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Intracorneal stromal hemorrhage in dogs and its associations with ocular and systemic disease: 39 cases

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Abstract

Objective To describe clinical features of dogs diagnosed with stromal intracorneal hemorrhage (ICH).

Animals studied Retrospective case series of 39 dogs (44 eyes) with ICH.

Procedures Medical records of dogs evaluated by the Cornell University ophthalmology service were searched to identify animals with a clinical diagnosis of ICH between 2005 and 2014. Signalment and clinical details, including concurrent ocular disease, concurrent systemic disease, diagnostic tests performed, outcome of hemorrhage, presenting client complaint, and treatment, were recorded.

Results Intracorneal hemorrhage was identified in 44 eyes of 39 dogs. The mean (±standard deviation) age of dogs was 11.5 years (±2.8 years). The Bichon Frise breed and older dogs were statistically over-represented relative to the entire ophthalmology service canine referral population during the same time period. Concurrent ocular disease was present in 40 eyes (91%) and included keratoconjunctivitis sicca, cataracts, and corneal ulcers. Twenty-three dogs (59%) suffered from concurrent systemic disease, most frequently diabetes mellitus, hyperadrenocorticism, hypothyroidism, and systemic hypertension. Less commonly, life-threatening systemic conditions were identified in dogs with ICH including immune-mediated hemolytic anemia, immune-mediated thrombocytopenia, metastatic neoplasia, and sepsis. Intracorneal hemorrhage was found in all corneal locations, and corneal vascularization was present in each affected eye.

Conclusions Intracorneal hemorrhage is an uncommon condition in dogs that occurs in association with corneal vascularization. The risk of ICH may be increased due to certain ocular and systemic diseases. Although uncommon, ICH may also be an ocular manifestation of severe immune-mediated, infectious, and neoplastic systemic diseases in dogs.

Key Words: cornea, corneal vascularization, dog, intracorneal hematoma, intracorneal hemorrhage, keratitis

INTRODUCTION

Hemorrhage into the cornea is an uncommon clinical finding in both human and veterinary medicine, with fewer than 100 cases reported in the physician-based literature and only one peer-reviewed veterinary medical journal article describing canine cases.[1,2] This condition is reportedly associated with corneal vascularization, which is a much more prevalent finding in both human beings and animals.[3–6] The difference in prevalence between the conditions could be explained by special pathophysiologic circumstances. Corneal vascularization and stromal intracorneal hemorrhage (ICH) are both complications that may threaten visual status.[1,2] In addition, these conditions are associated with similar insults to the cornea such as corneal grafting, infection, inflammatory corneal diseases, intraocular surgery, extraocular surgery, ocular trauma, and, in human beings, contact lens irritation.[7–9] In many cases, ICH resolves spontaneously over time with or without the use of specific topical treatments.[2,10] According to literature describing human ICH, severe cases may require surgical drainage of the hemorrhage or

corneal transplantation to salvage normal function of the eye.[11–14] Similar surgical intervention has not been documented in veterinary literature.[2] Despite resolution of the hemorrhage, ICH may have lasting adverse impacts on corneal transparency and structure such as corneal pigmentation, scarring, thinning, and ulceration.[15]

The purpose of this study was to describe clinical features of dogs diagnosed with ICH at a referral veterinary medical teaching hospital. Possible variables, including the association with other ocular and systemic diseases, causing and affecting the outcome of ICH were investigated to lead to better understanding and treatment of the condition in dogs.

MATERIALS AND METHODS

Medical records of dogs evaluated by the ophthalmology service at the Cornell University Hospital for Animals between January 1, 2005 and December 31, 2014 that displayed a clinical diagnosis of ICH were identified. Information gathered from the medical record included signalment, date of presentation, eye affected, presenting owner complaint, concurrent ocular diseases, concurrent systemic diseases, current ocular medications, current systemic medications, presence of corneal vessels, hemorrhage quadrant (nasal, temporal, superior, inferior), hemorrhage location (peripheral, mid-peripheral, and axial), additional hemorrhage locations elsewhere on the body, diagnostic tests performed, treatment of ICH, re-evaluation dates, and outcome of hemorrhage.

