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CLINICAL REVIEW

FELINE ALIMENTARY LYMPHOMA
1. Classification, risk factors, clinical signs and non-invasive diagnostics

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Practical relevance Alimentary lymphoma (AL) occurs commonly in cats and exists as distinct subtypes that differ in their clinical course, response to treatment and prognosis. Accurate diagnosis is important to guide appropriate treatment.

Clinical challenges Differentiation of low-grade alimentary lymphoma from lymphoplasmacytic enteritis can be challenging, especially where endoscopic intestinal biopsies, which sample only the mucosa and submucosa, are used. The major differentials for intermediate- and high-grade alimentary lymphoma are other neoplastic and non-neoplastic intestinal mass lesions. The diagnosis of large granular lymphocyte lymphoma requires vigilance as it may be missed with routine diagnostics.

Patient group AL affects predominantly middle- to old-aged domestic crossbred cats (median age 10–13 years).

Evidence base The evidence supporting this review is grade II, III and IV, derived from prospective studies, retrospective case series, reviews, extrapolation from other species, pathophysiological justification and the combined clinical experience of those working in the field.

PART 2
Part 2 of this two-part article, reviewing the benefits and limitations of various biopsy techniques, treatment options and prognosis for different subtypes of alimentary lymphoma, appears on pages 191–201 of this issue of *J Feline Med Surg* and at **DOI: 10.1177/1098612X12439266**

Alimentary lymphoma – and its three clinical entities

Alimentary lymphoma (AL), the most common anatomical form of lymphoma in cats, comprises a group of diseases centred on the gastrointestinal tract, with variable extraintestinal involvement. Three histological grades of AL are recognised: low (LGAL), intermediate (IGAL) and high (HGAL). A separate histological subclassification of AL, large granular lymphocyte lymphoma (LGLL), which can be of any grade, is also described. Although these different subtypes of lymphoma share features related to gastrointestinal dysfunction, such as weight loss, vomiting and diarrhoea, there are major differences in clinical presentation, techniques required for diagnosis, treatment and prognosis (Table 1). From a clinical perspective, LGAL and LGLL can be considered as separate entities and IGAL and HGAL can be considered together as a third entity because, other than histological grade, the clinical features of IGAL and HGAL are similar.[1] Accurate diagnosis is essential to differentiate these lymphomas from each other and from other primary and secondary gastrointestinal diseases so that appropriate treatment can be initiated.

Classification and prevalence

Lymphoma is the most common intestinal neoplasm of cats, followed by adenocarcinoma and then mast cell tumour. In a study of 1129 feline intestinal neoplasms diagnosed histologically, 55% were lymphomas, 32% were adenocarcinomas and 4% were mast cell tumours.[2] Feline lymphoma can be classified by anatomical location, histological grade and immunophenotype.

Anatomical classification

The traditional anatomical classification recognises mediastinal, multicentric, alimentary and extranodal forms. Of these, AL is the most common anatomical form identified.[3–10] The declining influence of feline leukaemia virus (FeLV) worldwide has resulted in an increase in the relative prevalence of AL, since AL has the weakest association with FeLV antigenaemia. Some studies suggest that the absolute incidence

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Table 1 Comparison of clinically relevant features of AL subtypes in cats

	Intermediate/high-grade alimentary lymphoma (IGAL/HGAL)	Low-grade alimentary lymphoma (LGAL)	Large granular lymphocyte lymphoma (LGLL)
Age at presentation (median)	12 years	13 years	10 years
FeLV antigen status	>70% negative	>99% negative	>96% negative
Abdominal palpation findings	Focal intestinal mass lesion typical. Extraintestinal lesions may be palpable (eg, mesenteric lymph node, hepatic, splenic or renal masses)	Normal or diffuse intestinal thickening. Palpable mesenteric lymph node enlargement or intestinal mass in 20–30% of cases	Focal intestinal mass lesion typical. Extraintestinal lesions may be palpable (eg, mesenteric lymph node, hepatic, splenic or renal masses)
Immunophenotype	B cell or T cell	>90% T cell	>90% T cell
Recommended chemotherapy protocol	Multi-agent CHOP-based	Prednisolone and chlorambucil	Multi-agent CHOP-based
Major route of chemotherapy administration	Intravenous	Oral	Intravenous
Complete remission (CR) rate	38–87%	56–96%	5%*
Median survival time (for cats achieving CR)	7–10 months	19–29 months	17 days*

*Results from 20 cats treated with a COP-based protocol[32]

From a clinical perspective, alimentary lymphoma can be divided into three separate entities: LGAL, LGLL and I/HGAL.

of feline lymphoma, particularly AL, is increasing.[6,11] In one institution, cases of retrovirus-negative lymphoma increased by 78% in the 10-year period after 1994, compared with the previous 10 years; this could only be partly accounted for by an increase (29%) in the feline caseload.[6] Whether this trend reflects a true increase in the incidence of AL or increased demand for, and availability of, further investigation of feline patients is unclear.

