Ocular Pathology Review Course– BSC 2016

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**Day 1**
8:00-8:15 Introduction
8:15-9:00 Overview of disease mechanisms (CR)
9:00-9:40 Eyelid-Conjunctiva-Orbit (PL)
9:40:10:10:30 Break
10:10-12:30 Uvea and OMSD (CN)
12:30-13:30 Lunch
13:30-13:40 Questions-messages
13:40-14:00 Lens (CN)
14:00-15:00 Vitreous-Retina-Optic nerve (PL)
15:00-15:30 Break
15:30-16:30 Glaucoma (CR)
16:30-17:00 Topics/Questions

**Day 2**
8:00-8:10 Intro-messages
8:10-10:10
Intro to neoplasia and IHC (PL)
Canine neoplasia
Ocular surface neoplasia (PL)
Uveal melanocytic neoplasia (PL)
Uveal non-melanocytic neoplasia (CN)
10:10-10:30 Break
10:30-11:30
Posterior segment/orbit neoplasia (CR)
Equine Neoplasia (CR)
11:30-12:30 Lunch
12:30-12:40 Questions-messages
Feline neoplasia
Ocular surface neoplasia (CR)
Uveal melanocytic neoplasia (CR)
Uveal non-melanocytic neoplasia (CN)
Orbital neoplasia (CN)
14:00-14:30 Break
14:30-16:30 Quiz
16:30-17:00 Topics/questions
Ocular histopathology Overview

Chris Reilly

The pathologic interrelationships in and around the eye are often complex and/or potentially multidirectional. For example, lens luxation may cause or be caused by glaucoma. The highly specialized anatomic relationships and visual significance of even small perturbations can further challenge meaningful and accurate histopathologic assessment. In many ways, ophthalmologists are ocular gross pathologists, and ocular histopathology is a natural, if complicated cliniopathologic correlation.

Pathology “hacks” for Real Life

- Pathology can help; not always “the answer”
- And we can’t cover it all in 2 days
- YOU can help us help you
- Choose a pathologist that you “get”
- Work WITH them, talk with them
- Provide relevant history

Submission

- History, history, history
- SIGNALMENT
- SIGNS, clinical diagnosis/Ddx
- DURATION
- Prior treatment
- LOCATION (if known, if applicable)
- If using big labs, ask ahead
- Some have eye-interested and/or trained pathologists (Phil, Carol, others)
- If ancillary diagnostics expected (frozen section IHC, EM, PCR) plan ahead – and prep client for $$$
- Formalin is not always appropriate
- For best results:
- Remove adnexa/muscles MOST of the time
- If orbital margins are complex or fornicial region is of interest, submit whole
- Can submit adnexal tissues separately – note if lesions of interest
- Inking of complex/important margins can help

Development/Congenital/Genetic

- Not always synonymous
- History can be essential (e.g. anterior chamber collapse v malformation)

Cellular degeneration

- Can be lethal (irreversible) or sublethal (reversible)
- Cytoplasmic swelling/vacuolization; nuclear swelling
- Cellular collapse, hypereosinophilia, nuclear pyknosis
- Not unique to eye, but specific visual consequences (e.g. cataract)

Intracellular accumulations

Intracellular edema
• Acute cellular swelling (hydropic degeneration)
• Corneal epithelium, lens fibers, iris pigment epithelium
• Often reversible

Others

• Lipid (lipid corneal dystrophy – can also be extracellular
• Hemosiderin – macrophages, chronic hemorrhage
• Lipofuscin – age related, storage diseases (neuronal ceroid lipofuscinosis)

Extracellular accumulations

Edema

• Typically clear space between cells in most tissues (including episclera, retina, uvea, dermis/lids)
• In cornea, reduced clear space/clefting (useful artifact of processing)
  o Overhydration of GAGs between collagen fibers causes a “washed out” appearance, even with processing.
  o When severe, pallor, irregular clefting, and variably stained fibers can predominate

Mineral

• Dystrophic – mineralization of dead tissue, with normal serum Ca 2+
• Metastatic – mineralization of viable tissue due to hypercalcemia
• Basophilic in H&E (pink with decalcification) – often shatters during sectioning
• Stains black with von Kossa, red with Alazarin red

Lethal Cellular Degeneration

Necrobiosis

• Normal death of cells as part of development
• Keratinization, lens fiber senescence
• Typically unnoticed (i.e. normal)

Necrosis

• Classically involves:
  • Cellular swelling (oncosis)
  • Hypereosinophilia (denatured protein)
  • Nuclear changes/karyorrhexis
  • Secondary inflammation
  • Difficult to determine in single cells
  • Overlap with apoptosis, etc
  • Can occur in stromal tissues (e.g. corneal sequestrum)

Apoptosis

• Programmed cell death – usually individual or small clusters of cells
• Shrunken cells with shrunken or fragmented nuclei
• None/Minimal inflammation
• Can be normal/developmental (retina, anterior segment, lymphocytes)

Tissue degeneration

Environmental
• Solar elastosis – thickening and basophilia of subepithelial and arteriolar elastin due to UV irradiation
  ○ Conjunctiva and skin, not cornea
  ○ Along with solar induced SCCs and vascular tumors

Atrophy

• Loss of tissue bulk, cells
• Optic nerve, iris, phthisis bulbi, corpora nigra
• Can be accompanied by hypercellularity (e.g. optic nerve; relative)