The collected data were then enumerated and summarized with descriptive statistics. Signalment data from the ICH population were compared to the entire Cornell University ophthalmology service referral canine population over the same time period. A two-tailed t-test was used to compare the distribution of mean age between dogs with ICH and the entire canine referral population. The distribution of breed and sex (male vs. female) was compared between dogs with ICH and the entire canine referral population using a chi-square or Fisher's exact test. The frequency of concurrent systemic disease detection was compared between dogs with unilateral and bilateral ICH using the Fisher's exact test. The occurrences of the most frequent systemic diseases identified in the ICH population were individually compared between dogs with ICH and the ophthalmology service referral canine population over the same time period using a chi-square test. The frequency of concurrent ocular and systemic disease was compared between younger and older dogs with ICH using the Fisher's exact test. Significance was set at $P < 0.05$ for all comparisons.

RESULTS

Medical records of 39 cases of dogs with ICH were reviewed. The mean (±standard deviation) age of the study population with ICH at diagnosis was 11.5 years (±2.8 years). The distribution of sex was 18 castrated males (46.1%), 14 spayed females (35.9%), six intact females (15.4%), and one intact male (2.6%). Twenty-two dog breeds were represented in the study, including Bichon Frise ($n = 6$ dogs), mixed breed ($n = 4$), Boston Terrier ($n = 3$), Labrador Retriever ($n = 3$), Boxer ($n = 2$), American Cocker Spaniel ($n = 2$), Lhasa Apso ($n = 2$), Shih Tzu ($n = 2$), and single dogs of the following breeds: Australian Terrier, Chihuahua, Cockapoo, Golden Retriever, Italian Greyhound, Miniature Pinscher, Miniature Poodle, Miniature Schnauzer, Norfolk Terrier, Standard Poodle, Pug, Rat Terrier, Samoyed, Shetland Sheepdog, and Standard Schnauzer.

The entire canine referral population of the ophthalmology service at the Cornell University Hospital for Animals over the same time period included 7948 unique individual dogs. The mean (±standard deviation) age of the entire canine referral population was 8.6 years (±5.1 years). The mean age of the ICH population and the canine referral population was significantly ($P \leq 0.001$) different. The distribution of sex in the entire referral population was 35.5% spayed females, 33.3% castrated males, 16.9% intact females, and 14.3% intact males. There was not a significant difference in sex distribution between the ICH population and the canine referral population. The prevalence of the eight most common breeds in the ICH population was reviewed and compared to the referral population. Analysis of the frequency of each breed revealed a significant difference between the ICH population and the referral population for only the Bichon Frise breed ($P = 0.005$), which represented just 1.6% of the entire canine referral population.

Intracorneal hemorrhage affected the left eye (OS) only in 18 dogs, the right eye (OD) only in 16 dogs, and both eyes (OU) in five dogs. Intracorneal hemorrhage was identified in dogs that were presented to the ophthalmology service for a variety of reasons. The most common reasons for initial presentation were redness in the eye or eyes (10/39 dogs), re-evaluation after ocular surgery (8/39), and corneal ulcer (3/39). Other reasons for evaluation included ocular discomfort, hyperadrenocorticism evaluation, and re-evaluation after other nonocular surgery. No dogs were presented for evaluation after known ocular trauma. Concurrent ocular findings were found in 40/44 of the eyes (91%) diagnosed with ICH including keratoconjunctivitis sicca ($n = 18$ eyes), cataracts ($n = 15$), corneal ulcer ($n = 9$), iris atrophy ($n = 7$), nuclear sclerosis ($n = 5$), pseudophakia ($n = 5$), calcific keratopathy ($n = 4$), pigmentary keratitis ($n = 4$), eyelid mass ($n = 3$), glaucoma ($n = 3$), progressive retinal atrophy ($n = 3$), bullous keratopathy ($n = 2$), bullous retinal detachment ($n = 2$), chronic superficial keratitis ($n = 2$), corneal degeneration ($n = 2$), panuveitis ($n = 2$), sudden acquired retinal degeneration syndrome ($n = 2$), and only one eye each suffered from asteroid hyalosis, chronic hemophthalmos, corneal

stromal abscess, corneal stromal facet, distichiasis, lens-induced uveitis, lens subluxation, nictitans gland prolapse, and phthisis bulbi. Eight of the corneal ulcers detected were adjacent or superficial to the site of stromal hemorrhage, and only one was unrelated to the corneal ulcer location.

