The Journal of Veterinary Medical Science

NOTE

Surgery

Intramedullary spinal nephroblastoma in a mixed breed dog

Michihito TAGAWA[1)]*, Genya SHIMBO[1)], Mizuki TOMIHARI[2)], Masashi YANAGAWA[2)], Ken-ichi WATANABE[3)], Noriyuki HORIUCHI[3)], Yoshiyasu KOBAYASHI[3)] and Kazuro MIYAHARA[1)]

[1)]Veterinary Medical Center, Obihiro University of Agriculture and Veterinary Medicine, Inada, Obihiro, Hokkaido 080-8555, Japan

[2)]Department of Clinical Veterinary Science, Obihiro University of Agriculture and Veterinary Medicine, Inada, Obihiro, Hokkaido 080-8555, Japan

[3)]Research Center for Global Agromedicine, Obihiro University of Agriculture and Veterinary Medicine, Inada, Obihiro, Hokkaido 080-8555, Japan

J. Vet. Med. Sci.
82(7): 917–921, 2020
doi: 10.1292/jvms.20-0068

Received: 8 February 2020
Accepted: 5 May 2020
Advanced Epub: 18 May 2020

ABSTRACT. A 1-year-old male mixed breed dog presented for the evaluation of progressive hindlimb paresis. Neurological examination indicated a spinal cord lesion between the 3rd thoracic and 3rd lumbar vertebrae. Magnetic resonance imaging (MRI) revealed an intramedullary spinal cord lesion located at the level of the 1st and 2nd lumbar vertebrae. Following cytoreductive surgery of the mass, palliative radiation therapy was administered. A diagnosis of nephroblastoma was made based on histological examination. After radiation therapy, the disappearance of the spinal lesion was confirmed by MRI. The dog was improved from gait abnormality and alive at 16 months postoperatively, with slight signs of neurological dysfunction.

KEY WORDS: dog, intramedullary, radiation therapy, spinal nephroblastoma

Nephroblastoma of the spinal cord is a rare neoplasm, typically affecting young dogs [6]. Large breed dogs including German shepherd and Retriever breeds seem to be predisposed to this tumor [6]. However, the condition has also been reported in small breeds [12]. The tumor usually occurs between the 10th thoracic and 3rd lumbar spinal cord segments in an intradural-extramedullary location and less frequently in intramedullary or extradural locations [6].

Intramedullary spinal cord tumors present a therapeutic challenge, and a past study revealed that intramedullary nephroblastoma is associated with a worse prognosis than intradural-extramedullary tumors [11]. Some case reports have described a therapeutic approach for nephroblastoma, wherein, the survival after cytoreductive surgery of the tumor ranged from 2 months to over 3 years [11, 12, 15]. Radiotherapy after cytoreductive surgery for spinal cord tumors in dogs may be beneficial, but it is not well-documented for treating nephroblastomas [1, 10, 11, 16]. This case report documented the diagnosis, treatment, and outcome of an intramedullary nephroblastoma in a dog.

A 1-year-old, 16.6 kg, male mixed breed dog was referred to the Veterinary Medical Center, Obihiro University of Agriculture and Veterinary Medicine for investigation of hindlimb gait abnormality since one month. At the time of presentation, the dog had ambulatory paraparesis with marked hindlimb ataxia that was worse on the left side than the right. On examination, general findings were unremarkable, except muscle weakness in the left hindlimb. Neurological examination found proprioceptive deficits in the left hindlimb. Both hindlimbs showed positive upper motor neuron signs, and the forelimbs were normal. Clinical findings suggested a lesion between the 3rd thoracic and 3rd lumbar spinal cord segments. No significant abnormalities were found in routine serum biochemical and hematological analyses. Abdominal ultrasonography and radiography of the thorax, abdomen, and entire spine were unremarkable.

