

POST-TRAUMATIC OCULAR LYMPHOMA IN THREE RABBITS (*ORYCTOLAGUS CUNICULUS*)



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Abstract

This report describes post-traumatic ocular lymphoma in 3 companion rabbits; 2 rabbits with unilateral disease and 1 with bilateral disease. Historical findings suggestive of a traumatic event included either external unilateral ocular trauma or bilateral phacoemulsification. Severe corneal changes, presence of an anterior chamber mass(es), low intraocular pressures, and ocular discomfort were noted on ophthalmic examinations. All eyes were treated for variable courses with standard ophthalmic topical medications (antibiotic, anti-inflammatories, and steroid) and systemic anti-inflammatories. Based upon progression of disease, all affected eyes were ultimately enucleated; lenticular capsular rupture and a round cell neoplasm effacing normal structures with variable mitotic indices were noted on histopathology. Neoplastic lymphocytes strongly expressed CD79a via immunohistochemistry and lacked expression for CD3, indicating B lymphocyte lineage and not of T cell lineage. A single animal had evidence of local metastasis to a regional lymph node. Post-traumatic sarcomas have been reported in this species previously, however, these cases are the first reports of this novel round cell variant, named post-traumatic ocular lymphoma due to the B cell lineage confirmed through immunohistochemistry. Clinicians should be aware of this clinical presentation and the possibility of metastasis when evaluating ocular pathology in this species. Copyright 2018 Elsevier Inc. All rights reserved.

Key words: lymphoma; post-traumatic sarcoma; ophthalmic; rabbit; neoplasia

CASE 1

An 8-year-old male castrated lop rabbit presented to a veterinary teaching hospital for evaluation of possible cataracts. Three months prior to presentation a heavy decorative, cylindrical object fell from a shelf onto this rabbit and its cage mate. The client reported that since this

incident the left eye had dramatically increased in cloudiness.

On presentation, the physical examination findings were unremarkable outside of mild matting of the perianal and inguinal fur. Ophthalmic examination revealed marked blepharospasm, mucopurulent discharge, conjunctival hyperemia and episcleral injection in

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the left eye. Corneal neovascularization was noted extending 4 to 5 mm from the limbus in a 360 degree distribution. The iris could not be fully evaluated due to moderate flare, fibrin and blood present in the anterior chamber. The lens appeared completely cataractous. Intraocular pressure (IOP) (TonoVet Tonometer, Jorgensen Labs, 1450 Van Buren Ave, Loveland, CO USA) in the left eye was too low to be measured. The right eye had no abnormal findings and the IOP was 6 mmHg. At that time, the most likely differentials for the unilateral ophthalmic findings were *Encephalitozoon cuniculi*-induced phacoclastic uveitis, trauma induced uveitis, or an intraocular neoplasm.

The complete blood count (CBC) and plasma biochemistry revealed mild elevation in alkaline phosphatase (ALP) concentration (107 IU/L, reference 4-16 IU/L¹) that was considered to be secondary to underlying osteoarthritic or biliary disease. Whole body radiographs indicated abnormal gas accumulation within the cecum with no other abnormal findings. Because of a normal clinical course of appetite and defecation and normal borborygmi ausculted during the physical examination, further investigation of the abnormal gas pattern was not performed. Options for surgical management of the unilateral ocular changes including phacoemulsification and enucleation were discussed with the client. The rabbit was discharged with meloxicam (0.5 mg/kg PO q 12 hrs, Metacam, Boehringer Ingelheim Vetmedica, Inc, S. Joseph, MO USA) and diclofenac (1 gtt OS q 8 hrs, Akorn, Lake Forest, IL USA) to treat the corneal and anterior chamber inflammation while the client decided on a future course. A recheck examination was planned for 2 weeks.

The rabbit represented 2 months later for enucleation after the eye became acutely worse. At

that time, physical examination parameters were similar to previous findings. Ophthalmic examination revealed corneal findings consistent with previous reports with the addition of corneal edema. The anterior chamber was filled with a large amount of white to yellow opacity (Fig. 1A). The IOP in the left eye was 16 mmHg. The ophthalmic examination of the right eye was unremarkable and the IOP was 12 mmHg.

