NOTE *Surgery*

Case of a miniature dachshund with a primitive neuroectodermal tumor confined to the forebrain region treated with a combination of surgery and chemotherapy

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(Received 23 May 2016/Accepted 6 July 2016/Published online in J-STAGE 18 July 2016)

ABSTRACT. A miniature dachshund aged 9 years and 7 months with a history of polyuria/polydipsia and depression was referred. General physical and neurological examinations revealed no obvious abnormalities. MRI of the brain revealed a large space-occupying lesion in the left frontal lobe. This was surgically removed and pathologically diagnosed as a primitive neuroectodermal tumor (PNET). Although the clinical signs had been improved, follow-up MRI revealed recurrence of the tumor. Lomustine was administered, but 1 year after surgery, the dog exhibited cluster seizures and died. This is the first reported case of a dog with PNET confined to the forebrain region treated by surgical resection in combination with chemotherapy, as observed by repeated follow-up MRI.

KEY WORDS: canine, chemotherapy, MRI, primitive neuroectodermal tumor, surgery

doi: 10.1292/jvms.16-0273; *J. Vet. Med. Sci.* 78(11): 1703–1707, 2016

Primitive neuroectodermal tumors (PNETs) are embryonal tumors derived from germinal neuroepithelial cells that are capable of differentiating into primary neuronal, ependymal or glial cells [9, 10]. According to their location, they are subdivided into either cerebellar PNETs, also termed medulloblastomas, or non-cerebellar PNETs [4, 11]. Non-cerebellar PNETs can arise within the central nervous system or peripherally in the soft tissues or bone (peripheral PNETs). In veterinary medicine, non-cerebellar PNETs have been reported in dogs [1, 3, 4, 6, 7, 15], with five of these studies involving magnetic resonance imaging (MRI). Non-cerebellar PNETs confined intracranially have only been reported for two dogs [1, 4], and only one of these reports [1] provided clinical information regarding treatment by surgical resection. Furthermore, no report has confirmed progress after treatment through continuous MRI examination. Here, we describe a canine case with PNET confined to the forebrain region that was treated by surgical resection in combination with chemotherapy, with progress after the treatment monitored by repeated MRI examination.

A 4.25-kg spayed female miniature dachshund aged 9 years and 7 months with a 1-month history of polyuria and polydipsia (PU/PD) was referred to the Kyoto Animal Referral Medical Center (KyotoAR) for evaluation, because of a depression improved by treatment with predonisone. The complete blood count measurements, serum biochemical analyses, urinalysis, ACTH stimulation test, thyroid hormone test (T4 and fT4) and radiographic survey of the chest and abdomen, which were performed by the referring veterinarian 3–10 days prior to the referral, were unremarkable.

On presentation at the KyotoAR (day 0), a physical examination revealed a body temperature of 38.2°C, pulse rate of 136 beats/min and respiratory rate of 15 breaths/min. On neurological examination, mental status, intellect, behavior, posture, gait, palpation, postural reactions, spinal reflexes, cranial nerves, sensation and urinary function were normal. Based on the clinical history and findings, MRI of the brain was recommended. This was performed the same day under general anesthesia using a 0.3 Tesla MR imaging system with a permanent magnet (Airis Vento, Hitachi, Tokyo, Japan), with the dog in the dorsal recumbent position. Using a human wrist coil, T2-weighted images (T2W: FSE, TR/TE=4,000/120), fluid-attenuated inversion recovery sequences (FLAIR: FIR, TR/TE/TI=8,500/2,100/120) and T1-weighted images (T1W: SE, TR/TE=400/15) with and without an intravenous gadodiamide contrast agent (0.2 ml/kg, Magnevist, Bayer, Tokyo, Japan) in the transverse, sagittal and dorsal planes were obtained. The MRI indicated the presence of an oval space-occupying mass that was located in the left frontal lobe (Figs. 1, 3A and 3B). The mass was iso- to mildly hyperintense on T2W and FLAIR, iso- to mildly hypointense on T1W and strongly enhanced on the post-contrast T1W with a ring-like enhancement. The center of the mass was also hyperintense on T2W, hypointense on T1W, but showed no enhancement on the post-contrast T1W.

