Correlation of clinical, diagnostic and histopathological parameters in dogs with chronic lymphocytic-plasmacytic enteropathy

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Keywords
Chronic enteropathy, lymphocytic-plasmacytic inflammation, histopathology, endoscopy

Summary
Objective: The objective of this study was to correlate clinical signs and diagnostic parameters with duodenal inflammatory and architectural changes in dogs with lymphocytic-plasmacytic enteropathy. **Material and methods:** In a retrospective study dogs presented between 2003 and 2014 with chronic gastrointestinal signs (duration > 3 weeks) and histologic evidence of intestinal lymphocytic-plasmacytic inflammation were evaluated. Clinical signs, serum albumin, cobalamin and folic acid concentrations were recorded and a sonographic, endoscopic, histologic and cytological inflammatory score was determined. Furthermore, the presence of lacteal dilation, villus stunting, crypt lesions, epithelial integrity and increased intraepithelial lymphocytes was evaluated. **Results:** A total of 270 dogs were retrospectively evaluated. No significant correlation was found between clinical signs and sonographic, endoscopic or duodenal inflammatory score. Dogs with histological signs of lacteal dilation ($p = 0.001$) and increased intraepithelial lymphocytes ($p = 0.005$) had significantly higher clinical scores compared to dogs without these changes. No correlation was found between clinical score and villous stunting or crypt lesions. Hypoalbuminemia and hypocobalaminemia correlated significantly with lacteal dilation ($p = 0.001$, $p = 0.009$) and increased intraepithelial lymphocytes ($p = 0.036$, $p = 0.018$). **Clinical significance:** Some clinical and diagnostic parameter correlate with histopathologic features whereas others do not. Morphological features seem to be more important than the intensity of the duodenal inflammation in the assessment of the disease.

Schlüsselwörter
Chronische Enteropathie, lymphoplasmazelluläre Entzündung, Histopathologie, Endoskopie

Zusammenfassung
Ziel dieser Studie war, bei Hunden mit lymphoplasmazellulären Enteropathien klinische und diagnostische Parameter mit histopathologischen Veränderungen im Duodenum zu vergleichen. **Material und Methoden:** Die retrospektive Studie umfasste die Daten von Hunden, die zwischen 2003 und 2014 mit chronischen (> 3 Wochen) gastrointestinalen Symptomen vorgestellt wurden und bei denen eine histologisch bestätigte lymphoplasmazelluläre Duodenitis vorlag. Erfasst wurden die klinischen Symptome und die Serumkonzentrationen von Albumin, Cobalamin und Folsäure. Ferner erfolgte die Zuteilung eines sonographischen, endoskopischen, histologischen und zytologischen Entzündungsscores. Die histologischen Befunde wurden auf Zottenatrophie, Kryptenläsionen, epitheliale Integrität, Lymphangiektasie sowie erhöhte Zahl intraepithelialer Lymphozyten untersucht. **Ergebnisse:** Insgesamt 270 Hunde erfüllten die Einschlusskriterien. Zwischen klinischen Symptomen und dem sonographischen, endoskopischen, histologischen oder zytologischen Score ergab sich keine signifikante Korrelation. Hunde mit Lymphangiektasien ($p = 0{,}001$) oder erhöhter Anzahl an intraepithelialen Lymphozyten ($p = 0{,}005$) hatten signifikant höhere klinische Scores als Hunde ohne diese histopathologischen Veränderungen. Eine Korrelation zwischen klinischem Score und Zottenatrophie oder Kryptenläsionen war nicht nachweisbar. Hypoalbuminämie und Hypocobalaminämie korrelierten signifikant mit Lymphangiektasie ($p = 0{,}001$, $p = 0{,}009$) und erhöhter Anzahl intraepithelialer Lymphozyten ($p = 0{,}036$, $p = 0{,}018$). **Schlussfolgerung:** Einzelne klinische und diagnostische Parameter korrelieren mit den histopathologischen Veränderungen des Duodenums. Die morphologischen Veränderungen scheinen in der Beurteilung der Enteropathie eine wichtigere Rolle zu spielen als der Grad der Entzündung.

