WEDNESDAY SLIDE CONFERENCE 2018-2019

Conference 7   **17 October 2018**

Conference Moderator:

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CASE I: UW Case 1 (JPC 4084541-00).

**Signalment:** 15-year-old female spayed Himalayan feline, *Felis catus*

History: The patient presented to the University of Wisconsin–Madison Veterinary Medical Teaching Hospital and was diagnosed with a blind left eye (OS), granulomatous infiltrate in the anterior chamber, posterior chamber and vitreous (OS) and bilateral corneal ulcers. The left eye was enucleated, formalin-fixed and submitted for histopathology.

Gross Pathology: The formalin-fixed left eye was section at the dorsoventral plane. There was a white homogeneous tissue carpeting the surfaces of the iris and ciliary body and extending into the posterior chamber and anterior vitreous, cradling the lens.

Laboratory results: Thoracic radiographic studies and abdominal ultrasound were within normal limits.

Microscopic Description: There is a poorly delineated, moderately cellular and hyper-eosinophilic neoplastic mass carpeting the posterior iris and ciliary body surfaces, infiltrating and expanding the inferior iris leaflet stroma and extending into the anterior chamber, posterior chamber and anterior vitreous, surrounding the lens capsule. The mass is composed of haphazardly arranged plump neoplastic cells surrounded by dense, highly basophilic chondromatous matrix. Neoplastic cells are individualized or aggregated in lacunae within the matrix and have a moderate amount of granular
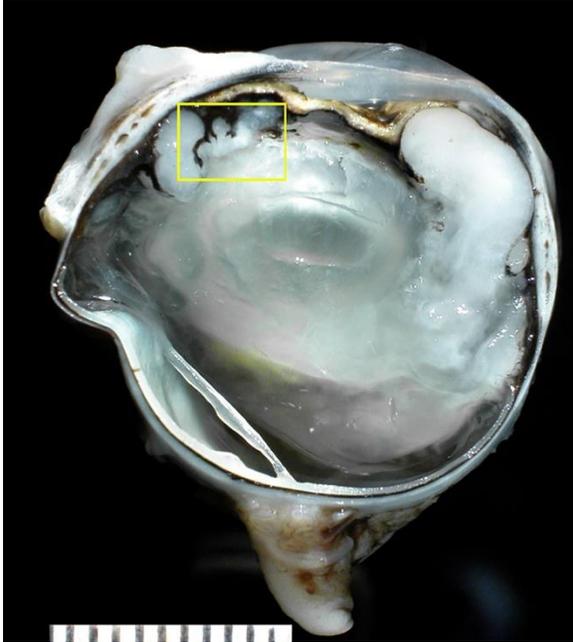
Globe, cat. A white homogenous tissue carpets the surfaces of the iris and ciliary body and extends into the posterior chamber and anterior vitreous, encircling the lens. (Photo courtesy of: Comparative Ocular Pathology Laboratory of Wisconsin – COPLOW, School of Veterinary Medicine, Department of Pathobiological Sciences, University of Wisconsin – Madison. http://www.vetmed.wisc.edu/departments/pathobiological-sciences/)

eosinophilic to basophilic cytoplasm. Nuclei are oval, have 1-2 magenta nucleoli and finely stippled chromatin. The mitotic rate averages less than one per 10 HPF. There are focally extensive areas of necrosis comprising approximately 20% of the mass. There is a fibrovascular membrane carpeting the anterior surface of the iris (preiridal fibrovascular membrane). There is moderate liquefaction of the cortical lens fibers with accumulation of round and lightly eosinophilic degenerated fibers (Morgagnian globules) and migration of the lens epithelial cells over the inner aspect of the posterior lens capsule. The retina is artifactually detached. The inner retina is devoid of ganglion cells and that are diminished numbers of nuclei in the inner nuclear layer. The optic nerve is markedly gliotic and atrophied (optic nerve not present in all sections).

Contributor's Morphologic Diagnoses:

Left eye:

a. Chondrosarcoma, primary.
b. Lens, circumferential and moderate cortical lens fiber degeneration and posterior lens epithelial migration (mature cortical cataract).
c. Retina, marked and diffuse inner retinal atrophy (secondary chronic glaucoma).
d. Optic nerve, marked and diffuse optic nerve gliosis and atrophy (secondary chronic glaucoma).

Contributor's Comment: Chondrosarcomas are uncommon malignant neoplasms with predominating cartilaginous matrix that account for the second most common primary skeletal tumor after osteosarcoma in both veterinary and human medicine.[5] The average age of cats affected by chondrosarcomas is 9.6 years, and there is a slight male predilection for the development of these tumors.[5] Extraskeletal
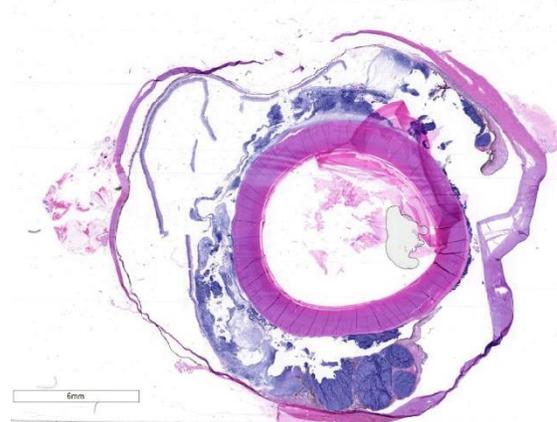
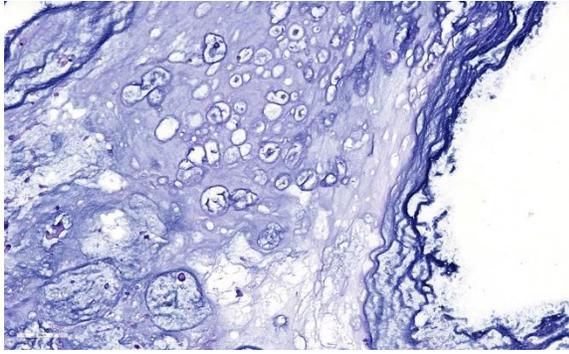
Globe, cat. At subgross magnification, a multilobular dark blue neoplasm carpets the iris, ciliary body and peripheral retinal surfaces, multifocally infiltrating the iris and ciliary body and surrounds the lens. (HE, 5X)

chondrosarcomas, and visceral ones in particular, are rare tumors in dogs, cats and people.[5,7] In a case series of 67 cats with chondrosarcomas, 47 were tumors of skeletal origin and 20 presented in subcutaneous sites, several of which were thought to be vaccine-site sarcomas.[5] Intraocular chondrosarcoma is reported in two dogs as a primary[11] or metastatic[8] neoplasm. Metastatic intraocular chondrosarcoma was also reported in one human patient.[6] In 1959, a single account was published describing an intraocular chondrosarcoma in a cat presenting with multiple intraocular tumors.[2] Recently, we reported 4 cases of presumed primary intraocular chondrosarcoma in cats (including the present case).[2] The mean age of the animals was 12.5 (range 9-16) and the tumors presented unilaterally as coalescing, poorly demarcated, white, friable masses filling the vitreous and intraocular chambers.

