Acute Pancreatitis in Dogs

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Introduction

Pancreatitis, the most common exocrine pancreatic disease of both dogs and cats, has remained a poorly understood and frustrating condition for veterinarians and clients alike. Many factors confound the diagnosis, treatment, and study of this condition; namely, the difficulty of accessing the pancreas for either clinical or academic purposes[1]. A vast array of etiologies have been proposed, but in most cases of pancreatitis the inciting cause is not determined. Furthermore, case presentations can vary widely in clinical signs, onset, and severity, thus requiring differing degrees of treatment, all of which are supportive[2]. Still, advances in diagnostics as well as an understanding of their limitations have proven instrumental in improving the outcome of small animal pancreatitis cases[2].

Pathophysiology

The exact mechanism of pancreatitis is not completely understood; however, studies have shown an insult to the pancreas occurs, which leads to a cascade of events that in turn allows trypsin to be inappropriately activated, ultimately leading to tissue autodigestion and inflammation[3]. Normally, the pancreas has a number of safeguards to protect itself from autodigestion. The first mechanism is the activation of zymogens, which are inert in the acinar cell and are activated once they are secreted into the duodenum. Second, zymogen and lysosomal granules remain separated within the acinar cell, further prohibiting autodigestion. Third, the pancreatic secretory trypsin inhibitor within acinar cells allows for inhibition of trypsin if it becomes activated in the cell. Finally, if any activated trypsin is released into circulation, antiproteases in the blood should be able to deactivate the trypsin[4].

The first step in the cascade to deactivate trypsin involves an apical block within the acinar cell, which allows zymogen granules and lysosomal proteases to colocalize and activates trypsinogen to trypsin. Once the pancreatic secretory trypsin inhibitor is overwhelmed by

pancreatic enzymes and trypsin, damage to the cell can occur, thus leading to inflammation. This inflammation is perpetuated by the recruitment of inflammatory cytokines and includes vasodilation of blood vessels, increased permeability of local capillaries, and migration of granulocytes to affected tissue and swelling of tissue cells. Generalized inflammation can lead to the initiation of several cascades that can result in systemic problems including hemorrhage, peritonitis, shock and disseminated intravascular coagulation[3].

Studies have found that inappropriate activation of trypsin can be incited by a change in intracellular pH and calcium, which can be caused by factors like hypotension and genetic abnormalities in processes that prevent the premature activation of trypsin. In humans, inappropriate activation of trypsin results from a mutation in the cationic trypsinogen gene, which leads to accumulation of trypsin in the acinar cell. In dogs, a genetic predisposition for pancreatitis has been found in breeds like the Miniature Schnauzer, but the exact mechanism remains unclear. Studies have shown that autoactivation of trypsinogen becomes more rapid as the pH of acinar cells become more neutral[4].

History and Clinical Signs

Pancreatitis typically affects middle-aged to older patients. Although acute pancreatitis can affect any breed, several breeds are over-represented like the Schnauzer, Yorkshire terrier, Spaniels, Shetland Sheepdog and Collies[5]. Potential etiologies that can cause pancreatitis can include, but are not limited to: dietary factors, hyperlipidemia, drugs, toxins, hypercalcemia, pancreatic trauma, ischemia and idiopathic causes[2,6]. Dogs that are overweight appear to have a greater risk of developing pancreatitis. This is speculated to be associated with abnormal dietary intake, altered lipid status, or a general predisposition to inflammation[2]. Reports have shown that

concurrent diseases including diabetes mellitus, hypothyroidism, and hyperadrenocorticism are commonly reported in pancreatitis cases. These diseases are associated with hyperlipidemia[2].

Dogs with acute pancreatitis present with vague gastrointestinal signs including anorexia, vomiting, abdominal pain, fever, and diarrhea. There are no physical exam findings that are specific for pancreatitis; instead, they vary with the severity and stage of disease[7]. Most patients will present with some degree of dehydration with signs including tachycardia, tachypnea, prolonged capillary refill time and dry mucous membranes[2]. Patients may also present with jaundice due to the development of an extrahepatic bile duct obstruction. This can occur secondary to local peritonitis or from a physical obstruction of the bile duct due to the proximity of the pancreas[2]. Other systemic complications include signs of clotting disorders, petechiae that may progress to DIC, and cardiac arrhythmias[5].

Diagnostics

Pancreatic biopsy is the gold standard for achieving a definitive diagnosis of acute pancreatitis. Biopsies are highly specific; however, sensitivity is poor because pancreatitis may be localized to small regions within the pancreas[5]. Biopsies are also not commonly performed due to invasiveness involved in obtaining them[8]. Due to this, a combination of other diagnostic tests and modalities must be used to diagnosis acute pancreatitis.

General blood work including a complete blood count, and serum chemistry should be performed in these patients. A complete blood count can reveal a neutrophilia with a degenerative left shift and leukocytosis. An increased packed cell volume can also be seen, indicative of hemoconcentration. Anemia and thrombocytopenia can also be present, which can be early signs of DIC[8].

