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Research Article

Investigation of Correlations Between Clinical Signs and Pathological Findings in Cats and Dogs with Inflammatory Bowel Disease

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Abstract

This paper compares the correlation between the clinical signs and the histopathological observations of the entire intestine in cats and dogs with inflammatory bowel disease (IBD). To perform this study, hospital records of 53 dogs and 20 cats of different sex, ages, and breed diagnosed with IBD following the histopathological criteria of the World Small Animal Veterinary Association (WSAVA) were evaluated. The results obtained in this study did show correlations between some clinical signs and the histopathological assessment of dogs and cats with IBD. Therefore, a slight association between diarrhea and lacteal dilation in the small bowel, and diarrhea and desquamation in the large bowel of dogs with IBD was seen, but no other associations were found between the rest of the lesions and symptoms. In contrast, cats only showed a correlation between anorexia with villous stunting and villous epithelial injury, without correspondence among other clinical signs and lesions. The results of this study propose that the evaluation of IBD can be complicated, especially with the use of retrospective records of archived intestinal biopsies and subjective clinical and histopathologic decisions.

Keywords: *Dog, Cat, Inflammatory Bowel Disease, IBD, Lesion, Clinical signs*

İnflamatuar Bağırsak Hastalığı Olan Kedi ve Köpeklerde Klinik Bulgular İle Patolojik Bulgular Arasındaki İlişkilerin Araştırılması

Öz

Bu makale, inflamatuar bağırsak hastalığı (IBD) olan kedi ve köpeklerde bütün bağırsakların klinik bulguları ile histopatolojik gözlemleri arasındaki korelasyonu karşılaştırmaktadır. Bu çalışmayı gerçekleştirmek için, World Small Animal Veterinary Association (WSAVA)'in histopatolojik kriterlerini izleyerek IBD tanısı konan farklı cinsiyet, yaş ve ırkta 53 köpek ve 20 kedinin hastane kayıtları değerlendirildi. Bu çalışmada elde edilen sonuçlar, IBD'li köpek ve kedilerde bazı klinik bulgular ile histopatolojik bulgular arasında korelasyon olduğunu gösterdi. Bu nedenle, IBD'li köpeklerde ince bağırsakta ishal ve lakteal dilatasyon ile kalın bağırsakta ishal ve deskuamasyon arasında hafif bir ilişki görülmüştür, ancak lezyonların geri kalanı ve semptomlar arasında başka bir ilişki bulunmamıştır. Buna karşın, kedilerde diğer klinik bulgular ve lezyonlar arasında ilişki saptanmezken, sadece anoreksi ile villöz gelişim eksikliği ve villöz epitel hasar arasında bir korelasyon vardı. Bu çalışmanın sonuçları, özellikle intestinal biyopsilerinin arşivlenmiş retrospektif kayıtlarının subjektif klinik ve histopatolojik kararlarının kullanılması ile IBD değerlendirmesinin karmaşık olabileceğini düşündürmektedir.

Anahtar sözcükler: *Köpek, Kedi, İnflamatuar Bağırsak Hastalığı, IBD, Lezyon, Klinik bulgu*

INTRODUCTION

Inflammatory bowel disease (IBD) refers to a chronic gastrointestinal (GI) disease of unknown cause and ill-defined pathogenesis [1]. It is characterized by persistent or recurrent GI signs with inflammatory infiltration of the mucous membrane in the lamina propria area [2-6]. The etiology of this process is multifactorial and may be produced by

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inappropriate and uncontrolled inflammation of gut-associated lymphoid tissue against harmless environmental antigens [7]. Clinical signs are highly variable [1], and these go from diarrhea and vomiting to appetite disturbance such as anorexia or polyphagia. Nonetheless, the lack of clinical, diagnostic, histopathologic, and therapeutic standards resulted in great challenges that led to the design of specific indexes [8-11], which did not support a correlation between the severity of clinical signs and histopathological score since findings interpretation varied widely between pathologists [12-15]. Despite this fact, the numeric index generated by some of these methods has been used to help clinicians and researchers to correlate inflammatory lesions with clinical signs [1]. Thus, Jergens et al.[1] proposed a set of assessment criteria called the Canine Inflammatory Bowel Disease Activity Index (CIBDAI). The suitability of this index as a monitoring tool was determined by the correlation between the clinical index and the histopathological lesions. Interestingly, a study suggested that the histopathological criteria for the diagnosis of GI tract inflammation in dogs and cats could be inconsistent [10]. Due to these concerns, the World Small Animal Veterinary Association (WSAVA) Gastrointestinal Standardization group developed a simplified histopathologic monograph that pictorially and textually defined inflammatory and morphologic features in endoscopic biopsy specimens obtained from the stomach, duodenum, and colon [10]. However, due to the particular individuality of IBD, only a sparse number of reports defining the severity of clinical signs in dogs with IBD and its relation with histopathological lesions have been published [13,15,16]. Therefore, this study aimed to compare the correlation between histopathological changes and clinical signs in dogs and cats affected with IBD.

