Student Paper Communication étudiante

Uveodermatologic syndrome in an Akita

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Abstract — An 8-year-old, spayed, female Japanese Akita was presented for acute blindness, cloudy eyes, and squinting. A presumptive diagnosis of uveodermatologic syndrome was made. Therapy with oral prednisone, topical prednisolone, and oral azathioprine was successful in eliminating most of the clinical signs and the Akita now has complete restoration of vision.

Résumé — Syndrome uvéodermatologique chez une chienne Akita. Une femelle Akita japonaise stérilisée âgée de 8 ans est présentée pour de la cécité aiguë, des yeux troubles et du strabisme. Un diagnostic présomptif de syndrome uvéodermatologique est posé. Une thérapie avec de la prednisone orale, de la prednisolone topique et de l'azathioprine orale a réussi à éliminer la plupart des signes cliniques et la chienne a maintenant complètement recouvré la vue.

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Introduction

An 8-year-old, spayed, female Akita was presented to the emergency service of the Calgary Animal Referral and Emergency Centre (C.A.R.E. Centre) for acute bilateral blindness of a few hours duration, squinting of approximately 1-month's duration, and cloudy looking eyes. Other than those ocular signs the Akita was said to be healthy and on no current medications. There had been no changes in eating or drinking, and no diarrhea or vomiting. A physical examination was unremarkable except for an elevation in blood pressure (BP of 209/127 mmHg; normal range: 160–180/100 mmHg). Schirmer tear tests (Schirmer Tear Test Strips; Alcon Canada, Mississauga, Ontario) on both eyes were within normal limits (reference range: 15–25 mm/min) as was the intraocular pressure of both eyes (reference range: 10–25 mmHg). A neurological examination revealed no abnormal findings. At this time, the owners were given the options of leaving the animal overnight so that its blood pressure could be monitored, or taking the animal home and returning the next day for an ophthalmology consultation; the latter choice was taken.

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Case description

The Akita was re-examined the following morning, and her physical examination revealed a bright, alert, and responsive dog; her temperature, pulse, and respiration were within normal limits. The patient had blepharospasm bilaterally. An ophthalmic examination revealed bilateral moderate aqueous flare, iris hyperemia, and keratic precipitates, indicating anterior uveitis. The intraocular pressure (IOP) in the right eye was within normal limits (12 mmHg; reference range: 10–25 mmHg), but was slightly low in the left eye (6 mmHg; reference range: 10–25 mmHg), which was likely due to the anterior uveitis. There was no menace response present in either eye and the direct pupillary light reflex was severely decreased in both eyes. The left eye had no dazzle reflex and there was a decreased dazzle reflex with the right eye. Bilateral bullous retinal detachment accompanied by a clear fluid underlying the retina was seen in both eyes, with the retina being detached 360° in the left eye and 270° in the right eye. The dorsal portion of the right retina remained attached. The rest of the neuro-ophthalmic examination was normal.

A problem list was created consisting of possible hypertension and bilateral anterior uveitis and bullous retinal detachments.

Differential diagnoses for anterior uveitis include immune-mediated diseases (uveodermatologic syndrome), neoplasia, trauma, infection (such as: viral hepatitis, brucellosis, systemic fungal, protozoal, rickettsial, or parasitic disease) and idiopathic causes. Differential diagnoses for bullous retinas include immune-mediated diseases, neoplasia (multiple myeloma), systemic hypertension, and infection.

A complete blood (cell) count (CBC), serum biochemistry profile, and urinalysis were carried out. The CBC showed a slightly low platelet count (133×10^{12}/L; reference range: $170–400 \times 10^{12}$/L). The serum biochemistry profile showed

a slight increase in globulins (36.8 g/L; reference range: 16–36 g/L), a decrease in the albumin/globulin ratio (0.7; reference range: 0.8–2.0) and a minor decrease in phosphorus (0.8 mmol/L; reference range: 0.81–1.94 mmol/L). The urine had a pH of 8.5 (reference range: 5.5–7.0) and a high number of red blood cells (3+; reference range: 0–3). These changes were all minor and nonspecific, so it was concluded that the blood count, serum biochemistry, and urinalysis results were unremarkable. Thoracic radiographs were taken and showed no abnormal findings. The dog's blood pressure was re-evaluated and was now at the higher end of normal values (BP of 155/96 mmHg); this was thought to be due to stress and excitement associated with coming to the clinic as the values had decreased from the previous day. At this time, the primary differential was uveodermatologic (UVD) syndrome.

Treatment was instituted with azathioprine (Imuran, GlaxoSmithKline, Mississauga, Ontario), 1.25 mg/kg, PO, q24h and prednisone (Novopharm, Toronto, Ontario), 1.25 mg/kg, PO, q24h. Topical prednisolone acetate 1% ophthalmic drops (Diopred drops, Sandoz, Boucherville, Quebec) OU, q6h were also added to the treatment protocol. A recheck was scheduled in 1 wk for a follow-up retinal examination.