One tumor presented as a solitary, well-demarcated, tan mass involving the iris and ciliary body. All four neoplasms were composed of haphazardly arranged plump neoplastic spindle cells surrounded by irregular islands and thick trabeculae of abundant, variably basophilic and Alcian-blue-positive chondromatous matrix. No other tumors or skeletal lesions were identified in these four cats that could suggest a metastatic tumor to the eye. Two of the four cats diagnosed with primary
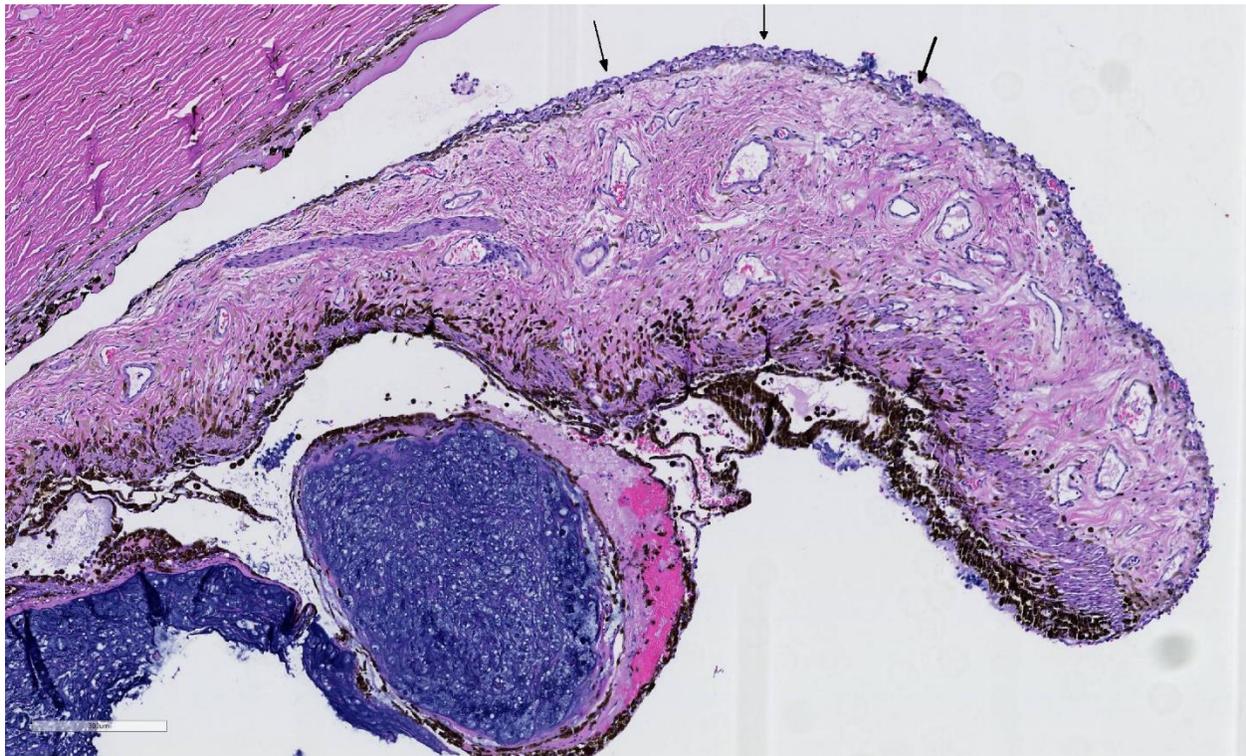
Globe, cat. The neoplasm (at left) carpets the posterior iris surface and the ciliary body. The anterior surface of the iris leaflet is covered by a fibrovascular membrane (arrows) (HE, 84X)

Globe, cat. Higher magnification of the neoplasm demonstrates variably sized cartilage lacunae containing polygonal cells. (HE, 260X)

ocular chondrosarcoma are still alive and healthy 2.5 years and 5 years following enucleation. One cat died 6 months after enucleation due to chronic kidney disease and diabetes and although no necropsy was performed, imaging done in the follow-up visits still did not revealed other masses. The last cat was lost to follow-up.

Due to the distribution of the neoplastic tissue on the eye (posterior chamber and anterior vitreous, surrounding the lens) and because of the chondromatous nature of the mass a post-traumatic sarcoma (chondro-sarcoma) is a possible differential diagnosis. Feline post-traumatic sarcomas (FPTS) are malignant, intraocular neoplasms that are usually associated with trauma that can be evidenced from the clinical history and/or histologic findings (e.g. lens capsule rupture, retinal detachment, and corneal perforation)[3,4]. We ruled out the diagnosis of FPTS in the present case based on the absence of a history of trauma and/or histologic features of trauma, especially lens capsule rupture, which appears to be a major step on the development of the post-traumatic sarcoma, allowing the lens epithelial cells to gain access to the extra-capsular space, proliferate over the ocular tissues and eventually become neoplastic.[1,11] Cats, similar to all mammals, do not have cartilage or bone within their globes and,

therefore, the tissue of origin of the primary ocular chondrosarcoma is unclear. It is likely that primary intraocular chondrosarcomas arise from ocular multipotent mesenchymal stem cells or cancer stem cells.[9] In human eyes, multipotent mesenchymal stem cells have been derived from the trabecular meshwork.[9] The trabecular meshwork could be a likely origin of the tumors seen in these cases, all of which showed extensive involvement in the vicinity of the iris, ciliary body and ciliary cleft.

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**JPC Diagnosis:** Eye, iris and ciliary body: Chondrosarcoma.

JPC Comment: The moderator, who was also the contributor of this case, has provided an excellent review of this uncommon lesion, as well as the primary differential diagnosis and secondary changes in the section.

In bone and beyond, a diagnosis of chondro-sarcoma may be complicated by a number of factors, not the least of which is small sampling. Both the production of osteoid (which changes a diagnosis of chondro-sarcoma to a diagnosis of osteosarcoma) as well as malignant features of neoplastic chondrocytes may be lacking in small samples and present in more liberal ones.[10]

Due to their poorly vascularized nature, many sarcomas contain extensive areas of necrosis and/or mineralization, and these areas should be avoided when evaluating the malignant features of a potential chondrosarcoma.[10] When evaluating for potential malignancy, the most obviously atypical area of the tumor deserves primary focus. Malignant features include: more than an occasional bi-nucleated cell (as seen in this case), numerous cells with prominent nuclei, and mitotic figures (which may be extremely rare in more well differentiated malignancies).[10] Chondrosarcomas often contain cellular populations of great morphological variety, including small cells with hyperchromatic nuclei resembling the mesenchymal precursors of cartilage,[10] which were seen in this section as well. Intercellular matrix may range in color from pink to blue, as well as the amount present, and mucinous or myxoid matrix may predominate.

