Diagnosing Doris

A Case Report of Canine Sinonasal Aspergillosis

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Class of 2019

Clinicopathologic Conference

August 31st, 2018

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Introduction

Rhinitis, or inflammation of the mucous membranes within the nose, is one of the most common upper respiratory tract diseases in dogs. In many cases, inflammation of the lining of sinuses, known as sinusitis, is also present. The nasal cavity is a bony canal with narrow points of entry and exit, called external nares and choanae, respectively. It is difficult to examine the nasal cavity thoroughly without expensive diagnostics; therefore, nasal disease can be a challenge for practitioners. Thus, it becomes important to use the patient's signalment and clinical signs as clues to obtain a diagnosis. In addition to performing a routine physical examination, there are other important parameters to assess when investigating a case of nasal disease. These include symmetry of the head and nose, palpation of the nose and hard palate, retropulsion of the eyeballs, examination of the nares with an otoscope, assessment of nasal airflow, a thorough dental examination, percussion of nasal cavity and sinuses, and palpation of the regional lymph nodes.[3]

There are multiple causes of nasal disease such as infectious, parasitic, non-infectious inflammation, dental disease, neoplasia, trauma, foreign body, and many others.[3] The most common infectious etiologies are viral, fungal, and/or bacterial. Despite the underlying cause, patients can present with similar clinical signs and unremarkable physical examination findings. The common clinical signs may include nasal discharge, sneezing, stertor, epistaxis, and rarely nasal pain. Nasal discharge typically starts as serous and clear but with chronicity can become mucoid or mucopurulent. Epistaxis can develop in the more advanced cases of nasal disease. Some clinical signs point to a more specific diagnosis: depigmentation of the nose is indicative of a fungal rhinitis while deformity of the nose, exophthalmos, and neurologic signs may indicate either cancer or a severe fungal infection, as those underlying causes are more locally invasive

and destructive. This report will outline a case of canine sinonasal aspergillosis and illustrate some of the difficulties encountered when dealing with nasal disease.

History and Presentation

On Wednesday, June 20th, 2018, an approximately 5 year old female, spayed mixed breed dog named Doris presented to Mississippi State University College of Veterinary Medicine's Small Animal Internal Medicine service for evaluation of a metallic foreign body in her left frontal sinus. She had a history of chronic sneezing, unilateral nasal discharge out of the left nostril, and recent episodes of epistaxis. Doris was adopted by her current owners approximately 3 years ago and was noted to have a chronic sneeze. Last year in 2017, Doris began having occasional, minor nosebleeds and constant mucopurulent discharge out of the left nostril. She was seen by her primary veterinarian multiple times over the course of a year and was prescribed antibiotics, which provided some improvement, but the nasal discharge never completely resolved. In December of 2017, skull radiographs revealed a metal opaque foreign object within her nasal cavity. During an attempt to remove the foreign object, it was inadvertently pushed into the frontal sinus. Her left nostril was lavaged with saline, and Doris was prescribed another round of antibiotics.

Approximately 2 weeks prior to presentation at MSU-CVM, Doris was running outside and returned with severe epistaxis coming from her left nostril but this resolved without medical intervention. Then, 9 days later, Doris returned home with severe, bilateral epistaxis. She was rushed to her primary veterinarian where the bleeding was controlled. Vitamin K and Keflex were prescribed at this visit, and the primary veterinarian recommended Doris be seen at MSU-CVM to further investigate her chronic nasal disease.

On presentation Doris was bright, alert, and responsive. She weighed 24.4 kg and had an ideal body condition score of 5/9. Doris was slightly hyperthermic with a temperature of 102.7, but all other vital parameters were within normal limits as her heart rate was 108 beats per minute, her respiration rate was panting, and her mucous membranes were pink and moist with a capillary refill time (CRT) of less than 2 seconds. Doris had dry, flaky skin with a mild amount of dandruff. Her heart and lungs auscultated normally with no murmurs, arrhythmias, crackles, or wheezes noted. Doris had unilateral, mucopurulent nasal discharge out of her left nostril. The left nostril was stenotic, compared to the right, and it was depigmented. The inside of the right nostril had normal pigmentation, while the inside of the left nostril was depigmented. There was sufficient airflow through both nostrils. There was mild soft tissue swelling noted on the left side of the nose that was slightly sensitive and painful upon palpation. There was normal percussion of her frontal sinuses and nasal cavity and normal retropulsion of both eyes. Her submandibular lymph nodes and all other peripheral lymph nodes palpated small and soft. All other physical examination parameters were within normal limits.