Thirty of the 39 dogs were already receiving at least one topical ophthalmic medication at the time of ICH diagnosis. Dogs were being administered different combinations of the following topical ophthalmic medications: cyclosporine (n = 11 dogs), atropine (n = 7), ofloxacin (n = 7), cefazolin (n = 4), dorzolamide–timolol (n = 3), neomycin–polymyxin b sulfates–dexamethasone (n = 3), artificial tears (n = 2), ciprofloxacin (n = 2), edetate disodium (EDTA) (n = 2), neomycin-polymyxin b sulfates–bacitracin (n = 2), prednisolone acetate (n = 2), autologous serum (n = 2), and only one case each received erythromycin, flurbiprofen, gatifloxacin, latanoprost, oxytetracycline, and tobramycin.

Concurrent systemic disease affected 23/39 dogs (59%) including diabetes mellitus (n = 8 dogs), hyperadrenocorticism (n = 7), hypertension (n = 6), hypothyroidism (n = 6), immune-mediated thrombocytopenia (n = 3), degenerative heart valve disease (n = 2), and only one dog each suffered from acquired portosystemic shunts, epileptic seizures, generalized lymphoma, hyperparathyroidism, immune-mediated hemolytic anemia, Lyme disease (including polyarthritis, pyrexia, and mild thrombocytopenia), metastatic hemangiosarcoma, and sepsis. These conditions included historically known diseases in the dogs and new diagnoses from the evaluation for the ICH. The frequency of concurrent systemic disease detection was not significantly (P = 0.72) different between dogs with unilateral and bilateral ICH. The frequency of the four most common concurrent systemic diseases identified in the ICH population was calculated for the entire canine referral population of the ophthalmology service over the same time period: diabetes mellitus (324 dogs, 4.08%), hyperadrenocorticism (84 dogs, 1.06%), hypertension (15 dogs, 0.19%), and hypothyroidism (65 dogs, 0.82%). Each of these four systemic diseases occurred significantly (P < 0.0005) more frequently in dogs with ICH compared to the general canine referral population.

Systemic medications were being administered in 17/39 dogs at the time of ICH diagnosis including amoxicillin trihydrate–clavulanate potassium (n = 4 dogs), enalapril (n = 4), amlodipine (n = 3), tramadol (n = 3), levothyroxine (n = 2), pregabalin (n = 2), trilostane (n = 2), and only one case each received Adequan,® Allerderm,® benazepril, carprofen, cephalexin, chemotherapy (CHOP protocol), complete vitamin supplement, cyclosporine, deracoxib, dexrazoxane, diphenhydramine, dl-methionine, doxorubicin, doxycycline, famotidine, furosemide, glucosamine, lactulose, levetiracetam, metronidazole, pancrelipase, pimobendan, potassium bromide, psyllium fiber supplement powder, selegiline, Traumeel tablets,® and zonisamide.

Corneal vascularization was associated with stromal ICH in all affected eyes (44/44 eyes). Hemorrhages were found in all quadrants of the cornea (Fig. 1). Intracorneal

