

New Concepts in Canine Pancreatitis

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Introduction

The incidence of exocrine pancreatic disorders in dogs is quite large. In a large retrospective study of necropsy findings, 1.5% of 9,342 canine pancreata showed significant pathological lesions. Approximately 50% of all canine patients with exocrine pancreatic disorders have pancreatitis and approximately 2/3 of dogs with pancreatitis have acute disease. According to the current classification system of human pancreatitis, acute pancreatitis is an inflammatory condition of the pancreas that is completely reversible after removal of the inciting cause.¹ Chronic pancreatitis is characterized by irreversible histopathologic changes (i.e., fibrosis and/or atrophy) of exocrine pancreatic tissue. Both forms can be mild or severe. Mild forms of pancreatitis are associated with no or little pancreatic necrosis and systemic complications and often allow recuperation of the patient. In contrast, severe forms of pancreatitis are associated with extensive pancreatic necrosis, multiple organ involvement, and often a poor prognosis.

Etiology and Pathogenesis

According to a generally accepted pathogenic model, pancreatic acinar cells ultimately respond in a common fashion to a variety of harmful stimuli, leading to inappropriate intracellular activation of trypsin and subsequently activation of other digestive zymogens.² The activated digestive enzymes cause local changes, such as inflammation, hemorrhage, acinar cell necrosis, and peripancreatic fat necrosis. Digestive enzymes released into the blood stream may cause systemic changes, including systemic inflammatory changes, systemic vasodilatation leading to hypotension, pulmonary edema, disseminated intravascular coagulation, central neurologic deficits, respiratory failure, renal failure, and multiorgan failure. However, more recently, cytokines are believed to play a more important role in the progression of pancreatitis and the development of systemic effects.³

Several diseases and risk factors have been associated with pancreatitis.⁴ Hyperlipidemia and dietary indiscretion have been implicated in causing pancreatitis in dogs but experimental evidence supporting this implication are sparse. Traumatic pancreatitis (due to road traffic accidents) has been reported as a cause of pancreatitis. Surgical trauma can cause pancreatitis but many human patients that undergo surgery of organs distant from the pancreas have also been shown to be at an increased risk for pancreatitis suggesting that hypoperfusion of the exocrine pancreas during anesthesia may be of bigger concern than surgical handling of the organ itself. Infectious agents, such as *Toxoplasma gondii* or hepatic fluke infestation have been shown to cause rare cases of pancreatitis in cats, but not in dogs. Many pharmaceutical compounds have been implicated in causing pancreatitis in human beings and dogs. Finally, more than 90% of all cases of canine pancreatitis are idiopathic.

Clinical picture

Clinical signs in dogs with pancreatitis depend on the severity of the disease. Mild cases may remain subclinical. More severe cases may present with anorexia (91%; data from a study of 70 dogs with fatal pancreatitis), vomiting (90%), weakness (79%), abdominal pain (58%), dehydration (46%), and diarrhea (33%).⁵ Severe cases can present with systemic clinical signs, such as fever or even cardiovascular shock. Clinical signs in patients with pancreatitis are due to pancreatic inflammation or systemic effects to the pancreatic inflammation. Recent data suggest that the exocrine pancreas responds to several different noxious stimuli by a decrease in secretion of pancreatic enzymes. This is followed by the formation of giant cytoplasmic vacuoles in acinar cells, visible only by electron microscopy. Biochemical studies have shown that these vacuoles are the product of co-localization of zymogens of digestive and lysosomal enzymes, which are normally strictly segregated. The ensuing decrease in pH and/or the presence of the lysosomal enzymes such as cathepsin B lead to premature activation of trypsinogen. Trypsin in turn activates other zymogens, leading to local effects such as inflammation, pancreatic edema and hemorrhage, pancreatic necrosis, and parapancreatic fat necrosis. These local effects are associated with clinical signs such as vomiting and abdominal pain. Until recently, it was believed that systemic signs commonly seen in pancreatitis patients, like local effects, are a direct result of circulating pancreatic enzymes. While there is little doubt that some of these systemic effects, such as systemic lipodystrophy, are caused by circulating pancreatic enzymes, recent data would suggest that other systemic sequelae are a consequence of the release of inflammatory mediators in response to pancreatic inflammation. A systemic inflammatory response, consisting of release of neutrophils from the bone marrow, chemotaxis of leucocytes, and degranulation of mast cells, basophils, and eosinophils, and platelet aggregation occur commonly in patients with severe forms of pancreatitis and can lead to fever. Other systemic effects seen in patients with severe pancreatitis are systemic vasodilation leading to hypotension and sometimes acute renal failure, pulmonary edema leading to respiratory failure, disseminated intravascular coagulation, and in some cases multi-organ failure. A few patients also develop systemic lipodystrophy, also known as pancreatitis associated panniculitis or Weber-Christian syndrome. Neurologic signs, such as disorientation have been seen in human and canine patients with severe pancreatitis and are sometimes referred to as pancreatic encephalopathy. While clinical signs are not specific for pancreatitis, vomiting and cranial abdominal pain are key clinical signs in dogs with pancreatitis and a dog presenting with both of these signs should be carefully evaluated for the presence of pancreatitis.

