HARRAN ÜNİVERSİTESİ VETERİNER FAKÜLTESİ DERGİSİ

Histopathological Grading of Idiopathic Gastroenteritis Diseases in Dogs

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Abstract: Idiopathic gastroenteritis is a disease that causes lesions in the stomach and intestines. Twenty dogs of different ages, genders, and breeds showing diarrhea, vomiting, weight loss, and other gastrointestinal findings brought to the Department of Pathology were performed necropsy. For pathological examinations, samples were taken from the cardia, fundus, antrum, and pylorus parts of the stomach and the duodenum, jejunum, ileum, cecum, colon, and mesenteric lymph nodes of the intestines. They were stained with hematoxylin and eosin (H&E). It was diagnosed as lymphocytic-plasmacytic gastritis with eosinophilic enteritis (n: 4), eosinophilic enteritis (n: 4), lymphocytic-plasmacytic gastroenteritis (n: 3), eosinophilic gastroenteritis (n: 4) and lymphocytic-plasmacytic enteritis (n: 5) histopathologically. Thus, it was determined that idiopathic gastroenteritis disease was thought to be common in Turkey and current data on incidence of the disease were provided.

Keywords: *Eosinophilic gastroenteritis, IBD, Lymphocytic-Plasmacytic gastroenteritis, Pathological grading method.*

Köpeklerde İdiyopatik Gastroenterit Hastalıklarının Histopatolojik Derecelendirilmesi

Özet: İdiyopatik gastroenteritis, mide ve bağırsaklarda lezyonlara neden olan bir hastalıktır. Patoloji Anabilim Dalı'na getirilen ishal, kusma, kilo kaybı ve diğer gastrointestinal bulguları gözlenen farklı yaş, cinsiyet ve ırktan yirmi köpeğin nekropsisi yapıldı. Patolojik incelemeler için midenin kardia, fundus, antrum ve pilorus kısımlarından ve bağırsakların duodenum, jejunum, ileum, sekum, kolon ile mezenterik lenf düğümlerinden örnekler alındı. Bunlar hematoksilen ve eozin (H&E) ile boyandı. Histopatolojik inceleme sonucunda eozinofilik enteritis (n: 4), eozinofilik enteritis (n: 4), lenfositik-plazmasitik gastroenteritis (n: 3), eozinofilik gastroenteritis (n: 4) ve lenfositik-plazmasitik enteritis (n: 5) ile lenfositik-plazmasitik gastritis tanısı konuldu. Bu nedenle idiyopatik gastroenteritis hastalığının Türkiye'de yaygın olduğu düşünülmektedir. Ayrıca hastalığın insidansı hakkında güncel veriler sağlanmıştır.

Anahtar Kelimeler: *Eozinofilik gastroenteritis, IBD, Lenfositik-Plazmasitik gastroenteritis, Patolojik dereceleme yöntemi.*

Introduction

Infectious agents (bacterial, viral, fungal, parasitic), toxins, exposure to foreign bodies, genetic predisposition, and food allergens play a role in the etiology of gastroenteritis diseases (Cerquetella et al., 2010), and these factors can be seen in three forms of the disease (peracute, acute, and chronic). However, the etiology of idiopathic inflammatory bowel disease (IBD), which occurs with the progression of the chronic form, is not fully known (Jergens and Simpson, 2012). There are opinions that the main mechanism of etiopathogenesis is that the lymphoid tissues related to the intestines show hypersensitivity to antigens in the gastrointestinal system, causing loss of tolerance (Cerquetella et al., 2010; Hall et al., 2005; Rychlik et al., 2007). In addition, breed predisposition, immune dysregulation and the interaction of environmental factors are also important factors in the etiology of the disease (Niina et al., 2021). The disease can be seen in dogs of all ages and breeds. It is more likely to be seen in Boxers, Border Collies, German Shepherds, Rottweilers (Farray et al., 2020; Kathrani et al., 2011) and in dogs five years of age and younger (Fonseca-Alves et al., 2012). The disease has no gender specificity (Cerquetella et al., 2010).