Because a spinal disease was suspected in the present case, MRI was performed for further investigation with a 0.4 Tesla open magnet (APERTO Lucent, Hitachi Medical Systems, Tokyo, Japan). Anesthesia was induced by slow intravenous administration of 8 mg/kg of propofol (PropoFlo28, DS Pharma Animal Health, Osaka, Japan) and maintained with a mixture of isoflurane and 100% oxygen. The imaging protocol included T2-weighted (T2W) images in transverse and sagittal planes, and T1-weighted (T1W) images before and immediately after manual intravenous administration of 0.1 mmol/kg gadoteridol (ProHance, Eisai, Tokyo, Japan) in transverse and sagittal planes. On T2W images, there was marked swelling of the spinal cord at the level of 1st to 2nd lumbar vertebrae and a solitary, rather heterogeneous mass, apparently intramedullary in location (Fig. 1A, 1B). The

*Correspondence to: Tagawa, M: mtagawa@obihiro.ac.jp

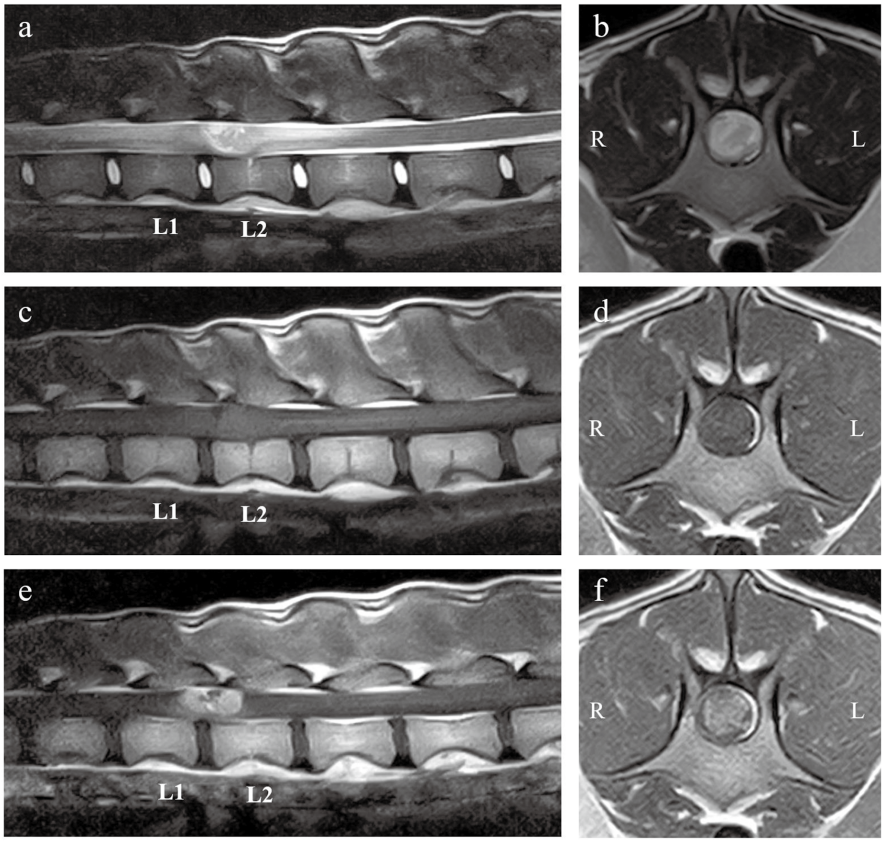

Fig. 1. Magnetic resonance imaging of the spinal cord of the dog. (a) Sagittal and (b) transverse T2-weighted images revealed swelling of the spinal cord at the level of 1st to 2nd lumbar vertebrae and a solitary, rather heterogeneous mass. (c) Sagittal and (d) transverse T1-weighted images. (e) Sagittal and (f) transverse T1-weighted postcontrast images revealed an enhanced intramedullary lesion.

lesion was isotense relative to normal spinal cord on T1W images (Fig. 1C, 1D) and was clearly demonstrated after gadolinium enhancement. The enhanced lesion was 20 mm in length, which indicates an intramedullary tumor. The lesion was located mainly to the left of the midline on the cranial side and occupied the whole spinal cord on the caudal side (Fig. 1E, 1F).

On the owner's request, the dog underwent a follow-up examination, and neurological deficits were found to be mildly worsened over the next 3 weeks. Twenty-seven days after MRI, a left-sided hemilaminectomy between the 1st and 2nd lumbar vertebra was performed. Anesthesia was induced by slow intravenous administration of propofol (8 mg/kg IV), fentanyl (0.005 mg/kg IV bolus followed by 0.01 mg/kg/hr IV infusion, Daiichi Sankyo Co., Tokyo, Japan), and was maintained with a mixture of isoflurane and 100% oxygen. After adopting a dorsal midline approach, the subcutaneous tissue and fat were bluntly detached. The multifidus muscle was then peeled from the spinous process and lamina of the vertebral arch. The left vertebral arch between the 1st and 2nd lumbar vertebra was removed using a rongeur and high-speed drill system with a 3-mm cutting round bar (Core console; Stryker, Kalamazoo, MI, USA). A reddish area of discoloration was observed through the dura, and after durotomy using surgical blade, part of the bulging mass was removed using a rongeur, but complete tumor resection was not possible because the border between the mass and spinal cord was unclear (Fig. 2). It was not possible to close the dura at the time of surgery, and the wound closed routinely. The lesion was fixed in 10% formalin solution and transferred to the pathology department at the Obihiro University of Agriculture and Veterinary Medicine for analysis.

