Chronic intestinal pseudo-obstruction in a Bernese Mountain Dog

Chronische intestinale pseudo-obstructie bij een Berner Sennenhond

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ABSTRACT

Chronic Intestinal Pseudo-Obstruction (CIPO) is a rare syndrome characterized by chronic intestinal dilation and dysmotility in the absence of mechanical obstruction. A definite diagnosis of CIPO can only be made after histological examination of intestinal tissues. The present case describes a CIPO in a 2.5-year-old Bernese Mountain dog with a history of recurrent gastro-intestinal complaints suggestive for pseudo-obstruction. Histological lesions of small intestinal samples consisted of severe loss of smooth muscle cells of the tunica muscularis and diffuse infiltration of mononuclear cells. In addition, a hypertrophy of the lamina muscularis mucosa of the small intestinal tract was present. On the basis of these findings and the results of immunohistochemistry, a myopathic form of CIPO was diagnosed.

SAMENVATTING

Chronische intestinale pseudo-obstructie (CIPO) is een zeldzame aandoening en wordt gekenmerkt door hypomotiliteit van het darmstelsel. Dit veroorzaakt symptomen van obstructie. Een histologisch onderzoek is noodzakelijk om een definitieve diagnose van CIPO te kunnen stellen. In dit artikel wordt een geval beschreven van CIPO bij een 2,5 jaar oude Berner Sennenhond met recidiverende gastro-intestinale klachten kenmerkend voor obstructie. Bij het histologisch onderzoek van de dunne darmen werd een sterke atrofie van de tunica muscularis waargenomen. Deze was diffuus geïnfiltreerd met monomorfe leukocyten. Daarnaast werd eveneens een hypertrofie van de lamina muscularis mucosa in de dunne darmen waargenomen. Deze bevindingen alsook de resultaten van het immunohistochemisch onderzoek wijzen in de richting van een myopathische vorm van CIPO.

INTRODUCTION

Chronic intestinal pseudo-obstruction is a rare and severe syndrome characterized by impaired intestinal function mimicking mechanical obstruction in the absence of any intestinal occluding lesion (Amleida and Penna, 2000). The diagnosis is mainly clinical, supported by radiographic and ultrasonographic examinations revealing dilated intestines with air-fluid level (Antonucci *et al.*, 2008). Full thickness biopsies of affected and non-affected alimentary tracts should be obtained for histopathological examination to make a definite diagnosis.

CIPO is a heterogeneous group of syndromes that mainly affect intestinal motility due to severe disease of the neuromuscular system. It is classified into three main categories: 1) neuropathies: disorders of myenteric plexi, which are further subdivided into inflammatory and degenerative neuropathies; 2) mesenchymopathies: abnormalities of the interstitial cells of Cajal; and 3) myopathies: primary involvement of smooth muscle cells. Immunohistochemistry is often helpful in establishing a correct diagnosis (Antonucci *et al.*).

In dogs, only a few cases of CIPO have been described (Arrick and Kleine, 1978; Moore and Carpenter, 1984; Swayne *et al.*, 1986; Lamb and France, 1994; Dvir *et al.*, 2001; Petrus *et al.*, 2001; Eastwood *et al.*, 2005; Couraud *et al.*, 2006; Johnson *et al.*, 2007). Histological samples of the small and large intestines of most cases demonstrated atrophy and infiltration with a mononuclear cell infiltration, as well as fibrosis of the tunica muscularis. Occasionally, degeneration of smooth muscle fibers and diffuse inflammatory cell infiltration in the tunica muscularis of the stomach and/or bladder were present. Although extensive immunohistochemistry was not performed in the cases described by Moore and Carpenter (1984), Swayne *et al.*(1986), Eastwood *et al.* (2005) and Couraud *et al.* (2006), they probably reflect a myopathic form of CIPO, in view of the high degree of involvement of smooth muscle cells. In three other cases, the neurological form of CIPO can be suspected, since lesions were observed in submucosal plexi and/or myenteric plexi (Lamb and France, 1994; Dvir *et al.*, 2001; Petrus *et al., 2001*).

Here, we report the histological and immunohistochemical characterization of myopathic CIPO with hypertrophy of the lamina muscularis mucosa in a Bernese Mountain Dog.

