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Ocular manifestation of lymphoma in newly diagnosed cats

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Abstract

Ocular manifestations of lymphoma are described in humans and dogs but rarely in cats. In this prospective study, cats with newly diagnosed and treatment-naïve lymphoma were evaluated concerning clinical stage and ophthalmologic findings. Twenty-six cats were included. In 12 cats (48%), ocular changes were documented. Uveitis anterior and posterior were predominant findings, being present in 58% of affected individuals. Other findings included exophthalmos, corneal surface lesions and chemosis. Eight cats received chemotherapy, two of which had ocular involvement. In these two cats, a complete remission of an anterior and a partial remission of a posterior uveitis were documented. Due to the detection of ocular involvement, a stage migration from stage IV to V occurred in four patients. In the light of these findings, an opthalmological examination may be considered as an important part of staging in feline lymphoma as well as of follow-up examination in affected cats.

Keywords
chemotherapy, eye, feline, stage migration, uveitis

Introduction

Lymphoma is the most common neoplasia in the cat.[1] The annual incidence is between 160 and 200 per 100 000 cats.[2]

As in the dog, lymphoma is a systemic disease in the cat, so the treatment of choice is chemotherapy.[1,3,4] Due to the systemic pattern of the disease, it is necessary to evaluate its extent and create a stage allocation according to WHO standards before treatment.[5]

The uveal tract of the eye is one of the most perfused tissues of the body and can be involved in a variety of systemic diseases.[6–8] Malignant lymphoma with a participation of the eye in humans have been described and comprehensively investigated.[6,9,10]

The ocular manifestations of lymphoma in humans are manifold and can affect nearly all parts of the eye.[9] Examples are exophthalmos,[6] eyelid ulceration,[10] infiltration of the conjunctiva and subsequent swelling,[11] corneal oedema, treatment-resistant episcleritis and scleritis or anterior uveitis.[12–15] In the posterior segment infiltration of the vitreous body,[8,16] posterior uveitis,[17] retinitis,[13,16,18] non-rhegmatogenous retinal detachment near the optic disc[19] and glaucoma[20] have been documented. In humans, manifestations in the eye or the ocular adnexae are most frequently seen in patients suffering from B-cell lymphomas.[9]

Malignant lymphoma is the most common secondary tumour in the eye of dogs.[21,22] This tumour type has also been described as being the underlying cause of anterior uveitis[23] as well as blindness subsequent to hyphaema and anterior uveitis.[24] Also, an involvement of the conjunctiva of the third eyelid has been documented.[25] In the majority of canine cases, both eyes are affected.[26]

To the authors' knowledge comparable information about the cat is missing. In the literature, lymphoma is only rarely described as a cause of uveitis in felines[27–31] and one case report showed participation of the conjunctiva with a high-grade swelling.[32]

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Therefore, the aim of this prospective study was to systematically evaluate the occurrence of ocular manifestations in cats with newly diagnosed, treatment-naive lymphoma and to document the ocular changes during the course of chemotherapy. Furthermore, it was the purpose of this study to compare staging results with and without an ophthalmic examination with respect to the possibility of subsequent stage migration.

Materials and methods

Patients

Cats presented with cytologically or histologically confirmed diagnosis of lymphoma from July 2010 to March 2012 were included in this study. Other eligibility criteria were no concurrent serious medical illness and signed owner consent. Cats that had received any cytostatic or glucocorticoid treatment prior to the presentation were excluded from this study.

Ocular examination

Ophthalmic examination included assessment of menace response, palpebral, dazzle and pupillary light reflexes. To measure the rate of tear production, a Schirmer Tear Test I (Intervet Deutschland GmbH, Unterschleißheim, Germany) was applied (reference range 8–18 mm min^{-1}).[33] The determination of intra-ocular pressure was accomplished by rebound tonometry using the TonoVet® (Tiolat Oy, Helsinki, Finland) (reference range 11–33 mmHg).[34] The corneal surface was evaluated using fluorescein (Fluorets®, Bausch and Lomb, Surrey, United Kingdom). The eyelids, conjunctiva, cornea, anterior chamber, pupil, iris and lens were examined using slit-lamp biomicroscopy (SL-15 Kowa, Tokio, Japan). Ophthalmoscopy was performed 20 min after application of tropicamide 0.5% (Mydrum®, Chauvin Ankerspharm, Berlin, Germany) with an indirect ophthalmoscope (Heine EN 20-1, Eickemeyer, Tuttlingen, Germany). To document possible fundic changes in the course of therapy, the fundus was photographed using the ClearView camera (Optibrand, Fort Collins, CO, USA).

