Presumed solitary intraocular or conjunctival lymphoma in dogs and cats: 9 cases (1985–2013)

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Objective—To determine prevalence, reason for evaluation, treatment, and outcome for dogs and cats with presumed solitary ocular lymphoma (PSOL).

Design—Retrospective case series.

Animals—7 dogs and 2 cats with PSOL.

Procedures—Medical records were reviewed. Progression-free survival time (PFST) and overall survival time (OST) were determined.

Results—Animals with intraocular (4 dogs and 1 cat) or conjunctival (3 dogs and 1 cat) lymphoma represented 0.1% and 0.08% of patients with lymphoma evaluated at the hospital during the study period, respectively. Animals with intraocular lymphoma represented 0.19% of all patients with uveitis; animals with conjunctival lymphoma represented 0.16% of all patients with conjunctivitis. Tumors included B-cell (2 intraocular and 1 conjunctival), non–B-cell, non–T-cell (1 intraocular), and T-cell (3 conjunctival) neoplasms; immunophenotype of 2 uveal lymphomas was not determined. Treatments included enucleation (4 intraocular) and chemotherapy (3 intraocular and 2 conjunctival). All dogs with intraocular lymphoma developed neurologic signs. Lymph node metastasis was detected in 2 patients with conjunctival lymphoma. Median PFST and OST were 178 days for all animals with PSOL, dogs with PSOL, and animals with intraocular lymphoma. Median PFST and OST for animals with conjunctival lymphoma were 221 and 549 days, respectively.

Conclusions and Clinical Relevance—Results indicated PSOL was uncommon, but should be considered a differential diagnosis for animals with uveitis or conjunctivitis. Performance of MRI and cytologic analysis of CSF and regional lymph node aspirate samples may be beneficial for such patients. Prognosis seemed to be better for animals with conjunctival lymphoma than it was for those with intraocular lymphoma. (*J Am Vet Med Assoc* 2014;244:460–470)

Lymphoma is a common neoplasm of small animals, accounting for 24% and 33% of neoplasms in dogs and cats, respectively.[1] The most common type in dogs is multicentric lymphoma, which accounts for nearly 80% of lymphomas in that species.[1] In cats, abdominal forms of lymphoma, including those with alimentary, hepatosplenic, or renal involvement, account for nearly 80% of lymphomas.[1] Ocular manifestations of lymphoma are variable in dogs. In 1 prospective study[2] of multicentric lymphoma in dogs, ocular disease was the second most common clinical finding after peripheral lymphadenomegaly, with 37% of dogs affected. However, in 2 other studies[3,4] of dogs with multicentric lymphoma, ocular involvement was found in 0.03% and 0.3% of animals. Although intraocular lymphoma has been described for dogs and cats,[5–8] a lack of systemic involvement was confirmed by necropsy in only 1 case report for a dog with uveal lymphoma that died as a result of vehicular trauma following enucleation of the neoplastic eye.[5] Conjunctival lymphoma in dogs and cats has also been reported;[9–14] however, a lack of systemic involvement was confirmed for dogs in only 2 reports.[11,14] Likewise, intraocular and primary conjunctival lymphomas each represent approximately 1% of non-Hodgkin's lymphomas in humans.[15–18] Thus, it seems that PSOL (ie, ocular [intraocular or conjunctival] lymphoma without proven involvement in other anatomic locations) is rare in dogs, cats, and humans.

Abbreviations

CETL	Cutaneous epitheliotropic lymphoma
OST	Overall survival time
PFST	Progression-free survival time
PSOL	Presumed solitary ocular lymphoma

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All animals in this study were evaluated and treated at the University of California-Davis Veterinary Medical Teaching Hospital.

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Primary anatomic location,[19,20] anatomic distribution (stage),[21–25] and presence or absence of clinical signs (substage)[23,24,26] may be prognostic factors for dogs and cats with lymphoid neoplasia. However, application of World Health Organization tumor staging guidelines[27] is problematic for animals with PSOL and further investigation is warranted. The conjunctiva has lymphatic vessels and a resident population of lymphoid cells and is part of the mucosa-associated lymphoid tissue.[28,29] As such, conjunctival lymphomas would typically be classified as stage 1 tumors.[27] By contrast, intraocular tissues (uveal tissues in particular) have typically been considered to be devoid of lymphatic vessels or cells.[30] Thus, intraocular lymphomas likely should be classified as stage 5 tumors on the basis of World Health Organization guidelines. However, results of recent studies of sheep[31] and humans[32,33] indicate uveal tissue may have lymphatic channels, suggesting that a revision of this classification scheme may be necessary to improve determination of a prognosis for patients with lymphoma at only an ocular site. To the authors' knowledge, only reports of single cats or dogs with PSOL have been published. Therefore, the purpose of the study reported here was to determine the prevalence, reason for evaluation, clinical signs, treatments, and outcomes (OST and PFST) of dogs and cats with PSOL evaluated at a single teaching hospital.

Materials and Methods

Animals—The electronic medical records system at the University of California-Davis Veterinary Medical Teaching Hospital was searched to identify dogs and cats evaluated between January 1985 and April 2013 with lymphoma of an ocular tissue without known involvement of nonocular tissues. To exclude animals with nonocular tissue involvement, results of physical examinations, CBCs, serum biochemical analyses, abdominal ultrasonography, and thoracic radiography (including left lateral, right lateral, and dorsoventral views) were assessed for each dog and cat. An ophthalmic examination had been performed by a board-certified ophthalmologist or resident in-training for all but 1 animal. Typically, additional testing, including serologic analyses for detection of infectious diseases and cytologic evaluation of aspirate samples of nonocular sites (liver, spleen, and lymph nodes), had been performed on ≥ 1 occasions. For 2 dogs, one or more of the following serologic tests were performed: ELISAs for detection of *Dirofilaria immitis* antigen or antibodies against *Anaplasma phagocytophilum*, *Borrelia burgdorferi*, and *Ehrlichia canis*; quantitative immunodiffusion assay for detection of antibodies against *Coccidioides immitis*; latex agglutination testing for detection of *Cryptococcus neoformans* antigen; and microscopic agglutination tests for detection of antibodies against *Leptospira interrogans* serovars Bratislava, Canicola, Grippotyphosa, Hardjo, Icterohaemorrhagiae, and Pomona. For 1 cat, serologic testing for FeLV antigen and antibodies against FIV was performed with ELISAs.

Data collection and analysis—For all patients, information retrieved from the medical records included age, sex, breed, hospital service that first examined the animal, diagnostic tests performed, method with which lymphoma was diagnosed, lymphoma immunophenotype, treatment, PFST, and OST. The PFST was defined as the time between histopathologic or cytologic diagnosis and detection of lymphoma recurrence locally or at a distant anatomic site. The OST was defined as the time between histopathologic or cytologic diagnosis and death. Survival times were censored if patients were alive at the time of data analysis or if follow-up data were not obtainable. Follow-up information was obtained by means of evaluating the electronic medical records for patients that died or were euthanized at University of California-Davis Veterinary Medical Teaching Hospital or by phone calls to owners or referring veterinarians for patients that were alive at the time of the last appointment. Median PFST and OST were estimated with the Kaplan-Meier product limit method. To identify reference populations of animals, the electronic medical records system was searched to identify dogs or cats with a diagnosis of any type of lymphoma, anterior uveitis of any cause, or conjunctivitis of any cause during the same period during which animals with lymphoma were identified.