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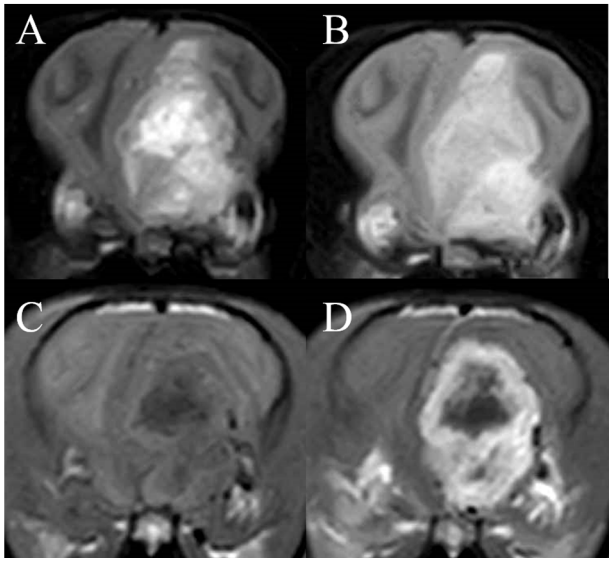

Fig. 1. Magnetic resonance images revealing the oval space-occupying mass in the left side of the frontal cerebrum. All images show the transverse plane at the level of the sulcus cruciatus. A: T2W image. B: FLAIR image. C: T1W image. D: Post-contrast T1W image. The mass was iso- to mildly hyperintense on T2W and FLAIR images, iso- to mildly hypointense on T1W image and strongly enhanced on the post-contrast T1W (with a ring-like enhancement). The center of the mass was also hyperintense on T2W, hypointense on T1W and FLAIR, and not enhanced on the post-contrast T1W image. Perilesional edema was present.

Perilesional edema was widely present. The owner opted for surgical removal of the mass. Predonisone (0.5 mg/kg SID) was used until the operation day.

Surgical resection on using a bilateral transfrontal sinus approach to the frontal lobe was performed on day 14. The dog was premedicated with midazolam (0.3 mg/kg IV) and was induced with propofol (6 mg/kg). The dog was intubated and maintained on oxygen and isofluothane using a mechanical ventilator controlling capnography and oximetry. Cefazolin (22 mg/kg), ranitidine (2 mg/kg), buprenorphine (0.02 mg/kg) and predonisone (0.5 mg/kg) were administered at the beginning of surgery. A diamond-shaped bone flap was removed in the bilateral transinusal approach. The oscillating bone saw was beveled to facilitate replacement and tight closure of the bone flap at the end of the surgery. The inner part of the frontal sinus bone was resected using a high speed burr, allowing access to the incised dura mater. The mass was located under the meninges and was weak and showed dark red color. The mass was removed using cavitron ultrasonic surgical aspirator under the magnifying glass. The border of the mass and the normal brain was indistinct; however, the mass was completely excised macroscopically. After the surgical resection, meninges were closed down using an artificial endocranium, and the diamond-shaped bone plate was repositioned.

Histological diagnosis was confirmed by examining tissue samples obtained during surgery. Tissues were fixed in 10% neutral buffered formalin. Paraffin sections were stained with hematoxylin and eosin. Histologically, the tumor mass comprised polygon- to spindle-shaped anaplastic cells that had clear nuclei and acidophilic cytoplasm (Fig. 2A). The tumor cells were strongly atypical. The perivascular tumor cells contained a large amount of cytoplasm. In other parts of the tumor, spindle-shaped tumor cells were the main constituent with a small amount of cytoplasm. Mitotic figures were also found in the tumor. In some parts of the mass, the tumor cells were arranged to form Homer Wright rosettes or pseudopalisading patterns. The tumor was also evaluated immunohistochemically for glial fibrillary acidic protein (GFAP), oligodendrocyte transcription factor 2 (Oligo-2), ionized calcium-binding adaptor molecule 1 (Iba1) and βIII-tubulin. The tumor cells were positive for GFAP (Fig. 2B), and some were also positive for βIII-tubulin (Fig. 2C), whereas they were completely negative for Oligo-2 and Iba 1 [5]. From these findings and the histological appearance, the lesion was diagnosed as PNET, in accordance with the WHO classification [5, 8].