CASE REPORT

Case history

A 2.5-year-old male Bernese Mountain Dog was referred to the Small Animal Clinic of the Faculty of Veterinary Medicine with a history of anorexia, diarrhea and vomiting for a period of 2 weeks and weight loss occurring over 2 months. Neither the antibiotics (ceftiofur, lincomycin and marbofloxacin) nor the antiemetics (primperan) given by the referring veterinarian had had any effect. On physical examination, poor body condition and a distended, painful abdomen were found. Abdominal auscultation did not reveal borborygmi. Complete blood count, urinalysis, and serum biochemistry profile including serum electrolyte concentrations showed no abnormalities. Abdominal radio-graphy demonstrated severely distended small intestinal loops filled with watery content and gas. The descending colon was dilated and filled with feces. The other parts of the colon were distended and filled with gas. Abdominal ultrasonography revealed severely dilated, fluid filled and flacid small intestines. Bacteriological and parasitological fecal examination were negative. Based on the clinical and radiographic findings, a diagnosis of intestinal obstruction was made. A midline exploratory celiotomy was performed. The small intestines were markedly distended and filled with fluid and gas. There was no evidence of peristalsis, but a mechanical obstruction could not be found. Large amounts of impacted contents were present in the large bowel. The intestinal content was removed by gentle massage. In addition, a moderate amount of serosanguineous fluid was present in the abdominal cavity. A jejunal biopsy revealed atrophy of the villi and multifocal necrosis of the mucosa. There was a significant mucosal infiltration with macrophages, lymphocytes and plasma cells that extended into the tunica muscularis. Several muscle cells of the tunica muscularis were hypereosinophilic and fragmentated. Postoperatively, the dog received fluid therapy, antibiotics (amoxicillin/clavulanic acid and metronidazole), ranitidine, primperan and cisapride, without improvement of the general condition. Because of the poor prognosis and the absence of response to treatment, the dog was euthanized 8 days after surgery.

Autopsy and histological findings

At necropsy, the duodenum was severely dilated and filled with yellow-brown fluid. The jejunum and ileum were moderately dilated and contained the same fluid, as well as impacted content. A moderate amount of impacted feces was present in the colon. Histological samples were taken from the esophagus, stomach, duodenum, jejunum, ileum, colon, trigeminal ganglion and urinary bladder. These tissues were fixed in 10% neutral buffered formalin and embedded in paraffin wax. Histological sections were stained with hemotoxylin-eosin (HE) and Van Gieson's staining. The tissues were immunolabeled with MAC 387 (reactive macrophages), CD 3 (T cells), CD 20 (B cells), smooth muscle actin (smooth muscle cells), S100 (enteroglial cells), GFAP (enteroglial cells), NSE (neurons), c-kit (interstitial cells of Cajal) and synaptophysin (degenerating neurons).

The lamina propria of the mucosa of the duodenum, jejunum and ileum was diffusely infiltrated with neutrophils, eosinophils, lymphocytes and plasma cells. Hypertrophy of the lamina muscularis mucosae was observed. The tunica submucosa was mildly edematous and infiltrated with moderate numbers of leukocytes. There was almost a complete loss of smooth muscle cells in both the longitudinal and the circular layers of the tunica muscularis (Figure 1). Both layers were also severely infiltrated with lymphocytes, plasma cells and histiocytes. As demonstrated with immunohistochemistry, T-cells, B-cells and macrophages were present, but there appeared to be a larger number of T-lymphocytes (mean of 51 T-cells/hpf to 14 B-

