Fungal rhinitis and sinusitis in three cats

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- Clinical signs of *Aspergillus* or *Penicillium* rhinitis and sinusitis in cats include chronic mucopurulent nasal discharge, epistaxis, and mandibular lymphadenopathy.
- Rhinoscopic, histologic, and diagnostic imaging findings in cats with *Aspergillus* or *Penicillium* rhinitis and sinusitis are compatible with a destructive inflammatory process of the nasal mucosa and underlying bony structures.
- In cats with *Aspergillus* rhinitis and sinusitis, results of immunoelectrophoresis of serum for antibodies against *Aspergillus fumigatus* may be positive even if results of fungal culture are negative.
- Oral administration of itraconazole may result in temporary improvement in cats with fungal rhinitis and sinusitis; however, hepatotoxicosis may develop. Intranasal infusion of clotrimazole may be an effective treatment for fungal rhinitis and sinusitis in cats.

A 2-year-old spayed female Siamese cat was referred for evaluation and treatment of chronic, unilateral, mucopurulent nasal discharge of 1 year's duration. Previous treatment with amoxicillin-clavulanate (12.5 mg/kg [5.7 mg/lb], PO, q 12 h) had resulted in transient improvement. The cat was currently vaccinated and had access to the outdoors.

Abnormalities evident on physical examination included left-sided mucopurulent nasal discharge and ipsilateral mild mandibular lymphadenopathy. Results of a CBC, serum biochemical profile, and urinalysis were unremarkable. The cat was anesthetized, and antegrade rhinoscopy was performed.[a] Diffuse reddening and swelling of the nasal mucosa, a large amount of gray-white discharge, and a white-yellow mass were found in the left nasal cavity. The right nasal cavity was unremarkable. Tissue specimens were taken blindly with cup biopsy forceps,[b] samples for bacterial and fungal culture were collected with culture swabs, and the nasal cavity was vigorously flushed with sterile saline solution. Results of serum immunoelectrophoresis[c] for antibodies against *Aspergillus fumigatus* were positive. Histologic examination revealed mixed-cell rhinitis with large agglomerates of fungal hyphae; neutrophils and eosinophils were seen on the mucosal surface. Bacterial culture yielded *Pasteurella dagmatis* and an α-hemolytic *Streptococcus* sp. Results of fungal culture were negative. A diagnosis of nasal aspergillosis was made on the basis of histologic and serologic findings. Clinical signs resolved after diagnostic rhinoscopy, and the cat was still healthy 1 year later.

A 12-year-old castrated male Persian cat was referred for evaluation of sneezing, bilateral purulent nasal discharge, and excessive lacrimation of 2 years' duration and recurrent epistaxis of 2 months' duration. There was no clinical improvement with antimicrobial treatment (drug and dosage unknown). The cat was allowed free access to the outdoors and was currently vaccinated.

Physical examination revealed signs of depression, oligodontia, anisocoria with poorly responsive pupils, and bilateral conjunctivitis with mucous discharge. A bilateral purulent foul-smelling nasal discharge and mandibular lymphadenopathy were also present. Results of a CBC, serum biochemical profile, and urinalysis were unremarkable. Results of serologic assays for FeLV, FIV, and feline coronavirus infection were negative. Ophthalmologic abnormalities included anterior uveitis with a large amount of fibrin in the anterior chamber of the left eye and retinal ablation with a giant retinal tear in the right eye. Computerized tomography of the skull was performed, and an irregularly shaped, approximately 1 × 1-cm object of density similar to that of a tooth was seen in the middle of the right nasal cavity (**Fig 1**). There was a moderate increase in soft-tissue density in the cranial part of the right nasal cavity and profound destruction of turbinate bones in the caudal