Phthisis bulbi

• Common end stage of ocular disease (glaucoma, uveitis)
• Globe shrinkage, intraocular atrophy, and intraocular tissue disorganization – defining features
• Cyclitic membranes are common
• Smaller size does not preclude neoplasia

Inflammation

• Acute – neutrophils, protein/fibrin
• Cornea, chamber exudates
  ○ +/- uvea, retina, lens
  ○ +/- hemorrhage
• Chronic – lymphocytes and plasma cells (uvea/retina, +/- cornea), fibrovascular membranes/neovascularization
• Either: macrophages, eosinophils; phakitis
  ○ Neutrophils may persist chronically
• Eosinophils – allergic, foreign body, idiopathic/”eosinophilic syndromes”, feline herpes
• Granulomatous – foreign body, ruptured lens, asymmetric uveitis, fungus, mycobacteria, lipid/chalazion
• Uveitis: Secondary glaucoma common with severity/chronicity

Patterns

• Anterior (iritis, cyclitis, iridocyclitis)
• Panuveitis (anterior + choroid)
• Endophthalmitis (any uvea + retina, +/- chamber exudates*)
• Panophthalmitis (all uvea, retina, cornea/sclera, +/- orbital/episcleral tissues*)
• Vitritis, hypopyon, phakitis, etc
• Keratitis, keratoconjunctivitis
• Optic neuritis, optic (nerve) meningitis, orbital cellulitis, episcleritis
• *Many ocular diseases have an inflammatory component, even if not primary pathology (e.g. uveitis in glaucoma, neoplasia)

Inflammation Types

Neutrophilic

  – Acute, innate
  – Tissue destruction, necrosis
  – Cavities/chambers
  – Surfaces; keratomalacia
Lymphocytic/plasmacytic

• Chronic, adaptive
  – At least a couple days, typically
• Tissue response (e.g. uvea)
• Often perivascular, sometimes nodular
• Etiologically nonspecific
  – Proportion can help (plasma cells in FIP)

Eosinophilic

• Acute or chronic
• Allergy, foreign body, parasites
• Immune/idiopathic
  – Eosinophilic keratitis
• Grossly characteristic
  – Granular on corneal surface
• Luna’s stain can highlight

Granulomatous

• Variably strict definitions
  – True granulomas
  – Granulomatous inflammation - sheets
  – Histiocytic infiltrates
• Idiopathic/Immune mediated histiocytoses
  Relatively common, very confusing
• Search for etiology
  – Fungal (stains – GMS, PAS, BCG IHC)
  – Mycobacterial (Fite’s, Ziehl-Neelsen AF, BCG)
  – Foreign body (polarized light for plants, plastic)
• Wrong diagnosis = wrong treatment
  – Steroids
• May need fresh tissue
  – Think before you fix
Fibrosis
• Common end result of inflammation
• Indicates chronicity
• Corneal fibrosis/scarring
• Uvea is resistant
  – But chambers and surfaces prone
• Pre-iridal, cyclitic, retrocorneal, vitreal, epiretinal
  – Often associated with prominent vessels

Dystrophy
• Inherited*, non-inflammatory, bilateral lesions
  – Corneal opacities in vet med
• Endothelial dystrophy
  – Better characterized in humans – Boston Terriers, Dachshunds, Chihuahuas
• Often secondary dysfunction in vet med

The ‘plasias
• Aplasia – complete failure to form
  – Ocular agenesis
  – Segmental: coloboma
• Hypoplasia – failure to reach normal size
  – Microophthalmia
  – Optic nerve hypoplasia
• Hyperplasia – non-neoplastic proliferation of cells
  – Corneal epithelial hyperplasia
  – v hyperTROPHY – increase in the size of individual cells
• RPE hypertrophy with detachment
• Dysplasia – abnormal development
  – Retinal dysplasia
  – Goniodysgenesis
• Metaplasia – transdifferentiation to another cell type
  – Osseous metaplasia
  – Epithelial-mesenchymal transition
- Squamous metaplasia of conjunctiva (vitamin A)

- Neoplasia – unregulated growth of cells
  - Benign or malignant

**Neoplasia**

- Round cell: leukocytes (melanoma?)
  - Sheets
  - No real pattern, architecture
- Epithelial – polygonal, cuboidal, columnar
  - Nests, cords, tubules, acini, “islands”
- Mesenchymal – spindle cells, stellate cells
  - More vague patterns, streams, whorls, fascicles, bundles, storiform etc

**Aging**

- Variably significant, can be subtle
  - Nuclear sclerosis, senile cataract
  - Thickening of DM and lens capsule
  - Hyaline material in ciliary body
  - Cystic degeneration of neuroepithelia
  - Asteroid hyalosis

**Systemic Disease**

- Metabolic
  - Diabetes mellitus (cataract, uveitis)
  - Hypertension (retinal hemorrhage, arteriolosclerosis, etc)
- Neoplasia
  - Metastasis
- Systemic infection
  - FIP, systemic mycoses, West Nile Virus, etc

**Common Special Stains**

- Periodic Acid-Schiff
  - Starch (glycogen, glycoproteins, fungi)
- Magenta

• Alcian Blue (Alb)
  - Mucopolysaccharides, GAGs
  - Bright blue
    - i.e. vitreous
    - Along with PAS
  - Deep Blue - Cartilage

• Periodic Acid-Schiff - PAS
  - Carbohydrates (BM, fungus, cellular debris, mucus, Lipofuscin)
  - Magenta
  - Often done w/ Alcian Blue

• Grocott’s/Gomori Methenamine Silver - GMS
  - Similar to PAS, can stain differently
  - Black – can be confusing in pigmented eyes
  - Light green counterstain

• Tissue Gram stain
  - Typically Brown & Brenn (B&B)
    - Gram +, Gram – (often weak)
    - Yellow background
    - Other techniques better for some
  - Brown and Hopps for Klebsiella spp.

