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Histopathological subtyping of actinic keratosis and it's coexistence with nonmelanotic skin cancers in Gaziantep and Malatya regions

Gaziantep ve Malatya bölgesinde aktinik keratoz olgularının histopatolojik alt gruplandırılması ve nonmelanotik deri kanserleri ile birliktelikleri

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Abstract

Background and Design: Actinic (solar) keratosis (AK) is a precancerous, epidermal lesion, which develops in sensitive skin exposed to sun for a long period. AKs are divided into different histopathological subtypes. There is a link between the clinical progression of the histopathological subtypes, the degree of cellular atypia, and the precancerous nature of the lesion. Different series have reported that the rate of transformation of AK to squamous cell carcinoma (SCC) ranges between 12% and 20%.
Materials and Methods: In this study, we reevaluated patients who were diagnosed with AK in the Pathology Departments of the Medical Faculties of İnönü and Gaziantep Universities over an eight-year period, and divided the patients into different histopathological subtypes. In addition, we investigated the association between the lesions, and basal cell carcinoma (BCC), SCC and both carcinomas.
Results: 29,6% of cases were proliferative AK, 27% of cases were hypertrophic AK.19% and 13% of all lesions was associated with BCC and SCC, respectively.
Conclusion: In this study, we found that the most frequent subtype was proliferative AK and the most frequent nonmelanotic skin cancer was BCC associated with AK.
Keywords: Actinic keratosis, solar keratosis, histopathology, non melanotic skin cancers

Öz

Amaç: Aktinik keratoz (AK) veya solar keratoz, uzun süreli güneşe maruz kalan hassas deri zemininde ortaya çıkan, prekanseröz epidermal lezyonlardır. AK histopatolojik olarak çeşitli alt gruplara ayrılabilmektedir. Bu histopatolojik alt grupların klinik seyirlerindeki farklılıklar kesin olarak aydınlatılmamışsa da bu alt gruplardaki hücresel atipi derecesi ile lezyonun prekanseröz olabilmesi arasında bir bağlantı vardır. AK'nin skuamoz hücreli kansere dönüşüm oranı değişik serilerde %12-20 arasında bildirilmektedir. Biz bu çalışmamızda Malatya ve Gaziantep bölgelerinde 8 yıl boyunca tanı almış 82 olguda 115 AK lezyonunun alt tipleri ile bazal hücreli karsinom (BHK) ve skuamoz hücreli karsinom (SHK) birlikteliklerini araştırdık.
Gereç ve Yöntem: Bu çalışmada İnönü Üniversitesi ve Gaziantep Üniversitesi Tıp Fakültesi Patoloji Anabilim Dalları'nda 8 yıllık dönem boyunca tanı almış AK olguları tekrar gözden geçirilerek histopatolojik alt gruplandırma yapılıp; BHK ve SHK birliktelikleri araştırıldı.
Bulgular: Olguların %29,6'sı proliferatif tip, %27'si hipertrofik tip AK olarak tespit edildi. Tüm lezyonların %19'u BHK, %13'ü ise SHK ile birliktelik göstermekteydi.
Sonuç: Tüm AK'lar içerisinde en sık proliferatif tip AK izlenirken ikinci sırada hipertrofik tip ve üçüncü sırada akantolitik tip AK tespit edildi. Olgulara ait lezyonların %13'ünde SHK, %19'unda ise BHK varlığı tespit edildi.
Anahtar Kelimeler: Aktinik keratoz, solar keratoz, histopatoloji, non melanotik deri kanserleri

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Introduction

Actinic keratosis (AK) refers to precancerous epidermal lesions that develop in the skin after long-term exposure to the sun[1].

AKs are divided into different histopathological subtypes. While it is hypothesized that there is a connection between the degree of cellular atypia and transformation to cancer, the differences in clinical progression are not fully known[2,3].

To date, different series have reported varying rates of transformation of AKs to non-melanocytic skin cancers. The rate of transformation to squamous cell carcinoma (SCC) ranges between 12 and 20% in the literature[2,4].

In this study, we retrospectively evaluated the medical records of patients who were diagnosed with AK over an eight-year period in the Pathology Departments of the Medical Faculties of İnönü and Gaziantep Universities, and investigated the possible association between AK and SCC and/or basal cell carcinoma (BCC).

Materials And Methods

One hundred fifteen patients, who were diagnosed with AK over an eight-year period in the Pathology Departments of the Medical Faculties of İnönü and Gaziantep Universities were included in the study. One hundred fifteen AK cases belonged to 82 patients, and 16 patients had multiple lesions.

