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Letter to the Editor

An asthmatic case of psoriasiform eruption caused by administration of dupilumab

Dear Editor,

Dupilumab is a humanized IgG4 monoclonal antibody that targets the IL-4 receptor alpha chain and inhibits type 2 inflammation. It is suitable for atopic dermatitis and asthma therapy and injected subcutaneously every two weeks. Some side effects reported to date are injection site reactions, conjunctivitis, and rarely anaphylaxis. Here, we present a patient with severe asthma who experienced the onset of psoriasis after treatment with dupilumab. Details of this case from the viewpoint of mechanisms connecting dupilumab and the pathophysiology of psoriasis are given. He gave us written informed consent for publication of this case report.

A 60-year-old man had been diagnosed with asthma and treated with an inhalation therapy of inhaled corticosteroids (ICS), long-acting beta agonist (LABA), and long-acting muscarinic antagonist (LAMA) for 6 years at our hospital. The patient had no history of skin disease including atopic dermatitis, urticaria and psoriasis. Despite these treatments, his respiratory symptoms were not well controlled, and short-term systemic corticosteroid administration was often required. Before initiating dupilumab, his forced vital capacity (FVC) was 82.4% of the predicted value, his forced expiratory volume (FEV_1) was 69.3% of the predicted value, and the FEV_1/FVC ratio was 69.0%. His FeNO level was 223 ppb, blood eosinophil counts were 232/μL and total serum IgE level was 1210 IU/ml. Allergen-specific IgE antibodies toward dust mites, house dust, cedar, cypress, and mugwort were positive. He had received no continuous systemic corticosteroids. In May 2018, he started dupilumab at a first dose of 600 mg and subsequent doses of 300 mg. After one month of treatment, FeNO level, eosinophil counts and total IgE level decreased to 61 ppb, 132/μL, and 722 IU/ml, respectively, and his symptoms also became well controlled (Fig. 1).

However, by July, skin rashes on his knees and right condyle precipitated a dermatology visit at our hospital for the first time. These rashes, erythemic with keratinous proliferation and scales, were suspected as psoriasis and were treated with steroid creams (alclometasone dipropionate on face and neck, clobetasol propionate on other lesions). By August, his skin rashes had spread from his knees and right condyle to his hands, elbows, and face. We then stopped dupilumab over concerns about this worsening psoriasiform dermatitis. The left knee skin rash was biopsied in September where hyperkeratosis, thinning and disappearance of the stratum

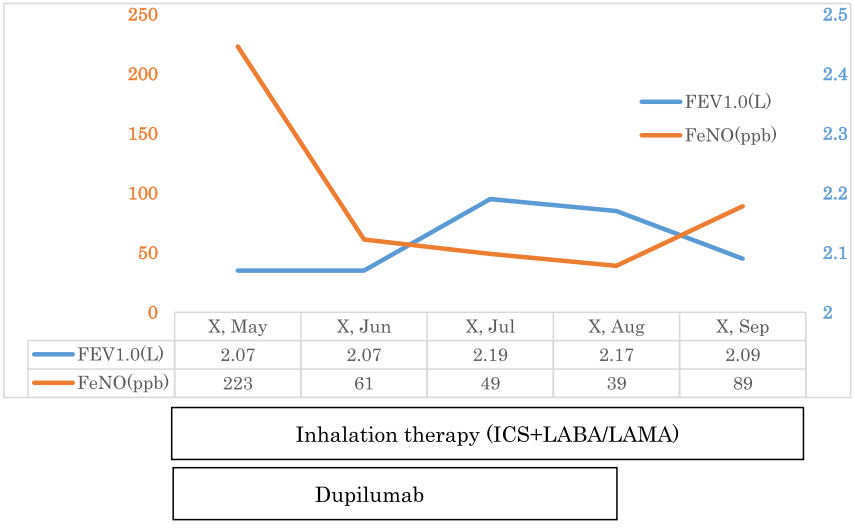

Fig. 1. The course of treatment of asthma.

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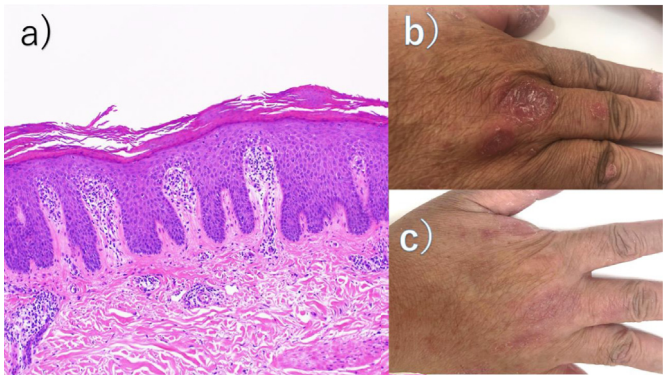

Fig. 2. Pictures and pathological findings of the course of the skin. **a)** Biopsy pathology of the skin. **b)** Skin after administration of Dupilumab. **c)** Skin findings 1 month after discontinuation of Dupilumab.

granulosum, and neutrophilic infiltration into the stratum corneum were observed in the epidermal tissue. This led to a diagnosis of psoriasiform dermatitis, consistent with psoriasiform eruption (Fig. 2a). By September, one month after stopping dupilumab, the skin rashes were less visible and the scaling had decreased (Fig. 2b, c).

