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SUCCESSFUL TREATMENT OF CHRONIC INFLAMMATORY ENTEROPATHY IN 2-YEAR-OLD YORKSHIRE TERIER. CASE REPORT

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ABSTRACT

Chronic enteropathy in dogs represents a significant clinical challenge that often requires innovative therapeutic strategies for effective management. This case study investigated the simultaneous use of budesonide, cannabidiol (CBD) oil and probiotics. Budesonide represents a corticoid therapy primarily used in human medicine for autoimmune diseases. Cannabidiol oil is one of the cannabinoids that does not affect sensory perception and is known for its anti-inflammatory properties. Probiotics help maintain gut microbiota balance as a treatment modality for chronic enteropathy in dogs. This report details the clinical symptoms, diagnosis, and treatment plan, highlighting the positive response seen in the patient. The findings suggested that the combination of budesonide, CBD oil, and probiotics may be a beneficial strategy for the treatment of chronic enteropathy in dogs.

Key words: budesonide; cannabidiol oil; chronic enteropathy; diarrhoea; probiotics

INTRODUCTION

Canine chronic inflammatory enteropathies (CIEs) represent a group of disorders characterized by persistent (lasting three weeks or longer) or recurrent gastrointestinal symptoms. Symptoms may include diarrhoea, vomiting, nausea, borborygmus, flatulence, eructation, abdominal pain, weight loss, or a combination. A diagnosis is confirmed by excluding other non-digestive ailments that could produce gastrointestinal symptoms, along with intestinal parasites and digestive neoplastic or infectious diseases [4].

Chronic inflammatory enteropathies are classified into four primary categories: food-responsive enteropathies (FREs), antibiotic-responsive enteropathies (AREs), immunosuppressant-responsive enteropathies (IREs), and non-responsive or refractory enteropathies (NREs). Inflammatory bowel diseases (IBDs) encompass IREs and NREs, both characterized by mucosal inflammation. Furthermore, there exists a specific category termed protein-losing enteropathies (PLEs), which includes all chronic enteropathies resulting in hypoalbuminemia, irrespective of their therapeutic response [5].

Chronic enteropathy in dogs mostly presents in two histological forms: lymphocytic-plasmacytic enteritis (LPE) and eosinophilic gastroenteritis (EGE). These diseases exemplify the most frequently found histological features linked to chronic inflammatory bowel disease (IBD) in canine patients. Although the clinical manifestations and histological characteristics of IBD in small animals do not consistently align with those seen in human Crohn's disease (CD) and ulcerative colitis (UC), it is posited that the fundamental mechanisms underlying these conditions exhibit considerable similarities [8].

The intensity of clinical manifestations in canine IBD correlates with the Canine IBD Activity Index (CIBDAI) or the Canine Chronic Enteropathy Clinical Activity Index (CCECAI). The CIBDAI is a commonly utilized clinical scoring instrument that evaluates six distinct indicators: attitude/activity, hunger, vomiting, stool consistency, stool frequency, and weight loss. The latest CCECAI incorporates additional criteria, including blood albumin levels, peripheral oedema, and pruritus severity, to provide a more comprehensive assessment of therapy effectiveness. Higher scores on these measures indicate an increased risk of adverse outcomes and can guide treatment decisions. Furthermore, low blood albumin levels (< 20 $g.l^{-1}$) and hypocobalaminaemia are recognized as negative prognostic indicators [1].

The primary cause of IBD in both dogs and humans is an abnormal immune response, which is thought to originate from reduced tolerance to various luminal antigens. Reduced tolerance is essential for the onset and progression of IBD in both species. The exact cause of IBD remains unknown, but it is generally accepted that the disorder results from a complex interplay of several factors. Elements such as genetic susceptibility, environmental influences, and disruption of the integrity of the intestinal epithelial barrier contribute to the onset and continuation of inflammation. Research showed that an amplified immune response in the gastrointestinal tract, triggered by normally tolerated antigens such as specific dietary elements or intestinal flora, leads to an inflammatory chain reaction. This increased immune response ultimately causes gastrointestinal damage, perpetuating the cycle of inflammation and worsening the clinical symptoms of IBD. Understanding these complex interactions is essential for the development of effective therapies to manage chronic enteropathy in dogs and improve their overall health and quality of life [15].

