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Bilateral Triamcinolone Induced Subconjunctival Granuloma in the Treatment of Scleritis Accompanied by Scleral Ectasia in a Dog

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Abstract : A 6-year-old spayed female American Cocker Spaniel presented with episcleritis in the right and then the left eye (OS) at eight month interval. Repeated intralesional triamcinolone acetonide was administered subconjunctivally to both eyes (OU). During this period, scleral ectasia was revealed on ocular funduscopy OS and then confirmed on ultrasonography and computed tomography. A year later, conjunctival hyperemia occurred around remnant triamcinolone particles and was treated by resection of these particles in the OU. A recurrence of episcleritis, which did not regress, required repeated triamcinolone subconjunctival injections four months later in the OU. Four months after these injections OU, the dog was presented with bilateral conjunctival mass, which had developed over the previous month. The round-shaped masses with diameters of 1 cm were surgically resected from exposed scleral ectasia lesion of thin and bulging scleral surface in the OU. The cross-section of both masses showed a white-colored accumulation at the center and triamcinolone induced granulomas enclosing necrotic tissue were confirmed by impression cytology and histopathological examination.

Key words : episcleritis, granuloma, scleritis, scleral ectasia, triamcinolone.

Introduction

Corticosteroid agents are injected subconjunctivally as a supplement to other routes for the administration of steroids in severe inflammatory diseases of the eye (19). Subconjunctival injection is known to be a very effective method for accomplishing a high drug concentration in the anterior ocular segment as it bypasses the epithelium and penetrates transsclerally (14).

Triamcinolone acetonide is one of the corticosteroid suspensions frequently used for intralesional or subconjunctival administration in dogs (14,19). The triamcinolone repositol preparation is known to be effective for up to 2~3 weeks. Complications that have been reported following periocular injection of corticosteroids in humans include globe perforation, ocular hypertension, conjunctival necrosis, cataract formation, blepharoptosis and granuloma formation (4). There have been rare reports of the occurrence of complications following subconjunctival injection of triamcinolone acetonide in dogs.

Inflammatory diseases involving episclera and sclera have been reported as the most common scleral diseases, but uncommon compared with other ocular diseases in dogs (13). Episcleritis and scleritis are known to be immune-mediated, may be associated with keratitis, uveitis, panophthalmitis, or chronic glaucoma, and usually responsive to corticosteroid therapy (13).

This case report present a case of bilateral subconjunctival granuloma formation induced by previous triamcinolone subconjunctival injections used to treat bilateral episcleritis and discusses the disease progression in a dog.

Case

A 6-year-old spayed female American Cocker Spaniel was presented with conjunctival hyperemia of the left eye (oculus sinister: OS) of 2 months duration. On history and physical examination, the abnormalities were limited to the ocular signs. The neuro-ophthalmic examinations, including menace response, dazzle and pupillary light reflexes, were normal in both eyes (oculus uterque: OU). On complete ophthalmic examination, including a tear production test (Schirmer tear test®, Schering Plough Animal Health, Kenilworth, NJ, USA), tonometry (Tonopen XL®, Mentor, Norwell, MA, USA), slit lamp biomicroscopy (SL-D7, Topcon Corp. Tokyo, Japan) and ophthalmoscopy (Vantage Indirect Ophthalmoscope®, Keeler Ltd., Windsor, UK), episcleritis accompanied by mild thickening of the lateral sclera with adjacent corneal edema was tentatively diagnosed (Fig 1A). Intraocular pressure (IOP) values were 19 mmHg in the right eye (oculus dexter: OD) and 11 mmHg in the OS, showing no flare with no fundus abnormalities in the OU. A mixture of triamcinolone acetonide (4 mg; Udenolon®, Kukje Pharm, Ansan, Republic of Korea) and gentamicin (4 mg; Gentapro®, Huons Co Ltd, Sungnam, Republic of Korea) was

