Long-Term Survival in a Dog with Anaplastic Oligodendroglioma Treated with Radiation Therapy and CCNU

Daisuke HASEGAWA1), Kazuyuki UCHIDA3), Takayuki KUWABARA1), Shunta MIZOGUCHI1), Naoko YAYOSHI2) and Michio FUJITA1)

1)Division of Veterinary Radiology, Department of Veterinary Science, Nippon Veterinary and Life Science University, 1–7–1 Kyounan-cho, Musashino-shi, Tokyo 180–8602, Japan
2)The Animal Medical Center, Department of Veterinary Science, Nippon Veterinary and Life Science University, 1–7–1 Kyounan-cho, Musashino-shi, Tokyo 180–8602, Japan
3)Department of Veterinary Pathology, The University of Tokyo, 1–1–1 Yayoi, Bunkyo-ku, Tokyo 113–8657, Japan

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ABSTRACT. A 9 year-old, neutered, male French Bulldog showing cluster seizures was diagnosed with a glioma in the right piriform cortex by MRI. Hypofractionated radiation therapy (RT) was performed using a linear accelerator. Although the lesion had involuted significantly at 2 months after RT, recurrence was observed at 4 months after RT. Chemotherapy was started using CCNU (60 mg/m² every 6–9 weeks) and was continued for one year. Follow-up MRI revealed involution of the lesion and the intervals of CCNU were increased to every 9–14 weeks. Two years after the first presentation, the dog suffered status epilepticus, followed by deficits of left sided postural reaction with cognitive dysfunction. The dog died on day 910, and histopathological diagnosis confirmed anaplastic oligodendroglioma.

KEY WORDS: canine, CCNU, MRI, glioma, radiation therapy.


Gliomas such as oligodendrogliomas and astrocytomas are relatively common intracranial and intraparenchymal tumors in dogs [19]. In contrast to meningiomas, gliomas may be treated with megavoltage radiation therapy (RT) and/or chemotherapy (nitrosoureas) because of their location and infiltration [2, 7, 15, 18]. Several reports have documented the results and prognosis of gliomas treated with RT [3, 4] and chemotherapy [6, 8, 9]. However, detailed descriptions of individual cases are very limited.

Here, we describe the long-term survival (2 years and 6 months) of a dog with glioma (final diagnosis: anaplastic oligodendroglioma) that was treated with megavoltage RT and CCNU (lomustine) therapy.

A 9 year-old, 13.0 kg, neutered male French Bulldog presented with a complaint of cluster seizures that had started 2 weeks earlier. The seizures consisted of focal seizures (mastication, salivation, and vomiting) with secondary generalization. Although the neurological examination was normal and the seizures were controlled by phenobarbital (PB) (2 mg/kg, PO, BID), magnetic resonance imaging (MRI) was performed to evaluate intracranial disease. Cranial MRI (1.5 Tesla) revealed a lesion showing hyperintensity on T2-weighted (T2W) and fluid-attenuated inversion recovery (FLAIR) images, and hypointensity on T1-weighted (T1W) images without contrast enhancement (on gadolinium enhancement (Gd-) T1W) in the right piriform area (piriform cortex and amygdala) with mild mass effect (Fig. 1A, 1B). From these MRI findings, a glioma, likely a low-grade astrocytoma or oligodendroglioma, was diagnosed clinically (day 0).