Corticosteroids are a common and often essential choice for treating IBD in dogs. Numerous studies have demonstrated the effectiveness of prednisone, a type of corticosteroid, in alleviating the symptoms associated with IBD in dogs. The importance of corticosteroids is not only in veterinary practices but also in the treatment of human inflammatory bowel disorders such as Crohn's disease and ulcerative colitis. Despite their therapeutic benefits, the systemic use of corticosteroids in both dogs and humans can sometimes lead to various side effects. In dogs, the adverse effects can be quite substantial and may include increased appetite, excessive urination, increased thirst, restlessness, panting, and notable changes in behaviour. Additionally, prolonged use of corticosteroids can have serious consequences like obesity, vacuolar liver disease, muscle wasting and weakness, ligament tears, urinary tract infections, skin infections, and the onset of diabetes mellitus. These possible side effects can significantly diminish pets' quality of life, even when the symptoms of IBD are well-managed. Therefore, even though corticosteroids provide an effective treatment for IBD, their long-term effects should be carefully considered to protect the overall well-being of dogs [6].

Budesonide is a corticosteroid drug predominantly utilized to diminish inflammation in multiple illnesses, particularly those impacting the respiratory and gastrointestinal systems. It possesses significant anti-inflammatory properties while exhibiting less systemic adverse effects than other corticosteroids such as prednisolone, owing to its extensive first-pass metabolism in the liver, which restricts its systemic absorption. Budesonide is frequently given for the management of chronic respiratory disorders, including asthma and chronic obstructive pulmonary disease, and is typically delivered using an inhaler or nebulizer to specifically address airway inflammation. Moreover, it is extensively utilized for the treatment of IBD, including Crohn's disease, ulcerative colitis, and microscopic colitis, all of which are marked by gastrointestinal tract inflammation. Budesonide's targeted action in the intestines mitigates inflammation while minimizing systemic effects compared to other corticosteroids. It functions by inhibiting the immune system, thereby reducing inflammation. Budesonide is available in several formulations that include inhalers, oral capsules, tablets, and nasal sprays, contingent upon the problem being addressed. While generally well tolerated, potential side effects may encompass

headaches, nausea, respiratory infections (associated with inhaled formulations), and the danger of adrenal suppression with prolonged treatment. Notwithstanding its reduced systemic absorption, it should still be administered under medical supervision [21].

Cannabidiol (CBD) oil is one of the cannabinoids that does not affect sensory perception. CBD is a non-intoxicating compound that interacts with the body's endocannabinoid system, which plays a role in controlling various physiological functions, like inflammation and immune response. In cases of inflammatory bowel disease (IBD), the immune system mistakenly attacks the gastrointestinal tract, leading to inflammation and harm to the intestinal lining. CBD oil is believed to modulate the immune response and reduce inflammation by interacting with the endocannabinoid system, specifically the CB1 and CB2 receptors situated in the gastrointestinal tract and immune cells. CBD has demonstrated anti-inflammatory properties in animal studies and limited human trials. It might help in decreasing the production of pro-inflammatory cytokines, which are elevated in individuals with inflammatory bowel disease (IBD). By lowering these inflammatory agents, CBD may aid in relieving symptoms such as pain, cramps, and diarrhoea [13].

CASE PRESENTATION

A two-years-old Yorkshire terrier was initially evaluated by a private veterinarian for persistent diarrhoea, decreased appetite and repeated vomiting. On examination, the private veterinarian diagnosed the patient with giardiasis. They administered metronidazole at a dose of 25 $mg.kg^{-1}$ for 10 days for the treatment of giardiasis. After the treatment, the disease showed a slight improvement; nevertheless, symptoms such as diarrhoea, borborygmi and general gastric distress continued. In addition, the private veterinarian recommended a hypoallergenic feed along with probiotics. Due to persistent gastrointestinal problems, this patient was referred to the Small Animal Clinic of the University of Veterinary Medicine and Pharmacy in Košice.

