



NOTE

Internal Medicine

Successful use of prednisolone and radiation therapy in a dog with intracranial histiocytic sarcoma

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ABSTRACT. The ideal treatment for intracranial histiocytic sarcoma (HS) remains unclear. Herein, we report a case of intracranial HS that was successfully treated using prednisolone and radiation therapy. The patient was a 9-year-old spayed female Pembroke Welsh Corgi that presented with epileptic seizures. Magnetic resonance imaging revealed a contrast-enhancing mass adjacent to the right piriform lobe. Prednisolone administration (1 mg/kg/day) decreased the lesion size. Additional palliative radiation therapy (total dose, 37 Gy) resulted in complete disappearance of the lesion. However, on day 164, the dog's neurological signs deteriorated, and she was euthanized. Necropsy revealed an intracranial metastasis of HS via the cerebrospinal fluid without any extracranial metastasis. Nonetheless, combined prednisolone and radiation therapy might be effective in treating intracranial HS.

KEY WORDS: brain tumor, canine, histiocytic sarcoma, magnetic resonance imaging, radiotherapy

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Canine intracranial histiocytic sarcoma (HS) is a rare disease. Although surgery, radiation therapy, and chemotherapy are reported to be effective against soft-tissue HS, the ideal treatment for intracranial HS remains unclear. Herein, we report a case of canine intracranial HS that was successfully treated using prednisolone and radiation therapy.

The patient was a 9-year-old spayed female Pembroke Welsh Corgi with approximately 2 months history of episodic epileptic seizures. She was treated using phenobarbital; however, the seizures could not be controlled. She was then referred to Animal Medical Center, Nihon University for brain imaging.

The patient weighed 16.5 kg. A physical examination, complete blood count, blood chemical analysis, and urinalysis revealed no abnormalities. A neurological examination revealed decreased proprioception in the left hind limb, but the spinal cord reflexes and cranial nerves were normal. This implied that the neuroanatomical location of the disease could be in the right forebrain. Magnetic resonance imaging (MRI) revealed an extra-axial solid mass adjacent to the right piriform lobe and thalamus, with a low signal intensity on T1-weighted images and well-defined homogenous enhancement after contrast injection (Fig. 1A and B). The brain parenchyma surrounding the mass showed increased signal intensity on T2-weighted images (T2WIs) and fluid-attenuated inversion recovery (FLAIR) images, suggesting brain edema (Fig. 1C and 1D). Therefore, we did not collect a cerebrospinal fluid (CSF) sample. Computed tomography (CT) did not reveal any abnormalities in the thorax or abdomen. The differential diagnosis was meningioma and intracranial HS [5]. Accordingly, she was prescribed prednisolone (1 mg/kg/day) and isosorbide (1 ml/kg bid) in addition to phenobarbital (3 mg/kg bid). After consulting with the owner, we also decided to start palliative radiation therapy for the brain mass.

On day 13, a neurological examination showed that the decreased proprioception in the left hind limb had improved to normal, and MR and CT images were acquired simultaneously for radiation planning. MRI revealed a size reduction of the contrast-enhancing mass lesion, probably caused by the administration of prednisolone (Fig. 1E). Moreover, T2WIs and FLAIR images revealed a reduction in the signal intensity around the mass, suggesting a reduction in the edematous lesion (Fig. 1F). Although the possibility of an intracranial lymphoma was considered, radiation therapy was initiated as planned. The administration of prednisolone was continued, and the isosorbide dose was tapered and subsequently discontinued.

Palliative radiation therapy was carried out using a three-dimensional conformal method, and dose distribution was calculated using a treatment planning software (XiO; Elekta, Tokyo, Japan) utilizing CT images. The gross tumor volume was defined from

