provide further insight into its clinical behavior and management. Additionally, the study sought to identify features associated with malignant transformation in KA.

METHODS

Ethical approval for this study was obtained from the Ethics Committee of Trakya University Faculty of Medicine (protocol no:

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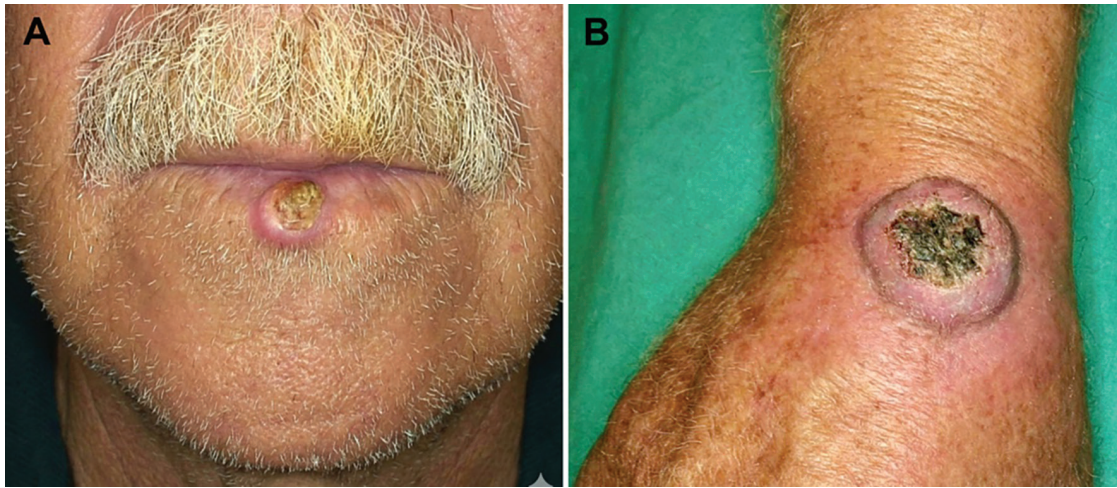


Figure 1. Clinical appearance of a crateriform lesion with central keratinous material (A). Clinical appearance of giant keratoacanthoma (B)

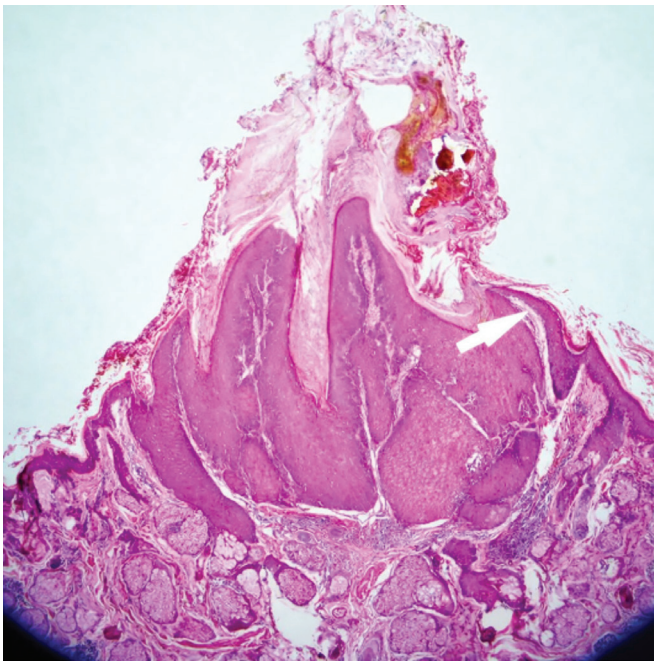


Figure 2. Keratin-filled crateriform epidermal proliferation demonstrating an inverted growth pattern, with peripheral epidermal "lippling" (overhanging epidermal edges) (white arrow) (H&E, $\times 100$)

H&E: Hematoxylin and eosin

TÜTF-GOBAEK 2025/380, decision no: 17/03, date: 22.09.2025).

