Irreversible Bilateral Cicatricial Keratoconjunctivitis after Dupilumab Therapy

Minh T. Nguyen  Mai Tsukikawa  Whitney Lomazow  Michele Lee

Department of Ophthalmology, University of Washington, Seattle, WA, USA

Abstract
This report highlights a case of irreversible bilateral cicatricial keratoconjunctivitis related to dupilumab therapy for the treatment of severe atopic dermatitis (AD). After 38 years of AD, the patient began dupilumab therapy and achieved disease control. Two years into treatment, his ophthalmic examination was significant for bilateral cicatricial keratoconjunctivitis with severe foreshortening of the inferior conjunctival fornices, symblepharon, and ankyloblepharon, which persisted even after topical steroid eye drops and discontinuation of dupilumab. Treating dermatologists should be aware of this potential irreversible adverse effect, and we recommend that patients are monitored for ocular complications while on dupilumab therapy.

Introduction
In 2017, the Food and Drug Administration approved dupilumab (Dupixent, Regeneron, and Sanofi, USA), the first biologic systemic treatment for moderate to severe atopic dermatitis (AD), asthma, and chronic sinusitis with nasal polyps [1]. One of the most common side effects of dupilumab is conjunctivitis, seen in up to 14–19% of AD patients in phase 3 clinical trials [2, 3]. While nearly all reported cases have been reversed with treatment or discontinuation of dupilumab, we describe a case of dupilumab-induced keratoconjunctivitis associated with irreversible ocular surface scarring due to delay in ophthalmic care.

Keywords
Dupilumab · Atopic dermatitis · Drug reaction · Cicatricial keratoconjunctivitis · Symblepharon · Ankyloblepharon
Case Report

A 53-year-old male patient with no prior history of blepharoconjunctivitis presented to our eye institute with 2 years of bilateral eye redness, irritation, and blurry vision. He had no prior ophthalmic issue except glaucoma suspect, for which he saw an ophthalmologist on a regular basis until 5 years prior to presentation. However, he had a history of severe AD since childhood with significant involvement of the face and body, which was recalcitrant to topical therapy and oral prednisone. Approximately 6 weeks after initiation of dupilumab therapy (loading dose of 600 mg followed by 300 mg every 2 weeks), he began experiencing the above ocular symptoms. He was told by his previous dermatologist that eye redness was a minor side effect of dupilumab and should resolve over time without the need for any treatment. He established care with a new dermatologist a few weeks prior to presentation who recommended topical tacrolimus without relief of symptoms, and a subsequent referral process was started.

At presentation, his best-corrected visual acuities were 20/80 in the right eye and 20/40 in the left eye, while his intraocular pressures were normal in both eyes. On examination, he had severe bilateral entropion, symblepharon, ankyloblepharon, severe eyelid fornix foreshortening, 3+ papillary reaction of the upper eyelids, as well as diffuse corneal inflammation with punctate epithelial erosion and stromal edema (Fig. 1). He was started on prednisolone acetate 1% drops four times a day in both eyes and elected to discontinue dupilumab due to the severity of his ocular symptoms. Three months after discontinuing dupilumab, subjective symptoms improved, his best-corrected visual acuity improved to 20/20 in both eyes, his intraocular pressure remained stable, and examination revealed resolution of conjunctival injection and corneal inflammation. However, entropion, symblepharon, ankyloblepharon, and fornical foreshortening persisted in both eyes. The patient continued to experience pain with eye movements due to conjunctival cicatization, which required extensive ocular surface and fornix reconstruction with buccal mucosal graft placement (Fig. 2). Biopsy of the inferior conjunctival fornix

Fig. 1. Right eye at presentation. Cicatricial keratoconjunctivitis with (a) lateral ankyloblepharon. (b) Cicatricial entropion and trichiasis. (c) Thick symblepharon band.

Fig. 2. Right eye, 3 months after discontinuation of dupilumab. (a) Persistent lateral ankyloblepharon. (b) Persistent entropion and trichiasis. (c) Persistent symblepharon.
showed chronic conjunctivitis with no evidence of ocular cicatricial pemphigoid on immunofluorescence staining.

Discussion

Dupilumab is an effective steroid-sparing treatment for moderate to severe AD. This human monoclonal antibody works by reducing the inflammatory process through the blockage of IL-4 and IL-13 downstream signaling [4]. Many patients with AD praise dupilumab as “life-changing” as it can rescue them from life-long pain, discomfort, and social stigma [5]. However, with an increasing number of patients starting dupilumab, there are increasing numbers of reported side effects such as dupilumab-induced conjunctivitis. The International Eczema Council thus recommends that patients should be made aware of this potential adverse reaction before the initiation of dupilumab; even so, there remains a consensus among AD experts that baseline conjunctivitis is not a contraindication to starting treatment, and those who develop ocular symptoms should continue treatment while awaiting ophthalmic evaluation [3].

