DIAGNOSTIC AND TREATMENT OPTIONS FOR FELINE GASTROINTESTINAL LYMPHOMAS

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DIAGNOSTIC OPTIONS.

Inflammatory bowel disease (IBD) and lymphomas are common diseases of the feline gastrointestinal tract, with similar clinical signs, laboratory and imaging findings. However, treatment and prognosis are different and it is crucial to have an accurate diagnosis. Gastrointestinal (GI) lymphoma is the most common presentation of lymphoma in cats, and some studies have documented an increase in its incidence in the last decades of the past century. Alimentary lymphomas can be divided in three clinical presentations: small cell (low-grade), large cell (high-grade) and large granular lymphocyte lymphoma, being the small cell the most common presentation (75% of cases).

Cytology.
For large granular lymphocyte lymphoma and large cell lymphoma, cytology can be a useful diagnostic tool. Large granular lymphocyte lymphoma is an uncommon and aggressive form of lymphoma with bad prognosis that is minimally responsive to chemotherapy. In a recent study that used cytology and histopathology for diagnosis, the cytoplasmic granules were recognized in all cases with cytology, and were not discerned in any case on hematoxylin and eosin-stained biopsies. Granzyme B is a frequent component of these granules and staining for this molecule can help to identify this clinical entity. Large cell lymphoma can be normally diagnosed with cytology based on a monomorphic population of large lymphocytes.

Histopathology.
Small T cells lymphoma and IBD are characterized by infiltrates of small lymphocytes. Cytology is not appropriate to accurately differentiate these entities and endoscopic or surgical biopsies for histopathology are required. Benefits of endoscopic samples include directed biopsy if mucosal changes are seen, collect multiple samples from different areas and begin therapy immediately after the procedure but endoscopy samples are limited to the mucosa, and is limited to proximal and distal GI tract. In the lymphomas, the lymphocytes may infiltrate not only the mucosa, but the submucosa, muscularis and serosa, but this transmural progression may take long time. Because endoscopic samples are limited to the mucosa, it may be difficult to differentiate between both diseases by histomorphology alone. On the other hand, surgical biopsies can collect transmural samples of any segment of the GI tract or other organs (lymph node, liver). Evans et al compared full-thickness and endoscopic diagnosing lymphoma in 10 cats with full-thickness samples. Only 3 of those cases were diagnosed with lymphoma with endoscopic samples (all three in stomach) highlighting the limitations of endoscopy to diagnose lesions in small intestine.

Molecular diagnosis.
Immunophenotyping and clonality tests are important tools to differentiate between IBD and small cell GI lymphoma. Immunophenotyping is useful in lymphocyte lineage assignment, and the PCR for Antigen Receptor Rearrangement (PARR) will detect clonal expansion of lymphocytes. Combination of histologic evaluation, immunophenotyping and clonality of lymphoid infiltrates results in more accurate differentiation of neoplastic versus inflammatory lymphocytes. Kiupel et al proposed an algorithm for diagnosis that shows that from 19 cases
Initially diagnosed as IBD based on morphologic evaluation, after running the immunophenotype and clonality tests only 9 had IBD and 10 had lymphoma. Similarly, Sabattini et al went from 20% of lymphoma diagnosed with histology, to 32% with histology and immunophenotype and to 50% with histology, IHC and PARR.

It is important to remember that while clonality is generally accepted as a property of neoplasia, benign clonal expansions are possible, in response to antigen stimulation for instance. Similarly, PARR is lineage associated, but cross-lineage rearrangements have been described, with B cells rearranging T cell loci and T cells that rearrange B cell loci as showed by Andrews et al. Where 9% of feline GI lymphomas had cross lineage rearrangement. Thus, PARR should not be used as the only test for lineage assignment. On the other hand, the sensitivity of PARR tests may be different in different diagnostic laboratories. Some reports show a sensitivity of 65%. Factors that can produce a false negative result include insufficient primer coverage or clonal peak obscured by a polyclonal background that could be recognized by a mixed cellular infiltrate or the distribution of B and T cells determined by immunophenotyping, showing again how important is the integration of all clinical and analytical data.

Flow cytometry is routinely used for diagnosis of canine lymphoproliferative disorders, but is less commonly used for feline lymphoma. Two potential reasons are poor-quality samples from abdominal lesions (because of sampling difficulties) and the limited availability for monoclonal antibodies binding to feline leukocyte antigens. However, recent papers show that flow cytometry can be diagnostic in 75% of the cases, with low cellularity being the main problem with some samples. Martini et al recommend to use a 21G needle that was associated in their study to a higher cellularity.

In summary, differentiating low grade GI lymphoma from IBD in cats is challenging. Owners should be informed about the advantages and cons of surgical biopsies versus endoscopic samples, and if endoscopy is performed, obtaining duodenal and ileal samples should be attempted. Lesions selection, histopathology, immunohistochemistry and PCR may be needed to have a definitive diagnosis and decrease the likelihood of misdiagnosis.

To have an accurate diagnosis allows the clinician to give appropriate prognostic information to the owners. Several studies show the better prognosis for the IBD, with 1, 2 and 3 years survival of 84%, 75% and 71% respectively for cases with IBD compared with 59%, 26% and 15% respectively in cases with small cell lymphoma.

