

Case Report

J Vet Intern Med 2016;30:647–652**Intraparenchymal Spinal Cord Ganglioneuroblastoma Originating from the Peripheral Sympathetic Nervous System in a Cat**

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Key words: Feline; Oncology-diagnosis; Neuroimaging; Neurology; Neurosurgery.

A 12-year-old castrated male mixed breed cat was presented to the University of Illinois Veterinary Teaching Hospital oncology service for evaluation of a progressive gait abnormality of 4 months duration. The referring veterinarian identified radiographic evidence of vertebral lysis before referral. Initial physical examination indicated a slightly overweight (body condition score [BCS] 7/9; 4.8 kg) cat with a systolic sternal grade III/VI heart murmur, with all other findings being normal. Computed tomography^a identified a large, mildly enhancing, expansile, soft tissue attenuating lesion within the vertebral canal of L5, L6, and L7 vertebral bodies (Fig 1). The expansile nature of the mass was evident by the circumferentially widened vertebral canal of L6 and L7, with moderate distortion, and thinning of the pedicles and dorsal lamina. The mass could be seen exiting a markedly widened left L7-S1 intervertebral foramen and extending ventral to the sacrum as the L7 left spinal nerve. It tapered to an abnormal size as it crossed the ischial body forming the sciatic nerve. Inspection of the left gluteal muscles showed moderate atrophy compared to the contralateral pelvic limb.

Eight days after the initial CT study, the cat was referred to the neurology service for further evaluation and diagnostic testing. The neurologic examination showed evidence of a plantigrade stance in the pelvic limbs (left more severe than the right) and mild paraparesis in the pelvic limbs bilaterally. The cat had proprioceptive deficits in the left pelvic limb with a decreased withdrawal reflex on the left and mild to moderate pelvic limb muscle atrophy. A large bladder was palpated. No other abnormalities were observed on neurologic examination. A neurolocalization of some combination of spinal cord segments, nerve roots and

Abbreviations:

BCS	body condition score
CT	computed tomography
FNA	fine needle aspirate
GFAP	glial fibrillary acidic protein
GNB	ganglioneuroblastoma
GN	ganglioneuroma
HPF	high power field
IHC	immunohistochemistry
MRI	magnetic resonance imaging
NPY	neuropeptide Y
STIR	short tau inversion recovery
TH	tyrosine hydroxylase

nerves of L4-S3 (left lateralized) was suspected. Based on the CT findings, neoplasia was the most likely differential diagnosis with peripheral nerve sheath tumor or round cell neoplasia considered most likely. The cat was prepared and anesthetized for the magnetic resonance imaging (MRI)^b; imaging included T2-weighted, T1-weighted and Short tau inversion recovery (STIR) sequences in all 3 planes, as well as repeated T1-weighted sequences following contrast administration. Magnetic resonance imaging (MRI) confirmed the mass extended from the midvertebral canal of L5 to the L7 spinal nerve root entering the pelvic canal (Figs 2, 3, 4A), with similar expansile changes to the L6 and L7 vertebral bodies. The mass lesion was homogenous and hyperintense on T2-weighted and STIR sequences compared to normal spinal cord seen cranial to L5 (Figs 2, 3). The mass was isointense on T1-weighted sequences with strong homogenous contrast enhancement (Fig 4A,B). The mass obliterated the cauda equina which was only identified caudal to the lumbosacral junction. It also had indistinct margins and displacement of the conus medullaris. A mixed intradural and infiltrative parenchymal mass was diagnosed.

Concurrent thickening and contrast enhancement of the urinary bladder was identified that had not been appreciated on the initial CT scan. Based on the imaging characteristics, the differential diagnoses included a peripheral nerve sheath tumor or round cell neoplasia, such as lymphoma or histiocytic sarcoma. Neuritis was considered less likely given the marked expansile nature of the lesion. The findings also suggested a neurogenic bladder and suspected disruption of colonic innervation causing fecal retention. However, the owner reported the cat to have normal urination and defecation at home.

