• Letter to the Editor •

Dupilumab-associated ulcerative keratitis

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Received: 2021-10-09 Accepted: 2021-12-09

DOI:10.18240/ijo.2022.06.23

Citation: Wilson MM, Roberts PK, Daniell M. Dupilumab-associated ulcerative keratitis. *Int J Ophthalmol* 2022;15(6):1020-1022

Dear Editor,

We present a case of a healthy 32-year-old man who developed bilateral corneal ulceration 3wk after commencing dupilumab for atopic dermatitis. Dupilumab is a recently introduced systemic monoclonal antibody used in the treatment of moderate-to-severe atopic dermatitis, showing efficacy in clinical trials[1-4]. Several publications have reported ocular surface complications associated with dupilumab, including conjunctivitis, blepharitis, and superficial keratitis, though we report a novel case of dupilumab-associated bilateral corneal ulceration. This study is in accordance with the tenets of the Declaration of Helsinki and written informed consent has been obtained from the patient.

A 32-year-old man presented to the Royal Victorian Eye and Ear Hospital (RVEEH), referred from a private ophthalmologist, with severe, worsening bilateral ulcerative keratitis for over a week.

The patient had initially noted right eye irritation and redness, with bilateral (OU) photophobia and epiphora, prompting ophthalmology review. He was treated with one week of ofloxacin and gentamycin eye drops OU 2 hourly while awake and chloramphenicol ointment at night. On re-review, his vision had deteriorated from 6/9 in each eye, to right visual acuity (RVA) of counting fingers at 1m (CF@1 m) and left visual acuity (LVA) of 6/18, and he was referred to the RVEEH.

Previous ocular history included a skin cancer removal from a left lower lid tear duct. Medical history was notable for atopic dermatitis, ulcerative bladder post childhood trauma and epilepsy. Systemic medication included sodium valproate, mycophenolate, oxybutynin and dupilumab subcutaneous injections. Dupilumab injections, including an initial 600 mg loading dose followed by a maintenance dose of 300 mg every second week, had been commenced 4wk prior. Onset of ocular symptoms were first noted 3wk post first dupilumab dose. All other systemic medications had remained unchanged for multiple years.

On presentation to the RVEEH, his best corrected visual acuity (BCVA) was 6/36 right eye (OD) and 6/6 left eye (OS). On slit lamp examination, he had peripheral ulcerative keratitis in the right eye worse than the left. The right eye had 2 corneal defects: a 6×2.5 mm^2 paralimbal, deep-stromal infiltrate from 3 to 6 o'clock with an overlying epithelial defect, and a 3×1 mm^2 deep-stromal infiltrate at 11 o'clock on the limbal edge with overlying epithelial defect (Figures 1 and 2). He had severe blepharitis of the lid margins bilaterally, with a lateral ectropion OD and medial ectropion OS. Anterior segment findings showed an injected limbal flush of the right eye. Flare was noted in the anterior chamber but no cells or hypopyon.

In his left eye, the cornea had no epithelial defect, though 2 sub-epithelial infiltrates (<1 mm diameter) were noted superiorly. Anterior chamber showed no signs of intraocular inflammation.

Right eye corneal scrape and swab was taken, including 2 glass slides for gram and blankophor stain, blood agar, chocolate agar, a fungal slope, broth, an acanthamoeba slope, a viral polymerase chain reaction (PCR) and a gonococcal and chlamydia PCR.

The patient was admitted and commenced on ofloxacin 0.3% eye drops OD 1 drop hourly day and night, sodium hyaluronate 0.2% eyedrops OS 2nd hourly during the day, oral valaciclovir 500 mg three times a day and oral doxycycline 50 mg twice a day. Patient remained stable with only minor improvements despite 72h of intensive treatment. Bacterial and fungal microbiology and viral PCR [including herpes simplex virus (HSV) type 1 & 2, and varicella zoster, cytomegalovirus and adenovirus] were negative for all organism growth and, on day 3 of admission, fluorometholone 0.1% eye drops four times a day (QID) OU was commenced and chloramphenicol ointment

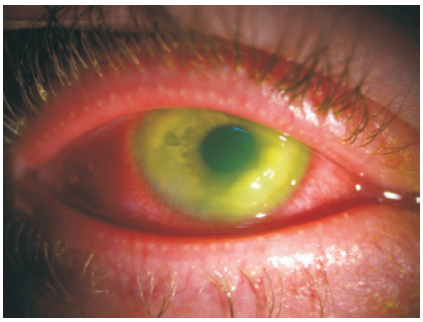

Figure 1 Right eye slit lamp photo The infiltrates in the patient's right eye superotemporally and inferonasally.