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Introduction

Chronic enteropathies are a common cause for persistent or recurrent gastrointestinal signs in dogs. Depending on the responsiveness to therapy, chronic enteropathies can be divided into food-responsive, antibiotic-responsive and steroid-responsive enteropathy (2, 7, 13). A thorough work-up is needed to exclude other causes of gastrointestinal signs (infectious, neoplastic, metabolic or endocrine diseases). This includes a detailed history and clinical examination, complete blood count and biochemistry, serum cobalamin, serum folic acid, canine pancreatic lipase immunoreactivity (cPLI), canine trypsin-like immunoreactivity (cTLI), as well as a complete fecal examination, abdominal ultrasound and histopathologic evaluation of gastrointestinal biopsies. Flexible endoscopy is a well-accepted method for obtaining biopsies of the stomach and duodenum and is less invasive than laparotomically obtained full-thickness biopsies (33, 39, 40). The interpretation of the obtained biopsies contributes to the classification of the severity and distribution of the disease (8). Depending on the type of the intestinal inflammatory infiltration of the lamina propria, canine enteropathies can be divided into neutrophilic, eosinophilic and lymphocytic-plasmacytic enteropathies (LPE) (14, 33). Neutrophilic inflammation can be seen with infectious disease, eosinophilic inflammation with parasites or food hypersensitivity reactions. The exact cause for LPE, even though it is described as the most frequent form of enteritis, is still unclear (7, 14, 17, 18).

Previous studies showed contrasting results regarding the association between clinical signs, diagnostic parameters and histopathology. Jergens et al. (19) demonstrated a correlation between clinical severity and histopathology. In several other studies no correlation between the canine inflammatory bowel disease activity index (CIBDAI) and the histologic score was observed (2, 7, 11, 16, 24, 28). A recent study reported different histopathologic features in dogs with or without hypoalbuminemia (37).

The objective of this retrospective study was to correlate duodenal inflammatory and architectural changes with clinical signs and diagnostic parameters in a large number of dogs. Our hypothesis was that duodenal morphological features influence clinical and diagnostic parameters more than the intensity of intestinal inflammation in the lamina propria.

Materials and methods

Patients

Medical data of all dogs presented between 2003 and 2014 with predominantly gastric and small-bowel signs were retrieved. Inclusion criteria were chronic persistent or intermittent gastrointestinal signs (> 3 weeks) and histologic evidence of intestinal lymphocytic-plasmacytic inflammation. All dogs had been tested negative for gastrointestinal parasites and bacteria. Dogs with endocrine, metabolic or neoplastic disease as primary cause for the gastrointestinal signs were excluded.

Evaluated parameters

The **CIBDAI** was used to assess the clinical signs based on the following clinical variables: attitude/activity, appetite, vomiting, stool consistency, stool frequency and weight loss (19). Depending on the sum of the score, the enteropathy was classified as clinically insignificant (0–3), mild (4–5), moderate (6–8) or severe disease (≥ 9).

Serum **albumin**, **cobalamin** and **folic acid** concentrations were recorded as normal or decreased (albumin < 2.8 g/dl, cobalamin < 234 ng/ml, folic acid < 9.3 ng/ml) based on the reference range of the laboratory performing the test (IDEXX, Germany). Serum cobalamin and folate concentrations were determined by use of an electrochemiluminescence immunoassay (E-170, Elecsys, Hoffmann-La Roche, Mannheim, Germany) and serum albumin by colometry (FUJI dri-chem, Sysmex Co, Norderstedt, Germany).

Sonography was performed using GE Logiq P6 and Vivid 7 (with an 8–12 mHz linear transducer) in every patient without sedation before endoscopy. The duodenal wall thickness, incorporating all layers of the duodenal long-axis segment, was used for the assessment of the **sonographic score** as follows: 1 = wall thickness < 4 mm, 2 = wall thickness 4–5 mm, 3 = wall thickness > 5 mm.

Endoscopy was performed with a flexible video endoscope (Video gastroduodenoscope, 9.8 mm optics, length 140 cm, Karl Storz®, Tuttlingen, Germany). At least 5–15 biopsies were taken from different areas of the duodenum using fenestrated forceps with oval cupped jaws, a spike and a diameter of 2.2 mm (Karl Storz®, Tuttlingen, Germany). The **endoscopic score** was classified based on the degree of mucosal irregularity, friability and hyperemia (normal mucosa = score 0; mild mucosal irregularity, mild friability, mild erythema = score 1; moderate mucosal irregularity, moderate friability, cobble stone appearance = score 2; severe mucosal irregularity, bleeds easily = score 3; erosive or nodular mucosal appearance, difficult insufflating the bowel = score 4).

Histopathologic analysis was performed by pathologists of the Specialty Practice for Veterinary Pathology, Munich, employing histologic criteria published by Jergens et al. (18), Day et al. (8), and Washabau et al. (36). Every dog was given a histologic inflammatory score by one board-certified pathologist (WvB) based on the severity of the lymphocytic-plasmacytic inflammation (0 = normal, 1 = mild, 2 = mild-moderate, 3 = moderate, 4 = moderate-severe, 5 = severe). Furthermore, the presence of lacteal dilation, villus stunting, crypt lesions, epithelial integrity and increased intraepithelial lymphocytes (IEL) was evaluated (0 = not present, 1 = present) using the standardized WSAVA guidelines (18).

