A Clinical Conundrum: Differentiating Chronic Inflammatory Enteropathy from Low-Grade Intestinal T-Cell Lymphoma

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1. The challenge presented

Both lymphocyte-rich chronic inflammatory enteropathy (CIE) and low-grade intestinal T-cell lymphoma (LGITL) are common disorders in cats that unfortunately present a large amount of overlap in clinical presentation, physical exam, lab results, imaging, and histopathology. While there is a general trend for LGITL to be more frequent in older cats, the age at diagnosis can range from 4 to 20 years.[1]

2. Why does the diagnosis matter? A practical medicine perspective

Many clinicians have dealt with the dilemma of differentiating feline LGITL from CIE by concluding that no differentiation is required. Clients often ask "if it's not going to make a difference, why go to the effort and cost of biopsy?" Although it may be a pragmatic and cost-saving option, it is worth considering what is missed when this approach is taken, and the potential cost of the compromise.

2.1 What else could it be?

It is worthwhile considering other causes of chronic enteropathy, including large cell lymphoma, adenocarcinoma, mast cell tumours, infectious diseases (fungal, viral) and eosinophilic diseases. Pancreatic inflammation and exocrine pancreatic insufficiency (EPI) can have similar symptoms of weight loss, vomiting and diarrhoea with or without loss of appetite. Imaging and blood tests can help in differentiating these causes to a degree, but histopathology is often required for a definitive diagnosis.

2.2 Treatment options

For both CIE and LGITL, the treatment usually involves prednisolone. Prednisolone is not without its side effects, potentially leading to muscle wasting, insulin resistance or diabetes mellitus. For cats with CIE, other options such as novel protein, hydrolysed or fibre modified diets can be explored, as these may allow the cat to avoid or reduce long term medications. Other treatments such as pro or prebiotics or faecal transplants can be trialled for improvement of the intestinal microbiota. These treatments are unlikely to be helpful in cats with LGITL and may lead to further clinical deterioration while waiting for a response.

Chlorambucil is a convenient and commonly used chemotherapy agent that is often used as an immunosuppressant in cats when steroids alone are inadequate. For this reason, many clinicians will use chlorambucil along with prednisolone if enteropathy symptoms are severe as it will treat both LGITL and CIE.

Several dosing schedules have been proposed for chlorambucil and prednisolone. These each have benefits and disadvantages and variable levels of toxicity. While side effects are low with chlorambucil compared to protocols using injectable chemotherapy agents, they are still important. Pope et al [2] found 33.9% of cats experienced adverse events related to chlorambucil treatment for LGITL. They were most commonly low-grade myelosuppression; some requiring treatment delays or discontinuation of prednisone and chlorambucil and subsequent initiation of a different chemotherapy protocol to continue treating their disease. Moderate to severe elevations in liver enzymes necessitating discontinuation or delay of treatment with dose reduction has also been documented.

The decision to use a cytotoxic drug can also impact the carers of the cat and husbandry practices may need to be altered to ensure safe handling of waste in the household. Given the risk of toxicities and the safety concerns, using a chemotherapy drug without evidence of neoplasia requires significant client counselling so that they can make an informed decision.

2.3 Prognosis

The prognosis for LGITL is good with chemotherapy; the prognosis for chronic enteropathy can be good to excellent, using diet modification and other treatments. However, without chemotherapy the prognosis for LGITL is poor, and pre-treatment with prednisolone may reduce the effectiveness of chemotherapy if added later into the treatment regime.

Early studies using chlorambucil rather than traditional “CHOP” based protocols showed good responses - overall clinical response rate was 96%, with a median clinical remission duration of 786 days.[3]

The 2008 Kiselow study had median remission duration of 428 days for cats achieving a partial response, compared with 897 days for cats achieving a complete response. No other factors were associated with remission duration. Overall median survival time was 704 days.[4]

A more recent 2015 paper treated cats with glucocorticoid and chlorambucil with discontinuation of treatment recommended at 1 year if complete clinical response was documented. Treatment was restarted if disease relapsed. Overall response rate was 85.7% with glucocorticoid and chlorambucil. Median progression-free survival was 1078 days; Median overall survival was 1317 days.[2]

These studies show that very good outcomes can be achieved with chemotherapy, balanced with the additional cost of medications, monitoring and potential for toxicity.

3. Making the diagnosis

3.1 Is biopsy the only way?

A less expensive and invasive diagnostic option is the holy grail, and several studies have looked at biomarkers as an alternative to biopsy, while ongoing studies continue to help with increasing the value of less invasive tests.

- Faecal calprotectin: A significant difference in faecal calprotectin concentrations was found between with CE and healthy control cats at baseline.[5]
- No significant difference in faecal calprotectin concentrations was found between cats with CIE and cats with LGITL at baseline
- Faecal AGP concentration shows promise to differentiate cats with SCGL from cats with IBD and FRE.[6]

Imaging is commonly used as part of the diagnostic pathway for a cat with gastrointestinal symptoms and weight loss. This can be helpful to identify other diseases, and to try to differentiate between focal and diffuse enteropathies. Imaging can help in planning biopsy procedures: A cat with a focal mass would be better suited to surgical biopsy, whereas diffuse mucosal changes suggest that the lesions will be accessible endoscopically. Enlarged lymph nodes can be sampled percutaneously under ultrasound guidance; while this has not been shown to be able to identify LGITL, it may identify non-neoplastic conditions (such as granulomatous or suppurative inflammation) or other neoplasia (e.g. mast cell tumour, adenocarcinoma). It is important to advise owners that ultrasound cannot give a cytological or histopathological diagnosis and that findings in the intestinal wall are not specific for one enteropathy over another.