Diagnostic Approach/Considerations

A CBC, chemistry profile, and coagulation profile revealed no abnormalities, which was expected since it is uncommon for nasal disease alone to cause significant hematologic or biochemical changes. Thoracic radiographs were performed in order to assess the lungs for evidence of pneumonia or potential metastasis from a nasal mass. There were no nodules or significant pathology within the lung fields. Doris was sedated and a computed tomography (CT) scan (with contrast) of her head was performed. There was diffuse destruction of the nasal turbinates, thickening of the mucosa, and a moderate amount of poorly defined, fluid and soft tissue dense material within the left nasal cavity. The material extended into the left frontal sinus.

There was moth eaten to permeative lysis of the left nasal, frontal bones, bony nasal septum, and vomer bone with thinning of the left palatine and maxillary bones. Within the left frontal bone and extending into the dorsal and left aspect of the calvarium at the level of the left frontal lobe, there was an ovoid, irregularly marginated, metal dense structure that measured 9.2 x 8.5 x 8.1 mm. There was another smaller metallic fragment and several metallic foci within the left frontal bone caudal and rostral to this larger structure. Thus, it was evident that Doris had left sided rhinitis and sinusitis with primary consideration given to infectious etiologies, such as fungal, likely introduced into the left frontal sinus by ballistic trauma.

The following morning a rhinoscopy was performed under general anesthesia. The right nasal cavity appeared grossly normal while the left nasal cavity had severe turbinate atrophy. There were multiple white to grey coalescing plaques throughout the left nasal cavity. The left frontal sinus was explored through a large opening from the left nasal cavity, and there were large plaques seen throughout the sinus as well. Biopsies and impression smears were taken of the nasal plaques and submitted for cytology and histopathology. The cytology revealed septic neutrophilic inflammation and fungal proliferation. The submitted slide was of high cellularity with mostly degenerate neutrophils with numerous rods extracellularly and within the neutrophils. There were also moderate numbers of hyphal structures that were approximately 5 microns wide and had straight parallel walls, prominent septation, and angular, non-dichotomous branching. The biopsy showed severe chronic fibrinosuppurative rhinitis with fungal plaques in the left nostril and moderate, chronic suppurative rhinitis in the right nostril. The pinch biopsies of the left nasal plaques were composed entirely of fungal hyphae with scattered colonies of bacteria and conidia. The fungi were parallel walled and approximately 7 microns wide. The nasal mucosa was unrecognizable due to inflammation, granulation tissue proliferation, loss of

epithelium and bone, and a thick covering of neutrophils and fibrin. The surface was completely ulcerated, with hyperplastic glands remaining in an edematous granulation tissue matrix. The right nose had turbinates that were thickened by edema, inflammation, and fibrosis that distorted its architecture. The character of the infiltrate was similar to the left side, but far less severe. The next diagnostic step in this case would have been to submit samples for culture to identify the species of the fungus, but ultimately a diagnosis of sinonasal aspergillosis was reached.

Pathophysiology

Aspergillus is a ubiquitous saprophytic fungus that occurs naturally in the environment and can act as an opportunistic pathogen, especially in an immunocompromised individual. It is by far the most common fungus affecting dogs, with *Penicillium* being a distant second.[3] *Aspergillus* grows on dead leaves, stored grain, soil, mold, compost piles, or other decaying vegetation. The fungus sheds microscopic spores, called conidia, that float in the air and are easily inhaled. The characteristic asexual structures producing the conidia consist of a conidiophore, a terminal bulbulous vesicle, and sterigmata.[1] Aspergillosis is acquired by inhalation, ingestion, or cavity invasion of the conidia spores.[1] Once the conidia is present within the nasal cavity, a healthy dog usually has effective defense mechanisms within the nasal passageways and sinuses to expel the fungus and therefore prevent infection. The mucosal lining of the respiratory tract traps debris and the muco-ciliary apparatus is in constant motion to sweep the debris-filled mucus out of the airways. Stimulation of phagocytic cell surface receptors within the nose, particularly toll-like receptor (TLR)-4, by *Aspergillus spp*. conidia results in macrophage production of pro-inflammatory cytokines, such as tumor necrosis factor (TNF)-α, interleukin (IL)-1α and IL-1β. The presence of fungal hyphae results in IL-10 production via TLR-2-mediated pathways.[4] However, if *Aspergillus* conidia are inhaled and able to avoid these

protective respiratory mechanisms and proliferate then they can cause infection and become more difficult for the body to remove. This could be due to reduced muco-ciliary clearance, decreased phagocytic cell numbers, or impairment in their capacity to destroy the organisms.[4]