• Von Kossa
  - Phosphate, black

• Prussian Blue (or Gomori’s, Perl’s)
  - Iron (hemosiderin)

• Masson’s Trichrome
  - Muscle = red; Collagen = Blue; Cytoplasm = Pink; Nuclei = Blue/black

• Luna’s Stain – eosinophil granules (even if degranulated)
  - Red/brown

• Giemsa/Toluidine blue – metachromatic
  - Mast cells (purple)
  - Bacteria (pink)

• Fontana Masson – Melanin
– Black in a VERY pale background

• Mucicarmine – Mucus
  – Pink, can highlight Cryptococcus

• Acid Fast (Ziehl-Neelson, Fite’s)
  – Mycobacteria, other Acid Fast
  – Red w blue background
  – Fite’s for atypical AFB (e.g. M. leprae)

• Oil Red O, Sudan Black
  – Lipid, can’t be on processed tissue
  – Can do fixed, unprocessed – LET PATHOLOGIST KNOW IF YOU SUSPECT LIPID

• Phosphatongstic acid-hematoxylin
  – Fibrin, black

• Vierhoff-van Gieson
  – Elastin, black

• Luxol Fast Blue
  – Myelin, blue

• Bodian’s
  – Axons, black

• Neuro Combos:
  – LFB/HE, LFB/Bodians, LFB/PAS
Pathology of the Eyelids, Conjunctiva and Orbit

Phil Labelle

Eyelid

Any skin disease can affect the eyelid skin (allergic/hypersensitivity disease, zinc-responsive dermatosis, pemphigus foliaceus, demodicosis, dermatophytosis, habronemiasis, etc). Eyelid skin reacts similarly to skin elsewhere. Eyelids may be the first or the most severely affected site. For more information: Veterinary Ocular Pathology (Dubielzig et al.), Veterinary Dermatopathology (Gross, Ihrke, Walder)

Demodicosis is caused by Demodex sp. The disease is often classified as either juvenile form or adult form. Lesions can be localized or generalized. Histologically the lesion consists of perivascular inflammation, periadnexal inflammation, folliculitis and furunculosis with intrafollicular organisms. Organisms may be free within the dermis if there is follicular rupture.

Dermatophytosis is caused by Microsporum sp and Trichophyton sp. Organisms can be seen with standard staining but are most obvious with either PAS of GMS stains. Fungal hyphae and spores colonize hairs. Histologically the condition presents as folliculitis and furunculosis. Lesions may be more subtle in cats and pustular disease may predominate. When furunculosis is present, bacterial furunculosis and demodicosis are the main dx.

Habronemiasis is caused by Draschia megastoma, Habronema majus or Habronema muscae. The histologic lesion consists of severe eosinophilic and granulomatous inflammation. Larvae are typically few in numbers. If no larvae are present, the final histologic diagnosis may be eosinophilic granuloma. This diagnosis does not exclude Habronemia as the cause.

Chalazion is a form of meibomian adenitis consisting histologically of lipogranulomatous inflammation. The lesion is secondary to leakage of meibomian gland secretions, most often from meibomian gland neoplasia. The inflammation consists of large numbers of macrophages and multinucleated giant cells. The cells contain acicular cytoplasmic clefts on HE. These clefts are refractile/birefringent material. Under polarized light, birefringent crystals may be present in macrophages. Not always demonstrable, this feature is unique to inflammation associated meibomian gland secretions and is absent with granulomatous inflammation associated with other sebaceous glands.

Idiopathic Marginal Blepharitis affects dogs. The lesion has features similar to those of Sterile granuloma syndrome and consists of granulomatous to pyogranulomatous inflammation typically with well formed granulomas. The lesion typically forms a mass effect, but can be poorly circumscribed or diffuse. The lesion can be bilateral. The etiology is unknown.

Conjunctiva

The conjunctiva has limited ways in which it responds to injury. Conjunctival biopsies rarely identify a specific cause for the conjunctivitis. There are few specific diseases and biopsies are taken late in the disease process often after treatment.

Conjunctival Overgrowth is a condition of rabbits also termed pseudopterigium (The lesion is termed “pseudo”-pterigium because a true pterygium should have solar/actinic changes (ie solar elastosis +/- actinic keratosis) and will invade the cornea following dissolution of Bowman’s membrane. The cause is unknown. The lesion consists of hyperplastic conjunctival tissue that has normal architecture. This tissue extends to cover the cornea. The tissue does not invade it is not adhered to the cornea.

