FULL PAPER *Internal Medicine*

A Retrospective Study in 21 Shiba Dogs with Chronic Enteropathy

Aki OHMI[1)], Koichi OHNO[1)], Kazuyuki UCHIDA[2)], Hiroyuki NAKAYAMA[2)], Yuko KOSHINO-GOTO[1)], Kenjiro FUKUSHIMA[1)], Masashi TAKAHASHI[1)], Ko NAKASHIMA[1)], Yasuhito FUJINO[1)] and Hajime TSUJIMOTO[1)]

[1)]Department of Veterinary Internal Medicine and [2)]Laboratory of Veterinary Pathology, Graduate School of Agricultural and Life Sciences, The University of Tokyo, 1–1–1 Yayoi, Bunkyo-ku, Tokyo 113–8657, Japan

(Received 13 April 2010/Accepted 29 July 2010/Published online in J-STAGE 12 August 2010)

ABSTRACT. We retrospectively studied the clinical and laboratory features and outcomes of chronic enteropathy in Shiba dogs. Among 99 dogs with chronic enteropathy, 21 Shiba dogs (21%) were included in the study (odds ratio, 7.14). No significant differences were seen in signalment, clinical signs, symptoms or laboratory profiles between the Shiba and non-Shiba groups. Severe histopathological lesions in the duodenum were a common finding in the Shiba group. The median overall duration of survival in the Shiba group was 74 days, while that of the dogs in the non-Shiba group could not be determined because more than half of the cases remained alive at the end of this study. The difference between the groups was statistically significant ($P<0.0001$). The 6-month and 1-year survival rates for the Shiba group were 46% and 31%, respectively. Conversely, the 6-month, 1-year and 3-year survival rates for the non-Shiba group were 83%, 74% and 67%. The results obtained here demonstrated that the Shiba dog is predisposed to chronic enteropathy and shows severe duodenum lesions and poor outcomes, indicating a breed-specific disease.

KEY WORDS: breed-specific enteropathy, chronic enteropathy, Shiba.

J. Vet. Med. Sci. 73(1): 1–5, 2011

Chronic enteropathy is one of the most common diagnoses in dogs with chronic gastrointestinal symptoms such as diarrhea and vomiting. Based on response to treatment, chronic enteropathy can be classified into 3 main groups: food-responsive diarrhea (FRD), antibiotic-responsive diarrhea (ARD) and inflammatory bowel disease (IBD) [1, 12, 13, 15]. Although the pathogenesis of the disease has not been completely clarified yet, some reports in human medicine and laboratory animals have demonstrated underlying genetic factors related to the disease [5]. In veterinary medicine, some breeds are known to be predisposed to specific types of chronic enteropathy, such as protein-losing enteropathy and nephropathy in the Soft Coated Wheaten Terrier [18], immunoproliferative enteropathy in the Basenji [3] and chronic enteropathy and ARD in the German Shepherd [2, 11]. The existence of so-called breed-specific chronic enteropathy implies that some kinds of genetic factors are associated with the pathogenesis of the disease in dogs.

In our previous report on dogs with lymphocytic-plasmacytic enteritis (LPE), Shiba dogs tended to be at higher risk of poor prognosis [19]. As only a small number of Shiba cases were analyzed, we could not clarify differences between the Shiba breed and other breeds. The present study compared clinical and laboratory features and outcomes of chronic enteropathy in Shiba dogs and compared results with previous reports.

* CORRESPONDENCE TO: OHNO, K., Department of Veterinary Internal Medicine, Graduate School of Agricultural and Life Sciences, The University of Tokyo, 1–1–1 Yayoi, Bunkyo-ku, Tokyo 113–8657, Japan.
e-mail: aohno@mail.ecc.u-tokyo.ac.jp

