

This is an Open Access article licensed under the terms of the Creative Commons Attribution-NonCommercial 3.0 Unported license (CC BY-NC) ([www.karger.com/OA-license](http://www.karger.com/OA-license)), applicable to the online version of the article only. Distribution permitted for non-commercial purposes only.

# Keratoacanthoma Accompanied by Multiple Lung Squamous Cell Carcinomas Developing in a Renal Transplant Recipient

Sadanori Furudate Taku Fujimura Aya Kakizaki Yumi Kambayashi  
Akira Hashimoto Setsuya Aiba

Department of Dermatology, Tohoku University Graduate School of Medicine, Sendai, Japan

## Key Words

Keratoacanthoma · Renal transplantation · Interleukin-27 · pSTAT1

## Abstract

Keratoacanthoma (KA) is a benign keratinocytic neoplasm that spontaneously regresses after 3–6 months and shares features with well-differentiated squamous cell carcinoma (SCC). An increased incidence of both KA and non-melanoma skin tumor, including SCC, is seen among immunosuppressed, organ-transplant recipients. In this report we describe a case of KA accompanied by multiple lung SCCs developing in a renal transplant recipient.

© 2014 S. Karger AG, Basel

## Introduction

Keratoacanthoma (KA) is a benign keratinocytic neoplasm that spontaneously regresses after 3–6 months and shares features with well-differentiated squamous cell carcinoma (SCC). Although the histopathologic diagnosis of KA is based on architecture as well as cytologic features [1], notably, Clausen et al. [2, 3] reported significantly different regions of genomic aberration in KA and SCC, based on chromosomal comparative genomic hybridization. In addition, as we previously reported, the profiles of tumor-infiltrating cells and tumor-expressing molecules differ between KA and SCC [4]. An increased incidence of KA is seen among immunosuppressed patients [5]. The risk factors for non-melanoma skin cancer in renal transplant recipients (RTRs) are related to the dosage and duration of administra-

Taku Fujimura  
Department of Dermatology, Tohoku University Graduate School of Medicine  
Seiryomachi 1-1, Aoba-ku, Sendai 980-8574 (Japan)  
E-Mail [tfujimura1@mac.com](mailto:tfujimura1@mac.com)

tion of immunosuppressive reagents [6]. In this report, we describe a case of KA accompanied by multiple lung SCCs developing in a RTR.

## Case Report

A 59-year-old Japanese male visited our outpatient clinic with a 2-month history of a rapid-growth red nodule on his left lower jaw. He had undergone renal transplantation and been administered cyclosporine 200 mg/day for 4 years. On his initial visit, physical examination revealed a dome-shaped, skin-colored, symmetrical, elastic-soft tumor covered with crust on his left lower jaw (fig. 1). The size of the tumor was approximately 17 mm in diameter. We excised the tumor with a 2-mm margin. Histological findings revealed a cup-shaped, symmetrical, well-differentiated squamous epithelium with a mild degree of pleomorphism, individual cell keratinization and keratin pearls (fig. 2). There was no sign of vascular or lymphatic invasion in the lesional skin. From the above findings, we diagnosed the cutaneous lesion as KA.

Unexpectedly, chest X-ray revealed multiple nodules on the patient's bilateral lungs. We subsequently screened for a possible internal malignancy with positron emission tomography-computed tomography, which revealed a significant enlargement of tumor masses on the lung (fig. 3a) and swelling of multiple pulmonary lymph nodes (maximum standardized uptake value 4.2–16.3) (fig. 3b). Needle biopsy from the lung lesion revealed that the nodule in the lung was primary, poorly differentiated lung SCC with multiple lymph node metastases. For the treatment of lung carcinoma, monthly carboplatin (443 mg/m<sup>2</sup>) with tri-weekly paclitaxel (45 mg/m<sup>2</sup>) was administered for 6 months. One year after the excision, there was no sign of recurrence of the skin lesion. As previously reported, well- or moderately-differentiated SCC and KA can be distinguished using interleukin-27 (IL-27) staining and pSTAT1 [4]. Therefore, to confirm our diagnosis for the cutaneous lesion, we employed immunohistochemical stainings for IL-27 (fig. 4a, c) and pSTAT1 (fig. 4b, d). As expected, immunohistochemical staining revealed a substantial number of IL-27-producing cells and pSTAT1-expressing tumor cells in the lesional skin of KA.

