Joint Pathology Center
Veterinary Pathology Services

WEDNESDAY SLIDE CONFERENCE 2022-2023

Conference #23 **19 April 2023**

CASE I:

Signalment:
16-years old, female spayed, French bulldog, (*Canis lupus familiaris) canine*

History:
The dog was presented to the animal hospital for mass of the right eye that had grown from two months ago. Marked exophthalmos was observed in the right eye and enucleation was performed.

Gross Pathology:
Most of formalin fixed material was neoplastic tissue and normal ocular structures were unclear. On cut surface, there was scattered bleeding and necrosis in the tumor tissue.

Laboratory Results:
No laboratory findings reported.

Microscopic Description:
The nonencapsulated and poorly demarcated mass surrounded the optic nerve behind the globe. The mass consisted of spindle or epithelioid polygonal cell arranged in whorls, bundles or sheets, and often formed tumor islands of variable size and lobules separated by fibrovascular stroma. These tumor cells had various amounts of pale eosinophilic cytoplasm with slightly distinct cell margins. The cells had ovoid nuclei with stippled chromatin and occasional clear nucleoli. Anisocytosis and anysokaryosis was mild. 11 mitotic figures were observed under 10 high-magnification fields of view. Several large to small foci of necrosis and hemorrhage were also seen. Although no tumor invasion was observed into the eye tissue, the neoplastic cells extensively invaded into peripheral adipose and muscle tissues. Clusters of neoplastic cells were seen in some lymphatic or blood vessels. The ocular structures markedly compressed by the tumor. In other specimens submitted, the corneal epithelium showed hyperplastic thickening with some small pustules and ulcer. In the substantia propria of cornea, severe fibrosis with mild hemorrhage, edema and infiltration of lymphocytes can be seen. The structures of the iris and ciliary body were collapsed, the lens and retinae were obscure.

Contributor's Morphologic Diagnosis:
Eye: Orbital meningioma, right eye, dog

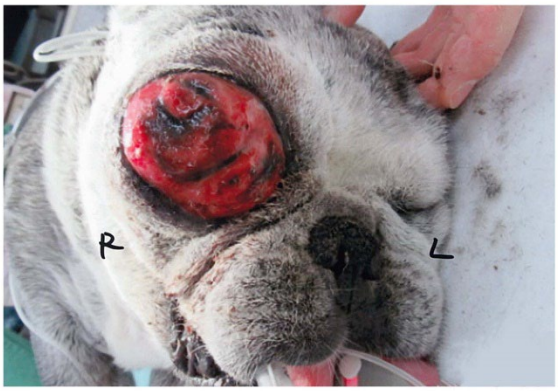

Figure 1-1. Presentation, dog. Marked exophthalmos was observed in the right eye (Photo courtesy of: Department of Veterinary Pathology and Public Health, Institute of Veterinary Science, Univ Laboratory of Pathology, Faculty of Pharmaceutical Sciences, Setsunan University, 45-1 Nagaotohge-cho, Hirakata, Osaka 573-0101, Japan)

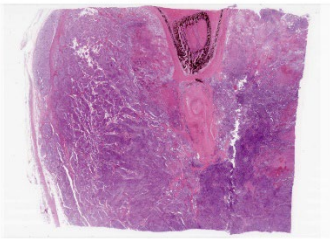

Figure 1-2. Orbit, dog. A single section of orbit containing a compressed phthitic globe and the optic nerve projecting downward (top center). An infiltrative mass effaces the orbital skeletal and periorbital fat. (HE

Contributor's Comment:

Meningioma is a common primary brain tumor in dogs (up to 45%) and cats (60%), and most intracranial meningiomas occur as well-demarcated solitary masses. However, meningioma in the retrobulbar site accounts for only 2 to 3 % of all meningiomas and develops surrounding optic nerve area with invasion into peripheral tissue.[14,15] Meningioma is derived from arachnoidal cap lining arachnoid villi. In veterinary medicine, orbital meningioma is considered a primary lesion originating in meninge covering intraorbital or intracanalicular optic nerve, while in human medicine, some are observed as secondary lesion occurring intracranially and extend along the optic nerve.[6,7]

Orbital meningioma is characterized by proliferation in sheets or cluster of various sized epithelioid cells with glassy eosinophilic cytoplasm and may form whorls or bundles as is the intracranial cases, but psammoma bodies are rare. While chondro-osseous metaplasia is rare in intracranial meningioma, it is frequently observed in orbital meningiomas and is useful for diagnosis.[13,14,18] In 3 previous cases in the Wednesday Slide Conference, epithelioid or spindle cells arranged in small lobules and whorls in 2 cases (Conference 19, 2013, Case 2; Conference 20, 2015; Case 4) , epithelioid cells arranged in nests and sheets predominated in 1 case (Conference 7, 2018, Case 4), and chondro-osseous metaplasia was seen in all cases. This case is thought to be typical orbital meningioma at the point of location and histological morphology except for the lack of chondro-osseous metaplasia.

Although immunohistochemistry is not always necessary in typical cases, it may be useful for excluding other differential diagnosis such as carcinoma. In general, neoplastic cells show positive reaction for vimentin, S100 and neuron specific enolase in varying degree, and negative for pancytokeratin and glial fibrillary acidic protein, however, cytokeratin expression was detected in few cases on a report .[2,11,13,15]

Orbital meningioma is slow growing and malignant variants are rarely reported. One study of 22 canine orbital meningiomas revealed that 6 of 17 recurred and furthermore 2 of them presented subsequent central blindness suggesting intracranial invasion of the tumor.[10] In addition, two other reports showed distant metastasis to lung.[12,16] These aggressive biologic behaviors of this tumor might be associated with stage and progression at the time of excision.

Malignancy of human orbital meningiomas are assessed by WHO grading system for intracranial meningioma, which depends on histologic subtypes and specific cytological features.[6,7] In canine intracranial meningioma, application of the system has been proposed because they are likely to exhibit biological similarities to their human

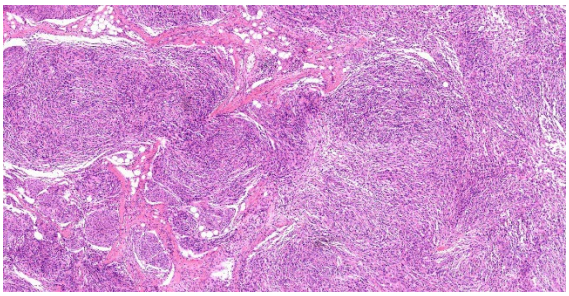

Figure 1-3. Orbit, dog. The neoplastic cells are arranged in long streams, bundles, and frequent whorls. (HE, 39X)

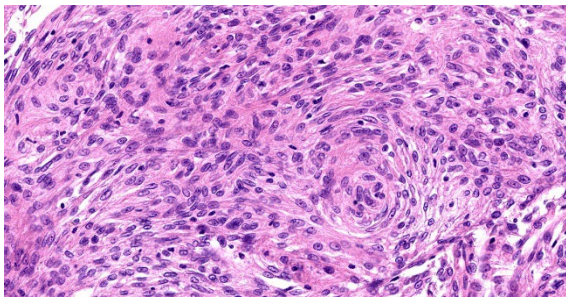

Figure 1-4. Orbit, dog. High magnification of neoplastic cells. (HE, 388X)

counterparts, but it is not yet used for orbital lesions. The number of cases of canine orbital meningioma is small and correlation be tween grading and prognosis with both types of meningioma has not been validated, therefore the standardization of grading system in canine meningioma needs further studies using larger caseloads.[1,11]

This case might have poor clinical outcome such as recurring and/or extension into cranium because of the histopathological features including prominent local invasion, lymphovascular invasion and frequent mitotic figures. It was suggested that loss of the eye structure was due to compression by the neoplastic tissue and secondary inflammatory change.

Contributing Institution:
Laboratory of Pathology, Faculty of Pharmaceutical Sciences, Setsunan University,
45-1 Nagaotohge-cho, Hirakata, Osaka 573-0101, Japan

JPC Diagnosis:
Globe, right: Orbital meningioma.

JPC Comment:
Meningioma was last seen in the Wednesday Slide Conference in 2021-2022, conference 7, case 2: this case was an intracranial neoplasm in a cat, and the contributor and conference comments delineate the pathologic and historical aspects of this common neoplasm.

Non-orbital canine meningiomas are classified according to the 2007 WHO human grading system. The two most common types of meningioma, the meningotheliomatous (epithelioid) and transitional (mixed) types, are both considered grade I, as are fibrous, psammomatous, angiomatous, microcystic, and myxoid types.[3] Grade II meningiomas include choroid and atypical meningiomas, which have a higher mitotic rate ($\geq$ 4 per 10 high power fields) and hypercellularity.[3] Grade III meningiomas include papillary, rhabdoid, and anaplastic forms, which have cytologic features of malignancy and greater than 20 mitotic figures per 10 high power fields.[3,17] While orbital meningiomas are not graded, this week's moderator, Dr. Jey Koehler from Auburn University, described several concerning features which could *potentially* be indicative of a more aggressive behavior (and would be characteristic of malignancy in a non-orbital meningioma): large areas of necrosis and regions with significant anisokaryosis and high mitotic rate.