After admission to our clinic, the patient underwent several examinations. Blood was first analysed (Procyte Dx Hematology Analyzer, IDEXX Laboratories, Inc., Westbrook, ME, USA) for both haematology count and serum biochemical evaluation. Haematology examination revealed no signs of inflammation. All other hematologic parameters fell within the reference standards. Biochemical analysis (Cobas c 111 analyzer Roche, Switzerland) showed borderline urea levels while creatinine and SDMA were within reference ranges. The results of haematological and biochemical analyses are presented in Table 1.

Parasitological analysis of faeces revealed no gastrointestinal parasites. The faeces used for the analysis were collected over three days at different time intervals.

The patient was referred for a sonographic examination of the abdominal cavity to complete the diagnosis. USG showed fluid stagnation in the stomach, with a thickened wall of 4–5 mm in the pyloric region, and the stomach appeared inactive. The pancreas appeared hyperechogenic and the gallbladder had a thin wall without significant thickening. In the duodenum, hyperechoic mucosa and a thickened wall were observed, accompanied by mild effusion in the bowel region (Fig. 1).

Table 1. Reference ranges of haematological and biochemical markers and their levels prior to therapy

RBC	HCT	HGB	WBC	NEU	LYM	MONO	EOS	BAS
5.6–8.8 x $10^{12}.l^{-1}$	37.3–61.7 %	13.1–20.5 $g.dl^{-1}$	5.0–16.7 x $10^{9}.l^{-1}$	2.9–11.6 x $10^{9}.l^{-1}$	1.05–5.1 x $10^{9}.l^{-1}$	0.16–1.12 x $10^{9}.l^{-1}$	0.06–1.23 x $10^{9}.l^{-1}$	0.0–0.1 x $10^{9}.l^{-1}$
6.38	44	15.7	11.6	3.71	5.67	1.09	0.58	0.01
CREA	**UREA**	**ALT**	**ALP**	**GLU**	**ALB**	**TP**	**AMYL**	**LIP**
46–88 $\mu mol.l^{-1}$	3.9–8.5 $mmol.l^{-1}$	< 0.949 $\mu kat.l^{-1}$	< 1.24 $\mu kat.l^{-1}$	3.6–5.8 $mmol.l^{-1}$	26–41 $g.l^{-1}$	47–74 $g.l^{-1}$	< 7.21 $\mu kat.l^{-1}$	< 1.66 $\mu kat.l^{-1}$
72.7	8.05	0.61	0.73	5.1	29.6	45.6	5.71	0.6

RBC – red blood cells; HCT – haematocrit; HGB – haemoglobin; WBC – white blood cells; NEU – neutrophils; LYM – lymphocytes; MONO – monocytes; EOS – eosinophils; BAS – basophils; CREA – creatinine; ALT – alanine aminotransferase; ALP - alkaline phosphatase; GLU – glucose; ALB – albumin; TP – total protein; AMYL – amylase; LIP – lipase

