A Thesis
For the Degree of Master of Veterinary Medicine

# The First Case of Cecal Malignant Peripheral Nerve Sheath Tumor in a Dog

Department of Veterinary Medicine
GRADUATE SCHOOL
JEJU NATIONAL UNIVERSITY

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Abstract

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A 12-year-old mixed-breed dog presented with a 2-month history of abdominal distension. Radiographic examination, abdominal ultrasonography and computed tomography revealed a mass in the cecum (15.0 × 11.9 × 4.5 cm). The cecal mass was surgically removed and examined histopathologically. Immunohistochemically, the neoplastic cells expressed S-100 and neuron specific enolase but not α-smooth muscle actin and CD117 (c-kit). These histologic and immunohistochemical features indicated that the mass was consistent with a malignant peripheral nerve sheath tumor (MPNST). In dogs, most MPNSTs arise from the brachial plexus, spinal nerve root, and skin of the extremities. However, gastrointestinal MPNSTs in dogs have not been described previously. To the best of my knowledge, this is the first report to describe cecal MPNST in a dog. MPNST might be included in differential diagnostic lists of gastrointestinal mass.

***Key words:*** cecal mass, dog, gastrointestinal mass, immunohistochemistry, malignant peripheral nerve sheath tumor.

# Contents

# I. Introduction

Peripheral nerve sheath tumors (PNSTs) are generally classified as soft tissue tumors that usually arise from Schwann cells, perineural cells, fibroblasts, or other cells comprising the nerve sheaths. PNSTs may be subdivided into benign and malignant PNST (MPNST) variants [24]. Schwannomas and neurofibromas are the most common types of human benign PNSTs. Most MPNSTs in humans are localized in the trunk, head, neck, extremities, and paravertebral regions. [12, 24] MPNSTs of the gastrointestinal tract are rare [12]. Only 6 cases were observed to originate from the colon, and MPNST of the cecum has not been reported previously to my knowledge [17]. The relationship between MPNST and neurofibromatosis 1 (NF1) is well known in humans. Neurofibromatosis is an autosomal dominant disorder, and up to 50% of MPNSTs are associated with NF1. NF1-related MPNSTs reportedly have a worse prognosis than non-NF1- related MPNST [5, 6, 11, 25].

In dogs, most MPNSTs arise from the brachial plexus, spinal nerve root, and skin of the extremities [4, 8, 23]. Canine MPNSTs have also been reported in other uncommon sites, such as the liver, spleen, adrenal gland, bladder, and diaphragm [1, 7, 10, 14, 15]. Two cases of benign PNSTs in the gastrointestinal tract were reported previously [21]. However, gastrointestinal MPNSTs in dogs have not been described previously. To the best of my knowledge, this is the first report of MPNST originating from the cecum in a dog.

# II. Materials and Methods

## *Patient*

A 12-year-old 5.6 kg neutered male mixed-breed dog with a 2-month history of abdominal distension was presented to the Veterinary Medical Teaching Hospital, College of Veterinary Medicine, Jeju National University in the Republic of Korea. Physical examination revealed a body condition score of 4/9, and the abdomen was markedly distended.

## *Laboratory examination*

Laboratory evaluations included a complete blood count (CBC) (Advia 2120i; Siemens, Erlangen, Germany), assessment of serum chemistry (Vetscan; Abaxis, CA, USA) and PT and APTT were evaluated using an automated coagulation analyzer (VetScan VSpro; Abaxis).

## *Imagimg examination*

The abdominal and thoracic radiographs were obtained using digital radiographic equipment (Listem, Seoul, Korea). Abdominal mass were evaluated by ultrasonography (Philips, Bothell, WA, USA) and Computed tomography (Somatom Emotion; Siemens).

*Pathologic examinations*

Tissue samples were stained with hematoxylin and eosin and immunochemistry at the laboratory of Veterinary Pathology in Jeju National University. For immunohistochemical analysis, a panel of 4 antibodies, including S-100 (DAKO, Denmark), neuron specific enolase (NSE; DAKO), α-smooth muscle actin (α-SMA; DAKO) and CD117 (c-kit; DAKO).