In conference, the moderator discussed three potential diagnoses for this case of an obvious chondromatous neoplasm within the globe: a) a primary ocular chondrosarcoma, b) a chondrosarcoma metastatic to the globe, and c) a post-traumatic sarcoma. The moderator noted the absence of any variation in the morphology of the neoplasm particularly that of in the absence of a spindle cell or osseous component, which would be unusual for a post-traumatic sarcoma, which often has a mix of morphologies. In addition, post traumatic sarcomas are often associated with a tear in the lenticular capsule, which is absent in this specimen.

He also noted that the pattern of "carpeting" of posterior aspect of the ciliary body, as well as the lack of infiltration into this tissue suggests a metastatic process. Other characteristics of ocular metastasis is the
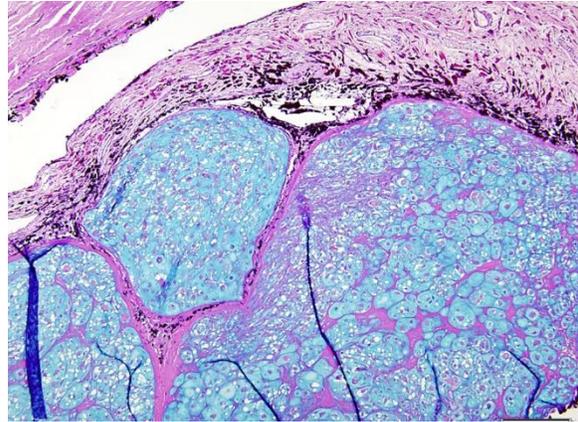
Globe cat: An Alcian blue/PAS stain highlights the composition of the chondromatous matrix. (Alcian blue/PAS 2.5, 100X) . (Photo courtesy of: Comparative Ocular Pathology Laboratory of Wisconsin – COPLOW, School of Veterinary Medicine, Department of Pathobiological Sciences, University of Wisconsin – Madison.
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formation of a well-demarcated mass within the globe. Presence of neoplastic emboli within the vessels of the choroid or uvea may or may be seen with metastatic tumors. The presence of a primary process elsewhere in the body is ultimately a major consideration, and this was a case submitted by the moderator, who was were unable to identify a primary process elsewhere in the body. COPLOW currently has a total of 7 similar lesions in cats in their database – 5/7 were alive after 2.5 years, the remaining two died of unrelated causes.

Another discussion centered upon whether the retina was artifactually or truly detached. For most of its circumference, photoreceptors remained attached to the RPE, suggesting artifactual detachment. However, there are focal areas in of RPE hypertrophy (tombstoning) as well scattered along the retina, suggesting the possibility of focal areas of detachment prior to processing.

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CASE II: 16RD2093 (JPC 4102435-00).

Signalment: 8-year-old male neutered Yorkshire terrier dog, *Canis familiaris*

History: The patient presented to a veterinary ophthalmologist and was diagnosed with a blind right eye (OD) with retinal detachment and potentially an opaque structure posterior to the lens with areas of hemorrhage. The right eye was enucleated, formalin-fixed, and submitted for histopathology.
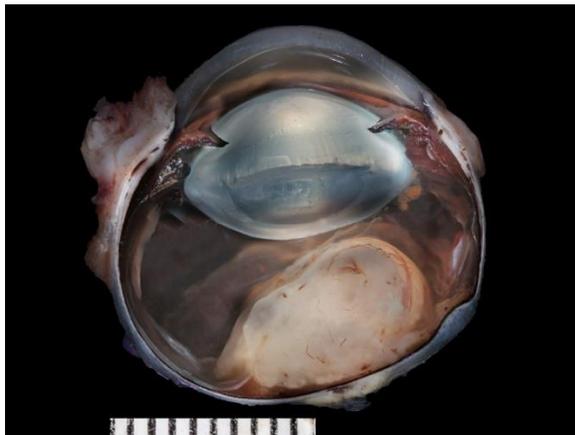
Gross Pathology: The formalin-fixed left eye was section at the dorsoventral plane. There was a soft, tan and homogeneous mass adjacent to the optic nerve protruding into the vitreous.

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Laboratory results: Ocular ultrasound revealed a soft tissue opacity extending from the optic nerve into the vitreal space.

Microscopic Description: There is an unencapsulated, well-delineated and densely cellular neoplastic mass infiltrating,

Eye, dog: A neoplasm arises from and effaces the central retina and optic nerve head protruding into the vitreous. (Photo courtesy of: Comparative Ocular Pathology Laboratory of Wisconsin – COPLOW, School of Veterinary Medicine, Department of Pathobiological Sciences, University of Wisconsin – Madison. http://www.vetmed.wisc.edu/departments/pathobiological-sciences/)

expanding and partially effacing the optic nerve head and central retina, protruding into the vitreous. The mass is composed of a mixture of polygonal, spindle and round cells arranged in short interlacing streams and bundles supported by a moderately dense fibrovascular stroma. The neoplastic cells have indistinct cell borders, a variable amount of pale eosinophilic fibrillar cytoplasm, oval to elongate nuclei with finely stippled chromatin and 1-3 variably distinct nucleoli. A subset of neoplastic cells presents vacuolated cytoplasm with round and eccentrically located nuclei. Anisocytosis and anisokaryosis are marked; with moderate numbers of karyomegalic cells and a few bi and multinucleated cells. There are 6 mitotic figures in 10 HPFs. There are multifocal to focally extensive areas of necrosis, characterized by tissue hypereosinophilia and accumulation of karyorrhectic debris that are surrounded by palisading neoplastic cells (not in all sections . There are multifocal cavitated areas filled with light amphophilic material thought the mass. At the periphery of the neoplasm and in the inner aspects of the retina adjacent to the mass there is prominent capillary proliferation with occasional formation of glomerular-like tufts. There is a mild accumulation of red blood cells in the anterior vitreous. The retina is diffusely detached and there is

Eye, dog Subgross magnification of the retinal mass infiltrating, expanding and partially effacing the central retina and optic nerve head and its placement within the vitreous.

moderate hypertrophy of the RPE cells and mild subretinal hemorrhage. The detached retina presents diffuse loss of ganglion cells, atrophy of the inner nuclear layer, and mild

and multifocal hemorrhage. The post-laminar portion of the optic nerve (not present in all slides) is markedly atrophied and presents increased numbers of non-neoplastic glial cells (gliosis).

Contributor's Morphologic Diagnoses:

Left eye:

- e. Optic nerve and retinal glioma/astrocytoma, high-grade.
- f. Retina, diffuse retinal detachment with inner retinal atrophy.
- g. Post-laminar optic nerve, moderate and diffuse atrophy and gliosis.

Additional results: Neoplastic cells present strong immunohistochemichal cytoplasmic positivity for glial fibrillary acidic protein (GFAP).

