A Canine Case of Skull Base Meningioma Treated with Hydroxyurea

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ABSTRACT. An 11-year-old female miniature schnauzer was tentatively diagnosed with the skull base meningioma, based on several examinations. Because surgical treatment was difficult, and outpatient radiation therapy was not available in the local area, chemotherapy with hydroxyurea combined with dexamethasone was selected. The patient’s clinical symptoms improved after one week of treatment, and the tumor size was obviously reduced on MRI performed 37 days after treatment began. The patient received hydroxyurea for 7 months, with symptoms remaining stable, and the tumor re-increased to almost the same size at 7 months as that at the initial examination. At that time, hydroxyurea was discontinued. The patient died from pulmonary edema 14 months after treatment began. Pathologically, the tumor was diagnosed as a meningioma.

KEY WORDS: canine, hydroxyurea, meningioma.

In dogs, unlike in humans and cats, intracranial meningioma is likely to infiltrate the surrounding tissues, making radical resection of the tumor difficult [10]. Although a combination of surgery and radiation therapy has been shown most effective for treatment of the disease, surgical intervention is sometimes more difficult in dogs than in humans, depending on the affected site, because the temporal muscles of dogs are much thicker than those of humans [1, 2]. Few veterinary hospitals provide radiation therapy for tumors, which requires anesthesia to be administered multiple times during the course of treatment. Therefore, veterinarians treating dogs with intracranial meningioma need other treatment options. We report a canine case of inoperable meningioma in the skull base that was treated with hydroxyurea, which has been used to treat human meningiomas [7, 8]. Hydroxyurea chemotherapy was combined with steroid treatment, resulting in reduced tumor size and improved clinical symptoms.

An 11-year-old female miniature schnauzer presented with a four-to-five-month history of progressive impairment of vision and hearing. On physical examination, bradycardia was observed. A neurological examination revealed a decreased level of consciousness, loss of pupillary light reflex, absence of menace response, and slightly reduced postural reactions in all limbs. No abnormalities were found with respect to hematology or blood chemistry, or in thoracic and abdominal X-ray examinations. Magnetic resonance imaging (MRI) of the brain (0.2T MRP20-EX; Hitachi Medico, Tokyo, Japan) revealed a mass in the extraparenchymal area spreading from the sella turcica to the right olfactory bulb, which was hypointense on T1-weighted images (T1WIs), hyperintense on T2-weighted images (T2WIs), uniformly strongly enhancing upon intravenous administration of 0.3 ml/kg meglumine gadopentetate (Magnevist; Schering Plough), and had a dural tail sign. Mid-sagittal plane images showed that the thalamus and midbrain were dislocated to the dorsocaudal side by the mass effect. Edema was also observed around the mass (Fig. 1). We compared changes in tumor size over time, using the maximum width and height (excluding the dural tail), on transverse MRI images at the pituitary level. Initially, the tumor was 14.2 mm × 10.3 mm in size (width × height). Meningioma in the skull base was suspected, but surgical excision was considered difficult because of the location and size of the tumor. We offered the patient’s owner several treatment options, including radiation ther-

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Fig. 1. Brain MRI scans obtained at presentation. A: Transverse T2WI at the pituitary level. B: T1WI at the same level. C: Post-contrast T1WI at the same level. D: Dorsal postcontrast T1WI. E: Sagittal postcontrast T1WI. A tumor mass with marked enhancement can be seen in the extraparenchymal area from the sella turcica to the right olfactory bulb. Edema in the adjacent thalamus can be seen on T2WI. Mass effect can be seen in the sagittal image.
apy, chemotherapy, symptomatic treatment with steroids, and any combination of these options. After discussion, we decided to administer hydroxyurea chemotherapy combined with symptomatic treatment with a steroid.

Initially, 30 mg/kg hydroxyurea was administered orally three times a week, plus 0.5 mg/day oral dexamethasone to treat the edema around the tumor. A complete blood count (CBC) was obtained every 2 weeks to detect any myelosuppression in response to hydroxyurea treatment. One week after treatment began, the dog’s vision and hearing recovered, and the level of consciousness returned to normal. On MRI performed at 37 days after treatment began, the tumor was smaller and the surrounding edema had disappeared. At that time, the tumor was 9.5 mm × 9.1 mm in size (Fig. 2).

Dexamethasone was tapered, and mild worsening of the neurological symptoms, particularly the visual and auditory ones, was observed at times. The symptoms were controlled by an increase in the dexamethasone dose. Five months after treatment began, loss of vision and depression developed. At that time, the tumor was 9.8 mm × 9.5 mm in size, with no edema (Fig. 2), and the dexamethasone dose was 0.5 mg/day. Increasing the hydroxyurea dose to 45 mg/kg three times a week with no change to the dexamethasone dose relieved these symptoms. Packed cell volume (PCV) gradually decreased during the course of treatment, which was possibly caused by the hydroxyurea. At 7 months after the initial presentation, when the PCV had decreased to 36% (from 48% at the initial presentation), hydroxyurea was discontinued. At that time, the dexamethasone dose was 0.25 mg/day. On MRI carried out at the same time as the PCV measurement (0.3T AIRIS2 Comfort; Hitachi Medico, Tokyo), the tumor was 14.0 mm × 11.4 mm in size, without edema (Fig. 2). One month after discontinuation of hydroxyurea treatment, the PCV fluctuated around 40%. Neutropenia was not observed at any time during treatment. Two months after treatment began, hepatomegaly and elevated hepatic enzyme levels were noted. Although these symptoms were considered to be related to dexamethasone, it was difficult to determine the appropriate time at which to discontinue the drug.

