Surgical Management of Fungal GI Diseases
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Key Points:
- Pythiosis should be considered as a differential for young large-breed dogs with clinical signs of gastrointestinal obstruction
- Diagnostic modalities such as serology and ultrasound are useful to confirm the diagnosis and assess resectability of the lesion while serology performed before and 2 months after surgery is helpful for predicting long-term outcome in dogs with GI pythiosis
- Surgical resection of gastrointestinal lesions is the treatment of choice for pythiosis; when possible, complete surgical resection with wide (5 cm) margins significantly improves prognosis compared to medical management
- Enlarged mesenteric lymph nodes are most often reactive rather than infected, and should be biopsied rather than removed

Although fungal diseases of the gastrointestinal (GI) tract that necessitate surgery are generally uncommon, in many parts of the US the pseudofungal pathogen *Pythium insidiosum* is encountered quite often in dogs as a cause of gastrointestinal lesions for which surgery is an important part of treatment. In addition, *Histoplasma capsulatum* is an endemic fungal pathogen that often causes infiltrative intestinal disease in dogs and cats. Because of the diffuse distribution of GI lesions associated with histoplasmosis, surgery is not generally helpful for treatment, but surgeons may encounter histoplasmosis in patients with protein-losing enteropathy that are referred for full-thickness intestinal biopsies. In most of these patients, a diagnosis can be made by detecting *Histoplasma* antigen in either urine or serum (available through MiraVista Labs), and/or by finding organisms on endoscopic biopsy or rectal scraping cytology, making surgical biopsy unnecessary.

As an aquatic oomycete rather than a true fungus, *Pythium insidiosum* has a cell wall that generally lacks chitin and a cytoplasmic membrane that lacks ergosterol. The absence of ergosterol makes medical treatment challenging because most of the commonly used anti-fungal medications target ergosterol in the fungal cell membrane. The infective form of *P. insidiosum* is thought to be the biflagellate zoospore that develops in wet environments and shows chemotaxis towards injured tissues. Infection is likely acquired when damaged skin or GI mucosa comes in contact with water that contains motile zoospores.

*Pythium insidiosum* is found in tropical and subtropical climates worldwide, with many human and animal cases reported from southeast Asia and Brazil. In the United States, infections are most common in the Gulf Coast states. However, pythiosis has also been reported in Arizona, California, Illinois, Ohio, Missouri, Kentucky, Oklahoma, Kansas, the Carolinas, Indiana, New Jersey and Virginia.

Pythiosis generally occurs in immunocompetent animals. It has been reported most commonly in horses and dogs, but has also been diagnosed in cats, calves, and various wild animals including bears and large cats. Affected dogs are typically young adults (1-4 years of age), with large breeds such as Labrador retrievers overrepresented. Many of these dogs have frequent access to lakes and ponds, but pythiosis also occurs in animals that lack historical
contact with aquatic environments. In cats, pythiosis usually occurs in very young animals and typically causes cutaneous or subcutaneous disease, with GI lesions being rare.

Clinical signs associated with GI pythiosis include vomiting, weight loss (often significant), intermittent diarrhea and anorexia. On physical examination, patients are generally in poor body condition and many have a palpable abdominal mass. Radiographs may show a soft tissue mass within the abdomen. However, ultrasound is the preferred imaging tool for assessing the location and extent of the lesion, which is essential for determining whether or not a lesion is surgically resectable, and for predicting prognosis.

When GI pythiosis is suspected, serology for evaluation of anti-*Pythium insidiosum* antibodies is usually the most straightforward means of diagnosis. This assay (offered as a diagnostic service through the Pythium Lab at LSU) has been shown to be 100% specific and greater than 95% sensitive for the diagnosis of pythiosis in dogs. Veterinarians interested in sending a sample for *Pythium* serology should contact Dr. Amy Grooters directly at agroot1@lsu.edu. In addition to providing a diagnosis, anti-*Pythium* serology is also an extremely useful post-operative monitoring tool. In dogs that have a complete resection and go on to have no recurrence of disease, antibody levels usually drop dramatically within 2-3 months after surgery.

Surgical resection with wide margins is the treatment of choice for both the cutaneous and gastrointestinal forms of pythiosis. Surgical resection should be aggressive with 5-10 cm margins, if possible. Unfortunately, the most common locations for GI pythiosis are the gastric outflow tract and the ileocolic junction, although mid-jejunal lesions can also be seen. Surgical resection and anastomosis can be performed using sutures or stapling equipment. Various stapling instruments such as GIA and TA staplers as well as the EEA stapler have been used successfully in human and veterinary gastrointestinal surgery. While they add expense to the surgery, they have been shown to significantly decrease operating times. No significant differences in complication rates have been found between sutured and stapled anastomoses in humans or small animals.