## Discussion

Long-term administration of immunosuppressive agents has been reported to cause DNA damage and deviations in natural immune surveillance [7]. Among various types of organ transplantation, previous reports suggested an association between renal transplantation and an increased incidence of non-melanoma skin cancer, likely caused by immunosuppression [7]. SCC, one of the major histological types of non-melanoma skin cancer, exhibits more aggressive biological and clinical courses in RTRs, with higher rates of recurrence and mortality than in the general population [7]. Other reports also suggested that immunosuppressed patients, such as RTRs, show a higher incidence of KAs [6]. In aggregate, RTRs could possess a higher incidence of both SCC and KA. Therefore, it is sometimes difficult for dermatologists to differentiate between KA and SCC in RTRs.

In this report, we describe a case of KA accompanied by multiple lung SCCs developing in a RTR. In our present case, as we previously reported [4], substantial numbers of IL-27-producing cells and pSTAT1-expressing tumor cells were detected in the lesional skin of KA, suggesting that the tumor microenvironment of KA is Th1-shifted. It was reported that IL-27 is produced by activated antigen-presenting cells and induces proliferation and expression

of T-bet in naive CD4+ T cells [8, 9]. WSX-1, which is highly expressed in CD4+ T cells, natural killer cells, natural killer T cells and macrophages [10], constitutes a functional, signal-transducing receptor for IL-27 with gp130 to induce STAT1 activation. Thus, the production of IL-27 results in the enhancement of naive CD4 T cell proliferation, the promotion of early Th1 differentiation, and suppression of the differentiation of Th2 and Th17 cells [11]. Notably, unlike a poorly differentiated SCC in the lung, the cutaneous tumor can be controlled with a small surgical margin, which also suggests that the biology of the cutaneous tumor was different from that of the lung tumor in our patient. Our present case suggests that immunohistochemical staining for pSTAT1 in combination with IL-27 might be one of the possible tools to differentiate KA from SCC.

