TRIADITIS

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DEFINITION AND STATEMENT OF THE PROBLEM

The term triaditis denotes an often cited but poorly
documented syndrome of concurrent cholangitis,
pancreatitis, and inflammatory bowel disease in cats.
The association of these entities may indicate a common
underlying disease mechanism. Ascending bacterial
infection from the duodenum into the liver and pancreas
may cause parenchymal inflammation in these organs;
while, inflammatory bowel disease may occur as a
consequence of aberrant host immune responses to
luminal bacteria. It is reported that in most cases of
triaditis, the predominant signs are attributable to
hepatobiliary disease, with pancreatitis and IBD
occurring as secondary complications.1

FELINE INFLAMMATORY DISEASE AS INDIVIDUAL
COMPONENTS

Pancreatitis
Pancreatitis denotes inflammation of the pancreatic
parenchyma classified temporally, by cause, or by
severity. Acute and chronic pancreatitis cannot be
differentiated clinically and may be mild or severe;
however, chronic cases are more commonly mild and
acute cases are more commonly fulminate. The inciting
cause of feline pancreatitis is usually unknown, but a
variety of potential risk factors have been identified
including parasites (Toxoplasma gondii, Amphimerus
pseudofilineus), blunt trauma, ischemic, and intercurrent
disease (particularly hepatobiliary disease). Regardless
of cause, pancreatitis is due to autodigestion of the
pancreas by prematurely activated digestive enzymes,
most importantly proteases and phospholipases.

History and clinical signs in cats are variable. Most
cats with severe disease will present with lethargy and
anorexia while vomiting and abdominal discomfort are
less common. Mild chronic pancreatitis may be
subclinical and may also cause anorexia and weight loss.
A clinical (e.g., antemortem) diagnosis of pancreatitis is
elusive. Changes in the complete blood count and
serum biochemistry profile are often mild and
nonspecific. Elevations in hepatic enzymes (ALP, ALT)
are common in severe cases and may indicate
concurrent hepatic lipidosis, cholangitis, and/or extra-
hepatic biliary obstruction. Diagnostic imaging may show
increased soft-tissue opacity and/or diminished
abdominal detail in the right cranial compartment.
Abdominal ultrasonography is more sensitive for
pancreatitis and may detect hypoechoic changes in the
parenchyma consistent with inflammation. An assay for
serum feline pancreatic lipase immunoreactivity (fPLI)
has recently been developed and appears highly
sensitive and specific as a serologic marker for
pancreatitis. Histopathology of pancreatic biopsy
confirms pancreatic inflammation.

Treatment of pancreatitis is broad-based and includes
maintenance of fluid/electrolyte balance, reduction of
pancreatic secretions, and symptomatic medical
therapies. Analgesic therapy may be required to provide
relief of pain and to facilitate patient recovery. Special
consideration should be given to nutritional support as
many cats with pancreatitis have histories of anorexia;
and, hepatic lipidosis may occur as a secondary
complication. Cats that do not vomit should be offered a
low-fat diet orally if tolerated. In anorectic animals,
enteral nutrition via nasogastric, esophageal,
gastrostomy, or percutaneous jejunostomy tube
(preferred) are reasonable and practical means of
alimentation. Avoid the use of antimicrobial agents
unless evidence of sepsis, an inflammatory leukogram,
or fever is present. The prognosis for cats with
pancreatitis is directly related to the severity of the
disease, concurrent complications, and tolerance to oral
alimentation.

Feline Cholangitis

A new classification scheme proposed by the WSAVA
liver disease standardization group recognizes three
distinct forms of cholangitis in cats. Under this new
classification scheme, cholangitis is used in preference
to cholangiohepatitis since disruption of the limiting plate
is not always a feature. The etiology for suppurrative
cholangitis is unknown but may involve causative factors
such as bacterial infection. One hypothesis suggests
that the bile duct and major pancreatic duct, which form
a common tract entering the duodenum, may predispose
cats to inflammatory hepatic disease. This connection
might favor the ascension of luminal bacteria or the
entrance of pancreatic enzymes into the biliary tract.
Lymphocytic cholangitis is postulated to be immune-
mediated in origin. Histologically, there is moderate to
marked infiltration of portal areas by small lymphocytes.