The diagnosis of lymphoma was confirmed for all patients in this study following histologic evaluation of sections of tissue samples by ≥ 1 board-certified pathologists (CMR or RRD). For determination of immunophenotype, results of immunohistochemical analyses performed at the time of the initial diagnosis were reviewed if available. If immunohistochemical analysis was not performed initially, such analysis was performed for the purposes of this study with various antibodies: rat anti-CD3[a] (T-cell marker; 1:10 dilution), mouse anti-CD79a[b] (B-cell marker; 1:150 dilution), rabbit anti-CD20[c] (B-cell marker; 1:300 dilution[34]), mouse anti-dog CD45[d] (panleukocyte marker; 1:50 dilution), mouse anti-dog CD18[e] (panleukocyte marker; 1:100 dilution), and mouse anti-dog CD45RA[f] (B-cell subset marker; 1:10 dilution). Tissue sample slides were incubated with primary antibodies at room temperature (21°C) for 1 hour, followed by heat antigen retrieval in citrate buffer[g] for 30 minutes at 100°C. Negative control slides were treated with PBS solution in lieu of primary antibody. For 1 dog with a lymphoma immunophenotype that was not clearly determined, molecular clonality testing for the T-cell receptor (T cells) and immunoglobulin heavy chain (B cells) was performed.[35]

Results

During the 28.3-year period reviewed, PSOL was diagnosed in 7 dogs and 2 cats, involving intraocular (4 dogs and 1 cat) or conjunctival (3 dogs and 1 cat) tissues. During the same period, among animals evaluated at the University of California-Davis Veterinary Medical Teaching Hospital, lymphoma at ≥ 1 site was diagnosed in 4,877 animals (3,161 dogs and 1,716 cats); anterior uveitis of any cause was diagnosed in 2,655 animals (2,147 dogs and 508 cats), and conjunctivitis of any cause was diagnosed in 2,573 animals (1,760 dogs and 813 cats). Thus, dogs or cats with PSOL represented 0.18% of all patients with lymphoma (dogs, 0.22%; cats, 0.12%). Patients with presumed solitary intraocular lymphoma represented 0.1% of all patients with

lymphoma (dogs, 0.13%; cats, 0.06%) and 0.19% of all patients with uveitis (dogs, 0.19%; cats, 0.2%). Patients with presumed solitary conjunctival lymphoma represented 0.08% of all patients with lymphoma (dogs, 0.09%; cats, 0.06%) and 0.16% of all patients with conjunctivitis (dogs, 0.17%; cats, 0.12%).

The mean ± SD (median [range]) ages of dogs with any type of PSOL (n = 7) and those with intraocular (4) and conjunctival (3) lymphoma only were 6.7 ± 3.3 (8 [1 to 11]), 8.5 ± 1.7 (8 [7 to 11]), and 4.3 ± 3.5 (4 [1 to 8]) years, respectively. The cats with intraocular or conjunctival lymphoma were 10 or 11 years old, respectively. Of the 7 dogs with PSOL, 4 were male and 3 were female. Various dog breeds were represented, including Labrador Retriever (n = 2), Staffordshire Terrier (2), and 1 each of Border Collie, Rottweiler, and mixed breed. Of the cats, 1 was female and 1 was male; both were domestic cats. Four dogs were first evaluated by personnel of the ophthalmology service. The other 5 patients (3 dogs and 2 cats) had lymphoma that was previously diagnosed on the basis of histopathologic findings (2 with intraocular and 3 with conjunctival lymphoma); these animals were first evaluated by personnel of the oncology service. Only 1 dog that was first evaluated by personnel of the ophthalmology service had lymphoma that had previously been diagnosed (by means of analysis of a conjunctival biopsy sample). All other dogs that were first evaluated by the ophthalmology service were referred for further evaluation of uveitis (n = 1), panophthalmitis (1), or chorioretinitis (1). All patients with intraocular lymphoma had clinically evident uveitis manifest as anterior uveitis (2 dogs and 1 cat) or endophthalmitis (2 dogs). In addition, 1 dog and 1 cat had glaucoma, 1 cat had anterior lens luxation, and 2 dogs had a visibly thickened iris detected during initial examination (**Figure 1**). Two dogs also had abnormalities of the contralateral eye (panuveitis and retinal detachment in one and anterior uveitis and hyalitis in the other). Two dogs with intraocular lymphoma were blind in the affected eye at the time of the initial evaluation at the hospital. Three patients with conjunctival lymphoma had an initial diagnosis of conjunctivitis. All patients had conjunctival thickening that was detected during the initial evaluation; 2 patients had regional thickening of the bulbar (1 dog) or palpebral (1 cat) conjunctiva, and 2 dogs had discrete conjunctival masses. Prior to referral, the 3 patients with an initial diagnosis of conjunctivitis received bacitracin-neomycin-polymyxin (n = 1), neomycin-polymyxin-dexamethasone (1), or dexamethasone (1) applied topically to the affected eye; none had improvement with such treatment.