A repeat CBC and plasma biochemistry revealed hyperfibrinogenemia (400 mg/dL) which was presumed to be secondary to the described inflammation within the globe. Systemic therapy with sulfamethoxazole-trimethoprim (30 mg/kg PO q 12 hrs, Sulfatrim, Actavis Mid Atlantic LLC, 1877 Kawai Road, Lincolnton, NC USA) was initiated to cover a possible bacterial infection and meloxicam therapy was continued as previously prescribed. On the next day, the rabbit was anesthetized and a routine transconjunctival enucleation was performed.¹ The rabbit recovered uneventfully from the procedure. An aspirate taken of the aqueous humor immediately after enucleation was submitted to a laboratory (Comparative Pathology Lab, School of Veterinary Medicine, University of California, One Shields Avenue, Davis, CA USA) and was negative for *E cuniculi* by PCR.

Histologically, intraocular structures were substantially effaced by a dense population of neoplastic round cells arranged in sheets and clusters within minimal fibrovascular stroma, and with coalescing foci of coagulative necrosis (Fig. 1B). Cells were 20 to 30 μ m in diameter, with indistinct cell margins and scant to small amounts of amphophilic cytoplasm. Nuclei were large and irregularly round with finely stippled chromatin and 1 to 2 variably distinct nucleoli. Anisocytosis and anisokaryosis were mild, with 42 mitotic figures per 10 400 \times

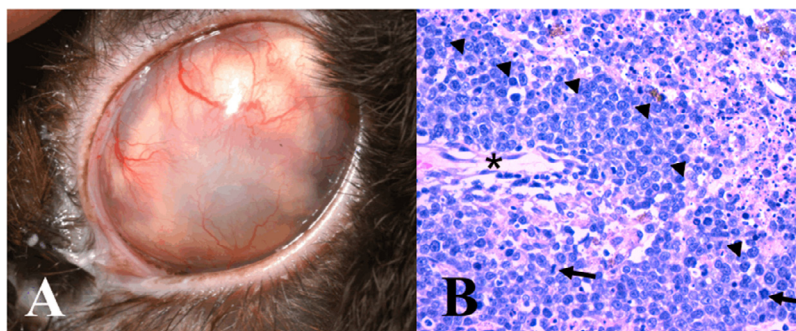


FIGURE 1. (A). Gross appearance of the left eye of an 8-year-old male neutered domestic rabbit diagnosed with post-traumatic ocular lymphoma after enucleation (Case 1). Note the mild mucopurulent discharge, marked neovascularization, corneal edema, and billowing white-yellow opaque material in the anterior chamber. (B). Photomicrograph of post-traumatic ocular lymphoma in Case 1. Atypical lymphocytes are intact around blood vessels (asterisk), with necrotic debris to the upper and right of the panel (arrowheads). Nuclei are large and atypical, with prominent nucleoli and scattered mitotic figures (arrow). HE, original magnification 400 \times .

fields. Immunohistochemistry (IHC) for T-cells (rat monoclonal anti-CD3, clone 3-12) and B-cells (mouse monoclonal anti-CD79a, clone MH57, AbD Serotec #MCA2538H) was performed as previously described.² Atypical lymphocytes had strong, membranous immunoreactivity to CD79a, with CD3-immunoreactive, inflammatory T-cells scattered throughout. Admixed in the atypical infiltrate and filling the ocular chambers were large mats of heterophils, macrophages, lymphocytes, plasma cells, free red blood cells, and fibrin. The lens capsule was ruptured multifocally with extensive cortical fiber swelling (morgagnian globules). There were multifocal accumulations of brightly eosinophilic lens material within the vitreous chamber admixed with neutrophils and foamy macrophages that extended into the anterior chamber. The retina was multifocally necrotic, atrophied, infiltrated by neoplastic cells, and admixed with an eosinophilic proteinaceous material. The corneal epithelium was minimally hyperplastic with regionally extensive areas of neovascularization. The histopathologic and IHC findings were consistent with uveal B-cell lymphoma, with lens capsule rupture and severe endophthalmitis. The clinical history, presence of lens epithelium disruption, and lack of documented systemic involvement led to a presumptive diagnosis of post-traumatic lymphoma, previously called round cell variant of post-traumatic sarcoma, as reported in cats.^{3,4}

Two weeks after discharge the rabbit presented for suture removal. The enucleation site was healed and the sutures were removed. An abdominal ultrasound examination was performed to rule out metastatic disease based upon the biopsy results. Tracking gas was noted in the biliary tree with a moderate amount of sludge present in the gallbladder. No evidence of mesenteric lymph node enlargement was present. A bone marrow biopsy was offered to the client for a full staging of systemic lymphoma, but declined.