A recent study described four cases of the uncommon rhabdoid meningioma in dogs.[17] In all cases, the neoplasms were located in the olfactory or frontal lobes and were locally invasive.[17] Rhabdoid cells comprised >70% of the tumor population, were arranged in

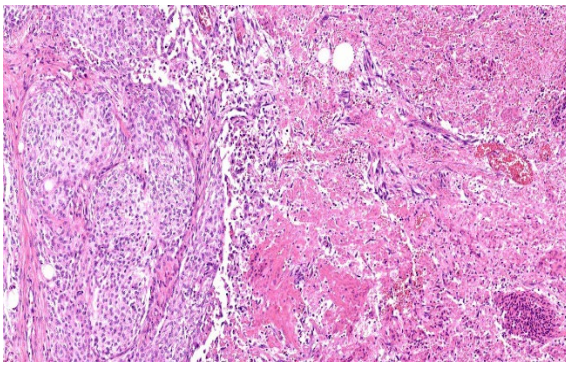

Figure 1-5. Orbit, dog. There are large areas of necrosis scattered throughout the neoplasm. (HE, 108X)

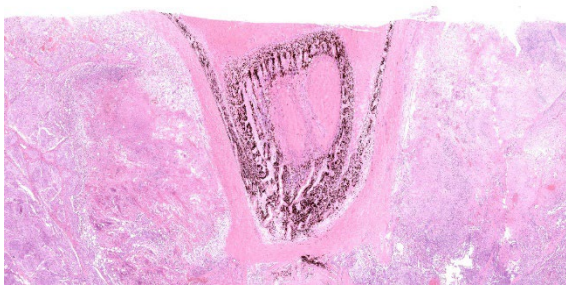

Figure 1-6. Orbit, dog. The compressed globe is phthitic – there is remnant pigment outlining the position of the ciliary body, uvea and choroid, but the anterior and posterior chamber are replaced by mature collagen (HE, 11X)

sheets, and had well-delineated cell borders, abundant eosinophilic cytoplasm, and hyaline to fibrillar inclusions which peripheralized the nucleus.[17] On electron microscopy, these inclusions were composed of whirling intermediate filaments (consistent with a rhabdoid morphology), a network of extensive cell process interdigitations (consistent with a rhabdoid-like morphology), or abundant mitochondria (consistent with an oncocytic meningioma).

In humans, expression of Ki-67, a marker of proliferation, and osteopontin, a cytokine with multiple activities important in tumor progression, are highly correlated to the histologic grade and recurrence rate of meningiomas.[8] Janssen et al recently evaluated 35 canine meningiomas and found that neither Ki-67 nor osteopontin were correlated with histologic grading according to the WHO classification system for human meningiomas.[8]

Meningiomas have a characteristic cytologic appearance, and samples may be obtained via impression smears or crush preparations of biopsy or by fine needle aspirate.[4,5] As on histology, samples from meningiomas may demonstrate whirling or acini formation and psammoma bodies on cytology. Additionally, neoplastic cells may have intracytoplasmic nuclear invaginations or an elongate nucleus with a longitudinal, dark blue linear bar imparting a "coffee bean" appearance to the nucleus.[4,5] These characteristic nuclei can be seen on histology throughout the neoplasm in this case as well.

Another primary neoplasm of the optic nerve described in dogs is an ocular astrocytoma.[9] This may arise in the optic nerve or within the retina and can lead to retinal detachment.[9]

References:

1. Avallone G, Rasotto R, *et al*. Review of Histological Grading Systems in Veterinary Medicine. *Vet Pathol*. 2021;58(5):809-828.
2. Barnhart KF, Wojcieszyn J, *et al*. Immunohistochemical staining patterns of canine meningiomas and correlation with published immunophenotypes. *Vet Pathol*. 2002;39(3):311-21.
3. Cantile C, Youssef S. Nervous system. In: Maxie, MG, ed. *Jubb, Kennedy, and Palmer's Pathology of Domestic Animals*, Vol I. 6th ed. Philadelphia, PA: Elsevier Ltd; 2016:396-398, 494.
4. DeLorenzi D, Mandara MT. The Central Nervous System. In: Raskin RE, Meyer DJ, eds. *Canine and Feline Cytology*. 3rd ed. St. Louis, MO: Elsevier. 2016: 396-400.
5. Gould A, Naskou MC, Brinker E. What is your diagnosis? Impression smear from a dog with an intracranial mass. *Vet Clin Pathol.* 2022; 00:1-5.
6. Grossnilaus HE, Eberhart CG, Kivelä TT. The 2016 World Health Organization Classification of Tumors of the Eye. 139.
7. Jain D, Ebrahimi KB, et al. Intraorbital meningiomas: a pathologic review using current World Health Organization criteria. *Arch Pathol Lab Med.* 2010;134(5):766-70.
8. Janssen J, Oevermann A, Walter I, Tichy A, Kummer S, Gradner G. Osteopontin and Ki-67 expression in World Health Organization graded canine meningioma.

9. Labelle P. The Eye. In: Zachary JF, ed. *Pathologic Basis of Veterinary Disease*. 7th ed. St. Louis, MO: 2022. 1423.
10. Mauldin EA, Deehr AJ, et al. Canine orbital meningiomas: a review of 22 cases. *Vet Ophthalmol*. 2000;3(1):11-16.
11. Montoliu P, Añor S, et al. Histological and immunohistochemical study of 30 cases of canine meningioma. *J Comp Pathol*. 2006;135(4):200-7.
12. Pérez V, Vidal E, et al. Orbital meningioma with a granular cell component in a dog, with extracranial metastasis. *J Comp Pathol.* 2005;133(2-3):212-7.
13. Regan DP, Kent M, *et al*. Clinicopathologic findings in a dog with a retrobulbar meningioma. *J Vet Diagn Invest.* 2011; 23(4):857-62.
14. Richard RD. Tumors of the Eye. In: Meuten DJ, ed., *Tumors in Domestic Animals.* 5th ed. Ames, IA. Wiley Blackwell. 915-916.
15. Robert JH, Andrew WB, *et al*.: Tumors of the Nervous System. In: Meuten DJ, ed., *Tumors in Domestic Animals.* 5th ed. Ames, IA. Wiley Blackwell. 864.
16. Schulman FY, Ribas JL, *et al*. Intracranial meningioma with pulmonary metastasis in three dogs. *Vet Pathol.* 1992;29(3):196-202.
17. Tabaran AF, Armien AG, Pluhar GE, O'Sullivan MG. Meningioma with rhabdoid features: Pathologic findings in dogs. *Vet Pathol*. 2022; 59(5): 759-762.
18. Wilcock BP: Special Senses. In: *Jubb Kennedy and Palmer's Pathology of Domestic Animals.* 6th ed. Vol 3. St. Louis, US: Elsevier; 2016:487-488.

CASE II:

Signalment:
14-year-old neutered male Persian cat (*Felis catus*)

History:
The cat had an acute onset of difficulty walking on the hind limbs, with a progressive worsening. The cat urinated and defecated in inappropriate places with sagging of the limbs during urination / defecation; had difficulty in jumping and appeared depressed. Palpation of the thoraco-lumbar spine caused discomfort. The cat underwent hospitalization and a complete diagnostic workflow. Due to a severe worsening of the symptoms and the health status, the cat was euthanized, and a necropsy was performed.

Gross Pathology:
An intramedullary neoformation was present in the thoraco-lumbar spinal cord (approximately T7).

Laboratory Results:
Hematobiochemistry: mild leucopenia; hyperazotemia.

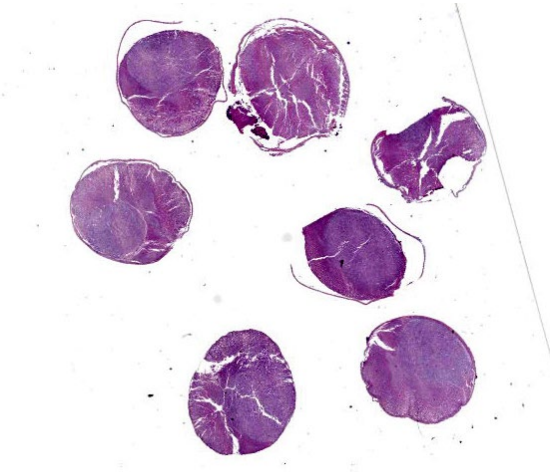

Figure 2-1. Spinal cord, cat. Multiple sections of spinal court are submitted for examination. At subgross magnification, an infiltrative neoplasm effaces 50-60% of the normal architecture. (HE, 6X)

Serology for FIV, FeLV, *Toxoplasma gondii*: negative.
PCR for Feline coronavirus, *Neospora caninum*, Feline parvovirus, *Toxoplasma gondii* (liquor): negative.
Liquor cytology: mixed pleocytosis, mainly monocytoid and neutrophilic.
Liver and spleen cytology: mild hepatocellular degeneration; splenic extramedullary hemopoiesis.

Microscopic Description:
Spinal cord. Focally effacing and replacing about 60% of the grey and white matter compressing the adjacent tissue, there is a nodular neoplasm of 4 mm that is moderately cellular, multifocally infiltrative, moderately demarcated and unencapsulated.

Neoplastic cells are variably arranged in interlacing streams, short bundles, and sheets with scant amounts of supporting fibrovascular stroma. A mixed cell population is present. The predominant neoplastic cells are round to angular, 20-50 microns large, with low nucleus/cytoplasm ratio, variably distinct cell borders and abundant eosinophilic cytoplasm that multifocally forms stout processes. Nuclei are 5-15 microns large, round to elongated to pleomorphic, eccentric, with open-faced chromatin and mostly single prominent nucleolus. Rare binucleated neoplastic cells and multifocal megakaryosis are observed. Anisokariosis and anisocytosis are severe (gemistocyte-like cells; 60%). The predominant population is admixed with spindle to stellate cells, 10-15 microns large, with high nucleus/cytoplasm ratio, indistinct cell borders and scant eosinophilic cytoplasm. Nuclei are oval to elongated, 6-8 micros large, central with finely stippled chromatin and rarely evident nucleoli. Anisokariosis and anisocytosis are mild (astrocytes; 40%). Mitoses are less than 1 in 2.37mm^2.

