

Bowenoid transformation in seborrheic keratosis: A retrospective analysis of 429 patients

Parvin Rajabi,¹ Neda Adibi,² Pardis Nematollahi,³ Mitra Heidarpour,³ Mehdi Eftekhari,⁴ Amir Hossein Siadat²

¹Professor, Department of Pathology, School of Medicine, Isfahan University of Medical Sciences, Isfahan, Iran.

²Assistant Professor, Department of Pathology, School of Medicine, Isfahan University of Medical Sciences, Isfahan, Iran.

³Assistant Professor, Department of Pathology, School of Medicine, Isfahan University of Medical Sciences, Isfahan, Iran.

⁴Resident of Pathology, Department of Pathology, School of Medicine, Isfahan University of Medical Sciences, Isfahan, Iran.

Background: Seborrheic keratosis is a common, benign skin tumor. Numerous reports have shown its possibility of malignant transformation. This study was designed to demonstrate the occurrence of concomitant seborrheic keratosis and skin cancers. **Materials and Methods:** Data was retrospectively reviewed from all patients with a diagnosis of seborrheic keratosis in pathology department of Alzahra Hospital and a private pathology laboratory in Isfahan, Iran over a 4-year period. We classified all demographic data and associated dysplasia or Bowen's disease and analyzed them by student-t or chi-square tests. **Results:** From all 429 specimens, 5 (1.2%) were found to be associated with Bowen's disease and one (0.2%) with mild dysplasia in squamous epithelium. All cases arose within the clinically, atypical seborrheic keratosis. More men were affected with lesions alone and with malignancy (230/423 (54.4%) and 5/6 (83.3%), respectively) compared to women. The average age of patients suffering from lesions with and without associated malignancy was 57 and 54 years, respectively. The common site of lesion alone was head and neck but lesions with malignancy involved lower extremities. The two lesions were significantly different in site of occurrence ($p < 0.001$). **Conclusion:** Generally, although the association between seborrheic keratosis and skin malignancy appears to be accidental, it must always be in mind. Therefore, histopathologic examination of all seborrheic keratosis should be considered, especially when seborrheic keratosis has atypical clinical manifestations.

Key words: Keratosis Seborrheic, Bowen's Disease, Dysplasia

INTRODUCTION

Seborrheic keratoses are common, benign, pigmented, epidermal tumors, usually developing after age 50 although occasionally in young adulthood.^[1,2] Males and females are equally affected.^[3] The common place of involvement includes the trunk, particularly interscapular area, sides of the neck, the face and the arms.^[3-5] The tumors are not however seen on the mucous membranes.^[6] Lesions are coin-like, exophytic, sharply demarcated, and stuck on the skin with a verrucous, rough, dull, or punched-out surface. Flat lesions often have a smooth surface and are scarcely elevated above the surface of the skin.^[3]

Patients are commonly assured of the benign nature of the lesions. It is thus an accepted practice to destroy the lesions without histopathologic proof. However, there have been numerous reports and studies highlighting the possibility of malignant transformation in these so-called benign lesions.

In this retrospective study, histopathological examination was performed on specimens from dermatological lesions. Our study was designed to

demonstrate the occurrence of concomitant seborrheic keratosis and skin cancers and their correlations with age, sex and clinical locations.

MATERIALS and METHODS

We carried out a retrospective analysis on 429 seborrheic keratosis cases proved by histological examination over a 4-year period in specimens from Alzahra Hospital and a private laboratory. The resulting histological reports were analyzed based on sex, age, and histological types. Seborrheic keratosis patients with other lesions were also noted. Data was presented as frequency, percentage, and range. Since we were unable to distinguish malignant transformation from adjacent tumors in curetted specimens, their data was excluded from the study. We used student-t and chi-square tests for comparison of data. P values less than 0.05 were considered significant.

Results

We studied 429 seborrheic keratosis cases that underwent excisional biopsy. They were all histologically confirmed as seborrheic keratosis

Address for correspondence: Mehdi Eftekhari, Resident of Pathology, Department of Pathology, School of Medicine, Isfahan University of Medical Sciences, Isfahan, Iran. E-mail:eftekhari@yahoo.com

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over a 4-year period. We found 6 (1.4%) lesions associated with malignant transformation among which five cases showed bowenoid transformation (Figure 1) and one revealed mild dysplasia in squamous epithelium. All lesions arose within the clinically, atypical seborrheic keratoses (malignant transformation).

We summarized all data in Table 1. Most patients with seborrheic keratosis alone or seborrheic keratosis associated with other lesions were in their sixties (Figure 2). Although mean age of individuals with seborrheic keratosis associated with other lesions was higher, the difference was not statistically significant ($p = 0.155$; student-t). The most common subtype of

seborrheic keratosis was acanthotic (72.1%) which was also observed in all 6 patients with bowenoid transformation.

