Joint Pathology Center
Veterinary Pathology Services

WEDNESDAY SLIDE CONFERENCE 2015-2016

C o n f e r e n c e 20

6 April 2016

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CASE I: 13-870 (JPC 4048070).

Signalment: 11-year-old female spayed miniature schnauzer (*Canis familiaris)*

History: The dog presented for evaluation of a cataract and it was discovered that the dog is blind in this eye and has a probable retinal detachment. An enucleation was performed.

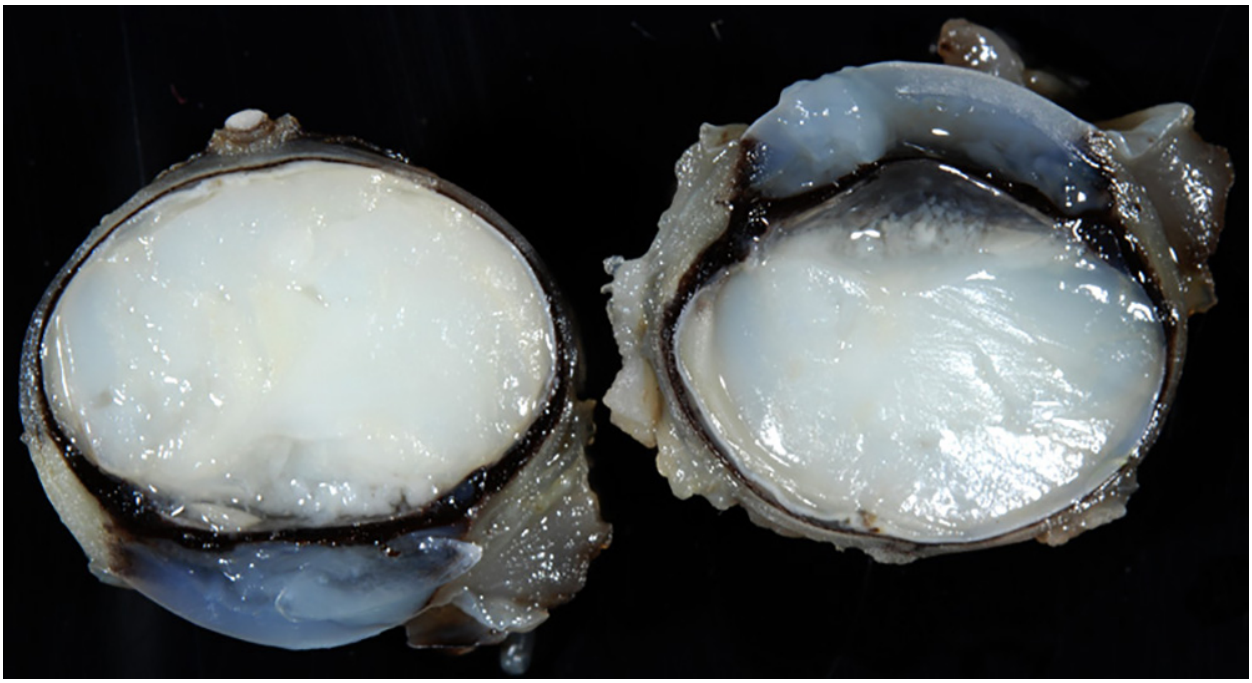
Gross Pathology: The interior of the eye is filled with an opaque white material that obscures all internal structures.

Laboratory Results: None

Histopathologic Description:
The vitreous and the anterior and posterior chambers are filled with a proteinaceous material containing many cholesterol crystals. A mild mixed inflammation of macrophages and lymphocytes is present at the margins of the fluid and a few macrophages are within the fluid. The retina has mild atrophy of the inner layers, a partial detachment, and a diffuse, mild inflammation of lymphocytes and plasma cells. The back of the iris is covered with a fibrous layer containing many lymphocytes. A few lens fibers are round, swollen and vacuolated. The lens is not present in all slides.

Contributor's Morphologic Diagnosis:
1. Cholesterolosis bulbi
2. Retinal atrophy, partial detachment and lymphoplasmacytic retinitis
3. Cataract

Contributor's Comment: Cholesterolosis bulbi is the accumulation of cholesterol within a degenerate vitreous humor that has become liquefied (syneresis). The condition may also involve the anterior and posterior chambers as in this case. It occurs in eyes that have suffered previous hemorrhage, inflammation or other degenerative changes.[2] The cause in this case is unknown but the cataract is a possibility.

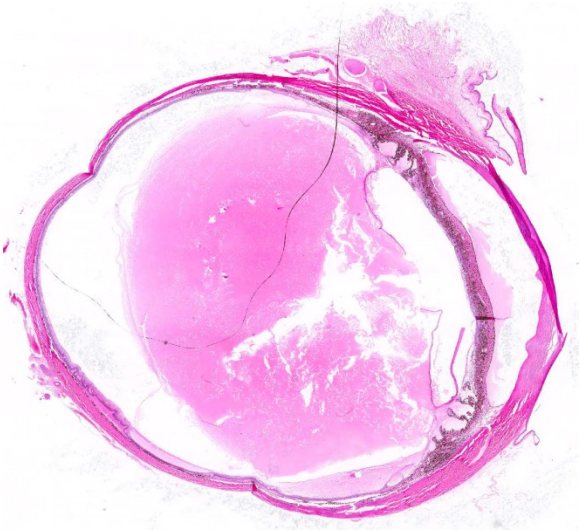


Globe, dog. The posterior chamber of the eye is filled with an opaque white material which obscures internal structure. (Photo courtesy of: College of Veterinary Medicine, Virginia Tech, Blacksburg, VA 24061, www.vetmed.vt.edu)

JPC Diagnosis: Eye, Globe: Panuveitis, lymphoplasmacytic and histiocytic, diffuse, moderate with protein and cholesterol-rich exudate, retinal detachment and atrophy, and drainage angle closure.

Conference Comment: Cholesterolosis bulbi is an uncommon condition and not well-documented in the professional veterinary literature. Although it is more well-documented in human medicine, it is still uncommon may also be referred to as "synchysis scintillans". The lesion is typically found in the vitreous and common causes include trauma and degenerative ocular disease, which may be associated with chronic inflammation and/or longstanding retinal detachment. The cholesterol crystals are thought to be derived from the breakdown of intraocular erythrocytes and, may also be found within the anterior chamber.[1,4] In people, cholesterolosis bulbi may be associated with a condition known as Coats' disease, which includes retinal telangiectasis with intra and subretinal exudation.[4] In cases of cholesterolosis in the absence of intraocular hemorrhage, it has been suggested that cholesterol crystals may enter eye through breaks in the retina and originate from the cholesterol rich subretinal fluid. Phacolysis has also been proposed as a source of cholesterol crystals.[3]

In addition to the proteinaceous, cholesterol-laden fluid filling most segments of the globe, conference participants noted retinal degeneration and atrophy, mild keratitis, uveal inflammation and choroidal edema. Fragmentation and fibrillation as well as cataractous changes were also described within the lens (not present in all sections), although the moderator cautioned against over-interpreting lens rupture due to the fragile nature of the lens and its tendency to fracture during sectioning. Specific retinal changes included retinal detachment, hypertrophy and hyperplasia of the retinal pigment epithelium, vacuolation of the nerve fiber layer, and degeneration of the ganglion



Globe, dog. The posterior chamber, and to a lesser extendt, the anterior chamber is filled by a flocculent brightly eosinophilic proteinaceous exudate. (HE, 5X)

cell and plexiform layers. The moderator commented on the rare nature of cholesterolosis bulbi, citing several potential underlying causes such as trauma and hemorrhage, although it should be noted that intraocular hemorrhage is a relatively common finding not specific to this uncommon condition. Asteroid hyalosis was also present and is typically characterized by the presence of 4-10um pale basophilic granules / globules within the posterior segment, consisting of lipids embedded in a matrix of calcium and phosphorus, and attached to the vitreous. The asteroid bodies appear as amorphous globules, are PAS positive and contain small birefringent crystals when viewed under polarized light. Diabetes mellitus is a risk factor in people for the development of asteroid hyalosis as are hypertension and atherosclerosis.[5]