Histological classification of AL subtypes

AL is characterised by infiltration of the gastrointestinal tract with neoplastic lymphocytes, with or without mesenteric lymph node involvement.[3,12,13] The histological classification systems most frequently applied to feline lymphoma are the National Cancer Institute Working Formulation (NCIWF) and the Revised European–American Lymphoma/World Health Organisation (REAL/WHO) schemes.[1,9,14–19] The NCIWF scheme classifies lymphoma according to its natural rate of progression, recognising three histological grades (high, intermediate and low) based on the frequency of mitoses. The REAL/WHO scheme classifies lymphoma into specific disease entities based primarily on immunophenotype and morphological features.[20] These schemes are complementary since neither considers both histological grade and immunophenotype.

LGAL has been increasingly recognised in cats over the past 10 years. Synonyms include 'well-differentiated', 'lymphocytic' and 'small cell' AL.

LGAL has been increasingly recognised in cats over the past 10 years.[19,21–27] Synonyms include 'well-differentiated', 'lymphocytic' and 'small cell' AL. Using the NCIWF scheme, most cases of LGAL can be further classified histologically as 'small lymphocytic lymphoma'.[1,15,22–26] Using the REAL/WHO scheme, feline LGAL has been most frequently categorised as 'epitheliotropic small T cell lymphoma', 'epitheliotropic T cell lymphoma', 'intestinal T cell lymphoma' or 'enteropathy-associated T cell lymphoma'.[1,15,16,21,22,27–29] LGLL is a separate subclassification of AL recognised in the REAL/WHO scheme which can be of any histological grade.[15,27,30–35]

How common are different AL subtypes in cats?

Low-grade lymphoma constitutes 10–13% of all feline lymphomas,[1,14,25] but it may be more common in the alimentary location.[1] LGAL comprised 37, 45 and 75% of all cases of AL in three different studies.[15,19,23] Histopathological reviews of AL are likely to be skewed towards selection of LGAL since this subtype cannot be diagnosed by aspirate cytology, whereas cases of IGAL and HGAL diagnosed by aspirate cytology are less likely to proceed to biopsy and histological classification. Taking this into account, a recent study found that LGAL accounted for 28% of all cases of AL (n = 53) presented to three feline clinics.[36] LGLL is the least common subtype of AL, comprising 6–7% of AL cases.[15,27,32] The true incidence could be higher as reliable demonstration of large granular lymphocytes (LGLs) in fixed tissues requires plastic embedding and use of Giemsa-stained sections or immunohistochemistry to detect the cytotoxic granule protein, granzyme B.[27,30]

What does immunophenotyping tell us?

Over 90% of LGALs and LGLLs are of T cell immunophenotype, whereas I/HGALs are variably of B or T cell origin.[5,9,12,14–17,21,25,27,31,37] A strong association between immunophenotype and location within the gastrointestinal tract has been identified.[15,38] In two studies, B cell lymphoma predominated in the stomach and large intestine while T cell lymphoma was most common in the small intestine.[15,27] In a retrospective study of small intestinal biopsies from 63 cats with lymphoma or inflammatory disease, 43/51 (84%) lymphomas were CD3-positive (CD3+), further supporting that primary small intestinal lymphomas in cats are typically of T cell origin.[21]

T cell lymphomas arise from the diffuse, mucosal-associated lymphoid tissue (MALT) of the small intestine, which includes lamina propria and intraepithelial compartments populated largely by CD3+ T cells. Key immunophenotypic features shared by neoplastic LGLs and intraepithelial lymphocytes (IELs) in the cat (CD3+, CD8αα+, CD103+) suggest that LGLLs arise from neoplastic transformation of natural killer cells and cytotoxic T lymphocytes within the intestinal epithelium.[31] Further, in contrast to lamina propria lymphocytes, 25–35% of normal feline intestinal IELs have LGL morphology.[39]

