http://dx.doi.org/10.5021/ad.2012.24.4.482

Induction of Vitiligo-Like Hypopigmentation after Imiquimod Treatment of Extramammary Paget's Disease

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Dear Editor:

Imiquimod 5% cream, an immune response modifier, is licensed for the treatment of extramammary Paget's disea se (EMPD). Although pigmentary changes associated with imiquimod treatment have been listed as possible side effects on the package insert, the reports are rare and sometimes inconsistent in the dermatology literature. Some studies described vitiligo-like hypopigmentation, while other studies reported hyperpigmentation after imiquimod use[1]. In our skin cancer clinic, we frequently applied imiquimod 5% cream every other night for 6～8 hours in EMPD patients who are poor surgical candidates or susceptible to local recurrence after surgery. After reviewing the clinical course of three male patients with EMPD, we found that whole skin lesions around scrotum applied with imiquimod were completely depigmented after 3 months in all cases (Fig. 1). The depigmentation did not extend beyond treatment area and affect other vitiligo-prone areas at all. Despite discontinuation of imiquimod, the hypopigmentation did not improve at all after at least 13 months follow-up in all cases. Imiquimod was the only product used and our patients did not have a history of vitiligo at all. Wood light examination shows an accentuation of the pigment loss, and H&E and Fontana Masson reveal decreased pigmentation in the basal layer of epidermis (Fig. 2). The average number of melanocytes in the basal layer counted by 3,4-dihydroxyphenylalanine staining and immunohistochemistry method using HMB-45 antibody was also significantly decreased (Fig. 3). Interestingly, two of our patients had experienced irritiation several times after cryotherapy and podophylline application before imiquimod treatment

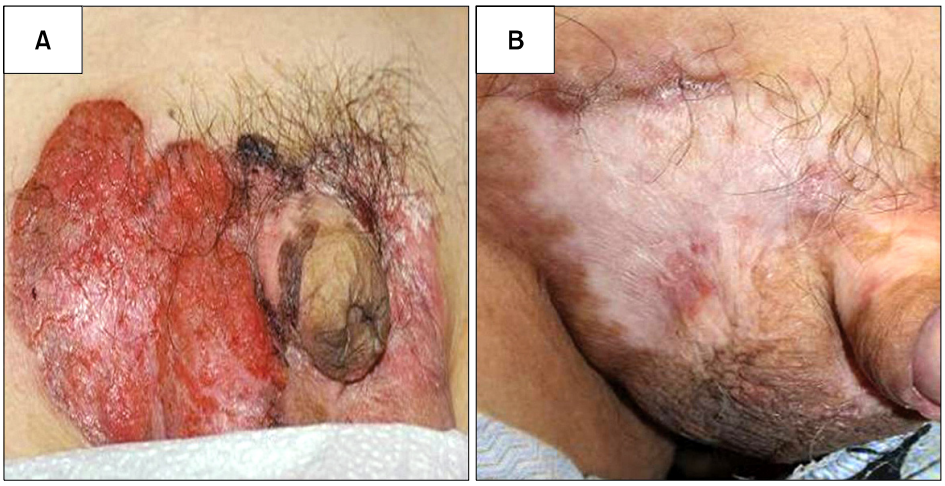

Fig. 1. (**A**) Extramammary Paget's disease lesions around pubic area. (B) Relatively well defined whitish depigmented patches on the imiquimod application sites after 3 months.

Received November 16, 2011, Revised January 10, 2012, Accepted for publication January 25, 2012

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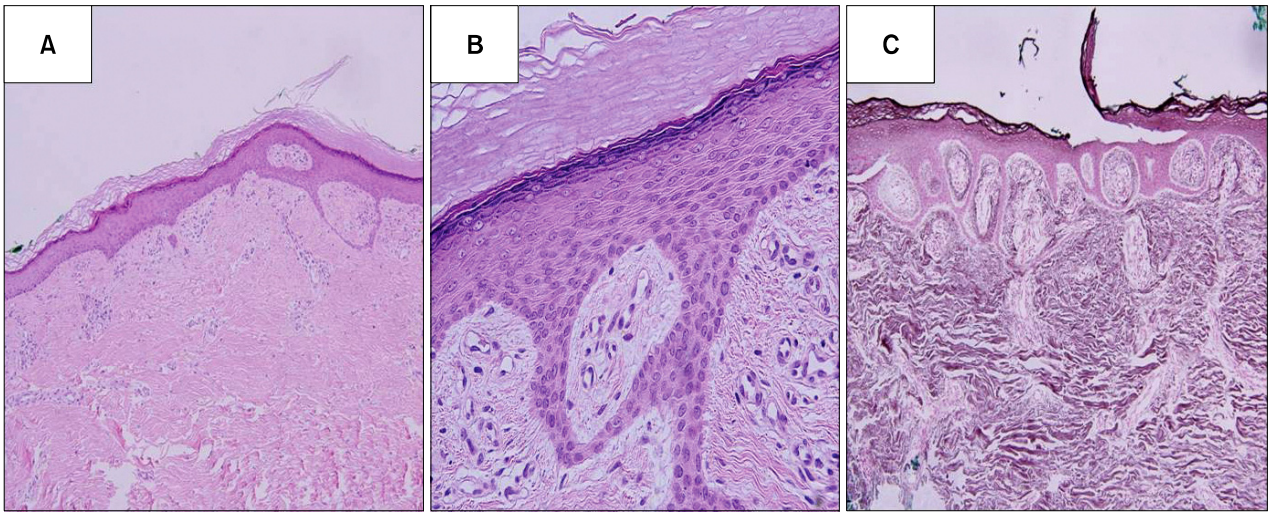

Fig. 2. The basal layer of epidermis shows no pigmentation (A) at a low magnification view (H&E stain, ×100), and (B) a high magnification view (×400). The basal layer of epidermis shows negative reaction for (C) Fontana-Masson staining (×100).