Contributing Institution:
College of Veterinary Medicine
Virginia Tech
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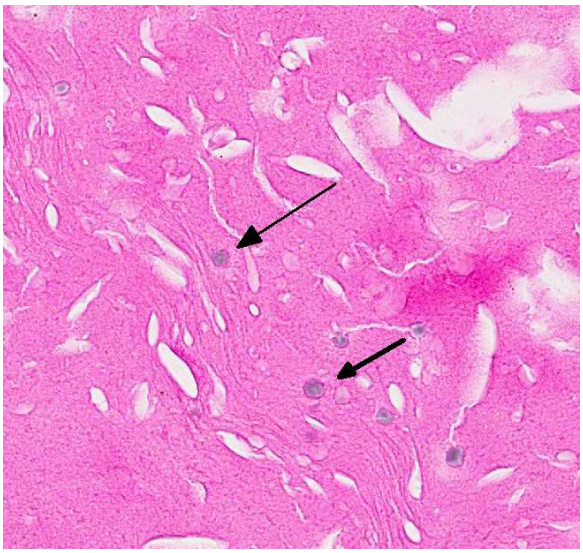

Globe dog. The exudate in the posterior chamber contains numerous acicular cholesterol clefts as well as numerous 10-20 um amphophilic globules (asteroid hyalosis). (HE, 320X)

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CASE II: 9650463 (JPC 4048848).

Signalment: 9-year-old male neutered Labrador retriever dog (*Canis familiaris*).

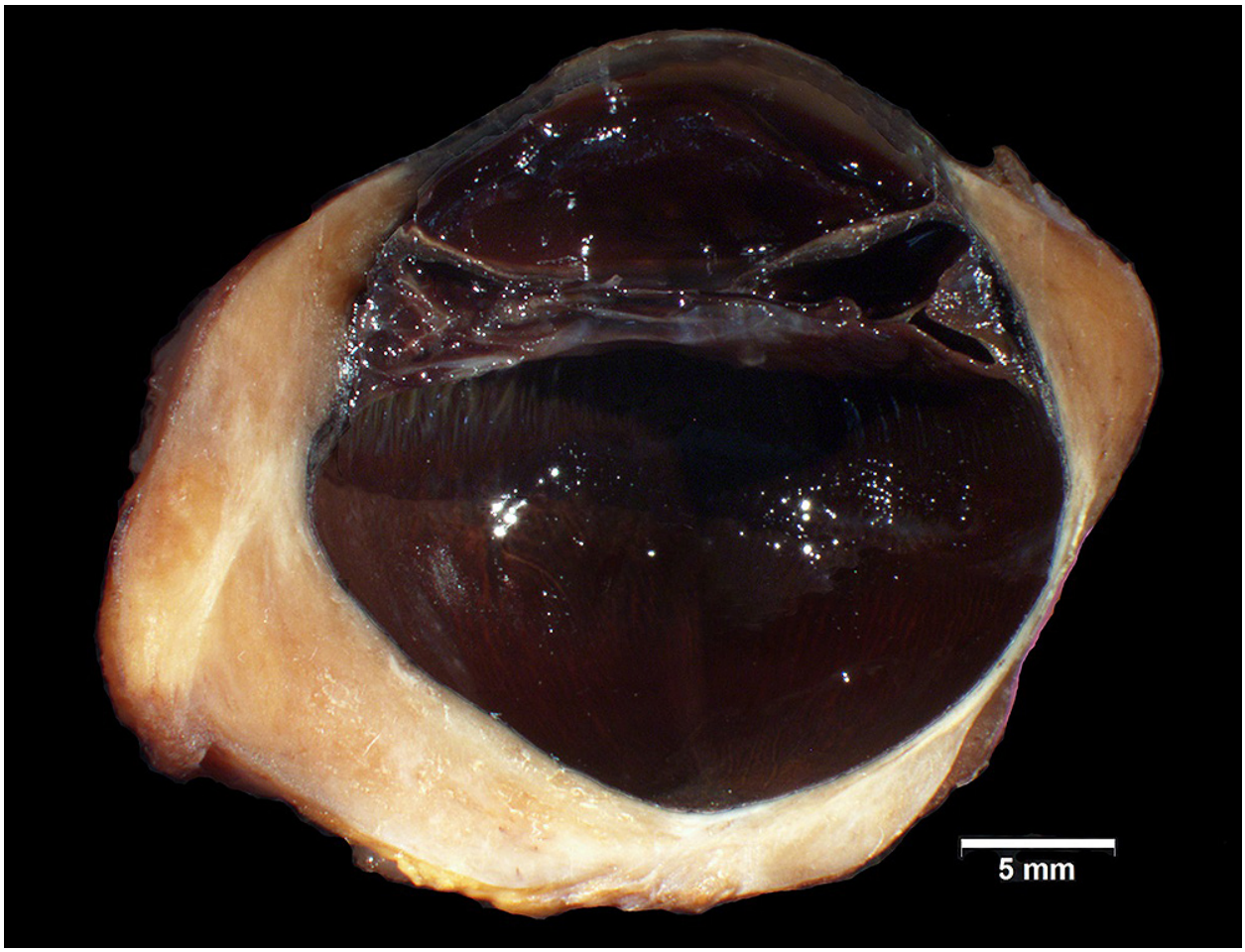
History: Chronic glaucoma of the left eye for approximately 1 year with pain and blindness. Glaucoma is poorly controlled with medical management and history of cataract with cataract surgery in the same eye 1.5 years prior.

Gross Pathology: The globe is enlarged and there is multifocal nodular to coalescing severe thickening of the sclera at the limbus and extending nearly circumferentially around the globe, measuring up to 0.7 cm in the thickest areas. There is intraocular blood and there is corneal opacity.

Laboratory Results: Results of complete blood count and chemistry panel are within reference interval.

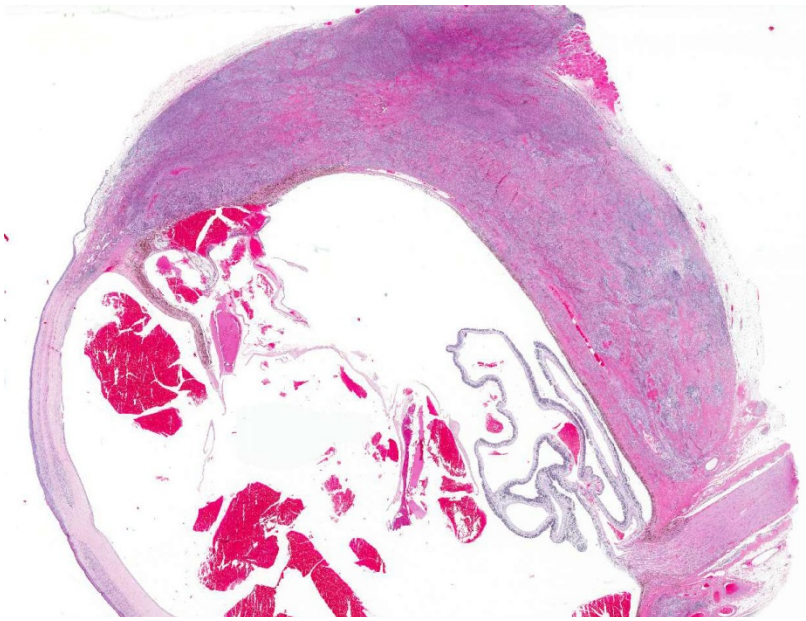
Histopathologic Description: Please note that the section available for participants contains the majority of the scleral lesion, but may not contain all of the internal lesions within the globe.