Contributor's Comment: Gliomas are among the most common primary tumors of the CNS in dogs, their prevalence being only exceeded by meningiomas.[4] Based on the World Health Organization (WHO) classification for domestic animal tumors,[6] which, in turn, is based on classification of human neoplasms, these tumors are classified according to their cell of origin into astrocytomas, oligodendrogliomas, mixed tumors (oligoastrocytomas), and ependymomas. According to their cytologic characteristics, astrocytomas are further classified into low-grade or well-differentiated, medium-grade or anaplastic, and high-grade or glioblastoma. Low-grade astrocytomas are classified as fibrillary,
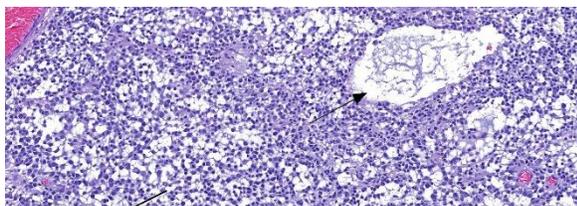
Eye, dog Neoplastic cells are polygonal to spindled on a mucinous matrix. There are large areas of dropout scattered throughout the mass (arrows) (HE, 286X)

protoplasmic, or gemistocytic.[4,6]

Optic nerve and retinal glioma are rare neoplasms that have been sporadically reported in dogs and cats.[2,3,9] These tumors can originate and infiltrate the retina, optic nerve head and the post-laminar optic nerve. Most optic nerve and retinal gliomas present morphologic features similar to astrocytomas as seen in other areas of the central nervous system, but rarely these tumors can resemble oligodendrogliomas or
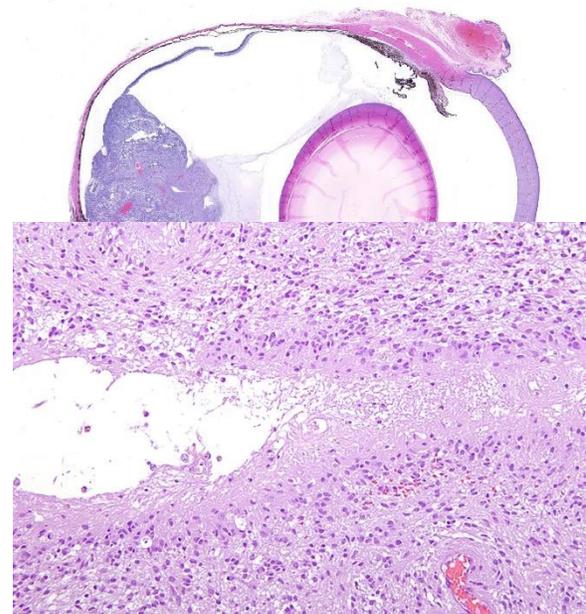
present a mixture of astrocytoma and oligodendroglioma features.[3,9]

Eye, dog. Neoplastic cells palisade around areas of dropout and necrosis. (HE, 100X) (Photo courtesy of: Comparative Ocular Pathology Laboratory of Wisconsin – COPLOW, School of Veterinary Medicine, Department of Pathobiological Sciences, University of Wisconsin – Madison.
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Optic nerve/retinal gliomas with predominantly astrocytic phenotype present immunohistochemical positivity for glial fibrillary acidic protein (GFAP) and the rare cases of oligodendrogliomas reported were GFAP-negative.[3,9] The present case is an

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example of a mixed glioma, with the tumor presenting predominantly astrocytic cells with areas of oligodendroglial differentiation. The decision to classify the present tumor as an astrocytoma was based on the predominance of the astrocytic component and the strong immunoreactivity to GFAP.

Regarding tumor grading, it has been reported that, based on the WHO classification,[6] the majority of optic nerve/retinal gliomas in dogs fit into the high-grade astrocytoma category.[9] Similarly, the hypercellularity, cellular pleomorphism, relatively high mitotic count (6/10 HPF) and the presence of intratumoral vascular proliferation and necrosis identified on the present tumor led to the classification of a high-grade astrocytoma. Interestingly, despite the high-grade classification of the majority of canine optic nerve/retinal gliomas these tumors rarely metastasize or recur when surgical margins are clean.[2,3,9] The most important prognostic feature is the presence of tumor invasion beyond the optic nerve surgical margins, which correlated with tumor recurrence (in the remaining optic pathways) and, in rare cases, tumor extension to the brain.[4]

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http://uwveterinarycare.wisc.edu/support-services/laboratory/anatomic-pathology/

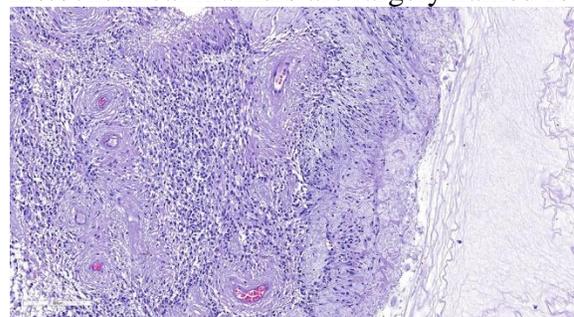**JPC Diagnosis:** Eye, retina and optic nerve: Astrocytoma, low-grade.

JPC Comment: The moderator, who was also the contributor of this case, has provided an excellent review of this uncommon lesion as well, and this case brings our two-week run of three gliomas(!) to an end.

The JPC ran GFAP and Olig-2 on sections from this case and well over 80% of the neoplastic cells were strongly positive for both markers in this particular case.

The naming of Olig2, like many other immunohistochemical markers, implies a

Eye, dog   Neoplastic cells palisade around vessels with numerous cytoplasmic projections adjacent to vessel walls. (HE, 134X)

specificity for oligodendroglia that is unfortunately lacking in the real world of the diagnostic pathologist. Immuno-histochemical markers are largely named for their targeted gene product. (Another example of this "false advertising" for immunohistochemical markers is thyroid transcription factor 1, which not only labels both thyroid follicular and C-cells, but also is an excellent marker for pulmonary carcinomas.)

Within the subcutaneous ventricular zone of the developing brain, undifferentiated progenitor cells may ultimately developing to neurons, astrocytes, or oligodendroglia. Expression of Olig2 specifies progenitor

cells to pattern glial versus neuronal lineage. By reprocessing the neuronal phenotype in these progenitor cells, only two expression permits production of astrocyte and oligodendrocyte precursors.[7] Undifferentiated retinal progenitor cells may also express Olig-2, although oligodendroglia are not found in the retina. In the retina it functions to maintain retinal progenitor cells in an undifferentiated state.[8] Olig-2 expression is downregulated in mature astrocytes.[7] This may explain the increased expression of Olig 2 in the progression of malignant astrocytomas[1], with highest levels in glioblastomas and anaplastic gliomas. A review of labeling indices (LI) in neuroepithelial tumors in humans revealed Olig-2 LI at 43.7% in diffuse astrocytomas, , 59.3 in oligoastrocytomas (mixed gliomas), and 76.1% in oligodendrogliomas.[10]

From a diagnostic standpoint, Olig2 is obviously widely expressed in both astrocytomas and oligodendrocytomas. It is not expressed in ependymomas, so a negative finding may help to differentiate pilocytic astrocytomas and glioblastomas which morphologically resemble ependymomas from tumors of true ependymal origin.[5]