Upon follow-up, a thorough ophthalmic examination revealed that the right retina had completely reattached. The left retina had reattached 180° along the dorsal portion, with the most ventral portion still remaining detached. The ventral portion is most often the final part of the retina to reattach due to fluid pooling ventrally in the subretinal space. The plan was to institute biweekly check-ups to determine if the left retina would fully reattach. If this were to occur, the dosages of the medications could be tapered, and hopefully discontinued.

Discussion

In this case, UVD syndrome was diagnosed based on clinical signs. The excellent response to treatment further confirmed this diagnosis.

Uveodermatologic syndrome was first reported in 1977 by Asakura et al (1) in 2 Akitas. There have been no age or sex predilections documented, although the disease is commonly seen in dogs between the ages of 6 mo and 6 y (1). The highest incidence of the disease is seen in the Akita, with this breed making up about 80% of the case reports (2). The syndrome is also seen in Siberian huskies, Irish setters, dachshunds, fox terriers, Shetland sheepdogs, St. Bernards, Old English sheepdogs, chow chows, samoyeds, shiba inus, and has been reported in a Brazilian fila dog (1,3,4). The increased incidence in Akitas could mean that there is a breed predisposition and that the syndrome is transmitted genetically (1). As this may be the case, owners of a dog with UVD syndrome should be discouraged from breeding their animal. The syndrome is not usually seen in mixed breed dogs, which is likely a function of the higher incidence of immune-mediated disease in purebreds due to the smaller gene pool (2).

The cause of UVD is yet to be determined. It is believed that an immune-mediated attack against the body's own melanocytes is to blame. It is also thought that exposure to ultraviolet radiation can exacerbate the symptoms (5,6). A theory that viral infection may trigger the immune system reaction has been postulated but is yet to be fully researched (1).

Uveodermatologic syndrome is characterized by chronic and recurrent bilateral uveitis and dermal depigmentation (1,3,5,6). Other clinical signs that can be seen include a diminished or absent pupillary light response, blepharospasm, photophobia, keratic precipitates, hyphema, chorioretinitis, retinal detachment, and occasionally iris bombe (1,4). Ocular signs are usually the first to appear and can occur up to a month before any dermatological signs such as depigmentation of the skin at the nasal planum, mucocutaneous junctions, perianal region, scrotum, and footpads (4). Often leukotrichia, whitening of the hair, will be seen and this can occur over a period of time where the hair progressively loses its pigment. Some dogs may be so severely affected that they have generalized depigmentation of the skin and hair or alopecia (4). It is important to remember that patients may not always exhibit both eye and skin abnormalities, as is shown in this particular case. When presented with a patient exhibiting bilateral uveitis, differential diagnoses should include immune-mediated disease, such as uveodermatologic syndrome, neoplasia, trauma, idiopathic, systemic hypertension, and infectious etiologies. When presented with a patient showing the dermatologic signs mentioned previously, the differential diagnosis list should include cutaneous lymphoma and other immune-mediated diseases such as pemphigus foliaceous, systemic lupus erythematosus, and discoid lupus, as well as UVD (5). One should also keep in mind that dogs do not have to present with bilateral uveitis to have this disease. It has been shown that in dogs with heterochromia irides, 2 different colored eyes, it is possible for only 1 eye to show signs of UVD. This is most likely due to asymmetrical uveal pigmentation (7).

Currently no diagnostic criteria are set out for dogs with UVD, so diagnosis is generally made based on clinical signs and histopathology of a skin biopsy (7). The CBC, serum biochemistry profile, and urinalysis are usually within normal limits (5). Intraocular pressure will be normal unless there is a secondary glaucoma, in which case it will be increased, or acute severe uveitis, in which case it will be decreased. A Schirmer tear test will be normal and a fluorescein dye test will be negative (1). Depending on geographical location, tests should be run to rule out infectious causes of anterior uveitis. A skin biopsy, normal retinal examination and negative ANA titers will aid in differentiating other skin disease from UVD syndrome (5). Histopathology of the skin biopsy will show histiocytic lichenoid dermatitis with an absence of pigment in the keratinocytes (1). There may be an aberrant deposition of melanin within the tissue. Melanophages may also be present within the dermis and a lympho-mononuclear infiltrate can be seen with lymphocytes as the predominant cell type. Occasionally, plasma cells will be seen (1,4). One study has shown that in skin lesions it is predominately T lymphocytes and macrophages that are present whereas in eye lesions B lymphocytes and macrophages predominate (8).