An acute inflammation of the inner structures of the eye was considered to be associated to the lymphoma. Flare in the anterior chamber was scored from 0, + to +++. An intraocular pressure below 10 mmHg, reddened or swollen iris, chorioretinitis and retinitis were defined as an acute inflammation. Furthermore, an exophthalmos caused by an orbital involvement of nasal lymphoma was also considered as a lymphoma-associated ocular finding.

Clinical staging

Clinical staging was based on physical examination, complete blood work including examination of feline leukaemia virus (FeLV) and feline immunodeficiency virus (FIV) [FeLV Antigen/FIV Antibody Test Kit (SNAP® Kombi Plus FeLV Antigen/FIV Antikörper Test, IDEXX GmbH, Ludwigsburg, Germany)], X-rays, abdominal ultrasound and cytology of liver and spleen. Subsequently, the findings of the ophthalmologic examination were added and this stage allocation was compared to the conventional stages.[5]

Treatment

Patients were treated with a cyclic combination chemotherapy protocol[4] consisting of L-asparaginase [Asparaginase (Asparaginase 5000, -10000 Medac®, Medac, Hamburg, Germany)], vincristine [Vincristine sulfate (Cellcristin®, cellpharm, Bad Vilbel, Germany)], cyclophosphamide [Cyclophosphamide (Endoxan®, Baxter Oncology, Frankfurt/Main, Germany)], doxorubicin [Doxorubicin-HCL (Doxo-cell®, Medac, Hamburg, Germany)] and prednisolone [Prednisolone (Prednisolon®, Jenapharm, Brehna, Germany)].

Patients with histologically classified low-grade lymphoma received chlorambucil (2 mg qm^{-1} PO every other day)[35] and prednisolone (2 mg kg^{-1} PO every day for the first week, 1 mg kg^{-1} PO for the second week, 0.5 mg kg^{-1} PO for the third week). In case of a corneal defect, topical antimicrobial treatment was started. Uveitis was treated with systemic corticosteroid as administered with the chemotherapy treatment. If necessary, the patients received systemic non-steroid antiphlogistic (robenacoxib 6 mg, one tablet for cats up to 6 kg and two tablets for cats over 6 kg).

Follow-up ophthalmic examinations

Before treatment as well as in the weeks 2, 5 and 11 of treatment, a detailed ophthalmic examination was performed. Further check-ups followed after 4 weeks, 3, 6 months and 1 year after chemotherapy.

Results

Patients

Twenty-six cats with newly diagnosed lymphoma entered the study between July 2010 and March 2012. The most commonly presented breed was European Short Hair ($n = 18$). Four cats were Maine Coon and the remaining four cats were represented by Persian, Siamese, Turkish Angora and Birman cat. The median age was 10 years (range 2–17 years) and the median body weight was 4.85 kg (range 2.6–8.1 kg). Sixteen cats were castrated male, nine cats were spayed female and the remaining last cat was female. An overview of all patients is presented in Table 1. One of the 26 patients was diagnosed with a low-grade lymphoma, all other cats had intermediate/high-grade disease.

Ocular findings

Fourteen cats (54%) neither showed ocular changes in the ophthalmologic examination nor were clinical signs of ocular origin reported by the owners. The 12 (46%) patients with changes detected in the ophthalmologic examination are shown in Table 2. The Schirmer Tear Test I was within the reference range for all patients. The fluorescein test was positive in three cases. Of these 12 affected cats, anatomical localization was as follows: $n = 9$ extranodal ($n = 3$ renal, $n = 4$ nasal, $n = 1$ cutaneous), $n = 3$ multicentric, $n = 1$ mediastinal.