Lymphocytic cholangitis occurs primarily in middle-
aged cats with chronic (>3 weeks) signs. Recurrent
signs are often interspersed with weeks or months or
normalcy, with abnormal or even increased appetites.
Cats are often less ill than those with the acute
neutrophilic form. The following clinical signs are most
commonly observed: 1) intermittent episodes of
inappetence or anorexia and lethargy; 2) weight loss;
3) fever with neutrophilic cholangitis; 4) ascites is
sometimes observed with lymphocytic cholangitis.

Diagnosis of cholangitis is based on routine diagnostic
parameters. Biochemical liver parameters show high
ALT, ALP, and total bilirubin concentrations. Increased
plasma globulin and decreased albumin are often
present in the lymphocytic form. Biliary obstruction
should be suspected in cats with lethargy, intermittent
fever and progressive jaundice. Definitive diagnosis
requires histologic evaluation of liver biopsy specimens.
Perform coagulation tests (ACT or APTT/OSPT or
PIVKA) prior to hepatic biopsy and initiate vitamin K1
therapy if abnormal. Bile and/or liver culture are
recommended in cats with suspected neutrophilic
cholangitis.
Specific treatment is dictated by the results of hepatic biopsy. Neutrophilic cholangitis will require antimicrobial therapy. Lymphocytic cholangitis is often responsive to immunosuppressive drugs. Administer ursodeoxycholic acid for choleretic and modulation of deleterious bile acids. S-adenosyl is recommended to reduce hepato cellular injury. Supportive care may include anticoagulant, fluid, and nutritional therapy. Jejunostomy or gastrostomy tubes are key to successful nutritional management. The prognosis for cholangitis is guarded. The prognosis with neutrophilic cholangitis is less favorable than that for the lymphocytic form. Cats with lymphocytic cholangitis may survive for months to years.

Feline Inflammatory Bowel Disease (FIBD)

FIBD is an important disease characterized by persistent gastrointestinal signs, histologic evidence of mucosal inflammation, and general responsiveness to immunotherapeutic intervention. It is considered to be one of the most common histologic diagnoses obtained in cats with chronic vomiting or diarrhea. The etiology for FIBD is unknown. Recent studies suggest interactions between the mucosal immune system, host genetic susceptibility and environmental factors (e.g., normal microflora). FIBD may occur as a consequence of aberrant host immune responses to the luminal resident microflora ultimately resulting in a loss of mucosal tolerance. Clinical signs in cats are related to mucosal cellular infiltrates and the effects of diverse inflammatory mediators. GIT signs are usually cyclical and predominantly reflect the organs of involvement. Chronic diarrhea, vomiting, anorexia, lethargy, and weight loss are indicative of small or large intestinal inflammation. Protein-losing enteropathy may occur in some cats with severe disease. Physical examination is often unremarkable with the exception of weight loss in some cats. Laboratory abnormalities are usually mild and nonspecific but may include alterations in protein concentrations, elevations in hepatic enzyme activities, and minor electrolyte disturbances with chronic vomiting. A diagnosis of FIBD is one of exclusion and requires ruling out many other diseases that cause intestinal inflammation. Systemic disease, chronic parasitism, dietary sensitivity (e.g., food responsive disorders), infectious diseases, and alimentary lymphosarcoma are the major differential diagnoses for FIBD. Clinical criteria for the diagnosis of FIBD have been described: 1) persistent GIT signs; 2) failed responses to dietary trials alone; 3) exclusion of other causes for GIT inflammation; 4) histopathological evidence of mucosal inflammation. Unfortunately, no standard microscopic grading system for defining IBD lesions has been established. Biopsy interpretation remains very subjective and is further hampered by the technical constraints of specimen size, procurement artifacts, and processing limitations inherent in the diagnostic evaluation of endoscopic specimens.

Treatment of FIBD includes the use of elimination diets, dietary fiber supplementation for IBD colitis, and administration of anti-inflammatory/immunosuppressive drugs. Well-designed therapeutic trails have not been performed and therapy remains largely empirical. The prognosis for control of FIBD is good to excellent in the vast majority of cases. Following completion of drug therapy, most animals are able to maintain remission with diet alone. Treatment failures are uncommon and usually due to an incorrect diagnosis, presence of severe disease, poor client compliance with drug/dietary recommendations, and/or the presence of concurrent disease such as antibiotic response diarrhea or hepatobiliary disease.

