

*Case report*

## SMALL INTESTINAL GANGLIONEUROMATOSIS ACCOMPANIED BY AN ULCER IN A 13-YEAR OLD DOG

HUBER Doroteja\*, GUDAN KURILJ Andrea, HOHŠTETER Marko

Department of Veterinary Pathology, Faculty of Veterinary Medicine, University of Zagreb, Zagreb, Croatia

(Received 05 October 2019, Accepted 18 February 2020)

Ganglioneuromatosis is a rare disorder characterized by hyperplasia of intestinal ganglia including myenteric plexus and enteric nerve fibers. This disorder is generally described in children, but sporadic cases have also been described in adults. Most human cases arise in the colon and rectum. The disorder has also been described in dogs, mostly juveniles, but rarely in mature dogs with the oldest dog reported with this change being 9 years old.

We report the first case in an older dog from Croatia. A 13-year old female, mixed-breed dog had a history of diarrhea and weight loss. Ultrasound revealed focally-extensive markedly thickened small intestine. The changed part of the intestine, measuring 7 mm x 20 mm, was removed on laparotomy and delivered for histopathologic examination. Grossly, the intestine showed circumferential expansion of the intestinal wall, which was whitish in color. Microscopic findings included diffuse hyperplasia of the myenteric and submucous plexus. Focally in the affected tissue a subacute ulcer was evident, which was probably not the cause of intestinal signs, as it presented a localized lesion, while ganglioneuromatosis was a diffuse change in the affected tissue.

So far, ganglioneuromatosis was reported in young dogs, rarely in adult dogs. Our report shows that ganglioneuromatosis can also be encountered in older dogs. Although the lesion presents a rare finding, it should be listed as a differential diagnosis in dogs where infectious and neoplastic etiology has been ruled out as cause of diarrhea.

**Key words:** dog, ganglioneuromatosis, histology, small intestine

### INTRODUCTION

Ganglioneuromatosis is a rare disorder characterized by poorly demarcated, multinodular to diffuse proliferation of intestinal ganglia including myenteric and enteric nerve fibers [1,2]. This disorder is primarily a human disease occurring anywhere in the alimentary tract, from the oral cavity to the rectum, but is mostly found in the colon [3,4].

---

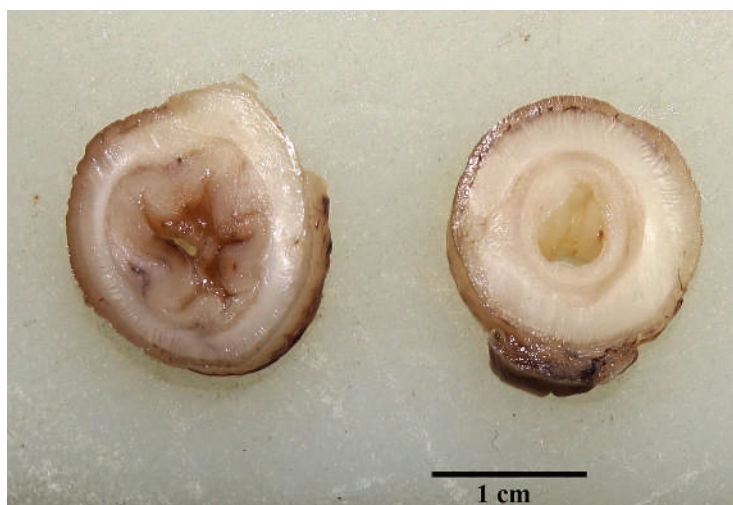
\*Corresponding author: e-mail: dhuber@vef.hr

Ganglioneuromatosis has been described in few dogs in the intestinal tract [5-8] and in the wall of the gallbladder [9]. It has so far been mostly reported in puppies and juveniles [5-7], rarely in adult dogs [8,9]. Reported clinical signs of ganglioneuromatosis include persistent diarrhea, intermittent vomiting, poor appetite, depression and poor body condition in small intestinal ganglioneuromatosis [6,8] and tenesmus, hematochezia and rectal prolapse in colorectal ganglioneuromatosis [5,7]. The etiology of the disease in dogs is unknown. In most reported canine cases it was speculated that the lesion was congenital due to young age of the patients and slowly progressive nature of the lesion [5-7]. Proposed theories in humans include overexpression of neural growth factor causing proliferation of nerve fibers, hyperplasia of nerve fibers, decreased expression of the tumor suppressor gene and increased expression of glial cell line-derived neurotrophic factor and neurturin [10-13].