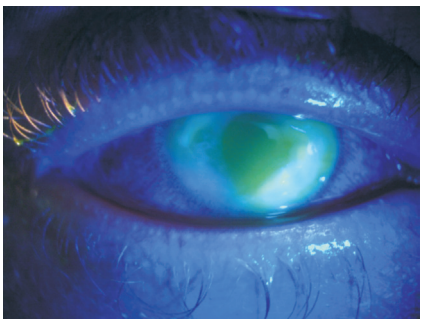

Figure 2 The cobalt blue filter shows corneal staining with fluorescein 2% of the epithelial defect overlying the larger infiltrate.

twice daily OU to the lids. On day 4, patient was noted to be improving clinically with the epithelial defect measuring less than 0.5 mm and dense infiltrate measuring 1.5×1.5 mm^2. He had almost complete resolution of his ocular symptoms and was discharged home for outpatient follow up.

On final follow up, 2wk post discharge, patient had received no further dupilumab treatment. His BCVA was 6/9 OD and 6/7.5 OS. His intraocular pressure (IOP) was 12 mm Hg OD and 17 mm Hg OS. His right eye had no further epithelial defect or stromal opacities and the left eye had some very mild peripheral punctate opacities. The blepharitis was noted to be mild OU, and the bilateral ectropions had largely resolved.

The onset of corneal ulceration, in a previously healthy cornea, in relation to the commencement of dupilumab treatment is highly suggestive of a dupilumab-induced effect. The patient had no previous history of ocular surface disease, and the corneal ulceration completely resolved with topical steroid treatment and cessation of dupilumab.

Associated with a genetic predisposition, atopic dermatitis is a chronic inflammatory skin disease, affecting 10% of adults and 20% of children worldwide. It is a complex immune and autonomic dysfunction disorder with a pathogenesis determined by Th2-mediated inflammation[1-2]. Characterised by severe pruritus, the mainstay of treatment has been topical corticosteroids. However, for the 20% of patients who suffer from moderate-to-severe atopic dermatitis, the requirement for prolonged topical and oral steroid use can result in severe side effects such as hypothalamo-pituitary adrenal (HPA) axis suppression and skin atrophy[2]. Dupilumab is a recently introduced systemic monoclonal antibody used in the treatment for moderate-to-severe atopic dermatitis. It works by binding to the alpha subunit of the interleukin (IL)-4 and IL-13 receptor, blocking the downstream signalling cascade of IL-4 and IL-13, downregulating inflammatory mediators and upregulating structural proteins, lipid metabolism proteins, and epidermal barrier proteins[1,5-6]. It is also reported to reduce serum levels of CCL17, a main regulator of Th2-mediated immunity[1-3]. Dupilumab has shown efficacy in the treatment of atopic dermatitis both in clinical trials and systematic review, observing a 70% reduction in Eczema Area and Severity Index (EASI) scores after 16wk of treatment[3-4]. The most commonly reported adverse side effect of dupilumab is conjunctivitis with 26.1%[3-4,7]. More common in patients with severe atopic dermatitis or previous episodes of allergic conjunctivitis, most cases were mild to moderate and resolved by the end of the treatment period[3-4]. In most studies the type of conjunctivitis was not described. Blepharitis was present in 9.6% and keratitis in 6.2%[3-4,7]. In most cases, keratitis only involved the superficial cornea, with diagnosis of superficial punctate keratopathy, inferior punctate keratitis or dry eye. More serious cases of ocular surface disease have been described, including a case of unilateral corneal ulceration, a cicatrising blepharoconjunctivitis with punctal stenosis and cicatricial ectropion and a case of conjunctival cicatrisation and symblepharon formation[5,8-9].