Because of the location of the lesion and by the owner’s request, megavoltage radiation therapy (RT) using a 4 MV X-ray linear accelerator was started on day 14. The radiation treatment area was planned with software based on CT images. The lesion was treated with hypofractionated radiation that was 6 Gy per fraction from 4 directions (0°, 90°, 180° and 270°) once a week for 6 weeks (total 36 Gy). During the period of RT, no clinical signs, including seizures, occurred under PB therapy, and no problems associated with the RT or anesthesia were observed. Two months after RT (day 56), follow-up MRI (day 116; 4 months after RT; 1.5 Tesla) was performed, and showed extension of the lesion with significant contrast enhancement and partial ring enhancement (Fig. 1C, 1D). The lesion infiltrated not only the internal capsule but also the thalamus beyond the piriform area. Because contrast enhancement of gliomas is more often associated with a higher grade of malignancy [1, 17,
these findings suggested a malignant transformation of the glioma, which reduced the efficacy of further RT for this case. Chemotherapy or symptomatic therapy/euthanasia was suggested to the owner, who chose chemotherapy. Chemotherapy with CCNU was started on day 120 at 60 mg/m² every 6 weeks per os. Obvious side effects of the CCNU treatment were not observed, except for mild leukopenia (pre-treatment average, 6,350/µl; 1 week post-CCNU average, 4,575/µl) that recovered within 2 weeks after each administration (average at just before each CCNU, 6,271/µl). During CCNU therapy, the clinical signs gradually improved and only a loss of proprioception of the left hind limb remained at the time of the third administration. Since the clinical signs had not changed, the interval of CCNU was increased to every 9 weeks after the 6th administration. After the 8th CCNU administration (day 575; approximately 1 year after starting CCNU), a third follow-up MRI (3.0 Tesla) was performed. On MR images, the mass lesion had almost disappeared, although subtle hyperintensities on T2W/FLAIR remained around the right lateral and third ventricles without contrast enhancement on Gd-T1W. In addition, these changes resulted in parenchymal atrophy, which extended the ventricular system (Fig. 1G, 1H). Based on the results of MRI and the improvement of clinical signs, the interval of CCNU was increased further to every 14 weeks. Two weeks after the 9th CCNU (day 600), focal seizures with secondary generalization relapsed occurred, and the dose of PB was increased from 2.0 to 3.5 mg/kg, BID, for 1 week. The seizures were controlled, but the dog showed severe depression. Although the serum concentration of PB was 24.4 µg/ml (therapeutic range: 15–35 µg/ml), it was thought that the depression was caused by the increased PB dosage. Therefore, 10 mg/kg, BID of zonisamide (ZNS) and 30 mg/kg, SID of potassium bromide (KBr) were started, and PB was gradually reduced and withdrawn over 2 months (reduced 0.5 mg/kg each week, total 8 weeks). The dog became lucid within 2 weeks after beginning PB reduction. Several seizures (average of 1.5 seizures/month) were observed, but CCNU therapy was continued. On day of 838 (1 week after the 11th CCNU administration), the dog suffered focal status epilepticus with secondary generalizations despite being under ZNS (36.4 µg/ml; therapeutic range: 10–40 µg/ml) and KBr (serum concentration was not measured) therapy. Status epilepticus was controlled by intravenous diazepam (0.5 mg/kg × 2 times) and loading of PB (4.0 mg/kg × 4 times). After recovering from status epilepticus, the dog became depressed again and then showed cognitive dysfunction (i.e. disorientation, aimless pacing/circling, loss of house training, failure to recognize his owner, etc.). From serum chemistry, hypothyroidism (T4:<0.5 µg/ml; reference range: 1.1–3.6 µg/ml) was revealed. Levothyroxine therapy and dietetic treatment (Hill’s b/d) were added. However, the clinical signs of cognitive dysfunction showed no improvement. Although there was no seizure recurrence, neurological deficits suggested right cerebral dysfunction and behavioral

Fig. 1. Time-course changes of MR findings. All images show the transverse plane at the level of the piriform area. A, C, E, and G are FLAIR images and B, D, F, and H are Gd-T1W images. A-F were obtained by a 1.5 Tesla MRI system, and G & H were obtained by 3.0 Tesla. A & B: The first MRI (day 0). The lesion shows hyperintensity on FLAIR, and hypointensity without enhancement on Gd-T1W was found in the right piriform area with slight mass effect. C & D: Two months after RT (day 56). The lesion was significantly regressed with mild hyperintensity on FLAIR and subtle enhancement on Gd-T1W. E & F: Four months after RT (day 116). The lesion showed regrowth and further extension to the thalamus with ring enhancement. Malignant transformation was suspected. G & H: After the 8th administration of CCNU (day 575). The lesion significantly regressed again. Although subtle hyperintensities are observed around the ventricular system on FLAIR, there was no contrast enhancement. The right lateral ventricle, foramen of Monro, and third ventricle were dilated by parenchymal atrophy.
problem (cognitive dysfunction). Symptomatic treatment was continued. However, the dog died calmly on day 910 (approximately 2 years and 6 months). Thirteen hours after the animal’s death, postmortem MRI and necropsy were performed. On the postmortem MRI, the mass lesion showing T2W hyperintensity and T1W hypointensity was recognized again, and sporadic spots of hypointensity on T2W that coincided with microhaemorrhage were found in the hippocampi and at the boundaries between the gray and white matter (Fig. 2). Histopathological examinations revealed lesions of a solid proliferation of tumor cells with small single or polymnucleated nuclei and a high nuclear/cytoplasmic ratio (Fig. 3). These tumor cells proliferated diffusely in the right piriform area, mainly in the white matter. Within the proliferation area, there was marked proliferation of small vessels, microhemorrhage, micronecrosis, and the deposition of calcium. Furthermore, pseudopalisading of tumor cells was observed around necrotic nests. Immunohistochemically, the tumor cells were intensely positive for olig2, and some were also positive for doublecortin (DCX), while completely negative for glial fibrillary acidic protein (GFAP), nestin, and beta III tubulin [5, 12]. Based on these findings, the lesion was diagnosed as anaplastic oligodendroglioma according with the WHO classification [12, 13].

