The Armed Forces Institute of Pathology
Department of Veterinary Pathology

Conference Coordinator:
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WEDNESDAY SLIDE CONFERENCE 2008-2009

Conference 20

11 March 2009

Conference Moderator:

Dr. F. Yvonne Schulman, DVM, Diplomate ACVP

CASE I – 07-1158 (AFIP 3102611)

Signalment: 6-year-old, spayed female, mixed breed dog (*Canis familiaris*)

History: 6-week history of progressive neurologic deficits that began as posterior paresis and progressed to cerebellar ataxia. Neurologic exam revealed cranial nerve V involvement and central vestibular signs.

Gross Pathology: No gross lesions in brain

Laboratory Results: MRI and CSF analysis are both normal. Immunohistochemistry for GFAP was negative.

Histopathologic Description: The pons and medulla have a diffuse infiltration of neoplastic elongate cells within gray and white matter. The cells have indistinct cytoplasm, elongate nuclei with dense, hyperchromatic chromatin, mild anisokaryosis and no mitotic figures. They resemble fibrillary astrocytes. The neoplasm does not form a distinct mass and has no borders, but infiltrates the neuropil diffusely without damaging the normal tissue. The cells tend to stream along the axis of white matter fiber tracts and often wrap around neurons, but no neuronal lesions are seen **(Fig. 1-1)**. Tumor cells form a thin subpial layer in the cerebellum and extend into the cerebellar folia with regional loss of Pukinje cells. An occasional perivascular cuff of lymphocytes is observed.

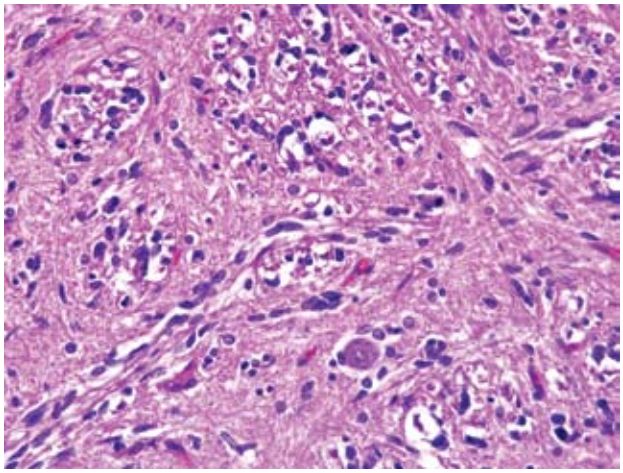
Contributor's Morphologic Diagnosis: Gliomatosis cerebri

Contributor's Comment: Gliomatosis cerebri is a neoplasm of unknown cell origin but is classified as a glial cell tumor in the WHO classification of tumors of the nervous system. The tumor cells resemble fibrillary astrocytes but GFAP immunostaining is variable; some tumors stain negative and others have few positive staining cells. Gliomatosis in man is divided into two subtypes. Type I is the most common and presents as a diffuse infiltration of the brain with no mass lesion. Type II gliomatosis presents as a mass lesion.

Gliomatosis cerebri was established in dogs in a report of 6 cases [5] and based upon lesions that are very similar to those in man. Four of the cases in dogs were type I, and two cases were type II. The case presented here represents type I gliomatosis. The neoplasm in dogs has many similarities to the disease in man, but GFAP staining has been consistently negative in dogs, as it was in this case.

AFIP Diagnosis: Brainstem: Gliomatosis cerebri

*Sponsored by the American Veterinary Medical Association, the American College of Veterinary Pathologists, and the C. L. Davis Foundation.



1-1. Brainstem, dog. Gliomatosis cerebri. Diffusely infiltrating grey and white matter, often surrounding axons, are high numbers of neoplastic glial cells. (HE 400X)

Conference Comment: The differential diagnosis including gliosis, diffuse astrocytoma, lymphoma, primitive neuroectodermal tumors (PNETs) and microgliomatosis was discussed at the conference. Widespread infiltration of the central nervous system, atypia and mitotic activity are typical for gliomatosis cerebri and help to differentiate it from gliosis. Gliomatosis cerebri is also more widespread than diffuse astrocytoma and, in dogs, is usually negative for GFAP.(5,6) In lymphoma, neoplastic cells are round with round to irregularly round nuclei and scant to small amounts of cytoplasm, and lymphomas tend to efface tissue. CD3 or CD79 positivity helps to identify lymphoma and prevent an incorrect diagnosis of gliomatosis cerebri. PNETs also tend to efface tissue and are usually seen in young animals. Microgliomatosis is a neoplasm of microglial origin, the resident macrophage of the central nervous system, and should be positive for CD18.