Additionally, several biopsy samples of the duodenum were blindly assessed by a cytologist to determine the cytological inflammatory score, using the squash-smear technique and Diff-Quick® stain as described by Mangelsdorf et al. (22, 23). According to this system the **lymphocytic-plasmacytic infiltration** is graded from score 0 (physiologic), score 1 (sparsely distributed thin layer of inflammatory cells adjacent to the epithelial cell layer), score 2

(thin, continuous layer of inflammatory cells), score 3 (1–2 inflammatory cell layers) score 4 (2–3 inflammatory cell layers) to score 5 (> 3 inflammatory cell layers).

Statistical analysis

For the statistical analysis, a commercially available standard statistic software (SPSS statistics 23, IBM corp. New York, United States) was used. Normal distribution of data was assessed using the Kolmogorov-Smirnov test. Non-parametric Kruskal-Wallis test and Mann-Whitney test were used to assess differences in continuous parameters between groups. Correlation between scores was performed by the Pearson correlation test. For testing differences among groups for ordinal or ratio data, the Pearson's chi-square test was used. A p-value < 0.05 was considered to be significant.

Results

A total of 270 **dogs**, 143 males and 127 females, were examined. The median age of the study population was 6.5 years (range 0.5–15 years). Seventy-eight mixed breed dogs and 192 purebred dogs were included. The most commonly affected breeds were West Highland White Terrier (n = 14), Jack Russell Terrier (n = 14) and German Shepherd Dogs (n = 13).

Eighty-six dogs had a **CIBDAI score** between 1 and 3 (clinically insignificant disease), 108 dogs a score of 4–5 (mild disease), 54 dogs a score between 6 and 8 (moderate disease) and 22 dogs a score ≥ 9 (severe disease). Clinical signs included vomiting (172/270), diarrhea (170/270), decreased activity (158/270), decreased appetite (104/270), increased defecation activity (41/270) and weight loss (73/270).

Due to the retrospective nature of this study clinical data were not available from all animals. **Albumin** levels were available from 173 dogs, **cobalamin** levels from 51 dogs and **folic acid** levels from 41 dogs. Thirty-three dogs had hypoalbuminemia, 11 dogs hypocobalaminemia and 13 dogs decreased folic acid levels. Breeds with hypoalbuminemia included: mixed breed dogs with > 10 kg body weight (14), Yorkshire Terrier (2), Cairn Terrier (2), Pomeranian, West Highland White Terrier, Boxer, Cocker Spaniel, Maltese, Fox Terrier, Schnauzer, Beauceron, Saluki, Belgian Shepherd Dog, Golden Retriever, Bavarian Hunting Dog, Border Collie, German Shepherd Dog, Podenco (each one per breed). Decreased cobalamin levels were found in two German Shepherd Dogs, two Jack Russell terriers, two Podencos, one mixed breed dog, one Sheltie, one pug, one Labrador Retriever and one Dalmatian.

Ninety-seven dogs were assigned a **sonographic score** of 1 (wall thickness < 4 mm), 76 dogs a score of 2 (wall thickness 4–5 mm) and 97 patients a score of 3 (wall thickness > 5 mm). The sonographic score did not correlate significantly with the CIBDAI (p = 0.801), with the endoscopic score (p = 0.269), with cobalamin (p = 0.738) nor with folic acid (p = 0.820) but was significantly correlated with albumin (p = 0.038).

Endoscopically, the duodenal mucosa of 28 dogs was within normal limits (score 0), 76 dogs had a mildly irregular mucosa (score 1), 59 dogs had a moderately irregular mucosa (score 2), 81 dogs had a severely irregular mucosa (score 3), and 26 dogs displayed erosive/ulcerative lesions (score 4).

The **histologic inflammatory infiltration** was mild in 170 dogs (score 1), mild-moderate in 18 dogs (score 2), moderate in 59 dogs (score 3), moderate-severe in 11 dogs (score 4) and severe in 12 dogs (score 5). The histologic inflammatory score was not significantly correlated with CIBDAI, sonographic score or blood parameters. A significant correlation (p = 0.042) was found with the endoscopic score. Dogs with higher inflammatory scores had significantly higher endoscopic scores.