### CASE REPORT

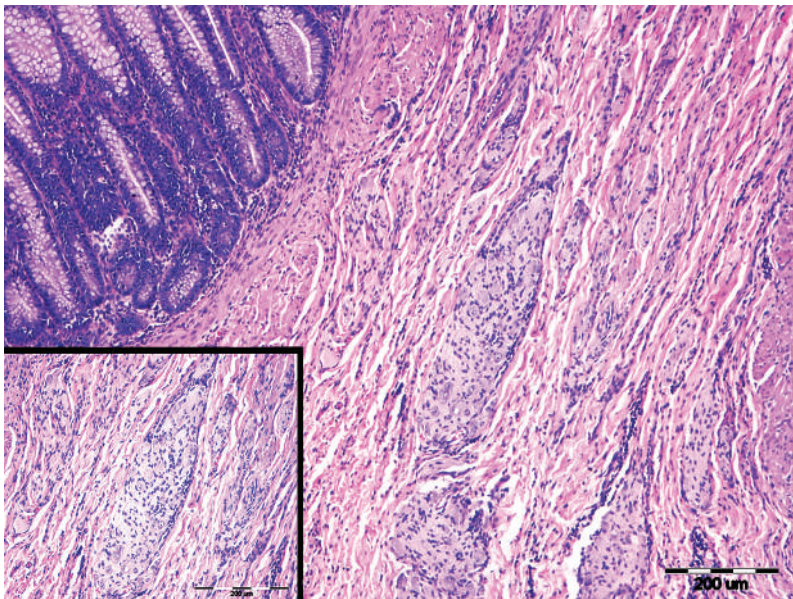
A 13-year-old female, mixed-breed dog from a shelter was presented to a local veterinarian with a history of diarrhea and weight loss of unknown duration. Ultrasound performed by referring veterinarian revealed focally-extensive markedly thickened segment of the small intestine. The changed part of the intestine was removed on laparotomy and delivered for histopathologic examination fixed in 10% neutral, buffered formalin. Surgery and histologic analysis were allowed by the owner of the dog (animal shelter).

The submitted tissue was a 7 mm x 20 mm part of the small intestine with a thickened wall (Fig. 1). Focally, there was a linear, dark brown to black colored defect in the mucosa measuring 7 mm in length and less than 1 mm in width.



**Figure 1.** Transverse cut section of affected intestine showing firm, whitish circumferential thickening of tissue

Histology revealed diffuse hyperplasia of myenteric and submucous plexus affecting the submucosa and muscularis of the whole submitted small intestine (Fig. 2). The cell bodies were polygonal in shape, with a large round to oval nucleus with coarse to vesicular chromatin and one pronounced nucleolus (Fig. 2 inset). The cytoplasm was eosinophilic, scant and with faintly to moderately visible cell borders. Neurons were surrounded by elongated cells with moderate to abundant eosinophilic, fibrillar, sometimes foamy, cytoplasm compatible with Schwann cells (Fig. 2 inset). The linear defect, seen grossly, was expanding from the mucosa to the proximal half of the circular layer of the muscularis and characterized by necrosis of all affected layers and accumulation of predominantly neutrophils and smaller number of macrophages, lymphocytes and plasma cells (Fig. 3). Around the defect were activated fibroblasts.



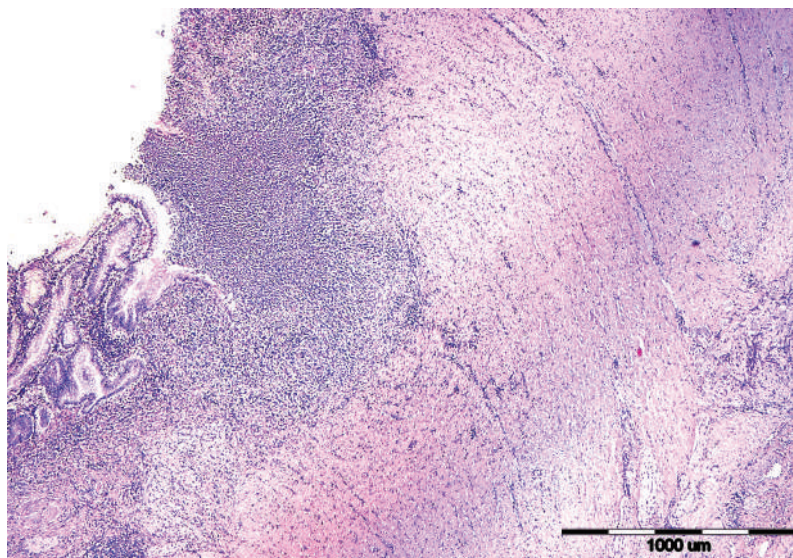
**Figure 2.** Throughout the submucosa and between the muscular layers of the muscularis, numerous well differentiated neuronal cell bodies were scattered. Hematoxylin and eosin (HE), objective magnification 10x. Inset: The neurons are uniform and well differentiated. Around the neurons are elongated Schwann cells. HE, 20x.