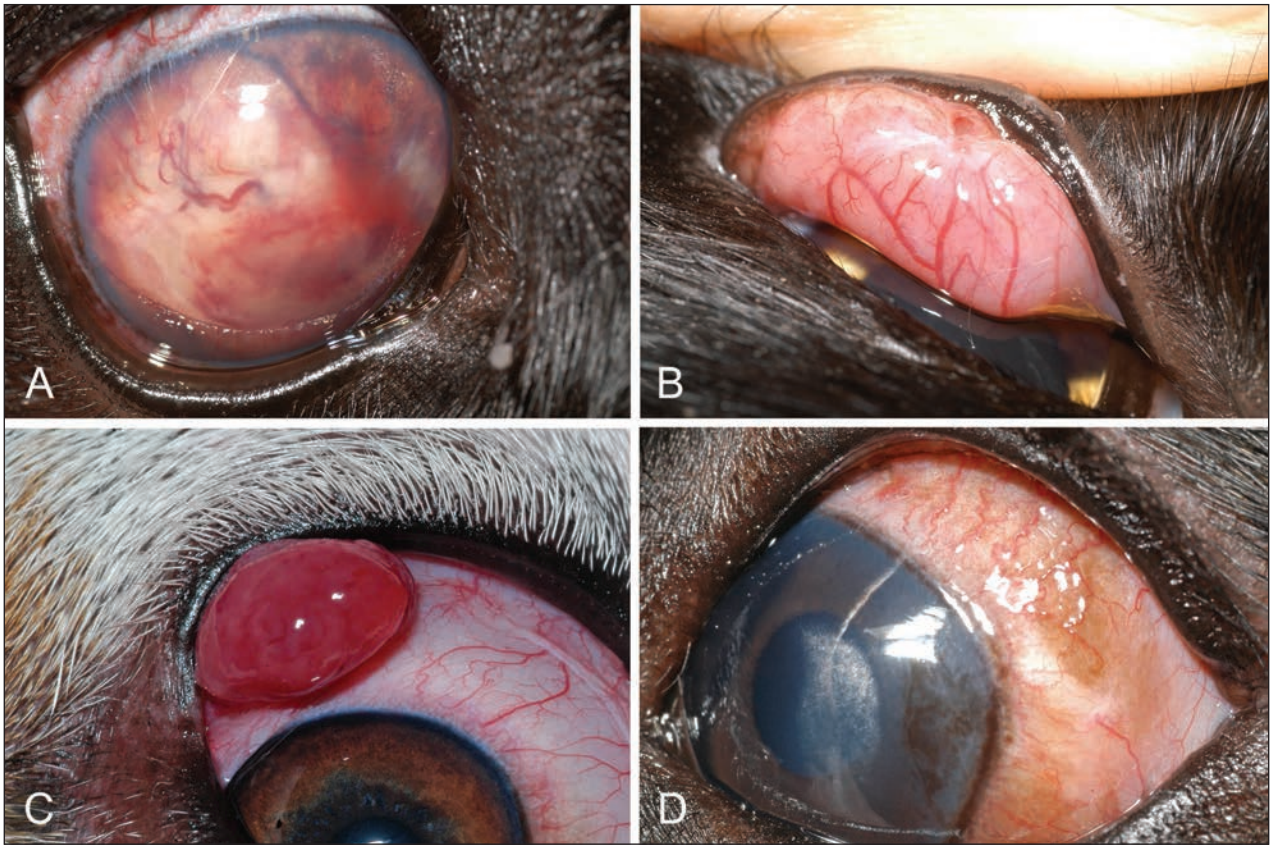

Figure 1—Representative photographs of eyes of cats and dogs with intraocular or conjunctival lymphoma. A—Right eye of a dog with intraocular lymphoma. Notice the hypopyon and hyphema, filling most of a shallow anterior chamber, and the rubeosis iridis. B—Left eye of a cat with conjunctival lymphoma. Notice the diffuse hyperemia and marked, lobulated thickening of the superior palpebral conjunctiva. C—Left eye of a dog with conjunctival lymphoma. Notice the marked, well-demarcated focal thickening of the medial aspect of the bulbar conjunctiva. D—Left eye of a dog with conjunctival lymphoma. Notice the mild thickening and irregularity of the lateral aspect of the bulbar conjunctiva; the dorsal and ventral aspects of the bulbar conjunctiva were similarly affected. There is also diffuse conjunctival pigmentation and superficial corneal vascularization laterally, as well as a semicircular area of corneal lipid or mineral accumulation in the lateral aspect of the paraxial region of the cornea.

Results of CBCs, serum biochemical analyses, thoracic radiography (3 views), and abdominal ultrasonography did not indicate evidence of neoplasia for any animal tested. In addition, urinalyses were performed for all animals with the exception of 2 dogs; results of these tests did not reveal evidence of neoplasia. Cytologic analysis of aspirate samples of nonocular sites was performed for 7 animals (5 dogs and 2 cats); these included bone marrow (n = 6) or other organs (8), including ≥ 1 lymph nodes (3), liver (2), or spleen (3). Results of these diagnostic tests did not indicate evidence of lymphoma at a nonocular site. Prior to determination of a diagnosis of lymphoma, infectious disease testing was performed for 3 animals (2 dogs and 1 cat) with uveitis. For 2 dogs, serologic testing for *D immitis* antigen (n = 1), *C neoformans* antigen (1), and antibodies against *A phagocytophilum* (1), *B burgdorferi* (2), *C immitis* (1), *E canis* (2), and *L interrogans* serovars Bratislava, Canicola, Grippotyphosa, Hardjo, Icterohaemorrhagiae, and Pomona (1) was performed; all results were negative. For 1 cat, serologic testing for FeLV antigen and antibodies against FIV was performed; results were negative for both tests. According to records provided by the referring veterinarians, 1 cat had circulating antibodies against FIV, and 1 cat had circulating antibodies against *Bartonella* spp.

Intraocular lymphoma was diagnosed for 1 dog by means of cytologic evaluation of a fine-needle aspirate of an iris mass and an aqueous humor sample obtained by means of aqueocentesis. This dog was included in another study.[36] All other diagnoses were made on the basis of results of histologic evaluation of conjunctival biopsy samples or enucleated globes. For all animals, the diagnosis of lymphoma was made on the basis of detection of a monomorphic population of atypical lymphoid cells, characterized by large round cells, scant basophilic cytoplasm, large round to indented nuclei, and mitotic activity (**Figure 2**). Conjunctival biopsy samples typically had a mixed inflammatory infil-