The lesions of the disease occur in the stomach and intestines. The disease is divided into three types according to the localization of immune system cells in the stomach and intestines: lymphocytic-plasmacytic, eosinophilic and granulomatous (Day et al., 2008, Simpson, 2010). The most common forms in dogs are lymphocytic-plasmacytic enteritis and eosinophilic gastroenteritis. Granulomatous inflammation is less common (Rychlik et al., 2007).

The Canine IBD Activity Index - CIBDAI, a clinical grading method, was developed to objectively correlate laboratory and histological indices of clinical findings in idiopathic gastroenteritis disease. This method is routinely accepted worldwide (Jergens et al., 2003). To better understand and examine IBD disease, a histopathological grading system was developed in the stomach and intestines (Allenspach et al., 2019; McCann et al., 2007). However, histopathological grading studies are rare (Farray et al., 2020). In this system, cell infiltration, eosinophil presence, fibrosis, atrophy of intestinal villi, expansion of crypts, and increase in goblet cells were evaluated (Fonseca-Alves et al., 2012; Lyles et al., 2009; McCann et al., 2007; Rychlik et al., 2007).

For the treatment to be applied to animals with IBD to have positive results, it is essential to grade the severity of the disease pathologically. The aim of the study was to examine the breed, gender, and age distribution in dogs with suspected IBD or showing gastrointestinal findings and to classify the inflammation in the stomach and intestines by grading.

Materials and Methods

In this study, 20 dogs of different ages, genders, and breeds showing diarrhea, vomiting, weight loss, and other gastrointestinal findings brought to the Department of Pathology were performed necropsy. This study was approved by the Ankara University Animal Experiments Local Ethics Committee, Ankara, Türkiye (Decision No: 2023-11-100).

Macroscopic examinations:

For pathological examinations, samples were taken from the cardia, fundus, antrum, and pylorus parts of the stomach and the duodenum, jejunum, ileum, cecum, colon, and mesenteric lymph nodes of the intestines. The mucosal surfaces of the stomach and intestines were examined macroscopically for parasites, hemorrhages, etc. Tissue samples were fixed in 10% buffered formalin.

Histopathological examinations:

After the routine tissue process, the cells were embedded in paraffin wax and sectioned at 4 µ. They were stained with hematoxylin and eosin (H&E). The results were evaluated under a light microscope (Leica DM 4000M) and photographed (Leica DFC-280).

Results

Breed, gender and age distributions of dogs:

The breed distribution of dogs (n:20) was as follows; mixed breed (n:5), German shepherd dog (n:3), Terrier (n:2), Rottweiler (n:2), Labrador (n:2), Pomeranian (n:1), Springer spaniel (n:1), Catalan shepherd dog (n:1), English cocker (n:1), Anatolian shepherd dog (n:1) and Pug (n:1). Age distribution was as follows; under 12 months (n:7), between 1-10 years (n:8) and over 10 years (n:5). The genders were determined as male (n:10) and female (n:10).

Macroscopic findings:

The lumens of the dogs' stomachs and intestines were opened entirely, and the gastrointestinal system was examined in detail. Foreign bodies (n:2), volvulus (n:1), and hemoabdomen (n:5) were observed in the stomach. Hemorrhages (n:3) were detected in the stomach and intestines, especially in the jejunum. Yellowish-greenish mucoid content was detected in the lumens of the intestines (n:15). However, there were no prominent ulcer areas in the GI tract. Parasites were not observed in any case.

Microscopic findings:

All stomach and intestinal sections were examined as modified according to the parameters in the histopathological scoring system of Allenspach et al. (2019) and McCann et al. (2007) (Table 1).