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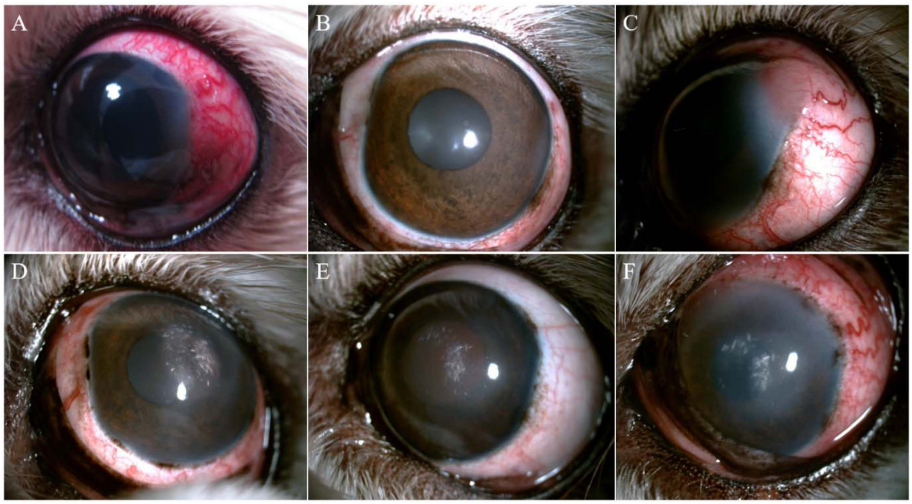

Fig 1. Appearance of the left eye (OS) in chronological order: (A) Initial presentation (first triamcinolone injection OS); (B) 1 month later; (C) 4 months later (second triamcinolone injection OS); (D) 8 months later; (E) 6 months later; (F) 5 months later (fourth triamcinolone injection OS). It was then four months before the conjunctival mass development.

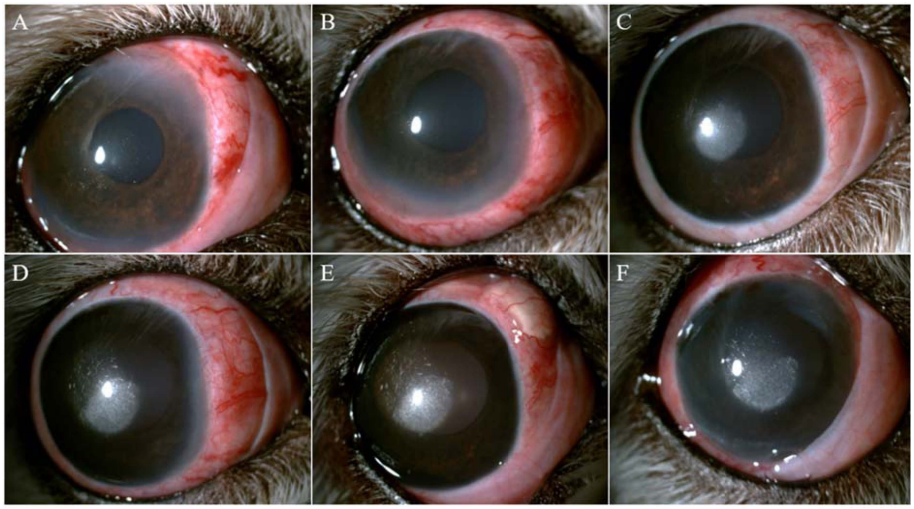

Fig 2. Appearance of the right eye (OD) in chronological order: (A) Initial presentation at eight months after OS initial presentation (first triamcinolone injection OD); (B) 5 months later (second triamcinolone injection OD). The same date as Fig. 1-D; (C) 2 months later (third triamcinolone injection in both eyes); (D) 4 months later (fourth triamcinolone injection OD). The same date as Fig. 1-E; (E) 1 month later. Both eyes showed conjunctival hyperemia around remnant triamcinolone particles; (F) 4 months later (fifth triamcinolone injection OD). It was four months before the conjunctival mass development, which was the same date as Fig. 1-F.

administered subconjunctivally (OS-1st) and neomycin-polymyxin B-dexamethasone (NPD) ophthalmic suspension (Maxitrol®, Alcon Laboratories, Fort Worth, TX, USA) and 0.2% cyclosporine ophthalmic ointment (Optimmune®, Schering-Plough Animal Health, Kenilworth, NJ, USA) were applied topically to the OS.

One month after treatment, the episcleritis lesion had resolved (Fig 1B). However, four months later, during the subsequent tapering off of topical agents, the episcleritis recurred in a more prominent nodular form at the same site (Fig 1C). A repeat intralesional triamcinolone injection (OS-2nd) was performed, the dosing frequency of the previous topical agents to the OS was increased, and 1% prednisolone acetate ophthalmic suspension (Pred Forte®, Allergan, Seoul, Republic of Korea) was added.

