PANCREATITIS IN DOGS AND CATS

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Pancreatitis is a relatively common diagnosis in dogs and is being diagnosed with increasing frequency in cats. The true incidence of pancreatitis in dogs and cats is uncertain. It is likely that many cases are missed and, conversely, pancreatitis may sometimes be diagnosed incorrectly in patients with other gastrointestinal diseases.

Pathophysiology

The fundamental mechanism of disease in pancreatitis is autodigestion of pancreatic tissue by digestive enzymes that are prematurely activated within the pancreatic acinar cells. Normally, pancreatic digestive enzymes are released from the pancreas as inactive precursor zymogen granules. Trypsinogen within these granules is proteolytically cleaved and activated when it reaches the duodenal lumen by an enzyme called enteropeptidase (previously named *enterokinase*). The newly-formed trypsin is then able to activate other zymogens in the duodenal lumen by proteolytically cleaving from each of them a small amino terminal peptide called the 'activation peptide'. In acinar cells, the developing granules are normally kept strictly separated from lysosomes, where they might inadvertently get activated. In many experimental models of acute pancreatitis, zymogen granules fuse abnormally with lysosomes inside acinar cells leading to inappropriate intra-pancreatic activation of the zymogens. Lysosomes contain proteases that, at low pH, are capable of activating the zymogens. For protection, the pancreas contains trypsin inhibitors. Also, trypsin can auto-catalyse its own degradation, further enhancing safety. However, the inhibitor present in zymogen granules is not active at the low pH present in lysosomes. If the zymogen activation process proceeds too vigorously, pancreatitis can result.

Pancreatitis can have severe systemic effects because activated proteolytic enzymes can circulate and cause damage distant from the pancreas. There are plasma protease inhibitors (*e.g.,* alpha-macroglobulins and alpha-1-proteinase inhibitor) that bind and inactivate circulating proteases and lead to their rapid clearance from circulation by the mononuclear phagocyte system. Unfortunately, these plasma protease inhibitors can be used up and overwhelmed in severe pancreatitis. This is one reason why fresh-frozen plasma transfusions can sometimes be life-saving in severe pancreatitis.

Some of the ways in which pancreatitis can be reproduced experimentally include: 1). hyper-stimulation of secretion; 2). obstruction of the pancreatic duct; and 3). retrograde, intraductal injection of bile or duodenal enzymes. These mechanisms may also be relevant in clinical situations. For example, in high-rise syndrome of cats retrograde flow of duodenal contents into the pancreatic duct may occur. Alternatively, blunt trauma to the pancreas may lead to ischaemic damage and consequent pancreatitis. In cats, viscous bile may lead to extra-hepatic bile duct obstruction (EHBDO). You may recall that the pancreatic duct joins the bile duct before entering the duodenum in cats. This means that biliary diseases more readily extend to involve the pancreas in this species.

Aetiology

In many patients with pancreatitis, the underlying cause for development of the disease is never determined. Some risk factors that are well recognised, but not necessarily well understood, include:-

- Ductal obstruction;
- Hyperlipidaemia (*e.g.,* familial forms);

- Dietary indiscretion (*e.g.,* a recent very fatty meal);
- Physical trauma (*e.g.,* high-rise syndrome, blunt abdominal trauma, surgery);
- Hypercalcaemia;
- Ischaemia / reperfusion / hypoxaemia (*e.g.,* gastric dilatation-volvulus, profound anaemia);
- Various drugs and toxins (*e.g.,* organophosphates, azathioprine, L-asparaginase, tetracycline potassium bromide); and
- Infections / infestations (*e.g.,* Toxoplasmosis, FIP, hepatic fluke [*Amphimerus pseudofelis*]).

In cats, as previously mentioned, pancreatitis commonly accompanies cholangitis / cholangiohepatitis and inflammatory bowel disease (IBD). In dogs, pancreatitis is thought to be more common in obese animals.