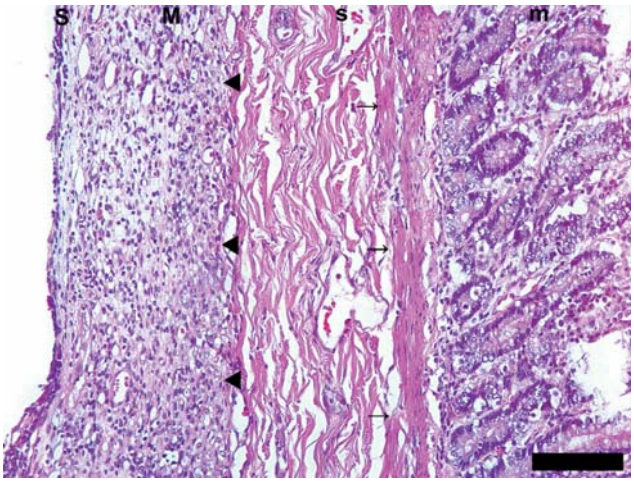

Figure 1. Small intestine, CIPO. The lamina muscularis mucosae is hypertrophic (→). The tunica muscularis is athrophic and infiltrated with inflammatory cells (►). M = tunica mucosa; s = tunica submucosa; M = tunica muscularis; S = tunica serosa. HE, Bar 100 µm.

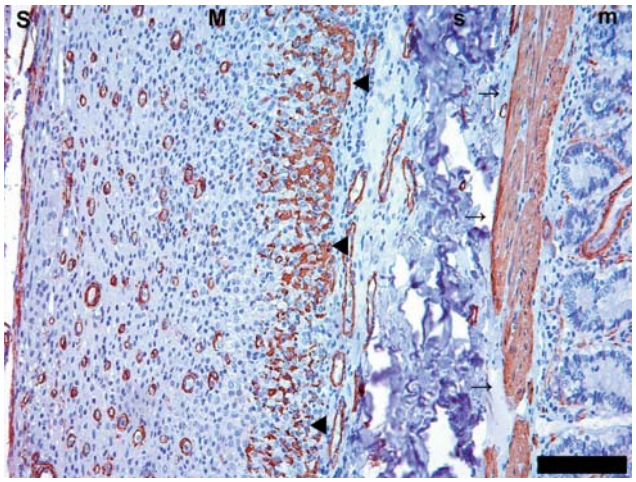

Figure 2. Small intestine, CIPO. Smooth muscle cells (colored brown) are prominent in the lamina muscularis mucosae (→) and almost absent in tunica muscularis (►). M = tunica mucosa; s = tunica submucosa; M = tunica muscularis; S = tunica serosa Smooth muscle actin immunolabeling, Bar 100 µm.

cells/hpf). Only small numbers of smooth muscle cells were present in the tunica muscularis, as demonstrated by actin immunolabeling (Figure 2). Fibrosis was not detected by Van Gieson's staining. Histological and immunohistochemical examination of the neuronal plexi and cells of Cajal did not reveal any abnormalities. A transition to the normal tunica muscularis was noted in the colon. In samples of esophagus, trigeminal ganglion and stomach, lesions were not observed. On the basis of these findings, a diagnosis of myopathic CIPO was made.

DISCUSSION

In human medicine, CIPO is a rare but well-known disease and is defined as an intestinal obstruction without mechanical basis. CIPO is idiopathic (primary) in the majority of cases (Antonucci *et al.*, 2008). However, every disease that affects one of the control mechanisms of intestinal functioning can be responsible for secondary CIPO, such as central and peripheral extrinsic autonomic nervous system disorders in neuropathies or myothonic dystrophy (congenital disorder characterized clinically by progressive muscle weakness and wasting) and systemic sclerosis (abnormal accumulation of fibrous tissue in skin and multiple organs) in myopathies. However, CIPO can also be observed in patients with hypothyroidism or hypoparathyroidism. In the present case, no indications of a concurrent disease affecting intestinal motility were obtained. Therefore, the CIPO in this Bernese Mountain Dog was most probably idiopathic.