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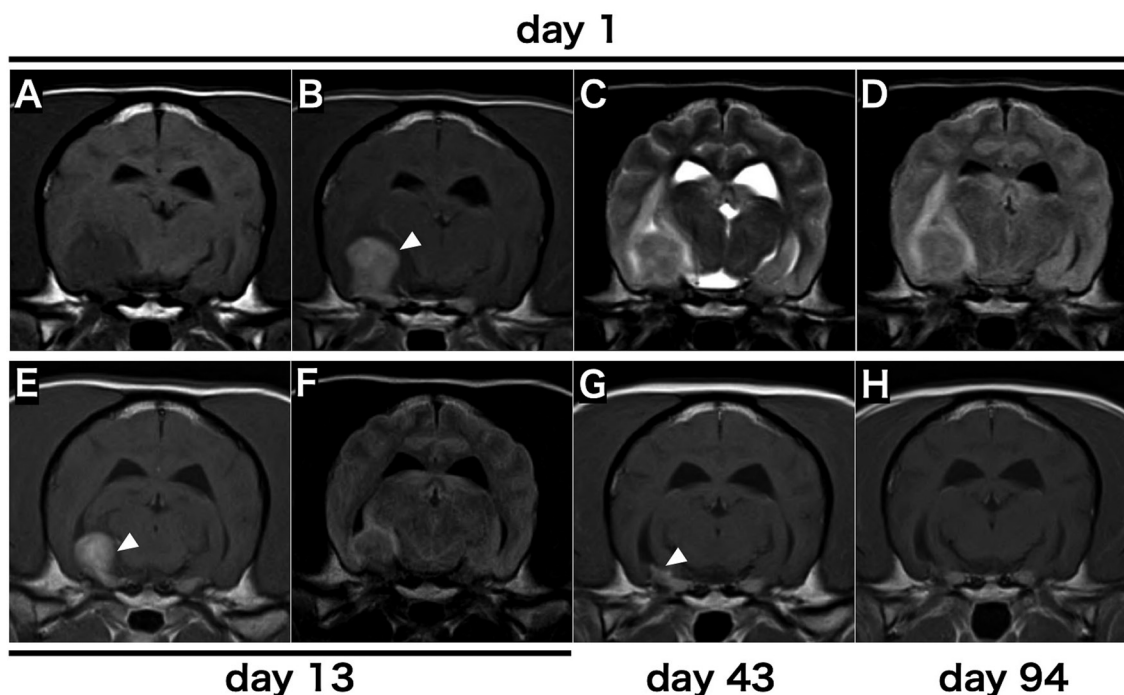


Fig. 1. Transverse magnetic resonance images (thalamus level) acquired on day 1 (A–D), day 13 (E, F), day 43 (G), and day 94 (F). (A) T1-weighted image (T1WI). A hypointense-signal lesion is observed adjacent to the right piriform lobe and thalamus. (B) Postcontrast T1WI. There is a mass at the center of the hypointense-signal lesion (arrowhead) (mass size: length 22 mm × width 14 mm × height 16 mm). It shows homogenous contrast enhancement. (C) T2-weighted image and (D) fluid-attenuated inversion recovery (FLAIR) image. A diffuse hyperintense signal is observed around the mass. (E) Postcontrast T1WI. The contrast-enhancing mass has shrunk (arrowhead) (mass size: length 19 mm × width 11 mm × height 13 mm). (F) FLAIR image. The area of the hyperintense signal around the mass is smaller on day 13 than on day 1. (G) Postcontrast T1WI. The contrast-enhancing mass has almost disappeared (arrowhead). (H) Postcontrast T1WI. The mass has completely disappeared.

the intracranial contrast-enhancing mass on MRI. The clinical target volume (CTV) was delineated as a contrast-enhancing mass on day 1, i.e., before the mass shrank. An additional 5-mm margin was added to the CTV. The radiation beam was delivered from 4 ports, and the prescription dose was calculated at the center of the CTV. A linear accelerator equipped with a multi-leaf collimator (4 MV X-ray, PRIMUS Mid-Energy; Canon Medical Systems, Ohtawara, Japan) was used for radiation therapy. The dog was treated with 5 doses once weekly (1×5 Gy, followed by 4×8 Gy; total dose, 37 Gy). Radiation therapy was completed as planned, without any apparent acute side effects.

On day 43, the last day of radiation therapy, MRI revealed that the contrast-enhancing mass was still shrinking and that the edematous lesion had completely disappeared (Fig. 1G). CT also revealed no abnormality. Accordingly, the prednisolone dose was tapered to 0.7 mg/kg/day. On day 94, MRI revealed complete disappearance of the intracranial abnormality, suggesting a complete response (Fig. 1H). The prednisolone dose was further tapered to 0.3 mg/kg/day, and the phenobarbital dose was tapered and subsequently discontinued.

