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CONSENSUS STATEMENT

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ACVIM consensus statement guidelines on diagnosing and distinguishing low-grade neoplastic from inflammatory lymphocytic chronic enteropathies in cats

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Abstract

Background: Lymphoplasmacytic enteritis (LPE) and low-grade intestinal T cell lymphoma (LGITL) are common diseases in older cats, but their diagnosis and differentiation remain challenging.

Objectives: To summarize the current literature on etiopathogenesis and diagnosis of LPE and LGITL in cats and provide guidance on the differentiation between LPE and LGITL in cats. To provide statements established using evidence-based approaches or

Abbreviations: ACVIM, American College of Veterinary Internal Medicine; AL, alimentary lymphoma; ALT, alanine transaminase; AUS, abdominal ultrasound; CBC, complete blood count; CE, chronic enteropathy; CT, computed tomography; EATL, enteropathy-associated T-cell lymphoma; EPI, exocrine pancreatic insufficiently; FCEAI, feline chronic enteropathy activity index; FFPE, formalin-fixed and paraffin-embedded; FIP, feline infections peritonitis; FIV, feline immunodeficiency virus; FeLV, feline leukemia virus; f-PLI, feline pancreatic lipase immunoreactivity; GRADE, Grading of Recommendations Assessment, Development and Evaluation; GI-TLPD, gastrointestinal T-cell lymphoproliferative disorder; H&E, hematoxylin and eosin; IBD, inflammatory bowel disease; IGH, immunoglobulin heavy chain; IHC, immunohistochemistry; JAK, Janus kinase; LDH, lactate dehydrogenase; LGITL, low-grade intestinal T-cell lymphoma; LPE, lymphoplasmacytic enteritis; MALT, mucosa-associated lymphoid tissue; MEITL, monomorphic epitheliotropic intestinal T-cell lymphoma; MMA, methylmalonic acid; MRI, magnetic resonance imaging; NK, natural killer; PARR, PCR for antigen receptor rearrangement; PCR, polymerase chain reaction; SCL, small cell lymphoma; STAT, signal transducer and activator of transcription; TCR, T-cell receptor; WHO, World Health Organization; WSAVA, World Small Animal Veterinary Association.

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where such evidence is lacking, statements based on consensus of experts in the field.

Animals: None.

Methods: A panel of 6 experts in the field (2 internists, 1 radiologist, 1 anatomic pathologist, 1 clonality expert, 1 oncologist) with the support of a human medical immunologist, was formed to assess and summarize evidence in the peer-reviewed literature and complement it with consensus recommendations.

Results: Despite increasing interest on the topic for clinicians and pathologists, few prospective studies were available, and interpretation of the pertinent literature often was challenging because of the heterogeneity of the cases. Most recommendations by the panel were supported by a moderate or low level of evidence. Several understudied areas were identified, including cellular markers using immunohistochemistry, genomics, and transcriptomic studies.

Conclusions and Clinical Importance: To date, no single diagnostic criterion or known biomarker reliably differentiates inflammatory lesions from neoplastic lymphoproliferations in the intestinal tract of cats and a diagnosis currently is established by integrating all available clinical and diagnostic data. Histopathology remains the mainstay to better differentiate LPE from LGITL in cats with chronic enteropathy.

KEYWORDS

alimentary, cat, chronic diarrhea, endoscopy, gastrointestinal, histology, immunohistochemistry, inflammatory bowel disease, lymphoma, lymphoplasmacytic enteritis, lymphoproliferative disorders, T-cell

1 | INTRODUCTION

Chronic enteropathy (CE) is a common disorder in cats, especially in the older cat population and its prevalence has increased over the past 2 decades.[1] Differentiating chronic inflammatory enteropathy from intestinal low-grade lymphoma in cats can be difficult because physical examination findings, laboratory data, diagnostic imaging findings, and even histopathologic features frequently overlap.

The most recent revision of the World Health Organization (WHO) classification of lymphoid neoplasms in people includes a primary, indolent clonal T-cell proliferation of the gastrointestinal tract as a provisional entity named indolent T-cell lymphoproliferative disorder of the gastrointestinal tract (GI-TLPD).[2] This disorder shares many similarities with intestinal low-grade lymphoma in cats, including the challenge to differentiate it from inflammatory disorders and its frequent misdiagnosis as enteropathy-associated T-cell lymphoma (EATL), formerly known as EATL type I, or monomorphic epitheliotropic intestinal T-cell lymphoma (MEITL), formerly known as EATL type II.[2,3] Lymphoproliferative disorders (LPDs) are characterized by an uncontrolled proliferation of lymphocytes and can be differentiated into lymphomas, leukemias, and monoclonal gammopathies.[2,4,5] Although LPDs including intestinal low-grade lymphomas in cats are characterized by monoclonal or oligoclonal rearrangements of the lymphocyte receptors, clonality is not equivalent with malignancy and clonality has been well described in reactive lesions in humans[6-10] and companion animals.[11] In fact, the capacity for clonal expansion upon antigen-recognition is a hallmark of both B-lymphocytes and T-lymphocytes.[12-16] Although all lymphomas are clonal, not all reactive lesions are polyclonal.[17]

Part of the veterinary community has argued that a comprehensive diagnostic evaluation of cats with CE may be unnecessary because it does not appear to change prognosis or treatment. However, data from more recent studies indicate that prognosis and treatment strategy may need adjustment based on the underlying diagnosis.[18,19] An evaluation including intestinal biopsies does not only exclude other differential diagnoses including large cell lymphomas, infectious, eosinophilic, or mast cell disease but also could allow for a more accurate prognosis and treatment plan in the future.

The following report by the American College of Veterinary Internal Medicine (ACVIM) consensus statement panel on CE in cats proposes a classification of CE based on the state-of-the-art diagnostic methods and provides recommendations for the diagnostic approach and management of cats with CE.

The panel recognizes that even after applying all currently available diagnostic tests, ambiguous cases will remain and that some diagnostic approaches are unclear and even arbitrary. Nonetheless, there appear to be correlations among certain clinical, laboratory, histopathological, immunohistochemical, and clonality features that predict a

different disease outcome and may lead to different treatment approaches in the future.

2 | MATERIALS AND METHODS

A panel of 6 experts in the field (2 internists [S. Marsilio, V. Freiche], 1 radiologist [E. Johnson], 1 anatomic pathologist [M. R. Ackermann], 1 clonality expert [I. Peters], 1 oncologist [C. Leo]) was formed to assess and summarize evidence in the peer-reviewed literature and complement it with consensus recommendations. An immunologist and clonality expert in human medicine served as a panel consultant [A. W. Langerak].

During the first consensus meeting, different options for building consensus were considered and included the Delphi method, the nominal group technique, and the Grading of Recommendations Assessment, Development and Evaluation (GRADE) method. The members decided to employ a modified Delphi method that incorporates a combination of anonymous commenting on a series of statement drafts in addition to regular video conferences. Committee members used a 5-point Likert scale to rank each statement (Table 1). Consensus was defined as reached if ≥6 of 7 committee members indicated strong agreement (score = 5) or agreement (score = 4) with the statement. Three review rounds were permitted per statement until a final decision was adopted. For the section on clonality analysis, the panel consulted with an external immunologist between review rounds. A Qualtrics survey was distributed among the panel experts for final and anonymous voting on the statements according to the adopted Likert scale (Table 1).

PubMed, Google Scholar, and Web of Science were used along with the following search terms to identify relevant articles (in alphabetical order): "alimentary lymphoma," "cat," "clonality," "clonal expansion," "enteropathy," "feline," "histopathology," "immunohistochemistry," "inflammatory bowel disease," "lymphoma," "lymphoplasmacytic enteritis," "lymphoproliferative disorders," "PCR for antigen receptor rearrangement," "radiology," "small cell lymphoma," "ultrasonography," "ultrasound." The group also added additional subtopic-relevant terminology. In addition, review articles were used to identify additional relevant articles not captured in the original searches. Articles were excluded if they were published only in abstract form, were not available in English, did not address relevant topics or only contained case reports or small case series.

TABLE 1 Likert scale.

Strongly disagree	Disagree	Undecided	Agree	Strongly agree
1	2	3	4	5

Note: The Likert Scale assumes that the strength/intensity of an attitude is linear, that is, on a continuum from strongly disagree to strongly agree, and that attitudes can be measured.

References documenting peer-reviewed published studies containing original data were reviewed by the panel and graded. A modified system of evidence (Table 2) was used to rate the level of evidence.[20,21] For each statement for which consensus was reached, a level of evidence was determined based on review of the literature (Table 2).

3 | RESULTS

3.1 | Terminology

The terminology for CE in cats used in the literature varies. Terms commonly used to describe inflammatory lesions are inflammatory bowel disease (IBD), lymphoplasmacytic enteritis (LPE), and eosinophilic enteritis. Terms commonly found to describe neoplastic lesions are small cell lymphoma, low-grade lymphoma, alimentary lymphoma (AL), lymphosarcoma, enteropathy-associated T-cell lymphoma (EATL), monomorphic epitheliotropic intestinal T-cell lymphoma (MEITL), and low-grade intestinal T-cell lymphoma (LGITL). For the purpose of this consensus statement, the experts adopted the following terms:

- Chronic enteropathy for cats with chronic (at least 3 weeks' duration) signs of gastrointestinal disease where extragastrointestinal, metabolic, and infectious causes have been ruled out.
- Lymphoplasmacytic enteritis for inflammatory lesions in the gastrointestinal tract of cats with CE that are dominated by lymphocytic infiltration in the lamina propria.
- Low-grade intestinal T-cell lymphoma for lesions in the gastrointestinal tract of cats with CE characterized by a monomorphic infiltration of the lamina propria or epithelium or both of cats with small, mature, neoplastic (clonal) T lymphocytes.

TABLE 2 Evidence levels.[20,21]

Evidence level	Key features
I	• Randomized controlled trials in cats • Prospective, nonrandomized controlled trials in cats, with adequate sample size and no major methodological flaws
II	• Experimental laboratory trials in cats • Prospective studies with inadequate sample size • Retrospective clinical studies with intervention and control groups
III	• Retrospective clinical studies and case series in cats without control groups
O	• Studies in other species
E	• Expert opinion

3.2 | Incidence

The true incidence of LPE or LGITL remains unknown. However, studies imply that the incidence of intestinal lymphoma may have increased since the advent of the FeLV vaccine[1] and that presently most AL cases do not exhibit circulating FeLV antigen.[22]

Whether this situation is a true increase in incidence or a reflection of other factors such as an increased caseload (i.e., because of urbanization), improved healthcare for cats, and increased longevity has not been studied.

