

Chronic Diarrhea in Cats

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Feline inflammatory bowel disease

Feline inflammatory bowel disease (IBD) is the term applied to a group of poorly understood intestinal disorders that are associated with vomiting, diarrhea and weight loss in cats. Diagnosis is usually based upon subjective analysis of intestinal mucosal biopsies and qualified according to the dominant mucosal infiltrate, typically lymphocytes and plasma cells. However, more objective studies have demonstrated increased expression of MHC class II antigen by leukocytes in the lamina propria and enterocytes, and upregulation of pro-inflammatory and immunoregulatory cytokines, rather than an increase in mucosal cellularity. Abnormalities in mucosal architecture, such as crypt distortion, villous blunting and fusion, and fibrosis have also been described, and have been associated with the severity of clinical signs, and the subjective histological grade of IBD. The cause of feline IBD has not been determined, but it is suspected that IBD in cats, like IBD in people, is a consequence of uncontrolled intestinal inflammation in response to a combination of elusive environmental, enteric microbial, and immunoregulatory factors in genetically susceptible individuals. Genetic susceptibility in people is linked increasingly to defects in innate immunity, exemplified by mutations in the innate immune receptor NOD2/CARD15, that in the presence of the enteric microflora may lead to up-regulated mucosal cytokine production, delayed bacterial clearance and increased bacterial translocation, thereby promoting and perpetuating intestinal inflammation. This possibility is supported by studies showing the pivotal importance of the enteric microflora in the development of IBD in rodents with engineered susceptibility and those demonstrating an abnormal mucosa-associated flora, considered to interact most closely with the innate immune system, in people with IBD. Knowledge of genetic susceptibility in cats with IBD is limited, with some studies reporting a predisposition for purebred cats such as Simease. Culture based studies have shown fewer luminal microaerophilic bacteria in the duodenal juice of cats with clinical signs of gastrointestinal disease than healthy cats. More recent studies have revealed changes in the intestinal microflora of cats with chronic gastrointestinal disease, termed dysbiosis. The number of mucosa-associated Enterobacteriaceae was higher in cats with signs of gastrointestinal disease than healthy cats ($P < 0.001$). Total numbers of mucosal bacteria were strongly associated with changes in mucosal architecture ($P < 0.001$) and the density of cellular infiltrates, particularly macrophages ($P < 0.002$) and $CD3^+$ lymphocytes ($P < 0.05$). The number of Enterobacteriaceae, *E. Coli*, and *Clostridium* spp. correlated with abnormalities in mucosal architecture (principally atrophy and fusion), upregulation of cytokine mRNA (particularly IL-1, -8 and -12), and the number of clinical signs exhibited by the affected cats. These data establish that the density and composition of the mucosal flora is related to the presence and severity of intestinal inflammation in cats, and suggest that mucosal bacteria are involved in the etiopathogenesis of feline IBD.

A stepwise approach to treating feline inflammatory bowel disease

How confident am I the cat has IBD?

- Clinical findings
- Clinicopathological tests
- Diagnostic imaging
- Intestinal biopsy

Have I ruled out

- Systemic/ metabolic disease
- Dietary intolerance/ food allergy
- Infectious agents
 - Protozoa
 - *Giardia*
 - *Tritrichomonas*
 - Pathogenic bacteria
 - *Campylobacter* / *Salmonella*
 - Viral?
- Structural/anatomic abnormalities
- Does the cat have multiple problems or organ systems involved?
- Is the cat deficient in cobalamin or folate?
- Do I need a biopsy?
- What and how should I biopsy?
- How do I interpret the biopsy results and integrate gastric and intestinal histopathology?
- Is it IBD or small cell lymphoma?

- What diet should I use?
- When should I use antimicrobials? corticosteroids? chlorambucil?
- How do I manage concurrent disease in the liver and pancreas?
- How do I assess response?

An overview of diagnosis and treatment

Clinical findings

Vomiting is the most common clinical sign in cats with IBD. Vomitus often contains bile. Other findings include diarrhea, changes in appetite, weight loss and less commonly excessive borborygmi and abdominal discomfort.

