

Defying the Odds

A Case Report of Surgical Excision of Gastrointestinal Pythiosis

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Introduction

Pythiosis is a non-transmissible disease caused by *Pythium insidiosum* which is generally found in standing inland waters and soil of tropical, subtropical, and temperate regions.³ Though these regions are the most common, the organism's ecological niche is spreading and surviving in non-traditional areas. Places such as Arizona and California have had reported cases even though their climates do not fit the disease's traditional criteria. To date, pythiosis has been recorded to infect many different species of mammals, but the most common mammals affected are dogs, horses, and humans.³

Pythiosis is referred to as an emerging disease process, but the literature first described this disease in 1884 while a veterinarian was working with horses in India.³ It was not until 1901 and 1924 where Dutch scientists were able to isolate the causative agent from horses. Based on their findings, the disease was initially named *Hyphomycosis destruens equi*. In 1961, the organism was renamed *Hypomyces destruens* and classified as a zygomycete based upon its fungal-like characteristics and lack of sporulation seen.³ It was not until 1974 where zoospores were observed changing its classification to Oomycete genus *Pythium* and the disease term was proposed as pythiosis. The causative agent *Pythium insidiosum* was officially defined when sexual sporulation was finally observed in 1987. Even though pythiosis is still classified as a fungus, research in the early 2000s suggested that *Pythium* spp. are more closely related to diatomeae and algae instead of a fungus.³

History and Presentation

Dixie, a 3-year-old spayed female German Shorthaired Pointer, presented to Mississippi State University College of Veterinary Medicine Internal Medicine Department on July 2, 2018 for a three-week history of vomiting/regurgitation and a decreased appetite. Prior to presentation,

Dixie's owner began noticing piles of vomit/regurgitation over multiple occasions, so she presented to her referring veterinarian on June 21, 2018 for evaluation. During this visit, she was presumptively diagnosed with gastritis and was treated symptomatically with subcutaneous fluids and Maropitant Citrate. Dixie did not improve and become more inappetent and dull, so she returned to the referring veterinarian on June 22, 2018. Three view abdominal radiographs were performed and did not reveal any obvious obstruction, so she was symptomatically redosed with Maropitant Citrate and Metronidazole was added to her treatment regime. On June 25, 2018, Dixie returned to her referring veterinarian for an exploratory laparotomy where a thickening of the pylorus was noticed. Multiple biopsies were taken, and she was sent home on Carprofen, Cefpodoxime, and Sucralfate. The biopsy revealed a chronic ulcerative, eosinophilic and lymphoplasmacytic gastritis with no fungal organisms.

When she presented to MSU-CVM Internal Medicine Department, a comprehensive physical exam was performed. Upon presentation, Dixie was dull but alert and responsive with all vital parameters within normal limits. Physical exam revealed a mild amount of mucopurulent discharge from her left eye, excessive salivation, a mildly enlarged right submandibular lymph node, and a quarter sized freely movable mass at the base of her tail. There was an incision present along her ventral midline, and it did not exhibit any signs of heat or swelling. A rectal exam was performed which revealed black, tarry feces. Cardiothoracic auscultation and abdominal palpation were unremarkable.

Diagnostic Approach/Considerations

A series of hematology testing (complete blood count, chemistry, baseline cortisol, Pythium titers) and a urinalysis were performed. The complete blood count revealed a mild to moderate leukocytosis, a moderate neutrophilia, and a moderate eosinophilia. The chemistry

panel revealed a mild to moderate hypoalbuminemia, mild decrease blood urea nitrogen, mild decrease in ALT, mild decrease osmolality and mild hypomagnesemia. Baseline cortisol was 2.7 ug/dL which ruled out hypoadrenocorticism disease. Pythium ELISA serology revealed a 93% positive result with the positive control being greater than 40%. Urinalysis revealed concentrated urine, trace proteinuria, and no evidence of bacteria.

