BJVP
Brazilian Journal of Veterinary Pathology

Case Report

Gliomatosis Cerebri in a Dog

Fabiano J. F. de Sant'Ana[1], Claudio S. L. Barros[2]

[1] Laboratório de Patologia Veterinária (LPV), Universidade Federal de Goiás (UFG), Jataí, GO, Brazil.
[2] Laboratório de Patologia Veterinária (LPV), Universidade Federal de Santa Maria (UFSM), Santa Maria, RS, Brazil.
Corresponding author: Fabiano J.F. de Sant'Ana, LPV, UFG, 75800-000, Jataí, GO, Brazil.
E-mail: santanafjf@yahoo.com

Submitted on February 2nd 2011, Accepted March 3rd 2011

Abstract

A 6-year-old, female, mixed-breed dog was presented for necropsy with history of prostration and incoordination followed by circling to the right and seizures. There were no gross findings in the brain. Histologically, there were numerous neoplastic glial cells throughout the thalamus, midbrain, pons and medulla oblongata. Moderate multifocal lymphoplasmacytic perivascular cuffings were also present in the same areas. In addition, severe multifocal proliferation of glial cells was observed in the leptomeninge and white matter of the cerebellum. The neoplastic cells observed in the brain stem were negative for GFAP, while in the cerebellum the neoplastic glial cells were strongly labeled with GFAP and vimentin. Based on the histopathological findings and on the immunohistochemical results, a diagnosis of gliomatosis cerebri was made.

Key Words: dog diseases; gliomatosis cerebri; CNS neoplasia; neuropathology.

Introduction

Gliomatosis cerebri is a neoplasm characterized by diffuse infiltration of glial cells in the central nervous system (9). The condition is diagnosed mainly in humans and dogs. Cases of gliomatosis cerebri are rare and generally affect middle age dogs (16, 17, 20, 21). Breed and sex predilections have not been determined (9, 16). This disorder is classified as a neuroepithelial neoplasm of unknown histogenesis (9). Some human authors classify this neoplasm as one type of astrocytoma (11). There are two morphological forms of presentation recognized in humans (12) and dogs (16). Type I is more frequent and is characterized by widespread infiltration in the brain without formation of detectable gross lesion. In type II, which can develop from type I, the histological lesion is associated with an conspicuous neoplastic mass detected by diagnostic imaging or at necropsy examination (15, 16).

Case Report

This report describes the pathological and immunohistochemical findings of a case of gliomatosis cerebri in a 6-year-old, female, mixed-breed dog submitted for necropsy with a clinical history of two days of prostration and incoordination followed of circling to the right and seizures. The dog died during sedation for clinical examination.

Grossly, multifocal subpleural hemorrhages in the lung and moderate congestion in the kidneys were observed. There were no gross alterations in the brain.

Samples of lung, kidney and the brain were collected and fixed in 10% buffered formalin. The tissues were processed for routine histopathological evaluation and stained with hematoxylin and eosin. The following antibodies were applied in appropriate dilutions on representative brain sections: anti-glial fibrillary acidic protein (GFAP) (polyclonal, 1:1.000, Dako, Carpinteria, California, USA) and anti-vimentin (monoclonal, 1:100, Dako, Carpinteria, California, USA). Immunohistochemistry (IHC) sections were counterstained with Mayer's hematoxylin. Positive controls for IHC consisted of normal dog brain for

GFAP and normal dog skin for vimentin. For negative controls, instead of the primary antibodies, a phosphate-buffered saline (PBS) solution was used. Streptavidin-biotin-peroxidase complex (Dako, Carpinteria, California, USA) and 3,3-diaminobenzidin (Sigma Chemical Co., St. Louis, Missouri, USA) were used as the detection system.

Microscopically, widespread infiltration of neoplastic glial cells was observed in the thalamus, midbrain, pons and medulla oblongata, forming areas with high cellularity (Fig. 1). These same regions presented moderate multifocal lymphoplasmacytic perivascular cuffing. The neoplastic cells presented indistinct cytoplasmic borders, mild pleomorphism, round, oval or mainly elongated nucleus and few mitosis. In addition, severe multifocal proliferation of glial cells was observed in the leptomeninge and white matter of the cerebellum. The neoplastic cells observed in the brain stem were negative for GFAP and moderately positive for vimentin (Fig. 2), while in the cerebellum the neoplastic glial cells were strongly labeled with GFAP (Fig. 3) and vimentin (Fig. 4). Few GFAP-positive astrocytes with prominent branching processes were identified in the thalamus and midbrain in the affected areas. These cells were interpreted as reactive astrocytes.