Archive slides of 115 lesions (belonging to 82 patients) were accessed, and histopathological subtyping was performed according to predetermined criteria[1,2]. At the same time, each patient's clinical and demographic features were obtained, and the association of AK lesions and nonmelanotic skin cancers was recorded.

Eighty-two patients were divided into five different age groups. The localizations of lesions were classified into 14 different regions. The facial skin included only the buccal region, molar region, maxilla, zygoma, and moustache region.

To identify the association between lesions and non-melanocytic cancers, the patients were divided into different groups (BCC; SCC, BCC+SCC, no association), and evaluated.

Histopathological subtypes were divided into nine groups according to the World Health Organization (WHO) and McKee criteria (Table 1)[1,2]. The lichenoid AK subtype was excluded from our series due to the absence of patients, and eight different subtypes were evaluated.

Table 1. Histopathological subtypes of actinic keratosis

Histopathological subtypes
Hypertrophic AK
Proliferative AK
Acantholytic AK
Bowenoid AK
Actinic cheilitis
Pigmented AK
Atrophic AK
Cutaneous horn
Lichenoid AK

AK: Actinic keratosis

For AK type lesions, the general common histopathological findings, as described by WHO and McKee[2], were determined at Table 2[1].

For keratinocytic atypia criteria, the following findings (described by McKee) were considered (Table 3).

In addition to the aforementioned criteria, the following histopathological findings were considered in different histopathological subtypes and were determined at Table 4[1-3].

SPSS v.17.0 software was used for statistical analysis. Descriptive statistics were used to analyze age, gender, frequency of localization, mean, and comparison of the two parameters.

Results

In our study, 42 of 82 patients (51%) were male, and 40 patients (48%) were female (M/F: 1.05). Among all patients, 43% of the patients were older than 71 years. Fifty-two percent of male patients and 35% of female patients were older than 71 years (Graphic 1).

Thirty percent of the lesions were localized in nose, 24% of the lesions were localized on the facial skin, and 9% of the lesions were localized on lips (Table 5).

The most frequent localization was the facial skin in females (12/40), and the nose in males (14/42). In addition, localization on hairy skin, the temporal region, and arms were not seen in female patients. In the case of male patients, localization on the mandible, skin of the feet, neck, and back were not seen. Sixteen patients had multiple lesions. A single patient had ten lesions with different subtypes, and at different localizations.

When we evaluated the distribution of histopathological subtypes, 30% were proliferative, 27% were hypertrophic, 18% were acantholytic, 10% were Bowenoid, and 9% were atrophic (Table 6) (Figures 1, 2, 3, 4).

Forty-eight percent of the patients with hypertrophic lesions were older than 71 years; 33% of the patients with proliferative lesions were older than 71 years. One of two patients with pigmented AK was in the 30-40 years age group, and the other patient was older than 71 years. Another type of AK that was seen in patients between 30-40 years was

Table 2. The general common histopathological findings for actinic keratosis

Irregular epidermal acanthosis
Thinning or loss of granular layer
Mild or prominent hyperkeratosis and parakeratosis
Keratinocytic atypia that does not reach the upper epidermis
Solar elastosis in superficial dermis
Lymphoid infiltrate and dilated vascular structures in dermis

Table 3. Keratinocytic atypia criteria described by McKee

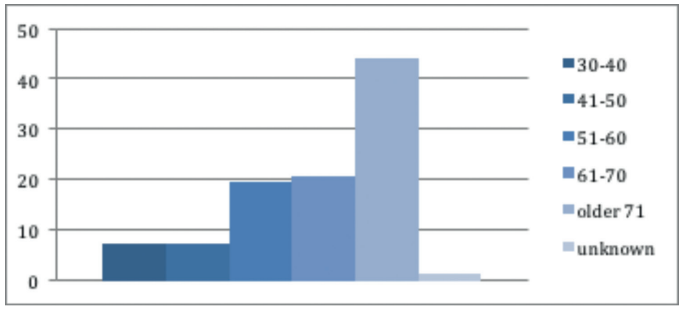
Keratinocytic atypia criteria
Defects in keratinocyte arrangement
Presence of variable mitosis
Single-cell keratinization (dyskeratosis)
Larger size (compared to normal keratinocytes) and differences in shape
Large nuclei with nucleolus

proliferative AK (PAK) (22%). Only one of ten atrophic AK cases was seen in patients between 30-40 years (Graphic 2). In our study, both patients (n=2) who had cutaneous horn were female.

