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The overlap between feline low-grade intestinal lymphoma and lymphoplasmacytic enteritis

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Lymphoplasmacytic enteritis (LPE) and low-grade lymphoma (LGL) are increasingly common chronic gastrointestinal diseases in cats. Both diseases share common clinical signs, biochemistry, and diagnostic imaging findings. Previous studies have reported between 15.6% to 53% of cases initially diagnosed as LPE on histopathology were subsequently reclassified as LGL when incorporating immunohistochemistry or clonality testing. Although such a large percentage of LPE cases have been reported to be reclassified as LGL, the converse does not as readily apply, whereby cases diagnosed with LGL were unlikely to be reclassified as LPE on histopathology. This reclassification highlights the significant overlap between these two conditions and the need for additional testing besides histopathology alone.

Feline alimentary lymphoma is the most common digestive tract neoplasm and anatomical form of lymphoma, comprising up to 75% of lymphoma cases in cats. Gastrointestinal lymphoma can currently be classified into three categories: low-grade intestinal lymphoma, high-grade alimentary lymphoma and large granular lymphocytic lymphoma (the most aggressive form).

Low-grade lymphoma, a predominant T-phenotype, is the most common subtype and accounts for up to 75% of the various lymphoma classifications. The histopathological findings typically are the infiltration of small to intermediate-sized neoplastic T-lymphocytes with or without regional lymph node involvement.
Confounding the diagnosis mentioned above, LPE is the most common form of inflammatory bowel disease (IBD) in cats, a group of chronic and recurrent inflammatory gastrointestinal disorders. The underlying pathogenesis is largely unknown but proposed due to disruption of the mucosal barrier, immune system dysregulation, microbiome alterations and dysregulation of immunologic tolerance to commensal and dietary antigens.

Signalment

Low-grade lymphoma has been proposed to affect older cats without a breed or sex predilection. In contrast, some authors suggest LPE affects cats of all ages without breed or sex predilection.

Clinical signs

The most common clinical signs in LPE and LGL cats are varying combinations of persistent or recurrent, chronic (> 3 weeks) lethargy, anorexia, weight loss, vomiting and diarrhoea. Additional signs that may be demonstrated include polyphagia, haematochezia, malaena, constipation and pyrexia. These signs are not specific to either disease; however, the median duration of signs has been reported longer in LGL compared to LPE.

Diagnosis

There is an extensive overlap between the disease entities of LPE and LGL concerning clinical signs, laboratory findings, diagnostic imaging and histopathology results. The relationship between LGL and LPE has also been intertwined, whereby up to 60% of LGL cases have been concurrently diagnosed with LPE, and LGL has been suggested to develop from LPE. A proposed initiating event is chronic antigenic stimulation from food, viral or bacterial components resulting in immunologic dysregulation, interleukin-6 upregulation and neoplastic emergence.

As with multiple chronic small intestine enteropathies, a thorough workup and exclusion of precipitating bacterial, helminth and dietary factors should be performed first. Diagnostics of both diseases should include: a minimum database with biochemistry and haematology, viral screening, vitamin B testing, abdominal ultrasound and ultimately intestinal biopsies (either endoscopically or via exploratory laparotomy) with the added modalities of immunohistochemistry and clonality testing. Of interest and changed over time, most cats affected with alimentary lymphoma test negative for Feline Leukaemia virus (FeLV) in recent studies.

The biochemistry finding of hypoalbuminaemia has been reported in 14% to 49% of LGL cases and 32% to 77% of LPE cases. Hypocobalaminaemia has been found in both diseases and is significantly more frequent in the LPE groups. Besides these findings, no other differences in biochemistry or fPLI concentrations were found between the groups reported by Freiche *et al*. Secondary changes on biochemistry panels such as electrolyte abnormalities, azotaemia, and leucocytosis may be present depending on disease chronicity and severity before presentation.