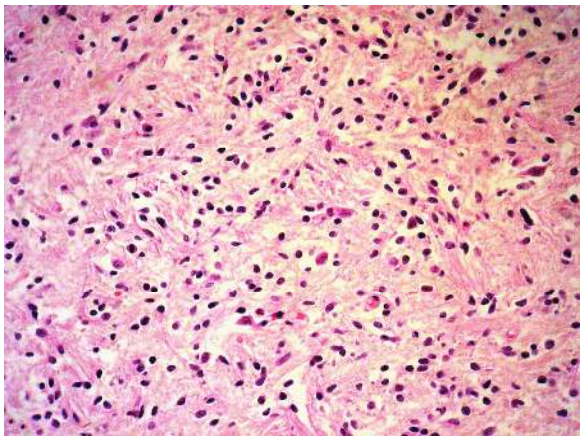

Fig. 1. Midbrain, dog, gliomatosis cerebri. Widespread infiltration of neoplastic glial cells. Hematoxylin and eosin, 40X.

Fig. 2. Midbrain, dog, gliomatosis cerebri. Neoplastic cells (arrows) present moderate positive reaction for vimentin. Mayer's hematoxylin counterstain. 20X.

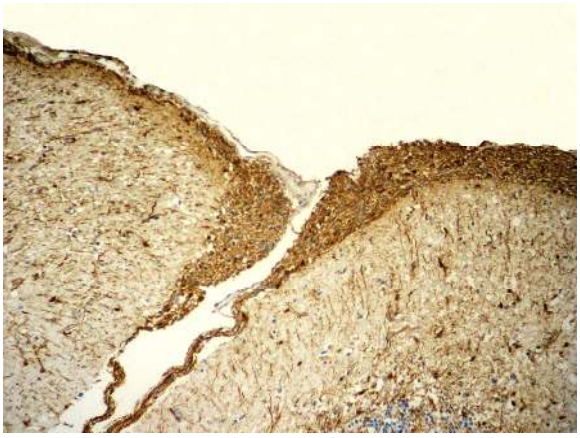

Fig. 3. Cerebellum (leptomeninge), dog, gliomatosis cerebri. The glial cells present strong labeling for GFAP. Mayer's hematoxylin counterstain. 20X.

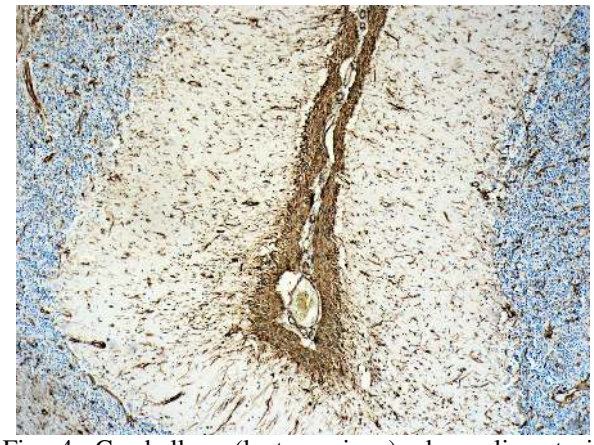

Fig. 4. Cerebellum (leptomeninge), dog, gliomatosis cerebri. There is strong labeling for vimentin in neoplastic glial cells. Mayer's hematoxylin counterstain. 20X.

Based on the morphologic and immunohistochemical findings, a diagnosis of gliomatosis cerebri was made.

Discussion

The term gliomatosis cerebri was initially coined to describe gliomatous neoplasms in the central nervous system in which the neoplastic elements were very diffuse in their distribution (14). In the World Health Organization (WHO) classification, gliomatosis cerebri is a specific neoplasm, distinct of other tumors of glial origin (9). The origin of the neoplasm remains unknown. Some authors suggest that infiltrating tumor cells are primitive in origin with astrocytic or oligodendroglial differentiation (15). It is apparent that further research is necessary to define the cell origin of this entity.

