

Clinical Communications

Amelioration of conjunctival giant papillae by dupilumab in patients with atopic keratoconjunctivitis

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Clinical Implications

- We report the successful treatment of 2 cases of conjunctival giant papillae associated with severe atopic keratoconjunctivitis by dupilumab administered for atopic dermatitis. Dupilumab is thus a potential alternative agent for the treatment of severe atopic and vernal keratoconjunctivitis.

TO THE EDITOR:

Severe ocular allergic diseases such as atopic and vernal keratoconjunctivitis are associated with the formation of giant papillae, proliferative lesions of the upper tarsal conjunctiva. The pronounced T helper 2 and eosinophilic inflammation characteristic of giant papillae can result in the development of corneal epithelial disorders and consequent visual disturbance. The control of such inflammation is thus critical for the treatment of severe ocular allergic disease.

Dupilumab is a human monoclonal antibody to the α subunit of the IL-4 receptor. Given that the IL-13 receptor shares this α subunit,¹ dupilumab inhibits signaling by both IL-4 and IL-13. Dupilumab was recently approved for the treatment of atopic dermatitis (AD), and we now report 2 cases of severe atopic keratoconjunctivitis with giant papillae that were ameliorated by dupilumab administered for the treatment of AD.

A 25-year-old man with atopic keratoconjunctivitis was referred to us for treatment. Slitlamp examination revealed giant papillae with discharge on the upper tarsal conjunctiva as well as a large shield ulcer with plaque on the cornea of the right eye (Figure 1, A and B). Administration of eyedrops containing tacrolimus (0.1%), betamethasone (0.1%), epinastine, and levofloxacin for 2 months did not improve his clinical condition. We then performed surgical resection of the giant papillae, but the lesions recurred within 1 month after surgery. We again performed resection of the giant papillae 2 months later, but again they regrew within 1 month of the second surgery (Figure 1, C and D). The patient had a history of AD developing in childhood, with adult onset severe dermatitis of the face and eyelids. His dermatitis had been treated with steroid ointment, tacrolimus ointment, and oral antihistamine. His dermatologist started treatment with dupilumab for AD, and at about the same time, we repeated surgical resection of the giant papillae in the right eye. Despite initial recurrence after this third resection (Figure 1, E and F), the papillae underwent complete regression and the corneal condition also improved at 3 months after this

surgery (Figure 1, G and H). There has been no subsequent recurrence of the giant papillae in the 8 months since their regression.

A 33-year-old man with AD noticed a foreign body sensation and discharge in both eyes and visited an eye clinic 3 months before his referral to us by his dermatologist. He was treated with eyedrops containing olopatadine and tacrolimus with a diagnosis of atopic keratoconjunctivitis. His subjective symptoms improved for 1 week, and he then interrupted treatment with tacrolimus. At his initial visit to us, slitlamp examination revealed giant papillae with hyperemia and discharge on the upper tarsal conjunctiva of both eyes (Figure 2, A and B). Giemsa staining of eye discharge revealed the presence of many eosinophils. The patient had a history of AD developing in childhood and had been treated with steroid ointment and oral antihistamine. The patient had never noticed any symptoms of allergic conjunctivitis including ocular itching. His AD was then treated with dupilumab injections by his dermatologist. Two weeks after the first dupilumab injection, the itch in both eyes disappeared and the giant papillae showed a reduced area and height (Figure 2, C and D). Four weeks after his initial visit to us (2 weeks after a second dupilumab injection), the giant papillae had further regressed and had flattened out (Figure 2, E and F).

As far as we are aware, this is the first report of a therapeutic effect of dupilumab on giant papillae in patients with atopic keratoconjunctivitis. The onset of dupilumab treatment was thus associated with regression of recurrent giant papillae after surgery in a case refractory to topical steroid and tacrolimus as well as with a rapid reduction in the size of giant papillae in another case.

Giant papillae form as a result of the deposition of extracellular matrix, the proliferation of conjunctival fibroblasts, and the invasion of inflammatory cells. We and others have previously shown that IL-4 and IL-13 act on conjunctival fibroblasts and thereby contribute to the pathogenesis of giant papillae.² These cytokines stimulate the migration and proliferation of conjunctival fibroblasts³ and inhibit their apoptotic death,⁴ resulting in overgrowth of the cells in giant papillae. IL-4 and IL-13 also stimulate the synthesis of extracellular matrix proteins such as collagen and fibronectin,⁴ inhibit the production of matrix metalloproteinases that degrade extracellular matrix,⁵ and increase that of tissue inhibitors of metalloproteinases² in conjunctival fibroblasts, effects that together result in the accumulation of extracellular matrix in giant papillae. The inhibition of both IL-4 and IL-13 signaling by dupilumab thus likely accounts for its therapeutic effect on giant papillae.