The next week, the cat was admitted to the neurology service for surgical biopsy and subtotal resection of the

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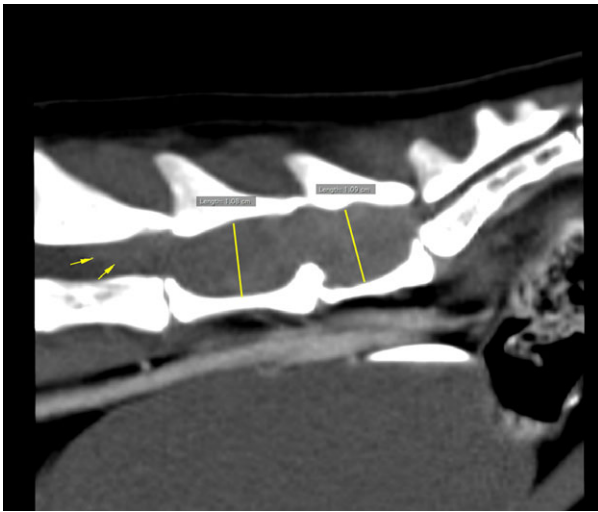


Fig 1. Sagittal CT image performed before surgical excision. Note the expansile widening of the L6 (1.08 cm) and L7 (1.9 cm) vertebral canal. The arrows highlight the cranial extent of the contrast-enhancing invasive mass lesion.

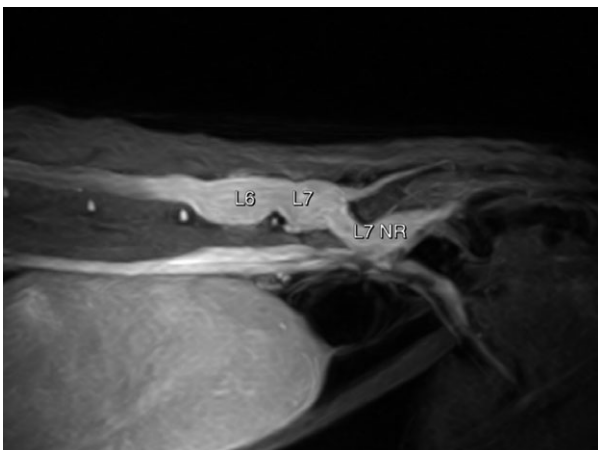


Fig 2. Sagittal STIR maximum intensity projection MR image of the lumbosacral region. The mass lesion can be seen entering via the L7 nerve root, and expanding the L6 and L7 vertebral canal.

spinal tumor. It was premedicated with dexmedetomidine and methadone, induced with propofol, and maintained on isoflurane, ketamine, and fentanyl throughout the procedure. A dorsal laminectomy was performed from the midbody L5 to the cranial aspect of L7 to provide access to the spinal canal, where the mass was identified and biopsy samples were taken for intraoperative analysis. Surgical debulking continued after receipt of intraoperative cytology results, which failed to show evidence of a round cell tumor. Intraoperatively, the mass appeared greyish pink in color and was located extradurally. Although a clear distinction could be made between the mass and surrounding normal neural tissue, the mass was friable and could not be removed completely. The majority of the mass located within the spinal canal was removed, but normal mar-

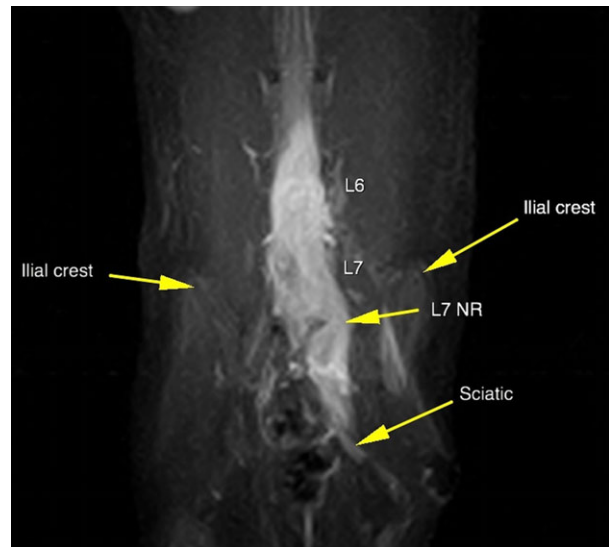


Fig 3. Dorsal STIR MR image showing the hyperintense mass lesion and extension.

gins could not be obtained. The caudal aspect of the tumor was not removed because of the very thin vertebral bone of L7 and the high risk of fracture or destabilization of the spine. The portion of the mass that extended ventrally along the left nerve root was not removed.