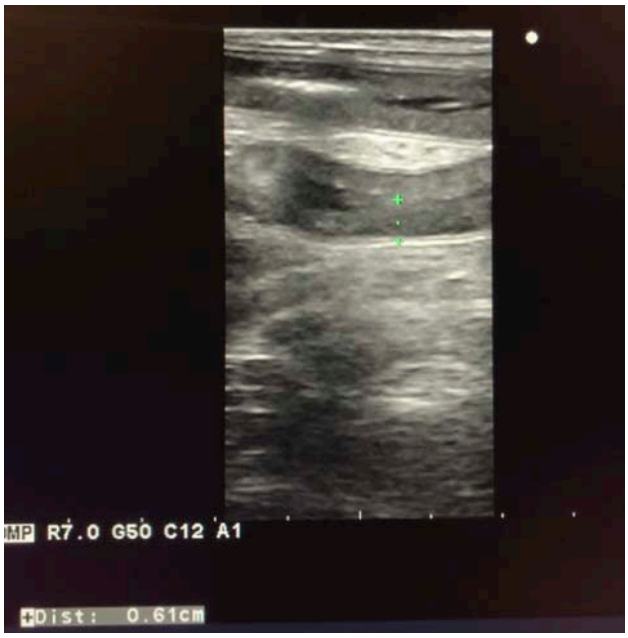

Fig. 1. Thickening of the intestinal wall

Based on previous examinations, the owner was advised to seek an endoscopic examination and to take a sample of the intestinal wall for histological analysis. The endoscopic examination of cardia revealed hyperaemia, and it was accompanied by mucosal oedema in the fundus area. Endoscopic examination of duodenum revealed hyperaemia, oedema, discoloration and granularity of wall (Fig. 2).

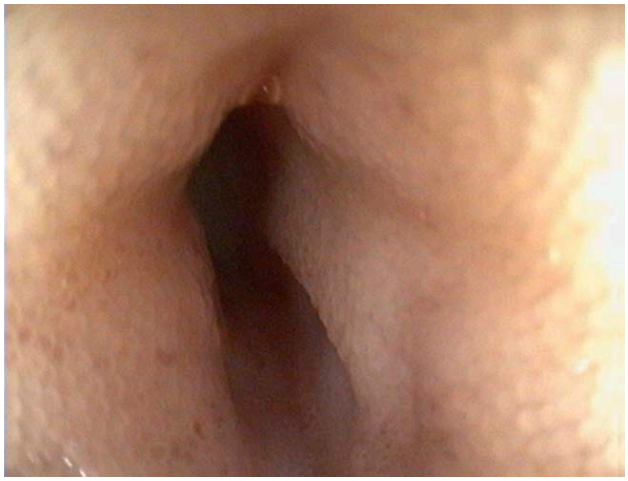

Fig. 2. Endoscopy of the duodenum

Changes were also observed in the large intestine, extending from the ampulla recti into the descending colon, characterized by wall thickening. Miliary haemorrhages and hyperaemic foci were infrequently noted.

Histological examination of the colon revealed crypt and glandular areas of the mucosa with round cell infiltration and epithelial exfoliation (Fig. 3).

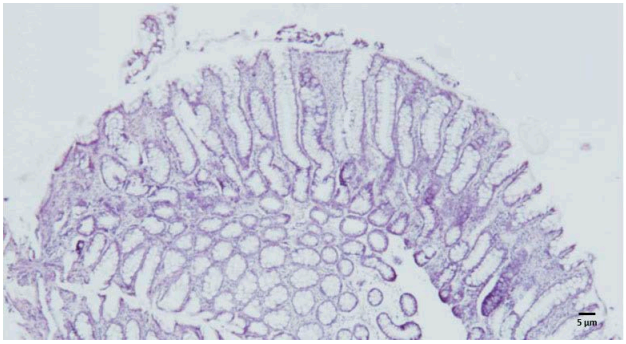

Fig. 3. Histology examination of the large intestine

The diagnosis of chronic catarrhal colitis with a predominance of lymphocyto-plasmacytes were established after excluding all causes of persistent diarrhoea and based on the results of histological analysis.

The manifestation of clinical symptoms and the concentration of albumin were included in the scoring assessment of the Canine Chronic Enteropathy Clinical Activity Index (CCECAI) which reflects the severity of the disease. The CCECAI was utilized to evaluate the severity of chronic enteropathy (Table 2).

Table 2. Canine Chronic Enteropathy Clinical Activity Index (CCECAI) before the treatment

Parameter	Score	Parameter	Score
Defecation frequency	2	Weight loss	0
Albumin	0	Ascites	0
Pruritus	0	Activity	1
Appetite	1	Vomiting	2
Faecal consistency	2	Total	8

The cumulative score of CCECAI was 8, indicating moderate chronic enteropathy requiring appropriate treatment. As a part of the therapy, we recommended the use of corticosteroids used in human medicine to control chronic enteropathies such as inflammatory bowel disease (IBD). The dosage was selected based on the dog's size, at 1 mg once daily. Furthermore, we prescribed CBD oil as a supportive anti-inflammatory drug at a concentration of 20 % at a dose of 6 drops three times daily. Budesonide was administered for one month followed by a steady reduction in dose until complete discontinuation. Long-term administration of CBD oil was recommended. We also recommend Purina® Pro Plan®Veterinary Diets; FortiFlora® Probiotic Supplement, Nestle Purina PetCare, St Louis, MO. We recommend commercial diet with less than 20 % fat to the owner.

