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Delayed periocular dermatitis as a rare side-effect of topical anti-glaucoma eyedrop instillation in two Shih-Tzu dogs with atopic dermatitis

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ABSTRACT

Two Shih-Tzu dogs with atopic dermatitis presented with delayed periocular dermatitis (PD) following the instillation of dorzolamide and dorzolamide/timolol combination eyedrops; the development of dermatologic signs took 94 and 104 d in cases 1 and 2, respectively. Hypersensitivity to anti-glaucoma eyedrops was highly suspected, and treatment was discontinued. Delayed PD was significantly relieved in cases 1 and 2, at days 155 and 64 after discontinuation, respectively. In this study, the clinical characteristics and progression of delayed PD were described to inform clinicians who may encounter this rare side effect.

Keywords: Atopic dermatitis; carbonic anhydrase inhibitor; dorzolamide; delayed periocular dermatitis; hypersensitivity

INTRODUCTION

Dorzolamide is a carbonic anhydrase inhibitor (CAI) that lowers intraocular pressure (IOP) by reducing bicarbonate production and consequently decreasing aqueous humor production [1]. It has long been used to manage canine glaucoma, and complications associated with its use have been reported [2]. Ocular irritation, conjunctivitis, blepharitis, and keratitis are well-known adverse effects [1,3]. However, periocular dermatitis (PD) has rarely been reported in either dogs or humans [1,4].

Hypersensitivity reactions can cause PD, which may be associated with various environmental contact allergens [5]. Some eyedrops, including dorzolamide, timolol, pilocarpine, and preservatives, are well-known contact allergens [6,7]. The associated allergic reactions can be easily misdiagnosed as periorbital cellulitis or infectious lesions [8] as many skin diseases induce similar clinical signs [9], and PD caused by eyedrops is a relatively rare condition [5,10].

Therefore, this study aimed to present cases of delayed PD caused by eyedrop administration and to suggest its proper management in dogs.

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Conflict of Interest
The authors declare no conflicts of interest.

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CASE PRESENTATION

Case 1

A 15-year-old spayed female Shih-Tzu presented with chronic glaucoma caused by anterior lens luxation of the cataractous lens in the right eye (OD). The dog was diagnosed with secondary glaucoma OD 1 mon before referral and was subsequently treated with 2% dorzolamide/0.5% timolol (Cosopt®; MSD, Korea) and neomycin-polymyxin B-dexamethasone (Maxitrol®; Alcon Laboratories Inc., USA) by the referring veterinarian. At the initial presentation, buphthalmos and moderate conjunctival hyperemia were observed in the OD. The left eye (OS) showed a fibrotic, chronic phthisical change with a hypermature cataract. The IOP was 25 mmHg (OD). The menace response, dazzle reflex, and direct pupillary light reflex were absent.

End-stage glaucoma OD was diagnosed, and an intravitreal cidofovir injection was administered for the pain relief salvage procedure. After the procedure, Cosopt® was prescribed three times a day (TID) for 10 d for OD.

The dog was re-presented 14 d later. After discontinuation of Cosopt® for 4 d, the OD was still hypertensive, with an IOP of 35 mmHg. However, because of the absence of clinical signs associated with ocular hypertension or pain, the dog's owner refused additional intravitreal injections of cidofovir. Therefore, Cosopt® TID in the OD and 0.3% sodium hyaluronate (Hyalein®; Santen Pharmaceutical, Japan) PRN in both eyes were administered.

After an additional 50 d of instillation of Cosopt®, the dog's owner initially reported a periocular skin abnormality. The photographs sent by the owner showed periocular erythema, lichenification, hyperpigmentation, and alopecia (**Fig. 1A**). Delayed PD caused by hypersensitivity to Cosopt® was considered, and Cosopt® was subsequently discontinued, with only the continuation of hyaluronate treatment.

