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CASE REPORT

Development of Vitiligo-Like Depigmentation after Treatment of Lentigo Maligna Melanoma with 5% Imiquimod Cream

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A 69-year-old man presented with a black irregular patch on his left cheek. Skin biopsy revealed lentigo maligna melanoma *in situ*. He was treated via partial excision of the melanoma, followed by the application of 5% imiquimod cream every other night for 6 to 8 hours. The patient experienced severe local inflammation accompanied by burning, edema, and erythema, as well as oozing and crusting. The patient discontinued using the imiquimod cream after 15 applications because of the inflammation. Depigmentation was noted in the treated area 3 months after the initiation of treatment with imiquimod cream. Histological examination using Melan-A staining of the depigmented area revealed an absence of melanocytes, which is consistent with vitiligo. The depigmented lesions improved considerably after a 5-year follow-up, and there was no recurrence of melanoma. **(Ann Dermatol 30(4) 454∼457, 2018)**

-Keywords-
Lentigo maligna, Melanoma, Toll-like receptor, Vitiligo

INTRODUCTION

Imiquimod, as a 5% cream, has been approved by the U.S. Food and Drug Administration for the treatment of genital and perianal warts. It is also used to treat actinic keratosis and superficial basal cell carcinoma; however, its range of applications is gradually expanding. In cases of lentigo maligna melanoma with lesions in areas where surgical intervention is not feasible, treatment with 5% imiquimod cream has been reported to have a high success rate. There is also a growing number of reports on the use of 5% imiquimod cream for the removal of residual lesions after surgery[1]. The following presentation is a case report of a patient with a resolving facial lentigo maligna melanoma who developed vitiligo-like depigmentation following treatment with 5% imiquimod cream.

CASE REPORT

A 69-year-old male patient presented with a black irregular patch on his left cheek. The patient had undergone laser treatment for the condition at a clinic 7 years ago; however, he had recurrences without receiving any additional treatment. At our hospital, he presented with a black patch on his left cheek measuring approximately 3.5×3.5 cm with unclear boundaries and uneven coloration (Fig. 1A). The skin biopsy identified the condition as lentigo maligna melanoma *in situ*. The patient was advised to undergo a skin graft or flap after a complete excision of the lesion; however, he declined this treatment to avoid scarring. The patient elected to undergo partial resection of the lesions including the darkest area (Fig. 1B), followed by the application of 5% imiquimod cream three times a week. Application of the imiquimod cream to the lesion was initiated 2 weeks after the partial

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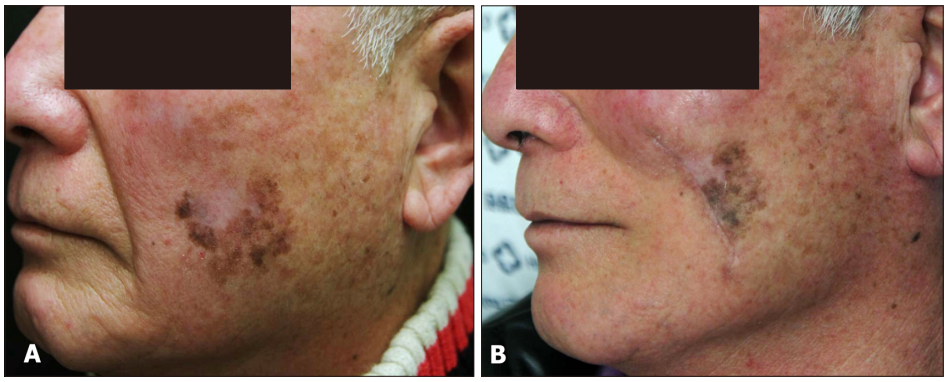

Fig. 1. Clinical photographs prior to and after partial excision of melanoma *in situ*. (A) A large black patch with an unclear boundary and uneven color on the left cheek prior to treatment. (B) Remaining black patch after partial excision of melanoma.