In the 3 weeks immediately after discharge, the owner reported that the cat exhibited noticeable improvement in neurologic and motor function in the pelvic limbs and voluntary tail movement that previously had been absent. However, the owner also noted that urinary and fecal incontinence began approximately 10 days postoperatively. The cat was treated with bethanechol (1 mg/kg PO q24h) and diazepam (0.4 mg/kg PO q12h) for urinary incontinence.

Eight weeks after surgery, the cat was reevaluated by the oncology service for progressive weakness in the pelvic limbs. Physical examination identified ambulatory paraparesis, lack of rectal tone, moderate amounts of palpable hard fecal material in the colon, and a large bladder, indicative of detrusor muscle areflexia with intact innervation of the internal urinary sphincter. Aggressive regrowth of the tumor was suspected and a CT scan of the spine was repeated. The CT scan showed moderate dorsal expansion of the mass through the laminectomy site, with static mild contrast enhancement. Due to the aggressive behavior of the neoplasm, a 6-dose course of palliative radiation therapy was initiated to slow tumor progression.

Four months after surgical removal and after the third round of palliative radiation therapy, the cat was presented to the emergency service for multiple episodes of vomiting and diarrhea. Abdominal ultrasound examination was performed, with no evidence of metastatic disease, and no overt explanation for the presenting signs. A CT scan (Fig 5) was performed to monitor neoplastic progression. The mass had extended cranially to cause mild to moderate expansile deformation to the

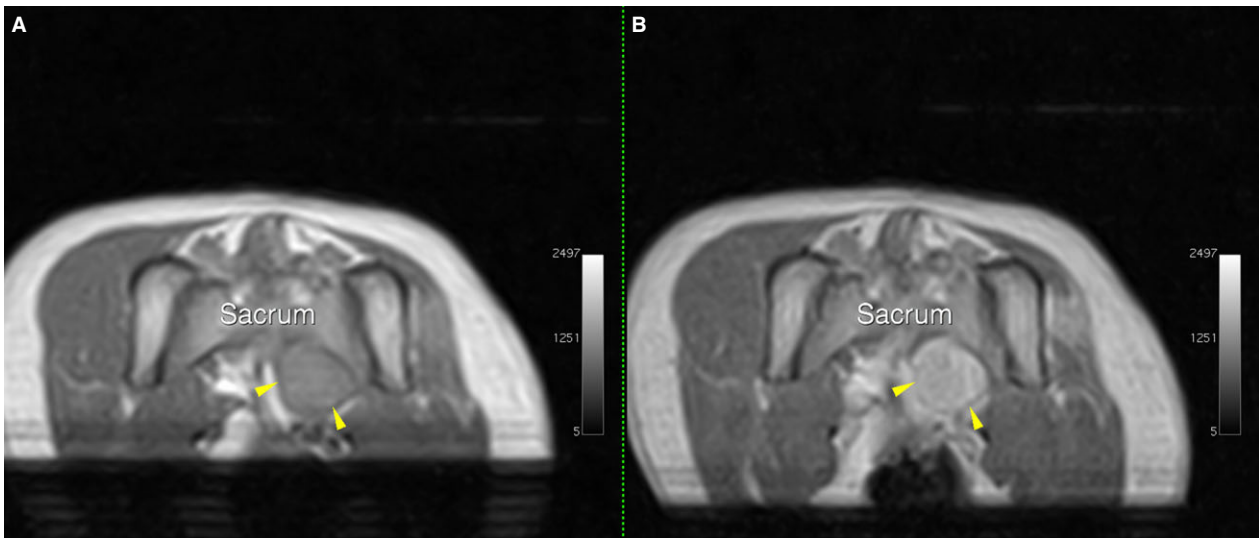


Fig 4. (A) Transverse T1-weighted precontrast MR image at the level of the sacrum showing the cross-sectional dimension of the mass lesion (arrowheads). (B) Transverse T1-weighted postcontrast MR image at the level of the sacrum showing strong homogeneous contrast enhancement of the mass lesion.

