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Case Report

Chronic gastrointestinal inflammation in a dog mimicking human russell body gastroduodenitis

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Abstract

Herein we describe an unusual benign chronic gastroduodenal inflammation associated with protein losing enteropathy in a dog. A 10-year-old Golden Retriever dog was presented for chronic weight loss associated with pica, ptyalism, vomiting and diarrhea. Blood chemistry showed hypoproteinaemia and hypoalbuminaemia. Gastric and duodenal full-thickness biopsies were collected and histopathological examination revealed severe mucosal infiltration with Mott cells, consistent with Russell body gastroduodenitis in humans. Warthin-starry stain showed no *Helicobacter* spp. proliferation in gastric biopsies. After treatment including anti-acid, antibiotics and corticosteroids, no recurrence of gastrointestinal signs was reported and improvement in clinical and biological condition was observed.

Key words: Russell bodies, Mott cell, IBD, plasma cell.

Introduction

Chronic gastroenteropathies are common in dogs and include predominantly inflammatory bowel disease (IBD), dysbiosis and dietary sensitivity (1). Inflammatory gastric and bowel disease is common in dogs, being part of the chronic enteropathies if lasting more than three weeks, and is properly defined when there is histological demonstration of mucosal inflammation and all other possible causes of enteritis, infiltrates or both have been investigated and excluded (2). Canine IBD are commonly categorised according to the nature of the predominant cellular infiltrate (e.g. eosinophilic, lymphoplasmacytic, granulomatous or lymphoid follicular), and lymphoplasmacytic gastroenteritis remains the most common form of canine chronic gastroenteropathy (3). The International Gastrointestinal Standardization Group of the World Small Animal Veterinary Association (WSAVA) guidelines suggest that the presence of neutrophils in the gastric and duodenal mucosa characterises an acute inflammatory process, while an increase in mucosal mononuclear leucocytes identifies a chronic gastroenteritis (3).

The aim of this communication is to describe an unusual chronic benign infiltration of Mott cells in the gastroduodenal tract of a dog, mimicking human Russell body (RB) gastroduodenitis. Russell body infiltration of the gastrointestinal tract was firstly described in 1998 (4) and the term ‘‘Russell body gastroenteritis’’ was coined in 2013 in order to describe an unusual benign inflammatory disease in the digestive tract of a human patient, characterised by the presence of a very high number of plasma cells containing a large amount of RBs in their cytoplasm (5). Since then, 24 cases were reported in human medicine (5, 6).

Case report

A 10-year-old neutered female Golden Retriever dog, weighing 28 kg, was admitted for 4-months history of

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chronic weight loss (2.5 kg). In the past year, the dog had several episodes of pica (geophagia and ground-licking), associated with intermittent episodes of ptyalism, diarrhea and vomiting. A symptomatic treatment with 1 g sucralfate (Ulcar; Sanofi-Aventis, France) oral every 12 hours, 0.5 mg/kg metoclopramide (Emeprid, CEVA Santé Animale, France) oral every 8 hours, and 12.5 mg/kg metronidazole (Flagyl; Sanofi-Aventis, France) by mouth every 12 hours was administered associated with an easily digestible diet, but the patient failed to respond to therapy.

At presentation, the dog was free of treatment for one month. Its body condition score was 3/9, according to the WSAVA Global Nutrition Committee criteria (7). On physical examination, the only detected abnormality was discomfort during palpation of the cranial abdominal region. Faecal samples pooled over a period of three consecutive days, were analysed by a flotation test with a low flotation solution (specific gravity 1.2), direct smear and by the Baermann migration-sedimentation technique, and all scored negative for parasites. Complete blood count values, blood smear and serum electrolytes concentration revealed no abnormality. Serum total protein (54 g/L [RI (reference interval) 60-75 g/L]) and albumin (20 g/L [RI 23-40 g/L]) concentrations were decreased. Serum protein electrophoresis was normal. Serum concentration of trypsin-like immunoreactivity (TLI), folates and B12-vitamin were within RI and specific pancreatic lipase concentration was normal. Urine analysis (specific gravity, urine dipstick, sulfo-salicylic acid test and urinary sediment examination) was unremarkable and urine protein/creatinine ratio was normal. On abdominal radiographs, a loss of serosal details related to emaciation was observed. Abdominal ultrasonography revealed diffuse gastric wall thickening, with normal layering and motility and no evidence of lymphadenopathy. Duodenum and jejunum wall thickness and layering were normal. Gastrointestinal full-thickness biopsies were obtained by laparotomy. Laparotomy was preferred to endoscopy in order to reduce the potential to miss lesions deep within the submucosal and muscular layers of the intestinal wall. During celiotomy, the gastrointestinal tract was macroscopically examined. The gastric and duodenal walls appeared pale and stiff. No foreign bodies were found at organ palpation. 380The histological examination of the gastric (four from fundus and two from pyloric antrum) biopsies showed a marked expansion of the lamina propria due to an infiltration of monomorphic cells with eosinophilic cytoplasm and eccentric nuclei (Fig. 1A). On high-power examination, the typical aspect of Mott cells (plasma cells with round eosinophilic intracytoplasmatic inclusions, so-called Russell bodies [Rbs]) was identified (Fig. 1B). Four duodenal biopsies revealed numerous disseminated Mott cells in the lamina propria. No evidence of lymphangectasia or crypt dilation was observed. The absence of mitotic figures and a low Ki-67 index (MIB-1 clone, Dako) disclosed an absence of a significant proliferative activity of the infiltrating cells. Immunohistochemistry against the Multiple Myeloma Oncogene 1 (MUM-1 antigen, MRQ43 clone, Acris Antibodies) confirmed the high prevalence of plasma cells in the gastric and duodenal infiltrate (Fig. 1C), while immunohistochemistry against cytokeratins (AE1/AE3 clone, DAKO) confirmed that the infiltrating cells were not of epithelial origin (Fig. 1D). Wartin-Starry stain showed no *Helicobacter* spp. proliferation in gastric specimens.

