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Detection of *Helicobacter*-like organisms in dogs with chronic gastric and intestinal inflammation

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Abstract

In humans, *Helicobacter pylori* and some other members of *Helicobacteraceae* are known to be implicated in both inflammatory and non-inflammatory gastrointestinal disorders. So far, conclusive evidence regarding the potential involvement of helicobacters in development of chronic inflammatory lesions of canine stomach and intestine is missing. The aim of the study was to determine the prevalence of *Helicobacter*-like organisms in endoscopic biopsy samples of different parts of the gastrointestinal tract of dogs with chronic inflammation and to reveal their potential relationship to the presence and severity of morphological and inflammatory changes. A total of 183 samples of inflammatory lesions were examined histologically and immunohistochemically. *Helicobacter*-like organisms were found in 64.1% of samples of gastritis, 5.3% of cases of duodenitis, 47.6% of cases of ileitis and 48% of cases of colitis. The most frequent gastric morphological change was surface epithelial injury. In duodenum epithelial injury together with villous stunting, and in ileum villous stunting were the most commonly observed morphological changes. Crypt dilation/ distortion was the most frequent morphological abnormality among colonic samples and was significantly more often a feature of colitis than duodenitis and ileitis. Our data show no effect of colonization with *Helicobacter*-like organisms on the presence of gastric pit epithelial injury and gastric mucosal fibrosis. No association was found between the presence/density of *Helicobacter*-like organisms and the presence or severity of morphological and inflammatory lesions of duodenal, ileal, and colonic mucosa.

Histopathology, immunohistochemistry, gastritis, enteropathy, Helicobacter spp.

Chronic gastric and intestinal inflammation is a common finding encountered during examination of endoscopic biopsy samples of the gastrointestinal (GI) tract of dogs. According to the literature 24–80% of dogs with chronic vomiting and/or other upper GI signs are diagnosed with chronic gastritis whereas 39–90% of dogs presented for chronic diarrhoea or other signs of lower GI tract disease have chronic enteritis (van der Gaag and Happé 1989; Allenspach et al. 2007; Lidbury et al. 2009; Leib et al. 2010; Maeda et al. 2016; Çolakoğlu et al. 2017; Kubota-Aizawa et al. 2017; Marchesi et al. 2017a, 2017b; Volkmann et al. 2017; Ivasovic et al. 2022). Chronic inflammatory diseases are usually diagnosed by means of clinical, laboratory, and imaging techniques but definitive diagnosis supported by characterization of the inflammatory reaction and accompanying architectural changes can only be achieved by histopathological examination of tissue samples (Day 2012; Jergens and Simpson 2012).

The genus *Helicobacter* comprises several species of gram-negative spiral-shaped bacteria normally inhabiting the GI tract of animals and human. Some species of *Helicobacter* spp. (especially *H. pylori*) have been associated with acute and chronic gastritis, gastric

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or duodenal ulceration as well as some proliferative gastrointestinal diseases in humans (Peek and Crabtree 2006; De Falco et al. 2015; Jafarzadeh et al. 2018). Members of the family *Helicobacteraceae* have frequently been isolated from stomachs of both healthy dogs and dogs suffering from chronic gastritis (Hermanns et al. 1995; Happonen et al. 1998; Hwang et al. 2002; Wiinberg et al. 2005; Polanco et al. 2011). Considerably less information is available regarding the presence of *Helicobacter* spp. in more distal parts of canine GI tract and their possible association with morphological and inflammatory changes of the mucosa (Wiinberg et al. 2005; Castiglioni et al. 2012; Amorim et al. 2015; Kubota-Aizawa et al. 2017).

The aim of the present study was to evaluate the presence of *Helicobacter*-like organisms (HLOs) in different parts of the GI tract of dogs with chronic inflammatory lesions and to compare the character and severity of morphological and inflammatory changes with the presence and density of HLOs.