In 6 of the 12 patients, anterior uveitis was diagnosed. In these cases, fibrin was seen unilaterally within the anterior chamber in five cats and bilaterally in one. In four of the five patients with a unilateral anterior uveitis, the intraocular pressure was decreased (mean 6.16 mmHg, 5–7 mmHg). In four of the six cats with an anterior uveitis, the iris was reddened and swollen (Fig. 1) and one of the six cats additionally had a chorioretinitis with an ablatio retinae and an iris mass. One patient was presented with chorioretinitis and retinal detachment.

Three patients were presented with unilateral exophthalmos and an increased intra-ocular pressure in the affected eye. Of these three cases, patient number 8 and 10 also had a corneal defect. In the subsequent computed tomographic examination, diagnosis of an orbital mass could be made in one case whereas the other two cats each exhibited an orbital mass arising from the nasal cavity. In all cases, fine needle aspiration of the masses led to the cytologic diagnosis of lymphoma. The corneal surface of patient number 11 was fluorescein positive and a large corneal defect was diagnosed. In this patient, a lymphoma in the nasal cavity was also diagnosed despite of absence of a visible exophthalmos.

The right eye of one cat (patient number 6, Table 2) was not examinable due to high-grade swelling of the conjunctiva. This was diagnosed to be due to lymphoma infiltration via cytologic examination of a cytobrush sample. The patient's left eye was without pathological findings.

Staging

The 26 examined patients were presented with variable and unspecific symptoms including vomiting, diarrhoea, inappetence, weight loss, dyspnoea, nasal stridor and apathy. The most common anatomical classification was extranodal lymphoma ($n = 15$, 58%; skin, kidney, pharyngeal, nasal and isolated intra-ocular). The four patients (15%) with a multicentric lymphoma did not have more than two lymph nodes involved. Intestinal lymphoma was diagnosed in five (19%), mediastinal in two (8%) cases (Table 1). Seventeen patients were negative for both the FIV and the FeLV. Three patients were tested positive for the FIV and one patient positive for the FeLV (Table 1).

In 17 patients, complete clinical staging was performed. The remaining nine patients were not completely staged due to their bad general condition or owners' decision. Stage distribution was as follows: stage I, $n = 2$, stage II, $n = 2$, stage III, $n = 2$, stage IV, $n = 10$ and stage V, $n = 1$.

Twelve patients were classified in substage b and 5 patients in substage a. Including the results

Table 1. Epidemiologic data of cats with malignant lymphoma

Patient no	Breed	Gender	Age	Anatomical classification	FeLV and FIV status
Patients without ocular involvement					
1	ESH	mc	8	Extranodal (renal)	FIV+
2	ESH	sf	3	Extranodal (subcutis)	Neg
3	ESH	mc	3	Extranodal (subcutis)	Neg
4	ESH	sf	12	Extranodal (pharyngeal)	Neg
5	ESH	mc	10	Extranodal (eye,spleen)	FIV+
6	ESH	sf	13	Intestinal	Neg
8	Birman Cat	mc	4	Intestinal	Neg
9	Maine Coon	mc	7	Extranodal (subcutis)	Neg
10	ESH	sf	10	Gastrointestinal	Neg
11	ESH	mc	2	Mediastinal	FeLV+
13	ESH	mc	11	Multicentric	Neg
14	Persian	sf	15	Multicentric	Neg
15	ESH	mc	9	Extranodal (renal)	Neg
17	ESH	sf	17	Gastrointestinal	Neg
Patients with ocular involvement					
7	ESH	sf	15	Extranodal (renal)	Neg
12	ESH	mc	10	Mediastinal	Neg
16	ESH	mc	12	Extranodal (nasal)	FIV+
18	Maine Coon	sf	10	Multicentric	Neg
19	ESH	mc	10	Extranodal (subcutis)	Np
20	ESH	mc	13	Gastrointestinal	Np
21	ESH	mc	11	Extranodal (nasal)	Neg
22	Maine Coon	f	15	Multicentric	Neg
23	Maine Coon	sf	11	Extranodal (nasal)	Np
24	ESH	mc	2	Extranodal (renal)	Neg
25	Siam	mc	10	Extranodal (renal)	Np
26	Turkish Angora	mc	11	Extranodal (nasal)	Np

ESH, European Short Hair; f, female; m, male; mc, male castrated; Neg, negative; Np, not performed; sf, spayed female.

of the ophthalmological examination into the stage evaluation, the number of cases in stage V increased to five and the number of cats in stage IV decreased from ten to six due to the reclassification of four patients.