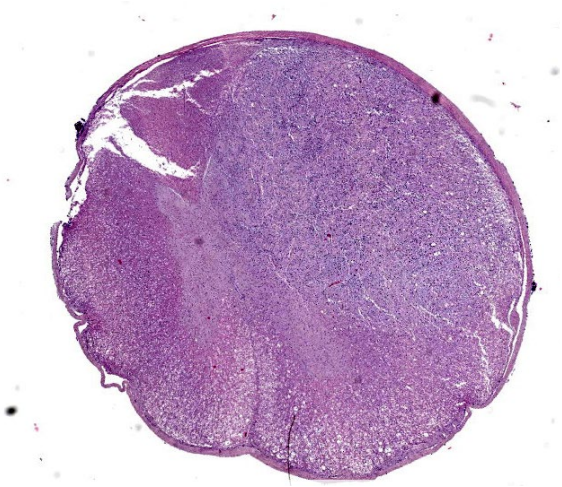

Figure 2-2. Spinal cord, cat. Slightly higher magnification of one section of spinal cord demonstrating the neoplasm (HE, 17X)

In the surrounding white matter axonal sheaths are moderately vacuolized (spongiosis). Vessels are hyperemic.

Immunohistochemistry: neoplastic cells are diffusely and strongly GFAP-positive, diffusely and moderately S100-positive; negative to CNPase.

Contributor's Morphologic Diagnosis:
Spinal cord. Gemistocytic astrocytoma, grade II

Contributor's Comment:
Gliomas are primary neoplasms of the central nervous system originating from glial cells.[18] Astrocytomas are common in dogs, whereas they are rare in cats. In cats, astrocytomas represent about 2.8% of intracranial neoplasms and 3.5% of spinal ones; the most common tumors of the spinal cord in cats are lymphoma and osteosarcoma.[1,8,18] The most frequent location of astrocytomas in cats, according to the literature, is telencephalon, with rarer reports in the brainstem, cerebellum and spinal cord.[8,9,12,18]

Astrocytomas have variable macroscopic appearance, although their presence might be hard to assess grossly. They can be firm,

palpable masses, ranging from white to gray, with ill-defined borders and possible areas of necrosis, especially with larger and more malignant tumors.[3]

Histologically, astrocytomas are neuroepithelial tumors classified in different histological subtypes which correlate to the grade. Based on the 2007 World Health Organization (WHO) classification of tumors of the central nervous system, there are:
• Low-grade astrocytomas (grade I), with the variants fibrillary astrocytoma, protoplasmic astrocytoma, pilocytic astrocytoma, and subependymal giant cell astrocytoma;
• Medium grade astrocytomas (grade II), with the gemistocytic variant;
• Anaplastic astrocytomas (grade III);
• High-grade astrocytomas (grade IV) or glioblastoma.[3,6]

Low-grade astrocytomas are mostly scarcely or moderately cellular, unencapsulated, expansile, with round to oval neoplastic cells replacing the pre-existing tissue. On the other hand, the medium grade astrocytomas usually are more densely cellular, showing more nuclear atypia. Anaplastic astrocytomas are characterized by cells with the greater extent of atypia and higher mitotic index. In high-grade astrocytomas there are frequent areas of haemorrhages and necrosis, around which neoplastic cells are pseudopalisading. Proliferation of the endothelium of blood vessels is present. In this entity high pleomorphism and atypia of the neoplastic cells are expected.[3]

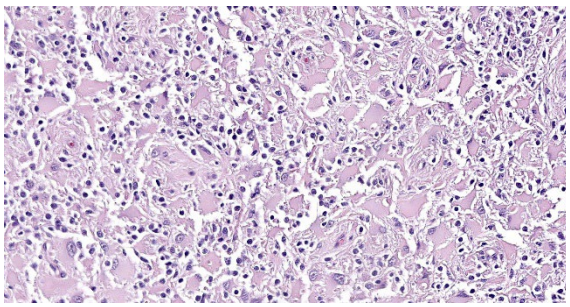

Figure 2-3. Spinal cord, cat. The neoplasm is composed of large polygonal gemistocytes which are separated by bundles of astrocyte process, numerous microglia, and fewer Schwann cells and non-neoplatic astrocytes. (HE, 337X)

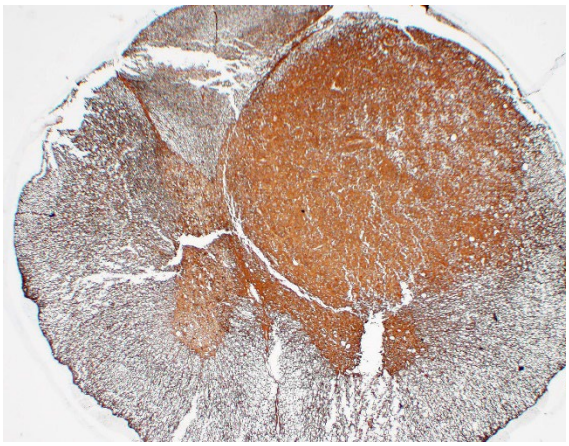

Figure 2-4. Spinal cord, cat. The neoplasm (and adjacent compressed grey matter) demonstrates strong immunopositivity for glial fibrillary acidic protein. (HE, 40X)

Alongside the well differentiated astrocytomas reported in cats, the rarer subtypes eg. pilocytic astrocytoma, granular cell astrocytoma, angiocentric astrocytoma and anaplastic gemistocytic astrocytoma are also described.[8,9,15,18] There are few reports of gemistocytic astrocytoma in cats. Gemistocytic astrocytoma is considered a medium-grade (grade II) tumor that is histologically characterized by the prevalence of large cells with abundant eosinophilic cytoplasm and eccentric oval nuclei (gemistocytic cells).[3] Nevertheless, in human pathology gemistocytic astrocytomas are no longer recognized as a histological subtype but rather as a pattern ("gemistocytic tissue pattern"), according to 2021 World Health Organization classification of tumors of the central nervous system.[7] A threshold of 20% gemistocytes in the neoplastic population is suggested to adopt this definition.[7]

On immunohistochemistry, neoplastic cells in gemistocytic astrocytomas are immunoreactive for glial fibrillar acidic protein (GFAP), S100, vimentin, whereas they do not stain for CNPase and epidermal growth factor receptor (EGFR), in contrast to

oligodendrolioma or glioblastoma, respectively.[1,3] Variable immunoreactivity for p53 was also described in one study, suggesting a possible abnormal biological behavior of this protein in the pathogenesis of feline astrocytoma.[1]

We classified the lesion we submitted as a gemistocytic astrocytoma taking into consideration the prevalence of gemistocytic cells observed on histology in association with the immunohistochemical positivity for S100 and GFAP and negativity for CNPase.

Contributing Institution:
San Marco Veterinary Clinic and Laboratory Pathology division
Viale dell'Industria 3, 35030
Veggiano (PD), Italy
https://www.clinicaveterinariasanmarco.it/

JPC Diagnosis:
Spinal cord: Gemistocytic astrocytoma.

JPC Comment:
A recent *Vet Pathol* review article by Rissi details the clinical, pathologic, diagnostic, and behavioral features of primary central nervous system neoplasms in cats. Most intracranial neoplasms in cats are primary brain tumors, and the most common primary brain tumor is the meningioma, representing 60%

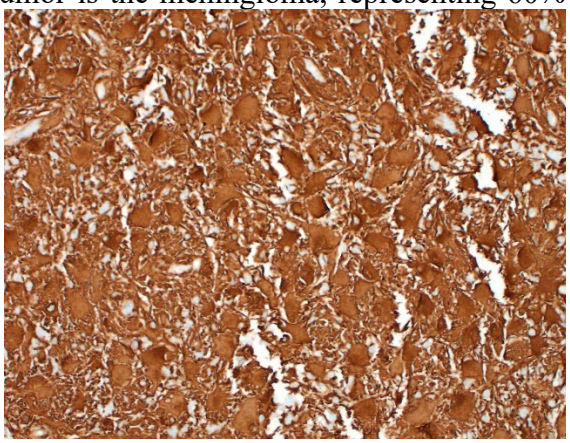

Figure 2-5. Spinal cord, cat. Neoplastic cells and their processes demonstrated strong immunopositivity for glial fibrillary acidic protein. (HE, 40X)

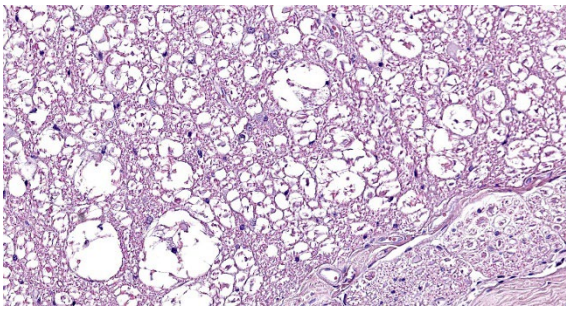

Figure 2-6. Spinal cord, cat. Adjacent to the neoplasm, there are few markedly dilated myelin sheaths continuing axonal debris and Gitter cells. (HE, 314X)

of all intracranial tumors and 85% of all primary brain tumors. [12] Gliomas are the second most common primary CNS tumor of the cat but, in the spinal cord and vertebral column, gliomas are slightly more common (8%) than meningiomas (7%).[12] The most commonly reported type of glioma in the cat is the astrocytoma; ependymoma and oligodendroglioma are reported at lower rates.[12]

Astrocytomas have variable staining for GFAP and OLIG-2, whereas oligodendrogliomas have strong labeling for OLIG-2 and variable reactivity for GFAP.[13] Round cell markers may also be useful to rule out lymphoma in neoplasms that lack OLIG-2 staining, as lymphoma is the most common spinal cord tumor of cats.[13] Recently, Elbert and Rissi reported on doublecortin immunolabeling in 11 feline gliomas. Doublecortin (DCX) is a protein of neuronal precursor cells. [13] DCX expression along the periphery of invasive human gliomas is suggestive of more invasive behavior. [13] In this study on feline gliomas, DCX was expressed in all 4 astrocytomas, with more intense staining along the margins of the neoplasms. [13] Neuronal nuclear protein (NeuN), expressed by mature neurons, was negative in all four astrocytomas of this study. [13]