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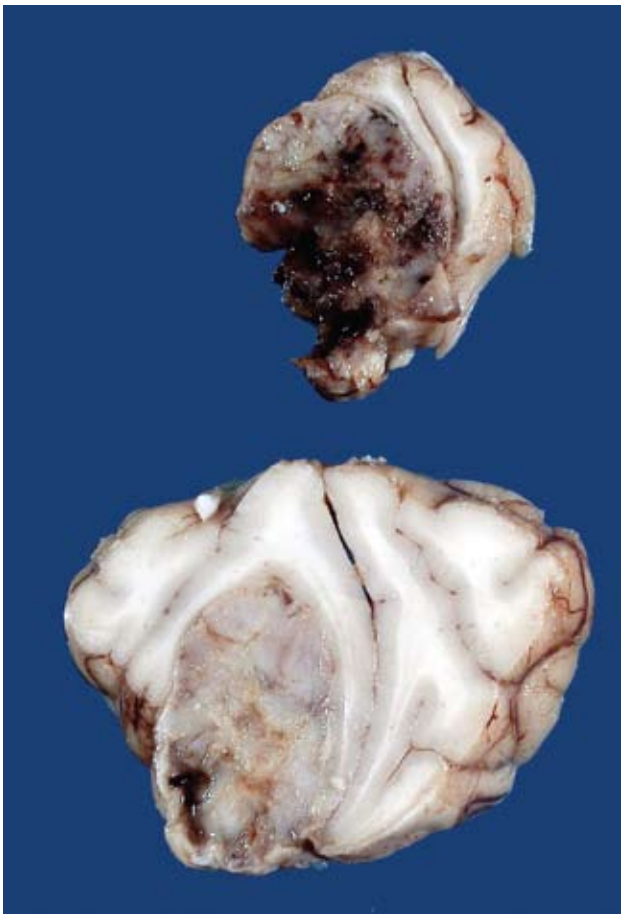
CASE II – UNAM Case 1 (AFIP 3102490)

Signalment: 10-year-old, male, Boxer dog, canine (*Canis familiaris*)

History: This dog presented with a one-week history of ataxia, general weakness and occasional temporary loss of consciousness. Neurological examination showed cranial nerve reflexes within normal limits. Two to three hours later, the animal had lost the sense of smell, palpebral and swallowing reflexes, perception of painful stimuli, and was blind. Two hours later the patient was in a coma. The owner elected euthanasia due to poor prognosis. The carcass was submitted for necropsy examination.

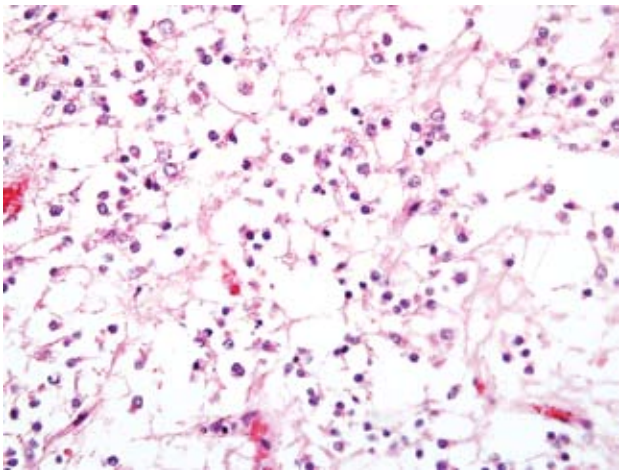
Gross Pathology: The left cerebral hemisphere showed moderate edematous swelling with flattening of the cortical gyri and narrowing of the sulci. In transverse section there was a mass primarily located in the subcortical white matter of the frontal lobe, which extended cranially to the olfactory bulb and caudally to the pellucid septum. The growth was infiltrative, poorly circumscribed, soft, gelatinous and grayish white, with extensive areas of hemorrhage. The mass compressed surrounding tissues and distorted the cerebral hemispheres **(Fig. 2-1)**.

Laboratory Results: None



2-1. Cerebrum, dog. Anaplastic oligodendroglioma within the left cerebral hemisphere with multifocal hemorrhage. Photograph courtesy of Departamento de Patologia, Facultad de Veterinaria, Universidad Nacional Autonoma de Mexico, Mexico City, Mexico.