The cytological inflammatory score was available for 242 dogs. Inflammation was scored as mild in 70 dogs (score 1), mild-moderate in 29 dogs (score 2), moderate in 88 dogs (score 3), moderate-severe in 30 dogs (score 4), and severe in 25 dogs (score 5). The cytological inflammatory score was not significantly correlated with CIBDAI, sonographic score or blood parameters, but there was a significant correlation (p < 0.001) with the endoscopic score. Dogs with higher inflammatory scores had significantly higher endoscopic scores.

Architectural changes of the duodenum were as follows: lacteal dilation in 71 dogs, villus stunting in 72 dogs, crypt distention in 13 dogs, epithelial injury in 16 dogs and increased IEL in 115 dogs. Lacteal dilation was significantly associated with higher CIBDAI (p = 0.001), hypoalbuminemia (p = 0.001) and hypocobalaminemia (p = 0.009), whereas no significant correlation was found with folic acid (p = 0.173) or the endoscopic score (p = 0.176). No significant correlation was found between villus stunting and CIBDAI, blood parameters or the endoscopic score. Crypt distention was not significantly correlated with CIBDAI or the endoscopic score. Due to the small number of dogs with crypt distention (n = 8) in which blood parameters were available, no significant correlation with crypt distention could be found. There was no correlation between epithelial injury and CIBDAI, albumin, cobalamin, folic acid or the endoscopic score. Dogs with increased IEL had significant higher CIBDAI scores (p = 0.005). Hypoalbuminemia (p = 0.036), hypocobalaminemia (p = 0.049) and decreased folic acid levels (p = 0.018) were significantly correlated with increased IEL.

Discussion

The median age of the dogs included in this study was similar to those previously described (2, 7, 11). A sex predisposition was not apparent in our study. Breeds included in the study cohort reflect the general hospital population but some breeds known to have a predisposition for chronic gastrointestinal disease were also represented (German Shepherd Dog, Golden Retriever, Jack Russell Terrier).

According to other studies, clinical signs most frequently observed in dogs with LPE are vomiting, diarrhea and weight loss (17, 18). We found vomiting, diarrhea and decreased activity to be the most frequent clinical signs at presentation. Decreased activity level is most commonly encountered in dogs with protein-losing enteropathy (21, 32). In our study however, decreased activity was also observed in non-hypoproteinemic dogs. Decreased activity is the most subjective parameter of the CIBDAI score and very much dependent on the perception and alertness of the owner. This could explain the discrepancy to other studies.

Dogs included in our study were predominantly presented with small bowel disease, with only 14% of the study population also having large bowel signs. Nevertheless, we used the CIBDAI score as a grading system for the clinical signs which summates small and large bowel signs. This may explain the high number of dogs with low CIBDAI score (classified as „mild disease“).

In the correlation analysis some clinical and diagnostic parameters correlated with each other, whereas others did not. The sonographic score, representing the duodenal wall thickness was not significantly correlated with CIBDAI. This was an expected finding, since it was the same conclusion obtained by previous studies (12, 30). However, hypoalbuminemia correlated significantly with higher sonographic scores, which was also observed by Gaschen et al. (12) in dogs with protein losing enteropathy.

As expected, the severity of the lymphocytic-plasmacytic inflammation in the lamina propria did not correlate with the severity of clinical signs. This missing correlation may explain why dogs with chronic enteropathies, who improved clinically after treatment, had no improvement in the inflammatory infiltration (1, 11, 31). Furthermore, the lymphocytic-plasmacytic inflammation did not correlate with serum albumin or cobalamin which is in agreement with previous studies (2, 7, 37).

In a recent study a statistical correlation between histologic and endoscopic scores was described, which was the same result we obtained in our study: the grade of lymphocytic-plasmacytic inflammation correlated significantly with the endoscopic score (29). The cause for this correlation is unclear, but probably the severe inflammatory patterns cause more irregular mucosal layers.

Although a recent study found a significant correlation between clinical signs and crypt distention (28) we did not find a significant correlation with CIBDAI. Only one dog with crypt distention was hypoalbuminemic in our study, even though crypt distention is thought to be a possible cause of protein-losing enteropathy (32, 38). We found crypt distention as a rare histologic finding which could be the cause of the contrasting result compared to other studies.

In human medicine malabsorption can be caused by villous stunting. This morphologic feature results from an increase in the crypt compartment and a decrease in the villous compartment as a consequence of intestinal inflammation (25). Also in veterinary medicine, villous stunting is observed in hypoalbuminemic dogs (29, 32, 37). Contrary to our expectation hypoalbuminemia or hypocobalaminemia did not correlate significantly with villus stunting in our study. A possible explanation for this discrepancy can be the segmental or multifocal distribution of the histopathologic lesions so that they can be missed in endoscopically obtained biopsies.