MATERIALS AND METHODS

Clinical cases: Medical records of dogs with chronic enteropathy referred to the Veterinary Medical Center at The University of Tokyo (VMC-UT) between April 2000 and March 2009 were reviewed. Criteria for selection included chronic (duration > 3 weeks) gastrointestinal symptoms such as vomiting, diarrhea and weight loss, failure to identify other causes of gastrointestinal diseases despite thorough diagnostic evaluation, condition refractory to dietary therapy (selected antigen or highly digestible diet) or symptomatic therapy (antibiotics, antiemetics or gastrointestinal protectants) alone and histopathological evidence of gastrointestinal inflammation after examination of endoscopically obtained biopsy specimens. The dogs were classified into a Shiba group (Shiba dogs) or non-Shiba group (breeds other than the Shiba) according to breed. A minimal diagnostic evaluation to exclude other diseases was performed that was comprised of complete blood cell count (CBC), serum chemistry, fecal examination, survey radiography and abdominal ultrasonography. Cases were excluded if underlying or concurrent disorders other than chronic enteropathy were confirmed.

Data analysis: Signalment, clinical signs and symptoms, laboratory findings, histopathological findings, diagnosis and outcomes were recorded. Clinical signs and symptoms at the first visit were evaluated by the presence or absence of vomiting, diarrhea, anorexia, lethargy, ascites and pruritus. Degree of weight loss was calculated when information was available. Laboratory analysis at the first examination included hematocrit, total white blood cell count, platelet count and serum chemistry profiles of total protein, albumin, blood urea nitrogen, creatinine, alkaline phosphatase, alanine aminotransferase, lactate dehydrogenase, total

bilirubin, total cholesterol, ammonia, magnesium, calcium, sodium, potassium, chloride and C-reactive protein (CRP). Histopathological severity was judged by pathologists and classified objectively into 4 grades (normal, mild, moderate and severe) based on the infiltration of inflammatory cells and structural changes in the gastrointestinal mucosa. In some cases, endoscopic biopsy samples were submitted for polymerase chain reaction (PCR) testing for lymphocyte antigen receptor rearrangement to detect the presence of clonal gene rearrangements indicating lymphoma, following a previously described method [4].

Statistical analysis: Categorical data are presented as either percentages or ratios. Numerical data are presented as medians (ranges). Fisher's exact tests were used to determine associations between categorical variables. Mann-Whitney U tests were used to compare numerical values. Kaplan-Meier survival curves and log-rank testing were used to analyze survival data. Values of $P<0.05$ were considered significant. The statistical analysis was performed using commercial statistical software (JMP 5.0.1, SAS Institute, Cary, NC, U.S.A.).

RESULTS

Signalment: Twenty-two Shiba dogs (Shiba group) and 77 non-Shiba breed dogs (non-Shiba group) were included in the study. Although 1 Shiba dog was diagnosed with eosinophilic enteritis, all other dogs (n=98) were diagnosed with LPE. We excluded the dog with eosinophilic enteritis from the subsequent analysis because of the small number of such cases. The Shiba group accounted for 21% of all the dogs. During the study period, a total of 9,100 dogs were referred to the VMC-UT, including 322 Shiba dogs. The odds ratio was calculated as 7.14. The non-Shiba group included breeds of dogs such as the Miniature Dachshund (n=8), Yorkshire Terrier (n=8), Shetland Sheepdog (n=7), Maltese (n=6), Border Collie (n=5), Welsh Corgi (n=4), French Bulldog (n=4), Pomeranian (n=4), Boston Terrier (n=3), Golden Retriever (n=3), Cavalier King Charles Spaniel (n=3), mongrel (n=3), Shih Tzu (n=2), West Highland White Terrier (n=2) and others (n=15). The Shiba group comprised 14 male dogs (intact, n=9; castrated, n=5) and 7 female dogs (all spayed). Median age at admission was 4.9 years (range, 1.3–13.9 years). The non-Shiba group included 39 male dogs (intact, n=30; castrated, n=9) and 38 female dogs (intact, n=18; spayed, n=20). The median age of these dogs was 7.0 years (range, 0.8–13.6 years). No significant differences in signalment were seen between the groups. These data are summarized in Table 1.

Clinical signs and symptoms: Clinical signs and symptoms for each group are shown in Table 1. Information on the degree of weight loss was available for 14 dogs in the Shiba group and 42 dogs in the non-Shiba group. Moderate to severe weight loss and diarrhea were common symptoms in both groups. Anorexia was frequently observed in the Shiba group. Vomiting and ascites tended to be more common in the non-Shiba group than in the Shiba group. No significant differences were observed.