The characteristics of patients with histopathologically confirmed KA after complete excision between 2015 and 2025 were retrospectively evaluated. Sociodemographic variables (age at diagnosis, sex, family history, and season of diagnosis) and clinical variables (immunosuppression status, tumor location on sun-exposed body sites, rapid tumor growth, history of trauma, history of prior NMSC, presence of concomitant actinic keratosis or NMSC at the time of diagnosis, pruritus, and recurrence) were obtained through a comprehensive review of medical records.

KA was clinically classified into two main categories: solitary and multiple forms. Solitary KAs were further subdivided into five subgroups: classical (typical), giant KA (diameter ≥ 2 cm), KA centrifugum marginatum, subungual KA, and mucosal KA (4,7,8).

Histopathological parameters including maximum tumor diameter (mm), depth of invasion (mm), ulceration, perineural and/or lymphovascular invasion, and lymphohistiocytic infiltration—were recorded for each case. Missing pathological data were reassessed and completed through re-evaluation by two experienced pathologists (N.C. and M.B.). Based on the criteria reported by Vilcea et al. (9), cases were categorized as benign KA or KA with malignant transformation; the latter was defined histopathologically as KAs containing areas of carcinoma *in situ*, microcarcinoma, well-differentiated SCC, moderately differentiated SCC, or acantholytic SCC.

Statistical Analysis

All statistical analyses were performed using IBM SPSS Statistics for Windows, version 25.0 (IBM Corp., Armonk, NY, USA). Descriptive statistics were presented as mean $\pm$ standard deviation for normally distributed continuous variables, median (interquartile range, range) for non-normally distributed continuous variables, and number (n) and percentage (%) for categorical variables. The normality of continuous variables was assessed using the Shapiro-Wilk test together with visual inspection of histograms and Q-Q plots. Comparisons between the benign KA and KA with malignant transformation groups were performed using the independent samples t-test for normally distributed continuous variables and the Mann-Whitney U test for non-normally distributed continuous variables. Categorical variables were compared using the Pearson chi-square test or Fisher's exact test, as appropriate. To identify factors associated with malignant transformation, univariate and multivariate binary logistic regression analyses were performed, and the results are presented as odds ratios (OR) with 95% confidence intervals (CI). A two-sided p-value < 0.05 was considered statistically significant.

RESULTS

The mean age of the 115 patients with KA was 65.1 ± 14.8 years, and the male-to-female ratio was 1.3:1. The highest proportion of diagnoses occurred in winter ($n=38$, 33.0%). A history of trauma was reported in 14.7% ($n=17$) of the patients, whereas rapid tumor growth was observed in 69.5% ($n=80$). The predominant clinical presentation was solitary KA ($n=114$, 99.1%), and classical KA was the most common clinical subtype ($n=109$, 94.8%). Because 20 patients were lost to follow-up, recurrence status was evaluated in the remaining 95 patients with available follow-up data. Accordingly, the recurrence rate was calculated as 9.5% ($n=9$) (Table 1).

Regarding the anatomical distribution, KA was most frequently located in the head and neck region ($n=88$, 76.5%). Among lesions located in the head region, the lips ($n=16$, 18.2%) and forehead ($n=13$, 14.8%) were the most commonly involved sites (Figure 3A and B).

On histopathological evaluation, 36.5% ($n=42$) of cases exhibited features of malignant transformation. Lymphohistiocytic infiltration was observed in 63.5% ($n=73$) of cases, whereas neither perineural nor lymphovascular invasion was identified in any case (Table 2).

When patients with benign KA were compared with those with KA exhibiting malignant transformation, maximum tumor diameter and depth of invasion were significantly greater in the malignant transformation group ($p=0.012$ and $p=0.040$, respectively) (Table 3).

In univariate logistic regression analysis, the largest tumor diameter and depth of tumor invasion were significantly associated with malignant transformation. The OR was 1.092 for largest tumor diameter (95% CI: 1.012-1.179, $p=0.023$) and 1.345 for depth of tumor invasion (95% CI: 1.006-1.799, $p=0.046$) (Table 4).

