“A Shih Tzu’s Rendition of Queen’s ‘Under Pressure’”

Canine Primary Glaucoma

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Introduction:

In general, glaucoma most commonly occurs due to aqueous humor outflow impairment. The overarching categories of glaucoma are separated into primary and secondary causes.[4,6] Focusing on primary glaucoma, this classification is further divided into primary open-angle glaucoma (POAG) and primary closed-angle glaucoma (PACG). While differentiated based on the normal (open) or narrowed to closed appearance of the iridocorneal angle on gonioscopy, primary glaucoma is thought to have no associated disorder within the eye or systemically. Primary glaucoma is characterized as a bilateral disease with a presumed genetic component based on several breed predispositions.[3,4,5,6,8,9,10,11]

Canine PACG has been shown to be approximately eight times more common than POAG; thus, PACG will be the primary focus of this paper.[5,6] Breeds noted to have a genetic predisposition for PACG include, but are not limited to, the following: Basset Hound, Bouvier des Flanders, Chow-Chow, Cocker Spaniels (American and English), Dachshund, Flat Coated Retriever, Golden Retriever, Springer Spaniels (English and Welsh), Samoyed, and Siberian Husky.[3,5,6,8,10,11] There is discrepancy if sex acts as a predisposition to PACG among various breeds, but it is believed that females are more predisposed than males due to anterior chamber size difference.[3,5,6,8,9,11] Age-related ocular changes may alter aqueous humor flow as well as lead to glaucoma development.[3,8,9] Thus, PACG usually occurs in middle-aged to older dogs.[5,6,10] Clinical signs of glaucoma usually are in association with or a consequence of increased intraocular pressure despite the predisposing cause. Depending on the stage and duration of disease, clinical signs can range from only periodic episcleral injection to more progressive indications such as corneal edema, iris atrophy, mydriasis, buphthalmos, optic disc cupping, and

retinal and optic nerve degeneration.[2,5,6,8] Ocular pain, visualized as blepharospasm, serves as an indicator of increased intraocular pressure as well.[6]

Glaucoma can result in permanent blindness if not diagnosed promptly.[6,8] A thorough ophthalmic examination can help to differentiate PACG from other causes of glaucoma. Common diagnostic tools employed are direct and indirect ophthalmoscopy to visualize abnormalities within the anterior and posterior segments of the eye with detailed fundic examination, gonioscopy to visualize the iridocorneal angle, and tonometry to measure the intraocular pressure.[6,8,9] In order to determine if vision can be spared, acute and chronic cases must be differentiated. Medical therapy is less beneficial in end-stage disease. Treating the primary cause of glaucoma and surgical correction are usually more effective measures. In addition, it is important to evaluate the other eye to begin prophylactic treatment for primary glaucoma. While clinical signs usually appear unilaterally, it is a bilateral disease, so the other eye has a high risk for developing glaucoma in the near future.[1,2,4,5,6,10]

History and Presentation:

Shelby is an approximately 6-year-old, female spayed Shih Tzu who presented to the MSU-CVM Ophthalmology Service on May 29, 2019 for glaucoma of the right eye. Shelby's owners began noticing changes to her right eye approximately 2-3 weeks prior to presentation. A progression of clinical signs occurred over time beginning with redness to her right eye that progressed to swelling and haziness of approximately a 1-week duration. On May 28, 2019, her primary veterinarian noted bulging of her right eye with scleral hyperemia and an absent pupillary light reflex. Applanation tonometry (Tonopen) measured her right eye intraocular pressure to be elevated at 60 mmHg. The primary veterinarian prescribed latanoprost 0.005% ophthalmic solution (2 drops topically into the right eye BID) and referred her to Dr. Betbeze for

a suspect posterior lens luxation. The owners administered the latanoprost once the night prior to her presentation to MSU-CVM. Shelby had no previous history of ocular problems; however, she did have historical back pain and a recent episode of gastrointestinal upset at the beginning of April. She was taking unspecified joint supplements.

On presentation to MSU-CVM, Shelby was bright, alert, and responsive. She was obese with a body condition score of 7/9 and weighed 7.10 kg. Her heart rate was 120 bpm and her respiratory rate was panting. No temperature was taken. On auscultation, no arrhythmias, murmurs, crackles, or wheezes were appreciated. All other parameters were within normal limits.