MATERIAL and METHODS

This retrospective study included hospital records of 53 dogs and 20 cats of different sex, ages, and breed diagnosed with IBD in the Small Animal Hospital of Las Palmas de Gran Canaria University and the Veterinary Hospital of Cordoba University. The study was performed from April 2016 to August 2018 following the approval of the Ethical Commission of Veterinary Medicine of Las Palmas de Gran Canaria University (agreement MV-2017/05). Criteria for animal selection were: clinical signs consistent with IBD such as anorexia, vomiting, diarrhea and weight loss (>3 weeks in duration), failure to respond to dietary (a commercially prepared select antigen or homemade diets) or symptomatic therapies alone, exclusion of other causes such as exocrine pancreatic insufficiency, infectious agents, endoparasites, neoplasia or food, and antibiotic responsive enteropathies; and histopathologic evidence of mucosal inflammation in biopsy specimens. The diagnostic evaluation in all animals with IBD consisted of medical records taken over 1 or more clinical examinations, hematological and serum biochemistry analyses, urinalysis, fecal test for parasites, diagnostic imaging, and histopathologic examination of GI mucosal biopsy specimens following the histopathologic scoring system of the WSAVA.

Seven dogs and four cats that were free of gastrointestinal signs over one or more clinical examinations, and showed normal hematological and serum biochemistry analyses, as well as free of parasites on fecal examinations, were used as a control group *(Table 1)*. Mucosal biopsies of the gut were also obtained from these animals as previously described in other studies [8,12].

Clinical Disease Activity Data

To evaluate the clinical disease activity, a retrospective assessment was performed following symptoms of the upper gastrointestinal part such as vomiting, diarrhea, anorexia (as appetite disorders) and weight loss, as well as symptoms of lower gastrointestinal signs such as hematochezia and mucoid feces.

Table 1. *Tissues sampled from small and large bowel of healthy dogs and cats*

Sampling Location	LD	CD	VEI	SQ	VS	MF	IEL	LPI
Duodenum (1)	+	-	+	+	-	-	+	+
Duodenum (1)	+	+	+	+	-	+	+	+
Duodenum (1)	+	-	-	-	-	+	+	+
Duodenum (1)	+	-	-	+	-	+	+	+
Colon (1)	+	+	+	+	+	+	+	+
Colon (1)	-	-	+	+	-	+	+	+
Cecum (1)	+	-	-	-	-	+	+	+
Duodenum (2)	+	+	-	-	-	-	-	-
Duodenum (2)	-	-	-	-	-	+	-	-
Duodenum (2)	+	-	-	-	-	+	-	-
Colon (2)	-	-	-	+	-	+	-	-

(1) Dog. (2) Cat. LD: Lacteal dilation; CD: Crypt dystention; VEI: Villous Epithelial Injury; SQ: desquamation; VS: Villous stunting; MF: Mucosal fibrosis; IEL: Intraepithelial lymphocytes; LPI: Lamina propria infiltrate

Histopathologic Examination

To perform the histopathological assessment, biopsy samples from the small and large bowel of diseased animals were used. These samples were fixed in 10% neutral-buffered formalin, dehydrated through graded alcohols, and embedded in paraffin wax. Sections (4 µm thick) were cut and stained with hematoxylin and eosin stain for histopathological examination. It was based on the morphological and inflammatory findings identified in the standard histopathologic system of the WSAVA Gastrointestinal Standardization group [12], as well as on those modifications done by Jergens et al.[10]. Therefore, for small and large bowel samples the main morphological features chosen were villous stunting, epithelial injury, crypt distention, lacteal dilation, desquamation, mucosal fibrosis, as well as intraepithelial lymphocyte and lamina propria infiltration. Clinical data and specific histopathological lesions were used and compared to search for significant associations.

