

MRI FEATURES OF GLIOMATOSIS CEREBRI IN A DOG

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The features of gliomatosis cerebri involving the brainstem and cerebellum in a 3-year-old dog are described. In magnetic resonance (MR) images, there was diffuse loss of the cerebellar folia and cerebellar gray and white matter contrast. Multiple illdefined T2-hyperintensities were present in the cerebellar parenchyma. A poorly defined, T2-hyperintense mass effect was present ventral to the pons and rostral medulla. No contrast enhancement was noted. Cerebrospinal fluid (CSF) was normal. Postmortem examination was consistent with gliomatosis cerebri, based on compatible histopathology and immunohistochemical findings. Although rare, gliomatosis cerebri should be included as a differential for diffuse infiltrative central nervous system (CNS) lesions. © 2012 *Veterinary Radiology & Ultrasound*.

Key words: brain tumor, dog, glioma, gliomatosis, MRI.

Signalment, History, and Clinical Findings

A 3-YEAR-OLD NEUTERED female mixed-breed dog (weight, 33.6 kg) had a 2-month history of slowly progressive incoordination and 1-week history of swaying movements of the head.

The dog was bright and alert. Intention tremors and a right-sided head tilt were present. There was severe vestibulocerebellar ataxia with a wide-based stance in the pelvic limbs and marked truncal sway. There were also a ventral strabismus of the right eye and positional vertical nystagmus of both eyes. Conscious proprioception and hopping were delayed on both right-sided limbs and mildly delayed in the left pelvic limb. Neuroanatomic localization was cerebellum (bilateral) and rostral medulla (mainly right-sided).

Imaging

Magnetic resonance (MR) imaging of the brain was performed using a 3.0 T magnet.* Turbo spin-echo T1-weighted and T2-weighted images were acquired in sagittal, transverse, and dorsal planes. Fluid-attenuated inversion-recovery (FLAIR) and gradient-echo images were acquired in the transverse plane. Postcontrast T1-weighted images were acquired in sagittal, transverse, and dorsal planes after

IV administration of gadodiamide.† There was diffuse loss of the cerebellar folia, as well as diffuse loss of the cerebellar gray and white matter contrast on sagittal T2-weighted images (Fig. 1A). An illdefined, T2-hyperintense and slightly T1-hypointense mass effect was also noted located within the ventral pons and rostral medulla on sagittal images (Figs. 1A and B). The mass effect was bilateral, but more marked on the right side of the brainstem and remained hyperintense on transverse FLAIR images (Figs. 2A and B). Multiple illdefined, patchy hyperintensities were noted bilaterally within the cerebellar parenchyma on dorsal and transverse T2-weighted images and FLAIR transverse images (Figs. 2C–E). Contrast enhancement was not present. Based on the imaging findings, the main differential diagnoses were an inflammatory process, either immune mediated, such as granulomatous meningoencephalitis or infectious, such as protozoal or fungal, or an infiltrative tumor such as lymphoma or histiocytic sarcoma.

Diagnosis and Outcome

Cerebrospinal fluid (CSF) collected from the cerebellomedullary cistern was normal with a protein content of 9.6 mg/dl (reference range, <25 mg/dl) and a white blood cell count of 3 cells/ μ l (reference range, <5 cells/ μ l). Serology for *Cryptococcus spp.* was negative. Polymerase chain-receptor analysis of the CSF for canine distemper virus, West Nile virus, *Toxoplasma gondii*, *Neospora caninum* and *Neospora hughesi*, *Ehrlichia canis*, *Anaplasma phagocytophilum*, *Rickettsia spp.*, and *Borrelia burgdorferi* was negative. Treatment with clindamycin and dexamethasone did not result in improvement and the dog was

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*Achieva 3.0 T, Philips Healthcare, Cleveland, OH.

†Omniscan™; GE Health Care, Oslo, Norway.

