Helicobacter IBD Lymphoma different forms of the same disease in cats

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Feline intestinal lymphoma

Lymphoma (malignant lymphoma, lymphosarcoma) is the most common haematopoietic tumour in cats, dogs and humans. In the cat, this neoplasia occurs about twice as often as in the dog and about 10 times more frequently than in humans (~ 200 or 100 or 20 cases per 100,000 individuals at risk). FeLV infections increase the risk of developing lymphoma by a factor of about 60, FIV by a factor of 5. Other potential risk factors are immunosuppression with cyclosporine (6-fold risk) and passive smoking (3-fold risk). Mediastinal lymphomas are very often associated with FeLV infection and typically occur in young cats. Gastrointestinal lymphomas, on the other hand, are much more variable in association with FeLV, although the PCR of biopsy material FeLV may also be positive in serologically negative cats.

Although FeLV-associated lymphomas have decreased dramatically in recent decades, the prevalence of feline lymphoma has increased (1). This increase is mainly attributed to the increase in the intestinal form of the lymphoma (alimentary form; 1). Compared to humans (1-4 %) and dogs (6.6 %, diploma thesis VetMedUni Vienna), the gastrointestinal / alimentary form of the lymphoma in cats accounts for ≥ 50 % of lymphomas (2,3). The alimentary lymphoma is thereby mostly in the small intestine (50-80 %) or in the stomach (25 %), whereas the ileocecal valve and colon are rarely affected. Compared with the WHO classification for human gastrointestinal lymphoma of 2016, in a new study in Vienna mainly the forms enteropathy associated T-cell lymphoma type I and II (EATL I and II; 41 and 34 %, respectively) and diffuse large B-cell lymphoma (DLBCL; 20 %) were found (4). However, the in humans quite common mucosa-associated lymphoid tissue (MALT) lymphoma has accounted for only 2 %. In 92 % of cases, immunohistochemistry was sufficient with CD3 and CD79, whereas in 5/61 an additional clonality test was necessary (4 T-cell and 1 B-cell lymphoma, 4).

Correlation with helicobacter and chronic inflammation?

In human medicine, many studies show a significantly increased risk of gastrointestinal lymphoma in celiac disease (mainly EATL), Crohn's disease (along with other small intestinal and colonic tumours) and Helicobacter (especially DLBCL in the stomach). A first possible association between Helicobacter spp. and lymphoma in the cat was revealed in 2001 (5). In gastric biopsies from 72 cats (25 with gastric lymphoma, 23 with gastritis, 24 with normal histology), 92 % of lymphomas were positive for Helicobacter spp. compared with 78 % in gastritis and 52 % in animals with normal histology. From this study, it was concluded that there could be a potential association between Helicobacter spp. in the stomach of the cat and the emergence of gastritis and / or gastric lymphoma. Another interesting study (from the same research group) on the potential association between Helicobacter and lymphoma in cats was published in 2008 (6). In 31 cats with MALT lymphoma and 14 cats with gastritis, Helicobacter heilmannii was significantly associated with diseased cats (22/29) and with lymphoblastic lymphoma (13/17). However, as depending on the study between 38 and 93 % of healthy cats are positive for Helicobacter heilmannii, it is currently unclear whether there is any real etiological link between Helicobacter infections and (MALT-) lymphoma in cats. In addition, these MALT lymphomas are very rare in the cat, since mainly DLBCL occur in the stomach. However, gastrointestinal lymphomas may also be PCR-positive in serologically FeLV-negative cats in the biopsy material, which is why it has been speculated that viral infections as well as other infectious agents (such as Helicobacter spp.) or potentially carcinogenic factors could lower the threshold for developing neoplasia. Obvious evidence for this, however, is missing.

Correlation with food and chronic inflammation?

Although the definitive proof is still missing, there is increasing evidence that the intestinal lymphoma could be associated with food modifications and chronic inflammation. There is no evidence of a direct connection with food. However, numerous modifications in cat food in the last 30 years may have contributed to the relative and absolute increase in intestinal lymphoma (1,7). A possible association with chronic inflammation has been present in the area of intestinal and nasal lymphoma for some time, were mainly a link between intestinal lymphoma and Inflammatory Bowel Disease (IBD) is suspected (1).

IBD and lymphoma – diagnostic dilemma?

While no direct evidence has been found in recent years, the indirect evidence has significantly increased that the intestinal lymphoma is associated with chronic inflammation and with IBD (1,7-9). Unfortunately, both the clinic (chronic vomiting and diarrhoea, weight loss) as well as the response to the therapy (elimination diets or hydrolysed diets, prednisolone) are partially overlapping (8) and do not facilitate the prognosis.

A first problem already exists in getting adequate biopsies to reliably differentiate IBD from intestinal lymphoma. Already in 2003, a study suggested that distinguishing epitheliotrophic intestinal lymphoma, non-epitheliotrophic intestinal lymphoma, and IBD is very difficult to impossible due to T cells (small to medium size) in the epithelium (9). Especially in endoscopic biopsies, this distinction is difficult and may lead to confusion (half of the alimentary lymphomas in the small intestine were missed with endoscopic biopsy specimens only; 10). To make matters worse, according to a study with endoscopic biopsies of 70 cats to distinguish between IBD and intestinal lymphoma (N = 18; 11) nearly half of the patients showed only changes in the ileum, which would be missed by only gastroduodenoscopy without (a more time consuming) ileoscopy.

