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Tulobuterol Patch (Hokunalin® Tape)-Induced Leukoderma: A Case Report

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Dear Editor:

Tulobuterol patch (Hokunalin Tape®; Abbott Japan Co., Ltd.) is the first transdermal delivery system for tulobuterol, a β2-adrenergic receptor (β2-AR) agonist; it is a bronchodilator used for managing asthma and obstructive pulmonary disease[1]. Due to its convenience of use, it is often applied in children for relieving asthma and bronchiolitis. The patch stays on chest or back for the entire treatment period since it requires only a once-daily change. Several studies have reported mild cutaneous adverse events such as itching, eruption and contact dermatitis[1]; however, depigmentation has not yet been reported so far. Herein, we present a case of transdermal tulobuterol patch-induced leukoderma.

A 3-year-old boy presented with a single, well-defined hypopigmented patch on the back that had developed 2 months ago, after a tulobuterol patch (0.5 mg) was applied for 1 month for treating bronchiolitis. The lesion location and shape matched with that of the patch, and the size was slightly larger (Fig. 1A). When the patch is applied, molecular tulobuterol is absorbed and diffused through the dermal layer, therefore affected area can be larger than the actual size. Under Wood's lamp, sharply demarcated whitish accentuation was noticed. He had no medical or family history of vitiligo. He was treated using a 308-nm excimer laser weekly for 8 months, 30 times

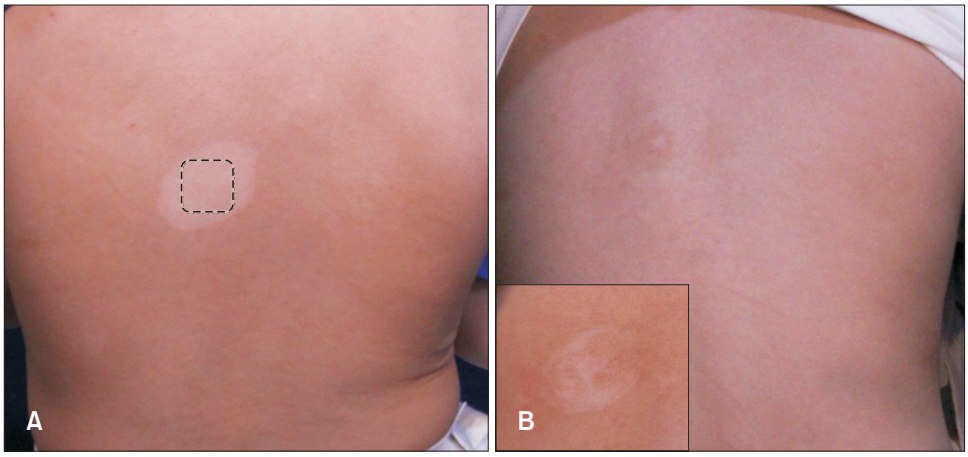

Fig. 1. Clinical presentation of the patient. (A) Well-defined 3 cm-sized hypopigmented patch on the back. Dotted line shows the location and size of the 0.5 mg tulobuterol patch (16 mm×16 mm) which had been applied. (B) Successful re-pigmentation after 8 months of excimer-laser treatment. The box inside the figure shows the progress after 3 months of treatment. We received the patient's consent form about publishing all photographic materials.

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in total. The depigmented area was almost completely repigmented after treatment (Fig. 1B).

Although not confirmed by biopsy, the pattern of depigmentation limited to the contact site and its appearance under Wood's light suggested that the lesion in our patient represented chemically-induced vitiligo. Vitiligo is an autoimmune depigmentation disorder caused by autoreactive T-cell-mediated loss of melanocytes[2]. Chemical exposure is a risk factor for the development of vitiligo caused by the initiation of cellular stress in melanocytes and keratinocytes[3].

Tulobuterol is a β2-AR agonist, and human melanocytes express β2-ARs. Previous studies have revealed that β2-AR activation in melanocytes promotes melanogenesis via cyclic adenosine monophosphate (cAMP) production while carvedilol, a nonselective β-AR inhibitor, suppresses melanogenesis by inhibiting cAMP signaling[4]. Contrary to preceding research, depigmentation was observed at the β2-AR activation site in our case. Activation of β2-AR has been shown to produce reactive oxygen species (ROS), thereby inducing endoplasmic reticulum stress in several cell types. Dysregulated ROS and unfolded protein response (UPR) have been proven to play an important role in the initiation and progression of vitiligo by triggering autoimmune reaction to melanocytes[3]. Melanocytes involved in vitiligo are thought to be more vulnerable to ROS because their function in melanin synthesis results in a pro-oxidant state. A study on 4-tertiary butyl phenol-induced chemical vitiligo revealed that UPR activation by phenol induces interleukin (IL)-6 and IL-8 production in melanocytes, and such pro-inflammatory cytokines promote oxidative stress, provoking innate immune responses[5]. These findings suggest that the tulobuterol patch might have disturbed the normal function of keratinocytes and melanocytes at its attachment site, and triggered cellular stress, resulting in depigmentation.

To our knowledge, this is the first case report of depigmentation after the use of a tulobuterol patch. Physicians should avoid placing the patch repeatedly on the same site to prevent depigmentation.

CONFLICTS OF INTEREST

The authors have nothing to disclose.

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