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Long-term Chemotherapy with Hydroxyurea in a Dog with Suspected Intracranial Meningioma

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Abstract : A 9-year-old female mixed breed dog was presented due to cluster seizure episode. A mass in the frontal lobe was noted on brain magnetic resonance imaging (MRI). The dural tail sign was identified on contrast MR images. Based on MRI findings, intracranial meningioma was suspected strongly. The patient's symptom was controlled well by a combination therapy of hydroxyurea and prednisolone, and survived for fourteen months after diagnosis. This case report demonstrated that the clinical findings, imaging characteristics of a dog with suspected intracranial meningioma and long-term survival after hydroxyurea plus prednisolone therapy.

Key words **:** hydroxyurea, magnetic resonance imaging (MRI), meningioma, dog

Introduction

Meningiomas are primary tumors of mesodermal origin which appear as intracranial and intraspinal tumors, and are common neoplasms of the central nervous system (CNS) in dogs and cats (1,2,6). Although malignant forms of meningioma could occur and rarely pulmonary metastasis has been reported, meningiomas are typically characterized by benign biological behavior. Treatments of dogs and cats with meningiomas are surgery with subsequent radiation therapy for accessible tumors and radiation therapy for non-resectable tumors and systemic chemotherapy (1). Non-resectable meningiomas have been posed a problem for veterinarians when clients refused radiation therapy. These patients have been given supportive therapy with corticosteroids and anticonvulsant drugs for managed clinical signs. Furthermore, there were limited reports of chemotherapeutic attempts to treat meningiomas in dogs (6,7). Recently, hydroxyurea has been shown to be an effective chemotherapeutic agent against meningioma in both human and veterinary medicine (5,9,11, 13,15-17,19).

We report here our experience with hydroxyurea therapy in a suspected case of intracranial meningioma without owner's consent to surgery and/or radiation therapy.

Case Report

A 9-year-old female mixed breed dog was presented due to cluster seizure episode. Isolated seizure was observed first, and the intensity and frequency of seizure worsened progressively as cluster seizure. Other neurological examination results were normal. The results of complete blood count (CBC) profiles were within the reference range. Serum chemistry profiles, thoracic and abdominal radiographic examination and abdominal ultrasonography showed no remarkable findings. Based on the above results, brain lesion was suspected.

Thus, we performed a brain magnetic resonance imaging (MRI) scan (E-scan; ESAOTE, Italy) using 0.2T unit. T1- and T2-weighted images and postcontrast T1-weight images were obtained. MRI scanning revealed a mass in right frontal lobe that was isointense on the T1-weighted images and hyperintense on T2-weighted images (Fig 1). A massive lesion occupied in right frontal lobe and the falx cerebri displaced to the left. This lesion was homogeneously enhanced after intravenous administration of gadolinium-diethylenetriamine pentaacetic acid (Omniscan; Nycomed, Inc., Princeton, NJ) (0.1 mmol/kg body weight, IV), and the dural tail sign was identified with marked linear enhancement to the same degree as the tumor (Fig 1B). The width of the mass was 16.5 mm, and its length was 14.8 mm. The lesion was highly suggestive of a neoplastic process. Before cerebrospinal fluid (CSF) collection, we used 15 % mannitol (1 g/kg CRI for 30 minutes; Daehan Pharm Co., Ltd., Korea) to decrease intracranial pressure and collected CSF from the cerebellomedullary cistern. The results of CSF analysis were normal. To rule out central nervous system (CNS) infections, canine distemper virus (RT-PCR) and toxoplasma IgG/IgM antibodies were tested, and all results were negative for