In a retrospective study of 120 cats with gastrointestinal lymphoma (12), 70 % were mucosal T-cell lymphomas (EATL II) with a median survival of 29 months. Survival decreased dramatically as T-cell lymphoma spread transmural (16 %, 1.5 months). In these 2 dominant types, molecular clonality analysis proved to be very helpful, as 90 % of the cats were positive for mono- or oligoclonal rearrangements of the T-cell receptor gamma (TCRG). Another 16 % were B-cell lymphomas (mainly DLBCL) with a mean survival time of 3.5 months.

Low grade alimentary lymphoma (LGAL, synonyms: well-differentiated, lymphocytic, small cell, mostly epitheliotrophic, EATL) is the most difficult form of intestinal lymphoma to differentiate from lymphoplasmacellular enteritis (IBD). In contrast to intermediate / high-grade alimentary lymphoma (IGAL / HGAL) and large granular lymphocyte lymphoma (LGLL), cats with LGAL generally show only diffuse thickening of the intestinal loops and only rarely intestinal masses like the other 3 forms (13). Accordingly, unlike the other forms, LGAL cannot / very rarely be diagnosed with aspiration cytology of intestinal masses. However, depending on the study, LGALs are responsible for 37, 45 or 75 % of alimentary lymphomas. An advantage of the LGAL is that these patients are usually very responsive to oral therapy with prednisolone and chlorambucil (such as IBD ...) and have a median survival of 19-29 months (14, if in complete remission, otherwise 15-25 months). In the other three forms, the survival time is significantly shorter and the therapy with CHOP-based protocols significantly more time consuming and expensive (13).

IBD and lymphoma – is there a connection?

In 2 studies, 60 % of cats with intestinal T-cell lymphoma (15) and 33 % of cats with LGLL (16) had a pre-existing diagnosis of IBD. It is difficult to decide if the pre-existing diagnosis was wrong or if IBD has progressed to lymphoma. 22/28 cats with intestinal T-cell lymphoma were monoclonal and 3 oligoclonal on testing TCRG VJ junctional diversity, whereas all cats with IBD were tested polyclonal (15). Lymphoplasmacellular enteritis (the most common form of IBD) was detected in up to 41 % of cats with LGAL in other regions of the intestine concomitantly with intestinal lymphoma (9,13,17). Finally, individual cases have been described with documented passage of lymphoplasmacellular enteritis to alimentary lymphoma (18,19). However, these were described at times when additional test systems such as clonality tests did not exist.

Diagnostic procedure for the distinction of LGAL and IBD

Although there is some evidence that alimentary lymphoma may develop as a result of chronic infection and lymphoplasmacellular enteritis / IBD, the main focus should be on a reliable diagnosis and distinction. Central points are (14,17,20):

LGAL and IBD

- both have either normal or diffusely thickened intestinal loops (IGAL / HGAL and LGLL yield mainly intestinal masses)
- both need histology for diagnosis (IGAL / HGAL and LGLL often fine needle aspiration and cytology sufficient)
- both respond to oral therapy with prednisolone +/- chlorambucil (IGAL / HGAL and LGLL need CHOP protocols)
- both occur mainly in the jejunum / ileum (> 90 %) and duodenum (> 70 %); IBD is more common in the stomach

LGAL

- more commonly also in muscularis and serosa
- more infiltration and changes in architecture
- almost always monomorphic T cell phenotype (possibly B cells in inflammation)
- full-thickness biopsies are recommended
- immunohistochemistry mostly necessary (CD3, CD79, possibly others)
- monoclonal or oligoclonal at TCRG VJ junctional diversity (78-90 %)
- possibly monoclonal or oligoclonal in B cell immunoglobulin heavy chain

IBD

- additional plasma cell infiltration
- almost always a mixture of T and B cells
- polyclonal at TCRG VJ junctional diversity (100 %)
- possibly polyclonal in B-cell immunoglobulin heavy chain

In an attempt to find an ideal algorithm for distinguishing between intestinal inflammation and lymphoma, the gradual combination of histology, immunohistochemistry (CD3e, CD79a) and clonality PCR was required for reliable differentiation of IBD and intestinal lymphoma (21). More than half of the histological IBD cats (10/19) were reclassified as intestinal lymphomas by immunohistochemistry and PCR, whereas only 3 out of 50 lymphoma cats were reclassified as IBD. Important histological features for detecting a lymphoma were lymphoid infiltration beyond the mucosa, epithelial biotrophism (especially intraepithelial nesting), heterogeneity and nuclear size of lymphocytes (21). Although the enzyme lactate dehydrogenase (LDH) is a negative prognostic factor in lymphoma, LDH does not seem to be really helpful to distinguishing between IBD and intestinal lymphoma (22).

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