Gliosarcoma is a rare subtype of the grade IV astrocytoma (glioblastoma), and the first documented case in a cat was reported by Alvarez et al in 2019. Gliosarcomas are composed

of bimorphic cell populations: a glial component and a sarcomatous component; both components are thought to arise from a common progenitor cell due to their similar genetic alterations.[2] This case was in a 5-year-old cat with 1.5-year history of mild neurologic signs that acutely progressed, and a gliosarcoma was discovered in the septum pellucidum. Within the glial component, neoplastic cells histologically resembled astrocytes and were positive for GFAP and negative for OLIG-2.[2] This case also contained all four types of structures of Scherer, which are histologic features of invasiveness in glial tumors.[2] Types of Scherer structures include spread within the subpial space, perivascular infiltration, and perineuronal and perivascular satellitosis.[2]

The glioma entity was first described over 200 years ago, and several notable pathologists have contributed to our knowledge of the entity. Rudolf Virchow coined the term glioma and provided the first histologic description of the neoplasm,[11] and Howard Tooth, Percival Bailey, and Harvey Cushing later expanded the knowledge of glioma histology. German pathologist Hans Joachim Scherer (1906-1945), the namesake for Scherer structures, also conducted extensive landmark research on gliomas.[11] One of the many observations made by Scherer that shape our understanding of gliomas is the pseudopalisading of neoplastic cells around areas of necrosis in glioblastoma multiforme (high grade astrocytoma).[17] As a researcher in Germany during the first half of the 20th century, Scherer's work was both influenced and interrupted by Nazi activities and World War II. After being arrested by the Gestapo in 1933, Scherer fled to Belgium, where published numerous studies on human gliomas while employed at the Institute Bunge in Antwerp.[10] In 1941, the German military ordered Scherer to return to Germany, and he began working at the Neurologic Institute in Breslau (now Poland).[10] There, he conducted post-mortem examinations on at least 209 euthanized children, most with neurologic disabilities.[5] Whether his work in this program was voluntary or conducted under coercion is still unknown, but his prior arrest, his exodus from Germany after Hitler rose to power, and personal accounts from his acquaintances suggest that he was not sympathetic to the Nazi party.[16] Scherer died in 1945 in a railway station attacked during one of the last Allied bombings.[11]

Readers are encouraged to review Case 1, Conference 7, 2021-2022, a grade IV astrocytoma in the dog. The contributor and conference comments provide an excellent review of features of canine astrocytoma, including a recently published grading scheme for canine gliomas.

References:

1. Aloisio F, Levine JM, Edwards JF. Immunohistochemical features of a feline spinal cord gemistocytic astrocytoma. *J Vet Diagn Invest*. 2008 Nov;20(6):836-8.
2. Alvarez P, Wessmann A, Pascual M, Comas O, Pi D, Pumarola M. Cerebral gliosarcoma with perivascular involvement in a cat. *JFMS Open Reports.* 2019; 5(2): 1-6.
3. Cantile C, Youssef S. Nervous System. In: Grant Maxie M, ed. *Jubb, Kennedy and Palmer's Pathology of Domestic Animals*. 6th ed. St. Louis, USA: Elsevier. 2016; 250-406.
4. Elbert JA, Rissi DR. Doublecortin immunolabeling and lack of neuronal nuclear protein immunolabeling in feline gliomas. *J Vet Diagn Invest.* 2022; 34(4):757-760.
5. Kleiheus P. Reply to Marc Scherer. *Brain Pathol.* 2013; 23(4): 488.
6. Louis DN, Ohgaki H, Wiestler OD, et al. The 2007 WHO classification of tumours

of the central nervous system. *Acta Neuropathol*. 2007; 114(2):97-109.
7. Louis DN, Perry A, Wesseling P, et al. The 2021 WHO Classification of Tumors of the Central Nervous System: a summary. *Neuro Oncol*. 2021 Aug 2;23(8):1231-1251.
8. Marioni-Henry K. Tumors affecting the spinal cord of cats: 85 cases (1980–2005). *J Am Vet Med Assoc*. 2008; 232: 237–243.
9. Murthy VD, Liepnieks ML, Roy MA, et al. Diagnosis and clinical outcome following surgical resection of an intracranial grade III anaplastic gemistocytic astrocytoma in a cat. *JFMS Open Rep*. 2020; 6(2): 2055116920939479.
10. Peiffer J, Kleiheus P. Hans-Joachim Scherer (1906-1945), pioneer in glioma research. *Brain Pathol.* 1999; 9(2): 241-245.
11. Reuter G, Lombard A, Molina ES, Scholtes F, Bianchi E. Hans Joachim Scherer: an under-recognized pioneer of glioma research in Belgium. *Acta Neurol Belg.* 2021; 121(4): 867-872.
12. Rissi DR. Feline glioma: a retrospective study and review of the literature. *J Feline Med Surg*. 2017; 19:1307–1314.
13. Rissi DR. A review of primary central nervous system neoplasms of cats. *Vet Pathol.* 2023. Online First.
14. Rissi DR, McHale BJ, Armién AG. Angiocentric astrocytoma in a cat. *J Vet Diagn Invest*. 2019; 31(4): 576-580.
15. Sant'Ana FJ. Pilocytic astrocytoma in a cat. *Vet Pathol*. 2002; 39: 759–761.
16. Scherer M. Some comments on the paper: Hans-Joachim Scherer (1906-1945), a pioneer in glioma research. *Brain Pathol*. 2013; 23(4):485-487.
17. Stoyanov GS, Petkova L, Dzenkov DL.Hans Joachim Scherer and His Impact on the Diagnostic, Clinical, and Modern Research Aspects of Glial Tumors. *Cureus.* 2019; 11(11): e6148.
18. Troxel MT. Feline intracranial neoplasia: retrospective review of 160 cases (1985–2001). *J Vet Intern Med*. 2003; 17: 850–859.

CASE III:

Signalment:
2-year-old, female-neutered domestic short hair cat (*Felis catus)*

History:
The cat was presented in a veterinary practice with acute back pain and mild ataxia after a jump from a cupboard. The clinical examination revealed no specific findings, and the cat was treated with non-steroidal anti-inflammatory drugs (NSAIDs) for a suspected traumatic injury of the vertebral bone and spinal cord. After 2 days without clinical improvement, blood work was performed and displayed mild hypophosphatemia (3.1 mg/dl, reference range: 3.4 – 8.5 mg/dl) and monocytosis (6.6%, reference range: 1 – 3%). The radiological examination showed no abnormalities in the skeleton or spinal cord but a mildly increased interstitial pattern in the

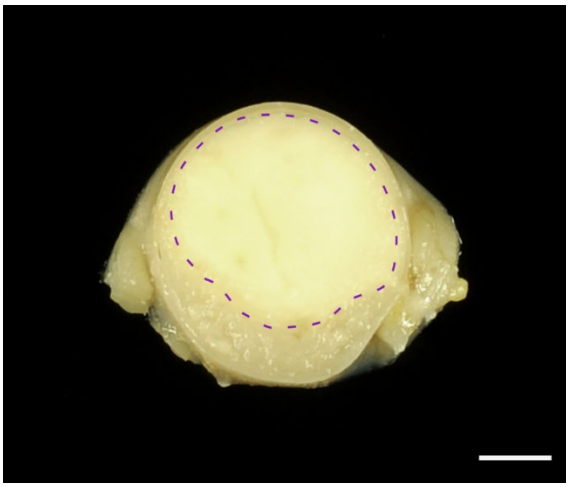

Figure 3-1. Spinal cord, cat. Cross-section with a leptomeningeal, circumferential, grey, solid neoplasm compressing the spinal cord (dashed line: junction tumor – spinal cord). Scale bar: 2 mm. (Photo courtesy of: Department of Pathology, University of Veterinary Medicine, Hannover, Buenteweg 17, 30559 Hannover, Germany. http://www.tiho-hannover.de/kliniken-institute/institute/institut-fuer-pathologie/)

craniodorsal lung. The cat was treated further with NSAIDs, antibiotics and vitamin B. Four days after initial presentation, the cat showed mild apathy and severe ataxia with markedly reduced proprioceptive reactions in all four limbs and reduced segmental reflexes in the thoracic limbs. The suspected neuroanatomical localization was the brain or the spinal cord cranially to Th2. No cells were found in the cerebrospinal fluid (CSF). Infection with feline coronavirus, bornavirus, *Toxoplasma gondii* and *Bartonella henselae* within the CSF was excluded via PCR. Computed tomography (CT) of the entire body was performed but showed no abnormalities of the central nervous system. During hospitalization, further progressive clinical decline and irresponsiveness to treatment resulted in lateral recumbency and spontaneous death within 6 days after initial presentation. The cat was subsequently submitted for necropsy.

Gross Pathology:
Leptomeninges were diffusely prominent, mostly pronounced within cervical segments with rostral extension to the medulla oblongata. After formalin fixation, cross sections revealed a well demarcated, gray-beige, soft, subdural thickening within the whole circumference of the spinal cord, involving primarily the cervical part, and the medulla oblongata with partial compression of the neuroparenchyma. No intraaxial mass was found in coronal sections of the brain and spinal cord.