B cell lymphomas appear to originate principally from organised lymphoid tissues, including Peyer's patches and mucosal lymphoid nodules, which are concentrated in the distal small intestine, caecum and colon.[38] Gastric B cell lymphomas in cats are proposed to arise from diffuse gastric MALT colonised by *Helicobacter heilmannii*[40] or from gastric mucosal lymphoid nodules.[38]

Risk factors

Feline leukaemia virus

FeLV is a directly oncogenic retrovirus and persistent antigenaemia confers a 60-fold increased risk of lymphoma development compared with antigen-negative status.[41] The strength of this FeLV association varies with anatomical type. Among thymic lymphoma cases, 80–90% test positive for FeLV antigen,[8,42,43] whereas AL has shown the lowest association, with FeLV antigenaemia generally being detected in 0–12% of cases.[3,5,8,12,13,19]

While the ability to detect FeLV provirus may shed more light on its potential role in lymphomagenesis in exposed but antigen-negative cats with regressive infection, consensus has not yet been reached. In three studies where FeLV antigen was detected in 4%, 2% and 38% of cases of AL, FeLV proviral DNA was detected in 60%, 21% and 53% of tumours.[10,36,44] In these studies, approximately equal numbers of T and B cell lymphomas were provirus-positive. In contrast, in 32 cats with AL, Stutzer et al detected much lower levels of FeLV infection and demonstrated concordance between tests; FeLV provirus was detected in only two cases, both of which were antigenaemic and expressed FeLV antigen in lymphoma tissue (6%).[8] The remaining 30 cats were negative for FeLV on all tests. A control group of 41 FeLV antigen-negative cats without malignancies all tested negative for FeLV provirus in the bone marrow. Immunophenotype was determined for 36/77 lymphomas of different anatomical forms. Lymphomas from FeLV antigen-positive cats were significantly more likely to be of T cell immunophenotype than those arising in FeLV antigen-negative cats.[8] This is consistent with previous studies which have demonstrated neoplastic transformation by FeLV of T lymphocytes, null cells and monocytes/macrophages.[45]

There is currently no evidence of an association between retroviral infection and LGAL or LGLL. However, the retrovirus status of all cats with AL should be determined, as it may have implications for prognosis or patient monitoring.

Feline immunodeficiency virus

Feline immunodeficiency virus (FIV) infection of cats increases the risk of lymphomagenesis by five-fold compared with uninfected cats.[41] An indirect role is favoured for FIV in lymphomagenesis.[46] FIV-associated lymphoma is typically extranodal, high grade and of B cell phenotype, including atypical lymphoma (eg, nasopharyngeal) and mixed lymphoma with involvement of multiple anatomical sites.[47–50] Lymphoma was diagnosed in 21% of FIV-infected cats in one report and AL was the most common anatomical form.[51]

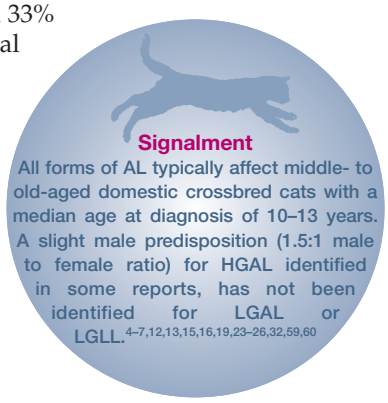
Retrovirus status

There is currently no evidence of an association between retroviral infection and LGAL or LGLL.[19,21,23–25,31,32,34,35] The retrovirus status of all cats diagnosed with AL should be determined since persistent FeLV antigenaemia carries a guarded prognosis and infection with either FIV or FeLV can cause immune dysfunction which may be compounded by chemotherapy, necessitating careful patient monitoring.

Other risk factors

- **Environmental exposure to tobacco smoke** was associated with a 2.4- or 3.2-fold increased risk of developing lymphoma in cats with any or more than 5 years' exposure, respectively.[52]
- **Chronic intestinal inflammation** is often proposed as a risk factor for the development of AL, but definitive proof has been lacking.[3,6,31,53] A direct association between coeliac disease, an inflammatory intestinal disease associated with gluten sensitivity, and the development

of AL has been established in humans. In genetically predisposed individuals, enteropathy-associated T cell lymphoma (EATCL) can arise from clonal transformation of intestinal IELs after chronic antigenic stimulation.[54,55] EATCL is the most common neoplastic complication of coeliac disease. Several lines of evidence support the proposition that intestinal inflammation is a risk factor for the development of T cell lymphoma (of any histological grade) and LGLL in cats. In two studies, 60% of cats with intestinal T cell lymphoma and 33% of cats with LGLL had chronic clinical illnesses suggestive of pre-existing inflammatory disease.[31,56] Concurrent lymphoplasmacytic enteritis (LPE) has been identified in other regions of the alimentary tract in up to 41% of cats with LGAL of T cell immunophenotype,[22–24] and apparent histological progression of LPE to AL has been documented in individual cases.[57,58]



