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Eric Dean and Valerie Meunier

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Eric Dean and Valerie Meunier

Abstract

The medical records of 45 cases (56 eyes) of feline eosinophilic keratoconjunctivitis (EKC) diagnosed between 2005 and 2011 were reviewed. Cats were included if a clinical diagnosis of EKC was recorded and eosinophils were found on corneal cytology. Median age at presentation was 5 years (interquartiles 5–9 years) for both males and females. Domestic shorthair was the predominant breed, accounting for 77.8% of the cats. The condition was unilateral in 75.6% of cases, with the superotemporal quadrant of the cornea the most frequently affected position (76.8% of eyes). A history of corneal ulceration was recorded in 37.8% of cases, and corneal ulcers were present at or before diagnosis in 66.7% of the cats. Eosinophils were found in 92.0% of conjunctival scrapings. We performed polymerase chain reaction (PCR) for feline herpesvirus type 1 (FHV-1) for 33/45 cats. Viral DNA was detected in 54.5% of these cats. FHV-1 DNA was detected by PCR in 66.7% of cats with a history and/or presence of a corneal ulcer at first presentation, which is significantly more than those with no corneal ulcer at any time (22.2% FHV-1 DNA detected). Our findings suggest that a corneal ulcer can be present prior to the development of eosinophilic keratitis. Further studies are mandatory to explore the role that FHV-1 could play in EKC-associated corneal ulceration.

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Introduction

Ocular surfaces inflammation has several causes and clinical presentations in the cat. First described as chronic eosinophilic keratitis or corneal eosinophilic granuloma,^{1,2} feline proliferative eosinophilic keratitis^{3,4} is a progressive, infiltrative keratopathy with distinctive clinical features that begins by a progressive and superficial vascularisation of the peri-limbal cornea.⁵ As the disease progresses, a pink–white infiltration results in corneal thickening and accumulation of gritty, yellowish material. The adjacent conjunctiva is also often involved and, more rarely, the third eyelid.^{3,4} Even though the cornea is always affected in this disease, the fact that other ocular surfaces may be affected renders the term keratitis too restrictive, hence, the recent suggestion to use the more inclusive term of keratoconjunctivitis rather than keratitis solely.⁶ The use of both terms would reflect more accurately the clinical presentation, but is lengthy, so we use the term eosinophilic keratoconjunctivitis (EKC) in the text. Another alternative could have been to name this entity ‘eosinophilic ocular surface disease’.

The terminology of this condition is not solely clinical, as infiltration by eosinophils is considered to be the hallmark of the disease. These cells may be observed on both cytological and histological examinations of corneal and conjunctival specimens.^{6,7} Based, in particular, on these observations, the pathogenesis proposed by Prasse and Winston⁷ is either type I or type IV hypersensitivity.

Several studies published on EKC in the 1980s and 1990s describing the clinical signs of the disease^{4,5} tried to identify its causative agent.⁸ More recent studies have proposed an alternative to corticosteroid treatment.³ In the current study, we based our investigation of the disease by retrospectively selecting cases based on their clinical presentation. We gathered data available on each

Vet-Oeil Ophthalmology Clinic, Lognes, France

Corresponding author:

Eric Dean DVM DESV-O, Vet-Oeil Ophthalmology Clinic, 17 rue des campanules, Lognes, 77185, France
Email: edean@club-internet.fr

case including clinical presentation and results of laboratory tests in order to explore possible relationship between the animal's history or laboratory tests results and disease progression, with a view to identifying appropriate treatment options.

Materials and methods

The medical records of cats presented from 2005 to 2011 at two ophthalmological practices in the Parisian region were systematically and retrospectively reviewed for eosinophilic keratitis/keratoconjunctivitis. Cases were selected based on typical clinical appearance of corneal lesions,^{4,6,9} such as proliferative, white-pink, oedematous, irregular and vascularised ingrowth of tissue and gritty, and white-yellow corneal plaques. Among these, only cases for which corneal cytology yielded eosinophils were included. In order to obtain a reference population, cats seen for any eye disease during the same time period were quantified from these medical records.

The data retrieved included breed, age, sex, ophthalmological history of each cat, eye(s) affected, position of the corneal lesion, presence of skin lesions, results of diagnostic tests performed, treatment prescribed and, when available, follow-up. Lesion localisations on the cornea were classified in either relevant corneal quadrant (supero-temporal, infero-temporal, supero-nasal, infero-nasal), central area or to the entire cornea when lesions encompassed most of corneal surface. Uncommon involvement was described specifically. The time of the year the cat was referred to our clinics was also recorded and expressed in terms of season.