3.3 | Etiopathogenesis

3.3.1 | Infectious agents

Although a causative relationship between high-grade lymphomas such as mediastinal lymphoma and FeLV infection has been well documented, the association between low grade lymphomas such as LGITL and FeLV and FIV infections is poorly documented. The majority of cats with LGITL test serologically negative for both FeLV and FIV.[1,23,24] However, some studies found FeLV genetic material in samples from cats with LGITL using immunohistochemistry (IHC) or polymerase chain reaction (PCR)[25,26] and hence the role of regressive infections in lymphomagenesis is still unclear.[27] To our knowledge, no studies have investigated the role of retroviruses in cats with LPE.

Bacterial mucosal colonization has been investigated as a driver of neoplastic transformation in humans, dogs, and cats. Gastric colonization with *Helicobacter pylori* is strongly associated with gastric inflammation and development of gastric adenocarcinomas and mucosa-associated lymphoid tissue (MALT) lymphoma in humans.[28,29] Although a statistically significant association of mucosa-invading and intravascular bacteria has been found in intestinal large cell lymphomas in cats, no association between LGITL and bacterial invasion has been reported.[30] Dysbiosis in humans and animal models of LPE has been found to promote inflammation and malignant transformation, especially the development of colorectal cancer.[31] The role of dysbiosis in CE of cats is poorly understood. Previous studies reported intestinal dysbiosis in cats with LPE and LGITL, which parallels findings in humans.[32,33] However, dysbiotic patterns were not significantly different between cats with LGITL and LPE.[32]

3.3.2 | Chronic inflammation

Chronic inflammation is a well-known promoter of oncogenesis, and several arguments support the hypothesis that LPE and LGITL represent a continuum rather than 2 separate disease entities. Progression of LPE to LGITL previously has been suspected based on the frequent coexistence of inflammatory and neoplastic lesions in cats with LGITL, a previous history of LPE or both.[34-36] In addition, concurrent inflammation in the same or other parts of the gastrointestinal tract has been documented in up to 60% of cats with LGITL.[35-39] The duration of clinical signs has been documented to be significantly longer in cats with LGITL compared with LPE.[40] Epitheliotropism can be found in both entities.[18,34,41,42] In some cases of LGITL, an apical-to-basal gradient has been described, suggesting chronic endoluminal antigenic stimulation; no LGITL cases have been shown to emerge from the depth of the mucosa.[18] Minimal and mostly gradual differences within the fecal microbiome and metabolome of cats with LGITL or LPE have been reported and there is high similarity with perturbations seen in humans with IBD.[32,43] Recently dysregulations of the janus kinase (JAK)-signal transducer and activator of transcription (STAT) pathway with high expression of STAT5 were documented in cats with LGITL.[3,19] The JAK^{-} STAT pathway plays a critical regulatory role in lymphocyte development, differentiation, and proliferation, and its dysregulation has been shown to be a major oncogenic driver in several lymphoma subtypes in humans.[44]

3.3.3 | Other factors

The role of exposure to environmental tobacco smoke in the pathogenesis of CE in cats has been evoked but remains controversial. One study found a significantly increased risk of development of lymphoma in cats exposed to environmental tobacco smoke. However, this study did not specify the type of lymphoma.[45] A second study did not find any association between hair nicotine concentration and the development of gastrointestinal lymphoma.[46]

3.4 | Signalment and clinical presentation

Statement

There are currently no known pathognomonic signalment or clinical findings that can reliably distinguish between LPE and LGITL in cats, because both conditions overlap with a wide range of presentations, including no clinical signs at all

Evidence level

II/III

Panel vote

6 out of 6 members strongly agreed

Cats with LGITL[38,47,48] have been reported to be older than cats with LPE[49-52] (median ages, 13 and 8, respectively). However, a significant age overlap exists with LPE ranging from 1.3 to 16 years vs LGITL ranging from 4 to 20 years. Interpretation of the pertinent literature is challenging because of inconsistent use of classification schemes. Recent studies imply that LGITL is very uncommon in cats under 8 years of age.[40] The role of breed is unclear. To date, no specific association has been found consistently between breed and LGITL in cats, although domestic shorthair and Siamese breeds are over-represented in some studies of AL.[38,39,53] Some studies also have mentioned an overrepresentation of male neutered cats.[39,40,54]

Duration of clinical signs before presentation is generally chronic in both cats with LPE and LGITL. However, a recent study found clinical signs to be present for longer in LGITL cats (median, 365 days; range, 62-1460 days) compared with LPE cats (median, 107 days; range, 7-1095 days; $P < .001$).[40] In contrast to dogs, the clinical phenotype of CE in cats is not dominated by diarrhea. Other common clinical signs include weight loss, lethargy, hyporexia, polyphagia, vomiting, and more rarely constipation.[32,36-38,43,47,48,52,55-63] No study found significantly different clinical signs in cats with LPE or LGITL, and cats with LGITL can present with minimal or even no clinical signs.[64] The absence of diarrhea does not rule out severe intestinal disease including LGITL. Although weight loss is the most common clinical sign, it often is overlooked by clients or even veterinarians. Cats can have substantial sarcopenia, especially of epaxial muscles whereas an abdominal fat pad is preserved.

Findings on physical examination may include abdominal pain or discomfort and diffusely thickened bowel loops. Mesenteric lymphadenopathy may be found on abdominal palpation and large abdominal masses or lymph nodes more often reflect higher grade gastrointestinal lymphomas or other diseases including other neoplasms, infectious diseases (e.g., feline infectious peritonitis [FIP], fungal disease, mycobacteria), or gastrointestinal eosinophilic sclerosing fibroplasia of cats. The clinical presentation can vary widely depending on the individual cat and possible comorbidities, such as hyperthyroidism, chronic kidney disease, chronic pancreatitis, chronic cholangitis, urolithiasis, and hypertrophic cardiomyopathy. Also, cats with LPE or LGITL may have a normal physical examination findings.

3.5 | Anatomical location

Any part of the gastrointestinal tract can be affected by LPE or LGITL, but some locations are more frequently reported in LGITL: jejunum, ileum, duodenum, stomach, and colon, in descending order of occurrence.[34,35,38] The stomach is more commonly involved in cats with large cell lymphomas,[34,38,65,66] but is rarely affected by LGITL and has not been reported to be exclusively affected without involvement of the small intestinal tract. Although colonic involvement in cats with LPE is more common, it is rare in cats with LGITL.

3.6 | Laboratory data

Statement

Laboratory tests cannot differentiate between LPE and LGITL and currently there are no specific cancer markers for LGITL in cats.

Low serum cobalamin concentrations are more frequent in cats with LGITL.

Evidence level

II

Panel recommendation

6 out of 6 members strongly agreed

Laboratory tests are always required to distinguish CE from other diseases causing chronic gastrointestinal signs and a typical diagnostic evaluation involves a CBC, serum biochemistry panel, urine and fecal analyses, and total thyroxine concentration. Cats with outdoor access or those in multi-cat households should be tested for FeLV and FIV, given the previously reported associations with intestinal lymphoma.[1,61]

Interpretation of the literature regarding laboratory data and biomarkers was substantially compromised because not all studies reliably differentiated between LPE and LGITL or provided information on the fraction of cats with biochemical changes. Today, there is no single biomarker or biomarker panel that reliably diagnoses LPE or LGITL in cats. However, laboratory tests are needed to rule out metabolic, endocrine, and infectious diseases as well as exocrine pancreatic insufficiency, pancreatitis, or chronic cholangitis, the latter 2 often occur concurrently with a CE.[52,55,58,67-74]

The current paradigm in veterinary medicine requires differentiating food-responsive enteropathies from CE using dietary trials. However, the differentiation of LPE and LGITL requires more advanced diagnostic techniques such as histopathology, immunohistochemistry and PCR for antigen receptor rearrangement (PARR). That said, even with the most advanced techniques, ambiguous cases still remain and the distinction between LPE and LGITL is not entirely clear today.

Hypoalbuminemia, although common, is usually mild and may be because of negative acute phase reactivity or enteral loss with reports ranging from 14% to 100% of cases.[40,50,75,76] Severe protein-losing enteropathy and marked hypoalbuminemia are extremely rare in cats with CE. Total protein concentration is often normal or even increased because of concurrent hyperglobulinemia and an increased total protein concentration is part of the feline chronic enteropathy activity index (FCEAI).[52] In addition, mild hypoglobulinemia and pan-hypoproteinemia also are described in both LPE (39%) and LGITL (55%).[40,75] Increased liver enzyme activities have been reported in cats with LPE and LGITL.[40,52,77] One study found increased ALT serum activity to be predictive of histopathological severity of LPE, and ALT activity was included as a parameter in the FCEAI.[52] Another recent study found increased liver enzyme activity in only 14% of cats with LGITL and in 0% of cats with LPE, and ALT was significantly different between the groups.[40]

Acute and chronic pancreatitis has been identified in humans with IBD.[78] Frequent reports also exist in cats with CE, based both on histopathological results and increased feline pancreatic lipase immunoreactivity (f-PLI) serum concentration.[68,71,72,79] Although the prevalence of pancreatitis appears to be higher in cats with CE, histopathological lesions consistent with pancreatitis are also common in clinically healthy older cats, and their occurrence has been correlated with age.[79] Anecdotal evidence seems to be high, but few comprehensive studies are available, and the true association or even causative relationship between CE and pancreatitis in cats remains to be assessed.[80] Similar to dogs, the presence of increased f-PLI serum concentration or

ultrasonographic changes alone may not be truly representative of disease status, and it is currently unclear whether extrapancreatic disease can lead to increased serum f-PLI concentrations in cats as reported in dogs.[81] Whether pancreatitis is truly linked to CE or an incidental comorbidity, it should be ruled out using a combination of clinical signs, serum f-PLI concentration, imaging findings and pancreatic histopathology.

Few retrospective studies have investigated signalment, clinical signs, and concurrent diseases in cats with exocrine pancreatic insufficiency (EPI).[74,82] They highlight EPI as an important differential diagnosis of CE in cats. One study showed an association between CE and EPI in cats based on ultrasonographic findings, intestinal biopsy results or both.[82] Therefore, feline trypsin-like immunoreactivity (f-TLI) should be assessed in cats with clinical signs of chronic gastrointestinal disease and EPI should be considered as a differential diagnosis as well as a potential comorbidity.