Abdominal ultrasound is a widely available non-invasive imaging modality and, therefore, commonly used. Multiple criteria evaluating the intestinal wall layering thickness and lymph node dimensions have been proposed to attempt disease differentiation with varying success. Many ultrasound features do not accurately differentiate between LPE and LGL.

Both diseases have been reported to demonstrate jejunal lymph node enlargement and thickened and altered intestinal wall layering. For example, a thickened muscularis layer has been reported in LGL, LPE, eosinophilic enteritis and mechanical obstruction, and as such, measurements cannot differentiate clearly between the diseases. In a recent study by Freiche *et al.*, the jejunal mucosal thickness was statistically significantly higher in LGL compared to LPE.

These median measurements were 1.4mm in the LGL group and 1mm in the LPE group. Although statistically different, using this difference practically in the private veterinary setting would be difficult. Freiche *et al.* also reported that jejunal lymphadenopathy with the following features: hypoechoic, rounded, thickened with surrounding hyperechoic fat and an abdominal effusion were more commonly seen in LGL cats compared to LPE cases.

In both LPE and LGL, the most representative and infiltrated portions of the small intestine are the jejunum and ileum, highlighting the importance of obtaining samples from both sites. In a study by Scott *et al*., comparing endoscopic biopsies of the duodenum versus the ileum, poor agreement of diagnosis between the sites was evident. In this study, in a greater population of cats, the diagnosis of LGL was made by ileal and not duodenal samples.

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Therefore if endoscopy is performed samples from the jejunum and ileum (where feasible and performed retrograde) should also be attempted. These findings should be considered when deciding on endoscopy versus exploratory laparotomy to obtain a diagnosis. Both diagnostic modalities have pros and cons regarding cost, degree of invasiveness, quality and number of representative samples obtained.

In order to confirm the diagnosis, immunohistochemistry is required whereby LPE demonstrates a combination of CD3+ T- and CD20+ B-cell phenotypes, whereas LGL displays a predominant CD3+ T- cell phenotype. Clonality testing using PCR to assess antigen receptor gene rearrangements (PARR) has demonstrated excellent sensitivity and specificity for disease differentiation and therefore suggested to be integrated into the diagnostic arsenal (where available). An additional marker that can be utilised is Ki67, an index of proliferation, which has been reported to be significantly higher in LGL groups compared to LPE cases. Therefore, the usage of IHC and clonality testing enhances and increases the diagnostic ability to detect lymphoma cases.

Treatment

Treatment for LPE generally involves combinations of antimicrobial, dietary and immunosuppressive protocols. Felines that do not respond favourably or for extended periods to antimicrobial and dietary management and that have histopathology / immunohistochemistry confirming disease require immunosuppression.

Corticosteroids are the mainstay of therapy, starting at 1-2 mg/kg or 5 mg per cat per os (PO) twice daily (BD), with positive responses to therapy seen within 1 to 2 weeks. The corticosteroid dose is tapered incrementally for 2- 4 weeks to achieve the lowest effective dose that controls disease and mitigates side effects. An achievable goal for long-term management is 0.25- 0.5 mg/kg every second day. Other formulations of corticosteroids, such as injectable methylprednisolone acetate and budesonide, should be utilised as alternatives if poor responses to prednisone are noted. Additional immunosuppressive agents can be considered for LPE cats unresponsive to corticosteroids, the most commonly being chlorambucil. A dosage of 5- 6mg/m^2 every second day can be instituted.

Low-grade lymphoma responds favourably to conservative therapies with durable remission and response rates of > 80% and median survival times ranging between 1.5 and 3 years. The more aggressive maximum tolerated dose CHOP (cyclophosphamide, doxorubicin, vincristine, prednisone) protocols are reserved for cases with high-grade lymphomas and when the conservative protocols are no longer effective. Treatment protocols for LGL utilise a combination of chlorambucil at 2mg per cat PO every second day and prednisone at 1- 2 mg/kg PO daily, which is subsequently reduced to 0.5- 1 mg/kg every second day over several weeks.