Common abnormalities that can be found on a serum chemistry include a pre-renal azotemia due to hypovolemia or shock. In addition to an increased packed cell volume, hyperproteinemia may be secondary to dehydration. Hyperbilirubinemia secondary to pancreatic inflammation occurs, especially if the common bile duct is obstructed Cholestasis can lead to an increase in AST, ALT, and ALP. An increase in hepatic enzymes suggests hepatic ischemia from local inflammation. Hypocalcemia may result due to deposition of calcium within the pancreas, which occurs secondary to pancreatic inflammation. The systemic inflammation associated with acute pancreatitis may lead to hypercholesterolemia, hyperlipidemia and hypoalbuminemia. Since the most common presentation of these patients is vomiting and anorexia, electrolyte abnormalities such as hyponatremia, hypochloremia, and hypokalemia are also common[5]. Complications such as systemic inflammatory response syndrome and/or multi-organ dysfunction may lead to patient decompensation, especially respiratory-wise.

Diagnostic imaging is not specific for pancreatitis but can aid in ruling out intestinal obstruction and can reveal other causes for clinical signs such as free gas within the abdomen or a distended, fluid-filled uterus[2]. Abdominal radiographs of patients with pancreatitis may reveal loss of serosal detail in the cranial abdomen, displacement of the stomach to the left, displacement of duodenum to the right and/or ventrally, and a widened pyloric-duodenal angle[8]. Abdominal ultrasound can be a valuable tool in aiding in the diagnosing of acute pancreatitis; however, the sensitivity and specificity is highly operator-dependent. This modality can reveal an enlarged, irregularly marginated, hypoechoic pancreas. The surrounding mesentery may be hyperechoic, and fluid accumulation may be detected. Due to its proximity to the pancreas, the descending duodenum may be thickened, fluid-filled and non-motile. Focal peritoneal effusion may be present. If the patient has an extrahepatic biliary obstruction secondary to the pancreatitis

fibrosis, edema and inflammation of the bile duct may be detected[9]. CT imaging is commonly used to diagnosis pancreatitis in humans; however, there is limited information in veterinary medicine about using it to diagnose the condition in dogs. Furthermore, CT requires sedation or anesthesia, which may not be safe to use in these cases[7].

Although previous studies have shown an increase in serum lipase and amylase in cases of pancreatitis, these enzymes are not specific to the disease. Since they also originate from gastrointestinal mucosa and are cleared by the kidneys, an elevated serum lipase may indicate acute enteritis, gastroenteritis, liver disease, renal failure or pancreatitis[2].

The most recent advancement in diagnosing canine pancreatitis is a pancreatic lipase immunoreactivity assay (cPLI). This is a sensitive indicator of exocrine pancreatic disease in the dog in that it reflects the release of pancreatic lipase into the serum as a result of pancreatic acinar cell damage[8]. There are two tests readily available to assess pancreatic lipase: spec cPL assay, which can specifically quantify the pancreatic lipase concentration, and semi-quantitative ELISA, which is a Snap® test that can be performed in hospital. The reference interval for these tests are 0-200 ug/L, with concentrations above 400ug/L being consistent with pancreatitis. Serum concentrations between 200-400ug/L are diagnostically ambiguous.

The Snap® cPl test includes a reference spot that corresponds to the upper limit of the reference interval (200ug/L). The color intensity of the sample spot is visually compared with the reference spot. Results are either normal or abnormal, based on the color of the sample spot compared to the reference spot. Cases that fall into the gray zone may be consistent with the result of an abnormal PL.

A study reported the sensitivity of the Snap® cPl to be 94% and a specificity of 77%, highlighting the test's ability to rule out pancreatitis rather than diagnose it[10]. The primary

benefit of using a Snap® cPl is the 10-minute wait time until results are obtained, as opposed to waiting at least 24 hours to receive the results of a send-out test. False negatives can happen in chronic pancreatitis cases where histopathologic lesions associated with chronic pancreatitis such as pancreatic fibrosis and atrophy are not associated with leakage of pancreatic enzymes. Due to these limitations, further testing using the quantitative reference method is recommended when an abnormal Snap® cPl is obtained.

Advancements in rapid diagnostics are providing clinicians with more options for diagnosing and quantifying pancreatitis. Vetscan cPL Rapid test is a quantitative immunoassay for the detection of cPL that combines rapid results with quantitative results. One study found that its sensitivity was 73.9% and specificity was 76.9%[11]. Precision PSL, another recently developed test, is a colorimetric assay that uses DGGR for the diagnosis of pancreatitis; however, it is not specific for pancreatic lipase. Its sensitivity is 85.7% and specificity is 64%[11]. Utilizing multiple forms of testing in cases of pancreatitis may be proven to be beneficial to case outcomes in the near future.