The diagnostic tests performed included cytological examination of corneal and conjunctival specimens and real-time quantitative polymerase chain reaction (PCR)¹⁰ for feline herpesvirus type 1 (FHV-1) (TaqMan technology, Scanelis Laboratories, Colomiers, France).

Samples were collected under topical anaesthetic (oxybuprocaine chlorhydrate; Cebesine, Chauvin, Bausch and Lomb Laboratories) by: (1) rolling a cytobrush along the inferior conjunctival sac (cytology and PCR) and over the cornea for cytology, and (2) applying a hydrophilic polyethersulfone membrane (Supor 200PES membrane disc filter; Pall Life Science) on the cornea for PCR.

Corneal and conjunctival cytologies were stained with a fast variation of May-Grünwald Giemsa technique, RAL 555 kit (Réactifs RAL). When both eyes were affected, samples from each eye were combined for PCR-based DNA detection.

Statistical analyses

For data management, a local database was established using the EpiData software (version 3.1; <http://www.epidata.dk>) for entering all raw data. Statistical analyses were performed with Epi-Info software version 3.5.3

(Centers for Disease Control). As age was not distributed normally, data are given as median and 25 and 75 interquartile ranges. Fisher's exact test¹¹ was used for analyses of associations of categorised variables when sample size was small (<5), with χ^2 tests carried out otherwise. Values of $P < 0.05$ were considered statistically significant. Logistic regression was used to obtain odds ratios (ORs) and 95% confidence limits for potential risk factors for corneal ulcers and FHV-1 infection.

For descriptive purposes, we used a sex ratio equal to 1 in the general feline population of our area.¹²⁻¹⁴

Results

During the study period, feline EKC was clinically diagnosed in 47 cats (58 eyes). Eosinophils were observed on corneal cytology from 45 of them (56 eyes), which were used as the study population. They corresponded to 2.3% of the feline cases seen by us for eye diseases during that period. The median age of affected cats was 5 years (interquartiles 5-9 years) and range was 1 to 15 years. A significant difference between female (22, 48.9%) and male (23, 51.1%) cats was not found ($P = 0.88$).

Domestic cats, including both the domestic shorthair and longhair breeds, were the most frequently affected (77.8%; 35/45). Eight other breeds were represented (Persian, Turkish Angora: each 2/45, 4.4%; Russian Blue, Norwegian Forest cat, Siamese, Abyssinian, Thai cat, Chartreux: each 1/45, 2.2%).

Only one eye was affected in most cats (75.6%, 34/45). Right and left eyes were affected with a similar frequency (29/56 right eyes, 27/56 left eyes), which was confirmed by a lack of statistical difference ($P = 0.79$). Corneal lesions were most frequently found in the superotemporal quadrant (76.8%, 43/56), then the inferior nasal quadrant (12.5%, 7/56), central area (3.6%, 2/56) and over the entire surface of the cornea (5.4%, 3/56). One of these three cases had 360° limbal involvement, while the cornea was infiltrated and had proliferative lesions in the nasal and temporal quadrant, and had proliferative lesions along the limbus in the other quadrants. Position was not specified in one case (1.8%, 1/56). Only one cat had skin lesions (flea allergic dermatitis), which did not belong to the eosinophilic granuloma complex.

A history of corneal ulcer before the onset of disease was recorded in 18/56 eyes (32.1%; 17/45 cats, 37.8%). A corneal ulcer was present at diagnosis in 16/56 eyes (28.6%; 15/45 cats, 33.3%) either on the lesion or elsewhere. Two cats (4.4%) had a corneal ulcer both at and before diagnosis, including one with bilateral involvement. Corneal ulcer was absent before and at initial presentation in 19/56 eyes (33.9%; 15/45 cats, 33.3%). The seasonal distribution of cases was even, with 12 cases referred in spring, 11 in summer, 14 in autumn and eight in winter.

