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CASE STUDY

Keratosis pilaris caused by dupilumab for the treatment of bronchial asthma

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Abstract

Here, we present two patients with bronchial asthma, who developed keratosis pilaris (KP) following treatment with dupilumab, a monoclonal antibody to IL-4 receptor. Both of them reported pruritic papules in their extremities in 1 months after initiation of dupilumab therapy. The lesions newly developed on the day of every administration of dupilumab at 2-week interval, however, they tended to resolve over time until the next treatment. A diagnosis of KP was made from clinical and histopathologic findings. Dermoscopic examination revealed keratotic plugs with coiled, curly hairs. We suspected that dupilumab might abruptly impact on growth of vellus hair to generate KP.

KEYWORDS
bronchial asthma, curly hair, dupilumab, hair follicle, keratosis pilaris, Th2 pathway

1 | INTRODUCTION

Dupilumab is a fully human monoclonal antibody specific for the alpha subunit of the IL-4 receptor and inhibits downstream signaling of IL-4 and IL-13, leading to attenuation of the Th2 pathway activation that plays a key role in the development of allergic disorders, including atopic dermatitis (AD), bronchial asthma (BA), and chronic rhinosinusitis with nasal polyposis.[1,2] Since the approval of dupulimab in 2018 in Japan, a number of patients with aforementioned disorders, who were resistant to conventional therapies, appreciate its clinical efficacy. However, until now there have been unexpected side effects of dupulimab; such as conjunctivitis,[1] hair regrowth in pre-existing alopecia areata (AA), hair loss resembling AA,[3] dissemination of molluscum contagiosum[4] and rosacea-like folliculitis.[5] The mechanisms underlying these conditions remain to be well understood. However, it is likely that dupilumab evokes "off-target" effects through unexpected immunological modulation, which may be associated with down-regulation of the Th2 pathway. Herein, we report two patients with BA, who developed keratosis pilaris (KP) after treatment with dupilumab. KP is a common dermatologic condition characterized by keratinous plugs in the follicular orifices and perifollicular erythema, although little is known about its etiology.[6] From observation of the clinical courses of two cases, we suspect that immunological perturbation by dupilumab treatment might affect hair follicles to develop KP.

2 | CASE REPORTS

2.1 | Case 1

A 34-year-old woman, who had no present or past history of atopic dermatitis, was referred to us with slightly pruritic papules on the shoulder and anterior aspects of thighs. She had more than 10-year history of severe bronchial asthma that was uncontrollable with a high dose of inhaled corticosteroids, 15 mg of oral prednisolone, 100 mg of azathioprine, and 600 mg of biweekly administration of omalizumab. Therefore, omalizumab was switched to dupilumab at a dose of 300 mg biweekly. After the 2nd treatment with dupilumab, her respiratory symptom became relieved. After the 3rd treatment

with dupilumab, papules appeared in her shoulders. She was referred to our outpatient clinic after 4 days of the 4th injection of dupilumab because of newly development of papules in the thighs. Slightly brownish-pigmented follicular keratotic papules and mild perifollicular erythema were found in the shoulders and extensor aspects of thighs (Figure 1A,B). Dermoscopic examination revealed coil-like circular hair (CH), looped hair shafts, multiple vellus hairs emerging from a single opening and semicircular hair embedded beneath the cornified layer (closed triangles, arrow, dotted arrow, and open triangle, respectively, Figure 1D,E). Also, perifollicular erythema was noted. These features were compatible with KP.[6,7] Histopathology of the papule in her shoulder revealed follicular dilation with keratin plugs and mild mononuclear cell infiltrates (Figure 2A). Notably, higher magnification showed that a dilated follicle infundibulum involved entrapped hair shafts (arrows, Figure 2B). This characteristic finding was relevant to KP with CH.[7] Collectively, a diagnosis of KP was made. The papules increased immediately after every administration of dupilumab; however, they tended to resolve over time until the next treatment. Topical glucocorticoid was some effective, but the lesion recurred after administration of dupilumab. When the administration period was extended, the papules almost disappeared in 3 weeks (Figure 1E).