The dog recovered from the surgery and was discharged the KyotoAR on day 21. Predonisone (0.25 mg/kg BID) had been used 3 days postoperatively. Ranitidine and buprenorphine had been used until discharged. Only cefazolin had been used as symptomatic therapy for 14 days after surgery. At the time of a discharge, the dog was a clinically normal, and PU/PD had been improved. The first follow-up MRI (on day 37) showed partial contrast enhancement (Fig. 3C and 3D). A second follow-up MRI (on day 73) showed extension of the lesion with significant contrast enhancement (Fig. 3E and 3F). Options of surgical resection, radiation therapy, chemotherapy or symptomatic therapy were suggested to the owner, who chose symptomatic therapy including predonisone (0.5 mg/kg SID). The third follow-up MRI (on day 144) showed further extension of the tumor (Fig. 3G and 3H). For about 6 months after surgery, the dog was neurologically normal, and the PU/PD had been improved. However, a slight protrusion of the left eyeball was observed; surgical treatment, radiotherapy, chemotherapy and symptomatic therapy were presented again to the owner, who chose chemotherapy.

Chemotherapy with lomustine was started on day 191 at 80 mg/ m^2. After the first lomustine administration, the dog exhibited fever (40.2°C) and inappetence and was treated in the hospital, with recovery after approximately 1 week. Based on this, lomustine was administered for the second time on day 226 at 40 mg/m^2, without obvious side effects. The third administration at 40 mg/m^2 was on day 251, again with no obvious side effects. A fourth follow-up MRI (on day 262) showed that the mass lesion had extended further and infiltrated subcutaneously (Fig. 3I and 3J). Based on the MRI findings, the owner chose symptomatic therapy and to stop chemotherapy. A fifth follow-up MRI (on day 345) showed significant extension of the lesion with contrast enhancement (Fig. 3K and 3L). A protrusion of the left eyeball became more obvious, and the subcutaneous bulge was notable. The dog could not close left eyelid and showed visual impairment. Results of other neurological examina-