Conjunctival cytology was performed on 25/45 cats (55.6%). Eosinophils were detected in 23 (92.0%),

Table 1 Treatments given to the cats with FHV-1 status

Number of cats	Topical steroids	CsA	Opatanol	Antiviral	Ulcer (history = H and/or concomitant = C)
FHV-1 PCR positive					
18	18 (100%)	3 (16.7%)	3 (16.7%)	15 (83.3%)	16 (10H 6C) (88.9%)
FHV-1 PCR negative					
15	13 (86.7%)	5 (33.3%)	2 (13.3%)	2 (13.3%)	8 (5H 5C) (53.3%)
FHV-1 PCR not performed					
12	12 (100%)	1 (8.3%)	0 (0%)	4 (33.3%)	6 (2H 4C) (50%)
Total 45	43 (95.6%)	9 (20.0%)	5 (11.1%)	21 (46.7%)	30 (17H 15C) (66.7%)

lymphocytes in eight (32.0%), neutrophils in four (16.0%) and mast cells in two (8.0%) of the 26 cats. Bacteria (cocci) were observed in two cases (8.0%). Both cats whose corneal cytologies were negative had nasal quadrant involvement and eosinophils were in high number on the conjunctival cytology of one of these cats.

Eye samples were taken from 33/45 cats for FHV-1 DNA detection by PCR. FHV-1 DNA was detected for 54.5% (18/33, 10 males and 8 females) of these cats and was not detected for 45.5% (15/33, eight males and seven females).

Fifteen of the 17 cats with a history of previous corneal ulcer were tested for FHV-1 (88.2%) and FHV-1 DNA was detected in 10 (66.7%) of the 15 cats tested. Eleven of the 15 cats presenting with a corneal ulcer at the time of EKC diagnosis were PCR tested for FHV-1 DNA detection (73.3%). Viral DNA was detected in six of them (6/11, 54.5%). FHV-1 DNA was detected only in 2/9 cats with no current or previous corneal ulcer (22.2%). This proportion was significantly lower than that for cats with a concomitant or previous corneal ulcer [Fisher's test: $P = 0.047$, OR = 7.00 (1.06–46.10)]. Such a difference was not found significant when considering solely cats with a history of corneal ulcer [Fisher's test: $P = 0.09$, OR = 7.00 (0.94–52.20)]. Similarly, the frequency of FHV-1 DNA detection was not significantly different ($P = 0.2$) for cats with concomitant corneal ulcers (6/11, 54.5%) than for those with no history of corneal ulcers (2/9, 22.2%).

Whenever both eyes were involved clinical records show that the same treatment was prescribed for both eyes. Topical corticosteroids were prescribed in almost all cases (43/45, 95.6%) (see Table 1). Topical steroids were used alone in 17 cats; nine of them did not have corneal ulcer. Among these 17 cats, eight had negative PCR results for FHV-1 DNA detection, two had positive results and seven were not tested. Topical steroids were associated with topical antiviral treatment (ganciclovir, Virgan; Thea Laboratories; omega interferon, Virbagen Omega; Virbac Laboratories) in a total of 21 cats. FHV-1 DNA was detected for 15 cats of these cats and not detected for two cats. Three cats were not tested. Corneal

ulcer was not observed in four cases. In one last case (not tested for FHV-1 DNA, bilateral involvement), corneal lesions worsened on the left eye (which had a corneal ulcer) after 1.5-month topical corticosteroid treatment alone, but improved quickly with the addition of topical interferon omega (Virbagen; Virbac) on that eye. In three cases (two with a history of corneal ulcer), in which FHV-1 DNA was detected by PCR, antiviral treatment was not instituted because clinical lesions had improved greatly by the time the animal was re-checked (with PCR results available). Conversely, in two cases in which FHV-1 DNA was not detected, antiviral treatment that was instituted at the first consultation was continued for another 4 weeks in one case (no ulcer); the other case was lost to follow-up (concomitant ulcer).

Topical cyclosporine A was prescribed alone at the first consultation in two cases (corneal ulcers, FHV-1 PCR test negative) but their outcome is unknown. In another case, the first treatment instituted was topical corticosteroids, which was discontinued after 3 months owing to deterioration (corneal sequestra and abscess). Once complications cleared, EKC was treated successfully with topical cyclosporine A alone (resolution in 3 months). FHV-1 DNA was not detected in any of these three cases. Cyclosporine A was associated with topical steroids in six cases (three cats for which FHV-1 DNA was detected, two cats for which it was not detected and one cat was not tested). One of these cats (PCR for FHV-1 detection not performed) underwent multiple relapses.