Three months later, i.e., eight months after the initial presentation of the OS, the OD also developed episcleritis with multiple raised scleral lesions and with corneal edema near the limbus (Fig 2A). An intralesional triamcinolone injection (OD-1st) was administered subconjunctivally and the same topical agents as for the other eye were prescribed. However, five months later, the episcleritis had persisted or rather progressed (Fig 2B) necessitating a repeat subconjunctival triamcinolone injection in the OD (OD-2nd). At the same time, scleral ectasia was suspected on the ocular fundus of the OS as examined by indirect ophthalmoscopy (Fig 3A-C). Ocular B-scan ultrasonography (Fig 3D and E) and computed tomography (Fig 3F) revealed a bulging of the sclera in the OS.

Two months later, a third subconjunctival injection of tri-

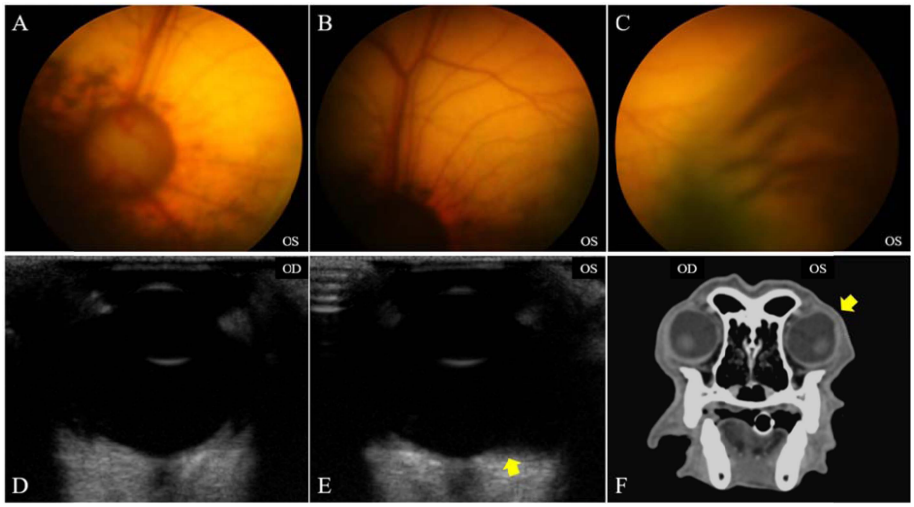

Fig 3. Fundus appearances and representative images of 10 MHz ocular ultrasonography and CT scanning. (A), (B) and (C) The left eye showed wrinkled retinal ingression at lateral fundus. The right eye showed normal fundus; (D) and (E) scleral ectasia in the left eye (arrow) was revealed on ultrasonogram; (F) The CT image also showed scleral ectasia in the left eye (arrow).