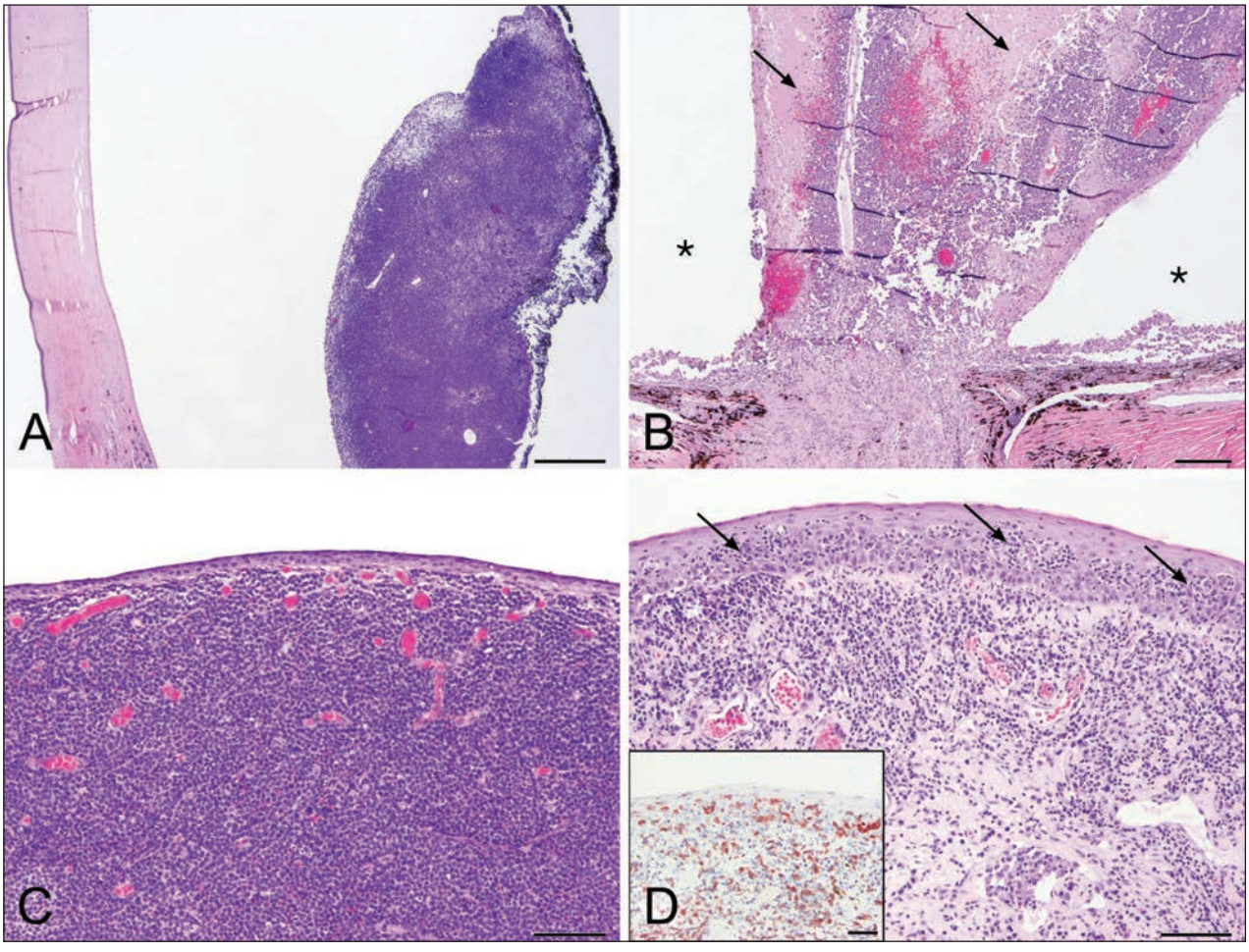

Figure 2—Representative photomicrographs of sections of eyes of cats or dogs with intraocular or conjunctival lymphoma. A—Photomicrograph of the iris (right side of the image) and cornea (left side of the image) of a cat with uveal B-cell lymphoma. Notice the marked infiltration of the iris with a monomorphic infiltrate of neoplastic lymphocytes. The separation of the posterior aspect of the iris epithelium is an artifact. H&E stain; bar = 500 μm. B—Photomicrograph of the retina, choroid, sclera, and optic nerve of a dog with retinal B-cell lymphoma. Neoplastic lymphocytes surround retinal blood vessels, interspersed with areas of necrosis (arrows). The retina is detached, expanding the subretinal space (asterisks). H&E stain; bar = 200 μm. C—Photomicrograph of the bulbar conjunctiva of a dog with conjunctival B-cell lymphoma. Neoplastic lymphocytes expand the substantia propria but do not invade the epithelium. H&E stain; bar = 100 μm. D—Photomicrograph of the bulbar conjunctiva of a dog with conjunctival epitheliotropic T-cell lymphoma. Large, atypical T lymphocytes infiltrate the epithelium (arrows) and are admixed with inflammatory cells in the substantia propria. H&E stain; bar = 100 μm. Inset—Photomicrograph of the bulbar conjunctiva of the same dog in D confirming the T-cell lineage of neoplastic lymphocytes in the epithelium and a subset of cells in the substantia propria. CD3 immunohistochemistry; bar = 50 μm.

trate of mature lymphocytes, plasma cells, neutrophils, and rare eosinophils. Immunophenotype was determined for 2 of 4 uveal lymphomas. One was classified as B-cell lymphoma. One was classified as non–B-cell and non–T-cell lymphoma on the basis of weak immunohistochemical labeling with the T-cell marker CD3 and lack of labeling with B-cell markers CD20, CD79a, and CD45r; results of molecular assays[35] indicated polyclonal results for both T-cell receptor and immunoglobulin heavy chain (B cells) gene rearrangements for this tumor. One uveal lymphoma could not be further classified because the lymphoid cells were not labeled with any antibody tested, including panleukocyte markers CD45, CD18, and CD45RA; however, the diagnosis of lymphoma for this patient was confirmed on the basis of cellular morphology by consensus of both pathologists (CMR and RRD). The fourth uveal tumor was diagnosed cytologically and immunophenotyping was not attempted. The final patient with intraocular lymphoma had a retinal tumor; this was classified as a B-cell lymphoma on the basis of results of assessment of CD79a immunoreactivity. All 4 conjunctival lymphomas were unilateral. Three of these tumors were classified as T-cell lymphoma (2 dogs and 1 cat), and 1 was classified as B-cell lymphoma (1 dog). Conjunctival lymphomas in 2 dogs were classified as epitheliotropic; one diffusely involved the bulbar conjunctiva, and the other was a discrete bulbar conjunctival nodule.

Four (3 dogs and 1 cat) of 5 patients with intraocular lymphoma underwent enucleation. Chemotherapy was started for 3 dogs with intraocular lymphoma, 2 of which also underwent enucleation prior to chemotherapy. These 3 dogs were treated with a 26 week-long modified University of Wisconsin-Madison chemotherapy protocol (ie, UW-25) with a split induction. That is, L-asparaginase (286 to 357 U/kg [130 to 162 U/lb], SC) was administered alone during the first week and vincristine (0.6 to 0.7 mg/m^2, IV) was administered alone during the second week. One dog received vinblastine (1.5 mg/m^2, IV) in place of vincristine after developing gastrointestinal tract toxic effects following vincristine administration IV (dose, 0.7 mg/m^2). Two of these dogs completed the full 26-week protocol; 1 dog received only the first 3 weeks of treatment prior to death at home following a seizure. One of the 3 dogs had received a single dose of lomustine (70 mg/m^2, PO) before being switched to the modified chemotherapy protocol because no improvement in vision had been detected. Topical application of ophthalmic medications was prescribed for 2 dogs with intraocular lymphoma; these included 1% prednisolone acetate (2 dogs; 1 drop, q 2 to 4 h), 0.1% diclofenac (1 dog; 1 drop, q 6 h), 0.5% timolol (1 dog; 1 drop, q 8 h), and 2% dorzolamide (1 dog; 1 drop, q 8 h). It was possible to monitor changes in ocular signs during chemotherapy for 2 of 3 dogs with intraocular lymphoma; both had some evidence of improvement. One dog underwent enucleation of its right eye and had evidence of panuveitis and a weak menace response in the left eye; this dog had subjective improvement in vision in the left eye 50 days after starting chemotherapy but seemed to be blind in that eye 60 days later and remained blind during the remainder of the treatment protocol. The other dog, which had an iridal mass in the right eye and uveitis in both eyes, had a reduction in severity of uveitis in both eyes and resolution of the iridal mass in the right eye approximately 1 week after initiation of chemotherapy. The severity of aqueous flare decreased during chemotherapy in both of these dogs.