Accordingly, in the stomach; lymphocytes and plasma cells, eosinophils, neutrophils in lamina propria, fibrosis and intraepithelial lymphocytes; in small intestines; crypt dilatation, lymphocytes and plasma cells, eosinophils, neutrophils in lamina propria, in large intestines (colon); crypt dilatation, fibrosis, goblet cell count, lymphocyte, plasma cell, eosinophil and macrophage in lamina propria were examined (Fig. 1a-h) and converted into numerical data per x400 field (Table 2). Each parameter was graded as 0 (Normal), 1 (Mild), 2 (Moderate) and 3 (Marked) and they were diagnosed.

Table 1. Modified scoring system for defining gastrointestinal inflammation.

Location	Histopathological Parameters	Grade			
		0	1	2	3
		(Normal)	(Mild)	(Moderate)	(Marked)
Stomach (Fundus)	Fibrosis (number of fibrocytes separating glands)	≤2	3–5	6–10	≥11
	Intraepithelial lymphocytes (lymphocytes per stretch of 50 epithelial cells)	≤2	3–10	11–20	≥21
	Lamina propria lymphocytes and plasma cells (cells per 400× field)	≤20	21–50	51-100	≥101
	Lamina propria eosinophils (cells per 400× field)	≤2	3–20	21–50	≥51
	Lamina propria neutrophils (cells per 400× field)	0	≤20	21–50	≥51
Stomach (Antrum)	Fibrosis (number of fibrocytes separating gastric pits or mucous glands)	≤10	11–15	16–20	≥21
	Intraepithelial lymphocytes (lymphocytes per stretch of 50 epithelial cells)	≤2	3–5	4–10	≥11
	Lamina propria eosinophils (cells per 400× field)	≤2	3–10	11–50	≥51
Duodenum and ileum	Crypt dilation (% of crypts that were dilated, distorted, or containing eosinophilic material/degenerate neutrophils)	≤2	3–10	11–25	≥26
	Lamina propria lymphocytes and plasma cells (% area of one 400× villous field or cells between crypts)	≤25, ≤2	26–50, 3–5	51–75, 6–10	≥76, ≥11
	Lamina propria eosinophils (cells per 400× field)	≤3	4–10	11–20	≥21
	Lamina propria neutrophils (cells per 400× field)	0	≤10	11–30	≥31
Colon	Crypt dilation and distension (% of crypts per section)	0	≤25	26–50	≥51
	Fibrosis (number of fibrocytes separating crypts)	≤2	3–5	6–10	≥11
	Goblet cell numbers (% reduction from normal)	0	≤25	26–50	≥51
	Lamina propria lymphocytes and plasma cells (cells between crypts)	≤5	6–10	11–20	≥21
	Lamina propria eosinophils (cells per 400× field)	≤2	3–10	11–20	≥21
	Lamina propria macrophages (cells per 400× field)	≤2	3–20	21–50	≥51

The cardia and fundus and the antrum and pylorus sections of the stomach were evaluated together because they gave the same results. Grading could not be done because the stomach (n: 1) was autolytic (Case 5). Therefore, histopathological grading was done on 19 cases.

The intestines, duodenum, jejunum, ileum, and colon were evaluated separately and concluded. The jejunum and ileum generally showed similar results. Since one of the samples in the ileum (Case 10) and colon (Case 17) was autolytic, the results were assessed in 19 cases.

No parasites, hemorrhages, inclusion bodies, bacterial clusters, or dense neutrophil leukocyte infiltrations were found in the stomach or intestinal sections.

After all these microscopic scoring and examinations, inflammation in the intestines was observed in all dogs. It was diagnosed as lymphocytic-plasmacytic gastritis with eosinophilic enteritis (n: 4), eosinophilic enteritis (n: 4), lymphocytic-plasmacytic gastroenteritis (n: 3), eosinophilic gastroenteritis (n: 4) and lymphocytic-plasmacytic enteritis (n: 5) histopathologically.