Treatment

Eight cats received combination chemotherapy with asparaginase, vincristine, cyclophosphamide and doxorubicin. Three of the cats completed the protocol and are still alive. Another three of the eight cats stopped chemotherapy: one after the first treatment because of owners' decision and 2 after 4 weeks of chemotherapy protocol because of progressive disease. Two cats were still in treatment when the study was closed. One cat received a chemotherapy protocol consisting of chlorambucil and prednisolone because of a low-grade intestinal lymphoma and was still under treatment at the time of study closure. Three cats received prednisolone monotherapy due to the owners' decision. The remaining 14 cats received no treatment due to owner decision.

Follow-up ophthalmic examination

Two of the 12 patients with ocular findings received combination chemotherapy.[4] Patient 7 with a renal lymphoma showed chorioretinitis, retinal detachment and proliferation of the optic nerve head in the right eye. After 1 week, the proliferation of the optic nerve head in the right eye decreased by 25%. The retinal detachment and posterior uveitis in the left eye decreased by 25% after the first and 50% after the second chemotherapy treatment (Fig. 2). This patient was in partial remission after first treatment. In patient 16, the uveitis decreased after the first week of therapy. In the ventral part of the anterior chamber, endothelial precipitate could be seen. One week later, the uveitis had completely resolved. This cat could be classified as being in clinically complete remission. Seven of the 14 patients without ocular findings received chemotherapy. All follow-up examinations at weeks

Table 2. Listing of ocular findings and diagnoses in cats with newly diagnosed lymphoma ($n = 12$)

	Adnexe		Anterior segment		Posterior segment		
Patient no.	OD	OS	OD	OS	OD	OS	Diagnoses
5	/	Enucleated	IOP 6 mmHg flare ++, rubeosis and diffuse swelling of Iris with mass effect	Enucleated	ca. 30% ablatio retinae non-tapetal scars	Enucleated	OD chorioretinitis, uveitis anterior OS enucleated
7	/	/	IOP 13 mmHg /	IOP 14 mmHg /	Papilledema ablatio retinae (ca. 20%)	Scars Papilledema ablatio retinae (ca. 50%)	OU chorioretinitis
12	/	/	IOP 7 mmHg flare++	IOP 6 mmHg flare++	/	/	OU uveitis anterior
16	/	/	IOP 16 mmHg /	IOP 15 mmHg flare+++ swollen iris	/	/	OS uveitis anterior
18	/	/	IOP 7 mmHg flare++	IOP 11 mmHg /	/	/	OD uveitis anterior
19	High-grade oedematous swelling redness conjunctivitis	/	Not evaluable	IOP 18 mmHg /	Not evaluable	/	OD chemosis
21	/	Exophthalmos	IOP 13 mmHg /	IOP 42 mmHg /	/	/	OS exophthalmos
22	/	/	IOP 5 mmHg /	IOP 6 mmHg flare++ rubeosis, iridis	/	/	OS uveitis anterior
23	/	Exophthalmos	IOP 15 mmHg /	IOP 35 mmHg fluorescein-positive lesion	/	/	OS exophthalmos glaucoma corneal defect
24	/	/	IOP 18 mmHg flare++ swollen iris	IOP 20 mmHg /	/	/	OD uveitis anterior
25	/	Exophthalmos	IOP 18 mmHg /	IOP 82 mmHg fluorescein-positive lesion	/	/	OS exophthalmos glaucoma corneal defect
26	/	/	IOP 15 mmHg fluorescein-positive lesion	IOP 14 mmHg /	/	/	OD corneal defect

/, no abnormal clinical findings; IOP, intraocular pressure; OD, oculus dexter; OS, oculus sinister; OU, oculus uterque.

2, 5, 11 and 1, 3 and 6 months after therapy were without any ocular findings. The patient with low-grade intestinal lymphoma went through the same follow-up exams and showed no ocular changes.