Further diagnostics were performed which consisted of thoracic radiographs, abdominal radiographs, an abdominal ultrasound and a computed tomography (CT) scan of her abdomen to evaluate the extent of the previously diagnosed pyloric mass. Thoracic radiographs revealed a mild diffuse bronchial pulmonary pattern. There was free gas in the abdomen which allowed for the diaphragm to be outline on all images. Abdominal ultrasound revealed free peritoneal gas and the gastric wall was hypoechoic and thickened in the region of the pylorus. The thickest portion measured 1.7 centimeters with normal wall thickness being 3 to 5 millimeters thick. There was loss of normal wall layering in the pyloric region as well.⁷ The CT scan revealed thickened pyloric wall that was heterogeneously contrast enhancing. There were multiple enlarged abdominal lymph nodes that were not originally detected on ultrasound that were also heterogeneously contrast enhancing.

Based on the diagnostic results, the surgical department was consulted to see if the mass could be removed. The surgeons recommended a Billroth 2 and a partial pancreatectomy with biliary rerouting. While this was the best surgical option, there are significant post-operative complications associated with the procedure along with a guarded post-operative prognosis. The surgical option was given to the owner and the post-operative care, complications, and prognosis were discussed in detail. After discussion, the owner elected to pursue surgery and Dixie was transferred to the MSU-CVM Surgery Department on July 5, 2018.

In surgery, a complete abdominal exploratory was performed and a large mass infiltrating the entire pylorus, pyloric antrum and pyloric sphincter, and the proximal portion of the duodenum was identified. The rest of the abdomen revealed no other affected areas of the GI tract, but an enlarged bile duct was noted. The margins of the pyloric mass were measured and marked five centimeters in all directions. Thoracoabdominal (TA) stapler was used to staple the mid stomach and distal duodenum at the measured margin. Once stapled, the involved bowel was excised, and the stapler line was over sewn with an inverting pattern to prevent leakage. The right and left lobes of the pancreas adjacent to the excised bowel were also excised and the bile duct was ligated and transected at its insertion in the duodenum. The jejunum was mobilized and a side-to-side anastomose to the remaining stomach was performed using a gastrointestinal stapler (GIA) and TA stapler. The gallbladder was freed from the hepatic fossa and a cholecystoduodenostomy was performed. The abdomen was copiously lavaged and a gastric tube was placed to assist feeding post-operatively. Dixie recovered uneventfully in the ICU.

Pathophysiology

Pythium insidiosum is not a true fungus because the cell walls lack chitin, but they are composed of cellulose and beta-glucans.³ After learning how the organism was composed, a phylogenetic analysis was completed suggesting that *Pythium* spp. were more closely related to algae and diatomeae. Their cytoplasmic membranes lack ergosterol and their zoospores develop biflagella when exposed to a wet environment. The zoospores and their ability to move are important aspects of the infective process having an affinity for hair, wounds, other damaged skin, intestinal mucosa, and injured/decaying plant tissue. Once the zoospores find an entrance, they will encyst and secrete glycoproteins to allow for adhesion formation to the tissues. After adhesion formation, the zoospores become well adapted to the host body temperature which

allows for hypha to develop and extend into the surrounding tissues and vessels.³ The hypha allows for the disease to spread rapidly and become life threatening if diagnosis and treatment are not initiated early.

Treatment and Management

In managing pythiosis, it is extremely important to detect the disease as early as possible, but early detection can be difficult in small animals. Once the disease is detected, the treatment options for pythiosis are dependent on the patient and the location of the disease. To date, the mainstay of pythium treatments for small animals are radical excision and antimycotic agents such as azoles and terbinafine.^{2,3} It is said that radical excision (ex. billroth 1 & 2, resection and anastomosis, amputation) is the most useful and effective treatment because it allows for removal of diseased tissue(s). Medical management is generally used in conjugation with surgical excision because complete excision is unlikely or not possible in most cases. Antimycotic agents are the drugs of choice due to their mechanism of action against fungal organisms which includes interfering with ergosterol biosynthesis.³ The azole drugs are known to change the permeability of the fungal cells which eventually leads to cell lysis. As *Pythium insidiosum* is not a true fungus and lacks ergosterol in the cytoplasmic membrane, the efficacy of the azole drugs for treatment is questionable. However, despite limited success with the use of these drugs, they are still used as no other options exist.