Histologic findings were consistent with ganglioneuromatosis and focally extensive, subacute intestinal ulcer.

The veterinarian submitting the tissue was contacted for follow-up at the time of writing of this manuscript (6 months after surgery). The dogs' recovery from surgery was uneventful, and the dog was doing well, without any therapy. Gastrointestinal signs reported at presentation ceased after surgical removal of the affected intestine.

So far, ganglioneuromatosis was reported predominantly in young dogs [5-7], rarely in adults [8,9]. The oldest reported dog with ganglioneuromatosis was 9 years old [8].

Our report shows that ganglioneuromatosis can also be encountered in older dogs, as our dog was 13 years old at the time of presentation.



**Figure 3.** Necrosis of the mucosal lining of the intestine (ulcer) extending to the circular layer of the muscularis. HE, 4x.

Radiographic or ultrasound examination may be useful in localizing the affected intestine, which is usually thickened due to accumulation of hyperplastic nerve cells [2,6]. Histologic examination of full thickness biopsy or completely excised affected tissue is required to make a definitive diagnosis of ganglioneuromatosis [6]. Immunohistochemical markers of nerve tissue (neurofilament protein, neuron-specific enolase and synaptophysin) can highlight ganglion cells and aid in diagnosis [6]. Diagnosis in this case was set based only on histology as the shelter caring for the dog declined immunohistochemical staining.

From the histologic findings and the clinical picture, it is not clear whether ganglioneuromatosis and the intestinal ulcer were associated lesions or presented independent pathology in the current dog. The intestinal ulcer was a localized lesion, and although presumably painful for the animal, was probably not the cause of intestinal signs, as only a small area of the intestine was affected. As the ganglioneuromatosis affected the whole intestinal biopsy of the intestine, we presumed that this was the primary cause of intestinal signs.

In summary, ganglioneuromatosis is a rare disorder of the gastrointestinal nervous system causing vomiting and diarrhea in dogs. Although a rare occurrence, this disorder should be considered as a differential diagnosis in dogs with diarrhea, when common infectious and neoplastic causes have been ruled out.

## Ethical approval

The conducted research is not related to animals use. No ethical approval was obtained because this study did not involve laboratory animals and only involved tissue obtained as a product of surgery used as treatment of the diseased animal.

## Authors' contributions

HD prepared the delivered surgically excised tissue for histologic examination, made gross pictures of the lesion, participated in histologic examination of the tissue and drafted the manuscript. GKA performed histologic examination of the tissue and set the diagnosis. HM participated in histologic examination of the sample and made histologic pictures of the lesion. All authors read and approved the final manuscript.