Around day 146, the dog appeared depressed and displayed ataxia but did not experience seizure relapse. On day 164, her left eye vision was suspected to have weakened because of a decreased menace response, and postural reaction in the left fore and hind limbs was decreased or absent. MRI revealed a faint contrast-enhancing lesion within the radiation field, as well as an edematous lesion spreading along the right lateral ventricle (Fig. 2). Multiple contrast-enhancing small nodules also appeared along the ventricles, and edematous changes spread adjacent to the cerebellum and optic chiasm. Additionally, the lateral ventricles were enlarged, possibly because of the obstruction of CSF flow at the mesencephalic aqueduct due to the mass lesion. Recurrence of the brain mass and intracranial metastasis via the CSF were suspected. After receiving the owner's consent, the dog was euthanized, and a whole-body necropsy was performed.

The tumor nodules were scattered along the brain ventricles. Histological analysis revealed that these nodules were composed of round cells containing abundant eosinophilic cytoplasm (Fig. 3). Immunohistochemical analysis, using same methods as described before, revealed that the tumor cells were diffusely positive for HLA-DR (anti-HLA-DR mouse monoclonal antibody [TAL.1B5], Dako, Tokyo, Japan) and Iba-1 (anti-Iba-1 polyclonal antibody, Wako, Osaka, Japan) [13]. This finding was consistent with that of HS. Within the irradiated area, no tumor was observed, but partial encephalomalacia, which was suspected to be due to delayed radiation toxicity, was observed. A CSF smear prepared using a sample obtained from the cistern showed many vacuole-containing, slightly atypical round cells, which were suspected to be the invasive and exfoliated tumor cells. No metastasis of HS was observed

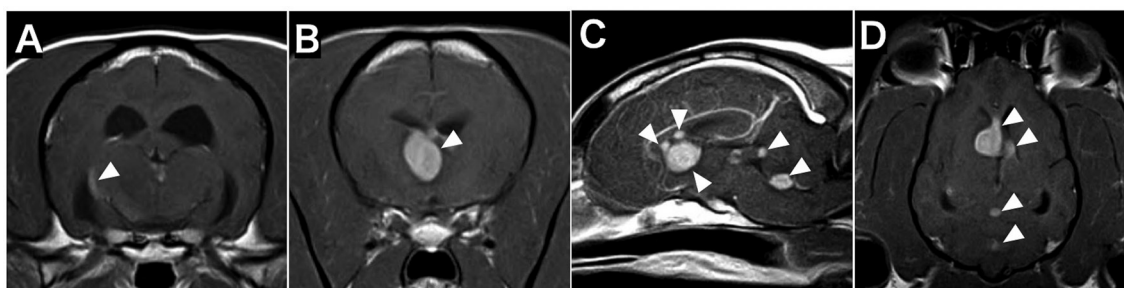


Fig. 2. Postcontrast T1-weighted images acquired on day 164. **(A)** A transverse section (thalamus level). A faint contrast-enhancing lesion (arrowhead) is observed, which is later confirmed as encephalomalacia. Note that the lateral ventricle has enlarged compared to previous images. **(B)** A transverse section at the level of the rostral edge of the lateral ventricle, **(C)** a mid-sagittal section, and **(D)** a dorsal section (mesencephalic aqueduct level). Note the new contrast-enhancing nodules (arrowhead) emerging along the ventricles.