# III. Results

The biochemical profile and complete blood count were normal. On the radiographic view, a large, round, soft tissue opaque mass was visualized in the ventral abdomen, and it was difficult to make the evaluation of the dorsocaudal part of the abdomen (Fig. 1). Abdominal ultrasonography revealed a large, heterogeneous echotexture mass (Fig. 2). Ultrasound-guided fine-needle aspiration of the abdominal mass revealed low cellularity with mesenchymal cells. Preoperative and post-contrast-enhanced computed tomography of the abdomen was performed for surgical planning.

A soft tissue-attenuating large mass (15.0 × 11.9 × 4.5 cm) was noted within the middle of the abdomen. A segment presumed to be the cecum was embedded from the back to the inside of the mass, which had relatively distinct margins (Fig. 3). An exploratory laparotomy was performed for diagnostic and therapeutic purposes. The dog was premedicated with 0.2 mg/kg intravenous midazolam (Bukwang Midazolam; Bukwang Pharm, Seoul, Korea) and anesthetic induction was achieved by injecting 6 mg/kg propofol (Anepol; Hana Pharm, Seoul, Korea) intravenously; it was maintained with isoflurane and oxygen (1.5-1.8% concentration of isoflurane in oxygen). A large, firm, and well-circumscribed round cecal mass weighing approximately 1.6 kg (approximately 28% of the body mass) was surgically resected (Fig. 4A) and submitted for histopathology. The samples were routinely processed for histopathology and stained with hematoxylin and eosin. The mass consisted of a papulation of neoplastic spindle cells present in the interwoven bundle that formed a herringbone pattern (Fig. 4B). Neoplastic cells exhibited hyperchromatic nuclei, and mild nuclear pleomorphism. Mitotic figures counted

in 10 high power fields (2.37 $mm^2$) (diameter of the field of view = 0.55 mm; 40× objective and 10× ocular field number (FN) 22 mm; Olympus BX43 microscope) were 0-1.

Immunohistochemically, the neoplastic cells were positive for S-100 and NSE and negative for α-SMA and CD117 (c-kit). Based on these histopathologic and immunohistochemical features, the mass was diagnosed as a malignant neoplasm of peripheral nerve sheath origin (Fig. 5 A-D). The dog was discharged from the hospital 9 days postoperatively. Further adjuvant chemotherapy and recheck ultrasonography for the cecum tumor were proposed but declined by the owner. The dog remained well for more than 400 days, however, died 478 days after surgery due to tumor recurrence.

# IV. Discussion

Gastrointestinal MPNSTs are rarely reported in cats, and only two cases have been reported to my knowledge [2, 18]. Ribas *et al.* reported a small intestinal MPNST without metastasis in a 5-year-old female spayed chinchilla cat that was treated with complete surgical excision. The cat remained free from clinical signs for up to six months [18]. Boland *et al.* described a colonic MPNST with hepatic metastasis in a 14-year-old male neutered domestic medium-hair cat that was treated with surgical resection and metronomic cyclophosphamide. The cat experienced recurrence, and post-mortem examination identified MPNST within the kidneys and liver 18 months postoperatively [2].

The diagnosis of MPNST is often difficult. because it is a diverse group of heterogeneous neoplasms. Histologically, MPNST are usually highly infiltrative lesions composed of pleomorphic spindle cells with ovoid or fusiform cells mostly arranged in interwoven bundles, palisades and whorls. [19, 20]. Immunohistochemistry is mainly used to confirm the neural origin and exclude other possible spindle cell tumors. But It has not yet been a clear diagnostic criteria for MPNST. S-100, NSE, Vimentin, nerve growth factor receptor (NGFR) and oligodendrocyte transcription factor 2 (Olig2) were suggested as MPNST markers [7, 20]. Although I could not perform immunohistochemistry using more neurologic markers such as vimentin, NGFR or Olig2 [7, 20], expression levels of S-100 protein and NSE which are highly related to neural-derived neoplasia [8, 13] were evaluated in this study. In addition, different markers are used to exclude other possible non-angiogenic, non-lymphogenic intestinal mesenchymal tumors [13]. α-SMA and desmin are used to rule out smooth muscle tumors, whereas CD117

(c-kit) and CD34 are used to rule out gastrointestinal stromal tumors [2, 8, 18, 20]. In this case, I observed positivity for S-100 protein and NSE and negativity for c-kit and α-SMA.

