**Clinical management of suspected intracranial meningioma in three dogs with pulsed high-dose hydroxyurea**

Jae-Geum Cho, Kun-Ho Song, Kyoung-Won Seo*

Department of Veterinary Internal Medicine, College of Veterinary Medicine, Chungnam National University, Daejeon 34134, Korea

(Received: March 21, 2018; Accepted: April 5, 2018)

**Abstract:** Three aged dogs, all over 15 years old, with multiple seizure events and various neurologic signs such as head turn and ataxia were brought to the referring hospital. Two cases were tentatively diagnosed with intracranial meningioma based on magnetic resonance imaging, and one case was histopathologically confirmed as meningioma at necropsy. All dogs improved after initiation of pulsed high-dose hydroxyurea (HU) treatment. Clinical sign relapses were managed by repeating high-dose HU without obvious side effects. Pulsed high-dose HU can be applied when clinical signs are refractory to the traditionally recommended dosage for intracranial meningioma in dogs.

**Keywords:** brain neoplasms, chemotherapy, hydroxyurea, meningioma, seizures

Meningioma is an extra-axial, primary tumor that originates from the meninges surrounding the brain, and comprises a large portion of space-occupying lesions in the cranium, with a prevalence of approximately 33–49% of primary brain tumors in aged dogs (median age, 9 years) [1, 3, 5]. Meningioma is generally considered as a benign tumor; however, 33% of cases in dogs is accompanied by invasion, unlike in other species [9]. Therefore, dogs with meningioma should be thoroughly evaluated using a tumor grading system to determine the accurate prognosis [4, 6, 7, 10]. The World Health Organization (WHO) international histological classification system was modified for use in dogs and includes the following grades: Grade 1 (benign), Grade 2 (atypical), and Grade 3 (malignant) [2, 4, 9].

The most common clinical signs of intracranial meningioma in dogs include seizures, ataxia, behavioral changes, visual deficits, circling, and other various neurologic dysfunctions [1, 4, 6]. Neurologic signs vary depending on the location and size of the tumor, and secondary effects such as inflammation, edema, and intracranial hypertension can also add to the severity of signs in the patient [3, 9].

Treatment options for intracranial meningioma in dogs can be divided into three types as follows: definitive (surgery and radiation), palliative (chemotherapy, anticonvulsant therapy, and decompressive agents), and alternative (gene, immune, and hormonal therapies) [1, 5, 9]. Surgical removal with adjunctive radiotherapy is the treatment of choice for improving patient quality of life and providing longer survival times (16–30 months) [1, 2, 4, 6, 9]. However, most cases are limited to only palliative treatment due to cost, owner compliance, high risk of anesthesia, and surgical inaccessibility of the tumor. As chemotherapeutics penetrating the blood brain barrier, hydroxyurea (HU) is reportedly used for meningioma as an adjunctive or sole therapy, since it is inexpensive and has minimal and reversible side effects in veterinary medicine [1, 4]. The traditional dosage of HU reported for the treatment of intracranial meningioma in dogs is 20–30 mg/kg daily, with or without glucocorticoids for vasogenic edema [4, 7, 8]. However, a number of studies in veterinary medicine have shown that managing clinical signs with the traditional dosage is more difficult as time progresses [3, 9].

A 19-year-old spayed female Maltese (Case 1) with a history of several generalized tonic-clonic seizures was presented neurologically stable to the Veterinary Teaching Hospital of Chungnam National University. The owner complained that the patient had displayed intermittent seizures and neurologic signs, such as altered mentation and circling, for the past year. On magnetic resonance imaging (MRI), a homogenous contrast mass (2.5 × 1.4 cm) with contrast enhancement in the right frontal lobe and olfactory bulb, along with an additional mass in the right nasal cavity, was identified and was accompanied by edema and compression of the lateral ventricle (Fig. 1A and B), and the patient was diagnosed with a probable intracranial meningioma, based on MRI features. Concurrent degenerative conditions, mitral valve diseases (ACVIM stage B2: hemodynamically significant valve
regurgitation but asymptomatic) and chronic kidney disease (IRIS stage 2: creatinine 1.4–1.8 mg/dL), were also diagnosed. Palliative chemotherapy was chosen in this case, since surgery was declined due to the difficulty of accessing the lesion. The patient’s neurologic status gradually improved with a high dose of HU (50 mg/kg/day), dexamethasone (0.25 mg/kg/day), and an anticonvulsant during the initial 7 days and stabilized while the dosage was reduced to 20 mg/kg/day. However, the patient died of cardio-renal syndrome with respiratory failure 4 months later.

A 16-year-old intact female Shih Tzu (Case 2) in status epilepticus and with a right-sided head turn was referred, and the clinical signs had worsened over the previous 2 years according to the owner. Along with multiple seizure episodes, a variety of neurologic signs, such as altered mentation, head tilt, and nystagmus, were observed in this case. On MRI, a mass with a dural tail sign (2.1 × 3.0 cm) in the right temporal lobe was identified and was compressing the brainstem and cerebellum, inducing severe peritumoral edema in T2-weighted transverse image (A) and T1-weighted transverse image (B). A 16-year-old castrated male Yorkshire Terrier (Case 3) after the second cluster seizure episodes. Mass (1.2 × 1.0 cm) formed from meninges at the level of optic chiasm and hypothalamus with peritumoral edema in T2-weighted transverse image (C) and T1-weighted transverse image, post contrast (D).

Fig. 1. A 19-year-old female Maltese (Case 1) with several generalized tonic-clonic seizures. Homogenous contrast mass (2.5 × 1.4 cm) with contrast enhancement in right frontal lobe and edematous lesion and compression of lateral ventricle in T2-weighted transverse image (A) and T1-weighted transverse image (B). A 16-year-old castrated male Yorkshire Terrier (Case 3) after the second cluster seizure episodes. Mass (1.2 × 1.0 cm) formed from meninges at the level of optic chiasm and hypothalamus with peritumoral edema in T2-weighted transverse image (C) and T1-weighted transverse image, post contrast (D).

Fig. 2. A 16-year-old intact female Shih Tzu (Case 2) with presentation of status epilepticus and right head turn. Mass with dural tail sign (2.1 × 3.0 cm) on right temporal lobe in T1-weighted transverse image (A) and decreased mass size (2.1 × 3.0 to 1.7 × 1.2 cm) at 6 months after HU and dexamethasone combination therapy T1-weighted transverse image, post-contrast (B).

Fig. 3. A 16-year-old intact female Shih Tzu (Case 2). Brain tissues obtained at necropsy representing inflamed and partially necrotic meningioma. H&E stain. 50× (A) and 400× (B).

1.2 cm) and peritumoral edema was noted on MRI recheck 6 months into treatment (Fig. 2B). When seizures or other neurologic signs occasionally recurred, the high-dose HU was again administered and then tapered back to the traditional dose (20–30 mg/kg/day), and the dog managed well with the adjustments. She survived for 10 months and was then euthanized due to uncontrollable neurologic dysfunctions, and the diagnosis of an inflamed and necrotic intracranial meningioma was confirmed by histopathological evaluation of biopsy samples taken at necropsy (Fig. 3).

A 16-year-old castrated male Yorkshire Terrier (Case 3) was presented after a second episode of cluster seizures, and the owner reported an abrupt onset of signs. On initial screening, hepatic neoplasia (suspected biliary adenoma) was identified, and MRI of the brain revealed a mass (1.2 × 1.0 cm) originating from the meninges at the level of the optic chiasm and hypothalamus with moderate peritumoral edema (Fig. 1C and D). The owner declined surgical treatment due
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