Histopathologic Description: Sections of the brain show a poorly circumscribed, hypercellular mass compressing the surrounding tissue. The tumor is primarily located in the white matter and is composed of dense sheets of small round cells. These cells have moderate amount of clear eosinophilic and vacuolated cytoplasm, with poorly defined cell boundaries**(Fig. 2-2)**. Nuclei are round to oval, hyperchromatic, with clumped chromatin, inconspicuous nucleoli, and show moderate anisokaryosis. Mitotic figures are present (0-3 per random 40x field). Rarely, atypical astrocytes are scattered among the neoplastic cells. Occasionally, in some areas, tumor cells show poorly stained cytoplasm (perinuclear halo) with distinct cell membrane. In other areas, cellularity is low to moderate, and tumor cells have euchromatic nuclei with a vesicular chromatin pattern, single small basophilic nucleoli, fibrillary processes, and microcystic degeneration.

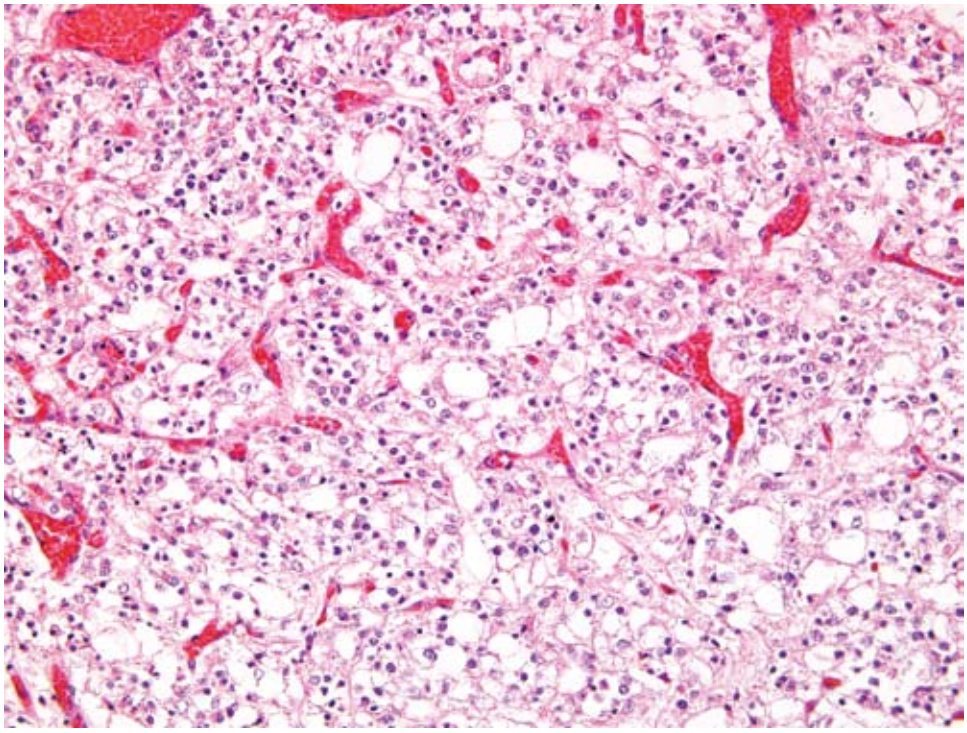


2-2. Cerebrum, dog. Anaplastic oligodendroglioma. Neoplastic cells have a dense nuclear chromatin pattern, poorly staining cytoplasm, and indistinct cell borders, giving the appearance of a perinuclear halo. (HE 400X)

