“Melvin Nose Better”

Christopher M. Lenahen

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Advisor: Patty Lathan, VMD, MS, DACVIM

Co-advisor: Katie Cooley-Lock, DVM, MS

Introduction

Nasal disease in the canine patient is one of the more commonly encountered diseases in small animal practice. [2] Clinical signs can be similar regardless of the underlying pathology, however, certain signs as well as the ability to determine the nature and chronicity of the discharge are paramount in developing a logical differentials list and an appropriate diagnostic workup. [1, 2] Fungal disease of the nasal cavity is relatively uncommon in veterinary medicine with *Aspergillus* species accounting for the majority of the cases. [1, 8] Aspergillosis is a debilitating and often times frustrating condition to treat despite the relative ease in diagnosis and years of research evaluating pathogenesis and treatment modalities. [8]

Aspergillosis can be an opportunistic primary or secondary pathogen, and the capacity for infection depends on host immunocompetency and virulence factors associated with the fungal organism. [8] Successful outcomes depend on the willingness of the owner to pursue expensive therapies as well as the extent of the damage caused by the fungal organism. [2]

History and Presentation

Dolicocephalic and Mesocephalic breeds are the most at risk for developing nasal disease. [2,8] There are no specific breeds that are at risk for developing sinonasal aspergillosis (SNA), however young to middle-age dogs tend to be at a higher risk for SNA most likely because of their behavioral disposition. [2, 8] Approximately 40% of dogs presenting for nasal aspergillosis are under 3 years of age, and 80% are under age 7. [1] There is currently no consistently supported evidence that males are more predisposed than are females. [2, 8] A thorough history and physical exam can provide valuable clues in determining the cause of clinical signs and can more appropriately direct the diagnostic workup. The three hallmarks of

canine nasal aspergillosis are a profuse mucoid to hemorrhagic chronic nasal discharge that may alternate with epistaxis, ulceration and depigmentation of the external nares and alar fold with crusting, and pain or discomfort of the facial region. [1, 2, 8] Nasal signs may be present for weeks to months to years with sneezing and epistaxis noted, decreased appetite, and depression being the most commonly observed signs by the owner. [8] Additionally, facial deformity and asymmetry can occur. [8] As with any nasal disease, signs may overlap, and although clinical suspicion may direct the diagnostic approach, it is important to rule out the various causes of sneezing, nasal discharge, and sinonasal pain.

Pathophysiology

There are a wide variety of described fungal infections in the dog, but the saprophytic *Aspergillus* spp. is by far the most common. Of this genus, *Aspergillus fumigatus* is the most common isolate with *A. niger, A. nidulans, and A. flavus* also being reported. [8] *A. fumigatus* is an ubiquitous soil saprophyte that is of ecological significance, as it is an organism involved in environmental recycling. [8] Host immunocompetence is one of the main determining factors in the development of infection as is the virulence of the organism itself. [1, 8] Fungal elements are inhaled daily as this organism is ubiquitous in nature, but the respiratory tract, mucociliary defenses are usually enough to halt further advances of the fungus. [1,8] If this mechanism is breached, additional innate immunity is incurred in the form of the alternative complement system, phagocytic cells, natural killer cells, and γδ T-cells. [8] Unfortunately, many otherwise healthy animals are unable to clear the pathogen and infection ensues. There are several factors that may counteract the hosts protective abilities. Stimulation of toll-like receptor 4 (TLR-4) by the *Aspergillus* conidia result in the release of the pro-inflammatory cytokines tumor necrosis factor alpha (TNF-α), interleukins IL-1α and IL-1β. [8] T-helper cells subsequently respond in a

balanced effort to eliminate infection with as little autoimmune injury as possible. [8] *A. fumigatus* produces several metabolites that may aid in survival and evasion from host immunity. [8] Gliotoxin, fumagillin, and helvolic acid are three such metabolites that cause reduced mucociliary apparatus clearance and increase the chance for epithelial damage. [8] Gliotoxin is implicated in dampening phagocytosis and impairing complement binding thus reducing the ability for the host organism to fight off infection. [8] Although the mechanisms behind infection has been extensively studied, the pathogenesis is poorly understood. [8]

A. fumigatus causes a non-invasive fungal infection which seemingly defies the pathology invoked by the organism. It is the dermonecrolytic toxins and local tissue damage invoked by the host immune system that causes the pathology seen with infection. Defects in the hosts innate and adaptive immunity are not commonly seen, nor are concurrent disease or systemic immunodeficiency; so there is much to be understood regarding the exact reason why otherwise healthy dogs are infected with SNA. [8] Trauma to the face, dental disease, and foreign bodies of the nasal passage are seen as inciting causes, most likely due to damage to the innate immune system allowing the opportunistic pathogen to thrive. [8]

Once *A. fumigatus* has breached the primary host defenses, a destructive rhinitis ensues. [1] Severe nasal turbinate destruction and rhinitis are identified. [1, 8] The disease has the capacity to extend into the periorbital soft tissue, frontal sinus, and destroy the integrity of the cribiform plate in more advanced cases. [1, 8] The extent of the pathology dictates the treatment modalities. As mentioned previously, the host inflammatory response as well as toxins are responsible for the pathology seen, not the fungal organism itself. [8]