Seborrheic keratosis was more prevalent in men (54.4%). In lesions associated with malignancy, the prevalence was much, but not significantly, higher in men (83.3%; $p = 0.157$, chi-square).

While seborrheic keratoses alone were mostly seen in the head and neck (78.3%), tumors accompanied with other lesions were more common in lower extremities (Figure 3). The difference between the two groups was statistically significant ($p < 0.001$, chi-square).

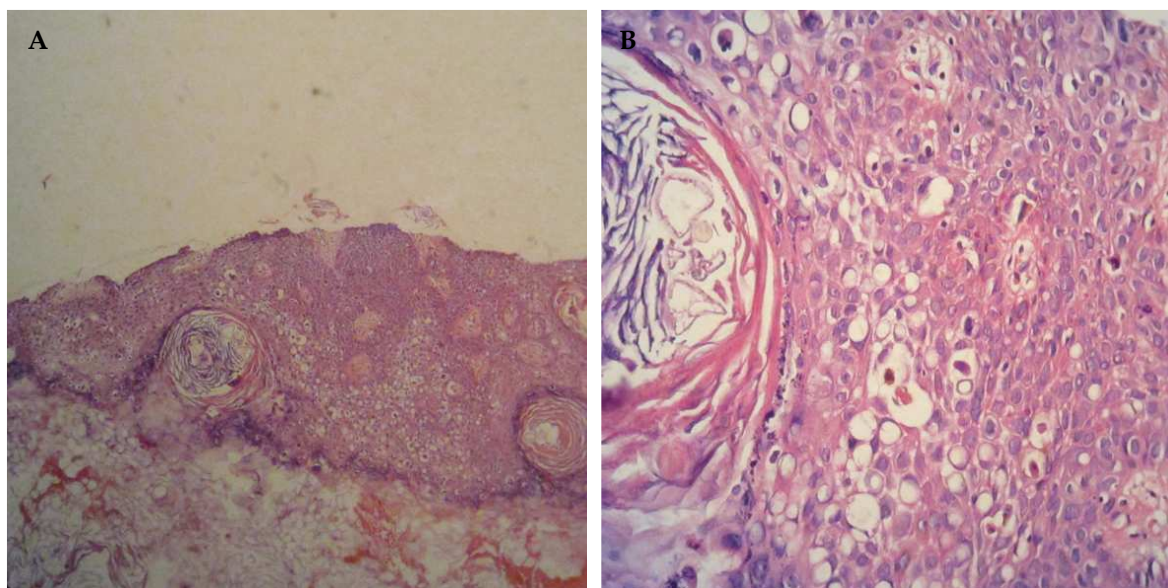


Figure 1. Acanthotic seborrheic keratosis with bowenoid transformation: (A) In this variant the surface is smooth and rounded and there is an obvious acanthosis, horn cysts and basaloid cell population (haematoxylin eosin (H&E) staining) ($\times 100$). (B) In high power, there is full-thickness cytological atypia. In addition, superficial clear cell changes and dyskeratotic cells are apparent.

Table 1. Demographic characteristics of patients in the two studied groups

| | SK alone | SK associated with malignancy | p |
|-------------------------------------|-------------------|-------------------------------|-------------|
| Male | 230 (54.4 %) | 5 (83.3%) | $p = 0.157$ |
| Age mean \pm SD | 54.48 \pm 12.81 | 57.33 \pm 6.74 | $p = 0.155$ |
| Seborrheic keratosis pattern | | | $p = 0.889$ |
| Acanthotic | 305 (72.1 %) | 6 (100%) | |
| Hyperkeratotic | 32 (7.6 %) | 0 | |
| Adenoid | 17 (4.0 %) | 0 | |
| Clonal | 34 (8.0 %) | 0 | |
| Desmoplastic | 1 (0.2 %) | 0 | |
| Irritated | 20 (4.7 %) | 0 | |
| Melanoacanthoma | 14 (3.3 %) | 0 | |
| Site | | | $p < 0.001$ |
| Head and neck | 331 (78.3%) | 0 | |
| Trunk | 41 (9.7%) | 0 | |
| Upper extremities | 32 (7.6%) | 1 (16.7%) | |
| Lower extremities | 19 (4.5%) | 5 (83.3%) | |

SK: seborrheic keratosis

Values are expressed as number (%) or mean \pm SD.