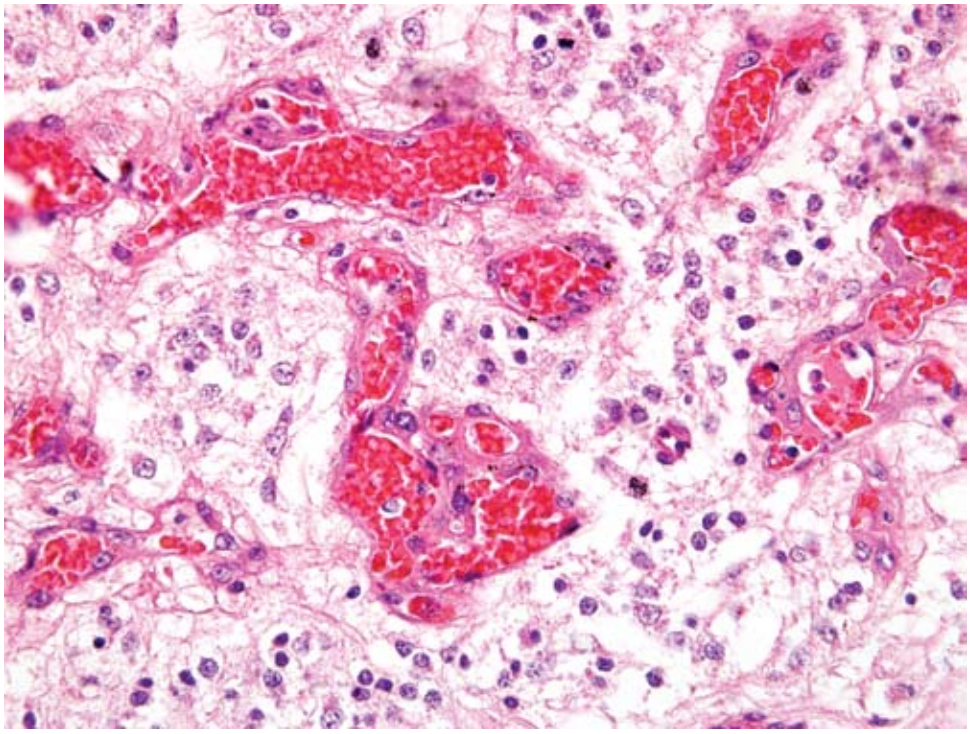
The neoplasm exhibits pronounced branching vascular proliferation **(Fig. 2-3)** with abundant glomeruloid vessels **(Fig. 2-4)**. Multifocal extensive areas of necrosis, with hemorrhages and small numbers of foamy macrophages (gitter cells) are also seen. In addition, small spaces filled with pale, gray-blue mucinous material (mucinous cystic degeneration) are also present in some sections (slides not submitted).

Contributor's Morphologic Diagnosis: Cerebrum: Oligodendroglioma, anaplastic

Contributor's Comment: Oligodendrogliomas appear to be the most common primary brain tumors in mature dogs (older than 5 years). Their overall incidence in dogs ranges from 5 to 12 %.(1) A predilection for brachycephalic dog breeds, such as the present case, has been recognized in glial tumors.(2,3) Oligodendroglioma is usually located in the subcortical white matter of the cerebral hemispheres, particularly the frontal lobe. In brachycephalic dog breeds, these tumors appear to arise within remnants of the germinal matrix adjacent to the lateral ventricles. Clinically, the dogs show depression, blindness, ataxia, and change in temperament from nerve damage.(3) Microscopically, the tumor cells have small, round, hyperchromatic nuclei with poorly stained cytoplasm. A perinuclear halo effect is common with delayed fixation which results in the artifactual but characteristically described "honeycomb" cell pattern. (1) Other important characteristics include pronounced branching capillary proliferation forming a delicate vascular "chicken-wire" pattern (2) and the formation of vascular loops or glomerular-like tufts often arranged



2-3. Cerebrum, dog. Anaplastic oligodendroglioma. Multifocally, there is pronounced branching vascular proliferation. (HE 200X)



2-4. Cerebrum, dog. Anaplastic oligodendroglioma. Occasionally, vascular proliferation have 'glomeruloid' morphology. (HE 400X)

in long lines or clusters, at the margins of or throughout the tumor.[1] Mucinous cystic degeneration and multifocal mineralization sometimes occur.(1,3) Other glial cells such as astrocytes and transitional forms between astrocytes and oligodendrocytes may be present in varying numbers.[2]

There are no antibodies for specific markers for oligodendrogliomas that have been formalin fixed and paraffin embedded.[1] The results of immunohistochemical staining of canine oligodendroglioma with antibody against myelin basic protein are generally negative. Many oligodendrogliomas show a mixture with GFAP-positive astroglial cells. The interpretation of the finding is controversial whether the astrocytes indicate a capacity for immature oligodendrocytes to express astrocytic differentiation or reactive astrocytes.[3]

In our case, the neoplasm was considered to be anaplastic due to the findings of high cellularity in some areas, frequent mitotic figures, nuclear pleomorphism, prominent proliferation of glomeruloid vascular tufts, and extensive necrosis. Anaplastic (malignant) oligodendroglioma and astrocytoma share several histomorphological features, including high cellularity, necrosis, high mitotic rate, and prominent proliferation of glomeruloid vessels; thus, distinguishing between these two glial neoplasms may be difficult.[2] In addition, the presence of intermingled astrocytic cells is common in anaplastic oligodendrogliomas and may further complicate the histologic picture. However, the presence of several distinguishing features in the tumor cells such as round, hyperchromatic nuclei surrounded by small amounts of clear to lightly stained cytoplasm, and distinct cell borders, as well as the branching capillary proliferation, support the diagnosis of oligodendroglioma in this case.