Chemotherapy was started for 1 dog and 1 cat with conjunctival lymphoma. The owners of the other 2 dogs with conjunctival lymphoma declined treatment. The dog that was treated had concurrent diabetes mellitus and received an initial dose of L-asparaginase (200 U/kg [91 U/lb], SC) followed by 5 doses of lomustine (4 doses of 70 mg/m^2 3 weeks apart followed by 1 dose of 60 mg/m^2 because of suspected hepatic toxic effects [determined on the basis of high activities of serum alkaline phosphatase, alanine aminotransferase, and γ-glutamyltransferase]) and 1% prednisolone acetate (1 drop topically in the left eye, q 8 h). No clinical evidence of infiltrative disease was detected 22 days after the start of chemotherapy; however, clinical evidence of conjunctivitis remained. Recurrence of conjunctival lymphoma was clinically detected 42 days after remission was achieved (85 days after initial diagnosis) in the dog. The cat with conjunctival lymphoma underwent the entire course of the modified chemotherapy protocol and received prednisone (1.5 mg/kg [0.68 mg/lb], PO, q 24 h) during that time; complete clinical remission was achieved. However, local recurrence was detected 221 days after determination of the diagnosis, and the cat was treated with radiation therapy (energy, 6 MeV) administered in 10 daily (Monday through Friday) 3-Gy doses. Local recurrence was detected again 311 days after determination of the diagnosis (90 days after radiation treatment); at that time, the cat was treated with various rescue protocols including reinitiation of drugs in the modified chemotherapy protocol, lomustine (37 mg/m^2), cytosine arabinoside (303 to 346 mg/m^2), and an intralesional injection of triamcinolone (10 mg). The cat had transient responses to all of these treatments; however, bilateral neoplastic involvement of mandibular lymph nodes was detected 467 days after determination of the diagnosis. The cat was euthanized 549 days after determination of the diagnosis.

Two dogs (1 with intraocular lymphoma and 1 with conjunctival lymphoma) underwent repeated diagnostic testing to determine disease status (at 136 or 208 days after determination of the diagnosis, respectively). These tests included a CBC (n = 2), serum biochemical analyses (2), thoracic radiography (2), abdominal ultrasonography (2), and cytologic evaluation of fine-needle aspirate samples of a lymph node (1), bone marrow (1), lung (1), liver (2), or spleen (2). No evidence of neoplasia was found in the dog that underwent enucleation for treatment of intraocular lymphoma. Results of cytologic examination and immunocytochemical analysis of aspirate samples of liver, lung, and lymph node tissues from the dog with conjunctival lymphoma confirmed metastatic T-cell lymphoma. Prior to death or euthanasia, all 4 dogs with intraocular lymphoma developed evidence of neurologic disease (seizures in 4 dogs, obtundation in 2 dogs, ataxia in 1 dog, and circling in 1 dog). One dog and 1 cat with conjunctival lymphoma developed mandibular (n = 2) or axillary region

(1) lymph node enlargement 136 and 467 days following determination of the diagnosis, respectively; lymphoma was confirmed at these sites by means of cytologic evaluation of fine-needle aspirate samples from both animals.

Four dogs and 1 cat were euthanized, 1 dog died, 1 cat was lost to follow-up, and 2 dogs with conjunctival lymphoma were alive and free of disease at 115 and 1,216 days after determination of the diagnosis. Of the animals that were euthanized, 3 dogs with intraocular lymphoma were euthanized because of progressive neurologic disease, and 1 dog and 1 cat with conjunctival lymphoma were euthanized 2 and 19 days, respectively, following a diagnosis metastatic disease. Necropsy was performed for only 1 patient (a dog with presumed solitary conjunctival lymphoma). Necropsy revealed T-cell lymphoma in the conjunctiva of the left eye, lungs, liver, stomach, mandibular lymph nodes, lymph nodes in the region of the hilus of the lungs, and lymph nodes in the mesentery of the small intestine.

Median PFST (**Figure 3**) and OST (**Figure 4**) for all animals with PSOL were both 178 days (range, 19 to 1,325 days). Median PFST (**Figure 5**) and OST (**Figure 6**) for all patients with intraocular lymphoma were also both 178 days (range, 19 to 1,325 days). Median (range) PFST (**Figure 7**) and OST (**Figure 8**) for all patients with conjunctival lymphoma were 221 days (115 to 1,216 days) and 549 days (115 to 1,216 days), respectively. For dogs only, the median PFST (**Figure 9**) and OST (**Figure 10**) were both 178 days (range, 19 to 1,325 days). Insufficient data were available to determine PFST and OST for cats only. For the 1 cat with conjunctival lymphoma, the PFST and OST were 221 and 549 days, respectively.

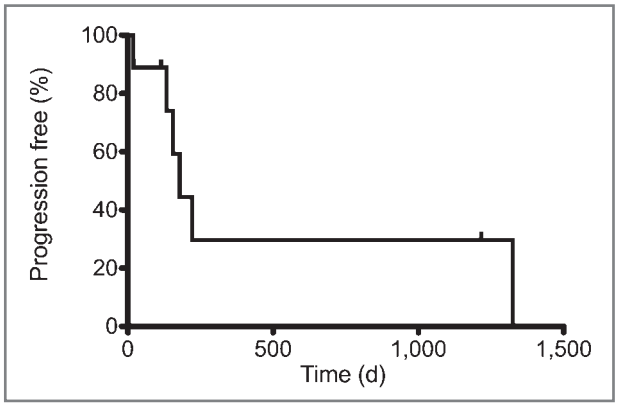

Figure 3—Kaplan-Meier curve of PFST for 9 animals (7 dogs and 2 cats) with PSOL. Median PFST for all animals was 178 days (range, 19 to 1,325 days).

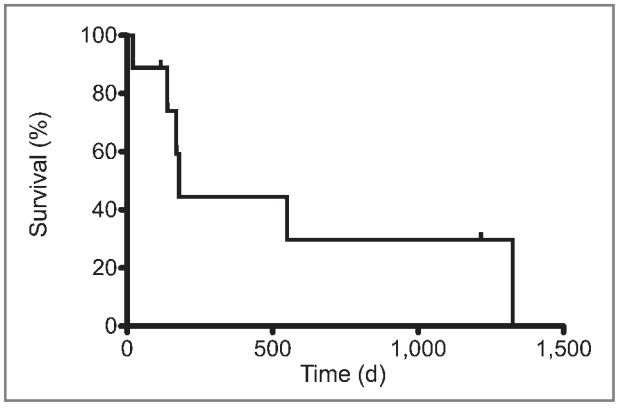

Figure 4—Kaplan-Meier curve of OST for 9 animals (7 dogs and 2 cats) with PSOL. Median OST for all animals was 178 days (range, 19 to 1,325 days).