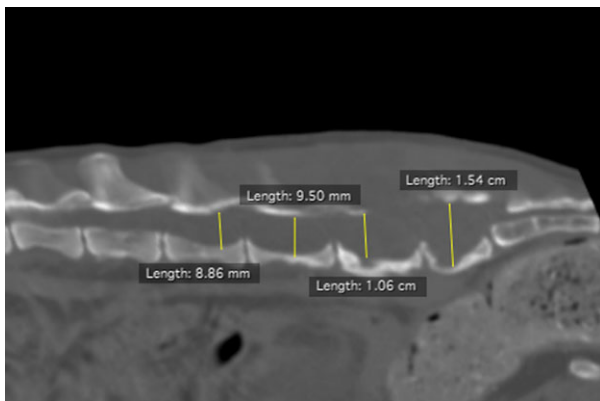


Fig 5. Sagittal CT image performed 4 months after surgical excision. Note the progressive cranial extension and associated vertebral canal widening involving vertebral bodies L4 and L5. There is continued bony destruction at the original sites of L6 and L7.

L4 and L5 vertebral canals. It also was invading the epaxial muscles dorsally with a thin peripheral contrast-enhancing rim. Additional lysis was seen affecting the L6 and L7 vertebral bodies ventral to the mass lesion. In addition to the already widened left L7 intervertebral foramen, widening of the left L6 foramen also was now present.

The cat was last evaluated 6 months postsurgery after completion of the palliative radiation therapy protocol. The owner reported that within the previous week, the cat had been moving around the house less frequently and was generally quieter at home. On neurological examination, the cat was mentally quiet, paraplegic with marked muscle atrophy of the pelvic limbs and had urinary and fecal incontinence. Because of continued deterioration of quality of life, the clients elected euthanasia by the referring veterinarian (7 months postsurgery).

The cat was not available for necropsy and postmortem histopathology.

Tissue samples from the surgical site were used for impression smears and stained with Giemsa, or fixed in formalin, paraffin embedded, and tissue sections stained with hematoxylin and eosin or used for immunohistochemistry (IHC). Histologically, neoplastic cells invaded nerves in the spinal canal (Fig 6A, stars), neoplastic cells were arranged in densely but variably cellular sheets and often grouped in small clusters separated by a variably thick eosinophilic stroma (Fig 6B). Cells were round to polygonal, with abundant basophilic cytoplasm and an eosinophilic paranuclear area (Fig 6B, arrows). Nuclei were round and large with finely stippled chromatin and large prominent nucleolus. Anisocytosis and anisokaryosis were moderate, with up to 3 mitoses per high power field (HPF) and frequent apoptotic cells. On impression smears, neoplastic cells had very similar features (Fig 6C).

Neoplastic cells showed a strong positive cytoplasmic labeling for synaptophysin (Fig 6D), BIII tubulin (Fig 6E) and were negative for both glial fibrillary acidic protein (GFAP); (Fig 6F), and chromogranin A (Fig 6G). The histological and cytological features and IHC results supported neoplasia with neuronal differentiation (Table 1) with ganglion cell differentiation without glial elements (ganglioneuroma [GN] or ganglioneuroblastoma [GNB]). Based on evidence of malignancy (tissue invasion, apoptosis, mitosis) the tumor was classified as a GNB. Analysis of sympathetic nervous system neuronal markers indicated that the neoplastic cells were positive for tyrosine hydroxylase (Fig 7G) and neuropeptide Y (Fig 7H) and negative for NeuN (Fig 7I) as were the sympathetic nervous ganglia from a control cat (Fig 7D,E,F). On the other hand, a dorsal root ganglion (and a spinal cord sample, data not shown) from a control cat were