Current treatment of MPNST in humans is similar to that of soft tissue sarcomas (STS). Complete surgical excision with wide negative margins is treatment of choice [9, 16]. The role of adjuvant radiotherapy and chemotherapy remains controversial. However, postoperative radiotherapy is often recommended to improve local control, especially after incomplete resection. No randomized trials have assessed the efficacy of specific adjuvant chemotherapy in MPNST [5, 6, 16, 17, 24]. However, Kroep *et al.* compared chemotherapy for MPNST and other STSs and reported similar outcomes. The retrospective data from 12 pooled trials indicated that a doxorubicin-ifosfamide combination was associated with a lower risk of relapse and better response rate [9]. Wang *et al.* reported that a patient with multiple metastatic NF-1 related MPNSTs was administered combination chemotherapy with ifosfamide, carboplatin, and etoposide, known as ICE chemotherapy after the primary lesion was resected. It has been 12 years since his first visit, and he remains disease-free [25]. Chaudhary and Borker described a case of a 10-year-old male dog with MPNST with NF-1 who achieved a complete response to metronomic therapy with etoposide, cyclophosphamide, and prednisolone [5].

Only a few instances of metronomic therapy as MPNST treatment have been reported for dogs and cats. Metronomic therapy with cyclophosphamide and piroxicam delays recurrence in dogs after incomplete surgical excision [3, 22]. In addition, in a cat with colonic MPNST treated with surgery and metronomic cyclophosphamide, clinical signs recurred 18 months postoperatively [2]. However, the optimal treatment for gastrointestinal MPNST remains poorly established due to its rare occurrence.

# V. Clinical relevance

To my knowledge, this is the first reported case of cecum MPNST in a dog. The dog remained free of clinical signs for 12 months postoperatively without adjuvant chemotherapy.

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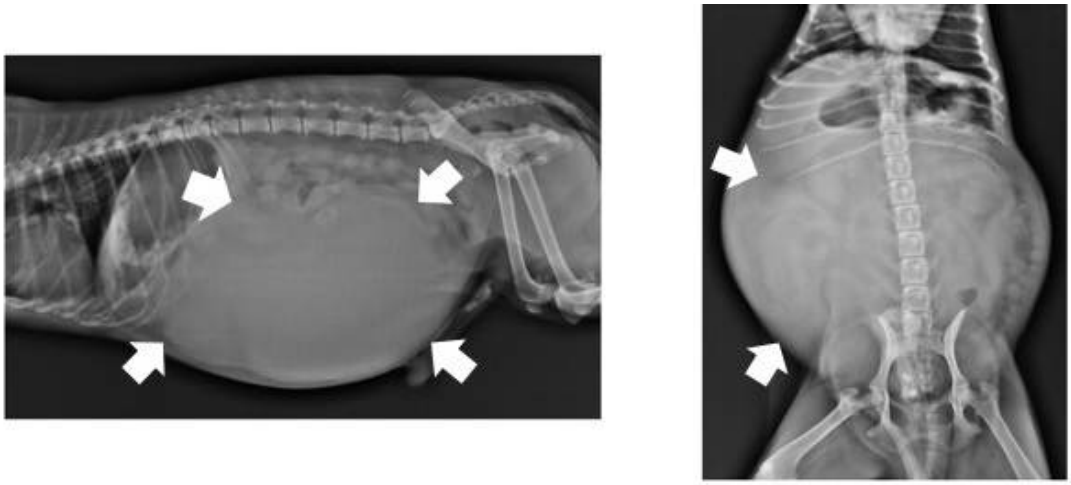

**Fig. 1. Radiographic images of the right lateral view and dorso-ventral view.** A large, round, soft tissue opaque mass (white arrow) was visualized in the ventral abdomen.

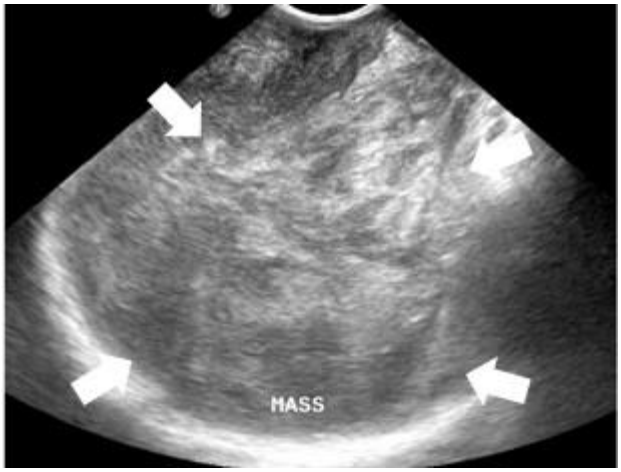


**Fig. 2. Sagittal ultrasound image of the mass.** Abdominal ultrasonography revealed a large, heterogeneous echotexture mass (white arrow).

