CASE REPORT

Bilateral orbital and nasal aspergillosis in a cat

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Abstract

A 12-year-old, 4 kg, castrated male Persian cat was referred with a 2-month history of sneezing and bilateral mucopurulent nasal discharge. Rhinoscopically acquired nasal biopsies at this time revealed bilateral lymphoplasmacytic rhinitis. A tapering dose of oral prednisone caused the complete remission of the clinical signs, but 2 months after discontinuation of the therapy, the rhinitis recurred and the OD became exophthalmic. Computed tomography showed a soft tissue mass in both sides of the nasal cavity, both frontal sinuses, the right orbit, and to a lesser extent the left orbit. A fine needle aspirate of the right orbit revealed pyogranulomatous inflammation and Aspergillus spp. hyphae. Repeat nasal biopsy demonstrated multi-focal necrosis and a mixed inflammatory cell process which now included macrophages and scattered septate fungal hyphae. A few days later the cat became bilaterally blind and a contrast enhancing lesion involving the optic chiasm was found on magnetic resonance imaging. Despite a poor prognosis, therapy consisted of exenteration of the right orbit and trephination of both frontal sinuses before the planned initiation of medical antifungal therapy. Unfortunately, the cat died of cardiac arrest intraoperatively. Aspergillus fumigatus was cultured from both orbits at necropsy. Orbital aspergillosis has been rarely reported in cats and its relationship with lymphoplasmacytic rhinitis is unclear. In this patient lymphoplasmacytic rhinitis or previous antibiotic/corticosteroid therapy may have allowed secondary fungal invasion of the nasal mucosa and subsequently both orbits and the brain. Alternatively, Aspergillus infection may have preceded the lymphoplasmacytic rhinitis.

Key Words: Aspergillus fumigatus, cat, exophthalmos, mycosis, orbit, rhinitis

INTRODUCTION

Deep fungal infections of the orbit and nasal passages are uncommonly reported in cats.1–5 Several organisms have been associated with this disorder in cats, especially Cryptococcus neoformans6–10 and, much less commonly, Aspergillus spp.1–5 Penicillium spp.2,3,11 and Pythium insidiosum.12 Orbital involvement may be the result of dissemination from a distant site, especially the lungs; extension into the orbit from a lesion involving the nasal passages, sinuses, or globe itself; or occur secondary to a penetrating wound of the orbit. The exact etiopathogenesis, however, is often unclear.

The factors that predispose cats to orbital mycosis are also unclear. Systemic mycoses are frequently suggested to be associated with immunosuppression (e.g. panleukopenia, feline infectious peritonitis, feline immunodeficiency virus, feline leukemia virus, multiple diseases, or glucocorticoid therapy), or with previous antibiotic therapy, but data supporting these assertions are often sparse.1,3,4,7,13,14 Local alterations in immune competency may also be important in allowing fungal colonization of the nasal passages or sinuses. Idiopathic chronic lymphoplasmacytic rhinitis (LPR) in cats has been associated with reduced mucociliary clearance of the nasal mucosa, which may allow fungal colonization and invasion of the upper respiratory tract.15 LPR is a relatively common nasal disorder in cats and dogs.15–18 The definitive etiology of this condition is still undetermined, although some authors believe that it is the
result of a chronic inflammatory response to an inhaled irritant, pollutant or allergen. An immune-mediated pathogenesis has also been suggested. Recent theories also support the possibility that LPR may have an infectious trigger. With chronic LPR, nasal secretions become progressively more mucoid as mucus-secreting glands within the nasal mucosa proliferate and become hypersecretory in response to chronic inflammation. Reduced mucociliary clearance of nasal secretions creates an ideal microenvironment for proliferation of bacteria or fungi, with a resultant increased susceptibility to secondary infections. Furthermore, corticosteroid therapy or antibiotic therapy may also serve as predisposing factor in deep fungal infections.

The purpose of this report is to document an unusual case of sino-nasal aspergillosis affecting both orbits and the optic chiasm in a cat.

