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Case Series

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Topical treatment of sinonasal aspergillosis with combined enilconazole infusion and frontal sinus deposition of clotrimazole cream in two cats

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Abstract

Case series summary Two cats presenting with chronic sneezing and nasal discharge were diagnosed with sinonasal aspergillosis (SNA) through a combination of CT, rhinoscopy, histopathological analysis and fungal culture of nasal biopsies. Treatment included trephination of the frontal sinuses, followed by a sinonasal flush using a 1% enilconazole solution and the application of 1% clotrimazole cream into the frontal sinuses. In one cat, unilateral treatment resulted in recurrence of SNA 8 months later; however, two bilateral treatments, 1 month apart, proved effective. The second cat underwent a single bilateral treatment. Short-term observations indicate that cats may experience mild to moderate systemic side effects, including anorexia, lethargy and hyperthermia. Clinical cure was achieved in the long term in both cases, although it was not confirmed by follow-up rhinoscopy.

Relevance and novel information To our knowledge, this paper is the first to describe the technique and outcome of depot therapy in cats presenting with SNA. This treatment approach circumvents the need for systemic antifungal therapy, which is often prolonged, costly and potentially associated with toxicity. However, the success rate and tolerance of this method should be evaluated in a larger cohort of cats.

Keywords: Sinonasal aspergillosis; depot therapy; antifungal; rhinitis

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Introduction

Feline rhinosinusal aspergillosis can present in two forms: sinonasal aspergillosis (SNA) and sino-orbital aspergillosis (SOA). SOA is characterised by orbital invasion featuring a fungal granuloma, while SNA is localised solely within the nasal cavities and sinuses. Comprehensive treatment for SNA often includes endoscopic debridement of fungal plaques, topical antifungal infusions and systemic antifungal therapy (SAF), typically administered in combination. A definitive treatment strategy for feline SNA remains undetermined because of the limited clinical documentation available. SAF poses several challenges, including prolonged treatment duration, high costs, difficulties in administering oral medications to cats and potential toxicity. An efficient topical treatment method would overcome these issues.

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Table 1 Main clinical, diagnostic and treatment data of two cases of feline sinonasal aspergillosis treated with combined enilconazole infusion and frontal sinus deposition of clotrimazole cream

	Case 1	Case 2
Signalment	11-year-old castrated male Persian cat	15-year-old castrated male Chartreux cat
Clinical signs	Sneezing, mucopurulent discharge and right epistaxis	Sneezing
CT scan	Increase in soft tissue attenuation (bilateral), moderate turbinate lysis and mild cribriform plate destruction (right nasal cavity)	Mild caudal thickening of the right nasal turbinates and mild right frontal sinusitis
Rhinoscopy	Hyperaemia, mucopurulent secretions, fungal plaques (right nasal cavity)	Fungal plaques in the right nasal cavity
Histopathology of nasal biopsies	Lymphoplasmacytic and neutrophilic inflammation, fungal hyphae at the epithelial surface	Fungal hyphae at the epithelial surface
Culture	*Aspergillus* section *Fumigati*	*Aspergillus nidulans*
Number of treatments	One unilateral (right) After recurrence: two bilateral	One bilateral
Adverse effects	Depression	Anorexia, depression, mild hyperthermia
Length of follow-up (without recurrence)	4 years	2 years

Case series description

The main clinical, diagnostic and treatment data of both cases are provided in Table 1.

Case 1

An 11-year-old castrated male Persian cat was presented for a chronic mucopurulent nasal discharge, right unilateral epistaxis and sneezing. Clinical examination revealed a right nasal mucopurulent discharge. A complete blood count (CBC) revealed a mild hypochromic non-regenerative normocytic anaemia (haematocrit 28%; reference interval [RI] 37.3–61.7). A CT scan (Somatom Emotion 16; Siemens) of the head revealed an increase in soft tissue attenuation in both nasal cavities (right > left), moderate turbinate lysis and mild cribriform plate destruction (Figure 1). During rhinoscopy (Pediatric Cysto-Urethroscope Set 9.5; Karl Storz) and nasopharyngeal endoscopy (Olympus CLV-160, flexible endoscope XV10; Olympus), the right nasal cavity showed moderate mucosal hyperaemia and turbinate lysis, and the ventral nasal meatus was obstructed by a consolidated whitish material resembling fungal plaque (Figure 2). Mild mucopurulent secretions were observed in the left nasal cavity. The histopathological evaluation of biopsies from the right nasal cavity showed a severe lymphoplasmacytic and neutrophilic infiltrate in the lamina propria, and a large number of fungal hyphae at the epithelial surface. Fungal culture of the nasal biopsies was negative. The cat was prescribed amoxicillin/clavulanate (20 mg/kg PO q12h) for 2 weeks to treat secondary bacterial rhinitis, pending results of histopathology and fungal culture.