AFIP Diagnosis: Cerebrum: Oligodendroglioma, anaplastic

Conference Comment: Oligodendrogliomas have been reported in several animal species including dogs, cats, horses, and cattle. Grossly, these tumors are generally well demarcated, gray, grey-pink or pink -red, soft, gelatinous and may have cystic foci.[3,5] Necrosis and hemorrhage are uncommonly present.

The differential diagnosis discussed during the conference included oligoastrocytoma and neurocytoma.

Oligoastrocytomas (mixed gliomas) are glial neoplasms with astrocytes and oligodendroglial cells either intermingled or separated into distinct groups of cells.[4] When the cell populations are distinct, the diagnosis is uncomplicated. When the two cell populations are intermixed, at least 25% of the cells must be astrocytes to be classified as an oligoastrocytoma.[4] Tumors with less than this threshold of astrocytes are considered anaplastic oligodendrogliomas with reactive astrocytes.[4] Interpretation of the histogenesis of intratumoral cells can be complicated by the presence of minigemistocytes (gliofibrillary oligodendrocytes) which are neoplastic cells with round, oligodendroglial-type nuclei and GFAP-positive, eccentric eosinophilic cytoplasm.

The first reported case of a neurocytoma in domestic animals involved the spinal cord of a dog and was published in 2008.[2] Neurocytomas stain strongly positive for synaptophysin allowing differentiation from oligodendrogliomas.[3]

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CASE III – AFIP 08 CASE 1 (AFIP 3115317)

Signalment: Domestic feline, less than 1 yr. of age (*Felis domesticus*)

History: Euthanized because of non-responsive weight loss, generalized poor condition.

Gross Pathology: Not available.

Laboratory Results: Not performed

Histopathologic Description: Two sections of kidney are on the slide. Evident at the low magnification are an irregular cortex and multiple basophilic areas that comprise approximately 20 – 30% of each of the sections with some sections having up to 50% involvement. The irregular serosa has multifocal areas of predominantly plasma cell infiltrates with scattered areas of mixed inflammatory cells and fibrosis. The basophilic areas localized to the cortical regions consist of inflammatory cells infiltrates, which vary in composition. Some areas consist of primarily plasma cells, some areas are mixtures of plasma cells with neutrophils and macrophages, and there are areas of granulomatous inflammation with confluent infiltrates of macrophages **(Fig. 3-1)**. The infiltrates separate relatively normal tubules in some areas, while in other areas there is tubular degeneration and necrosis **(Fig. 3-2)**, and the inflammation has replaced the renal parenchyma with fibrosis. There is one focus of necrosis approximately 1- 2 mm in diameter that is occupied with hemorrhage and fibrin. Multiple glomeruli in the affected areas have hypertrophied parietal epithelium, but glomeruli in the non-involved regions are normal in appearance.

Other changes consist of occasional scattered minor proteinaceous tubular casts and diffuse moderate vacuolation of the tubular epithelium consistent with lipid accumulation that was considered excessive for the feline species and suggestive of perhaps a metabolic abnormality in addition to the obvious inflammatory disease process.

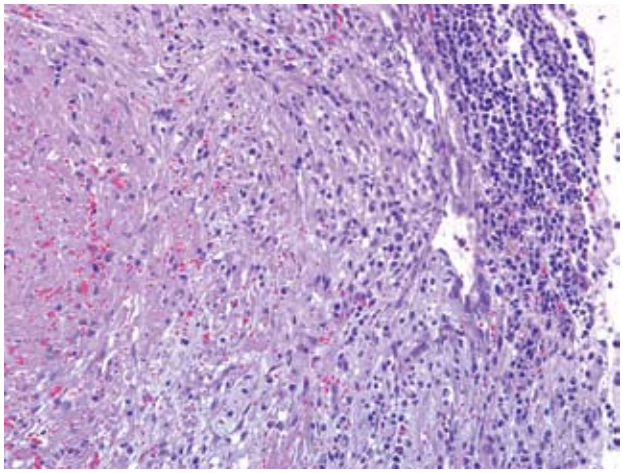
Contributor's Morphologic Diagnosis: Moderate bilateral multifocal mixed cell to granulomatous inflammation, kidney

