Veterinary Ophthalmology (2001) 4, 69–74

Feline eosinophilic conjunctivitis

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Abstract

Objective To review 12 cases of histologically confirmed feline eosinophilic conjunctivitis, their clinical, cytologic, histologic and electronmicroscopic findings, results on PCR for FeHV-1, treatment and outcome.

Animals studied Twelve naturally occurring cases presented during a period of 26 months.

Procedures Thorough ophthalmologic examination, conjunctival scrapings performed with the cytobrush method; histologic samples from the palpebral conjunctiva; PCR for FeHV-1 on Schirmer Tear Test (STT) strips; saliva and nasal swabs, and retrospective evaluation of all results.

Results The breed most commonly affected was the Domestic Shorthair ($n = 8$), followed by Persians ($n = 2$), Somali ($n = 1$) and Siamese ($n = 1$). Age at presentation was 1–15 years with a mean age of 7.2 years. Nine cats were castrated males; three cats were females: two of them were spayed. Unilateral ($n = 7$) or bilateral ($n = 5$) involvement with depigmentation and erosions of lid margin, blepharospasm, swelling and redness of conjunctiva and third eyelid were the most common clinical findings. Frequency of eosinophils in cytologic samples was more than 10% in every patient. PCR for FeHV-1 on STT was negative in all cases. Histologically, eosinophils, lymphocytes, plasma cells, mast cells and macrophages were involved. On electronmicroscopy, viral particles were not detected. Ten cases needed long-term anti-inflammatory treatment.

Conclusions The 12 reviewed cases suggest that feline eosinophilic conjunctivitis is a chronic inflammatory uni- or bilateral disease of the adult cat. Typically the lid margin was also involved, and was thickened, depigmented and erosive. Cytological examination of conjunctival scrapings was a valuable tool for detecting eosinophilic conjunctivitis. The cytological findings correlated well with the histopathological findings in our patients. Topical or systemic anti-inflammatory drugs resolved the clinical symptoms in our cases within a short period of time. Neither electronmicroscopy nor PCR were able to detect involvement of FHV1 in the represented cases. The etiopathogenic role of FeHV-1 remains undetermined.

Key Words: cat, eosinophilic conjunctivitis, feline, herpesvirus

INTRODUCTION

Feline eosinophilic keratitis and eosinophilic keratitis-keratoconjunctivitis are inflammatory diseases that primarily affect the cornea.[1–6] They are described as slowly progressive, infiltrative, uni- or bilaterally occurring corneal diseases of undetermined origin. Bilateral eosinophilic infiltration of the nictitans was described in one cat.[6] The presence of eosinophils with or without mast cells on corneal scrapings is considered diagnostic of eosinophilic keratitis.[3] Eosinophilic infiltration of the conjunctiva without corneal involvement has been described in five cats.[7] Eosinophilic conjunctivitis and eosinophilic keratitis-keratoconjunctivitis may have similar etiopathogenesis, but they do appear to be separate clinical entities.[7] This paper describes 12 cases of feline eosinophilic conjunctivitis focusing on their clinical, cytological and histological characteristics.

MATERIALS AND METHODS

The records of 12 cats with eosinophilic conjunctivitis presented to the Small Animal Clinic at the Free University of Berlin, Germany between March 1997

and May 1999 were reviewed. Clinical diagnosis was based upon the presence of conjunctivitis and the finding of abundant eosinophils and/or mast cells on cytologic and/or histologic examination of scrapings and biopsies of the conjunctiva.

Data reviewed from the records included the breed, gender, which eyes were affected, duration of clinical signs prior to presentation, results of diagnostic tests, the applied treatment, and outcome. Cases were included in this study if cytologic and/or histologic examination of conjunctiva had been performed and conjunctival tissue samples were available for electronmicroscopic examination. Histologic specimens were available on all 12 cytologic scraping sites of eight cases.

The scrapings were obtained from the inferior cul de sac under topical anesthesia with proxymetacainhydrochlorid (Proparakain-POS® O.5%, Ursapharm, Saarbrücken, Germany) by the cytobrush method (Cytobrush Plus GT, Medscand AB, Malmö, Sweden).[10,11] The specimens were air-dried and stained according to May-Grünwald-Giemsa. Cytological examination was performed by light microscopy using 400× and 1000× magnification. The slides were analyzed for quality, cellularity, degree of conjunctival cellular dysplasia, ratio of epithelial and inflammatory cells, degree of free mast cell granules, and frequency of different inflammatory cell population.