After approximately two months, a follow-up examination was performed. Haematological blood test results

Table 3. Reference ranges of haematological and biochemical markers and their levels during therapy

RBC	HCT	HGB	WBC	NEU	LYM	MONO	EOS	BAS
5.6–8.8	37.3–61.7	13.1–20.5	5.0–16.7	2.9–11.6	1.05–5.1	0.16–1.12	0.06–1.23	0.0–0.1
x $10^{12}.l^{-1}$	%	$g.dl^{-1}$	x $10^{9}.l^{-1}$	x $10^{9}.l^{-1}$	x $10^{9}.l^{-1}$	x $10^{9}.l^{-1}$	x $10^{9}.l^{-1}$	x $10^{9}.l^{-1}$
7.02	46	15.9	5.98	2.57	2.31	1.05	0.05	0.0
CREA	**UREA**	**ALT**	**ALP**	**GLU**	**ALB**	**TP**	**AMYL**	**LIP**
46–88	3.9–8.5	< 0.949	< 1.24	3.6–5.8	26–41	47–74	< 7.21	< 1.66
$\mu mol.l^{-1}$	$mmol.l^{-1}$	$\mu kat.l^{-1}$	$\mu kat.l^{-1}$	$mmol.l^{-1}$	$g.l^{-1}$	$g.l^{-1}$	$\mu kat.l^{-1}$	$\mu kat.l^{-1}$
80.1	8.0	0.88	0.95	5.1	30.9	50.1	6.25	0.8

RBC – red blood cells; HCT – haematocrit; HGB – haemoglobin; WBC – white blood cells; NEU – neutrophils; LYM – lymphocytes; MONO – monocytes; EOS – eosinophils; BAS – basophils; CREA – creatinine; ALT – alanine aminotransferase; ALP - alkaline phosphatase; GLU – glucose; ALB – albumin; TP – total protein; AMYL – amylase; LIP – lipase

were within reference range, and serum biochemical analysis was also normal. Table 3 shows the various parameters of the haematobiological blood tests after medication. Ultrasound examination revealed changes in the thickness and characteristics of the intestinal wall.

Two months after the start of the therapy, we again evaluated the CCECAI, which showed physiological values in all monitored parameters (Table 4). The final score was 4, indicating substantial improvement after therapy.

Table 4. Canine Chronic Enteropathy Clinical Activity Index after treatment

Parameter	Score	Parameter	Score
Defecation frequency	1	Weight loss	0
Albumin	0	Ascites	0
Pruritus	0	Activity	0
Appetite	1	Vomiting	1
Faecal consistency	1	TOTAL	4

For the next 9 months, the therapy consisted of 20 % CBD, 5 drops three times a day, and the probiotic preparation PURINA PRO PLAN, Fortiflora Canine Probiotic. The condition did not deteriorate during therapy. No side symptoms of therapy such as polyuria/polydipsia, poor coat quality, cystitis or loss of appetite were noted. The dog strictly adhered to a low-fat diet containing less than 15–20 % fat.

DISCUSSION

Budesonide, a nonhalogenated potent glucocorticoid, is 15 times more potent than prednisolone [26]. Its high-water solubility enables good distribution to mucosal surfaces, with the drug converting into a lipophilic ester in local tissue cells. This gradual hydrolysis releases active budesonide, providing a lasting local anti-inflammatory impact, as the active form possesses a strong binding affinity for intracellular glucocorticoid receptors [19, 26].

