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Anaplastic oligodendroglioma with leptomeningeal dissemination in a French Bulldog

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ABSTRACT. A 2.5-year-old male French Bulldog was evaluated for seizures. Cranial magnetic resonance imaging (MRI) suggested a glioma in the left piriform area. Radiation therapy (RT) and continuous chemotherapy were administered. Although the lesion had regressed significantly 2 months after RT, a follow-up MRI revealed meningeal enhancement in the left piriform area, which expanded further, with hydrocephalus, by day 310 (8 months after RT). Because of the poor prognosis, the dog was euthanized on day 356 and necropsy was performed. Histopathological examination confirmed anaplastic oligodendroglioma with leptomeningeal dissemination. This case suggests that the possibility of leptomeningeal dissemination and hydrocephalus should be considered even after RT and chemotherapy for anaplastic oligodendroglioma.

KEY WORDS: canine, glioma, leptomeningeal dissemination, MRI, treatment

Intracranial neoplasms are common in dogs, with one study reporting an incidence of 14.5/100,000 [16], and another estimating a prevalence of 3.0% [23]. Gliomas such as astrocytoma and oligodendroglioma occur frequently in dogs [6, 23, 24, 28], and depending on their location and infiltration, may be treated with radiation therapy (RT) and/or chemotherapy [6, 10, 17, 19].

Oligodendrogliomas are the second most common primary brain tumors in dogs [23, 24, 28], with certain brachycephalic breeds, such as French Bulldogs, Boxers, and Boston Terriers, being particularly susceptible [6, 23, 24, 28]. There have been several histological reports of oligodendrogliomas extending through the ependyma and along the cerebrospinal fluid (CSF) pathway [14, 21, 30]; however, detailed descriptions of the use of RT and/or chemotherapy in individual cases are very limited [30]. Here, we describe the case of a dog with anaplastic oligodendroglioma that exhibited leptomeningeal dissemination and hydrocephalus despite treatment of the isolated mass with megavoltage RT and chemotherapy with lomustine.

A 2.5-year-old male French Bulldog weighing 12 kg was referred to the Kyoto Animal Referral Medical Center with complaints of seizure. An acute-onset, non-progressive, mild gait abnormality of the hindlimbs had been recognized over the previous year. Physical examination upon presentation (day 1) revealed a body temperature of 38.3°C, pulse rate of 144 beats/min, and respiratory rate of 30 breaths/min. Neurologic examination revealed normal mental status, behavior, posture, palpation, cranial nerves, sensation, and urinary function. Postural reactions were unremarkable in the forelimbs but were reduced in the hindlimbs. Spinal reflexes were unremarkable in all four limbs and no spinal hyperesthesia was elicited. Results of complete blood count measurements, serum biochemical analyses, and thoracic radiographs were unremarkable.

The clinical history and findings suggested intracranial and thoracolumbar spinal disease, and magnetic resonance imaging (MRI) was therefore performed to investigate these possibilities. Cranial and thoracolumbar MRI was performed on the same day with the dog under general anesthesia, using a 0.3-T MRI system with a permanent magnet (Airis Vento, Hitachi, Tokyo, Japan). For cranial MRI, T2-weighted (T2W) images (fast spin echo), fluid attenuated inversion recovery (FLAIR) images (finite impulse response), and T1-weighted (T1W) images (spin echo) were obtained in transverse, sagittal, and dorsal planes using a multipurpose joint coil. In addition, transverse, sagittal, and dorsal post-contrast T1W images were also acquired after administering intravenous

