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Solitary Keratoacanthoma at the Recipient Site of a Full-Thickness Skin Graft: A Case Report and Review of the literature

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Abstract:
A 57-year-old man presented with a pigmented papule, 0.4 cm in diameter, on the left lower eyelid. Skin biopsy revealed a basal cell carcinoma, which was excised through a wide excision followed by a full-thickness skin graft (FTSG). Two weeks after the surgery, an erythematous nodule developed in the lower margin of the graft recipient site. The nodule size increased rapidly over 2 weeks, becoming dome-shaped with a central hyperkeratotic plug. A diagnosis of keratoacanthoma (KA) was made, and surgical excision was performed. Histological findings revealed a large, well-differentiated squamous tumor with a central keratin-filled crater and buttress. The HPV genotyping results were negative.

Risk factors for KA include trauma, old age, exposure to UV radiation, immunosuppression, and HPV infection. KA has most often been reported to develop at the donor site. Although the pathogenesis of KA is unclear, trauma is believed to act as a second insult to a preceding oncogenic insult, such as exposure to UV radiation, resulting in a koebnerization. Herein, we report a case of solitary KA at a FTSG recipient site. This report presents information that may provide guidance during dermatologic surgeries.

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Solitary Keratoacanthoma at the Recipient Site of a Full-Thickness Skin Graft: A Case Report and Review of the literature

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Abstract

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Risk factors for KA include trauma, old age, exposure to UV radiation, immunosuppression, and HPV infection. KA has most often been reported to develop at the donor site. Although the pathogenesis of KA is unclear, trauma is believed to act as a second insult to a preceding oncogenic insult, such as exposure to UV radiation,
resulting in a koebnerization. Herein, we report a case of solitary KA at a FTSG recipient site. This report presents information that may provide guidance during dermatologic surgeries.

Keywords
Keratoacanthoma
Koebnerization
full-thickness skin graft

Introduction
The term, keratoacanthoma (KA) was first coined in the 1940s [1]. KA are historically considered to be a variant of squamous cell carcinoma (SCC); however, it has been suggested to be defined as a benign tumor due to the numerous cases of spontaneous regression [2]. Despite the controversy, KA remains classified as a variant of SCC in the 2018 WHO classification [3]. KA typically presents as a rapidly growing dome-shaped umbilicated nodule with a central hyperkeratotic plug [4], undergoing three stages: proliferative, mature, and regression phase [2]. The similarity of the triphasic nature of KA to the follicular morphogenesis of anagen, catagen, and telogen cycles, suggests that KA has a follicular origin and may be associated with Wnt signaling [2]. Representative KA types include solitary, centrifugum et marginatum, and giant [2]. Excluding solitary KA, all other types are reportedly associated with human papilloma virus (HPV) infection [2].

In addition to the SCC associated risk factors, trauma, including surgery, is also a potential risk factor for KA [2,4]. There are few reports on trauma after skin grafting. If KA occurs after skin grafting, it may be misdiagnosed as SCC without consultation with a dermatologist, which in turn can lead to invasive treatment such as wide excision. This report highlights a case of KA that occurred at the recipient site of full-thickness skin graft (FTSG), which has educational value.

Case report
A 57-year-old Korean man without any contributory medical history visited the dermatology department with a solitary pigmented papule, 0.4 cm in diameter, on the left lower eyelid (Figure 1a). Skin biopsy revealed a basal cell carcinoma (BCC) with peripheral palisading and peritumoral cleft. (Figure 1b). After wide excision, FTSG from left preauricular area was used for reconstruction during plastic surgery (Figure 1c).

Two weeks post-operatively, an erythematous nodule developed in the lower margin of the skin graft recipient
site. The nodule rapidly attained a dome shape with a central hyperkeratotic plug over the following two weeks (Figure 2a). During dermatologic consultation, the patient was diagnosed with KA, and a surgical excision with 3 mm margin was performed (Figure 2b). Histopathological findings revealed a large, well differentiated, squamous tumor with central keratin filled crater (Figure 2c). A buttress of normal epidermis surrounded the crater. Keratin horn pearls, bland squamous cells with abundant eosinophilic or glassy cytoplasm with minimal atypia, were also observed. The tissue tested negative for HPV genotyping. The remaining defect was closed with a split-thickness skin graft harvested from the left lateral thigh (Figure 2d). No signs of recurrence were observed three months postoperatively.

Discussion

KA classically presents as a firm, dome-shaped nodule filled with a keratinous plug [2,4]. It has been associated with old age, HPV infection, immunosuppression, ultraviolet (UV) exposure, and cutaneous traumas such as surgery, laser resurfacing, and burns [2]. The patient in the present case tested negative for HPV DNA on polymerase chain reaction analysis. Considering his age and medical history, it is unlikely that the patient was immunosuppressed. Table 1 summarizes the reported cases of KA after skin grafting according to the patient demographic and case data. The occurrence of KA at the skin graft site is rare, and in most of the 11 reported cases, the KA developed at the donor site [5-7]. Moreover, the cases that report KA development on the recipient site are recurrences of multiple KAs in the extremities of older patients [5,8-10]. The mechanism of KA formation after receiving a skin graft are unclear due to its multifactorial etiology [10]. A two-step pathogenesis, characterized by two triggering insults to the epidermis, has been proposed [6,7,10]. The first insult (initiator) may be oncogenic UV exposure of the epidermis or the mutation of cell-cycle regulators due from a chemical carcinogen. The KA in our patient also occurred in a sun-exposed area (lower eyelid) where BCC had previously presented. We believe that a potential first insult may have been a mutation in the cell-cycle regulator due to UV exposure. The trauma associated with surgery may have been the second insult (promoter) to induce epithelial proliferation. The local upregulation of cytokines and chemokines from recruitment of neutrophil, macrophage, and T cells may be involved in the acute wound healing process [10]. Helper T cells enhance skin carcinogenesis [11]. Fibroblast growth factor is involved in the Koebner phenomenon of psoriasis [12], characterized by the appearance of skin lesions following trauma in a previously affected site. Therefore, epithelial proliferation and angiogenesis may be induced by these cells after acute epidermal injury [10]. Contrastingly, cytotoxic T cells are involved in KA regression. After skin grafting, microscarring reduces lymphatic regeneration, thereby decreasing local immunosurveillance; this factor places higher risk among older
patients with immunosenescence [10]. In a previously reported case of recurrent multiple KA in older patients, local and systemic immunosuppression were presumably involved. Considering these findings and reports, the two-step pathogenesis presents an acceptable explanation for the koebnerization [7,10].