Twelve months after enucleation, the rabbit presented for euthanasia. The clients reported worsening ambulation and lack of fecal and urinary continence and were concerned with quality of life. Six months prior, a wellness examination was performed and CBC, chemistry and whole body radiographs were consistent with previous findings outside of development of severe elbow arthrosis. A physical examination at the time of euthanasia showed no abnormalities outside of poor body condition and moderate fecal and urinary staining of the inguinal region, presumed secondary to the recent fecal and urinary

incontinence. The rabbit was euthanized routinely and a postmortem evaluation was not permitted.

CASE 2

A 4-year-old female spayed rabbit presented to a private veterinary specialty clinic for evaluation of cloudiness of the left eye. After a presumed diagnosis of hereditary or developmental cataracts, the rabbit had previously undergone staged bilateral phacoemulsification 10 and 11 months prior for the right and left eyes, respectively. Ophthalmic examination of the left eye revealed periocular swelling, conjunctival hyperemia, and neovascularization of the cornea. Multiple dense light-yellow masses and moderate cellular flare within the anterior chamber made further evaluation of the iris, lens and fundus impossible. Fluorescein stain (Ful-Glo, Akorn, Inc, 1925 West Field Court, Suite 300, Lake Forest, IL USA) was positive in the left eye. The right eye had changes consistent with the previous surgery (mild focal corneal edema, neovascularization, posterior synechia) and appeared comfortable. The IOP (TonoVet Tonometer, Jorgensen Labs, 1450 Van Buren Ave, Loveland, CO USA) in the left eye was 8 mmHg and the right eye was 5 mmHg. Lens induced uveitis or a foreign body reaction was suspected at that time and the prognosis for vision in the left eye was considered guarded. The rabbit was prescribed ketorolac ophthalmic drops (1 ggt OS q 8 hrs, Acular LS, Allergan, Inc, 2525 Dupont Dr, Irvine, CA USA) and an aqueous ocular lubricant (1 ggt OS q 8 hrs, Refresh Celluvisc, Allergan, 2525 Dupont Dr, Irvine, CA USA) to treat the corneal ulceration present and reduce inflammation. Three days later the fluorescein stain test was negative in the left eye; however, the left sided ocular changes were otherwise unchanged. The previously described ketorolac drops were discontinued and prednisone acetate ophthalmic suspension (1 gtt OS q 12 hrs, Pred Forte, Allergan, 2525 Dupont Dr, Irvine, CA USA) was instituted to treat anterior uveitis.

Ten days later, the ocular changes in the left eye had reduced in severity. Corneal neovascularization was still present, but flare was negative and the iridial margins could be visualized to have 360 degree posterior synechia to the anterior lens capsule. Moderate lens fiber regrowth was evident which has previously been reported in rabbits.^{5,6} Intraocular pressures were 3 mmHg OD and 7 mm Hg OS. The marked inflammation was presumed to be secondary to the lens fiber regrowth in this animal. The frequency of the

prednisone ocular drops was decreased to once daily.

Over the next 10 weeks, the rabbit was rechecked 4 times. Over this time a mass, presumed to be lens regrowth, began to occupy the majority of the left anterior chamber and had vascularization apparent upon the surface. Clinical presumption of lens regrowth was also present in the right eye, with anterior protrusion of the dorsal iris that was thought to be secondary to proliferation of lens material posterior to this region. Prednisone acetate drops were continued in the left eye once daily and anti-inflammatory drops were prescribed once daily to the right eye. On the last of these visits, the rabbit was blepharospastic and ophthalmic examination showed obliteration of the left anterior chamber with presumed lens material and associated vessels. Enucleation was recommended at that time due to grave prognosis for vision in that eye as well as associated discomfort associated with the marked recurrent anterior uveitis.