Other treatments included L-lysine (seven cases, FHV-1 DNA was detected for all of them), topical olopatadine (Opatanol; Alcon Laboratories) (five cases), and topical cyclosporine (Optimmune, MSD Animal Health) alone (two cases). Systemic corticosteroids (prednisolone, 1–2 mg/kg/day) were used in four cases for a short period (<3 weeks) owing to the extent of corneal involvement (see Supplementary Table).

Mean and median times to improvement were, respectively, 2.3 months and 1.5 months (1–2.5 months) (range, 3 weeks to 8 months). Follow-up data (1–60 months) were available for 17 cats (37.8%), among which recurrence is documented in eight cats (range, 3–60

months). Owners had discontinued treatment in all these cases. One of the cats in which FHV-1 DNA was detected had a corneal ulcer after 7 months of topical corticosteroids and two cats had multiple recurrences.

Discussion

In the present study, we investigated data on each cat's history of corneal disease. More than a third (37.8%) of cats with EKC had a history of previous corneal disease and 66.7% had a corneal ulcer at or before diagnosis of the disease. The proportion of cats with concomitant corneal ulcers (33.3%) was similar to that reported in two previous studies — 28.6%³ and 24%⁴ — higher than that reported by Paulsen (13%).⁵

Much of the data reported here are consistent with published results:^{3–5,8} age at diagnosis (median, 4–6 years),^{3,4} position on the cornea, involvement mostly unilateral. The right and left eyes were affected with equal frequency in this study. In other studies, the left eye^{4,5} or the right eye³ were affected more frequently.

Male cats were over-represented in three studies,^{3–5} whereas the sex ratio was close to 1 in our study and in that by Nasisse et al.⁸

Domestic cats were the most frequently affected breeds in all studies, including ours.^{3–5,8} They account for 80.5% of cats presented to veterinary practitioners in the Paris area.¹⁵ This breed cannot, therefore, be considered to be over-represented in this study. Among the eight pure cat breeds encountered in this study, Persians accounted for 4.4%, which is similar to the 6.1% of the cats seen in the Parisian region.¹⁵ The Persian breed is known to be overrepresented among cats suffering from corneal ulcers — 31% in the study of La Croix et al.¹⁶ A similar over-representation was not observed among the cats suffering from both corneal ulcer and EKC in the present study.

FHV-1 DNA was detected in 66.7% of the cats with current or past corneal ulcer that were tested, which is significantly higher than the 22.2% of cats without current or previous corneal ulcer. Cats with concomitant or previous corneal ulcers were more frequently PCR-tested for FHV-1 (80.0%) than cats without ulcers (60.0%). Although this difference was not significant, we cannot rule out the existence of a bias. Nevertheless, these findings suggest that it would be indicated to test for FHV-1 EKC cats with corneal ulcers at presentation or a history of such ulcers. The converse view (no corneal ulcer suggesting low risk of FHV-1) cannot be justified given the possible existence of bias. To our knowledge, observations suggesting a possible association between the detection of FHV-1 DNA and corneal ulceration has never before been published in EKC.

Other studies on EKC have investigated the presence of herpesvirus DNA on the cornea or conjunctiva. Fewer cats tested positive in our study (54.5%) than in that by

Nasisse et al.⁸ (76.3%). It was higher than that in the study by Morgan et al.⁴ (33%), in which FHV-1 was detected by immunofluorescence, a technique shown to be less sensitive than PCR.

FHV-1-related clinical signs can arise from inoculation by young cats experiencing primary herpetic disease or by reactivation of latent virus in the trigeminal ganglia of adult carrier cats undergoing recrudescence herpetic disease.^{17,18} In the present study, the affected cats were adults. It is unclear whether the FHV-1 DNA detected arose from viral reactivation from the trigeminal ganglia; the virus may also have stayed latent in the cornea or, alternatively, the PCR may have detected free DNA.¹⁹ The origin of the FHV-1 virus DNA detected by PCR in samples from cat corneas is unclear. As cats are more frequently outside during the spring and summer, they are more likely to meet other cats. Nevertheless, we found no influence of the season on the number of cases seen. In published studies,^{8,20–23} FHV-1 DNA was detected in 5.9–31% of cornea and/or conjunctiva of cats without ocular disease or history of respiratory disease when sampled by swab or brush, which is less than in the present study. When corneal biopsies during necropsy are used, FHV-1 DNA was detected in up to 49% of normal cats.^{19,24} The reasons for this increased detection may include factors relating to the biology and pathogenicity of FHV-1, differences in sample collection, contamination, PCR methodology, procedure of normal cat recruitment (shelter versus veterinary practices).^{25,26}