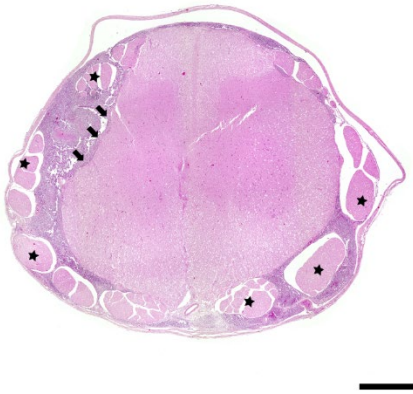

Figure 3-2. Spinal cord, cat. The neoplasm is highly cellular and restricted to the subarachnoidal space with compression of the adjacent neuroparenchyma (arrows) and omission of the spinal nerves (asterisks). HE, bar: 2 mm. (Photo courtesy of: Department of Pathology, University of Veterinary Medicine, Hannover, Buenteweg 17, 30559 Hannover, Germany. http://www.tiho-hannover.de/kliniken-institute/institute/institut-fuer-pathologie/)

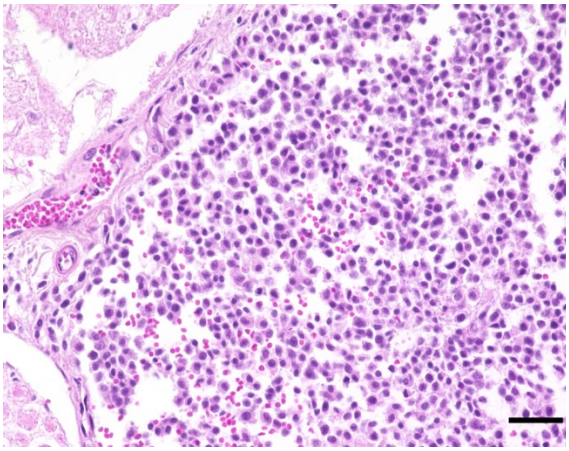

Figure 3-3. Spinal cord, cat. The leptomeningeal neoplasm is composed of numerous round cells arranged in sheets and containing a large hyperchromatic nucleus. HE, bar: 50 µm. (Photo courtesy of: Department of Pathology, University of Veterinary Medicine, Hannover, Buenteweg 17, 30559 Hannover, Germany. http://www.tiho-hannover.de/kliniken-institute/institute/institut-fuer-pathologie/)

Laboratory Results:
The mass was immunostained using the ABC method with commercially available antibodies. Neoplastic cells showed a diffuse, intranuclear expression of oligodendrocyte transcription factor 2 (OLIG2) and doublecortin. Moreover, tumor cells exhibited a diffuse cytoplasmic expression of microtubule-associated protein 2 (MAP2), CNPase and synaptophysin. Some of the neoplastic cells displayed a cytoplasmic vimentin expression. Ki-67 as a proliferation marker protein was detected in more than 50% of the neoplastic cells. Scattered ionized calcium-binding adapter molecule 1 (Iba1)-positive cells and few scattered glial fibrillary acid protein (GFAP)-positive cells were present within the neoplasm (interpreted as reactive

macrophages/microglia and astrocytes, respectively). Neoplastic cells lacked immunoreactivity for neurofilament (NF), S100 protein, neuron specific enolase (NSE), myelin basic protein, p75 neurotrophin receptor, neuronal nuclear protein (NeuN), periaxin, pan-cytokeratin, CD3, CD20, CD79a, paired box 5 transcription factor (PAX5) and multiple myeloma oncogene 1 (MUM1).

Microscopic Description:
Spinal cord: Expanding the subarachnoidal space, there is a solid, non-encapsulated, cell-rich, circumferential accumulation of neoplastic cells extending from the arachnoidea to the margins of the spinal cord. The neoplasm is composed of closely packed, round, mononuclear cells arranged in sheets, accompanied by low amounts of fine fibrovascular stroma. The medium-sized cells possess variably distinct cell borders and contain low amounts of finely granular eosinophilic cytoplasm. Nuclei measure 10–15 µm in diameter, are centrally to eccentrically located, round to oval and frequently hyperchromatic with one distinct small nucleolus. Multifocally, large necrotic areas with complete loss of cytological details are present. Tumor cells exhibit mild anisocytosis and –karyosis with a mitotic count of 10 mitoses per 2.37 mm² (with variation throughout the samples). Occasionally, mild hemorrhages are present. The neuroparenchyma adjacent to the tumor multifocally shows compression and marked degenerative changes including spheroid formation and vacuolation of the white and gray matter.

Contributor's Morphologic Diagnosis:
Spinal cord: Leptomeningeal oligodendrogliomatosis, feline.

Contributor's Comment:
The presented findings relate to a rare case of primary diffuse leptomeningeal oligodendrogliomatosis, which represents an oligodendroglioma-like tumor with an unusual distribution.

In contrast to other glial tumors, which mostly arise intracranially within the neuroparenchyma and may secondarily infiltrate the leptomeninges, primary diffuse leptomeningeal gliomatosis (PDLG) is defined as a diffuse infiltration of the subarachnoidal space by neoplastic glial cells without evidence of a primary intraaxial tumor.[27] Having been described in humans and in dogs before, this entity has recently been reported in an older cat.[1,10,21,28] The presented case is the second report of feline PDLG.[2]

Histologically, oligodendroglial tumors are typically characterized by uniform, densely packed cells with vacuolated or eosinophilic cytoplasm, a round hyperchromatic nucleus and distinct cell borders with variable patterns of cell arrangement. Delayed formalin fixation often causes a perinuclear halo, resulting in a "honeycomb pattern" appearance.[25] However, these tumors can vary in their appearance and origin, which requires distinction from other neoplasms (such as lymphomas and neurocytomas) by

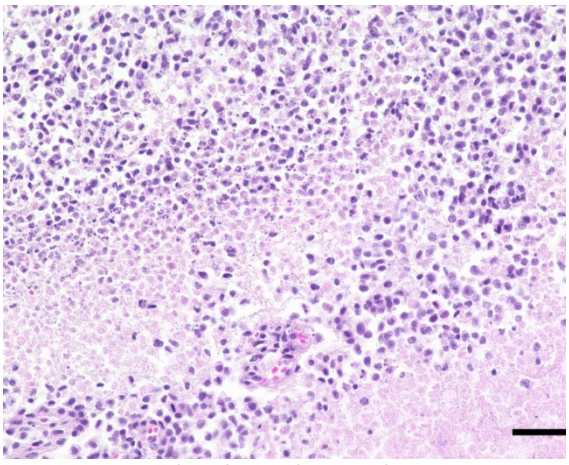

Figure 3-4. Spinal cord, cat. There are large necrotic areas within the neoplasm. HE; bar: 50 µm. (Photo courtesy of: Department of Pathology, University of Veterinary Medicine, Hannover, Buenteweg 17, 30559 Hannover, Germany. http://www.tiho-hannover.de/kliniken-institute/institute/institut-fuer-pathologie/)

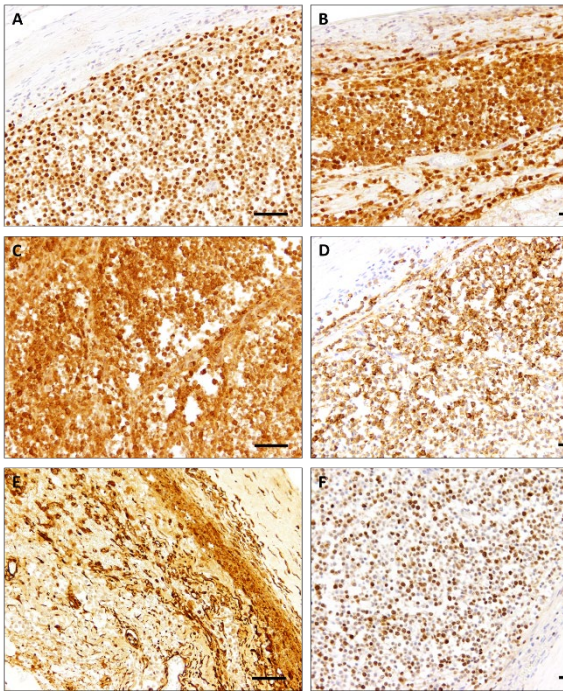

Figure 3-5. Spinal cord, cat. The tumor shows diffuse immunopositivity for OLIG2 (A), doublecortin (B) and MAP2 (C). Most tumor cells were also immunopositive for synaptophysin (D). Tumor-associated vasculature stained positive for vimentin (E). Positive nuclear staining for Ki-67 demonstrates high proliferation activity (F). bars: 50 µm. (Photo courtesy of: Department of Pathology, University of Veterinary Medicine, Hannover, Buenteweg 17, 30559 Hannover, Germany. http://www.tiho-hannover.de/kliniken-institute/institute/institut-fuer-pathologie/)

immunohistochemistry, as performed in the present case. Tumor cells in the present case exhibited an expression of oligodendrocyte transcription factor 2 (OLIG2), doublecortin, microtubule-associated protein 2 (MAP2), CNPase and synaptophysin. Some of the neoplastic cells displayed a cytoplasmic vimentin expression.

Further differentials in humans and domestic animals for leptomeningeal cell infiltrates include secondary leptomeningeal gliomatosis, ependymoma, pilocytic astrocytoma, or multicentric neoplasia and meningitis of autoimmune or infectious etiology.[1,5,11,27] In felines, the most frequently reported extraparenchymatous tumors of the spinal cord are lymphomas and osteosarcomas.[14] An infectious disease that needs to be considered in cats for this localization is feline infectious peritonitis (FIP).[7,22]

To date, the exact origin of PDLG remains unknown. Several authors postulated that PDLG arises from so-called heterotopic glial cell nests, which represent small aggregates of glial cells within the subarachnoid space arising from protrusions of mature glia cells from the neuraxis, but this hypothesis remains controversial.[4,5,19] Occasional simultaneous immunopositivity for OLIG2 and neuronal markers like synaptophysin or doublecortin, as also observed in the present case, suggests a histiogenesis from a common progenitor cell.[15,16,18]

In humans, the incidence of diffuse leptomeningeal oligodendroglioma-like neoplasms is higher in children and young adults when compared to other age groups.[20] Several genetic abnormalities have been attributed to oligodendroglial neoplasms in humans including a 1p/19q deletion.[26] Concerning domestic animals, brachycephalic dog breeds are predisposed to develop oligodendroglioma with a suspected defect on chromosome 26.[23,24] The exclusive representation of brachycephalic dogs (4 boxer dogs, 1 Staffordshire bull terrier, 1 Cane Corso) in published cases of canine diffuse leptomeningeal gliomatosis may propose a similar breed disposition to PDLG.[1,8,10,12] However, further case data need to be obtained to confirm this assumption. No specific genetic alterations have been determined so far for PDLG in domestic animals.