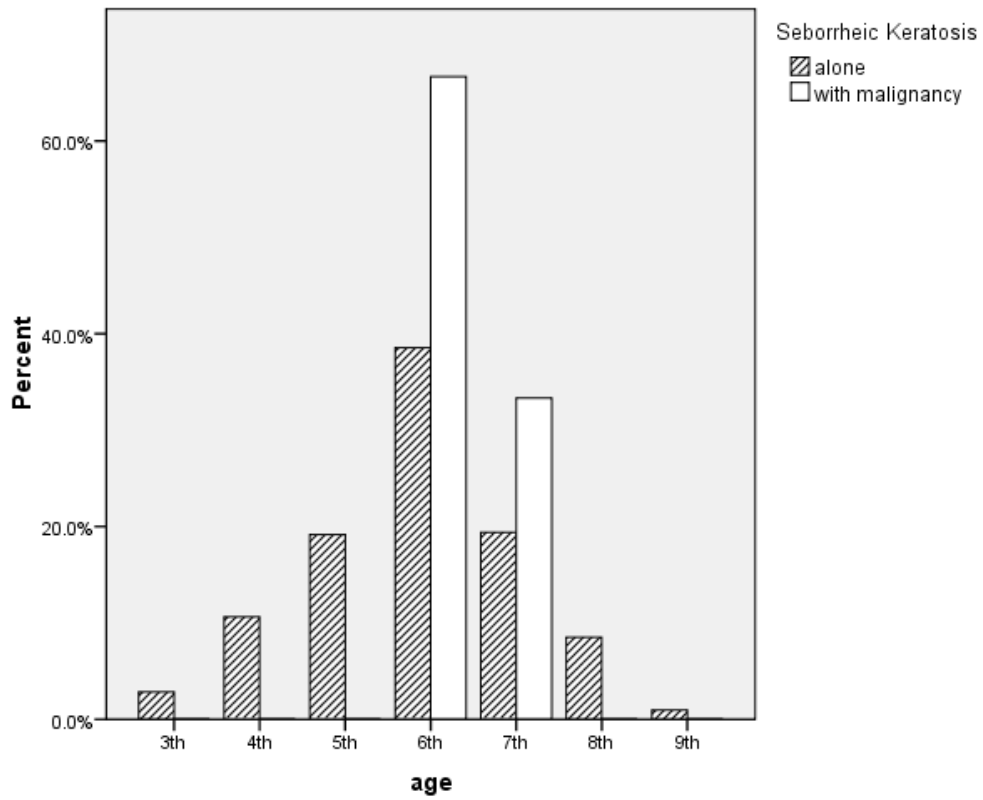


Figure 2. The association between seborrheic keratosis (with malignant transformation and alone) and age of specimens

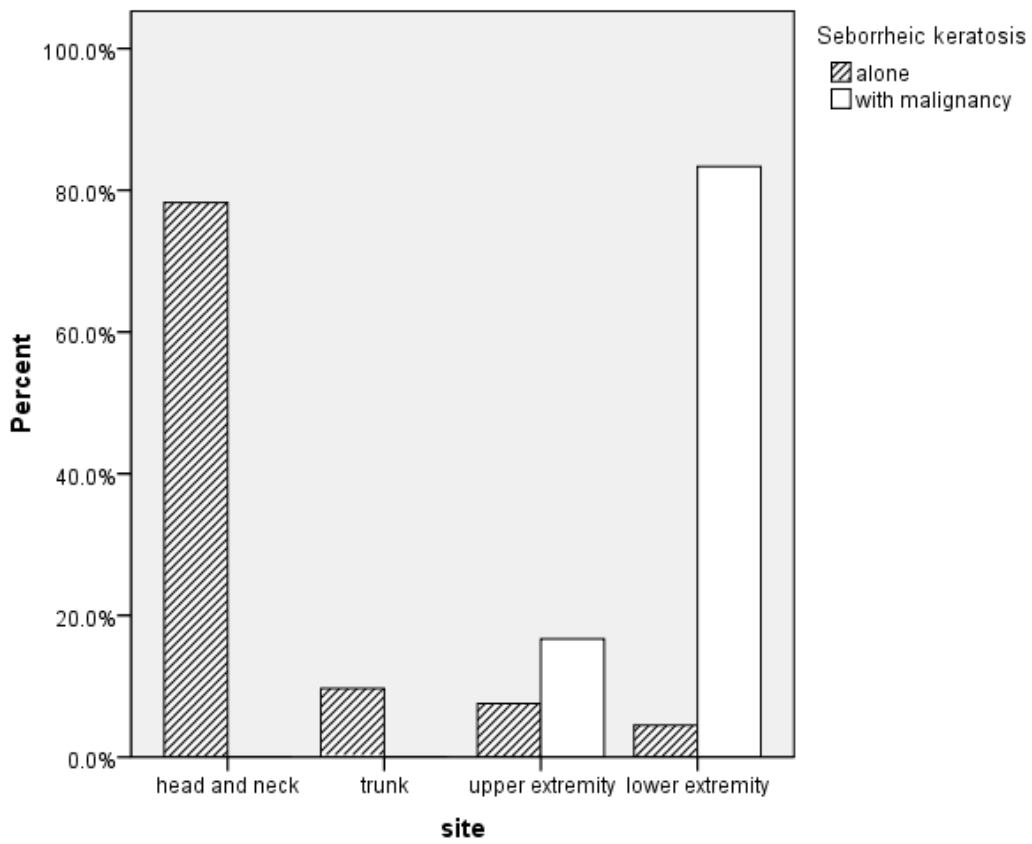


Figure 3. The association between seborrheic keratosis (with malignant transformation and alone) and site of specimens