Studies are limited as to irradiation and/or chemotherapy for canine brain tumors, especially for individual cases. Furthermore, only a few reports have described the pathological diagnosis of the tumor type and repeated imaging follow-ups. With the application of MRI in the veterinary field, it is incumbent upon physicians to review this information.

In the present case, the lesion showed parenchymal swelling with mild mass effect and T2W hyperintense and T1W hypointense areas without contrast enhancement in the piriform area on the first set of MRI (Fig. 1A, 1B), which was finally diagnosed as oligodendroglioma. Canine gliomas, especially oligodendrogliomas, are recognized as parenchymal (intra-axial) swellings with T2-hyperintensity and T1-hypointensity with or without contrast enhancement, and tend to develop in the piriform and temporal lobe [19, 20]. Similar MR findings in this area are often observed as reversible lesions following severe seizure activities [16]. These seizure-related lesions are generally recognized as acute changes and do not persist for a long time, especially the associated swelling. Further, more severe lesions, i.e. irreversible lesions, may result in necrotic and/or atrophic lesions and may extend to the hippocampi [10, 11]. The first MRI of this case was obtained at 2 weeks after the cluster...
seizures, and the lesion was restricted to the piriform area. Therefore, we diagnosed the initial lesion of this case as low-grade glioma. The imaging findings of oligodendrogliomas are discussed below.

In a latest study of megavoltage RT using the conventional protocol alone for 46 canine brain tumors, the median survival time was 699 days [3]. Although this study included various tumor types such as meningiomas and pituitary tumors, most were of uncertain histology. The RT protocol used in this case was hypofractionated radiation, which has been reported previously, and its efficiency was thought to be similar to those of the conventional protocol at the time [4]. Although the hypofractionated protocol seems to be inferior compared with the latest study cited above [3], we did not choose the conventional protocol because of systemic problems in our institution. In the present case, RT was very effective initially, but clinical worsening and regrowth of the lesion developed comparatively early (4 months after RT). This relatively fast regrowth may be associated with malignant transformation or the malignant nature of the glioma rather than the RT protocol, since significant changes of MR findings, such as ring enhancement, were observed on the second imaging follow-up. Although malignant transformation of gliomas is well known in humans [1, 14], no report has confirmed this phenomenon in canine glioma. Recently, the MR characteristics of canine gliomas have been reported, and low-grade oligodendrogliomas are not enhanced by contrast agents, while high-grade oligodendrogliomas are significantly enhanced and are involved mainly with ring-enhancement [17, 20]. These findings also support our speculation that the oligodendroglioma in the present case was transformed into malignancy. However, it remains unclear whether the anaplastic oligodendroglioma in the present case developed de novo or was a secondary transformation.

On the other hand, it appears that chemotherapy for canine brain tumor is not as advanced as RT. Most of the current textbooks [2, 7, 15, 18] that describe dosage and prognosis are based on comparatively old studies [6, 8, 9]. Nitrosoureas such as carmustine (BCNU) and CCNU, are alkylating agents that are recommended for canine brain tumors, because these compounds are highly lipid-soluble and cross the blood-brain barrier comparatively easily. The recommended dose of BCNU and/or CCNU for canine brain tumors is controversial, because the dosage that has been used and documented for gliomas (i.e. 60–80 mg/m$^2$, every 6–8 weeks) is lower than that used by oncologists for other tumors (e.g. 70–90 mg/m$^2$, every 3–6 weeks for lymphomas, mastocytomas, etc.). The reason as to why the dosage for canine gliomas is low has not been explained. However, we also used CCNU according to the protocol by Fulton and Steinberg [9] for the present case. Although its efficacy was not expected in the beginning because the lesion presented with relapsing and malignant signs, the lesion almost completely disappeared on MRI at one year after starting CCNU therapy as mass effect and signal intensity were normalized. Finally, although it appeared that extended administration intervals of CCNU caused the recurrence of the lesion, we cannot deny the possibility of the recurrence caused by the nature of malignant glioma. However, long-term survival with the owner’s satisfaction was achieved by treatment with CCNU. Previous studies have shown that several cases of glioma (astrocytoma and oligodendroglioma) treated with CCNU/BCNU (+/− surgery) survived for comparatively long periods (3–21 months) [6, 9]. These facts suggest that canine oligodendroglioma, even though malignant and/or recurrent after RT, may have a high sensitivity to CCNU.

In the present report, long-term survival was achieved in a dog with anaplastic oligodendroglioma treated with RT and CCNU. Follow-up MRI may yield very useful therapeutic biomarkers for brain tumors, as in the present case. The efficacy of both RT and chemotherapy, especially with CCNU, for brain tumors has not been determined sufficiently. Information available concerning these therapies will be improved by accumulating more cases in the future.

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