Animals with gastric lesions may be treated with a partial gastrectomy. Lesions at the pylorus or proximal duodenum may be treated with a pylorectomy and gastroduodenal anastomosis (Billroth I), although due to the extent of disease and need for wide margins, partial gastrectomy and gastrojejunal anastomosis (Billroth II) is often necessary.

Infection can spread to local lymph nodes (especially those at the root of the mesentery), pancreas or biliary system. However, although local lymph nodes are often significantly enlarged, they are typically reactive rather than infected, so the presence of severe mesenteric lymphadenopathy should not dissuade the surgeon from attempting resection of the associated GI lesions. It is essential to biopsy local lymph nodes during surgery for histopathologic evaluation because lymph node infection significantly changes the treatment protocol and the patient’s prognosis after surgery. Lymph node biopsies can be obtained using a wedge biopsy technique with a #11 scalpel blade or with a skin biopsy punch.

All samples of GI lesions and lymph nodes should be submitted for histopathologic analysis, especially if pre-operative serology was not performed. Histopathologic characteristics of *P. insidiosum* lesions generally include eosinophilic and pyogranulomatous inflammation along with hyphae that are non-septate, wide (2-7 micron diameter), have non-parallel undulating walls, and branch at 90-degree angles. Hyphae may not be identified on routine H&E-stained sections, but should be readily visualized using a GMS stain. It is important to note that these histologic characteristics are not specific for *P. insidiosum*, as pathogenic oomycetes in the genus
Lagenidium as well as the zygomycete fungi Basidiobolus and Conidiobolus cause a similar histologic appearance. However, Lagenidium spp have not been associated with GI lesions to date, and the zygomycetes are rare pathogens compared to P. insidiosum. Therefore, the majority of dogs with GI lesions that display these histologic characteristics will have pythiosis. Still, because of potential differences in treatment and prognosis, it is recommended to make a definitive diagnosis either through anti-Pythium serology or culture of fresh tissues.

Medical management can be attempted in animals with unresectable masses or following incomplete surgical excisions. The combination of itraconazole (10 mg/kg/day) and terbinafine (5-10 mg/kg/day) has been used successfully for the treatment of a limited number of dogs with unresectable GI pythiosis. However, the response rate is less than 10-15%, treatment often has to be continued for more than 6-9 months, and the cost of therapy can be very high in large breed dogs. Corticosteroids administered at anti-inflammatory doses to dogs with unresectable GI pythiosis often result in rapid improvement in clinical signs, and can be used to reduce vomiting in dogs that are receiving oral anti-fungal medication. Although the majority of these dogs will go on to have worsening of their signs within weeks to months, occasionally complete resolution of disease will occur in a dog with GI pythiosis following treatment with corticosteroids.

Given the low rate of response associated with medical therapy, surgery is clearly the treatment of choice for GI lesions that can be completely resected with wide margins. Therefore, even aggressive surgical procedures with high morbidity and mortality rates such as Billroth procedures are likely to give the patient a better chance of survival than medical treatment alone. The author's current approach in dogs for which the surgeon is not certain that clean 5 cm margins were obtained is to treat with itraconazole and terbinafine for two months post-operatively. If repeat serology at that time shows a greater than 50% reduction in anti-Pythium antibody levels, then the resection was likely complete and the medications are discontinued. If antibody levels do not drop, then medical therapy is continued, with monitoring of serology and abdominal ultrasound performed every 3 months.

An immunotherapy product developed for use in horses with pythiosis is currently available and has been used to treat dogs with unresectable disease. Unfortunately, although this product has been shown to have fairly good efficacy in horses (response in approximately 50% of cases), response rates in dogs appear to be low (probably less than 5%), and published data regarding efficacy in dogs is limited to anecdotal reports. Side effects associated with the current immunotherapy product are uncommon, but would potentially include induction of immune-mediated disease such as immune mediated hemolytic anemia and immune mediated thrombocytopenia. In addition, it is not known to what degree administration of the immunotherapy product alters anti-Pythium antibody levels and thus interferes with the use of serology as a monitoring tool. Therefore, the immunotherapy product is not recommended for use in dogs with surgically resectable lesions, but is better suited for use along with medical therapy in dogs with unresectable disease. It should be noted that the immunotherapy product is not a preventative, and should not be administered to healthy dogs.

In conclusion, rapid diagnosis and early treatment, ideally with surgery, are essential in the management of this GI pythiosis in dogs. Although there are some exceptions, the prognosis for most dogs with unresectable disease is poor, with most patients succumbing to the disease within weeks to months despite medical therapy. Surgery can be curative and should be the mainstay of treatment for any animal with a resectable mass.