Medical treatment was initiated with 1 mg/kg omeprazole (Mopral; AstraZeneca, France) oral every 24 hours, 0.2 mg/kg metoclopramide (Emeprid, CEVA Santé Animale, France) subcutaneously every 8 hours and 12.5 mg/kg metronidazole (Flagyl; Sanofi-Aventis, France) intravenously every 12 hours for five days. The dog was given an easily digestible diet and discharged with 12.5 mg/kg metronidazole (Flagyl; Sanofi-Aventis, France) oral every 12 hours for the next ten days, 1 mg/kg omeprazole (Mopral; AstraZeneca, France) oral every 24 hours and 0.1 mg/kg budesonide (Entocort, AstraZeneca, France) oral every 24 hours for the next two months. The dog weight was checked every week. An improvement in physical and clinical conditions were observed ten days after starting therapy with oral budesonide. Serum total protein (68 g/L [RI 60-75 g/L]) and albumin (29 g/L [RI 23-40 g/L]) concentrations were within RI one month after starting therapy. The corticosteroid treatment was progressively decreased over a period of two months. No vomiting, diarrhea or pica were then reported by the owner. Since physical and clinical improvement was observed, the owner declined endoscopic biopsies after ending treatment.

Discussion

The development of canine IBD is thought to originate as a consequence of a deregulation of mucosal immunity in predisposed animals (1, 2), and the loss of tolerance to antigens, such as food or intestinal bacteria, is one of the most studied mechanisms that could justify the development of chronic intestinal inflammation (2). A number of previous studies have addressed the role of immunologic mechanisms in the pathogenesis of canine gastroenteropathies (1, 2). In this regard, high numbers of immunoglobulins (Ig)-G and IgA secreting plasma cells have been found in duodenal lamina propria of dogs with IBD, antibiotic-responsive diarrhoea and with adverse reactions to food (1, 2). The infiltration of plasma cells is a hallmark of gastrointestinal chronic inflammation (8). Under the stimulation of antigens, plasma cells produce Ig involved in the immune response. The aggregation of high quantity of Ig within the rough endoplasmic reticulum and Golgi apparatus of plasma cells may result in RBs formation (9). Morphologically, RBs are eosinophilic, large, homogeneous immunoglobulin-containing cytoplasmic inclusions usually found in a plasma cell undergoing excessive synthesis of Ig and is characteristic

of the distended endoplasmic reticulum and Golgi apparatus resulting from secretion disturbance (9). Therefore, RBs represent a general response of the cell to the accumulation of abundant, non-degradable proteins that fail to exit from the endoplasmic reticulum (6).