The dog was taken to the ophthalmology department 8 d after delayed PD was reported. The IOP was lower than normal at 5 mmHg, so only hyaluronate was maintained. Dermatological examinations of the periocular lesions were performed by the dermatology department of the same hospital. Mild erythema, alopecia, lichenification, and hyperpigmentation were observed on the periocular skin of the OD. In addition, mild erythema and crust were observed in the forepaws and perianal areas. To rule out infectious diseases, glass slide impressions and hair plucking tests were performed to identify infectious microorganisms. The onset of delayed PD was believed to be related to the instillation of anti-glaucoma eyedrops, as distinct lesions were not observed in the OS (eyedrops were not administered), but were observed in the OD. Systemic atopic dermatitis was tentatively diagnosed by excluding other possible causes through a dermatological examination, detailed history taking, and interpretation of the clinical characteristics of the dog. As contact hypersensitivity to Cosopt® was strongly indicated, an elimination trial treatment was considered. Furthermore, after only 8 d of discontinuation of Cosopt®, the dog's owner noticed a partial improvement in delayed PD.

A significant improvement in delayed PD was observed 25 d after discontinuing Cosopt® (**Fig. 1B**). The 155 d after discontinuing the drug, the OD showed normalized periocular skin without use of any further medication (**Fig. 1C**). Until the last follow-up on day 422, no delayed PD or recurrence of symptoms were observed.