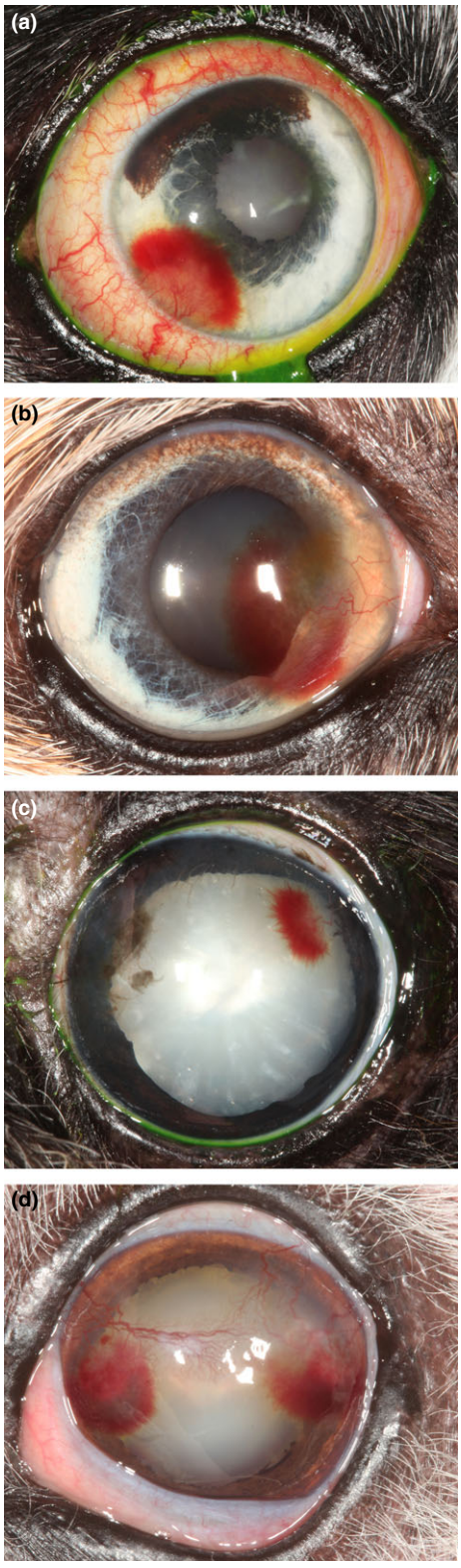

Figure 1. Clinical photographs of right (a, b) and left (c, d) eyes of four dogs with corneal vascularization and intracorneal hemorrhage.

hemorrhage was least common in the inferior quadrant ($n = 6$ eyes) and more evenly distributed throughout the other quadrants (nasal = 17 eyes, temporal = 13 eyes, superior = 13 eyes). In some eyes, ICH affected multiple quadrants. When evaluating ICH distribution, the mid-peripheral location most frequently exhibited hemorrhage ($n = 21$ eyes), followed by peripheral ($n = 13$) and axial ($n = 12$) locations. In some eyes, ICH affected multiple corneal locations (Fig. 1).

Two dogs with immune-mediated thrombocytopenia were severely thrombocytopenic and showed clinical signs of abnormalities in primary hemostasis which included petechiae on abdominal skin, limb skin, and oral mucosa in one dog and ecchymosis over the entire ventrum in the other dog. Another dog exhibited bilateral retinal hemorrhages as well as bilateral ICH, but no specific etiology for the hemorrhages, or additional systemic abnormalities, were identified during hemogram, serum biochemistry panel, abdominal ultrasound, coagulation panel, thyroid panel, and systemic blood pressure measurements. No additional dogs with ICH displayed abnormal hemorrhages in noncorneal sites.

Diagnostic testing was performed on 30/39 dogs at the time of ICH diagnosis, either specifically for the ICH or for other medical conditions. The tests included serum biochemistry panel ($n = 25$ dogs), hemogram ($n = 24$), urinalysis ($n = 15$), systemic blood pressure measurements ($n = 10$), aerobic bacterial culture of the cornea ($n = 6$), anaerobic bacterial culture of the cornea ($n = 6$), thyroid panel ($n = 6$), thoracic radiographs ($n = 3$), adrenocorticotropic hormone level assay ($n = 2$), coagulation panel ($n = 2$), cytological evaluation of a corneal scraping ($n = 2$), and only one case each received an abdominal ultrasound, bone marrow cytology, fructosamine level assay, insulin level, liver biochemistry panel, low dose dexamethasone suppression test, renal biochemistry panel, total protein creatinine ratio, and SNAP 4DX plus test (IDEXX Laboratories Inc., Westbrook, Maine; ELISA for heartworm disease, Lyme disease, ehrlichiosis, and anaplasmosis).

All dogs identified with ICH had at least one potential predisposing factor including older age (>10 years old), concurrent ocular disease, or concurrent systemic disease. Of the younger 10 dogs of the study population (≤10 years old), 10 dogs had concurrent ocular disease and three dogs had concurrent systemic disease. Of the older 29 dogs of the study population (>10 years old), 26 dogs had concurrent ocular disease and 18 dogs had concurrent systemic disease. The frequency of concurrent ocular ($P = 0.56$) or systemic ($P = 0.14$) diseases was not significantly different between younger and older dogs.

Forty of the 44 affected eyes received ocular medication after ICH diagnosis. These medications were administered specifically for the ICH or for other concurrent ocular conditions. Treatment often involved a combination of topical ophthalmic drugs including cyclosporine ($n = 25$ eyes), diclofenac ($n = 9$), prednisolone acetate ($n = 6$), atropine ($n = 5$), neomycin–polymyxin b sulfates–dexamethasone ($n = 5$), flurbiprofen ($n = 4$), ciprofloxacin ($n = 3$), dorzolamide–timolol ($n = 3$), gatifloxacin ($n = 3$), latanoprost ($n = 3$), neomycin–polymyxin b sulfates–bacitracin ($n = 3$), artificial tears ($n = 2$), cefazolin ($n = 2$), and only one case each received EDTA, dexamethasone, tacrolimus, and tobramycin.