However, in multivariate analysis, none of the variables remained statistically significant as an independent predictor. The largest tumor diameter showed borderline significance (OR: 1.072, 95%

Table 1. Baseline demographic, clinical, and tumor characteristics of patients with keratoacanthoma (KA)

Characteristic		Total (n=115)
Age at diagnosis, years, mean $\pm$ SD*		65.1 $\pm$ 14.8
Sex, n (%)	Female	50 (43.5)
	Male	65 (56.5)
Family history n (%)	Yes	7 (6.0)
	No	108 (94.0)
Season at diagnosis, n (%)	Spring	23 (20.0)
	Summer	28 (24.3)
	Autumn	26 (22.6)
	Winter	38 (33.0)
Immunosuppression, n (%)	Yes	21 (18.3)
	No	94 (81.7)
Sun-exposed body site, n (%)	Yes	99 (86.1)
	No	16 (13.9)
History of trauma, n (%)	Yes	17 (14.7)
	No	98 (85.3)
Rapid tumor growth, n (%)	Yes	80 (69.5)
	No	35 (30.5)
Solitary vs multiple KA, n (%)	Solitary	114 (99.1)
	Multiple	1 (0.9)
History of non-melanoma skin cancer, n (%)	Present	19 (16.5)
	Absent	96 (83.5)
Concurrent non-melanoma skin cancer at diagnosis, n (%)	Present	20 (17.4)
	Absent	95 (82.6)
Actinic keratosis at diagnosis, n (%)	Present	25 (21.7)
	Absent	90 (78.3)

Table 1. Continued

Characteristic		Total (n=115)
Clinical variants, n (%)	Classic	109 (94.8)
	Giant KA	6 (5.2)
	KA centrifugum marginatum	0 (0)
	Subungual KA	0 (0)
	Mucosal KA	0 (0)
Recurrence, n (%)	Yes	9 (9.5)
	No	86 (90.5)
	Unknown	20 (17.4)
Time to recurrence, months, median (IQR)**		31 (20-63)
Site of recurrence, (n=9), n (%)	Same site	4 (44.4)
	Different site	5 (55.6)

*: Normally distributed continuous variables are presented as mean $\pm$ standard deviation, **: Non-normally distributed continuous variables are presented as median (IQR), SD: Standard deviation, n: Number of patients, IQR: Interquartile range

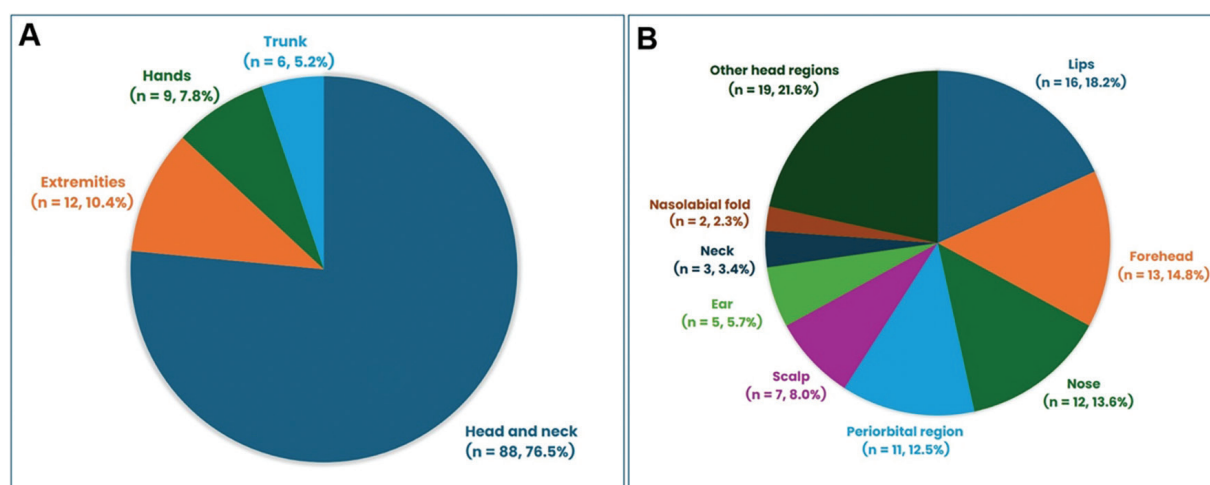


Figure 3. Anatomical distribution of lesion locations in patients with keratoacanthoma (n=115) (A). Distribution of keratoacanthoma lesions within the head and neck region (n=88) (B)

