Treatment of Keratoacanthoma with 5% Imiquimod Cream

Na Young Ko, M.D., Jun-Ha Park, M.D., Sang-Wook Son, M.D., Il-Hwan Kim, M.D.

Department of Dermatology, Korea University Ansan Hospital, Kyunggido, Korea

Keratoacanthoma is a rapidly growing tumor that histologically resembles squamous cell carcinoma. Surgical excision is a desirable therapeutic option, but several other treatment modalities are available. We report on two cases of keratoacanthoma that were treated with imiquimod 5% cream. Imiquimod was applied daily for the first 6 or 7 days, and then reduced to alternate days according to the tolerance and erythema severity of the patient. In both patients, the tumors fully regressed after five weeks of treatment.
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Key Words: Imiquimod 5% cream, Keratoacanthoma

INTRODUCTION

Keratoacanthoma is a rapidly growing, locally destructive tumor that develops from a pilosebaceous follicle and histologically resembles squamous cell carcinoma[1]. It usually presents as a solitary lesion which grows rapidly within a few weeks to a dome-shaped tumor with a central keratotic plug. Surgical excision is a preferred treatment, but several other treatment modalities are currently available, such as curettage, radiotherapy, laser therapy, and intralesional injections of 5-fluorouracil, bleomycin, methotrexate or interferon-α have been successfully used[1].

The imidazoquinoline imiquimod (Aldara™) is a novel immune response modifier that promotes antiviral and antitumor immune response. Recently, many investigators have reported that imiquimod is effective in a variety of benign, premalignant, and malignant diseases[2]. Herein, we report on two cases of keratoacanthoma treated with imiquimod 5% cream.

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Reprint request to: Il-Hwan Kim, M.D., Ph.D., Department of Dermatology, Korea University Ansan Hospital, 516 Gojan-dong, Ansan, Kyunggi-do 425-707, Korea. Tel. 031-412-5180, Fax: 031-412-5985, E-mail. kumcihk@unitel.co.kr
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CASE REPORTS

Case 1

A 35-year-old Korean man presented with a rapidly growing nodule on the right side of his nose of four weeks duration. An examination revealed a dome-shaped mass of diameter 1.5 cm with a central keratotic core (Fig. 1A). Histological evaluation of a punch biopsy demonstrated well-differentiated squamous epithelium proliferation that extended down to the epidermis, which raised the possibility of keratoacanthoma or squamous cell carcinoma. However, a diagnosis of keratoacanthoma was made based on its short history and its typical morphologic features. The patient refused surgical excision for cosmetic reasons and agreed to the therapeutic use of imiquimod 5% cream. Initially, imiquimod 5% cream was applied every night for six days, and then reduced to alternate days because of irritation at the treatment site. Within two weeks of treatment the skin lesion had started to reduce, and at five weeks the tumor had completely regressed leaving peripheral erythema. Treatment was then discontinued. One month after treatment, the surrounding erythema had disappeared and only a depressed scar was observed (Fig. 1B).

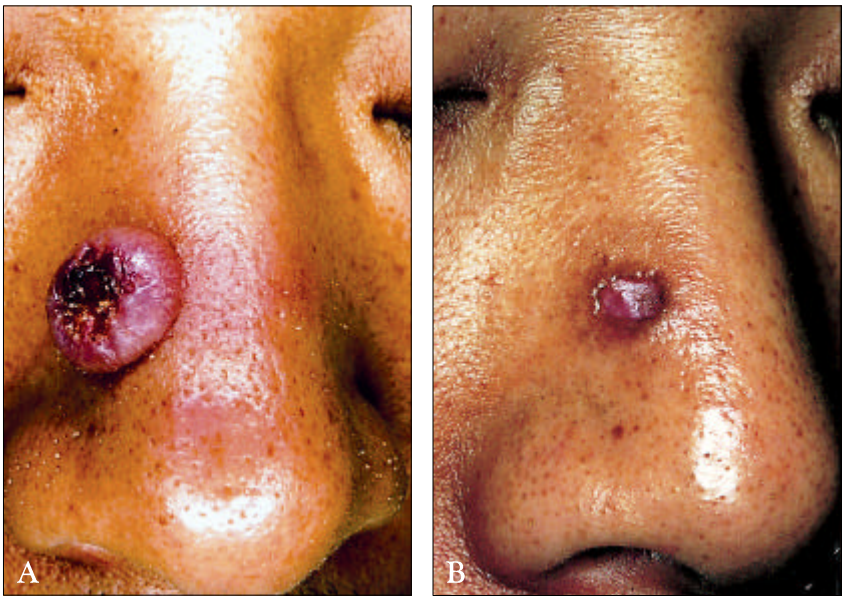

Fig. 1. (A) Keratoacanthoma before treatment. (B) After five weeks of treatment with imiquimod 5% cream, the tumor had disappeared leaving only a depressed scar.

