International Journal of Clinical Dermatology & Research (IJCDR)
ISSN: 2332-2977

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 riskfactor in the development of SCCis ultra-violet (UV) light exposure; in addition, immunosuppressive therapy after organ transplantation is closely related to the carcinogenesis [2]. A 20.5% 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 transplantrecipients is60- 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.

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Received: January 28, 2022
Accepted: February 22, 2022
Published: March 26, 2022

Citation: Keiji Sugiura, Mariko Sugiura, Kazuharu Uchida, KunioMorozumi. A Keratoacanthoma With Squamous Cell Carcinoma Under Immunosuppressive Therapy After Renal Transplantation. *Int J Clin Dermatol Res.* 2022;10(1):275-277. doi: http://dx.doi.org/10.19070/2332-2977-2200061

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 greaterover the following month(Figure 1-b). The results of a second skin biopsy indicated akeratoacanthoma 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,hehad 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 nitrogenhad been used to treatmany warts.

Discussion

The incidence of non-melanotic skin cancer among tissue-transplant recipients is higher 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 sunblock be used for protecting the skin's DNA against UV radiation, and in Australia, the use of sunblock is a standard recommendation for patients undergoing immunosuppressive therapy [16, 17]. Our patient hadnever used sunblock, as is true of many elderly males in Japan. The use of sunblock in that population has been considered to be similar to the use of make-up 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

Figure 1. (a)Clinical findings at the first biopsy.(b) Clinical findings at the second biopsy.

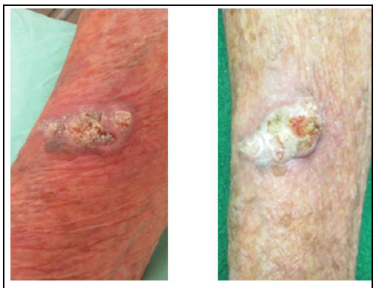
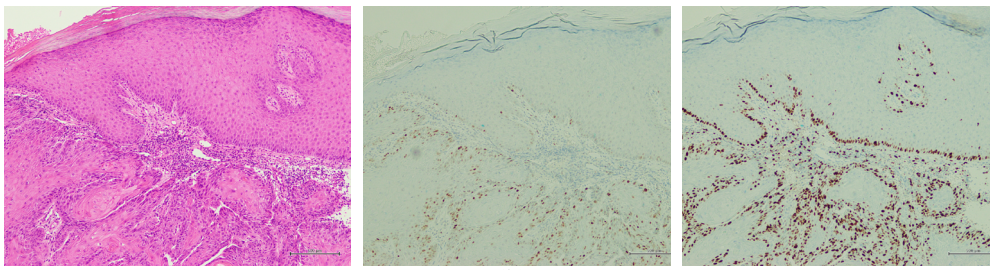
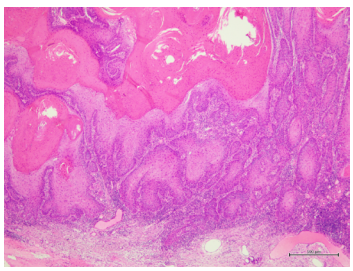


Figure 2. Immunohistopathological findings of second skin biopsy by (a) hematoxylin-eosin (HE), ×20 (b)Ki-67, ×20, and (c)p53, ×20.



(a) (b) (c)

Figure 3. Histopathological findings after the tumor's removal; HE×20.



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 hadreceived treatment for many warts, and these warts 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 latterkeratoacanthoma 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 akeratoacanthoma 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.

References

[1]. Paolino G, Donati M, Didona D, Mercuri SR, Cantisani C. Histology of Non-Melanoma Skin Cancers: An Update. Biomedicines. 2017 Dec 20;5(4):71. PubMed PMID: 29261131.

[2]. Kim JYS, Kozlow JH, Mittal B, Moyer J, Olenecki T, Rodgers P. Guidelines of care for the management of cutaneous squamous cell carcinoma. J Am AcadDermatol. 2018 Mar;78(3):560-578. PubMed PMID: 29331386.

[3]. Ulrich C, Arnold R, Frei U, Hetzer R, Neuhaus P, Stockfleth E. Skin changes following organ transplantation: an interdisciplinary challenge. DtschArztebl Int. 2014 Mar 14;111(11):188-94. PubMed PMID: 24698074.

[4]. Kasiske BL, Snyder JJ, Gilbertson DT, Wang C. Cancer after kidney transplantation in the United States. Am J Transplant. 2004 Jun;4(6):905-13. PubMed PMID: 15147424.

[5]. Miao Y, Everly JJ, Gross TG, Tevar AD, First MR, Alloway RR, et al. De novo cancers arising in organ transplant recipients are associated with adverse outcomes compared with the general population. Transplantation. 2009 May 15;87(9):1347-59. PubMed PMID: 19424035.

[6]. Apel H, Walschburger-Zorn K, Häberle L, Wach S, Engehausen DG, Wullich B. De novo malignancies in renal transplant recipients: experience at a single center with 1882 transplant patients over 39 yr. Clin Transplant. 2013 Jan-Feb;27(1):E30-6. PubMed PMID: 23278453.

[7]. Wimmer CD, Rentsch M, Crispin A, Illner WD, Arbogast H, Graeb C, et al. The janus face of immunosuppression - de novo malignancy after renal transplantation: the experience of the Transplantation Center Munich. Kidney Int. 2007 Jun;71(12):1271-8. PubMed PMID: 17332737.

[8]. Hartevelt MM, Bavinck JN, Kootte AM, Vermeer BJ, Vandenbroucke JP. Incidence of skin cancer after renal transplantation in The Netherlands.Transplantation. 1990 Mar;49(3):506-9. PubMed PMID: 2316011.