Materials and Methods

Endoscopic biopsy samples from 105 dogs submitted to the Department of Pathological Morphology and Parasitology of Faculty of Veterinary Medicine, University of Veterinary Sciences Brno between 2009 and 2021 were included in the study. Samples were included if inflammatory lesions of gastric and/or intestinal mucosa were present, and the amount of tissue was sufficient for serial sectioning. All tissue samples were fixed in 10% buffered formalin and processed routinely. Four µm thick sections were made from each tissue sample and stained with haematoxylin and eosin (HE) for evaluation of inflammatory and morphological changes according to previously published guideline (Day et al. 2008). Histopathological diagnosis was established for each sample. Assessment of the presence of HLOs was performed by examining sections stained with HE, immunohistochemistry (IHC), or both. The amount of HLOs was broadly quantified as follows: 0 – absence of spiral-shaped organisms/antigen; 1 – presence of spiral-shaped organisms/antigen in < 5% of the mucosal surface/gastric pits/gastric glands/crypts of Lieberkuhn/lamina propria; 2 – presence of spiral-shaped organisms/antigen in 5–50% of the mucosal surface/gastric pits/gastric glands/crypts of Lieberkuhn/lamina propria; 3 – presence of spiral-shaped organisms/antigen in at least 50% of the mucosal surface/gastric pits/gastric glands/crypts of Lieberkuhn/lamina propria (Scanziani et al. 2001; Recordati et al. 2009).

Immunohistochemistry

Immunohistochemistry was performed on deparaffinized 4 µm thick sections which were hydrated and incubated in a water bath of 98 °C, pH 9.0 for 20 min for retrieval of antigens. Endogenous peroxidase activity was blocked using 3% hydrogen peroxide and a monoclonal rabbit anti-*Helicobacter pylori* antibody (Abcam, Waltham, USA; clone nr.: EPR10353) was applied at a dilution 1:2,500 for 60 min. Mouse and Rabbit Specific HRP/DAB IHC Detection Kit - Micro-polymer (Abcam) was used for visualisation of the reaction. Mayer's haematoxylin was used to counterstain the nuclei. A visible dark brown coloration was considered positive.

Statistical analysis

Statistical analysis was performed using statistical software Statistica for Windows version 12 (StatSoft, Inc., 2014). Pearson's chi-square test was used to determine the significance of the association between two or more variables. The significance level was set at 0.05.

Results

Evaluation of mucosal inflammation

In total, 183 biopsy samples of gastrointestinal mucosa from 105 dogs were analysed. Of the 183 samples there were 78 cases of gastritis (43%), 57 cases of duodenitis (31%), 21 cases of ileitis (12%) and 27 cases of colitis (15%). Chronic lymphoplasmacytic inflammation was the most common histopathological diagnosis in all organs (87%), other diagnoses included mixed inflammation (6%), lymphoplasmacytic and eosinophilic (LPE) inflammation (4%), lymphoplasmacytic and neutrophilic (LPN) inflammation (3%), and histiocytic inflammation (0,6%). Severity of the inflammation was mostly mild (61%), however in duodenum and ileum moderate inflammation was the most frequent (56% and 57%, respectively) (Table 1). Ileum was the organ with the highest average intensity of the inflammation.

Table 1. Severity grade, type of infiltration and morphological changes in different parts of the gastrointestinal tract.

	Total (n = 183)	Gastritis (n = 78)	Duodenitis (n = 57)	Ileitis (n = 21)	Colitis (n = 27)
Severity grade					
Mild	112	67	21	6	18
Moderate	63	10	32	12	9
Severe	8	1	4	3	0
Type of infiltrate					
LP	159	70	50	15	24
LPE	7	0	3	3	1
LPN	6	3	2	0	1
MIXED	10	5	2	3	0
H	1	0	0	0	1
Morphological changes					
Epithelial injury	96	33	32	14	17
Mucosal fibrosis/atrophy	37	15	10	2	10
Crypt dilation/distortion	45	-	19	6	20

LP - lymphoplasmacytic, LPE - lymphoplasmacytic and eosinophilic, LPN - lymphoplasmacytic and neutrophilic, H - histiocytic

Absence of morphological changes was detected in 36/78, 5/57, 0/21 and 3/27 cases of gastritis, duodenitis, ileitis and colitis, respectively. The most frequent gastric morphological change was surface epithelial injury (n = 33/78), which was also present in more than 50% of cases of duodenitis, ileitis, and colitis. In duodenum epithelial injury together with villous stunting, and in ileum villous stunting were the most commonly observed morphological changes (n = 32/57 and n = 15/21, respectively). Crypt dilation/distortion (n = 20/27) was the most frequent morphological abnormality among colonic samples (mostly of mild intensity) and was significantly more frequent in colon than in duodenum and ileum ($P < 0.05$). Mucosal fibrosis/atrophy was most commonly detected in the colon (n = 10/27) with less than 20% of cases in the rest of the organs, however, the difference in frequency was not significant. The comparison of intensity of epithelial injury, cryptal distension/distortion and mucosal fibrosis/atrophy revealed that all these changes were the most severe in duodenum.