On histopathological examination, the mass was composed of a biphasic cellular population of epithelial and mesenchymal cells (Fig. 3a). The epithelial cells consisted of tubular and acinar structures but no glomeruloid structure. The epithelial components were surrounded by mesenchymal cells, which exhibited mild to moderate anisokaryosis. Mitotic figures were up to 36, as noted in 10 high-power fields. Neoplastic tissue was infiltrated with a few mononuclear cells. Immunohistochemically, the epithelial tubular and acinar cells were strongly positive for cytokeratin and mesenchymal cells were positive for vimentin (Fig. 3b, 3c). Based on the biphasic component, immunohistochemical findings, and location, the mass was diagnosed as nephroblastoma.

The dog was discharged 2 days after surgery. A palliative course of radiation therapy was prescribed in accordance with the owner's decision and radiation began 7 days after surgery. The source of radiation was an orthovoltage X-ray therapy machine (300 kVp, 20 mA, half value layer; 0.5 mmCu and 0.5 mmAl). A total dose of 26 Gy was administered in doses of 6.5 Gy fractions per week, and the dog was placed in dorsal recumbency. The radiation plan consisted of right- and left-lateral opposed fields with a margin area of 5 × 5 cm. At the time of the third radiation dose, 18 days after surgery, hindlimb ataxia of the dog was improved

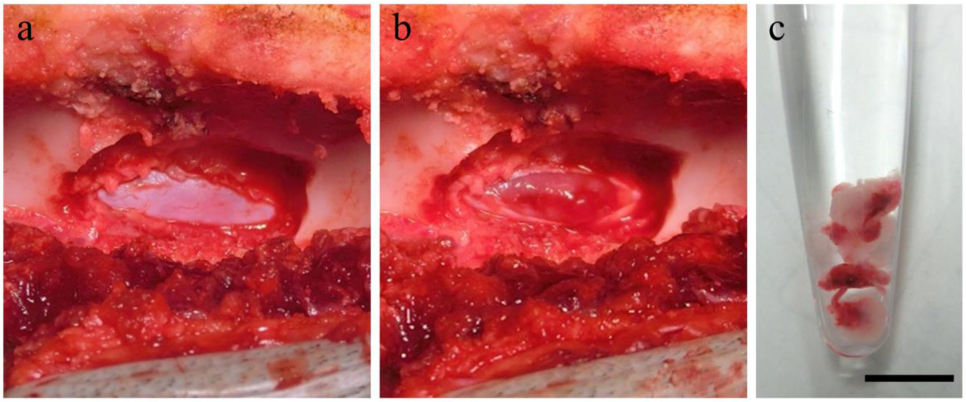

Fig. 2. Macroscopic findings of the spinal cord lesion. (a) A reddish area of discoloration was observed through the dura. (b) After myelotomy, a bulging dark-red colored mass was observed. (c) A part of the mass was removed for the histopathological examination. Bar=1 cm.