Laboratory findings: The CBC and serum chemistry profiles of each group at the first examination are shown in Table 2. Leukocytosis, hypoproteinemia, hypoalbuminemia, low blood urea nitrogen, low creatinine, low total cholesterol, low magnesium and elevated CRP were common findings in both groups. No significant differences were found between the groups.

Histopathological examination: All dogs showed evident inflammatory infiltration of lymphocytes and plasma cells, which led to the diagnosis of LPE. Other findings included epithelial injury, stunting and fusion of villi, crypt distension and lacteal dilation. The sites and severity of lesions in the cases are shown in Table 3. Severe lesions were more frequently documented in the duodenum and ileum than in the stomach and colon. In the non-Shiba group, severe lesions in the duodenum were documented in 37% of the cases. Conversely, no less than 75% of the dogs in the Shiba group were judged as having severe lesions in the duodenum. A significant difference was thus evident between the groups ($P<0.0046$).

PCR testing: PCR testing to detect the clonal rearrangement of lymphocyte antigen receptor was performed for 8 dogs in the Shiba group. A single T-cell receptor (TCR) gene rearrangement was identified in 2 of the 8 cases.

Table 1. Signalment, clinical signs and symptoms in the Shiba and non-Shiba groups

	Shiba group (n=21)	n	Non-Shiba group (n=77)	n	*P*
Signalment					
Gender, M : MC : F : FS	9 : 5 : 7 : 0	21	30 : 9 : 18 : 20	77	ND
Male : Female ratio		2 : 1	21	1.03 : 1	770.2239
Age, median (range)	4.9 years (1.3–13.9 years)	21	7.0 years (0.8–13.6 years)	77	0.1009
Clinical signs and symptoms					
Degree of weight loss, median (range)	20% (6–35%)	14	21% (5–45%)	42	0.4663
Vomit, n (%)	7 (33%)	21	41 (53%)	77	0.1407
Diarrhea, n (%)	19 (90%)	21	68 (88%)	77	1
Anorexia, n (%)	12 (57%)	21	29 (38%)	77	0.1367
Lethargy, n (%)	9 (43%)	21	36 (47%)	77	0.8087
Ascites, n (%)	3 (14%)	21	28 (36%)	77	0.066
Pruritus, n (%)	2 (10%)	21	7 (9%)	77	1

M, male; MC, male castrated; F, female; FS, female spayed.

Table 2. Results of hematological and biochemical tests in the Shiba and non-Shiba groups

	Shiba group (n=21)	n	Non-Shiba group (n=77)	n	*P*
CBC					
Hematocrit (%)	40 (23–56)	21	41 (17–61)	77	0.2281
Total white blood cells (/μl)	21,100 (7,800–66,100)	21	14,900 (5,300–87,600)	76	0.0603
Platelets (/μl)	389,000 (185,000–864,000)	21	446,000 (57,000–1,254,000)	76	0.4053
Serum chemistry					
Total protein (g/d*l*)	4.4 (1.8–8.0)	21	4.0 (1.8–7.3)	77	0.606
Albumin (g/d*l*)	1.9 (1.1–3.5)	21	1.9 (0.6–3.9)	75	0.6161
Blood urea nitrogen (mg/d*l*)	14.3 (2.3–37.7)	21	14.1 (4.2–51.3)	77	0.9035
Creatinine (mg/d*l*)	0.6 (0.2–1.3)	21	0.6 (0.1–1.9)	77	0.9132
Alkaline phosphatase (U/*l*)	218 (21–10,140)	21	197 (33–3,500)	77	0.2513
Alanine aminotransferase (U/*l*)	72 (20–540)	21	61 (14–655)	77	0.5854
Lactate dehydrogenase (U/*l*)	152 (7–418)	10	104 (33–254)	29	0.5845
Total bilirubin (mg/d*l*)	0.7 (0.2–1.4)	5	0.3 (0.2–0.4)	7	0.1332
Total cholesterol (mg/d*l*)	78 (55–163)	11	133 (33–266)	49	0.0666
Ammonia (μg/d*l*)	73 (31–159)	6	52 (25–91)	17	0.2934
Magnesium (mg/d*l*)	1.3 (0.4–2.0)	9	1.6 (0.5–2.1)	19	0.5053
Calcium (mg/d*l*)	9.9 (7.3–12.1)	15	10.3 (6.8–14.2)	46	0.5747
Sodium (mEq/*l*)	146 (128–149)	17	146 (129–152)	65	0.8316
Potassium (mEq/*l*)	4.0 (2.9–4.9)	17	4.0 (2.8–5.5)	65	0.4257
Chloride (mEq/*l*)	109 (91–121)	17	110 (92–128)	65	0.4394
C–reactive protein (mg/d*l*)	1.65 (0.0–12)	20	0.4 (0.0–20)	74	0.1534