The globe is enlarged and severely expanding the sclera at the limbus and extending nearly circumferentially, there is a nodular to diffuse inflammatory infiltrate with extensive fibroplasia and fibrosis. The



Globe, dog. The sclera of this enlarged globe is thickened segmentally, up to 0.7cm in some areas. The retina is detached. (Photo courtesy of: Animal Medical Center, 510 East 62nd Street, New York, NY 10065, www.amcny.org)

inflammation is composed of predominantly epithelioid macrophages, lymphocytes, and plasma cells, with fewer neutrophils. There are occasional discrete granulomatous foci with central altered collagen that is hypereosinophilic and smudged ("collagenolysis"), surrounded by a rim of epithelioid macrophages. There is extensive collagen deposition within the inflammatory lesion, and in some areas the collagenous tissue is in a storiform-like pattern that multifocally has central similarly altered collagen that is hypereosinophilic with smudging ("collagenolysis"). The inflammatory lesion and collagen deposition extends from the nodular area of the limbus posteriorly to adjacent to the optic nerve, and extends outward into the adjacent extraocular skeletal muscle.



Globe, dog. Subgross image of the eye, showing the profound fibrosis and inflammatory change of the sclera. The retina is diffusely detached and there is hyphema with in the anterior and posterior chambers. There is multifocal inflammatory infiltrates within the cornea (HE, 5X)

Within the cornea, there is hyperplasia of the epithelium with irregular rete ridge formation, and within the stroma, there is fibrosis, neovascularization, and a mild inflammatory infiltrate, composed of lymphocytes, plasma cells, and neutrophils. There is a focal break in Descemet's membrane (corneal stria) filled in with fibroplasia and fibrosis. Within the anterior uvea, there is iris and ciliary body atrophy, a pre-iridal fibrovascular membrane that spans across the filtration angle, and a mild to moderate perivascular accumulation of lymphocytes and plasma cells. There is blood within the anterior and posterior chambers, as well as in the vitreous. A fragment of lens is present, which includes lens capsule, and the lens fibers are fragmented, hypereosinophilic, and have occasional Morgagnian globules and bladder cells. There is a fibrovascular membrane adhered to the posterior aspect of the lens capsule. There is diffuse retinal detachment with hypertrophy of the retinal pigmented epithelium, and there is mild atrophy of the inner nuclear and ganglion cell layers of the retina.

Masson's trichrome: There is segmental red staining of the lesional collagen with Masson's trichrome.

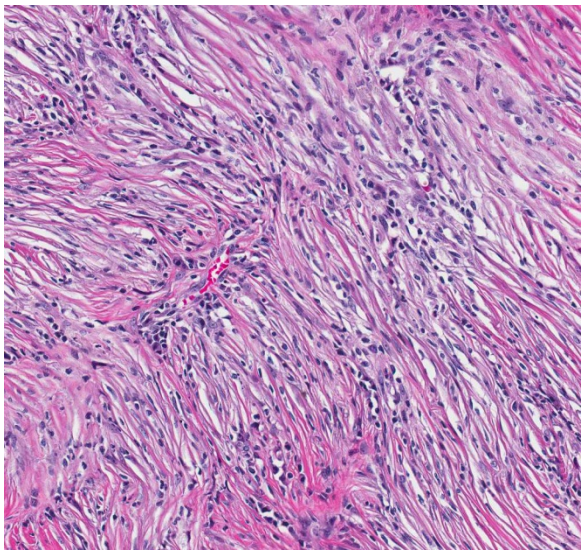
Contributor's Morphologic Diagnosis:

Eye (left):

1. Severe granulomatous scleritis with altered collagen, consistent with necrotizing scleritis (also known as granulomatous scleritis).

2. Buphthalmia; corneal fibrosis, neovascularization, keratitis, and focal rupture of Descemet's membrane (corneal stria); mild lymphoplasmacytic anterior uveitis with pre-iridal fibrovascular membrane, occlusion of filtration angle and hyphema; retinal detachment with inner retinal atrophy; and lens cataractous change.

Contributor's Comment: The scleritis in this case is consistent with the disease entity known as necrotizing scleritis. The most diagnostic features are the formation of discrete granulomas within the inflammatory lesion, as well as the altered collagen appearance, which is often referred to as "collagenolysis" or "collagen necrosis." Necrotizing scleritis is discussed in more detail below. The other intraocular lesions described in this globe, as well as the clinical glaucoma, may be secondary to the scleritis[2], although the granulomatous inflammation does not extend into the intraocular structures in this case. Another possible pathogenesis for the glaucoma is a lens-induced uveitis or other idiopathic or immune-mediated lymphoplasmacytic uveitis leading to formation of a pre-iridal fibrovascular membrane and subsequent occlusion of the filtration angle. Histologic evidence supporting the clinical diagnosis of secondary glaucoma includes the buphthalmia, iris and ciliary body atrophy, keratitis with focal rupture of Descemet's membrane (corneal stria), retinal detachment with retinal pigmented epithelial hypertrophy, and inner retinal atrophy.



Globe, dog. The sclera is expanded by abundant mature collagen, throughout which is an infiltrate of large numbers of macrophages and lymphocytes. (HE, 200X)

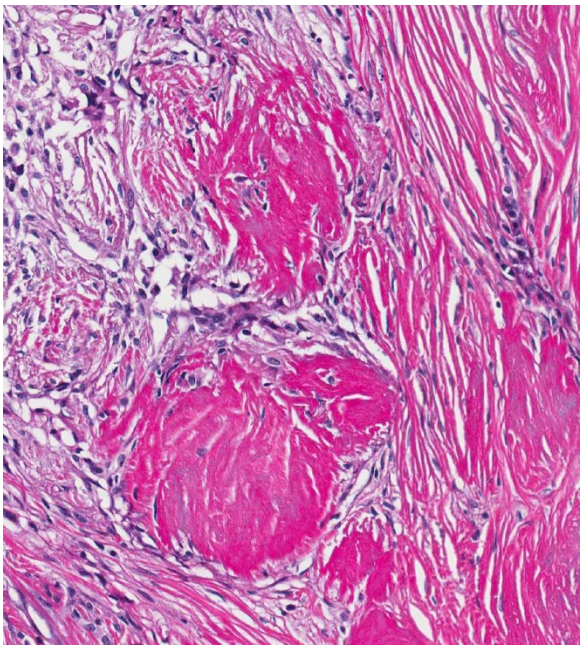
The majority of scleral disease in dogs is inflammatory in nature and is most often the result of secondary involvement of the sclera with either intraocular inflammation or extension from an orbital cellulitis,[7] as with a penetrating foreign body, trauma, or infectious etiology.[5] Primary scleral/episcleral inflammation can be clinically divided into unilateral versus bilateral, nodular versus diffuse, and scleral versus episcleral categories, but there is often overlap in the clinical presentation of these entities and of secondary scleritis/episcleritis.[5] One of the most common primary inflammatory diseases of the sclera/episcera is nodular granulomatous episcleritis, while necrotizing scleritis is rare in comparison.

Nodular granulomatous episcleritis, not present in this case, is also referred to as ocular nodular fasciitis, among other names, and is a proliferative nodular inflammatory lesion at the limbus of the eye that behaves somewhat like a neoplasm in its locally infiltrative growth.[7] The histologic lesion consists of a proliferation of histiocytes, spindle cells and lymphocytes and plasma cells. The inflammation has a diffuse granulomatous pattern, but discrete granulomatous foci are not present, and collagenolysis is not a feature.[7]

Necrotizing scleritis, the disease entity in the present case, is also an inflammatory and proliferative process within the sclera, and has more recently been referred to by some as granulomatous scleritis.[1,3] For the remainder of the discussion, this entity will be referred to as necrotizing scleritis, the more well-known name for the condition. In necrotizing scleritis, there is a similar composition of inflammatory cell types to that identified in cases of nodular gran-

ulomatous episcleritis, including histiocytes, lymphocytes, plasma cells and spindle cells. Some lesions also have a neutrophilic component, as in the present case, or an eosinophilic component.[6] The two main distinguishing features of necrotizing scleritis from nodular granulomatous episcleritis are the formation of discrete granulomatous foci, and the presence of altered collagen ("collagenolysis").[6,7] The altered collagen is often surrounded by epithelioid macrophages to form the discrete granulomas. Altered collagen may have an abnormal tinctorial staining quality with Masson's trichrome,[2] which is identified in the present case as segmental red-staining of the collagen rather than the usual blue. The terms collagenolysis and collagen necrosis are somewhat controversial since collagen is considered inert and therefore cannot technically become "necrotic." There is also often a granulomatous vasculitis, but this is not present in every case[3]. In the current case, although the inflammation appears somewhat vasocentric in some areas, overt vasculitis is not identified.