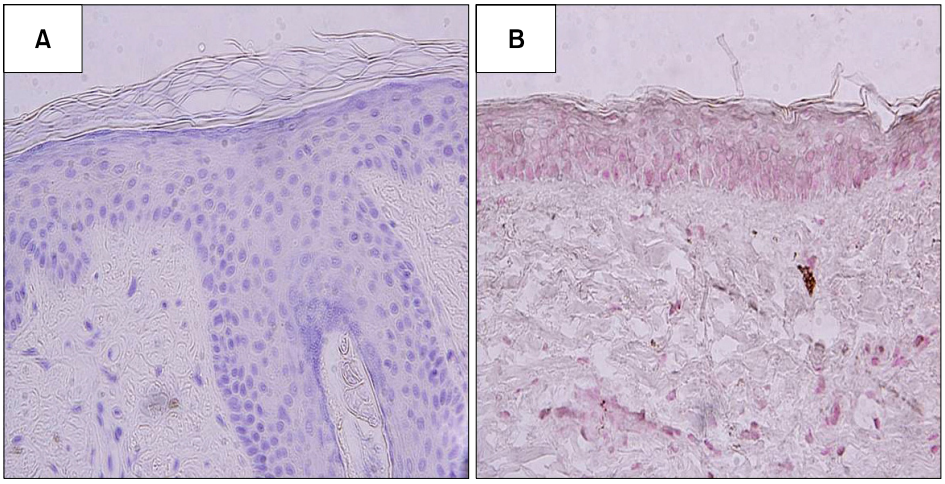

Fig. 3. Melanocytes in the basal layer of epidermis stained by immunohistochemistry methods using (A) HMB-45 (×400) antibody, and (B) 3,4-dihydroxyphenylalanine staining (×400) were rarely observed in the depigmented lesions.

without inducing any depigmentation, respectively. This supports the likelihood that imiquimod may have caused the vitiligo-like hypopigmentation by a mechanism other than simple irritation. Several possible mechanisms could explain this hypopigmentation. Imiquimod binds to the Toll-like receptors (TLR) 7 and 8 which are cell-surface receptors recognizing ligands associated with pathogenic organisms. TLR-7 activates the T-helper (Th) 1 response and increases the production of pro-inflammatory cytokines mainly interferon-α, tumor necrosis factor-α and interleukin (IL)-12, all of which play a role in the pathogenesis of vitiligo[2]. The stimulation of the Th1 pathway also results in a predominantly perilesional CD4+ T cell infiltrate and many CD8+ T cells. The CD4+ cells are stimulated by IL-12 to produce IFN-α and IL-2. In addition, imiquimod promotes secretion of IL-6, IL-8, and IL-10, which are pro-inflammatory and pro-apoptosis cytokines that can also cause vitiligo[3,4]. A previous case report stated that a trial with macrolide immunomodulators could benefit patients, although lacking sufficient evidence[5]. Expanded use of imiquimod may increase localized depigmentation as observed in our case. Since patients could be emotionally sensitive to the depigmentation of pubic areas, we believe that dermatologists should be aware of this annoying side effect, particularly when using imiquimod on EMPD.

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http://dx.doi.org/10.5021/ad.2012.24.4.484

Delayed Diagnosis of Squamous Cell Carcinoma of the Scrotum in a Patient with Behçet's Disease

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Dear Editor:

Behçet's disease (BD), a chronic inflammatory disease, is characterized by oral apthae and genital ulcer, arthritis, cutaneous lesions, such as non-bacterial folliculitis, and erythema nodosum, as well as ocular, gastrointestinal and neurological manifestations. Although genital ulcers are histologically similar to oral aphthae, they are deeper than oral aphthous ulcers and are a major criterion for diagnosis. We present a case of scrotal squamous cell carcinoma (SCC) in a patient diagnosed with BD.

A 39-year-old male patient was admitted to our clinic with recurrent oral aphthae and a deep ulcer, covering the scrotum and perineal regions. The patient had been suffering from recurrent oral aphthous lesions for almost 11 years, and he had been medicated with 1.5 mg/day of colchicine, with a diagnosis of BD. Over the preceding 2 years, the genital ulcer had gradually enlarged and deepened. During this period, the patient received topical treatment and systemic antibiotics therapy; however, he was lost to follow-up.

Dermatological examination revealed a large and painless ulcer, extending from the scrotum to perineal region, which was approximately 8 cm in diameter (Fig. 1). This ulcer had an indurated floor and also sharp and irregular edges. No growth was observed in the bacterial and fungal cultures of the genital ulcer. No inguinal lymphadenopathy was noted and syphilis tests were negative.

The ulcer had a foul odored heavy discharge; it was considered as a secondary bacterial infection and systemic antibiotics therapy was initiated. After the treatment of wound infection, the lesion was excised with a margin of at least 1 cm of normal skin. The surgical specimen showed neoplastic proliferation of squamous differentiated tumour cells in the epidermis (Fig. 2). The test of the tumor cells for anti-human papilloma viruses (HPVs) antibodies was negative; furthermore, HPVs DNA was not detected by direct polymerase chain reaction (PCR) method in excisional tissue specimen. In addition, abdominal, chest and pelvic computed tomography scan showed no evident distant metastasis, including the regional lymph nodes. Six months after surgical treatment, local recurrence or metastasis was not detected yet.

Genital ulcers in BD are sometimes large and deeply located; however, they heal with scarring in 4 weeks[1]. Our patient had been suffering from genital ulcer for two

Received July 27, 2011, Revised January 26, 2012, Accepted for publication February 1, 2012

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