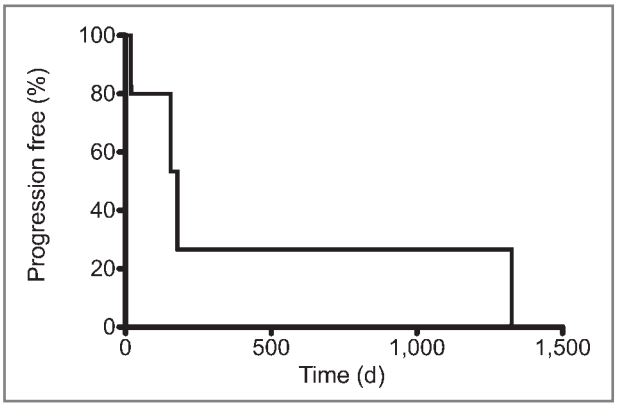

Figure 5—Kaplan-Meier curve of PFST for 5 animals (4 dogs and 1 cat) with presumed solitary intraocular lymphoma. Median PFST was 178 days (range, 19 to 1,325 days).

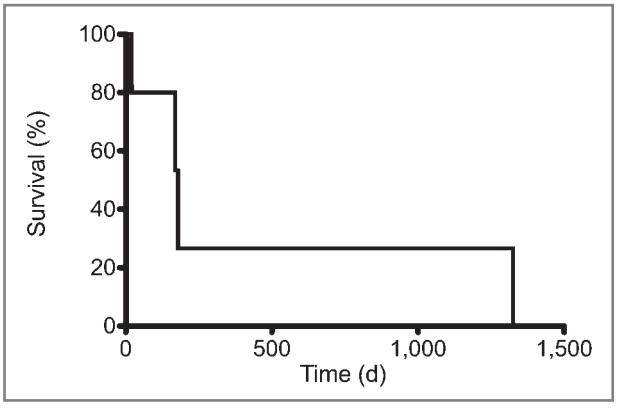

Figure 6—Kaplan-Meier curve of OST for 5 animals (4 dogs and 1 cat) with presumed solitary intraocular lymphoma. Median OST was 178 days (range, 19 to 1,325 days).

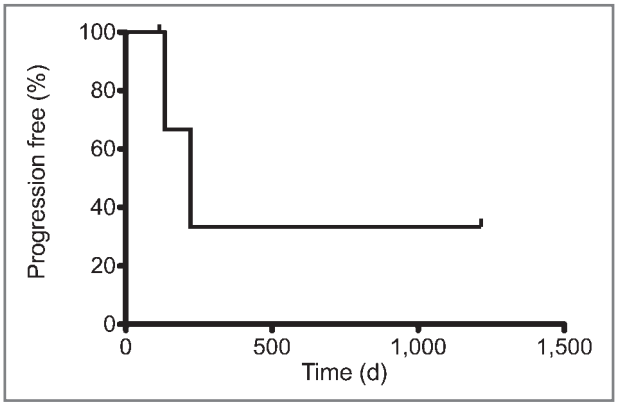

Figure 7—Kaplan-Meier curve of PFST for 4 animals (3 dogs and 1 cat) with presumed solitary conjunctival lymphoma. Median PFST was 221 days (range, 115 to 1,216 days).

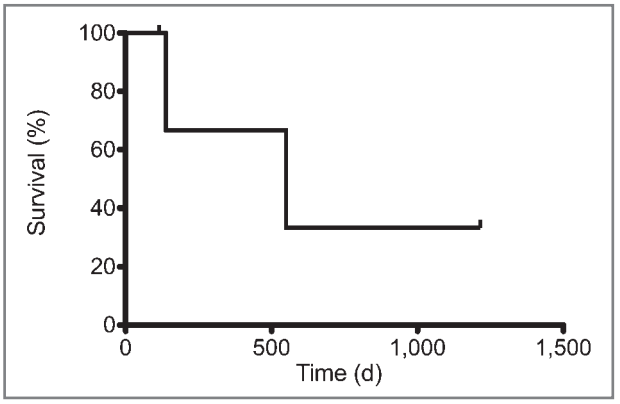

Figure 8—Kaplan-Meier curve of OST for 4 animals (3 dogs and 1 cat) with presumed solitary conjunctival lymphoma. Median OST was 549 days (range, 115 to 1,216 days).

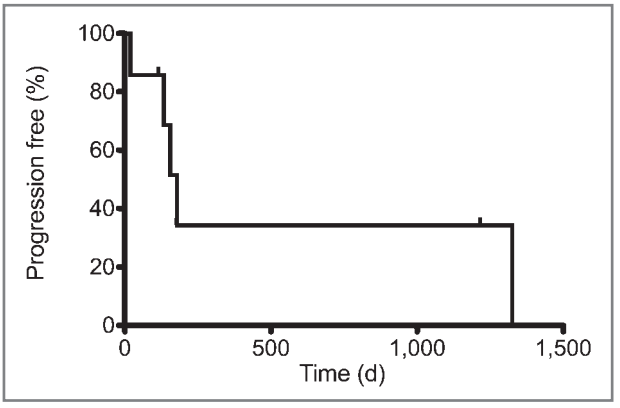

Figure 9—Kaplan-Meier curve of PFST for 7 dogs with PSOL. Median PFST for all dogs was 178 days (range, 19 to 1,325 days).

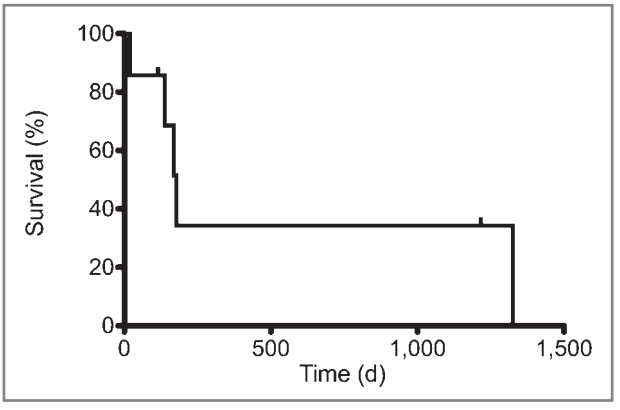

Figure 10—Kaplan-Meier curve of OST for 7 dogs with PSOL. Median OST for all dogs was 178 days (range, 19 to 1,325 days).

Discussion

Results of the present study suggested that PSOL develops infrequently in dogs and cats; such tumors represented only 0.18% of all lymphoma diagnoses at the institution of this study. Conjunctival lymphoma developed in animals at a frequency that was 80% of the frequency for intraocular lymphomas (percentage of all lymphomas detected, 0.08% and 0.1%, respectively). This is similar to but lower than the reported[15–18] prevalence of PSOL in humans (approx 1%). The true prevalence of solitary conjunctival and intraocular lymphoma may have been lower than that determined in the present study because the selection criteria would not have excluded patients with unrecognized systemic involvement. All patients in the present study were assessed by means of physical examinations, CBCs, serum biochemical analyses, abdominal ultrasonography, and thoracic radiography. In addition, urinalyses were performed for all but 2 patients and cytologic analysis of aspirate samples obtained from nonocular tissues was performed for all but 1 patient. However, all diagnostic tests were not performed for every patient; therefore, neoplasia at nonocular sites may not have been detected in some patients. The low prevalence of PSOL in this study was consistent with the low number of animals with that problem in other reports. We are aware of only 6 reports[9–14] of conjunctival lymphoma in 4 dogs and 2 cats. For animals in only 2 of the reports[11,14] (2 dogs), results of diagnostic testing indicated there was no involvement of nonocular tissues. To the authors' knowledge, there is only 1 report[5] of presumed solitary intraocular lymphoma in a dog. In that dog, the absence of lymphoma in a nonocular site was confirmed during necropsy that was performed after the patient died as a result of vehicular trauma at an unspecified time following determination of the diagnosis of intraocular lymphoma. To the authors' knowledge, no reports of confirmed solitary intraocular lymphoma in cats have been published. Although ocular lymphoma has been reported[6,8] for 2 cats, results of antemortem nonocular tissue staging were not described.