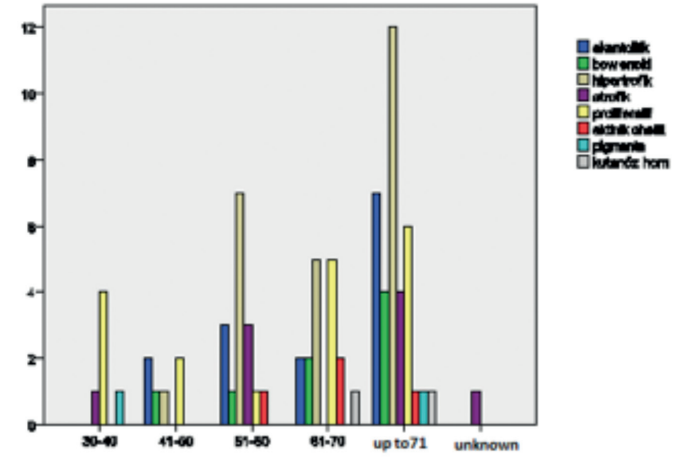
When we evaluated the association between all lesions and tumors, we found that 63% of the lesions were associated with any non-melanocytic skin cancer.

When we evaluated the association of lesions with non-melanocytic skin cancers, 19% of the lesions were associated with BCC, 13% of the lesions were associated with SCC, and 4% of the lesions were associated with BCC+SCC (Table 7) (Figures 5, 6).

Acantholytic subtype showed the highest association with BCC (28%). Hypertrophic subtype showed the highest association with SCC (22%). Acantholytic subtype showed the highest association with BCC+SCC (9.5%) (Graphic 3). Pigmented AK did not show association with any non-melanocytic tumor.



Graphic 1. The distribution of patients with respect to age groups



Graphic 2. The histopathological subtypes distribution of age groups

Table 4. Additional histopathological findings in different histopathological subtypes

Histopathological subtypes	Histopathological findings
Atrophic AK	Epidermal atrophy and loss of rete peg
Keratin horn	Keratotic mass with half height (minimum) of the lesion base width
Acantholytic AK	Acantholysis in lower epidermis
Proliferative AK	Progression keratinocytes in the lower epidermis to the sebaceous gland level
Hypertrophic AK	Atypia progression into the middle layer of the epidermis and dyskeratosis
Bowenoid AK	Single-cell keratinization and full-layer atypia that does not involve cutaneous adnexa
Pigmented AK	Presence of increased melanin in atypical keratinocytes
Actinic cheilitis	Atypical basal layer cells with labial localization, and presence of intense inflammation in dermis

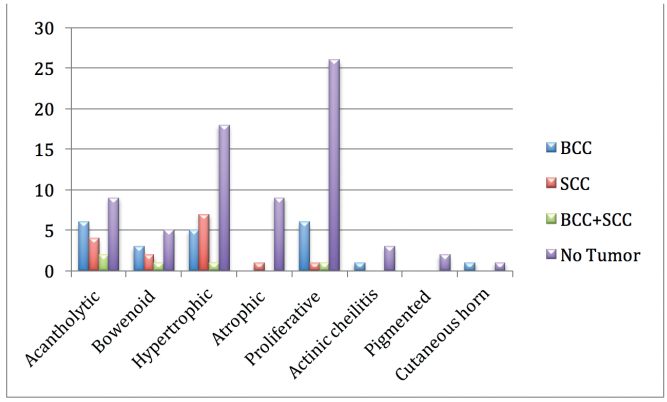
AK: Actinic keratosis

Discussion

AKs are more common in males compared to females[2,7]. In our study, 51% of the patients were male, and the male/female ratio was 1.05. In our previous study, this ratio was 2.2[5]. On the other hand, Akyılmaz ve Özpoyraz[8] found an equal gender distribution in their studies.

AKs are generally seen in middle-to-advanced age group, and its incidence increases with increasing age. It is known that exposure to chronic sunlight has an important role in its etiopathogenesis[1-3]. In our study, 43% of the patients were older than 71 years, and this finding was consistent with the literature[1,5,6].