Two weeks later, the rabbit represented for enucleation of the left eye. The rabbit was anesthetized, and a routine transconjunctival enucleation was performed.² The rabbit recovered without incident and prescribed meloxicam (0.7 mg/kg PO q 24 h) for 7 days for postoperative analgesia.

The subgross appearance of the eye is shown in Fig. 2. Histologic features of the enucleated left eye were similar to those described in Case 1, including an atypical round cell mass in the uvea and ocular chambers, and mixed inflammation, necrosis and hemorrhage. Differences included a lower mitotic rate in the atypical lymphoid population, (3 mitotic figures per 10,400× fields), a retinal detachment, and multifocal retinal necrosis. There was cataractous lens regrowth with regional liquefaction, with a broad anterior lens capsule rupture (associated with prior surgery). Histologic staining characteristics were similar to those described in Case 1 with strong positive CD79a staining indicating lymphocytes of B cell origin

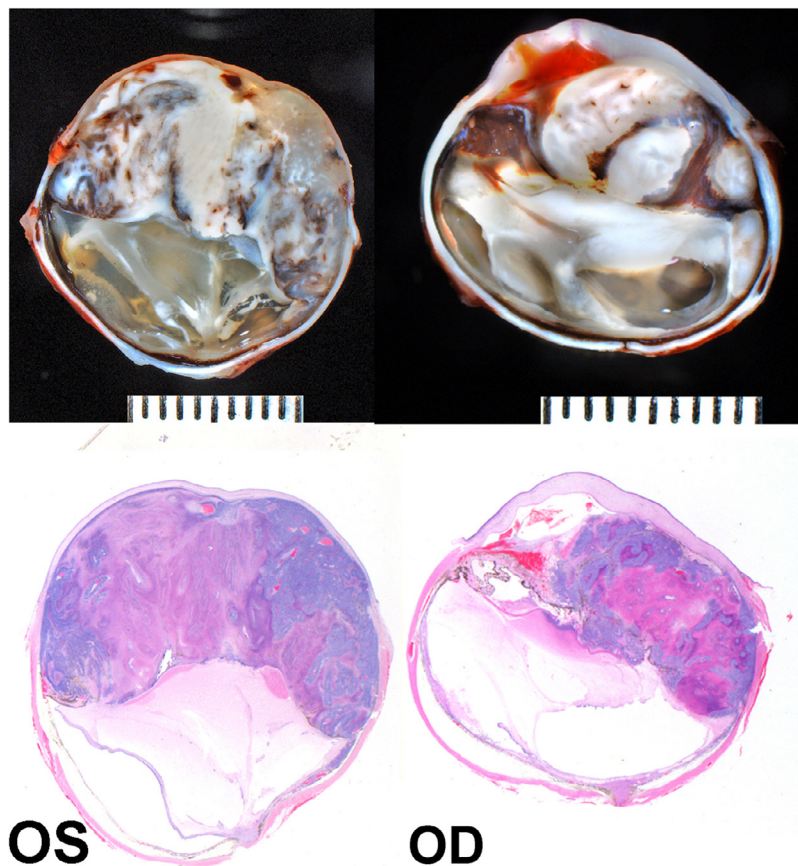


FIGURE 2. Gross (top) and subgross (bottom) images of both eyes from a 4-year-old female spayed rabbit diagnosed with bilateral post-traumatic ocular lymphoma after staged phacoemulsification (Case 2). Note that all anterior chamber structures are effaced by a mass, mostly white to cream in color with some areas of pigmentation. Subgross slides are HE stain.

(Fig. 3A). These findings were consistent with post-traumatic lymphoma.

Three months after OS enucleation surgery, the rabbit was being managed at home with anti-inflammatory drops in the right eye and was doing well clinically. Upon recheck examination, the lens regrowth in the right eye was mildly progressive and a 2.5 × 2.0 cm freely movable mass was palpable below the chin that could not be localized to either the right or left side. Whole body radiographs were performed and were unremarkable. Main differentials for the mass included a subcutaneous abscess or a primary or metastatic neoplastic process. Excision of the mass under general anesthesia was performed. Histologically, lymph node architecture was largely effaced by neoplastic lymphocytes. The neoplastic cells were larger and more anaplastic than those noted in the eye, and had small amounts of amphophilic cytoplasm, with prominent nucleoli, nuclear atypia and numerous karyomegalic and binucleate cells. There were 29 mitotic figures per 10 high power fields (400×). Atypical lymphocytes strongly expressed CD79a consistent with a B-cell phenotype. CD3-expressing, non-neoplastic T-cells were scattered between sheets of neoplastic B-cells. The lymph node was encapsulated and the surgical margins were free of neoplastic cells. Based on the clinical course and histologic features of the lymph node infiltrate, this was interpreted as spread of ocular lymphoma to a regional node, with increased atypia.