In necrotizing scleritis, the inflammation and spindle cell proliferation typically begins in the anterior sclera and slowly spreads circumferentially and posteriorly with eventual progression to involvement of the uvea and retina.[7] On gross evaluation, the sclera is severely thickened and bright white.[3] Staphyloma, which is a protrusion of uveal tissue through a weakened portion of the sclera, is a possible sequela in some cases, along with disinsertion of the extraocular muscles.[4,5] Necrotizing scleritis is most commonly bilateral, but the second eye may not be affected until later in the course of the disease.[3,7] It is critical to alert clinicians to the likelihood of involvement of the contralateral eye, given the important prognostic implications for vision[3]. The treatment for necrotizing scleritis is



Globe, dog. Scattered throughout the fibrous and inflammatory infiltrates are focal areas of brightly eosinophilic, degenerate collagen referred to in the literature as "collagenolysis". (HE, 172X)

aggressive life-long anti-inflammatory or immunosuppressive therapy, but complete remission is rare and medical management fails in many cases, leading to enucleation of the affected eye(s).[5,7]

The pathogenesis of necrotizing scleritis is not well-understood. No etiologic agents have been identified in these cases,[7] although necrotizing scleritis has been reported in dogs with ehrlichiosis.[3] An immune-mediated pathogenesis has been suggested, particularly due to the comparable lesion in humans, which is an autoimmune disease process, as well as the partial response to immunosuppressive therapy in dogs.[1,2,5] Most cases reported appear to be localized to the eye, with rare reports that have evidence for other systemic immune-mediated disease, which is the case for humans with necrotizing scleritis.[1] There is some evidence for a type III and type IV hypersensitivity mechanism to the pathogenesis of necrotizing scleritis in dogs, but there is variability in the literature as to whether T- or B-lymphocytes predominate

in the lymphocytic component of the inflammation.[1,2] Some pathologists have made the comparison between necrotizing scleritis and systemic reactive histiocytosis in dogs and consider that these entities may be related (personal communication, R. Dubielzig). This is in particular due to the vasocentric nature of the cellular infiltrate in necrotizing scleritis (personal communication, R. Dubielzig).

In conclusion, this case is a classic example of necrotizing scleritis in the eye of a dog, highlighting the characteristic histologic features of this condition including the granulomatous inflammation and the altered collagen within the lesion.

JPC Diagnosis**:**

1. Eye, sclera: Scleritis, granulomatous and sclerosing, focally extensive, severe with optic nerve demyelination.

2. Eye: Panuveitis, lymphoplasmacytic, chronic, diffuse, moderate with hyphema, pre and post iridial fibrovascular membranes, retinal detachment and atrophy, and hypermature cataract.

Conference Comment**:** The contributor provides a comprehensive and very informative review of this entity. The conference analysis of this case included separating the ocular lesions into two separate processes as alluded to in the contributor's discussion. The first process, the scleritis with formation of vague granulomas, includes a tremendous fibroblastic response (fibrosis) initiated by inflammation and necrosis. The second, primarily intraocular process is quite extensive, and encompasses the corneal changes (squamous metaplasia of the corneal epithelium and a break in Descemet's membrane), cataract, pre- and post-iridal fibrovascular membrane formation with drainage angle obstruction,. changes in the ciliary body and iris, intraocular hemorrhage, and retinal detachment. The moderator cautioned against over interpreting retinal degenerative changes particularly in a detached retina that has been artifactually folded and distorted. Some sections contain optic nerve in which moderate to severe degenerative changes (i.e. axonal degeneration and gitter cells) are seen.

Contributing Institution:
Animal Medical Center
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www.amcny.org

References:

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2. Denk N, et al. A retrospective study of the clinical, histological, and immunohistochemical manifestations of 5 dogs originally diagnosed histologically as necrotizing scleritis. *Vet Ophthalmol*. 2012; 15:102-109.

3. Dubielzig RR. Diseases of the cornea and sclera. In*: Veterinary Ocular Pathology a comparative review*. Saunders Elsevier: New York, NY; 2010: 232-234.

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CASE III: 12B2550 (JPC 4066796).

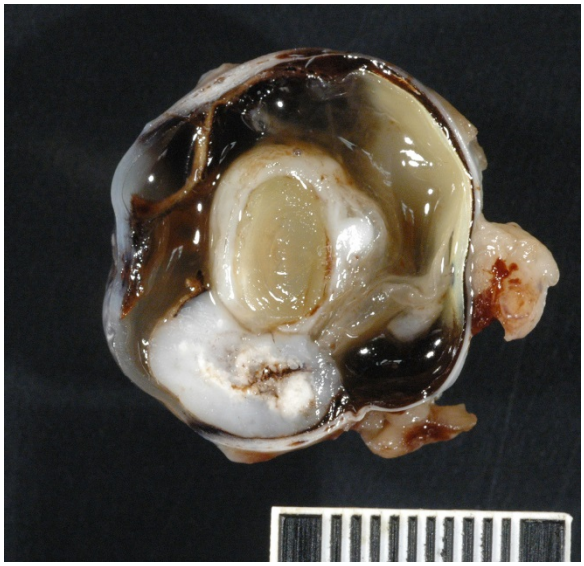
Signalment: 12-year-old intact domestic short hair cat (*Felis catus*)

History: Corneal perforation of unknown duration in the right eye (OD). Suspect cataracts and anterior lens luxation OD. Presented to ophthalmologist for enucleation OD. Eye was submitted to the referring institution for biopsy.

Gross Pathology: The entire right globe was received. The globe was 1.9 cm in nasolateral diameter, and had a white-tan, raised mass at 3-6 o'clock. On cut section, the mass was firm to slightly gritty, and obscured the ciliary body and a portion of the iris. The lens was opaque, and slightly irregular. The retina was detached, and the peripheral iris was irregular segmentally.

Laboratory Results: N/A

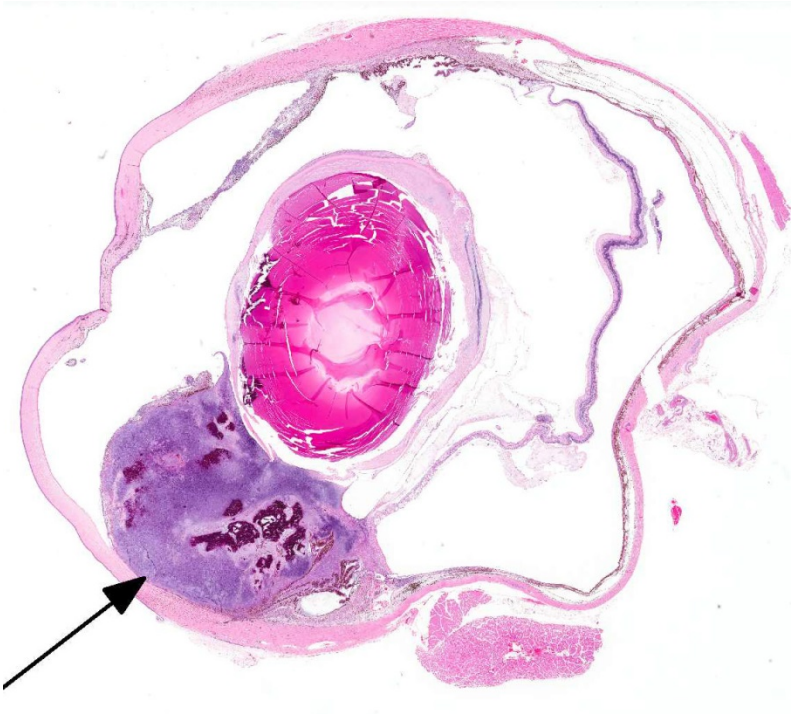
Histopathologic Description: Examined is a parasagittal section of the globe, in which there is a discrete, unencapsulated, mesenchymal mass filling the posterior chamber, abutting the equator of the lens, and partially obliterating the anterior uvea. The cornea is distorted axially by implanted uveal pigment, fibrosis, and segmental rupture of Descemet's membrane. Portions of smooth muscle, iris pigment epithelium, and nodules of lymphocytes and plasma cells are also adherent to the exposed posterior stroma. The surrounding stroma is densely eosinophilic and slightly hypercellular (fibrosis), and the epithelium is hyperplastic. Peripherally, the stroma lacks clefting (edema) and the epithelium is thinned. The posterior chamber/uveal mass is composed of irregular clusters of chondrocytes, sheets of spindle to stellate cells, and abundant granular to hyaline basophilic chondroid matrix, which abuts the posterior cornea and is intermittently covered by extensions of an inflamed fibrovascular membrane; there is a segment of Descemet's membrane surrounded by this membrane. The cells have scant amounts of amphophilic cytoplasm, and distinct borders.



