Pancreatitis: Under-Recognized or Over-Diagnosed?

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Like cholangitits the term pancreatitis describes a number of different processes and outcomes rather than a single entity. Human medicine classifies pancreatitis as acute or as chronic. Using a similar scoring system in cats, DeCock describes acute pancreatitis (AP) to consist of neutrophilic inflammatory changes with concurrent interstitial edema and mesenteric fat necrosis. In chronic pancreatitis (CP), fibrosis is more notable than is inflammation, and the inflammatory cell infiltrate favours lymphocytes along with some macrophages and eosinophils. Additionally, cystic dilation and changes in lobulation were seen in the chronic form of the disease. Unlike human CP, there were only minimal pancreatic duct changes in cats.

From a clinical standpoint, AP is a short term, disease, often completely reversible unless it is acute necrotizing disease, a completely different entity. Because chronic pancreatitis, the more common form of pancreatitis in cats, represents a long-term process and is associated with irreversible pathological changes, (i.e., fibrosis), it isn't curable, however, it can generally be controlled and is less fatal than acute necrotizing pancreatitis (ANP). It has been suggested that CP may become, or result from, ANP in some cases.

Both acute and chronic pancreatitis can be mild or severe, but acute cases tend to be more severe, and chronic cases milder. Mild pancreatitis generally results in minimal clinical signs, minimal necrosis, and low mortality. Histopathologic classification may help in designing appropriate therapeutic protocols for our patients. DeCock suggests one schema (found online at: http://vet.sagepub.com/content/44/1/39.full.pdf+html). It is important to get a good pathologic description when submitting pancreatic biopsies.

Etiology and pathogenesis of pancreatitis

In the majority of cases, the etiology is unknown. More than 90% of the cases of feline pancreatitis are idiopathic. As the De Cock study speculates, one reason for the high prevalence of CP in cats may be that the pancreas is very sensitive to drugs, stress, metabolic derangements, or ischemia associated with a wide variety of clinical conditions. Anaesthesia-related hypoperfusion or hypovolemia from any cause might also result in ischemia. Additional causes include trauma, infectious agents, toxins (e.g., fenthion) and potentially drugs as recognized in human pancreatitis. Infectious agents have been implicated including feline parvovirus, Toxoplasma organisms (of 45 pancreata examined in 100 cats infected with Toxoplasma, 38 had lesions), feline herpesvirus I, Eurytrema procyonis (raccoon pancreatic fluke), feline infectious peritonitis (FIP), and, rarely, Amphimerus pseudofelineus.

Data evaluating the presence and distribution of bacteria within 46 inflamed feline pancreatae using fluorescent in situ hybridization (FISH) was presented at AVCIM 2011. A 16S rDNA probe was used to identify bacteria, using further probes to specifically identify E.coli and Streptococcus spp. Thirty-five percent (11/31) of cats with histologically defined moderate to severe pancreatitis, had intra-pancreatic bacteria. Infection was most common in those with AP more so than CP. Localization and type of bacteria suggest translocation of enteric organisms possibly from the colon.

Clinical findings

Pancreatitis should be included in a diagnostic rule-out list whenever there is a history of lethargy, anorexia, dehydration, hypothermia, vomiting (in only 35% in one paper), abdominal pain, abdominal mass effect, dyspnea, diarrhea and ataxia. Concurrent problems may include hepatic lipidosis, cholangitis, inflammatory bowel disease (IBD), enteritis, diabetes mellitus, and vitamin K1 responsive coagulopathy. Clinical findings for pancreatitis are, therefore, extremely vague and a diagnosis requires a combination of clinical suspicion, abdominal ultrasound findings and feline pancreatic lipase immunoreactivity (fPLI). .A retrospective study published in 2003 looked at 63 histologically confirmed cases of feline pancreatitis to identify differences between acute necrotizing and chronic nonsuppurative forms of pancreatitis. The conclusion was that ANP and CP in cats cannot be distinguished on the basis of history, physical examination findings, results of clinicopathologic testing, radiographic abnormalities, or ultrasonographic abnormalities. Histology (and/or cytology) is needed.

