A Keratoacanthoma With Squamous Cell Carcinoma Under Immunosuppressive Therapy After Renal Transplantation

Case Report

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Abstract

A 69-year-old Japanese male developed a solitary keratoacanthoma with squamous cell carcinoma (SCC) on his right arm. He had undergone kidney transplantation from his father due to chronic renal failure approx. 45 years earlier and had since been under immunosuppressive treatment (azathioprine and prednisolone). An immunohistopathological examination revealed Ki-67- and p53-positive cells in the tumor bed of the keratoacanthoma, and our final diagnosis was a solitary keratoacanthoma with SCC. In this case, several factors apparently caused the solitary keratoacanthoma with SCC: the long duration of immunosuppression, the use of azathioprine after renal transplantation, and UV exposure. Immunohistopathological studying is important for the diagnosis of SCC or keratoacanthoma. Keratoacanthomas have malignant potential, and this patient’s SCC could have been caused by the keratoacanthoma.

Keywords: Keratoacanthoma; Squamous Cell Carcinoma (SCC); Renal Transplantation; Immunosuppressive Condition; Azathioprine.

Introduction

Three kinds of keratinocyte tumor, squamous cell carcinoma (SCC), basal cell carcinoma (BCC), and actinic keratosis (AK), account for 99% of non-melanoma skin cancers, and 20% of cutaneous malignancies are SCC [1]. The incidence of SCC is increasing worldwide. A major risk factor in the development of SCC is ultra-violet (UV) light exposure; in addition, immunosuppressive therapy after organ transplantation is closely related to the carcinogenesis [2]. A 20.8% incidence of non-melanotic skin cancer in patients who underwent organ transplantation in the years from 1978 to 2005 was reported [3]. In the USA, >7% of 35,000 renal transplant recipients with 3 years of immunosuppression treatment developed non-melanotic skin cancer, and this incidence is 20-fold higher compared to that in immunocompetent individuals [4]. Kidney transplant recipients were reported to have a 3- to 12-fold increased risk of solid organ cancer compared to general populations [5, 6], and another study indicated that the incidence of non-melanotic skin cancer in transplant recipients was elevated by 52.7-fold [7]. Remarkably, the high risk incidence of non-melanotic skin cancers such as SCC and BCC in kidney transplant recipients is 60- to 250-fold increasing [8, 9].

Keratoacanthoma, first described by Jonathon Hutchison in 1889 [10], is a benign skin tumor raised from hair follicles [11, 12], and it often arises on skin exposed to UV light. The characteristics of keratoacanthoma are single-cause, dome-shaped, and rapid growth and development in elderly people [11-13], and a keratoacanthoma possesses malignant potential. The histological findings of keratoacanthoma are similar to those of well-differentiated SCC. The removal of a keratoacanthoma is recommended for diagnosis and treatment.
Case Presentation

A 69-year-old Japanese male noticed skin swelling on his right arm beginning in March 2021 (Figure 1-a). The first diagnosis based on a skin biopsy was irritated seborrheic keratosis, but the swelling continued and became greater over the following month (Figure 1-b). The results of a second skin biopsy indicated a keratoacanthoma with Ki-67-positive and p53-positive cells in the tumor bed (Figure 2a–c).

We removed the tumor under local anesthesia with a 1-cm safe margin, with suspicion of SCC. The final diagnosis based on the histopathological findings was a solitary keratoacanthoma with SCC (Figure 3). Forty-five years earlier, due to the patient's chronic renal failure, he had received a kidney from his father, and he had been under immunosuppressive treatment with azathioprine and prednisolone since then. His several warts had increased in number after the start of the immunosuppressive treatment, and liquid nitrogen had been used to treat many warts.

Discussion

The incidence of non-melanotic skin cancer among tissue-transplant recipients is higher than that of general populations, and SCC is most common skin cancer. SCC is related to UV exposure. More than 90% of skin tumors among organ transplant recipients developed in UV-exposed areas of skin [14]. This feature may be responsible for the approximately fourfold higher incidence of SCC compared to that of BCC among transplant recipients; moreover, the causal factors of invasive SCC are also related to the dose and duration of immunosuppressive therapy and UV exposure [15].

UV is thus a greater causal factor of skin cancer in immunosuppressed patients compared to general populations [16]. It is important that sunscreen be used for protecting the skin's DNA against UV radiation, and in Australia, the use of sunscreen is a standard recommendation for patients undergoing immunosuppressive therapy [16, 17]. Our patient had never used sunscreen, as is true of many elderly males in Japan. The use of sunscreen in that population has been considered to be similar to the use of makeup by females (and thus "unmanly" behavior).

Skin cancer in patients with immunosuppressive therapy is associated with the dose, kinds of immunosuppressant medicine used, and the duration of immunosuppression. A particular immunosuppressive agent, azathioprine, is related to the development of multiple SCCs and warts, and it is better to use mammalian target of rapamycin inhibitors (mTORi) instead of azathioprine for immunosuppressive protocols in light of the risk of skin cancer [18]. A common immunosuppressive agent that is catabolized to 6-mercaptopurine, azathioprine affects the synthesis of purines and can block DNA repair [19, 20], and this agent produces reactive oxygen species under UV exposure [19, 21]. Azathioprine was reported to increase the risk of SCC development by fivefold [19, 21]. The use of mTORi has shown significantly lower incidences of skin cancer compared to that of azathioprine.
of both AKand SCC, because these agents have an inhibitory effect on tumor angiogenesis and an antiproliferative effect on tumor cells.

A retrospective study showed that risk factors of cancer development were age and male gender [23]. The cancer risk in kidney transplant recipients is threefold-increased compared to that of patients with dialysis [24]. Our patient had received treatment for many wars, and these wars might be related to him being in an immunosuppressive condition. His risk factors for skin cancer were being male, elderly, with a UV-exposed area, not using sunblock, a long duration of immunosuppression, and immunosuppressive therapy with azathioprine.

The etiology of keratoacanthoma is uncertain, but keratoacanthoma can be associated with immunosuppressive conditions such as UV exposure, drug treatments, and the use of X-rays [25]. Keratoacanthoma has been classified in the group of benign epithelial tumors with malignant potential, and it sometimes shows SCC differentiation within the lesion. The histological features of keratoacanthoma and SCC are similar, and it is often difficult to differentiate these tumors. Because keratoacanthoma and SCC are often admixed, there are a few proposed terms such as keratoacanthoma-like SCC [26] and keratoacanthoma with an SCC component (KASCC) [27, 28]. The latter keratoacanthoma has been classified as SCC keratoacanthoma type [29]. Immunohistochemistry using p53 and Ki-67 may be helpful for distinguishing between subungual keratoacanthoma and subungual SCC [30].

Conclusion

We reported a case of SCC in keratoacanthoma related mainly to the patient’s immunosuppressive condition. This case emphasizes that performing a skin biopsy or tumor removal and the immunohistopathological findings are important for the diagnosis and treatment of a keratoacanthoma and/or SCC in patients who have undergone organ transplantation.

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