Over the next 3 months, lesions suggestive of intraocular mass developed in the right eye. The owner elected enucleation and the eye was enucleated in a similar fashion as the left eye. Histologic and IHC features were similar to the left eye, with more extensive hemorrhage and necrosis and a mitotic rate more similar to the lymph node mass. There was also a perilimbal corneal scar

(surgical) and multifocal proliferation of lens epithelial cells along the inner lens capsule, consistent with the previous phacoemulsification surgery. *E. cuniculi* PCR on tissues from both the left and right eye was negative (Comparative Pathology Lab, School of Veterinary Medicine, University of California, One Shields Avenue, Davis, CA USA).

One year after the second enucleation, the rabbit was presented to another veterinarian for euthanasia after a rapid clinical decline. The client declined a full postmortem evaluation, and 2 skin masses were submitted for histopathology and the results were unrelated to lymphoma but unavailable for review.

CASE 3

A 5-year-old female spayed Holland lop rabbit presented to a private veterinary clinic for evaluation of an abnormal left eye. The rabbit had a history of a mature cataract OS with no associated aqueous flare noted on previous exams. There were no abnormalities in activity, appetite or urinary or fecal outputs according to the client.

Ophthalmic examination revealed moderate flare with mild generalized corneal edema and moderate conjunctival vessel injection. A CBC, plasma biochemistry panel, and radiographs were offered but declined. *E. cuniculi* ELISA optical density delta values (Animal Health Diagnostic Center, Cornell University, 240 Farrier Rd, Ithaca, NY USA) were 2.243, consistent with infection. Therapy including fenbendazole (5 mg/kg PO q 24 hrs, Panacur suspension, Merck Animal Health, 1102 South Hills Dr, Ames, IA USA), enrofloxacin (10 mg/kg PO q 12 hrs, Bayer Animal Health, 5975 S Quebec St, Englewood, CO USA), and flurbiprofen (1 gtt OS q 8 hrs, Bausch + Lomb, 100 Bausch and Lomb Pl, Rochester, NY USA) was

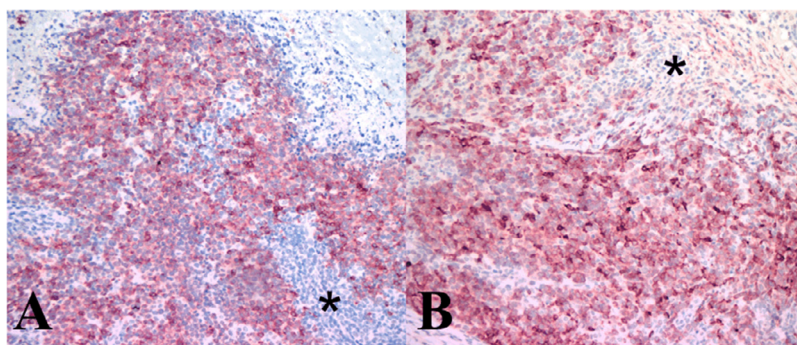


FIGURE 3. Immunohistochemistry (IHC) for CD 79a – a B-cell antigen – in Cases 2 (A) and 3 (B), with strong membranous to cytoplasmic staining (orange-red) in large, atypical lymphocytes. Smaller, unlabeled lymphocytes (asterisks) were confirmed to be T-cells with CD3 IHC (data not shown), and interpreted as non-neoplastic. Vector red chromagen, Meyer's hematoxylin counter stain. Original magnification 200×.

initiated as there was a strong clinical suspicion of *E. cuniculi* infection.