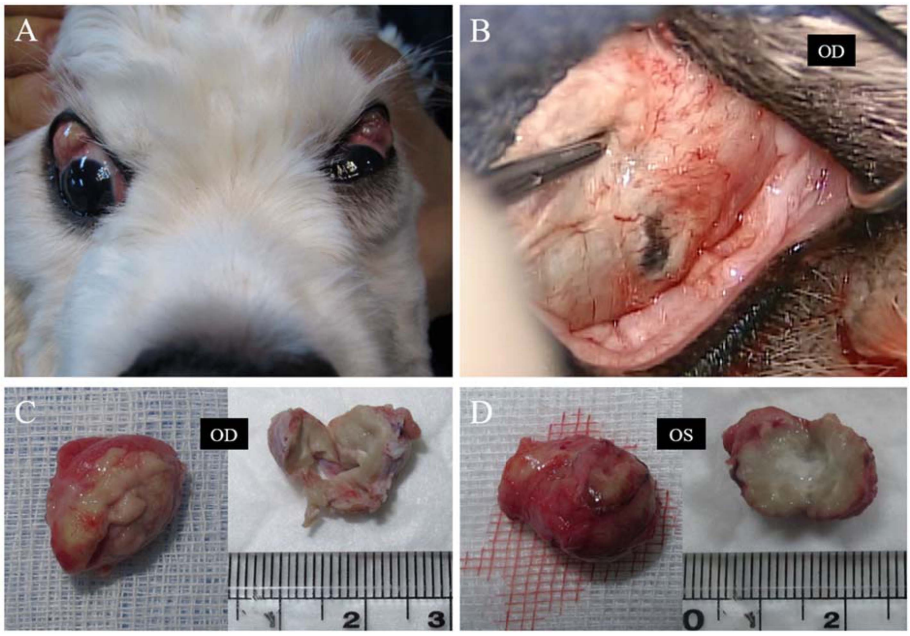

Fig 4. Bilateral conjunctival masses in a 6-year-old American Cocker Spaniel. (A) Front view; these masses occurred at dorsolateral bulbar conjunctival sites in both eyes. (B) After the mass resection, the sclera was bulging in both eyes and extremely thin surface was exposed in the right eye (OD), at which the uvea was almost exposed. (C) and (D) Gross appearance of the resected masses; the masses were round-shaped with a diameter of 1 cm and the cross-section of these masses revealed wide necrotic area at the center of each mass.

amcinolone (OD/OS-3rd) was administered in the OU (Fig 2C) and a fourth injection in the OD (OD-4th) was performed 4 months later (Fig 2D). During this period, corneal infiltration with lipid degeneration became obvious in the OU, even though serum total cholesterol, triglyceride levels and thyroid function test results were within normal range (Fig 1D-F and 2C-F). One month later, conjunctival hyperemia occurred in the OU around remnant triamcinolone particles (Fig 2E). These triamcinolone particles were resected through conjunctival incision in the OU under topical 1% proparacaine anesthesia (Alcaine®, Alcon, Fort Worth, TX, USA) and healed well. There was then a recurrence of the episcleritis, which did not regress despite topical application of NPD and cyclosporine, requiring a repeat triamcinolone subconjunctival injection (OD-5th/OS-4th) 4 months later in the OU (Fig 1F and 2F). Four months after these injections OU, the dog was presented with bilateral dorsal conjunctival masses that had developed during the previous month (Fig 4A). These masses occurred at dorsolateral bulbar conjunctival sites in the OU. Both eyes were able to close completely and there were no corneal lesions involved in the exposure keratitis. Preoperative complete blood count, serum chemis-

try, and thoracic radiography were performed and showed no significant findings.

General anesthesia was induced through routine procedures and maintained using isoflurane (Ifran Solution®, Hana Pharm, Seoul, Republic of Korea) inhalation. Both eyes were aseptically prepared with diluted 0.5% povidone iodine solution after clipping. The conjunctiva was incised and partially resected together with the mass in the OU. Both masses were well delineated and loosely attached to the anterior Tenon's capsule on the surface of extremely thin and bulging sclera, which was exposed after the mass resection. In the OD, the sclera was so thin that the uvea was almost exposed (Fig 4B). A horizontal mattress suture was performed on the margin of the scleral ectasia. The conjunctiva was routinely closed and had healed well without apparent pain or inflammation 10 days after surgery. Topical application of NPD, 1% prednisolone acetate, and cyclosporine were maintained for the treatment of the episcleritis.

Both masses were round-shaped with a diameter of 1 cm. The cross-section of both masses OU showed a white-colored accumulation at the center of each mass (Fig 4C and D). On the application of impression cytology, chronic inflammation was identified (Fig 5), and then the masses were immediately fixed in 10% neutral buffered formalin. The presence of granuloma enclosing necrotic tissue was confirmed by histopathological examination, including the presence of macrophages and lymphocytes (Fig 6). No microorganisms or neoplastic lesions were detected. Triamcinolone particles could not be observed due to their dissolution in the presence of routine hematoxylin-eosin staining, but there were multiple empty spaces within both masses.

Four months later, 360° perilimbal corneal edema and infiltration with peripheral corneal neovascularization and severe conjunctival hyperemia developed in the OU (Fig 7E and F). Slit lamp biomicroscopy revealed mild aqueous flare in the OU with the IOP of 4 mmHg in the OD and 5 mmHg in the OS. The fundus examination using the indirect ophthalmoscope and a portable fundus camera (Genesis®, Kowa, Tokyo, Japan) revealed regional areas of retinal degeneration accompanied by multifocal pigmentation in the OU (Fig 7C and D), compared with previous fundus photographs (Fig 7A and B). Bilateral anterior and posterior diffuse scleritis was tentatively diagnosed by confirming uveitis and retinal involvement (8,9). Serum total cholesterol, triglyceride levels and thyroid function parameters were measured again and the results were normal with no significant changes in routine serum chemistry and electrolyte levels. A mixture of dexamethasone disodium phosphate (0.5 mg; dexamethasone jeil inj®, Jeil Pharm, Seoul, Republic of Korea) and gentamicin (4 mg) was administered subconjunctivally and topical NPD, 1% prednisolone acetate, and cyclosporine were applied. Additionally, oral prednisolone (0.2 mg/kg BID; Solondo Tab®, YuHan Corp., Seoul, Republic of Korea) was prescribed for two weeks and tapered thereafter.