Nasal polyps associated with severe eosinophilic rhinosinusitis are characterized by a protruding mass of inflammatory nasal mucosa and are similar to conjunctival giant papillae both morphologically and pathophysiologically.^{2,6,7} Both atopic keratoconjunctivitis with giant papillae and eosinophilic rhinosinusitis with nasal polyposis are thus thought to be related to T helper 2 and eosinophilic inflammation. A randomized clinical trial showed that dupilumab induced a significant reduction in nasal polyp burden in patients with nasal polyposis refractory to

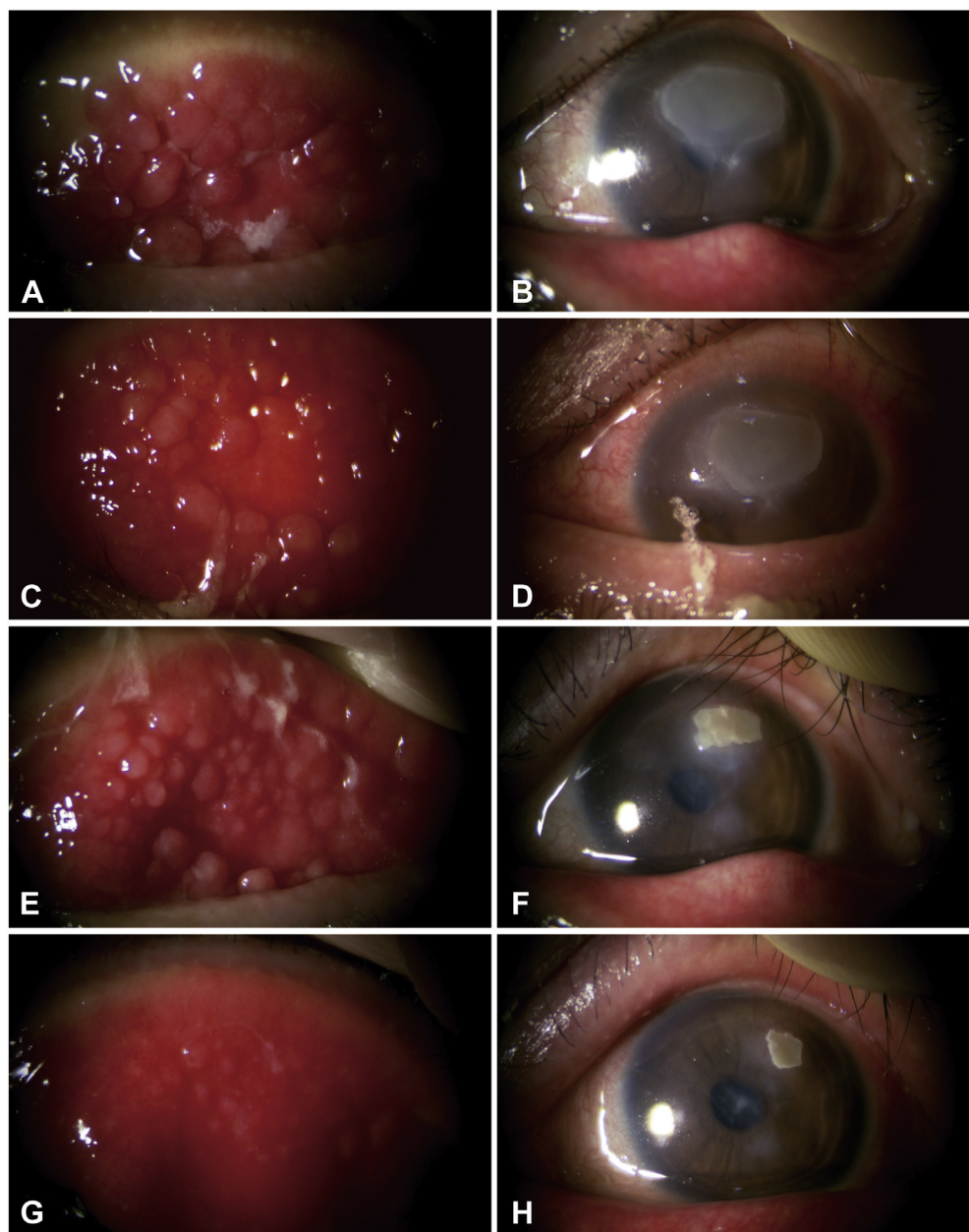


FIGURE 1. Slitlamp images for case 1. Giant papillae and corneal ulcer were apparent at the initial visit (**A** and **B**), 1 month after the second surgery (**C** and **D**), and 1 month after the third surgery and onset of dupilumab treatment (**E** and **F**). Both conditions had ameliorated at 3 months after the third surgery (**G** and **H**).

corticosteroids.⁸ We recently performed transcriptome profiling of giant papillae in patients with atopic keratoconjunctivitis refractory to topical treatment with tacrolimus and corticosteroid.⁹ Among transcripts encoding cytokines and their receptors, those for IL-4 and IL-13 were the most abundant, suggesting that insufficient suppression of these 2 cytokines may contribute to treatment resistance. These observations further support a therapeutic role for dupilumab in severe ocular allergic diseases with giant papillae as well as in nasal polyposis.