Diagnosis

Pancreatitis is most common in middle-aged and older dogs that are often overweight. In cats, a much wider age range may be affected. Dogs with acute pancreatitis usually have vomiting, abdominal pain, depression and sometimes fever and diarrhoea. Peracute disease may be associated with stupor, collapse and rapidly progressive deterioration in haemodynamic status. Signs of disseminated intravascular coagulation (*e.g.,* petechiae, ecchymoses) may develop within hours. In subacute or chronic cases, a cranial abdominal mass may be palpable after one or two days. This can sometimes be quite firm, and may be associated with peripancreatic fat saponification.

Cats usually have less obvious clinical signs than dogs. Lethargy, anorexia and weight loss predominate. The disease can also vary enormously in severity. Vomiting and abdominal pain are absent in a majority of affected cats.

Radiography may be helpful in dogs, but only in a minority of affected patients. There may be increased radiopacity and reduced contrast in the right cranial abdomen (with a so-called 'ground glass' appearance). The descending duodenum may be displaced to the right and have some gas in it. This gas may be persistently present on more than one radiograph. Sometimes the gas within the duodenum reveals a corrugated 'angry' appearance to the descending duodenum, or the impression of thickened duodenal walls. Similar changes may also be detected in the ascending/transverse colon.

Animals were severe pancreatitis may have a small pleural effusion, more likely to be observed on the right side.

Ultrasonography can be highly specific for diagnosis of pancreatitis in the hands of an expert operator, but sensitivity is rather low. It ranges from 70% in dogs to as low as 30% in cats. Ultrasonographic diagnosis of pancreatitis is particularly challenging in cats because many have mild or chronic morphological changes. Contrast enhanced computed tomography in cats has been reported to be even less sensitive than ultrasonography for the detection of pancreatitis.

Peripheral blood neutrophilia, often with a left shift, is a common feature of pancreatitis. Thrombocytopenia, if present, may be evidence of developing DIC. Azotaemia may be present. It may be prerenal or renal, since pancreatitis can induce secondary acute renal failure. This form of acute renal failure can resolve if the pancreatitis is successfully managed. Liver enzymes are usually increased as a consequence of local inflammation and flow of toxins in venous blood from the inflamed pancreas to the liver. EHBDO may develop because of external pressure on the common bile duct. This can lead to hyperbilirubinaemia, hyperbilirubinuria and sometimes jaundice. Cholestasis of sepsis may contribute to hyperbilirubinaemia and jaundice in some patients. Hyperglycaemia may be present as a

result of stress and, in some patients, islet cell destruction. Hypoalbuminaemia and hypocalcaemia may develop. Low blood calcium may only reflect the albumin concentration or may be a consequence of calcium consumption in the formation of peripancreatic soap. Hypoalbuminaemia may be a consequence of systemic inflammation. Albumin may also be lost from leaky blood vessels into the extracellular space and into 'third spaces' (*e.g.,* peritoneal cavity, pleural cavity) as a result of pancreatitis-induced vasculitis. Hyperlipidaemia may be present despite anorexia and may interfere with a measurement of many other serum biochemical analytes.

Serum amylase and lipase have been used for many years in the assessment of suspected pancreatitis. Unfortunately, they are far from ideal for this purpose. In one study, the sensitivity and specificity of elevated serum amylase for detection of canine pancreatitis were 62% and 57%, respectively. For elevated serum lipase the sensitivity and specificity were 73% and 55%, respectively. In pancreatitis, these enzymes may become depleted or their synthesis may be disrupted. This may explain the poor sensitivity values and also why the severity of clinical disease does not correlate well with the degree of enzyme elevation. The poor specificity values may be explained by sources of enzyme outside the pancreas, failure of clearance of serum enzyme in renal failure and glucocorticoid-induced increases in serum lipase activity, in the absence of pancreatitis. In contrast, glucocorticoids are reported to decrease serum amylase activity.