Ligneous Conjunctivitis a condition of dog which has been reported in the Doberman Pinscher, Yorkshire terrier, Golden Retriever, and Scottish terrier. Clinically the lesion presents as conjunctivitis with a hard consistency and pseudomembranous exudate. Histologically there is subepithelial deposition of mostly acellular hyalinized eosinophilic matrix. This material is positive with phosphatungstic acid-hematoxylin (PTAH) indicating fibrin (or fibrin-like). And negative for Congo Red/amylaid. Fibrin deposition occurs in the conjunctiva, oral cavity, esophagus and +/- glomeruli and other sites. In humans the lesion is caused by plasminogen deficiency. Plasminogen deficiency has also been identified in some
dogs. The deficiency is suspected to result in the deposition of material/fibrin as plasma and fibronolytic. See Mason et al, JSAP, 2016; Mason et al, JSAP, 2012; Torres et al, VO 2009; McLean et al JAVMA, 2008; Ramsey et al, JAAHA , 1996.

Solar Elastosis, Fibrosis and Vasculopathy are solar-induced lesions within the conjunctival substantia propria. The lesions can be seen in some cases of conjunctival squamous cell carcinoma, hemangioma or hemangiosarcoma. Solar elastosis consists of altered fibers within the superficial substantia propria. The abnormal fibers represent mostly new production with some degradation of collagen and elastin. Normal elastin fibers require special stains to be visualized. Solar elastosis fibers are thick, basophilic and irregularly aligned. The cornea does not develop this change, likely due to few elastin fibers. Generally mild in dogs, it can form plaques in horses. Solar “fibrosis” consists of altered collagen that forms a pale, hypocellular (sclerotic) band underlying the epithelium. Solar fibrosis is not true fibrosis. Solar vasculopathy is more common with cutaneous solar changes. The lesion consists of thickened hyalin vessel walls. Some vessels have swollen endothelium.

Lymphoplasmacytic conjunctivitis is the most common inflammatory response in the conjunctiva. This form of inflammation does not suggest a specific etiology. It can be the result of infectious and non-infectious causes. Histologically the lesion can be predominantly perivascular in mild cases or diffuse and more severe cases. The lesion is typically not ulcerative. This diagnosis is not without value: The inflammation can be severe enough to warrant clinical concern for neoplasia which can be excluded by the biopsy.

Lipogranulomatous Conjunctivitis is a condition in cats. The lesion consists of nodular inflammation comprise of macrophages with lipid lakes Mmultinucleated giant cells may be present. Although it can be a stand-alone lesion, is often seen associated with neoplasia.the diagnosis of lipogranulomatous conjunctivitis should always warrant concern for neoplasia/monitoring of the site for neoplasia.

Triamcinolone Granuloma is a nodular inflammatory reaction comprised of macrophages and multinucleated giant cells. Inflammation is centered on large rounded rectangular vacuoles. Most often recognize clinically, these lesions are rarely biopsied.

Nodular Granulomatous Episcleritis (Episclerokeratitis, episcleritis, NGE) is an inflammatory disease with a variety of histological presentations. The exact cause is not known but suspected to be an immune mediated process. Despite the name the lesion is almost always within the conjunctival substantia propria. The episclera is rarely involved.the lesion may be limbal/bulbar but can be found at other conjunctival sites, and even in the orbit. Typical lesions consist of smooth nodules to diffuse thickening. Histologically the lesion consists of epithelioid and spindle macrophages admixed with lymphocytes and plasma cells. The macrophages do not form distinct granulomas. Some of the spindle cells are myofibroblasts. The relative proportion of inflammatory cell types is highly variable between cases. Cases with a predominance of spindle cells have been called nodular fasciitis. Some cases may include multinucleated giant cells or eosinophils. Special stains for infectious organisms are always negative (and must be). The proportion of T-cells and B-cells has been said to be predictive of response to treatment (B-cell predominant were more refractory). See Breaux et al. VO, 2007 (T vs B); Barnes et al, VO 2010 (orbit)

Eosinophilic conjunctivitis is a common condition in both dogs and cats. By definition eosinophils are a component of the inflammation. However they are very often not the predominant cell type. Many lesions consists predominantly of lymphocytes and plasma cells with fewer eosinophils. The infiltrate may be perivascular to diffuse, depending on severity. Most lesions represent allergic/ hypersensitivity disease. The role of Herpesvirus infection in catis is unclear; viral inclusionsare never seen histologically.

Herpes Keratoconjunctivitis is a disease of cats, primarily kittens. These cases are unlikely to be biopsies. Viral inclusions are transient and only present for a small period of time; they are unlikely to be present in biopsy samples. Eosinophils can be a component of the inflammatory reaction. The role of Herpervirus in feline keratoconjunctivitis in adult cats is controversial. Clinical lesions suspected to be, diagnosed as, and treated for herpes viral infection lack any histologic evidence to specifically support a viral cause. The presence of eosinophils is not a helpful feature as many hypersensitivity diseases have eosinophils as a hallmark of the lesion.