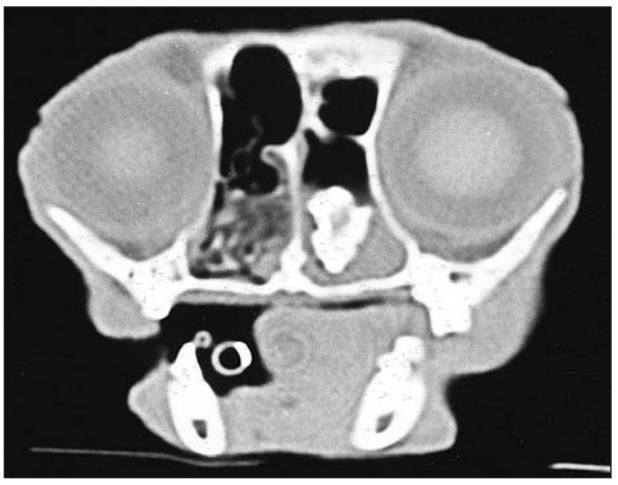

Figure 1—Computed tomographic scan of the nasal and paranasal cavities in a cat examined because of sneezing, bilateral purulent nasal discharge, and epistaxis. The left nasal cavity and part of the frontal sinus appear normal. In contrast, fine turbinate markings in the right nasal cavity are lost, and there is increased soft-tissue density ventrally. A high-density object (1,542 Hounsfield units [HU]), similar to the density of the teeth (2,030 HU), is evident in the right nasal cavity.

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part of the right nasal cavity with no deviation of the nasal septum. On rhinoscopy,[d] the right nasal cavity appeared empty with profound destruction and atrophy of the turbinates. A large white-yellow mass was seen (**Fig 2**) and removed with biopsy forceps.[b] The mass had a gritty structure, similar to turbinate bone, and histologic findings were necrotic rhinitis with large colony of segmented fungal hyphae and calcification of the affected tissue. Bacterial culture of a nasal swab specimen yielded moderate growth of *Escherichia coli*. Results of serum immunoelectrophoresis[c] for antibodies against *Aspergillus* spp were negative, and fungal culture did not yield any growth. A diagnosis of fungal rhinitis, presumably attributable to *Aspergillus* or *Penicillium* spp complicated by bilateral anterior uveitis, was made. No further diagnostic testing or treatment was performed, as the owner elected euthanasia.

An 8-year-old castrated male Persian cat was referred because of chronic mucopurulent greenish nasal discharge from the right nostril for the past 6 months. The cat had free access to the outdoors and was currently vaccinated. Treatment with doxycycline (3 mg/kg [1.4 mg/lb], PO, q 8 h) had led to transient improvement of clinical signs on multiple occasions.

Physical examination abnormalities included high rectal temperature (39.4°C [103°F]) and a unilateral purulent nasal discharge. On abdominal palpation, both kidneys were considered slightly larger than normal. Serum biochemical abnormalities included high urea (15.7 mmol/L; reference range, 8 to 14 mmol/L) and creatinine (175 μmol/L; reference range, 84 to 161 μmol/L) concentrations. There were no hematologic abnormalities, and a urinalysis was not performed. Polycystic kidney disease was evident during abdominal ultrasonography. Computed tomography of the skull revealed loss of the turbinate bones, filling of the frontal and sphenoid sinuses with fluid, thinning of the orbital bones on the right side, and deviation of the vomer bone to the left. On rhinoscopy,[d] a large amount of white-gray discharge was present in the right nasal cavity; however, the entire cavity lacked turbinates, and the rhinoscope could be guided directly into the frontal sinus. Histologic examination of biopsy specimens from the frontal sinus revealed mixed-cell inflammation with fungal hyphae. Histologic examination of biopsy specimens from the nasal cavity revealed mixed-cell rhinitis without evidence of fungal colonies. Bacterial and fungal cultures of nasal swab specimens did not yield any growth. Results of serologic testing[c] for antibodies against *A fumigatus* were positive.