Aspergillus fumigatus is a common cause of rhinitis and sinusitis in dogs and has been found in 12%-34% of dogs evaluated for chronic sinonasal disease.[2] Nasal aspergillosis from *Aspergillus fumigatus* occurs mainly in middle-aged, outdoor, dolichocephalic breeds, affecting the nasal passages and paranasal sinuses.[3] It causes atrophic rhinitis, which is destruction of the nasal turbinates, resulting in nasal discharge. Discharge can vary from mucopurulent to hemorrhagic. Although it often begins as a unilateral disease, it frequently affects both nasal cavities as the fungus can lyse part of the bony nasal septum and infiltrate the contralateral nostril. Dogs with nasal aspergillosis frequently have depigmentation of the nares, pain on palpation of the nasal cavity, weight loss, and may be systemically unwell with varying degrees of lethargy. Diagnosis is made through a combination of clinical signs, evidence of turbinate lysis on either nasal radiography or CT, serology, culture, rhinoscopy findings, cytology and histopathology. Rhinoscopy commonly reveals fungal colonies of affected turbinates visualized as white plaques.

Treatment and Management

Treatment success of aspergillosis has improved over the last decade; however, it still proves to be challenging and multiple rounds of therapy may be required. Topical treatment with either enilconazole, which is not available in the U.S., or clotrimazole formulated in a polyethylene glycol has resulted in approximately 60-80% success in dogs with nasal aspergillosis. These agents are imidazoles, that impede ergosterol biosynthesis, which is an integral component of fungal membranes. It impedes synthesis, via the p450 enzyme system by

blocking 14α-sterol demethylase, which results in lanosterol accumulation within fungal membranes. Topical azoles such as clotrimazole and miconazole also have a direct lytic effect.[4] In order for topical treatment to be an acceptable option the cribriform plate should be intact. In Doris's case, there was one area on the left dorsal surface that was questionable on her CT images. Therefore, if this procedure were to be performed on Doris, it would need to be done very carefully and would carry a risk of neurological deficits or potentially death. However, recent studies have shown that topical clotrimazole solution was not associated with adverse neurologic effects in neurologically normal dogs with sinonasal aspergillosis and cribriform plate lysis diagnosed via CT scan.[2,5] Typical treatment protocols include placing the pet under general anesthesia and debriding the fungal plaques through a rhinoscope. Once debridement occurs, catheters are placed within the nasal cavities to infuse the anti-fungal therapy into the affected area. The nasopharynx is packed off with gauze sponges to prevent aspiration or pharyngeal mucosal irritation/contact with clotrimazole. Typical infusion time is 15 minutes per side, for 60 minutes. Cost for this procedure and the necessary drugs may range from $800 to $1200. This procedure should be repeated at least 2-3 times, possibly more depending on clinical signs, with approximately 4-8 weeks in between treatments.

Since Doris had involvement in the left frontal sinus, a second step would include drilling holes into the frontal sinus cavities, called trephination. This would need to be performed by a board-certified surgeon and would allow for better evaluation of the left frontal sinus and debridement of any fungal plaques seen. The sinus cavity would then be infused with clotrimazole. This procedure would carry the greatest risk as the suspected area of cribriform plate destruction was intimately associated with the left sinus cavity, and it would add an

additional $300-400 to the total cost. During this procedure, the 2 metallic fragments within Doris's left frontal sinus would be removed, as they were likely acting as a nidus for infection.

When there is evidence that the infection has eroded through bone and penetrated into the brain, oral anti-fungal medication may be elected. This typically does not have the same efficacy that infused clotrimazole provides; however, it has been shown to have some penetration into the sinonasal cavities. Common medications used are posaconazole, itraconazole, and voriconazole. Several months of oral therapy is needed, and a 50% success rate has been reported in older studies. Newer triazoles, such as fluconazole and itraconazole, improve success up to 70% in more recent studies.[4] Side-effects from oral anti-fungal medications include gastrointestinal upset and hepatotoxicity. A repeat CT scan helps to determine the efficacy of oral therapy. Approximated cost for oral fungal treatment is $500-700/month.

Doris's Outcome

Due to financial constraint, no treatment option has been initiated for Doris. Doris's disease carries a guarded prognosis without treatment. As of last week, her owner reported that Doris has been doing well at home over the past 2 months and no epistaxis has been noted since presenting to MSU-CVM. She is still having unilateral nasal discharge from her left nostril and has developed inspiratory stertor. Doris has been kept mostly indoors and is being fed only canned food, which appears to be helping her gain some weight back.

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