Signalment

All forms of AL typically affect middle- to old-aged domestic crossbred cats with a median age at diagnosis of 10–13 years. A slight male predisposition (1.5:1 male to female ratio) for HGAL identified in some reports, has not been identified for LGAL or LGLL.[4–7,12,13,15,16,19,23–26,32,59,60]

Differential diagnosis

The presenting signs of AL are common to many primary and secondary gastrointestinal diseases. LPE is a major differential diagnosis for LGAL in particular. A comparison between cats with LPE and LGAL found no correlation between clinical findings and the final diagnosis.[61] In cats with intestinal mural mass lesions, epithelial and mast cell neoplasia are major differentials. Diagnostic tests recommended to rule out other primary and secondary gastrointestinal diseases are listed in the box on page 186.

Non-invasive diagnostics

Routine laboratory testing

Haematology The most common haematological abnormalities in cats with AL are anaemia, due to chronic disease and/or gastrointestinal blood loss, and neutrophilia.[3,24,25,31,32,63] While routine haematology is of low diagnostic yield for LGAL and I/HGAL, careful evaluation of a peripheral blood film is an essential step for the diagnosis of LGLL. In LGLL, marked

History and clinical signs

LGAL

The most common clinical signs of LGAL are weight loss (Figure 1; ≥80%), vomiting (≥70%), diarrhoea (≥60%) and partial or complete anorexia (≥50%). The appetite may be normal or, occasionally, polyphagia is noted. Less frequently reported signs include lethargy and polydipsia.[19,23–25,61] In the majority of cases, clinical signs are chronic (present for >1 month).[23,24,61] Abdominal palpation is often abnormal (Figure 2); diffusely thickened intestinal loops are detected in a third to more than half of affected cats. An abdominal mass is palpable in 20–30% of cases, attributable to mesenteric lymph node enlargement or, rarely, to a focal intestinal mass.[19,23,24]

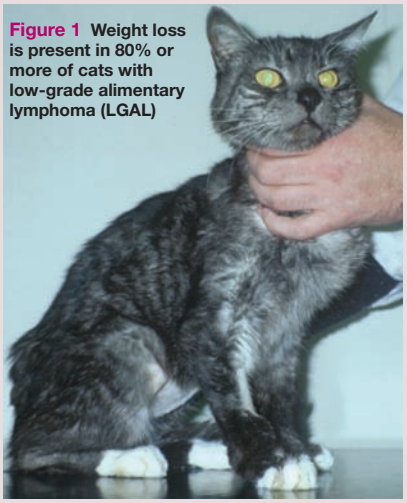


Figure 1 Weight loss is present in 80% or more of cats with low-grade alimentary lymphoma (LGAL)

Abdominal palpation can be normal in cats with LGAL . . . By contrast an abdominal mass is palpable in most cats with I/HGAL and LGLL.

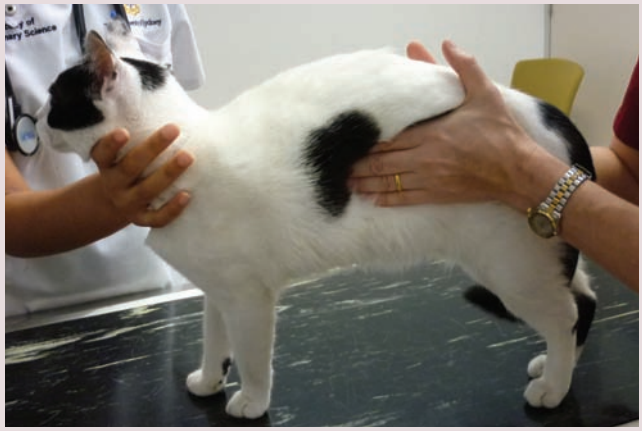


Figure 2 Abdominal palpation can be normal in cats with LGAL, but common abnormalities include diffusely thickened intestinal loops or a palpably enlarged mesenteric lymph node

