GI-LYMPHOMA AND IBD IN CATS: PITFALLS AND PROGRESS IN DIAGNOSIS AND DIFFERENTIATION
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Feline lymphoma in general
Lymphoma in the cat represents a diverse group of lesions that vary in cell type, rate of dissemination, and progression. The National Cancer Institute (NCI) Working Formulation (WF) has been used to histologically classify feline lymphomas into low, intermediate, and high-grade categories. The majority of lymphoma in cats has been classified as intermediate (35%) or high (54%) grade and behaves similarly as rapidly progressive diseases that are almost uniformly fatal despite aggressive chemotherapy. Approximately 10% of feline lymphomas are composed of small, relatively well-differentiated, neoplastic lymphoid cells and can be histomorphologically described as low-grade. A recent study describing clinical spectrum of lymphoma since the decline in Feline Leukemia Virus indicates that there has been a progressive rise in the diagnosis of alimentary lymphoma in cats.

The emergence of low grade T-cell alimentary lymphoma
Gastrointestinal lymphoma is typically characterized by the mucosal and sub-mucosal infiltration of neoplastic lymphocytes that may lead to ulceration, perforation, and malabsorption. Focal forms of lymphoma may cause obstruction. While lymphoma has often been related to feline leukemia virus cats with GI lymphoma are usually FeLV negative. Concurrent involvement of the GI tract and the kidney, liver, pancreas or spleen may be observed. In cats GI lymphoma has been classified histologically as B, T and LGL in origin. The relative frequency of each type appears to vary according to geographical location and perhaps the time the study was performed (e.g. before or after the decline in FelV). Studies in Australia and UK report predominantly medium to High grade B cell lymphoma. In contrast recent studies in the US report the predominance of low grade T cell lymphoma, and have presented a simplified approach to categorizing GI lymphoma as lymphocytic (Low grade T cell) or lymphoblastic (generally B cell). This has meaningful clinical application as the low-grade lymphocytic form usually responds very well to chemotherapy.

Clinical findings
Middle aged and older cats, predominantly DSH cats are reported. Weight loss, vomiting, chronic small bowel diarrhea and progressive inappetance 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 TLI or PLI concentrations are found in some cats and may indicate concurrent pancreatitis or pancreatic lymphoma. Ultrasound is useful for evaluating intestinal thickness / layering and detecting mesenteric lymphadenopathy and abnormalities in liver/kidney/spleen and pancreas. 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. 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 hypocobalaminemia, 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.

**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 and mesenteric lymphadenopathy suggests lymphoma but is by no means pathognomonic. 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 causes low-grade small cell 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 infectious stimulus such as *Helicobacter pylori* (gastric MALT). Intratumoral T cells responding to *Helicobacter* antigens are believed to drive the proliferation of B cells, and eradication of *Helicobacter* in early gastric MALT can be curative. Recent studies have shown that chromosomal translocations in pathways that regulate nuclear factor \( \kappa \)B signaling e.g. t(11;18)(q21;q21) which leads to generation of an API2-MALT-1 fusion protein capable of activating nuclear factor \( \kappa \)B, are significant risk factors for the development of MALT in *Helicobacter* infected people. Thus it is plausible that low-grade lymphoma in cats is the result of a chronic infectious or inflammatory stimulus in a genetically predisposed individual.

These observations with respect to MALT lymphoma are very much in step with current think in IBD. IBD in people is thought to arise as a consequence of an overaggressive immune response to a subset of the enteric flora in genetically susceptible individuals. The best-characterized genetic defects in people with IBD involve the innate immune system and its interactions with the enteric microflora. e.g. NOD2. A recent study in cats with IBD has shown that the number of mucosa-associated *Enterobacteriaceae* is higher in cats with signs of gastrointestinal disease than healthy cats. Total numbers of mucosal bacteria were strongly associated with changes in mucosal architecture and the density of cellular infiltrates, particularly macrophages. *Enterobacteriaceae* spp, *E. Coli*, and *Clostridium* spp. were associated with significant changes in mucosal architecture (principally atrophy and fusion), upregulation of cytokines (particularly IL-8), and the number of

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clinical signs exhibited by the affected cats. It is possible that this abnormal mucosal environment associated with IBD in cats may stimulate transformation of T cells and the progression to low grade lymphoma.

References