Uveodermatologic syndrome is similar to Vogt-Koyanagi-Harada (VKH) syndrome in humans and this is why UVD is often called VKH-like syndrome. Most of the data for the disease in dogs has been extrapolated from the human literature

on VKH. This syndrome in humans is characterized by bilateral granulomatous uveitis with poliosis, vitiligo, dysacousia, and meningitis (3). Meningitis and dysacousia are rarely seen in dogs, and this is thought to be due to the fact that dogs do not have melanocytes in their meninges or auditory tissues (2). The common link between the central nervous system, ocular, and cutaneous signs is a similar embryonic development of pigment containing cells, which are the target of the granulomatous inflammation (8). Cutaneous injury and viral disease have been implicated as factors that exacerbate the disease in humans (7,8). As with UVD, VKH syndrome is thought to develop as a result of Th-1-lymphocytic, cell-mediated, autoimmune attack against melanocytes in the uvea, skin, central nervous system, and inner ear in humans (7). People of Asian, Italian, Native American, and Hispanic ancestry are more prone to the disease, perhaps due to the melanin expressed in their skin (7). In humans, the strongest candidate antigens thought to play a role in the development of the syndrome are tyrosinase and tyrosinase-related proteins (4). Tyrosinase proteins are enzymes involved in melanin formation and are also expressed by melanocytes (8). A study was conducted in which lymphocytes were taken from humans diagnosed with VKH and were exposed to tyrosinase proteins. The result was a proliferation of lymphocytes (8). Another study showed that when Akitas were immunized with tyrosinase-related proteins they developed a disease closely resembling human VKH (7,8). Anti-retinal and anti-melanocytic antibodies have been detected in dogs also (7). Other research is being undertaken to see how much of a role the Major Histocompatibility Complexes play in this disease (8).

There are 2 main medications involved in treating UVD. Ocular signs are the most important signs to be treated, as these can have detrimental effects on the eye, whereas the skin/coat problems are purely cosmetic. Every dog should receive systemic corticosteroids beginning with an immunosuppressive dose (4). Most cases should be started on prednisone at an induction dose of 1–3 mg/kg, PO, q12–24h (4). Topical corticosteroids should also be prescribed in every case. These will decrease inflammation within the eye, stabilize the blood-aqueous barrier, and suppress the auto-immune response (7). Common drugs used in cases of uveodermatologic syndrome include 1% prednisolone ophthalmic drops (1 drop, OU, q4h) and 0.1% dexamethasone ophthalmic solution (1 drop, OU, q4h) (4). It has also been reported that using certain drugs subconjunctivally can reduce the signs of inflammation in the eye. Drugs that have been studied include dexamethasone (1–2 mg), triamcinolone (10–20 mg), and depot betamethasone (6 mg) all injected just once (4). A topical cycloplegic, such as 1% atropine ophthalmic solution, may be applied to the eyes every 6 to 24 h, to effect, if the pupil is miotic (4). Dilating the pupil will help prevent synechiae formation. Both topical and systemic steroids should be continued until there is resolution of the clinical signs. Once this has occurred (usually around 4 to 8 wk), the dose can be tapered over several weeks until the lowest possible dose can be given every other day without reoccurrence of symptoms (maintenance dose for prednisone is 0.5–2 mg/kg, PO, q24h) (4). If there has been no improvement in the clinical signs in 2 wk, an alternative glucocorticoid should be used instead of the prednisone. Dexamethasone and triamcinolone are often used in these refractory cases (4). If the glucocorticoid is ineffective at controlling the syndrome or adverse side effects occur, an immunosuppressant drug can be added to the medication regimen. Azathioprine is widely used at a dose of 1.5–2.5 mg/kg, PO, q24–48h. Cyclosporine, a combination of tetracycline and niacinamide, or cyclophosphamide can also be used, and all these drugs may have a steroid-sparing effect (4). A response to these treatments should be seen within 8 to 12 wk. The dose can be tapered to the lowest possible dose that will maintain the animal (for example, the maintenance dose of azathioprine is 1.5–2.5 mg/kg, PO, q48–72h) (4). If a response is seen with this treatment, then the glucocorticoids can be tapered and finally discontinued with the animal remaining on the immunosuppressive drug (4). Animals with UVD may need life-long therapy with 1 or both drugs depending on the response (4). Using intravitreal administration of triamcinolone has been documented, but only in humans (7).

Weekly retinal examinations are the preferred means of monitoring progress but biweekly examinations are also acceptable. It is important to monitor the retinal changes, as improvement of dermatological signs may not affect retinal pathology (5).

If treatment is successful, any hair lost will usually re-grow and any hair that had lost its coloring can become pigmented again. All signs of inflammation within the eye should resolve and the retina may reattach (1). Sequelae that may occur even after the clinical signs have improved include secondary glaucoma due to inflammatory debris within the eye blocking the irdiocorneal angle, cataracts, permanent blindness, or the cutaneous depigmentation may become permanent (3,4). The prognosis for most cases is guarded (1).

A 1-wk recheck of this case revealed that the right retina had completely reattached and the left retina had reattached 180° with the ventral portion still being detached, due to fluid pooling. The uveitis was clearing up and most of the other clinical signs had resolved. A recheck 2 wk later showed that the left retina was only now detached 45° and vision in both eyes had been restored. Important points gleaned from this case include the fact that clinical signs and histopathology, if skin lesions are present, are the mainstays of diagnosis. Treatment may be required throughout the life of the animal, but should be initiated as soon as possible to allow the patient the greatest chance at complete recovery.

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