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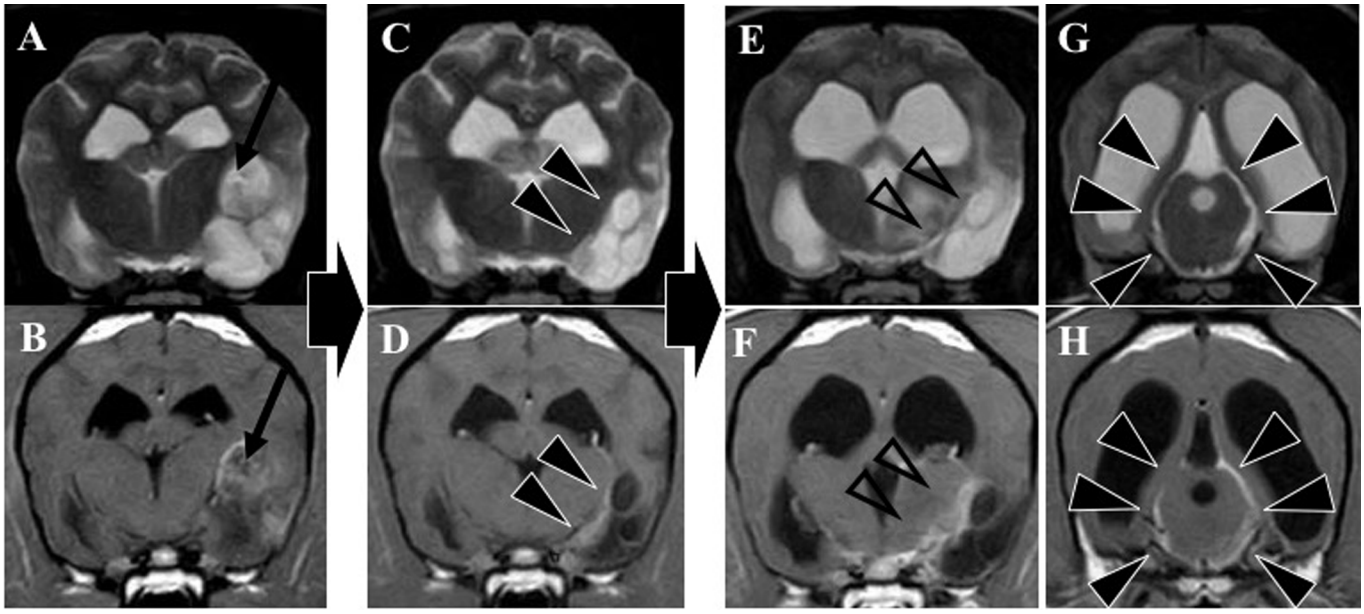

Fig. 1. Time-course of changes in magnetic resonance imaging (MRI) results. (A–F) Transverse plane at the level of the piriform area. (G, H) Transverse plane at the level of the midbrain. (A, C, E, G) T2-weighted (T2W) images; (B, D, F, H) post-contrast T1-weighted (T1W) images recorded following the intravenous injection of gadodiamide contrast agent (0.2 m//kg); (A–H) obtained by 0.3-T MRI. (A, B) Day 1 MRI. The lesion shows hyperintensity on T2W with mild enhancement on post-contrast T1W images in the left piriform area with slight mass effect (arrow). (C, D) Two months after radiation therapy (RT; day 142). The initial lesion is still clearly present but smaller, and necrosis of the left piriform area can be seen. Moreover, mild enhancement on post-contrast T1W image is recognizable between the left side of the diencephalon and the piriform cortex (arrowheads). (E–H) Eight months after RT (day 310). (E, F) The left crus cerebri between the diencephalon and piriform cortex shows hyperintensity on T2W and strong enhancement on post-contrast T1W image (open arrowheads). (G, H) The brainstem meninges show hyperintensity on T2W image and strong enhancement on post-contrast T1W image (arrowheads).

gadodiamide contrast agent (0.2 m//kg) (Magnevist, Bayer, Tokyo, Japan). Thoracolumbar MRI was then performed using a knee coil, and T2W and post-contrast T1W images were obtained in transverse and sagittal planes. The cranial MRI results indicated the presence of a mass in the left piriform area (piriform cortex and amygdala) with a mild mass effect. The mass was mildly hyperintense on T2W and FLAIR images, iso- to mildly hypointense on T1W images, and mildly enhanced on post-contrast T1W images (Fig. 1A and 1B). Thoracolumbar MRI indicated the presence of a localized signal-intensity abnormality in the spinal parenchyma at the 8th and 9th thoracic vertebral levels. The region was mildly hyperintense on T2W images and mildly hypointense on post-contrast T1W images. Intervertebral disc disease was present but unremarkable. Examination of CSF from the cisternal puncture was unremarkable. Based on these findings and clinical history, a glioma and a spinal cord infarction were suspected (day 1). Because the glioma was thought to be the cause of the seizure and the spinal cord infarction was considered an old lesion, treatment options for glioma were considered.