Discussion and Conclusion

IBD, or idiopathic gastroenteritis, is a disease that causes lesions in the stomach and intestines. Due to its etiological uncertainty, it is an area to be investigated, especially in animals. Different methods must be used to define the disease because clinical findings and diagnostic tests are not specific and because of the possible side effects of the drugs used in treatment (Dye et al., 2013).

The distribution of dogs in the study by gender (n: 10 each) and age (5 years and under (n: 11)) supports previous studies (Cerquetella et al., 2010). In addition, the disease was more common in Rottweilers, German shepherds, and mixed breeds in this study and detected similar results to previous studies (Kathrani et al., 2011; Minnat et al., 2017).

Macroscopic findings in IBD are mostly detected in the proximal part of the stomach and intestines (German et al., 1999). Mild redness, erosion and ulcer areas, occasional folds, and diphtheroid formations are seen in the mucosa (Rychlik et al., 2007). Additionally, mild thickening in the duodenum and areas of serosal hyperemia in the ileum have been observed (McTavish, 2002). Microscopic findings show that all layers of the small intestine are thicker than usual, there are mononuclear cell infiltrations, connective tissue hyperplasia, fibrosis, atrophy of intestinal villi and expansion of crypts, disruption of the integrity of the gastric and intestinal epithelium, leukocytosis and epithelial cell necrosis in the mucosa in general (Fonseca-Alves et al., 2012; McCann et al., 2007; Rychlik et al., 2007). An increase in eosinophils, lymphocytes and plasma cells was observed as a differential diagnosis (Lyles et al., 2009). The results obtained were mainly consistent with the macroscopic and microscopic findings.

In a study of Kanat and Ortatatlı (2022) in examination of histopatlogical in intestines, the cases in which epithelial degeneration, desquamation, hyperaemia, oedema, neutrophil granulocyte and macrophage infiltrations in propria are preponderant, were described as acute; mononuclear cell infiltrations and fibrosis/atrophy formed cases as chronic; and the cases formed with only dense