Data are shown as medians (ranges).

Table 3. Number and percent of dogs with each severity of histopathological lesion in different sites of the gastrointestinal tract

Site and severity	Shiba group (n=21)	Non-Shiba group (n=77)
Stomach		
Normal	4/11 (36%)	21/46 (46%)
Mild	7/11 (64%)	13/46 (28%)
Moderate	0/11 (0%)	6/46 (13%)
Severe	0/11 (0%)	6/46 (13%)
Duodenum		
Normal	0/20 (0%)	1/76 (1%)
Mild	2/20 (10%)	7/76 (9%)
Moderate	3/20 (15%)	40/76 (53%)
Severe	15/20 (75%)	28/76 (37%)
Ileum		
Normal	0/8 (0%)	3/20 (15%)
Mild	1/8 (13%)	6/20 (30%)
Moderate	3/8 (38%)	5/20 (25%)
Severe	4/8 (50%)	6/20 (30%)
Colon		
Normal	0/12 (0%)	7/32 (22%)
Mild	4/12 (33%)	7/32 (22%)
Moderate	8/12 (67%)	15/32 (47%)
Severe	0/12 (0%)	3/32 (9%)

Data are shown as no. of dogs/total no. of dogs (%).

Clonal immunoglobulin heavy chain (IgH) gene rearrangement was not detected in any cases.

Treatment: All dogs received prednisolone (0.5–2 mg/kg/day) as an initial treatment. Other treatments included prescription diet, medications such as metronidazole, tylosin, famotidine, sucralfate, azathioprine, cyclosporine A and sulfasalazine and some other drugs based on the condition of each case and preferences of the practitioner. Statistical analysis was not performed because of the large variety of treatments.

Outcomes: Of the 21 dogs in the Shiba group, only 1 dog was still alive (> 927 days) at the end of this study. Sixteen dogs became refractory to treatment and died as the disease progressed. One dog died due to an undetermined disease. The remaining 4 dogs were lost to follow-up after 31, 84, 196, and 240 days. In the non-Shiba group, 18 dogs were still alive at the end of the study, 20 dogs died of enteropathy, 1 dog was euthanized due to enteropathy, and 5 dogs died of undetermined or unrelated diseases. The remaining 33 dogs were lost to follow-up, with a median follow-up period of 418 days (range, 35–959 days). The median overall duration of survival for the dogs in the Shiba group was 74 days, while that of the dogs in the non-Shiba group could not be determined because more than half of the cases remained alive at the end of this study (Fig. 1). The difference between groups was significant ($P<0.0001$). The 6-month and 1-year survival rates for the Shiba group were 46% and 31%, respectively. In contrast, the 6-month, 1-year and 3-year survival rates for the non-Shiba group were 83%, 74% and 67%.