Statistical Analysis

The lesions and clinical signs of the animals involved in this research were categorical variables summarized as frequencies and percentages. These percentages were compared using the Chi-square test. Statistical significance was set at $P<0.05$. The values in duodenum-jejunum-ileum as small intestine, and cecum-colon-rectum as large intestine were fused in order to check accurately the correlations between clinical signs and pathological findings of animals with IBD.

RESULTS

Histopathological lesions and clinical signs of 53 dogs and 20 cats of different breed and sex with IBD are shown in *Table 2* and *Table 3* (dogs), and *Table 4* and *Table 5* (cats).

The location-based on histopathologic lesions present in biopsy of dog specimens was as follows: upper intestinal part (n=27 cases) that included duodenum (n=24 cases), jejunum (n=2 cases) and ileum (n=1 case); and lower intestinal part (n=26 cases), with cecum (n=2), colon (n=17 cases), and rectum (n=7 cases). These patients showed highly variable histopathological lesions. Therefore, according to WSAVA guidelines, lacteal dilation was found in 37 out of 53 animals, crypt distention in 28 out of 53 animals, 24 animals showed villous epithelial injury, desquamation was found in 23 out of 53 animals, villous stunting just in 14 animals, and mucosal fibrosis in 35 animals in total *(Fig. 1. a-d)*.

In case of cats, the distribution on histopathologic lesions present in biopsy specimens was as follows: upper intestinal part (n=14 cases) that included duodenum (n=14 cases); and lower intestinal part (n=6 cases), where only colon lesions (n=6 cases) were detected. Among these cases lacteal dilation was identified in 12 out of 20 cats, crypt

Table 2. *Histopathologic assesment of small and large bowel of dogs with IBD*

Intestine	LD	CD	VEI	SQ	VS	MF	IEL	LPI
Small bowel (n: 27)	20	14	12	11	7	16	26	27
Duodenum (24)	17	12	11	10	6	14	23	24
Jejenum (2)	2	1	-	-		1	2	2
Ileum (1)	1	1	1	1	1	1	1	1
Large Bowel (n: 26)	17	14	12	12	7	19	26	26
Colon (17)	12	12	10	11	6	15	20	20
Rectum (7)	4	2	2	1	1	3	5	5
Cecum (2)	1	-	-	-	-	1	1	1

LD: Lacteal dilation; CD: Crypt dystention; VEI: Villous Epithelial Injury; SQ: desquamation; VS: Villous stunting; MF: Mucosal fibrosis; IEL: Intraepithelial lymphocytes; LPI: Lamina propria infiltrate

Table 3. *Relation between samples and clinical signs in small and large bowel of IBD dogs*

Intestine	Vomiting	Diarrhea	Anorexia	Weight Loss	Hematochezia	Mucoid Feces
Small bowel (n: 27)	16	21	7	7	1	-
Duodenum (24)	14	18	7	7	1	-
Jejenum (2)	2	2	-	-	-	-
Ileum (1)	-	1	-	-	-	-
Large Bowel (n: 26)	7	21	1	2	15	11
Colon (17)	5	17	1	1	11	10
Rectum (7)	1	3	-	1	4	1
Cecum (2)	1	1	-	-	-	-

Table 4. *Histopathologic assessment of small and large bowels of cats with IBD*

Intestine	LD	CD	VEI	SQ	VS	MF	IEL	LPI
Small bowel (n: 14)	9	10	6	6	2	14	14	14
Duodenum (14)	9	10	6	5	2	14	14	14
Large Bowel (n: 6)	3	4	2	4	1	3	6	6
Colon (6)	3	4	2	4	1	3	6	6

LD: Lacteal dilation; CD: Crypt dystention; VEI: Villous Epithelial Injury; SQ: desquamation; VS: Villous stunting; MF: Mucosal fibrosis; IEL: Intraepithelial lymphocytes; LPI: Lamina propria infiltrate

Table 5. *Relation between samples and clinical signs in small and large bowel of IBD cats*

Intestine	Vomiting	Diarrhea	Anorexia	Weight Loss	Hematochezia	Mucoid Feces
Small bowel (n: 14)	5	8	2	1	-	-
Duodenum (14)	5	8	2	1	-	-
Large Bowel (n: 6)	3	4	1	-	1	1
Colon (6)	3	4	1	-	1	1