In veterinary medicine, 11 cases of CIPO in dogs have been described, without predisposition for breed, age or sex (Arrick and Kleine, 1978; Moore and Carpenter, 1984; Swayne *et al.*, 1986; Lamb and France, 1994; Dvir *et al.*, 2001; Petrus *et al.*, 2001; Eastwood *et al.*, 2005; Couraud *et al.*, 2006; Johnson *et al.*, 2007). The present case is the second case reported in a Bernese Mountain Dog. All dogs had symptoms of recurrent gastrointestinal problems, mostly vomiting and inappetance (Moore and Carpenter, 1984; Swayne *et al.*, 1986; Lamb and France, 1994; Dvir *et al.*, 2001; Eastwood *et al.*, 2005; Couraud *et al.*, 2006). Based on the clinical and radiographic findings, most cases, as in human medicine, were suspected of intestinal obstruction. At laparascopy or laparatomy, the intestinal loops were severely dilated, but no physical obstruction was found (Moore and Carpenter, 1984; Lamb and France, 1994; Dvir *et al.*, 2001; Couraud *et al.*, 2006). In one case, cecal impaction was present (Eastwood *et al.*, 2005). In our case, as well as in the cases reported in the literature, treatment did not have any effect and most dogs died or were euthanized. If a necropsy was performed, severely dilated intestinal loops with a flaccid wall and watery contents were found (Lamb and France, 1994; Dvir *et al.*, 2001). In one case, necropsy revealed thickened small intestine (Swayne *et al.*, 1986). Both in the present case and in most of the reported cases in the literature, histological samples of the intestines demonstrated atrophy and infiltration with a mononuclear cell infiltration of the tunica muscularis (Moore and Carpenter, 1984; Lamb and France, 1994; Dvir *et al.*, 2001; Eastwood *et al.*, 2005; Couraud *et al.*, 2006). In contrast to our case, fibrosis of the tunica muscularis is a common finding in dogs with CIPO (Moore and Carpenter, 1984; Swayne *et al.*, 1986; Lamb and France, 1994; Dvir *et al.*, 2001). An abrupt transition between affected and normal tunica muscularis was present at the transition between ileum and colon. It is tempting to speculate that this could be due to a specific reaction to the small intestinal tract. However, information in the literature concerning tissue specificity of CIPO is lacking. Interestingly, in the present case, hypertrophy of the lamina muscularis mucosa was observed. This has only been described in 2 dogs (Arick and Kleine, 1978; Swayne *et al.*, 1986). The reason for this finding is not clear, although it could reflect a compensatory phenomenon.

In the present case, a definite diagnosis of CIPO was made after necropsy and histological examination. Although a full thickness biopsy of the jejunum was histologically examined, CIPO was not definitely diagnosed. Since only 1 biopsy of the small intestinal tract was examined, the observed lesions could represent a focal process. Also, it was not evident that tunica muscularis was primarily affected, since inflammation was also observed in the tunica submucosa and necrotic enterocytes were present. For this reason, and also because CIPO is an extremely rare disease in dogs, other conditions affecting the small intestinal tract were suspected, rather than a primary myopathy. As a consequence, several full thickness biopsies from dilated and non-dilated tracts of the alimentary canal should be obtained for histopathological examination (Antonucci *et al.*, 2008).

In human medicine, several different immunohistochemical markers are applied on histological slides of full thickness biopsies to characterize neuropathic, mesenchymopathic and myopathic forms of CIPO. Neuronal markers, such as GFAP, S100, NSE and synaptophysin, can be used to demonstrate loss of neurons or neuronal degeneration in myenteric plexi. If the inflammation or degeneration is invariably confined to the myenteric plexus, a neuropathic form of CIPO can be suspected. The enteric mesenchymopathic form is associated with lesions in the interstitial cells of Cajal. The decreased density of these cells can be assessed using immunohistochemical markers such as KIT (Antonucci *et al.*, 2008). The myopathic form is characterized by a selective decrease or even absence of smooth muscle actin in tunica muscularis. Hence, immunolabelling for smooth muscle actin is considered a biological marker for this type of CIPO. In the present case, several immunohistochemical markers were used and a myopathic form of CIPO was suggested, based on the decrease in smooth muscle cells in tunica muscularis and the absence of lesions in myenteric plexi and in cells of Cajal.

Immunolabeling for leukocytes revealed the predominant presence of T-cells. This is in agreement with a case of fibrosing myositis (Johnson *et al.*,

2007). Also in humans, a large population of T-cells (mainly CD8+) is observed in patients with CIPO and an autoimmune enteric leiomyositis is suggested as possible underlying cause (Haas *et al*., 2005; Ruuska *et al.*, 2002).

In conclusion, clinical suspicion of CIPO should be confirmed by histological examination of full thickness biopsies of different sites of the intestinal tract. Furthermore, immunolabeling can be performed to better characterize the lesion.

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