On ophthalmic examination, her right eye had several abnormalities, including negative menace and tracking responses, which suggested a lack of vision. Her right eye was slightly buphthalmic with mild episcleral injection. The cornea was vascularized with pigmentation, and diffuse, mild corneal edema was present. She also had an absent dazzle reflex in the right eye with a mydriatic, fixed, and dyscoric pupil, which did not respond directly to light. An iris/ciliary body pigmented mass was seen laterally, and her lens was subluxated. The right anterior chamber had trace flare with vitreous present at the site of lens subluxation. Mild vitreal syneresis was seen in the right eye as well. The left eye had a positive menace response, tracking response, and dazzle reflex. The left eye had a normal size, position, and motility. A chalazion in the middle of the left dorsal eyelid and mild nasal entropion were present in her left eye, but her intraocular structures appeared normal. The left cornea had faint fibrosis ventromedially. Vitreal syneresis was noted in the left eye as well. Mild mucoid discharge was present bilaterally.

Diagnostic Approach & Considerations:

Initial diagnostics revealed a Schirmer tear test within normal limits bilaterally (16 OD/15 OS mm/min) and negative fluorescein stain bilaterally. Rebound tonometry (TonoVet)

measured an elevated intraocular pressure in her right eye and a normal pressure in her left eye (48 mmHg OD/20 mmHg OS). On fundic examination of her right eye, attenuated vessels and mild optic nerve cupping were noted. The left fundic examination was within normal limits.

Gonioscopy was also performed in her left eye, where pectinate ligament dysplasia with a narrow iridocorneal angle was observed. Analyzing the contralateral eye for iridocorneal angle and pectinate ligament abnormalities via gonioscopy is a valuable diagnostic tool to understand the structural abnormalities present in the affected eye that may be visually obstructed by ocular changes caused by the elevated intraocular pressure.

Because Shelby's right eye was irreversibly blind, had an elevated intraocular pressure despite medical therapy, and contained an iris/ciliary body mass, it was deemed necessary to obtain histopathology of the right eye via enucleation to relieve pain and accurately confirm her diagnosis of primary glaucoma. Histopathology was especially important, because she had abnormalities on gonioscopy which supported a diagnosis of primary glaucoma and an iris/ciliary body mass of the right eye, which can cause secondary glaucoma.

Pathophysiology:

While the exact pathophysiology is poorly understood, PACG classically occurs as a rapid and significant increase in intraocular pressure unilaterally in middle-aged to older dog breeds that appear to have a genetic predisposition.[2,5,6,10,11] Physiologically, aqueous humor has various pathways to leave the eye. The 'traditional outflow route' involves the aqueous humor entering from the posterior chamber and passing into the anterior chamber through the pupil. When exiting the eye, the aqueous humor goes through the pectinate ligaments into the trabecular meshwork of the ciliary cleft to the angular aqueous plexus and into the scleral venous plexus. After the scleral venous plexus, the humor is drained via episcleral and conjunctival

veins or via the vortex venous system, which ultimately enters the systemic circulation. While most of the aqueous humor exits via this route, the uveoscleral pathway removes the rest ultimately through either the supraciliary space or the suprachoroidal space.[6]

Multiple risk factors have been established for PACG. Pectinate ligament dysplasia (i.e., goniodysgenesis) appears to be associated with PACG as a risk factor but does not cause glaucoma alone.[2,3,5,6,8,9] This congenital condition is characterized by increased thickness to dysplastic sheets of pectinate ligaments spanning the trabecular meshwork and underlying structures to various degrees.[6,8,10,11] It is estimated that 1% of dogs with pectinate ligament dysplasia develops PACG.[6] The pectinate ligament dysplasia can relate to the iridocorneal angle narrowing, which is another factor linked to glaucoma initiation.[3]

In various breeds, genetic loci have been discovered that may predispose the patient to PACG. For example, CFA8 was identified in Dandie Dinmont terriers to be one gene involved in a polygenic disorder.[8] In Shih Tzu's with PACG, the *SRBD1* susceptibility gene seems to play a role in disease; therefore, while Shih Tzus are not commonly classified as high risk for PACG, risk factors for primary glaucoma are present.[4,5] Other potential risk factors associated with PACG include female predisposition, dim lighting, and stress/excitement.[3,5,6,8,9,11]