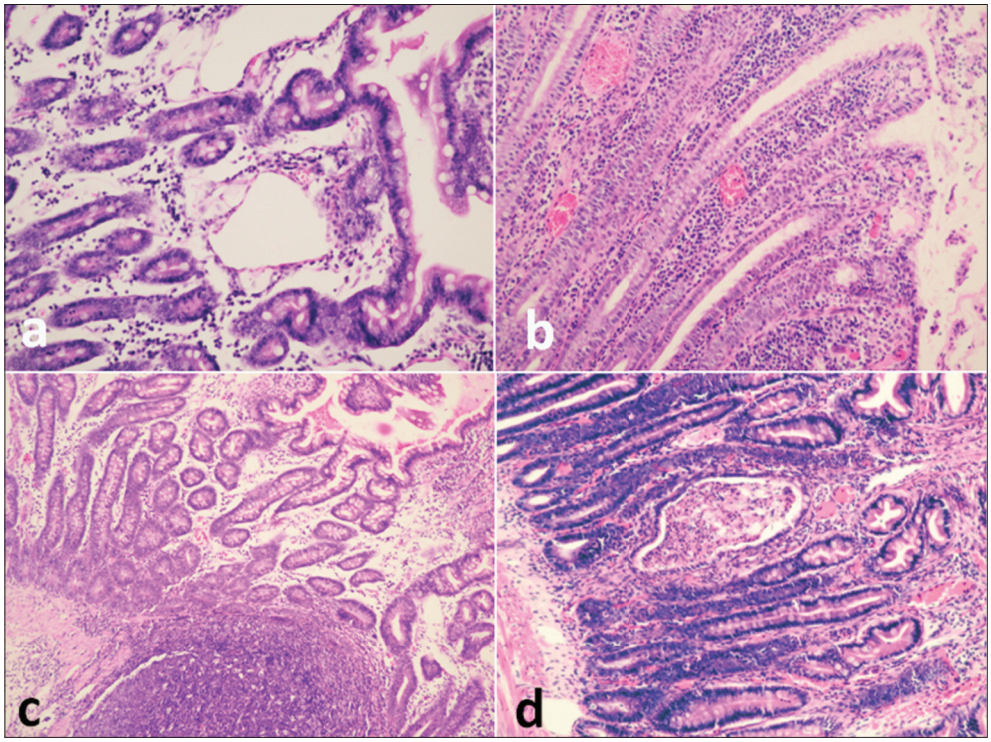

Fig 1. a) Villi appear markedly distended, with mild mononuclear infiltration, interstitial oedema of the lamina propria and moderate lacteal dilation. Haematoxylin & Eosin x200, **b)** Mild-diffuse mononuclear infiltration into the lamina propria. Haematoxylin & Eosin, x100, **c)** Mononuclear infiltration and oedema of the lamina propria, and mild hyperplasia of crypts and lymphoid aggregates. Haematoxylin & Eosin x40, **d)** Distension of a crypt, filled with mucus, inflammatory cells and cellular debris, and surrounded with attenuated epithelial cells, as well as mononuclear cell infiltration into the lamina propria. Haematoxylin & Eosin x100

distension was found in 14 out of 20 animals, 8 cats showed villous epithelial injury, desquamation was found in 10 out of 20 animals, whereas villous stunting and mucosal fibrosis were identified in 3 and 17 cats, respectively.

The cellular infiltrate in all mucosal specimens was predominantly composed of lymphocytes and plasma cells, sometimes accompanied by an admixture of sparse numbers of eosinophils, neutrophils, and macrophages. Lymphocyte infiltration in the duodenum of animals with IBD was significantly increased compared with controls, and these were mainly located in the upper part of the villi, as well as within the epithelial layer. In contrast, in the colonic mucosa, there was smaller variability between control individuals and animals with IBD.

The statistical analysis revealed a slight association between diarrhea and lacteal dilation in the small bowel (P=0.0098),

Table 6. *Frequencies and Chi-square test for the different variables considered in the small bowel and obtained from the histopathologic examination and clinical signs in dogs with IBD*

Clinical Signs	Total N =27	Lacteal Dilation		P-Value	Crypt Distension		P-Value	Villous Epithelia		P-Value	Squamation		P-Value	Villous Stunting		P-Value	Mucosal Fibrosis		P-Value
		Yes N=20	No N=7		Yes N=14	No N=13		Yes N=12	No N=15		Yes N=11	No N=16		Yes N=7	No N=20		Yes N=16	No N=11	
Vomiting	16	11	5	0.4464	9	7	0.5812	6	10	0.3811	5	11	0.2261	5	11	0.4464	11	5	0.2261
Diarrhea	21	18	3	0.0098	11	10	0.9180	10	11	0.5346	10	11	0.1736	3	18	**0.0098**	13	8	0.6007
Anorexia	7	6	1	0.4142	4	3	0.7448	1	6	0.0621	1	6	0.0979	4	3	0.0285	5	2	0.4464
Weight loss	7	5	2	0.8528	2	5	0.1521	2	5	0.3261	2	5	0.4464	2	5	0.8528	3	4	0.3048
Hematochezia	1	1	0	0.5466	1	0	0.3261	0	1	0.3621	0	1	0.3981	0	1	0.5466	1	0	0.39810

