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Abstract
Canine conjunctival tumors of vascular endothelial origin are common, although under-reported. The purpose of this study was to evaluate the epidemiology of and potential risk factors for these tumors. This study evaluated 108 cases (70 hemangiomas, 38 hemangiosarcomas) from 8300 canine submissions between 1989 and 2004. Signalment, location, pigmentation, size, duration, diagnosis, margins, ancillary therapy, and geographic location were recorded. Follow-up information was available for 49 cases. Each case was matched with two unaffected controls and compared using logistic regression analysis. Average age upon presentation was 8.6 years; there was no sex predilection. Risk of conjunctival tumors was statistically different among breed groups (P = 0.0010), demonstrating a propensity to occur in groups likely to have increased outdoor activity. Primary involvement occurred within nonpigmented epithelium along the leading edge of the nictitating membrane (41/108) and temporal bulbar conjunctiva (33/108). The etiology remains unknown; however, the strong site predilection, involvement of nonpigmented epithelium, and development within specific breed classes strongly suggest ultraviolet (UV) light as a significant risk factor. In a full-logistic model including breed, gender, age, and UV exposure, UV was not a statistically significant variable (P = 0.1215). In a reduced-model including UV only, significance was approached (P = 0.0696) and posthoc contrast demonstrated a significant linear trend with increasing UV exposure (P = 0.0147). In separate analysis of risks associated with hemangiosarcoma, compared with hemangioma, breed was not significant while increasing UV exposure was significant (P = 0.0381). Early surgical therapy is recommended and may be curative; however, recurrence is possible and more likely with hemangiosarcomas (11/20).

Key Words: conjunctiva, dog, hemangioma, hemangiosarcoma

INTRODUCTION
Primary conjunctival tumors of vascular endothelial origin, typically diagnosed as hemangioma or hemangiosarcoma, are infrequently reported. These tumors occur most commonly in dogs, although other species including horses and cats have been reported to be affected.1–10 To date in the veterinary literature, information regarding these tumors is based on a few individual case reports or on small case series, with limited information pertaining to their biologic behavior. The largest case series to date, examined by Wilcock, evaluated 22 cases of canine conjunctival vascular tumors.11

Dogs with vascular tumors involving the conjunctiva usually present within the adult to geriatric age group.1–6 Based on a previous study, the average age at presentation is 8½ years, with no sex predilection.11 The site of primary involvement is typically the leading edge of the nictitating membrane or the temporal bulbar conjunctiva, with or without encroachment onto the cornea.1–6 Lesions tend to be unilateral in distribution. However, bilateral involvement has been reported.4 Clinically, lesions are typically described as superficial, red to brown, exophytic nodules that are smooth to multilobulated, and focal in their distribution.12
Diagnosis is often based on typical clinical ophthalmic findings, but histologic evaluation by incisional or excisional biopsy is required for a definitive diagnosis. Histologically, hemangiomas are characterized by localized accumulations of cavernous spaces lined by morphologically normal endothelial cells without surrounding smooth muscles or pericytes. Hemangiosarcomas, however, are locally invasive with marked cellularity, hyperchromasia, anisokaryosis, and mitotic figures. Current treatment recommendations consist of early, wide surgical excision, because of the superficial and presumed locally invasive behavior of these tumors. However, primary conjunctival hemangiosarcoma should be distinguished from hemangiosarcoma metastatic to the eye from other sites. Several ancillary treatment modalities, including radiation, laser, or cryotherapy, are often employed, although there is no evidence to date that they improve outcome.

Conjunctival hemangiomas and hemangiosarcomas are associated with a good prognosis. Histologically, a distinction between hemangioma and hemangiosarcoma is made based on the histologic degree of differentiation and local tissue invasion. Although complete surgical excision may be curative, local recurrence has been reported. To our knowledge, there have been no previous reports of metastatic disease arising from a primary conjunctival hemangiosarcoma. The etiology of these tumors and the factors contributing to their pathogenesis remain unknown. However, in a study by Hargis et al. and subsequent case reports, environmental, pigmentary, and behavioral risk factors have been proposed, as is true for cutaneous vascular endothelial tumors.