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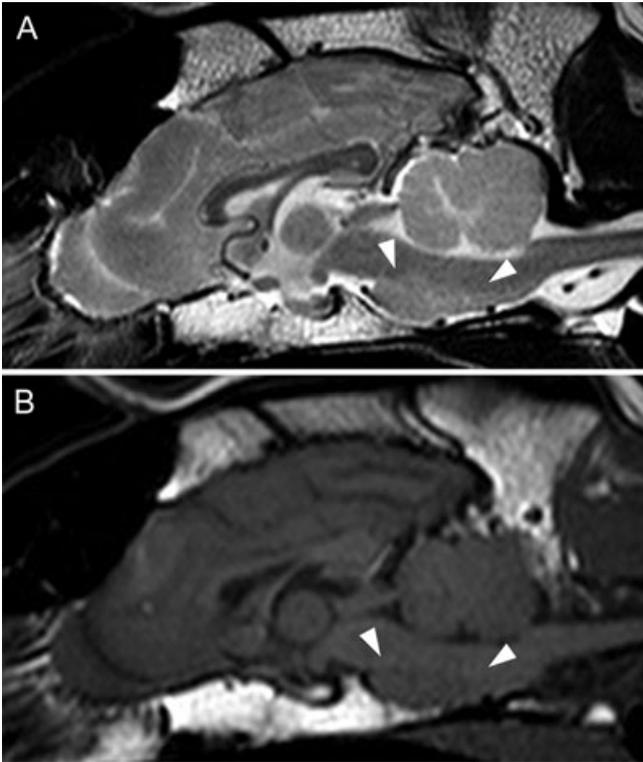


FIG. 1. (A) Sagittal T2-weighted image (TR = 3000 ms, TE = 80 ms, slice thickness = 2 mm) and (B) sagittal T1-weighted image (TR = 608.2 ms, TE = 10 ms, slice thickness = 2 mm). There is diffuse loss of the cerebellar folia, as well as diffuse loss of the cerebellar gray and white matter contrast on the sagittal T2-weighted image. An ill-defined, T2-hyperintense and slightly T1-hypointense mass effect is present in the ventral pons and rostral medulla on the sagittal image (arrowheads).

euthanized 4 weeks later due to progression of the clinical signs.

The brain was normal grossly. The white matter of the pons, rostral medulla, and cerebellum contained an extensive and poorly defined hypercellular region containing multiple small foci of pan-necrosis (Fig. 3A). The infiltrating cells were embedded in otherwise undisturbed neural parenchyma and were characterized by round to oval nuclei with coarsely granular to condensed chromatin and scant eosinophilic cytoplasm with short fibrillar cell processes (Fig. 3B). These were interpreted to be neoplastic glial cells. Differential diagnoses for a diffusely proliferative glial neoplasm included diffuse astrocytoma, oligodendroglioma, microgliomatosis, and gliomatosis cerebri. Immunohistochemistry (IHC) for glial fibrillary acidic protein (GFAP) was negative. Additionally, IHC for CD18 (a pan-leukocyte marker) was negative in neoplastic cells, but strongly positive in activated microglia found within the regions of pan-necrosis. The tumor cell morphology and growth pattern was consistent with a diagnosis of gliomatosis cerebri. Cell morphology and IHC results did not allow a precise characterization of glial cell origin. However, IHC and morphology did rule out lymphoma, the primary