The severity of disease ranges from intermittent vomiting in mild cases to intractable small bowel diarrhea, inappetence and weight loss in severe ones. The severity of the disease correlates with the degree of intestinal damage, particularly villus atrophy and fusion

Physical findings range from normal to thickened intestines, mesenteric lymphadenopathy and loss of muscle mass. Ascites or edema are extremely rare in cats with IBD.

Routine laboratory testing may reveal mild to moderately elevated liver enzymes as a result of GI barrier dysfunction. However, IBD can be associated with concurrent hepatobiliary disease and pancreatitis- “triaditis”- so the clinician must consider these disorders (Ultrasonography and fPLI aid detection of intercurrent disease). The presence of hypocalcemia would ring alarm bells for pancreatitis. Hypoalbuminemia is rare. CBC is usually normal. Eosinophilia is encountered in some cats with LP enteritis, and should prompt consideration of parasites or food intolerance/allergy, as well as mastocytosis or hypereosinophilic syndrome. Measurement of serum cobalamin and folate can aid the detection of intestinal disease- low cobalamin concentrations are common in cats with IBD (EPI should be excluded by TLI assay). Cobalamin deficiency can produce identical signs to those associated with IBD. A combination of low folate and cobalamin tends to support a diagnosis of severe IBD or GI lymphoma.

Ultrasonographic findings in cats with IBD overlap with those of cats with lymphoma i.e. muscularis hypertrophy and mesenteric lymphadenopathy

Diagnosis

A diagnosis of idiopathic IBD is made by excluding systemic, parasitic, infectious, pancreatic and structural causes of chronic vomiting, weight loss or diarrhea and demonstrating histopathological abnormalities in intestinal biopsies. Keep in mind that IBD may co-exist with hepatobiliary disease and/or pancreatitis.

Treatment

Treatment of IBD is usually a “best guess least harm” approach employing dietary modification, vitamin supplementation, antimicrobial agents and immunosuppression. Treatment is to some extent based on the severity of the disease.

Mild to moderate disease may be associated with dietary sensitivity / intolerance, cobalamin deficiency or antibiotic responsive enteropathy.

A therapeutic dietary trial can be performed with either: 1) a highly digestible diet which is gluten-free, 2) a diet limited to a single novel protein source or 3) a diet containing protein hydrolysate, to determine if dietary sensitivity or intolerance are present. A response is usually observed within one to two weeks. Re-challenge with the original diet is required to demonstrate intolerance.

Cobalamin deficiency is treated with parenteral cobalamin (0.5ml SC q 2-3wks). Folate should be given orally if serum concentrations are low.

A therapeutic trial (21 days) with Tylosin (10mg/kg PO TID), metronidazole (15mg/kg PO BID) or oxytetracycline (10-20mg/kg PO TID) can be undertaken to determine if an antibiotic responsive enteropathy is present.

In patients who fail these trials and in those with moderate to severe disease, or hypoproteinaemia, immunosuppressive agents are usually added to achieve a response. Oral prednisolone (1-2mg/kg PO BID) is the initial drug of choice. It is usually administered at an immunosuppressive dose for 2-3 weeks and then decreased by 50% every 2-3 weeks, and continued on an alternate day basis for 2-3 months. If clinical response is poor, chlorambucil (6mg/m² PO PO EOD (@2mg/5.3kg cat) and prednisone (5mg PO /cat/day) are initiated. Metronidazole (15mg/kg PO BID 10-14d then SID 10-14d) is frequently used in conjunction with corticosteroids to modify the microflora. However metronidazole is a potential mutagen and the author avoids long-term therapy.

Successful treatment is accompanied by a decrease in clinical signs, and an increase in plasma proteins (though low albumin is uncommon in IBD). Once a patient has had 2-3 months remission from signs it may be possible to gradually withdraw immunosuppressive therapy. If signs recur daily medication is continued until signs resolve then gradually reduced. In patients who respond poorly to therapy or relapse after an initial response lymphoma should be ruled out.