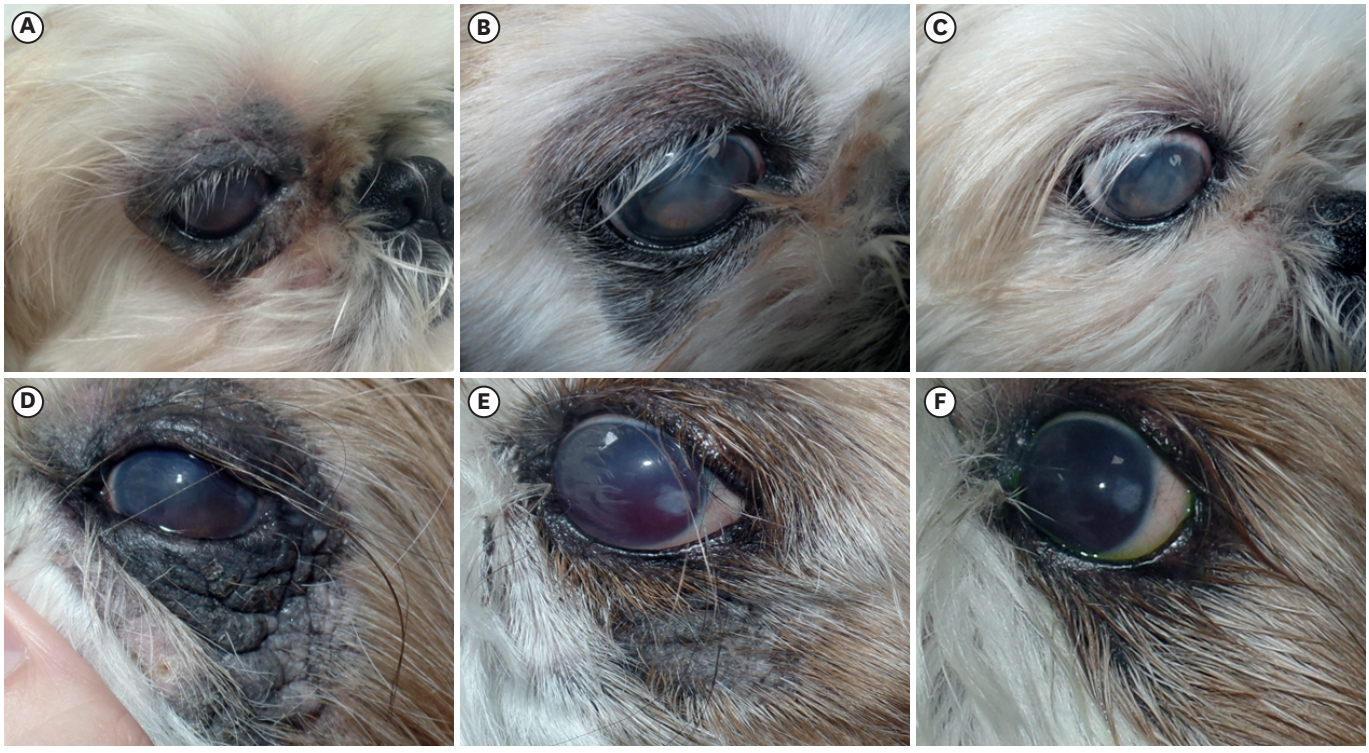

Fig. 1. Clinical presentation and progression of delayed PD induced by topical dorzolamide and dorzolamide/timolol combination in two dogs. (A-C) Case 1; (D-F) Case 2. (A, D) The initial presentation with periocular skin problem in cases 1 and 2, respectively (day 0). Note the appearance of periocular erythema, lichenification, hyperpigmentation, and alopecia. Dermatologic examination, history, and clinical characteristics strongly indicated hypersensitivity to topical anti-glaucoma eyedrops. (B, E) After discontinuation of anti-glaucoma eyedrops, a significant improvement in delayed PD was observed in both cases (days 25 and 36, in cases 1 and 2, respectively). (C, F) Delayed PD showed more improvement compared to previous examination (days 155 and 64, in cases 1 and 2, respectively). PD, periocular dermatitis.

Case 2

A 15-year-old castrated male Shih-Tzu presented to the emergency room with red-eye OS. At the initial evaluation, the IOP of the OS was 45 mmHg, and menace response and dazzle reflex were absent due to hyphema with ocular hypertension OS. Incipient cataract OD and secondary uveitic glaucoma OS were diagnosed, and topical medication of 2% dorzolamide (Trusopt®; MSD) TID in the OS and 0.3% sodium hyaluronate TID in both eyes were to be administered for 2 d.

The dog was re-evaluated 2 d later at the ophthalmology department of the same hospital. The IOP of the OS had decreased to 10 mmHg. Severe hyphema concealed the posterior part of the eye; therefore, ocular ultrasonography was performed, and posterior lens luxation was confirmed. No signs of intraocular mass were observed on the ultrasonography. As the IOP was adequately controlled, the prescription for the OS was reduced to 2% dorzolamide BID. To treat uveitis, a subconjunctival injection of 4 mg of triamcinolone (Udenolon; Kukje Pharm, Korea) was administered in the OS. In both eyes, topical administration of 0.3% sodium hyaluronate was maintained, and use of topical cyclosporine ointment (Optimmune®; Schering Plough Animal Health, USA) BID was resumed, as prescribed by a referring veterinarian.

At follow-up (104 d after dorzolamide instillation), the dog presented to the ophthalmology department with delayed PD OS, showing clinical signs that included lichenification, erythema, hyperpigmentation, and alopecia (**Fig. 1D**). For more than a year, this dog had received ear

cleaning and medicated shampoo for atopic dermatitis, but this time he had severe localized skin symptoms only around the OS. A hair plucking test and slide glass impression test were performed by the dermatology department of the same hospital, revealing no infectious agents. Considering the dog's history and dermatologic examination results, hypersensitivity to topical dorzolamide was strongly indicated; therefore, an elimination trial for dorzolamide was recommended by the consulting dermatologist. Furthermore, since IOP had stabilized at 4 mmHg, 2% dorzolamide was discontinued and only artificial tears were prescribed PRN. The follow-up appointment was scheduled for 1 mon later.

A significant improvement in delayed PD was observed at 36 d after dorzolamide discontinuation (**Fig. 1E**), and delayed PD showed much improvement at 64 d after dorzolamide discontinuation (**Fig. 1F**).