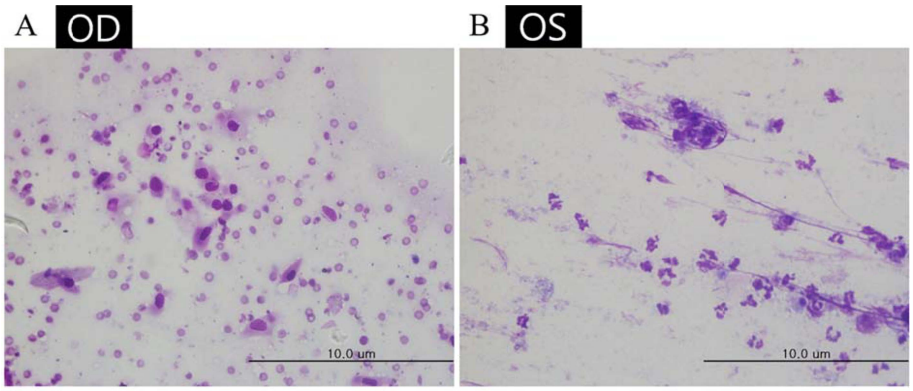

Fig 5. Microscopic images of the impression cytology of the mass of (A) the right eye and (B) the left eye, respectively (Bar = 10 μm). Chronic inflammation with the presence of non-degenerative neutrophils and macrophages was identified. There is no evidence of microorganisms.

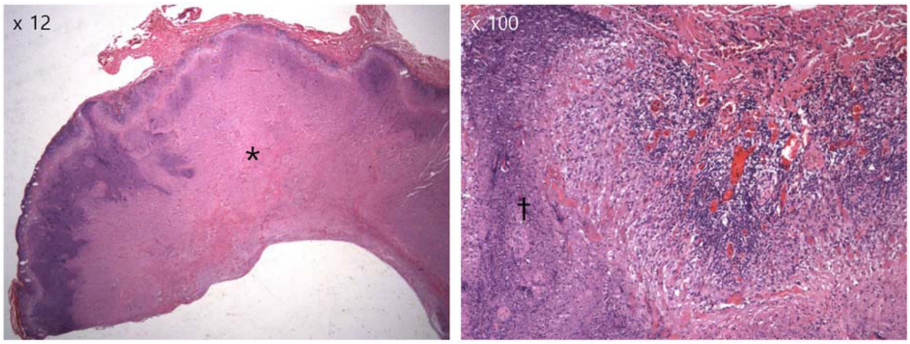

Fig 6. Histopathologic appearance of the masses. Granuloma enclosing necrotic tissue (*) was confirmed by histopathological examination, with the presence of neutrophils, macrophages, and lymphocytes (†). Microorganisms and neoplastic lesions were not detected.