Besides malabsorption, hypocobalaminemia can be caused by excess cobalamin consumption from the intestinal bacteria (3, 13) and congenital disorders described in the breeds Giant Schnauzer (10), Beagle (9), Border Collie (26) Australian Shepherd (16) and Shar-Pei (4). All dogs predisposed to hypocobalaminemia due to their breeds were normocobalaminemic in our study.

Increased IEL correlated significantly with every clinical and diagnostic parameter in our study. In human medicine increased numbers of IEL point to specific gastrointestinal diseases including celiac disease, *Helicobacter pylori* infection, immunodeficiency, small intestinal bacterial overgrowth (SIBO), viral enteritis or idiopathic inflammatory bowel disease (5, 27). In veterinary medicine a specificity is lacking. Increased IEL, as well as lacteal dilation, correlated significantly with higher CIBDAI scores, which suggests that they influence the severity of clinical signs. Furthermore, increased IEL and lacteal dilation correlated significantly with hypoalbuminemia and hypocobalaminemia. This result corresponds to previous studies. In one study the degree of hypoalbuminemia correlated with the degree of lacteal dilation (29). The second study compared histopathological findings in dogs with chronic enteropathies and hypoalbuminemia or normoalbuminemia. Lacteal dilation and increased IEL were more frequently observed in the hypoalbuminemic group (37). Additionally, a significant correlation between lacteal dilation and hypoalbuminemia was found by three of four pathologists evaluating the same histopathological slides (40).

Hypoalbuminemia and hypocobalaminemia may occur concurrently in dogs with chronic enteropathies (2) and together with higher CIBDAI scores they are risk factors for a negative outcome (2, 7).

Walker et al. (35) proposed, that duodenal morphologic changes are as important as inflammatory changes in the assessment of chronic enteropathies. Our results suggest, that morphologic changes as lacteal dilation and increased IEL are even more important in the pathogenesis of the disease. The fact that these two changes correlate significantly with CIBDAI, albumin and cobalamin suggests that such morphologic changes may indicate a more severe form of enteropathy. To evaluate the impact of these features in the responsiveness to treatment and the outcome further prospective studies are needed.

All biopsies were taken endoscopically, which is a well-accepted method even though the sensitivity of the histologic lesions is strongly dependent on the quality of the biopsies (39). Full-thickness biopsies may be more reliable in evaluating lesions deep within the submucosa and muscularis layer and to diagnose intestinal lymphoma (20). Ileal biopsies were not evaluated, which is clearly a limitation of this study, especially because recent studies documented different histopathologic features among ileum and duodenum (6, 28). Based on the multifocal nature of the disease

Conclusion for practice

Some clinical and diagnostic parameter correlate with histopathologic features whereas others do not. The intensity of the lymphocytic-plasmacytic inflammation in the lamina propria did not correlate with the severity of clinical disease, serum albumin and cobalamin, whereas increased intraepithelial lymphocytes and lacteal dilation correlated significantly with clinical signs, hypoalbuminemia and hypocobalaminemia and may represent a more severe form of chronic enteropathies. In the assessment of the disease morphological features seem to be more important than the intensity of the duodenal inflammation.

lesions can be easily missed, contributing to the discrepancy between histopathology and clinical signs.

The retrospective nature of the study is a further limitation, as not all biomarker levels were available and follow-up information was not complete in all dogs. For this reason, we could not correlate clinical, diagnostic or histopathology parameters with patient outcome, which would have been of great interest. Furthermore, we did not systematically classify our dogs as food-responsive, antibiotic-responsive or steroid-responsive enteropathy due to the changing treatment regime in our clinic over time. Some dogs were treated with more than one therapy.

Inter-observer variation in interpreting histopathology is possible, because more than one pathologist was involved in our study (40). Inter-observer variation in assessing the endoscopic score is a further limitation (34).

In conclusion, some clinical and diagnostic parameters correlate with histopathologic features whereas others do not. The intensity of the lymphocytic-plasmacytic inflammation in the lamina propria did not correlate with the severity of clinical disease, serum albumin and cobalamin, whereas increased IEL and lacteal dilation correlated significantly with clinical signs, hypoalbuminemia and hypocobalaminemia and may indicate a more severe form of chronic enteropathies. Further prospective studies are needed to evaluate the impact of increased IEL and lacteal dilation on the responsiveness to treatment and outcome.

Clinicians should not rely on only one scoring system to categorize the enteropathy, but the summation of clinical and diagnostic information gives an overall picture of the disease.

Conflict of interest

The authors confirm that they do not have any conflict of interest.

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