Conjunctival Histoplasmosis is caused by Histoplasma capsulatumand is essentially a disease of cats. The lesion consists of pyogranulomas inflammation forming subconjunctival nodules. Special stains (GMS) are often needed to visualize the organisms.
Conjunctival/Orbital Onchocerciasis is caused by Onchocerca lupi. It is a disease of dogs and cats. It is mostly seen in Europe and in the Southwestern United States. Feline cases have only been described in the United States. According to a 2015 review paper, there have been 205 canine, 2 feline and 18 human infections in Europe, Tunisia, Turkey, Iran and the USA described in the literature. The condition presents as subconjunctival or periscleral/orbital nodules. Histologically most lesions consist of granulomatous inflammation. Eosinophils may be present in large numbers and there may be fibrosis. In some cases the parasites do not elicit inflammation. The organisms must be differentiated from other nematodes with microfilariae. Onchocerca sp have annular/circumferential ridges. This distinguishes the organisms from Dirofilaria immitis which have longitudinal ridges. There is an association with onchocerciasis and glaucoma in humans. It is unclear if such association exists in dogs and cats. In the feline and some canine cases, there were intraocular lesions (uveitis, PIFMs, retinal atrophy/glaucoma) of unclear significance. The life cycle includes lower pole development in blackflies. The nematodes require the endosymbiotic bacteria Wolbachia for survival. It is a current topic of interest and there are numerous recent publications on the topic including not limited to: Canine disease Tudor et al Parasitol Res 2016; Otranto D et al. Emerg Infect Dis 2015; Otranto D et al Parasit Vectors 2015; Otranto D et al. Emerg Infect Dis 2013; Labelle AL et al. Vet Parasitol, 2013; Fascia P et al VO 2010; Zarfoss et al. Vet Pathol 2007; Komnenou A et al. VO 2002; Egyed Z et al. Vet Parasitol, 2001; Intraocular k9 Komnenou AT et al. VO 2015; Feline Labelle AL et al. VO 2011; Review Gracio AJ et al. Parasitol Res 2015.

Orbital extraocular polymyositis affects all the extraocular muscles except the retractor bulbi muscle. It is a rare disease, typically affecting young dogs. Patients present with bilateral and variably symmetric exophthalmos, retraction of the upper eyelid, and mild chemosis. There may be enophthalmos and strabismus in chronic cases. Histologically the lesion is a CD3+ predominant lymphocytic myositis with myonecrosis. Attempts at regeneration with muscle atrophy and fibrosis may also be present. The lesion likely represents an immune-mediated attack directed specifically against the extraocular muscles. Because the clinical presentation can often be diagnostic and the tissue is difficult to biopsy, these cases are unlikely to be biopsied.
Pathology of the Cornea and Sclera

Phil Labelle

Congenital/dystrophies/degenerations

General Considerations: the cornea has limited ways it responds to injury and limited healing capacity (to maintain function).

Dermoid describes an ectopic island of skin on cornea (or conjunctiva). It is also termed congenital choristoma. The lesions have many or all features of normal skin. The term “cutaneous metaplasia” occasionally used to describe corneal changes is not analogous to a dermoid. “cutaneous metaplasia” is seen with chronic keratitis and refers to hyperplasia, pigmentation and keratinization of the corneal epithelium.

Corneal Dystrophies and Degenerations may be epithelial, stromal or endothelial. True dystrophy is bilateral and symmetric. Lesions secondary to other diseases are not true dystrophies and best termed “degeneration”. Most dystrophies are breed-related/heritable

Corneal Epithelial Dystrophy are most often recognized in Shetland Sheepdogs; Longhaired Dachshunds. The lesions can be described as superficial punctate corneal dystrophy. Histologically there is dysplasia of basement membrane with dyskeratosis and necrosis of epithelium. These cases are unlikely to be biopsied.

Mineral/Band Keratopathy describes the deposition of mineral in the basement membrane of the corneal epithelium and/or superficial stroma. The lesion is usually secondary (not a true dystrophy). Inflammation and hypercalcemia are potential causes of secondary mineral deposition. In the horses uveitis and steroid and phosphate containing topical solutions maybe contributing factors. Calcareous corneal degeneration of older dogs affects both the basement membrane area and the deep stroma. Some cases present in the absence of any other ocular disease. The von Kossa is commonly used and highlights the phosphorus of the calcium-phosphorus complex. Alizarine Red can be used to specifically stain the calcium.

Stromal Lipid Dystrophy is often simply termed “Corneal dystrophy”. The condition is bilateral and symmetrical with no association to metabolic disease. Histologically the lesion consists of accumulation of lipids within the stroma. Macrophages may border these foci. Lipids are dissolved during routine processing and lipids appear as clear space/vacuoles/clefts. Cholesterol clefts are angular or needle shaped clearings. It is one form of lipid accumulation. Special stains for lipid (Oil Red O, Sudan Black) can on be performed on fresh, frozen or fixed but unprocessed sections. Acquired lipid keratopathy can be associated with corneal or adjacent disease, or metabolic disease.

Endothelial Dystrophy is most often secondary (not true dystrophy). It may be primary in Boston terrier, Chihuahua. The condition initially affects the temporal cornea and leads to corneal edema +/- ulceration. Histologically the lesion consists of endothelial cell attenuation. The lesion can be very subtle and difficult to recognize histologically. Furthermore formalin fixation can cause artifactual vacuolation of the endothelium. Anterior uveitis, glaucoma, surgery, anterior lens luxation, are possible causes of secondary endothelial degeneration. Fibrometaplasia/ retrocorneal membranes may be present with endothelial degeneration. The endothelium can slide but cannot replicate (post-miotic) with rare exceptions (rabbits + dogs).