Contributor's Comment: Signalment (age) and morphologic changes were consistent with feline infectious peritonitis.[2,6]

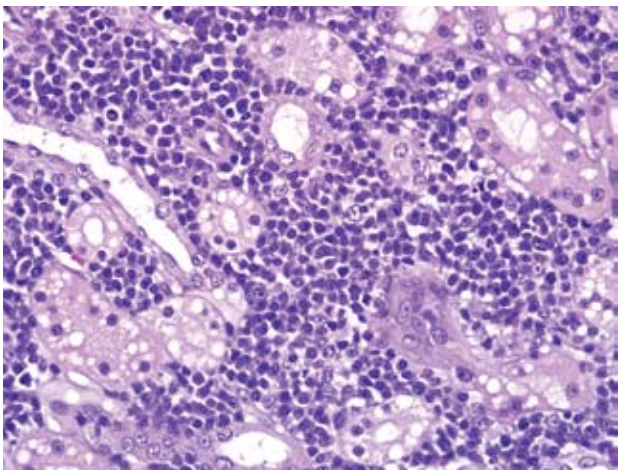
AFIP Diagnosis: Kidney: Nephritis and phlebitis, granulomatous, necrotizing, chronic, multifocal, severe, with multifocal mild tubular degeneration, necrosis, and regeneration

Conference Comment: Feline infectious peritonitis (FIP) is caused by feline coronavirus (FCoV), an enveloped, positive-stranded, RNA virus.[1] Cats that develop FIP are usually less than two years of age and come from a multi-cat environment.[2]

FCoV is spread via fecal-oral transmission, and the



3-1. Kidney, cat. Multifocally within the cortex and medulla, there is phlebitis, characterized by loss of endothelium and vascular tunics and replacement by necrotic debris, macrophages, fibroblasts, and variable numbers of plasma cells. Vessel lumens often contain fibrin thrombi. (HE 200X)



3-2. Kidney, cat. Multifocally, the interstitium is expanded by large numbers of plasma cells and fewer lymphocytes and macrophages. Multifocally, tubular epithelium is attenuated or regenerative. (HE 400X)

prevalence of coronavirus infection is high but the number of clinical cases of FIP is low.[1,7] The most commonly accepted theory for this peculiar finding is that FCoV undergoes a mutation and acquires virulence factors by deletions in open reading frames 3 and 7 to cause FIP.[7] Recent studies also strongly suggest that monocytes not only disseminate the virus, but also mediate the development of phlebitis associated with FIP.[7]

A strong cell mediated immune response is essential for protection against developing FIP.[1,2] Two forms of FIP, wet and dry, are generally referred to when describing FIP. If a weak cell-mediated immunity is mounted, the virus can persist in macrophages for months causing release of a variety of inflammatory mediators leading to perivascular pyogranulomatous inflammation in affected organs. This is the dry form. The wet or effusive form occurs when no cell mediated immunity is present and continued viral replication leads to the production of large quantities of non-neutralizing antibodies and immune complex deposition.[1,2]

Peritonitis is common in both the dry and wet forms. In the effusive form, copious amounts of flocculent yellow exudate may be found in the abdominal cavity, and serosal surfaces are often covered with fibrin.[1,2] Pyogranulomas are commonly found in the kidney, uvea, and peritoneum. Cervical and thoracic lymph nodes are often enlarged, and hydrocephalus is often found in cats with neurologic symptoms.[2] The classic histologic lesion of FIP is phlebitis with circumferential rings of pyogranulomatous inflammation.[2] Immunohiostochemical detection of coronavirus antigen in macrophages can be used to confirm a diagnosis of FIP.

A recent report associated FIP with papular cutaneous lesions [4] and fatal systemic coronavirus infections have recently been reported in ferrets [5] and dogs.[3]

Contributing Institution: Wyeth Research, 641 Ridge Rd, Chazy, NY

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CASE IV – 08N0486 (AFIP 3102517)

Signalment: 10-year-old, female, mixed Labrador retriever, (Canis familiaris)

History: The dog was presented for evaluation of decreased mobility of 3 weeks duration culminating in intermittent tetraparesis. On neurological examination the dog had severe ataxia, was able to stand with support, but would knuckle in all limbs and was most weak on the right thoracic limb, which had noticeable biceps and triceps muscle atrophy. Decreased withdrawal was observed in the right thoracic limb. Conscious proprioceptive deficits were present in all four limbs. There was severe pain on cervical palpation or manipulation. With magnetic resonance neuroimaging, axial slices from cervical cord segments C1 to C3 detected a well defined dural-based mass in the right dorsal lateral aspect of the spinal canal cranial to C2, causing severe compression and displacement of the spinal cord ventrally and to the left. The mass caused focal dilatation of the subarachnoid space at C2. The mass was isointense and hyperintense on T1 and T2 weighted images respectively. There was homogeneous intense contrast enhancement of the mass. From a surgical biopsy of the mass a diagnosis of chordoid meningioma was made and the dog was euthanized at the owners' request seven days later due to a poor prognosis.