Diagnostics

Given the poor predictive value of any clinical finding in achieving the diagnosis, we must rely on a combination of examination, imaging, biochemical changes and, lacking clinical improvement, ultimately tissue evaluation (cytology and/or histopathology).

Imaging

The classical signs of abdominal tenderness or mass in the right anterior quadrant along with haziness in this region and displacement of abdominal viscera on abdominal radiographs and/or visualization of a (nodular) hyperechogenicity or peripancreatic fluid or a pancreatic abscess or mass on ultrasound examination support the presumptive diagnosis of pancreatitis.

Ultrasonographic findings may include the following changes in the pancreas -- swelling, increased echogenicity, mass effects, and fluid accumulation around the pancreas or there may be no ultrasonographic changes. Abdominal ultrasound is sensitive in cats with

moderate-severe pancreatitis and specific (reliable negative predictive value) in healthy cats. Two studies have been done to assess the effects of age on the normal pancreas and pancreatic duct. Both have shown that pancreatic size and echogenicity do not change with age, and that pancreatic duct diameter increases with age. A dilated duct should not be used as the definitive indicator of pancreatitis in an elderly cat.

A study was performed to evaluate the usefulness of endosonography as a tool for diagnosing pancreatitis. The conclusion was that this technique did not alter the diagnosis in the six cats with pancreatitis or the 11 normal cats when compared to abdominal ultrasound. It is a technique that may be useful when ultrasound is limited by obesity, intestinal gas or a hyperechoic mesentery. Contrast-enhanced computed tomography (CT) is used in humans to diagnose and stage the severity of pancreatitis with its ability to detect and delineate areas of necrosis. In cats, contrast enhancement may improve diagnostic acuity in cats.

Of the imaging modalities most readily available, ultrasound is the most sensitive, non-invasive evaluative tool that we have at this time.

Serum biochemistry and hematology

Changes are most commonly mild and nonspecific. There may be mild, non-regenerative anemia in chronic pancreatitis or a severe anemia terminally in acute, necrotizing pancreatitis. An inflammatory or stress leukon may be present, and in the case of a pancreatic abscess or a suppurative pancreatitis, a left shift may be seen. Concurrent elevations of SAP and ALT are not uncommon and reflect inflammatory or lipidotic involvement of adjacent tissue. Nonspecific changes, such as hyperglycemia (stress or concurrent diabetes), hypocalcemia, hypokalemia (innapetance), hypercholesterolemia, azotemia (prerenal and/or renal), and hyperbilirubinemia have all been reported. Hypoalbuminemia may be present in moderate-severe pancreatitis. The lack of sensitivity and specificity of amylase and lipase is a source of frustration in diagnosing feline pancreatitis. The lack of hyperlipasemia cannot be depended on to rule-out pancreatitis. Elevations in serum amylase may occur with pancreatitis, but more commonly are a result of other gastrointestinal diseases, as well as from decreased renal clearance of this enzyme.

Trypsin-like immunoreactivity (TLI) has been shown to be diagnostic for severe acute pancreatitis. However, this fails to detect the more common, chronic and milder forms of pancreatitis. Trypsinogen and trypsin are pancreas-specific in origin, and both are detected by the trypsin-like immunoreactivity (TLI) assay. TLI test is very specific but has poor sensitivity. Even though published reference intervals are 17-48 micrograms/dl values under 150-200 are equivocal. TLI seems most reliable in identifying acute pancreatitis. Later in the course of disease it may not be elevated because either the sick pancreas has leaked all of the enzymes that it had made and isn't capable of producing more (after several days of inflammation) or the pancreatic blood flow has decreased following the worst phase of the inflammatory response. Mild inflammation may also just not stimulate much leakage of enzyme.

