A Retrospective Study in 21 Shiba Dogs with Chronic Enteropathy

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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.

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.

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...
biliurbin, 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 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

<table>
<thead>
<tr>
<th></th>
<th>Shiba group (n=21)</th>
<th>Non-Shiba group (n=77)</th>
<th>P</th>
</tr>
</thead>
<tbody>
<tr>
<td>Signalment</td>
<td>Gender, M : MC : F : FS</td>
<td>9 : 5 : 7 : 0</td>
<td>21</td>
</tr>
<tr>
<td></td>
<td>Male : Female ratio</td>
<td>2 : 1</td>
<td>21</td>
</tr>
<tr>
<td></td>
<td>Age, median (range)</td>
<td>4.9 years (1.3–13.9 years)</td>
<td>21</td>
</tr>
<tr>
<td>Clinical signs and symptoms</td>
<td></td>
<td>9 : 5 : 7 : 0</td>
<td>21</td>
</tr>
<tr>
<td></td>
<td>Degree of weight loss, median (range)</td>
<td>20% (6–35%)</td>
<td>14</td>
</tr>
<tr>
<td></td>
<td>Vomit, n (%)</td>
<td>7 (33%)</td>
<td>21</td>
</tr>
<tr>
<td></td>
<td>Diarrhea, n (%)</td>
<td>19 (90%)</td>
<td>21</td>
</tr>
<tr>
<td></td>
<td>Anorexia, n (%)</td>
<td>12 (57%)</td>
<td>21</td>
</tr>
<tr>
<td></td>
<td>Lethargy, n (%)</td>
<td>9 (43%)</td>
<td>21</td>
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<tr>
<td></td>
<td>Ascites, n (%)</td>
<td>3 (14%)</td>
<td>21</td>
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<tr>
<td></td>
<td>Pruritus, n (%)</td>
<td>2 (10%)</td>
<td>21</td>
</tr>
</tbody>
</table>

M, male; MC, male castrated; F, female; FS, female spayed.
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
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 plasma cells 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, 14, 16].