Follow-up examinations after diagnosis of ICH were highly variable between dogs. The majority of dogs (28/39 dogs) were re-evaluated by the Cornell University ophthalmology service at least once after the initial diagnosis of ICH. Of those dogs, most came back for multiple re-evaluation visits. The time period until first re-evaluation ranged from 10 to 413 days (median = 40 days). Eleven dogs were lost to follow-up. Of the 28 dogs (31 eyes with ICH) that were re-evaluated, the hemorrhage resolved by the final evaluation in 20 eyes and persisted in 11 eyes. In some dogs, the resolved hemorrhages had various persistent effects on the cornea including degeneration, edema, fibrosis, hypoperfused corneal blood vessels, and pigmentation. Persistence of hemorrhage was characterized as blood visibly present in the cornea at the last re-evaluation. In dogs where the hemorrhage resolved, the mean (±standard deviation) number of days between the date of diagnosis and date of complete ICH resolution was 198 days (±189 days) and ranged from 10 to 631 days.

DISCUSSION

Intracorneal hemorrhage in dogs has been described in one peer-reviewed veterinary medical publication.[2] This study retrospectively evaluated ICH in 22 eyes of 19 dogs with data collected from an ophthalmology referral population.[2] The authors reported no breed or sex predisposition to ICH and older dogs were more frequently affected compared to the institution's entire ophthalmologic referral population.[2] All affected eyes had corneal vascularization, hemorrhage was found in all locations of the cornea, and other ocular diseases were frequently present concurrent with ICH. No apparent links between systemic disease and specific ocular disease and the development of ICH were identified in the previous study.[2] The authors further reported that ICH commonly reabsorbs over time with or without the use of medical treatment and no dogs required surgical intervention.[2]

The current study's findings display many parallels with the previous study describing canine ICH, including the presence of corneal vascularization in all dogs, frequent association of ocular disease with ICH, and effects of treatment.[2] In addition, both studies showed large variability in time to ICH resolution. The present study found a significantly higher prevalence of the Bichon Frise breed in the ICH group compared to the referral population, indicating a possible predisposition in that breed. The Bichon Frise was also the most prevalent breed with

ICH in the report by Matas *et al.*[2] A significant difference in the mean age of the current study's ICH population compared to the age of the referral population was found, with older dogs over-represented in the ICH group. Similarly, older human patients have been found to have an increased risk for ICH.[16] No other statistical discrepancies between the signalment data for the entire Cornell University ophthalmology service canine referral population and the ICH population were identified in the present study.

The association of ocular disease with ICH is likely a result of the angiogenesis caused by the processes of those diseases rather than initiating the hemorrhage itself. The new vessels created during angiogenesis may be particularly fragile or have certain characteristics that make them more susceptible to bleeding.[17] It is difficult to separate those variables in clinical studies to determine whether a specific ocular disease actually increases the chances of corneal vessel hemorrhage. No particular ocular disease appears to have a strong association with ICH, and many different ocular conditions were identified in the present study. Physician-based literature describes many ocular insults that produce corneal vascularization and subsequent ICH.[16] It is likely that there are specific factors that influence capillary fragility in the cornea and cause subsequent hemorrhage. Contrary to the conclusions of Matas *et al.*, results of the present study suggest that systemic disease may play a role in development of ICH in some dogs.[2] The majority of dogs affected with ICH in the present study also suffered from one or more systemic diseases, although not every systemic disease identified in this study is considered likely to cause increased bleeding tendency. This finding may be a product of the older dog population evaluated with ICH, or it may represent possible risk factors for canine ICH. Reasons for the large difference in the detection frequency of concurrent systemic diseases between the present and previous study describing canine ICH could relate to differences in the evaluated study populations or differences in the frequency of diagnostic testing.[2] Most dogs in the present study received one or more diagnostic evaluations to screen for systemic abnormalities (30 of 39 dogs), where in the previous study these evaluations were performed uncommonly (6 of 19 dogs).[2]