## Declaration of conflicting interests

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

## REFERENCES

1. D'Amore ESG, Manivel JC, Pettinato G, Niehans GG, Snover DC: Intestinal ganglioneuromatosis: mucosal and transmural types. A clinicopathologic and immunohistochemical study of six cases. *Hum Pathol* 1991, 22:276-286.
2. Higgins RJ, Bollen AW, Dickinson PJ, Sisó-Llonch S: Tumors of the Nervous System. In: *Tumors in Domestic Animals*, 5<sup>th</sup> ed. USA: Wiley-Blackwell, 2017, 856-858.
3. Shekitka KM, Sobin LH: Ganglioneuromas of the gastrointestinal tract. Relation to Von Recklinghausen disease and other multiple tumor syndromes. *Am J Surg Pathol* 1994, 18:250-257.
4. Thway K, Fisher C: Diffuse ganglioneuromatosis in small intestine associated with neurofibromatosis type 1. *Ann Pathol* 2009, 13:50-54.
5. Fairley RA, McEntee F: Colorectal Ganglioneuromatosis in a Young Female Dog (Lhasa Apso). *Vet Pathol* 1990, 27:206-207.
6. Hazell KLA, Reeves MP, Swift IM, Sullivan N: Small intestinal ganglioneuromatosis in a dog. *Aust Vet J* 2011, 89:15-18.
7. Bemelmans I, Küry S, Albaric O, Hordeaux J, Bertrand L, Nguyen F, Abadie J: Colorectal Hamartomatous Polyposis and Ganglioneuromatosis in a Dog. *Vet Pathol* 2012, 48(5):1012-1015.
8. Paris JK, McCandlish IAP, Schwarz T, Simpson JW, Smith SH: Small Intestinal Ganglioneuromatosis in a Dog. *J Comp Path* 2013, 148:323-328.
9. Ramírez GA, Altimira J, Vilafranca M: Ganglioneuromatosis of the Gallbladder in a Dog with Cholecystitis and Cholestasis. *J Comp Path* 2018, 163:29-32.

10. DeSchryver-Kecskemeti K, Clouse RE, Goldstein NM, Gersell D, O'Neal L: Intestinal ganglioneuromatosis. A manifestation of overproduction of nerve growth factor. *N Eng J Med* 1983, 308:635-639.
11. Lee NC, Norton JA: Multiple endocrine neoplasia type 2b: Genetic basis and clinical expression. *Surg Oncol* 2000, 9:111-118.
12. Qiao S, Iwashita T, Ichihara M, Murakumo Y, Yamaguchi A, Isogai M, Sakata K, Takahashi M: Increased expression of glial cell line-derived neurotrophic factor and neurturin in a case of colon adenocarcinoma associated with diffuse ganglioneuromatosis. *Clin Neuropathol* 2009, 28:105-112.
13. O'Donnell AM, Puri P: A role for PTEN in paediatric intestinal dysmotility disorders. *Pediatr Surg Int* 2011,27:491-493.

## **GANGLIONEUROMATOZA TANKIH CREVA PRAĆENA ULCERACIJOM KOD PSA STAROG 13 GODINA**

HUBER Doroteja, GUDAN KURILJ Andrea, HOHŠTETER Marko

Ganglioneuromatoza je redak poremećaj koji se karakteriše hiperplazijom intestinalnih ganglija uključujući mijenterični pleksus i intestinalne nervne strukture. Ovaj se poremećaj uopšteno opisuje kod dece, međutim sporadični slučajevi mogu da se nađu i kod odraslih ljudi. Većinom se slučajevi kod ljudi nalaze u kolonu i u rektumu. Poremećaj je opisan i kod pasa, uglavnom kod mladih jedinki, a retko se sreće kod odraslih životinja pri čemu je poremećaj primećen kod najstarijeg psa koji je imao 9 godina.

Predstavljen je prvi slučaj kod starijeg psa u Hrvatskoj, kuje starosti 13 godina, mešanac kod koje je u anamnezi navedena dijareja i gubitak telesne mase. Ultrazvučnim pregledom uočene su naglašena fokalna zadebljanja tankih creva. Promenjeni segmenti creva, dimenzije 7 mm x 20 mm, uklonjeni su laparatomijom. Uzorci uklonjenih tkiva su poslani na histopatološku analizu. Patomorfološki, uočeno je cirkumferentno povećanje debljine crevnog zida, beličaste boje. Mikroskopskim pregledom, uočena je difuzna hiperplazija mijenteričnih submukoznih pleksusa. Fokalno, u promenjenim tkivima evidentno je bilo prisustvo subakutnog ulcera, koji najverovatnije nije bio uzrok promena u intestinalnom traktu s obzirom da se radi o lokalizovanoj promeni, dok je ganglioneuromatoza bila u vidu difuzne lezije promenjenog tkiva.

Do sada, ganglioneuromatoza je opisivana kod mladih pasa, a retko kod odraslih životinja. Naš rad ukazuje da ganglioneuromatoza može da se nađe i kod starijih pasa. Iako promena koja je prikazana predstavlja redak nalaz, ipak treba da se uvrsti u diferencijalnu dijagnozu kod pasa kod kojih su isključena infektivna oboljenja i neoplazije, a kod kojih postoji dijareja.