An interesting study on the effects of budesonide was conducted by P i e t r a et al. [16] involving 11 dogs with chronic enteropathies over a 30-day period. The concentrations of budesonide and its metabolite, 16-α-hydroxyprednisolone, were monitored in plasma and urine samples collected on day 1 and 8 of the treatment. Samples were taken before administering budesonide and five times during the day at regular intervals to determine the duration of action of the administered medication. The evaluation of the therapy's effect on the improvement of clinical signs was assessed on the 20th day of treatment and on the 30th day from the start of medication. The highest plasma concentrations of budesonide and 16-α-hydroxyprednisolone on the 1st day were found 1 hour and 2 hours after drug administration, indicating rapid absorption of the medication in all dogs. Comparison of urinary concentrations of budesonide and 16-α-hydroxyprednisolone on day 1 and 8 of the therapy showed that by the 8th day, the concentrations of these medications were higher in the monitored dogs. The drug gradually accumulated, leading to an adequate therapeutic response without adverse effects. The analysis of the clinical response of dogs 20 days after the start of treatment revealed significant clinical improvement of the disease, evidenced by a marked reduction in CIBDAI scores, and the effect persisted even 30 days after the infiltration of therapy. In three out of the 11 monitored dogs, a greater effect of budesonide on the small intestine was observed compared to the large intestine. In fact, it is possible that the primary site of action of budesonide in dogs is more in the small intestine

than in the large intestine. It is important to emphasize that regardless of the therapeutic response to budesonide, none of the dogs exhibited polyuria, polydipsia, or other clinical signs compatible with iatrogenic hyperadrenocorticism 30 days after starting treatment. It was confirmed that although budesonide is largely metabolized and may have an inhibitory effect on the hypothalamic-pituitary-adrenal axis, there was no increase in serum alkaline phosphatase activity in the dogs.

Changes in biochemical parameters were significantly monitored in many studies that compared the treatment of IBD patients using prednisolone and budesonide [6].

D y e et al. [6], in a similar comparative study involving 40 dogs with IBD, divided the dogs into two groups based on therapy and found that both medications, prednisolone and budesonide, demonstrated high efficacy in reducing the severity scores of clinical symptoms of the disease. However, budesonide led to a significant increase in albumin levels, a change that was not observed in the prednisolone group of dogs with IBD. Furthermore, in the group receiving prednisolone therapy, there was a significant increase in liver enzymes and an increase in the number of leukocytes, primarily neutrophils.

T u m u l t y et al. [24] also found no significant changes in serum alkaline phosphatase activity, water consumption, frequency of urination, or appetite before and after treatment with budesonide.

A similar effect of budesonide therapy was observed in our case, where biochemical examinations did not confirm elevated concentrations of alkaline phosphatase or any other parameters in the dogs.

Furthermore, multiple studies concerning human medicine [18] compared budesonide therapy with mesalazine therapy, confirming a rapid achievement of remission in patients with IBD, particularly those with moderate disease severity, using both medications. Although budesonide may not be as effective as conventional steroids in treating severe IBD, it remains a valuable option for patients with moderate diseases, especially for those at a higher risk of adverse effects from conventional high-dose corticosteroids [7, 9].

A n g e l u c c i et al. [2] also confirmed fewer side effects in the treatment of IBD using budesonide in their studies involving patients with Crohn's disease. They found that therapy with methylprednisolone and budesonide had a similar remission rate, particularly in patients with moderate IBD severity, but budesonide caused fewer metabolic side effects in patients.

In our patient, the disease was of moderate severity, with a CCECAI score of 8, which provided an excellent reason to use budesonide for therapy, given its cumulative effect on the body.

Another study by S z w e d a et al. [22], which focused on evaluating the effects of budesonide on antigen-induced cell proliferation and apoptosis in dogs with IBD, also confirmed that budesonide is a next-generation glucocorticoid and may be effective in managing gastrointestinal disorders, such as IBD, associated with increased levels of apoptosis.