I/HGAL and LGLL

Clinical signs in cats with I/HGAL and LGLL are similar to those for LGAL but tend to be more acute and/or severe. A major clinical difference, compared with LGAL, is the presence of a palpable abdominal mass at diagnosis in the majority of cases of I/HGAL and LGLL. The mass comprises focal intestinal thickening and/or extraintestinal lesions, such as mesenteric lymphadenomegaly, hepatomegaly or renomegaly. Intussusception, intestinal obstruction and intestinal perforation are more common in cases of I/HGAL than in LGAL.[3,12,19,31,32,35,62]

Diagnostic investigation

Tests to rule out other primary and secondary gastrointestinal diseases in older cats with chronic weight loss, vomiting and/or diarrhoea

Blood and urine tests
- Complete blood count
- Serum biochemical profile
- Serum total T_4
- Serum cobalamin and folate
- FIV and FeLV serology
- Feline pancreatic lipase (Spec fPL; Idexx Laboratories)
- Urinalysis

Faecal tests

If small bowel diarrhoea is predominant:
- Faecal flotation assays
- Faecal immunoassays/direct fluorescent antigen tests/PCR assays for detection of:
  - *Giardia* species
  - *Cryptosporidium* species
  - *Campylobacter* species
  - Enteropathogenic bacterial toxins

If mixed/large bowel diarrhoea is predominant:
- Faecal smears/culture/PCR assays for detection of *Tritrichomonas fetus*

If there is bloody diarrhoea, especially in cats with fever and an inflammatory leukogram:
- Faecal culture for enteropathogenic bacteria (*Salmonella* species, *Clostridium* species, *Campylobacter* species)

Diagnostic imaging
- Abdominal ultrasonography
- Thoracic radiography

Therapeutic trials
- Fenbendazole (50 mg/kg PO q24h for 5 days)

Dietary elimination trials

To investigate possible adverse food reactions:
- Single novel protein + carbohydrate
- Hydrolysed protein diet

neutrophilic leukocytosis is usually present, which may be accompanied by a regenerative left shift.[31–33] A peripheral lymphocytosis (with LGL morphology) was documented in over 80% of cats with LGLL in two studies.[31,35] However, in two other studies lymphocytosis was uncommon in cats with LGLL, although peripheral lymphoblasts were present in 15% of cats.[32,33] Since LGLs can be identified with routine haematological stains, peripheral blood smears should be examined thoroughly in the assessment of all cats where AL is suspected.

Serum albumin The most common serum biochemical abnormality in AL is hypoalbuminaemia. In intestinal disease, hypoalbuminaemia occurs when loss of albumin into the lumen through a compromised intestinal wall exceeds the capacity of the liver to synthesise albumin. Hypoalbuminaemia is less common in cats with LGAL than in other forms of AL, probably because the integrity of the intestinal wall can be maintained until late in the disease process.[3,19,23,32,33,63] Elevations in bilirubin or liver enzymes, or azotaemia, may occur in cats with AL with hepatic or renal involvement.[23,24,32,60,63]

Serum cobalamin Up to 80% of cats with LGAL are hypocobalaminaemic.[25] This finding is not unexpected since cobalamin is absorbed from the ileum, and the ileum and jejunum are the most common locations for LGAL.[22,23,27] Utilisation of cobalamin by proliferating intestinal microflora in the proximal intestine can further reduce available cobalamin.[64]

Serum folate Folate levels may be low, normal or high in cats with LGAL.[24,25] Folate deconjugase, a brush border enzyme, and a carrier protein required for folate absorption are located only in proximal intestinal enterocytes. Hence, low serum folate levels occur with proximal intestinal disease due to reduced mucosal absorption. High serum folate levels can occur due to proliferation of intestinal microflora that synthesise folate.[64] Serum folate levels were low in 4% and high in 37% of cats with LGAL in one report.[25]

The frequency of perturbations in serum folate and cobalamin with other forms of AL has not been evaluated.

Abdominal ultrasonography

Abdominal ultrasonography facilitates evaluation of the gastrointestinal tract by assessment of wall thickness, layering, motility and luminal content. Normal intestinal wall appears as a five-layered image, with alternating hyper- and hypoechoic layers corresponding to the luminal surface, mucosa, submucosa, muscularis and serosa. Normal ultrasonographic intestinal wall thicknesses are: duodenum and jejunum ≤2.8 mm, ileum ≤3.2 mm and colon ≤1.7 mm.[65] Mesenteric lymph node diameter is generally ≤5 mm.[66] Mural thickening can be further characterised by symmetry, anatomical location and whether it is focal, multifocal or diffuse.