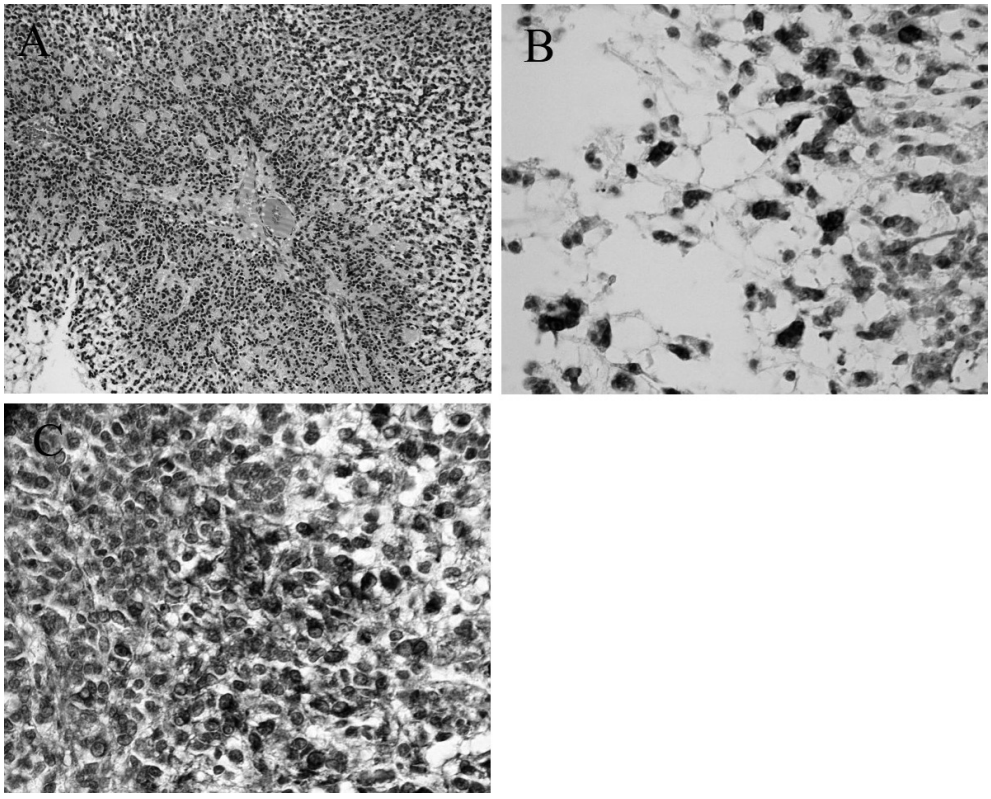

Fig. 2. Histopathology. A: The tumor cells were arranged to form Homer Wright rosettes or pseudopalisading patterns (H&E stain, ×100). B: The tumor cells displayed strong expression of glial fibrillary acidic protein (immunohistochemistry for GFAP, ×200). C: The tumor cells displayed mild expression of βIII-tubulin (immunohistochemistry for βIII-tubulin, ×200).

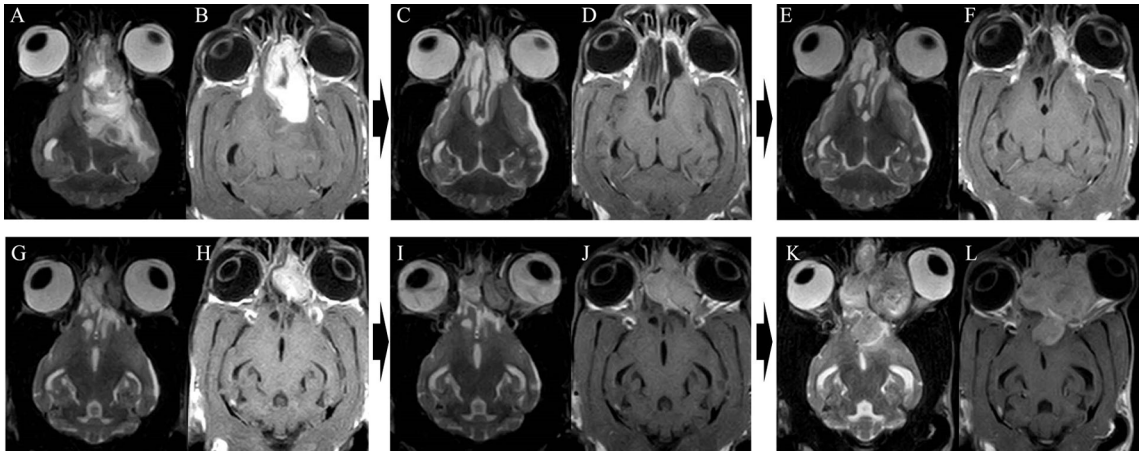

Fig. 3. Changes in magnetic resonance imaging (MRI) findings from day 0 to day 345. All images show the coronal plane at the level of the dorsal images at the level of the quadrigeminal bodies. The first of each pair of images (A, C, E, G, I and K) is a T2W image, and the second (B, D, F, H, J and L) is a post-contrast T1W image. A & B: MRI at first referral (day 0). The lesion shows hyperintensity on the T2W image and ring enhancement on the post-contrast T1W image. C & D: Two weeks after surgery (day 37). The lesion shows partial contrast enhancement on the post-contrast T1W image. E & F: Five weeks after surgery (day 73). The lesion has extended with significant contrast enhancement on the post-contrast T1W image. G & H: Four months after surgery (day 144). The lesion shows further extension of the tumor. I & J: Approximately 8 months after surgery (day 262). The lesion has extended further and infiltrated subcutaneously. K & L: Ten months after surgery (day 345). The lesion shows significant extension with contrast enhancement on the post-contrast T1W image.

tion were normal. The dog was able to lead a normal daily life. However, cluster seizures were recognized, and the dog could not stand up afterwards on days 360 and 361; the dog died calmly. It was not possible to perform an autopsy.