Table 7. *Frequencies and Chi-square test for the different variables considered in the large bowel and obtained from the histopathologic examination and clinical signs in dogs with IBD*

Clinical Signs	Total N =26	Lacteal Dilation		P-value*	Crypt Distensio		P-Value	Villous Epithelia		P-Value	Squamation		P-Value	Villous Stunting		P-Value	Mucosal Fibrosis		P-Value
		Yes N=17	No N=9		Yes N=14	No N =12		Yes N=12	No N=14		Yes N=12	No N=14		Yes N=7	No N=19		Yes N=19	No N=7	
Vomiting	7	5	2	0.6942	3	4	0.4951	5	2	0.1166	3	4	0.8378	1	6	0.3779	5	2	0.9084
Diarrhea	21	14	7	0.7782	13	8	0.0912	11	10	0.1918	12	9	**0.0213**	7	14	0.1310	16	5	0.4632
Anorexia	1	1	0	0.4581	1	0	0.3451	1	0	0.2707	1	0	0.2707	0	1	0.5359	1	0	0.5359
Weight loss	2	1	1	0.6341	1	1	0.9096	1	1	0.9096	1	1	0.9096	0	2	0.3716	1	1	0.4438
Hematochezia	15	10	5	0.8725	9	6	0.4623	9	6	0.0982	8	7	0.3912	4	11	0.9725	11	4	0.9725
Mucoid Fec	11	6	5	0.3198	7	4	0.3912	7	4	0.1257	6	5	0.4623	3	8	0.9725	7	4	0.3527

Table 8. *Frequencies and Chi-square test for the different variables obtained from the histopathologic examination and clinical signs in cats with IBD*

Clinical Signs	Total N = 20	Lacteal Dilation		P	Crypt Distensio, n		P	Villous Epithelia, n		P	Squamation, n		P	Villous Stunting,n		p	Mucosal Fibrosis		P
		Yes N=12	No N =8		Yes N =14	No N =6		Yes N =8	No N =12		Yes N =10	No N =10		Yes N =3	No N =17		Yes N =17	No N =3	
Vomiting	8	3	5	0.0935	4	4	0.1110	3	5	0.8522	4	4	1	2	6	0.3065	6	2	0.3065
Diarrhea	12	6	6	0.2636	8	4	0.6903	4	8	0.4561	7	5	0.3613	2	10	0.7982	9	3	0.1250
Anorexia	3	3	0	0.1250	3	0	0.2187	3	0	0.0214	3	0	0.0603	2	1	***0.0066***	3	0	0.4300
Weight lossn	1	0	1	0.2089	0	1	0.5018	0	1	0.4022	0	1	0.3049	0	1	0.6665	1	0	0.6665
Hematochezia	1	1	0	0.4022	1	0	0.5018	1	0	0.2089	1	0	0.3049	0	1	0.6665	1	0	0.6665
Mucoid Feces	1	1	0	0.4022	1	0	0.5018	1	0	0.2089	1	0	0.3049	0	1	0.6665	1	0	0.6665

and diarrhea and desquamation in the large bowel (P=0.0213) of dogs with IBD. The results of this analysis are shown in *Table 6* and *Table 7*, respectively. Concerning cats, the statistical analysis showed a high association between villous stunting (P=0.0066) and villous epithelial injury (P=0.0214) with anorexia. The results of this analysis are shown in *Table 8*, where the odds ratio with the confidence intervals is presented. No significant associations were identified among the rest of the lesions and clinical signs of dogs and cats affected with IBD.