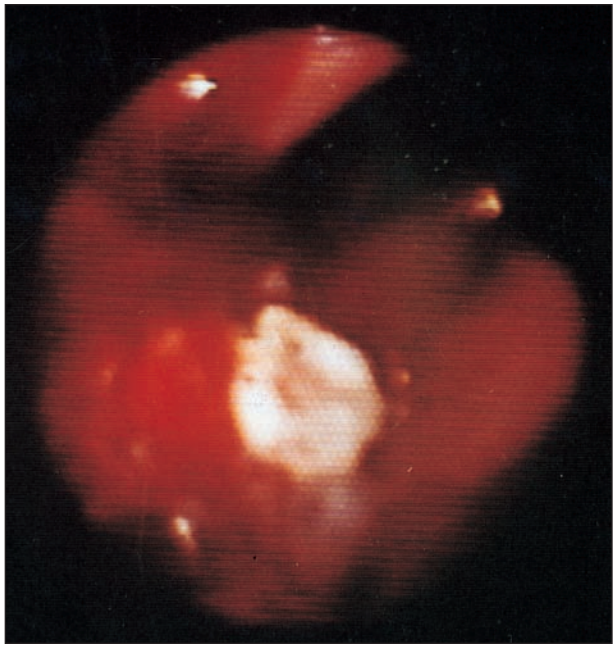

Figure 2—Rhinoscopic view of the right nasal cavity in the cat in Figure 1. The nasal cavity appears more cavernous than normal, and there is severe reddening and irregularity of the nasal mucosa. A white-yellow mass, corresponding to the high-density object seen on the computed tomographic scan, is lying on the mucosa.

The cat was treated with itraconazole (10 mg/kg [4.5 mg/lb], PO, q 24 h) for 6 weeks, and its condition improved, with a reduction in the amount of nasal discharge. However, after 6 weeks of treatment with itraconazole, the cat became anorectic. On physical examination, the cat appeared healthy; the only abnormality was a small amount of crusting at the right nostril. Serum biochemical abnormalities included mild azotemia (urea, 14.3 mmol/L; creatinine, 200 μmol/L) and high alanine aminotransferase activity (178 U/L; reference range, 41 to 140 U/L). Itraconazole toxicosis was suspected, and treatment was discontinued. The owner insisted on taking the cat home without further treatment.

One month later, the cat was readmitted because of recurrence of purulent nasal discharge. The cat was anesthetized, and bilateral intranasal infusion of 1% clotrimazole solution in propylene glycol was performed as described,[1] with minor modifications. Briefly, with the cat in dorsal recumbency, a 14-F Foley catheter was introduced through the right nasal opening and advanced through the ventral meatus into the pharynx. With the balloon fully inflated, the catheter was pulled rostrally to lodge tightly in the rhinopharynx and prevent caudal leakage of infusate. In addition, gauze sponges were used to pack the pharynx. An 8-F Foley catheter was introduced into the left and right nasal opening each, and their balloons were fully inflated to prevent rostral leakage. Clotrimazole solution was instilled under mild pressure through the rostral Foley catheters until it started to leak slowly out of both nasal openings; at this time, complete filling of the nasal and paranasal cavities was assumed to have occurred. Additional infusate was given as necessary to maintain pressure in the nasal cavity, and the clotrimazole solution was left in the nasal cavity for 1 hour. Because of the risk of posttreatment anorexia, a gastrostomy tube was placed during the same anesthetic episode.

The cat recovered without complications and was treated with enrofloxacin (10 mg/kg, q 24 h) through the gastrostomy tube to prevent secondary bacterial infection. Anorexia did not develop, but a transient bilateral purulent blood-tinged nasal discharge was noticed shortly after the procedure. This gradually resolved over the subsequent 10 days of hospitalization. The gastrostomy tube was removed after 1 week. One year later, the owner reported by telephone that the cat appeared healthy.

There are few published reports of localized *Aspergillus* or *Penicillium* infection of the nasal, paranasal, or orbital cavities in cats.[2-6] Clinical and histologic differentiation between infections caused by fungi of these 2 genera is difficult, and fungal culture is required to distinguish them.[7] However, whether differentiation is of therapeutic importance is unknown, and because the diagnosis is often made on the basis of histologic examination alone, the disease might best be called aspergillosis-penicilliosis.