AK lesions tend to localize in regions that are exposed to more sunlight (face, neck, and dorsal faces of the hands and arms)[2,6,7,9]. Frost ve Green10 reported that 80% of AK lesions tend to localize in the head-



Graphic 3. The association between histopathological subtypes and non-melanocytic tumors

SCC: Squamous cell carcinoma, BCC: Basal cell carcinoma

Table 5. The distribution of actinic keratosis lesions with respect to their localization

Localization	Frequency (n)	Percentage (%)
Nose	35	30.4
Face	27	23.5
Lips	10	8.7
Ears	9	7.8
Eyebrow	7	6.1
Supraorbital	6	5.2
Hairy skin	4	3.5
Back of the hand	4	3.5
Mandible	3	2.6
Arms	3	2.6
Total	**115**	**100**

neck region, forearms, and hands. We aimed to specify lesions with facial localization, and to determine the most frequent localizations on the face. We found that AK lesions were localized on the nose in 30% of the patients. Similarly, Şahin et al.[5] found nasal localization in 32% of the patients.

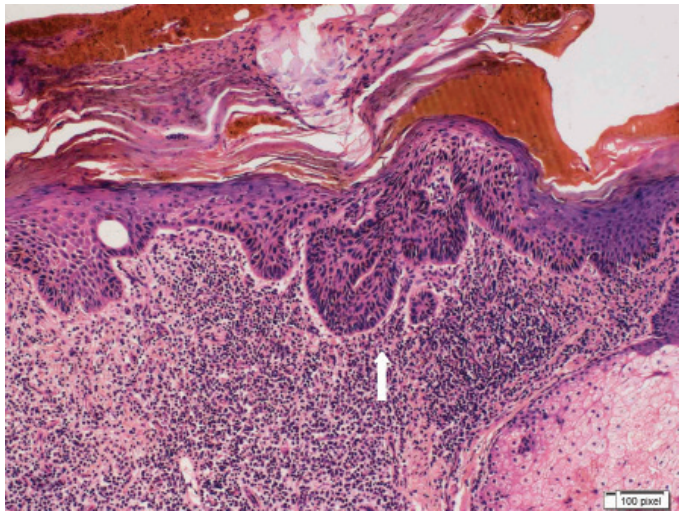


Figure 1. Proliferative actinic keratosis. Below parakeratotic hyperkeratosis; progression keratinocytes in the lower epidermis to the sebaceous gland level (H&E x100)

Table 6. The frequency of histopathological subtypes

Histopathological subtype	Frequency (n)	Percentage (%)
Proliferative	34	29.6
Hypertrophic	31	27
Acantholytic	21	18.3
Bowenoid	11	9.6
Atrophic	10	8.7
Actinic cheilitis	4	3.5
Pigmented AK	2	1.7
Cutaneous horn	2	1.7
Total	**115**	**100**

AK: Actinic keratosis

In 1996, for the first time, AKs were classified as precancerous, benign, epidermal tumors in the World Health Organization's classification of skin tumors, and AKs were divided into different subtypes[2,11]. Investigating the potential differences in biological behaviors of these subtypes

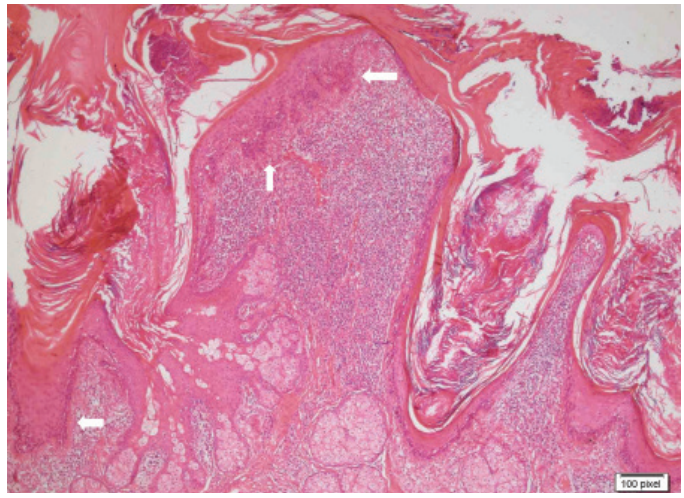


Figure 2. Hypertrophic actinic keratosis. Atypia progression into the middle layer of the epidermis and dyskeratosis (H&E x40)

