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Proliferative Actinic Keratosis: An Invasive Squamous Cell Carcinoma or not?

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ABSTRACT Actinic keratoses have variants that differ clinically and pathologically. Proliferative actinic keratoses (PAK) are known to be resistant against standard therapies and to create a tendency for the development of invasive squamous cell carcinoma (SCC). This study retrospectively reviewed the medical records of 50 patients with 51 PAK lesions. Fifty patients (40 male, 10 female) with a mean age of 68.5 were included in the study. Thirty-two (63%) PAK lesions were clinically selected for total excision but only 27 of them could be totally excised. Among the excised lesions, 13 were reported to be PAK, 13 were SCC, and 1 was keratoacanthoma. There was no significant difference between the PAK and SCC groups. Overall, the groups with excised and unexcised lesions were statistically similar with respect to age, sex, lesion duration, localization, size, and surface features, but induration was more common in the SCC group. The mean follow-up time was 19.7 and 17.0 months in the PAK and SCC group, respectively. In conclusion, 25% (13/51) of lesions diagnosed as PAK were invasive SCC, which is of clinical and histopathological significance. Our results suggest that the definition of PAK should be histopathologically revised and that total excisional biopsy instead of punch biopsy should be considered, especially for lesions with a proliferative appearance.

KEY WORDS: actinic keratosis, proliferative actinic keratosis, squamous cell carcinoma

INTRODUCTION

Actinic keratoses (AK) are keratinocyte-associated premalignant lesions found in light-skinned people due to chronic solar injury (1). Clinically, they are characterized as reddish-brown patches, plaques, or tumors whose surface may have a rough appearance (1). The annual progression rate of an AK lesion to invasive squamous cell carcinoma (SCC) was reported to be 0.025% to 16% (2). However, some authors have advocated that AK is an early-stage SCC lesion or a true SCC lesion (3,4). Actinic keratoses have been clinically and histopathologically categorized as hypertrophic, atrophic, bowenoid, acantholytic, pigmented, lichenoid, and proliferative variants (5,6). Proliferative actinic keratosis (PAK) was first defined

by Goldberg *et al.* in 1994, and was implicated for SCC development due to the spread of anaplastic cells to hair follicles and sweat glands and its resistance to standard treatments (7,8). In our clinic, we observed that histopathological examination of excision materials found SCC in some of our patients who were diagnosed with PAK with the punch biopsy method and who subsequently underwent excision for clinical high suspicion of an invasive tumor. Therefore, patients diagnosed with PAK were systematically and retrospectively assessed on their sociodemographic, clinical, histopathological, treatment, and follow-up features.

METHODS

We retrospectively reviewed the digital records, photographs, and medical records of 50 patients with 51 lesions diagnosed as PAK with the punch biopsy method at Health Sciences University (HSU) Istanbul Training and Research Hospital, Dermatology Outpatient Clinic between January 2010 and October 2016. The study was approved by the Local Ethics Committee of the Health Sciences University (HSU) Istanbul Training and Research Hospital. The missing information was acquired through telephone interviews with the patients.

1. Sociodemographic, clinical, and histopathological features: Age, sex, time from symptom onset to diagnosis (months), follow-up duration (months), lesion localization, size (mm), surface features such as ulceration, induration, inflammation, and crusts, punch biopsy results, and excisional biopsy results if available were recorded.

2. Treatment and follow-up features: Treatment modalities (conservative follow-up, surgical treatment, cryosurgery), treatment response (complete response, partial response), persistence of treatment response (stable complete response, recurrence) were recorded.

RESULTS

Sociodemographic, clinical, and histopathological features: Fifty patients with 51 lesions were included in the study. Forty (80%) patients were male and 10 (20%) were female, with a mean age of 68.5±14.3 (mean ± Standard Deviation) years. The number and percentage distributions of the sociodemographic, clinical, histopathological features of the enrolled patients are presented in Table 1.

Treatment and follow-up features: As shown in Figure 1, thirty-two (63%) lesions were clinically selected for excision, but only 27 of them could be totally excised. Five patients refused excision despite our recommendation or their results could not be accessed. The histopathological examination of the totally excised lesions that were histopathologically diagnosed as PAK after punch biopsy revealed that 13 (25.5%) of these were PAK, 13 (25.5%) were SCC, and 1 (2.0%) was keratoacanthoma. All SCC lesions were invasive and well-differentiated, with none showing systemic or lymph node metastasis or neurovascular invasion.

