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Original article

Evaluation of clinicopathological features in cats with chronic gastrointestinal signs

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Abstract

Food-responsive enteropathy (FRE), idiopathic inflammatory bowel disease (IBD), and alimentary tract lymphoma (AL) are often the remaining differentials for cats presenting with chronic gastrointestinal (GI) signs. Differential diagnosis is further complicated by overlapping clinicopathological features and histopathological changes, however.

In this study we describe the clinical presentation of cats with chronic GI signs secondary to FRE, IBD, and AL, and evaluate possible associations between clinical, clinicopathological, ultrasonographic findings and diagnosis.

The medical records of client-owned cats with chronic GI signs secondary to FRE, IBD, and AL were reviewed. Univariate and multivariate logistic regression models and receiver-operating characteristic curve (ROC) analysis were used for testing the data.

Of the 56 cats included in the study, 22 were diagnosed with FRE (mean age, 70 months ± 49), 17 with IBD (mean age, 101 months ± 40), and 17 with AL (mean age, 122 months ± 45). Cats with FRE were younger and presented more often with diarrhea and less frequently with muscle wasting than cats with IBD or AL. In cats with AL, serum cobalamin levels were lower than in those with FRE or IBD (239 ± 190 ng/L vs. 762 ± 408 ng/L and 625 ± 443 ng/L, respectively) and folate levels were higher than in cats with IBD (18.2 ± 4.2 µg/L vs. 9.1 ± 4.7 ,g/L, respectively). Multivariate/ROC curve analysis showed increased values of BUN (sensitivity 100, specificity 29.4, criterion >37 mg/dl) and serum folate (sensitivity 80, specificity 100, criterion >15.6 µg/L) and reduced values of cobalamin (sensitivity 100, specificity 62.5, criterion ≤540 ng/L), which suggested a diagnosis of AL versus IBD.

Some clinicopathological features evaluated at diagnosis might suggest AL; however, because differentiating AL from IBD is often difficult, definitive diagnosis should be based on invasive diagnostic workup.

Key words: feline, food-responsive enteropathy, inflammatory bowel disease, alimentary lymphoma

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Introduction

Chronic clinical signs of gastrointestinal (GI) disease are a common presenting complaint in cats of all ages; however, such manifestations are not disease-specific and frequently overlap with other non GI-disorders (Jergens 2012). After excluding the possibility of infectious/parasitic agents, non GI-disorders, exocrine pancreatic insufficiency, and abnormalities requiring surgery, the remaining differentials include food-responsive enteropathy (FRE), idiopathic inflammatory bowel disease (IBD), and alimentary lymphoma (AL) (Guilford et al. 1998, Guilford et al. 2001, Janeczko et al. 2008, Krick et al. 2008, Lingard et al. 2009, Washabau et al. 2010, Barrs and Beatty 2012, Jergens 2012). While dietary trials will usually rule out FRE (Guilford et al. 2001, Trepanier 2009, Mandigers and German 2010), differentiation of IBD from small-cell AL poses a diagnostic challenge because histological features can overlap (Waly et al. 2005, Briscoe et al. 2011, Kiupel et al. 2011) and because small-cell AL and inflammatory infiltrates can coexist (Briscoe et al. 2011, Kiupel et al. 2011). Other factors that may lead to misdiagnosis include the potential for IBD to progress to AL (Davenport et al. 1987, Hart et al. 1994), differences in histopathologic evaluation among pathologists (Willard et al. 2002), inadequacy of endoscopic biopsy specimens, and incorrect anatomic sampling from the GI tract (Evans et al. 2006, Kleinschmidt et al. 2010, Kiupel et al. 2011). Differentiation between IBD and AL relies on a diagnostic approach that combines morphologic with immunohistochemical and clonality analysis (Moore et al. 2005, Waly et al. 2005, Kiupel et al. 2011).

Studies comparing IBD and AL are numerous (Waly et al. 2005, Evans et al. 2006, Kleinschmidt et al. 2010, Zwingenberger et al. 2010, Briscoe et al. 2011, Kiupel et al. 2011, Scott et al. 2011, Swanson et al. 2012, Al-Ghazlat et al. 2013, Burke et al. 2013, Daniaux et al. 2014); however, to the authors' knowledge, information comparing clinical, clinicopathological data and ultrasonographic findings in cats with chronic GI disease is scattered or lacking (Ruaux et al. 2005, Jugan and August 2017). To fill this gap, the present study describes the clinical presentation of cats with chronic GI disease secondary to FRE, IBD and AL, and evaluates possible associations between clinical, clinicopathological data, and ultrasonographic findings.