Measurement of amylase and lipase activities in peritoneal fluid, or fluid obtained by peritoneal lavage, has been suggested and is used by many clinicians. Whether it provides advantages over measuring serum activities is uncertain.

In cats, measurement of serum amylase and lipase activities has been shown to have no diagnostic usefulness.

Serum trypsin-like immunoreactivity (TLI) is familiar to many companion animal veterinary nurses because it is used in the diagnosis of canine (and more recently feline) exocrine pancreatic insufficiency. Unfortunately, TLI is an insensitive way of assessing dogs and cats with naturally-occurring pancreatitis. Elevated levels were observed in less than 40% of dogs and 30-60% of cats with naturally-occurring pancreatitis. It has high specificity, except in azotaemic cats.

A relatively new kind of test detects serum pancreatic lipase immunoreactivity in both cats (fPLI) and dogs (cPLI). Unfortunately, few laboratories are able to carry out these analyses. However, many clinical pathology labs are willing to forward samples to the labs that do it. The reference range for serum cPLI is reportedly 2.2–102 µg/L. Using a cut-off value of 200µg/L, the test was 82% sensitive and 100% specific. In cats, fPLI detection is reported to be sensitive and specific in the diagnosis of pancreatitis.

Treatment

In severely affected patients this can be very challenging. Here as a summary of things to consider in most cases:-

- Removal of any identified underlying cause
- Analgesia
- Intravenous crystalloid fluid therapy, with monitoring of electrolytes and acid-base status in severely ill patients
- Insulin if diabetic
- Plasma or whole blood transfusion in severely ill patients
- Control of vomiting
- Offer water and if vomiting does not follow, provide enteral nutrition with a fat-restricted, highly digestible food. In cats, tube feeding is likely to be needed.

EXOCRINE PANCREATIC INSUFFICIENCY (EPI)

EPI is uncommon to rare in cats and much better characterised in dogs. In cats, it is most often caused by chronic pancreatitis.

In dogs, EPI may arise because of selective loss of pancreatic acinar cells (PAA), chronic pancreatitis and, less commonly, pancreatic hypoplasia or pancreatic neoplasia. By far the most common cause is PAA.

PAA results from selective destruction or loss of the pancreatic acinar cells with consequent failure to produce and secrete pancreatic digestive enzymes. This results in clinical signs of voluminous, fatty stools, weight loss and (typically) ravenous hunger. Coprophagia may be a feature. Diabetes mellitus is not a feature.

PAA is most common in German shepherd dogs and, to a lesser extent, in Rough collies. In these breeds, lymphocytic infiltration of the pancreas has been detected before overt pancreatic insufficiency develops. It is therefore thought that this disease may be immune-mediated or, indeed, autoimmune. For this reason, the name PAA (which stands for pancreatic acinar *atrophy*) should perhaps be discarded and replaced with a name that more accurately describes the suspected underlying pathogenesis.

Diagnosis

The typical clinical picture is of a young German shepherd dog with pale, voluminous faeces, ravenous hunger and weight loss. Flatulence and intermittent diarrhoea may be reported. The hair coat may be dull.

Routine blood work does not provide a specific diagnosis. ALT is often elevated. This is thought to be a consequence of increased gastrointestinal toxins reaching the liver, perhaps as a consequence of small intestinal bacterial overgrowth (SIBO).

