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Letter to the Editor

Development of conjunctivitis with a conjunctival proliferative lesion in a patient treated with dupilumab for atopic dermatitis

Dear Editor,

Dupilumab is a human monoclonal antibody to the α subunit of the IL-4 receptor (IL-4R α), which is also shared by the IL-13 receptor.¹ It thus inhibits signaling by both of these Th2 cytokines, and it has recently been approved for the treatment of atopic dermatitis. Clinical trials identified conjunctivitis as one of the most common adverse events of dupilumab treatment in patients with atopic dermatitis,^{2–4} with this side effect also having been encountered in clinical practice.^{5,6} Here we present a case of proliferative conjunctivitis associated with dupilumab treatment.

A 35-year-old woman with a history of atopic dermatitis since the age of 5 years presented with bilateral ocular itch and discharge that developed several days after the initiation of dupilumab treatment 3 months previously. The patient did not notice any symptoms of conjunctivitis including ocular itching and eye discharge before treatment with dupilumab. Atopic dermatitis (eczema) never occurred on her face even before treatment with dupilumab. Although she was treated with olopatadine eyedrops and levofloxacin eyedrops prescribed by her dermatologist, her symptoms did not improve. At her initial visit to our hospital, bilateral hyperemia of the tarsal conjunctiva as well as the presence of papillae and a follicular reaction in the upper and lower tarsal conjunctiva, respectively (Fig. 1A, B), were observed by slitlamp examination. Some giant papillae were also detected on the left upper tarsal conjunctiva. In addition, hyperemia of the bulbar conjunctiva and a lesion (7 by 3 mm) protruding from the upper fornix (Fig. 1C) were apparent in her left eye. Giemsa staining of eye discharge revealed the presence of many neutrophils and a smaller number of eosinophils (Fig. 1D). No pathogens were found in eye discharge by Gram staining. We treated her conjunctivitis with 0.1% fluorometholone eyedrops three times a day without discontinuation of dupilumab injections. The itch disappeared within 5 days, and both the giant papillae on the left upper tarsal conjunctiva and the proliferative lesion in the left conjunctiva had regressed after 1 month (Fig. 2).

The clinical features of 13 cases of dupilumab-induced conjunctivitis were recently described.⁶ The conjunctivitis was bilateral, with hyperemia of the limbus being a prominent feature. Nodular swelling of the limbus resembling Trantas' dots was also present in severe cases. Two cases of follicular conjunctivitis associated with dupilumab injection have also been reported.⁵ However, dupilumab-induced conjunctivitis with a conjunctival proliferative

lesion like that in the present case has not been previously described.

We have shown that fibroblasts at the ocular surface express IL-4R α ,^{1,7} and both IL-4 and IL-13 play key roles in the pathogenesis of proliferative lesions of the conjunctiva.⁸ We have thus also shown that the chemotactic, mitogenic, and antiapoptotic effects of IL-4 and IL-13 on conjunctival fibroblasts result in hyperplasia of these cells,^{7,8} as well as that IL-4 and IL-13 stimulate the synthesis of extracellular matrix (ECM) proteins including collagen types I and III and fibronectin by conjunctival fibroblasts.⁷ Furthermore, these cytokines inhibit the release from conjunctival fibroblasts of matrix metalloproteinases (MMPs),⁹ which mediate the degradation of ECM, as well as promote the release from these cells of tissue inhibitors of metalloproteinases (TIMPs),⁸ which inhibit the activity of MMPs. Together, these effects of IL-4 and IL-13—stimulation of ECM synthesis and attenuation of ECM degradation—may result in the excessive deposition of ECM in giant papillae of patients with vernal keratoconjunctivitis.⁸ In the present case, however, inhibition of signaling by IL-4 and IL-13 by dupilumab was accompanied by the development of a proliferative lesion of the conjunctiva resembling those associated with vernal keratoconjunctivitis. The mechanism responsible for this paradoxical effect is unclear. In clinical trials, conjunctivitis has been associated with dupilumab treatment for atopic dermatitis but not with that for other allergic diseases including asthma, nasal polyposis, and eosinophilic esophagitis, suggesting that a factor specific to atopic dermatitis underlies the development of this adverse event. Examination of the conjunctival cytokine profile of T cells in subjects with chronic allergic eye diseases revealed a Th2 cytokine array in patients with vernal keratoconjunctivitis or giant papillary conjunctivitis but a shift toward a Th1 pattern in patients with atopic keratoconjunctivitis.¹⁰ Th1 cells in the conjunctiva of individuals with atopic dermatitis might thus contribute to the pathogenesis of dupilumab-induced conjunctivitis.