A total of 19 PAK lesions were not excised; 17 of them were treated with cryosurgery and 2 lesions were conservatively managed. The mean duration of follow-up was 17.1±16.3 months. Fifteen of the seventeen lesions treated with cryosurgery showed complete response and no recurrence. One lesion developed recurrence after complete response, while one lesion achieved partial response.

The comparison of the PAK and SCC groups separately is shown in Table 2. Seven lesions were excluded because one lesion was identified as keratoacanthoma and follow-up information of 5 patients with 6 lesions were missing. Thirty patients in total from the PAK group and 14 patients from the SCC groups were analyzed.

The PAK and SCC groups did not significantly differ with respect to age, sex, lesion duration, localization, size, and surface features ($P>0.05$). Although no significant difference existed among surface features, induration was more common in the SCC group than the PAK group (78.5% vs 53.3%). The PAK group had a mean follow-up duration of 19.7±18.7 months, whereas the SCC group was followed for a mean of 17.0±13.6 months ($P>0.05$) (Table 2). Some clinical images of patients with PAK and SCC at various different localizations are shown in Figure 2 and Figure 3 (a-d).

The group with lesions that were clinically selected for excision was compared against the group whose lesions were not excised (Table 3). Overall the excision and follow-up group were also statistically similar with regard to age, sex, lesion duration, localization, size, and surface features. The induration, ulceration, and inflammation were common in the excision group compared with the follow-up group, but the difference was not significant ($P>0.05$).

DISCUSSION

AK is the most common epithelial precancerous disease that shows predilection for the face, ear, scalp, dorsum of hand, and forearms due to chronic ultraviolet (UV) exposure (9). Clinically and pathologically it may appear as hypertrophic, atrophic, bowenoid,

Table 1. Sociodemographic, clinical, and histopathological features of the study population

	N (%) or mean ± SD*
Sex	
Female	10 (20)
Male	40 (80)
Age (year)	68.5 ± 14.3 (min: 9 – max: 92)
Disease duration (months)	32.1 ± 11.8
Disease follow-up duration (months)	17.1 ± 16.3 (min: 1 – max: 156)
Lesion size (mm)	11.8 ± 10.9
Lesion localization	
Lip	15 (29.4)
Nose	14 (27.5)
Cheek	7 (13.7)
Ear	5 (9.8)
Scalp	5 (9.8)
Forehead	2 (3.9)
Trunk	2 (3.9)
Neck	1 (2.0)
Surface features	
Ulceration	25 (49.0)
Induration	31 (60.8)
Inflammation	25 (49.0)
Crust	42 (82.4)
None	2 (3.9)
Punch biopsy result	
Bowenoid- proliferative AK*	2 (3.9)
Hyperkeratotic- proliferative AK	7 (13.7)
Insitu SCC- proliferative AK	2 (3.9)
Proliferative AK	40 (78.4)

**SD: Standard Deviation, AK: Actinic keratosis*

acantholytic, pigmented, lichenoid, and proliferative variants (5,6). Occupational UV exposure, male sex, immunosuppression, and a UV-sensitive skin type are the risk factors for AK development (10).

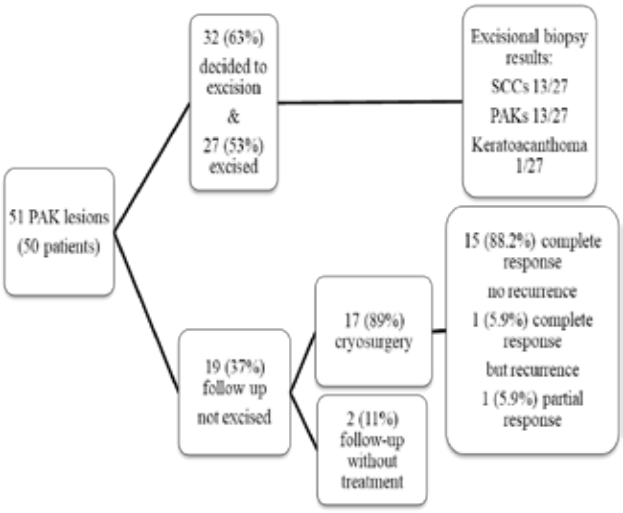

Figure 1. Flow diagram of patient treatment. (*SCC: Squamous cell carcinoma, PAK: Proliferative actinic keratosis).