While most species do not have oligodendroglia in the retina, dogs and rabbits have a myelinated optic nerve head which and may contain oligodendroglia. However, the strongly positive GFAP in this case rules out the possibility of an oligodendroglioma in the case.
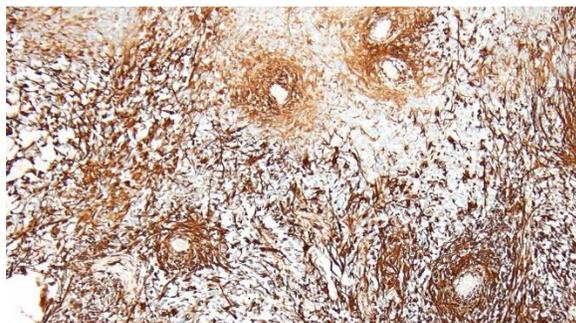
Eye, dog   Palisading neoplastic cells and their projections demonstrate strong cytoplasmic immunopositivity for glial fibrillary acidic protein. (anti-GFAP, 134X)

In the conference, the moderator drew the attendees' attention to the proliferation of blood vessels within the inner layers of the retina (particularly the ganglion cell layer and inner nerve fiber layer) similar to that seen within the tumor as well, suggesting the possibility of local diffusion of growth factors produced by tumor cells. Another incidental change noted by the moderator is the presence of melanin within the
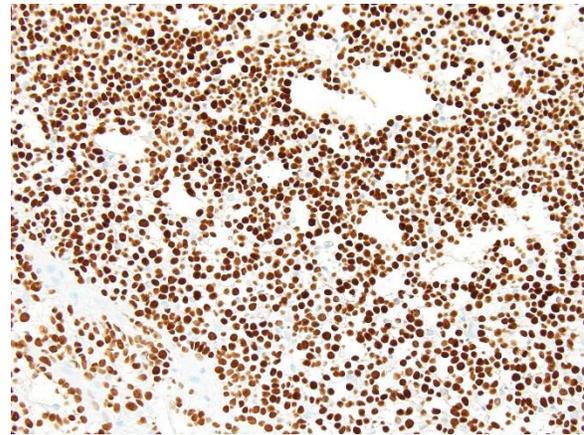
Eye, dog   Neoplastic cells demonstrate strong nuclear immunopositivity for OLIG-2. (anti-OLIG-2, 200X)

connective tissues of the drainage angle, suggestion previous damage to the pigmented epithelium of the ciliary body. While not a problem in this globe at this particular time, infiltration of macrophages may occur at some point in the future to phagocytize the pigment and initiate inflammatory changes that may ultimately result in fibrosis and closure of the drainage angle.

The moderator commented on the thickness of the sclera, which some participants had interpreted as thinned. Three points are helpful in evaluation of scleral thickness – first the moderator says that evaluation of thickness should be made at the limbus. Second, the normal spatial relationship of other structures, such as the iridal leaves will be abnormal in buphthalmic eyes, and finally, comparison to suspected

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buphthalmic globes to globes from other dogs (even other breeds) may be useful, as the difference in globe size between dogs, even of different breeds, is not very significant.

The JPC diagnosis of astrocytoma, low grade is based on the presence of over 80% of cells which are morphologically identifiable of astrocytes on the HE, a mitotic rate of 2 per 2.37mm^2 field, and strong GFAP and Olig2+ positivity (not available to participants before the conference). The moderator said that COPLOW would likely call this a mixed glioma of the retina/optic nerve but the JPC diagnosis was essentially the same.

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CASE III: 15/444 (JPC 4068158-00).

Signalment: 20-year-old horse, Appaloosa, unknown sex (*Equus caballus*)

History: The horse was blind on the left eye, and had glaucoma that was suspected to
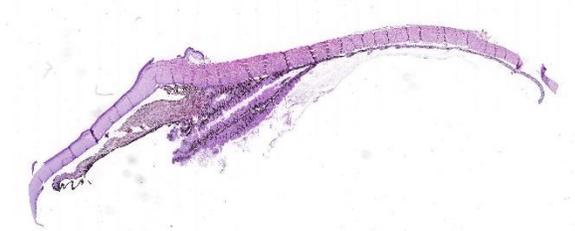
be secondary to chronic (possibly recurrent) uveitis and posterior lens luxation. The eye was enucleated due to increased ocular pressure that could not be medically controlled, and submitted for histo-pathological examination.

Gross Pathology: The lens of the eye was posteriorly luxated and attached in only a few lens fibers. Other gross changes were not detected.

Laboratory results: N/A.

Microscopic Description: Eye, horse: In the conjunctiva, there was a mild lympho-plasmacytic infiltration. Multiple ruptures was observed in the Descemet's membrane in conjunctiva. The filtration angle appeared to be pressed posteriorly, and consisted of compact tissue without obvious trabecular tissue. The iris appeared normal. Along the non-pigmented epithelium of the ciliary body, there was a diffuse thick membrane consisting of eosinophilic homogeneous to slightly fibrillar material. Intensely eosinophilic rod-shaped inclusions were found in some of the non-pigmented epithelial cells. There was a very mild multifocal infiltration of lymphocytes and plasma cells in the ciliary body. The retina was atrophic, with few ganglion cells, a thin inner nuclear layer that multifocally merged with the outer nuclear layer. In the lens, there was mild multifocal degenerative changes.

In Congo-red stained sections, there was intense positive apple green birefringence under polarized light (amyloid) in the eosinophilic membrane associated with the non-pigmented epithelium. Small amounts of positive material was also detected in the filtration angle and the iris. In some sections, there are vascular invasion in the cornea and corneal edema.

Due to the large size of the eye, pieces containing limbal cornea, iris, ciliary body and anterior sclera, choroid and retina was excised for submission for Wednesday Slide Conference. In a few sections the tip of the iris is missing in the slide, however as described above this area of the ocular tissue was without morphological lesions. The number of intracytoplasmic inclusion and inflammatory infiltrates were few, and thus not present in every slide. The main lesion, the amyloid, was extensive and is present in every slide.

Contributor's Morphologic Diagnoses: Eye, ciliary body: amyloidosis, severe, diffuse with mild multifocal lympho-plasmacytic uveitis and ciliary non-pigmented epithelial intracytoplasmic inclusions
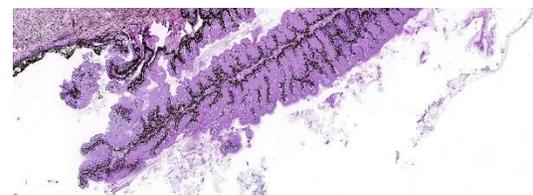
Eye: secondary glaucoma and posterior lens luxation

Contributor's Comment: Equine recurrent uveitis is a leading cause of blindness in horses. The cause is unknown, and autoimmune disease, infection with

Eye, horse: The ciliary processes are markedly expanded. (HE, 14X)

leptospires or a stereotypic response to chronic intraocular inflammation following a variety of insults have been proposed to cause the disease.[2,5,6,11,12] Inflammation in the ciliary body of this horse was very mild and consisted of multifocal infiltration of few lymphocytes and plasma cells. Another histopathologic feature of equine recurrent uveitis in the horse is rod-shaped intracytoplasmic inclusions in the non-pigmented ciliary epithelium,[1,4] and although sparse, such inclusions were present in this case.