Diagnostic Approach

Careful consideration of the onset, severity, and duration of the clinical signs will help in developing a logical approach to diagnostic testing. Determining if the process began as a unilateral or a bilateral nasal discharge is normally helpful, however laterality can sometimes cause confusion as many processes may initially begin as a unilateral discharge before progressing to both sides. [1, 2] This can be accomplished using a chilled microscope slide held up to the dog's nares and assessing condensation development. [1] A thorough physical exam should be performed in order to prioritize differentials as well as rule out causes for secondary invasion. An assessment of the symmetry of the head, nasal planum, and palate can aid in identifying masses, bony defects, or localized pain. Retropulsion of the eyes can identify asymmetries associated with a mass in the nasal cavity that restricts movement of the globe. [1, 2] An oral exam, which includes probing of the sulci of the teeth, is important in ruling out tooth root abscesses, oronasal fistulas, fractures, and osteomyelitis. [2]

Clinical signs as well as history of the disease process can increase clinical suspicion in favor of SNA, however many diagnostic tests are worthwhile because of their low cost even if diagnostic value is low. [2, 8] A good example is performing a fine needle aspirate of a submandibular lymph node in order to rule out metastatic neoplasia. [2] A complete blood cell count (CBC), serum biochemistry, urinalysis is recommended in order to rule out concurrent disease. [1] If epistaxis is present, a coagulation panel should be run as well as other hemotologic testing if the patient is intact or has not undergone a previous surgery. [1] Serology, using agar gel immunodiffusion (AGID), has been performed in the past, but its usefulness has been challenged due to its high specificity but low sensitivity. [1, 8] A positive serology must be interpreted in light of other diagnostic modalities, and because of this, its diagnostic value is questionable. [1]

Diagnostic imaging is an important tool in diagnosing nasal disease in dogs. [1, 2, 8] Advantages and disadvantages exist with each imaging modality. [2] Plain film nasal radiographs require accurate head positioning and general anesthesia for quality images. [1, 2] Radiographs cost significantly less, however superimposition of structures as well as low sensitivity to detect bony and soft tissue changes allow for CT to be a more attractive option. [1, 2, 8] Radiographic changes include turbinate destruction via wide spread punctate lucencies. [8] Mixed density patterns with an increase in opacity can be seen with fungal plaques, debris, or discharge. [8] The use of thoracic radiography is questionable because nasal tumors are unlikely to metastasize to the lungs. [2] Thoracic radiographs are however useful in those cases that do have thoracic metastasis in that treatment is likely altered. [2] Computed tomography (CT) of the skull with contrast enhancement is a viable option in that it provides excellent detection of bony changes within the nasal cavity. [2] CT is superior at discriminating between mucus and tissue, defining extension of lesions into adjacent structures, and determining laterality of the lesions via cross-sectioning. [1, 2] CT must be performed before rhinoscopic evaluation in order to eliminate artifacts from lavage, tissue manipulation, and most importantly, hemorrhage. [1] Because of the advantage CT has in cost, availability, and detection of bony changes, it is a preferred modality to magnetic resonance imaging (MRI). [2]

Rhinoscopy allows for direct visualization of the nasal passage and is important in diagnosis and therapy of nasal aspergillosis. [1, 2] The rhinoscope should be measured from the nasal planum to the medial canthus and marked with a piece of tape in order to avoid penetrating the cribiform plate. [1, 6] The least affected side should be evaluated first. [1] With the patient in sternal recumbency, the scope is inserted in antegrade fashion at the ventral medial aspect of the nostril using the nasal septum as a landmark. [6] The three primary meatus should be examined and

assessed for inflammation, discoloration, and structural integrity. [6] Visualization of fungal plaques on the nasal mucosa is highly suggestive of aspergillosis, however biopsy of these lesions is confirmative with histopathology. [1] The classic rhinoscopic lesion is a grey-green or white necrotic plaque with reactive turbinate hyperplasia. [1, 6] The cribiform plate and frontal sinus should be assessed in order to effectively treat all areas affected with fungal elements. [6] It is crucial to biopsy the plaque since the surrounding tissues may likely indicate a lymphoplamacytic or neutrophilic rhinitis like many nasal disease processes. [1] Visualization of fungal hyphal elements on histopathology is confirmative of SNA. [1] Rhinotomy, sinusotomy, and frontal sinus trephinations are the most invasive options but are utilized in those cases where identification of fungal plaques is not possible using the aforementioned techniques. [2]

Other diagnostic modalities such as fungal culture, cytology, and bacterial culture are of little diagnostic value. Cytology of nasal discharge could reflect normal nasal colonization since *Aspergillus* is a commensal organism making diagnosis unlikely. [8] Fungal culture has the potential for false positives and requires a substantial amount of time for fungal growth. [2, 8] The visualization of fungal plaques is often enough to confirm the diagnosis without necessitating a culture be performed. [2] Bacterial culture is of limited value because the nasal passages of normal healthy dogs is not a sterile environment and primary bacterial rhinitis is rare in dogs. [2]

