

# Seborrheic keratosis evolution into squamous cell carcinoma: A truly modified sun-related tumor? A case report and review of the literature

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## Abstract

The incidence of seborrheic keratosis (SK) generally increases with age and are mostly localized on the trunk, face and neck, especially on sun-exposed areas. The association between SK and skin malignancies appears to be accidental, but *in situ* transformation occurs more frequently in sun-exposed areas. Histopathological examination of all SK cases should be considered, especially when SK lesions exhibit atypical clinical manifestations, such as ulceration and crusting, as they may herald malignant transformation. In addition, other features associated with malignant transformation include excoriations or hemorrhages identified on the lesion, modification and evolution of the macroscopic characteristics, and the presence of local erythema or pruritus. Immunocompromised patients exhibit an increased risk of malignant transformation, even when radiation is involved.

## Introduction

The incidence of seborrheic keratosis (SK) generally increases with age. These lesions are mostly localized on the trunk, face and neck, especially on sun-exposed areas. Basal cell carcinoma (BCC), squamous cell carcinoma (SCC) and melanoma associated with SK may arise from the basaloid cells, squamous cells and melanocytes that are contained in SK. Here, we report the *in situ* transformation of SK into SCC that was unfortunately treated by local cryotherapy a few months prior to surgical treatment.

## Case Report

A 69-year-old male who worked out-

doors and lacked medical history, with the exception of heliodermatitis, presented to our dermatological department for an SK lesion localized on the right flank. The lesion appeared few years ago but became painful in recent months, exhibiting peripheral inflammation and superficial bleeding (Figure 1). The lesion was treated by local cryotherapy, but the lesion recurred. Given the clinical appearance of the lesion, we performed surgical treatment because SCC was suspected and confirmed by histopathology analysis (Figures 2 and 3). Follow-up (7 years) showed no tumor recurrence.

## Discussion

The incidence of SK typically increases with age, and most lesions occur on the trunk, face and neck. The lesion size can vary from 0.5 cm to 3.0 cm or larger in diameter. The etiology is misunderstood. Lesions appear to be genetically stable despite multiple somatic alterations.<sup>1</sup> Increased FGFR3 mutation levels are associated with increased FOXN1 levels, and a positive feedback loop is hypothesized to favorize malignant progression in UV-prone areas.<sup>2</sup> Histologically, hyperkeratosis, papillomatosis or acanthosis are features observed in SK, and these lesions tend to be reticulated, pigmented, clonal, irritated or flat. Clinically, keratinocyte proliferation can lead to the formation of an endophytic or exophytic nodule. The lesion typically exhibits a well-defined border with the underlying dermis. Some lesions may be symptomatic due to pruritus and are often treated by local cryotherapy. Multiple lesions are occasionally observed in cases with an internal neoplasm called a Leser-Trelat sign, which is sometimes present in gastrointestinal tract adenocarcinoma; breast, lung, liver, pancreas, and prostate cancers; hematopoietic diseases<sup>3</sup> and metastasized melanoma.<sup>4</sup> A pseudo Leser-Trelat sign is associated with chemotherapy and epidermal growth factor antagonists therapy.<sup>5</sup> Non-malignant cases with Leser-Trelat signs are rarely described. Malignant transformation raises questions about the true nature of these benign lesions. The malignant transformation of SK appears more frequently in the elderly on the head and neck. Malignant lesions are occasionally associated with a recent history of pruritus, ulceration or increasing size. Potential etiological factors include prolonged sun damage and chronic low-dose radiation exposure.<sup>6</sup> In a study involving more than 23000 histopathological examinations, 11.9% of clinically apparent of SK lesions

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were diagnosed as BCC, 3.4% as SCC and 1.01% as melanoma.<sup>7</sup> In another retrospective study of 813 SK lesions, neoplasia was noted in 5.3%; superficial SCC was the most common, followed by BCC and invasive SCC. Most lesions may represent SK an *in situ* transformation.<sup>8</sup> On the other hand, a review of greater than 10000 SK revealed 14 cases of BCC; however, the majority of these lesions were in direct contact with the epidermis<sup>9</sup> as presented by Ishida who suggested that BCC does not arise directly from SK but that SK is distinct from the carcinoma based on immunohistochemical results.<sup>10</sup> The presence of a melanoma inside of an SK lesion prompts the question – does this lesion represent a coincidental association or true malignant transformation? Given that this association is very rare, it seems to be coincidental. However, dermoscopic analysis of any suspicious or changing SK lesion is essential.<sup>11</sup> In a study of 9204 cases, melanoma was identified in 0.66% of cases submitted for histological examination with a clinical diagnosis that included SK. Melanoma was in the clinical differential diagnosis of 51% lesions. Of the remaining lesions, 28% had a differential diagnosis of SK vs melanocytic nevus, 12% BCC, or 5% squamous cell proliferation. All the histological types of melanoma were described.<sup>12</sup> Although rare, the association SK and eccrine porocarcinoma has been described.<sup>13</sup> The molecular mechanism of a malignant transformation is not completely understood. Proposed theories implicate the alter-

ation of proteins involved in cell cycle regulation. In general, epidermal growth factor receptors (EGFR) are present on basal keratinocytes, but EGFR levels decrease as the keratinocytes differentiate in the upper epidermal layers. The loss of the membrane receptor with the absence of cytoplasmic EGFR, which is similar to actinic keratosis, or cytoplasmic receptor accumulation, which is similar to Bowen's disease, has been observed.<sup>14</sup> Somatic fibroblast growth factor receptor 3 (FGFR3) and phosphatidylinositol 3-kinase catalytic subunit  $\alpha$  (PIK3CA) mutations are found in 89% of SK lesions and may be important in the development of cutaneous epithelial malignancies,<sup>15</sup> especially those associated with increased age and localization on sun-exposed areas of the head and neck.<sup>16</sup> Dupperet *et al.* suggested FGFR3 activation in skin keratinocytes might play a tumor-suppressive role by driving differentiation and antagonizing RAS signaling. These authors postulated that activating FGFR3 mutations alone are insufficient to drive KS and do not alter the growth kinetics or differentiation status of SCC and that FGFR3 pro-