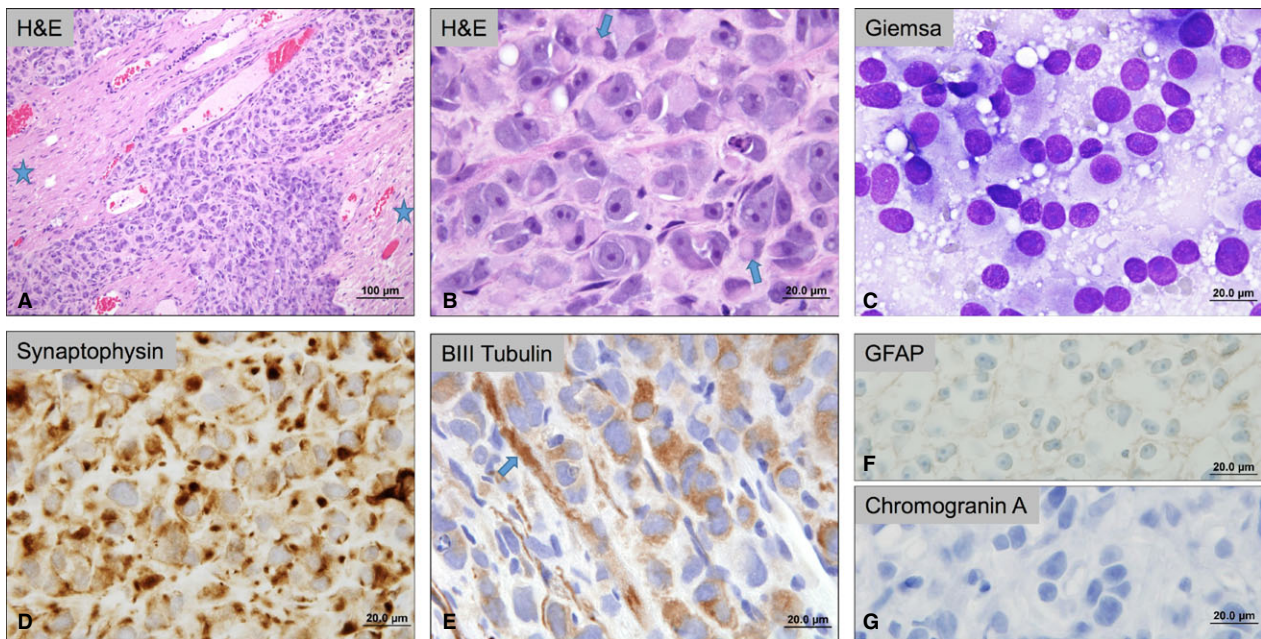


Fig 6. (A) Neoplastic cells invade nerve bundles (H&E staining); (B) Neoplastic cells at higher magnification (H&E staining); (C) Impression smear stained with Giemsa; (D) Neoplastic cells are strongly positive for Synaptophysin; (E) Neoplastic cells also are positive for BIII tubulin that also labels remaining axons (arrow); (F & G) Neoplastic cells are negative for both GFAP and Chromogranin A.