Colonization with HLOs

Out of 105 dogs, 64 (61%) had one or more parts of the GI tract infected with HLOs. HLOs were present in 64.1% of cases of gastritis, 5.3% of cases of duodenitis, 47.6% of cases of ileitis and 48% of cases of colitis. Colonization of two or more organs was present in 9 dogs (14% of HLOs positive dogs), of which one dog had all four parts infected (i.e. stomach, duodenum, ileum and colon), two dogs had stomach, ileum and colon infected, 3 dogs had ileum and colon infected and the remaining dogs had their stomach and colon, stomach and duodenum and stomach, duodenum and colon infected, respectively. Details about the degree of colonization of the different organs and localization of the bacteria are summarised in Table 2.

HLOs and relationship to morphological changes

All HLOs positive cases of duodenitis and ileitis and 44% and 85% of HLOs positive cases of gastritis and colitis, respectively, were accompanied by at least one morphological

Table 2. Presence and density of *Helicobacter*-like organisms (HLOs) in different parts of the GI tract in samples included in the study (n = 183).

	Number of HLOs positive cases (mean intensity ± SD)					
	HLOs positive	Mucosal surface	Gastric pits	Gastric glands	Crypts	Lamina propria
Gastritis (n = 78)	50 (2.0 ± 0.9)	34 (1.9 ± 0.9)	34 (2.2 ± 0.8)	42 (2.4 ± 0.7)	-	-
Duodenitis (n = 57)	3 (0.3 ± 0.0)	3 (1.0 ± 0.0)	-	-	0	0
Ileitis (n = 21)	10 (0.5 ± 0.3)	10 (1.4 ± 0.7)	-	-	2 (1.0 ± 0.0)	0
Colitis (n = 27)	13 (0.6 ± 0.4)	10 (1.5 ± 0.9)	-	-	3 (1.0 ± 0.0)	1 (2.0 ± 0.0)

SD - standard deviation

and/or inflammatory change other than infiltration with lymphocytes and plasma cells, whereas at least one change was also present in 94%, 100%, 79% and 100% of HLOs negative cases of duodenitis, ileitis, gastritis, and colitis, respectively. A significant difference in frequency was found between uncolonized and colonized gastric biopsies for variables gastric pit epithelial injury and mucosal fibrosis/atrophy ($P < 0.05$). When intensity of morphological/ inflammatory changes was compared to the density of HLOs, a significant difference in frequency was observed between uncolonized/poorly (0/1) colonized gastric samples with mild/moderate mucosal fibrosis/atrophy and moderately/ heavily (2/3) colonized samples without fibrosis ($P < 0.05$). No significant association was found between the presence and density of HLOs and the presence and intensity of morphological/inflammatory changes in other organs.

Discussion

Among the different types of chronic inflammatory reaction in the GI tract of dogs, lymphoplasmacytic (LP) inflammation, characterised by predominant infiltration of the mucosa with lymphocytes and plasma cells, is most frequently diagnosed histologically. Consistently, in this study LP inflammation was the most prevalent type accounting for more than 87% of cases of gastritis, duodenitis and colitis and 71% of cases of ileitis. Compared to that, only 7 dogs were diagnosed having lymphoplasmacytic and eosinophilic (LPE) inflammation, 6 of them with LPE enteritis and one dog with LPE colitis, which represents 6% and 2% of dogs that had their small intestine and colon examined, respectively. This is in agreement with other studies which also showed relatively low prevalence of LPE enteritis (5.6–8.7% of dogs with chronic GI signs) (Craven et al. 2004; Lidbury et al. 2009; Đorđević et al. 2012; Volkmann et al. 2017; Ivasovic et al. 2022). As regards mixed inflammation, we detected only 5% of cases of enteritis being characterized by this type of inflammation, whereas Craven et al. (2004) and Volkmann et al. (2017) reported the prevalence of mixed intestinal inflammation to be 38% and 53%, respectively. The disparity in frequency of mixed type inflammation likely reflects high degree of subjectivity in evaluating GI endoscopic biopsies and persistently poor agreement on differentiating the respective type of inflammation among histopathologists (Willard et al. 2002; Washabau et al. 2010).

