Immunosuppression and Systemic Candidiasis in the Canine Patient

A Case Report

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Introduction

Candidiasis is a fungal infection caused by yeasts from the genus *Candida*. There are over 20 species of *Candida* capable of infecting humans, but the most common amongst people and animals, alike, is *Candida albicans* (Boden, 2005). *C. albicans* is a commensal organism and an opportunistic pathogen (Brandt, et. al., 2016). The most well-known form of this disease is oropharyngeal candidiasis, more commonly referred to as “thrush”. While local *Candida* infections are not typically life-threatening, the yeast can enter the bloodstream and become systemic, resulting in morbidity and mortality. Systemic candidiasis is the fourth most frequent cause of nosocomial bloodstream infections in the U.S. (Grubb, et. al., 2008). As a commensal organism, *C. albicans* is not a pathogen that can be fought off with hand-washing or protective equipment, rather it requires our internal defenses. The body’s immune system is responsible for keeping its own microbiota within appropriate concentrations. Any disturbance in the immune system may result in an imbalance of microbes within the body. A disrupted microflora can result in numerous infections, with systemic candidiasis being one of the least favorable. The following case report investigating long-term steroid use, immunosuppression, and systemic candidiasis in a canine patient aims to identify the relationship between these topics and highlight their importance to patient health and disease.

Case Report

A one-year-old spayed female Weimaraner, named Molly, first presented to Mississippi State University Animal Health Center (MSU-AHC) in March of 2009 for inability to open her mouth. She was presumptively diagnosed with masticatory muscle myositis (MMM). MMM is an autoimmune inflammatory myopathy involving the muscles of mastication. Autoantibodies target these type 2M muscle fibers, causing swelling and trismus in the acute phase, followed by

severe muscle atrophy as the disease becomes chronic. Early detection and aggressive immunosuppressive therapy are key to controlling MMM (Melmed, et. al., 2004). Molly was sent home with an immunosuppressive dose of prednisolone at 2mg/kg. Over the next 16 months, Molly was continually given prednisolone, tapering from the immunosuppressive dose, to an anti-inflammatory dose of 0.5mg/kg.

It was not until January of 2017 that Molly was seen again by MSU-AHC when she presented for a one-week-history of abdominal pain and vomiting. On presentation, the patient was quiet, alert, and estimated 5% dehydrated. Her physical exam revealed no abnormal findings other than moderate cranial abdominal pain. Bloodwork revealed neutrophilia (Segs = 23584 /ul with reference range 3500-14200), lymphopenia (Lymphocytes = 804 /ul with reference range 1200-6500), and monocytosis (Monocytes = 1876/ul with reference range 175-1700), indicative of either chronic inflammation or a stress leukogram consistent with chronic steroid exposure. The bloodwork also revealed a mild azotemia (BUN = 47mg/dl with reference range 8-24, Creatinine = 2.70mg/dl with reference range 0.50-1.40) and hypoalbuminemia (Albumin = 1.9 g/dl with a reference range 2.5-3.9). A urinalysis revealed a urine specific gravity of 1.022. Abdominal radiographs and ultrasound revealed splenomegaly and a hyperechoic pancreas. The kidneys exhibited bilaterally dilated renal pelvises, hyperechoic regions within the renal cortices, cortical cysts, and urinary bladder debris. A Snap PLI test, an ELISA used to measure pancreas-specific lipase levels, concluded abnormal. Molly also tested negative for 8 serotypes of Leptospirosis at this time. She was diagnosed with a urinary tract infection, pyelonephritis, and pancreatitis at this time. Unfortunately, Molly became inappetent, tachypneic, hypertensive, and oliguric, even with hospitalization and supportive care. Given her deteriorating status, Molly’s owners elected for humane euthanasia, just three days after bringing her in to MSU-AHC.

On necropsy, gross exam revealed bilaterally enlarged, pale, and soft kidneys. The parenchyma bulged upon cross section and appeared diffusely mottled with tan and bright red, obscuring of the corticomedullary delineation. The spleen was enlarged, in addition to the liver with a diffuse enhanced lobular pattern. The pancreas was diffusely reddened, dappled with ecchymotic hemorrhages. The lungs were poorly collapsed and mottled with black and gray discoloration in all lobes. The necropsy report details interstitial nephritis, adrenalitis, lymphadenitis, enteritis, suppurative bronchopneumonia, and severe suppurative myositis and atrophy of the masticatory muscles. Histologic evaluation revealed severe inflammation within the kidneys, adrenal glands, and lungs, characterized primarily by large numbers of neutrophils and moderate macrophage populations. Fungal organisms characterized by narrow-based budding and pseudohyphae were found within lung tissue. *Candida spp.* were cultured from the bladder wall. Germ tubes were formed in the presence of 5% serum in growth medium and pseudohyphae were again identified off agar plates, confirming the presence of a pathogenic species of *Candida*. These findings are supportive of systemic Candidiasis secondary to immunosuppression.

Pathogenesis

Candida spp. are commensal organisms of humans, dogs, and certain livestock species, which exhibit overgrowth in the presence of either long-term use of antibiotics, disrupting the normal flora, or an immunosuppressive state (Pressler, et. al., 2003). While antibiotics were not a part of Molly's history, the referring veterinarian had Molly on long-term glucocorticoids for skin issues that were tapered off in the six months prior to presenting at MSU-AHC. This was the second known long-term steroid use in this patient, given the previously mentioned course she received for management of her MMM.