In our case, the KA occurred at the FTSG recipient site following the surgical excision of a BCC in a relatively young patient. Without dermatological consultation, this pathogenic presentation may have been misdiagnosed as a SCC and treated invasively with wide excision margins. Since a possibility of KA regression exists, treatment with bleomycin ILI administration can be considered, instead of surgical resection [2,4]. This report presents information that may provide guidance to clinicians performing dermatologic surgeries and identify better therapeutic strategies. In addition, the possibility of postoperative KA development should be explained to patients when skin grafts are used in a surgical site of previous oncogenic insult. Since most of the previously reported cases developed KA within 2 months, careful follow-up should be done at least 2 months post-operatively.

**Patient consent**
The patient provided written informed consent for the publication and use of their images.

**Previous presentation**
None.

**Author contributions**

**Funding**
The authors have no funding sources to declare.

**Conflict of Interest**
The authors have no conflict of interests to declare.
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References


Figure 1. Clinical and histopathological features of preceding skin lesion. (a) Solitary rodent-ulcer like
pigmented papule on the Lt. lower eyelid. (b) Histopathological specimen was compatible with basal cell carcinoma, showing numerous nests of basaloid tumors with peripheral palisading and peritumoral cleft. (c-1) preoperative design on the left lower eyelid. (c-2) photograph immediately after tumor removal. (c-3) preauricular donor site. (c-4) photograph immediately after skin graft.

**Figure 2.** Clinical and histopathological features of keratoacanthoma (KA). (a) Solitary dome-shaped nodule with central keratotic plug on the left lower eyelid. (b) The center of nodule located on the lower margin of skin graft (red arrow head). (c) Large, well differentiated squamous tumor with central keratin filled crater, consistent with KA. (d) Excision with split-thickness skin graft was performed.
Table 1. Keratoacanthomas associated with previous skin graft

<table>
<thead>
<tr>
<th>Author (year)</th>
<th>Age/Sex</th>
<th>Preceding Lesion</th>
<th>Time interval between SG and appearance of KA</th>
<th>Type of SG</th>
<th>Location of KA</th>
</tr>
</thead>
<tbody>
<tr>
<td>†Dibden and Fowler (1955)</td>
<td>76/M</td>
<td>Keratoacanthoma</td>
<td>2 mo</td>
<td>Unspecified</td>
<td>Donor and Recipient sites</td>
</tr>
<tr>
<td>Wulsin (1958)</td>
<td>unspecified</td>
<td>Unspecified</td>
<td>3 wk</td>
<td>Unspecified</td>
<td>Donor site</td>
</tr>
<tr>
<td>†Schwartz (1979)</td>
<td>59/F</td>
<td>Keratoacanthoma</td>
<td>unspecified</td>
<td>Unspecified</td>
<td>Donor site</td>
</tr>
<tr>
<td>Soto-de-Delas et al (1989)</td>
<td>38/F</td>
<td>Melanoma</td>
<td>3 wk</td>
<td>Split-thickness</td>
<td>Donor site</td>
</tr>
<tr>
<td>Hamilton et al (1997)</td>
<td>61/F</td>
<td>Burn</td>
<td>1 mo</td>
<td>Split-thickness</td>
<td>Donor site</td>
</tr>
<tr>
<td>Taylor et al (1998)</td>
<td>55/M</td>
<td>Burn</td>
<td>3 wk</td>
<td>Split-thickness</td>
<td>Donor site</td>
</tr>
<tr>
<td>Tamir et al (1999)</td>
<td>54/M</td>
<td>Burn</td>
<td>4 mo</td>
<td>Split-thickness</td>
<td>Donor site</td>
</tr>
<tr>
<td>†Vergara et al (2007)</td>
<td>80/F</td>
<td>Keratoacanthoma</td>
<td>1 mo</td>
<td>Split-thickness</td>
<td>Recipient site</td>
</tr>
<tr>
<td>Nagase et al (2016)</td>
<td>78/F</td>
<td>Actinic Keratosis</td>
<td>23 days</td>
<td>Full-thickness</td>
<td>Donor site</td>
</tr>
<tr>
<td>†Nishibaba et al (2017)</td>
<td>89/F</td>
<td>Keratoacanthoma</td>
<td>2 mo</td>
<td>Full-thickness</td>
<td>Recipient site</td>
</tr>
<tr>
<td>†Lee et al (2017)</td>
<td>93/F</td>
<td>Keratoacanthoma</td>
<td>3 mo</td>
<td>Split-thickness</td>
<td>Donor And Recipient sites</td>
</tr>
</tbody>
</table>
our case (2022) 57/M Basal Cell Carcinoma 2 wk Full-thickness Recipient site

Similar cases are bolded.

KA, Keratoacanthoma; SG, Skin graft.

†Case of **multiple** and **recurrent** KA all around the edge of the skin graft site.
lower margin of skin graft