Eosinophils were present in 92% of the conjunctival samples analysed (23/25). Eosinophils and/or mast cells are not found on healthy feline corneas, and their presence has been assumed to be pathognomonic of EKC,⁷ even though the reason for their presence remains unclear. They are also found in the eosinophilic complex in cats. Nevertheless, our observations are in accordance with published findings, which indicate that cats with EKC rarely have skin diseases, including eosinophilic granuloma.^{4,6}

Owing to the abundance of lytic enzymes and toxic proteins they release, eosinophils are often associated with lesions. The presence of eosinophils and eosinophilic granule proteins beneath the intact cornea has been suggested to account for the vulnerability of the corneal epithelium.²⁷ This may also be the case for EKC, as corneal ulceration was more frequent than in other ophthalmological diseases. Nevertheless, eosinophils may have a more positive effect, for example, by promoting primary antiviral host defence.²⁸ Human eosinophils express multiple pattern-recognition receptors on their surfaces, including Toll-like receptor 9, which recognises viral DNA.²⁹ Rosenberg et al.²⁸ reported the uptake of respiratory syncytial virus by human eosinophils, but were unable to demonstrate viral replication within cells. Several studies, including ours, report a tendency of

FHV-1 to be associated with EKC, but further studies are required to investigate this possible link further.

Topical steroids are reported to be highly effective in EKC,⁶ which is consistent with the present results. Cyclosporine A was shown recently to be effective when used alone in 31/35 cats with EKC.³ In our study, this drug was administered in 9/45 cats because corticosteroid treatment alone was ineffective or corneal lesions worsened, and it was found to be a useful alternative to topical corticosteroids. Antiviral agents were administered mostly to cats that tested positive for FHV-1.³⁰ In two cases, lesions had improved sufficiently by the time the positive PCR results were obtained so that antiviral treatment was considered unnecessary.

Olopatadine inhibits mast cell mediator release, has selective histamine H₁ receptor antagonist activity, and inhibits inflammatory lipid mediators release from human polymorphonuclear leukocytes and eosinophils.³¹ In rats, olopatadine inhibits antigen-induced eosinophil infiltration and represses the IL-5-induced expression of LFA-1 and Mac-1 on eosinophils.³² We have attempted to use olopatadine solely in five cases suspected to be infected with FHV-1 in order not to use corticosteroids before PCR results were available. As this drug alone was found not to be effective, it was not used in more cases. Nevertheless, as treatment duration was <10 days and the number of cases low, further investigations are necessary to confirm this observation.

Megestrol acetate was the first medical treatment found to be consistently effective against EKC at a time at which the recommended treatment was keratectomy.^{1,2} Its potentially serious side effects preclude its use as a first-line treatment³ and it was not used in the present study.

Mean time to resolution was 2.3 months, and the median value was 1.5 month (1–2.5 months). These findings are consistent with those reported by Morgan et al (2.5 months),⁴ who also reported disease recurrence to be common (65%) in cats with long-term follow-up. Paulsen et al⁵ reported follow-up data for 9/15 cats (60%), three of which presented recurrence. In the present study, follow-up was available for only 37.8% of cases, as most owners return to their usual veterinary surgeon once a diagnosis has been obtained.

Conclusions

In the present study our findings indicate that a previous history and/or a concurrent corneal ulcer is significantly more frequent when FHV-1 DNA is detected in corneal samples taken during the course of EKC. Both conditions are severe and require specific treatment. The present observations suggest that in animals with corneal ulcer or a history of such ulcers associated with EKC, antiviral treatment could be initiated before PCR results are obtained. The present series confirms that topical

steroids are very effective, even though cyclosporine A was found useful in a minority of cases. Some cases presented here had a favourable outcome with topical steroids alone despite the detection of FHV-1 DNA on these cats' corneas. In the present series, in all cases for which relapses were documented, treatment had been stopped, which supports the maintenance of the treatment for several weeks to months to ensure disease remission. Prospective studies comparing topical steroids alone and topical steroids associated with antiviral treatment are necessary to further investigate the present results on cats suffering from EKC and on which FHV-1 DNA is found on the cornea.

Supplementary data A table of treatments given to each cat, FHV-1 status, presence of ulcer and outcome.

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