2.2 | Case 2

A 61-year-old woman with a history of severe BA, which was controlled with 300 mg of Dupilumab biweekly, was referred to us complaining of slightly pruritic papules of her shoulders. She had past histories of allergic bronchopulmonary fungal disease, eosinophilic sinusitis, eosinophilic otitis, and drug allergy, but not AD. One month after the first administration of dupilumab, she noticed

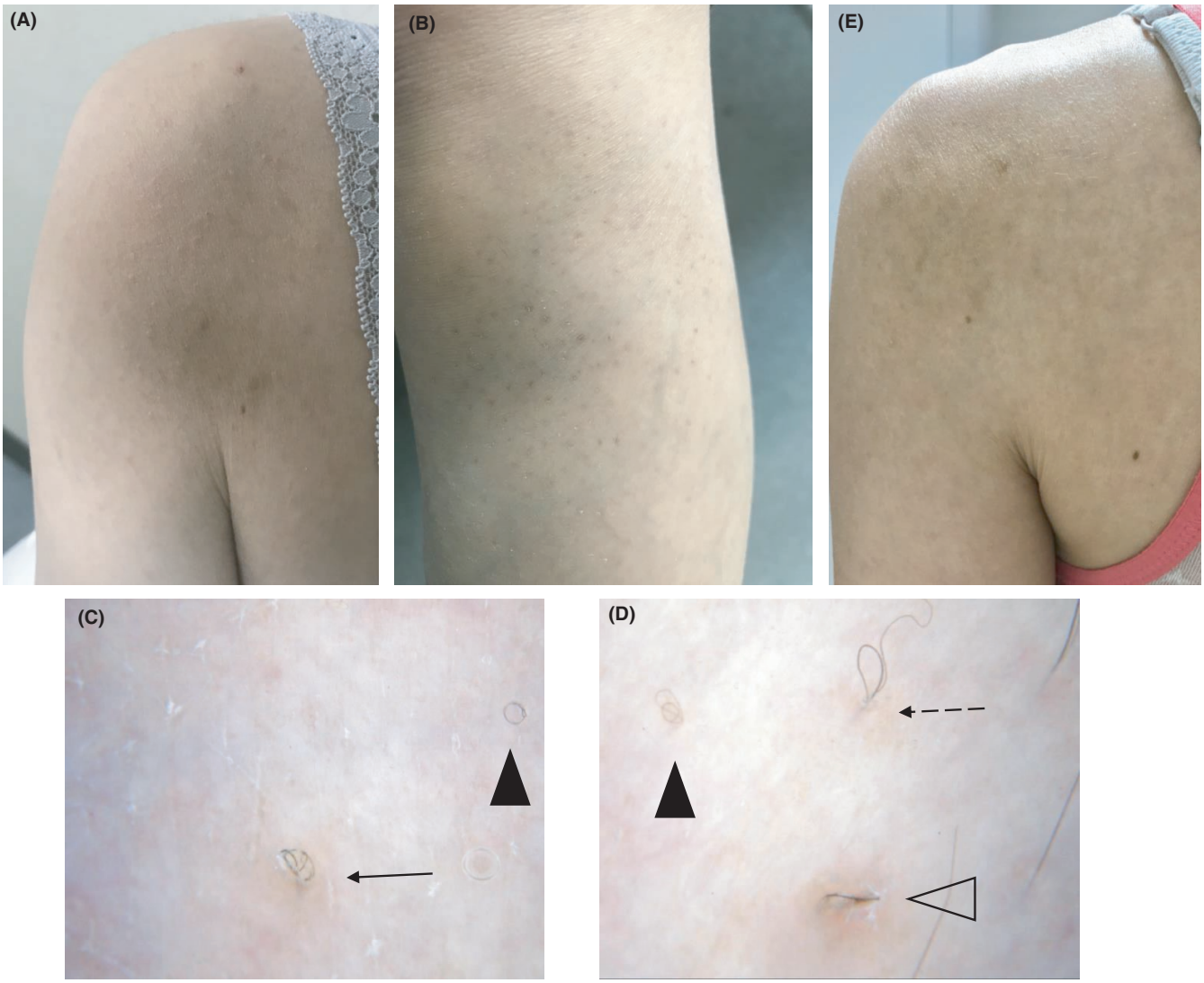

FIGURE 1 Clinical manifestations of keratosis pilaris (KP) in Case 1. (A, B) Follicular papules were present at day 3 of subcutaneous treatment with dupiumab. (C) KP was resolved after 3 weeks. (E, F) Dermoscopic views of KP. Closed triangles, coil-like circular hair (CH); arrow, looped hair shafts; dotted arrow, multiple vellus hairs emerging from a single opening; open triangle, semicircular hair embedded beneath the cornified layer