Although a recommended treatment has not been established for dupilumab-induced conjunctivitis, topical corticosteroids or tacrolimus, but not antihistamines or artificial tears, have been found to be effective in some cases.⁶ Consistent with these previous findings, treatment with fluorometholone eyedrops, but not that with antihistamine eyedrops, also led to clinical improvement in the present case. These previous and present findings thus suggest that dupilumab-associated conjunctivitis may be manageable by topical treatment with steroids or tacrolimus. Further studies are warranted to clarify the risk factors, mechanisms, and effective treatments for dupilumab-associated conjunctivitis.

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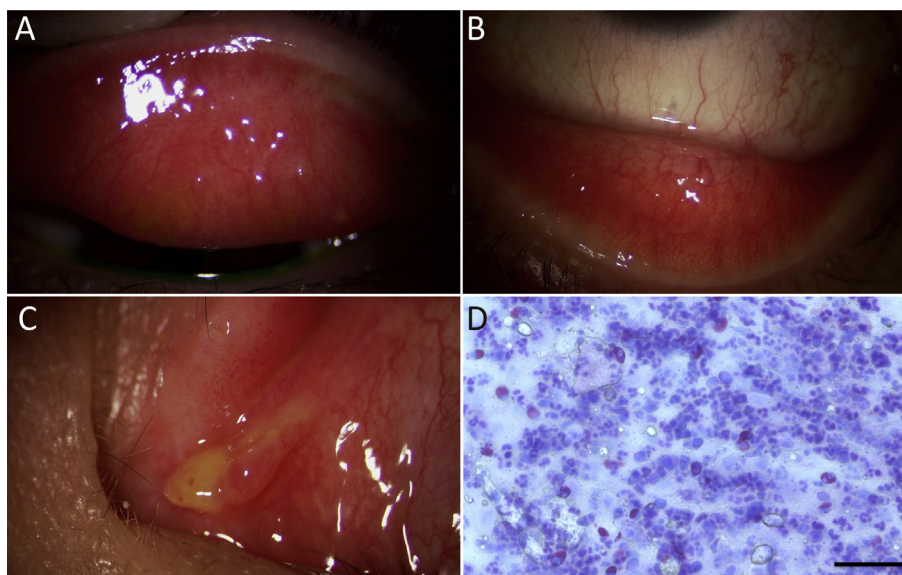


Fig. 1. Slitlamp images of the left eye and Giemsa staining of eye discharge at the initial visit. Papillae formation (A) and a follicular reaction (B) were apparent in the upper and lower tarsal conjunctiva, respectively. A lesion protruding from the upper fornix was also detected (C). Giemsa staining of eye discharge revealed the presence (red staining) of neutrophils and a smaller number of eosinophils (D). Scale bar, 50 µm.

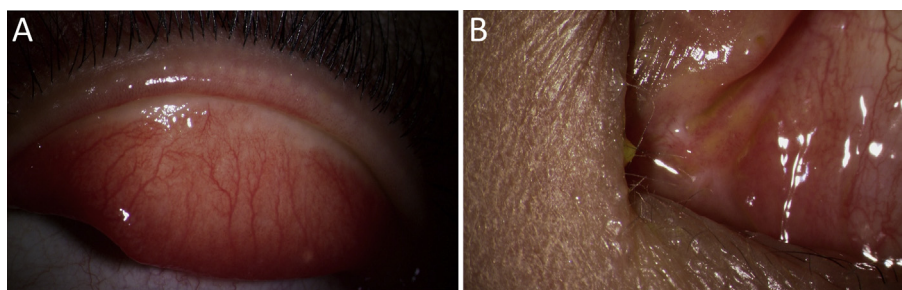


Fig. 2. Slitlamp images of the left eye 1 month after the initial visit. Giant papillae (A) and the protruding lesion (B) had regressed.

Conflict of interest

The authors have no conflict of interest to declare.

Ken Fukuda *, Waka Ishida, Tatsuma Kishimoto, Atsuki Fukushima

Department of Ophthalmology and Visual Science, Kochi Medical School, Kochi University, Kochi, Japan

* Corresponding author. Department of Ophthalmology and Visual Science, Kochi Medical School, Kochi University, Kohasu, Oko-cho, Nankoku, Kochi 783-8505, Japan.

E-mail address: k.fukuda@kochi-u.ac.jp (K. Fukuda).

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