Globe, cat. The globe contains a white mass which obscures the ciliary body, prolapses the ventral iris leaflet, and opposes the lens. The lens is opaque, and the retina is segmentally detached. (Photo courtesy of: University of California Davis, Department of Pathology, Microbiology, Immunology, 1 Garrod Dr, UC Davis, Davis CA 95616)

Nuclei are plump and oval, with coarse chromatin and prominent nucleoli. There is moderate anisocytosis and anisokaryosis, and about 35 mitotic figures per 10 400x fields. There are many scattered cells that are shrunken and hypereosinophilic, and there are several regions of mineralization. The mass and associated matrix is contiguous with the break in the lens capsule and the variably cellular layer of fibrous tissue that lines the inner capsule that replaces the cortex; there are foci of cartilage within the lens. The lens nucleus lacks fiber definition, and has a few swollen fibers and irregular clefts. Fibrous tissue with moderate nuclear atypia and scattered mitotic figures surround the outer capsule, as well.

The unaffected iris leaflet is expanded by edema and mononulcear inflammation, and the iridocorneal angle is collapsed. Reactive fibrovascular tissue lines the inner ciliary body. The entire retina is detached, with variable outer retinal atrophy, minimal subretinal exudate, and diffuse hypertrophy of the retinal pigmented epithelium. Peripherally, the full thickness of the retina is disorganized with fluid filled clefts/cavities. The inner retina is largely devoid of ganglion cells, particularly the non tapetal aspect. There is perivascular retinal infiltration by lymphocytes and plasma cells. The optic nerve head is vacuolated and anteriorly displaced. The optic nerve parenchyma is essentially normal. There are a few foci of lymphocytes and plasma cells in the sclera.



Globe, cat. Subgross magnification of the affected globe, with a cartilaginous neoplasm within the posterior segment (arrow). There is circumferential spindle cell metaplasia subjacent to the lens capsule, a detached retina, and the dorsal iris leaflet is adhered to the cornea (anterior synechia). (HE, 5X)

Contributor's Morphologic Diagnosis:

1. Right eye: Lens capsule rupture with uveal chondrosarcoma (post traumatic ocular sarcoma)
2. Right eye: Lymphonodular panuveitis
3. Right eye: Iridocorneal angle collapse with inner retinal atrophy (chronic glaucoma)
4. Right eye: Complete chronic retinal detachment and chronic retinitis
5. Right eye: Mild to moderate chronic keratitis with focal Descemet's membrane rupture and uveal implantation

Contributor's Comment: Taken together, the constellation of lesions (corneal rupture with uveal incorporation, lens capsule rupture, and ocular sarcoma) are classic for feline post-traumatic ocular sarcoma (FPTOS). The relationship of the chondrosarcoma to the lens and to the lenticular rupture was highlighted, as was the extent of

retinal and optic nerve lesions. There was no evidence of extra-ocular extension in examined sections, which suggests that recurrence/extension is unlikely following enucleation in this case.

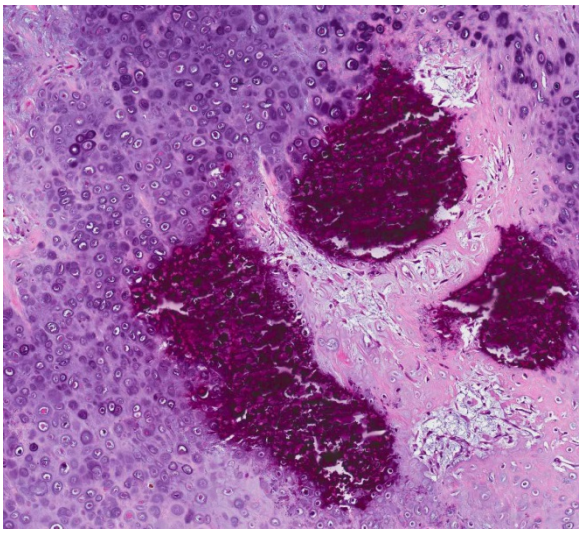
Feline ocular sarcomas are malignant, intraocular neoplasms that are usually associated with evidence of trauma (i.e. FPTOS) from the clinical history and/or histologic findings (e.g. lens capsule rupture, retinal detachment, and corneal perforation). The time from trauma to the development of FPTOS varies widely, uncommonly in as little as 2 months, and more commonly several years; up to 10 years of latency has been reported.[3] The average time between trauma and enucleation is 7 years.[3] Extra-ocular invasion can occur and is typically at the limbus through the sclera, or at the optic nerve.[2,5] For this reason, prophylactic enucleation of a feline eye after trauma should be considered if the eye is nonvisual.[3] Metastasis is uncommonly reported in this disease, but current studies are small and/or have limited follow up.

FPTOS have a typical distribution. Tumors commonly occupy the posterior iris with expansion to the posterior chamber, posterior lenticular capsule, retina, and choroid.[2] Invariably the lens is destroyed, either from initiating trauma or from tumor invasion, and significant inflammation accompanies these tumors (i.e. lens-induced uveitis).[2,7] There are three variants of FPTOS, the most common of which is the spindle cell variant, followed by round cell variant, and lastly osteosarcoma/chondrosarcoma.[3] The cell of origin in spindle cell variants is likely lenticular epithelium.[3,7]

The phenomenon of FPTOS is similar to vaccine-associated feline sarcomas. The latter is associated with vaccination of cats for infectious diseases, most commonly rabies and feline leukemia virus.[5] Vaccine-associated feline sarcomas are most commonly fibrosarcomas, but many different sarcoma variants have been reported, similar to FPTOS.[5,7] Although the pathogenesis of both types of tumors is unknown, inflammation is an antecedent feature, suggesting a causal relationship is possible.

JPC Diagnosis:

1. Eye, globe: Chondrosarcoma (post-traumatic ocular sarcoma).
2. Eye, lens: Lenticular rupture with subcapsular chondroid metaplasia.
3. Eye: Anterior uveitis, lymphoplasmacytic, multifocal, mild.