The histologic samples were taken under topical anesthesia from the temporal lower and upper palpebral conjunctiva, fixed in 10% formalin and embedded in paraffin wax. The sections were stained with hematoxylin and eosin (H & E) and examined by light microscopy. Tissue samples (1 mm^3) of the paraffin wax-embedded blocks from six cases were immersed in xylol, transferred to a wash solution by passing an ascending alcohol series and fixed in osmium. The tissue samples were then twice transferred to Epon 812 over an ascending alcohol series, propylenoxid and a mixture of Epon and propylenoxid (1:1). The blocks polymerized at 60 °C. Semithin (1 mm) sections were toluidin stained (1%). After the location in the epithelium was determined the blocks were trimmed. Ultrathin sections were produced, compared with uranylacetate and Pb-citrate, and examined and photographed by transmission electron microscopy (Zeiss, Oberkochen, Germany).

In eight cats a polymerase chain reaction (PCR) for Feline Herpes Virus 1 (FeHV-1) was performed on Schirmer tear test strips, saliva and a nasal swap. The samples were processed with the QIAamp DNA Mini Kit (QIAGEN, Basel, Switzerland) to extract DNA. Details of the method will be published elsewhere (Leutenegger *et al.* in preparation). The reaction was performed on an ABI PRISM 7700 sequence detection system. Primers and a TaqMan-probe (PE, Applied Biosystems, Rotkreuz, Switzerland) were designed to amplify a 81-bp sequence within the open reading frame of the glycoprotein B gene of FeHV-1.

RESULTS

Signalment

Table 1 summarizes signalment and duration of clinical signs prior to presentation.

Eosinophilic conjunctivitis was diagnosed in 12 cats at the Small Animal Clinic at the Free University in Berlin, Germany over a period of 26 months. The breed most commonly affected was the Domestic Shorthair ($n = 8$), followed by Persians ($n = 2$), Somali ($n = 1$) and Siamese ($n = 1$). Age at presentation was 1–15 years with a mean age of 7.2 years. Nine cats were castrated males, three cats were females; two of them were spayed. The right eye was involved in five cats, the left eye in two cats. Five cats showed bilateral eye involvement. The duration of the clinical signs of eosinophilic conjunctivitis prior to presentation ranged from 4 weeks to over 1 year.

Clinical findings

All cats showed involvement of the lid in the affected eye(s) with swelling, depigmentation and erosive changes of the lower lid margin ($n = 12$) and nasal canthus ($n = 4$). Other common clinical findings were blepharospasm ($n = 12$),

Table 1 Clinical data for the 12 cats with eosinophilic conjunctivitis: signalment, eye involved and duration of signs prior to presentation

No.	Breed	Gender	Age (years)	Eye	Duration of signs prior to presentation (weeks)
1	Domestic Shorthair	cm	7	OS	9
2	Domestic Shorthair	cm	3	OS	32
3	Somali	cm	7	OD	8
4	Domestic Shorthair	cm	15	OU	7
5	Persian	cm	1	OU	28
6	Perisan	sf	12	OD	6
7	Domestic Shorthair	cm	7	OD	10
8	Domestic Shorthair	cm	9	OU	> 52
9	Domestic Shorthair	f	9	OD	10
10	Domestic Shorthair	cm	12	OD	24
11	Domestic Shorthair	cm	3	OU	4
12	Siamese	sf	1.5	OU	4

Cm, castrated male; f, female; sf, spayed female. OS, oculus sinister; OD, oculus dexter; OU, oculi uterqui.

swelling and redness of conjunctiva and third eyelid ($n = 12$) as well as mucous to mucopurulent discharge ($n = 11$) of the affected eye(s) (Figs 1–4). None of the cases had any pathologic corneal changes at the time of presentation. One cat had been treated for bilateral corneal sequestrum 1 year prior to the actual presentation (bilateral keratectomy and placement of a conjunctival flap). The ophthalmologic examination of the unaffected eye in the seven unilateral cases revealed no abnormalities.