Discussion

The aim of this study was to examine cats with lymphoma and to document the presence and type of ocular changes they exhibit as well as to assess the impact of ocular findings on clinical stage. Additionally, these patients who received chemotherapy were examined at predetermined time points during the course of treatment in order to evaluate development of ocular characteristics over the course of time.

Uveitis is described as being a possible secondary involvement of systemic lymphoma in cats.[29,30] To the best of the author's knowledge however, information about the frequency of ocular findings

Figure 1. Photographs of two newly diagnosed patients with malignant lymphoma. Both cats show a unilateral involvement of iris tissue by swelling and redness (rubeosis iridis). Both anterior chambers are narrow due to the thickening of the iris, there is + to ++ flare of the aqueous humour and endothelial precipitates at the ventral cornea.

in cats with malignant lymphoma and the appearance of unilateral or bilateral manifestation are lacking.

In this study, close to half of the cats diagnosed with lymphoma exhibited ocular findings on ophthalmologic examination. Changes ranged from low-grade uveitis anterior or small corneal defects over high-grade uveitis, ablatio retinae, significant iris swelling and exophthalmos due to retrobulbar mass effects. The detected frequency of 48% of the examined cats with ocular changes within this study population is high in comparison to the number of dogs showing ocular involvement and also high in comparison of the rate of ocular changes seen in humans with lymphoma.[9,12] In dogs, Gwin *et al.* and Krohne *et al.* showed that an ocular manifestation of lymphoma existed in nearly one-third of all examined cases.[21,22] A secondary involvement of the third eyelid is described as the most common ocular manifestation.[27] In the majority of cases both eyes are affected.[26] In one study, older dogs were predisposed.[23] In humans, ocular involvement also mostly affects older lymphoma patients, with a mean age of 63 years[11] but can also occur in young children.[15] There is no sex predilection.[7] In this study, the median age of cats with ocular involvement was 10 years, as it is described in the literature for cats with lymphoma.[4] There was no sex predilection in our study. Differing from the findings in dogs, the presented feline patient population exhibited bilateral ocular findings only in two of the 26 patients.[26]

The most frequent finding in the presented cats with ocular manifestation of lymphoma was uveitis in that 50% of the patients with ocular involvement had a unilateral or bilateral uveitis anterior. Uveitis is frequently described in humans, dogs and cats as an accompanying symptom of systemic diseases due to the breakdown of the blood–aqueous and blood–retina barrier.[6–8,29,30] Possible causes in the cat are an infection with FeLV, FIV, toxoplasmosis or feline infectious peritonitis as well as lymphoma. In this study, the status of FeLV and FIV was evaluated in 17/26 cats revealing a low incidence of positive cases.

The phenomenon of stage migration was first described in 1985 and subsequently demonstrated for various human neoplasia.[36] It is based on