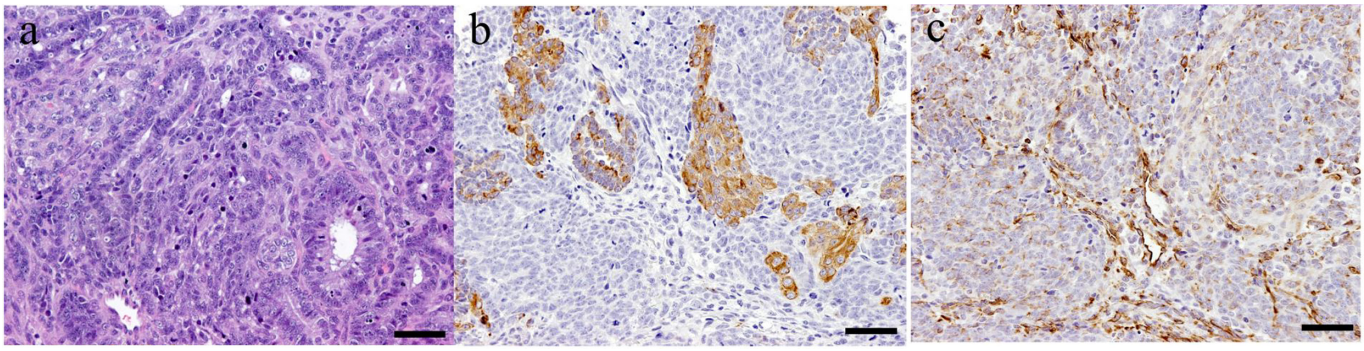

Fig. 3. Microscopic appearance of the mass. A biphasic population of proliferating cells was noted. Epithelial cell consisted of tubules and acinar structures. The epithelial structures were surrounded by mesenchymal spindloid cells. Few mononuclear cells infiltrated the neoplastic tissue. (a) Hematoxylin eosin, (b) cytokeratin, and (c) vimentin staining. Bar=50 μm.

remarkably. Radiation toxicity was limited to alopecia of the treated skin.

At 4 months after surgery, the dog walked with a slight hindlimb lameness but had no other abnormalities. Subsequent MRI evaluation at that time revealed no enhanced area in the spinal cord (Fig. 4). Sexteen months following diagnosis the dog was alive and well, with no evidence of clinical signs according to a telephone inquiry made to the owner.

Spinal cord nephroblastoma is a rare but a well-recognized neoplasm of the canine spinal cord that generally occurs in dogs less than 3 years of age [6]. It is suspected that the tumors arise from embryonic renal tissue that becomes entrapped in the dura of the spinal canal during fetal development [15]. The tumor generally presents as an intradural-extramedullary solitary mass, which is consistently located between the 10th thoracic and 3rd lumbar spinal cord segments. Clinical signs including hindlimb paresis and ataxia associated with spinal cord nephroblastoma are due to the compression caused by the mass on the spinal cord [12, 18].

In humans, nephroblastoma is the most common primary renal tumor of childhood, and intraspinal lesions were not reported except in some cases of invasion of spinal canal by the abdominal mass and metastasis [14, 19]. Currently, multi-modal treatment including surgical resection, chemotherapy, and radiotherapy is recommended for the treatment of human patients with nephroblastoma [4]. On the other hand, the therapeutic approach of spinal nephroblastoma in dogs is poorly documented as the tumor is rare and dogs are often euthanized following diagnosis [5, 15, 17, 18]. Varied outcomes of dogs with spinal cord nephroblastoma after surgical management are reported and the prognosis of a tumor in an intramedullary location is poor compared with that of an intradural-extramedullary location [11, 12, 15]. In addition, radiation therapy combined with surgery is not well documented in canine nephroblastoma [7, 10, 11].

Differential diagnosis of preoperative imaging included intramedullary tumors (e.g., nephroblastoma or lymphoma) and fibrocartilaginous embolism. In this case, cytoreductive surgery was performed, however, complete excision was difficult and the neurological signs of the case did not improve immediately after surgery. After the 3rd fraction of radiation therapy, a remarkable improvement in the clinical signs was observed. Thus, we thought that cytoreductive surgery and radiotherapy were effective for the case in terms of improvement of neurologic function and longer survival time. In addition, the dura was not closed after cytoreductive surgery because of the large dural defect and to facilitate spinal cord decompression. Durotomy complications were