Materials and Methods

The medical records of cats with chronic GI signs of FRE, IBD, and AL diagnosed at the Veterinary Teaching Hospitals of Bologna, Teramo, and Turin Universities, Italy, between June 2008 and December 2013 were retrospectively reviewed. Information gleaned from the medical records included breed, sex, age, body condition score (BCS, 1 to 5), complaints/clinical signs, cell blood count, serum biochemistry profile, feline immunodeficiency virus/feline leukemia virus (FIV/FeLV) status (SNAP® FIV, FeLV Combo, IDEXX), serum folate and cobalamin concentrations, abdominal ultrasound changes [(increased GI wall thickness, loss of GI layering, lymphadenomegaly) according to a modified scoring system (Ripollès et al. 2013)], type of GI biopsy (endoscopic vs full-thickness), GI cytological/histopathological findings, clonality of GI lymphoid infiltrates, treatment, response to treatment (persistence, complete or partial remission of clinical signs), definitive diagnosis (FRE, IBD, AL) and follow-up (alive vs. date and cause of death). Cats with infectious disorders, non GI-disorders, exocrine pancreatic insufficiency and/or abnormalities requiring surgery were excluded, as were cats treated with immunosuppressive therapy before intestinal biopsy. The instrument used to evaluate cell blood count was an ADVIA 120 Hematology System (Siemens Healthcare, Germany), in addition to cytological blood smear evaluation. Instruments used for serum biochemistry profile evaluation were ILab Aries Instrumentation Laboratory (IL, Italy), and an AU400 Chemistry Analyzer (Beckman Coulter, Italy). The reference ranges reported by the clinical laboratories were similar. In all cats in which histologic examination was performed, the procedure was compliant with the histopathological standards of the World Small Animal Veterinary Association (WSAVA) Gastrointestinal Standardization Group. With regard to definitive diagnosis, cats that responded to hydrolysed protein or restricted antigen diets fed for at least 7 days (clinical signs resolved) were categorized as having FRE (Guilford et al. 2001). Cats with chronic (≥ 2 weeks) persistent or recurrent GI tract signs, inadequate response to dietary (hydrolysed protein or restricted antigen diets fed for at least 7 days), antimicrobial (metronidazole 15 mg/kg PO, SID for 14 days) or anthelmintic (fenbendazole 50 mg/kg PO, SID for 5 days) trials alone, histopathologic evidence of mucosal inflammation, absence of other causes of GI signs/inflammation and clinical response to prednisolone (1 mg/kg PO, SID for at least 2 weeks before considering dose reduction) were categorized as having IBD (Al-Ghazlat et al. 2013). In some cases in which the histopathologic examination was not performed, the clinical response to prednisolone and follow-up information were considered suggestive of IBD. Endoscopic or full-thickness biopsies of the GI tract had been obtained to

assess disruption of normal architecture by neoplastic infiltrates. Endoscopic and exploratory laparotomy procedures were performed under general anesthesia in all cats. Anesthesia protocols were individualized. Gastroduodenoscopy and colonoscopy to obtain GI tract biopsy specimens were performed by some of the authors in standardized fashion (Sum and Ward 2009) using a flexible-video gastroscope (6 mm x 100 cm Pentax EG1840). Mucosal surfaces of the esophagus, stomach, duodenum and colon were evaluated and multiple representative specimens were obtained for histologic evaluation. Exploratory laparotomy was performed by different staff surgeons and full-thickness biopsy specimens of the stomach, duodenum, jejunum and ileum were obtained. In addition, liver, pancreas and enteric lymph nodes with grossly abnormal appearance were biopsied. The biopsy sites and abdominal incision were closed routinely. Postoperative care was routine. In selected cases, aspiration cytology of focal intestinal wall masses or enlarged mesenteric lymph nodes was considered adequate to diagnose high-grade AL or large granular AL (Barrs and Beatty 2012). To more accurately differentiate severe forms of IBD from small-cell AL, the histological findings and results of immunophenotype and clonality analysis were combined (Kiupel et al. 2011, Barrs and Beatty 2012), along with response to therapy and follow-up information (Barrs and Beatty 2012, Jergens 2012). Endoscopic and full-thickness biopsy samples were formalin fixed and paraffin-embedded. Serial sections from paraffin tissue blocks from each sample were cut for routine hematoxylin and eosin (HE) staining, and subsequently deparaffinized for DNA extraction and PCR amplification in order to detect rearrangements of T and B cell variable regions.