The pathogenesis of dupilumab-associated ocular adverse effects remains unclear. With dupilumab inhibiting goblet cell and mucin production through IL-4 & IL-13 blockade this may contribute to tear film insufficiencies and subsequent corneal erosions[10]. Other plausible hypotheses postulate the unmasking of pre-existent subclinical atopic or allergic inflammatory processes; increased expression of pro-inflammatory molecules (*i.e.*, OX40L) and a local immunodeficiency resulting in local bacterial and viral infections[6]. Interestingly, there was no apparent difference in ocular adverse effects between dupilumab and placebo in patients treated for other allergic disease such as asthma, nasal polyposis or eosinophilic oesophagitis[3-4]. This suggests that rather than the effect of dupilumab being the implicit cause of ocular surface disease, there may be an underlying inflammatory mechanism (or co-existing ocular condition) associated with the interaction between atopic dermatitis and dupilumab. With an association between atopic dermatitis and a higher incidence of ocular surface disease, we postulate that combined with the effect of tear film disruption and subsequent dry eye of dupilumab, may create a compounding environment that predisposes an individual to ocular surface diseases such as keratitis.

It is also noted that the patients' lower eyelid ectropions were largely resolved on final follow up. This is likely due to the clinical improvement of the patients inflamed, blepharitic eyelid margins after cessation of dupilumab and the implementation of medical treatment. Recent reports of eyelid related adverse effects, including ectropion, associated with dupilumab use warrants further ongoing research[11].

As the use of dupilumab increases in the population, we may see an increase in associated ocular surface disease, including corneal ulceration. Dermatologists prescribing dupilumab should be aware of these risks and be vigilant for ocular symptoms such as changes in vision, pain, redness and discharge. We also believe that these patients should have a prompt evaluation with an ophthalmologist to exclude any corneal infiltration.

ACKNOWLEDGEMENTS

Conflicts of Interest: Wilson MM, None; **Roberts PK,** None; **Daniell M,** None.

REFERENCES

1 Gooderham MJ, Hong HCH, Eshtiaghi P, Papp KA. Dupilumab: a review of its use in the treatment of atopic dermatitis. *J Am Acad Dermatol* 2018;78(3 Suppl 1):S28-S36.

2 Mayba JN, Gooderham MJ. Review of atopic dermatitis and topical therapies. *J Cutan Med Surg* 2017;21(3):227-236.

3 Wang FP, Tang XJ, Wei CQ, Xu LR, Mao H, Luo FM. Dupilumab treatment in moderate-to-severe atopic dermatitis: a systematic review and meta-analysis. *J Dermatol Sci* 2018;90(2):190-198.

4 Halling AS, Loft N, Silverberg JI, Guttman-Yassky E, Thyssen JP. Real-world evidence of dupilumab efficacy and risk of adverse events: a systematic review and meta-analysis. *J Am Acad Dermatol* 2021;84(1):139-147.

5 Li G, Berkenstock M, Soiberman U. Corneal ulceration associated with dupilumab use in a patient with atopic dermatitis. *Am J Ophthalmol Case Rep* 2020;19:100848.

6 Wohlrab J, Werfel T, Wollenberg A. Pathomechanism of dupilumab-associated inflammatory eye symptoms. *J Eur Acad Dermatol Venereol* 2019;33(11):e435-e436.

7 Akinlade B, Guttman-Yassky E, de Bruin-Weller M, *et al*. Conjunctivitis in dupilumab clinical trials. *Br J Dermatol* 2019;181(3):459-473.

8 Levine RM, Tattersall IW, Gaudio PA, King BA. Cicatrizing blepharoconjunctivitis occurring during dupilumab treatment and a proposed algorithm for its management. *JAMA Dermatol* 2018;154(12):1485-1486.

9 Lee DH, Cohen LM, Yoon MK, Tao JP. Punctal stenosis associated with dupilumab therapy for atopic dermatitis. *J Dermatolog Treat* 2021;32(7):737-740.

10 Gooderham M, McDonald J, Papp K. Diagnosis and management of conjunctivitis for the dermatologist. *J Cutan Med Surg* 2018;22(2):200-206.

11 Park S, Lee JH, Park JH, Park SH, Park SY, Jung YW, Choi SA. Ocular surface disorders associated with the use of dupilumab based on WHO VigiBase. *Sci Rep* 2021;11(1):14293.