CASE REPORT

A 12-year-old, 4 kg, castrated male Persian cat was referred with a 2-month history of bilateral mucopurulent nasal discharge, more evident on the right side. Before the onset of the discharge there was no history of trauma, previous respiratory or ocular disease, and the cat was reported to be otherwise healthy. Previous therapy with oral enrofloxacin (5 mg/kg once a day for 20 days) and subsequently ibafloxacin (15 mg/kg once a day for 20 days) by the referring veterinarian did not improve the clinical signs of the rhinitis. Open mouth radiographs of the nasal cavities by the referring veterinarian showed a diffuse opacity of the right nasal cavity and a posterior turbinate opacity in the left side.

At presentation to our facility in Milan, Italy, the cat was active, but reportedly partially inappetant for the past 3 weeks. On physical examination he had no fever, no weight loss and a mildly enlarged right submandibular lymph node. The cat exhibited sneezing and mucopurulent nasal discharge from the right nares, but air could pass through both nares.

At this time the owner declined further imaging studies to better define the extent of nasal cavity lesions. The owner did, however, consent to rhinoscopy and biopsy of the lesion. Rhinoscopy under general anesthesia using a rigid endoscope (2.7 mm diameter frontal vision) revealed a bilateral mucopurulent exudate, hyperemic nasal mucosa and a pinkish mass in both nasal cavities that bled readily when touched (Fig. 1). The mass occupied the entire nasal passage, had a soft consistency, a broad base and indistinct borders. Histologic examination of multiple, endoscopically-guided pinch biopsies revealed irregularly moderately hyperplastic epithelium with goblet cell hyperplasia, multifocal epithelial erosions, mucosal edema and a diffuse inflammatory infiltrate that consisted primarily of lymphocytes, plasma cells and a smaller number of eosinophils and neutrophils (Fig. 2). No organisms were seen on Gram and PAS stain. The histologic diagnosis was severe bilateral LPR of undetermined cause.

The cat was initially treated with oral doxycycline 10 mg/kg once a day for three weeks in an effort to provide broad spectrum antibiotic coverage for common feline respiratory tract bacterial pathogens, and to take advantage of the immunomodulatory properties of this drug over the previously used fluoroquinolones in the event the disease was immune-mediated in nature. This initially resulted in a partial improvement (reduced sneezing) but after 2 weeks, and while still receiving doxycycline, the clinical signs of the rhinitis worsened. The owner declined further work-up at this time and a course of oral prednisone (1 mg/kg once a day for one week, then 0.2 mg/kg once every other day for 3 weeks) was prescribed on the presumption that the proliferative lesions were immune-mediated in nature.

Oral prednisone resulted in a rapid improvement in the clinical signs of rhinitis, and there were no clinical signs of rhinitis for 2 months after prednisone therapy was discontinued. Two months after stopping corticosteroid therapy, however, the cat was again referred for recurrent rhinitis and also for
progressive exophthalmos of the OD. On this examination the OD was exophthalmic, deviated dorso-laterally, and exhibited pronounced resistance to retropulsion. The motility of the globe was impaired in all directions and resisted forced duction testing. The conjunctiva of this eye was moderately hyperemic, and the third eyelid was prominent, hyperemic and slightly thickened. The right cornea also had an exposure keratitis characterized by extensive corneal edema and a 1-cm diameter, deeply vascularized, central corneal ulcer and corneal edema.

Figure 3. External photograph showing exophthalmos and dorso-lateral deviation of the right eye with concurrent third eyelid elevation, hyperemia and thickening. The cornea shows an exposure keratitis with a 1 cm diameter, deeply vascularized, central corneal ulcer and corneal edema.

deficiency virus (FIV) and coronavirus antibody also proved negative. The cat was then anesthetized for evaluation of the nasal cavities, sinuses and orbits by computed tomography (CT) and repeat rhinoscopy. Computed tomography revealed a large soft-tissue mass present in both sides of the nasal cavity. This mass slightly indented the right globe (Fig. 4). In addition to the changes in the right orbit there also was a moderately sized, soft tissue density mass ventro-medially within the right orbit which was displacing the globe dorso-laterally, focal lysis of the right lacrimal bone, and abnormal soft tissue density in both frontal sinuses and both sides of the nasal cavity. This tissue had indistinct borders and completely invaded the frontal sinuses, nasal conchae, and portions of the right ventral nasal meatus. The optic chiasm and both optic nerves did not show any abnormalities. Transpalpebral fine-needle aspirates of the mass in the right orbit were acquired with CT guidance.