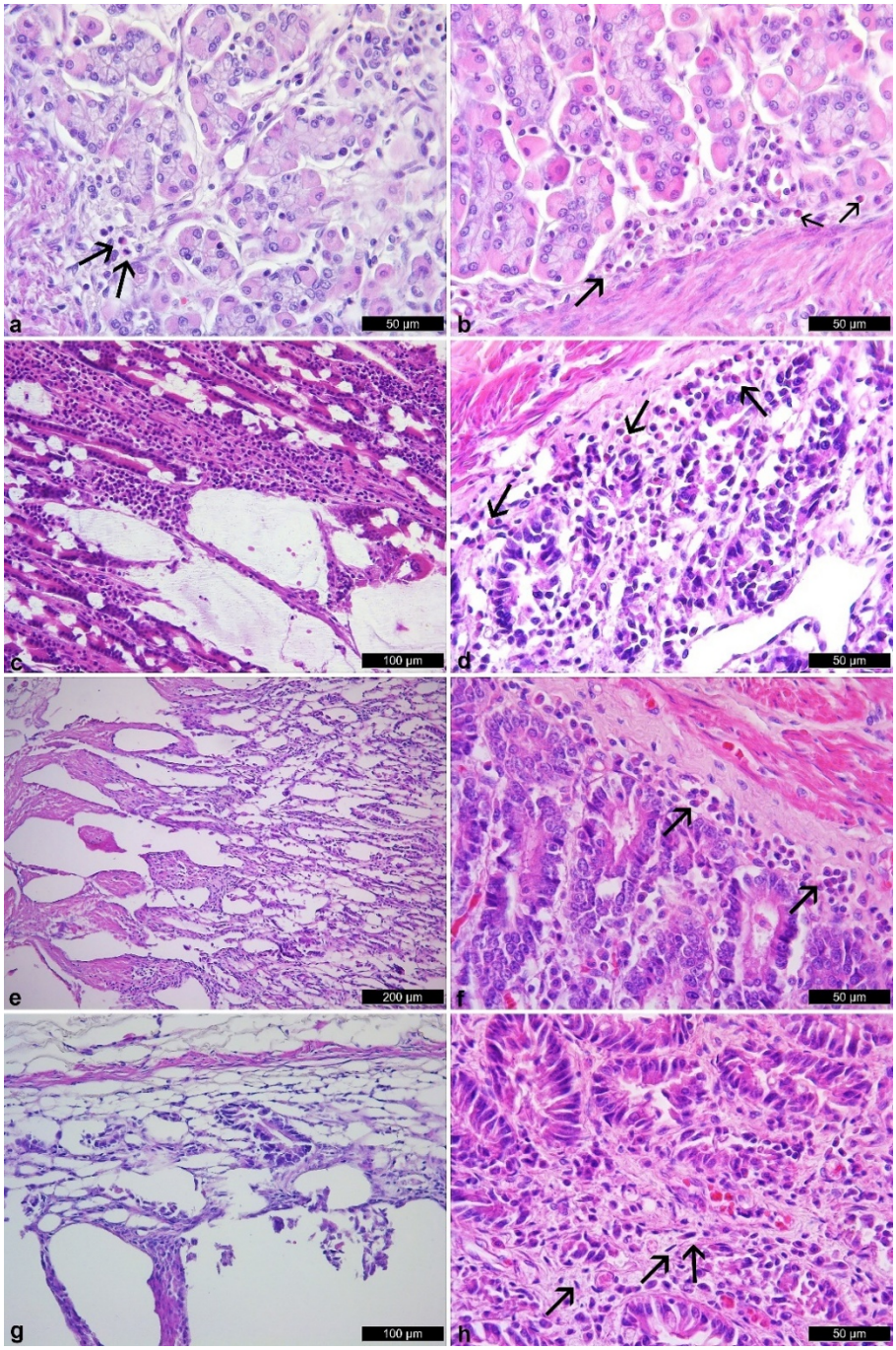

Figure 1a: Few eosinophils (arrows) in the lamina propria of the stomach (grade 1), b: Many eosinophils (arrows) in the lamina propria of the stomach (grade 3), c: Crypt dilatation in the duodenum (grade 2), d: Eosinophils (arrows) in the lamina propria of the duodenum (grade 2), e: Crypt dilatation in the jejunum (grade 3), f: Eosinophils (arrows) in the lamina propria of the jejunum (grade 2), g: Crypt dilatation in the colon (grade 3), h: Connective tissue cells (arrows) that cause fibrosis in the colon (grade 2), HE.

lymphocyte and plasma cell accumulations in mucosa were defined as lymphocytic and plasmacytic enteritis. However, since this study aimed to examine idiopathic gastroenteritis diseases in dogs histopathologically, the stomach sections were reviewed along with the intestines. Here, some parameters in the histopathological scoring system of Allenspach et al. (2019) and McCann et al. (2007) were used. Accordingly, in the stomach; lymphocytes and plasma cells, eosinophils, neutrophils in lamina propria, fibrosis and intraepithelial lymphocytes; in small intestines; crypt dilation, lymphocytes and plasma cells, eosinophils, neutrophils in lamina propria, in large intestines (colon); crypt dilatation, fibrosis, goblet cell count, lymphocyte, plasma cell, eosinophil and macrophage in lamina propria were examined and they were diagnosed only as eosinophilic or lymphocytic-plasmocytic gastro and/or enteritis, (Table 2). Thus, the results and diagnoses were compatible with the previously applied scoring system.

Table 2. Histological grading and diagnosis in all cases histological grading and diagnosis in all cases.