A new therapy being researched for the treatment of Pythium is the phenylamide compound mefenoxam.^{3,6} Mefenoxam is a fungicide used for plants that are infected with pathogenic oomycetes. It has a specific mechanism of action which acts as an inhibitor of the oomycete's RNA polymerases. There are precautions listed such as moderate eye irritation and can be harmful if swallowed or absorbed through the skin.⁹ Though these are the listed

precautions for humans, there is not documentation on its side effects for animals.⁶ The thought behind using it for animals infected with pythiosis is to inhibit the RNA polymerase from replicating and halt the proliferation of the disease process. Further research is needed to elucidate adverse effects with animal use.

Case Outcome

Dixie was finally discharged on July 13, 2018 when she began intermittently eating on her own. She was sent home on Viokase Powder, Terbinafine, Itraconazole, Acetaminophen with Codeine (Tylenol 4), Gabapentin, Metronidazole, Enrofloxacin (Baytril), Omeprazole, and Maropitant Citrate. The owners were instructed on how to manage the gastric tube at home. At her two-week recheck on August 8, 2018, her skin staples were removed, and the gastric tube was left in place since she was not completely eating on her own. At this check, Dixie's bloodwork revealed elevated liver enzymes and ascending hepatitis (a common side effect from biliary rerouting surgery) was suspected. At this time antibiotic therapy was reinstated.

At her one-month recheck on September 7, 2018, she showed signs of improvement and began eating on her own, but the gastric tube was left in place to supplement oral intake. Her bloodwork revealed improving yet ongoing hepatitis, and antibiotic therapy was continued. Blood was also drawn for a *Pythium* titer recheck which revealed a titer decreased from 93% to 62%. At this time, Dixie was started on Mefenoxam (Subdue MAXX Fungicide, Syngenta) 22% based on successful management of *Pythium insidiosum* in a case report in the Medical Mycology Journal.⁶ Being that the use of Mefenoxam had only been reported in one other patient, Dixie needed monthly rechecks to ensure she was not experiencing any adverse effects to the drug.

On January 11, 2019, Dixie presented to MSU-CVM Internal Medicine for a recheck where bloodwork, a Pythium titer, and an abdominal ultrasound were performed. Dixie was back to her normal self and eating actual dog food again. Her abdominal ultrasound did not reveal any regions that suggested regrowth. Bloodwork revealed moderately elevated liver enzymes suggesting a hepatitis flare, so she was placed back on antibiotic therapy. The Pythium titer revealed a decrease from 63% to 24% which is considered a negative titer. With this positive result, Dixie was kept on all medications until her next titer recheck in three-months. At this time, the plan discussed with the owner was Dixie would need three negative titers in a row before her Pythium medications could be discontinued.

Dixie's next Pythium titer was obtained on April 3, 2019 which revealed another negative titer result (26%). She continues to be her normal self and continues to follow the previously discussed plan. Dixie will be having another Pythium titer run in July 2019 to determine whether she can discontinue her Pythium therapy.

Summary/Conclusion

In summary, *Pythium insidiosum* is classified as a fungus even though it is not a true fungus when evaluating its cellular characteristics. The zoospores have an affinity for injured or decaying plant and mammalian tissues. Once infected, adhesions form allowing for the disease to seed and develop. This disease has no known effective treatment, but the general treatments used are surgical excision and antimycotics. Emerging treatment options such as the phenylamide compound Mefenoxam show promise, but further research is warranted to determine safety and efficacy.

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