In our study we noted that epithelial injury was the most prevalent mucosal structural lesion among gastric biopsies. In contrast, Lidbury et al. (2009) reported mucosal fibrosis to be the most frequent morphological abnormality in the gastric mucosa, accounting for 19% of gastric biopsies (Lidbury et al. 2009). This number agrees with both our results and results of Çolakoğlu et al. (2017) (19% and 17% of cases of chronic gastritis, respectively). Compared to that, we observed lower frequency of fibrosis/atrophy

in duodenal and ileal mucosa of symptomatic dogs than Procoli et al. (2013) did. On the other hand, lacteal dilation was just as common or even more common in our group of samples (28% of cases of duodenitis and 43% of cases of ileitis) than in previously published studies (2.2–29.0% of cases of duodenitis and 38% of cases of ileitis) (Lidbury et al. 2009; Đorđević et al. 2012; Procoli et al. 2013; Çolakoğlu et al. 2017). We can conclude that both villous stunting and lacteal dilation were more frequent in ileum compared to duodenum which corresponds to the observation of Casamian-Sorrosal et al. (2010) that morphological abnormalities are sometimes more readily detectable in ileal mucosa. Moreover, we observed cryptal dilation to be significantly more frequent feature of colitis compared to ileitis or duodenitis.

Another aim of our study was to evaluate the presence of *Helicobacter* species along the GI tract of dogs with chronic gastrointestinal inflammation. So far, the prevalence of gastric helicobacters in dogs was reported the most, with percentage of *Helicobacter* spp. positive diseased dogs ranging mostly from 78% to 100% (Hermanns et al. 1995; Hwang et al. 2002; Polanco et al. 2011; Amorim et al. 2015). An exception to this range exists, as Kubota-Aizawa et al. (2017) reported the prevalence of only 35% of dogs with GI disease in Japan. In the present study, we observed helicobacters in 64% of dogs with chronic gastritis, which is somewhat lower percentage than in most of the reports. However, most of the prevalence values mentioned were obtained using highly sensitive methods, in particular polymerase chain reaction (PCR). When more traditional means of detecting helicobacters were employed, the prevalence of 82% and 87% out of a group of diseased dogs was reported (Hermanns et al. 1995; Amorim et al. 2015). Compared to these data, the prevalence found by us is still lower; this can reflect local differences in distribution of *Helicobacter* spp. infection among the population of dogs (Kubota-Aizawa et al. 2017). As we are lacking data about previous therapeutical interventions, another possible explanation for this discrepancy could be a history of administration of antimicrobial therapeutics prior to the endoscopic examination. In the present study, of the dogs diagnosed with chronic duodenitis and ileitis, 5.3% and 47.6% were colonized with HLOs, respectively. To the best of our knowledge, there is no literature currently available regarding the prevalence of *Helicobacter* spp. in the small intestine of dogs with chronic enteritis, although these bacteria have been isolated from dogs with chronic diarrhoea (Rossi et al. 2008; Recordati et al. 2009; Giaretta et al. 2020). As regards the colon, we observed lower percentage of infected dogs compared to a study of Castiglioni et al. (2012) which can be due to different methods used to detect helicobacters (histopathology and/or immunohistochemistry and PCR, respectively).

In recent years, some features of chronic inflammation (i.e., increased numbers of IEL, epithelial injury and gastric lymphofollicular hyperplasia) were associated with *Helicobacter* spp. infection of canine gastric mucosa (Eaton et al. 1996; Ali Shabes et al. 2008; Amorim et al. 2017; Kubota-Aizawa et al. 2017; Biénès et al. 2022). In contrast, our results show that colonization of gastric mucosa in dogs with chronic gastritis has no effect on the presence of specific morphological changes, i.e., mucosal fibrosis/atrophy and gastric pit epithelial injury. Regarding more distal parts of the GI tract, Castiglioni et al. (2012) demonstrated a correlation between the presence of *Helicobacter* spp. in colon and occurrence and severity of mucosal fibrosis/atrophy. In our study, we observed slightly increased frequency of fibrosis/atrophy in HLOs positive samples of colonic mucosa than in those without helicobacters, however, the difference in frequency was not statistically significant. As regards the ileum, IEL, villous stunting and lacteal dilation were more frequent among positive samples in this study, but the difference was also non-significant. Further studies on this topic are needed to reveal the actual prevalence of *Helicobacter* spp. along different parts of the intestine of dogs and to elucidate its potential relationship to pathological changes of the mucosa.

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