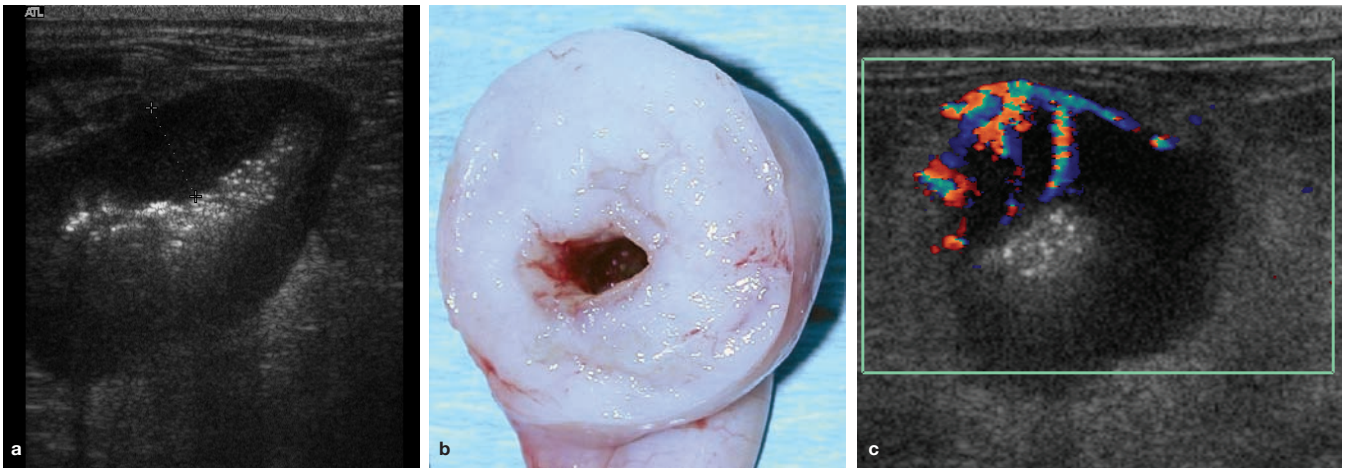


Figure 3 **(a) Ultrasonographic and (b) gross appearance of a focal jejunal mass due to high-grade alimentary lymphoma (HGAL). The intestinal wall is thickened (1 cm) and has lost its normal alternating hyperechoic and hypoechoic wall layering pattern. The symmetrical concentrically thickened intestinal wall is visualised in (c) and vascularity identified using power Doppler. Extraintestinal involvement, such as concurrent renal (d) and hepatic (e) masses, is common in HGAL.** *Images (a), (c), (d) and (e) courtesy of Karon Hoffman, University Veterinary Teaching Hospital, Sydney*

I/HGAL The ultrasonographic features of I/HGAL include transmural intestinal thickening with disruption of normal wall layering, reduced wall echogenicity, localised hypomotility and abdominal lymphadenomegaly. Loss of intestinal wall layering occurs due to infiltration of the intestinal wall with neoplastic or inflammatory cells, necrosis, oedema and/or haemorrhage (Figure 3).[3,67,68] Transmural intestinal thickening in I/HGAL is usually symmetrical or concentric, in contrast to intestinal mast cell tumours and adenocarcinomas where intestinal wall thickening is often asymmetrical or eccentric.[69,70] Ultrasonographically, evidence of extraintestinal involvement is common in I/HGAL.[3,12]

Transmural intestinal thickening in I/HGAL is usually symmetrical or concentric.