TREATMENT OPTIONS.
Small cell lymphoma is normally treated with glucocorticoid and chlorambucil, with a high response rate (80-90%) and median survival times of 30-40 months. An important prognostic factor is the response to the therapy, with longer remission duration for those cats that have complete response compared with partial response. The time to response may be up to three months, with one study finding that there was 20% of non-responders at one month of therapy, and only 9% at three months. This study found that the percentage of cats in complete remission was 23% at one month and it rose to 50% at three months. It seems to be important then give time to the therapy before we can assess the response. For those cases that do not respond to chlorambucil, lomustine and prednisone has been used as a rescue therapy, obtaining a median progression free interval of 7 months in small cell GI lymphoma.

Some authors have proposed to discontinue the therapy with prednisone and chlorambucil at one year if the cat is in complete remission with reintroduction of both drugs as a rescue therapy when needed. This approach was associated to a better outcome (survival of 50 months) that the use of prednisone and lomustine as rescue protocol (16 months of survival). About 30% of cases were in complete remission after one year of therapy and discontinued the treatment.

Chlorambucil may have interactions with other immunosuppressive drugs (as cyclosporine or cyclophosphamide) increasing the risk of infection. The doses normally used include 2 mg (total dose) every 48 hours for cats greater than 4 Kg or every 72 hours for cats less than 4 Kg.

The treatment recommended for high-grade alimentary lymphoma is a multidrug protocol. Response rates vary from 40 to 90%. A modified version of university of Wisconsin-Madison protocol was associated to a median
survival time of 3 months. The survival was associated to the response, being 7 month for those with complete remission, 2 months for partial remission and less than one month for those that didn’t respond to therapy. Although this study included multiple locations, most of the cases were GI large cell lymphomas. There is a possibility that some large granular lymphocyte lymphomas were included due to the difficulty of identify these cases on histopathology.

A COP-based protocol used in 114 cats (50% of them with GI large cell lymphoma) achieved a 47% response rate. The response to the therapy was again an important prognostic factor, with median survival times of 20 moths for responders versus 2.5 months for non-responders. For cases non responding, doxorubicin-based chemotherapy can be evaluated as a rescue therapy. Although 22% of cases had a positive response, all were small cell lymphomas and none of the large cell lymphomas responded to doxorubicin what shows that is not an effective rescue protocol.

Methotrexate (MTX) may have interactions with some drugs. These interactions have been either reported or are theoretical interactions:
- Cyclosporine: my increase MTX levels.
- Folic acid: may decrease MTX efficacy, but folate deficiency increase MTX toxicity.
- Neomycin given by mouth concomitantly may decrease absorption of MTX.
- Penicillins: may decrease MTX renal elimination.

Doxorubicin is a potential nephrotoxin in cats and renal function should be checked before and during therapy. Some interactions include cyclosporine (can increase doxorubicin levels) or phenobarbital (may increase elimination of doxorubicin and reduce levels).

Lomustine has been used to treat intermediate to large cell gastrointestinal lymphoma as a first line therapy, with a response rate of 50% (22% complete response and 28% partial response) with a median duration of the response of 10 months. Although the median survival time for all the cats was only 3 months, for those in complete or partial response, the median survival time was 11 months. Dosages higher than 40 mg/m² were associated to better outcome than dosages lower than 40 mg/m². When used as rescue therapy in large cell lymphomas the median progression free interval was short (25 days).

Large granular lymphocyte lymphomas were treated with lomustine there was a 33% of complete responses, 22% of partial responses, 11% of stable disease and the remaining 33% had progressive disease. Median survival time was 4 months. A review of 109 cases found short median survival times regardless the type of therapy, with 2 months if treated with CHOP-based therapy and 3 months with lomustine. Cases treated only with corticosteroids had a median survival time of 15 days.

When treating cats with GI lymphoma, perforation is a concern. In a study about spontaneous gastrointestinal perforation, six out of 11 cats that had histopathological examination of the perforated area, had GI lymphoma and the other five had non neoplastic diseases as IBD or necrotic enteritis. Post-chemotherapy perforation is as well a risk in cats with intermediate to large cells GI lymphoma; 17% of cases treated in one study had a perforation that occurred between 3 weeks and 3 months of initiation of therapy.

**Supportive therapy.**
Most cats with GI Lymphomas present with low body condition score. Frequent diseases in elder cats as hyperthyroidism or renal disease, have to be ruled out or treated and monitored during the therapy of the lymphoma.

Appetite stimulants, antiemetics and dietary modification may be needed. Nutritional support has been already covered in other lectures of the seminar.
Both, the GI lymphoma and the chemotherapy can cause vomiting. Maropitant (1 mg/kg SC or PO every 24 hours), or ondansetron (0.5 mg/kg IV loading dose followed by 0.5 mg/kg IV infusion for six hours, or 0.5-1 mg/kg PO every 12-24 hours) are the drugs normally used in our clinic.

Low levels of serum cobalamin are common in cats with GI lymphoma and the majority of cases have serum levels below 300 ng/l. Cobalamin should be supplemented because cats with untreated hypocobalaminemia may have suboptimal response to chemotherapy. Commonly is supplemented with SQ injections, weekly during the first month and then monthly. Oral supplementation is possible and effective. Treatment with 0.25 mg of cyanocobalamin tablets once daily changed a median serum concentration from 128 pmol/l before the treatment to 2701 pmol/l after 30-90 days of therapy.

REFERENCES.


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