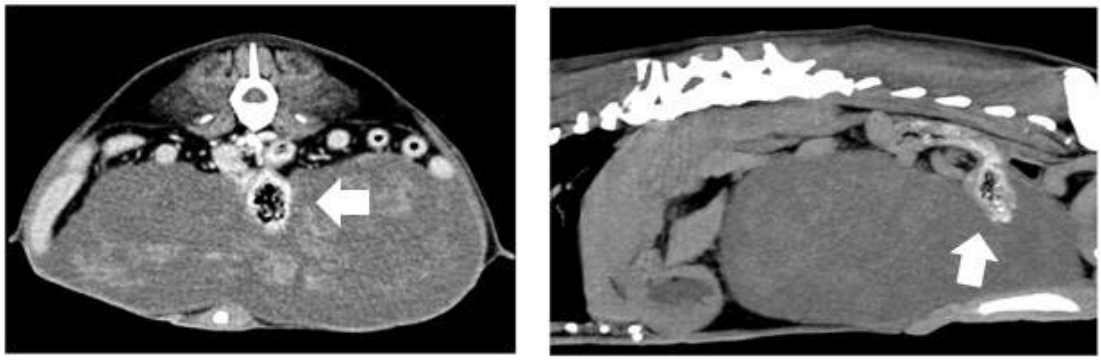

**Fig. 3. Computed tomography of the transverse and sagittal view fo the abdomen.** A soft tissue-attenuating large mass (15.0 × 11.9 × 4.5 cm) was noted within the middle of the abdomen. A segment presumed to be the cecum (white arrow) was embedded from the back to the inside of the mass.

A B

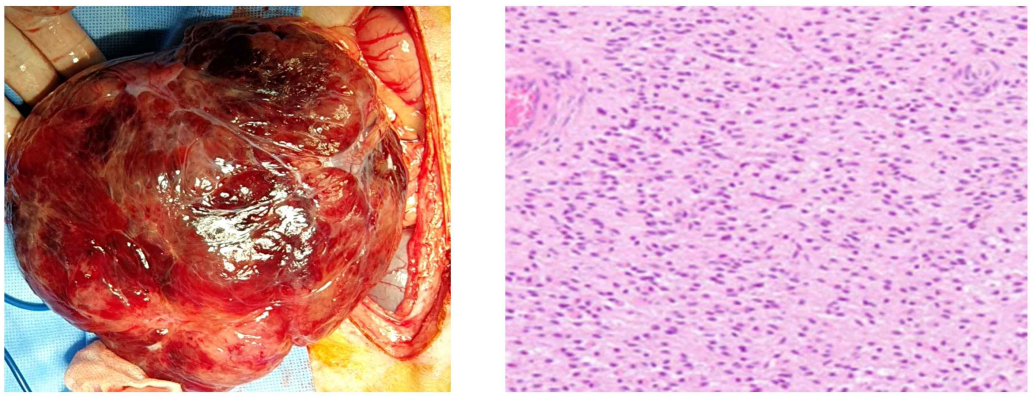

**Fig. 4. Intraoperative image of the cecal mass and histopathology with hematoxylin and eosin staning of the mass.** (A) A large, firm, and well-circumscribed round cecal mass weighing approximately 28% of the body mass. (B) The mass consisted of a papulation of neoplastic spindle cells present in the interwoven bundle that formed a herringbone pattern (× 200).