Intravital diagnosis of PDLG, which is predominantly based on MRI findings and exclusion of other diseases, is challenging due to relatively unspecific clinical and CSF findings and requires histopathological confirmation.[1,5,6,8,10,12,27,28] In most cases, final diagnosis is made at necropsy due to the rapid progression and poor prognosis of the tumor.[5]

Contributing Institution:
Department of Pathology,
University of Veterinary Medicine,
Hannover,
Buenteweg 17,
30559 Hannover, Germany.

http://www.tiho-hannover.de/kliniken-institute/institute/institut-fuer-pathologie/

JPC Diagnosis:
Leptomeninges, spinal cord: Oligodendrogliomatosis.

JPC Comment:
The moderator and conference participants had a spirited discussion over the morphologic diagnosis in this case. As the contributor mentions, it is impossible to determine whether the oligodendrogliomatosis is a primary lesion, or if it arose secondary to a small primary tumor not in section. Due to this uncertainty, some participants favored a broader diagnosis of oligodendroglioma; however, most felt that the term oligodendrogliomatosis would provide valuable information for the clinicians, as a focal oligodendroglioma would not be consistent with the neurologic signs, advanced imaging patterns (MRI with contrast), and gross lesions produced by a diffuse leptomeningeal lesion.

In this section, there is a small focus of fibrosis within the meninges, and some participants considered a second morphologic diagnosis of fibroma. The moderator explained that focal fibrosis within the meninges and in the nerve sheath is a common aging change in geriatric animals and is not considered abnormal in this case.

In a 2020 *Vet Pathol* article, Kauer et al described leptomeningeal olgodendrogliomatosis in a 4.5 year old cow which died after progressive neurologic signs, including ataxia, circling, and tremors.[9] Grossly, the leptomeninges spanning the cerebellum, ventral occipital lobe, and first cervical spinal cord segment were expanded by a gelatinous, tan to gray mass that protruded into the third and fourth ventricles and extended into the thalamus.[9] Histologically, the neoplastic cells were uniformly round and hyperchromatic, arranged in sheets, nests, and cords, and surrounded by a myxoid matrix.[9] There were multifocal microcysts filled with mucin. Multifocal areas of necrosis, microvascular proliferation, and a high mitotic rate were indicative of malignancy.[9] The vast majority of tumor cells had strong nuclear immunoreactivity for Olig-2.[9] These features were consistent with a diffuse high-grade leptomeningeal oligodendrogliomatosis.[9] While this is the first documented bovine case of diffuse leptomeningeal oligodendrogliomatosis, two previously documented cases of oligodendrogliomas in cows also featured this diffuse leptomeningeal growth without identification of a primary neoplasm. The authors suggest that these prior cases may also be instances of diffuse leptomeningeal oligodendrogliomatosis.[9]

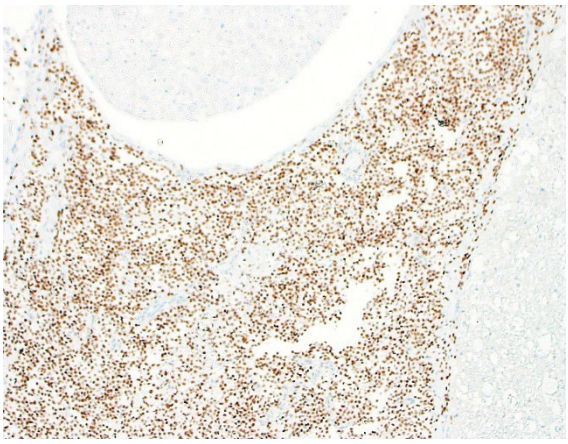

Figure 3-6. Spinal cord, cat. Neoplastic cells stain demonstrates strong nuclear immunopositivity for Olig-2. (anti-Olig-2, 200X)

Two other rare proliferative lesions of the leptomeninges have recently been reported in cats: angiocentric astrocytoma and

meningiomatosis.[3,17] In a 2019 *Vet Pathol* article, Rissi et. al described the first veterinary case of angiocentric astrocytoma in a 15 year old cat with seizures refractory to medical therapy.[17] On necropsy examination, the leptomeninges surrounding the olfactory bulbs were swollen and firm with multifocal hemorrhage.[17] Histologically, blood vessels within the leptomeninges of the olfactory bulb and extending caudally to the thalamus were surrounded by polygonal to elongate, sometimes palisading neoplastic cells.[17] No primary neoplasm was identified. On IHC, these cells had strong reactivity for GFAP, S100, and vimentin.[17] The histologic morphology, IHC staining, and ultrastructure features of this case were all consistent with a diagnosis of astrocytoma, and this case bears many similarities to human angiocentric astrocytoma, a rare entity in children and young adults.[17]

The first documented case of meningioangiomatosis in a cat was recently reported by Corbett et al.[3] Previously, this rare entity has been described in humans and dogs. Corbett's report details a 13 year old cat with history of acute behavioral changes, open mouth breathing, and facial twitching that progressed to generalized seizures.[3] The animal died despite 5 days of hospitalization, and on necropsy, a unilateral hemorrhagic plaque expanded the meninges over the right pyriform, temporal, and ventral aspect of the occipital lobes and extended into the subjacent cerebral cortex.[3] Histologically, the leptomeninges were thickened by proliferations of vimentin-positive spindle cells streaming and whirling around blood vessels.[3] The histomorphology and IHC profile were consistent with the cases of meningioangiomatosis documented in humans and dogs.[3]

References:

1. Canal S, Bernardini M, Pavone S, et al. Primary diffuse leptomeningeal gliomatosis in 2 dogs. *Can Vet J*. 2013;**54:** 1075–1079.
2. Chludzinski E, Puff C, Weber J, et al. Case Report: Primary diffuse leptomeningeal oligodendrogliomatosis in a young adult cat. *Front Vet Sci*. 2021;**8:** 795126.
3. Corbett MP, Kopec BL, Kent M, Rissi DR. Encephalic meningioangiomatosis in a cat. *J Vet Diagn Invest.* 2022; 34(5): 889-893.
4. Cooper IS, Kernohan JW. Heterotopic glial nests in the subarachnoid space; histopathologic characteristics, mode of origin and relation to meningeal gliomas. *J Neuropathol Exp Neurol*. 1951;**10:** 16–29.
5. Debono B, Derrey S, Rabehenoina C, et al. Primary diffuse multinodular leptomeningeal gliomatosis: case report and review of the literature. *Surg Neurol*. 2006;**65:** 273–282; discussion 282.
6. Dietrich PY, Aapro MS, Rieder A, et al. Primary diffuse leptomeningeal gliomatosis (PDLG): a neoplastic cause of chronic meningitis. *J Neurooncol*. 1993;**15:** 275–283.
7. Fondevila D, Vilafranca M, Pumarola M. Primary central nervous system T-cell lymphoma in a cat. *Vet Pathol*. 1998;**35:** 550–553.
8. Giron C, Paquette D, Culang D, et al. Diffuse meningeal oligodendrogliomatosis characterized by spinal intra-parenchymal nodules on magnetic resonance imaging in a dog. *Can Vet J*. 2020;61**:** 1312–1318.
9. Kauer RV, Bagatella S, Oevermann A. Diffuse Leptomeningeal Oligodendrogliomatosis in a Cow. *Vet Pathol*. 2020; 57(2): 253-257.
10. Kovi RC, Wünschmann A, Armién AG, et al. Spinal meningeal oligodendrogliomatosis in two boxer dogs. *Vet Pathol*. 2013;**50:** 761–764.

11. Lee JK, Ko HC, Choi JG, et al. A Case of diffuse leptomeningeal glioneuronal tumor misdiagnosed as chronic tuberculous meningitis without brain biopsy. *Case Rep Neurol Med*. 2018;**2018:** 1391943.
12. Lobacz MA, Serra F, Hammond G, et al. Imaging diagnosis – magnetic resonance imaging of diffuse leptomeningeal oligodendrogliomatosis in a dog with "dural tail sign". *Vet Radiol Ultrasound*. 2018;**59:** E1–e6.
13. Louis DN, Perry A, Reifenberger G, et al. The 2016 World Health Organization classification of tumors of the central nervous system: a summary. *Acta Neuropathol*. 2016;**131:** 803–820.
14. Marioni-Henry K, Van Winkle TJ, Smith SH, et al. Tumors affecting the spinal cord of cats: 85 cases (1980-2005). *J Am Vet Med Ass*. 2008;**232:** 237–243.
15. Perry A, Scheithauer BW, Macaulay RJ, et al. Oligodendrogliomas with neurocytic differentiation. A report of 4 cases with diagnostic and histogenetic implications. *J Neuropathol Exp Neurol*. 2002;**61:** 947–955.
16. Rissi DR, Levine JM, Eden KB, et al. Cerebral oligodendroglioma mimicking intraventricular neoplasia in three dogs. *J Vet Diagn Invest*. 2015;**27:** 396-400.
17. Rissi DR, McHale BJ, Armien AG. Angiocentric astrocytoma in a cat. *J Vet Diagn Invest.* 2019; 31(40: 576-580.
18. Rissi DR, Miller AD. Feline glioma: a retrospective study and review of the literature. *J Feline Med Surg*. 2017;**19:** 1307–1314.
19. Riva M, Bacigaluppi S, Galli C, Citterio A, Collice M. Primary leptomeningeal gliomatosis: case report and review of the literature. *Neurol Sci*. 2005;**26:** 129–134.
20. Rodriguez FJ, Perry A, Rosenblum MK, et al. Disseminated oligodendroglial-like leptomeningeal tumor of childhood: a distinctive clinicopathologic entity. *Acta Neuropathol*. 2012;**124:** 627–641.
21. Roussy G, Cornil L, Leroux R. *Tumeur meningee a type glial*. vol. 30. Paris: Rev. Neurologique.1923:**30**: 294–298.
22. Shrader S, Lai S, Cline K, et al. Gliomatosis cerebri in the brain of a cat. *Vet Sci*. 2016;**3** (3): 13. doi: 10.3390/vetsci3030013.
23. Snyder JM, Shofer FS, Van Winkle TJ, et al. Canine intracranial primary neoplasia: 173 cases (1986-2003). *J Vet Intern Med*. 2006;**20:** 669–675.
24. Truvé K, Dickinson P, Xiong A, et al. Utilizing the dog genome in the search for novel candidate genes involved in glioma development - genome wide association mapping followed by targeted massive parallel sequencing identifies a strongly associated locus. *PLoS Genet*. 2016;**12** (5)**:** e1006000. doi: 10.1371/journal.pgen.1006000.
25. Vandevelde M, Higgins R, Oevermann A. Neoplasia. In: *Veterinary Neuropathology: Essentials of Theory and Practice*. Ames, IA, USA: Wiley-Blackwell; 2012:137–139.
26. Wesseling P, van den Bent M, Perry A. Oligodendroglioma: pathology, molecular mechanisms and markers. *Acta Neuropathol*. 2015;**129:** 809–827.
27. Yomo S, Tada T, Hirayama S, et al. A case report and review of the literature. *J Neurooncol*. 2007;**81:** 209–216.
28. Zoll WM, Miller AD, Bandt C, et al. Primary leptomeningeal gliomatosis