At around 11 months after the first presentation, signs of Cushing’s syndrome began to appear, and at 14 months, the patient died at her owner’s home from pulmonary edema of unknown cause. On post-mortem MRI, no definitive evaluation was possible because contrast media could not be used, although the tumor was seen to be enlarged on several T2WIs relative to images obtained at 7 months.

At necropsy, a large extramedullary mass, 15.2 mm × 12.2 mm in diameter, white to red in color, was found on the ventral surface of the brain. Histopathological examinations revealed that the mass consisted of solid proliferation of ovoid to spindle-shaped tumor cells, sometimes forming whorl structures and a few psammoma bodies. In the stroma, there were mild neutrophilic infiltration and cholesterol deposits. Based on these findings, the tumor was diagnosed as meningioma, meningotheelial type (Fig. 3). Based on findings including systemic calcinosis (in the lungs, kidneys, spleen, liver, and cerebrovascular vessels), severe vacuolar degeneration of hepatic cells, and atrophy of the adrenal cortex, we determined that the patient had eventually developed iatrogenic Cushing’s syndrome. Apart from these changes, pulmonary congestive edema was also observed.

Hydroxyurea is an antimetabolite that specifically affects the S stage of the cell cycle [4]. Hydroxyurea can be used for years with acceptable and reversible toxicity in humans, and for this reason it may be the optimal drug for treating slow-growing tumors with low mitotic indices, such as
unresectable and recurrent meningioma, despite the controversy over its efficacy [4]. In dogs, hydroxyurea is used for the treatment of chronic lymphocytic leukemia (CLL) [6], polycythemia [9], and essential thrombocythemia [3]. Lomustine and carmustine, which pass through the blood-brain barrier and are used for certain human brain tumors, are not effective treatments for canine meningioma [1]. A previous case report described a dog with meningioma that survived for 13 months on lomustine and prednisolone [5], although no data on tumor size after treatment were provided. For these reasons we selected hydroxyurea to treat the present case.

In the present case, the cytostatic and tumor-shrinking effects of hydroxyurea in combination with the antiedema effect of dexamethasone appeared to result in symptom relief. Specifically, when symptoms worsened after 5 months of treatment, the hydroxyurea dose was increased, resulting in suppression of tumor growth and reduction in tumor size. After a discussion about treatment with the owner, hydroxyurea chemotherapy was started at a low dose of 30 mg/kg, based on the therapeutic dose range used for dogs with CLL. One of the side effects of hydroxyurea is progressive myelosuppression, which can be attenuated before it becomes severe by temporarily decreasing the dose or discontinuing the medication when neutropenia is detected during routine CBC monitoring [6]. We discontinued hydroxyurea treatment because of a persistent decrease in PCV, although neutropenia did not occur in this case. It is unclear whether the gradual decrease in PCV was due to hydroxyurea-induced myelosuppression, or in fact whether discontinuation of treatment was appropriate. Although hydroxyurea is used at a dose of 30–50 mg/kg in dogs with CLL, further investigation of the optimal dose range for treating canine meningiomas is necessary.

In the present case, symptomatic treatment with dexamethasone eventually induced iatrogenic Cushing’s syndrome. When using steroids, matters warranting consideration are selection of steroids, temporary use of steroids only when clinical symptoms worsen, and combined use with other antiedema agents such as acetazolamide.

In a review of the treatment outcomes for intracranial meningioma in dogs, it was found that the median survival time was approximately 3.9 months with symptomatic treatment with steroids alone, 7 months with surgery alone, and 16.5 months with surgery and radiation therapy [1]. In that analysis, however, the location of the tumor, the tumor size at diagnosis, the histological type of the tumor, and the patient’s age were not taken into consideration. Therefore, although our patient survived for 14 months with chemotherapy combined with a steroid, care should be taken when comparing her survival time with those of other reported cases. In the present case, more important is the fact that the combination of steroid and hydroxyurea chemotherapy reduced the tumor size, which suggests that this combination therapy may be an effective approach for treating meningiomas in dogs. Multimodal therapies combining chemotherapy with surgery or radiation therapy can also be considered. There is little information available in the literature about chemotherapy for canine brain tumors, including meningiomas, and the matter has not yet been extensively investigated [1]. More hydroxyurea-treated cases of canine meningioma should be studied in order to further investigate the optimal dosage and efficacy of this chemotherapeutic agent.

REFERENCES