Histological evaluation is essential for the diagnosis in all cases, but currently imaging have been used more frequently as an auxiliary diagnostic tool. Magnetic resonance imaging (MRI) is an important technique for aid in the diagnosis of gliomatosis cerebri in dogs (5) and humans (3) and it is the method of

choice because can reveal brain areas of signal hyperintensity on T2-weighted images, suggesting proliferation of cells (3, 15).

Most cases of gliomatosis cerebri occur in humans between 30 and 50 years and both sexes are equally affected (7, 15, 19), while the few cases described in dogs, the median age is 6 years old (1, 16), as in the present report.

The main microscopic pathologic findings described in this report may be related to nervous disturbances observed clinically. Incoordination, prostration and circling can be associated with tumor lesions in brain stem or diencephalus (13). Clinical signs of this condition are extremely variable, because many different regions of the central nervous system can be affected (16).

In the present case, the neoplastic infiltration was observed in the thalamus, midbrain, pons, cerebellum and medulla oblongata. In humans, usually gliomatosis cerebri involve also the telencephalus and the spinal cord, showing the diffuse aspect of this disorder (6, 8).

Gliomatosis cerebri present many similar morphologic aspects between human and canine cases, such as the preservation of anatomical architecture and the sparing of neurons (1, 2, 5). These findings occurred in the present case. In some canine cases, the infiltration of neoplastic cells can cause disruption on normal architecture, satelitosis, neuronal degeneration, edema, mild cavitation with accumulation of gitter cells and marked nuclear tropism in the brain stem (15). Perivascular cuffings are observed in human and animal cases (1, 16, 22). This alteration is more commonly found in gliomatosis cerebri type I of humans (15). The meaning of this microscopic finding has not been determined (6, 16). Based on the histological findings presented in this case, the neoplasm was classified as type I, because there is no formation of grossly evident mass. In humans, gliomatosis cerebri type II (with formation of mass) present poor prognosis and survival (15).

In this report, the imnunohistochemical findings were partially similar to those described in dogs (5, 16). Negative-GFAP staining was observed in the neoplastic infiltration in the thalamus and brain stem, while only in the cerebellum positive cell were present. GFAP reactivity in humans with gliomatosis cerebri is extremely variable (6, 15) and in dogs it is commonly negative (1, 16). On the other hand, there were two canine cases described in the literature with positive-GFAP labeling (5, 20). In the present case, positive-vimentin staining was observed in the affected cerebellum and brain stem. Vimentin reaction was also detected in cases of human gliomatosis cerebri (6, 22). Vimentin, an intermediate filament that comprise a large family of cytoskeletal proteins, is not only present in all mesenchymal tissue but also appears transitionally in a variety of cells during development and may be expressed in the central nervous system (4). The two major intermediate filament proteins of astrocytes are vimentin and GFAP. Early during development, immature astrocytes express mainly vimentin. Towards the end of gestation, vimentin is progressively replaced by GFAP in differentiated astroglial cells. The IHC findings reported here demonstrate the expression of vimentin in many cells in gliomatosis cerebri. These results suggest that the infiltrated cells can be undifferentiated astrocytes and/or cells with great motility. Positive GFAP labeling was detected in cells in the cerebellar leptomeninges, as visualized in human cases (6).

Main differential diagnoses included gliosis, diffuse astrocytoma, lymphoma and primitive neuroectodermal tumors (PNETs). Gliosis do not present with widespread infiltration and atypia of glial cells, as visualized in gliomatosis cerebri (18). Gliomatosis cerebri is also more widespread than diffuse astrocytoma and, in dogs, is usually GFAP negative (16, 20), although some human authors include gliomatosis cerebri as one type of astrocytoma (11). In lymphoma, neoplastic cells are round with round to irregularly round nuclei and scant to small amounts of cytoplasm, and lymphomas tend to efface surrounding tissues. These findings were not observed in the present case. PNETs also tend to efface tissue, are usually seing in young animals and are commonly limited to the cerebellum (9).

Acknowledgements

The authors thank Prof. Janildo L. Reis Jr. (UnB, Brasília, Brazil) for technical assistance of this article.

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