After completion of the CT scan a repeat rhinoscopy was performed so as to acquire additional biopsy specimens from the nasal cavity. The findings on rhinoscopy were similar to those seen at the first presentation, but there was a more intense turbinate hyperplasia and a hypertrophic nasal mucosa.
A white-pinkish mass was present in both nasal cavities, but it was more evident on the left. This lesion occupied the entire nasal passage and was translucent, had a soft fatty consistency, a broad base and indistinct borders (Fig. 5). Multiple biopsies of the nasal lesions were performed.

A few days after the CT scan and repeat rhinoscopy, and while waiting for the results of the orbital cytology and repeat nasal biopsies, the cat represented with bilateral vision loss and absence of a menace response or pupillary light reflexes in both eyes. The left fundus appeared normal, and the lesion causing vision loss was clinically localized to either both optic nerves or the optic chiasm. Thoracic radiographs were unremarkable, and serological tests for systemic mycoses were not pursued because of the absence of other systemic signs. Magnetic resonance imaging (MRI) was performed to more critically evaluate the optic chiasm and to determine the full extent of the soft-tissue component of the disease. The MRI confirmed the alterations seen by CT and, after the administration of contrast medium, it also showed an enhancement of the right portion of the optic chiasm (Fig. 6) that could not be appreciated on review of the CT scan acquired a few days earlier. The lesion involving the optic chiasm was felt to exhibit the characteristic appearance of an inflammatory process that could explain the bilateral vision loss.

Cytologic evaluation of the orbital aspirates acquired at the time of CT now became available and revealed abundant necrotic cellular debris and a mixed inflammatory infiltration composed of neutrophils, macrophages, lymphocytes, and plasma cells. Numerous PAS stain-positive, septate, fungal hyphae were also visible. The morphologic appearance of the organism was consistent with Aspergillus spp. Histopathology of the nasal mucosa biopsies revealed a mixed inflammatory cell population, mostly composed of lymphocytes, plasma cells and scattered eosinophils. In contrast to the first rhinoscopically acquired biopsy, however, a significant number of macrophages were also present, indicating that the inflammatory response had acquired a granulomatous component since the first biopsy several months before. A small number of fungal hyphae were detected within areas of coagulative necrosis on the surface of ulcerated nasal turbinates (Fig. 7). These were characterized by parallel walls, relatively uniform width (3–7 μm), occasional acute-angle dichotomous branching, and apical bulbous dilations, consistent with Aspergillus spp. Intense turbinate bone remodeling was also present. A diagnosis of fungal rhinitis, presumptive fungal sinusitis, fungal orbital cellulitis, and inflammation of the optic chiasm was made. Given the rhinoscopic appearance of the nasal passages, the clinical course of the cat and the finding of septate fungal hyphae on multiple biopsy samples it was elected not to pursue further testing for C. neoformans and other systemic mycoses.
Although the prognosis was poor, the owner wished to attempt to aggressively pursue therapy. Despite the disease progression the cat was only partially inappetant and remained in good body condition. A complete blood count, serum biochemical analysis and routine urinalysis were still unremarkable. Therefore, a decision was made to exenterate the right orbit to alleviate ocular pain and to attempt to debulk the main fungal load in preparation for systemic antifungal therapy in the post-operative period. The cat was anesthetized using midazolam (0.25 mg/kg i.m.) and buprenorphine (15 μg/kg i.m.) for premedication, propofol (1 mg/kg i.v.) for induction and isoflurane for maintenance of anesthesia. Main cardiovascular and respiratory parameters were evaluated for intra-anesthetic monitoring by using a pulse oximeter, a capnometer, an electrocardiograph, a Doppler indirect arterial blood pressure monitor and subjective clinical signs every 5 min.

At the time of surgery the mass in the right orbit was friable, yellow-gray in color, fatty in appearance and diffusely infiltrated the soft tissues of the orbit. Erosion was present in lacrimal bone creating a direct communication between the orbit and the right nasal cavity. After the exenteration had been completed, both frontal sinuses were trephinated to adequately drain these structures and further reduce the fungal load. This resulted in the aspiration of a large amount of mucopurulent material from the sinuses. The sinuses were then flushed with a dilute (1/100) povidine iodine solution and 0.9% saline solution. Excised tissues were submitted for histopathological evaluation and for aerobic and anaerobic bacterial and fungal culture.