The purpose of this retrospective study was to evaluate the epidemiology of primary conjunctival hemangiomas and hemangiosarcomas of dogs and to examine potential predisposing risk factors.

MATERIALS AND METHODS

All 108 cases of canine conjunctival vascular tumors were taken from a database consisting of 8300 canine cases submitted to the comparative ocular pathology laboratory of Madison-Wisconsin (COPLOW), during the time period 1989–2004. The tissues were fixed in 10% buffered formalin or Bouin’s solution. Paraffin-embedded tissue was sectioned at 5 µm and stained with hematoxylin and eosin for evaluation.

All cases were evaluated by the author (RRD) between 1989 and 2004 and re-evaluated for the purpose of this study. Case inclusion criteria included the appropriate species and anatomic location, adequate patient information, and a definitive histologic diagnosis. Anatomic locations deemed appropriate included the bulbar or palpebral conjunctiva (superior, inferior, nasal, or temporal), nictitating membrane (bulbar, palpebral, or leading edge), and corneal surface. The cornea was included for the purposes of the study, as the authors believe that vascular tumors in the avascular cornea arise from limbal blood vessels.

Upon submission, each sample sent to COPLOW was assigned an accession number. For comparative purposes, two control cases were selected from the same database for each case included in the study. Standardized sampling of control cases was performed by selecting one control case five accessions prior to, and five accessions following each case used in this study. Control case inclusion criteria included appropriate species and adequate patient information. If a control case did not meet inclusion criteria, sampling continued, one accession prior to or following the previously generated control case, respectively, until an appropriate control was identified. This standardized method of sampling was performed to minimize geographic variation of submissions during the study period (1989–2004). Furthermore, validation of the study control population was performed, comparing breed proportions by the total number of accesses, regardless of diagnosis, submitted to the veterinary medical database (VMDB) during the study period. This method of comparison was chosen because the authors believe the VMDB most closely relates to the COPLOW database, suffering similar limitations and bias.

Canine breed, age, gender, globe involvement, anatomic location, size, duration, pigmentation, diagnosis, margins, ancillary treatment, recurrence, geographic location, and additional complications were determined. Breeds were analyzed both individually and by breed class, based on accepted American Kennel Club (AKC) classifications, which included the Sporting, Non-sporting, Herding, Hound, Working, Terrier, Toy, and Mixed breed classes. The degree of pigmentation was determined histologically and graded as less than or greater than 10% of epithelial pigmentation. The occurrence of squamous metaplasia, an indicator of chronic inflammation, in association with epithelial pigmentation was noted. Geographic location was recorded by the state of origin of each sample submission and used for analytic purposes, comparing calculated average state UV levels and geographic location.

The National Oceanic and Atmospheric Administration/National Weather Service and Centers for Environmental Prediction generously provided incident UV light levels for major US cities, ranging from 0 to 12, during the time period 1995–2003. To calculate a single average UV value per state, we averaged monthly means of major cities within that state. Follow-up information was obtained from submitting veterinarians, initially by letter and subsequently by telephone conversation, where possible. A total of 86 replies were obtained for this retrospective study.

Statistical methods

There were 324 observations and 15 variables in the data analyzed. The number of cases deleted because of missing data was tabulated for all of the 15 variables. A logistic regression model (Proc Logistic, SAS Institute Inc., Cary, NC, USA) was used to describe the nature of the association between the response variable (e.g. diagnosis) and a set of explanatory variables (e.g. age, breed, UV exposure, etc.).

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Estimation of odds ratios (OR) was carried out for the explanatory variables entered into a given model. The OR, while not directly comparable, may be viewed as analogous to slope coefficients that are estimated in multiple regression analyzes conducted on continuous data. OR take values from zero to infinity. OR with values > 1 indicate a direct relationship between the explanatory variable and the response variable, while OR with values < 1 indicate an inverse relationship between explanatory and response variables. OR equal or close to 1 indicate that the explanatory variable provides no discrimination or predictive relationship with the response variable, and were eliminated during the stepwise model-fitting process.18

Model fitting employed a backward elimination procedure that used significance of the Wald chi-square statistic as the criteria to remain in the model. Significance was defined as P ≤ 0.05. Likelihood ratio chi-square and Pearson goodness-of-fit chi-square statistics were used to assess whether the model adequately fit the data.