Central PNETs have been reported in dogs aged 18 months to 6 years [1, 3, 4, 7]. In the present case, a non-cerebellar PNET was diagnosed for the tumor based on immunohistochemical differentiation of the glial cells and nerve cells, the histological appearance and the MRI findings. The dog was 9 years and 7 months old at the time of onset; thus, although this type of tumor may be rare, it should be recognized that PNET can develop in older dogs.

The clinical signs of canine central PNETs have been reported as including vestibular syndrome (80%), mentation changes (60%), blindness (40%) and neck pain (20%) [15]. This report was included in PNET of mesencephalon/metencephalom, myelecephalon and cerebellum origin; however, clinical signs associated with posterior cranial fossa disorders have been frequently observed. Other reports of a forebrain disordered by a central PNET have described depression, circling behavior, walking disturbances, abnormal behaviors, dyspnea, vomiting, repeated episodes of fainting and seizures [4, 7]. In the present case, disturbance of consciousness and PU/PD were the main complaints. The cause of PU/PD including chronic kidney disease, hyperadrenocorticism and hypothyroidism was excluded. The exact cause of the PU/PD was unknown, but the clinical manifestations improved after surgery. This may indicate that the tumor disturbed the function of the hypothalamus.

In humans, lesions have been observed to be hypointense and hyperintense on T1W and T2W MR imaging, respectively, and were heterogeneously enhanced by the contrast medium according to the extent of vascularity [12–14]. In addition, a ring-like contrast enhancement was present, and brain edema around the tumor varied from slight to marked [12, 13]. In the present study, the MRI findings were similar to those observed in humans. Our results show that central PNET should be taken into consideration when lesions in the frontal lobe have been observed to be hypointense and hyperintense on T1W and T2W MR imaging, and a ring-like contrast enhancement was present by the contrast medium. However, in another dog where the PNET extended into the cranial vault, the MRI findings were isointense on T1W, moderately hyperintense on T2W, and showed moderate and slightly heterogeneous enhancement [3]. Common MRI findings of canine PNET may become apparent as further cases accumulate.

The outcomes for treatment, including surgery, in dogs with central PNET are unknown. In the majority of previously reported cases, the dogs were euthanized or died suddenly [3, 4, 7]. In one report, the dog was surgically treated and survived for 6 months after surgery [1]. Chemotherapy has traditionally been regarded as ineffective for canine brain tumors, mainly because of the poor ability of most drugs to cross the blood–brain barrier, even when disturbed by the presence of a tumor [2]. Nitrosoureas, such as carmustine and lomustine, are alkylating agents recommended for canine brain tumors, although this is controversial [16]. The recommended dose of lomustine for central PNET remains unknown, although a dosage of 60 mg/m^2 every 6 to 8 weeks has been used and documented for glioma [2]. In the present case, the dosage was decided by taking into consideration the body weight and shape of the lomustine tablet. The optimal treatment regimen for non-cerebellar origin PNET has not yet been established in humans. In humans, long-term survivors are rare among both adults and children, despite aggressive therapy with surgery, radiation therapy and chemotherapy, with outcomes possibly being worse for aged patients than for young adults [14]. Sufficient reduction of tumor volume before chemotherapy and additional therapeutic modalities may be needed to improve outcome [14]. In the present case, the dog returned to clinical normal after surgery; however, the tumor had increased in size during chemotherapy treatment using lomustine. The surgery was therefore regarded as effective, but it is difficult to judge the curative effect of the chemotherapy because it commenced after a recurrence of the tumor. In humans, chemotherapy with nitorosourea and/or a platinum-based agent and/or vincristine was given to long-term survivors [14]. A combination of some of the above agents may be expected to be effective in veterinary medicine. However, the efficacy of surgery and chemotherapy for canine central PNET has not yet been sufficiently determined; information concerning these therapies will be improved by the accumulation of further cases.

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