Univariate analysis: To identify candidate prognostic factors for chronic enteropathy in Shiba dogs, univariate analysis was performed (Table 4). Dogs surviving >6 months were classified as survivors, whereas those that did not were considered non-survivors. Each parameter was examined as to whether a significant difference would be detected between the groups. Anorexia, lethargy, leukocytosis, hypoproteinemia, hypoalbuminemia and low Cre value at the first examination were more frequently observed, and the differences were statistically significant. The number of cases was not sufficient to allow multivariate

Table 4. Comparison of survivors and non-survivors with regard to clinical and laboratory profiles in the Shiba group

	Survivors (n=8)	Non-survivors (n=11)	*P*
Clinical signs and symptoms			
Anorexia, n (%)	1 (13%)	10 (91%)	0.0012
Lethargy, n (%)	1 (13%)	8 (73%)	0.0198
CBC			
WBC (/μl), median (range)	11,600 (7,800–39,400)	27,600 (11,500–66,100)	0.0232
Serum chemistry			
Total protein (g/d*l*), median (range)	5.6 (2.6–8.0)	4.0 (1.8–4.8)	0.013
Albumin (g/d*l*), median (range)	2.7 (1.2–3.0)	1.6 (1.0–2.4)	0.0072
Creatinine (mg/d*l*), median (range)	0.8 (0.4–1.0)	0.5 (0.2–1.1)	0.0462

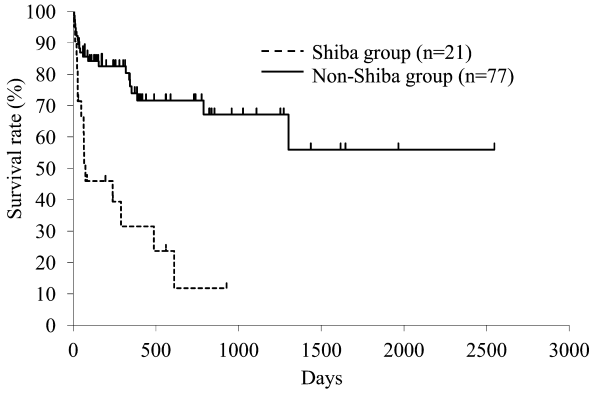

Fig. 1. Kaplan-Meier survival curves for the Shiba and non-Shiba groups. The difference between groups was significant (P<0.0001).

analysis.

DISCUSSION

In this study, LPE was the most common cause of chronic enteropathy in dogs. Shiba dogs were overrepresented among the breeds, accounting for 21% of the cases (odds ratio, 7.14). This suggests that the Shiba breed is predisposed to chronic enteropathy. All dogs in the Shiba group were treated intensively, but few dogs responded to treatment or survived for long. The median survival time in the Shiba group in this study was as short as 74 days, and the prognosis was significantly worse compared with the non-Shiba group. The 6-month and 1-year survival rates were calculated as 46% and 31%, respectively. In previous studies, more favorable prognoses have been reported. In one report, 80 dogs diagnosed with IBD were retrospectively analyzed, but only 3 dogs were euthanized due to refractory IBD within 6 months, and 77 dogs (96%) remained alive after >6 months. Ten of the 80 dogs (13%) were euthanized because of disease in the study period [7]. In another prospective study, 70 dogs with chronic enteropathy were classified into 3 groups as a food-responsive diarrhea group, a steroid-treatment group and a protein-losing enteropathy group. The 3-year survival rate was 97% (38/39) in the food-responsive diarrhea group, 57% (12/21) in the steroid-treatment group and 70% (7/10) in the protein-losing group [1]. In our previous report of non-Shiba dogs with LPE, the 6-month survival rate was determined to be 74% (29/39) [19]. Compared with these reports, the present results strongly imply poor outcomes for Shiba dogs with chronic enteropathy.

To date, factors such as anorexia, hypoalbuminemia and hypoproteinemia have been reported to be associated with poor prognosis in dogs with chronic enteropathy [1, 7, 19]. However, no significant differences in symptoms or laboratory findings were detected between the Shiba and non-Shiba groups. Interpretation of clinical signs is inevitably subjective and might have some effect on the results. Recently, clinical indices to assess the severity of canine IBD (canine inflammatory bowel disease activity index (CIBDAI)) and canine chronic enteropathy (canine chronic enteropathy activity index (CCECAI)) have been described, and some studies have indicated their clinical usefulness [1, 14, 16]. In the present study, however, data for CIBDAI or CCECAI could not be obtained because of the retrospective study design.