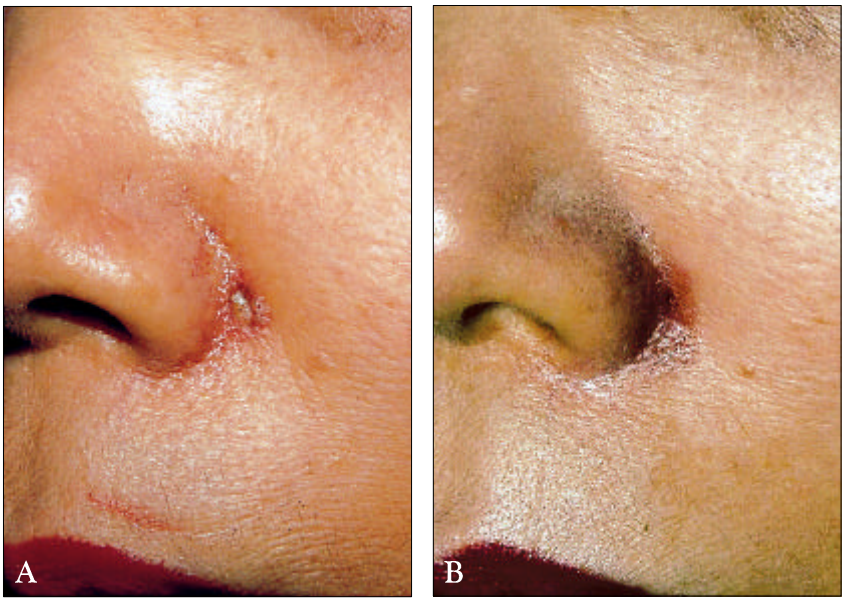

Fig. 2. (A) Keratoacanthoma before treatment. (B) After five weeks of treatment with imiquimod 5% cream, the tumor had disappeared leaving only residual erythema.

Case 2

A 56-year-old Korean woman presented with a 0.4 × 0.2 cm sized whitish papule with a mildly erythematous rolled border on her left nasolabial fold (Fig. 2A). The lesion had been excised at a local dermatologic clinic one year ago, but recurred three weeks prior to this presentation. Histological evaluation of the papule indicated keratoacanthoma, but highly differentiated squamous cell carcinoma could not be excluded (Fig. 3A). Initially, imiquimod 5%