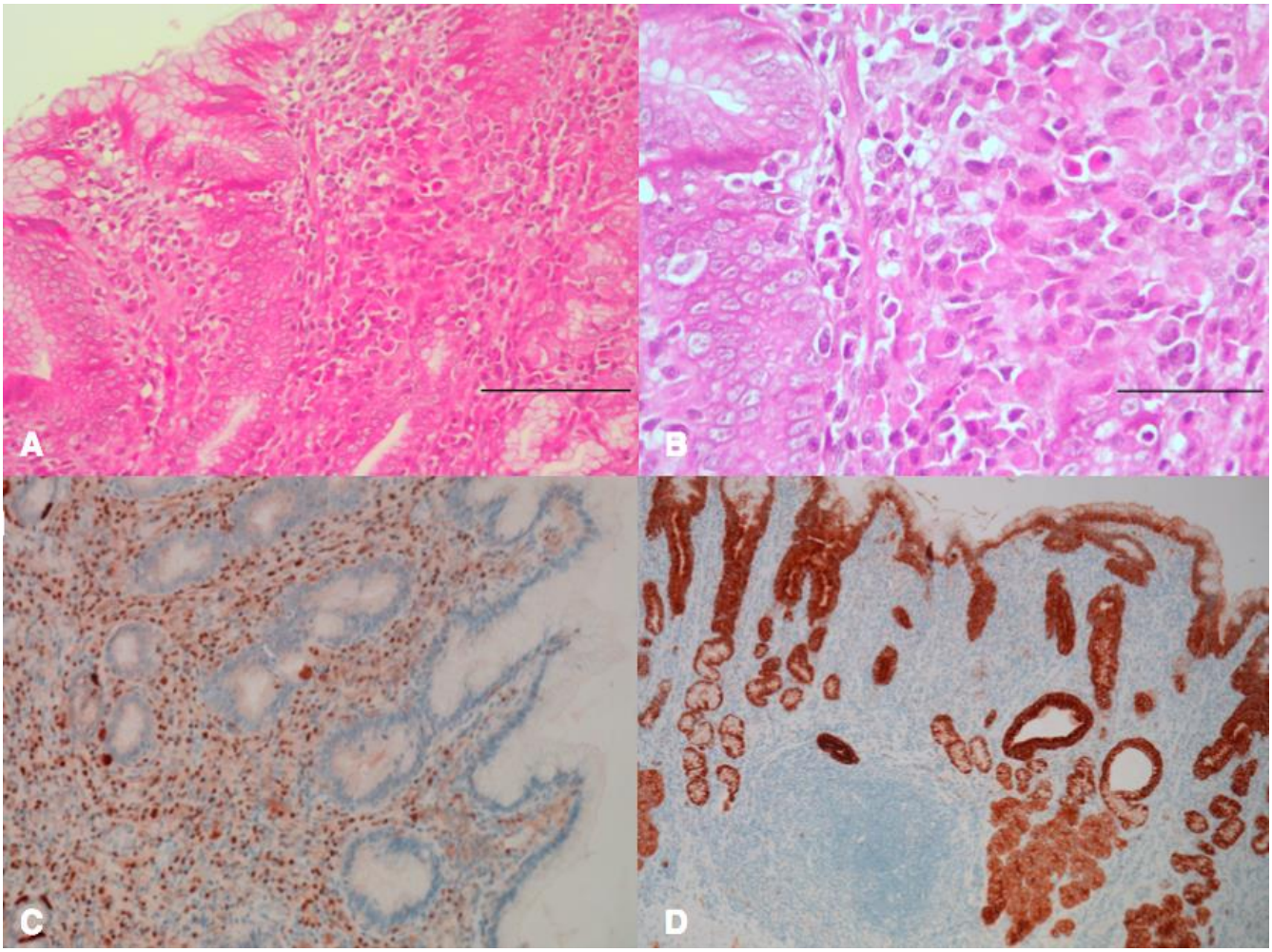

Figure 1. A. Hematoxylin and eosin, 200x. Gastric biopsy showing marked expansion of the lamina propria by numerous monomorphic plasma cells with eccentric nuclei and abundant eosinophilic cytoplasm (so-called Mott cells). **B.** Hematoxylin and eosin, 400x. High-power view of infiltrating plasma cells with round eosinophilic inclusions (Russell bodies). **C.** MUM1 immunostaining (DAB chromogen and hematoxylin counterstain), 200x. Nuclei of plasma cells in the lamina propria are highlighted by MUM1 positivity, a plasma cell marker. These cells represent 60 to 80% of the leucocyte population in the *lamina propria* of the stomach. **D.** Pancytokeratin immunostaining (clones AE1/AE3, DAB chromogen and hematoxylin counterstain), 200x. Expression of the pancytokeratin markers by epithelial superficial and glandular cells but none by cells in the lamina propria demonstrating the non-epithelial nature of the infiltrating cells.

Human RBG is a rare benign gastroenteropathy characterized by the accumulation of numerous plasma cells filled with eosinophilic globules, so-called Rbs, in the lamina propria of the gastric and duodenal mucosa and more rarely, in the oesophageal wall (8). Clinically, RBG is strongly associated with upper gastrointestinal signs in human patients, such as abdominal discomfort, nausea and dyspepsia, anorexia, weight loss, emesis and more rarely, acute diarrhea (8). The presence of microorganisms, such as *H. pylori*, Human Immunodeficiency Virus, Hepatitis C virus and Epstein-Barr virus, have been hypothesized to induce RBs formation in the gastric and duodenal lamina propria, as a consequence of a robust inflammatory response (8). A link between RBG and *H. pylori* infection of the gastric mucosa has been postulated, but the clinical importance and the relationships with this pathogen are still unclear, and *H. pylori* negative-RBG have been described in human patients (6). In the dog herein examined, no evidence of *Helicobacter* spp. infection was observed in the gastric mucosa after Whartin-Starry staining. However, the importance of *Helicobacter* spp. infections in the development of gastric lesions in dogs remains controversial (10).