We have described 2 cases of giant papillae that were ameliorated by dupilumab. These cases suggest that dupilumab is

a potential alternative therapeutic agent for patients with severe atopic or vernal keratoconjunctivitis, although further studies including clinical trials will be required to confirm such efficacy. In contrast to the present cases, mild conjunctivitis has been reported as an adverse effect of dupilumab in patients with AD but not in those with asthma or nasal polyps.¹⁰ Conjunctivitis occurring during dupilumab treatment has been observed in approximately 9% to 28%, and the incidence of conjunctivitis was associated with higher baseline AD severity, prior history of conjunctivitis, and atopic comorbidities.¹⁰ Although the mechanism of dupilumab-induced conjunctivitis is unclear, most of

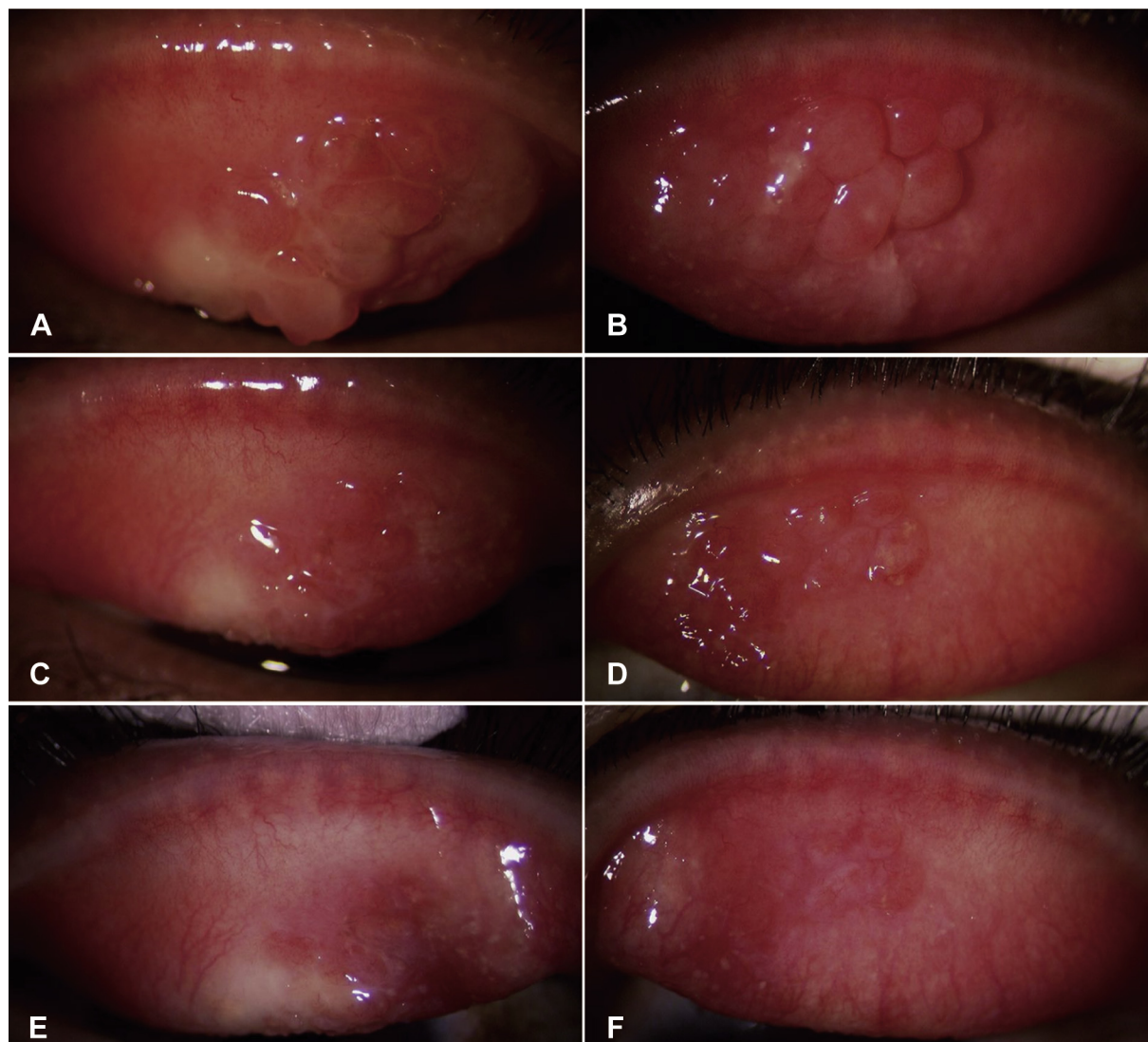


FIGURE 2. Slitlamp images of the upper tarsal conjunctiva for case 2. Giant papillae were apparent in both the right (A) and left (B) eyes at the initial visit. The giant papillae had regressed 2 weeks after the first injection of dupilumab (C and D) and had completely flattened out 2 weeks after the second injection of dupilumab (E and F).

the reported cases responded to treatment with topical corticosteroid or tacrolimus. To clarify the background of patients showing an adverse effect or a therapeutic effect of dupilumab, screening patients by an ophthalmologist before and during dupilumab treatment may be needed.

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