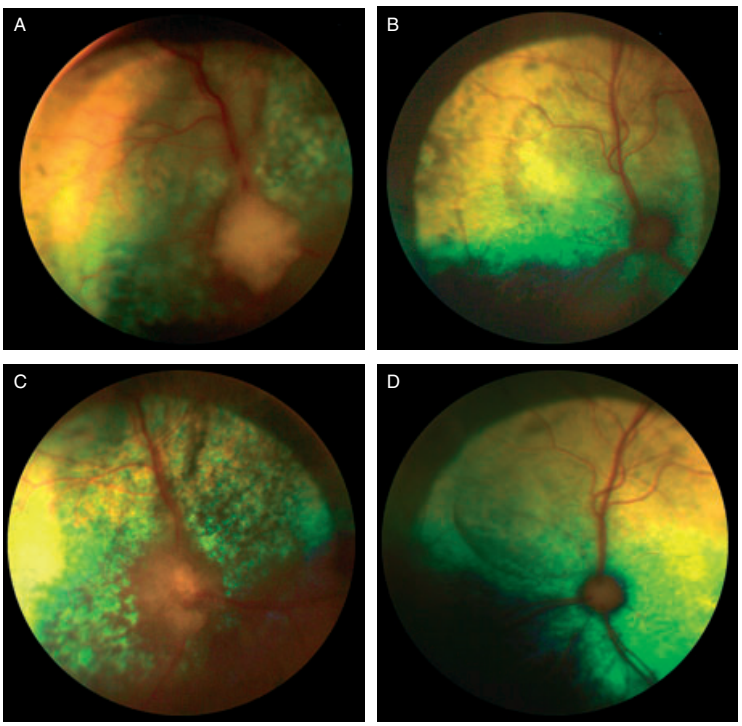

Figure 2. (A–D) Photographs of the ocular fundi of patient 7 with renal lymphoma. (A) Chorioretinitis, retinal detachment and proliferation of the optic nerve head in the right eye. (B) The right eye 1 week after therapy initiation with decrease of retinal detachment and the proliferation. (C) Retinal detachment and posterior uveitis in the left eye. (D) Decrease of posterior uveitis in the left eye 1 week after treatment induction.

the fact that with increasing sensitivity of the applied diagnostic methods previously undetected tumour burden may become apparent, leading to an assignment to higher stages. Flory *et al.* showed significant stage migration with advanced staging methods like abdominal ultrasound and bone marrow cytology in canine patients. However, this study could not demonstrate an impact of stage migration on outcome.[37]

In this study, reclassification subsequent to detection of ocular changes from stage IV to V took place in 24% of all cases. Whether this stage migration has an influence on prognosis of these patients is however unclear at this time and further studies addressing this question are warranted in the future. Unfortunately, clinical staging was not complete in nine patients, therefore these cats could not be included into the stage migration evaluation so that a possible reclassification of these remains open.

In both treated cats that had ocular findings a significant improvement of the ocular as well as the general condition could be documented, but it remains unclear, whether the cytostatic therapy or treatment with prednisolone led to the remission of the ocular changes. This demonstrates however, that follow-up ophthalmic examinations are indicated in cats that have been documented to display ocular involvement. In human patients with central nervous system lymphoma, 20–25% patients have ocular involvement while patients initially presented with ocular lymphoma subsequently develop cerebral lymphoma in 56–85% of cases.[38,39] Central nervous system lymphoma and intra-ocular involvement are described as having a poor prognosis for survival time.[40] In dogs, survival time is also described as being decreased when intra-ocular involvement is present.[22] In contrast to this, one case report[24] describes long-term survival time of 4.5 years in a dog with multicentric B-cell lymphoma and intra-ocular involvement.

One limitation of this study is that further more invasive examinations such as fine-needle aspiration of the aqueous humour or vitreous body were not performed; therefore a definitive

diagnosis of the ocular changes is missing. In the human literature, aspiration is described as a routine technique to establish a diagnosis.[9] Aspiration of the aqueous humour or vitreous body however is an invasive diagnostic method necessitating anaesthesia in veterinary patients. In this study, aspiration of the aqueous humour or vitreous body was not performed due to this reason. Future studies including these investigations should however be performed in order to verify whether cytologic proof of lymphoma infiltration can be demonstrated in cases of feline lymphoma with suspected ocular involvement. Only in the patient with chemosis, the diagnosis of a lymphoma involvement was confirmed by cytobrush examination. Additionally, all cats with retrobulbar or nasal masses were diagnosed using cytological examinations. Finally, an infection with, e.g., toxoplasmosis or feline infectious peritonitis could not be excluded in cases with uveitis. These diagnostic tests should be considered in further studies in order to verify the association of ocular findings and lymphoma.[8,29,30] Additionally, the small number of patients represents an additional limitation. Future investigations with higher numbers will give more representative data.

Furthermore unfortunately only two patients with ocular findings received chemotherapy treatment and were available for follow-up examination. Therefore, no evaluation of the impact of ocular involvement on prognosis in treated patients could be performed. Further studies are therefore needed to investigate the influence of ocular manifestation in cats with lymphoma with regard to the prognosis, survival time and outcome after chemotherapy.

In summary, the occurrence of ocular changes in approximately half of the cats presented with lymphoma could be documented resulting in stage migration in a subset of cases. An ophthalmic examination is recommended to be included in the routine staging procedure when cats are presented with a lymphoma independently of the anatomical localization and the extent of disease.

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