Over the next 4 weeks the rabbit was rechecked every other week to monitor progression of the ophthalmic signs. During these examinations, a white mass like structure was noted within the anterior chamber. On the last recheck the eye had become buphthalmic with fulminant inflammation present within the globe based upon evidence of worsening aqueous flare, corneal edema, conjunctival vessel injection, and epiphora. The previously noted mass was larger in size and occupied a majority of the anterior chamber space. Enucleation was recommended due to lack of response to therapy and perceived discomfort to the animal. A routine transconjunctival enucleation was performed² and the rabbit recovered uneventfully.

Histologic and IHC features were similar to Case 1 and 2, (Fig. 3B) including atypical lymphoid infiltrates, mixed inflammation, lens capsule rupture, and necrosis. Other features included scleral and peripheral corneal extension, more extensive retinal necrosis, and extruded lens material into the ocular chambers. *E. cuniculi* PCR (Comparative Pathology Lab, School of Veterinary Medicine, University of California, One Shields Avenue, Davis, CA USA) on formalin-fixed, paraffin-embedded tissue was negative; the tissue passed DNA quality control assessments. Based upon the biopsy results, further diagnostics were offered to the client but declined.

Approximately four and half years after the first enucleation, the rabbit was presented for euthanasia after becoming blind in the remaining eye and having a poor perceived quality of life. A full postmortem was performed. There was no gross or histologic evidence of lymphoma in the remaining right eye or in any other body tissue. Ocular lesions in the right eye included: extensive cortical lens fiber swelling and disorganization (cataract); complete retinal detachment with advanced outer retinal atrophy and retinal pigment epithelial cell hypertrophy; ciliary cleft narrowing, optic nerve head cupping, and mild ganglion cell loss (consistent with chronic glaucoma). There was also a mild, histiocytic, lymphoplasmacytic, and fibrinous vitritis and chronic ulcerative keratitis. An unequivocal sequence of lesions in the right eye was not established due to the limited history however, retinal detachment, cataract, and glaucoma are all potentially blinding conditions. Systemic lesions considered incidental included: small, scattered wedges of renal infarction; regional arteriolar thickening (arteriolosclerosis), rare fibrinoid necrosis in cerebellar vessels, and rare,

small aggregates (2-5 cells) of hemosiderin-laden macrophages in cerebral sections (indicating prior hemorrhage). These lesions were considered age-related and clinically incidental based on limited history. There was regional epidermal hyperplasia, hyperkeratosis, and mild otitis externa in sections of the pinna. Other examined organs (heart, lungs, liver, pancreas, spleen) were considered normal for an aged rabbit.

DISCUSSION

This report highlights the historical and clinical presentation, diagnostic criteria and the long-term outcome of 3 rabbits with ocular lymphoma following lens capsule rupture, similar to the previously named round-cell variant of post-traumatic sarcoma previously described in cats.³⁻⁴ Spindle cell variants of post-traumatic sarcoma have previously been described in rabbits,^{7,8} cats,⁹⁻¹⁴ and a dog.¹⁵ This neoplasm arises secondary to any cause of lens rupture, including iatrogenic surgical causes and long-term ocular inflammation.^{3,9,13} The cases presented here appear to be distinct from previous reports of post-traumatic sarcoma, as represented by round cell morphology and immunohistochemistry to support B cell lineage. Although not yet reported, it has been observed by the authors (CRM, RDD) that the neoplastic lymphocytes present in round cell variants of post-traumatic sarcomas in cats are of B-cell lineage as well. Pathologists are moving toward the terminology of post-traumatic ocular lymphoma, rather than round cell variant of post-traumatic sarcoma to more accurately reflect the cell of origin. Key histologic features supporting this diagnosis – over other ocular manifestations of lymphoma – include lens capsule rupture, irregular mass-like expansion of the uvea, and large regions of coagulative necrosis. These features are not entirely specific, but they may alert the pathologist to the possibility of a post-traumatic etiology, and may suggest to the clinician that lymphoma may be limited to the eye, rather than an ocular manifestation of systemic lymphoma.