The most striking lesion was the thick eosinophilic membrane associated with the non-pigmented ciliary epithelium that was confirmed to be amyloid in Congo red stained slides viewed under polarized light. This finding is by some authors considered to be specific for equine recurrent uveitis and diagnostic for the condition.[4,13] The ocular amyloid in two horses suffering from equine recurrent uveitis was characterized immuno-histochemically and by mass spectrometry to be localized ocular AA amyloid.[9] Several morphologic features in the ciliary body in the eye from this horse

was consistent with equine recurrent uveitis: amyloid deposition - lymphoplasmacytic uveitis and intraepithelial eosinophilic rod shaped inclusions - although the two latter were very mild.

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JPC Diagnosis: 1. Eye, surface of ciliary body: Amyloidosis, diffuse, severe.

2. Eye, iris: Anterior synechiae with occlusion of the iridocorneal angle.

JPC Comment: Ocular amyloidosis is an uncommon finding in the horse; to date, all reported cases of intraocular amyloid have been associated with equine recurrent uveitis. Conjunctival amyloid has also been identified in the horse eye, most often in conjunction with nasal amyloidosis.[10]
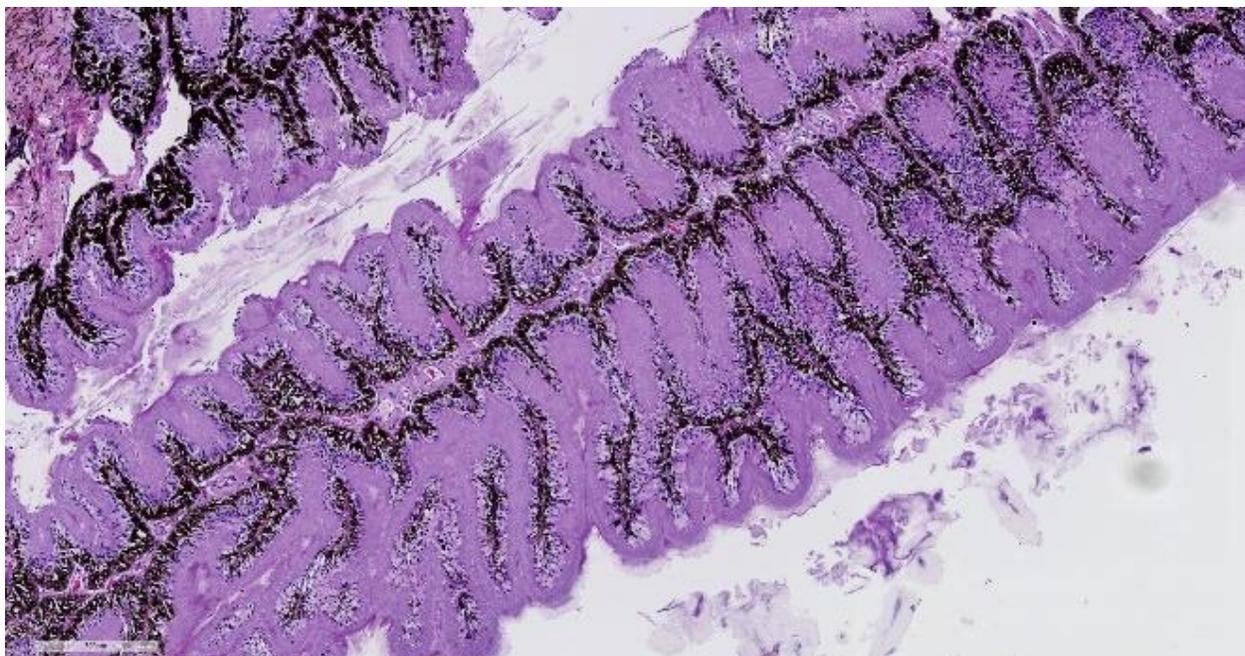
Eye, ciliary processes, horse: A 35um-thick layer of amyloid carpets the non-pigmented epithelium. (HE, 73X)

Several syndromes have been identified with amyloidosis in the horse. Systemic amyloidosis occur secondary to chronic inflammatory conditions, horses used for the production of immunoglobulins, and neoplasia. Reactive systemic amyloidosis (seen in chronic inflammatory conditions and immunoglobulin-producing horses) results from the production of excessive serum amyloid A (SAA), and deposition of the non-degradable protein within tissues. SAA is preferentially deposited in the liver but may also be seen in the spleen, kidneys, GI tract, adrenal glands, and lymph nodes. Systemic amyloidosis resulting from the deposition of amyloid light chains (AL) is rare in the horse and has been seen in association with multiple myeloma.[6]

There are several forms of localized amyloidosis in the horse as well. Nasal amyloidosis results from the nodular deposition of AL amyloid within the nasal cavity and elsewhere in the respiratory system. These deposits may result in epistaxis, stertor, exercise intolerance, and nasal obstruction. Conjunctival amyloid
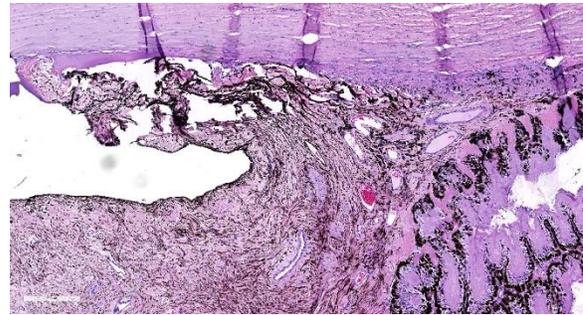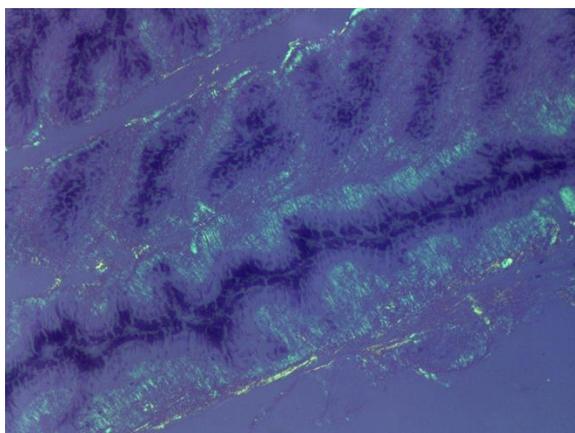

Eye, drainage angle, horse: The drainage angle presents a narrowed ciliary cleft and a collapsed trabecular meshwork (HE, 73X).

deposits have been seen in two cases. Progression to systemic AL amyloidosis has not been reported in the horse.[10]

A final type of localized AL-amyloidosis seen in the horse is cutaneous amyloidosis (and has also been documented in man, dogs, and cats. In the horse, these nodules are most often seen within the panniculus of the head, neck, shoulders and chest, and may be associated with granulomatous dermatitis and panniculitis.[8] They may wax and wane, and of the cases that have been associated with extraskeletal plasmacytoma and lymphoma, a pathogenesis for most cases has not yet been identified. They are occasionally seen with other forms of localized amyloid, but not with systemic forms of amyloid in the horse.[8]