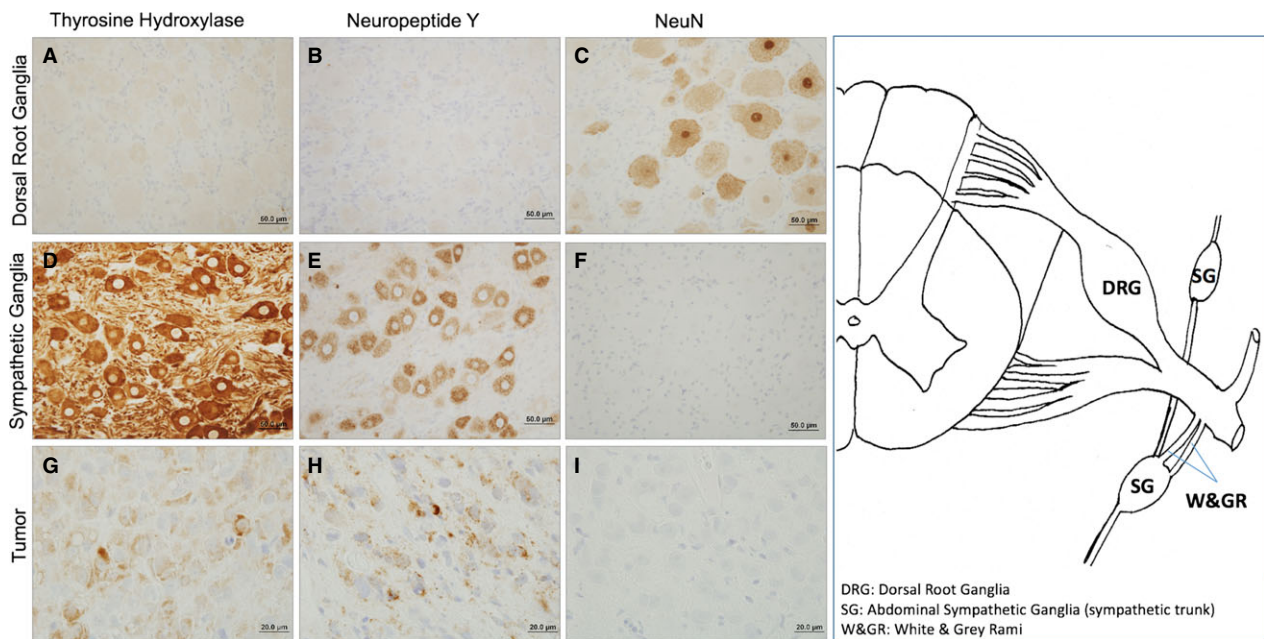


Fig 7. Tyrosine Hydroxylase, Neuropeptide Y, and NeuN staining characteristics of normal dorsal root ganglia cells (first row), and sympathetic ganglia cells (second row) from a control cat, and tumor cells (third row).

positive for NeuN (Fig 7C) and negative for both tyrosine hydroxylase (Fig 7A) and neuropeptide Y (Fig 7B). Interestingly, GNs usually are positive for NeuN, but neurons of the sympathetic nervous system are negative for this marker,¹ reinforcing the hypothesis that this tumor originated from the sympathetic nervous system.

A spinal cord paraganglioma could have been suspected in the lumbar spinal cord as previously described,² but the histopathology and IHC findings support a ganglioneuroblastoma likely originating from the abdominal sympathetic chain. A neuroendocrine pattern would be expected in a paraganglioma³ as well as positivity for chromogranin A (Table 1).

Table 1. Features of neuronal and mixed neuronal-glial tumors^{19,20}

Tumors	Histological Features	Main IHC Markers
Ganglioneuroma	Irregular groups of large neurons often multipolar with dysplastic features (peripheralized Nissl substance)	SYN, NeuN, NSE, NeuroF, BIII Tubulin
Ganglioglioma	Same as ganglioneuroma admixed glial cells elements (reactive or neoplastic)	SYN, NeuN, NSE, NeuroF, BIII Tubulin GFAP for the glial cell population
Ganglioneuroblastoma	Embryonic tumor composed of undifferentiated or poorly differentiated neuroepithelial cells admixed ganglion cells	SYN, NeuN, NSE, NeuroF, BIII Tubulin GFAP (±)
Neuroblastoma (Primitive neuro-ectodermal tumors)	Embryonic tumor composed of small undifferentiated or poorly differentiated neuroepithelial cells	SYN, NeuN, NSE, NeuroF, BIII Tubulin GFAP (±)
Neurocytoma	Uniform small round cells with some neuroendocrine pattern, sometimes with rosettes or pseudorosettes, and with areas fibrillary areas mimicking the neuropil	SYN, NeuN, NSE
Paraganglioma	Islands, nests or small cords of small/medium size, polygonal to round uniform cells surrounded by a regular delicate capillary network (neuroendocrine pattern) May contain mature ganglion cells—large neurons—gangliocytic paragangliomas	SYN, NSE, NeuroF, CgA. GFAP for interstitial cells (Sustentacular cells)

CgA, chromogranin A; GFAP, glial fibrillary acidic protein; NeuroF, neurofilaments; NSE, neuron specific enolase; CNS, central nervous system; SYN, synaptophysin.