Feline pancreatic lipase immunoreactivity (fPLI) has been shown to be sensitive in cats with moderate-severe pancreatitis as well as having a high negative predictive value (i.e., specific) in healthy cats. A weakness of this test is its high interassay variability, meaning that results may vary significantly from run to run. This limits its usefulness for monitoring therapeutic efficacy as well as reliability in making a diagnosis. It is most reproducible in its middle range. The other concern is that observed: expected ratios are very wide. An observed: expected ratio describes the amount of a substance recovered when a known amount is utilized. Ideally, a test "should" detect 100% of a substance it is measuring (O: E = 1). The O: E for when a known amount of pancreatic lipase was added in various concentrations to feline serum, ranged from 76.9% (not detecting all) to 147.6% (detecting more than was added).

The levels of fPLI concentrations have been evaluated in cats with diabetes mellitus in one study. This report found that cats with diabetes had higher fPLI levels than cats without diabetes. This increased fPLI value was unrelated to the degree of control of the diabetes and interestingly, there were no significant differences in reported clinical signs between cats with or without DM regardless of serum fPLI concentration. A study comparing fPLI concentrations in cats with histologically diagnosed IBD found that whether they had normal or increased fPLI levels, was not associated with a difference in clinical outcome, treatment and clinical response.

Cobalamin levels are often subnormal in cats with pancreatitis because, in this species, the pancreas is the only known source of intrinsic factor. Intrinsic factor is complexed to dietary cobalamin to allow absorption into the body after which it is transferred to transcobalamin proteins, and then finally taken up by cells.

Definitive diagnosis

Ultimately, surgical biopsy is required to make the histopathological diagnosis. Whilst dogma was that biopsying the pancreas is a pathophysiologically dangerous undertaking, in the cat, this does not appear to be the case. The author routinely biopsies the pancreas in all of her exploratory patients. Gently isolate the pancreas from the surrounding viscera and pack it off with a moistened gauze swabs being careful to not exteriorize the organ. Doing this results in rapid, dramatic hypotension. Using fine scissors (e.g., iris scissors), take a 4 X 4 mm wedge from both poles as well as any gross lesion. Submit a small piece in a culture medium as well as formalin preserved samples, in case the lesion is reported as septic suppurative. Ultrasound guided aspiration of the pancreas is a less invasive tool which may also yield useful clinical clues when performed with care.

Therapy

Therapy for pancreatitis is best designed about the histologic type of pancreatitis. Fluid therapy and pain relief are the cornerstones in supportive care. Fluids sustain blood and plasma volume and blood pressure to ensure adequate perfusion and to correct acid-base and electrolyte disorders. Even if obvious abdominal pain isn't present, a test dose of 0.1-0.2-mg/kg oxymorphone IV or buprenorphine IV, SC may be considered to see if the patient improves over the approximately 6 hour effective period. If that is the case, then constant rate infusion of a narcotic may be considered or a transdermal fentanyl patch for continuous relief.

NSAIDs may be selected for their usefulness both as anti-inflammatory agents as well as their analgesic component. As always, adequate hydration of a patient, knowledge of appropriate renal function and the lack of gastrointestinal bleeding are important before choosing this class of drugs. Use of COX-2 inhibitors minimizes the risk to feline patients as does appropriate dosing and dosing intervals.

Concurrent problems (such as lipidosis or enteritis) should be addressed as well. A noteworthy difference between the dog and cat is the recommendation to feed, rather than fast, those patients suspected of (or confirmed as) having pancreatitis unless they are vomiting. Even with the vomiting cat, designing a nutritionally supportive protocol is of great importance due to this species' ease of developing lipidosis. The author fasts cats for no longer than 24 hours utilizing anti-emetics as necessary. In these few intractably vomiting cats, total parenteral nutrition or jejunostomy tube feeding may be required for 7-10 days. Discussion of tube feeding (nasogastric, esophageal, gastrotomy, jejunostomy) may be found in numerous texts, and therefore won't be discussed here. Trickle feeding may be of value when emesis persists despite pharmacologic intervention.