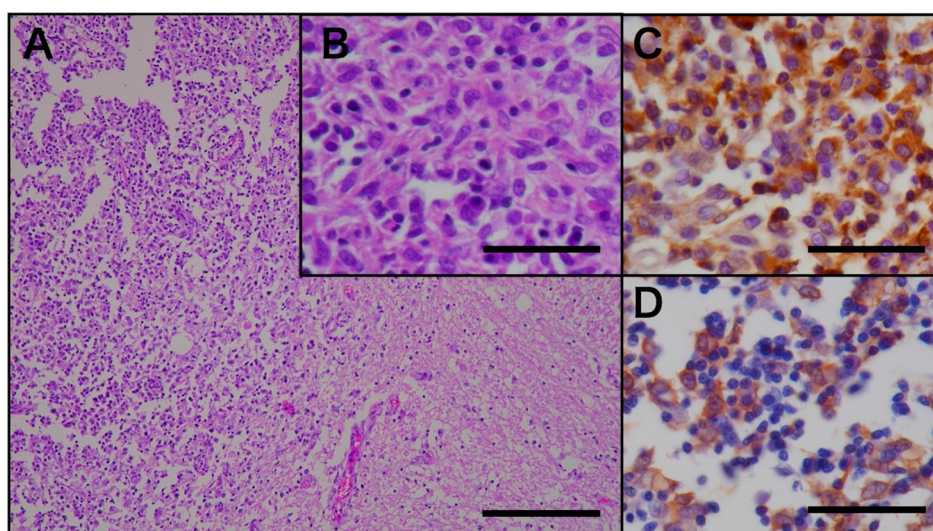


Fig. 3. Histopathological features of one of the nodules showing contrast enhancement on magnetic resonance imaging on day 164. **(A, B)** Hematoxylin-eosin stain. The nodule is composed of round cells containing abundant eosinophilic cytoplasm. **(C)** Immunohistochemically, the round tumor cells are diffusely positive for HLA-DR and **(D)** Iba-1. Bar=200 μ m (A) and 50 μ m (B–D).

in the thorax or abdomen. Nevertheless, a 10-mm mass was observed at the left fourth mammary chain and was diagnosed as a low-grade mammary adenocarcinoma.

On the basis of the case findings, we identified two important clinical issues. First, prednisolone has an antitumor effect on intracranial HS even when used as the sole treatment at anti-inflammatory doses. Second, radiation therapy is effective in treating intracranial HS when used in combination with prednisolone.

Prednisolone revealed an antitumor effect on intracranial HS. Prednisolone was prescribed as a symptomatic treatment for brain edema, and approximately 2 weeks later, the brain mass was found to have shrunk. Although the duration of the effect of prednisolone remains unclear, it demonstrated a tumor-shrinking effect in intracranial HS, even when used at anti-inflammatory doses. Although the metastatic rate is low for intracranial HS, the absence of metastatic lesions other than in the brain at necropsy may be attributed to this effect of prednisolone [8]. Prednisolone is one of the multiagent chemotherapeutic drugs used for treating HS; however, its effect as a sole treatment remains unclear [1, 10, 11]. A previous report documented a case of enlargement of the intracranial HS lesion after prednisolone administration [12]. A few studies also reported that the time to tumor progression was shorter when prednisolone was administered for periarticular HS [3, 6]. Therefore, the effect of prednisolone could differ from patient to patient; however, when intracranial HS is suspected, prednisolone is worth prescribing not only for its anti-inflammatory effect but also for its expected anti-tumor effect [5, 8].

Although radiation therapy was effective in intracranial HS when used in combination with prednisolone, we cannot prove its effectiveness as a sole treatment. Nevertheless, our findings suggest it could have additive or synergistic effects. Only a few reports have documented using radiation therapy for treating primary intracranial HS, and none of them could prove its effectiveness [9]. To the best of our knowledge, this is the first report to demonstrate the effects of radiation therapy on intracranial HS. Since no

neoplastic lesion was observed within the radiation treatment field at necropsy, intracranial HS seemed radiosensitive. Moreover, no metastatic lesions were observed other than in the cranial vault; therefore, radiation therapy could be selected as a powerful local treatment modality. Radiation therapy has also been reported to be effective in periarticular HS [3, 7]. Nevertheless, the optimal radiation therapy protocol and dose for the treatment of intracranial HS require further clarification.

In cases where intracranial HS is suspected, care should be taken to prevent its intracranial spread rather than distant metastasis. In the present case, an edematous area was observed around the contrast-enhancing mass at the first presentation, and this was possibly a tumor-invasion area. If intracranial HS is highly invasive, its intracranial dissemination can be prevented or delayed by setting up a radiation treatment margin wide enough to cover the edematous area. A previous study reported four cases of intracranial HS that invaded the meninges and brain parenchyma [12]. Another case report documented intracranial HS invading the brain parenchyma and spreading into the ventricles, even though MRI revealed that the tumor lesions seemed to developed outside of the brain [4]. When intracranial HS is presumed to spread via the CSF, whole-ventricular irradiation using a cutting-edge radiation machine, if available, might be ideal [2]. Of course, widening the radiation field treated increases severe side effects. Furthermore, the administration of chemotherapeutic agents, such as lomustine, may be effective in preventing intracranial dissemination via the CSF, but this option was not selected in the current case [1, 10, 11].

In conclusion, we found that prednisolone administration as a sole treatment had an antitumor effect on intracranial HS, even at anti-inflammatory doses. Radiation therapy was also effective in treating intracranial HS when used in combination with prednisolone. Therefore, combination treatment using prednisolone and radiation therapy could be an effective strategy for treating intracranial HS.

POTENTIAL CONFLICTS OF INTEREST. The authors have nothing to disclose.

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