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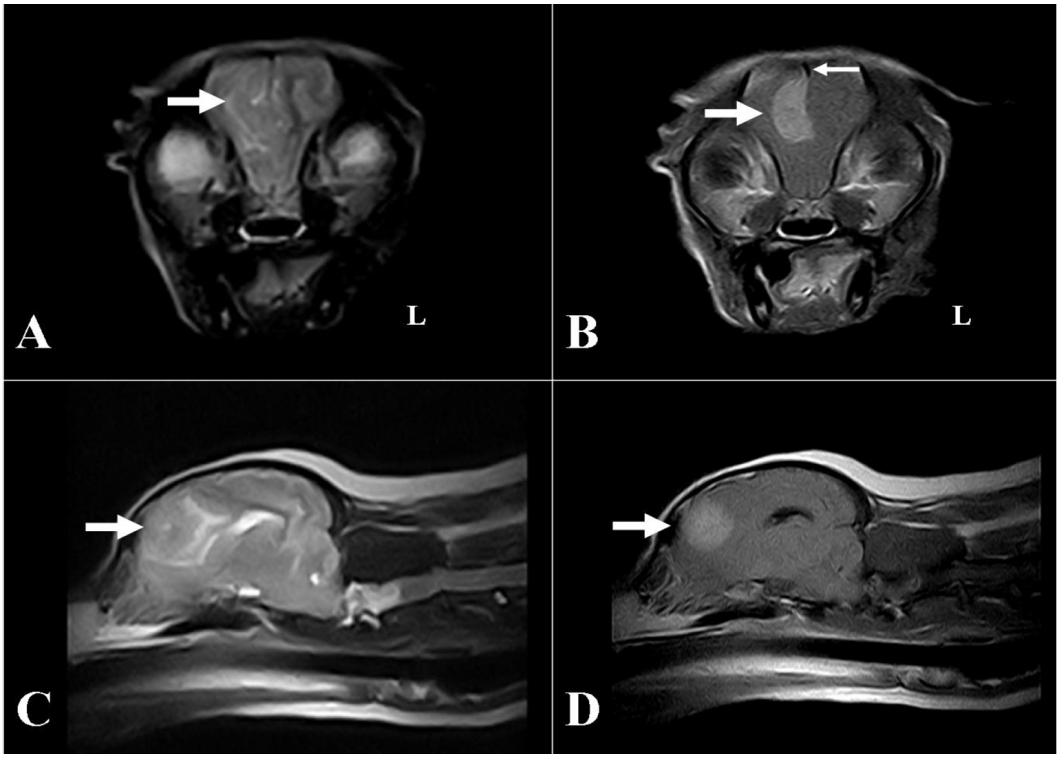

Fig 1. MR images of a dog with suspected meningioma. On transverse and sagittal T2-weighted images, hyperintensed lesion is detected in the right frontal lobe of forebrain (A and C: arrow). A well defined hyperintense lesion is seen on postcontrast T1-weighted images (B and D: arrow) at the same level as panel A and C, respectively. And adjacent dura is thickened and enhanced (dural tail sign) (B: small arrow).

the CSF. In addition, the results of bacterial and fungal culture on the CSF were all negative.

Based on these results, we tentatively diagnosed this case as intracranial meningioma. The client declined surgical intervention and radiation therapy due to the expense of the treatment and the age of the patient. Thus, hydroxyurea (Hydrin®, Korea United Pharm., Korea; 50 mg/kg, PO, three times a week) with phenobarbital (Phenobarbital®, Myung In Pharm., Korea; 3 mg/kg, PO, BID) was administered and seizure was controlled for 6 months. However, seizure episode was relapsed 6 months after therapy. Although phenobarbital dosage was increased to 5 mg/kg and potassium bromide (KBr, Sigma, USA; 40 mg/kg, PO, SID) was administered, clinical sign was not improved and worsened gradually. Therefore, prednisolone (Prednisolone®, Korea Phama, Korea; 0.5 mg/kg, PO, q 12 hours) was then administered with hydroxyurea and clinical sign was controlled. Prednisolone dosage was tapered to 0.25 mg/kg, gradually. The patient's symptom was controlled well by hydroxyurea and prednisolone therapy without significant side effects for fourteen months. Fourteen months after initial therapy, neurological signs including seizure, ataxia and cranial nerve deficits were relapsed and not responded on medical therapy. Ultimately, the patient was euthanized due to worsening neurological dysfunctions. Necropsy was not performed due to refusal of the client.