RESULTS

Control population
Two hundred and sixteen control cases were selected from the COPLOW database during the study period (1989–2004). A total of 52 pure-breeds and mixed-breed dogs were represented. The largest classes of dogs included mixed breeds (44), Labrador Retrievers (24), Golden Retrievers (23), and American Cocker Spaniels (14). The cases fell into the following AKC breed groupings: The Sporting group (73), Mixed breeds (44), Non-sporting (24), Working (20), Toy (16), Hound (14), Terrier (13), and Herding (12). There were 34 intact male, 66 castrated male, 17 intact female, and 81 spayed female cases, in addition to 17 cases with unspecified gender. The average age on submission was 9.1 ± 3.2 years (range: 0.5–16 years), with a median of 9.25 years. The states representing the largest control submissions included California (32), Florida (25), and New York (21), respectively (Fig. 1).

Hemangioma population
One hundred and eight cases of primary conjunctival vascular tumors received between 1989 and 2004 were selected from the COPLOW database. Seventy hemangiomas were identified out of the 108 conjunctival vascular tumors. Thirty-eight cases of conjunctival hemangiosarcoma were identified (Table 1). These 70 tumors comprised 0.84% of total canine submissions and 2.01% of canine ocular neoplasms examined during that time period. Geographically, 23 states were represented, with California (10), Florida (6), and Minnesota (6) providing 31% of all hemangiomas (Fig. 1). Twenty-seven pure-breeds and nine mixed-breed dogs were represented. Over-represented breeds included the Basset hound (7), English Springer Spaniel (6), Boxer (5), Labrador Retriever (5), and English Setter (4). The largest AKC breed grouping represented was the Sporting group (24), followed by the Hound (14), Mixed breed (9), Working (8), Herding (8), Terrier (3), Non-sporting (3), and Toy (3) groups. There were 10 intact male, 27 castrated male, five intact female, and 24 spayed female dogs, and four dogs of unknown sex. The average age at presentation was 8.4 ± 2.6 years (range: 3–13 years), with a median age of 8 years.

Thirty-six cases involved the right eye (OD), 27 cases involved the left eye (OS), three cases had bilateral involvement (OU), and in four cases the affected eye was not identified. Thirty-one cases developed within the bulbar conjunctiva, including 19 temporal, five nasal, two superior, two inferior, and three cases with unspecified location. Thirty-three cases were limited to the nictitating membrane, of which 30 involved the leading edge and three the palpebral surface. The remaining six cases involved the palpebral conjunctiva; all of these were located inferiorly. Three cases involved solely the cornea. The average tumor size at presentation was 26.4 ± 36.7 mm² (range: 0.79–200 mm²), with a median size of 12.28 mm². Average duration prior to presentation was 4 ± 4.5 months (range: 0.5–24 months). The median duration was three months. Epithelial pigmentation was absent in 57 cases. Ten cases were found to contain pigmentation in less than 10% of epithelial cells; six of these cases had pigmentation secondary to squamous metaplasia. Only three cases had > 10% epithelial pigmentation; of these, two cases also had squamous metaplasia. Evaluation of histologic margins identified 40 cases with completely tumor-free surgical margins, 23 cases with histologic evidence of incomplete excision, and seven cases with undetermined tumor margins, due to sample size and/or orientation.

Follow-up information was available for 29 cases. Of these, 14 cases with complete surgical excision and two cases with undetermined margins had no reported recurrence. Two animals (case #37 and #43) had recurrence at the primary tumor site, despite apparently complete surgical excision. The times to recurrence was 24 months (case #43) and unspecified (case #37). Cases #16 and #30 were submissions of tumor re-growths; the re-growths were removed by enucleation and evaluated as completely excised, based on tumor margins. No information regarding the initial excision or evaluation of tumor margins was available. The time interval to recurrence was 0.5 and 9 months for case #30 and #16, respectively. No additional recurrences were reported. Of the 23 cases identified with surgical margins suggesting incomplete excision, follow-up information was available for nine cases; eight of the nine cases had no reported tumor regrowth. Following diagnosis and identification of incomplete excised tumor, an enucleation was performed in one case (#9). Recurrence was reported in only one case with histologic evidence of incomplete excision (#47), and no information regarding time to recurrence was available. Use of ancillary therapy, including cryotherapy (12), CO₂ laser (1), and cautery (1), was reported in 14 cases. Follow-up information was available for 10 cases following CO₂ laser (1), cautery (1), or cryotherapy (8); in all cases, no recurrence was reported.