Topical treatment was attempted 4 weeks later. After endotracheal intubation and the placement of a gauze pack in the pharynx, the cat was placed in sternal recumbency with its head tilted downwards. After surgical preparation, a median 2 cm-skin stab incision was performed at the level of the frontal sinuses, followed by trephination of the right frontal sinus using a 4 mm bone drill. Efforts to debride the fungal plaques present in the nasal cavity and frontal sinus were conducted; however, only a limited amount was successfully removed. An 8 Fr Foley catheter was placed through the trephination opening, followed by the irrigation of the sinus with 50 ml of warmed 0.9% sodium chloride, which facilitated the removal of whitish and greenish material. Subsequently, 50 ml of a 1% enilconazole solution was slowly administered through the Foley catheter over 5 mins. The Foley catheter was then removed, and the right frontal sinus was filled with a 1% clotrimazole cream (Mycohydralin; Bayer Healthcare) before skin closure. The head was

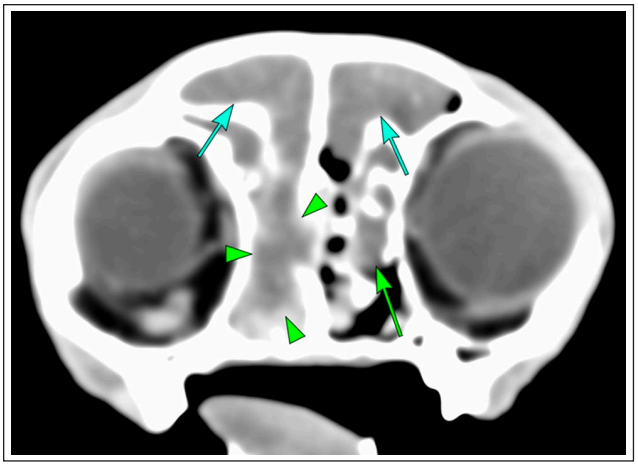


Figure 1 Post-contrast transverse reconstruction of the head of an 11-year-old male Persian cat diagnosed with sinonasal aspergillosis showing hyperattenuating material in the left and right frontal sinuses (blue arrows) and in the left caudal nasal cavity (green arrow), and a soft tissue mass in the right caudal nasal cavity (green arrowheads)