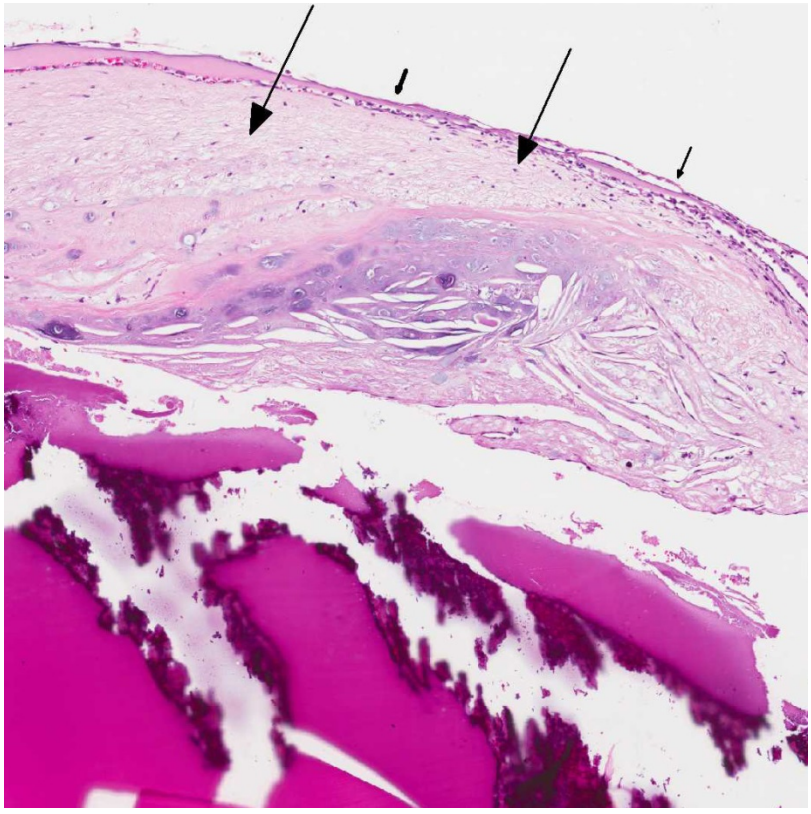


Globe, cat. Neoplastic cells within the chondrosarcoma are well differentiated and present within lacuna with a dense blue (glycosaminoglycan-rich matrix.) There is multifocal mineralization within the matrix as well. (HE, 124X)

Conference Comment: Interestingly, studies in rabbits, macaques and human infants have shown that when a cataractous lens is removed, but the lens capsule and lens epithelium (which cover the anterior surface of the lens) are left intact, they result

in functional lens regeneration - indicating these epithelial cells (or a subpopulation thereof) have stem cell / progenitor cell properties.[6] This may explain their ability to undergo mesenchymal neoplastic transformation in the cat. A subset of feline post traumatic intraocular sarcomas have been found to arise from the lens epithelium, although this phenomenon has not been documented to occur in people or dogs.[7] Features of FPTOS that support a lens epithelial origin include the frequent presence of lens capsule rupture, tumor development around the lens, lens capsule basement membrane being present around the neoplasm and alpha A crystallin positivity.[3]

Aside from cats, intraocular sarcoma has also been documented in rabbits with a history of chronic intraocular inflammatory disease. The two documented cases in rabbits were negative for *E. cuniculi* and bacterial infection via histochemical staining and polymerase chain reaction. The neoplasms expressed vimentin but were negative for smooth muscle actin, desmin, cytokeratin and S100. The neoplasms consisted of a population of anaplastic mesenchymal cells with the presence of lens fragments in the tumor. Trauma was not documented in the rabbits but the neoplasms were particularly aggressive and they were associated with the lens, similar to what is seen in many cases of FPTOS. Neoplastic cells extended through the sclera into adjacent extraocular tissues as well.[4] Non-trauma related feline intraocular chondrosarcoma has been documented in cats, although it is very uncommon. Given that mammals do not have cartilage within the globe, the tissue origin in non-trauma related intraocular sarcoma is unclear. It is proposed to arise from multipotent mesenchymal stem cells which may be present within the trabecular meshwork, cancer stem cells, or potentially from vascular pericytes. In all four documented cases in cats the neoplasm was contained within the globe.[1]



Lens, cat. Subjacent to the lens capsule (small arrows) is a thick layer of spindle cell metaplasia of lens fibers with a focal area of chondroid metaplasia, acicular cleft formation, and mineralization of lens fibers. (HE, 120X)

Conference participants discussed the spatial association of the neoplastic mass with the lens and how it may relate to the pathogenesis of this neoplasm, as well as the origin of the mass of cartilage distant from the neoplasm at the posterior aspect of the lens. A possible origin for this area is spindle cell and chondroid metaplasia of subcapsular lens fibers separate from the neoplastic transformation on-going elsewhere.

The trabecular meshwork of the iridocorneal angle was described as being collapsed and/or obscured by anterior uveitis, and glaucomatous changes were described in the retina including loss of ganglion cells as described above, as well as retinal atrophy. Anterior uvietisi is a common finding in the cat with quite a number of potential etiologies, and its connection to the neoplasm in this case could not be definitively proven. There are also areas with normal retina in this case, and the most severe thinning and loss of nuclei are present in the non-tapetal region.

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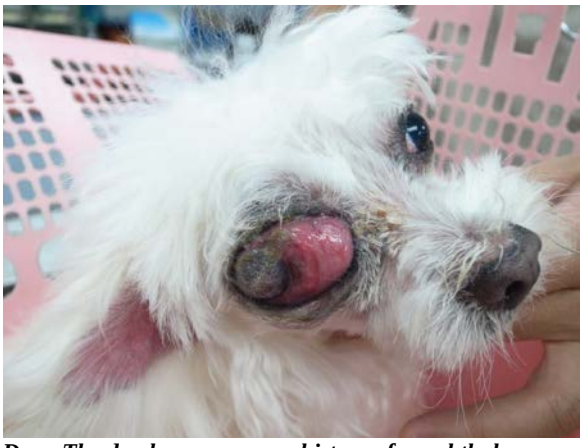
CASE IV: NTU20-12-1750 (JPC 4035591).

Signalment: 7-year-old neutered female Maltese, dog (*Canis familiaris)*

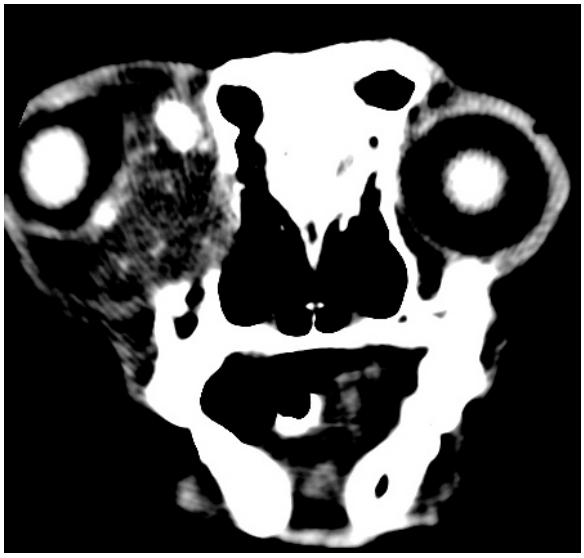
History: The animal presented signs of exophthalmos in the right eye, with mucopurulent discharge, for over half a year. Computed tomography scan revealed an irregular, retrobulbar, space-occupying mass with osteolytic lesion. A retrobulbar



Dog. The dog has a one-year history of exophthalmos with a mucous discharge. (Photo courtesy of: Graduate Institute of Molecular and Comparative Pathobiology, School of Veterinary Medicine, National Taiwan University, No. 1, Sec. 4, Roosevelt Road, Taiwan 106-17, Taiwan (ROC))

tumor was highly suspected. After five months of follow-up, the patient was presented for enucleation to relieve the discomfort, poor condition of right eye, and blindness. Right eye transconjunctival exenteration was performed and submitted for histopathological examinations.

Gross Pathology: The submitted specimens included (1) the right eye and periorbital mass, (2) right eyelids, (3) third eyelids, and (4) the mass in deep orbit. The periorbital mass, which was solitary, firm, yellowish, and space-occupying, encompassed and surrounded the globe. On cross section, the mass was multilobulated, leading to deformation of eyeball, but the delineation of eyeball was still identified. There was also a solitary, firm, and brownish tissue of irregular shape and with uneven surface along with the globe. Pieces of the eyelid displayed a firm and solitary appearance, partially containing haired skin coat. The third eyelid with an uneven surface was meaty, brownish, solitary and firm. The tissues obtained from the deep orbit comprised several solitary and firm tissues of variable shape and size. Submitted specimens were trimmed and selected for histopathological examination.