Hemangiosarcoma population
Thirty-eight cases of conjunctival hemangiosarcoma were identified out of the 108 conjunctival vascular tumors. Estimation of odds ratios (OR) was carried out for the explanatory variables entered into a given model. The OR, while not directly comparable, may be viewed as analogous to slope coefficients that are estimated in multiple regression analyzes conducted on continuous data. OR take values from zero to infinity. OR with values > 1 indicate a direct relationship between the explanatory variable and the response variable, while OR with values < 1 indicate an inverse relationship between explanatory and response variables. OR equal or close to 1 indicate that the explanatory variable provides no discrimination or predictive relationship with the response variable, and were eliminated during the stepwise model-fitting process.18

Model fitting employed a backward elimination procedure that used significance of the Wald chi-square statistic as the criteria to remain in the model. Significance was defined as \( P \leq 0.05 \). Likelihood ratio chi-square and Pearson goodness-of-fit chi-square statistics were used to assess whether the model adequately fit the data.
Controls

Hemangioma

Hemangiosarcoma

Figure 1. Geographic distribution of controls, hemangioma, and hemangiosarcoma cases, respectively.
Table 1. Signalment and clinical data of conjunctival hemangioma cases (1989–2004)

<table>
<thead>
<tr>
<th>Case</th>
<th>Breeds</th>
<th>Sex</th>
<th>Age*</th>
<th>Globe</th>
<th>Location</th>
<th>Duration†</th>
<th>Margins</th>
<th>Recurrence</th>
<th>State/UV</th>
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<td>TX/6</td>
</tr>
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<td>TX/6</td>
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<td>WI/2</td>
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<td>OS</td>
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<td>OD</td>
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<td>Fs</td>
<td>7.5</td>
<td>OD</td>
<td>Bulb, S</td>
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<td>Mc</td>
<td>11</td>
<td>OD</td>
<td>Bulb, N</td>
<td>8</td>
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<td>Mc</td>
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<td>OS</td>
<td>Palp, I</td>
<td>3.5</td>
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<td>1 : 4 months</td>
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<td>OS</td>
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<td>None</td>
<td>FL/6</td>
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<tr>
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<td>Mc</td>
<td>10</td>
<td>OS</td>
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<td>NM</td>
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submitted to COPLOW. Hemangiosarcomas comprised 0.46% of total canine submissions and 1.14% of canine ocular neoplasms (Table 2) examined during the period of study. Geographically, 17 states were represented, with California (9), Florida (6), and Utah (4) contributing 50% of all hemangiosarcomas (Fig. 1). Twenty-four pure-breds and five mixed-breed dogs were represented. The pure-breds most commonly represented included Beagles (3) and Dalmatians (3), followed by the Australian Cattle dog and Shepherd, Basset Hound, Boxer, and Great Dane, each of which were composed of two cases. By AKC breed groupings, the two largest groups were the Working (8) and Hound groups (7), followed by the Herding (5), Mixed breed (5), Non-sporting (4), Sporting (3), Terrier (3), and Toy groups (1). There were nine intact male, 12 castrated male, four intact female, and 13 spayed female dogs. Average age upon presentation was 9.1 ± 2.8 years (range: 4–15 years), with a median age of 9 years.