A review of the literature revealed multiple case reports describing cicatricial eye disease as a complication of dupilumab; all of which were reversible with discontinuation of therapy and/or treatment with topical steroid or immunomodulator eye drops [6]. It is also possible that ocular side effects from this medication are underreported. A small cohort study from Ivert et al. [7] found that 9 out of 10 patients who were treated with dupilumab had ocular issues, including seven with conjunctivitis. Similarly, a case series reported ocular surface disease in 14 patients of 28 consecutive patients who were taking dupilumab, and of these, 9 patients had conjunctivitis [6]. Even more vision-threatening side effects could also occur; as Far et al. [8] published a case of bilateral dupilumab-induced peripheral ulcerative keratitis that resolved after 3 weeks of therapy discontinuation and topical prednisolone. Our patient’s ocular symptoms, though severe, went unchecked for almost 2 years. This case motivates us to search for a robust protocol to aid clinicians in recognizing and referring to ophthalmologists.

One such grading scale has been described in a cohort of 57 patients with dupilumab-associated ocular surface disease [9]. In this 5-point grading system, 1 point was assigned for each of the most common symptoms of dupilumab-associated ocular surface disease: discharge, irritation/pain, photophobia, pruritus, and redness. It was then proposed that mild disease (score ≤2) can be treated with over-the-counter mast cell stabilizers, and severe disease (score ≥3) should be evaluated promptly by ophthalmology for possible treatment with topical corticosteroids and/or calcineurin inhibitors.

The delayed referral and resultant permanent conjunctival scarring in our patient illustrate a need for widespread awareness as well as implementation of a grading system and/or criteria to diagnose, treat, and refer to ophthalmology. We also recommend that all AD patients on dupilumab therapy stay vigilant and seek ophthalmic care with any new and concerning eye symptoms.

Conclusions

This case illustrates sight-threatening and potentially irreversible side effects from dupilumab in the setting of delay in ophthalmic care. We advocate for early ophthalmologic referral for all patients with moderate to severe AD who are treated with this medication and start to show ocular signs or symptoms. In the future, there may be a role for
baseline monitoring for higher risk patients, such as those with severe AD requiring a higher dose of dupilumab.

**Statement of Ethics**

This study protocol adhered to the tenets of the Declaration of Helsinki. This retrospective review of patient data did not require ethical approval in accordance with local or national guidelines. Written informed consent was obtained from the patient for publication of the details of their medical case and any accompanying images.

**Conflict of Interest Statement**

All the authors have no financial disclosures or conflicts of interest.

**Funding Sources**

The design and conduct of the study; collection, management, analysis, and interpretation of the data; preparation, review, or approval of the manuscript; and decision to submit the manuscript for publication were supported by an unrestricted grant from Research to Prevent Blindness Inc. NYC to the University of Washington Department of Ophthalmology.

**Author Contributions**

Minh T. Nguyen, MD – preparation of the manuscript, corresponding author. Mai Tsukikawa, MD – preparation of the manuscript. Whitney Lomazow, MD – preparation of the manuscript. Michele Lee, MD – preparation of the manuscript.

**Data Availability Statement**

All data generated or analyzed during this study are included in this article. Further inquiries can be directed to the corresponding author.

**References**

1. Gandhi NA, Bennett BL, Graham NMH, Pirozzi G, Stahl N, Yancopoulos GD. Targeting key proximal drivers of type 2 inflammation in disease. *Nat Rev Drug Discov*. 2016;15(1):35–50.
2. Blauvelt A, de Bruin-Weller M, Gooderham M, Cather JC, Weisman J, Pariser D, et al. Long-term management of moderate-to-severe atopic dermatitis with dupilumab and concomitant topical corticosteroids (LIBERTY AD CHRONOS): a 1-year, randomized, double-blinded, placebo-controlled, phase 3 trial. *Lancet*. 2017;389(10086):2287–303.
3. Thyssen JP, de Bruin-Weller MS, Paller AS, Vestergaard C, Deleuran M, et al. Conjunctivitis in atopic dermatitis patients with and without dupilumab therapy – International Eczema Council survey and opinion. *J Eur Acad Dermatol Venereol*. 2019;33(7):1224–31.
4. Beck KM, Seitzman GD, Yang EJ, Sanchez IM, Liao W. Ocular co-morbidities of atopic dermatitis. Part II: ocular disease secondary to treatments. *Am J Clin Dermatol*. 2019;20(6):807–15.
5. Clinical review report: Dupilumab (Dupixent): [Sanofi-Aventis Canada Inc]. Canadian Agency for Drugs and Technologies in Health; 2018.
6. Popiela MZ, Barbara R, Turnbull AMJ, Corden E, Martinez-Falero BS, O’Driscoll D, et al. Dupilumab-associated ocular surface disease: presentation, management and long-term sequelae. *Eye*. 2021;35(12):3277–84.

7. Ivert LU, Wahlgren CF, Ivert L, Lundqvist M, Bradley M. Eye complications during dupilumab treatment for severe atopic dermatitis. *Acta Derm Venereol*. 2019;99(4):375–8.

8. Far PM, Quinn MP, Johnson D. Bilateral peripheral ulcerative keratitis associated with Dupilumab. *Ophthalmology*. 2022;129(5):561.

9. Bohner A, Topham C, Strunk J, Haynes D, Brazil M, Clements J, et al. Dupilumab-associated ocular surface disease: clinical characteristics, treatment, and follow-up. *Cornea*. 2021;40(5):584–9.