Near the conclusion of surgery the cat experienced ventricular fibrillation and cardiac arrest. Attempts at resuscitation were unsuccessful and the cat died. A complete necropsy was performed. Both orbital masses were composed of multiple, coalescing pyogranulomas and abundant coagulative necrosis in which 3–5 μm irregularly septate fungal hyphae of variable length with acute-angle dichotomous branching, consistent with Aspergillus spp. were embedded (Fig. 8). The right globe showed a central exposure corneal ulcer and a keratitis with a predominantly neutrophilic infiltrate, corneal edema and neovascularization, hypopyon and moderate lymphocytic-plasmacytic anterior uveitis. A moderate mucopurulent sinusitis affected the frontal sinuses. The optic chiasm exhibited diffuse, moderate gliosis and spongiosis and a mild lymphocytic-plasmacytic meningitis. All other organs, including the central nervous system and the left globe were unremarkable. Fungal hyphae were detected only in the orbital contents, following staining with hematoxylin and eosin, periodic acid-Schiff, and Gomori’s methenamine silver stain.

Aerobic, anaerobic and fungal cultures from both frontal sinuses and orbits were plated on Sheep Blood Agar (Oxoid, Italy) for bacteria and on Sabouraud Dextrose Agar (Oxoid, Italy) for fungi and incubated at 37 °C. Aspergillus fumigatus was grown from both orbits but no fungi were isolated from the sinuses. Proteus mirabilis was found in both sinuses but not in the orbits.

Figure 8. Photomicrograph of the orbital mass. Irregularly septate, 3–5-μm wide fungal hyphae of variable length with parallel walls and acute angle dichotomous branching are embedded in abundant necrotic and karyorrhectic debris (Periodic Acid-Schiff, 400x).

DISCUSSION

Fungal nasal infections, with or without orbital involvement, are rare in cats, with C. neoformans being the most frequently reported etiologic agent. To date, only 10 cases of sino-nasal aspergillosis have been reported in cats. All (10) of these cats had rhinitis, sinusitis and a mucopurulent nasal discharge. Epistaxis was also present in several cats. In three of the 10 cats a lymphocytic-plasmacytic rhinitis was present, but fungal hyphae were found only in one or both frontal sinuses and not in the nasal passages. Rhinoscopy in eight of the cases demonstrated white masses in the nasal cavities and/or sinuses, whereas CT (performed in seven cats) showed destruction of the turbinale bones. Two cats with sino-nasal disease also had involvement of the orbit. In one case this was associated with fungal sinusitis, and in the other it was associated with fungal sinusitis and rhinitis. The literature also contains another case of orbital aspergillosis in a cat in which there were no reported signs of fungal rhinitis nor sinusitis. Therefore, although fungal orbital disease can be an extension of a fungal sino-nasal infection as in the case reported here, this does not appear to always be the case.

Of the 10 previously reported cases of feline sino-nasal aspergillosis, five were Persians (as was the cat reported here) and two were a closely related breed (Himalayan). Only one of these 10 cats was seropositive for FeLV, all were negative for FIV, and none had a history of immunosuppressive therapy or other diseases, indicating that most cats with sino-nasal aspergillosis do not have an obvious immunosuppressive condition. Although a specific breed-related or immunogenetic susceptibility to sino-nasal aspergillosis cannot be ruled out, it seems feasible that a brachycephalic facial conformation may be an important risk factor for the development of sino-nasal aspergillosis in cats. Additionally, it is possible that Persian and Himalayan cats may have a specific
breed predisposition to systemic infection with *Aspergillus* spp. much as is seen in young adult female German Shepherds, although no sex predisposition has been reported for cats.