Although no significant differences were seen between the Shiba and non-Shiba groups, anorexia, lethargy, leukocytosis, hypoproteinemia, hypoalbuminemia and low creatinine values were associated with death within 6 months among the Shiba group dogs. Leukocytosis indicated the presence of severe inflammatory response. Moreover, bacterial translocations or endotoxemia might have taken place in some cases with marked leukocytosis. Low creatinine levels might suggest a loss of lean body mass or cachexia. The number of cases was not large enough to allow multivariate analysis. Further studies are needed to validate prognostic factors in Shiba dogs.

Histopathological examination revealed severe inflammatory lesions in the duodenums of most of the Shiba dogs with LPE. Infiltration of abundant lymphocytes and plasmacytes and architectural changes such as blunt villi and lymphangiectasia were common. These disastrous inflammations would have caused malabsorption and loss of nutritional substances such as protein and minerals into the gastrointestinal tract, which might lead to critical malnutrition. Severe changes in the duodenum may be one of the clinical features of LPE in Shiba dogs. However, several reports have described no association between histopathological changes and clinical severity or outcome [1, 7, 10,

19]. The severe duodenum lesions cannot account for the poor prognosis of LPE in the Shiba dogs. Furthermore, histopathological evaluation was performed in this study by several pathologists, and interobserver variation might have been present. Further investigation with evaluation by a single pathologist based on the histopathological standard for gastrointestinal inflammation [8] is warranted.

Lymphoma is one of the most common neoplasias occurring in the intestinal tract for dogs [6]. Distinguishing gastrointestinal lymphoma from LPE is sometimes difficult, particularly when the lymphoma is well-differentiated and low-grade. In our study, all dogs in the Shiba group were diagnosed by endoscopic biopsy, and only 3 of 21 dogs were confirmed to have no evidence of lymphoma on necropsy. Although we usually take more than 6 tissue samples each from the upper and lower tracts, including the stomach, duodenum, ileum and colon, lymphoma cannot be excluded completely. PCR testing for clonal rearrangement of lymphocyte antigen was performed for 8 dogs in the Shiba group, and TCR gene clonal rearrangement was detected in 2 dogs. As the sensitivity and specificity of PCR testing are reportedly questionable to some extent for detecting alimentary lymphoma [9, 17], there is some possibility that these were false-positive results. Unfortunately, necropsy could not be conducted on the 2 dogs, and we could not completely exclude the possibility of lymphoma. When we analyzed the 6 dogs in the Shiba group that had negative PCR test results, the differences in survival time between the Shiba and non-Shiba groups were still significant (data not shown).

In conclusion, Shiba dogs appear predisposed to chronic enteropathy/LPE and show severe duodenal lesions and poor prognosis. Although we could not clarify specific clinical or laboratory features other than shortened survived time, chronic enteropathy in Shiba dogs should be considered a breed-specific disease.

ACKNOWLEDGMENT. This work was partially supported by the Ministry of Education, Culture, Sports, Science and Technology through a Grant-in-Aid for Scientific Research.