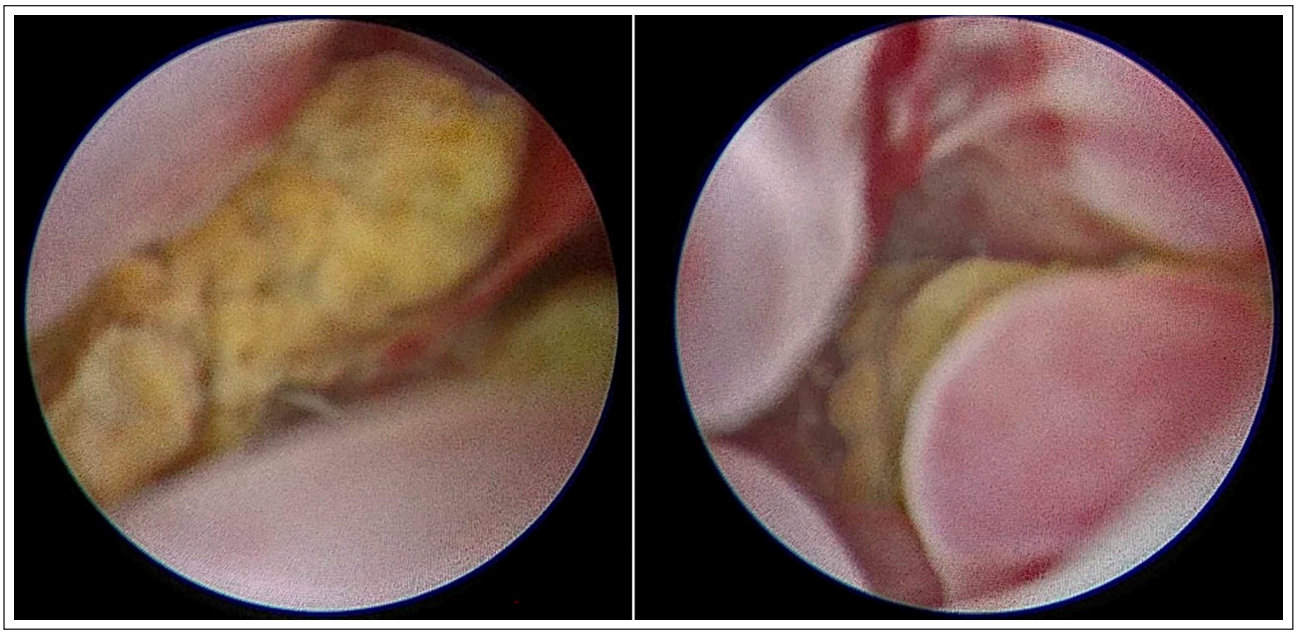


Figure 2 Rhinoscopic images from an 11-year-old male Persian cat diagnosed with sinonasal aspergillosis showing consolidated yellowish material obstructing the right ventral nasal meatus compatible with fungal plaque

maintained in a downward position until the nasal discharge ceased, after which the pharyngeal pack was removed. Amoxicillin/clavulanate (20 mg/kg PO q12h) and meloxicam (0.1 mg/kg PO q24h) were prescribed for 10 days. In addition, buprenorphine was prescribed (20 µg/kg q8h) oromucosally for 4 days. The cat exhibited self-limiting, moderate depression for 48 h after the treatment. This treatment was repeated 1 month later. After the second treatment, the clinical signs completely resolved; however, recurrence of unilateral mucopurulent discharge and sneezing was observed 8 months later. Repeat rhinoscopy and histopathological assessment of nasal biopsies confirmed the relapse of SNA. Fungal culture of nasal biopsies revealed the presence of an *Aspergillus* section *Fumigati*. The same treatment was performed twice, 1 month apart; however, both sinuses were treated, as it was believed that the recurrence may have been caused by the persistence of fungal organisms in the left frontal sinus. Since the last treatment (4 years), no respiratory clinical signs have been reported.

Case 2

A 15-year-old castrated male Chartreux cat was presented for chronic sneezing for 3 months, which had been unresponsive to previous treatments, including nebulisations, alpha-interferon, antibiotics and glucocorticoids. He had been treated for hyperthyroidism with radioactive iodine 5 years prior and had been reported to be euthyroid since then. Clinical examination revealed a body condition score of 5/5 and a 3 mm right cervical nodule. The CBC and biochemical panel did not reveal any abnormalities. The CT scan of the head and neck showed mild caudal thickening of the right nasal turbinates, mild right frontal sinusitis and a right thyroid nodule with contralateral atrophy. Rhinoscopy revealed yellow-greenish amorphous material located caudally in the right dorsal nasal meatus. Histopathological analysis of endoscopic biopsies revealed branched and septated hyphae on the surface of the mucosa, staining strongly positive to periodic acid–Schiff. Fungal culture showed growth of *Aspergillus nidulans*. After initial treatment with amoxicillin/clavulanate (20 mg/kg PO q12h for 5 days), topical treatment was performed bilaterally 2 weeks later, as described for case 1. Two days after the first treatment, the cat was presented for anorexia, depression and sneezing. Clinical examination revealed mild hyperthermia (39.2°C) and a slight mucopurulent discharge. The cat was hospitalised for 2 days. He received intravenous fluids (lactated Ringer's solution), amoxicillin/clavulanate (12.5 mg/kg IV q12h), meloxicam (0.05 mg/kg SC q24h), buprenorphine (20 µg/kg IV q6h) and mirtazapine (1.88 mg PO q24h). A second treatment was recommended but declined by the owners. At the time of writing (2 years since the treatment), no clinical sign suggesting clinical recurrence has been observed by the owners.

Discussion

There is no consensus on the best treatment strategy for feline SNA. Of the 35 cases reported in the literature, 25 cases received SAF for a duration in the range of 1–9 months, with most being treated for more than 2 months.[1–7] Topical treatment has been documented in 15 cats, often associated with SAF (8/15);[1,3,4,7,8] however, one

study reported the successful treatment of SNA in two cats with topical treatment only (clotrimazole infusion).[8] Debridement of fungal plaques has been reported in 17 cases,[1–3,7] typically associated with topical treatment and/or SAF. Overall, the prognosis appears to be guarded, with 17/31 cases with follow-up available considered cured.[1–4,6–9]

Treatment with SAF is associated with several drawbacks. Notably, the potential for toxicosis is significant: of the 25 cats reported that have been treated by SAF for SNA, four developed hepatotoxicity (all treated with itraconazole).[2,4,6,7] All azole antifungals may be associated with toxicity, but this risk is higher with itraconazole than with other antifungals.[10] In one study reporting its use to treat cryptococcosis, 26% of the cats developed toxicity during the course of treatment.[11] When toxicity is observed, discontinuation of the treatment is necessary. Resuming treatment at a lower dose can be attempted but may be subtherapeutic, leading to treatment failure.