Diagnostic tests

Complete blood count and serum chemistry profile often show mild and nonspecific changes.⁵ More severe changes can be observed in patients with severe forms of pancreatitis. Serum amylase and lipase activities have a limited clinical utility for the diagnosis of canine pancreatitis. The specificity of both of these parameters is only approximately 50%, even when stringent criteria are applied.⁶ Thus, serum amylase and lipase activities should only be used if they can be performed in-house and only until more definitive diagnostic tests can be performed. Radiographic changes seen in some patients include a decreased contrast in the cranial abdomen and displacement of abdominal organs. However, these changes are rather subjective and abdominal radiography is non-specific for canine pancreatitis. In contrast, abdominal ultrasound is quite useful for the diagnosis of canine pancreatitis. The sensitivity of abdominal ultrasonography is up to 68% in dogs.⁵ However, this number is largely operator-dependant. Changes identified include pancreatic swelling, changes in echogenicity of the pancreas

(hypoechogenicity in cases of pancreatic necrosis and rarely hyperechogenicity in cases of pancreatic fibrosis) and of peripancreatic fat (hyperechogenicity in cases of peripancreatic fat necrosis), fluid accumulation around the pancreas, and less frequently a mass effect in the area of the pancreas. Other findings that have been described are a dilated pancreatic duct or an enlarged duodenal papilla. Abdominal computed tomography is a routine procedure in humans suspected of having pancreatitis, but appears to be very insensitive for the diagnosis of pancreatitis in dogs.

Trypsin-like immunoreactivity is specific for exocrine pancreatic function. However, the sensitivity of serum TLI concentration for pancreatitis in dogs is only approximately 30-60%, making it a suboptimal diagnostic test for pancreatitis. However, serum canine TLI concentration remains the diagnostic test of choice for the diagnosis of EPI in dogs.

Recently, an assay for the measurement of pancreatic lipase immunoreactivity in dogs (cPLI, now measured as Spec cPL™) has been developed and validated. Many different cell types in the body synthesize and secrete lipases. In contrast to catalytic assays for the measurement of lipase activity, use of an immunoassay does allow for the specific measurement of lipase originated from the exocrine pancreas.

Serum cPLI was measured in a group of dogs with exocrine pancreatic insufficiency and the median serum cPLI concentration was significantly decreased compared to clinically healthy dogs. In addition, serum cPLI concentration was non-detectable in most of the dogs and minimal serum cPLI concentrations were observed in the rest of the dogs, indicating that serum cPLI concentration originates from the exocrine pancreas and is specific for exocrine pancreatic function. In another study, serum cPLI concentrations were evaluated in dogs with experimentally induced chronic renal failure. While serum cPLI was significantly higher in dogs with experimentally induced chronic renal failure than in clinically healthy dogs, most dogs had serum cPLI concentrations within the reference range and none of the dogs had a serum cPLI concentration that was above the currently recommended cut-off value for pancreatitis. These data would suggest that serum cPLI concentration can be used as a diagnostic test for pancreatitis even in dogs with renal failure. Also, long-term oral administration of prednisone did not have any effect on serum cPLI concentration. Finally, the sensitivity of different minimally-invasive diagnostic tests was compared in dogs with proven pancreatitis. The sensitivity of serum TLI concentration was below 35% and that of serum lipase activity was less than 55%. In contrast, the sensitivity for serum cPLI concentration for pancreatitis was above 80%.⁷ Thus, serum cPLI concentration is the most sensitive and specific diagnostic test for canine pancreatitis currently available. Recently, a commercial assay, Spec cPL™, has been introduced. This new assay is more robust than the original in-house assay developed at the Gastrointestinal Laboratory and has now replaced the original cPLI assay world-wide. Spec cPL concentration shows remarkable correlation with cPLI concentration and all data presented for the cPLI assay can be directly applied to the new Spec cPL assay.

Traditionally, a pancreatic biopsy has been viewed as the most definitive diagnostic tool for pancreatitis. Pancreatic biopsies can be collected during abdominal exploratory or by laparoscopy. The presence of pancreatitis is easily diagnosed by gross appearance of the pancreas in many cases. However, the absence of pancreatitis can be difficult to prove. In a recent study histopathological findings in dogs with pancreatitis were evaluated. Pancreata were sectioned every 2 cm. In approximately 50% of all dogs with pancreatitis and in 2/3 of dogs with chronic pancreatitis evidence of pancreatic inflammation was found in less than 25% of all sections. Thus, even if multiple biopsies are being collected, pancreatic inflammation, especially in cases of chronic pancreatitis, may easily be missed. This also would suggest that laparoscopy

is inferior for the collection of a pancreatic biopsy as it is much more difficult to evaluate the entire organ during laparoscopy. It should also be noted that while a pancreatic biopsy in itself is not associated with many complications, many patients with pancreatitis are a poor anesthetic risk.