Cobalamin and folate are water soluble vitamins present in dietary proteins and folates are synthesized by intestinal bacteria. Cobalamin binds to intrinsic factor which, in cats, originates exclusively from pancreatic secretion.[83,84] Although folate is absorbed in the proximal small intestinal tract, cobalamin mainly is absorbed in the distal small intestinal tract, especially the ileum.[83,85] Therefore, decreased serum concentrations of either or both B vitamins may give clues to disease localization. Hypocobalaminemia frequently has been documented in cats with CE with a reported prevalence between 18% and 80%.[40,47,67,73,75,86-93] In studies that compared serum cobalamin concentrations between cats with LPE and those with LGITL, the prevalence of hypocobalaminemia was reported to be significantly higher in cats with LGITL.[40,67,88,89,94] An increase in serum methylmalonic acid (MMA) concentration indicates cellular cobalamin deficiency and hence has been investigated in correlation with serum cobalamin concentrations in cats.[87,88,95,96] Serum cobalamin concentrations of <209 and 290 ng/L have been shown to have sensitivities of 51% and 74% and specificities of 96% and 80% for an increase of serum MMA indicating cellular cobalamin deficiency.[88,95] However, given the safety profile of cobalamin supplementation, identification of the serum concentration with the highest sensitivity for increases in MMA would be desirable. Conversely, cats with clinically relevant gastrointestinal disease may have normal serum cobalamin concentrations, and the absence of hypocobalaminemia does not exclude any gastrointestinal disease.[89] Increased serum cobalamin concentrations have been associated with inflammatory, immune-mediated, hepatic, and neoplastic diseases in cats.[97,98]

Both, hypofolatemia and hyperfolatemia have been reported in cats with CE.[47,67,75,87] Increased folate concentrations have been associated with small intestinal bacterial overgrowth in people,[99,100] but an association with dysbiosis in dogs and cats is not documented. One study reported serum folate concentrations of 15.5 µg/L to have a 80% sensitivity and 100% specificity for a diagnosis of LGITL in cats. However, hemolysis can cause clinically relevant increases in serum folate concentrations and thus should be considered when interpreting results.[89,101] Folate supplementation has been shown to be beneficial in people with IBD and hypofolatemia[102] but no data has been published in cats.

Other biochemical abnormalities reported in cats with chronic gastrointestinal disease are iron deficiency anemia, hypophosphatemia, hypovitaminosis D, increased serum lactate dehydrogenase (LDH) activity.[60,86,96,103] However, none of these markers has been shown to differentiate LPE from LGIT in cats. Feline thymidine kinase 1 recently has been suggested as a new specific biomarker in cats with lymphoma.[104,105] However, studies have not specifically investigated its value for LGITL, but included multiple lymphoma subtypes or lacked an appropriate control group including inflammatory intestinal lesions.[104,105]

3.7 | Diagnostic imaging

Statement

Abdominal ultrasonography is an important diagnostic tool in the diagnostic evaluation of cats with CE. It allows for cross-sectional evaluation, anatomical localization, characterization of bowel wall mural architecture, and mesenteric lymph nodes as well as evaluation of other abdominal organs. The sonographic abnormalities of CE have been well described, however, substantial crossover between the LGITL and LPE exists and clinically relevant pathology can be present in the bowel with a normal ultrasound appearance. Thus, currently no imaging technology reliably differentiates LPE from LGITL, and intestinal histopathology is required for establishing the diagnosis of CE.

Evidence level

II/III

Panel recommendation

5 out of 6 members strongly agreed, 1 member agreed

3.7.1 | Radiography

Limited data on the diagnostic utility of abdominal radiographs in cats and only few studies in dogs with clinical signs of CE are available.[76,106-110] Two studies comparing planar radiographs to abdominal ultrasound examination (AUS) in cats found radiographs either nondiagnostic[76] or diagnostic in only 1.9% of cases.[107] In cats with clinical signs of abdominal disease, combined assessment of radiographs and AUS allowed for a final diagnosis of renal disease or abdominal masses in 23.8% of cases; none of the cats was diagnosed with diffuse gastrointestinal disease.[107] Although radiographs may be useful to exclude abdominal masses and obstructions,[106] they appear rarely to provide additional benefits to AUS.

3.7.2 | Abdominal ultrasound examination

Various studies have investigated the diagnostic utility of AUS for the diagnosis and differentiation of LPE from LGITL in cats,[40,52,58,62,65,67,69,111] and evidence suggests that AUS is a critical step in the diagnostic evaluation of cats with clinical signs of chronic gastrointestinal disease. Besides the assessment of the intestinal tract, AUS allows for diagnostic evaluation of other organs, including the liver and biliary system, the pancreas, abdominal lymph nodes, the spleen, and the urinary tract. This feature is particularly important because multiple comorbidities often are identified in older cats and the term triaditis has been coined to describe the concurrent occurrence of LPE, pancreatitis, and cholangitis in cats.[71,72,112] In addition, AUS is a useful tool for identifying abnormal intestinal segments and helps with planning subsequent diagnostic procedures such as full-thickness laparotomic vs endoscopic biopsies. It also can be used in AUS-assisted fine needle aspiration of enlarged lymph nodes, abdominal masses, or aspirates of the liver and spleen.

Diffuse thickening of the muscularis propria, submucosa, or mucosa layer in the small bowel is the most common ultrasonographic finding and has been observed in 50% to 95% of cats with CE.[3,38,40,58,62,65,69,93,111] Again, the interpretation of the pertinent literature is challenging because the evaluated variables vary between total intestinal wall thickness and muscularis or mucosal layer, and not all studies specify the segment imaged by ultrasonography. Currently available data suggest that substantial overlap exists for ultrasonographic changes of the intestinal wall between cats with LPE and LGITL. Two studies showed that cats with LGITL had significantly increased thickness of the muscularis propria layer[111] or the mucosa,[40] compared with cats with LPE. A single prospective study showed that the jejunal mucosal wall layer was significantly thicker in cats with LGITL (median, 1.4 mm; range, 0.7-2.3 mm) compared with LPE (median, 1.0 mm; range, 0.4-2.8 mm).[40] Various studies have investigated the predictive value of ultrasonographic findings for the identification of histopathologic lesions with highly variable results.[69,111,113] Although 2 studies found high predictive value of ultrasonographic changes for the presence of transmural disease[111] or unspecified histopathologic small intestinal disease,[69] these findings were not confirmed by others.[113] The latter study found that although ultrasonographic abnormalities in the mucosa were highly predictive of mucosal histologic lesions, the presence of thickened submucosa or muscularis layer did not correlate with histopathologic lesions in these segments.[113] A major caveat of these approaches is that a substantial overlap exists between healthy cats and cats with CE and that both ultrasonographic and histopathologic changes also have been documented even in clinically healthy cats.[64,65,111] Hence, the presence of either is not necessarily predictive of clinical disease. One study evaluated the muscularis-to-submucosa ratio and the muscularis-to-mucosa ratio in cats with LPE and LGITL compared with healthy cats (Figure 1). Although the muscularis-to-submucosa ratio was lower in healthy cats than in cats with LPE or LGITL, in some small intestinal segments, the muscularis-to-submucosa ratio was not significantly different between groups.[65] In this study, a muscularis-to-submucosa ratio >1 was indicative of an abnormal bowel segment, but no difference was found between LPE and LGITL.[65] Eosinophilic enteritis has been identified as an important differential diagnosis in cats with diffuse thickening of the muscularis layer.[114] In a retrospective study, cats with eosinophilic enteritis had a significantly thicker muscularis layer than cats with lymphoplasmacytic enteritis.[114]

Several studies have investigated abdominal lymphadenopathy in cats with LPE and LGITL compared with healthy cats.[40,65,111] Results of 2 studies found median or mean lymph node size to be significantly higher in cats with LGITL compared with healthy cats, but no difference between LPE and LGITL was found.[65,111] One study found that jejunal lymph node size, echogenicity, and structure was significantly different in cats with LGITL compared with cats with LPE. Jejunal lymph nodes in cats with LGITL were significantly thicker (LGITL: median, 6.7 mm; range, 2.9-12 mm; LPE: median, 4.2 mm; range, 1.8-8.8 mm), significantly rounder and more hypoechoic compared with cats with LPE (Figure 2).[40] The same study showed that the presence of mild abdominal effusion tended to be associated with a final diagnosis of LGITL (45% in cats with LGITL vs 14% in cats with LPE).[40,94] Specific lesions in liver and spleen that allow for differentiation of LPE from LGITL have not been reported in cats.

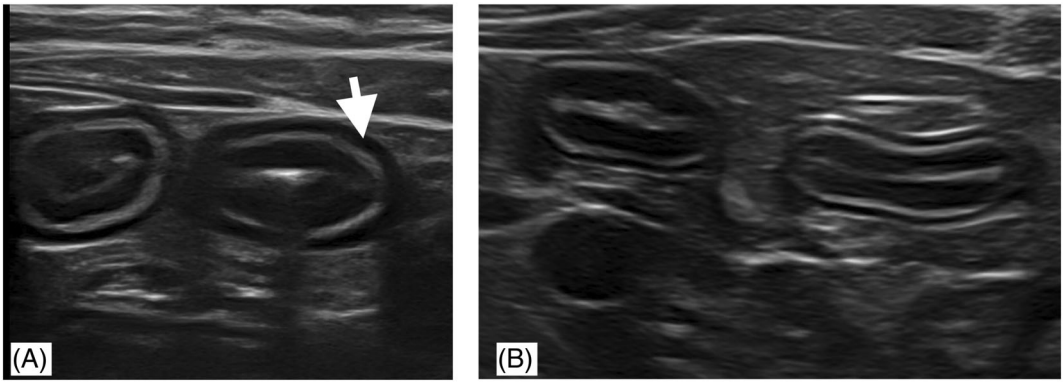


FIGURE 1 (A) Ultrasonographic aspect of the jejunum in cats finally diagnosed with a CE (LPE or LGITL): the muscularis layer is diffusely thickened (arrow). (B) Normal aspect of the jejunal wall.