In dogs, topical treatment with antifungals is the standard of care. Irrigation or prolonged soaks of the nasal cavities and frontal sinuses with antifungal solutions were originally described; however, these methods required repetitive treatments and extended anaesthetic time. More recently, the application of an antifungal cream ('depot therapy') into the frontal sinuses has been described. This approach is believed to increase the contact time between the drug and the mucosa because of the more viscous nature of the formulation.[12] The success rate of this method is high: 58–86% of dogs are cured after only one treatment and 94–100% if several treatments (range 1–4) are performed.[12–15] Another advantage is the reduced anaesthetic time compared with other techniques.[16] Topical treatment with clotrimazole cream has been reported anecdotally in cats, but the technique and associated outcome and adverse effects have not been specifically described.[1,7]

There has been concern regarding the safety of topical treatment when destruction of the cribriform plate is identified on CT scan. However, depot therapy has been reported in dogs with SNA and evidence of cribriform plate destruction without identifiable adverse events.[13,14] Furthermore, in case 1, cribriform plate lysis was identified on CT and no neurological adverse effect of treatment was observed.

Recently, the deposition of an antifungal cream into the frontal sinus via flexible endoscopy through the sinonasal ostium has been described in dogs.[12,14] This minimally invasive technique avoids the need for sinus trephination; however, it may not be feasible in cats because of the smaller size of the sinonasal ostium and the extensive tissue destruction that would be needed to access the frontal sinus.

Meticulous debridement of fungal plaques is recommended before topical treatment with antifungals. In humans, a non-invasive form of fungal rhinosinusitis is characterised by the formation of fungal masses known as fungal balls, which are associated with minimal mucosal inflammation. The recommended treatment for this condition is endosurgical debridement, and antifungals are usually not prescribed.[17] Given the similarities between fungal balls and canine and feline SNA, meticulous debridement of fungal plaques is believed to be integral part of the treatment. However, in our cases, because of the technical difficulties associated with the size of the patients, extensive and meticulous debridement of the fungal plaques was not achieved, as it would have required a particularly long anaesthetic time. Nevertheless, this did not preclude successful treatment.

Reported complications of depot therapy in dogs are mild swelling, discharge of antifungal cream, subcutaneous abscess or emphysema at the site of sinus trephination, aspiration pneumonia and epistaxis.[13,15] After treatment, our cats displayed depression, anorexia and mild hyperthermia, with one case requiring hospitalisation. This could be attributed to inflammation and pain at the site of the procedure or obstruction of the nasal passages by the cream, which is often not well tolerated by cats.[18] No local complication (such as abscesses or emphysema) occurred.

Our cases were considered cured given the long follow-up time without clinical signs; however, clinical cure does not always equate to complete disease resolution. In the case reported by Fawsitt et al,[3] a cat successfully treated for SNA was euthanased 8 months later for unrelated reasons, and evidence of persistent infection was found on necropsy. The lack of follow-up rhinoscopy is a limitation of our analysis.

Conclusions

Topical treatment of SNA using depot therapy is feasible in cats. Its main advantage is that it avoids the use of SAF, which, when used for prolonged periods, is associated with toxicity, high cost and decreased quality of life for some cats. Short-term complications (such as anorexia, lethargy and hyperthermia) have been observed in our cats and could limit the applicability of this treatment. However, further evaluation of this treatment in a larger cohort of animals is warranted.

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Ethical approval The work described in this manuscript involved the use of non-experimental (owned or unowned) animals. Established internationally recognised high standards ('best practice') of veterinary clinical care for the individual patient were always followed and/or this work involved the

use of cadavers. Ethical approval from a committee was therefore not specifically required for publication in *JFMS Open Reports*. Although not required, where ethical approval was still obtained, it is stated in the manuscript.

Informed consent Informed consent (verbal or written) was obtained from the owner or legal custodian of all animal(s) described in this work (experimental or non-experimental animals, including cadavers, tissues and samples) for all procedure(s) undertaken (prospective or retrospective studies). For any animals or people individually identifiable within this publication, informed consent (verbal or written) for their use in the publication was obtained from the people involved.

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