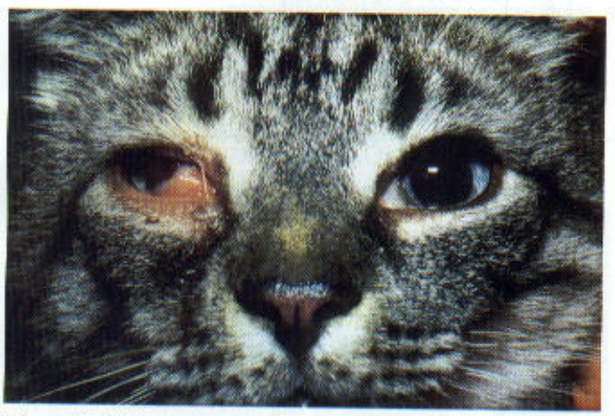

Figure 1. Clinical appearance of case 7 at presentation.

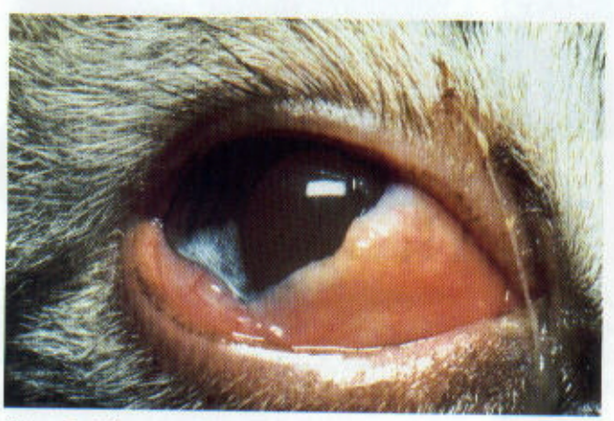

Figure 2. Close up of the right eye of case 7.

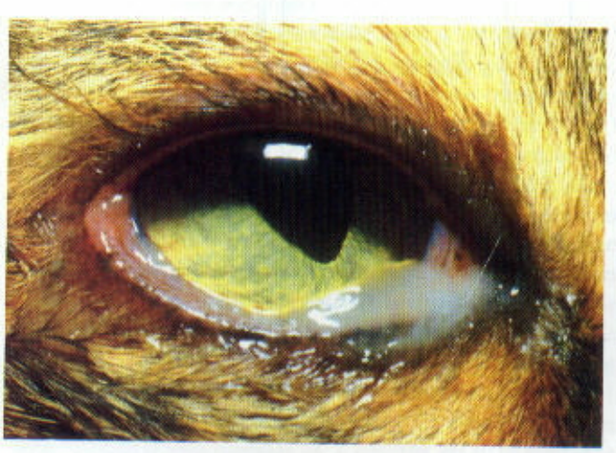

Figure 3. Clinical appearance of case 9 at presentation. Right eye. Note the lid margin involvement.

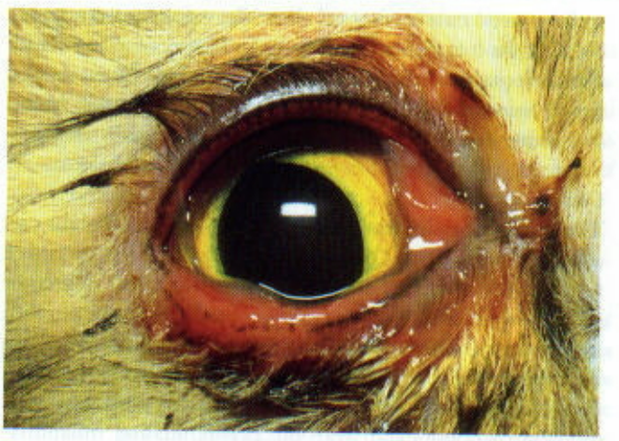

Figure 4. Clinical appearance of case 5 at presentation. Right eye. Note the lid margin involvement.

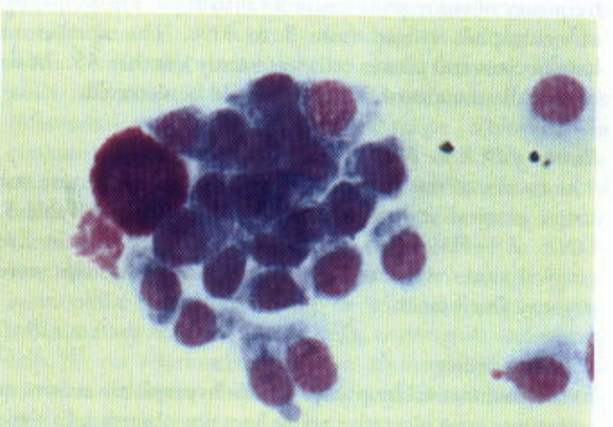

Figure 5. Cytologic specimen (May-Grünwald-Giemsa, × 1000) with mast cells and conjunctival epithelium.