Due to the diffuse nature of neoplastic cells within the intestinal segments, surgery for LGL is not recommended. It is somewhat reserved for high-grade lymphoma cases that demonstrate focal lesions presenting with intestinal perforation or obstruction. There is a current debate without consensus if focal lesions without perforation should have surgery performed or not.

Cats with chronic enteropathies are often hypocobalaminaemic. Therefore, supplementation with cobalamin 250ug intramuscularly or subcutaneous weekly for a six-week duration followed by two to four weeks should be added to the treatment regime.

Monitoring

Cases treated with chlorambucil immunosuppressive treatment should be routinely monitored for myelosuppression and hepatotoxicity by performing full blood counts and biochemistry profiles. It is also essential to monitor these cases' albumin, total protein, phosphorus and electrolyte values as they can be negatively affected.

Conclusion

Low-grade lymphoma and LPE demonstrate a wide overlap in clinical signs, biochemistry results and diagnostic imaging findings. In order to improve the diagnostic accuracy between these diseases, all cases that undergo biopsies should have multiple samples of the jejunum and ileum biopsied as well as immunohistochemistry (with or without clonality testing if available) performed.

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MULTIPLE-CHOICE QUESTIONS

QUESTION 1

When performing intestinal biopsies, the most representative locations where biopsies should be sampled are?
a) The duodenum and jejunum
b) The duodenum and ileum
c) The jejunum and ileum
d) The ileum and colon
e) The duodenum, jejunum and ileum

QUESTION 2

Lymphoplasmacytic enteritis demonstrates which T-phenotype appearance on immunohistochemistry?
a) Predominantly CD3+
b) Predominantly CD20+
c) A combination of CD3+ and CD20+
d) A combination of CD3+ and CD21+
e) A combination of CD3+ and CD4+

QUESTION 3

Which common clinical signs are evident in both LGL and LPE?
a) Acute haematochezia, malaena and constipation
b) Chronic haematochezia, malaena and constipation
c) Acute anorexia, weight loss vomiting
d) Chronic anorexia, weight loss and vomiting
e) None of the above

QUESTION 4

Histopathology and immunohistochemistry confirmed low-grade lymphoma should be treated with the following recommendation:
a) Sectional enterectomies
b) CHOP based chemotherapy protocol
c) Chlorambucil only
d) Corticosteroids only
e) Corticosteroids and Chlorambucil

QUESTION 5

The most common subtype of alimentary lymphoma in cats is:
a) Large granular lymphocytic lymphoma
b) High grade lymphoma
c) Low grade lymphoma
d) All of the above
e) None of the above

QUESTION 6

Jejunal lymphadenopathy with the following features is more often found in LPE:
a) Hyperechoic, rounded and thickened size
b) Hypoechoic, rounded and thickened size
c) Hypoechoic, rounded and reduced size
d) Hyperechoic, rounded and reduced size
e) None of the above

QUESTION 7

The most common anatomical form of feline lymphoma is:
a) Renal
b) Multicentric
c) CNS
d) Alimentary
e) Mediastinal

QUESTION 8

Hypoalbuminaemia is a common biochemistry findings in:
a) Both low-grade lymphoma and lymphoplasmacytic enteritis
b) Low-grade lymphoma cases only
c) Lymphoplasmacytic cases only
d) Hypoalbuminaemia is rarely demonstrated
e) None of the above

QUESTION 9

Hypocobalaminaemic cats should be initially supplemented with:
a) 250ug of cobalamin weekly
b) 250mg of cobalamin weekly
c) 250ug of cobalamin monthly
d) 250mg of cobalamin monthly
e) None of the above

QUESTION 10

Which intestinal wall layering finding on ultrasound can differentiate between LGL and LPE?
a) Thickened muscularis layer
b) Thickened submucosal layer
c) Diffuse wall thickening
d) Loss of intestinal layering
e) None of the above

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