A theory has been developed that the inciting factor causing PACG begins at the pupil where outflow is disrupted. It is theorized that an increase in heart rate causes a larger amount of aqueous humor to enter the anterior chamber via the pupil while in systole. Because pectinate ligament dysplasia is present, the additional humor cannot exit due to lack of ability of the iridocorneal angle to provide the necessary channel. Age can also play a factor, because trabecular meshwork function becomes impaired, so the dog loses additional capacity to release the pressure increase caused by the larger amount of aqueous humor. When the pupil size is

midrange during this increase, a reverse pupillary block results. The iris presses against the lens causing a block during the next systole and further increases the anterior chamber pressure.[6,8,9] This pupillary block is significant in PACG pathogenesis, causing downstream iris pigment loss of the iris epithelium and inflammation.[7,8,9,11] These downstream effects appear to be inciting causes of glaucoma in dogs with PACG.[6,8,11] If the block persists, the iridocorneal angle and ciliary cleft continue to collapse downstream, creating additional challenges in treatment.[6]

Based on the intraocular pressure and other clinical signs, PACG is further divided into subcategories: latent, intermittent, acute congestive, postcongestive, chronic, and absolute. Latent refers to an eye that needs prophylactic therapy due to increased risk of developing PACG but is still normotensive. Absolute describes end-stage disease, where the eye is blind and often buphthalmic with secondary changes. Examples of secondary changes are buphthalmos and lens subluxation. Based on the stage of disease, treatment options vary.[6,8]

Treatment and Management:

Various treatment and management options are implemented based on the presence of vision of the PACG affected eye with the goal to reduce intraocular pressure.[1,6] In both cases, the primary cause should be identified.[6] If the eye is visual or thought to be early in disease (based on fundic exam changes), medical therapy should be instituted. Many types of medications have been prescribed for primary glaucoma with varying success: cholinergic agonists (e.g., pilocarpine), adrenergic agonists (e.g., dipivefrin), adrenergic antagonists (e.g., timolol), carbonic anhydrase inhibitors (e.g., dorzolamide), prostaglandin analogues (e.g., latanoprost), and osmotic agents (e.g., mannitol).[1,6] Latanoprost 0.005%, a prostaglandin analogue, is usually the medical treatment of choice for primary glaucoma at 1 drop once to twice daily topically. Alternatives include mannitol (1.0 – 1.5 g/kg IV), methazolamide or dichlorphenamide (2.2-4.4

mg/kg PO BID to TID), or pilocarpine 2% (QID after initial 1 drop per 10 minutes over 30 minutes).[6] Many of these medications are now obsolete or not readily available to the practitioner. Commonly, therapy consists of a beta-blocker, such as timolol 0.5%, a carbonic anhydrase inhibitor, such as dorzolamide 2%, and a prostaglandin analogue, such as latanoprost 0.005%. After 1-2 hours of treatment initiation, the intraocular pressure should be reevaluated. If less than 20 mmHg, the medical therapy can be instituted until the pressure increases over 20 mmHg. If using latanoprost, the frequency has been debated, but the most common frequency is every 12 hours. Once over 20 mmHg, surgical therapy should be performed. Surgical options may include transscleral cyclophotocoagulation, endolaser cyclophotocoagulation, gonioimplantation, or combined procedures. Gonioimplantation aids in aqueous humor outflow, while cyclophotocoagulation reduces its production.[6]

If the eye is irreversibly blind, the primary goal is to eliminate pain through a salvage surgery. Enucleation, evisceration/prosthesis, and a cyclodestructive procedure are potential options. Evisceration/prosthesis is usually performed when the owner prefers a more cosmetic procedure; however, enucleation is usually the treatment of choice due to the low complication rate and quick recovery time.[6]

In primary glaucoma, the contralateral eye should be examined, monitored, and prophylactically treated.[1,2,6,8,9] The two most common therapies prescribed are dorzolamide 0.25% and timolol 0.5%. The dorzolamide is administered topically every 24 hours often with a topical corticosteroid. Timolol is prescribed topically every 12 hours.[6]