Despite the inference of a traumatic lesion occurring, the definition of trauma in the naming of this neoplasm is indicative of any process causing disruption of the lens capsule; this may or may not include an external traumatic injury and may include surgical causes. In 3 of the 4 eyes and 2 of the 3 rabbits reported here, an event known to cause lens rupture was reported in the history; the rabbit in case 1 had a large object fall upon it causing ocular trauma and the rabbit in case 2 had bilateral phacoemulsification performed. The rabbit in case 3

did not have a known history of a traumatic event or prior ocular disease. In the prior reports of intraocular sarcomas no previous traumatic events were noted in rabbits^{7,8} and less than half of the cats reported had a history of a traumatic event.⁹ This neoplasia has also been associated with phacoemulsification, lensectomy and intravitreal injections of gentamicin in cats.^{4,11,13}

In rabbits presenting to a veterinarian with ophthalmic findings including a mass in the anterior chamber, anterior uveitis, and associated corneal disease the main differentials should include *E. cuniculi*-induced phacoclastic uveitis, *Pasteurella* spp. abscessation, and intraocular neoplasms.^{7,8,16} In two of the rabbits in this report (Cases 1, 3) *E. cuniculi* infection was suspected either based upon clinical findings or titers that were performed that indicated potential infection. The rabbit in Case 3, treatment for *E. cuniculi* was pursued based upon elevated titer values. In the rabbit in Case 1, treatment for potential *E. cuniculi* was not pursued after discussion with the client about risks of benzamidazoles,¹⁷ the grave prognosis for return of function of that eye, and lack of other clinical findings of *E. cuniculi* infection. In both rabbits, an ultimate decision was made to enucleate the affected globe based upon lack of response to therapy, perceived ocular discomfort, and apparent lack of ability to recover vision in that eye. On tissue samples from the 4 eyes presented here, no *E. cuniculi* organisms were noted histologically and PCR performed either on the aqueous (Case 1) or on paraffin embedded tissues (Cases 2 and 3) were negative for this organism. Clinicians presented with rabbits exhibiting clinical signs and ophthalmic findings described here should be aware of the potential of primary ocular lymphoma so that early therapy is pursued.

In all of the eyes presented here, ocular structures were variably effaced with a lymphoid neoplasm exhibiting pleomorphism and a variable, but generally high, mitotic index. The neoplastic round cells exhibited characteristics of malignancy including cellular and nuclear pleomorphism and prominent nucleoli. Based upon morphology and immunohistochemical staining, the diagnosis was B cell lymphoma with a differential being secondary to trauma. The B cell immunohistochemical marker, CD79a has been previously used to diagnose B cell lineage tissue in rabbits.¹⁸ In other domestic species (dogs, cats, horses), molecular clonality assays for both B-cell and T-cells are available.¹⁹⁻²² At this time, molecular assays for lymphocyte clonality have not been developed for rabbits.

Although complete antemortem diagnostics were only performed for a single rabbit (Case 1) and complete postmortem diagnostics were only performed for a single rabbit (Case 3) in this report, the long follow up periods (12-54 months) that were described make a diagnosis of systemic lymphoma extremely unlikely and diagnosis of a primary post-traumatic ocular lymphoma far more likely. In one case (Case 2), there was metastasis to a regional lymph node. It is interesting that, in this case, the fellow eye was eventually involved. This may represent spread from the first eye affected, or *de novo* development of intraocular neoplasm, as both eyes had surgically induced lens capsule rupture. Previous reports of the spindle cell variant of post-traumatic sarcoma have not reported metastasis in this species.^{7,8} The presence of local metastasis in this report should prompt clinicians to pursue follow up diagnostics and examinations after diagnosis of this neoplasm in rabbits.

This case series highlights a novel ocular neoplasm in rabbits, post-traumatic ocular lymphoma that is postulated to be similar to previously described post-traumatic sarcomas in this species and other domestic animals. Clinicians should include this neoplasm on the differential list of a rabbit presenting with unilateral lenticular, anterior chamber and corneal abnormalities. As there is considerable clinical overlap with *E. cuniculi*-associated phacoclastic uveitis, the importance of clinical diagnostics (serology, PCR) for *E. cuniculi* and, if enucleation is indicated, histopathology cannot be overrated. Given the metastatic potential of this neoplasm, clinicians should pursue a full diagnostic work up at the time of diagnosis and in the months following diagnosis if this neoplasm is suspected or diagnostically confirmed.

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