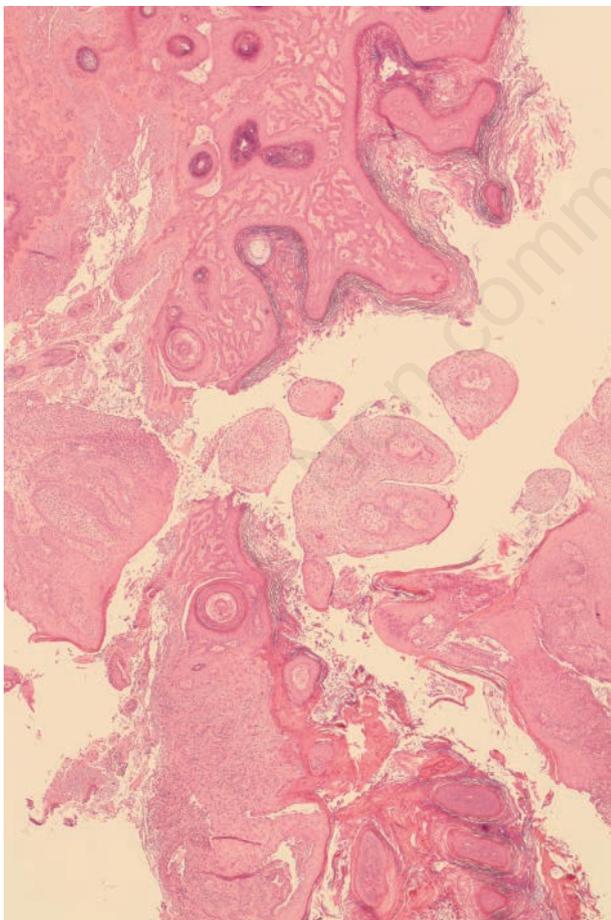
tein itself is dispensable for Ras-driven SCC.<sup>17</sup> The expression of glioma tumor-suppressor candidate region gene 2 (GLTSCR2) regulates the stability of the tumor suppressor PTEN, and the tumor suppressive function of GLTSCR2 is reduced in SK.<sup>18</sup>

## Conclusions

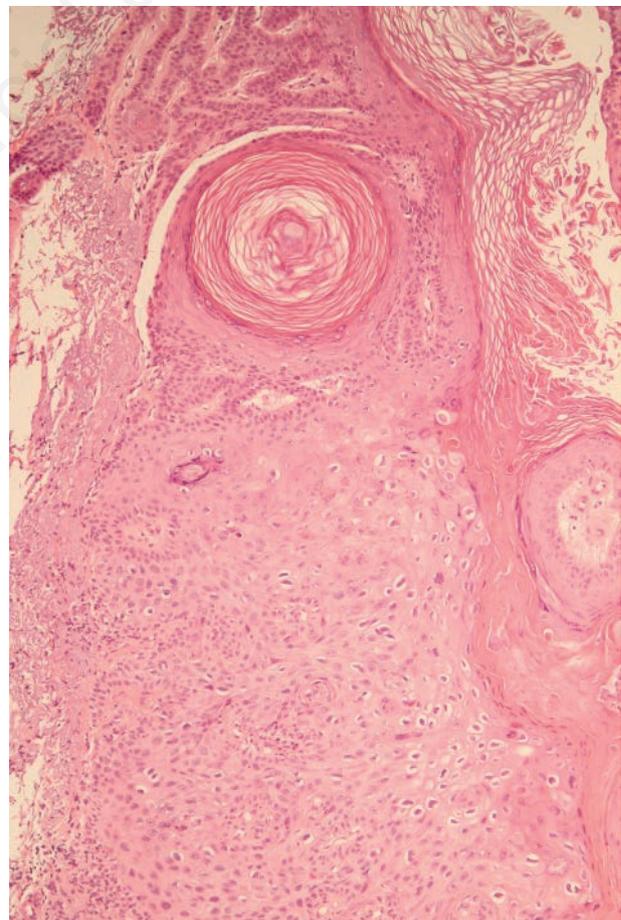
In general, the association between SK and skin malignancies appears to be accidental, but *in situ* transformation occurs



**Figure 1. Painful seborrheic keratosis with peripheral inflammation and superficial bleeding on the half right part.**



**Figure 2. Papillomatous seborrheic keratosis with massive hyperkeratosis and papillomatosis (Haematoxylin Eosin magnification  $\times 2.5$ ).**



**Figure 3. Foci of transformation with atypical nuclei and anisokaryosis (Haematoxylin Eosin magnification  $\times 10$ ).**

more frequently in sun-exposed areas.<sup>6</sup> Histopathological examination of all SK cases should be considered, especially when SK lesions exhibit atypical clinical manifestations, such as ulceration and crusting, as they may herald malignant transformation. In addition, other features associated with malignant transformation include excoriations or hemorrhages identified on the lesion, modification and evolution of the macroscopic characteristics, and the presence of local erythema or pruritus. Immunocompromised patients exhibit an increased risk of malignant transformation,<sup>19</sup> even when radiation is involved.<sup>20</sup>

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