Prognosis

The prognosis for lymphoplasmacytic enteritis is variable and depends on its severity and the presence of concurrent disease. Many patients require prolonged treatment with glucocorticoids and diet. As no accurate criteria exist for predicting response it is wise to give a guarded prognosis.

Alimentary lymphoma

The changing and variable phenotype of feline alimentary lymphoma:

Lymphomas represent up to ninety percent of hematopoietic tumors in the cat and are one of the most frequently diagnosed tumors of domestic cats. During the feline leukemia virus (FeLV) era of the 1960s through the 1980s, FeLV was the most common cause of up to 70% of cases of lymphoma that were predominantly cranial mediastinal, multicentric, renal and central nervous forms, associated with FeLV antigenemia. However, despite a decline in FeLV-associated lymphoma and contrary to expectations the prevalence of lymphoma has increased in the post-FeLV era, and there has been a change in the frequency of affected anatomic sites and patient demographics. Alimentary lymphoma is now the most common anatomic form and predominantly affects middle age to older cats, in contrast to mediastinal or multicentric lymphoma that typically affect younger cats. This increase in alimentary lymphoma has also been accompanied by a change in immunophenotype, from predominantly high grade B cell to predominantly low grade T cell. In a study of 41 cats with low-grade lymphocytic lymphoma evaluated at the Cornell University Hospital for Animals and South Carolina Veterinary Internal Medicine between 1995-2005, the median age at diagnosis was 13 years 148 (range, 6-17 years) and 40/41 were Domestic Shorthair (n = 33) or Domestic Longhair (n = 7). Lymphoma was confined to the gastrointestinal tract in 68% of cats and eighty-nine percent (32 of 36) of lymphomas were determined to be of T-cell origin by immunohistochemistry, while 8% (3 of 36) were of B-cell origin. A search of our pathology database for feline alimentary lymphoma during the years 2007 to 2011 yielded a total of 136 small cell lymphoma (SCL) and 16 cases of large cell lymphoma (LCL). The immunophenotype of a randomly chosen subset of 33 of the 136 cats with SCL indicated they were all T-cell. Surprisingly, we found that LCL were divided evenly between T- (8/16) and B-cell (7/6), with one tumor considered B&T-cell. This diversity in cell morphology and immunophenotype has potential implications for etiopathogenesis and treatment, and subsequent studies should be stratified on the basis of tumor immunophenotype and cell morphology.

The response to therapy has also changed, with overall median survival time reaching 704 days in low-grade lymphoma versus weeks to months in high-grade large cell lymphoma. Until, recently the large B cell phenotype predominated in Australia and the UK, but small T- cell phenotype has recently emerged. The sequential temporal emergence of low-grade alimentary lymphoma in the USA, Great Britain and Australia echoes the appearance of feline hyperthyroidism and raises the possibility of an underlying environmental or infectious etiology. The factors responsible for the changes in prevalence, immunophenotype and biology of feline alimentary lymphoma are not known.

Clinical findings

Middle aged and older cats (median 13yrs), predominantly DSH cats are reported. Weight loss, vomiting, chronic small bowel diarrhea and progressive inappetence are common features of GI lymphoma. Physical examination may reveal diffusely thickened or nodular intestines ± mesenteric lymphadenopathy. Hepatosplenomegaly, renomegaly, generalized lymphadenopathy and abdominal mass may also be detected. Acute abdominal pain and shock may be present if intestinal perforation has occurred.

Diagnosis

Routine biochemistry may reveal hypoalbuminemia. Anemia which is either normocytic normochromic non-regenerative or microcytic and hypochromic, and neutrophilia may also be present. Serum concentrations of cobalamin are often very low in cats with GI lymphoma and serum folate concentrations may also be reduced. High PLI concentrations are found in some cats and may indicate concurrent pancreatitis or pancreatic lymphoma. Ultrasound is useful for evaluating intestinal thickness / layering, presence or absence of mucularis hypertrophy, and detecting mesenteric lymphadenopathy and abnormalities in liver/kidney/spleen and pancreas. However it cannot distinguish lymphoma from IBD. Diagnosis can be made by demonstrating neoplastic lymphocytes in aspirates or biopsies from enlarged intestinal or peripheral lymph nodes, but is more often made by intestinal biopsy. The absence of lymphoma in a fine needle aspirate does not rule it out : there is a high degree of discordance between FNA and biopsy results of LN aspirates from cats with confirmed alimentary lymphoma. Endoscopic visualization and biopsy can enable the accurate diagnosis of GI lymphoma. However, endoscopy can also miss submucosal and serosal lesions or yield a diagnosis of "lymphoplasmacytic enteritis". Many cats with signs of intestinal disease including GI lymphoma have concurrent evidence of hepatic and pancreatic disease and undergo exploratory laparotomy and circumvent the endoscopy surgery debate.