Previous case reports in human medicine suggest that RBG should be differentiated from neoplastic diseases, such as signet ring cell adenocarcinoma, malignant lymphoma, plasma cell tumor, multiple myeloma and monoclonal gammopathy of uncertain significance (MGUS) (8). Furthermore, three cases of gastrointestinal Mott cell tumor have been previously reported in veterinary medicine (11, 12, 13). Signet ring cell adenocarcinoma of the canine stomach is characterised by a diffuse infiltration of signet ring tumour cells in the gastric wall. Histologically, this gastric neoplasm consists of isolated or small groups of malignant cells containing intracytoplasmic mucin with eccentric nuclei**,** whose morphology may mimic a Mott cells infiltration of the gastric mucosa (14). In addition, the 2010 WHO classification of human tumor recognises other variants of gastric carcinomas, such as 'poorly cohesive carcinomas' and "mixed carcinomas", which correspond to a mixture of non-signet ring cells, morphologically resembling histiocytes, lymphocytes and plasma cells (14). Therefore, in the dog herein examined immunostaining for cytokeratins was performed to completely rule out the possibility of a gastric carcinoma malignancy.

A differential diagnosis with an extramedullary plasma cell tumor originating from the mucosa-associated lymphoid tissue has also been suggested in our patient. Gastric plasmacytoma has been rarely described in veterinary medicine, with only four cases reports in dogs (15). Even if a positive polyclonal immuno-reactivity may be required to rule out with certainty the possibility of a gastric extra-medullary plasmacytoma, in the dog herein examined the typical presentation of an extramedullary plasmacytoma was not observed.

The absence of cell and nuclear polymorphism atypia, and mitosis, as well as a low proliferation Ki67 index were factors that favoured a diagnosis of RBG in our patient, excluding a plasmacytic or lymphocytic malignancy, such as a gastrointestinal B-cell lymphoma or Mott cell tumor (6). In dogs, these are rare neoplastic conditions, described as solid, multiple masses, characterized by the frequent presence of distant metastases at time of diagnosis (13). Additionally, in these neoplastic conditions Mott cells and Rbs are usually found in small numbers among a larger population of polymorphous lymphocytic infiltrate (13). Finally, MGUS has also been reported in veterinary patient (16, 17). This condition, as well as the possibility of multiple myeloma, were not very plausible in our patient, based on the absence of a monoclonal gammopathy at serum protein electrophoresis.

Concerning the treatment of RBG, no consensus exists in human medicine. Its management involves *Helicobacter* eradication therapy and exclusion of associated conditions (5). Furthermore, even in the absence of *H. pylori* infection, some case reports showed improvement in RBG if an antibiotic treatment is undertaken (6). In the dog herein examined, a treatment with oral metronidazole was administered associated with an oral corticosteroid. The administration of corticosteroids was based on the presence of chronic upper gastrointestinal signs and the evidence of a non-infectious or dietary responsive gastroenteropathy. Furthermore, several studies have shown that corticosteroids may be beneficial in the treatment of IBD in dogs (3, 18). The only serum biochemical abnormalities detected in our patient were hypoproteinaemia and hypoalbuminaemia. Causes of protein-losing enteropathy are numerous, including diseases that result in infiltration, inflammation, haemorrhage, or edema of the GI tract, including intestinal lymphangiectasia, alimentary lymphoma, hookworm infestation, infection by *Histoplasma capsulatum*, and intestinal intussusception (19). Furthermore, chronic enteropathies can result in protein-losing enteropathy and hypoalbuminaemia has been strongly associated with a poor outcome in canine IBD, correlating with diseases of greater severity (18, 19). Therefore, oral budesonide was preferred to prednisolone, based on its capacity to increase serum albumin concentration as compared with prednisolone (20). In dog herein examined, eight months after treatment no recurrence of gastrointestinal signs was reported by the owner and improvement in serum total protein and albumin concentration was observed.

In conclusion we describe an aberrant manifestation of chronic gastrointestinal inflammation in a dog, strongly resembling RBG in human patients. The description of a single clinical case can neither support the uniqueness of this condition in canine patients nor confirm the possibility of an another variant of IBD in dogs. Thus, further studies are required to confirm its involvement in veterinary medicine, as well as the usefulness of glucocorticoid in its medical approach.

Conflict of interest

The author declared no potential conflicts of interest with respect to the research, authorship, and/or publication of this article.

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