Based on the location of the lesion and the owner's request, megavoltage RT using a 4 MV X-ray linear accelerator (Primus Mid-Energy 4 MV linear accelerator, Siemens Healthcare, Malvern, PA, U.S.A.) was initiated on day 24 at the Animal Medical Center at Gifu University. The target area for RT was determined based on computed tomography (CT) images. Gross tumor volume (GTV) was defined as the gross lesion size on CT images, and the planning target volume (PTV) was GTV + 2 mm margin. The lesion was treated with hypofractionated radiation at 7 Gy per fraction from nine directions (0°, 40°, 80°, 120°, 160°, 200°, 240°, 280°, and 320°) once a week for 7 weeks (total, 49 Gy); 49 Gy was administered to the isocenter, and 95% of PTV was covered with a 28 Gy isodose line. Chemotherapy with oral lomustine (CeeNU, Bristol Myers-Squibb Australia Pty Ltd., Mulgrave, Australia) was initiated on day 30 at 60 mg/m^2 every 3 weeks, with no observed adverse effects. No clinical signs (except mild paraparesis) and/or complications associated with RT or anesthesia were observed during RT and chemotherapy. A second follow-up MRI (0.4 T; APERTO Lucent, Hitachi, Tokyo, Japan) was performed after RT (day 67) and revealed a reduction in the size of the lesion. Oral lomustine administration was continued at 60 mg/m^2 every 4 weeks, and prednisolone (0.5 mg/kg once daily; Prelon, Teva Takeda Pharma Ltd., Aichi, Japan) and phenobarbital (3 mg/kg twice daily; Phenobal, Daiichi Sankyo Co., Ltd., Tokyo, Japan) were administered pre-RT, and during RT and chemotherapy.

A focal seizure (akin to myoclonus) was reported on day 112 followed by a tonic-clonic seizure on day 140. A third follow-up MRI (day 142; 2 months after RT; 0.3 T) was performed, which revealed significant regression of the lesion. The imaging findings of hyperintensity on T2W, hypointensity on FLAIR, T1W, and post-contrast T1W images led to suspected necrosis of the left piriform area. Mild enhancement was also observed on post-contrast T1W images on the left side of the crus cerebri region, between the diencephalon and the piriform cortex (Fig. 1C and 1D). Although cerebral necrosis due to radiation damage and tumor

recurrence were considered, lomustine administration was continued at the same dose and interval on the owner's request. A fourth follow-up MRI was performed on day 310 (8 months after RT; 0.3 T). Neurologic examinations revealed left cerebral signs (absence of the menace response of the right eye, head turn to the left side, circling movement to the left side, proprioceptive and postural reaction deficits more marked on the right side). The MRI showed hyperintensity of the left diencephalon, the region of the left crus cerebri between the diencephalon and piriform cortex, and the meninges of the brainstem and cervical cord on T2W and FLAIR images, iso- to mild hypointensity on T1W images, and strong enhancement on post-contrast T1W images (Figs. 1E–H and 2B–C). The cervical cord parenchyma showed hyperintensity on T2W images, mild hypointensity on T1W images, and unremarkable enhancement on post-contrast T1W images. These findings, together with unclear cerebral sulci, lateral ventricle rounding, and third and fourth ventricle expansion suggested increased intracranial pressure and obstructive hydrocephalus. Isosorbide (1 m//kg twice daily: Isobaide, Kowa Pharmaceutical Co., Ltd., Kyoto, Japan) was, therefore, added to the treatment.

The dog was finally euthanized on day 356 (approximately 1 year) because of the increased frequency and duration of seizures, and its brain was obtained for necropsy. Post-mortem MRI was not performed. The tissue was fixed in 10% neutral-buffered formalin and paraffin sections were stained with hematoxylin and eosin. A significant gross lesion was observed extending from the right frontal lobe to the parietal and temporal lobes and from the left temporal lobe to the hippocampus. Atrophy and yellow material were observed in the left piriformal area. Histopathological examination revealed lesions comprising a solid proliferation of tumor cells with small single or multiple nuclei and a high nucleus/cytoplasm ratio. These tumor cells proliferated diffusely in the right frontal lobe, right cerebellum, meninges of the midbrain to the inferior cerebellar surface, and the fourth ventricle (Fig. 3). Tumor cells formed foci along the meninges (under the pia mater). Necrosis of the brain parenchyma and blood vessels, extensive neighboring dropsy, and inflammatory cell permeation were observed in the region extending from the left temporal lobe to the hippocampus. Within the necrotic area, a marked proliferation of small vessels, microhemorrhages, and a deposition of calcium, hemosiderin, and hematoidin were detected. Tumor cells were absent in the necrotic area. The tumor was also evaluated immunohistochemically and found to be positive for oligodendrocyte transcription factor 2 and negative for glial fibrillary acidic protein. Based on these findings, the lesion was diagnosed as anaplastic oligodendroglioma according to the World Health Organization classification, with leptomeningeal dissemination and brain necrosis [12, 15, 28].