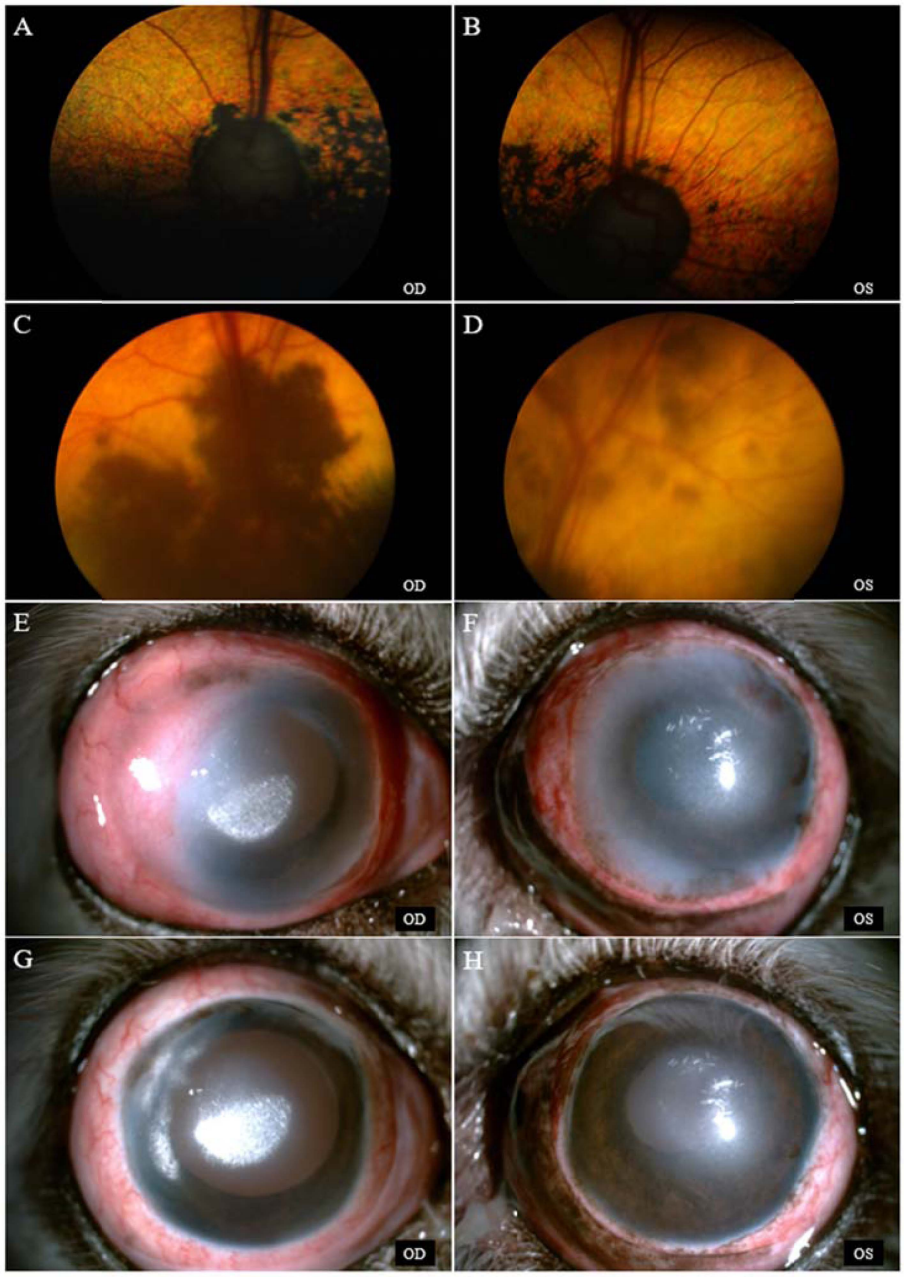

Fig 7. Fundus and clinical appearances showing scleritis progression. (A) and (B) Normal fundus of the right (OD) and the left (OS) eye. (C-F) Two years after the A and B, retinal degeneration accompanied by multifocal pigmentation was revealed with recurrent and progressed scleritis in both eyes. (G) and (H) The conjunctival hyperemia and perilimbal corneal edema were improved 3 months after treatment.

Three months later, there was improvement of the conjunctival hyperemia, perilimbal corneal edema and uveitis OU (Fig 7G and H). Slit lamp biomicroscopy revealed no aqueous flare with regressed uveitis in the OU. The IOP was 9 mmHg in the OD and 11 mmHg in the OS. The retinal degenerative lesions did not progress with the menace response remaining positive in the OU.

Discussion

In this case, subconjunctival mass formed during treatment for recurrent episcleritis, occurring bilaterally, with triamcinolone subconjunctival injections. Conjunctival neoplasia, inflammatory nodules, cysts, or displaced orbital fat were all considered in differential diagnoses for the subconjunctival mass (12). Triamcinolone crystals have been known to induce inflammation (4). In the current case, eight months before the granuloma formation OU, and one month after the OS-third and the OD-fourth subconjunctival injections of triamcinolone, conjunctival hyperemia had developed around the triamcinolone particles only. These particles were removed by conjunctival incision and the conjunctival hyperemia subsided in the OU. In spite of maintaining topical application of eye drops, episcleritis recurred 4 months later

in the OU and there was no choice but to subconjunctivally inject additional triamcinolone for the OS-fourth and OD-fifth (20). Four months later, granulomas had formed at the dorsal conjunctiva in both eyes. The gross appearance after transecting both masses showed white-colored material, similar to triamcinolone particles, accumulated at the center of each mass. However, in this study, the triamcinolone material was not visually evident on histopathological examination. A previous study described that triamcinolone particles can be dissolved during the pathologic processing with only empty spaces remaining after dehydration of the tissue sample (4); this describes what was seen in the histopathologic sample in this study. In the previous study, triamcinolone particles were distinctly demonstrated by examination of the frozen specimen using polarized light (4).