Gross Pathology: On the right dorsolateral aspect of C2, a grayish, smooth, gelatinous, partly translucent, poorly demarcated intradural mass measuring 1.5 cm x 1 cm x 0.5

cm was firmly attached to the dura mater. On transverse section the mass had indistinct borders and compressed the spinal cord to the left and ventrally **(Fig. 4-1)**.

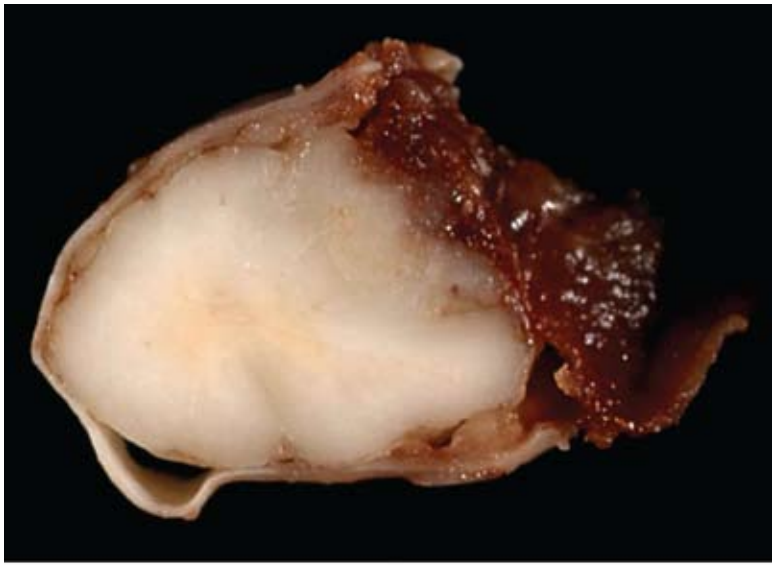
Laboratory Results: None

Histopathologic Description: On histological exam of transverse sections of the spinal mass an intradural, extraparenchymal, well-demarcated tumor was on the right dorsal aspect of the spinal cord, causing severe displacement of the cord ventrally and to the left. The tumor was organized in a pattern of trabeculae, clusters, or columns of cells in a basophilic mucinous matrix**(Fig. 4-2)**. The cells were uniformly polygonal with an abundant eosinophilic cytoplasm, with a round to oval nucleus and sometimes with a prominent nucleolus and had a well-defined cytoplasmic border. Mitotic figures were rare. At the periphery of the mass were prominent blood vessels while intratumorally there were multifocal inflammatory cell infiltrates of predominant lymphocytes. One dorsal nerve root fascicle was invaded by neoplastic cells. On the lateral aspect of the cord, there was also extensive hemorrhage and fibrin deposition in addition to an amorphous basophilic foreign material consistent with surgical gelfoam associated with the previous biopsy site. The white matter of the spinal cord, compressed by and adjacent to the tumor, had multifocal sites of axon spheroids, axonal necrosis, demyelination and macrophages. The neoplastic cells were uniformly strongly immunoreactive for vimentin and focal subpopulations of cells (about 15% total) were immunoreactive for cytokeratins using a low and high molecular weight antibody cocktail (Lu5, Biocare Medical). The proliferative index, assessed by MIB1 immunoreactivity, was approximately 1%.

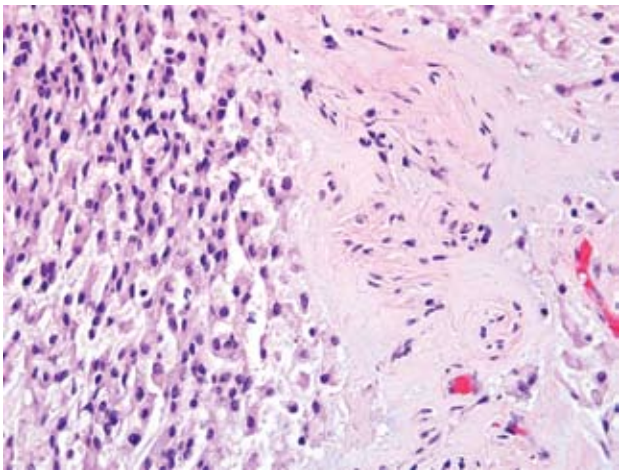
Contributor's Morphologic Diagnosis: Spinal Cord (Segments C2-3): Chordoid Meningioma