In contrast, a large number of cats with disseminated aspergillosis have been described in the literature.[8] Most cats with disseminated aspergillosis were emaciated, had concurrent immunosuppressive diseases, or had received glucocorticoids or antimicrobials. Clinical signs were usually referable to gastrointestinal tract or pulmonary involvement.[8]

The striking clinical difference between cats with disseminated aspergillosis and the cats in the present report with nasal aspergillosis-penicilliosis reflects a similar dichotomy in human patients with aspergillosis.[9-12] In immunocompetent humans, localized noninvasive infections (eg, aspergilloma, allergic bronchopulmonary aspergillosis, and allergic fungal sinusitis) are most commonly observed,[9-11] although isolated invasive fungal infection of the paranasal sinuses can occur in otherwise healthy patients.[11,12] Localized noninvasive and invasive infections are differentiated on the basis of whether fungal hyphae are seen within affected tissues, with associated granulomatous reaction, vascular invasion, or tissue necrosis.[9,11] Noninvasive infections may become invasive if untreated.[11,12] In contrast, immunosuppressed human patients are more likely to develop severe and usually fatal disseminated invasive aspergillosis.[9-11]

Aspergillus fumigatus is one of the most common airborne saprophytic fungi, and humans and animals constantly inhale numerous conidia of this fungus.[9-11] While no data concerning the environmental distribution of *Penicillium* spp exist, *Aspergillus* spp can readily be isolated, even from commercial dry pet foods.[13] Cellular properties of *Aspergillus* spp make it particularly suited to cause nasal infection and resultant inflammation. Direct expression of adhesion molecules on the cell membrane of *A fumigatus* conidia is responsible for adherence of the organism.[9] The fungus also produces virulence factors (eg, gliotoxin, a potent inhibitor of mucociliary clearance, a conidial inhibitory factor, and a complement inhibitory factor) that inhibit phagocytosis and opsonization.[9,14,15] Fungal 18-kDa RNase, known as restrictocin, is extremely toxic to cells, leading to cell death.[9] Vasculitis and tissue necrosis are well known complications of *Aspergillus* infections.[7,11,12]

Although host immunocompetence must be considered in humans and animals with nasal infection with opportunistic fungi, systemic immunosuppression is not critical to the development of nasal or paranasal aspergillosis.[7,11,12] A thorough evaluation of immune status was not performed in the cats described in the present report; however, results of serologic assays for FeLV, FIV, and feline coronavirus infection were negative in 1 cat. In a previous report[4] of a cat with nasal aspergillosis, results of a FeLV antigen assay were positive. Substantial colonization of the skin and mucous surfaces with a multitude of fungal organisms, including *Aspergillus* spp, has been documented in healthy cats and cats with systemic retroviral infections without any signs of localized or systemic fungal disease.[16]

Patients with localized nasal fungal infection mount an adequate, predominantly cellular, immune response that prevents systemic spread; however, some defects of local defense mechanisms or other underlying disease still permit persistence of the infection.[7,12] Physical barriers (mucociliary clearance) eliminate most airborne conidia, macrophages kill adhered conidia, and neutrophils combat the mycelial form of *Aspergillus* spp.[9,10] Multiple morphologic and functional variables influence the efficiency of mucociliary clearance of the nasal cavity and paranasal sinuses.[17-19] Abnormalities of mucociliary clearance are observed in human patients with septal deviations and other morphological variations, such as complicated facial deformities or obstructions of the nasal passages or paranasal sinus ostia.[18,19] Clear morphologic abnormalities exist in brachycephalic cats and dogs, causing turbulent airflow and mucosal edema,[20] and 2 of the cats in the present report were Persians. In addition, a previously reported case also involved a Persian cat,[5] and we believe that pronounced brachycephaly might alter airflow, cause changes in the vasomotor action of the vasculature, and decrease mucociliary clearance, thereby increasing the susceptibility to localized fungal infection.