Although PSOL is rare, patients with multicentric lymphoma often have concurrent ocular signs. Results of 1 prospective study[2] of 94 dogs with multicentric lymphoma indicated that 35 (37%) of those animals had signs of ocular disease; the most common finding was anterior uveitis, which was detected in 25 of 35 (71%) dogs with ocular involvement. Likewise, results of a retrospective study[37] of 102 dogs with anterior uveitis indicated that lymphoma was the most common neoplastic cause of that problem (approx 10% of animals). However, in both of those studies,[2,37] all dogs with lymphoma also had signs of nonocular disease. The development of some ocular signs in patients with lymphoma is attributed to perivascular infiltration by neoplastic cells.[38] Therefore, anterior uveitis may occur as a result of breakdown of the blood-aqueous barrier following neoplastic infiltration of the uvea.[2] Additionally, hematologic abnormalities such as anemia and thrombocytopenia secondary to bone marrow infiltration are theorized to cause some ocular lesions such as retinal hemorrhage.[2] However, results of a prospective study[39] of dogs with anemia and thrombocytopenia did not indicate a significant association between the presence of anemia and ocular lesions. In another study,[2] hematologic abnormalities were more commonly detected in dogs with intraocular lesions than they were in dogs without intraocular lesions; that finding prompted the recommendation that recognition of ocular involvement indicates stage 5 lymphoma. By contrast, none of the 3 animals in the present study with intraocular lymphoma for which bone marrow aspirate samples were

evaluated had neoplastic infiltration of bone marrow. Additionally, other than mild normocytic, normochromic anemia in 1 dog (Hct, 37.6%; reference range, 40% to 55%), no evidence of anemia or thrombocytopenia was detected for any animals in the present study.

Determination of primary anatomic location,[19,20] stage,[21–25] and substage[23,24,26] may be important for determination of a prognosis for dogs and cats with lymphoid neoplasia, but this has not been consistently proven, as results of other studies[40–44] indicate that these factors are not significantly correlated with prognosis. Established guidelines for staging of lymphoid neoplasia in domestic animals[27] suggest that involvement of a single lymph node or lymphoid tissue in a single organ represents stage 1 disease, whereas involvement of blood, bone marrow, or organs other than the liver and spleen represents stage 5 disease. Importantly, stage 5 disease may develop without lymph node, lymphoid organ, spleen, or liver involvement.[27] Given the notion that the globe is devoid of lymphatic vessels[30] and a mature population of lymphocytes,[45] it seems that intraocular lymphoma should be considered stage 5 disease. However, results of recent studies[32,33] suggest that lymphatic vessels exist in the anterior aspect of the uvea of clinically normal sheep and humans. Thus, although the absence of a mature population of lymphocytes in eyes precludes its classification as a secondary lymphoid organ, the presence of lymphatic vessels may indicate eyes are a tertiary lymphoid organ; this would indicate intraocular lymphoma should be classified as stage 1 disease for species with uveal lymphatic vessels. To the authors' knowledge, uveal lymphatic vessels have not been detected in dogs or cats. In contrast to the uveal tract, the presence of mature lymphoid tissue in conjunctiva of dogs and cats[28,29] suggests that solitary conjunctival lymphomas should be classified as stage 1 tumors.

Primary intraocular lymphoma in humans is considered to be a subtype of primary CNS lymphoma and is subcategorized by location (vitreoretinal, choroidal, iridal, or secondary uveal); the vitreoretinal location is most common.[18] Primary intraocular lymphoma comprises 0.3% to 1% of all extranodal non–Hodgkin's lymphoma cases in humans,[16–18] and the predominant phenotype is B-cell lymphoma.[17,18] Ocular involvement precedes the development of CNS signs in 50% to 80% of humans, and most patients develop CNS disease within 2 years after diagnosis.[17] Humans with intraocular lymphoma often have chronic uveitis that is unresponsive to corticosteroid treatment.[17,18] Therefore, in addition to obtaining intraocular tissue samples for cytologic evaluation, performance of MRI and evaluation of CSF samples are recommended for assessment of CNS involvement in such patients.[46] Metastasis to tissues outside of the CNS has been reported for only 6% of humans with primary intraocular lymphoma.[46] Treatment of humans with primary intraocular lymphoma has not been standardized because of the low number of reported cases. However, systemic,[47–49] intrathecal,[50,51] and intraocular[52–56] administration of chemotherapeutic drugs with or without adjunctive orbital radiation therapy[57–59] have been used. Cytosine arabinoside and methotrexate are the most commonly used chemotherapeutic agents because they penetrate the blood-ocular barrier. Results of a retrospective study[57] of humans with primary intraocular lymphoma indicate that the combination of chemotherapy and radiation therapy results in a median survival time of 47 months, which is significantly longer than that for chemotherapy (9.5 months) or radiation therapy (10 months) alone.

Comparison of the data determined in the present study regarding presumed solitary intraocular lymphoma in dogs and cats with data determined in studies of humans with primary intraocular lymphoma indicated interesting similarities. For all 3 species, the prevalence (approx 0.1% in dogs and cats vs 0.3% to 1% in humans), reason for evaluation (anterior uveitis typically unresponsive to anti-inflammatory treatments), immunophenotype (typically B cell), and extension to involve the CNS were common features. All 4 dogs with presumed solitary intraocular lymphoma in the present study developed neurologic signs prior to death or euthanasia, suggesting metastasis or extension into the CNS. Thus, it seemed that there may be a propensity for presumed solitary intraocular lymphoma to subsequently involve the CNS, possibly by means of direct invasion along the optic nerve. One patient in the present study that died because of seizures did not undergo enucleation, and another patient in which 1 eye was enucleated developed seizures prior to euthanasia. Two other patients with unilateral disease that underwent enucleation also developed progressive neurologic signs. In these 2 animals, disease in the contralateral eye may not have been apparent at the time of the initial diagnosis and neither patient was evaluated by an ophthalmologist immediately prior to euthanasia. Necropsies were not performed for any patient with neurologic signs in this study. Other authors[8] described a cat with unilateral anterior uveitis, secondary glaucoma, and blindness for which histologic evidence of lymphoma was detected in the retina, optic nerve, meninges, and anterior aspect of the uvea. After enucleation, that cat developed hypothermia, inappetence, and aggression and was subsequently euthanized. Lymphoma was histologically detected in brain tissue but no other assessed organs of the cat; B-cell lymphoma was diagnosed on the basis of results of evaluation of immunohistochemically stained tissue sections. Animals with presumed solitary intraocular lymphoma in the present study typically developed clinical signs consistent with CNS disease, even without histologic evidence of optic nerve involvement in enucleated eyes. Therefore, results of this study suggested that histologic examination of the optic nerve may not be sufficient to exclude CNS involvement at the time of diagnosis and that MRI and CSF sample analysis should be considered for veterinary patients with presumed solitary intraocular lymphoma. This recommendation is supported by data for humans with solitary intraocular lymphoma[46] and a cat with oculocerebral lymphoma.[8] Confirmation of lymphoma in the CNS would support use of chemotherapeutic drugs with excellent blood-brain barrier penetration. In addition, aqueocentesis should be considered to aid diagnosis of intraocular lymphoma, given that results of cytologic analysis of an aqueous humor sample and an iris mass aspirate sample collected from