Although one study by R y c h l i k et al. [17] questioned the efficacy of budesonide in improving clinical symptoms in dogs with IBD, the latest large study by H o d e l et al. [9], who monitored 60 dogs with chronic enteropathies, confirmed that budesonide effectively controlled the clinical signs of the disease in the long term. The authors even described treatment courses where budesonide was primarily used, which in combination with dietary changes significantly improved the severity scores of the disease. In many cases, dogs with chronic inflammatory bowel disease initially classified in the IRE group (immune-suppressive therapy responders) transitioned to the FRE group (diet-responsive dogs) with long-term quality survival of over a year. In our case, a similar treatment approach was confirmed, where the initial use of budesonide for 2 months, along with dietary changes, resulted in a significant healing effect on the intestinal mucosa lasting almost a year.

Similar results are described by K a t h r a n i et al. [10], who also recommend reducing fat intake to manage severe clinical conditions related to intestinal mucosal inflammation through a low-fat or ultra-low-fat diet. It is believed that these diets reduce lymphatic flow and pressure, thereby preventing issues such as lacteal dilation and lymph leakage. The authors recommended to follow with a diet with a fat content of less than 20 % (or less than 15 % for ultra-low-fat diets), preferably prepared at home. In our case, we also recommended to the owner to provide a commercial diet with a fat content below 20 %.

Many veterinarians and researchers are also exploring additional options to support therapy for dogs as well as humans with IBD. Over the past decade, there has been a significant progress in cannabinoid research. This ad-

vancement is largely attributed to the identification of cannabinoid receptors CB1 and CB2, which have been found in most mammals [3]. The CB1 receptor is predominantly expressed in the central nervous system, while the CB2 receptor is mainly expressed by immune system cells, where it is particularly abundant.

Furthermore, numerous studies [3, 11, 12] have demonstrated that cannabinoids largely inhibit the release of cytokines in both innate and adaptive immune responses in animal models and human cell cultures. This suppression of pro-inflammatory cytokines and chemokines suggests that these substances may possess anti-inflammatory properties and could potentially be utilized in the management of chronic inflammatory conditions.

Cannabinoids have demonstrated anti-inflammatory properties in a mouse model with chemically induced colitis. Administration of cannabinoids led to a reduction in colonic tissue ulceration and inflammatory reactions, as well as a decrease in tissue myeloperoxidase activity. Conversely, mice lacking CB1 receptors or treated with a CB1 antagonist exhibited heightened ulceration and inflammation. This indicates that cannabinoids may regulate the tissue's inflammatory response in the colon, possibly by moderating the smooth muscle reaction to pro-inflammatory agents and inhibiting the production of such agents. More research is required to fully comprehend the specific mechanisms underlying this regulation [14]. We administered cannabidiol (CBD) oil as a treatment, a cannabinoid that does not impact sensory perception and is known for its anti-inflammatory properties.

Research conducted by T i z a r d et al. [23] indicated that affected dogs often show an increase in Proteobacteria, such as *E. coli* or Pseudomonas, while experiencing a decrease in Firmicutes and Bacteroidetes. Additional contributors to inflammation may include greater bacterial adherence to the mucosa, diminished bacterial diversity, and bacterial overgrowth. Utilizing probiotic and prebiotic products effectively improves canine gut health. These products offer benefits to dogs by rebalancing the intestinal microbiota, regulating the immune system, mitigating inflammation, fortifying the intestinal mucosal barrier, and influencing intestinal metabolites [25]. In our case, we also used the probiotic supplement Purina® Pro Plan® Veterinary Diets FortiFlora® Probiotic Supplement for the dog.

Similar conclusions regarding the use of probiotics were published by S u c h o d o l s k i et al. [20] who focused on the role of gut microbiota in the gastrointestinal health of dogs. They emphasized the potential benefits of using probiotics to manage intestinal dysbiosis. They found that probiotics could be recommended as a supportive treatment for chronic enteropathies to restore balance in the gut microbiome and improve gastrointestinal function in dogs.

CONCLUSIONS

In conclusion, the combination of budesonide, CBD oil, and probiotics proved to be a successful therapeutic strategy for the treatment of chronic enteropathy in the presented case. The therapy effectively managed the patient's symptoms, leading to a significant clinical improvement. No adverse side effects were observed throughout the treatment period.

Conflict of interest

The authors have no conflicts of interest to declare.

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