Table 2. Histopathological characteristics of keratoacanthoma (KA) lesions

Characteristic	Total (n=115)
KA with malignant transformation, n (%)	42 (36.5)
Benign KA, n (%)	73 (63.5)
Maximum tumor diameter (mm), median (IQR)*	6 (5)
Depth of invasion (mm), median (IQR)*	2 (2)
Ulceration, n (%)	28 (24.3)
Perineural invasion, n (%)	0 (0)
Lymphovascular invasion, n (%)	0 (0)
Lymphohistiocytic infiltrate, n (%)	73 (63.5)

*: Non-normally distributed continuous variables are presented as median (IQR), n: Number of patients, IQR: interquartile range

Table 3. Comparison of clinical and histopathologic characteristics between benign keratoacanthoma (KA) and KA with malignant transformation

Characteristic		Benign KA (n=73)	KA with malignant transformation (n=42)	p-value*
Age at diagnosis, years, mean $\pm$ SD		63.12 $\pm$ 14.94	68.52 $\pm$ 14.20	0.060
Sex, n (%)	Female	34 (46.6)	16 (38.1)	0.377
	Male	39 (53.4)	26 (61.9)	
Family history, n (%)		5 (6.8)	2 (4.8)	0.175
Immunosuppression, n (%)		11 (15.1)	10 (23.8)	0.243
Tumor location, n (%)	Trunk	4 (5.5)	2 (4.8)	0.870
	Extremities	8 (11.0)	4 (9.5)	0.790
	Head and neck	58 (79.5)	30 (71.4)	0.328
	Hands	3 (4.1)	6 (14.3)	0.061
History of non-melanoma skin cancer, n (%)		12 (16.4)	7 (16.7)	0.802
Concurrent non-melanoma skin cancer at diagnosis, n (%)		15 (20.5)	5 (11.9)	0.239
Actinic keratosis at diagnosis, n (%)		19 (26.0)	6 (14.2)	0.231
Maximum tumor diameter (mm), median (IQR)**		6 (5.5)	8 (6)	0.012
Depth of invasion, (mm), median (IQR)**		2 (1.5)	2 (1.5)	0.040
Ulceration, n (%)		15 (20.5)	13 (31.0)	0.211
Lymphohistiocytic infiltrate, n (%)		42 (57.5)	31 (73.8)	0.081

*: Continuous variables were compared using the independent samples t-test or Mann-Whitney U test, as appropriate. Categorical variables were compared using Pearson's chi-square test or Fisher's exact test, **: Non-normally distributed continuous variables are presented as median (IQR), n: Number of patients, IQR: Interquartile range, SD: Standard deviation

Table 4. Factors associated with malignant transformation of keratoacanthoma: univariate and multivariate logistic regression analyses*

Characteristic	Univariate		Multivariate	
	OR (95% CI)	p-value	OR (95% CI)	p-value
Largest diameter of the tumor (mm)	1.092 (1.012-1.179)	0.023	1.072 (0.992-1.158)	0.078
Depth of tumor invasion (mm)	1.345 (1.006-1.799)	0.046	1.208 (0.888-1.643)	0.229

*: Univariate and multivariate binary logistic regression analyses were performed, and the results are presented as odds ratios (ORs) with 95% confidence intervals (CIs)

CI: 0.992-1.158, $p=0.078$), while depth of tumor invasion was no longer significant (OR: 1.208, 95% CI: 0.888-1.643, $p=0.229$) (Table 4).

DISCUSSION

The incidence of KA peaks between 50 and 69 years of age, with a higher prevalence in males (4,10). Consistent with the literature, our study demonstrated a predominance of middle-to- older age and male sex among patients with KA.