In this patient, the temporal relationship between the initiation of dupilumab treatment and psoriatic onset, coupled with the improvement in psoriasis after discontinuation of dupilumab, indicated a causative link between dupilumab and development of the psoriatic lesions.

The pathophysiology of psoriasis is based on interactions between dendritic cells, T cells, keratinocytes, neutrophils, and cytokines that likely contribute to the cutaneous inflammation seen in psoriasis.[1] The Th17 and the Th1 subsets of CD4+ T cells are especially related to psoriatic pathogenesis as Th17 cells produce inflammatory cytokines, including IL-17A, IL-17F, IL-21, IL-22, IL-6, and TNF-alpha, while Th1 cells produce the IFN-γ also implicated in psoriasis.[2] Th2 cytokines can negatively regulate Th17 cytokine expression[3]; it has been proposed that targeting Th2 cytokines promotes Th17-dependent neutrophilic airway inflammation[4] and that alternative treatment of psoriasis with IL-4 modulates the immune response from a Th17 phenotype.[5] We therefore hypothesized that inhibition of IL-4/IL-13 signaling by dupilumab may have stimulated the Th1 and Th17 differentiation that mechanistically promoted the psoriasiform dermatitis seen in our case.

In addition, IL-4R signaling in human neutrophils, through modulation of several neutrophil effector functions, seems to directly limit neutrophil actions, protect against the harmful consequences of uncontrolled neutrophils and promote resolution of neutrophil-mediated tissue injury.[6] Given that recent reports indicate that oxidative stress, granular components, and neutrophil extracellular traps from psoriatic neutrophils are related to the initial and maintenance phases of psoriasis,[7] dupilumab may have been crucial in the development of psoriasiform dermatitis by enhancing neutrophil functions in our case.

In addition to the current case, cutaneous psoriatic lesions had also reportedly occurred in patients treated by dupilumab for atopic dermatitis.[8,9] Therefore, although type 2-targeted biologic therapies have revolutionized the treatment of uncontrolled severe asthma by reducing (or even eliminating) the need for oral corticosteroids, vigilance against cutaneous symptoms is required, especially when asthma patients are treated with dupilumab.

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Conflict of interest

HY has received lecture fees from AstraZeneca and Boehringer Ingelheim. NHiz. has received lecture fees from AstraZeneca, GSK, Novartis and Boehringer Ingelheim. The rest of the authors have no conflict of interest.

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References

1. Nestle FO, Kaplan DH, Barker J. Psoriasis. *N Engl J Med* 2009;**361**:496–509.
2. Dainichi T, Kitoh A, Otsuka A, Nakajima S, Nomura T, Kaplan DH, et al. The epithelial immune microenvironment (EIME) in atopic dermatitis and psoriasis. *Nat Immunol* 2018;**19**:1286–98.
3. Newcomb DC, Boswell MG, Zhou W, Huckabee MM, Goleniewska K, Sevin CM, et al. Human TH17 cells express a functional IL-13 receptor and IL-13 attenuates IL-17A production. *J Allergy Clin Immunol* 2011;**127**:1006–13.
4. Newcomb DC, Peebles Jr RS. Th17-mediated inflammation in asthma. *Curr Opin Immunol* 2013;**25**:755–60.
5. Hahn M, Ghoreschi K. The role of IL-4 in psoriasis. *Expert Rev Clin Immunol* 2017;**13**:171–3.
6. Impellizzieri D, Ridder F, Raeber ME, Egholm C, Woytschak J, Kolios AGA, et al. IL-4 receptor engagement in human neutrophils impairs their migration and extracellular trap formation. *J Allergy Clin Immunol* 2019;**144**:267–79.
7. Chiang CC, Cheng WJ, Korinek M, Lin CY, Hwang TL. Neutrophils in psoriasis. *Front Immunol* 2019;**10**:2376.
8. Safa G, Paumier V. Psoriasis induced by dupilumab therapy. *Clin Exp Dermatol* 2019;**44**:e49–50.
9. de Wijs LEM, Nguyen NT, Kunkeler ACM, Nijsten T, Damman J, Hijnen DJ. Clinical and histopathological characterization of paradoxical head and neck erythema in patients with atopic dermatitis treated with dupilumab: a case series. *Br J Dermatol* 2019. https://doi.org/10.1111/bjd.18730.

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