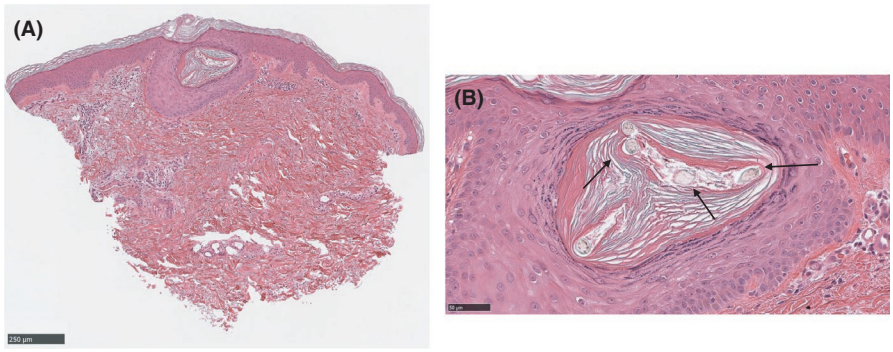

FIGURE 2 Histopathology of KP in Case 1. (A) A papule in her shoulder revealed follicular dilation with keratin plugs and mild mononuclear cell infiltrates. (B) A higher magnification showed that a dilated follicle infundibulum involved entrapped hair shafts (arrows). Scale bars, 250 μm (A), 50 μm (B). Hematoxylin-eosin staining

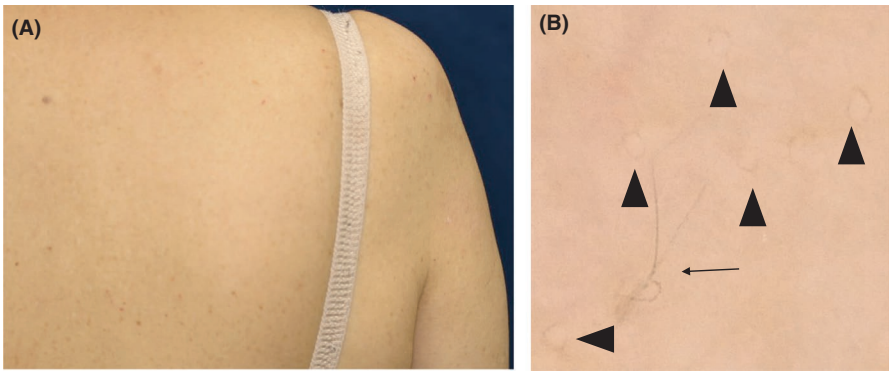

FIGURE 3 Clinical and dermoscopic views of KP in Case 2. (A) Small, brownish-colored keratotic papules were disseminated in the upper back and shoulder. (B) Dermoscopic observation revealed a number of CHs (triangles) and looped hairs emerging from a single opening (arrow)

erythematous papules on the upper arms and scapulae (Figure 3A). Dermoscopic observation revealed CH and looped hairs emerging from a single opening (triangles and arrow, respectively, Figure 3B). The symptoms peaked at 3-4 days after the injection of dupilumab but improved over time before the next administration. The diagnosis of KP was made. Since her symptoms were mild, she remained to be under observation without medication or discontinuance of dupilumab treatment.

3 | DISCUSSION

Dupilumab is a monoclonal antibody that binds to the α-subunit of the IL-4 receptor, leading to attenuation of the Th2 pathway.[1,2] It was approved for the treatment of AD in 2018 and severe BA in 2019 in Japan and has been widely used. In common with the two cases in this study, the cutaneous manifestation developed about 1 month after the initiation of dupilumab. The timing for the emergence of KP in both cases coincided with the reported timing of the effect of dupilumab on BA.[8] In fact, these two cases also experienced remission of the respiratory symptoms by dupilumab treatment, which, however, simultaneously induced KP. Also, both cases showed an exacerbation of KP within a few days after the injection of dupilumab, but KP became resolved over time before the next administration, suggesting of a cause-effect relationship between dupilumab and KP.

The prevalence of KP in adolescents is at least 50% with a female predominance.[9] There was a past history of KP in the case 1 in puberty but it was gradually relieved with age. The patient of case 2 did not have previous KP. Although the pathoetiology of KP is not well understood, it has been shown to be associated with AD, ichthyosis vulgaris,[9] but neither of the patients had a history of these conditions. The fact that patients have less background associated with the development of KP also suggested that the administration of dupilumab was associated with the development of KP. KP is suggested to be associated with CH, which leads to rupture of the follicular epithelium, inflammation, and abnormal follicular keratinization.[6] In addition, CH is also observed in patients with alopecia areata (AA).[10,11]