Statistical analysis

Statistical analysis was performed with a commercially available program (MedCalc®). Values of $p<0.05$ were considered significant. Assessment of data for normality was calculated by applying the D'Agostino-Pearson test. Data are expressed as mean (± standard deviation [SD]) or median (95% confidence interval [95% CI]). Complaints/clinical signs (vomiting, diarrhea, changes in appetite, weight loss, muscle wasting, icterus, pruritus, attitude/activity) were reported in a dichotomous manner (0, not present; 1, present) and were compared by applying a chi-square test. The following parameters at inclusion [sex, age, BCS, packed cell volume, white blood cell count, platelets, blood urea nitrogen, serum total protein, albumin, globulin, total cholesterol, alanine aminotransferase, alkaline phosphatase, γ-glutamiltransferase, total bilirubin, phosphorus, sodium, calcium, serum cobalamin, serum folate, FIV/FeLV status and abdominal ultrasound changes (GI wall thickening, loss of GI layering, lymphadenomegaly)] were compared using one-way-analysis of variance (ANOVA) or a Kruskall-Wallis test and a post hoc test (Student-Newman-Keuls test or Dunns test). Univariate logistic regression was performed on the data from cats with IBD and AL to screen for potential predictors for subsequent inclusion in a multivariable model. Variables with a value <0.15 at univariate analysis were entered in a final model-building process using a forward conditional method. The variables were then removed one at a time until the model with the best fit was identified. A receiver-operating characteristic (ROC) curve was used to select the optimum cut-off value of significant variables in the multivariate analysis to discriminate cats with IBD from those with AL.

Results

History and physical examination

The medical records of 56 client-owned cats with chronic GI signs secondary to FRE, IBD or AL diagnosed between June 2008 and December 2013 were reviewed. The group of 22 cats with FRE included 9 males (8 neutered) and 13 females (9 spayed) and ranged in age from 5 to 190 months (mean, 70 ± 49). Breeds included 1 each of Chartreux, Norwegian Forest, Persian, Ragdoll, Siamese and Sphynx, and 16 European Shorthair cats. The group of 17 cats with IBD included 9 males (7 neutered) and 8 females (6 spayed) and ranged in age from 36 to 176 months (mean, 101 ± 40). Breeds included 1 each of Maine Coon, Persian, and Scottish Fold cats, and 14 European Shorthair cats. The group of 17 cats with AL included 11 males (9 neutered) and 6 spayed females and ranged in age from 30 to 172 months (mean, 122 ± 45). Breeds included 1 each of Persian and Maine Coon, and 15 European Shorthair cats. There was no statistically significant difference in sex between the three groups. Cats with FRE were significantly younger than those with IBD or AL ($p<0.01$) and presented more often with diarrhea and less often with muscle wasting than the other two groups. Table 1 reports the complaints/clinical signs and BCS of the three groups.

Table 1. List of presenting complaints/clinical signs and BCS scores in cats with FRE, IBD, and AL.

Variable	FRE (n=22)	IBD (n=17)	AL (n=17)
Vomiting (%)	54.5	76.5	70.6
Diarrhea (%)	81.8	47	47
Decreased appetite (%)	13.6	23.5	5.9
Increased appetite (%)	50	47	58.8
Weight loss (%)	54.5	70.6	82.3
Muscle wasting (%)	31.8	58.8	76.5
Icterus (%)	4.5	11.8	–
Pruritus (%)	4.5	5.9	5.9
Reduced attitude/activity (%)	54.5	52.9	29.4
BCS (mean ± SD)	2.8 ± 1	3.1 ± 1.7	2.3 ± 1.2

n=number of cats
FRE – denotes food-responsive enteropathy; IBD – inflammatory bowel disease; AL – alimentary tract lymphoma; BCS – body condition score

Table 2. Laboratory findings in cats with FRE, IBD, and AL.