DISCUSSION

Literature defining clinical and histopathological indexes to value the activity of the chronic inflammatory bowel disease is scarce. Therefore, its assessment in dogs and cats is quite difficult. This is particularly important in cats with a diffuse enteric disease, which exhibits mixed bowel signs and requires biopsy of both the small and large intestines for diagnosis [7]. In our study, we included hospital records that comprised biopsies of the small and large bowel. Interestingly, most of the clinical signs observed in these animals were quite similar to other studies performed on IBD that used the Canine Inflammatory Bowel Disease Activity Index (CIBDAI) or the feline chronic enteropathy activity index (FCEAI) [1,7,15,17]. A previous study based its analysis on the intensity of different clinical signs [1]. However, in our research, the intensity and degree of the disease was partially ignored, and focused on the presence or absence of injury, avoiding interpretative ambiguity among pathologists as has been suggested by WSAVA new guidelines [10]. These subjective elements that do not always represent the existing inflammatory burden can lead to discordance between the results of different surveys using CIBDAI or FCEAI as described in other reports [13-17].

In this study, there were correlation between clinical signs and some histopathologic scores. This association was positive for lacteal dilation, desquamation, villous epithelial injury, and villus stunting. Interestingly, there was no correlation between the intensity of intraepithelial lymphocytes, lamina propria infiltrate, and mucosal fibrosis with IBD clinical signs.

Lymphangiectasia in animals is assumed to be an acquired disease, and its etiology is generally idiopathic [3]. It may also result from any type of obstruction to lymph flow in the lacteals, mesenteric lymph vessels or nodes, most frequently secondary to inflammation [8,12]. In our series, lacteal dilatation was in correlation with diarrhea, but it is important to consider that this clinical sign has been associated with chronic diarrhea [15,18]. Nonetheless, other important parameters associated with dilated lacteals such as hypoalbuminemia could not be evaluated as a consequence of the retrospective nature of our study. Other important changes observed in the mucosal architecture such as desquamation correlated well with diarrhea. A recent study indicated that changes in mucosal architecture were related to the presence and severity of GI disease [13]. Nonetheless, further prospective studies are needed to properly evaluate the meaning of these correlations.

In this study, the severity of the lymphocytic infiltration in the lamina propria did not correlate with the intensity of clinical signs. Different studies have reported that characterize the extent and severity of the inflammatory infiltrate in intestinal biopsies from dogs and cats is a difficult task [12-15]. Hence, some authors suggest that the presence of increased numbers of lymphocytes deposited in the lamina propria and their contribution to the IBD process are better explained when the intestine is checked as a big picture [8]. Moreover, studies performed in dogs and cats with IBD did show a predominant proinflammatory cytokine upregulation in the inflamed colonic and duodenal mucosa in animals with lymphoplasmacytic colitis or enteritis as happens in people, although not correlations were done [13,19]. In the present study, many similarities between the inflammatory response in the small and large intestine of dogs and cats affected with IBD were observed. Comparable findings were described in other studies [10,11,14] that showed better clinical evaluation without doing a distinction between the upper or lower intestine.

The histopathological lesions identified in the animals of this study showed significant fibrosis associated with major damage to the mucous membrane of the small and large intestine. Similar features were reported in a study done in the small intestine of animals with severe IBD [6].

Different circumstances can interfere with the histopathologic interpretation of intestinal samples such as the correct area of the GI tract to be sampled, the quality of tissue samples analyzed, and the lack of consistency in interpretation of histopathologic changes among pathologists [13-15]. These circumstances led to the WSAVA GI Standardization Group to develop a histopathologic template to avoid these concerns, but even with this histopathologic scoring system, important variations have been observed in the diagnostic interpretation of intestinal samples since the above-mentioned method did not include evaluation of all intestinal segments. Therefore, in the present study, we extended its use to other sections of the GI tract, and interestingly, its use did not show significant differences in the evaluation of the intestinal samples done among pathologists. Identical results were obtained in a recent study performed in dogs using a similar scoring system [13].

In conclusion, the histopathologic scoring system used in this study provided important information on the extent of mucosal inflammation in the GI tract of dogs and cats with IBD. However, this work proposes that the evaluation of inflammatory bowel disease can be complicated, especially with the use of retrospective records of archived intestinal

biopsies and subjective clinical and histopathologic decisions. To perform better results, it is important to follow-up on the affected animals and to evaluate outcome factors as an accurate assessment of the health status of patients as suggest reports on human chronic disease [20]. All these premises would be of great help in the uniformity of a standard for the evaluation, and monitoring of the inflammatory bowel disease.

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Statements Authors Contributions

DF, FR and JRJ designed the experiment, made the histologic interpretation, and wrote the manuscript. ARG and CF made the statistical analysis. ASB made a substantial contribution to interpretation of data. All authors discussed the results and contributed to the final manuscript.

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