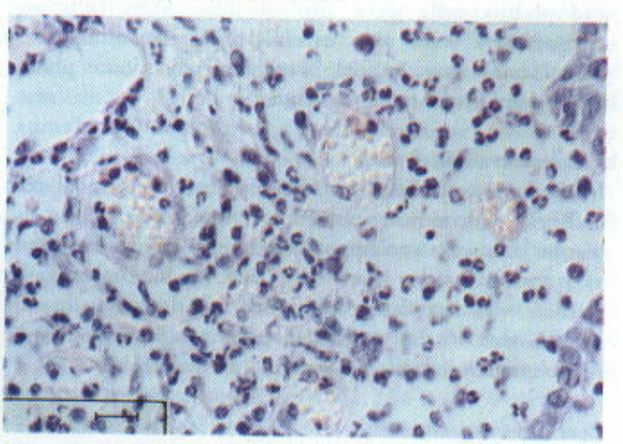

Figure 6. Photomicrograph of a histologic section of a conjunctival biopsy. Note the neovascularized stroma with abundant eosinophils. H&E, bar 16 μm, differential interference contrast (DIC).

A Schirmer tear test (STT) was performed in all cats at the time of diagnosis and ranged from 8 to 27 mm/min (mean: 17 mm/min) in the affected eyes and from 7 to 28 mm/min (mean: 16 mm/min) in the unaffected eyes.

On general examination no other abnormalities were found. None of the cats showed signs or had a history of allergies with dermatologic, gastrointestinal or respiratory signs. None showed typical lesions for the eosinophilic granuloma complex. Moreover, none had signs of upper respiratory disease.

Cytologic findings

The results of individual cytological parameters of eight cats are given in Table 2. Quality and cellularity of the specimen were mostly moderate to good. There was a low degree of cellular dysplasia in most cases. In several slides with moderate specimen quality the degree of cellular dysplasia was increased. The relative portions of inflammatory cell populations was variable. Mast cells were detected with moderate amounts and were the predominating inflammatory cell type in two patients (Fig. 5). High levels of eosinophils were seen in every patient. In every case the frequency of eosinophils was more than 10%. The frequency of neutrophils ranged from 5 to 82%. The number of lymphocytes and plasma cells was mostly less than 5%. In six cats small amounts of fibroblasts could be detected.

Results of PCR for FeHV-1

The results of the PCR for FeHV-1 on Schirmer tear test strips, gingival and nasal swabs are presented in Table 3. DNA of FeHV-1 was detected in one nasal and in five gingival swabs whereas the Schirmer tear test strips were negative in all cases.

Histologic findings

In the conjunctival biopsy specimens hyperplastic erosive or sometimes even ulcerative epithelium was observed. In some cases neovascularized stroma was noted. The most prominent cell type was the eosinophil, but clusters of lymphocytes and plasma cells were also obvious. Mast cells and macrophages were also involved (Fig. 6). Emigrating granulocytes were located intraepithelially. Some plasma cells accumulated immunoglobulin.

Electronmicroscopic findings

In the lamina epithelialis of the conjunctiva epithelial cells and cells with ultrastructural features of macrophages and plasma cells were encountered. Epithelial cells with granula and coated vesicles were seen (Fig. 7). Cytoplasmic or nuclear viral particles could not be detected. In the cytoplasma of the epithelial cells rough endoplasmic reticulum and tonofilaments were infrequently present.