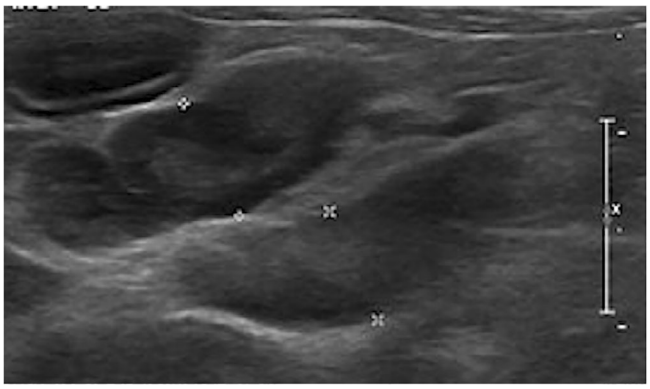


FIGURE 2 Ultrasonographic aspect of the jejunal lymph node in a LGITL case. The lymph node appears rounded and hypoechoic.

Conversely, a study on ultrasonographic findings in 22 cats with hypocobalaminemia reported the absence of ultrasonographic changes in 54% of cats with LPE, in 15% in cats with LGITL, and in 12% with other intestinal neoplasia. One cat with unremarkable abdominal ultrasound examination was later diagnosed with histoplasmosis.[93] This observation indicates that the absence of ultrasonographic changes does not exclude the presence of clinically relevant gastrointestinal disease in cats.

Similar to other diagnostic tests, interpretation of relevant literature evaluating ultrasonography is difficult because of variable equipment (especially over time), interobserver variability, the nature of the study (prospective vs retrospective, study approach [i.e., from a radiology, internal medicine, or pathology point of view]), the number of cases, enrollment criteria of healthy or diseased cats, segmental or subclinical disease, the presence of concurrent diseases, different lymphomas, and previous treatments including antimicrobials, and immunosuppressants.

No studies currently are available on the merit of other imaging modalities such as computer tomography (CT) or magnetic resonance imaging (MRI) for the diagnosis or differentiation of cats with LPE or LGITL.

3.8 | Cytology

Statement

Although cytology is helpful to exclude important differential diagnoses in cats with CE, cytology cannot be used to differentiate LPE from LGITL.

Evidence level

III

Panel recommendation

5 out of 6 members strongly agreed, 1 member agreed

Cytology can be of benefit in the diagnostic evaluation of cats with clinical signs of CE and is often the first line of diagnosis in cats with abdominal masses, lymphadenomegaly, or organomegaly. Fine needle aspirates can be helpful in excluding important differential diagnoses such as high-grade lymphomas, other round-cell neoplasia, or fungal disease.[23,61,115-120]

However, because of the lack of architectural information and overlapping cellular morphology, cytologic examination of fine needle aspirates from the intestinal wall is not helpful for reaching a definitive diagnosis of either LPE or LGITL (Figure 3). Lymphoplasmacytic enteritis in cats is characterized by a mixed infiltrate of mature lymphocytes and plasma cells. The infiltration generally is located in the lamina propria and in some areas extending into the epithelium. Inflammatory lesions can occur with architectural changes such as crypt distortion and villus blunting.[41,42] Well-differentiated, mature, small lymphocytes are the hallmark of LGITL in cats. Architectural alteration of the lamina propria and epithelium can vary from minimal compromise to complete effacement.[18,37,61,63,121-124] Concurrent inflammatory changes are seen often.[34,35,55,58,69,125] No value is added by performing a jejunal lymph node fine needle aspirate compared with histopathologic evaluation of the intestinal wall alone. A recent study investigated the use of needle rinse cell block technique for the diagnostic evaluation of gastrointestinal nodular lesions.[126] In this technique, a cell pellet is formed from fine needle aspirates, embedded in formalin and processed conventionally into a hematoxylin and eosin (H&E)-stained histology slide. However, although this technique appears to be an interesting ancillary tool for gastrointestinal nodular lesions, it does not add architectural context over that obtained using conventional cytology.

3.9 | Biopsies

Statement

The collection of intestinal tissue biopsy specimens is the current gold standard for the diagnosis of and differentiation between LPE vs LGITL in cats. No clearly demonstrated superiority in quality exists for biopsy specimens obtained by laparotomy (full thickness) vs endoscopic biopsy specimens, because poor technique can affect sample quality and hamper diagnostic evaluation for both methods.

It has been shown that all inflammatory and neoplastic lesions are present in the lamina propria and hence, if mucosal samples of sufficient quality are procured endoscopically, a diagnosis is possible without obtaining full-thickness biopsy specimens. However, because of limited access to the jejunum by endoscopy, jejunal lesions cannot be reliably sampled although this small intestinal segment is frequently abnormal.

Evidence level

II

Panel recommendation

4 out of 6 members strongly agreed, 2 members agreed

The current gold standard for the diagnosis and differentiation of CE in cats requires collection and histopathologic examination of intestinal tissue biopsy specimens. However, the optimal sampling technique is still a matter of controversy.

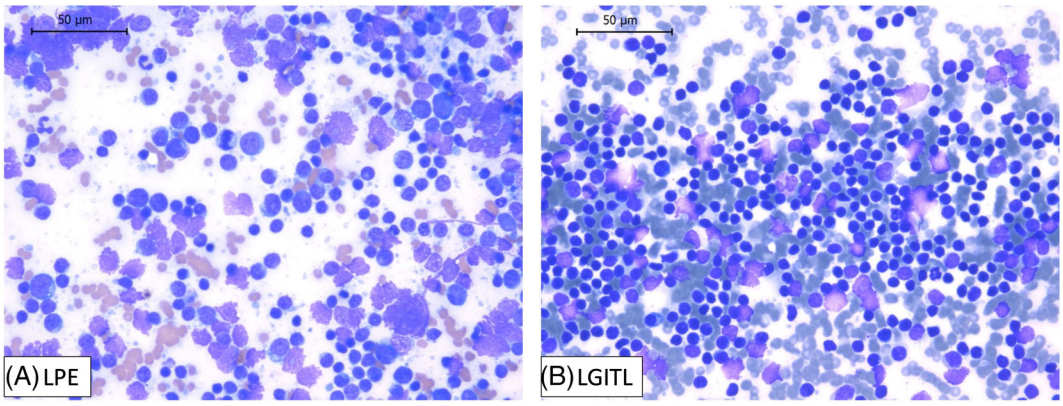


FIGURE 3 (A) Fine needle aspirate of an enlarged mesenteric lymph node from a cat later diagnosed with lymphoplasmacytic enteritis on small intestinal tissue biopsies. The aspirate mostly comprises small mature lymphocytes and reactive lymphocytes. One mitotic figure is visible (×100). (B) Fine needle aspirate of an enlarged mesenteric lymph node from a cat later diagnosed with small cell lymphoma on small intestinal tissue biopsies (×100). The aspirate mostly comprises small mature lymphocytes with few plasma cells in a blood-contaminated background. The number of small lymphocytes is not predictive of the final diagnosis and the sample is not diagnostic for small cell lymphoma.

Laparotomy is a widely available technique that can be performed in most small animal hospitals. It allows for sampling of full-thickness intestinal biopsy specimens and extraintestinal biopsy specimens. Furthermore, with laparotomy, jejunal samples can be collected, which can be important because the jejunum has been reported to be the most frequently affected intestinal segment in both diseases.[34,37,38] In addition, extraintestinal samples can be of value in cats with comorbidities such as hepatic or pancreatic disease or in cases with localized or eccentric intestinal lesions based on prior ultrasonographic assessment. Biopsy specimens obtained by laparotomy allow for the assessment of the entire gastrointestinal wall, but lesions of LPE and LGITL generally originate in the mucosa and may expand transmurally from there.[18,34] Transmural infiltration however has not yet been convincingly shown to be associated with shorter survival in cats with LGITL. One study comparing survival times in cats with mucosal and transmural infiltrates found cats with transmural T-cell lymphomas to have shorter survival times (median, 1.5 months) compared with cats with mucosal T-cell lymphomas (median, 29 months).[34] However, most transmural lymphomas were classified as large cell lymphomas including large granular lymphocyte lymphomas, the latter of which typically carry a grave prognosis with reported median survival times of 5 to 90 days.[127] Survival data on transmural LGITLs was only available for 4 cats with a range of survival between 3 days and 28 months. The limited number of samples (usually ≤5 biopsy specimens are collected) taken at laparotomy and the inability to see the mucosa while selecting a site for sample collection are major limitation of this technique. The low number of specimens results in a limited mucosal area available for analysis. Additional disadvantages include risks associated with surgery such as dehiscence, prolonged recovery time, wound healing complications, and the necessity to postpone treatment until wound healing is complete. Also, the diagnostic yield of the technique can be hampered when wedge-shaped biopsy specimens are obtained, which represents a common operator-related error. Wedge-shaped biopsy specimens have a large serosal area that funnels down through the muscularis into the mucosa. These biopsy specimens often appear of sufficient size, but the assessable mucosal area is small, damaged, or even absent. Occasionally, the mucosa, submucosa or both detaches from the muscularis and is lost during processing (Figure 4).

By contrast, endoscopy is mostly available at referral centers and few animal hospitals. It allows for direct visual examination of the mucosal surface and is minimally invasive. Targeted biopsy specimens from mucosal sites with gross lesions can be collected, which can be advantageous when lesions are distributed in a multifocal pattern. Furthermore, if necessary, medical treatment can be started immediately after endoscopy pending histopathology results. With appropriate endoscopic equipment, the proximal jejunum can regularly be examined and biopsied, although lesions located in the mid to distal jejunum are outside the range of the endoscope. Limiting factors for endoscopic procedures include difficult pyloric intubation, loss of pyloric elasticity, and acquired pyloric narrowing in cats with CE.[128] Moreover, intubation of the ileum may present a challenge in some cases where the angulation of the ileo-colic junction does not allow for entry into the distal ileum. Operator-related errors include inadequate sample number or quality (e.g., superficial samples consisting only of crushed villi). One study reported that a minimum of 6 mucosal biopsy specimens of adequate quality from the duodenum of cats and 3 to 5 from the ileum are required for a reliable histopathological evaluation.[129] However, another study determined that 10 to 15 duodenal biopsy specimens were required to confirm mild inflammatory lesions with confidence of at least 90%.[129] Studies in dogs[130] and cats[131] indicated that size of the forceps was correlated with the quality of the biopsy specimens and that larger capacity forceps provide superior sample quality. The presence of a spike in the center of the biopsy forceps was not found to have any effect on sample quality in dogs.[130] A study evaluating quality and adequacy of biopsy specimens collected using reusable or single-use forceps did not identify any difference in the quality of biopsy specimens in dogs.[132]