Treatment and Management

Treatment of dogs with SNA is challenging despite the numerous therapeutic options. [8] In instances where only the sinuses are involved, trephination is recommended in order to accurately visualize and diagnose the condition, as well as facilitate topical therapy and debridement. [1] The frontal sinus is entered via a large non-grooved Steinmann pin and bone chuck using the orbital rim, zygomatic process of the frontal bone, and midline of the skull as

landmarks. [1] Most infections involve the nasal cavity and frontal sinus; therefore, it is imperative to assess the integrity of the cribiform plate to decide whether topical therapy is feasible. [1] The mainstay of therapy is the use of the azole class of drugs including the imidazoles (ketoconazole, clotrimazole, enilconazole, miconazole) and triazoles (fluconazole, itraconazole, posaconazole, voriconazole). [4, 8] The azoles inhibit ergosterol biosynthesis, a key component of the fungal cell membrane, via the p450 enzyme system by blocking 14α-sterol demethylase which in turn creates a build-up of toxic sterols and ergosterol depletion in the cell membrane. [4, 8]

Oral therapy has been described as a therapeutic option, however poor clinical responses when used alone, limit their use in treating SNA. [8] Clinical responses of 50-70% have been described in older studies. [8] This can be attributed to the concept that *Aspergillus* is a non-invasive infection as seen on histopathology. [8] The use of azoles such as fluconazole and itraconazole for oral therapy has been proven efficacious for systemic mycosis such as blastomycosis and histoplasmosis, however, poor responses with long term therapy has been reported in treating SNA. [1, 4, 8] Two second generation triazoles, posaconazole and voriconazole, show great promise in being effective therapeutics, however their efficacy is unproven in veterinary medicine and they are currently very expensive, limiting the options for therapy at this time, but may prove useful in refractory cases. [4, 8]

Topical administration of clotrimazole or enilconazole are shown to be more effective than the administration of oral antifungal agents. [1] Topical therapy allows for direct access to fungal plaques for distribution of drug across the area of the infection. [8] Topical therapy includes a variety of techniques including: Surgically implanted catheters in the frontal sinus for administration of antifungal agents, placement of temporary frontal sinus catheters via endoscopy, nasal catheter administration, and trephination with depot therapy. [8] Indwelling

catheterization via surgery has fallen out of favor due to prolonged hospitalization and associated morbidity despite positive success rates. [8]

Noninvasive protocols involve administration of either a 1% clotrimazole or a 1% to 2% enilconazole via temporary endoscopically placed catheters under general anesthesia. [1, 4, 8] Following debridement of visible fungal plaques, approximately 50 mL of solution is inserted into the nasal cavity while in dorsal recumbency. [1, 8] This is a sufficient volume to fill the nasal passage and frontal sinus as described in a study on cadaver dogs. [1, 8] The head is then rotated 90 degrees every 15 minutes to allow for the topical agent to coat the surface of the entire nasal cavity and frontal sinus. [1, 8] This treatment is generally well tolerated with the only side effects being severe pharyngeal inflammation due to the propylene glycol in the clotrimazole formulation. [1, 4, 8] Because of this, it is recommended to use the human clotrimazole product which contains polyethylene glycol and is not associated with pharyngeal inflammation. [4] Topical therapy has been deemed an effective method in treating SNA in the canine patient with resolution of fungal plaques in 65% of patients after one treatment and up to 87% after multiple treatments. [1, 4, 8] An important consideration when deciding to pursue topical clotrimazole as a therapeutic option is the structural integrity of the cribiform plate. If the cribiform plate is damaged, meningitis and encephalitis are sequelae and the use of clotrimazole is not advised. [1] Systemic options such as oral ketoconazole, itraconazole, and fluconazole have been described in such cases. [8] Treatment in this case is expensive and may be prolonged for many months with a guarded outcome. [8]

Treatment failures are often times attributed to disease severity, however location of disease may be more indicative of impending treatment failure rather than the extent of the damage due to the *Aspergillus* organism. [8] This is most likely due to the ability for adequate

debridement and ability of topical therapies to penetrate into the fungal plaques. [8] The most accepted reason for treatment failure is inadequate distribution and retention of antifungal agents in the nasal cavity and sinus. [8] Unfortunately, ideal retention times have yet to be established. [8] Treatment of SNA has proven to be frustrating to owners and clinicians as first treatment success rates are variable. The extent of the disease, ability for adequate debridement, host immune system, and drugs chosen all appear to influence the outcome on a case by case level. [8]

Case Outcome

Sino-nasal aspergillosis is an uncommon disease that can be difficult and frustrating to treat. There is a lot to be understood as to why certain dogs are unaffected while others succumb to infection. Altered host immunity and virulence factors of the organism seem to be logical, but unproven explanations. Prognosis appears good in those patients that are free of the fungus post anti-fungal therapy. Focal disease in locations where debridement is difficult or where there is cribiform plate involvement carry a worse prognosis.

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