Very interestingly, it has been recognized that dupilumab is therapeutic not only for eczematous dermatitis but also for hair regrowth in pre-existing AA in patients with AD,[12,13] suggesting that there may be an interaction between immunological modulation by dupilumab and hair follicle growth.[3] The association between AA and AD is likely due to shared immune pathways involving Th2 over-activation.[3,14] More specifically, dupilumab has been shown to maintain regulatory T cell (Treg) by deterring the transition of Treg to Ex-Treg, which loses immunosuppressive effect with FoxP3.[2] In the skin, Tregs are abundant in the perifollicular region of the hair follicles; thereby, they can escape the immune cell attack to initiate the growth phase transition through Jag1-Notch interaction with stem cells.[15]

Given the above, we propose a following mechanism underlying the development of KP in this study. Dupilumab induced an increase in Treg number to initiate hair follicles in vellus hairs to switch from telogen to "temporal" anagen, which caused CH. However, due to insufficient hair growth to penetrate the cornified layer, it remains in the follicular infundibulum to develop KP. However, it is undetermined whether hair follicles in patients with BA are potentially immunologically impaired like those in AD under the influence of the Th2 over-activation, or whether CH/KP develops also in patients with AD. This is the first report of KP in patients with BA presumably induced by dupilumab treatment. Therefore, detailed observation of follicular changes will be necessary in AD and BA, who receive dupilumab treatment, in the future.

DECLARATION SECTION

Approval of the research protocol: N/A.

Informed Consent: Verbal informed consent was obtained from a legally authorized representative for anonymized patient information to be published in this article.

Registry and the Registration No. of the study/trial: N/A.

Animal Studies: N/A.

CONFLICT OF INTEREST

The authors declare no conflict of interest. Dr. Shigetoshi Sano is a member of the Journal of Cutaneous Immunology and Allergy Editorial Board. Management of the peer review process, and all editorial decision-making, for this article was undertaken by Editor in Chief.

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REFERENCES

1. Sastre J, Dávila I. Dupilumab: a new paradigm for the treatment of allergic diseases. J Invest Allerg Clin Immunol. 2018;28:139–50.
2. Harb H, Chatila TA. Mechanisms of dupilumab. Clin Exp Allergy. 2020;50:5–14.
3. Hendricks AJ, Lio PA, Shi VY. Dupilumab and alopecia: causative or therapeutic? Dermatology. 2019;235:306–7.
4. Sevray M, Dupré D, Misery L, Abasq-Thomas C. Hair regrowth and dissemination of molluscum contagiosum: two unexpected effects with dupilumab. J Eur Acd Dermatol Venereol. 2019;33:e296–8.
5. Quint T, Brunner PM, Sinz C, Steiner I, Ristl R, Vigl K, et al. Dupilumab for the treatment of atopic dermatitis in an Austrian cohort-real-life data shows rosacea-like folliculitis. J Clin Med. 2020;9:1241.
6. Thomas M, Khopkar US. Keratosis pilaris revisited: is it more than just a follicular keratosis? Int J Trichology. 2012;4:255–8.
7. Panchaprateep R, Tanus A, Tosti A. Clinical, dermoscopic, and histopathologic features of body hair disorders. J Am Acad Dermatol. 2015;72:890–900.
8. Castro M, Corren J, Pavord ID, Maspero J, Wenzel S, Rabe KF, et al. Dupilumab efficacy and safety in moderate-to-severe uncontrolled asthma. New Engl J Med. 2018;378:2486–96.
9. Hwang S, Schwartz RA. Keratosis pilaris: a common follicular hyperkeratosis. Cutis. 2008;82:177–80.
10. Esteves ALV, Serafini NB, Lemes LR, Melo DF. Circular hairs: nomenclature and meanings. An Bras Dermatol. 2017;92:874–6.
11. Waśkiel A, Rakowska A, Sikora M, Olszewska M, Rudnicka L. Trichoscopy of alopecia areata: an update. J Dermatol. 2018;45:692–700.
12. Darrigade A-S, Legrand A, Andreu N, Jacquemin C, Boniface K, Taïeb A, et al. Dual efficacy of dupilumab in a patient with concomitant atopic dermatitis and alopecia areata. Br J Dermatol. 2018;179:534–6.
13. Babino G, Fulgione E, D'Ambra I, Calabrese G, Alfano R, Argenziano G. Rapid hair regrowth induced by dupilumab in a patient affected by alopecia totalis of 28 years' duration: clinical and dermoscopic features. Dermatol Ther. 2020;33:e13582.
14. Renert-Yuval Y, Guttman-Yassky E. The changing landscape of alopecia areata: the therapeutic paradigm. Adv Ther. 2017;34:1594–609.
15. Maryanovich M, Frenette PS. T-regulating hair follicle stem cells. Immunity. 2017;46:979–81.

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