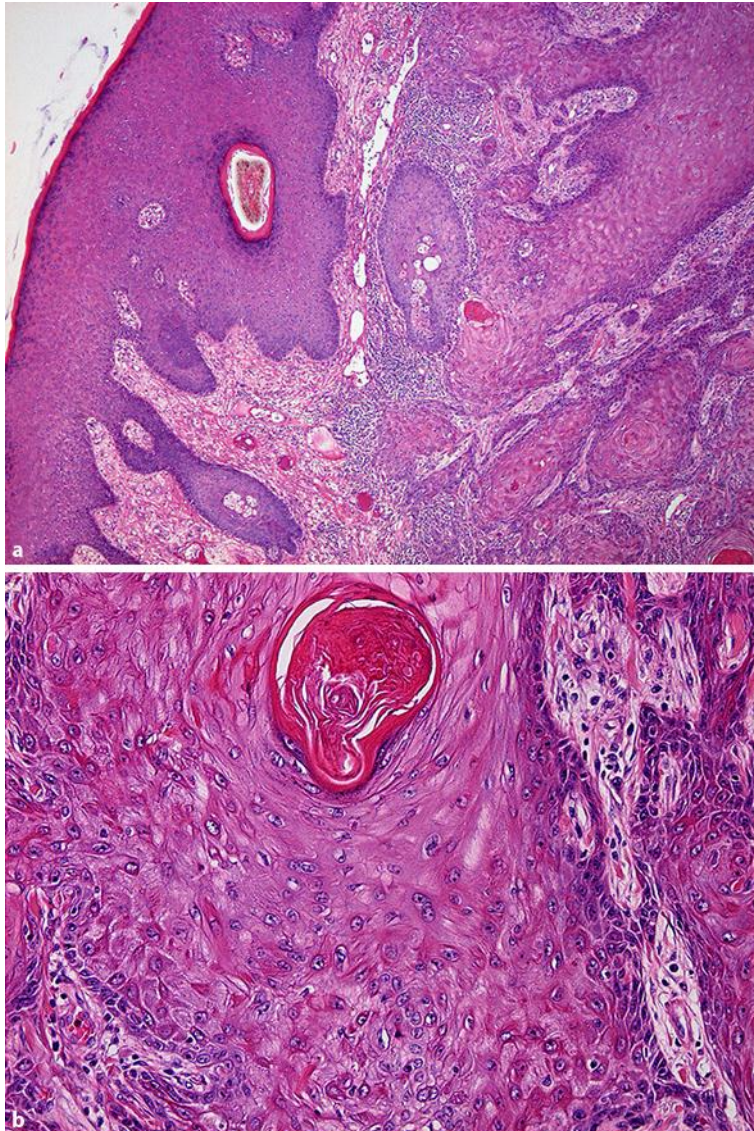
## References

- 1 Elder DE, Elemenitsas R, Johnson BL Jr, Murphy GF: *Lever's Histopathology of the Skin*, ed 10. Philadelphia, Lippincott-Raven, 2008.
- 2 Clausen OP, Beigi M, Bolund L, Kølvråa S, Gjersvik PJ, Mørk G, de Angelis PM: Keratoacanthomas frequently show chromosomal aberrations as assessed by comparative genomic hybridization. *J Invest Dermatol* 2002;119:1367–1372.
- 3 Clausen OP, Aass HC, Beigi M, Purdie KJ, Proby CM, Brown VL, Mattingsdal M, Micci F, Kølvråa S, Bolund L, Deangelis PM: Are keratoacanthomas variants of squamous cell carcinomas? A comparison of chromosomal aberrations by comparative genomic hybridization. *J Invest Dermatol* 2006;126:2308–2315.
- 4 Kambayashi Y, Fujimura T, Aiba S: Comparison of immunosuppressive cells and immunomodulatory cells in keratoacanthoma and invasive squamous cell carcinoma. *Acta Derm Venereol* 2013;93:663–668.
- 5 Pini AM, Koch S, Schärer L, French LE, Läuchli S, Hofbauer GF: Eruptive keratoacanthoma following topical imiquimod for in situ squamous cell carcinoma of the skin in a renal transplant recipient. *J Am Acad Dermatol* 2008;59(5 suppl):S116–S117.
- 6 Zavos G, Karidis NP, Tsourouflis G, Bokos J, Diles K, Sotirchos G, Theodoropoulou E, Kostakis A: Nonmelanoma skin cancer after renal transplantation: a single-center experience in 1736 transplantations. *Int J Dermatol* 2011;50:1496–1500.
- 7 Kasiske BL, Snyder JJ, Gilbertson DT, Wang C: Cancer after kidney transplantation in the United States. *Am J Transplant* 2004;4:905–913.
- 8 Pflanz S, Timans JC, Cheung J, Rosales R, Kanzler H, Gilbert J, Hibbert L, Churakova T, Travis M, Vaisberg E, Blumenschein WM, Mattson JD, Wagner JL, To W, Zurawski S, McClanahan TK, Gorman DM, Bazan JF, de Waal Malefyt R, Rennick D, Kastelein RA: IL-27, a heterodimeric cytokine composed of EB13 and p28 protein, induces proliferation of naive CD4(+) T cells. *Immunity* 2002;16:779–790.
- 9 Takeda A, Hamano S, Yamanaka A, Hanada T, Ishibashi T, Mak TW, Yoshimura A, Yoshida H: Cutting edge: role of IL-27/WSX-1 signaling for induction of T-bet through activation of STAT1 during initial Th1 commitment. *J Immunol* 2003;170:4886–4890.
- 10 Sugiyama N, Nakashima H, Yoshimura T, Sadanaga A, Shimizu S, Masutani K, Igawa T, Akahoshi M, Miyake K, Takeda A, Yoshimura A, Hamano S, Yoshida H: Amelioration of human lupus-like phenotypes in MRL/lpr mice by overexpression of interleukin 27 receptor alpha (WSX-1). *Ann Rheum Dis* 2008;67:1461–1467.
- 11 André S, Tough DF, Lacroix-Desmazes S, Kaveri SV, Bayry J: Surveillance of antigen-presenting cells by CD4+ CD25+ regulatory T cells in autoimmunity: immunopathogenesis and therapeutic implications. *Am J Pathol* 2009;174:1575–1587.