In our clinic, we observed that some of our patients who were diagnosed with PAK with the punch biopsy method and who subsequently underwent excision for clinical high suspicion of an invasive tumor were found to have SCC by histopathological examination of excision materials. We conducted this retrospec-

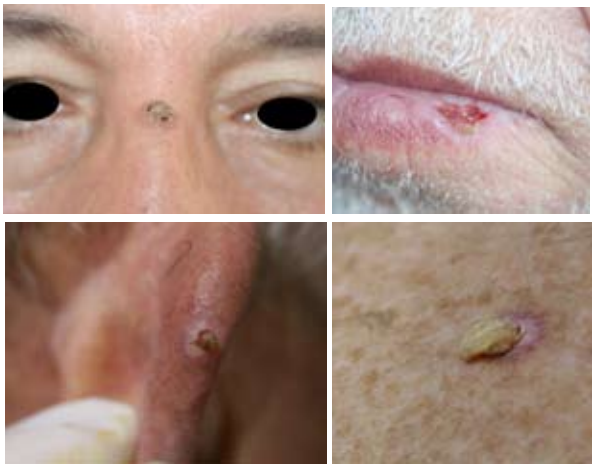

Figure 2. Clinical images of patients with proliferative actinic keratosis (PAK) at various different localizations (a-d).

Table 2. Comparison of the sociodemographic, clinical, and histopathological features of the squamous cell carcinoma (SCC) and proliferative actinic keratosis (PAK) groups separately

	PAK N (%) or mean ± SD*	SCC N (%) or mean ± SD	*P*
Age	68.5±11.2	65.8±21.2	.820
Sex			
Female	7 (23.3)	2 (14.3)	.488
Male	23 (76.7)	12 (85.7)	
Age at lesion onset	65.8±11.6	71.3±16.4	.140
Size (mm)	10.7±10.5	10.5±4.8	.383
Lesion duration (months)	16.5±24.9	20.8±50.8	.155
Follow-up duration (months)	19.7±18.7	17.0±13.6	.890
Lesion localization			
Lip	8 (26.7)	4 (28.6)	.817
Nose	11 (36.7)	1 (7.1)	.092
Cheek	2 (6.7)	4 (28.6)	.133
Ear	3 (10.0)	1 (7.1)	.798
Scalp	4 (13.3)	1 (7.1)	.926
Forehead	0 (0.0)	2 (14.3)	.096
Trunk	2 (6.7)	0 (0.0)	1.000
Neck	0 (0.0)	1 (7.1)	.318
Surface features			
None	0	2	
Yes	30	12	
-Ulceration	16 (53.3)	7 (50.0)	.837
-Induration	16 (53.3)	11 (78.6)	.109
-Inflammation	15 (50.0)	7 (50.0)	1.000
-Crust	25 (83.3)	11 (78.6)	.703

*SD: Standard Deviation

tive study to assess the relationship between PAK and SCC. Invasive SCC was detected in 13 (25.5%) patients among 51 lesions initially diagnosed as PAK.

In 1994, Goldberg et al. showed the spread of dysplastic keratinocytes to cutaneous adnexa and defined the proliferative variant of AK in histopathological examination of 4 patients with treatment resistant AK (7). In that study it was reported that PAK can be clinically differentiated from classical AK by its lesion width and growth and that classical AKs are frequently smaller than 1 cm (7). Our study revealed a mean lesion size of 11.8±10.9 mm.

AKs are classified as AK I when atypical keratinocytes invade the upper 1/3 epidermis, as AK II when they invade the upper 2/3, and AK III when they invade the full thickness of the epidermis (11). Even though it is classically assumed that full-thickness epidermal transformation is required for SCC development, AK I has been observed to be the most common precursor, unlike the classical pathway (12). It was

Table 3. Comparison of the clinical features of the group with lesions that were clinically selected for excision and the group with lesions not selected for excision

	Excision (+) (N: 27) N (%) or median	Excision (-) (N: 24) N (%) or median	*P*
Size (mm)	min:4, max: 50, median:10	min:2, max:50, median:9	.284
Surface features			
- Ulceration	14 (52)	11 (46)	.668
- Induration	19 (70)	12 (50)	.137
- Inflammation	15 (55)	10 (42)	.322
- Crust	22 (81)	20 (83)	1.000