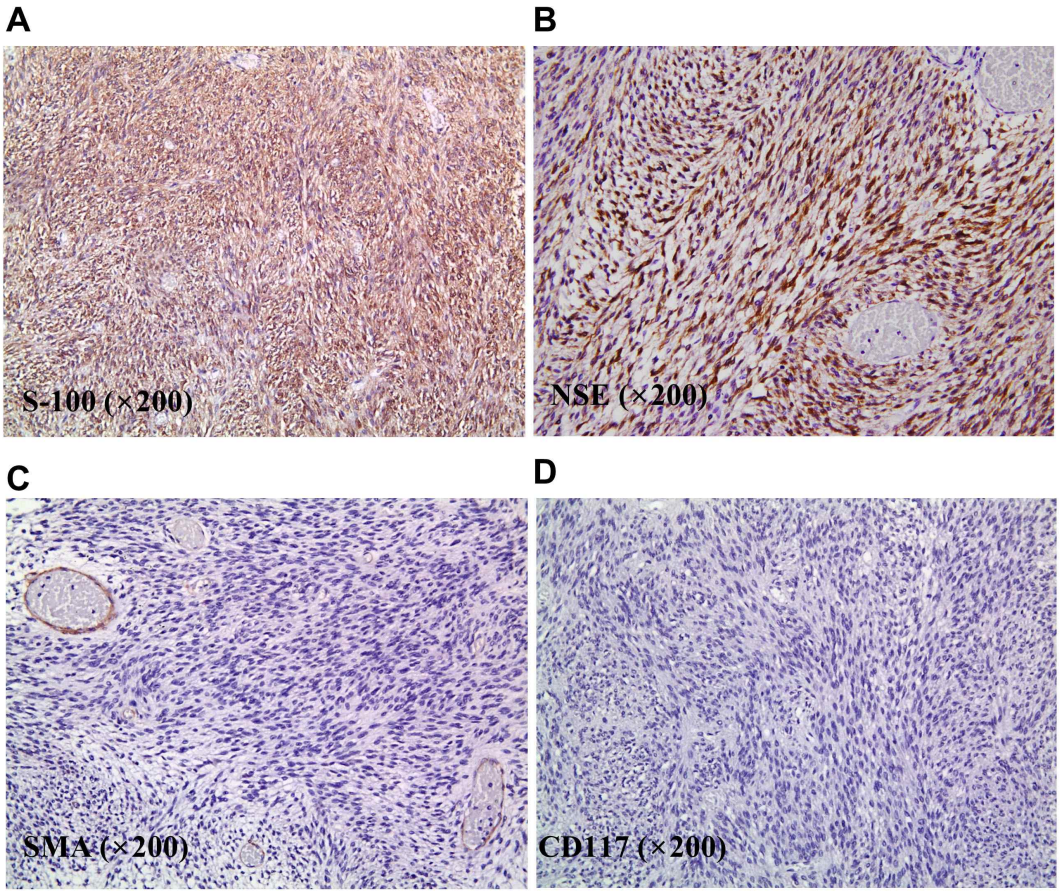


**Fig. 5. Immunohistochemical staining of the neoplastic cells in the tumor (× 200).** The neoplastic cells are positive for (A) S-100, (B) neuron specific enolase, and (C) negative for α-smooth muscle actin, and (D) CD117.

국문 초록

# 개의 맹장유래 악성 말초신경집 종양의 첫 증례

안혜린

(지도교수: 송우진)

제주대학교 대학원 수의학과

12살 잡종견이 2달간의 복부 팽만을 주증상으로 내원하였고 방사선검사, 복부 초음파 및 CT 촬영을 통해 맹장 종괴를 확인하였다. 맹장 종괴를 수술적으로 제거하고 조직병리학적 검사를 수행하였다. 맹장 종괴를 구성하는 방추형의 종양세포들에 대한 면역조직화학 염색 결과 S-100, neuron specific enolase는 양성, α-smooth muscle actin, CD117 (c-kit)은 음성을 나타내었다. 면역조직화학적 특징을 토대로 맹장 종괴는 악성 말초신경집 종양으로 진단하였다. 개에서 대부분의 악성 말초신경집 종양은 상완신경총, 척수 신경 뿌리, 사지의 피부에서 발생하지만 개에서 위장관 유래 악성 말초신경집 종양은 아직까지 보고된 바 없다. 이 논문은 개의 맹장에서 유래한 악성 말초신경집 종양의 첫 번째 증례 보고이다. 따라서 개의 위장관 내 종괴가 발생하였을 경우 악성 말초신경집 종양도 감별 진단 대상 종양으로 고려되어야 할 것으로 사료된다.

***Key words:*** 개, 맹장종괴, 면역조직화학 염색법, 악성 말초신경집종양, 위장관 종괴