3.2 How to biopsy?

When planning biopsy for histopathology, a decision needs to be made about whether to use a surgical approach or to take endoscopic biopsies. Factors to consider include:

Surgical biopsies

- Allow biopsy of liver, pancreas, sampling of bile (when multiple organs appear to be affected)
- Allow resection of focal lesions
- Provide access to the jejunum and ileum, known to be early and significant sites of LGITL
- Typically provide good quality samples
- Can be performed without specialized equipment
- Require significant time for healing prior to commencing chemotherapy or prednisolone treatment
- Carry higher risk of complications and morbidity

Endoscopic biopsies

- Allow evaluation of the appearance of the mucosa
- Allow evaluation of the oesophagus and colon (in addition to stomach, duodenum and ileum)
- Carry very low risk of complications
- Allows procurement of multiple samples from different locations
- Are typically superficial
- Require specialized equipment & training.
- Require bowel preparation (for ileal biopsies)
- Allow commencement of prednisolone or chemotherapy without delay.

3.3 Quality of biopsies

Procurement of biopsies both surgically and endoscopically affect the histopathological findings. A recent paper[7] specifically looked at techniques used to procure and preserve endoscopic biopsies and found that:

- The fixation method was a key factor that affected the quality of histopathologic specimens. In addition, the independent factors that decreased the quality of histopathologic specimens were the duodenal biopsy site and smaller forceps size in dogs, and the ileal biopsy site and older age in cats

- A filter paper-fixation method (using filter paper put in cassettes rather than placing the samples loose in formalin), affixed mucosal samples to the filter paper with the villi facing up, making it easy to determine the orientation of the samples
- Forceps for a 2.8 mm channel are recommended if an endoscope with a 2.8 mm channel can be inserted into the small intestine in dogs.
- Previous review articles[8] have recommended the attainment of 10–15 good quality endoscopic biopsy samples for the canine duodenum and six good quality endoscopic biopsy samples for the feline duodenum. Furthermore, the same review articles recommended the attainment of 3–5 good quality endoscopic biopsy samples for the canine and feline ileum, although the exact number remains uncertain.

3.4 Interpretation of biopsies

From the perspective of the pathologist, full thickness surgical biopsies of the intestine are almost always easier to interpret due to reduced crush artefact and fragmentation, ease of proper sample orientation during the paraffin embedding procedure, and ability to assess submucosal, neural, and muscular components in addition to the mucosal layer. In the past, there was often a reluctance to confidently diagnose small cell low grade intestinal lymphoma without demonstration of invasion into the submucosa, which generally could not be confirmed with more superficial endoscopic biopsies.

There is now better understanding of mucosal architectural changes specific to epitheliotropic small cell intestinal lymphoma (intraepithelial nests and plaques),[9] often allowing diagnosis or suspicion of LGITL on endoscopic biopsies without reliance on deeper infiltration, increasing the potential value of these samples.

Advances have also been made in the grading of inflammatory and degenerative mucosal lesions, with development of objective criteria for assessing multiple features including degree of mucosal epithelial injury, fibrosis, crypt and lacteal dilation, numbers of intraepithelial lymphocytes, and lamina propria inflammatory cells.[10] This standardised approach to assessing gastrointestinal biopsies is intended to decrease intra- and inter-pathologist variation in reporting.

3.5 Ancillary testing

In some cases, histological findings may still be equivocal such as when intraepithelial nests and plaques are rare and there is a significant concurrent inflammatory component which may potentially mask a neoplastic population. The potential for chronic inflammatory enteropathy to progress to LGITL means that some samples may have very mixed features. In this situation

ancillary testing can be valuable and can usually be performed on the same histological specimen without need for an additional surgical procedure.

Immunohistochemistry for CD3 is often used to label the population of T lymphocytes within the mucosa, both confirming if the cell population of concern is T-cell origin and facilitating detection of intraepithelial nests and plaques.

In cases where immunohistochemistry also remains equivocal or an extra layer of confidence is required, PCR for Antigen Receptor Rearrangements (PARR) is an additional tool that can be used to support presence of a clonal neoplastic population. This technology has two targets: T-cell receptor gamma (TCRG) and B-cell immunoglobulin heavy chain (IGH). PARR analysis complements immunohistochemistry and routine histopathology but is not a replacement for these modalities:

- It is possible to have cross-lineage rearrangements where a T-cell lymphoma has IGH clonality rather than TCRG clonality [11] and therefore PARR does not replace other immunophenotyping
- Some non-lymphoid neoplasms may show clonality with PARR analysis (e.g. plasmacytomas)
- False negatives may occur if insufficient neoplastic DNA is extracted, or primers otherwise fail to bind
- False positives may occur with some infections and neoplasms (e.g. leishmaniasis, ehrlichiosis, canine histiocytoma)

4. Summary

Differentiating between feline chronic inflammatory enteropathy and low-grade intestinal lymphoma can present a significant challenge as there is no one clinical criterion or biomarker that can reliably differentiate lymphocytic inflammation from neoplastic lymphoproliferative disease in the intestinal tract of cats. Nonetheless, it is worthwhile to pursue a diagnosis in order to make the best, and safest, treatment choices and improve outcomes.

While histopathology is often considered to be the main diagnostic tool for these disorders, there may still be challenges presented especially in cases of chronic inflammatory diseases potentially transitioning to LGITL. Immunohistochemistry and PARR testing can help to support a diagnosis in these equivocal cases, but ancillary tests ultimately should be interpreted in light of all available clinical and diagnostic information.

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