Histopathologic Parameter		**Case No**																			
		1	**2**	**3**	**4**	**5**	**6**	**7**	**8**	**9**	**10**	**11**	**12**	**13**	**14**	**15**	**16**	**17**	**18**	**19**	**20**
Stomach (Cardia + Fundus)	Fibrosis	0	0	0	0	*	0	0	0	0	1	0	0	0	0	0	0	0	0	0	0
	Intraepithelial lymphocytes	2	0	0	0	*	1	1	0	0	0	0	3	1	0	0	0	2	0	0	0
	Lymphocytes and plasma cells in LP	3	0	1	1	*	1	1	0	0	1	0	3	1	1	2	0	2	0	0	0
	Eosinophils in LP	1	0	0	0	*	0	2	0	0	0	0	1	1	0	1	0	0	0	1	1
	Neutrophils in LP	1	0	0	0	*	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0
Stomach (Pylorus)	Fibrosis	0	0	0	0	*	0	0	0	0	2	0	0	0	1	0	0	0	0	0	0
	Intraepithelial lymphocytes	0	0	0	0	*	1	1	0	0	1	0	2	2	1	0	0	1	0	0	0
	Eosinophils in LP	1	0	1	0	*	0	1	0	0	0	0	3	1	0	0	0	0	0	0	0
Duodenum	Crypt dilation	0	0	1	0	0	1	1	2	0	0	1	0	2	1	1	0	2	3	1	1
	Lymphocytes and plasma cells in LP	3	1	2	1	1	3	3	3	1	2	3	3	3	3	2	3	3	1	2	3
	Eosinophils in LP	3	0	1	0	0	2	2	1	0	0	0	3	3	2	2	3	3	0	3	1
	Neutrophils in LP	0	0	1	0	1	1	0	1	0	0	0	1	0	0	1	1	1	1	0	0
Ileum	Crypt dilation	0	0	0	0	0	1	2	1	0	*	1	0	2	1	1	2	2	3	1	0
	Lymphocytes and plasma cells in LP	3	2	2	1	1	3	3	3	1	*	3	3	2	2	1	3	1	1	2	3
	Eosinophils in LP	3	1	0	0	0	2	3	2	0	*	2	2	3	2	3	1	0	0	3	0
	Neutrophils in LP	1	1	1	0	1	1	0	1	0	*	0	0	0	0	1	0	0	1	0	0
Colon	Crypt dilation	1	1	1	1	1	1	2	1	0	2	2	1	3	1	1	1	*	3	1	1
	Fibrosis	0	0	0	0	0	1	2	0	0	1	0	3	0	2	2	0	*	1	1	0
	Goblet cell numbers	3	3	1	2	2	3	2	1	2	0	2	3	3	1	2	2	*	0	1	1
	Lymphocytes and plasma cells in LP	3	2	2	1	1	2	3	1	1	1	2	2	1	2	3	2	*	1	1	2
	Eosinophils in LP	0	1	1	0	0	3	3	0	0	0	1	1	1	2	2	1	*	0	0	0
	Macrophages in LP	0	0	0	0	0	0	0	0	0	0	0	1	0	0	1	0	*	0	0	0
Histopathological Diagnosis		**EGE**	**EE**	**LPGE**	**LPE**	**LPE**	**LPG+EE**	**EGE**	**EE**	**LPE**	**LPGE**	**EE**	**EGE**	**EGE**	**LPG+EE**	**LPG+EE**	**EE**	**LPGE**	**LPE**	**LPG+EE**	**LPE**

LP:Lamina propria L: Lymphocyte count, P: Plasma cell count, *: Autolytic, EGE: Eosinophilic Gastroenteritis, EE: Eosinophilic Enteritis, LPGE: Lymphocytic-Plasmocytic Gastroenteritis, LPE: Lymphocytic-Plasmocytic Enteritis, LPG+EE: Lymphocytic-Plasmocytic Gastritis and Eosinophilic Enteritis