FELINE INFLAMMATORY DISEASE AS COMBINED COMPONENTS

Published data supporting the simultaneous association between cholangitis, pancreatitis, and FIBD is sparse:

1) Weiss et al\(^6\) reported a relationship between inflammatory hepatic disease and IBD, pancreatitis, and interstitial nephritis in 78 cats at necropsy. The prevalence of IBD (83%) and pancreatitis (50%) was greater in cats having cholangiohepatitis compared with cats without inflammatory hepatic disease. Pancreatitis was mild in all cats. The authors concluded that cats with cholangiohepatitis should be evaluated for concurrent IBD and pancreatitis, although the temporal relationship between disease entities could not be determined.

2) Ascending infection from the intestine is believed to be an important predisposing factor in the development of pancreatitis.

3) Pancreatitis has been recognized in combination with lymphocytic cholangitis although previous reports do not reveal documented evidence of an association.\(^3\)

4) Feline IBD may be associated with increases in liver enzyme activities and with histologic evidence of liver injury. Breached mucosal epithelial integrity subsequent to mucosal inflammation (IBD) may permit inflammatory mediators, endotoxins, and microbial components access to the portal circulation and exceeding the capacity for hepatic Kupffer cells to remove and degrade them. The net result is the deposition of immune complexes in the liver, complement system activation, and hepatocellular necrosis. Additionally, gut permeability changes may allow the passage of select bacterial- and colonic epithelial cell-antigens which promote production of autoreactive antibodies that damage the liver.\(^4\)

5) Simpson et al\(^5\) reported the simultaneous presence of inflammatory disease of the intestines (most cats having IBD), pancreas, or hepatobiliary system in 22/49 cats with subnormal concentrations of cobalamin.
In this retrospective study, diagnosis of gastrointestinal inflammation was made by a combination of histopathologic, ultrasonographic, and select serologic (feline TLI assay) parameters.

(6) In separate studies, Akol et al\textsuperscript{6} and Hill et al\textsuperscript{7} report on the association between hepatobiliary disease and pancreatitis occurring concurrently in cats. In the former study, cats with both acute pancreatitis and hepatic lipidosis were observed to have a poorer prognosis in comparison to cats having lipidosis alone. Comparative data defining intestinal inflammation in these cats was not reported. In Hill’s study, only a postmortem diagnosis of acute pancreatitis or pancreatic necrosis was established for selection of cases. This excluded milder forms of acute pancreatitis and biased toward a fatal form of the disease. Interestingly, these same investigators showed no relationship between acute pancreatitis and cholangiohepatitis (as well as nephritis for that matter) in the cats of their study.

**FELINE TRIADITIS – THE CURRENT PERSPECTIVE**

While superficially there would appear to be an abundance of evidence supporting simultaneous inflammation in feline gastrointestinal tissues, critical appraisal of the literature does not necessarily substantiate this claim. Most studies to date have been retrospective in nature, focused on distinct subsets of feline patients, utilized less advanced diagnostic tools for specific diseases, and/or have not demonstrated a distinct temporal relationship between pancreatitis, cholangitis, and FIBD – namely that they occur simultaneously. Nevertheless, these earlier reports do have merit. They have further defined the individual components of triaditis to a greater extent and they do provide some relevant, evidence-based observations. Taken together, they suggest a reasonable association between feline liver disease (predominantly inflammatory in nature) and pancreatitis; although their association with FIBD is considerably less well-defined in the literature. The inability to fully document the role of FIBD in this syndrome is not surprising given the controversy surrounding the histopathologic evaluation of endoscopic biopsy specimens. With the exception of Weiss et al\textsuperscript{2}, objective histologic grading criteria for a diagnosis of FIBD were not described by other authors. A WSAVA (World Small Animal Veterinary Association) subgroup is presently working to develop standardized guidelines for GIT endoscopic procedures and the histopathologic evaluation of endoscopic biopsy specimens.

**References**