Given that the exposure of the upper respiratory tract of both humans and animals to the conidia of *Aspergillus* spp. is almost constant, it is possible that the brachycephalic airway of Persians and Himalayan cats may at times become overwhelmed in its ability to clear *Aspergillus* from the cat’s upper airway. Although *A. fumigatus* can be both a primary and an opportunistic pathogen (as well as a major allergen in humans), extensive investigations of its genome suggest that it is able to create disease not because it possesses true virulence genes, but instead because it has distinct sets of temperature-dependent genes that allow it to survive in environments that are either thermally (e.g. at body temperature) or oxidatively stressful. In dogs, *Aspergillus* fungal endotoxins that are hemolytic and dermonecrotic have also been associated with a vasculitis and vascular necrosis of the submucosal vessels that leads to destruction and necrosis of the nasal mucosa and underlying turbinate bones. Based on the few reports in the literature and the case reported here, cats may also experience a similar phenomenon.

Chronic LPR because of nonfungal etiologies may further exacerbate the anatomic compromise in brachycephalic cats by causing further luminal narrowing or even complete obstruction of nasal passages. It is tempting to speculate that the lower frequency of sino-aspergillosis in nonbrachycephalic cats is attributable to an initially more open nasal passageway that is more difficult to obstruct. Proliferation of mucus secreting glands in the nasal mucosa in response to chronic inflammation also may result in more mucoid nasal secretions and reduced mucociliary clearance of organisms from the nasal passages. In concert, these events may create an ideal microenvironment for proliferation of bacteria and/or fungi, with resultant increased susceptibility to secondary infections.

In the case reported here it is also possible that prior treatment with anti-inflammatory doses of systemic corticosteroids and/or three courses of broad spectrum antibiotics may have shifted the local environment towards one that favored proliferation of, and tissue invasion by, fungal elements, although the cat was off all therapy for 2 months before the clinical onset of orbital disease. Additionally, multiple biopsies of the nasal passages acquired at the first rhinoscopic examination failed to reveal fungal elements and did not demonstrate a granulomatous component to the inflammatory process at that time. However, we cannot exclude the possibility that the initial samples obtained by pinch biopsy were not truly representative of the disease process at that time, as pinch biopsies could conceivably have been too superficial.

The etiopathogenesis of LPR in cats is unclear but it may represent a chronic inflammatory response to an inhaled irritant, pollutant or allergen; a chronic immune-mediated (rather than irritant or allergic) disorder; or perhaps a response that is triggered by infectious agents such as feline herpesvirus type-1 (FHV-1) in cats or *Aspergillus* spp. in dogs. In humans, *A. fumigatus* is also regarded as a potential cause of allergic rhinitis and sinusitis. In at least one study, however, the frequency of FHV-1 infections in cats with chronic rhinosinusitis was comparable to that found in a control population of cats without rhinosinusitis, and fungal organisms could not be isolated from any cat affected with rhinosinusitis. Furthermore, another study of dogs with lymphoplasmocytic rhinitis found that the profile of gene expression of cytokines and chemokines with idiopathic LPR is different from that in dogs with sino-nasal aspergillosis, indicating that the majority of cases of idiopathic LPR in dogs are not likely to be cases of undiagnosed aspergillosis. Whether this is also true for cats is unclear, as the fundamental nature of the immune response reported for cats with LPR (Th1) is different from dogs with LPR (a partial Th2 response), although it is comparable to dogs with sino-nasal aspergillosis (Th1 and Th2) and nasal samples from cats positive for FHV-1 mRNA (also Th1). Given the above it is difficult to conclusively determine in the case reported here whether the LPR preceded colonization of the respiratory tract by *A. fumigatus* or whether the fungal organism initiated the LPR. The initial absence of fungi on multiple biopsy specimens, the relatively prolonged positive response to immunomodulating/immunosuppressive (doxycycline and glucocorticoids) agents, and the shift towards a granulomatous inflammatory component on the second set of biopsies in this case, however, partially substantiate the hypothesis that in this cat the LPR occurred first.

With regard to the therapy, our initial plan was to exenterate the orbit and then initiate systemic antifungal therapy in the post-operative period once the main fungal load had been surgically reduced. This plan was based on a previous report of a similarly affected cat in which posaconazole was successfully used as an adjunct to surgical exenteration. Posaconazole was selected because it is a broad spectrum triazole and has been suggested to have the lowest minimal inhibitory concentration for *A. fumigatus* on sensitivity testing. Unfortunately, the cat presented in our report died before systemic antifungal therapy could be initiated.

In summary, orbital aspergillosis may be a serious disorder affecting cats, and further studies are required in order to better understand the role of LPR in fungal sino-nasal infections in cats.

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