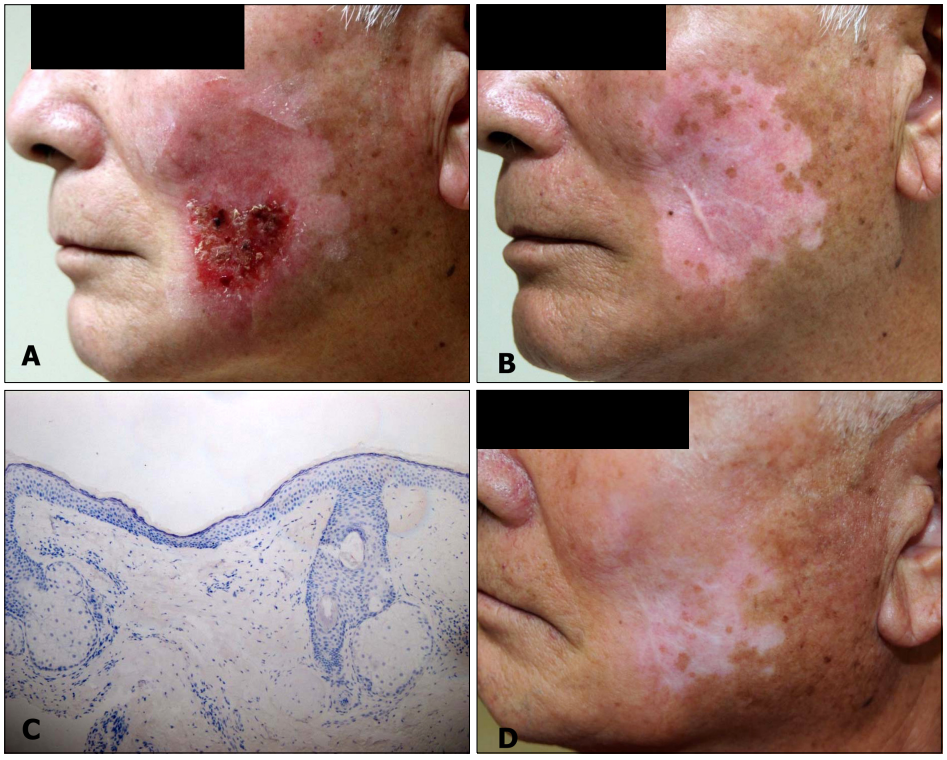

Fig. 2. (A) Severe local inflammatory reaction occurred after application of 5% imiquimod cream. (B) Depigmented lesions are observed in the treated area after 3 months. (C) Histological examination using Melan-A staining of the depigmented area revealed the absence of melanocytes (×100). (D) Partial improvement in vitiligo-like depigmentation after 5-year treatment without recurrence of melanoma.

resection. The cream induced a severe local inflammatory reaction, which caused burning, edema, erythema, oozing, and crusting (Fig. 2A). Because of the reaction, the use of the cream was limited to 15 applications over 3 months. Depigmented lesions were observed in the treated area 3 months after the initiation of topical imiquimod therapy (Fig. 2B). Histological examination using Melan-A staining of the depigmented area revealed the absence of melanocytes, which was consistent with vitiligo (Fig. 2C). The depigmented lesions improved greatly after a 5-year follow-up and the melanoma has not recurred (Fig. 2D). We received the patient's consent about publishing all photographic materials.

DISCUSSION

The number of reports on the use of 5% imiquimod cream for the treatment of melanoma *in situ*, especially lentigo maligna, is growing. Ellis et al.[2] reviewed 46 previous studies in which patients with melanoma *in situ* were treated with imiquimod cream. The reports indicated that 220 of 264 (83.3%) patients showed clinical or histological clearance of the melanomas. Similarly, a recently published study[1] indicated an overall clinical clearance rate of 86.2% was obtained at a mean follow-up of 42.1 months when 5% imiquimod cream was used as the primary or adjuvant therapy for lentigo maligna. However, there is still a lack of efficacy and safety data from

randomized controlled studies on the use of imiquimod cream for treating melanoma *in situ*, whereas studies on palliative surgical treatment are widely available. Therefore, imiquimod cream is currently used to treat melanoma *in situ* on an off-label basis.