Dufresne et al. (11) reported a higher incidence of KA during the spring and summer months, attributing this pattern to ultraviolet (UV) exposure. In contrast, our study identified the highest proportion of diagnoses in winter. This discrepancy may be explained by either (i) true geographic or environmental variation in seasonal patterns or (ii) a temporal lag between lesion onset

and clinical diagnosis. Although lesions may develop during periods of increased UV exposure, the rapid growth of KA over weeks to months—potentially combined with delayed patient presentation—may shift the timing of diagnosis to winter (10). Future studies comparing the season of diagnosis with the estimated onset of lesions may further clarify this association.

The etiology of KA remains incompletely understood. It is believed to originate from the hair follicle and most commonly arises on hair-bearing, chronically sun-exposed skin in older adults. Proposed etiological factors include UV radiation, chemical carcinogens (e.g., tar), immunosuppression, and foreign materials such as tattoos or collagen fillers. KA has also been associated with genetic syndromes (including Muir-Torre syndrome and xeroderma pigmentosum), trauma (e.g., surgery, laser therapy, or cryotherapy), and certain medications, including BRAF inhibitors (vemurafenib, dabrafenib) and immunosuppressive disease-

modifying antirheumatic drugs such as leflunomide (1,4). These risk factors substantially overlap with those reported for cSCC (12). This shared risk profile, together with the frequent involvement of sun-exposed body sites of the head and neck, may complicate clinical differentiation between KA and cSCC. In our study, KA lesions were most frequently located on the head, particularly the lips, consistent with the findings of Vilcea et al. (9). Several studies have identified the lower lip or vermilion border as a common site for cSCC (13). This shared anatomic predilection further complicates clinical differentiation between KA and cSCC.

Solitary KA is the most common clinical variant and typically presents as a well-circumscribed, firm, pink nodule measuring approximately 1-2 cm in diameter, with a characteristic central keratotic plug (14). Giant KA is a rare variant that may exceed 2 cm in diameter and, in some cases, fail to undergo spontaneous regression. Histopathologically, giant KA shares similar features with classical solitary KA (15). Due to their size and anatomical location, giant KAs may be associated with greater functional and cosmetic morbidity (16). Consistent with previous reports, solitary KA was the predominant variant in our study. It is possible that some giant KA cases represent initially solitary lesions that enlarged due to delayed presentation or diagnosis. These findings highlight the importance of improving awareness among clinicians and patients to promote early presentation, timely diagnosis, and appropriate management.

KA is associated with the presence or subsequent development of other NMSCs and premalignant lesions, such as actinic keratosis, and is considered a clinically relevant marker of increased cutaneous cancer risk (9). In a large population-based study, 89% of individuals with KA had a prior history of treatment for at least one skin cancer or actinic keratosis (17). In our study, a prior history of NMSC was documented in 16% of cases, while concomitant NMSC at diagnosis was observed in 21.7%. The lower rates observed in our cohort may partly reflect incomplete documentation inherent to retrospective study designs. Nonetheless, careful screening for coexisting NMSCs and premalignant lesions in patients with KA remains clinically warranted.

Distinguishing benign KA from KA with malignant transformation may be challenging because of substantial clinical and histopathological overlap. Features suggestive of malignancy include metastatic potential, aggressive clinical behavior (such as local recurrence or destructive growth), marked cytological atypia, vascular and/or perineural invasion, an infiltrative growth pattern, and an increased proliferative index (14). Vilcea et al. (9) reported a malignant transformation rate of 73.71% and concluded that clinical features alone were insufficient predictors of transformation. The lower rate of malignant transformation (36.5%) observed in our series may be attributed to variations in sample characteristics, case selection criteria, or differences in diagnostic thresholds. Collectively, these findings support the notion that clinical characteristics alone may be insufficient for definitive differentiation; rather, tumor size and depth of invasion appear to be more discriminative parameters.

The literature indicates that KA cases with malignant transformation are more likely to occur in older individuals (9,18). In line with these reports, malignant transformation was also observed more frequently in older patients in our study. One possible explanation is that age-related immunosenescence and cumulative UV exposure may contribute to a cutaneous microenvironment that facilitates malignant transformation (19).