[9]. Penn I. Skin disorders in organ transplant recipients. External anogenital lesions.Arch Dermatol. 1997 Feb;133(2):221-3. PubMed PMID: 9041837.

[10]. Hutchinson J. The crateriform ulcer of the face: A form of epithelial cancer. Trans PatholSoc London. 1889;40:275-81.

[11]. Miot HA, Miot LD, da Costa AL, Matsuo CY, Stolf HO, Marques ME. Association between solitary keratoacanthoma and cigarette smoking: a case-control study. Dermatol Online J. 2006 Feb 28;12(2):2. PubMed PMID: 16638395.

[12]. Jeon HC, Choi M, Paik SH, Ahn CH, Park HS, Cho KH. Treatment of keratoacanthoma with 5% imiquimod cream and review of the previous report. Ann Dermatol. 2011 Aug;23(3):357-61. PubMed PMID: 21909208.

[13]. Chauhan A, Chaudhary S, Agnihotri PG, Aadithya B. A solitary crateriform ulcer of the lower lip: a case report with review of literature. Indian J Dermatol. 2011 Jul;56(4):435-8. PubMed PMID: 21965859.

[14]. Joly P, Bastuji-Garin S, Frances C, Lebbe C, Aubin F, Penso-Assathiany D, et al. Squamous cell carcinomas are associated with verrucokeratotic cutaneous lesions but not with common warts in organ-transplant patients. A case-control study.Transplantation. 2010 May 27;89(10):1224-30. PubMed PMID: 20559031.

[15]. Euvrard S, Kanitakis J, Claudy A. Skin cancers after organ transplantation. N Engl J Med. 2003 Apr 24;348(17):1681-91. PubMed PMID: 12711744.

[16]. Kripke ML. Ultraviolet radiation and immunology: something new under the sun--presidential address. Cancer Res. 1994 Dec 1;54(23):6102-5. PubMed PMID: 7954455.

[17]. O'Donovan P, Perrett CM, Zhang X, Montaner B, Xu YZ, Harwood CA, McGregor JM, Walker SL, Hanaoka F, Karran P. Azathioprine and UVA light generate mutagenic oxidative DNA damage. Science. 2005 Sep 16;309(5742):1871-4. PubMed PMID: 16166520.

[18]. Hofbauer GF, Attard NR, Harwood CA, McGregor JM, Dziunycz P, Iotzova-Weiss G, et al. Reversal of UVA skin photosensitivity and DNA damage in kidney transplant recipients by replacing azathioprine. Am J Transplant. 2012 Jan;12(1):218-25. PubMed PMID: 21943390.

[19]. O'Donovan P, Perrett CM, Zhang X, Montaner B, Xu YZ, Harwood CA, McGregor JM, Walker SL, Hanaoka F, Karran P. Azathioprine and UVA light generate mutagenic oxidative DNA damage. Science. 2005 Sep 16;309(5742):1871-4. PubMed PMID: 16166520.

[20]. Zhang X, Jeffs G, Ren X, O'Donovan P, Montaner B, Perrett CM, et al. Novel DNA lesions generated by the interaction between therapeutic thiopurines and UVA light. DNA Repair (Amst). 2007 Mar 1;6(3):344-54. PubMed PMID: 17188583.

[21]. Gueranger Q, Kia A, Frith D, Karran P. Crosslinking of DNA repair and replication proteins to DNA in cells treated with 6-thioguanine and UVA. Nucleic Acids Res. 2011 Jul;39(12):5057-66. PubMed PMID: 21398635.

[22]. Paolino G, Donati M, Didona D, Mercuri SR, Cantisani C. Histology of Non-Melanoma Skin Cancers: An Update. Biomedicines. 2017 Dec 20;5(4):71. PubMed PMID: 29261131.

[23]. Marcén R, Pascual J, Tato AM, Teruel JL, Villafruela JJ, Fernández M, et al. Influence of immunosuppression on the prevalence of cancer after kidney transplantation. Transplant Proc. 2003 Aug;35(5):1714-6. PubMed PMID: 12962768.

[24]. Vajdic CM, McDonald SP, McCredie MR, van Leeuwen MT, Stewart JH, Law M, et al. Cancer incidence before and after kidney transplantation. JAMA. 2006 Dec 20;296(23):2823-31. PubMed PMID: 17179459.

[25]. Kwiek B, Schwartz RA. Keratoacanthoma (KA): An update and review. J Am AcadDermatol. 2016 Jun;74(6):1220-33. PubMed PMID: 26853179.

[26]. Misago N, Inoue T, Koba S, Narisawa Y. Keratoacanthoma and other types of squamous cell carcinoma with crateriform architecture: classification and identification. J Dermatol. 2013 Jun;40(6):443-52. PubMed PMID: 23414327.

[27]. Takai T. Advances in histopathological diagnosis of keratoacanthoma. J Dermatol. 2017 Mar;44(3):304-314. PubMed PMID: 28256761.

[28]. Ogita A, Ansai SI, Misago N, Anan T, Fukumoto T, Saeki H. Histopathological diagnosis of epithelial crateriform tumors: Keratoacanthoma and other epithelial crateriform tumors. J Dermatol. 2016 Nov;43(11):1321-1331. PubMed PMID: 27076258.

[29]. Zito PM, Scharf R. Keratoacanthoma. 2021 Nov 15. In: StatPearls [Internet]. Treasure Island (FL): StatPearls Publishing; 2022 Jan–. PubMed PMID: 29763106.

[30]. Connolly M, Narayan S, Oxley J, de Berker DA. Immunohistochemical staining for the differentiation of subungual keratoacanthoma from subungual squamous cell carcinoma.ClinExpDermatol. 2008 Aug;33(5):625-8. PubMed PMID: 18616725.