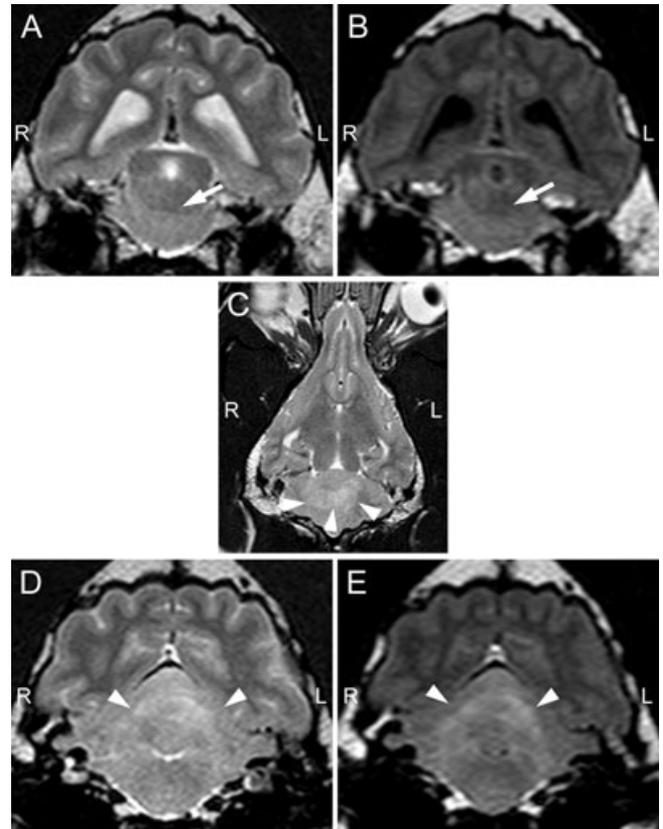


FIG. 2. (A) T2-weighted (TR = 3000 ms, TE = 80 ms, slice thickness = 2 mm) and (B) FLAIR transverse images at the level of the caudal mesencephalic aqueduct (TR = 11,000 ms, TE = 125 ms, slice thickness = 2 mm). (C) Dorsal T2-weighted image (TR = 3000 ms, TE = 80 ms, slice thickness = 2 mm) and (E) FLAIR transverse images at the level of the cochlea (TR = 3000 ms, TE = 80 ms, slice thickness = 2 mm). An ill-defined, T2-hyperintense mass effect is present in the ventral pons and rostral medulla (arrows). The mass effect is bilateral, but more marked on the right side of the brainstem. Multiple ill-defined, patchy T2-hyperintensities are noted bilaterally within the cerebellar parenchyma on dorsal and transverse images (arrowheads).

differential for an infiltrative neoplasm of nonglial (mesenchymal) origin.

Discussion

Gliomatosis cerebri is a rare neoplasm characterized by diffuse and widespread infiltration of the central nervous system (CNS) by neoplastic glial cells with relative preservation of the neural tissue architecture.¹⁻³ Until recently, gliomatosis cerebri had been classified as a neuroepithelial neoplasm of unknown origin.³ However, the 2007 World Health Organization classification of tumors redefined gliomatosis cerebri as a malignant (grade III) neuroepithelial tumor of astrocytic origin, presenting most commonly as a diffuse astrocytoma, but which occasionally can have the growth pattern of an oligodendroglioma or a mixed glioma.^{4,5} This condition was first described in

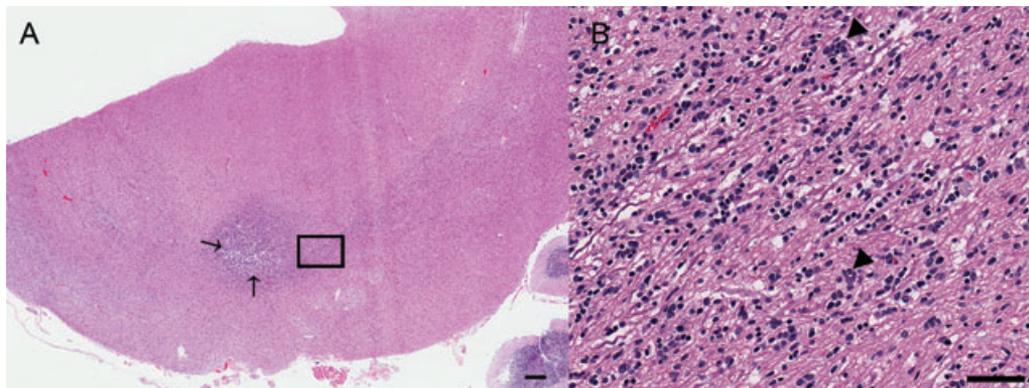


FIG. 3. (A) The white matter of the pons is diffusely hypercellular and contains a focus of pannecrosis characterized by rarefaction (arrows). [1X, hematoxylin, and eosin. Scale bar = 500 μ m] (B) A higher magnification of (A). Markedly increased numbers of cells with short eosinophilic fibrillar cytoplasmic processes are seen in clusters (arrow heads), infiltrating among axons and other glial cells. [25 \times , hematoxylin, and eosin. Scale bar = 50 μ m]

people in 1938 and slightly over than 300 cases have been reported since then.⁵⁻⁹ Gliomatosis cerebri has been reported in a few dogs, a cat, and a goat.^{3,10-17}

Two forms of gliomatosis cerebri are recognized in people.^{3,5,7,18} Type I is the classical form, in which there is extensive CNS infiltration of neoplastic cells without the formation of a focal mass at the time of initial clinical presentation. In type II gliomatosis cerebri, the diffuse infiltration is also accompanied by a focal mass, usually a high-grade glioma.^{3,5,7,18} The MR images of the dog we present here had a mass effect within the ventral brainstem, but no mass was identified at necropsy. Only diffuse infiltration of neoplastic cells was noted in this dog, which would be more consistent with type I gliomatosis cerebri.