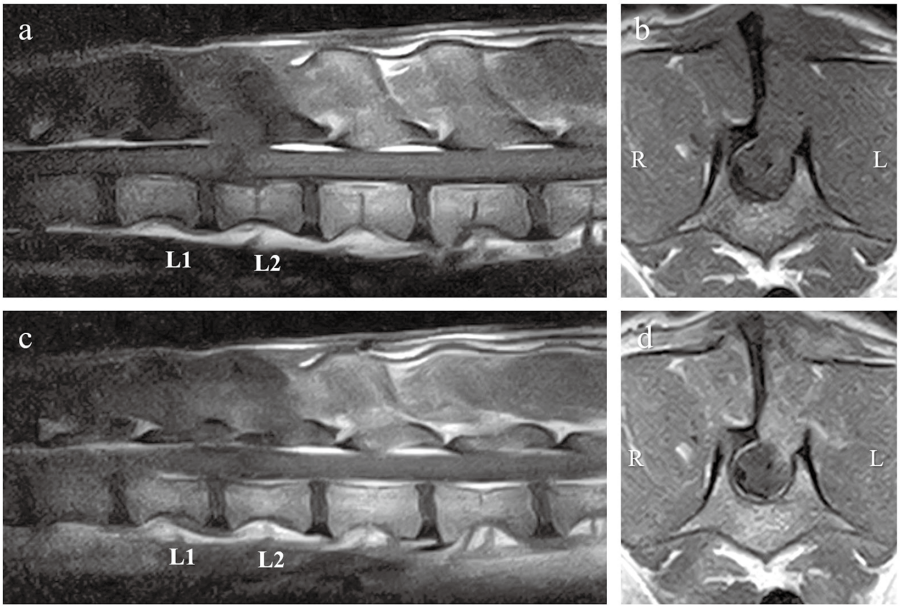

Fig. 4. Magnetic resonance imaging of the spinal cord of the dog at four months after surgery. (a) Sagittal and (b) transverse T1-weighted images. (c) Sagittal and (d) transverse T1-weighted postcontrast images revealed no enhanced area in the spinal cord.

not observed in this case during the follow-up period.

Radiation-induced osteosarcoma was reported in a case as an adjuvant to external beam radiation therapy of intradural-extramedullary spinal cord nephroblastoma [2]. In the report, a lower dose of 3 Gy/fraction or less was recommended when irradiating young dogs [2]. Stromal damage was more severe with large single doses, and the sequence of a course of fractionated irradiation followed by a large single dose seemed to enhance the carcinogenicity [3]. Moreover, an estimated 20-fold increase of second cancers is observed after radiotherapy or chemotherapy for childhood malignancies [13]. In addition, radiation-induced myelopathy (RIM) is one of the most severe complications of radiation treatment of the spinal area [8]. The human spinal cord was estimated to have a probability of RIM of less than 5% in 5 years following a dose of 47–50 Gy delivered in a standard 1.8–2 Gy/fraction schedule [9]. In this case, a palliative course of radiation therapy was chosen based on the owner's decision, and a total dose of 26 Gy was administered in 6.5 Gy fractions. Recently reported results of animal and human studies revealed that the biological equivalent dose to induce 5% (BED5) of RIM was calculated to be 83.9 Gy in 2 Gy/fraction schedule [8]. The 26 Gy/4fractions is equivalent to 69 Gy in 2 Gy fractions, according to the liner quadratic model using an α/β ratio of 3.9 Gy [8]. Long-term follow-up is needed for the case to track the occurrence of any radiation-induced complications.

The biological behavior of spinal nephroblastomas in dogs is poorly documented, and only two cases of multifocal or metastatic spinal cord nephroblastoma have been reported in canines [5, 17]. The prognosis for canine spinal cord nephroblastoma may depend on the neuroinvasive and metastatic potential of the neoplasm [11]. Because of the high radiosensitivity of the tumor, cytoreductive surgery and radiotherapy might be effective even if the mass is at an intramedullary location [4]. Further prospective studies are necessary to establish a standard treatment and radiation planning of the tumor.