The association between malignant transformation in KA and tumor location remains uncertain. One study reported that most KAs with malignant transformation were located on sun-exposed body sites (18). In line with the study by Vilcea et al. (9), tumor location was not significantly associated with malignant transformation in the present study. Further studies are needed to clarify this relationship.

The natural course of KA involves sequential proliferation, stabilization and regression, with spontaneous involution attributed to increased apoptosis, Wnt-retinoic acid pathway crosstalk, and heightened antitumor immune activity; when these regulatory pathways are inadequate, lesions may fail to regress and instead resemble the biology of cSCC (3). Previous studies have reported lower rates of spontaneous regression in KA cases with malignant transformation (20). This may be associated with the larger tumor diameter and greater depth of tumor invasion observed in KAs with malignant transformation, as also demonstrated in our study. However, the available evidence on this issue remains limited. Our findings may therefore provide useful guidance for clinicians in this regard.

A review examining the histopathological features of KA and cSCC noted that ulceration and perineural invasion occurred more frequently in cSCC, suggesting that these findings may reflect more aggressive biological behavior (4). Another study reported lymphohistiocytic infiltration in all KA cases, whereas no instances of vascular or perineural invasion were observed. (9). The absence of lymphovascular and perineural invasion may be considered a supportive histopathological finding favoring KA in the appropriate clinicopathological context; however, this finding alone is not sufficient to reliably distinguish KA from cSCC, particularly in the absence of a direct cSCC control group.

Complete surgical excision remains the first-line treatment and the gold standard for KA, as it allows definitive histopathological assessment and is associated with favorable outcomes. Recurrence has been reported in approximately 8% of cases following surgical treatment (1,21). Our recurrence rate of 9.5% was somewhat higher than previously reported rates, which may be partly attributable to differences in follow-up duration, patient characteristics, or treatment approaches.

In our study, univariate analysis identified the largest tumor diameter and depth of tumor invasion as predictive factors for malignant transformation in KA. However, these associations were not confirmed in the multivariate analysis. This may largely be explained by the limited sample size and by the biological and statistical overlap between clinicopathological parameters,

particularly tumor diameter and depth of invasion. Therefore, the independent prognostic significance of these variables in malignant transformation should be validated in larger prospective studies.

Study Limitations

This study has several limitations. First, its retrospective design may introduce inherent bias. Second, patients' sociodemographic characteristics could not be fully analyzed due to missing or incomplete medical records. Third, the assessment of recurrence may have been limited by the loss of 20 patients to follow-up and the relatively short mean follow-up duration of 31 months, which may have precluded a comprehensive evaluation of long-term recurrence. Fourth, in the comparison between benign KA and KA with malignant transformation, only the largest tumor diameter and depth of tumor invasion were statistically significant. Therefore, only these two variables were included in the multivariable logistic regression analysis. The limited number of events may have affected the reliability of the multivariable analysis.

CONCLUSION

In conclusion, our findings suggest that KA follows a clinical and demographic pattern similar to cSCC, predominantly affecting elderly males on sun-exposed body sites. Histopathologically, the absence of lymphovascular and perineural invasion may support the diagnosis of KA. Moreover, in cases exhibiting malignant transformation, tumor diameter and depth of invasion appear to be more discriminative parameters than clinical or sociodemographic variables. Histopathological examination remains the most reliable and essential method for diagnosing malignant transformation in KA.

Ethics

Ethics Committee Approval: Ethical approval for this study was obtained from the ethics committee of Trakya University Faculty of Medicine (protocol no: TÜTF-GOBAEK 2025/380, decision no: 17/03, date: 22.09.2025).

Informed Consent: Retrospective study.

Footnotes

Author Contributions: Concept - M.Ü., Y.G.Ü.; Design - M.Ü., G.K., Y.G.Ü.; Data Collection and/or Processing - G.K., M.B., N.C.; Analysis and/or Interpretation - M.Ü., Y.G.Ü., N.C.; Literature Search - M.Ü., G.K., M.B., Y.G.Ü., N.C.; Writing - M.Ü., G.K., M.B., Y.G.Ü., N.C.

Conflict of Interest: The authors have no conflicts of interest to declare.

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