CT of head, dog: Computed tomography scan revealed an irregular, retrobulbar space-occupying mass with osteolytic lesion. (Photo courtesy of: Graduate Institute of Molecular and Comparative Pathobiology, School of Veterinary Medicine, National Taiwan University, No. 1, Sec. 4, Roosevelt Road, Taipei 106-17, Taiwan (ROC))

Laboratory Results: N/A

Histopathologic Description:
The periorbital mass, which is located behind the globe, is unencapsulated and poorly demarcated, and is causing the deformation of globe. The neoplastic cells are arranged in islands, small lobules and tight whorls or bundles, and are separated by a delicate fibrous stroma. These tumor cells have epithelioid appearance with ample eosinophilic cytoplasm, fairly distinct cell margins, and large open-faced nucleoli. Mitoses are rare. Islands of chondroid and osseous metaplasia, and varied size of vacuolation resembling adipose tissue, are present in the tumor area. The neoplasm invades the peripheral adipose tissues and extra-ocular muscles. Tumor cells infiltrate the lamina propria of the bulbar conjunctiva and partially replace the outer sclera. Multifocal necrosis is remarkable in the tumor area, but may be rare in the tissue of the submitted slide. Aggregations of lymphocytes and hemorrhage are also noted at the marginal area of the tumor. Retinal detachment, with remarkable hypertrophy of retinal pigment epithelium and degeneration of ganglion cells, is noted. Edema is present in the conjunctival epithelia. At the area behind the globe, the tumor cells encompassed an obscure nerve bundle with degenerative changes, suggestive of an orbital nerve.

By tissue immunohistochemistry tumor cells are immunopositive for vimentin, S-100 and neuron-specific enolase (NSE), and are immunonegative for cytokeratin (CK), desmin, glial fibrillary acidic protein (GFAP), Melan-A, and neurofilament (-).

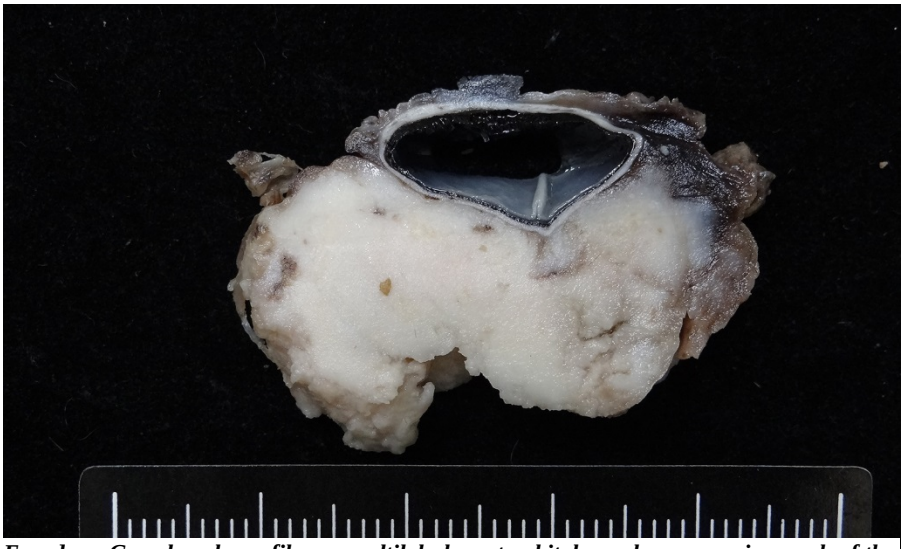
The epithelia of eyelid and third eyelid demonstrate severe hyperplasia, and the lamina propria displays extensive plasmacytic infiltration and hemorrhage. The tissues from the deep mass display numerous aggregates of lymphocytes, edema, hemorrhage, and necrosis, with presence of suspected neoplastic cells as described.

Contributor's Morphologic Diagnosis:

Orbit: Orbital meningioma, excisional biopsy, right eye, dog

Contributor's Comment: Although meningiomas are common tumors in the central nervous system of dogs, orbital meningioma is rare. Orbital meningiomas can arise from secondary extension of an intracranial neoplasm along the optic nerve or, as in the case of primary orbital tumors, from neoplastic transformation of arachnoid cap cells outside the optic nerve sheath.[3] Orbital meningiomas in dogs and humans usually grow slowly, compress the peripheral connective tissues, and may involve bilateral optic nerves with rare extracranial metastasis.[3,6,7] On immunohistochemistry, they may show variable positivity for S-100 and vimentin, but are generally negative for cytokeratin.[3] It is reported that an orbital meningioma with extracranial metastasis to the lung and heart in a dog demonstrated intracytoplasmic PAS+ granules.[7]

The histological features of meningiomas can be classified as meningotheliomatous, fibromatous, psammomatous or transitional pattern. In a study from the Comparative Ocular Pathology Laboratory of Wisconsin,[3] in 22 canine orbital meningiomas collected from 1981-1997, most of them were meningotheliomatous with rare fibromatous foci. The tumors characteristically have large epithelial-like neoplastic cells with nuclei containing disperse chromatin and prominent nucleoli. Psammoma bodies, which are commonly found in intracranial meningiomas, were not found in this study. In addition, islands of bone and cartilage metaplasia, which are very rare in the intracranial meningiomas, are very commonly present.[3] Metaplasia is very rare in human and canine meningiomas, but is more common in the orbital meningioma, which can be a diagnostic aid for both histologic and ultrasound analysis.[3] In the present case, the histology findings are very similar to the Wisconsin's study; nevertheless, prominent



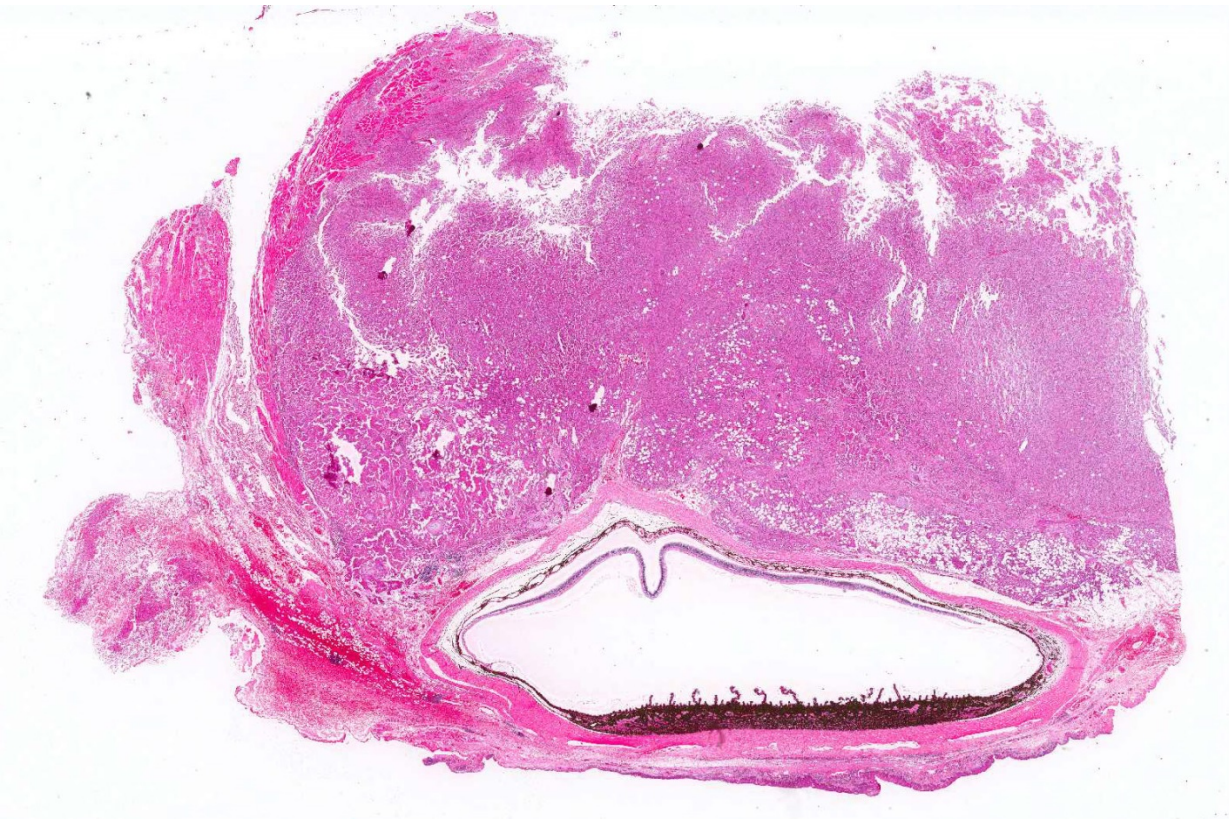
Eye, dog: Grossly, a large fibrous multilobular retrorbital neoplasm occupies much of the orbit, pushing the globe forward and transversely compresses it. (Photo courtesy of: Graduate Institute of Molecular and Comparative Pathobiology, School of Veterinary Medicine, National Taiwan University, No. 1, Sec. 4, Roosevelt Road, Taipei 106-17, Taiwan (ROC))

local invasion suggesting malignancy is noted in our case.