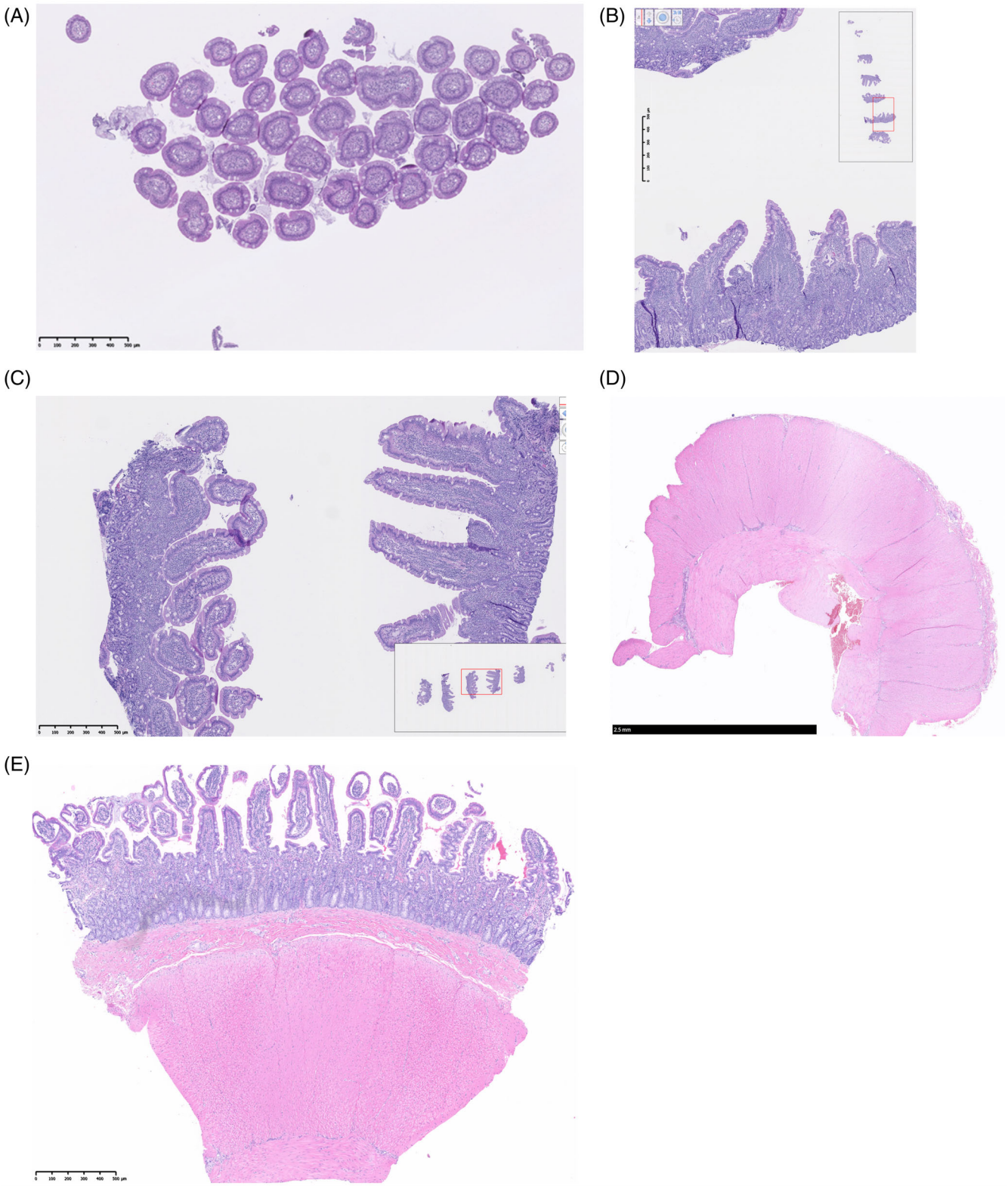


FIGURE 4 (Orientation) Hematoxylin and Eosin-stained endoscopically obtained biopsy specimens from cats with chronic enteropathies illustrating common errors associated with endoscopic (A-C) or surgical (D, E) biopsies. (A) Suboptimal sample orientation led to cutting this biopsy specimen tangentially, resulting in "villus slaw." The biopsy specimen is uninterpretable. (B,C) Examples of optimally oriented biopsy specimens from the same slide. Villi and crypts are cut parallel to the lamina propria and the entire lamina propria is visible for optimal interpretation. The images are the ×5 magnification of the red square in the slide map on the bottom right of images B and C. (D) Full-thickness duodenal biopsy specimen. While the biopsy is large and well-oriented the entire mucosa is missing making this specimen uninterpretable. (E) Full-thickness duodenal biopsy specimen. The biopsy specimen is well-oriented and fully accessible for histopathologic assessment. All biopsies on the slide are optimally oriented.

One prospective study directly compared endoscopically-obtained gastric and duodenal biopsy specimens with full-thickness biopsies obtained from the stomach, duodenum, jejunum, and ileum via laparotomy or laparoscopy in 22 cats with LPE or AL.[62] The authors concluded that endoscopically-collected biopsy specimens were inadequate for accurate differentiation of LPE from LGITL and that surgically-acquired full-thickness biopsy specimens from the jejunum and ileum were necessary for accurate diagnosis. However, the study only required the collection of 6 endoscopic duodenal biopsy specimens, and not all duodenal specimens were deemed adequate by the pathologist. In at least 5 cats, the endoscope was not passed through the pylorus into the duodenum and biopsy specimens were collected blindly with ≥3 specimens collected.

A second retrospective study assessed the diagnostic value of full-thickness intestinal biopsy specimens utilizing a 4 mm punch biopsy and extraintestinal biopsy specimens from cats with chronic signs of gastrointestinal disease. The authors concluded that full-thickness biopsy specimens were helpful in the diagnosis. However, they did not directly compare full-thickness and endoscopic biopsy specimens or investigate the agreement between diagnoses when considering all available samples vs limiting diagnosis to the mucosa.[133]

3.10 | Histopathology and immunohistochemistry

Statement

Histology is required for the diagnosis and differentiation of LPE from LGITL in cats. It requires proper sampling, processing, and interpretation of key lesions (which includes inflammatory infiltrates, neoplastic cells, and other intestinal wall changes).

Ambiguous cases often require ancillary tests such at immunohistochemistry and clonality tests.

Evidence level

II/O

Panel recommendation

6 out of 6 members strongly agreed

3.10.1 | Histology

Histopathologic examination of H&E-stained biopsy specimens remains the gold standard for the diagnosis and differentiation of CE in cats, and preparation of biopsy specimens (including orientation) is critical. Even adequately collected samples can lead to suboptimal or even inadequate H&E staining if specimens are misoriented (Figure 4). One study compared mounting intestinal biopsy specimens on cucumber slices or moisturized synthetic foam sponges to free flotation in formalin[134] and determined that mounted samples had significantly fewer artifacts and that pathologists had higher confidence in their histopathologic interpretation. Some histopathology laboratories orient free-floating samples before paraffin embedding. Like mounting, proper orientation of the sample during embedding can improve diagnostic accuracy. Figure 5 and Video S1 explain the process of orientation before embedding the sample in paraffin.

Even with adequate sample numbers and quality and optimal processing, it can be difficult to arrive at a precise diagnosis. Such cases require additional diagnostic tests including immunohistochemistry and clonality tests as discussed in later sections.

Clinicians should attempt to build a strong communication connection with their pathologist to optimize sample quality and report interpretation for the best possible patient care.

Interobserver variability among pathologists can be a concern. One study investigating the agreement among 5 different pathologists assessed the degree of cellular infiltrates in the intestinal mucosa of dogs and cats and identified a very high rate of interobserver variability.[135] As a response, the World Small Animal Veterinary Association (WSAVA) histopathology standardization group was formed and published criteria for the histopathologic assessment of endoscopic samples from the gastrointestinal tract in dogs and cats in 2008. A standard form was developed including a grading scheme from 0 (normal) to 3 (severe), assessing architectural changes (epithelial injury, villus blunting, crypt distention, fibrosis, and lacteal dilatation) and the degree and quality of cellular infiltrates in the mucosa.[41,42] However, interobserver variability remains an issue despite attempts to simplify the grading scheme.[136] In addition, the scope of the WSAVA standardization did not encompass the differentiation of LGITL from LPE in cats, and the standardization was designed and validated only for IBD. Since the WSAVA recommendations were published, a new histopathological assessment scheme for the assessment of intestinal biopsy samples from cats with CE has been proposed.[18] The scheme is based on the 2016 revision of the World Health Organization (WHO) classification of lymphoid neoplasms in humans,[2] the WHO classification of lymphoma in dogs, immunohistochemical expression of CD3, upregulation of STAT 5, and Ki67 expression (see Section 3.10.2), and clonality analysis in cases with lymphoma. Different patterns of cellular distribution in LGITLs have been recognized by pathologists, ranging from massive infiltration of the lamina propria with complete effacement of the lamina propria and loss of architecture, and marked epitheliotropism, to more subtle forms including specific patterns such as gradients within the lamina propria or nests or plaques or both within the intraepithelial compartment (Figure 6). Based on findings in a variety of cases, lesions appear to originate in the apical part of the villi and expand through the lamina propria or even transmurally. In the newly proposed histopathology grading scheme created for cats, differentiating LPE from LGITL can be improved if epithelium and lamina propria are assessed separately and in a structured fashion.[18]

Regardless of the assessment scheme used, histopathologic examination of H&E-stained biopsy specimens can be insufficient to reach a final diagnosis, and immunohistochemistry can be a valuable tool in ambiguous cases. Ambiguous cases present both inflammatory and neoplastic features, such as epitheliotropism in a polymorphic background, inconsistent nest or plaque identification within single villi, and areas of monomorphic lymphocytes within the lamina propria in an otherwise polymorphic background.