Ganglioneuromas, ganglioneuromatosis and GNBs are rare tumors in veterinary patients and have been reported in the literature in both dogs⁴⁻⁸ and in cats⁹⁻¹¹. Today, however, there has yet to be a published report of a GNB with histologic evidence of sympathetic differentiation or origin, such as in this case. Ganglioneuromas generally are benign in nature, consisting of ganglion cells and neurofibrils in a fibrous connective tissue stroma¹² with reports of intestinal or cardiac occurrence in cats.^{9,10} Spinal involvement of GN previously has been reported in a dog,⁸ but that neoplasm involved the cervical spine and was amenable to surgical resection with benign biologic behavior. In contrast to the majority of reported occurrences of GN, the neoplasm in the cat of our report had characteristics that strongly suggest malignancy, such as the CT and MRI findings of the aggressive and expansile invasion of the spinal canal, subsequent vertebral lysis and extreme dilatation of the left sided L7-S1 intervertebral foramen. Moreover, rapid tumor regrowth and recurrence of neurologic clinical signs leading to bilateral pelvic limb paresis in a matter of weeks after surgical debulking all support the aggressive nature of this tumor. Although the inability to completely excise the tumor with clean margins likely contributed to the recurrence of the tumor and clinical signs, the rapid decline of neurologic function after a brief postoperative period of improvement as well as the continuation of expansile changes to the vertebral canal cranially to L4 are suggestive of malignancy. Finally, this tumor was classified as a GNB, the malignant counterpart of the GN.

In humans, peripheral neuroblastic tumors include neuroblastomas, GNBs, and GN; these tumors are very rare and belong to the neuroblastoma group. Ganglioneuromas are considered benign tumors that develop from the autonomic nerve cells and most commonly arise in the paravertebral sympathetic chains,

from the cervical to pelvic areas or in the adrenal glands. Paravertebral GN in humans also can invade the spinal canal. Their malignant counterparts, GNBs, present with features of malignancy including less differentiated neuronal cells, mitoses, necrosis, tissue invasion, metastases, or some combination of these findings. These tumors are extremely rare.^{13,14}

Despite the initial suspicion of a peripheral nerve sheath tumor, the CT and MRI findings allowed for the hypothesized origin of the tumor in the abdominal sympathetic trunk ganglia that courses along the vertebral muscles, with subsequent spinal cord invasion. The patient's urinary incontinence and exceedingly large bladder as noted on physical examinations and observed on MRI (Fig 1A) likely resulted from involvement of the lower motor neuron segments of the pelvic nerve leading to detrusor muscle dysfunction, inability to urinate, and consequent overfilling of the urinary bladder.

The IHC results, including the positive tyrosine hydroxylase and neuropeptide Y staining, associated with negative NeuN staining strongly support the hypothesis that this neoplasm originated in the sympathetic ganglia. An alternative hypothesis is that during embryogenesis, neuronal sympathetic precursors migrated abnormally into the spinal cord, and transformed into a neoplasm later in life. However, the advanced age of the cat and the sudden onset of neurologic clinical signs suggest that the neoplasm was not embryonal in nature. A recently published case report of a GN in the urinary bladder of an 11-year-old dog⁴ and the previously mentioned cardiac GN in a 12-year cat⁹ are similar in late-stage presentation. Had these occurrences of GN been present throughout embryonic development and early-stage life, onset of clinical signs would be expected at a younger age, as described for primitive neuroectodermal tumors (eg, medulloblastomas). Published case reports show a predilection of

young patients for intestinal GN and ganglioneuromatosis,^{7,10,15} affected patient range in age from 6 weeks to 18-months, with a recent case report of intestinal ganglioneuromatosis in a 9-year-old dog¹⁶ being an exception to the general trend. A larger sample size would be necessary to provide a definitive age correlation. The malignant counterpart of the GN identified in this case report, GNB, also occurs more frequently in young human patients and is usually identified in patients under 15 years of age.¹³ The veterinary literature reports of GNB show a range in patient age of 8 months¹⁷ to 15 years of age¹⁸ in dogs, and a single published case of feline GNB in an 8-year-old cat.¹¹ In addition, none of the previously published veterinary reports of GNB reported spinal cord involvement. Because of the range in age, presentation, tumor location, and rarity of occurrence in veterinary patients, any predication of age predilection for GNB in veterinary patients would likely be premature without a larger sample size of similar cases for comparison.

To the author's knowledge, this is the first report documenting clinical signs, CT findings, MRI, and histopathology of an intraparenchymal spinal cord GNB originating from the peripheral sympathetic nervous system in a cat.