Discussion

Generally, intracranial tumors should be strongly suspected in elderly patients with progressive neurological signs. However, definitive diagnosis of intracranial tumor requires histopathological confirmation, although a confident tentative diagnosis can often be attained by advanced imaging results. CBC and serum biochemical analysis should be examined before performing the advanced imaging. And thoracic radiography and abdominal ultrasonography should be obtained to help rule out the possibility of metastatic neoplasia. In the present case, CBC, serum biochemical analysis, thoracic radiography and abdominal ultrasonography revelaed no remarkable findings. Based on these results, metastatic neoplasia was rule out.

According to previous studies, MRI proved to be more accurate for detection of an intracranial mass than computed tomography (CT) (1,18). MRI findings in dogs with specific intracranial tumors are not clearly determined and appeared variously. However, some typical features distinguish meningioma from other intracranial tumors. Previous reports described that meningiomas tend to have a broad-based, extra-axial attachment, exhibit distinct tumor margins, and have contrast-enhanced signs as dural tail sign (1,6,7,18,19). These MRI findings were also observed in the present case.

Hydroxyurea is an antineoplastic agent that inhibits ribonu-

cleotide reductase, an enzyme essential for DNA synthesis without effect on RNA or protein biosynthesis (11,16). And hydroxyurea induce to induction of cell death in the S phase of the cell cycle (16). In veterinary medicine, hydroxyurea is a myelosuppressive agent that has been used to treat polycythemia due to noncardiovascular disease, chronic myelogenous leukemia, chronic basophilic leukemia, mast cell tumors, hypereosinophilic syndrome, and essential thrombocythemia (3,4,8,10,12,14). A previous report (16) demonstrated that hydroxyurea induces apoptosis in meningiotheliomatous tissue in vitro and in vivo. In human medicine, there were several reports of hydroxyurea used in the treatment of meningioma patients (5,9,13,15,17). However, there were a few reports of hydroxyurea attempts to treat meningiomas in veterinary medicine (11,19). According to one previous report (19), hydroxyurea with steroid therapy in a intracranial meningioma dog showed reducing tumor size and improving clinical symptoms. Moreover, this dog survived for 14 months after hydroxyurea with steroid therapy and ultimately diagnosed as a psammomatous-type meningioma based on histopathological findings.

Survival times with brain tumors that are managed only symptomatically with steroids and/or anticonvulsants are poor, with the reported median survival time being 59 to 81 days from diagnosis (1,2). Another report (5) demonstrated a median of 6 days with no therapy or symptomatic therapy only.

Definitive therapy may consist of chemotherapy, surgical removal, radiation therapy, or a combination of two or more methods. The prognosis for treatment of canine meningioma is guarded. One report (1) indicated that the median survival time was 3.9 months with only steroid therapy. In recent reports of canine intracranial meningioma, the median postoperative survival time was approximately 7 months (3,5,20). Radiation therapy for canine meningioma as the sole therapy resulted in median survival times between 5 and 9 months, and dogs that surgery with radiation therapy had a median survival time of 16.5 months (3,5,16,20). Recently, long-term survival after lomustine therapy for intracranial meningioma in two dogs was reported (6,7). In that reports (6,7), two dogs with meningioma survived for 8 and 13 months with only combination chemotherapy of lomustine and prednisolone. The present patient with intracranial meningioma survived for 14 months with combination chemotherapy of hydroxyurea and prednisolone. Radical surgical therapy of meningiomas causes high morbidity rates, and the risks and limitations of surgery and radiation therapy are well known (17).

In the present case, surgical removal and radiation therapy was not performed because the client declined this treatment. Although necropsy was not performed due to refusal of the client, the present case was strongly suspected to intracranial meningioma based on MRI findings. Thus, we used hydroxyurea chemotherapeutic agent and the response was good. We postulated that apoptotic and antiproliferateive effect of hydroxyurea to meningioma cells and antiedema effect of prednisolone might be improved the neurological symptom in the present case (16,17). Previously reported side effects of hydroxyurea were myelosuppression, gastrointestinal problems and dermatological toxicity (11,13,17,19). In this case, there were no significant side effects during hydroxyurea therapy.

Although the present case was not definitely diagnosed and only a single case report, our experience suggests that medical therapy with hydroxyurea in intracranial meningioma could be lesser life-threatening useful method than surgery and radiation therapy in geriatric patients.

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