Corneal epithelial cysts/epithelial downgrowth are common findings. The cysts may be congenital or traumatic. It is a common finding at corneal surgical sites. Epithelial down growth can be seen following trauma or ulceration. Although most lesions have limited clinical significance, some cans have disastrous consequence for the globe. In its mildest form there can be small dust of epithelium or small cysts within the stroma, typically at sites of surgery or previous trauma. In rare cases the epithelium will extend beyond a ruptured Descemet’s membrane in the globe to carpet the posterior cornea and/or the iris.

Descemet’s Duplication describes a double layer of basement membrane. It is a relatively common finding in globe submitted for examination. Trauma, lens luxation, glaucoma, surgery are possible causes. The duplication may accompany breaks in Descemet’s membrane and there may be endothelium lining
one or both layers. the lesion is unlikely to be significant in most cases. It may be significant if associated with extension on the iris or if associated with traumatic lesions elsewhere. See Kafarnik et al. Vet Path 2009.

**Endothelial Pigment** is most often seen secondary to release of uveal pigment. Neoplasia, inflammation, anterior synechia, ruptured uveal cyst, iris-cornea PPM are possible causes. the lesion does not appear to affect function (not associated with corneal edema).

**Keratitis**

General Considerations: Keratitis can be categorized in a number of ways. From a histologic perspective, keratitis is usually characterized as ulcerative or non-ulcerative and by the nature of the inflammatory cellular infiltrate. When possible the lesions may be that characterized by the specific agent or condition. In general most forms of acute keratitis will have her predominance of neutrophils whereas chronic keratitis is typically a lymphoplasmacytic predominant process. Corneal edema and stromal neovascularization are common changes seen with various forms of keratitis.

**Corneal edema** is recognized histologically as loss of normal lamellar arrangement of the stroma. It must be differentiated from fixation artifact causing separation of lamellae. Corneal stromal neovascularization can begin within 48-72 hours after injury and can progress up to 1mm/24h. Although this can suggest a “minimum” age for the keratitis, this is rarely clinically helpful.

**Ulcerative keratitis** can be seen part of a variety of corneal insults as well as specific conditions. In general, ulcerative keratitis described corneal injury where segments of the epithelium are absent exposing the basement membrane and/or stroma. Epithelial changes in the remaining epithelium will typically include sliding, rounding of the epithelial edges, hyperplasia. Neutrophils predominate in acute cases. Ulcerative keratitis: Neutrophils predominate in acute cases. Lymphocytes and plasma cells may be admixed with neutrophils with chronicity and there may be stromal fibrosis and neovascularization.

**Ulcerative Keratitis with Keratomalacia** is also known as melting ulcer. It is most often seen in horses and dogs (brachycephalic), and less commonly in cats. The lesion is characterized by marked degeneration of stromal collagen typically underlying an area of ulceration. The stromal changes are the result of the actions of metalloproteinases and serine proteases. These may be of endogenous (inflammation/neutrophils) origin. Some bacteria and fungi produce proteases (exogenous origin).

**Chronic Keratitis (Nonspecific)** is also termed “Chronic keratitis, superficial”. It is not a disease, but a response pattern that represents the end result of a variety of corneal insults. Buphthalmos, lagophthalmos/exophthalmos, neurogenic disorders, lacrimal/Meibomian disorders (KCS), irritation from a mass or eyelid issue, etc. possible causes. It is a frequent finding in enucleated globes. Severe cases may mimic Chronic Superficial Keratitis/Pannus. Histologically the lesion consists of epithelial lesions (hyperplasia, pigmentation + - keratinization), lymphoplasmacytic stromal inflammation, pigmentary incontinence, stromal fibrosis and neovascularization. Pigmentary incontinence describes the “leakage” of pigment from the epithelium that is then phagocytized by macrophages in the underlying stroma, a common feature of chronic dermatitis.

**Specific diseases/conditions**

**Chronic Superficial Keratitis (Pannus)** is an immune mediated disease most often seen in German shepherds and sighthounds. The main histologic lesion consists of chronic lichenoid lymphoplasmacytic inflammation. Lichenoid inflammation describes a band of inflammation in the superficial stroma (or dermis) that abuts the epithelium. When the inflammation breaches the epithelial-stromal junction, it is termed interface (or lichenoid-interface) inflammation. Stromal fibrosis and neovascularization are frequent findings in there can be epithelial lesions such as hyperplasia, pigmentation + - keratinization. These cases are typically recognized clinically and are unlikely to be biopsied.

**Spontaneous Chronic Corneal Epithelial Defects (SCCEDs)** mostly occur in dogs (Boxers) but are also seen in cats and horses. The lesion consists of separation of the epithelium and stroma results in erosion/ulceration. The flap of separated epithelium shows dysmaturation with loss of organized layering.
There may be thin, acellular, hyalinized band in the superficial stroma, less so in horses. See Murphy et al, IOVS, 2001; Bentley et al, IOVS, 2002; Gosling et al, VO, 2013; Hempstead JE et al VO, 2014.