Treatment and outcome

Initial treatment administered in all cases consisted of topical dexamethasone ointment (Ultracortenol®, Ciba Vision, Wessling, Germany) six times daily. Systemic treatment

Table 2 Cytologic features of the conjunctival specimens

No.	Quality	Cellularity	Dysplasia	Ratio F:I	Pigmented epithelial cells	Lymphocytes and plasma cells (%)	Eosinophils (%)	Mast cells (%)	Neutrophils (%)	Fibrocytes (%)	Free granules
1	+++	++	0–1	9 : 1	+	3	36	26	32	3	+
5	++	+++	0–1	8 : 1	0	1	52	20	24	2	0
7	++	++	2	3 : 1	+++	3	23	62	5	7	+++
8	++	+++	0	6 : 1	+	25	11	11	53	–	0
9	+++	+++	2	8 : 1	+	1	40	5	10	2	+
10	++	+++	0–1	8 : 1	+	1	20	73	6	–	+
11	+++	+++	0–1	8 : 1	0	2	49	36	11	2	++
12	+	+++	2	4 : 1	+	3	11	2	82	2	0

Ratio F:I, ratio of epithelial and inflammatory cells; 0, none; +, mild/low; ++, moderate; +++, high.

Table 3 Results of the PCR for FeHV-1 on Schirmer tear test strips, nasal and gingival swabs

No.	STT strip OD	STT strip OS	Gingival swap	Nasal swab
1	–	–	+	–
2	–	–	–	–
3	–	–	–	–
5	–	–	+	+
6	–	–	–	–
8	–	–	+	–
10	–	–	+	–
11	–	–	–	–
12	–	–	+	–

STT, Schirmer tear test; OD, oculus dexter; OS, oculus sinister.

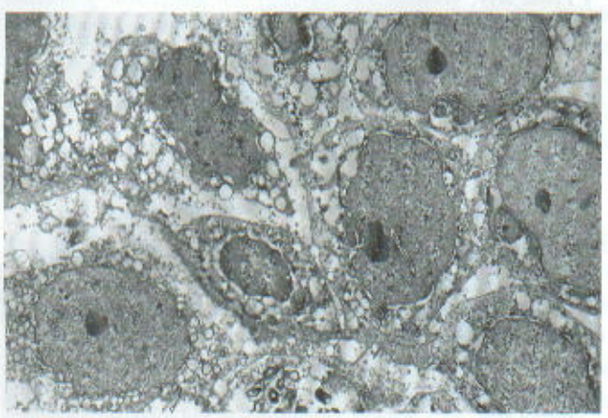

Figure 7. Transmissions electron microscopic appearance of conjunctival epithelium. Note: there are no nuclear inclusion bodies present. ×9400.

with megestrol acetate (Minipil®, Apharmo B.V., Arnheim, Netherlands) 0.5 mg/kg orally SID was utilized in two cases because the cats disposition would not allow intensive topical treatment. One cat had to be sedated for the examination and received triamcinolonacetonid (Volon A®, Bristol-Myers Suibb, München, Germany) 0.01 mg/kg subconjunctivally as the owner was unable to treat it topically or orally. Resolution of the most common clinical signs (blepharospasm, changes of the lower lid margin, swelling and redness of conjunctiva and third eyelid) were considered as response to the therapy. Resolution times ranged between 3 and 6 weeks. In five cats the treatment was then switched to topical cyclosporin (Optimmune®, Essex, München, Germany) BID. This resulted in severe reactions in three cats (irritation, chemosis and conjunctival hyperemia) within the first or second day after the treatment change. In these cats the original treatment was started again. In all cases the frequency of the topical treatment was tapered to the smallest yet effective dose. In the two cases receiving systemic treatment, the dosage was slowly tapered to 0.1 mg/kg megestrol acetate orally every 21 days. The cases were followed over periods of 3 months up to 2 years. As soon as the frequency of topically applied medication dropped below every other day the clinical signs recurred slowly, starting with blepharospasm in all but two cats. In two cases the treatment was completely weaned off without recurrence of clinical signs over a period of 6 months. All other cats stayed on long-term treatment. In seven cases the disease was strictly unilateral. In none of these cases did the second eye show similar changes during the period of observation. One cat developed a cicatrical entropion of the lower lid after resolution of the erosive lesions on the lid margins which required surgical correction. None of the cats progressed to corneal involvement during the period of observation.