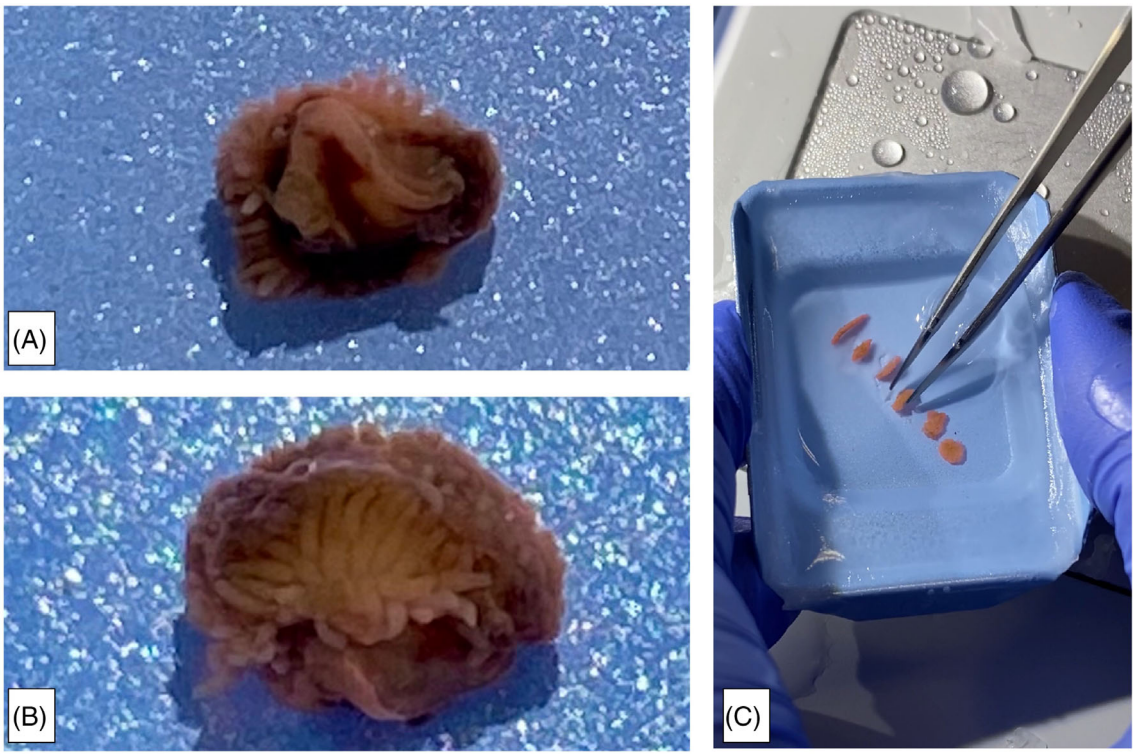


FIGURE 5 (Orientation): Histologic processing of endoscopically obtained formalin-fixed biopsy specimens by a histologist. (A) Jejunal biopsy specimen. The specimen is upside down with the villi facing downward. (B) Jejunal biopsy after reorientation, Villi are visible, pointing upward. (C) The histologist is orienting biopsy specimens in a position that allows for cutting the specimen parallel to the lamina propria. In this image the four specimens on top have been reoriented, whereas the two bottom specimens are still in a tangential position. Courtesy of Kelly Mallet, Texas A&M Gastrointestinal Laboratory, College Station, TX.

Chronic inflammation potentially can increase the risk of developing LGITL, and concurrent LPE has been described in up to 60% of cases with LGITL.[34,36-39] Thus, it has been hypothesized that LPE may precede or promote gastrointestinal neoplasia.[38,61,63,121-123]

In addition, some cats diagnosed with LGITL have been observed to develop large cell lymphoma over time.[137] It is currently unknown whether these neoplasms represent true disease progression or are separate entities because the co-existence of lymphomas originating from distinct clones has been documented.[34] At this point, no single diagnostic test is available to reliably differentiate LPE from LGITL. The combination of clinical data (e.g., age, duration of clinical signs), imaging, laboratory data, histopathology, immunohistochemistry, and clonality assays appear to be the best approach to reach a final diagnosis. However, grading schemes and diagnostic tests are expected to evolve over time and eventually improve the accuracy of diagnostic testing and, most importantly, treatment options for affected cats. More biomarkers also are being developed and tested for sensitivity and specificity.

3.10.2 | Special stains and immunohistochemistry

Immunohistochemistry can be readily performed as a complementary technique to standard histology on formalin-fixed and paraffin-embedded (FFPE) biopsy specimens (see Table 3). For ambiguous cases, it is an essential ancillary diagnostic tool. Immunohistochemistry utilizes specific antibodies to recognize and bind antigenic determinants (epitopes), enabling microscopic detection of biomarkers for differentiation and proliferation.[34,36,51,121,138-141] Cellular infiltrates seen on H&E-stained sections can be interrogated for their differentiation by applying antibody markers thereby investigating whether an infiltrate appears monomorphic or mixed. Monomorphic infiltrates imply the presence of cellular clones whereas a mixed infiltrate implies the presence of antigenic stimulation during inflammation. However, this technique does not allow for absolute differentiation. Concurrent inflammation frequently is identified in adjacent or the same intestinal location in cats with LGITL.[35-39] On the other hand, chronic antigenic stimulation has been described to lead to monoclonal lymphocyte proliferations.[9] Commonly used antibodies for cellular phenotyping include cluster of differentiation (CD)3 to detect T-lymphocytes,[34,36,51,56,121,139,141,142] CD20, CD79a, B lymphocyte antigen 36 (BLA.36), and paired box gene 5 (Pax5) for B-lymphocytes,[34,36,51,138,140,143] macrophage marker antibody 387 (MAC387) for macrophages,[18,144-146] and granzyme B to detect natural killer (NK) cells. Finally, the proliferative cell fraction can be assessed using Ki67 expression,[147,148] a nuclear protein with maximal expression during M phase that is absent after mitosis is completed.[147] Most intestinal lymphomas in cats appear to be CD3 positive small cell

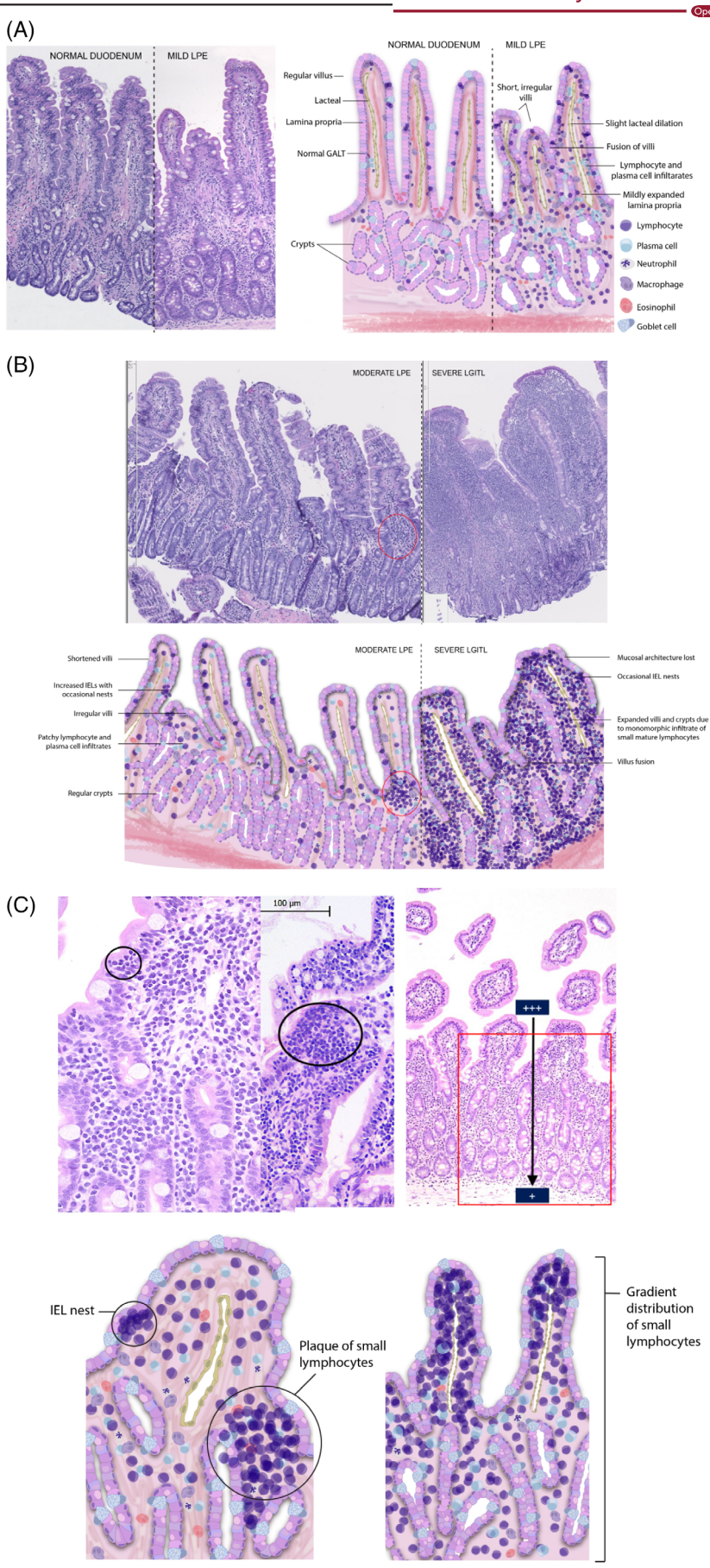


FIGURE 6 Legend on next page.

lymphomas that reportedly represent from 63% to 74% of all intestinal lymphomas (Figure 7).[34,36] Other types of lymphoma include large cell T-cell lymphomas, B-cell lymphomas, NK cell lymphomas, and large granular lymphocyte lymphomas. However, interpretation of the pertinent literature is obscured because of highly variable inclusion criteria such as different anatomic sites, mucosal vs transmural lymphomas, different subtypes, FeLV+ vs FeLV− cats, and interobserver variability.[54,63,140,149-152]

Since the advent of whole genome sequencing of the canine and more recently the feline genome, the field of comparative pathology has made considerable efforts to establish small animals as models for spontaneously occurring diseases in humans.[153] Canine and feline companions share many disease characteristics, including environment, biological behavior, histological appearance, genetic tumor mutations, and response to treatment with their owners. The EATL-type tumors are rare peripheral T-cell lymphomas arising from intraepithelial intestinal cytotoxic T-cell lymphocytes. Two disease variants are recognized by the current WHO classification in people, namely enteropathy-associated T-cell lymphoma (EATL)-Type I and EATL-Type II (recently renamed monomorphic epitheliotropic intestinal T-cell lymphoma [MEITL] or monomorphic $CD56^+$ intestinal T-cell lymphoma).[2] Although EATL-Type I is associated with celiac disease, EATL-Type II (MEITL) is less common and infrequently associated with celiac disease. Because of its morphologic features, including size of lymphocytes and epitheliotropism, previous studies suggested LGITL as a relevant model of MEITL.[19,34,154] However, despite LGITL having histologic similarities with MEITL, the clinical course of these 2 diseases and their immunophenotyping differ markedly. The MEITL neoplasms in humans co-express CD3 and CD56 (a natural killer cell marker), have high mitotic index with high expression rate of Ki-67, do not feature concurrent inflammatory lesions, and have an aggressive clinical course with a median survival time of only 7 months.[2,57,155-157] In contrast, LGITLs in cats are generally slowly progressing, indolent neoplasms, with a low mitotic index and a low expression of Ki-67 (Figure 8), frequently featuring concurrent inflammatory lesions, and are characterized by $CD3^+$/$CD56^-$ cells.[18,142] Moreover, 2 recent studies described a high expression of signal transducer and activator of transcription (STAT)5 in LGITL cases.[3,41] In this context, STAT5 phosphorylation suggests that the JAK/STAT signaling pathway could play a key role in LGITL (Figure 9).