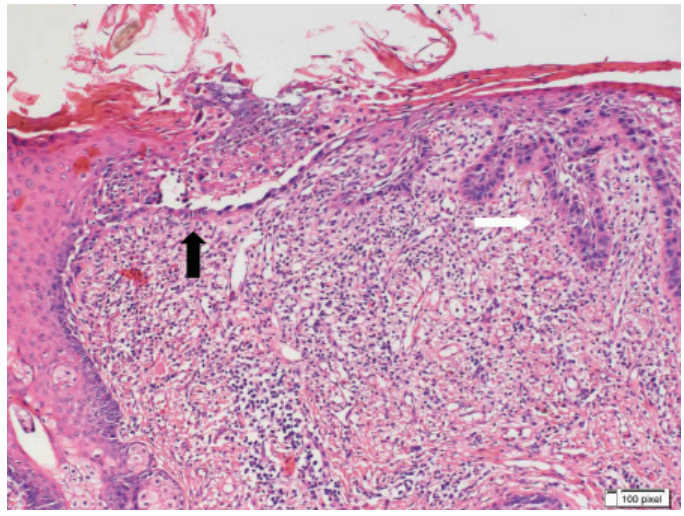


Figure 3. Acantholytic actinic keratosis. Atypical basal layer cells with acantholytic epidermis (H&E x100)

Table 7. The association between histopathological subtypes and non-melanocytic tumors

Histopathological subtype	BCC (%)	SCC (%)	BCC+SCC (%)	No tumor (%)	Total
Acantholytic	6 (28.5)	4 (19)	2 (9.5)	9 (42.8)	21
Bowenoid	3 (27.2)	2 (18.1)	1 (9.09)	5 (45.4)	11
Hypertrophic	5 (16.1)	7 (22.5)	1 (3.2)	18 (58)	31
Atrophic	-	1 (10)	-	9 (90)	10
Proliferative	6 (17.6)	1 (0.02)	1 (0.02)	26 (76.4)	34
Actinic cheilitis	1 (25)	-	-	3 (75)	4
Pigmented AK	-	-	-	2 (100)	2
Cutaneous horn	1 (50)	-	-	1 (50)	2
Total	**22 (19.1)**	**15 (13.4)**	**5 (4.3)**	**73 (63.4)**	**115**

AK: Actinic keratosis

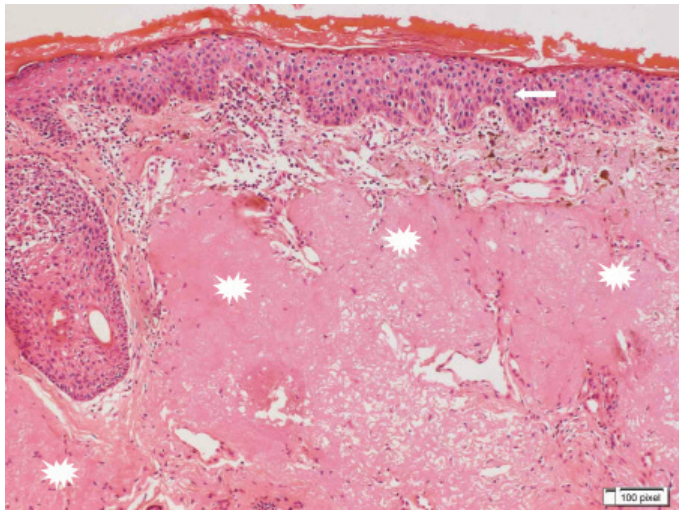


Figure 4. Bowenoid actinic keratosis. Full-layer atypia in the epidermis and dermaş solar elastosis (H&E x100)

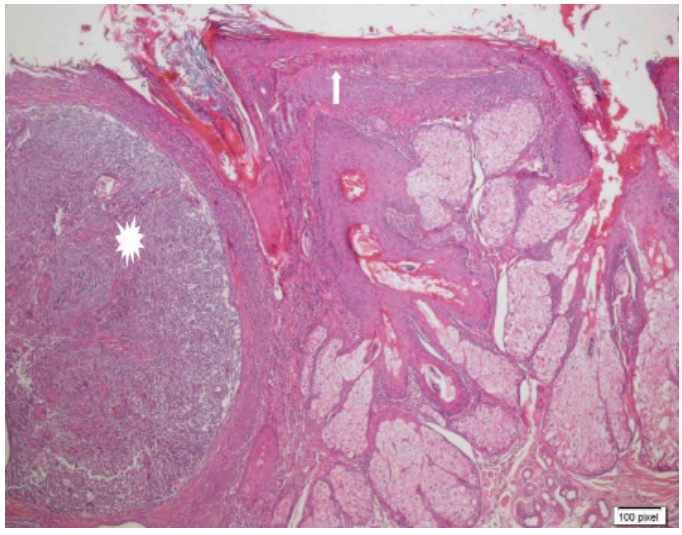


Figure 5. Proliferative actinic keratosis+basal cell carcinoma (H&E x40)