DISCUSSION

The prevalence of topical eye drop-induced PD in patients with atopic dermatitis remains controversial [6,11,12]. In a previous study, patients with atopic dermatitis were found to be less sensitive than those who did not have the condition [12]. However, other studies have supported the popular hypothesis that patients with atopic dermatitis may be more sensitive to the ingredients of eyedrops; therefore, chronic use of anti-glaucoma eyedrops might be a predisposing factor to developing PD [6,11]. In this study, both dogs that expressed PD had atopic dermatitis as an underlying disease. In case 1, atopic dermatitis was diagnosed when PD occurred, and in case 2, the dog had been treated for atopic dermatitis for more than 1 yr. Blepharoconjunctivitis is known to commonly occur in association with atopic dermatitis in humans and dogs [13], and both cases in this study involved delayed PD, as well as atopic dermatitis-related blepharoconjunctivitis. This may be because the potential for blepharitis in the eye receiving topical ophthalmic solutions may result in additional lesions [14]. Therefore, for dogs that are treated or show symptoms of atopic dermatitis and need to use eyedrops periodically, PD should be considered a possible side effect of the instillation of eyedrops. However, since only two cases of Shih-Tzu dogs were investigated in this study, further studies on more canine patients considering different ages, sexes, and especially breeds would be necessary.

In the present cases, dorzolamide was suggested to be a contact allergen that induces delayed PD. However, in case 1, it was difficult to determine which compound induced hypersensitivity because dorzolamide, timolol, and the preservative contained in the eyedrops (e.g., benzalkonium chloride) were discontinued together as a combination eyedrop. There have been no previous reports of ocular complications associated with topical timolol instillation in dogs [1,7]. However, timolol, along with dorzolamide, may still be a cause of delayed PD. Side effects of topical dorzolamide instillation have occasionally been reported, which include keratitis and blepharitis, as well as irritation of tissues due to low pH [1]. Furthermore, the delayed PD pattern observed in case 1 was similar to the lesion caused by dorzolamide alone in case 2. Therefore, in this study, dorzolamide was more likely to cause hypersensitivity manifesting as delayed PD. A patch test that provides clues to the allergen involved could have been performed to determine the exact cause of hypersensitivity [15]; however, it was not performed in this case.

The onset of hypersensitivity has been reported to vary between patients [7,16]. Hypersensitivity was first observed following the initiation of topical anti-glaucoma eyedrop

instillation in cases 1 and 2, after 94 and 104 d, respectively. A previous study reported a median of 266 d (range, 133–679 d) for the occurrence of adverse effects after CAI eyedrop instillation in dogs [7]. These results are similar to those of a human counterpart study, that reported a range of 90–360 d of delayed onset [16]. When hypersensitivity occurs, the most important factor for healing is the discontinuation of contact allergens [9]. A previous report revealed inflammatory lesions on histopathological examination in dogs with CAI-induced keratitis that failed to respond to steroid treatment [7]. Instead, the lesion improved 12–25 d after discontinuing topical dorzolamide. No further recurrence was observed until the median follow-up time (25.5 mon) [7]. Similar outcomes have been reported in humans, where PD caused by hypersensitivity to eyedrops is resistant to topical corticosteroid therapy, and the lesion is usually persistent until the eyedrops (contact allergen) are discontinued [9]. The results of this study were consistent with those of previous studies [7,9]. In this study, delayed PD started to regress significantly after discontinuation of anti-glaucoma eyedrops without steroid therapy at 25 and 36 d in cases 1 and 2, respectively, and no recurrence was observed until the final follow-up. Therefore, in this study, discontinuation of anti-glaucoma eyedrops was shown to be the most important treatment for delayed PD, as it was in previous studies.

In conclusion, delayed PD should be considered as a potential adverse effect of topical eyedrop instillation in dogs, particularly when associated with atopic dermatitis. To the best of our knowledge, this is the first case report of delayed PD following instillation of topical anti-glaucoma eyedrops in dogs with atopic dermatitis. Chronic use of eyedrops may increase the possibility of side effects. Recognition of the causative agent and its elimination are essential steps to achieve complete regression of the adverse effects. Additionally, patch tests would be helpful in determining the causative agent.

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