Globally, depigmentation or hypopigmentation occurring after treatment with imiquimod cream has been reported in 15 previous case reports on 17 patients. In nine of the cases, the imiquimod treatment was for genital warts or extramammary Paget's disease[3-8]. The extragenital cases of imiquimod-induced depigmentation or hypopigmentation occurred after treatment of basal cell carcinomas at various locations including the face, chest, and upper extremities[9-11]. However, to the best of our knowledge, no case of vitiligo has been reported after the application of imiquimod cream for melanoma treatment.

It has been shown that cryotherapy or podophyllin application for extramammary Paget's disease prior to topical imiquimod treatment results in severe irritation but no pigmentary changes[3,6]. Similarly, no pigmentary changes were observed when fluorouracil injection, trichloroacetic acid solution, or cryotherapy were used to treat genital warts prior to imiquimod treatment. Thus, pigmentary changes after imiquimod treatment are not thought to be due to hypopigmentation induced by simple skin irritation[3,4,6].

Schön et al.[12] reported on imiquimod-induced apoptosis in melanoma cells *in vitro* and *in vivo*. Kim et al.[13] also reported that an imiquimod-induced immune response mediates vitiligo-like reactions and apoptosis in human melanocytes. Imiquimod binds to Toll-like receptors (TLR) 7 and 8. TLR7 activates the T-helper 1 response and increases the production of pro-inflammatory cytokines such as interferon alpha, tumor necrosis factor alpha, and interleukin (IL)-12, which play an important role in the pathogenesis of vitiligo[14]. In addition, imiquimod directly increases the expressions of pro-inflammatory cytokines such as IL-6, IL-8, and IL-10, and pro-apoptotic molecules, which can also cause vitiligo[15].

In a study by Kumar and Narang[7], 22 immunocompetent male patients with genital warts were treated with 5% imiquimod cream thrice weekly. However, during the 7-week follow-up period, one of the patients presented with vitiligo lesions and severe adverse reactions in the treated area. A prolonged period between the application of imiquimod cream and a follow-up visit may result in difficulty in evaluating the onset of depigmentation.

A review of related literature shows that some studies have reported a 4-week[4], 8-week[5], 10-week[9], and 12-week[6,10] period between the application of imiquimod cream and the onset of depigmentation. In the present case, depigmented lesions were observed prominently 3 months after the start of treatment. The vast majority of cases where there were long periods between the application of imiquimod cream and hospital revisits have reported the confirmation of depigmented lesions within 6 months of treatment[3]. Therefore, if a patient has esthetic outcome concerns or undergoes treatment on body areas that are easily visible, follow-up visits at short intervals within the first 3 months of treatment would be useful.

The occurrence of depigmented lesions after the application of imiquimod cream in a patient who had a family history of vitiligo has been reported[4]. In addition, halo nevi was reported to have occurred in areas outside the sites of imiquimod cream application[8]. In previous studies describing depigmented lesions due to treatment with imiquimod cream, the maximum follow-up period was 18 months. In most of those cases, there was no repigmentation; however, Stefanaki et al.[4] observed a 2% repigmentation after a 3-month follow-up. In the present case, after treatment with imiquimod cream commenced, there was a follow-up treatment period of 5 years, which was much longer than that in any of the previous reports. At 5 years, more than 50% repigmentation had been achieved. In this case, we did not perform any treatments for the depigmentation, therefore, it is thought that spontaneous repigmentation of the lesions was obtained due to discontinuation from the imiquimod-induced immune response and long term follow-up.

In conclusion, vitiligo-like depigmentation occurrence after the application of imiquimod cream is one of the immunological adverse reactions that may be associated with the mechanism of action of imiquimod. But also, unlike any other vitiligo, it can show spontaneous repigmentation over time. Thus, it is important for clinicians to be aware that imiquimod cream can treat residual lentigo melanoma *in situ* effectively after partial excision. In addition, the development of vitiligo-like depigmentation, and then repigmentation following treatment with imiquimod cream occurs.

CONFLICTS OF INTEREST

The authors have nothing to disclose.

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