Treatment

Due to dehydration as a result of vomiting and decreased food and water intake, a mainstay of management is fluid therapy. Fluids are used to not only correct dehydration, but also to correct electrolyte abnormalities and increase perfusion, especially to the pancreas. There is a hypothesized benefit in using alkalinizing fluids such as Lactated Ringers solution to increase pH and therefore prevent further trypsin activation. Plasma transfusions may also be indicated, with benefits thought to include replacement of circulating alpha-macroglobulins, coagulation factors, and anti-inflammatory factors. Still, no benefits have been proven in the

treatment of human or canine cases of pancreatitis. Due to this and the expense, it should be reserved only for dogs with coagulation abnormalities[12].

Since the presenting complaint of many of the patients with pancreatitis is vomiting, another primary aim of treatment is anti-emesis. The most commonly used antiemetic is maropitant citrate, or Cerenia, which blocks the neurokinin (NK)1 receptor, which in turn blocks both centrally and peripherally mediated emesis[2]. Many clinicians also implement gastric acid suppression management, since it is theorized that a higher gastric pH will lead to decreased pancreatic stimulation. It is also thought that acute pancreatitis predisposes to the development of gastric ulceration because of hypovolemia and local peritonitis[2].

Another common presenting complaint of patients with pancreatitis is anorexia. It was traditionally thought that these patients should not be fed in order to give the gastrointestinal tract time to “rest”, which would provide no exocrine stimulation[2]. However recent studies have shown that imposed anorexia may be counterproductive to gastrointestinal health[13]. Enteral feeding can prevent mucosal atrophy, which may reduce the risk of bacterial translocation and septic complications[6]. Studies have shown that dogs benefit from enteral feeding if initiated within 48 hours of being hospitalized or immediately if five days of anorexia has occurred[13]. Assisted feeding may need to be implemented in patients that will not voluntarily eat sufficient daily caloric needs[13].

Abdominal pain is a common presentation of pancreatitis in dogs, due to the inflammation of the pancreas. Opioids are the most commonly chosen pain medication in these hospitalized patients, such as methadone, hydromorphone, or fentanyl. Morphine should be avoided in patients with conditions of the gallbladder and biliary tract[12].

Other treatments for managing pancreatitis can be instituted on case by case basis, depending on severity and clinical signs. In cases of infection or bacterial translocation, antibiotics that are broadly effective against gut pathogens like amoxicillin-clavulanate should be given parenterally. Proton pump inhibitors should be considered if melena, hematochezia or hematemesis are present. Likewise, ranitidine or cisapride can be instituted if the patient has poor intestinal motility[2].

Expected outcome and prognosis

Cases of pancreatitis can vary from mild to severe with prognoses from good to grave. The reported mortality rate for acute pancreatitis in dogs ranges from 27%-58%[14]. The point at which clinical signs are first noticed to the time of treatment is initiated can significantly improve case outcome. Although severe cases have a high mortality rate, histological and functional damage can be reversed in patients that recover[1]. Negative prognostic indicators for pancreatitis include: an elevation of BUN, creatinine, decreased platelet count and remarkable elevation of specific cPL concentrations[15].

Potential sequela to pancreatitis include the development of pancreatic pseudocysts or pancreatic abscesses. Both of these can be seen on ultrasound but are note easily differentiated using this imaging modality alone[9]. Pancreatic pseudocysts are sterile fluid accumulations with the pancreatic parenchyma[12]. Current recommendations are to perform percutaneous drainage of pseudocysts if it is determined that the fluid is causing pain to the patient. Otherwise, they should not be drained as there is evidence that this fluid may spontaneously resolve on its own[12]. Abscesses are areas of necrotic tissue or purulent debris within the pancreas[9]. The reported mortality rates for dogs with pancreatic abscesses are greater than 50%; however, this includes

those treated surgically with subsequent complications[2]. Current recommendations are to treat pancreatic abscesses with antimicrobials[2].

In severe cases, pancreatitis can lead to systemic complications. Acute renal failure may develop secondary to hypovolemia, ischemia, intravascular coagulopathy or direct inflammation resulting from peritonitis. Acute lung injury may result in inflammation, damage of endothelial cells, interstitial edema, and intra-alveolar hemorrhage[16]. Other systemic complications include disseminated intravascular coagulation and cardiac arrhythmias[3]. Even after recovery, chronic relapsing pancreatitis and development of exocrine pancreatic insufficiency may occur[3].

Conclusion

Although much remains to be learned about pancreatitis in companion animals, advancements in diagnostics as well as the study of prognostic indicators and outcomes show that in many cases the acute form of disease can be successfully treated with rapid diagnosis and early supportive intervention. Middle-aged to older dogs are more at risk for developing pancreatitis, as are overweight animals and specific breeds like Schnauzers[5]. Vague gastrointestinal signs are often the only clinical signs, with variation according to the severity of the disease. Due to the possibility for mortality and systemic complication, pancreatitis should always be a top differential in a dog presenting with acute vomiting and diarrhea.

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