Variable	FRE (n=22)	IBD (n=17)	AL (n=17)	
Variable	Mean (± SD)	Mean (± SD)	Mean (± SD)	Reference values
PCV	36.1 (± 4.6) %	32.9 (± 9.4) %	33.7 (± 10.3) %	27.7-46.8%
WBC	12,771 (± 7,936) cells/µL	14,758 (± 11,272) cells/µL	19,744 (± 12,854) cells/µL	6,300-19,600 cells/µL
Platelets	366,832 (± 139,462) cells/µL	656,156 (± 114,056) cells/µL	344,069 (± 226,864) cells/µL	156,400-626,4000 cells/µL
Blood Urea Nitrogen	62 (± 35) mg/dL	52 (± 19) mg/dL	66 (± 25) mg/dL	43-64 mg/dL
Total Protein	6.9 (± 1.0) g/dL	6.9 (± 1.4) g/dL	6.3 (± 1.3) g/dL	5.4-7.8 g/dL
Albumin	3.0 (± 0.7) g/dL	2.8 (± 0.7) g/dL	2.8 (± 0.5) g/dL	3.0-4.6 g/dL
Globulin	4.0 (± 0.9) g/dL	4.0 (± 1.3) g/dL	3.5 (± 0.7) g/dL	2.4-3.2 g/dL
Total Cholesterol	156 (± 66) mg/dL	168 (± 79) mg/dL	119 (± 45) mg/dL	95-130 mg/dL
Alanine Aminotransferase	450 (± 146) U/L	95 (± 97) U/L	68 (± 47) U/L	30-100 U/L
Alkaline Phosphatase	191 (± 123) U/L	46 (± 36) U/L	54 (± 40) U/L	25-93 U/L
Gamma Glutamyl Transferase	1.3 (± 3.1) U/L	1.1 (± 2.2) U/L	0.4 (± 0.6) U/L	1.3-5.1 U/L
Total Bilirubin	0.14 (± 0.07) mg/dL	0.21 (± 0.15) mg/dL	0.10 (± 0.10) mg/dL	0.15-0.20 mg/dL
Phosphorus	5.12 (± 1.5)	4.37 (± 1.5)	4.10 (± 0.90)	4.5-8.1 mg/dL
Sodium	151 (± 5) mEq/L	149 (± 6) mEq/L	150 (± 4) mEq/L	153-162 mEq/L
Potassium	4.5 (± 0.6) mEq/L	4.1 (± 1.2) mEq/L	4.3 (± 0.5) mEq/L	3.6-5.8 mEq/L
Total Calcium	9.8 (± 0.9) mg/dL	9.5 (± 0.8) mg/dL	9.2 (± 0.9) mg/dl	6.2-10.2 mg/dL
Cobalamin	762 (± 408) ng/L	625 (± 443) ng/L	239 (± 190) ng/L	290-1500 ng/L
Folate	12.9-6.1 µg/L	9.1 (± 4.7) µg/L	18.2 (± 4.2) µg/L	9.5-21.5 µ/L

n=number of cats
PCV – denotes packed cell volume; WBC – white blood cell

Table 3. Selected haematological, biochemical and SNAP test variables tested in cats with FRE, IBD, and AL.

Variable	FRE (n=22)	IBD (n=17)	AL (n=17)
Sodium	77.3	100	88.2
Variable	%	%	%
Potassium	77.3	100	88.2
PCV	86.4	100	100
Total Calcium	77.3	94.1	88.2
WBC	86.4	94.1	94.1
Cobalamin	63.6	47	35.3
Platelets	86.4	94.1	94.1
Folate	63.6	47	29.4
Blood Urea Nitrogen	81.8	100	100
FeLV SNAP®	90.9	64.7	64.7
Total Protein	81.8	100	100
FIV SNAP®	95.4	70.6	70.6
Albumin	77.3	100	100
Globulin	72.7	100	100
Total Cholesterol	72.7	94.1	88.2
Alanine Aminotransferase	81.8	100	100
Alkaline Phosphatase	81.8	100	100
Gamma Glutamyl Transferase	81.8	94.1	94.1
Total Bilirubin	81.8	100	88.2
Phosphorus	77.3	94.1	88.2

n = number of cats
FRE – denotes food-responsive enteropathy; IBD – inflammatory bowel disease; AL – alimentary tract lymphoma; PCV – packed cell volume; WBC – white blood cell; FeLV SNAP® – feline leukemia virus test (Idexx); FIV SNAP® – feline immunodeficiency virus test (Idexx).