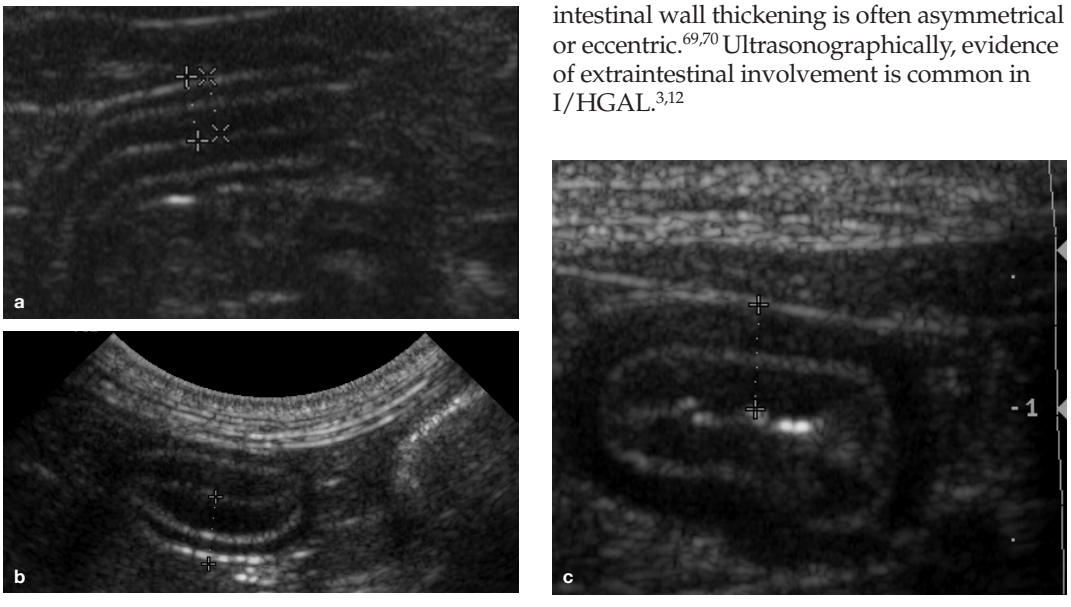


Figure 4 **(a) Mild diffuse small intestinal wall thickening (wall thickness 3.4 mm) in a cat with LGAL; (b and c) severe small intestinal wall thickening in a cat with LGAL (wall thickness 4.9 mm in b, and 4 mm in c). Note that the alternating hyperechoic and hypoechoic appearance of intestinal layers seen in healthy cats is preserved in cats with LGAL**

✣ **LGAL** In LGAL, intestinal wall thickness is normal or increased, with preservation of wall layering (Figure 4). In one study of cats with LGAL and diffuse small intestinal thickening, mean wall thickness was 4.3 mm (median 4.5 mm, range 3.4–5.0 mm).[23] Mesenteric lymph node enlargement was also common. In another report, 81% of cats with LGAL had evidence of intestinal thickening on abdominal ultrasonography.[26] Importantly, the ultrasonographic features of LGAL do not distinguish it from LPE or other enteropathies.[61,71] Thickening of the muscularis propria layer, which was found to be significantly associated with LGAL and not LPE or normal small intestine, may assist in the ranking of differentials.[72] It should be emphasised that the finding of normal intestinal wall thickness and normal mesenteric lymph nodes on abdominal ultrasonography does not rule out a diagnosis of LGAL; in patients with consistent clinical signs, intestinal biopsy is indicated. Less common findings on ultrasonographic examination of cats with LGAL include a focal intestinal mass or intussusception.[23,24] Diffuse infiltration of the liver may be present histologically but is not readily identifiable ultrasonographically.[23]

✣ **LGLL** The ultrasonographic features of LGLL in cats have not been described in detail but appear similar to I/HGAL.[32]

The finding of normal intestinal wall thickness and normal mesenteric lymph nodes on ultrasonography does not rule out a diagnosis of LGAL.

KEY POINTS

- I/HGAL typically presents acutely and can often be diagnosed by aspirate cytology of a mural intestinal mass or mesenteric lymph node.
- The clinical course of LGAL is chronic and LPE is a major differential. Definitive diagnosis may not be possible on histological evaluation of intestinal biopsy specimens alone. Immunohistochemistry and clonality testing, in addition to routine histopathology, can assist in differentiating LGAL from inflammatory disease.
- LGLL is the least common subtype and runs an acute clinical course. An index of suspicion is required to diagnose LGLL. Cytological evaluation of peripheral blood films and fine-needle aspirate biopsies is useful for diagnosis. For histological diagnosis, Giemsa-stained plastic-embedded biopsy specimens are necessary for reliable detection of granules within neoplastic lymphocytes. Alternatively, immunohistochemistry can be performed to detect the cytotoxic granule protein, granzyme B.
- Where the REAL/WHO histological classification scheme is used for diagnosis of AL, clinicians should additionally request that pathologists include the histological grade of the lymphoma to help guide therapeutic decisions.

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Conflict of interest

The authors declare that there is no conflict of interest.

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