The goal of future glaucoma treatment is to use specific molecular targets (e.g., Rho kinases) and to improve topical administration of medications via alternative drug delivery

systems (e.g., sustained release implants). The development of these alternatives aims to improve our treatment options and lessen the limitations currently faced.[1]

Case Outcome:

Because of the right iris/ciliary body mass, blindness, and refractory glaucoma, right eye enucleation was elected to be performed on June 5, 2019. It was also explained that since primary glaucoma was suspected, prophylactic medical therapy and monitoring of her left eye should occur. In the interim to surgery, timolol 0.5% ophthalmic solution (1 drop) was prescribed topically every 12 hours bilaterally. Latanoprost 0.005% ophthalmic solution was continued in her right eye, administering 1 drop topically every 12 hours. Both timolol and latanoprost were instituted to decrease intraocular pressure. The owners were instructed to wait 5 minutes between medications for adequate absorption time.

Upon return to MSU-CVM on June 4, 2019 for her enucleation, her physical and ophthalmic exams were unchanged from the previous visit. The owner reported that Shelby was doing well at home, and no medications were given the morning of June 4. No significant clinical abnormalities were noted on complete blood count and serum chemistry panel.

A subconjunctival enucleation of her right eye was performed on June 5, 2019 after receiving an inferotemporal retrobulbar block using bupivacaine. There were no complications during surgery, and she recovered uneventfully from anesthesia. The right eye was placed in neutral buffered formalin and submitted for histopathology to obtain a definitive diagnosis for her right eye and a prognosis for her left eye. Post-surgical medications in hospital were carprofen (1.7 mg/kg PO BID), timolol 0.5% ophthalmic solution (1 drop OS BID), Refresh artificial tear drops (1 to 2 drops OS TID), and trazodone (3.4 mg/kg PO TID PRN). A pain

score of the enucleation site was performed at treatments. A score of 0/24 was noted at each time point.

She was discharged the afternoon of June 6, 2019. The owners were instructed to monitor for any bleeding or discharge of the surgical site. Additional instructions included maintaining hard E-collar placement and resting her for the next 2 weeks until recheck at the Veterinary Specialty Center to remove her sutures. Timolol 0.5% ophthalmic solution was continued in her left eye (1 drop BID) to assist in delay of glaucoma onset. Carprofen (1.7 mg/kg PO BID) was also continued for 5-7 days to control pain and inflammation. Latanoprost (1 drop) was indicated for use if Shelby's left eye suddenly became blind with an immediate phone call to the Ophthalmology Service.

At her recheck appointment on June 21, 2019, the surgical site was healed, so the sutures were removed. The histopathology results were discussed at this time. The histopathology confirmed primary glaucoma via goniodysgenesis. The iris/ciliary body mass was diagnosed as a benign ciliary body adenoma. Therefore, prophylactic treatment of her left eye was continued with timolol 0.5% ophthalmic solution (1 drop OS BID). It is suspected that the elevated intraocular pressure was multifactorial in Shelby. She had the propensity to have glaucoma because she had PACG, but the growth of the mass may have contributed to her development of glaucoma in the right eye. Additionally, she was diagnosed with keratoconjunctivitis sicca of her left eye, so treatment was initiated and multiple rechecks of her left eye have been performed at the Veterinary Specialty Center. As of her last recheck on November 26, 2019, Shelby's left eye has not displayed any clinical signs of glaucoma development and is responding well to topical cyclosporine for keratoconjunctivitis sicca.

Conclusion:

Primary glaucoma is a painful condition characterized initially by a rapid increase in intraocular pressure associated with genetics, sex, age, and other predisposing factors. Primary closed-angle glaucoma (PACG) is the most common form of primary glaucoma. Pectinate ligament dysplasia and narrowing of the iridocorneal angle have been associated with PACG development. The diagnosis of PACG is based on signalment, clinical signs, ophthalmic exam, and gonioscopy. If enucleation is pursued, histopathology acts a confirmatory tool. Treatment depends on the cause of glaucoma and visual status of the affected eye. Medical options are available for visual eyes either alone or in combination with surgical procedures to prolong vision. Irreversible blindness is a common consequence of PACG, so surgical intervention is often needed to eliminate pain caused by the high intraocular pressure. Since PACG is a bilateral disease, prophylactic medical treatment of the contralateral eye is imperative to delay onset of glaucoma in the normotensive eye.

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