The resolution of clinical signs following diagnostic rhinoscopy in 1 of the cats in the present report might suggest that an unidentified foreign body acted as a predisposing factor to infection. Similarly, previous infection by **feline rhinotracheitis virus (FRV)** or **feline calicivirus (FCV)** may have changed mucosal health and local defense mechanisms. In particular, FRV infection can lead to severe disruption of nasal cavity architecture because of intense inflammatory reaction of the turbinates with subsequent osteolysis.[21] We did not attempt to identify latent FRV infection in the cats described in the present report, and given the chronicity of clinical signs in these cats, it would seem impossible to establish whether fungal infection was a primary event or a sequela of an underlying disorder.

All of the cats described in this report had received antimicrobials for various times prior to referral to our hospital, and antimicrobial treatment is commonly discussed as playing a predisposing role in fungal infection. However, although this may be true for *Candida* infections,[22] antimicrobials are not usually considered an important predisposing factor for aspergillosis in human patients.[10] Given that so few cases of aspergillosis-penicilliosis in cats have been documented, such an association also seems rather unlikely in cats, considering the common occurrence of fungal organisms on the skin and mucosal surfaces of healthy cats[16] and the widespread use of antimicrobials in cats. In addition, isolated fungal infections of the paranasal sinuses do occur in healthy human patients with no history of previous antimicrobial treatment.[11,12]

Clinical signs of fungal rhinitis and sinusitis are indistinguishable from clinical signs associated with other pathologic conditions of the nasal and paranasal cavities.[21,23] The nasal cavity can respond to insults in a limited number of ways, and mucopurulent nasal discharge, sneezing, epistaxis, and epiphora are common with viral and fungal rhinitis and nasal and paranasal neoplasia.[23] Because secondary bacterial rhinitis is common, a transient response to antimicrobial treatment does not exclude nasal neoplasia or fungal rhinitis.[7,23]

Anterior uveitis was documented in 1 of the cats described in the present report. We can only speculate that it may have been caused by fungal invasion of the globes (local or systemic) or by secondary chronic activation of immunocompetent lymphocytes by fungal antigens or deposition of fungal antigen-antibody complexes.[24]

An antemortem diagnosis of aspergillosis-penicilliosis should not be made on the basis of a single positive test result, as false-positive and false-negative results can occur with all available tests.[7,11] In the cats described in the present report, white-gray exudate, fungal plaques, or a nasal cavity devoid of turbinates were seen, as is common in dogs.[7] Histologic examination of biopsy specimens revealed fungal hyphae with mixed-cellular or necrotic rhinitis, as is common in human and canine patients.[7,11,12] Biopsy during direct examination is the best way to obtain fungal colonies, which may be missed during blind collection of biopsy specimens.[7] In 1 cat described in the present report, fungal colonies were not found in nasal biopsy specimens but were found in biopsy specimens from the frontal sinus. Unfortunately, the size of the nostrils in cats in relation to currently available rhinoscopic equipment may limit inspection of all recesses of the nasal cavity. In particular, unless the turbinates are destroyed, the paranasal sinuses may not be reached.

Results of skull radiography and computed tomography were suggestive of destruction of the turbinate bones together with focal increased soft-tissue densities. These changes are nonspecific and common with intranasal neoplasia and chronic rhinitis in cats.[25] The irregular calcified density that was found in 1 cat in this report was necrotic tissue that had presumably undergone dystrophic calcification. Deposition of calcium oxalate or phosphate crystals in tissues occurs frequently in association with *Aspergillus* infection in humans[26,27] and was reported recently in an alpaca with *A niger* pneumonia.[28] It is, therefore, uncertain whether calcification in the cat in the present report was dystrophic or a result of calcium oxalate deposits by the fungus itself. *Aspergillus* spp is known to produce oxalic acid, which causes substantial tissue necrosis.[28] Regardless, identification of mineralized densities in the nasal and paranasal cavities should raise the suspicion of *Aspergillus* infection.[12,27,28] Nothing is known about whether *Penicillium* spp has a similar ability.