in a domestic shorthaired cat. *J Vet Diagn Invest*. 2019;**31:** 94–97.

CASE IV:

Signalment:
1-year and 4-month-old, male entire, Lagotto Romagnolo dog (*Canis lupus familiaris).*

History:
The dog was presented with a 4-month progressive history of intention head tremors, head bobbing, hypermetria in all limbs, indicating a cerebellar disease, which were slowly progressing in severity. The clinical signs started to be present at 4 months of age. Magnetic Resonance Imaging (MRI) was performed and revealed a diffuse cerebellar cortical atrophy, characterized by a moderately and diffusely reduced in size cerebellum, accompanied by prominent cerebellar folia and sulci. Based on the clinical sings and MRI findings, the main clinical differential diagnosis was a neurodegenerative disease, such as altered autophagy and cerebellar storage disease of the Lagotto Romagnolo due to an unidentified mutation, or another form of cerebellar abiotrophy.

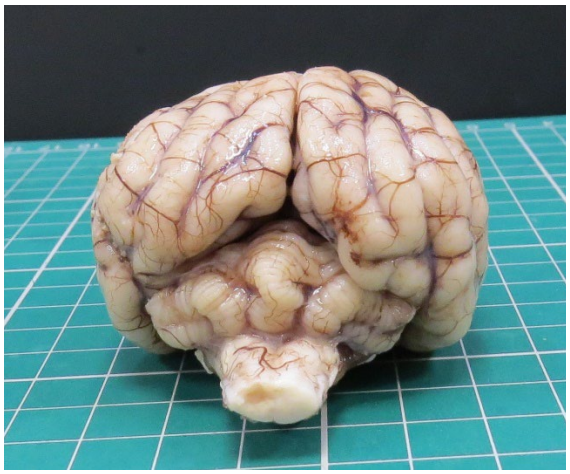

Figure 4-1. Cerebellum, dog. The cerebellum was diffusely reduced in size. (Photo courtesy of: Veterinary Pathology Service, School of Veterinary Medicine and Science, University of Nottingham, College Road, Sutton Bonington, Loughborough, LE12 5RA, United Kingdom https://www.nottingham.ac.uk/vet/service-for-business/veterinary-pathology-service/index.aspx)

The dog was humanely euthanized and submitted for a post-mortem examination (PME).

Gross Pathology:
At PME, macroscopic lesions were restricted to the cerebellum, which was diffusely and moderately reduced in size. Upon sectioning of the formalin-fixed cerebellum, the cortical cerebellar folia appeared markedly thinned.

Laboratory Results:
The genetic test LSD for the ATG4D gene mutation, as a specific DNA test for cerebellar storage disease in Lagotto Romagnolo, was negative.

Microscopic Description:
Cerebellum**:** Diffusely, the cerebellar folia are markedly flattened and there is diffuse, marked thinning and hypocellularity of the granular cell layer with marked loss of granular cells, leading to almost complete absence of this layer accompanied by moderate to marked vacuolation of the neuropil (spongiosis). Rarely, remaining granular cells are either swollen with a vacuolated cytoplasm (degeneration), or shrunken with pyknotic nucleus (necrosis). Glial and microglial cells are diffusely observed replacing the granular layer.

The Purkinje cell layer appears rarely affected with occasional loss of Purkinje cells which are often replaced by large, irregularly round, clear areas (empty baskets). Multifocally, scattered Purkinje cells are either shrunken with angular cellular profile, have a hypereosinophilic cytoplasm and pyknotic nucleus (necrosis) or are rarely swollen with central chromatolysis (degeneration). Rarely, swollen, pale eosinophilic proximal Purkinje

cell axons (torpedoes) are observed extending into the granular cell layer.

Diffusely, the molecular layer appears reduced in thickness, but is otherwise unremarkable.

Contributor's Morphologic Diagnosis:
Cerebellum**:** Diffuse, severe, granular cell degeneration and loss, with spongiosis, and mild, multifocal Purkinje cell loss

Contributor's Comment:
Detailed macroscopic examination in a 1-year and 4-month-old Lagotto Romagnolo dog revealed a severe, diffuse, and symmetric cerebellar atrophy, histologically characterized by a diffuse depletion of the cerebellar granular cell layer neurons, with relative sparing of the Purkinje cell layer, compatible with a cerebellar granuloprival degeneration (CGD). CGD is a type of cerebellar cortical degeneration, also termed cerebellar atrophy or abiotrophy.

Cerebellar cortical abiotrophies (CCAs) are a group of rare diseases characterized by premature or accelerated and progressive degeneration and loss of fully developed neurons, secondary to a presumed intrinsic metabolic defect.[2] CCA has been described as a hereditary defect in various species, such as various dog breeds[7,-9,12,18], Arabian horses[14,17], rabbits[16], goats[10], and rarely in cats[2,18].

Animals with CCA are usually neurologically normal at birth and then start to develop progressive signs of cerebellar disease in weeks, months or less commonly years after birth. Histologically, there is a characteristic degeneration and loss of Purkinje cells, which could be accompanied by secondary loss of granule cell neurons, as a retrograde degeneration.[4,6]

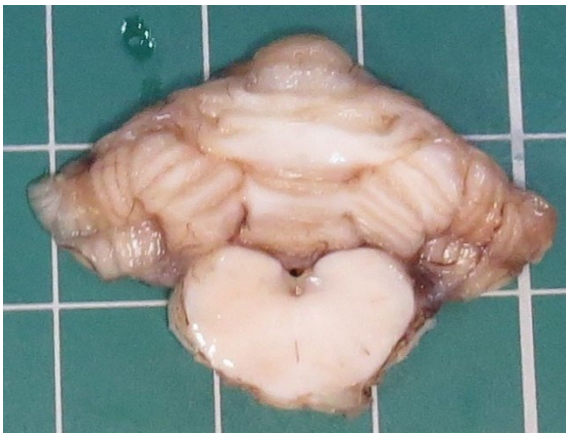

Figure 4-2. Cerebellum, dog. The cortical cerebellar folia appeared markedly thinned (Photo courtesy of: Veterinary Pathology Service, School of Veterinary Medicine and Science, University of Nottingham, College Road, Sutton Bonington, Loughborough, LE12 5RA, United Kingdom https://www.nottingham.ac.uk/vet/service-for-business/veterinary-pathology-service/index.aspx

The case presented herein, represents an unusual presentation of cerebellar cortical degeneration/abiotrophy in a Lagotto Romagnolo dog, characterized by marked degeneration and loss of granular cell neurons with relative sparing of Purkinje cells. Based on these histopathological features, this condition has been named cerebellar granuloprival degeneration (CGD).

The main differential diagnosis based on the breed, clinical signs, and MRI findings was altered autophagy and cerebellar storage disease of the Lagotto Romagnolo. This disease is characterized by progressive cerebellar ataxia and cerebellar atrophy as the main MRI finding, as observed in this case. However, the characteristic histopathological changes of the cerebellar storage disease of the Lagotto Romagnolo, consisting of widespread neuronal cytoplasmic vacuolization within both the central and peripheral nervous system, marked progressive Purkinje cell loss accompanied by reduction of granular cell neurons, as well as spheroid formation and cytoplasmic vacuolation in extra-neural tissues (e.g., pancreatic acinar cells, prostate, mammary gland)[11], were not observed in the

reported case, excluding this disease as a definitive diagnosis.

CGD has been occasionally reported in various dog breeds, including an Australian kelpie and a Labrador retriever, an Italian hound, a Chihuahua, and Border collies, Bavarian mountain and Lagotto Romagnolo dogs.[3,7-9,12,15]

The etiology and pathogenetic mechanisms leading to CGD are still not completely understood, and, although the development of CCA in some dog breed has been attributed to a genetic abnormality, no specific genetic mutation has been yet identified for canine CGD. Inflammatory and infectious diseases have been considered as differential causes for CGD. In Coton de Tulear dogs, two forms have been recognized: the neonatal cerebellar ataxia (aka Bandera's neonatal ataxia) caused by a mutation of the GRM1 gene [4], and a suggested immune-mediated form where the destruction of granular cell neurons results from an immune system defect.[19]

In the presented case, the pathogenetic mechanism leading to CGD was unclear although the histopathological features were not consistent with an inflammatory/infectious etiology. Therefore, a genetic origin was considered more likely. Further studies are needed to elucidate the pathogenesis of this condition in dog breeds.