REFERENCES

1. Brewer, D. M., Cerda-Gonzalez, S., Dewey, C. W., Diep, A. N., Van Horne, K. and McDonough, S. P. 2011. Spinal cord nephroblastoma in dogs: 11 cases (1985–2007). *J. Am. Vet. Med. Assoc.* **238**: 618–624. [Medline] [CrossRef]
2. Dickinson, P. J., McEntee, M. C., Lipsitz, D., Keel, K. and LeCouteur, R. A. 2001. Radiation induced vertebral osteosarcoma following treatment of an intradural extramedullary spinal cord tumor in a dog. *Vet. Radiol. Ultrasound* **42**: 463–470. [Medline] [CrossRef]
3. Gillette, S. M., Gillette, E. L., Powers, B. E. and Withrow, S. J. 1990. Radiation-induced osteosarcoma in dogs after external beam or intraoperative radiation therapy. *Cancer Res.* **50**: 54–57. [Medline]
4. Grundy, P., Perlman, E., Rosen, N. S., Warwick, A. B., Glade Bender, J., Ehrlich, P., Hoffer, F. A. and Lee, N. D. 2005. Current issues in Wilms tumor management. *Curr. Probl. Cancer* **29**: 221–260. [Medline] [CrossRef]
5. Henker, L. C., Bianchi, R. M., Vargas, T. P., de Oliveira, E. C., Driemeier, D. and Pavarini, S. P. 2018. Multifocal spinal cord nephroblastoma in a dog. *J. Comp. Pathol.* **158**: 12–16. [Medline] [CrossRef]
6. Higgins, R. J., Bollen, A. W., Dickinson, P. J. and Sisó-Llonch, S. 2017. Tumors of the nervous system. pp. 834–891. *In*: Tumors in Domestic Animals, 5th ed. (Meuten, D. J. ed.), John Wiley & Sons Inc, Ames.
7. Jeffery, N. D. and Phillips, S. M. 1995. Surgical treatment of intramedullary spinal cord neoplasia in two dogs. *J. Small Anim. Pract.* **36**: 553–557. [Medline] [CrossRef]
8. Jin, J. Y., Huang, Y., Brown, S. L., Movsas, B., Kaminski, J., Chetty, I. J., Ryu, S. and Kong, F. S. 2015. Radiation dose-fractionation effects in spinal cord: comparison of animal and human data. *J. Radiat. Oncol.* **4**: 225–233. [Medline] [CrossRef]

9. Kirkpatrick, J. P., van der Kogel, A. J. and Schultheiss, T. E. 2010. Radiation dose-volume effects in the spinal cord. *Int. J. Radiat. Oncol. Biol. Phys.* **76** Suppl: S42–S49. [Medline] [CrossRef]
10. Langen, N., von Pückler, K., Tillmanns, C., Bornand, V., Kramer, M. and Schmidt, M. J. 2017. [Spinal nephroblastoma at an uncommon localization in a dog]. *Tierarztl. Prax. Ausg. K Klientiere. Heimtiere* **45**: 115–121 (in German). [Medline]
11. Liebel, F. X., Rossmeisl, J. H. Jr., Lanz, O. I. and Robertson, J. L. 2011. Canine spinal nephroblastoma: long-term outcomes associated with treatment of 10 cases (1996–2009). *Vet. Surg.* **40**: 244–252. [Medline] [CrossRef]
12. Nakade, T., Inoue, A., Shimazaki, H., Miyoshi, K., Takeuchi, N., Kadosawa, T., Akihara, Y., Taniyama, H. and Ishida, O. 2006. Spinal nephroblastoma in a miniature Dachshund. *J. Vet. Med. Sci.* **68**: 1383–1385. [Medline] [CrossRef]
13. Penn, I. 1982. Second neoplasms following radiotherapy or chemotherapy for cancer. *Am. J. Clin. Oncol.* **5**: 83–96. [Medline] [CrossRef]
14. Ramdial, P. K., Hadley, G. P. and Sing, Y. 2010. Spinal cord compression in children with Wilms' tumour. *Pediatr. Surg. Int.* **26**: 349–353. [Medline] [CrossRef]
15. Sale, C. S., Skerritt, G. C. and Smith, K. C. 2004. Spinal nephroblastoma in a crossbreed dog. *J. Small Anim. Pract.* **45**: 267–271. [Medline] [CrossRef]
16. Siegel, S., Kornegay, J. N. and Thrall, D. E. 1996. Postoperative irradiation of spinal cord tumors in 9 dogs. *Vet. Radiol. Ultrasound* **37**: 150–153. [CrossRef]
17. Terrell, S. P., Platt, S. R., Chrisman, C. L., Homer, B. L., de Lahunta, A. and Summers, B. A. 2000. Possible intraspinal metastasis of a canine spinal cord nephroblastoma. *Vet. Pathol.* **37**: 94–97. [Medline] [CrossRef]
18. Vural, S. A., Kutlu, T., Besalti, O. and Can, P. 2016. Spinal nephroblastoma in a dog. *Glob. Adv. Res. J.Med. Med. Sci.* **5**: 283–286.
19. Watanabe, R., Takahashi, A., Suzuki, M., Toki, F., Kanazawa, T., Hirato, J., Morikawa, A. and Kuwano, H. 2009. Adolescent wilms tumor with intraspinal and bone metastases: a case report and the review of literature. *J. Pediatr. Hematol. Oncol.* **31**: 45–48. [Medline] [CrossRef]