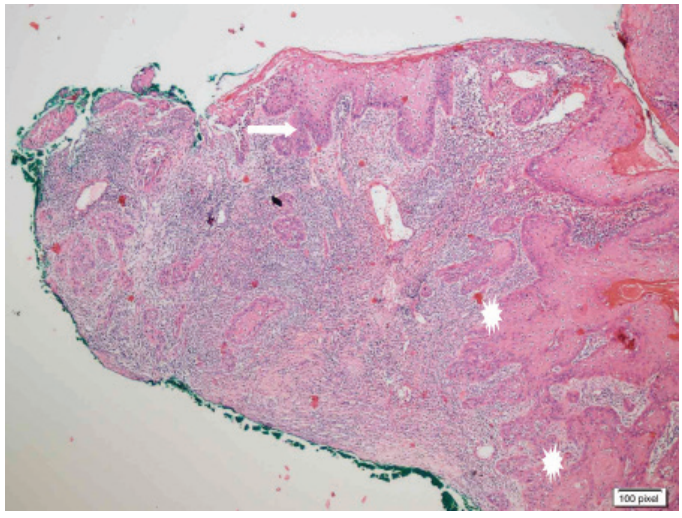


Figure 6. Actinic keratosis+squamous cell carcinoma (H&E x40)

plays a crucial role in determining the progression of carcinomas, and treatment planning[3,7,12-14]. Currently, there is no consensus on the number of subtypes. In addition, there is no consensus on the nomenclature of subtypes and definition of morphological features.

According to the literature, the most frequent histopathological subtype is hypertrophic AK[2,7]; on the other hand, we found that the most frequent subtype was PAK (29.6%).

In 1994, Goldberg et al.[12] recommended that PAK should be evaluated individually from other subtypes due to its resistance to conventional treatments[3]. At the same time, Suchniak et al.[15] reported that the association between PAK, hypertrophic AK (HAK), and SCC is common[13]. In our study, we determined that 17.6% of patients with PAK exhibited an association with BCC, whereas 76% of the patients did not show any association with any tumor. In addition, we determined that only 0.02% of the patients showed an association with SCC.

Different series have reported that the rate of transformation of AKs to malignancies ranges between 0.25 and 20%[13,15]. In case of patients with multiple lesions, this rate ranges between 0.1 and 10%[2].

In our study, we found an association between AKs and nonmelanotic skin cancer in 63% of the patients. With respect to the tumor type, the most frequent association was BCC (19%), which was contrary to the literature. The second most common association was SCC (13%).

In Turkey, the studies on AKs are limited, and the majority of these studies have focused on demographic features of AK lesions (age, gender, and localization), clinical features, and treatment[16,17]. The first study involving histopathological examination was carried out Atılganoğlu et al.[18], and investigated the effect of treatment on histopathological findings, and the efficacy of treatment. In addition, in 1984, Sabuncu et al.[19] reported a study on four patients and four lesions, but the authors did not perform histopathological subtyping. In Turkey, the first study on histopathological subtyping of AKs was conducted in our department as a thesis study in 1998, and the present study is an extension of the initial study. Again, in 2009, a thesis study on clinical and histopathological features of AKs in the Çukurova region investigated AK subtypes with respect to skin types[8].

Conclusion

While it has been proven that AKs are premalignant lesions, the number of studies on the cancer formation rate of AK subtypes is not sufficient. Given the fact that sun exposure is higher due to the geographical location of Turkey, we believe that further studies on AKs and the tendency of AK subtypes to malignancies should be conducted. We hope that this study will contribute to the research in this field.

Ethics

Ethics Committee Approval: The study were approved by the İnönü University of Local Ethics Committee, Informed Consent: Consent form was filled out by all participants.

Peer-review: Externally peer-reviewed.

Authorship Contributions

Surgical and Medical Practices: Serpil Şener, Concept: Nasuhi Engin, Aydın, Design: Nurhan Şahin, Data Collection or Processing: Suna Erkılıç, Zehra Bozdağ, Nurhan Şahin, Analysis or Interpretation: Nurhan Şahin, Nasuhi Engin Aydın, Literature Search: Zehra Bozdağ, Writing: Nurhan Şahin.

Conflict of Interest: No conflict of interest was declared by the authors.
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