Lymphocytic-plasmacytic gastroenteritis, the most common type of IBD in dogs, consists of numerous lymphocytes, plasma cells, and other inflammatory cells in the lamina propria and submucosa of the stomach and intestines (Bhavani et al., 2023; Lee et al., 2021; Rousseau, 2005). Eosinophilic gastroenteritis is characterized by an increase in eosinophils in the lamina propria and submucosa and is the second most common type of IBD (Fonseca-Alves et al., 2012; Sattasathuchana and Steiner, 2014). There is no specific diagnostic method for eosinophilic gastroenteritis. Since eosinophils in dogs are increased in parasitic diseases (*Physaloptera* spp., *Ollulanustricuspis* spp., *Gnathostoma* spp. and *Spirocerca* spp. for eosinophilic gastritis; *Ancylostoma caninum* for eosinophilic enteritis), these diseases need to be eliminated, and the disease is diagnosed according to clinical findings (Neiger, 2008; Simpson, 2010). In addition to parasitic diseases, mast cell tumors and lymphomas also cause the release of cytokines that secrete eosinophil polymorphonuclear leukocyte chemotaxis factors. As a result of this stimulation, paraneoplastic eosinophilia and eosinophilic infiltrations occur in the gastrointestinal system (Marchetti et al., 2005; Ozaki et al., 2006; Tomiyasu et al., 2010). In a study in Turkey, the oral mucosa, esophagus, stomach, and intestines of dogs were examined, and the results related to microbiological, parasitological, parvoviral enteritis, and distemper diseases were investigated (Kanat and Ortatatlı, 2011; Kanat and Ortatatlı, 2022). All these diseases were excluded in this study, and idiopathic diagnoses were examined as a preliminary diagnosis. Twenty dogs with no suspected viral, bacterial or parasitic diseases and showing idiopathic IBD or gastrointestinal findings were used in this study. Considering both anamnesis/clinical and macroscopic findings and histopathological results of dogs, viral, bacterial or parasitic diseases were easily excluded. No parasites, hemorrhages, inclusion bodies, bacterial clusters or dense neutrophil leukocyte infiltrations were found in the stomach and intestinal examinations. In all these dogs, gastritis, enteritis or gastroenteritis was diagnosed histopathologically. Most of the materials diagnosed with enteritis were eosinophilic form (n: 12) and 4 of them were mixed (eosinophilic gastroenteritis). Of the lymphocytic-plasmacytic gastroenteritis, 5 were only in the intestines (enteritis), and 3 were in the mixed form (lymphocytic-plasmacytic gastroenteritis), and a total of 8 lymphocytic-plasmacytic enteritis were detected. In short, although it is mentioned in the literature that lymphocytic-plasmacytic enteritis is more common (Rychlik et al., 2007), in this study, it was determined that eosinophilic gastro/enteritis was more frequently defined in routine necropsy materials.

In this study, breed, gender, and age distribution were examined, and histopathologically graded and diagnosed. Thus, idiopathic gastroenteritis disease was thought to be common in Turkey and current data on incidence were provided. The limitation of this study is the small number of samples. However, further studies are thought to provide more information and data on this subject.

For a positive treatment outcome, pathological grading of the severity of the disease is very significant. Idiopathic gastroenteritis disease is still a subject clear to research in the field of clinical pathology in terms of histopathological grading and appropriate pharmacological drug treatment for the severity of the disease obtained, and it has become a subject that requires pathology and pharmacology branches to focus more on this subject and work towards preventing the disease.

Conflict of Interest

The authors declare no conflicts of interest with respect to the publication of this manuscript.

Ethical Approval

This study was approved by the Ankara University Animal Experiments Local Ethics Committee, Ankara, Türkiye (2023-11-100).

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Similarity Rate

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Authors Contribution

Motivation / Concept: AST
Design: CÇ
Control/Supervision: AST
Data Collection and/or Processing: CÇ, AST
Analysis and / or Interpretation: CÇ, AST
Literature Review: CÇ
Writing the Article: CÇ
Critical Review: AST

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