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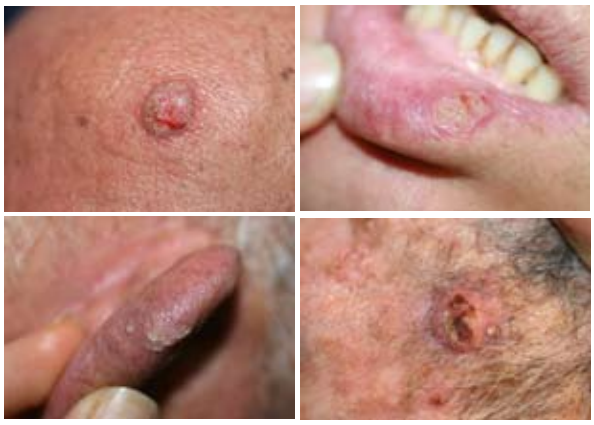

Figure 3. Clinical images of patients with squamous cell carcinoma (SCC) at various different localizations (a-d).

suggested that the adnexal involvement of atypical keratinocytes is more common for AK I lesions, which is implicated for development of invasive malignant lesions in PAKs (12).

One study reported a risk of invasive malignancy of 50% among hyperkeratotic type AKs and noted that clinical appearance is a significant factor for malignancy development from AK lesions (13). Quaedvlieg *et al.* reported that AKs greater than 1 cm in size and erythema, induration, ulceration, inflammation, rapid growth, and bleeding were markers of the development of invasive SCC (14). The AK treatment guidelines published in 2015 state that biopsy sampling should be considered for excluding the possibility of invasive malignancy development for lesions showing infiltration, induration, ulceration, pigmentation, rapid growth, and pain (15). In contrast to these reports, we did not detect any significant differences between the total excision and follow up groups with regard to age, sex, lesion duration, localization, size, and surface features such as ulceration, induration, inflammation, and crusts. We also did not observe any significant difference in terms of the same parameters when the PAK and SCC groups were separately analyzed due to a potential margin of error. This suggests that the need for excisional biopsy for a definitive diagnosis cannot be clinically predicted. However, more common, albeit statistically non-significant, development of induration in the SCC group compared with the PAK group (78.5% vs. 53.3%) suggests that the excision of indurated lesions may be considered for excluding SCC.

Although literature reports suggest that AK is frequently an epithelial precancerous disease, some research has labeled it as an early stage of SCC or true SCC (5,6). Stockfleth *et al.* advocated that all AK lesions should be assumed to be SCC since it is unknown which lesions will progress into SCC (16). In our study, the time from PAK diagnosis by punch biopsy to SCC diagnosis made by excisional biopsy was less than 1 month. This suggests that SCC lesions in our study did not develop from PAK lesions but were already SCC. As the proliferative appearance of actinic keratoses may show a malignant proliferation behavior, we are of the opinion that the definition of PAK should be histopathologically revised.

The limitation of our study was the lack of a second independent dermatopathologist to examine the pathology preparations diagnosed with punch biopsy.

While lesion-focused treatments alone can be applied for AK treatment, recent studies have indicated that field treatment actually reduces recurrences via subclinical UV injury (2). The treatment options include cryosurgery, curettage, imiquimod, ingenol mebutate, 5-fluoruracil (FU), photodynamic treatment, and laser (17). Cryosurgery is an easy-to-access treatment option that is mostly preferred for isolated lesions. Since it is a lesion-focused therapy, recurrence rates after treatment have been reported as high as 95% (18). In our study, at a mean follow-up time of 19.7±18.7 months 15 (88.2%) of 17 patients treated with cryosurgery had a complete treatment response, whereas 1 (5.9%) patient developed recurrence after complete response.

CONCLUSIONS

It is of clinical and histopathological importance that invasive SCC was detected in 25.5% of lesions diagnosed as PAK. The fact that there was no statistical difference between the clinical features of the PAK and SCC groups as well as the excision and follow up groups suggests that the need for excisional biopsy for a definitive diagnosis cannot be clinically predicted. A greater prevalence of induration in the SCC group suggests that excision should be considered in order to exclude the SCC diagnosis for indurated lesions. Our results suggest that the definition of proliferative actinic keratosis should be histopathologically revised and that total excisional biopsy instead of punch biopsy should be considered, especially for lesions with a proliferative appearance.

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