Therapy

Removal of Cause and Supportive Care - Whenever possible the inciting cause should be removed. Exposure to unnecessary drugs, especially those implicated in causing pancreatitis in dogs or other species, should be avoided. Aggressive fluid therapy is the mainstay of supportive therapy. Fluid, electrolyte, and acid-base imbalances need to be assessed, and corrected as early as possible.

Alimentation - The traditional recommendation for any patient with pancreatitis is to give nothing per os for three to four days. This recommendation is justified in patients that vomit, but there is little evidence to justify this strategy in patients that do not. In fact, in people with severe acute pancreatitis, early feeding is considered beneficial.⁸ Preferred routes of alimentation in patients kept NPO are a jejunostomy tube or total parenteral nutrition. However, these strategies are impractical in many cases and a gastrostomy tube or a nasogastric tube are acceptable alternatives if the patient does not vomit. However, in dogs that do vomit, and where the patient should be held NPO for 3-4 days. After this time water is slowly reintroduced, followed by small amounts of a carbohydrate-rich and low-fat diet.

Analgesia - Abdominal pain is commonly recognized in dogs with pancreatitis. However, the presence of abdominal pain should be assumed and analgesic drugs are indicated in all canine patients with pancreatitis. Meperidine, butorphanol tartrate, or morphine can be used parenterally. Other alternatives are a fentanyl patch or the intraabdominal administration of lidocaine.

Plasma - Studies in dogs suggest that when α_2 -macroglobulin, one of the scavenger proteins for activated proteases in serum, is depleted, death ensues rapidly. Fresh frozen plasma (FFP) and fresh whole blood not only contain α_2 -macroglobulin, but also albumin, which has many beneficial effects in patients with severe pancreatitis. However, in clinical trials in human patients with acute pancreatitis no benefit of plasma administration could be identified.⁹ Regardless, the author believes that FFP administration is useful in dogs with severe forms of pancreatitis.

Antibiotic Therapy - In contrast to humans, infectious complications in canine patients with pancreatitis are rare in dogs. Therefore, the use of antibiotic agents should be limited to those cases when an infectious complication can be identified or is heavily suspected.

Anti-inflammatory Agents - There is no data on the use of anti-inflammatory agents in dogs with severe pancreatitis, but no benefit was found in human patients. In dogs with severe pancreatitis, corticosteroids should only be used when secondary cardiovascular shock occurs. Corticosteroids may be needed to treat dogs with IBD and concurrent mild chronic pancreatitis, and do not appear to be harmful in these patients.

Other Therapeutic Strategies - Many other therapeutic strategies, such as the administration of trypsin-inhibitors (e.g., trasyolol), platelet activating factor inhibitors (PAFANTs), dopamine, antacids, antisecretory agents (i.e., anticholinergics, calcitonin, glucagon, or somatostatin), or antioxidants and surgical intervention all have been evaluated in human patients with pancreatitis. With the exception of PAFANTs and selenium, none of these have shown any beneficial effect at this point. The efficacy of selenium, which has also been shown to decrease mortality in dogs with pancreatitis in an uncontrolled study, needs to be further evaluated before its use can be recommended.

Mild chronic pancreatitis - It should also be noted that many dogs have mild forms of chronic pancreatitis. Often times these patients have concurrent conditions, most notably IBD. Very little is known about appropriate therapy for these animals and management is often limited to evaluation and treatment of the concurrent condition, and careful monitoring of the pancreatitis. Serum calcium and triglyceride concentrations should always be evaluated in these patients in order to identify any risk factors that can potentially be addressed therapeutically. Also, the use of low fat diets is recommended in these patients. The use of corticosteroids in patients with mild chronic pancreatitis is controversial. A subset of human pancreatitis patients is being diagnosed with immune-mediated pancreatitis. These patients respond well to corticosteroid administration. Many dogs with chronic pancreatitis show lymphocytic-plasmacytic infiltration of the exocrine pancreas, similarly to what can be observed in human patients with immune-mediated pancreatitis. Thus, dogs with mild chronic pancreatitis may also respond favorably to corticosteroid administration. Just as in human patients with chronic pancreatitis, patients with mild chronic pancreatitis are at risk for developing episodes of severe pancreatitis at any time or exocrine pancreatic insufficiency later in life.

Prognosis

The prognosis for dogs with pancreatitis is directly related to disease severity, extent of pancreatic necrosis, occurrence of systemic and pancreatic complications, duration of the condition, and the presence of concurrent disease.

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