Measurement of serum trypsin-like immunoreactivity (TLI) has become the standard way of diagnosing EPI. An abnormally low level (<2.5ng/L in dogs) is found in affected animals. A fasting serum sample is required (12 hour fast) to avoid confusion that may be caused by release of small amounts of enzyme into the blood during feeding (if the animal has any residual pancreatic secretory capacity). The test has excellent sensitivity and specificity and high positive and negative predictive values when applied to patients with a compatible clinical picture. Occasionally, a 'grey area' result will be obtained (2.5–5.0 ng/L). Repeat evaluation is recommended in these cases. Sometimes such dogs go on to produce clearly positive results but more often the TLI level will subsequently be found to be normal. Sometimes such animals will remain persistently in the 'grey area'. These animals may have chronic, grumbling pancreatitis with marginal exocrine secretory capability. In a non-German shepherd dog with clinical signs strongly suggestive of EPI, a single normal TLI value cannot be used to rule out a diagnosis of EPI. Such dogs may have chronic pancreatitis causing EPI. Pancreatitis tends to cause elevation of serum TLI whereas EPI, as previously stated, lowers it. In dogs that have chronic pancreatitis as the underlying cause of their EPI, these opposing influences make it impossible to predict what TLI value will be obtained on any given day.

There are some other diagnostic tests that can be used for diagnosis of EPI (*e.g.,* faecal proteolytic activity, faecal elastase activity), but these have been largely superseded by TLI. Small intestinal bacterial overgrowth (SIBO) often complicates EPI. Serum cobalamin (vitamin B_{12}) can be measured and a vitamin supplement provided it is found to be low. Serum folate can also be measured or, alternatively, it may be appropriate to assume that SIBO is present and treat accordingly.

Treatment

As mentioned above, PAA seems to be an immune-mediated disease. Unfortunately, there is no evidence that early immunosuppressant therapy of dogs that may be heading towards PAA-associated EPI (i.e., with biopsy-proven lymphocytic pancreatic infiltration) provides any benefit. Of course, few dogs have been diagnosed and treated at such an early, pre-clinical stage of disease.

Enzyme replacement therapy is indicated for EPI. Various enzyme extracts are commercially available. Powdered, non-enteric-coated supplements are recommended (~ 1 teaspoon added to each meal). Enteric-coated forms are reported not to work so well, because they are retained in the stomach. Alternatively, in some countries, it is legal to purchase and use raw pancreas to treat EPI.

H2 receptor antagonists can be used if response to enzyme supplementation is poor. These antacid drugs may increase the amount of enzyme supplement that survives passage through the stomach. Pre-incubation of soft food with enzyme supplements has been advocated, but whether it provide any benefit is uncertain.

A highly digestible, low fibre, moderate fat food may be helpful in some patients but many animals do not need to be fed a special diet. Fat restriction may be advisable because enzyme supplementation is insufficient to match normal lipase production.

Antibiotic therapy (*e.g.,* tetracycline, metronidazole) can be used in selected animals in which SIBO is demonstrated or strongly suspected. If response to enzyme supplementation alone is satisfactory, antibiotic is not needed.

In some dogs with EPI, cobalamin deficiency can be demonstrated. Enzyme supplementation should not be expected to resolve this problem. Parenteral supplementation (250-500µg/dose) and monitoring of serum levels may be necessary.

Prognosis

There is usually a prompt response to therapy with improved faecal consistency, decreased polyphagia and weight gain. Treatment must be continued indefinitely and can be too expensive for some clients. Over the long term, it has been reported that approximately 50% of dogs can be rendered essentially normal. 20% have a relatively poor response. Euthanasia is carried out in about 20% of cases during the first year after the diagnosis is made. The cost of treatment and/or poor response to treatment are thought to be the reasons why euthanasia is chosen.

Other pancreatic diseases of dogs and cats

There are numerous other kinds of exocrine pancreatic disease that are relatively uncommon. These include:-

- pancreatic pseudocyst;
- pancreatic abscess;
- exocrine pancreatic neoplasia;
- pancreatic parasites; and
- nodular hyperplasia.

Further reading

Steiner JM, Williams DA. Feline exocrine pancreatic disease. In: S.J. Ettinger & E.C. Feldman (Eds.) *Textbook of Veterinary Internal Medicine, Sixth Edition*. St Louis, Mo: Elsevier/Saunders, 2005; 1489-1492.

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