Clinicopathologic findings

Data regarding clinicopathological abnormalities and the number of cats that had undergone testing are shown in Tables 2 and 3, respectively. Among the cats with known FIV (45/56) and FeLV (42/56) status, 1 with IBD tested positive for FIV and 1 with AL tested positive for FeLV. Serum cobalamin levels were lower in cats with AL than in those with FRE or IBD (239 ± 190 ng/L vs. 762 ± 408 ng/L and 625 ± 443 ng/L, respectively); and serum folate levels were higher in cats with AL than in those with IBD (18.2 ± 4.2 µg/L vs. 9.1 ± 4.7 µg/L, respectively). Multivariate/ROC curve analysis showed increased values for BUN (sensitivity 100, specificity 29.4, criterion >37 mg/dl) and serum folate (sensitivity 80, specificity 100, criterion >15.6 µg/L) and reduced values for cobalamin (sensitivity 100, specificity 62.5, criterion ≤ 540 ng/L), which suggested a diagnosis of AL vs. IBD.

Abdominal ultrasonographic findings

Abdominal ultrasonography findings were reported for 13/22 cats with FRE, 15/17 with IBD, and 17/17 with AL. GI wall thickening was detected in 7/22 cats with FRE, 7/17 with IBD, and 7/17 with AL; loss of GI layering was detected in 5/22 cats with FRE, 2/17 with IBD, and 4/17 with AL; lymphadenomegaly was detected in 4/22 cats with FRE, 4/17 with IBD, and 5/17 with AL. There were no significant differences in ultrasonographic findings between the three groups.

Gastrointestinal cytology/histopathology results, and clonality

Gastroduodenoscopy was performed in 9 cats (1 with FRE, 4 with IBD, and 4 with AL), followed by

colonoscopy in 2 cats with IBD and in 1 with AL. Laparotomy was performed in 37 cats (13 with FRE, 11 with IBD, and 13 with AL). Tissue quality was classified as adequate in all cases. The most common abnormalities in the cats with IBD were lymphocytic plasmacytic (n=13 cats), eosinophilic (n=1 cat), and mixed lymphocytic plasmacytic and eosinophilic inflammation (n=1 cat). Low-grade AL was identified in 12 cats, intermediate-grade AL in 2, high-grade AL in 2, and large granular AL in 1 cat. Large granular AL, intermediate-grade, and high-grade AL were diagnosed on the basis of transabdominal fine-needle aspiration cytology of the intestinal wall and mesenteric lymph nodes. B- and T-cell clonality analysis was performed in the 14 cases (5 IBD and 9 low-grade AL) with severe lymphocytic intestinal infiltration. The monoclonal nature of the T-cell populations was considered neoplastic in 9 cases and polyclonal rearrangements were detected in 5. There was no disagreement between histopathologic findings and clonality analysis results within the groups.

Response to therapy and follow-up

All 22 cats with FRE received a hydrolysed (8 cats) or a restricted antigen diet (14 cats), with complete remission of clinical signs achieved in all but 2 cats which then underwent a second dietary trial with a different restricted antigen diet. At the time of medical record review (February 2015; 80 months) all FRE cats were alive and asymptomatic. All 17 cats with IBD received a highly digestible, hydrolysed or restricted antigen diet in addition to prednisolone (1 mg/kg PO q12h for at least 2 weeks before considering dose reduction). Complete or partial remission of clinical signs was achieved in all cats. In the cats with partial remission, combined therapy with prednisolone and metronidazole (15 mg/kg PO q24h) was administered to achieve complete remission of clinical signs. At the time of medical record review, 5/17 cats with IBD were dead or had been euthanized (median survival time, 0.4-12 months, 95% Confidence Interval [CI] 5.5) and the remaining 12 cats were alive and asymptomatic or paucisymptomatic. The most frequent cause of death or reason for euthanasia was deterioration of clinical conditions reportedly due to malabsorption. Two of the 17 cats with AL (1 with high-grade AL and 1 with large granular AL) were euthanized at diagnosis upon owner request. The remaining 15 cats underwent various chemotherapy protocols [CHOP (Hydroxydaunorubicin, Oncovin-vincristine, Prednisolone) or COP (Cyclophosphamide, Oncovin-vincristine, Prednisolone)-based protocols; prednisolone and chlorambucil]. Four of these cats died (high-grade AL in 1, intermediate-grade AL in 1, low-grade AL in 2) within 2 to 24 weeks of diagnosis. The duration of remission in the remaining 11 cats (all with low-grade AL) varied widely (median duration, 2.9 to 24.5 months, 95% CI 15) and were all dead at the time of medical record review. Regardless of the diagnosis, parenteral cobalamin supplementation was given to all cats with subnormal cobalamin levels.