Ocular involvement consisted of 21 OD, 14 OS, and three cases in which the eye affected could not be determined. Twenty-two hemangiosarcomas developed within the bulbar conjunctiva, including 14 temporal, one nasal, and one superior location, with six cases in unspecified locations (Fig. 2). Thirteen cases involved the nictitating membrane, with 11 cases occurring along the leading edge and two cases on the palpebral surface. The remaining three cases involved the superior palpebral conjunctiva, the cornea, and one unknown site. The average tumor size at presentation was 27.4 ± 26 mm² (range: 3.14–100 mm²), with a median size of 20 mm². Duration before surgery was 3.16 ± 3.37 months (range: 0.5–12 months), with a median time of 1.5 months. Histologic evaluation revealed that all 38 cases were conjunctival hemangiosarcomas devoid of epithelial pigmentation. Furthermore, evaluation of margins identified 12 cases to have complete surgical excision, 24 cases with incomplete surgical excision, and two cases in which margins could not be determined, due to sample size and/or orientation.

Follow-up information was available for 20 cases; all seven cases with incomplete excision reported no recurrence. However, for two of these cases (cases #27 and #37), surgical re-excision, including removal of the nictitating membrane (case #27) and superficial keratectomy (case #37), was performed, following histologic diagnosis and identification of incomplete surgical excision. No recurrence was reported for these two cases. Cases #2 and #16 were submissions of tumor re-growths, both in enucleated eyes, which were evaluated to have complete surgical excision. Case #2 recurred twice, with an initial interval of 12 months followed by a five-month time period after the first recurrence. Case #16 recurred one month following initial excision. No information regarding the initial excision or evaluation of surgical margins was available; however, no further recurrences were reported. Of the remaining cases for which follow-up information was provided, 11 of 20 cases reported recurrence. Five cases were evaluated to have complete excision, and six cases had incomplete excision. The average time interval before recurrence for cases with complete and incomplete excision was 10.8 ± 9.8 months (range: 2–24 months) and 1.6 ± 1.6 months (range: 0.75–4 months), respectively. Ancillary therapy, including cryotherapy (7) and CO₂ laser therapy (1), was performed in eight cases. Of these, three cases with complete excision and two cases with incomplete excision recurred following...
cryotherapy. In case #24, recurrence developed following cryotherapy; however, no information was available regarding histologic evaluation of the initial tumor. Case #26 recurred, despite apparently complete excision and CO2 laser therapy. Case #35 had no further recurrence following cryotherapy treatment, despite apparently incomplete excision.

### Statistical analysis

A comparison between the study control population and total VMDB case submissions, regardless of diagnosis, was performed to evaluate breed group proportions (Fig. 3). Breeds over-represented in the control population (maximum difference of 5.43%) included, in decreasing proportions,
Golden Retrievers, Labrador Retrievers, Beagles, Standard Poodles, and American Cocker Spaniel dogs. Breeds underrepresented (maximum difference of 2.87%), in decreasing order, included German Shepherds, Miniature Poodles, and mixed-breed dogs (1.2%).

Evaluation of clinical data, comparing case and control animals, was performed using a logistic regression model. Variables examined included age, gender, breed groups, and UV exposure based on geographic distribution. Using this model, only the difference between case and control animal breed groups was noted to be statistically significant ($P = 0.0010$). Furthermore, using a pair-wise backwards elimination model, the Hound (OR = 4.97), Working (OR = 3.08), and Herding (OR = 3.36) groups were noted to be at increased risk of tumor development compared to mixed breeds. Individual breed evaluation found the Basset Hound, Boxer, English Setter, and Springer Spaniel to be disproportionately represented (> 5% difference) within the hemangioma population, compared to controls. Dalmatians were the only breed disproportionately represented within the hemangiosarcoma population (> 5% difference). Differences between case and control animals in UV exposure did not meet statistical significance ($P = 0.1215$) using this full regression model. However, when a restricted model was used to evaluate UV exposure and control vs. case status, differences in UV exposure approached statistical significance ($P = 0.0696$). Additionally, posthoc analysis demonstrated a significant ($P = 0.0147$) linear trend with increasing UV exposure. The risk of tumor development at an annual UV exposure level of 4, 5, and 6, compared to 3, was OR = 0.96, OR = 1.84, and OR = 1.9 times more likely, respectively.