When the use of anti-emetics is being considered, a reduced clearance rate should be considered in dosing if the agent requires hepatic metabolism. Doses should be reduced accordingly. Anti-emetics commonly used in the cat include metoclopromide and chlorpromazine. Each of these drugs also has its own, inherent side effects, such as the central nervous system (CNS) sedation or frenzied behaviour or disorientation of metoclopromide in the cat or the hypotensive effect of the chlorpromazine. Ondansetron and dolasetron, while costly, are very beneficial in the intractably vomiting patient. Mirtazapine is very useful due to the infrequency of administration as well as its potential appetite stimulating effects. Maropitant is effective in many cats.

Anti-emetics for use in the cat

Generic name	Brand name	Dose for cats
Chlorpromazine	Thorazine, Largactil	0.5 mg/kg q8h IM
Prochlorpromazine	Compazine	0.1 mg/kg q6h IM
Diphenhydramine	Benadryl	2.0-4.0 mg/kg q8h PO, 2.0 mg/kg q8h IM
Dimenhydrinate	Dramamine, Gravol	8.0 mg/kg q8h PO
Metoclopramide	Reglan	1-2 mg/kg IV CRI over 24hours
Ondansentron	Zofran	0.1-0.15 mg/kg slow push IV q6-12 hours prn
Dolasetron	Anzemet	0.6 mg/kg IV, SC, PO q24h
Mirtazapine	Remeron	2-3 mg PO q72h
Maropitant	Cerenia	0.5-1 mg/kg SC, IV or PO q24 hr for up to 5 days

In the past, it was suggested that bland, low fat, high carbohydrate diets are most suitable however, there is no research done to support this recommendation that the author is aware of. Cats, being obligate carnivores, don't normally utilize carbohydrates well. The goal should be to feed a balanced, non protein-restricted diet. Ensure that the cat receives 50 kcal/kg ideal weight/day.

Modification of gastric acidity has been advised; the gastric pH can be checked by measuring pH of vomitus or by gastric suctioning. An H2 blocker, such as famotidine (0.5 mg/kg PO, IV q24h) or a proton pump inhibitor, such as omeprazole (0.5-1.0 mg/kg PO q24h) may be used.

Antibiotics are indicated if the diagnosis of a suppurative pancreatitis has been made. In this case, antimicrobial selection is best made with the knowledge of a sensitivity spectrum. Note that a suppurative pattern may be seen on histology in a sterile pancreatitis caused by enzyme damage. In patients with ANP, broad-spectrum antibiotics should be utilized before culture results are known to prevent bacterial translocation. Based on Simpson's work with culture-independent bacterial identification (FISH probes), antimicrobials may have a place in therapy of AP as well.

Corticosteroids are indicated if a lymphocytic/plasmacytic form is reported or in an acute shock presentation. For most cats with pancreatitis, the attempt is made to reduce inflammation and fibrosis. Prednisolone +/- metronidazole therapy is warranted for this. As with IBD and lymphocytic cholangitis, maintenance dietary and medical therapy is needed to interrupt the escalation of inflammation.

While pancreatic enzymes are not indicated other than in the rare case of feline exocrine pancreatic insufficiency, they are used in some human pancreatitis patients in order to reduce pain through feedback to the pancreas inhibiting further enzyme release (and leakage). Whether this is the case in cats is unknown. No benefits have been seen with the use of anticholinergics, GI hormones (somatostatin, glucagon), or calcitonin. Dopamine has been useful in acute experimental feline pancreatitis. Fresh frozen plasma may be considered in cats with severe pancreatitis to replace plasma proteases, albumin and alpha 2 macroglobulins. An interesting case

report describes using a synthetic protease inhibitor in addition to these agents. Its action is to inhibit thrombin, plasmin, trypsin and other agents.

The prognosis depends on the type, duration and severity of the disease. Many cats have chronic, low-grade smoldering pancreatitis and live long lives, but do better with diagnosis and appropriate therapy.

References available upon request