Some interesting parallels can be made between intracranial hemorrhage and stromal ICH in dogs and human beings. Primary nontraumatic intracranial hemorrhage results from leakage or spontaneous rupture of penetrating cerebral vessels without associated coagulopathy or vascular malformation. In both human beings and dogs, small intracranial hemorrhages form due to lack of integrity and fragility of capillary walls.[18] In terms of basic capillary pathology, ICH and intracranial hemorrhage may have similar pathophysiologic mechanisms. Established clinical risk factors for intracranial hemorrhage in human beings include hypertension, bleeding disorders, older age, hypothyroidism, and anticoagulant medication.[19,20] Systemic hypertension and clotting disorders have also been found to increase the risk for subconjunctival hemorrhage in human beings.[21] Some of these risk factors align with underlying systemic conditions that may be associated with, and have been found in, cases of canine intracranial hemorrhage. These conditions in dogs include hypothyroidism, neoplasia, sepsis, bleeding disorders, hypertension, diabetes mellitus, and hyperadrenocorticism.[18,22] All of these conditions also affected dogs reviewed in the present study of ICH. This finding indicates a possible association between these systemic conditions and ICH in situations where corneal vascularization is present.

Many of the systemic diseases suspected to have potential impact on ICH development have possible mechanisms that may elucidate their potential cause or contribution to the corneal hemorrhage. Hypothyroidism, diabetes mellitus, and to a lesser extent hyperadrenocorticism have all been identified to be associated with atherosclerosis.[22,23] In addition, advancing age is a major factor contributing to development and progression of atherosclerosis.[24] This process of fibrofatty plaque buildup has been found to weaken penetrating cerebral vessels. In human beings, diabetes mellitus is demonstrated to be a major cardiovascular risk factor for atherosclerosis due its promotion of inflammation and vascularization.[25] Atherosclerosis may potentially play a role in canine ICH by promoting corneal vessel fragility.

Hypothyroidism has been demonstrated to modify the coagulation-fibrinolytic balance and therefore disrupt the physiological processes of primary and secondary hemostasis leading to bleeding or thrombosis.[26] In addition, bleeding disorders such as immune-mediated thrombocytopenia directly impact primary hemostasis which will increase risk of spontaneous bleeding.[27] Hyperadrenocorticism may also play a role in hemostasis. It has been found that hyperadrenocorticism can cause a complex coagulopathy involving hypercoagulability and platelet hyporeactivity or dysfunction.[28] Additionally, retinal hemorrhage and intraocular hemorrhage have been associated with systemic hypertension.[29,30] Hypertension has a multitude of potential effects on vasculature that increase chances of hemorrhage in different anatomic locations of the canine eye.[31] Systemic hypertension has also been found to frequently be associated with other systemic disease in dogs, including hyperadrenocorticism and diabetes mellitus.[32,33] Five of the six dogs with systemic hypertension in this study had the disease in conjunction with hyperadrenocorticism or diabetes mellitus.

Neoplasia commonly results in an abnormal hemostatic state in dogs, including the induction of hypocoagulable states and thrombocytopenia.[34–36] Sepsis also increases the risk of hemorrhage by creating a deficiency in clotting factors.[37] The properties of these aforementioned endocrine, hematologic, infectious, immune-mediated, and vascular systemic diseases may contribute to the circumstances that promote ICH in an eye already affected with corneal

vascularization. In addition to promoting hemorrhage from established corneal blood vessels, some systemic diseases may also indirectly lead to the development of corneal vascularization and therefore increase the risk of ICH. For example, some canine endocrine diseases, including diabetes mellitus, hypothyroidism, and hyperadrenocorticism, may contribute to reduced aqueous tear production and development of keratoconjunctivitis sicca.[38]

This study suggests that, in rare cases, ICH may be an ocular manifestation of severe, life-threatening immune-mediated, neoplastic, and infectious systemic disease in dogs. Clinicians should recognize the possibility of this situation when a dog is presented with ICH. At a minimum, a thorough physical examination (including evaluation for signs of abnormal hemorrhage elsewhere in the dog and ophthalmic examination) should be performed to rule-out severe or life-threatening systemic etiologies of ICH. On a case-by-case basis, a more thorough evaluation of systemic health should be considered including additional diagnostic assays.

The present study described a relatively small population of dogs with ICH and was associated with several limitations typical of retrospective studies, including inconsistent or limited data availability for some study dogs. Although correlation between ICH and several other clinical factors was identified in this study, additional research is required to demonstrate causation and to further elucidate the pathophysiology of this potentially complex and multifactorial condition.

Canine stromal ICH is a relatively uncommon condition that is closely associated with corneal vascularization. In most cases, ICH clears with time but continued monitoring for complications is recommended. Ocular disease can promote corneal vascularization, but direct association with hemorrhage of those vessels is not clear. Certain concurrent systemic diseases may be risk factors for stromal ICH, and in rare cases, ICH can be associated with serious life-threatening systemic conditions.

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