1 dog in the present study indicated malignant lymphocytes. Assessment of aqueous humor samples with a PCR assay for detection of receptor gene rearrangement has also been described for diagnosis and immunophenotyping of lymphoma in a dog with ocular signs attributed to multicentric lymphoma.[7] Such analysis would be particularly advantageous if cytologic results were inconclusive or for assessment of the contralateral eye in patients undergoing unilateral enucleation.

Conjunctival lymphoma in humans is primarily B-cell in origin and a rare primary neoplasm, comprising 1% to 2% of all extranodal non-Hodgkin's lymphomas and 32% of ocular adnexal lymphomas.[16,60] T-cell conjunctival lymphomas and epitheliotropic T-cell lymphoma involving the conjunctiva have been reported less commonly for humans.[61–63] Humans with conjunctival lymphoma typically have nonspecific signs of conjunctivitis such as conjunctival swelling, redness, and irritation[64–66] or subsequent development of discrete conjunctival masses, which can extend posteriorly leading to progressive proptosis.[67] Treatment options include surgical resection, combination chemotherapy (vincristine, cyclophosphamide, prednisone, and doxorubicin), single-agent chemotherapy (chlorambucil),[68–70] radiation therapy,[70–72] immunotherapy,[73,74] or antimicrobials.[75] Median disease-free intervals for humans with conjunctival lymphoma range from 8 to 66 months.[60] Data for dogs and cats in the present study should be carefully compared with data for humans because only 4 animals with conjunctival lymphoma were identified in this study and that problem had a very low prevalence (0.08% of all lymphoma patients at our institution). However, similar to humans, 3 of 4 patients in the present study and 2 domestic animals in other reports[9,12] had conjunctivitis that was unresponsive to topical treatment. Unlike humans, however, T-cell lymphoma was the most common phenotype detected in the present study; 2 dogs had conjunctival CETL. Mucocutaneous junctions may be involved in dogs with CETL, but eyelids are less commonly affected than other areas.[76,77] Additionally, lymph node involvement and systemic spread have been reported in 0% to 4%[76] and 15% to 20%[77] of dogs with CETL in 2 retrospective studies. Treatment with lomustine results in the highest response rates (78% to 83%) in dogs, with remission durations of approximately 3 months.[76,78] Information in a report[9] of diffuse conjunctival CETL in a dog indicates that topical treatment with prednisolone acetate followed by additional treatment with synthetic retinoid (isoretinoin) administered orally is sufficient to maintain comfort in animals and prevent worsening of a lesion 6 months after starting isoretinoin treatment. A dog with a focal palpebral conjunctival nonepitheliotropic T-cell lymphoma in another report[11] was free of evidence of recurrence 1 year after surgical resection alone. The prognosis for dogs and cats with generalized CETL is not well described but seems to be poor, although outcomes for dogs and cats with localized disease may be better.[79] The locally aggressive, infiltrative behavior described for conjunctival lymphomas in humans was not detected in any animal in the present study, but metastasis to local lymph nodes was detected in 1 dog and 1 cat. Cytologic evaluation of an aspirate of a local lymph node was not performed in all animals with conjunctival lymphoma at the time of diagnosis, but should be considered as a diagnostic test for staging of this disease, given that 2 of 4 patients subsequently developed mandibular lymphadenomegaly.

Limitations of the present study were attributed to the retrospective study design, particularly the small amount of available follow-up information and the low number of animals meeting inclusion criteria. The small sample size precluded meaningful statistical analysis of PFST or OST with respect to tumor location, species, or treatment. Although prospective, case-controlled studies would be more useful for determination of such information, the very low incidence of solitary ocular lymphoma in animals make such studies difficult to conduct. Results of this study also indicated challenges of immunohistochemical analysis of tissue samples. Specifically, analysis with antibodies against 2 antigens (eg, CD3 for detection of T cells and CD20 or CD79a for detection of B cells) may not be sufficient for determination of immunophenotype for every tumor, particularly B-cell neoplasms. Treatments may be difficult to determine when results of immunophenotyping are inconclusive. In addition, if immunophenotyping is not performed at the time of the initial diagnosis, subsequent determination of immunophenotype may not be possible because archived tissue samples may not contain tissue from a lesion.

Results of the present study suggested that solitary ocular lymphoma is uncommon in dogs and cats and that such animals typically have initial diagnoses of uveitis (solitary intraocular lymphoma) or conjunctivitis (solitary conjunctival lymphoma) unresponsive to common treatments. Patients with these clinical signs may benefit from cytologic or histologic assessment of ocular tissue or fluid samples. Diagnosis of conjunctival or intraocular lymphoma should prompt diagnostic testing of tissue or fluid samples obtained from common metastatic sites including local lymph nodes (for conjunctival lymphoma) and CNS tissues (for intraocular lymphoma). Although the number of animals with those problems was low and PFSTs and OSTs had wide ranges in this study, the prognosis seemed to be better for animals with conjunctival lymphoma than it was for those with intraocular lymphoma. Survival times for animals with intraocular lymphoma may be increased by performance of enucleation.

a. Clone 3-12, PF Moore, Leukocyte Antigen Biology Lab, University of California-Davis, Davis, Calif.
b. Clone MH57, MCA2538H, AbD Serotec, Kidlington, Oxfordshire, England.
c. NeoMarker RB-9013-P1, Thermo Fisher Scientific, Fremont, Calif.
d. Clone CA12.10C12, PF Moore, Leukocyte Antigen Biology Lab, University of California-Davis, Davis, Calif.
e. Clone CA18.3C10, PF Moore, Leukocyte Antigen Biology Lab, University of California-Davis, Davis, Calif.
f. Clone CA21.4B3, PF Moore, Leukocyte Antigen Biology Lab, University of California-Davis, Davis, Calif.
g. Target Retrieval Solution 1699, Dako, Carpinteria, Calif.

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