According to the pathologists of the Comparative Ocular Pathology Laboratory of Wisconsin (COPLOW), equine recurrent uveitis (ERU) is the most common cause of cataract, glaucoma, phthisis bulbi, and blindness in the horse. It is characterized by recurrent bouts of inflammatory disease resulting in progressive ocular degeneration. Its pathogenesis has not been definitively established, although previous infection with various *Leptospira* serovars, breakdown of the ocular-blood barrier, and autoimmunity

Eye, non-pigmented ciliary body epithelium: Linear inclusions of hypereosinophilic crystalline proteins are present within non-pigmented ciliary body epithelium. (HE, 400X) (Photo courtesy of: Institute of Basic Sciences and Aquatic Medicine, Norwegian University of Life Science, School of Veterinary Medicine, www.nmbu.no)
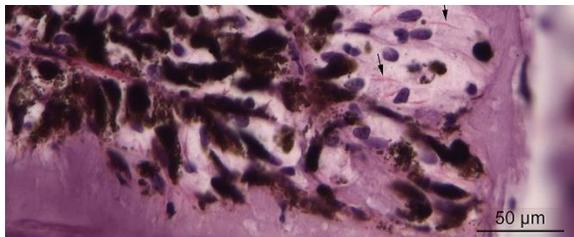
all play a significant part. The involvement of *Leptospira* sp. is a well-known yet often inconsistent finding, and the latter two factors are likely the most important driver in this disease. Appaloosas have a yet undefined breed predisposition.[3]

Affected eyes have a wide range of morphologic appearances, but the following have been noted with regularity in this condition: lymphoplasmacytic uveitis with lymphoid follicle formation; lymphocytes and/or plasma cells within the nonpigmented ciliary epithelium; eosinophilic linear inclusions within the cytoplasm of nonpigmented ciliary body epithelial cells, amyloid; and the deposition of a cell-poor hyaline protein on the inner surface of the nonpigmented ciliary body epithelium.[4] A wide range of non-specific secondary changes may be seen in affected eyes, including cataracts, anterior and posterior synechiae, iridal fibrovascular membranes, retinal degeneration and attachment, and optic neuritis.[4]

On a cellular level, the distribution of lymphocytes is characteristic of a TH1-like inflammatory response with a predominance of CD4 plus T cells and increased transcription of IL-2 and interferon gamma. Retinal autoantigens, including intra-photo receptor binding protein, cellular rectum aldehyde binding protein, recover in, and retinal S antigen have been demonstrated in experimental models and spontaneous cases of the ERU.[4]

The presence of corpora nigra (a normal structure in the eye of the horse which assists in filtering light coming into the globe) is useful in orienting horse eyes, as they are primarily found in the dorsal iris leaflet.

The formation of the JPC morphologic was a subject of spirited discussion. Due to the lack of significant inflammation, the term "uveitis" was not considered appropriate in this case. The combination of amyloid and crystalline inclusions within non-pigmented ciliary body epithelium in the first morphologic diagnosis above was made more out of convention than a shared pathogenesis. While references refer to the inclusions as "amyloid-like"[13], amyloid is an extracellular protein, and ultrastructurally, many of these inclusions are present in the mitochondria in ciliary body epithelium. The true nature of these inclusions is yet to be determined. The second morphologic diagnosis of anterior Synechiae with drainage angle occlusion is likely the result of recurrent episodes of now-resolved inflammation and subsequent fibrosis within the drainage angle. While this change is

certainly consistent with the contributor's diagnosis of secondary glaucoma, we are unable to confirm this finding with the limited number of intraocular tissue available on the slide. While the contributor identified retinal atrophy (possibly from being able to evaluate the whole globe), the conference slides only contain peripheral retina, the evaluation of which, in the moderator's (and JPC staff) experience, for atrophy is problematic at best.

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CASE IV: AVC C5181-11 (JPC 4019356-00).

Signalment: 5 year old, castrated male Boxer, (*Canis familiaris*)

History: A mass was located behind the eye in the region of the optic nerve resulting in exophthalmia. It was noticed 4 months prior to presentation. There was no evidence of metastasis.

Eye, dog. A whitish conical neoplasm encircles the optic nerve and infiltrates the orbital connective tissue but does not infiltrate the posterior sclera. (Photo courtesy of: Atlantic Veterinary College, University of Prince Edward Island http://avc.upei.ca)

Gross Pathology: A globe with attached orbital soft tissue and eyelids was submitted. A firm to hard lobulated white mass which measured approximately 2 cm x 3 cm x 3 cm surrounded the optic nerve and infiltrated the orbital soft tissues on the posterior aspect of the globe.

Laboratory results: NA

Microscopic Description: The non-encapsulated, well-delineated, moderately cellular mass surrounds the optic nerve, invades the orbital adipose and skeletal tissue, and extends slightly into the sclera. The mass is composed of nests and sheets of moderately densely packed neoplastic cells separated into lobules by fibrous connective tissue septa with scattered nodules of myxoid tissue and multifocal osseous and chondroid metaplasia. The majority of the neoplastic cells are large and polygonal with distinct cell margins, a moderate to abundant amount of glassy eosinophilic cytoplasm, and a large eccentric ovoid vesicular nucleus, occasionally with peripheralized chromatin, and one or two small distinct nucleoli. Scattered neoplastic cells contain intranuclear cytoplasmic invaginations. There is moderate to marked anisocytosis and anisokaryosis and scattered cells contain lobulated or multiple nuclei. Five mitotic figures are counted in 10 randomly selected HPF (40x) and rare mitotic atypia is noted. Small foci of necrosis, suppurative infiltration, and hemorrhage are present multifocally and small aggregates of lymphocytes are scattered amongst the neoplastic cells.

Contributor's Morphologic Diagnoses: Orbital (retrobulbar) meningioma

Contributor's Comment: Along with the gross appearance and location (surrounding the optic nerve), the histomorphologic features, which include dense aggregates of large epithelioid cells and foci of cartilaginous and osseous metaplasia, are characteristic of orbital (retrobulbar) meningioma.[8]

Meningiomas are considered common tumors of dogs and Boxers may be one of several breeds with a predilection for developing these masses.[9,10] Most meningiomas arise intracranially; tumors in the retrobulbar location are considered rare[1,3,9,14] accounting for only 3% of meningiomas in the dog.[7] Retrobulbar meningiomas may be primary (also called orbital meningioma), arising from the arachnoidal cap cells of optic nerve sheath,
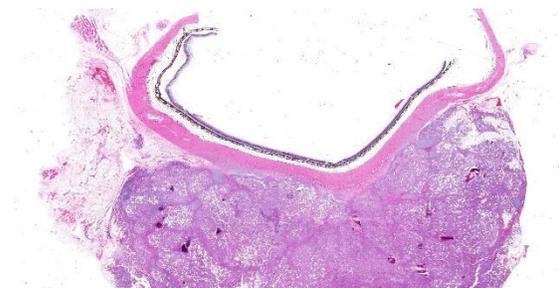