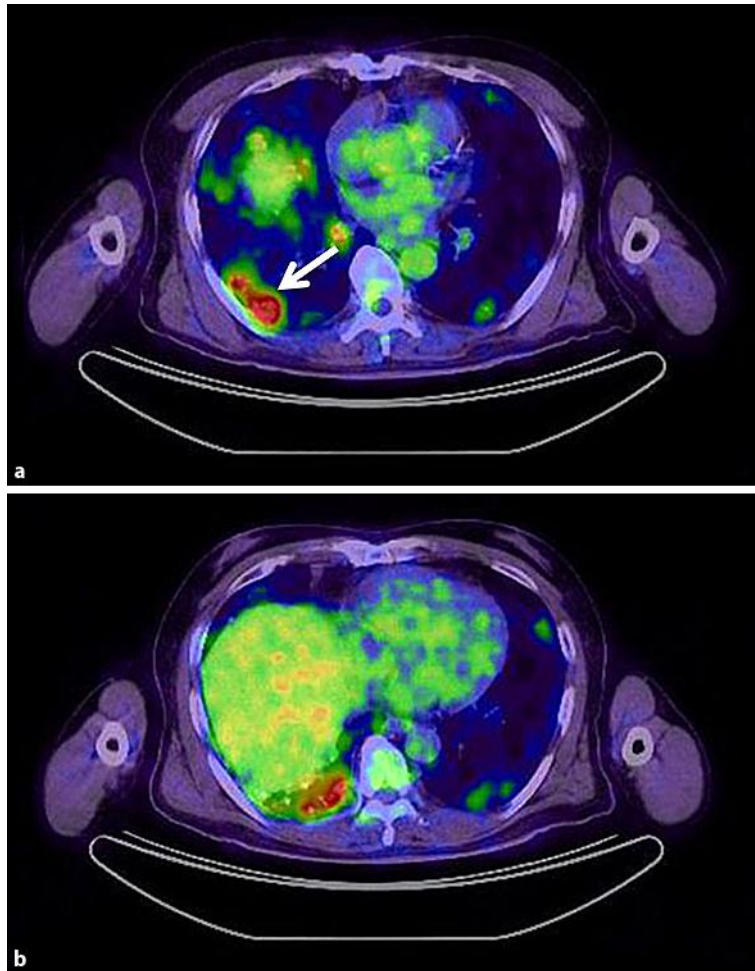


**Fig. 1.** Dome-shaped, skin-colored, symmetrical, elastic-soft tumor covered with crust on the left lower jaw.

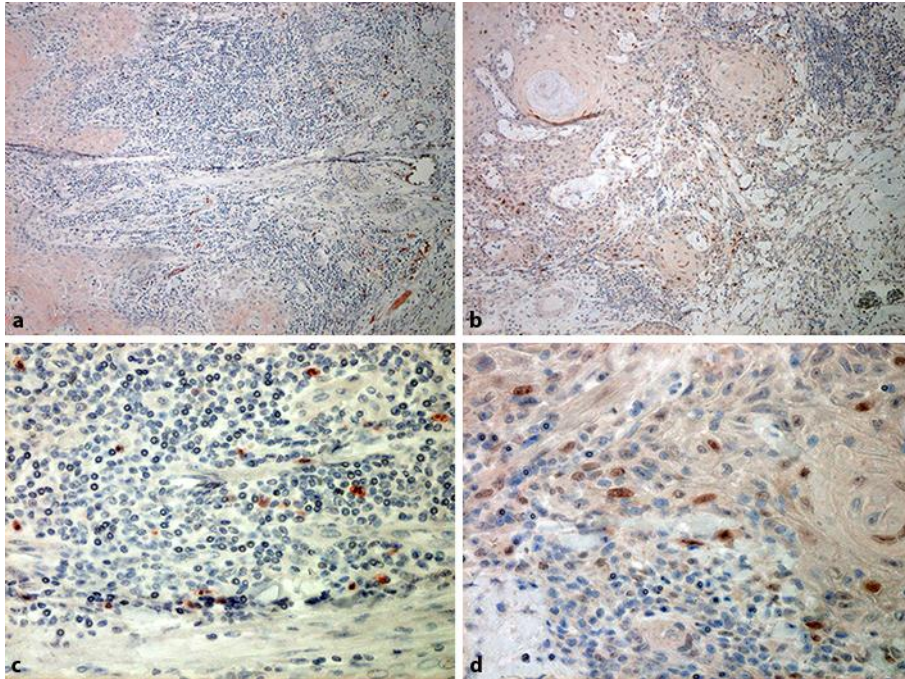
Furudate et al.: Keratoacanthoma Accompanied by Multiple Lung Squamous Cell Carcinomas Developing in a Renal Transplant Recipient



**Fig. 2.** Cup-shaped, symmetrical, well-differentiated squamous epithelium with a mild degree of pleomorphism, individual cell keratinization and keratin pearls. Original magnification:  $\times 100$  (a),  $\times 400$  (b).



**Fig. 3.** Positron emission tomography-computed tomography revealed significant enlargement of tumor masses on the lung (**a**; arrow) and swelling of multiple pulmonary lymph nodes (**b**) (maximum standardized uptake value 4.2–16.3).



**Fig. 4.** Paraffin-embedded tissue samples were deparaffinized and stained using anti-IL-27 antibody (**a, c**) or anti-pSTAT1 antibody (**b, d**). Sections were developed with liquid permanent red (red). Original magnification:  $\times 100$  (**a, b**),  $\times 400$  (**c, d**).