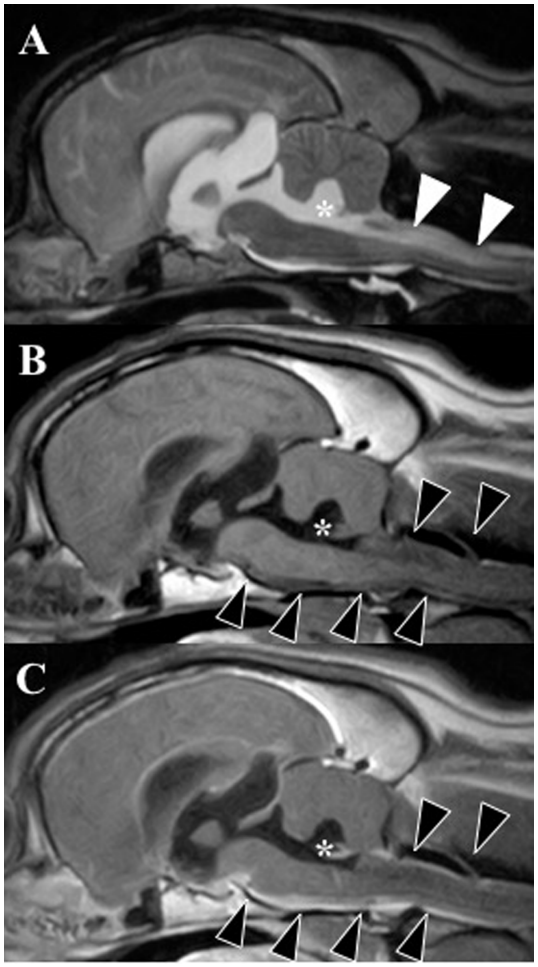

Fig. 2. Sagittal magnetic resonance image (MRI) at the midline of the brain 8 months after RT (day 310). (A) T2-weighted (T2W) image, (B) T1-weighted (T1W) image, and (C) post-contrast T1W image recorded following the intravenous injection of meglumine gadopentetate at 0.2 m//kg. (A–C) 0.3-T MRI. Cerebral groove obscurity, lateral ventricle rounding, and third and fourth ventricle expansion (asterisk) are revealed. The brainstem and cervical cord meninges show strong enhancement on post-contrast T1W images (black arrowheads), and cervical cord parenchyma showed hyperintensity on T2W images (white arrowheads), mild hypointensity on T1W images, and unremarkable enhancement on post-contrast T1W images.

Canine gliomas, such as oligodendrogliomas or astrocytomas, are recognized as parenchymal (intra-axial) swollen masses with hyperintensity on T2W images and hypointensity on T1W images, with or without contrast enhancement, and develop in the piriform, frontal, and temporal lobes [6, 23, 31]. Similar findings were observed on the first MRI in the present case. We thus diagnosed the initial lesion as a glioma, specifically an oligodendroglioma. However, subsequent follow-up MRI scans revealed meninges with enhanced contrast. Meningeal enhancement on MRI after the administration of an intravenous contrast agent has been observed in human and veterinary medicine [18, 22]. In humans, such enhancement has been associated with inflammation, neoplasia, ischemia, elevated intracranial pressure, changes secondary to radiation, and subarachnoid hemorrhage [22], while similar changes in veterinary cases have been associated with bacterial and cryptococcal meningitis, plasmacytic meningitis, granulomatous meningoencephalitis, neoplasia (lymphoproliferative cancers and histiocytic sarcoma), and inflammation secondary to otitis interna [18]. In the present case, meninges with enhanced contrast were observed in the irradiated region on the third follow-up MRI, and we therefore concluded that the enhancement was secondary to radiation. However, the meningeal enhancement region had expanded on the fourth follow-up MRI. In veterinary medicine, meningeal enhancement has also been reported in CSF drop metastasis [30]. Dissemination within the ventricular system, including the central canal, along with local invasion into or widespread metastases to the meninges is recognized in canine anaplastic oligodendrogliomas [28], though clinical reports are