Contributor's Comment: This tumor was classified histologically as a chordoid meningioma based on location, morphology and immunohistochemistry and using criteria from the latest update of the human WHO classification of tumors of the central nervous system.[5] Although this tumor was relatively benign cytologically, in humans chordoid meningiomas are graded as atypical (WHO Grade II) based on the high incidence of post surgical recurrence.[2,5] Certainly the invasive nature of this tumor within nerve roots fascicles would support this grade. Classification of canine meningiomas using the human WHO classification into one of three histological grades (benign, atypical, anaplastic) using carefully defined and clinically tested criteria in humans may also be useful for predicting clinical behavior and outcome in dogs.[6,8]

In dogs spinal cord chordoid meningiomas have been reported with a predilection site in the cervical region as in this case; [6,8] however, in another series of canine meningiomas this type occurred in the forebrain.[1] Confusingly, these tumors have been classified for unknown reasons as myxoid meningiomas in the veterinary literature. The chordoid type is a histological variant of meningioma, defined histologically by cords or trabeculae of polygonal cells with an eosinophilic cytoplasm in an abundant basophilic mucinous matrix. Chronic inflammatory cell infiltrates may be prominent as in this case.[2,5] In humans this chordoid pattern is not an uncommon focal pattern in atypical or aggressive meningiomas, however it is rare in pure form.[2] Meningiomas in people and dogs are uniform and strongly immunoreactive for vimentin and



4-1. Spinal cord, dog. Chordoid meningioma. The gray, gelatinous neoplasm compresses and distorts the contour of the spinal cord. There is an adjacent area of hemorrhage possibly associated with a previous biopsy procedure. Photograph courtesy of University of California, Davis, Veterinary Medical Teaching Hospital VM3A, Anatomic Pathology, 1 Garrod Drive, Davis, CA 95616 http://www.vetmed.ucdavis.edu/pmi/



4-2. Spinal cord, dog. Chordoid meningioma. Trabeculae of neoplastic cells are often surrounded by an amphophilic to lightly basophilic mucinous matrix. (HE 400X)

subpopulations of cells are variably immunoreactive for pancytokeratins.[1,2,5,9] Many human meningiomas are immunoreactive for epithelial membrane antigen and this is therefore a useful diagnostic feature, but unfortunately this epitope is not expressed in the dog.

The differential diagnoses for chordoid meningiomas include: chordoma, myxoid chondrosarcoma, and metastatic carcinoma. Chordomas arise from the axial skeleton, have characteristic fibrous lobularity, the hallmark physaliphorous cells and are strongly uniformly immunoreactive for low-molecular-weight cytokeratin. Myxoid chondrosarcomas do not exhibit immunoreactivity for keratin. Chordoid meningiomas lack the anaplasia of metastatic carcinomas. [2]

AFIP Diagnosis: Cervical spinal cord, meninges: Meningioma, chordoid (myxoid) with focal hemorrhage and surgical gel

Conference Comment: Meningiomas are derived from meningothelial cells of the arachnoid membrane.[4] Meningiomas tend to be discrete, well-demarcated tumors with a broad attachment to the meninges.[4] They rarely metastasize.[7]

There are nine meningioma subtypes listed in the second series of the WHO International Histological Classification of Tumors of Domestic Animals: meningotheliomatous, fibrous, transitional, psammomatous, angiomatous, papillary, granular cell, myxoid, and anaplastic.[3] The myxoid variant is comparable to the chordoid variant as seen in humans. As one of the aims of the WHO International Histological Classification of Tumors in Domestic Animals was to follow the WHO histological classification for human tumors as closely as possible to facilitate communication between pathologists, diagnosticians and researchers, perhaps the chordoid terminology should have been used.

In a recent publication, canine meningiomas were divided into histologic grades according to the WHO classification used for human meningiomas. 56% of canine meningiomas were grade I, 43% were grade II and 1% were grade III, as compared to 80% grade I, 8% grade II and <3% grade III meningiomas reported in humans.(8) The biological significance of these differences is not known.

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http://www.vetmed.ucdavis.edu/pmi/

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