DISCUSSION

Numerous studies have previously highlighted the possibility of malignant transformation in seborrheic keratosis lesions. Reports of seborrheic keratosis in association with malignancy have raised questions about the true nature of these benign lesions. Basal cell carcinoma (BCC) and other common skin cancers have rarely been suggested to be associated with seborrheic keratosis.^[7-9] More evaluation toward malignancy leads to the appearance of malignant melanoma,^[10-13] squamous cell carcinoma (SCC),^[14-16] keratoacanthoma,^[13] Bowen's disease,^[13,16,17] and eccrine carcinoma.^[18-20]

Vun and et al. studied 813 histological specimens of seborrheic keratosis. They found 43 cases (5.3%) associated with non-melanoma skin cancer among which intraepidermal carcinoma (SCC in situ) was the most common (4.4 %).^[5] Lim analyzed 639 consecutive histologically diagnosed seborrheic keratosis cases and suggested 44 (7%) to be associated with malignant lesions. These malignant lesions included nearly equal numbers of BCCs, SCCs and melanomas.^[21] It may therefore be concluded that various malignant neoplasms related to seborrheic keratosis might be found in 3 different cell types including layer cells, spinous layer cells and melanocytes.^[13]

Bowen's disease is a form of SCC in situ with the potential for significant lateral spread. It was first described by John T. Bowen in 1912.^[22] In 1991, annual average rate of Bowen's disease was reported as 14.9 cases per 100,000 whites.^[23] In 1994 however, the rate was reported to have increased by 10 times, i.e. 142 cases per 100,000 whites.^[24] On the other hand, the incidence of Bowen's disease in seborrheic keratosis in the present study was 1.4%. The rate of apparent bowenoid transformation was more than what seen in general population affected by Bowen's disease. Note, that it could exist, because an element of bias, in fact our hospital and pathological lab are professional center sites; therefore there was an increased likelihood of receiving atypical seborrheic keratosis for histological examination.

Although the etiology of seborrheic keratosis is not well understood, some epidemiologic studies have suggested a number of possible causes such as genetic predisposition, sunlight exposure, and human papilloma virus (HPV).^[1,25-28] However, none of these factors has been considered as the only cause of seborrheic keratosis. Several relevant etiological factors

including irradiation (solar photochemotherapy and radiotherapy), carcinogens (arsenic), immunosuppression, and HPV infection have also been suggested for Bowen's disease.^[29] It is clearly seen that the two diseases share some common etiologies.

Malignant changes especially SCC (both in situ and invasive) seem to occur in the seborrheic keratoses located in the head and neck.^[5,14,16,30] Prolonged sun damage, chronic low dose radiation exposure,^[16] and in some studies HPV infection have been proposed as etiological factors for this phenomenon.^[31-33] However, some case reports have also indicated bowenoid transformation in seborrheic keratosis on other sites.^[18,34,35] Interestingly, in contrast to previous studies, the most common location in our study was head and neck in seborrheic keratosis alone and lower extremities in seborrheic keratosis with malignant transformation. Such inconsistencies in the site of bowenoid transformation may imply that excisional biopsy of seborrheic keratosis should not be only performed from sites of lesions.

Previous authors have used the term collision tumor to designate lesions in which two distinctive neoplasms arise together.^[13] However, it is not yet clear whether malignant skin tumors and seborrheic keratosis are accidental lesions or seborrheic keratosis is a precursor lesion. About three-quarters of patients with Bowen's disease have lesions on the lower leg (60-85%).^[36,37] Therefore, bowenoid transformation is more likely an accidental lesion in seborrheic keratosis. In addition, the high prevalence of seborrheic keratosis suggests that coincidental occurrence is more logical. On the other hand, specific fibroblast-growth-factor-receptor-3 (FGFR3) mutations and frequent FGFR3 overexpression were observed in seborrheic keratosis. Thus, activation of the FGFR3 signaling pathway might be a common feature of tumorigenesis in seborrheic keratosis, although the activation might not induce typical oncogenic signals in epidermal keratinocytes.^[38] We should expect the accelerated cell division to increase the chance of mutation and induce malignancy.

Generally, the association between seborrheic keratosis and skin malignancy appears to be accidental but the probability must always be kept in mind. Therefore, histopathologic examination of all seborrheic keratosis cases should be considered, especially when seborrheic keratosis has atypical clinical manifestations.

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