Eye, dog. Subgross image of the neoplasm, better demonstrating infiltration of the orbital connective tissue and compression, but not invasion, of the posterior globe. (HE, 5X)

or secondary, representing extension of an intracranial neoplasm along the optic nerve.[6,7] In addition to dogs[1,2,4,8,9,11,12] and humans[6], meningiomas arising from the optic nerve have been reported in a cat,[5] F334 rats,[16] and a Simmental cow.[13]

Grossly orbital meningiomas are tan solid conical masses that surround the optic nerve and are firmly adhered to the posterior aspect of the globe with tapering towards the optic canal.[3] These tumors compress the optic nerve and circumferentially invade the adipose and muscular tissue of the orbit.[3]

Several histomorphologic subtypes of meningioma have been recognized in domestic species including: meningothelial, fibroblastic, transitional, psammomatous, papillary, microcystic, myxoid, angiomatous/angioblastic, and atypical/anaplastic.[7,9,14] Histologically, orbital meningiomas of dogs (and humans) fit best within the meningothelial and/or transitional types.[1,3,6,8,12] Granular cell differentiation, which has previously been described in meningothelial meningiomas,[7] has recently been recognized within a retrobulbar meningioma in a Golden Retriever dog.[11] More typically however, the neoplastic cells form lobules and dense aggregates and are epithelioid in appearance being polygonal with moderate to abundant
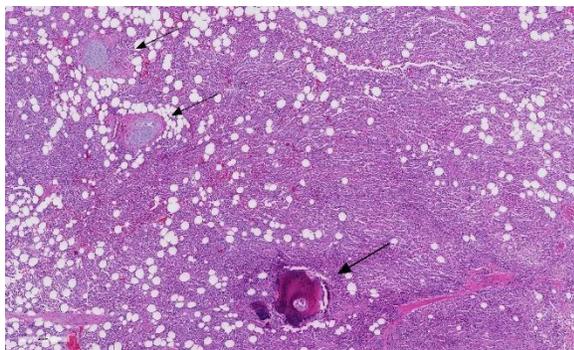
Eye, dog. There are scattered foci of cartilaginous and osseous metaplasia throughout the neoplasm. The adipose tissue is pre-existent orbital fat. (HE, 52X)

eosinophilic cytoplasm and round to oval,
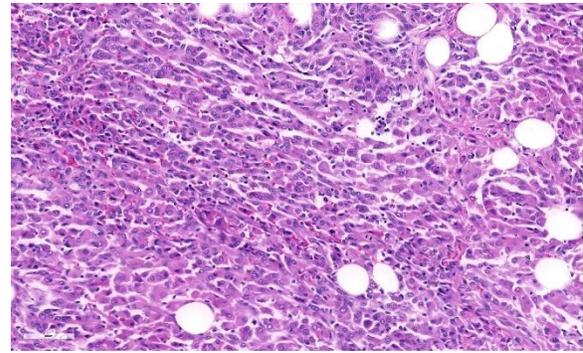
Eye, dog. Neoplastic cells range from polygonal (epithelioid) to spindled. (HE, 260X)

often vesicular, nuclei.[1,3,8,9,12,15] The presence of myxoid, cartilaginous and osseous metaplasia are common features[1,2,4,8,9,11,15] and may be useful aids in both the histologic and radiographic or ultrasound diagnosis of these tumours.[3,8]

Immunohistochemistry is useful in ruling out carcinoma, an important differential diagnosis in these cases.[3,14] Unlike carcinomas, the cells of orbital meningioma typically stain positively for vimentin and S-100 (although variably) and are usually negative for cytokeratin.[8,11] In one reported case,[12] tumor cells stained positively for vimentin (cytoplasmic), E-cadherin (membranous), and were negative for S100, pancytokeratin, and cytokeratins AE1 and AE3. Ultrastructurally, these masses have the typical features of meningioma[14] with interdigitating processes containing intermediate filaments and occasional desmosomes present between the cell membranes.[8]

Dogs with orbital meningioma are usually aged (mean age of 9 years)[8] and present with orbital swelling or exophthalmos with[2,4,8,12] or without[1,8] blindness. These tumors are generally thought to be slow-growing and benign, however tumor recurrence following extenoration,[2,4,11] intraocular invasion,[1,2] and malignant variants with extracranial

metastasis (mainly to the lungs)[2,4,11] have been reported. In one review paper[8] evaluating orbital meningioma in 22 dogs, follow-up information was available in 17 cases: enucleation with excisional biopsy was therapeutically effective in 11 cases (median follow-up time 1.7 years) and local recurrence was reported in 6 cases. While none of the 22 dogs had evidence of metastases, 2 of the 6 dogs with tumor recurrence developed central blindness in the opposite eye, suggesting spread along the optic nerve to the level of the optic chiasm.[8]

Contributing Institution:
Atlantic Veterinary College, University of Prince Edward Island
http://avc.upei.ca

JPC Diagnosis: Eye: Orbital meningioma.

JPC Comment: The contributor has done an outstanding job in describing this unique classification of meningioma. There are few differentials for this fairly characteristic neoplasm of the orbit; the morphologic appearance of epithelioid to spindle cells infiltrating the periorbital tissues with multiple areas of osseous and chondroid differentiation is unique, even in the absence of immunohistochemical findings. In
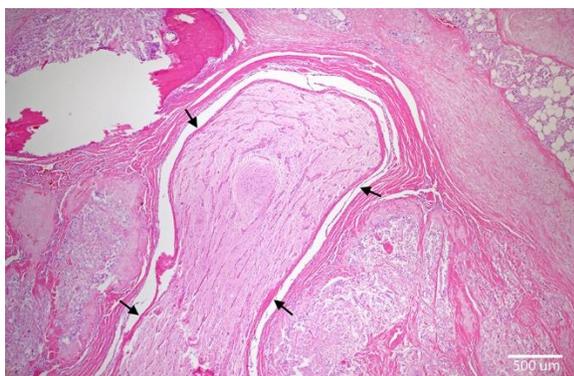
Eye, dog. The neoplasm surrounds the optic nerve (arrows). (Photo courtesy of: Atlantic Veterinary College, University of Prince Edward Island http://avc.upei.ca)

addition to being strongly immunopositive for vimentin, canine meningiomas may be multifocally positive for other neural markers, such as S-100 and NSE (WSC 2015-2016, Conference 20, Case 4). An S-100 immunostain was performed on this case at the JPC; neoplastic cells were strongly immunopositive.

Differential diagnosis would include malignant peripheral nerve sheath tumor (especially epithelioid variants), multilobular tumor of bone, and possibly orbital lobular adenoma. Of these three, only the multilobular tumor of bone would be expected to have any significant osseous or cartilaginous differentiation, and obviously far exceeding that which is seen in this slide. Histiocytic sarcoma commonly metastasizes to the eye and may also have a dimorphic appearance with both epithelioid and spindle cells, but lacks osseous and chondrous metaplasia and possesses a different immunohistochemical profile (immunopositive for vimentin and IBA-1 and other leukocyte markers, while negative for S-100 and NSE.)

The conical gross appearance of orbital meningiomas is a characteristic finding, tapering in proximity to the brain. Infiltration through the optic foramen may be life-threatening; metastasis of this tumor is extremely rare.[3]

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