The effects of variables on case status (hemangioma vs. hemangiosarcoma) were tested using a logistic regression model. Variables evaluated included age, gender, breed groups, histologic margins, and UV exposure based on geographic location. In this model, 104 observations remained, with four removed due to missing data. Specifically, backwards elimination removed age, margin, and breed group, as statistically significant, leaving UV exposure, which was statistically significant ($P = 0.0381$). Additionally, a dose response was noted, demonstrating increased risk of hemangiosarcoma development with increased UV exposure level. Compared to an annual reference UV exposure level of 3, levels 4 and 5 were 2.08 and 6 times more likely to develop hemangiosarcoma, respectively. A risk of 2.9 was noted with a UV exposure level of 6; this relatively low odds ratio was attributed to limited enrollment of cases of hemangiosarcoma at this exposure level.

We attempted to evaluate variables predictive of recurrence; however, due to sparse follow-up data and difficulty meeting convergence, no statistical analysis was possible.

**DISCUSSION**

Hemangioma and hemangiosarcoma, tumors of vascular endothelial origin, occur commonly in dogs. These tumors can occur in any organ with a blood supply.19 There is no sex predilection and the age at onset is variable, with a range of 8–13 years.20–23 Dogs that develop hemangioma are typically younger than those with hemangiosarcoma.24 Commonly reported breeds include German Shepherd dogs, Golden Retrievers, and Labrador Retrievers; however, numerous other breeds are also affected. Some authors report that any large breed dog may be at risk.20,22,24–26 Solar radiation is believed to be a risk factor for cutaneous hemangiomas and hemangiosarcomas, because of a tendency for these tumors
to occur in sparsely haired, poorly pigmented regions of skin. In humans, vascular stasis, radiation, trauma, and solar radiation are suspected risk factors for cutaneous vascular endothelial tumors. In one study, dogs receiving greater than 20 Gy of radiation were at risk of visceral hemangiosarcoma development and, similarly, risk factors for visceral hemangiosarcoma in humans include vinyl chloride, thorium dioxide, X-rays, and arsenic salts.

Primary hemangiomas and hemangiosarcomas in dogs occur at numerous sites, with a predilection for the spleen and skin. Cutaneous hemangiomas and hemangiosarcomas often develop in poorly pigmented, sparsely haired skin. Hemangioma is reportedly more common than hemangiosarcoma at such sites. Other anatomic sites reported to be affected by vascular endothelial tumors include the right atrium, liver, lung, kidneys, bladder, omentum, peritoneum, intestine, tongue, prostate, vulva/vagina, muscle, bone, iris, and ocular adnexa.

Metastasis is reported to occur in more than 80% of cases of hemangiosarcoma, with common sites of spread including the omentum, mesentery, liver, and lung. Concurrent hemostatic abnormalities are frequently reported including hemorrhage, thrombocytopenia, platelet dysfunction, and consumptive coagulopathy consistent with disseminated intravascular coagulopathy. Stage of disease at diagnosis does not appear to correlate with survival time for dogs with hemangiosarcoma. Despite multimodality therapy, one-year survival times are reported to be less than 10%. However, with tumors located primarily in the dermis, the incidence of metastasis is reportedly low.

In hemangiosarcomas confined to the dermis, completeness of excision is the most important predictor of outcome. In humans, prognostic factors include tumor size and degree of lymphatic involvement.

Primary conjunctival tumors in dogs include squamous cell carcinoma, melanoma, mast cell tumor, angiookeratoma, lymphoma, hemangioma, and hemangiosarcoma. Conjunctival tumors of vascular origin occur with the greatest frequency in dogs; however, these tumors have been reported in several other species. In the present study, 108 primary conjunctival vascular tumors, including 70 hemangiomas and 38 hemangiosarcomas, were identified in dogs. These tumors account for 2.01 and 1.14% of COPLOW canine neoplasia submissions to date, respectively. In humans, vascular tumors of the conjunctiva include capillary hemangioma, varices, lymphangioma, hemangiopericytoma, and Kaposi's sarcoma.

Hemangiomas account for approximately 2% of conjunctival tumors in humans; these tumors remain asymptomatic for extended periods of time and demonstrate benign clinical behavior.