**Corneal Sequestrum** is mostly a feline (Persian) disease also occurs in horses and dogs. Corneal sequestrum describes a well-circumscribed area of stromal devitalization, often with pigmentation. Some are not overtly pigmented. The areas bordered by inflammation and neovascularization and the overlying epithelium is typically ulcerated. Melanin, iron and porphyrins have been proposed and investigated as the source of the pigment with unconvincing results. An association of feline herpesvirus with sequestrum was proposed in some studies, not in others. See Stiles et al, AJVR 1997; Nassisse et al, AJVR 1998; Ejima et al, Science 1993; Featherstone et al, VO, 2004; Cullen et al, VO 2005; Newkirk et al, VO, 2011;

**Florida Keratopathy** is also known as Florida spots. Although recognize clinically there are no convincing histologic lesions. Of note, the material in the picture in G5 may be acid fast positive but it is not acid-fast bacteria. Sarfaty (ECVO 2008) suggests fire ants as a possible cause.

**Fungal Keratitis** is mostly seen in horses and less often in dogs, rarely cats. The lesion is typically neutrophilic +/- keratomalacia +/- stromal abscess, and typically ulcerative. Fungal hyphae may be numerous or rare; the number of organisms does not correspond to the severity of the lesion. Fungal hyphae are mostly in the deep stroma and may invade Descemet’s membrane. Aspergillus spp and Fusarium spp. are commonly cultured. Secondary opportunistic fungal colinization of injured corneas will be only superficial (surface colonization).

**Protozoal Keratitis/Conjunctivitis** has been described in dogs and is a rare condition. Clinically the lesion presents as a mass effect in the cornea +/- conjunctiva. Histologically the lesion consists of granulomatous to pyogranulomatous inflammation. In most cases have a history of preexisting ocular surface disease (typically KCS) and have been treated with immunomodulatory therapy (cyclosporine, tacrolimus +/- others). Cases where the organisms have been conclusively identified include cases with Amoeba, T. gondii, Leishmania (Beckwith-Cohen B et al. VO, 2016; Swinger RL et al. VO 2009), as well as as Sarcoctis sp. (PL).

**Eosinophilic Keratitis/Keratoconjunctivitis** as mostly seen in cats and horses. In cats it has been previously termed proliferative keratitis because of the proliferative gross appearance. As expected, eosinophils are a component of the inflammation. In many cases however, especially does that have been treated for extended periods of time eosinophils may not be the predominant cell type (lymphoplasmacytic). The role of infection such as Herpesvirus infection, Mycoplasma, Chlamydophila is unclear. Typical cases are unlikely to be biopsied.

**Acute Bullous Keratopathy** (corneal hydrops) is a disease of cats which consists of severe corneal edema following rupture of Descemet’s membrane. The cause is not known but an association with systemic anti-inflammatory/immunosuppressive drugs has been proposed. See Pierce ke et al. VO 2016 Epub; Pederson Sl et al. VO 2016 Epub.

**Malignant Catarrhal Fever** is a disease of bovidae caused by Alcelaphine herpesvirus 1 and ovine herpesvirus 2. Slightly infection causes endotheliitis. Such cases are unlikely to present specifically for ocular evaluation.

**Canine Adenovirus** lesions have been described with infection as well as some vaccines. The infection is caused by Adenovirus type 1 and 2. Histologically the lesion consists of endothelial necrosis +/- inclusions which results in severe corneal edema ("blue eye")

**Sclera**

**Staphyloma** describes a full or partial thickness scleral (or corneal) defect lined by protruding uvea. The lesion may be congenital or acquired. Some cases with staphyloma present as a suspicion of neoplasia (melanocytic neoplasia).

**Granulomatous Scleritis** has also been termed granulomatous-necrotizing scleritis. The term “necrotizing” causes confusion as it has been used in reference to cases with collagen degeneration/lysis or cases with neutrophils. This condition has an unclear pathogenesis, although an immune mediated process has been proposed. The lesion is characterized by inflammation predominantly centered on sclera. The inflammation can expand and the globe to cause uveitis and retinal detachment; however the bulk of the inflammation is always targeting the sclera. The inflammatory infiltrate consists of macrophages with
fewer lymphocytes and plasma cells. Neutrophils may be part of the infiltrate in some cases. The condition is often bilateral. There is no known association with immune-mediated diseases affecting other sites (except 1 dog). See Denk et al, VO, 2012; Day et al. VO, 2008.

**Scleral Mineralization/Metaplasia** is seen in a few species. In courses the lesion consists of mineralization and is an age associated change. In sheep the lesion consists of cartilage typically within the dorsal sclera. The significance of this change is unclear. In goats the lesion consists of cartilage and occasionally bone typically affecting the dorsal sclera or surrounding the optic nerve. In Fischer rats the lesion consists of bone or cartilage affecting the dorsal sclera it isn’t age associated change. See Smith et al, Vet Path, 201; Tusler CA et al. VO.
PATHOLOGY OF THE UVEA
Carol Naranjo Freixa

I. Congenital disease

- Iris hypoplasia: typically affects the stroma, which appears thin or bulging, in a patchy fashion. In Siamese cats may be accompanied with inherited congenital glaucoma.
- Aniridia: absence of iris tissue. Most are examples of severe hypoplasia, since some rudimentary iridal tissue can be recognized. May be associated with congenital cataract or dermoid.
- Persistent pupillary membranes (PPM): remnants of the vessels and mesenchyme that form the anterior tunica vasculosa lentis (TVL) or pupillary membrane, a sheet that overlies the anterior surface of the lens during development. PPMs are usually a delay in or a failure of normal regression of anterior TVL. May be associated with focal cataract or focal corneal opacity if the membranes are attached to the anterior lens capsule or corneal endothelium.

