Feline intestinal small cell lymphoma or chronic enteropathy? How to differentiate them and treat them.

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Introduction

Intestinal small cell lymphoma (also called low grade alimentary lymphoma) is more common than intermediate grade alimentary lymphoma in cats and can be difficult to differentiate from other causes of chronic enteropathy.

Typically, signalment, clinical presentation, and laboratory findings such as serum biochemistry and complete blood count are not helpful to differentiate between both diseases. Measuring vitamin B12 concentration should be considered as hypocobalaminaemia is a negative prognostic factor for cats with small cell lymphoma and vitamin B12 should be supplemented if present. Siamese are reported to be at higher risk and although cats of any age can present with the disease, it is usually diagnosed in older cats (over 10 years old). Lymphoma is the most common intestinal tumour type in the cat and more frequently localized in the small rather than large intestine where adenocarcinoma is more common.

Ultimately, after ruling out extra-intestinal diseases and food responsive enteropathy, abdomen imaging and biopsies are needed to further assess the intestinal tract for inflammation and to rule out a lymphoma.

How to obtain biopsies

Biopsies are usually taken either via explorative laparotomy (full thickness) or endoscopy (pinch mucosal biopsies). There are no well-designed studies to compare both modalities to reach a diagnosis, but limitations and advantages of each methods is summarized in table 1. Endoscopy requires specific instrumentation and specific training to obtain adequate biopsies. Any animal undergoing an endoscopy or laparotomy should have biopsies taken regardless of the gross findings as significant microscopic lesions can be present without macroscopic changes.

<table>
<thead>
<tr>
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<th>Endoscopy</th>
<th>Laparotomy</th>
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<tbody>
<tr>
<td>Invasiveness</td>
<td>Less</td>
<td>More</td>
</tr>
<tr>
<td>Cost</td>
<td>Less</td>
<td>More</td>
</tr>
<tr>
<td>Biopsies</td>
<td>Mucosa/sub-mucosa</td>
<td>Full thickness</td>
</tr>
<tr>
<td>Sampling</td>
<td>Stomach/duodenum</td>
<td>Entire small intestine</td>
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<tr>
<td>Visualization</td>
<td>Intestinal mucosa</td>
<td>Intestinal serosa</td>
</tr>
<tr>
<td>Palpation</td>
<td>Yes</td>
<td>No</td>
</tr>
<tr>
<td>Risk of rupture/dehiscence</td>
<td>Less</td>
<td>More</td>
</tr>
</tbody>
</table>

Table 1. Comparison of endoscopy and laparotomy to obtain intestinal biopsies.

The number of surgical biopsies taken is typically 1 or 2 per small intestinal segment (duodenum, jejunum, and ileum) as well as gastric biopsies. If an intestinal segment is abnormal, sampling from normal and abnormal tissue should be considered.
The number of endoscopic biopsies required to detect a lesion varies. To identify the presence of villous blunting with a high confidence, 5 to 6 biopsies of good quality are needed (Willard, 2008). For this reason, I would routinely take 10 to 12 biopsies to ensure collection of enough good quality biopsies from the stomach and the duodenum. Sampling the ileum (via colonoscopy) is also recommended to increase diagnostic yield.

**What to do with the biopsies**

Biopsies are routinely sent for histopathology using haemotoxylin and eosin staining. As differentiating between an inflammatory infiltrate in the intestines or a small cell lymphoma can be very difficult, additional methodology can be used.

**Immunohistochemistry (IHC)** is helpful to differentiate between B- and T- lymphocytes. A monomorphic population with some other histologic features such as intra-epithelial lymphocytes accumulation, can increase the suspicion for small cell lymphoma whereas mixed inflammation with B- and T-lymphocytes is more suggestive of an inflammatory process.

Molecular testing using polymerase chain reaction (PCR) to identify antigen receptor rearrangements (PARR) has also been described. This method is used to assess if the B- or T-lymphocytes originate from a single cell (clonal) or not (polyclonal). If there is a clonal population, then a lymphoma is strongly suspected. Although some cases of lymphoma will not be detected (the test sensitivity is not 100%), it can be very helpful to further support a diagnosis of lymphoma.

None of these tests is perfect and they always need to be correlated with the clinical findings. However, a study comparing histopathology with IHC, and PARR (Sabattini, 2016) from endoscopic biopsies, found that PARR testing was superior than other modalities to diagnose low grade alimentary lymphoma.

The advantage from IHC and PARR is that both tests can be run on formalin-fixed biopsies. Therefore, it is possible to run these tests on sample obtained for histopathology. However, although IHC is routinely available, PARR testing currently requires samples to be sent overseas and is more expensive.

Although the prognosis for cats with low grade alimentary lymphoma is much better with treatment than high grade alimentary lymphoma, survival remains lower than cats with CE. For this reason, a thorough work up can be helpful for the owners to obtain prognostic information.

**Treatment considerations**

Cats with T-cell low grade alimentary lymphoma (majority of cases) usually respond well (90% of cases have resolution of their clinical signs) with a combination of chlorambucil (2mg PO q48-72h) and prednisolone (initial dose 1-2mg/kg PO q24h). Median survival time of 2 years or longer have been reported with this treatment. In comparison, cats with steroid-responsive enteropathy will usually have a median survival time over 4 years.

Cats re-lapsing with low grade alimentary lymphoma might respond to rescue protocols.

**Conclusion**

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CE and low grade alimentary lymphoma can be difficult to differentiate one from another, but different laboratory methods using paraffin-fixed biopsies (for histopathology, IHC and PARR) can be very helpful. Although a staged treatment starting with steroids and adding chlorambucil in the absence of response can be used, determining from the outset if a low grade alimentary lymphoma is present can be helpful for prognosis and to increase confidence that aggressive treatment is indicated.

References