Discussion

This retrospective multicenter study compares, for the first time, clinical, clinicopathological data and ultrasonographic findings in cats with GI signs caused by FRE, IBD, and AL, and investigates potential associations with diagnosis. Consistent with previous observations, the cats with FRE were significantly younger than those with IBD or AL (Guilford et al. 2001, Jergens 2012, Al-Ghazlat et al. 2013). Although sex (male) and breed (Siamese and other Asian breeds) are known to predispose for AL and IBD, respectively (Guilford 1996, Fondacaro et al. 1999), we found no significant differences in the occurrence of either disease in relation to sex or breed. Cats with FRE, IBD and AL may present with any combination of weight loss, changes in appetite, vomiting, lethargy, and diarrhea (Guilford et al. 2001, Jergens 2012, Al-Ghazlat et al. 2013). We observed that weight loss was the most common presenting complaint/clinical sign, followed by vomiting and diarrhea, and that the cats with FRE presented more often with diarrhea and less often with muscle wasting than those with IBD or AL. Taken together, these results suggest that young-adult cats with a chronic history of weight loss, diarrhea, and minimal muscle wasting may potentially be affected by FRE.

In veterinary medicine, decreased serum cobalamin and folate concentrations are routinely used as a marker of GI absorptive dysfunction, distal and proximal, respectively (Simpson et al. 2001, Reed et al. 2007, Ruaux 2008, Berghoff and Steiner 2011), while increased serum folate concentrations may suggest small intestine dysbiosis (Ruaux et al. 2005). Previous studies have variously documented the prevalence of hypocobalaminemia in cats with GI disease (Simpson et al. 2001, Ibarrola et al. 2005, Reed et al. 2007, Barron et al. 2009). Moreover, failure to recognize and correct hypocobalaminemia can delay clinical recovery, even when specific therapy for IBD is instituted (Ruaux et al. 2005). In the present study, the serum cobalamin levels were lower in the cats with AL than in those with FRE or IBD and the serum folate concentrations were higher than in those with IBD. Although more sensitive measurements of clini-

cal hypocobalaminemia have been investigated in cats (Ruaux et al. 2009), the results of this study suggest that AL causes severe absorptive intestinal dysfunction and dysbiosis and that serum cobalamin is a practical indicator of severe gastrointestinal disease, such as AL (Simpson et al. 2001). In the majority of healthy cats, the cobalamin level is ≥500 ng/L (Ruaux et al. 2001, 2009, Maunder et al. 2012) and <500 ng/L in most cats with GI disease, regardless of the diagnosis (Simpson et al. 2001). In this study, AL could be ruled out with a serum cobalamin level ≤540 ng/L.

An ultrasonographic pattern of muscularis propria thickening has been recognized in cats with low-grade AL and IBD (Lingard et al. 2009, Zwingenberger et al. 2010), while intermediate and low-grade AL typically cause single or multiple masses in the stomach, intestines or colon (Penninck et al. 1994). However, the absence of abnormal findings at ultrasonography does not exclude inflammatory/neoplastic infiltrations (Daniaux et al. 2014). More recently, no differences in wall-layering were found when the two diseases were compared (Daniaux et al. 2014). Similarly, we found no significant differences in ultrasonographic findings between the three groups.

The major limitation of this study is its retrospective nature. Furthermore, each cat was examined by a variable number of clinicians and ultrasonographers. Finally, the diagnostic procedures were not strictly standardized and not all cats underwent endoscopy/laparotomy and clonality testing. It should be noted, however, that the response to therapy and the long-term follow-up supported the clinicians in making the final diagnosis.

In conclusion, adult and elderly cats with muscle wasting, increased values of BUN and serum folate and reduced values of cobalamin at presentation may suffer from AL. However, the definitive diagnosis should always be based on the evaluation of clinical signs, invasive diagnostic workup, response to therapy, and findings at follow-up.

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