While the immunosuppressive effect of steroids is desired in combating many diseases processes of a hyperactive immune response, the effect is not localized. Long-term use of systemic steroids suppress the entire immune system, rendering the patient at an increased susceptibility to novel infection, or reactivation of latent infections. Glucocorticoids suppress the inflammatory process by interacting with specific intracellular receptor proteins, altering their genetic makeup, synthesizing novel proteins, and blocking the production of mediators, such as prostaglandins, leukotrienes, and interleukins (Edwards, 2016). While steroids are effective in improving many different conditions, it is important to remember their numerous harmful effects that may put the patient at a greater health risk.

As a normal component of healthy gastrointestinal, respiratory, and genital mucosal flora, it is understood that *Candida spp.* transitioning from commensal to pathogenic is secondary to an immunogenic impairment. Accepted predisposing factors associated with candidiasis are drugs, including antibiotics and immunosuppressives, underlying disease, and iatrogenic factors, such as indwelling catheters (Greene and Chandler, 1998) (Warren and Hazen, 1999) (Brandt, et. al., 2016). In one study involving 20 dogs and cats with urinary tract infections where *Candida spp.* were isolated, all of the animals exhibited local or systemic immune compromise, that was suggested to have predisposed them to infection. Additionally, 6 of these animals (30%) were treated with exogenous corticosteroids within 1 month prior of the diagnosis of their infections (Pressler, et. al., 2003).

While overgrowth of *Candida spp.* most commonly manifests as oral (thrush) or urinary tract infections, it may progress to candidemia and become systemic (López-Martínez, 2010) (Ryan, 2004). Once the disease becomes systemic through hematogenous spread, lesions may be multisystemic (esophagus, central nervous system, kidneys, vagina, spleen, endocardium, liver,

eyes, meninges, respiratory, urinary tracts, and cardiac valves) (Brandt, et. al., 2016). Systemic candidiasis most commonly affects the kidneys and the lungs in dogs. Human studies report fewer than 10% of cases to progress to candidemia from candiduria, but a high mortality rate (33-54%) in patients with candidemia elevates this disease as a legitimate concern (Grubb, et. al., 2008).

Diagnosis

The diagnosis of candidiasis proves difficult in that both clinical signs, of which most are nonspecific, and laboratory evidence are required (Macdonald and Odds, 1980). A definitive diagnosis is found with microscopic demonstration of yeast and/or pseudohyphae in infected tissue with characteristics consistent with those of *Candida spp*. (Brandt, et. al., 2016). Out of 77 total species of Candida, there are five main species that are pathogenic in canines; these are *C. tropicalis, C. pseudotropicalis, C. dubliniensis, C. glabrata,* and the most prevalent, *C. albicans* (Muller, et. al., 1985). All of these species, except *C. glabrata*, form pseudohyphae, in which the host response is the cause of the associated tissue pathology.

C. albicans is a diploid, polymorphic fungus with a carbohydrate outer layer and the presence of pseudophypahe, blastoconidia, chlamydospores, and the absence of arthroconidia. The *Candida spp.* organisms occur as either thin-walled, ovoid, narrow-based budding yeast or in chains that produce pseudohyphae (Taboada, 2016). Numerous stains can be used to highlight these organisms, including Periodic acid-Schiff (PAS) and Gomori's methenamine silver (GMS) (Raskin, Meyer Cytology 2nd ed). In one case study of fungal endophthalmitis in a dog with confirmed *Candida albicans,* histopathology revealed severe inflammation, primarily comprised of neutrophils and macrophages, similar to the inflammatory cell population in Molly's kidneys, adrenal glands, and lungs. The fungal organisms were found both intra- and extracellularly and

stained positive with GMS. Yeast exhibited narrow-based budding and formed pseudohyphae with parallel walls (Enders, et. al., 2017). These organisms are often difficult to find, but once identified, a definitive diagnosis can be made.

Treatment

Treatment of *Candidia spp.* infections in dogs is controversial due to the associated risks of antifungal therapy and the necessity of treatment, as patients can spontaneously recover from these infections. Amphotericin B administered intravenously is the drug of choice for systemic candidiasis (Fisher, et. al., 1995). Other options include azole antifungals, such as Ketoconazole and Fluconazole (Brandt, et. al., 2016). A third class of antifungals, echinocandins, exist, but are cost prohibitive in veterinary medicine. While it is temping to treat any animal suspected of candidiasis in hopes of preventing systemic spread of the deadly disease, increasing resistance to antifungals demands a public health consideration before each use.

An emerging species of *Candida, C. auris,* was first identified in Japan, but as of May 2017, there have been 77 reported human clinical cases of *C. auris* in the U.S. This type of *Candida* poses a significant health threat as it has been proven capable of resistance to all three major classes of antifungal drugs. C. auris may affect animals and people, alike, and is to be reported to state or local public health authorities and CDC if detected (Tsay, et al., 2017).

Candida spp. is found worldwide and can be isolated from soil, animals, hospitals, fomites, and food. The impressive prevalence, combined with the capability of systemic infection, proves candidiasis a complex disease that is best managed by prevention. As the directed use of iatrogenic steroids belongs entirely to the clinician, it is our responsibility to understand all of the potential risks and make informed, cognizant decisions as to when their use is warranted.

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