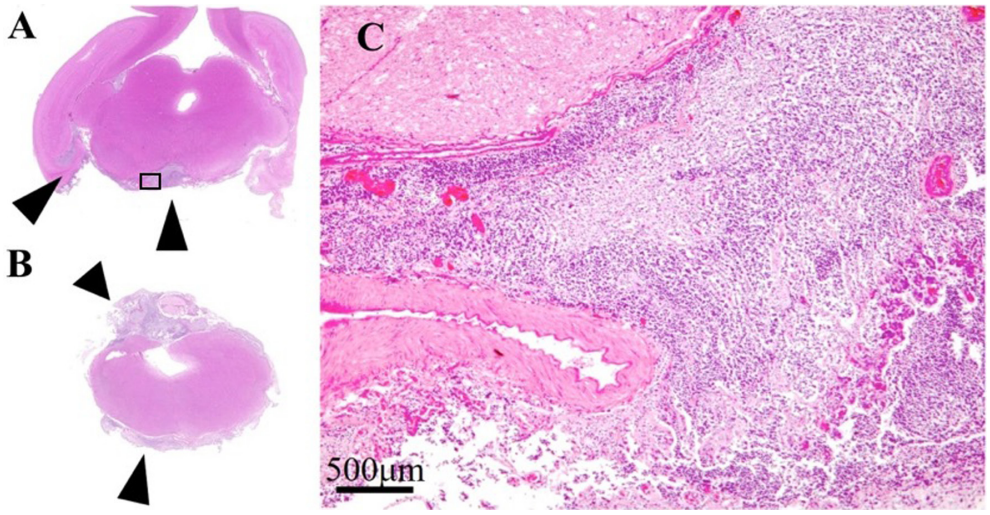

Fig. 3. Hematoxylin and eosin-stained brain sections. (A) Midbrain, (B) medulla oblongata, and (C) meninges of midbrain (black square in (A)) (bar=500 μm). Lesions are composed of a solid proliferation of tumor cells in the meninges of the midbrain to the inferior cerebellar surface and the ventral cerebellar area (black arrowheads).

few [14, 21, 30]. Peritumoral nuclear atypia and multiple large-walled vessels are often found in anaplastic oligodendrogliomas [28]. Local expansion from the primary site with spread into the adjacent subarachnoid space in the meninges and the ventricular system can occur. During CSF drop metastasis, the tumor extends through the ependyma and along the CSF pathway, and new lesions develop in a caudal direction, accompanied by the formation of tumor masses [14, 28, 30]. Leptomeningeal dissemination of oligodendroglioma and anaplastic oligodendroglioma has rarely been reported in humans [20, 25]. In the present case, histopathological examination revealed tumor cells forming tumor foci along the meninges (under the pia mater). Based on these facts, we concluded that leptomeningeal dissemination had occurred in the current case. Leptomeningeal dissemination of the tumor should thus be considered when meningeal enhancement is observed on MRI examination in association with gliomas, particularly oligodendrogliomas. Histopathological examination of the cervical cord was not carried out; however, the cervical cord parenchyma showed abnormal signal intensity on MRI, which was considered to indicate spinal cord edema, tumor infiltration, inflammation, and central canal expansion. We therefore considered a disorder of the CSF pathway, with development of hydrocephalus.