Footnotes

^a GE Lightspeed[®] 16 Slice Scanner, Milwaukee, WI, USA

^b 0.25T Esaote Vet Grande[®], Genoa, Italy

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Conflict of Interest Declaration: Authors disclose no conflict of interest.

Off-label Antimicrobial Declaration: Authors declare no off-label use of antimicrobials.

References

1. Wolf HK, Buslei R, Schmidt-Kastner R, et al. NeuN: A useful neuronal marker for diagnostic histopathology. *J Histochem Cytochem* 1996;44:1167–1171.
2. Davis WP, Watson GL, Koehler LK, Brown CA. Malignant cauda equina paraganglioma in a cat. *Vet Pathol* 1997;34:243–246.
3. Kim D-Y, Hodgin EC, Lopez MK, et al. Paraganglioma in the vertebral canal of a cow. *J Vet Diagn Invest* 1994;6:389–392.
4. Sakai H, Yonemaru K, Takeda M, et al. Ganglioneuroma in the urinary bladder of a dog. *J Vet Med Sci* 2011;73:801–803.
5. Ribas JL, Kwapien RP, Pope ER. Immunohistochemistry and ultrastructure of intestinal ganglioneuroma in a dog. *Vet Pathol* 1990;27:376–379.
6. Hermeyer K, Kühn M, Kuchelmeister K, et al. Multiple cutaneous ganglioneuromas in a dog. *Vet Dermatol* 2007;18:360–364.
7. Reimer M, Leib M, Reimer M, et al. Rectal ganglioneuroma in a dog. *J Am Anim Hosp Assoc* 1999;35:107–110.
8. Schueler RO, Roush JK, Oyster RA. Spinal ganglioneuroma in a dog. *J Am Vet Med Assoc* 1993;203:539–541.
9. Kobayashi R, Ohsaki Y, Yasuno K, et al. A malignant and metastasizing feline cardiac ganglioneuroma. *J Vet Diagn Invest* 2012;24:412–417.
10. Patnaik AK, Lieberman PH, Johnson GF. Intestinal ganglioneuroma in a kitten—a case report and review of literature. *J Small Anim Pract* 1978;19:735–742.
11. Spugnini EP, Citro G, Dotsinsky I, et al. Ganglioneuroblastoma in a cat: A rare neoplasm treated with electrochemotherapy. *Vet J* 2008;178:291–293.
12. McGavin DM, Zachary JS. *Pathologic Basis of Veterinary Disease*, 4th ed. Mosby: Elsevier; 2007.
13. Lonergan GJ, Schwab CM, Suarez ES, Carlson CL. Neuroblastoma, ganglioneuroblastoma, and ganglioneuroma: radiologic-pathologic correlation. *Radiographics* 2002;22:911–934.
14. Spinelli C, Rossi L, Barbeta A, et al. Incidental ganglioneuromas: A presentation of 14 surgical cases and literature review. *J Endocrinol Invest* 2014;38:547–554.
15. Hazell K, Reeves M, Swift I. Small intestinal ganglioneuromatosis in a dog. *Aust Vet J* 2011;89:15–18.
16. Paris JK, McCandlish IAP, Schwarz T, et al. Small intestinal ganglioneuromatosis in a dog. *J Comp Pathol* 2013;148:323–328.
17. Kuwamura M, Kotera T, Yamate J, et al. Cerebral ganglioneuroblastoma in a golden retriever dog. *Vet Pathol* 2004;41:282–284.
18. Mattix ME, Mattix RJ, Williams BH, et al. Olfactory ganglioneuroblastoma in a dog: A light, ultrastructural, and immunohistochemical study. *Vet Pathol* 1994;31:262–265.
19. Louis DN, Ohgaki H, Wiestler OD, Cavenee WK (Eds.) *WHO Classification of Tumours of the Central Nervous System*. IARC. Lyon: WHO Press, World Health Organization; 2007.
20. Vandeveld M, Higgins RJ, Overmann A. *Veterinary Neuropathology, Essentials of Theory and Practice*, 1st ed. New York: Wiley-Blackwell; 2012.