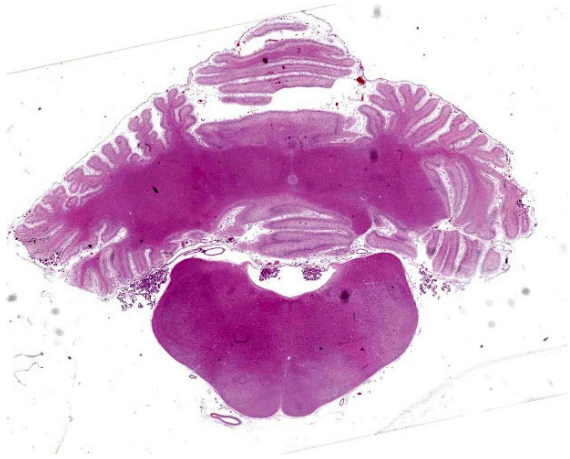

Figure 4-3. Cerebellum, dog. Cerebellar folia are markedly thinned and hypocellular. (HE, 5X)

Contributing Institution:
https://www.nottingham.ac.uk/vet/service-for-business/veterinary-pathology-service/index.aspx

JPC Diagnosis:
Cerebellum: Granule neuron degeneration and loss, diffuse, severe, with mild multifocal Purkinje cell loss.

JPC Comment:
The contributor provides an interesting and uncommon presentation for cerebellar degeneration which was last seen in case 1, conference 12, 2016, in a Coton de Tulear dog.

The moderator explained that granule cells receive most of their stimulation from Purkinje cells, thus are quite susceptible to transsynaptic degeneration during Purkinje cell injury. In the case of granule cell injury, however, Purkinje cells continue to receive stimulation from other neurons (such as the climbing fibers from the olive nucleus), making them more resistant to transsynaptic degeneration. This explains why the secondary Purkinje cell loss was less severe than the primary granule cell loss in this case.

Certain viruses can infect and destroy neuroblast precursors of granule cells in the cerebellum, so an important differential for cerebellar degeneration in young animal to consider is in utero viral infection.[20] In addition to granule cell loss, immature Purkinje cells may be fewer in number or malpositioned in the molecular layer, as granule cells to form the scaffolding for migration.[13,20] Viruses associated with cerebellar dysplasia include feline and rat parvoviruses; porcine and bovine pestiviruses (classical swine fever virus and bovine viral diarrhea virus), and certain bunyaviruses (Akabane virus, Cache valley

virus, and Ainovirus).[1,20] Kilham's rat parvovirus and minute virus of mice (mouse parvovirus) cause cerebellar hypoplasia in rats and mice, respectively, and both of these rodent parvoviruses can also cause cerebellar hypoplasia in experimentally infected Syrian hamsters.[1] In pigs, cerebellar hypoplasia can also be induced in utero when sows are treated with certain organophosphates late in gestation.[20]

Purkinje cells are named after their discoverer, 19th century Czech physiologist Jan Evangelista Purkinje (1787-1869).[5] Purkinje conducted extensive research and contributed to the advancement of multiple disciplines, including histology, embryology, and anatomy. The abundance of his research is evidenced in the variety of histoanatomic structures and physiologic phenomena that bear his name. In ocular physiology, Purkinje described dark adaptation, now known as the Purkinje phenomenon, where the perceived intensity of the color red decreases faster than green and blue as light intensity increases. He also described how a bright light in dim surroundings produces four images (Purkinje-Sanson images). These images are generated by the planes of transition as light passes through the eye: the anterior corneal surface, posterior corneal surface, anterior lens surface, and posterior lens surface. With the benefit of improved microscope technology, Purkinje also provide the first description of cells in the cerebellum. Camillo Golgi (with his newly developed silver stain) and

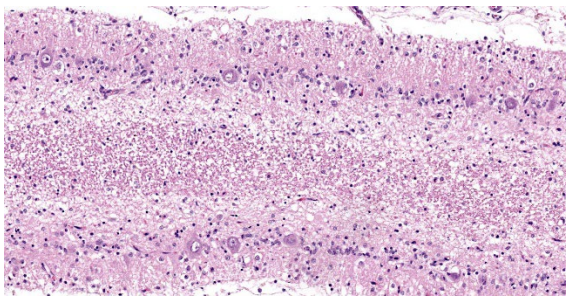

Figure 4-4. Cerebellum, dog. There is almost total depletion of the granular cell layer. (HE, 180X)

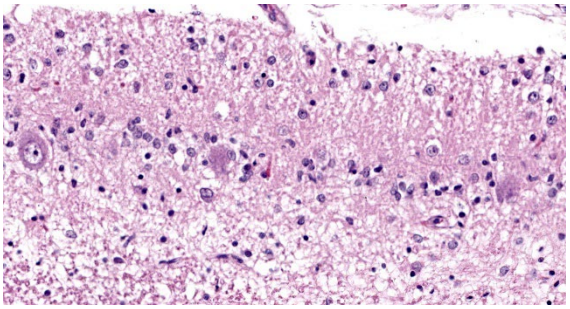

Figure 4-5. Cerebellum, dog. There is multifocal loss of Purkinje cells with proliferation of Begmann's astocytes. (HE, 370X)

Santiago Ramon y Cajal later described structure and processes of these cells, and Cajal recommended the cells be dubbed Purkinje cells. Purkinje's pursuit of knowledge did not stop with the external world; he also conducted pharmacologic experiments on himself, investigating the effects of agents such as digitalis extract, belladonna, camphor, and turpentine. There is some irony in the long list of discoveries which bear Purkinje's name, as Purkinje himself stated, "Science is not about names but discoveries."[5]

References:

1. Barthold SW, Griffey SM, Percy DH. *Path,ology of Laboratory Rodents and Rabbits.* Ames, IO: John Wiley & Sons, Inc. 2016; 18, 124, 175.
2. Biolatti C, Gianella P, Capucchio MT, et al. Late onset and rapid progression of cerebellar abiotrophy in a domestic shorthair cat. *J Small Anim Pract*. 2010;51:123–126.
3. Cantile C, Salvadori C, Modenato M, et al. Cerebellar Granuloprival Degeneration in an Italian Hound. *J Vet Med*. A 49, 523–525 (2002).
4. Cantile C, Youssef S. Nervous system. Maxie MG ed. In: Jubb Kennedy and Palmer's Pathology of Domestic Animals. Vol 1. 6th ed. Philadelphia, PA: Elsevier Saunders; 2016:276, 318-320.
5. Cavero I, Guillon JM, Holzgrefe HH. Reminiscing about Jan Evangelista

Purkinje: a pioneer of modern experimental physiology.
6. Coates JR, O'Brien DP, Kline KL, et al. Neonatal Cerebellar Ataxia in Coton de Tulear Dogs. *J Vet Intern Med*. 2002;16:680–689.
7. Flegel T, Matiasek K, Henke D, et al. Cerebellar cortical degeneration with selective granule cell loss in Bavarian mountain dogs. *J Small Anim Pract*. 2007;48, 462–465.
8. Huska J, Gaitero L, Heindrich N Snyman, et al. Cerebellar granuloprival degeneration in an Australian kelpie and a Labrador retriever dog. *Can Vet J*. 2013;54:55–60.
9. Jokinen TS, Rusbridge C, Steffen F, et al. Cerebellar cortical abiotrophy in Lagotto Romagnolo dogs. *J Small Anim Pract*. 2007;48:470–473.
10. Koehler JW, Newcomer BW, Holland M, et al. A Novel Inherited Cerebellar Abiotrophy in a Cohort of Related Goats. *J Comp Path*. 2015;153:135-139.
11. Kyöstilä K, Syrjä P, Jagannathan V, et al. A Missense Change in the ATG4D Gene Links Aberrant Autophagy to a Neurodegenerative Vacuolar Storage Disease. *PLoS Genet*. 2015;11(4): e1005169.
12. López Betran M, Mascort J, Pumarola M, et al. Cerebellar granuloprival and transsynaptic degeneration in a Chihuahua. *Vet Rec Case Rep*. 2020;8:e000873.
13. Miller AD, Zachary JF. Nervous System. In: Zachary JF, ed. Pathologic Basis of Veterinary Disease. 7th ed. Saint Louis, MO: Elsevier; 2022: 964.
14. Sabada SA, Madariaga GJ, Cobi Botto CM, et al. First report of cerebellar abiotrophy in an Arabian foal from Argentina. *Open Vet J.* 2016; 6(3): 259–262.
15. Sandy JR, Slocombe RF, Mitten RW, et al. Cerebellar Abiotrophy in a Family of Border Collie Dogs. Vet Pathol. 2002;39:736–738.
16. Sato J, Sasaki S, Yamada N, et al. Hereditary Cerebellar Degenerative Disease (Cerebellar Cortical Abiotrophy) in Rabbits. *Vet Pathol*. 2012;49(4):621-8.
17. Scott EY, Penedo MCT, Murray JD, et al. Defining Trends in Global Gene Expression in Arabian Horses with Cerebellar Abiotrophy. *Cerebellum*. 2017;16(2):462-472.
18. Taniyama H, Takayanagi S, Izumisawa Y, et al. Cerebellar Cortical Atrophy in a Kitten. *Vet Pathol.* 1994;31:710-713.
19. Tipold A, Fatzer R, Jaggy A, et al. Presumed immune-mediated cerebellar granular degeneration in the Coton de Tuléar breed. *J Neuroimmunol*. 2000;10(1-2):130-133.
20. Vandevelde M, et al. *Veterinary Neuropathology*. Ames, IA: Wiley-Blackwell; 2012: 96-98.