REFERENCES

1. Allenspach, K., Wieland, B., Grone, A. and Gaschen, F. 2007. Chronic enteropathies in dogs: evaluation of risk factors for negative outcome. *J. Vet. Intern. Med.* **21**: 700–708.
2. Batt, R. M., Needham, J. R. and Carter, M. W. 1983. Bacterial overgrowth associated with a naturally occurring enteropathy in the German shepherd dog. *Res. Vet. Sci.* **35**: 42–46.
3. Breitschwerdt, E. B., Ochoa, R., Barta, M., Barta, O., Mcclure, J. and Waltman, C. 1984. Clinical and laboratory characterization of Basenjis with immunoproliferative small intestinal disease. *Am. J. Vet. Res.* **45**: 267–273.
4. Burnett, R. C., Vernau, W., Modiano, J. F., Olver, C. S., Moore, P. F. and Avery, A. C. 2003. Diagnosis of canine lymphoid neoplasia using clonal rearrangements of antigen receptor genes. *Vet. Pathol.* **40**: 32–41.
5. Cooney, R. and Jewell, D. 2009. The genetic basis of inflammatory bowel disease. *Dig. Dis.* **27**: 428–442.
6. Couto, C. G., Rutgers, H. C., Sherding, R. G. and Rojko, J. 1989. Gastrointestinal lymphoma in 20 dogs. A retrospective study. *J. Vet. Intern. Med.* **3**: 73–78.
7. Craven, M., Simpson, J. W., Ridyard, A. E. and Chandler, M. L. 2004. Canine inflammatory bowel disease: retrospective analysis of diagnosis and outcome in 80 cases (1995–2002). *J. Small Anim. Pract.* **45**: 336–342.
8. Day, M. J., Bilzer, T., Mansell, J., Wilcock, B., Hall, E. J., Jergens, A., Minami, T., Willard, M. and Washabau, R. 2008. Histopathological standards for the diagnosis of gastrointestinal inflammation in endoscopic biopsy samples from the dog and cat: a report from the World Small Animal Veterinary Association Gastrointestinal Standardization Group. *J. Comp. Pathol.* **138** (Suppl.) **1**: S1–43.
9. Fukushima, K., Ohno, K., Koshino-Goto, Y., Uchida, K., Nomura, K., Takahashi, M., Nakashima, K., Fujino, Y. and Tsujimoto, H. 2009. Sensitivity for the detection of a clonally rearranged antigen receptor gene in endoscopically obtained biopsy specimens from canine alimentary lymphoma. *J. Vet. Med. Sci.* **71**: 1673–1676.
10. Garcia-Sancho, M., Rodriguez-Franco, F., Sainz, A., Mancho, C. and Rodriguez, A. 2007. Evaluation of clinical, macroscopic, and histopathologic response to treatment in nonhypoproteinemic dogs with lymphocytic-plasmacytic enteritis. *J. Vet. Intern. Med.* **21**: 11–17.
11. German, A. J., Day, M. J., Ruaux, C. G., Steiner, J. M., Williams, D. A. and Hall, E. J. 2003. Comparison of direct and indirect tests for small intestinal bacterial overgrowth and antibiotic-responsive diarrhea in dogs. *J. Vet. Intern. Med.* **17**: 33–43.
12. German, A. J., Hall, E. J. and Day, M. J. 2003. Chronic intestinal inflammation and intestinal disease in dogs. *J. Vet. Intern. Med.* **17**: 8–20.
13. Jergens, A. E. 1999. Inflammatory bowel disease. Current perspectives. *Vet. Clin. North. Am. Small Anim. Pract.* **29**: 501–521, vii.
14. Jergens, A. E. 2004. Clinical assessment of disease activity for canine inflammatory bowel disease. *J. Am. Anim. Hosp. Assoc.* **40**: 437–445.
15. Jergens, A. E., Moore, F. M., Haynes, J. S. and Miles, K. G. 1992. Idiopathic inflammatory bowel disease in dogs and cats: 84 cases (1987–1990). *J. Am. Vet. Med. Assoc.* **201**: 1603–1608.
16. Jergens, A. E., Schreiner, C. A., Frank, D. E., Niyo, Y., Ahrens, F. E., Eckersall, P. D., Benson, T. J. and Evans, R. 2003. A scoring index for disease activity in canine inflammatory bowel disease. *J. Vet. Intern. Med.* **17**: 291–297.
17. Kaneko, N., Yamamoto, Y., Wada, Y., Shimokawa Miyama, T., Hiraoka, H., Itamoto, K., Mizuno, T., Nakaichi, M., Takahashi, T., Watari, T. and Okuda, M. 2009. Application of polymerase chain reaction to analysis of antigen receptor rearrangements to support endoscopic diagnosis of canine alimentary lymphoma. *J. Vet. Med. Sci.* **71**: 555–559.
18. Littman, M. P., Dambach, D. M., Vaden, S. L. and Giger, U. 2000. Familial protein-losing enteropathy and protein-losing nephropathy in Soft Coated Wheaten Terriers: 222 cases (1983–1997). *J. Vet. Intern. Med.* **14**: 68–80.
19. Ohno, K., Konishi, S., Kobayashi, S., Nakashima, K., Setoguchi, A., Fujino, Y., Nakayama, H. and Tsujimoto, H. 2006. Prognostic factors associated with survival in dogs with lymphocytic-plasmacytic enteritis. *J. Vet. Med. Sci.* **68**: 929–933.