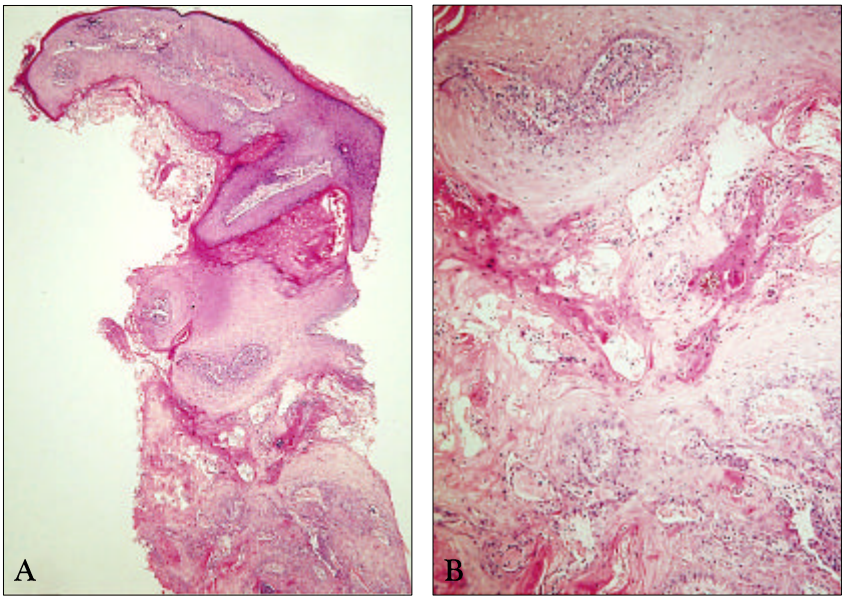

Fig. 3. (A) Histopathologic examination before treatment. The well-differentiated proliferation of squamous epithelium extended down to the dermis (H & E, × 40). (B) Histopathologic examination after five weeks of treatment with imiquimod 5% cream. Only lymphocytic infiltration was observed with no sign of residual malignancy (H & E, ×40).

cream was applied daily, and after seven days reduced to alternate days due to severe erythema. After five weeks of treatment the tumor had totally disappeared leaving mild erythema (Fig. 2B). A second biopsy was then performed at the lesion, and only lymphocytic infiltration was observed with no sign of malignancy (Fig. 3B).

DISCUSSION

Keratoacanthoma is a common epithelial tumor-that is characterized by rapid growth, histopathologic features similar to those of cutaneous squamous cell carcinoma, and a tendency toward spontaneous regression. Although keratoacanthoma may regress spontaneously, usually active treatment is required due to its rapid growth, unpredictable final size, and the possibility of vast tissue destruction due to ulceration and secondary infection[1]. Because it is difficult to differentiate keratoacanthoma from squamous cell carcinoma, complete surgical excision is advisable in most cases. However, other therapeutic options can be used for those receiving anticoagulation therapy, those who cannot tolerate surgery for medical reasons, or those with skin lesions difficult to treat surgically.

The imidazoquinoline imiquimod (Aldara^{TM}) is a novel immune response modifier that promotes antiviral and antitumor immune response. Recently, many investigators have reported that imiquimod is effective in a variety of benign, premalignant, and malignant diseases[3-5]. It enhances both acquired and innate immune functions by inducing the release of proinflammatory cytokines such as interferon-α, β, γ, interleukin-6, 8, and tumor necrosis factor-α via Toll-like receptors[2]. Spontaneous regression of keratoacanthoma seems to be promoted by T cell mediated immune reactions as activated T cells infiltrate tumor tissue[6]. Therefore, enhancement of local immune defense by imiquimod appears to be a reasonable approach to keratoacanthoma treatment[7].

Seven cases of keratoacanthoma treated with imiquimod 5% cream have been reported to date with times to total clearance varying from four to eleven weeks[7-9] (Table 1). Although in most reported cases imiquimod was applied every other day, no effective dosing schedule for keratoacanthoma was demonstrated. In our cases, imiquimod was applied every day for the first 6 or 7 days and then reduced to alternate days according to the tolerance

Table 1. Reported cases of keratoacanthoma treated with imiquimod 5% cream

Reporters	Sex/Age	Size of the keratoacanthoma	Duration of the keratoacanthoma	Frequency of the application	Duration to complete resolution
Dendorfer et al[7]	M/64	0.7 cm	5 weeks	Alternate day	11 weeks
	F/63	1.0 cm	6 weeks	Alternate day	4 weeks
	F/47	0.8 cm	4 weeks	Alternate day	6 weeks
	M/82	0.7 cm	8 days	Alternate day	6 weeks
Bhatia[8]	F/?	3.0 × 3.2 cm	?	Alternate → daily	? (maybe, >1 and <2 months)
Di Lervia et al[9]	F/54	1.0 cm	20 days	3 times a week	8 weeks
	F/63	0.9 cm	?	5 times a week	8 weeks
Authors	M/35	1.5 cm	4 weeks	Daily → alternate day	5 weeks
	F/67	0.4 × 0.2 cm	3 weeks	Daily → alternate day	5 weeks

of patient and erythema severity at the treatment site. Both tumors completely regressed after five weeks of treatment, which is shorter than that previously reported. The promptness of this regression suggested that more frequent imiquimod application considerably enhances its effectiveness against keratoacanthoma by promoting the local immune mechanisms. Therefore, we suggest that more frequent application of imiquimod at the beginning of treatment and subsequent adjustment according to the tolerance of patient and observed response may have clinical utility in the treatment of keratoacanthoma.

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