In this case series, the average age at onset of vascular tumors of the conjunctiva in dogs, regardless of histologic diagnosis, was 8.6 years, similarly to previous reports of 8.5 years. Interestingly, conjunctival hemangiomas demonstrated a slight tendency to develop in younger dogs compared to hemangiosarcomas, with an average age at presentation of 8.4 and 9.1 years, respectively. However, this difference was not statistically significant. We found no sex predilection for either tumor type, as previously reported. Breeds disproportionately represented in the case population included the Basset Hound, Boxer, English Setter, and English Springer Spaniel for hemangioma, and Dalmatians for hemangiosarcoma. This finding may relate to the presence of poorly pigmented periocular skin and hair in these breeds. In the present study, breed group was found to be the only statistically significant variable when cases were compared to controls. Specifically, groups likely to spend a greater amount of time outdoors, including the Hound, Working, and Herding groups, were noted to be at an increased risk of tumor development, compared to mixed-breed canines. Upon evaluation of VMDB case submissions (Fig. 3), only the Sporting group was over-represented, compared to our study control population (COPLOW). However, breeds within this class included the American Cocker Spaniel, and Golden and Labrador Retriever, which were over-represented on an individual breed basis. These findings were expected, due to the nature of COPLOW submissions, and believed to result in minimal bias.

The etiology of these vascular tumors remains unknown, although previous reports have proposed UV light as a risk factor. In 1896, UV light was first recognized to be associated with skin cancer in humans and, since that time, numerous research studies using laboratory animal models have demonstrated the carcinogenic effects of UV radiation. Naturally occurring tumors of cutaneous origin have been associated with UV exposure in animals, including squamous cell carcinoma of the ocular adnexa in white faced cattle, squamous cell carcinoma of the pinna and external nares of white cats, and cutaneous hemangioma and hemangiosarcoma in dogs. In one study evaluating cutaneous vascular tumors in dogs, a significant association between hemangiosarcoma and solar dermatosis was noted. UV exposure and effect depend on numerous variables including environmental, pigimentary, and behavioral factors. Specifically, environmental exposure to, and spectral distribution of sunlight depends on solar elevation, which is influenced by season and latitude, altitude, ozone, cloud cover, local air pollution, and ground reflectivity. In the present study comparing case and control status, UV exposure based on geographic location was not a statistically significant variable. However, a linear trend was noted that showed an increased risk of tumor development with increased UV exposure. These findings suggest a role for UV radiation in the etiology of hemangiomas and hemangiosarcomas of the conjunctiva in dogs. In addition, there was a statistically significant risk for conjunctival hemangiosarcoma development, compared to hemangioma, with increased UV levels.

We have demonstrated that these tumors have a strong predilection for the leading edge of the nictitating membrane and on the temporal bulbar conjunctiva. The leading edge of the
nictitating membrane was the most common site of involvement (41/108, 38%), followed by the temporal bulbar conjunctiva (33/108, 30.6%). Hemangiosarcomas occurred with a greater frequency at the temporal bulbar conjunctiva than hemangiomas, but this difference was not statistically significant. These findings may indicate a specific site predilection based on tumor type; however, further evaluation is required. In cases of both hemangioma (36) and hemangiosarcoma (21), there was a tendency for the conjunctival surface of the right eye to be affected, compared to the left eye. This is in contrast to findings from a review of previous case reports; however, this difference was not statistically significant.

Specific anatomic features of the skin, including epidermal thickness, the presence of hair follicles, and degree of pigmentation contribute to individual UV exposure levels and thus the risk of tissue damage. Kirby-Smith et al. demonstrated a greater penetration depth and increased risk of UV induced neoplastic transformation in regions lined by a thin epidermis, as is true of the conjunctival surface. Furthermore, the conjunctiva is naturally devoid of hair follicles, with a highly variable, breed-dependent degree of epithelial pigmentation. Pigmentation has been shown to be a significant inhibitory factor for the development of squamous cell carcinomas of the conjunctiva in cattle. All 38 cases of hemangiosarcoma and 57 of 70 (81.4%) cases of hemangioma in our series of tumors demonstrated a lack of pigmentation in nonaffected areas of the tissue sampled. Of the 13 cases where pigmentation was noted, eight cases demonstrated evidence of chronic inflammation, with pigmentation likely occurring secondarily.

