Rapid Enlargement of Vitiligo Vulgaris after Initiation of Dupilumab for Atopic Dermatitis: A Case Report

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Dupilumab, a monoclonal antibody targeting interleukin-4 receptor α, demonstrated high efficacy and effectiveness for atopic dermatitis (AD) with tolerable safety in clinical trials (1) and real-world data (2, 3). Vitiligo vulgaris is an acquired leukoderma characterized by depigmentation of the epidermis resulting from destruction of melanocytes. We report here a patient with AD with a small incomplete patch of depigmentation of vitiligo vulgaris on his forehead, which enlarged after initiation of dupilumab.

CASE REPORT

A 17-year-old male with severe AD presented to our clinic with refractory nodules accompanied by severe pruritus spreading over his entire body (**Fig. 1**A). He had received topical corticosteroids, oral antihistamine, and phototherapy for severe AD since he was diagnosed with AD at the age of 2 years. He initiated dupilumab when it became available for the treatment of AD in Japan. When dupilumab treatment was started, his Eczema Area and Severity Index (EASI) was 44.5, af-

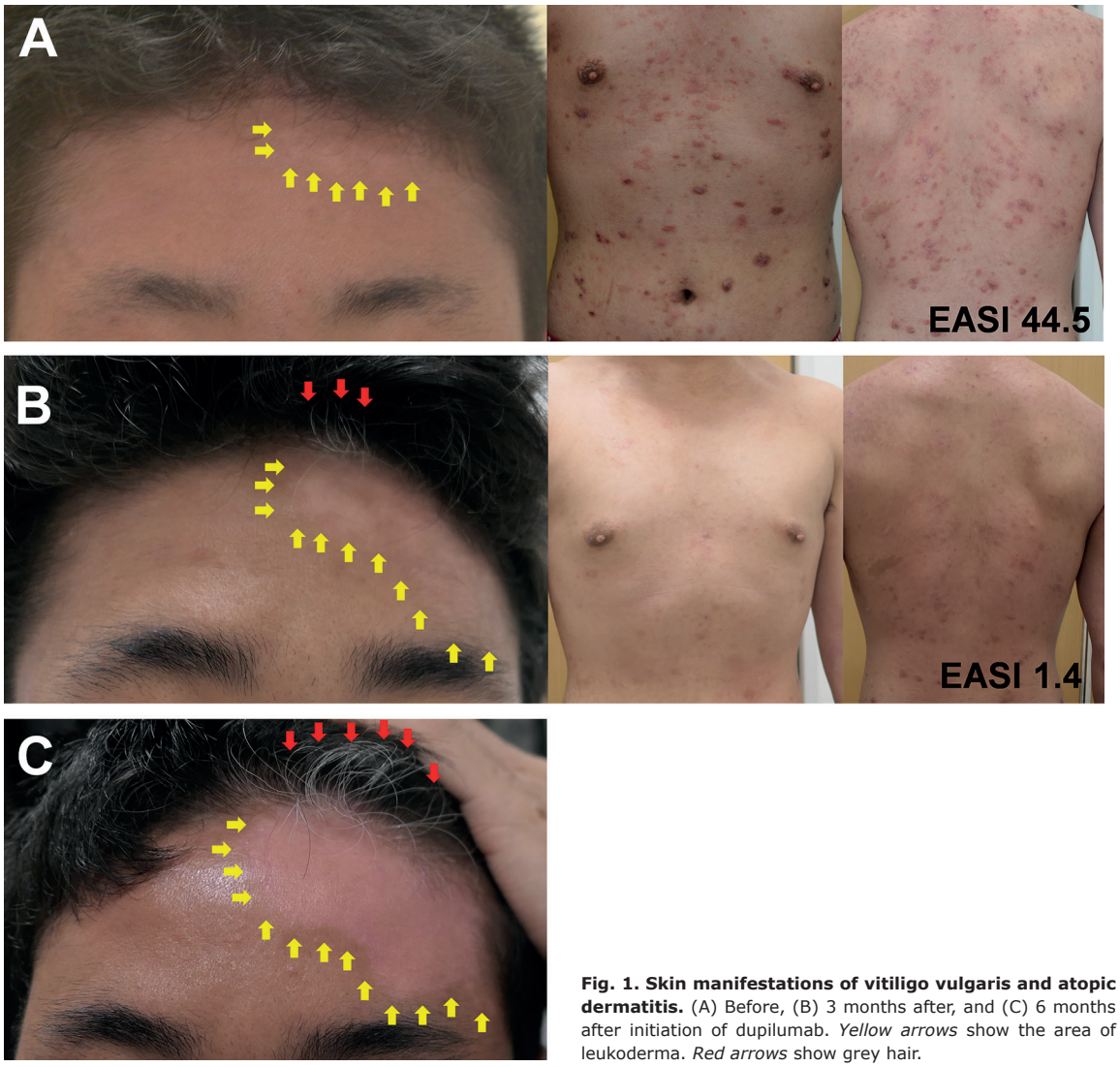

Fig. 1. Skin manifestations of vitiligo vulgaris and atopic dermatitis. (A) Before, (B) 3 months after, and (C) 6 months after initiation of dupilumab. *Yellow arrows* show the area of leukoderma. *Red arrows* show grey hair.

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fected body surface area (BSA) 75%, and Investigator Global Assessment (IGA) score 4. The serum levels of thymus and activation-regulated chemokine (TARC) and IgE were 1,980 pg/ml and 9,648 IU/ml, respectively. Photographs taken at the time of initiation of dupilumab showed a patch of incomplete depigmentation on his forehead (Fig. 1A); however, because the leukoderma was slight and small, neither he nor the physician noticed it at that time. Although dupilumab significantly improved skin manifestations of AD, including nodules and pruritus, as shown in Fig. 1B (EASI 1.4, affected BSA 4%, IGA 1, serum TARC level 271 