Granuloma formation resulting from the periocular injection of repository triamcinolone has been reported recently in humans (1,4,5,7). In veterinary medicine, this complication of granuloma formation has been reported following subconjunctival injection with methylprednisolone acetate in three dogs (6) and following subconjunctival injection with triamcinolone in two dogs (10). However, to the best of the authors' knowledge, this is the first report of large granulomas arising bilaterally in dogs after triamcinolone subconjunctival injection for the treatment of scleritis and accompanied by scleral ectasia. Scleral ectasia has been reported to result from scleral thinning secondary to the resolving of scleritis (3,8,16). Scleritis was known to divide into nonnecrotizing granulomatous and rare necrotizing granulomatous scleritis (13). There is a breed predisposition in the spaniel breeds, especially the American Cocker Spaniel, commonly diagnosed bilaterally, similar to the dog in this case study (8,9). Scleral inflammation can extend into adjacent uvea in advanced cases, and lead to anterior uveitis and/or choroiditis, with secondary retinal involvement, as seen in this case. Anterior scleritis has been reported as accounting for 99% of most cases of scleritis (17). In humans, scleritis may or may not be associated with systemic inflammatory disease (13,17). In 30-40% of patients with scleritis, underlying systemic disorders were described and the treatment of scleritis was known to be partially dictated by the systemic disorders (17). However, it was reported that clinical laboratory parameters measured at diagnosis in systemic collagen diseases were mostly negative in dogs with scleritis (13). In the current case, no other body organ was involved with this disease process. A limitation of this report is the absence of histopathologic confirmation using partial thickness biopsies at the scleral lesion. Nevertheless, our clinical findings could support the diagnosis of scleritis in that these lesions were resistant to topical therapy alone, associated with uveitis, retinal degeneration, and corneal stromal infiltration despite the normal range of serum lipid profile, and accompanied by scleral ectasia (8,9,13).

On the other hand, it has been suggested that periocular corticosteroid injections might promote scleral thinning and perforation. However, for resistant cases of non-necrotizing scleritis, subconjunctival triamcinolone injection has been known as an effective and safe method (20). The subconjunctival administration of corticosteroid suspensions is a treatment method with a prolonged effect as a large amount of the drug is absorbed transsclerally, which leads to minimal systemic side effects in recurrent, chronic, or severe inflammatory ocular disease, including episcleritis, anterior uveitis, and non-infectious keratoconjunctivitis in dogs (1,2,11,15,18-20). Subconjunctival corticosteroid injection can be especially appropriate in treating inflammatory ocular diseases in patients showing systemic conditions with potential side effects, including generalized infections, Cushing syndrome, diabetes mellitus, osteoporosis, and liver toxicity (19,20) or, especially in veterinary medicine, in uncooperative patients that do not tolerate topical treatment (19). Subconjunctivally injected triamcinolone has been known to persist for 7-10 days or 1-5 weeks and to have a prolonged effect when injected weekly in small animals (10). Encapsulation around a steroid depot was probably poorly penetrated thus making the steroid ineffective (4). Granuloma formation following subconjunctival injection of triamcinolone has been reported as an unusual complication, so such injection would be considered in ocular disease requiring intensive anti-inflammatory treatment (10).

Conclusion

Bilateral subconjunctival granulomas developed by triamcinolone subconjunctival injections on eyes diagnosed with episcleritis. Previous long-acting steroid injection should be considered during differential diagnosis of conjunctival mass in dogs. Scleral ectasia was incidentally found and suturing the site of the scleral thinning along with surgical resection of the granuloma was performed. Despite maintaining topical therapy, episcleritis progressed and posterior scleritis developed. Aggressive treatment including systemic, topical, and intralesional corticosteroids led to regression of the scleritis with maintaining vision and the eyes.

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