The most recent WHO classification of lymphoid neoplasms in people was the first to include a new class of indolent gastrointestinal T-cell lymphoma in humans, gastrointestinal T-cell lymphoproliferative disorder (GI-TLPD).[2,158] This subtype of intestinal lymphoma has a slow clinical course with a median follow-up time of >5 years (median survival time not reached).[155,158-164] The disorder is characterized by small lymphocytes within the mucosa with variable epitheliotropism, high expression of CD3 (100%), variable expression of STAT5 (0%-44%), low expression of Ki 67 and STAT3, and absent expression of CD56.[155] Dysregulation of the JAK/STAT pathway has been well described in several lymphoma subtypes.[44,165] The LGITL in cats bear striking similarities to GI-TLPDs in humans with respect to receptor expression profiles, mitotic indices, and clinical course and thus LGITL in cats recently has been validated as a relevant model for GI-TLPD in humans.[18,57,142] Although LGITL in cats and GI-TLPD share many features including biological behavior, histopathologic characteristics, and immunophenotype ($CD3^+$, $STAT5^+$, $CD56^-$) further research to determine whether the cell types are truly identical is required.[57]

TABLE 3 Common immunohistochemical markers used in diagnostic samples from cats with lymphoplasmacytic enteritis and low-grade intestinal T-cell lymphoma (LGITL).

Cellular population or function	Antibody
T-cells	CD3
B-cells	CD 20, CD79a, BLA36, Pax5
NK-cells	Granzyme B, CD56
Macrophages	MAC387 (recognizes L1 protein, Calprotectin)
M-phase (cellular mitosis)	Ki-67
Upregulation of signal transduction as oncogenic markers	STAT3, STAT5
Cytotoxic T cells	TIA1
Calcium-binding protein expressed in neutrophils among other cells	S100/Calgranulin

FIGURE 6 Examples of histologic appearance of intestinal biopsy specimens from cats diagnosed with feline lymphoplasmacytic enteritis (LPE) or low-grade intestinal T-cell lymphoma (LGITL). (A) Hematoxylin and eosin (H&E) stained biopsy specimen of a normal feline intestine and mild LPE and their schematic views. There is a normal resident population of lymphocytes, plasma cells, macrophages, neutrophils, and eosinophils within the lamina propria. A small number of resident intraepithelial lymphocytes is present. Schematic view of a case of mild LPE (right). There is an increased population of lymphocytes and plasma cells present in the lamina propria. The number of IELs can be slightly increased. Architectural changes such as villus blunting, crypt distention, fibrosis, and epithelial injury may be present. (B) H&E-stained duodenal biopsy specimen from a cat with moderate LPE and marked LGITL and their schematic view. Left: Moderate numbers of lymphocytes and plasma cells are present in the lamina propria. An increased number of IEL as well as villus blunting can be observed. Right. H&E-stained biopsy specimen of a feline duodenum with unambiguous LGITL. A monomorphic population of small mature lymphocytes diffusely infiltrates and expands the lamina propria. Architectural changes such as severe villus blunting, fusion of villi, and crypt distention and distortion are frequently present. The villus-to-crypt transition is blurred and a clear distinction is often lost. (C) H&E-stained jejunal biopsies specimens histologic features in LGITL cases and their schematic view: nests, plaques, and gradient.

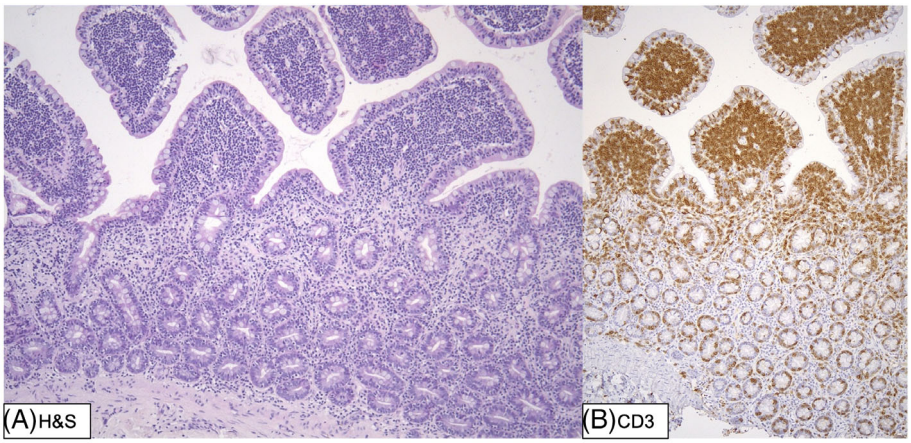


FIGURE 7 (A) H&E-stained jejunal biopsy specimen of a cat with LGITL. A monomorphic population of small mature lymphocytes with a gradient distribution most dense in the villus tips with a gradual decline toward the crypt area. (B) Anti-CD3 antibody staining of a jejunal biopsy specimen from a cat with LGITL with a gradient distribution as shown in A.

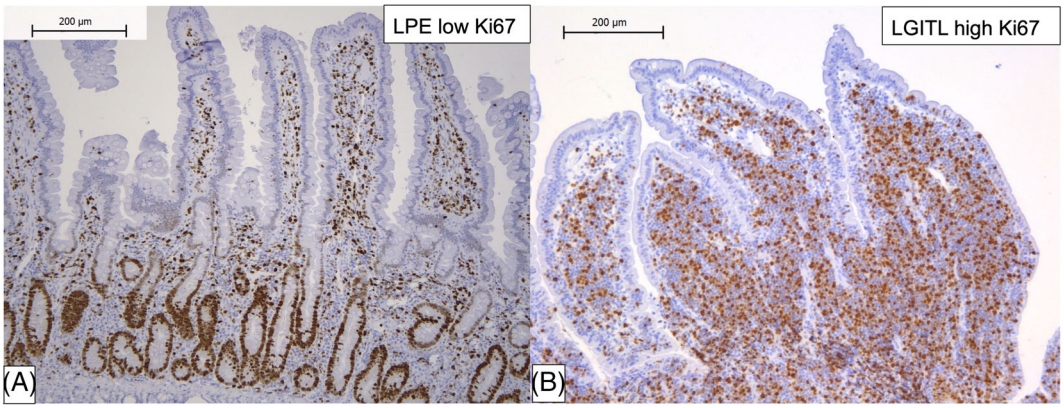
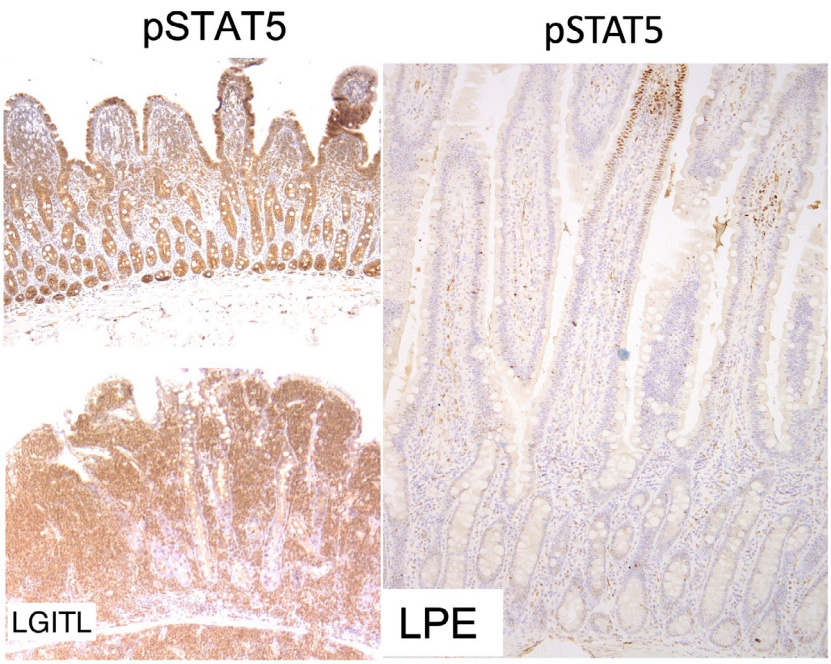


FIGURE 8 Comparative expression of Ki 67 in a LPE case (A) and a LGITL case (B).

FIGURE 9 Comparative expression of STAT5 in a LGITL case (left) and a LPE case (right).



Recent studies investigated additional diagnostic and prognostic markers including TIA1 cytotoxic granule-associated RNA binding protein and S100/Calgranulin. The presence of intraepithelial TIA1$^+$ cytotoxic lymphocytes was associated with poor prognosis in cats with LGITL[166]; S100/Calgranulin was not discriminant between LGITL and LPE.[94]

3.11 | Clonality analysis

Statement

Clonality can be an important part of the diagnostic evaluation of cats with CE. However, clonality must be interpreted in conjunction with clinical, histopathological, and immunohistochemical results and cannot be used as a sole means to reclassify cases.