pg/ml, and serum IgE level 3,051 IU/ml at 3 months after initiation of dupilumab), the leukoderma enlarged rapidly, was accompanied by grey hair, and became clinically conspicuous (Fig. 1B, C). He was treated with hydrocortisone butyrate ointment, and, subsequently, delgocitinib ointment, in addition to 10 sessions of excimer light therapy for the patch of complete depigmentation, but it did not ameliorate vitiligo vulgaris. He withdrew from dupilumab treatment 13 months after the initiation of dupilumab due to economic reasons. To date, 17 months after the cessation of dupilumab, slight repigmentation has been observed, but its area has not shrunk.

DISCUSSION

In this patient, although dupilumab rapidly improved AD, the existing vitiligo lesions expanded and depigmentation progressed, which could be accounted for by the hypothesis that dupilumab affected the balance of the immune system towards polarizing Th/Tc1 by blocking Th2. In vitiligo, both $CD4^+$ and $CD8^+$ T cells play an important role by producing interferon (IFN)-γ and tumour necrosis factor-α (4, 5), which are the signature cytokines of Th1/Tc1. Furthermore, Cheuk et al. (6) reported that, in skin from patients with vitiligo, where melanocytes are eradicated locally, $CD8^+CD49a^+$ resident memory T cells producing IFN-γ accumulated in both the epidermis and dermis. In the current case, dupilumab suppressed Th2 cytokines, which may have activated existing Th/Tc1 cells and $CD8^+CD49a^+$ resident memory T cells in small vitiligo lesions, resulting in enlargement of the skin patch affected by vitiligo vulgaris. Similarly, there have been several reports that dupilumab caused alopecia areata (7–9), which could be driven by Th/Tc1 activation (10). As a possible mechanism, it was considered that dupilumab downregulates the Th2 pathway, thereby amplifying the Th1 pathway and promoting the development of alopecia areata (10). However, further research is needed to elucidate the mechanism of rapid progression of vitiligo vulgaris in patients who are receiving dupilumab.

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