Several veterinary reports have documented the results and prognosis of gliomas treated with RT [1, 2, 10, 30] and chemotherapy [5, 7, 8, 10, 11, 29]. In one case, an oligodendroglioma was effectively reduced in size after RT (stereotactic ablative RT), though a new mass suspected as CSF drop metastasis was observed 5 weeks after therapy [30]. Although reduction of the new mass was observed following the second RT, ventral leptomeningeal enhancement had extended, and cervical lesions were observed [30]. In another case of anaplastic oligodendroglioma treated with RT (hypofractionated RT), the mass showed significant regression 2 months post-therapy, though clinical worsening and lesion regrowth was observed 4 months after RT [10]. Similarly, in the present case, although the lesion showed significant regression, regrowth was observed 8 months after RT. Based on these facts, RT is considered to have a short-term tumor-reduction effect. In the present case, RT became palliative (0 mm for CTV, 2 mm for PTV, hypofractionated protocol) to fit with the owner's financial situation and convenience. A deviation of 4 mm at the fixed position has been reported, even if a cranial-fixation device is used [9], suggesting that leptomeningeal dissemination may have occurred owing to the strict margin setting and geographical miss in the present case. Different results may thus be obtained by changing the irradiation range of RT. To the best of our knowledge, no studies have reported on the effects of changing the irradiation range of RT, and further research should therefore be conducted to investigate this. In human medicine, whole-brain radiotherapy (WBR) for brain metastases has mostly been used to treat patients with multiple brain metastases [3], and has resulted in complete resolution of all visible lesions in a patient with choroid plexus lymphoma [13]. However, WBR is no longer the default treatment for patients with brain metastases because of the risk of cognitive decline [3]. To the best of our knowledge, no veterinary studies have yet reported on the effect of WBR for leptomeningeal dissemination, and further research is thus needed.

Chemotherapy is not considered to be better than RT for canine brain tumors, and the its effects remain controversial [6, 10, 11, 29]. The recommended dose of lomustine for gliomas is undetermined. In this case, chemotherapy with oral lomustine was initiated at 60 mg/m^2 every 3 weeks, continued with and after RT. However, the tumor recurred and expanded, with leptomeningeal dissemination and hydrocephalus. In a previous report, a recurrent post-RT tumor in a dog, diagnosed as anaplastic oligodendroglioma, showed reduction following chemotherapy with oral lomustine (60 mg/m^2 every 6 weeks), resulting in long-term survival (2 years and 6 months) [10]. In that report, the effect of chemotherapy was recognized about 1 year after starting oral lomustine [10]. However, the dog in our case was finally euthanized after approximately 1 year because of a poor prognosis, with leptomeningeal dissemination and hydrocephalus, and it is possible that the dog was euthanized before the effect of lomustine was

evident. It is possible that surgical treatment using a ventriculoperitoneal shunt might have temporarily relieved the symptoms until the chemotherapy could have had an effect. Lomustine has been administered to small animals at doses of 70–90 mg/m^2 orally every 4 weeks [19], and doses of 60–80 mg/m^2 orally every 6–8 weeks have been used for brain tumors [8]. In human medicine, doses as high as 150–200 mg/m^2 have been recommended [19]. Based on these findings, we considered that changing the dose and frequency of administration of lomustine may have had an effect. In other reports, treatment of gliomas such as oligodendroglioma or astrocytoma with lomustine or carmustine resulted in comparatively long survival periods (3–21 months) [5, 8]. Based on these observations, the role of chemotherapy remains inconclusive, though canine oligodendroglioma may have high sensitivity to lomustine. In human medicine, chemotherapeutic regimens such as procarbazine+lomustine+vincristine have demonstrated good efficacy in patients with 1p19q co-deleted anaplastic oligodendroglioma [4], while patients without 1p19q co-deletion generally have a poor prognosis [27]. However, one report has suggested that 1p19q co-deletions were rare in canine oligodendrogliomas [26]. These findings suggest that the susceptibility to lomustine or chemotherapy may differ depending on the genotype of the canine oligodendroglioma, and further studies are needed to clarify the effect of chemotherapy in preventing CSF drop metastasis. The presence of leptomeningeal dissemination and hydrocephalus in the present case suggest that these features may be associated with a poor therapeutic effect.

In summary, we report on a dog with anaplastic oligodendroglioma treated with combined RT and chemotherapy, with the development of local recurrence and leptomeningeal dissemination to the diencephalon, brainstem and cervical cord 8 months after RT. Studies involving irradiation and/or chemotherapy for canine gliomas, especially in individual cases, are limited, and very few reports have described the pathological findings based on repeated MRI examinations. The widespread use of MRI, the high incidence of anaplastic oligodendrogliomas, and the challenges associated with treating these tumors with RT and/or chemotherapy in the veterinary field make it necessary for veterinary clinicians to review this information.

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