In human gliomatosis cerebri, all age groups can be affected, with the peak incidence between 40 and 50 years.^{1,5,7} In affected dogs, age has ranged from 3 to 9 years.^{3,10-14} In humans, both genders are affected equally.⁵ No clear gender predilection has been noted in dogs.

Clinical signs in gliomatosis cerebri are variable and typically reflect the location of the neoplastic infiltrates.^{3,5,7,8} Reports of gliomatosis cerebri in people indicate remarkable variation in the area of CNS involvement, with the cerebral hemispheres being the most commonly affected sites, often accompanied by concurrent infiltration of the brainstem.^{1,5,7,9} Involvement of the cerebellum in people is less common compared to the dogs with gliomatosis cerebri reported to date.^{3,5,9-11,14} None of the 22 humans with gliomatosis cerebri had cerebellar involvement based on MR images.⁹ In contrast, five of six dogs with gliomatosis cerebri had diffuse infiltration of the cerebellum at the time of necropsy.³ In contrast to the majority of human and canine gliomatosis cerebri patients reported, no cerebral hemisphere involvement was noted in this dog on either MR images or necropsy. In people, gliomatosis cerebri

lesions are most often bilateral, with a predilection for the right side of the brain, which was also noted in this dog.⁵

MR imaging is the modality of choice for the diagnosis of gliomatosis cerebri in people.^{5,19-24} In humans, MR features of gliomatosis cerebri include diffuse, extensive, and often poorly delineated T2-hyperintense lesions, which tend to be T1-iso to T1-hypointense and have variable contrast enhancement.^{5,18-24} FLAIR sequences are currently preferred over T2-weighted images because they provide superior delineation of gliomatosis cerebri lesions compared to standard T2-weighted images.^{5,22} The MR findings of seven dogs with canine gliomatosis cerebri have been described briefly.^{3,11,13} However, only two of the seven dogs included MR images are available for review.^{11,13} The dog we present shares many similarities with previously reported MR findings in both people and dogs, such as diffuse and poorly delineated hyperintensities on T2-weighted and FLAIR images. In people, the signal hyperintensities noted on T2-weighted or FLAIR images typically correlate well with areas of tumor cell infiltration.^{5,20} In the dog presented here, the hyperintense areas in the brainstem and cerebellum corresponded with diffuse infiltration of neoplastic glial cells at necropsy. No contrast enhancement was noted in this dog, similar to other canine reports.¹¹ Enhancement is usually minimal or absent in human gliomatosis cerebri suggesting a relatively well-preserved blood-brain barrier.^{18,19} If enhancement is seen, it usually represents either more aggressive disease, more dense infiltration, or late-stage disease.^{18,19}

MR findings are nonspecific and have been misinterpreted frequently in people as other infiltrative neoplasms, leukodystrophies, encephalitis, ischemia, multiple sclerosis, or vasculitis.^{8,18-21} A dog with oligodendroglial gliomatosis cerebri was diagnosed as necrotizing meningoencephalitis based on computed tomography and CSF analysis.¹⁴ Similarly, another dog with gliomatosis cerebri was

misdiagnosed as leukoencephalopathy of unknown origin based on the MR features.¹³

Results of CSF analysis were normal in this dog. A consistent and significant feature of human gliomatosis cerebri is the minimal degree of abnormalities in the CSF.^{1,18,23} In the few cases of gliomatosis cerebri reported in veterinary medicine that included CSF analysis, the results were non-specific and ranged from normal to mild elevations in total protein and/or total nucleated cell count.^{3,14}

Because clinical presentation, CSF analysis, and neuroimaging are often nonspecific, stereotactic brain biopsy for histopathologic examination is ultimately necessary

to confirm an antemortem diagnosis of gliomatosis cerebri in people.^{9,23} To date, all gliomatosis cerebri patients reported in veterinary medicine have been diagnosed at necropsy.^{3,10–17}

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DISCLOSURE

The authors have nothing to disclose.

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