Treatment and prognosis

In a recent study of 41 cats with low-grade lymphoma, lymphoma was confined to the gastrointestinal tract in 68% of cats, while 32% had other organ systems affected with or without gastrointestinal involvement. Extra-gastrointestinal sites involved included mesenteric lymph nodes (n = 6), liver (n = 10), spleen (n = 1), and pancreas (n = 1). Some cats had more than 1 site affected. Eighty-nine percent (32 of 36) of lymphomas were determined to be of T-cell origin via immunohistochemistry, while 8% (3 of 36) were of B-cell origin.

Fifty-five per cent of cats achieved a complete response to therapy and 37% achieved a partial response. The majority of cats (n = 31; 76%) received prednisone at a dose of 5 mg, PO, q 12-24 hrs and most (n = 35; 85%) received chlorambucil at a dose of 2 mg, PO, every other day. Eight percent of the cats experienced no response. There was no association between any risk factors and response to therapy. Overall median remission duration was 948 days. Partial response to therapy was associated with shorter remission duration (P = 0.002). Overall median survival time was 704 days. No factors were significantly associated with survival time. Interestingly,

78% of cats tested in this study had hypcobalaminemia, which was associated with short remission duration, but only in the univariable analysis. Thus supplemental cobalamin (0.5ml SC q 2-3wks) and folate should be given as required. Lymphoblastic lymphoma, is much more aggressive than lymphocytic lymphoma, is generally treated with combination chemotherapy, and carries a poor prognosis.

Given the dramatic differences in outcome of lymphocytic vs. lymphoblastic lymphoma is there any way to distinguish these forms of the disease without a biopsy?

In the study of Fondacaro et al clinical signs, physical exam findings and endoscopic localization of disease overlapped in cats with lymphoblastic and lymphocytic lymphoma. Lethargy and the presence of an abdominal mass tended to be more frequent in cats with lymphoblastic lymphoma.

Can I diagnose intestinal lymphoma with an endoscopic biopsy?

Yes and No! Endoscopic visualization and biopsy can enable the accurate diagnosis of GI lymphoma. However, endoscopy can miss submucosal and serosal lesions or yield a diagnosis of "lymphoplasmacytic enteritis". Many cats with signs of intestinal disease including GI lymphoma have concurrent evidence of hepatic and pancreatic disease and undergo exploratory laparotomy circumventing the endoscopy surgery debacle. Diagnosis also depends on the pathologist! Some pathologists are unwilling to diagnose lymphoma on endoscopic biopsies.

How can I distinguish gastrointestinal lymphoma from inflammatory bowel disease?

The signalment, clinical presentation, physical examination and results of clinical investigation are often very similar in cats with IBD and alimentary lymphoma. Hypoalbuminemia is a rare feature of IBD in cats and it's presence makes me think of high grade IBD or lymphoma. Intestinal perforation should place lymphoma high up the list. Concurrent renomegaly or splenomegaly should also prompt consideration of lymphoma and aspiration/biopsy. The presence of intestinal thickening, muscularis hypertrophy and mesenteric lymphadenopathy is consistent with IBD and lymphoma. Moreover, fine needle aspiration of enlarged lymph nodes can yield reactive hyperplasia in cats with GI lymphoma. Endoscopy may reveal marked thickening of the gastric mucosa and increased friability of the intestinal mucosa in cats with lymphoma, but there is an overlap between cats with IBD and alimentary lymphoma. At the present time the accurate distinction of GI lymphoma from IBD relies on histopathological evaluation. This can be relatively straightforward where biopsies are considered adequate in size and number, and unequivocal lymphoblastic cells or a monomorphic population of small lymphocytes are present. However, some biopsies display features of lymphoma and IBD, and others such as endoscopic biopsies do not allow thorough evaluation of all tissue compartments, and make it difficult to distinguish IBD from lymphoma. Immunophenotyping for T and B cell lineage, and PCR to detect clonal expansion of B (feline immunoglobulin heavy chain variable region genes) and T cells (T cell receptor gamma variable region genes) have been developed to aid this process.