Fungal culture of nasal swab specimens from the 3 cats in the present report did not yield fungal growth. While missing the lesion (fungal colony) during sample acquisition is the most likely explanation, similar observations have been made in human patients, in whom biopsy specimens are generally taken during surgical exploration of the diseased cavities.[11,12] As results of fungal culture do not distinguish between colonization and active infection,[7,9] and histologic findings are diagnostic, we consider fungal culture to be ineffective in terms of time and cost. Nevertheless, when a sample can be obtained directly from the site of visible fungal infection, positive results of fungal culture would provide useful adjunct diagnostic information. In 2 previous cases,[2,5] fungal growth (*Penicillium* spp and *Aspergillus* spp) was documented.

Detection of serum anti-*Aspergillus* antibodies strongly supports a clinical suspicion of aspergillosis in patients with compatible rhinoscopic, histologic, or diagnostic imaging findings,[7] and serologic testing is very helpful in the diagnosis of aspergillosis in immunocompetent human patients. Although growth of the fungus within tissues is limited, a strong humoral response frequently occurs.[9,10] In contrast, immunosuppressed patients have little capacity to develop high concentrations of specific anti-*Aspergillus* antibodies, regardless of the extent of growth of *Aspergillus* spp within tissues.[9,10] In addition, immunodiffusion and immunoelectrophoresis are sufficiently insensitive to virtually eliminate false-positive results occurring as a result of the low titers of anti-*Aspergillus* antibodies in most healthy individuals.[9,10] Results of an agar double diffusion test were positive in 10 dogs with *A fumigatus* infection of the nasal cavity and in none of 27 control dogs with various other nasal disorders.[29] A positive precipitin reaction for *A fumigatus* was reported previously in 1 cat with nasal aspergillosis.[4] Results of serum immunoelectrophoresis for antibodies against *A fumigatus* were positive for 2 of 3 cats in the present report, suggesting that this may be a useful diagnostic test. Further evaluation of this test in clinically healthy cats from the same geographic area and in cats with nasal cavity diseases of other causes would be necessary, however, before the diagnostic utility could be determined.

A recent development in the diagnosis of systemic and local aspergillosis in human patients is the use of polymerase chain reaction assays.[30,31] This may be particularly useful in immunocompromised individuals that are not able to mount an adequate immune response and are seronegative.[32]

Itraconazole has been suggested for empirical treatment of aspergillosis-penicilliosis in cats,[6] but to our knowledge, no reports of successful treatment of nasal or paranasal aspergillosis-penicilliosis in cats have been published, other than a description of rhinotomy and turbinectomy in 1 cat.[4] Itraconazole treatment led to marked improvement in clinical signs in 1 of the cats in the present report but was stopped abruptly because of associated hepatotoxicosis.

A single noninvasive intranasal infusion of 1% clotrimazole solution was performed in 1 cat in the present report, as described previously for dogs.[1] The technical simplicity of the procedure, combined with the complete resolution of signs afterwards, suggests that it may be an interesting therapeutic modality. Clotrimazole instillation through a frontal sinus trephination was reported recently in a cat with nasal, paranasal, and orbital aspergillosis, but no statement

was made about treatment success.[5] Anatomically, cats have 2 paranasal sinuses (frontal and sphenoid sinuses). Both sinuses communicate with the nasal cavity through broad openings[33]; therefore, we believe that in cats, the distribution of topical agents administered through the noninvasive technique would be similar to that in dogs.[34] A short-term worsening of clinical signs must be expected after clotrimazole instillation because of local irritation, and we consider gastrostomy tube placement to be advisable.

[a]Flexible pediatric bronchoscope URF P2, Olympus Optical Co Ltd, Tokyo, Japan.
[b]Biopsy forceps FB-15C-1, Olympus Optical Co Ltd, Tokyo, Japan.
[c]Institute of Medical Microbiology, University of Zurich, Switzerland.
[d]Flexible bronchoscope BF 1T30, Olympus Optical Co Ltd, Tokyo, Japan.

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