Evidence level

II/O

Panel recommendation

6 out of 6 members strongly agreed

To differentiate neoplastic lymphoid proliferations from reactive lesions, tests assessing clonality increasingly have been used in veterinary pathology in conjunction with other diagnostic techniques, but only a few have been validated.[34,35,167-179] Clonality assessment can be performed using different techniques including flow cytometry, Southern blot analysis and PCR. Polymerase chain reaction for receptor antigen rearrangement is currently the only technique that can be applied to FFPE tissue samples and thus it is the most commonly performed technique on biopsy specimens from cats with CE.[35,167,169,180] The test is based on amplification of the CDR3 region of the T-cell receptor (TCR) for T-cells and immunoglobulin heavy chain genes for B-cells during repeat PCR cycles.[11,17,35,37,174,175,180,181] A previous study was the first to report this diagnostic tool for intestinal T-cell lymphoma in cats.[35] A priori neoplastic lesions such as LGITLs are thought to consist of the proliferation of a single or few cell populations resulting in a clonal PCR product (monoclonal or oligoclonal), whereas reactive lesions are expected to consist of heterogenous lymphocyte populations leading to a polyclonal PCR product.[34,35] However, deviations from this rule are occasionally described, which, beside technical challenges, limit the value of PARR as the final determining diagnostic technique as it has commonly been promoted in veterinary medicine.[56,167,182]

Several technical challenges exist, including poor DNA quality, low amounts of target DNA (i.e., low numbers of T-cells, in patchy disease), and limited primer coverage. Formalin-fixation has been shown to cause cross-links and fragmenting of nucleic acid resulting in decreased fragment size in purified DNA.[183] The impact of fixation on an individual sample is difficult to predict but is likely related to the duration of fixation, temperature, and whether adequately buffered formalin is used.[183] In addition, the relatively small amount of tissue present in paraffin shavings used for DNA extraction further limits the potential DNA yield.[17] Standardized protocols in human medicine include a control PCR amplifying multiple differently-sized gene fragments to help identify problems related to sample quality[17] and previous studies in cats included a germline DNA PCR amplification control.[34,35] Small DNA fragments will result in a loss of larger PCR products, affecting the size profile obtained from the PCR reactions, and thus complicating result interpretation. Poor quality DNA, especially if low numbers of lymphocytes are present, can result in apparent clonal rearrangement patterns that are not reproducible among reaction repeats (pseudo-clonality) and therefore reaction duplicates should be run.[17,181,183] Formalin fixation issues can be overcome by contemporaneous collection of biopsy specimens that are stored frozen for subsequent clonality analysis, which has been shown to improve sensitivity.[184] T-cells are present within both the lamina propria and the epithelial layer of the mucosa of the intestine of cats and considered part of the normal resident gut-associated lymphoid tissue.[139,145,185] Clonality analysis will amplify the T-cell receptor gene DNA from all T-cells present within a sample, regardless of whether they are considered clinically relevant (i.e., suspicious for LGITL) or not. In emerging LGITLs or patchy disease, the DNA from T-cells of interest may only comprise a small proportion of the total T-cell DNA. The proportion of clonal T-cells required for a clonal result is reported to be as low as 5% to 10%,[35] but this likely varies among different samples based upon gene usage in the clonal vs polyclonal population. Conversely, low numbers of lymphocytes have been reported to result in coincidental dominant peaks causing overinterpretation of results.[181]

Besides technical challenges, predicaments concerning the misinterpretation and overinterpretation of clonality assays are common. Clonality assays occasionally are used as a determinant for the cellular phenotype (i.e., whether a population of cells is of T-cell or B-cell lineage). However, cross-linage rearrangements, where T-cells rearrange B-cell receptor genes and vice versa, have been reported in lymphomas of humans,[6-8] dogs,[186] and cats.[11] One study showed 8 of 92 cases of LGITLs in cats to have clonal rearrangement of that of B-cells whereas IHC determined these populations to in fact be of T-cell lineage.[11] Therefore, PARR complements rather than replaces the use of IHC because it cannot determine lymphocyte phenotype.

Some authors have reclassified cases based on clonality results alone and 1 study implied that clonality was associated with shorter survival times.[36,182]

First, a subset of cats with clonal rearrangements did show long-term survival of >500 days in this study.[182] Second, although the authors did not report the age of cats for the 2 separate groups, cats with LGITL tend to be older than cats with IBD and hence shorter survival times are to be expected in that population.[38,47,48] Third, shorter survival times could be a related to longer standing or more severe intestinal inflammation leading to benign clonal expansion rather than representing true malignancy. Most importantly, the group of cats with clonal results did include cats that were already diagnosed by histopathology with LGITL and hence a shorter survival time is not unexpected. It would be of value to see whether cats that were reclassified on the basis of clonality results alone also show shorter survival times compared with cats with polyclonal results. In human medicine, only 5% to 15% of cases are considered to benefit from additional molecular clonality diagnostic testing and hence the recent trend to use molecular clonality as the single determining factor in the decision on malignancy vs begin lesions is unjustified and far from common practice in human medicine.[17,187] Much data indicates that clonality is not synonymous with malignancy and it has been shown that any strong chronic antigenic stimulation can promote selective proliferation of lymphocyte clones. Benign clonal expansions have

been documented in humans,[188-193] dogs,[194-196] and cats with infectious diseases[197] (e.g., ehrlichiosis, leishmaniasis, feline immunodeficiency virus), chronic inflammatory intestinal disorders, neoplasia, and drug administration. In addition, it has been reported that inflammatory and low-grade neoplastic lymphoid lesions can coexist in the same cat.[34,65]

Previous studies have focused primarily on the sensitivity of clonality. The reported sensitivity of PARR on FFPE tissue in cats is reported to be between 89% and 91%.[34,35,167] Insufficient primer coverage of all possible rearrangements may have previously limited sensitivity.[167] Recently, a new multiplex assay was developed for T-cell lymphomas in cats targeting the T-cell receptor beta, delta, and gamma loci and the new assay was reported to have 95.5% sensitivity.[167] However, clonality assays are designed to differentiate inflammatory from neoplastic lesions, and hence specificity is of much greater concern. Although studies reported a specificity of up to 100% for PARR analysis in T-cell neoplasia of cats, these studies mostly included biopsy specimens from healthy young cats and cats with nonlymphoproliferative disorders or nongastrointestinal tissue as controls.[35,167] However, assessment of a specificity relevant for clinical practice (i.e., differentiation of LPE from LGITL in cats) would require systematic comparison of intestinal biopsy specimens from cats with LPE to those from cats with LGITL. Studies in humans and cats have shown the TCR gamma PARR assay to have specificities as low as 54%[10] and 33%,[18,64] respectively, for the differentiation of inflammatory from neoplastic lesions. The specificity of the new multiplex clonality assay targeting the TCR gamma, delta, and beta loci has not yet been investigated comparatively in a clinical study.

After recognition of the above-mentioned limitations of clonality assays in human medicine, the EuroClonality (BIOMED-2) consortium was founded in 2003.[17,181,198] The group aimed to standardize the preanalytical[17] (e.g., sample requirements), analytical[17] (eg, standardized primer sets), and postanalytical[181] (e.g., assay interpretation) steps of the assay and provided stringent guidelines accordingly. Unfortunately, no standardization for the performance and interpretation of clonality assays currently is available in the veterinary community.[198]

In light of these limitations, clinicians should refrain from reclassification of cases based on clonality results alone. Instead, clinical, morphological, and immunophenotypical data should be integrated with clonality analysis to decrease the chance of a misdiagnosis, as practiced in human medicine.[17,34,36,57,144,180,181]

4 | CONCLUSION

To date, no single diagnostic criterion or known biomarker is available that reliably differentiates inflammatory lesions from neoplastic lymphoproliferations in the intestinal tract of cats, and both frequently coexist in the same individual. To further investigate the relationship between LPE and LGITL, studies using immunohistochemical and genetic research tools are needed. Cancer genomics refers to the study of tumor genomes using various profiling strategies including whole genome DNA sequencing and characterization of the transcriptome (ie, the RNA transcripts of DNA). A wide range of emerging "omics" and multiview clustering algorithms now provide unprecedented opportunities to further classify cancers into subtypes, improve the survival prediction and therapeutic outcome of these subtypes, and understand key pathophysiological processes through different molecular layers.[199-201] These and other techniques currently are contributing to rapid advancements in the field of oncology. In addition to novel research techniques, longitudinal studies including long-term follow-up of cats with chronic enteropathy are needed; until then, ambiguous cases will remain. However, defining the differences between inflammatory and neoplastic lesions may have impact at both the individual and the population level. Further definition of the disorder may lead to a better understanding of etiopathogenesis and predisposing factors, new targets for diagnosis and treatment, and improve patient outcome. Finally, LGITL in cats has been shown to be a suitable model for of GI-LPDs in humans under the One Health concept. This consensus statement summarizes the state-of-the-art knowledge about CE in cats for the veterinary community within and beyond the ACVIM.

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CONFLICT OF INTEREST DECLARATION

Dr. S. Marsilio is a paid consultant for Dutch Pet, Inc., an online veterinary pet telehealth service and a paid speaker for Idexx Laboratories, Westbrook, ME.

Dr. V. Freiche is a paid speaker for Royal Canin, Aimargues, France, Dômes Pharma Vétérinaire, Lempdes, France, and Nestlé Purina, St Louis, MO.

Dr. E Johnson has nothing to disclose.

Dr. C. Leo is a paid consultant for Mars Anicura Inc., a paid teleconsultant for Vet-CT, an online veterinary pet telehealth service based in the UK and a paid speaker for UNISVET, an Italy-based continuing education company.

Dr. A.W. Langerak is the director of the Laboratory Medical Immunology (LMI) (ISO 15189 certified) at the Erasmus MC, University Medical Center, Rotterdam, The Netherlands. The LMI provides patient services including clonality testing on a fee-for-service basis. Dr. A.-W. Langerak receives funding for research support from Roche-Genentech, South San Francisco, CA, Janssen, Beerse, Belgium, and Gilead, Foster City, CA. Dr. A.W. Langerak is a paid speaker for Janssen, Beerse, Belgium, Gilead, Foster City, CA, and AbbVie, North

Chicago, IL. Dr. A.W. Langerak is also a founding member of the EuroClonality/BIOMED-2 group, a non-profit organization providing analytical guidelines for the performance of clonality assays in human medicine.

Dr. I. Peters is an employee at the Veterinary Pathology Group (VPG), Exeter, Devon, UK which provides clonality testing and other laboratory services on a fee-for-service basis. None of these organizations influenced the outcome of this consensus statement.

Dr. M. Ackermann has nothing to disclose.

OFF-LABEL ANTIMICROBIAL DECLARATION

Authors declare no-off label use of antimicrobials.

INSTITUTIONAL ANIMAL CARE AND USE COMMITTEE (IACUC) OR OTHER APPROVAL DECLARATION

Authors declare no IACUC or other approval was needed.

HUMAN ETHICS APPROVAL DECLARATION

Authors declare human ethics approval was not needed for this study.

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SUPPORTING INFORMATION

Additional supporting information can be found online in the Supporting Information section at the end of this article.

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