What is driving the development of feline alimentary lymphoma?

Low-grade alimentary lymphoma in cats does not appear to be related to FeLV or FIV. There is strong evidence in people that low grade mucosa associated lymphomas develop as a consequence of a genetic predisposition (typically chromosomal translocations that impact mucosal inflammation or apoptosis) and a chronic infections with bacteria and viruses are increasingly associated with lymphoma. In people, infections with *Helicobacter*, *Borrelia*, *Chlamydia* and *Campylobacter* are associated with gastric, cutaneous, periorcular and intestinal B cell MALT-lymphomas, respectively. The observation that 8-13% of people with celiac disease develop non-Hodgkin's enteropathy-associated T cell lymphoma is of high relevance to cats with alimentary lymphoma. Lymphomatous transformation in celiac disease is associated with unresolved chronic lymphocytic inflammation, villus blunting, an IL-6 and IL-8 rich cytokine environment, and global shifts in the enteric polymicrobial environment, towards proteobacteria and *E.coli*. We have established that cats with lymphoplasmacytic enteritis have shifts in mucosal Enterobacteriaceae, *E. coli*, and *Clostridium* spp. that correlate with abnormalities in mucosal architecture (principally atrophy and fusion), proinflammatory cytokine upregulation (IL-1, -8 and -12), and clinical severity, that parallel human coeliac disease. In preliminary studies, we found that the mucosal cytokine environment in feline alimentary lymphoma is dominated by IL-6 upregulation, and have detected invasive bacteria in 14/17 large cell lymphomas (a mix of T and B cell lymphomas) and 6 of 33 small cell lymphomas (T cell) relative to 0/18 controls.

While it is well established that persistent viral infections can drive lymphoma in cats, the relationship of FeLV to alimentary lymphoma in cats is controversial, with discordance between antigenemia (0-38%) and PCR positivity of tissues for viral sequences. It is conceivable that latent FeLV infection drives feline alimentary lymphoma, but this possibility has to be weighed against the falling prevalence of FeLV in the cat population. In people a variety of viruses have been associated with lymphoma including: the γ -herpesvirus Epstein Barr Virus (EBV), which is associated with Hodgkin's lymphoma and various non-Hodgkin's lymphomas, including B-cell lymphoma in immunocompromised patients, Kaposi Sarcoma herpesvirus in individuals with immunosuppressive conditions, Human T-cell Leukemia Virus-I with Adult T-cell leukemia-lymphoma (ATLL), a peripheral T-cell malignancy and Hepatitis C virus (HCV), which has been implicated in the development of some cases of non-Hodgkin lymphoma (NHL). Recent studies have expanded our knowledge of the role that viruses may play in promoting chronic intestinal inflammation, which is a known risk factor for tumorigenesis. A new dimension in understanding the multifactorial basis of chronic inflammatory diseases such as Crohn's disease has emerged from the discovery that a virus trigger (norovirus) is required to observe intestinal abnormalities in IBD susceptible *Atg16l1*^{HM} mice. Mucosal inflammation depended on the presence of the intestinal microbiome and pro-inflammatory cytokines.

Thus, variations in a host autophagy gene, exposure to a specific virus and the microbiome can act together to trigger intestinal inflammation in mice that is similar to that in patients with Crohn's disease.

Taken as a whole, the evidence to date supports the possibility that an underlying bacterial or viral infection could be involved in the etiopathogenesis of feline alimentary lymphoma

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