In the present case, due to the overlapping expression of neural markers, the diagnosis should rely on histologic findings of classic chondroid and osseous metaplasia with myxomatous changes. It's reported that canine meningiomas reveal variable positive results for neural markers, such as S-100 and NSE.[2] Correlated to the location, morphology, and IHC results, the differential diagnosis should include an epithelioid variant of malignant peripheral nerve sheath tumor. The orbital meningioma classically shows that epithelioid tumor cells envelope the optic nerve, expand into the peripheral adipose and loose connective tissues with myxomatous stroma, and chondroid and osseous metaplasia is present.[6] In the veterinary literature, epithelioid malignant PNST involving multiple organs with a mixture of spindle and epithelioid cells histologically has been reported.[4]

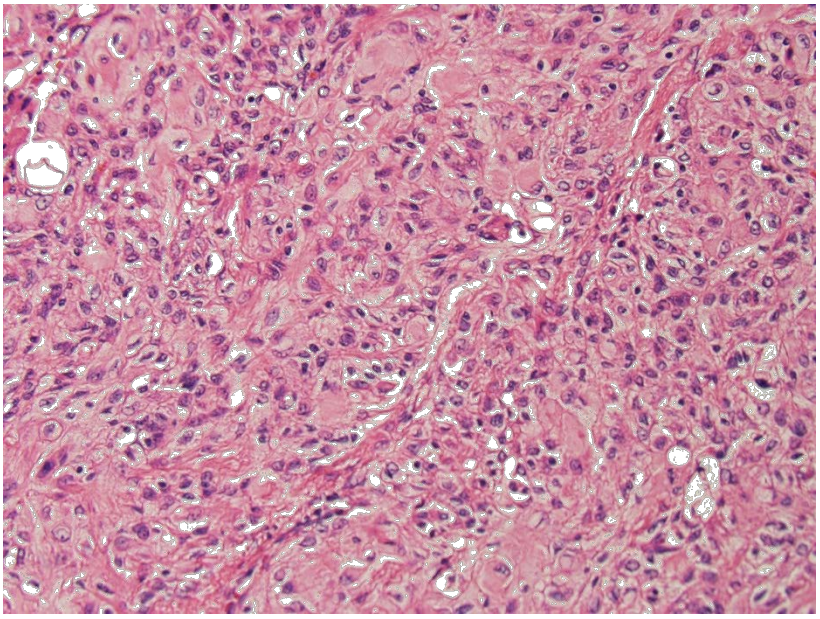
JPC Diagnosis: Eye, extraocular tissues: Orbital meningioma.

Conference Comment: Orbital meningiomas are generally regarded as slow growing and benign, but intraocular invasion may occur and metastasis has also been documented. Local recurrence is seen with intermediate frequency due in part to the difficulty in obtaining complete excision. The tumors are often found to be closely associated with the optic nerve and may appear to originate from the optic nerve sheath.[6] Fine needle aspiration or diagnostic imaging may be included in the initial diagnostic process. The cytologic appearance of meningioma cells upon



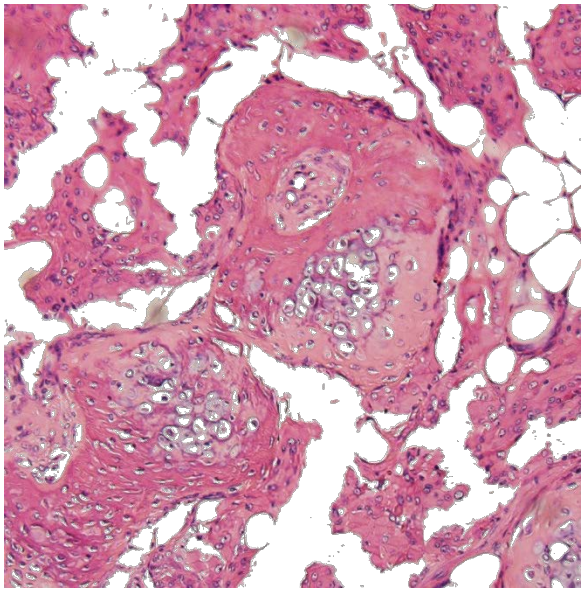
Eye, dog: Subgross magnification of the retro-orbital neoplasm. (HE, 5X)

aspiration may include round to polygonal to indistinctly shaped spindle cells which have moderate to abundant pale blue to grey cytoplasm, round to ovoid nuclei, mild anisokaryosis, a granular chromatin pattern, and small or indistinct nucleoli.[8,10] The features may be consistent with a mesenchymal neoplasm without prominent signs of malignancy, but may also present a diagnostic challenge due to the variable appearance of cells. Cells of the adjacent retina may also be obtained during aspiration and various components of the retina, including pigment epithelium, rods and cones, and nerve fibers, which have a distinctive cytologic appearance, should not be interpreted as part of the neoplasm.[10] Central blindness has been found to develop in the opposite eye in some cases of orbital meningioma, which suggests infiltration of the tumor along the optic nerve to the level of the optic chiasm.[6] Aside from being reported in dogs and cats, orbital meningioma has also been reported in large animals, such as cattle, although much less commonly.[9]



Eye, dog: The neoplasm is composed of tightly arranged streams and bundles of polygonal to spindled cells which are arranged in various planes. There is mild anisokaryosis and a low mitotic rate. (HE, 400X)

The moderator discussed the classic appearance of orbital meningioma in dogs and suggested that in an orbital neoplasm composed of large polygonal to spindle cells containing areas of cartilaginous and osseous differentiation, meningioma should be the first consideration. The differential diagnosis for orbital tumors in the dog includes multilobular tumor of bone, a mesenchymal neoplasm which also contains areas of cartilage and bone; these tumors have a characteristic lobulated pattern, and lobules are surrounded by spindle cells embedded in a rich collagenous matrix. Soft tissue sarcoma is an additional consideration for an orbital spindle cell neoplasm containing abundant collagen; these tumors typically lack bone and cartilage; however, and in dogs, morphologically low-grade but biologically high-grade fibrosarcoma would be the primary concern. Other considerations for orbital neoplasia include lymphoma, osteosarcoma, lacrimal or sa-livary gland adenocarcinoma, hem-angiosarcoma, liposarcoma (including hibernoma) and canine lobular orbital adenoma. Microscopically, the presence of osteoid would be the discriminating feature for osteosarcoma; and the presence of strap cells, rowed nuclei, and cross striations are characteristic features of rhab-domyosarcoma.[3] Macroscopically, canine orbital multilobular adenoma has a discriminating appearance and texture that may help differentiate it from other neoplasms, including the presence of friable, translucent lobules with a delicate capsule and often found to be challenging to manipulate and remove



Eye, dog. Scattered throughout the neoplasm are small nodules of cartilage and bone. Adipocytes likely represent remnants of the infiltrated retro-orbital fat. (HE, 200X)

during surgery. Histologically, multilobular adenoma consists of well-differentiated lacrimal or salivary gland tissue with the absence of ducts, and may have PAS positive material within the cytoplasm.[5]

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