The distinction between hemangioma and hemangiosarcoma is based on the histologic degree of differentiation and extent of local tissue invasion. This distinction is of particular importance as it pertains to the biologic behavior of the tumor, specifically growth and recurrence rates. Examination of tumor size and duration prior to initial presentation demonstrated that conjunctival hemangiosarcomas were larger and were of shorter duration than hemangiomas, with average durations of 1.5 and 3 months, respectively. Conjunctival hemangiosarcomas were more likely to reoccur at the primary site (11/20, 55%) than hemangiomas (3/29, 10.3%). These findings confirm that hemangiosarcomas demonstrate more aggressive behavior than hemangiomas, as would be expected based on histologic evaluation. Interestingly, eight recurrent cases involved the bulbar conjunctiva and support previous suggestions that the bulbar conjunctiva is at an increased risk of recurrence due to initial incomplete excision. Surprisingly, the tendency to recur did not correlate with the appearance of tumor-free surgical margins. However, a discrepancy between margin status and recurrence rates in this study may be attributed to improper tissue orientation because of small sample size and/or to local micrometastasis at the time of excision.

Primary conjunctival vascular tumors are of endothelial origin. None of the tumors evaluated in this study had evidence of metastasis at the time of excision, in keeping with the absence of published reports of ocular vascular tumor metastasis. The current treatment recommendation for these tumors is early, wide surgical excision to obtain tumor-free margins. Such surgery may be curative, although recurrence is possible. Three cases in this study underwent surgical re-excision following histologic evidence of incomplete excision; none of these tumors recurred. Some authors advocate the use of ancillary therapy, but there are no published reports demonstrating any additional benefit or greater efficacy from such additional treatments. In this study, adjunctive therapy was used postexcision for 22 cases (14 hemangiomas, eight hemangiosarcomas), with cryotherapy being the most common. Although follow-up data were limited and statistical analysis was not possible, use of such treatments appeared to result in decreased risk of recurrence for both hemangiomas and hemangiosarcomas. In six of the 22 cases, there was recurrence (four hemangiomas, two hemangiosarcomas) that did not correlate with histologic evaluation of tumor margins.

There are many limitations of a retrospective study pertaining to the acquisition of clinical data, and the current study suffers from some of those limitations. A total of 86 out of a requested 108 replies were obtained from veterinarians, and follow-up information was available for only 49 of these cases. The most common reasons for lack of follow-up information were the failure of the owners to return for subsequent examination and purging of medical records. Additionally, the estimation of UV exposure based solely on geographic location of case submissions may not truly represent individual environmental exposure, as several variables including housing, activity, and travel history are not accounted for.

In conclusion, conjunctival hemangiomas and hemangiosarcomas are tumors of vascular endothelial origin. There is a trend for these tumors to occur in dog breeds likely to spend large amounts of time outdoors and in breeds with poorly pigmented ocular adnexa. These tumors often present as superficial, red, and smooth to multilobulated exophytic nodules, which are focal in distribution and involve the nonpigmented conjunctiva along the leading edge of the nictitating membrane or temporal bulbar surface. The etiology of these vascular tumors remains unknown; however, their strong site predilection, involvement of nonpigmented conjunctival epithelium, and development within breed classes with increased outdoor activity are all strongly suggestive of UV light as a significant risk factor. There was a significant correlation between development of hemangiosarcomas and increased UV levels. For these tumors definitive histologic diagnosis is required and is predictive of tumor behavior. Hemangiosarcomas demonstrate aggressive locally invasive tissue involvement, with an increased risk of recurrence compared to hemangiomas. It is critical to differentiate primary ocular hemangiosarcoma from metastatic hemangiosarcoma. Early, complete surgical excision is recommended for ocular hemangiomas and hemangiosarcomas and may be curative, although recurrence is possible. Use of ancillary therapy, specifically cryotherapy, appears to be beneficial in decreasing recurrence; however, further evaluation is required.
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