DISCUSSION

Clinically the 12 cases described in this paper showed similar appearance with involvement of the lower lid margin being a striking feature that had not been reported before. Typically the lid margin was thickened, depigmented and erosive. The complete lack of corneal lesions in all our cats was also different from what was described by Pentlarge.[7]

Feline eosinophilic conjunctivitis is characterized by profound eosinophilic infiltration of the conjunctiva, which can be detected cytologically on scrapings. In the normal feline conjunctiva eosinophils are rarely detected. Eosinophilic infiltration in cats is regarded as indication of allergic inflammation.[8] The finding of a single eosinophil in conjunctival cytological specimens of 91 cats with chronic conjunctivitis suggests allergy to be an infrequent cause of feline chronic conjunctivitis.[12] Although feline eosinophilic keratitis as well as eosinophilic conjunctivitis closely resemble histologically eosinophilic ulcer of the feline eosinophilic granuloma complex with the predominant inflammatory cells being mast cells, eosinophils and plasma cells,[3,11] no relationship between eosinophilic granuloma complex and eosinophilic keratitis or eosinophilic conjunctivitis has been confirmed so far.

Etiopathogenetically hypersensitivity reactions (type I and IV) have been proposed for the eosinophilic keratitis.[4] A type I hypersensitivity, mediated by IgE, mast cell degranulation, and subsequent chronic tissue injury from degranulating eosinophils as well as a type IV reaction mediated by sensitized T-lymphocytes, interleukin 5 production, and stimulation of local eosinophil response followed by eosinophil-mediated reaction of conjunctival tissue could explain the cellular profile in eosinophilic conjunctivitis.

As with eosinophilic keratitis, feline herpesvirus 1 (FeHV-1) has been suggested as a possible etiologic agent.[5,7] Immunofluorescent antibody assays performed on conjunctival scrapings of cats with eosinophilic keratitis were positive for FeHV-1 in only 50% of the cases.[5] On the other hand, FeHV-1-DNA could be detected in 76.3% of corneal scrapings of cats with eosinophilic keratitis by PCR.[13] In a recent study FeHV-1-DNA was found in 31% of cats with no ocular signs. Because of the occurrence of healthy carriers FeHV-1 PCR was considered of limiting value as a diagnostic test for FeHV-1-associated disease.[14] Interestingly, intradermal skin testing in

cats that had been challenged with FeHV-1 produced a positive delayed type skin reaction predominantly with eosinophils and neutrophils.[15] Nine of our 12 cats were tested for FeHV-1 by PCR (tears, nasal discharge and saliva). A positive result could be obtained in five cases of the gingival swab as well as on the nasal swab in one case; all other samples were negative. The inflammatory cells that were found on histology and transmission electron microscopy did not imply a viral etiology. In particular, the nuclear appearance of the epithelial cells was not compatible with a herpes virus or comparable infection.

All our cases received immunosuppressive drugs topically or systemically. If FeHV-1 played a major pathogenic role in feline eosinophilic conjunctivitis longterm immunosuppressive treatment would theoretically facilitate a relapse of a FeHV-1 infection. None of our cats showed any clinical signs of FeHV-1 infection either prior to the onset of eosinophilic conjunctivitis or after treatment. However, the possible pathogenic role of FeHV-1 for feline eosinophilic conjunctivitis needs further investigation.

Topical or systemic anti-inflammatory drugs resolved the clinical signs in our cases within a short period of time (3 to 6 weeks), but could not be stopped completely in most of the cases as signs would recur. This is in accordance with what has been reported for eosinophilic keratitis.[5] In five cats we used topical cyclosporin ointment (Optimmune®, Essex, München, Germany). This is an immunosuppressive drug approved for dogs only. It was well tolerated by two cats and able to successfully suppress the inflammation. However it lead to severe local reactions in three cats. Whether this was due to the drug itself, to the ointment base, or due to discontinuation of the topical steroid, was not determined.

Cytological examination of conjunctival scrapings was a valuable tool in detecting eosinophilic conjunctivitis. The cytological findings correlated well with the histopathological findings in our patients. Cellularity and quality of the slides was mostly good using the cytobrush method except for one patient, for whom there was a high degree of postvital cellular reactions due to a bad spreading of cellular material on the glass slide. The frequency of mast cells and eosinophils was increased in all cats although the ratio of these cells was variable. This was in contrast to neutrophils, which was the major inflammatory cell type in some cats. Lymphocytes, plasma cells and fibrocytes were detected rarely. The high degree of neutrophils in some cats may have been caused by secondary bacterial infection.

Feline eosinophilic conjunctivitis is a chronic inflammatory response of the conjunctiva. Whether it is etiopathogenetically related to other feline eosinophilic inflammatory corneal (eosinophilic keratitis) or dermatologic (eosinophilic granuloma complex) diseases remains undetermined, as does the etiopathogenic role of FeHV-1.

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