II. Degenerative, hyperplastic and age related changes

- Iris atrophy: seen in older animals, with progressive thinning of the iris. Iris atrophy can be seen also in trauma or chronic glaucoma.
- Cysts of the iridociliary epithelium
  - Sporadic iridal cysts: cysts of the posterior epithelium (less commonly, of the inner ciliary body epithelium). Seen in any species, but common in dogs, especially in Labrador o Golden retriever and Boston Terriers. They are typically considered non-significant clinically, but in some breeds there is an association with glaucoma (Golden retriever, see below, Great Dane and American Bulldog).
  - Pars plana cysts: seen in aged cats and horses. There is hyperplasia of the non-pigmented epithelium at the pars plana. They have no known clinical significance.

Multiple thin-walled iridociliary cysts in Golden retriever dogs (pigmentary and cystic glaucoma of Golden retrievers)

Formerly known as “Golden retriever uveitis” or “pigmentary uveitis”, this is a syndrome characterized by the presence of multiple cysts of iridociliary epithelium origin, which lead to glaucoma in Golden Retrievers, basically in the US. Occasionally, it has been reported in Great Danes in Europe and in other breeds. In Great Danes, though, the cysts appear poorly pigmented.

The disease is bilateral, although not symmetrical. There is no goniodysgenesis seen in these eyes, neither clinically no microscopically.

Grossly it may be difficult to locate the cysts in the fixed globe, but there may be evidence of pigment in the back of the cornea and anterior lens capsule.

To understand the microscopic appearance, one has to acknowledge that there are differences between the clinical and histologic presentation of the disease:

- Clinically, this dogs present with uveitis, with aqueous flare and pigment in the anterior chamber and adherent to the lens capsule or back of the cornea.
- Histologically there is sparse to no inflammation within the uvea. There are thin-walled cysts in the posterior chamber. The cysts, or part of them, are best found at the lens equator and/or anterior vitreal face. The cysts are lined by a single layer of cuboidal to squamous (flattened) epithelium, variably pigmented. The globes are typically heavily pigmented and there is free melanin in the iridocorneal angle.
A PAS stain may help highlight a delicate membrane supporting the cyst wall. There is also a collagenous matrix supporting the cysts, especially when they adhere to the lens capsule; this matrix is best identified by a blue staining with Masson’s trichrome.

Immunohistochemically, the cysts are positive for vimentin, NSE (Neuron-Specific Enolase) and S-100, which indicates they are of ciliary body epithelium origin. Some of the cysts are positive for cytokeratin.

The globes are typically removed for secondary glaucoma, the pathogenesis of which is uncertain. The physical obstruction cause by the iris, which is pushed forward by the cysts, the presence of free melanin in the iridocorneal angle, the preiridal fibrovascular membranes with peripheral anterior and/or posterior synechia or iris bombé that frequently develops all may contribute.

Recently, a paper described glaucoma associated with multiple uveal cysts with concurrent goniodysgenesis in American Bulldogs. These cases, besides showing goniodysgenesis, had a significant amount of inflammatory infiltrates histologically, pigment dispersion and prominent preiridal fibrovascular membrane formation. The authors hypothesize that cyst formation and pigment release from cyst rupture may contribute to chronic inflammation, which in turn, may trigger glaucoma in dogs already predisposed by the presence of glaucoma.

References


Canine ocular melanosis

Formerly known as “pigmentary glaucoma”, ocular melanosis occurs mainly in Cairn terriers, but other breeds can be affected too.

In Cairn Terriers, the disease is typically bilateral, but frequently asymmetrical. The disease courses with a progressive pigmentation of the uveal tissues, extending from the uvea to the sclera, typically at the limbus, eventually leading to glaucoma.

Grossly, the globes may show pigmentation of the sclera at the limbus and peripheral cornea. There is diffuse thickening and distortion of the uvea, which appears dark brown to black.

Histologically, the uveal contour is markedly distorted by the presence of round, heavily pigmented cells that circumferentially infiltrate the uvea, altering its normal profile, invading the iridocorneal angle and extending to the limbal sclera. Although the anterior segment is more heavily involved, the choroid, retina, sclera surrounding the optic nerve, optic nerve meninges and optic nerve itself may be affected. Some cases may have a lymphoplasmacytic anterior uveitis.
Immunohistochemical and ultrastructural studies reveal that most of the pigmented cells are melanocytes (HMB45 and MITF-positive, but negative for Melan A), with a small proportion melanophages (CD18-positive) admixed.

The main differential diagnoses are uveal melanocytic tumors. Uveal melanocytoma typically forms a discrete mass lesion, although it can also involve the iris and/or ciliary body with a diffuse pattern. The definitive distinction is made because melanocytoma shows two populations of cells; besides the round cells, there are variably pigmented spindle cells within the tumor. Distinction between ocular melanosis and malignant melanoma is typically not a problem, since malignant melanoma will show pleomorphic cells with atypical cytologic features and a high mitotic index. One has to keep in mind that there may be a melanocytoma or a malignant melanoma arising within ocular melanosis.

In breeds other than the Cairn terrier gross and histologic features are similar to what has been described. Breeds more commonly affected are the Boxer, Labrador and Dachshund, but it has been seen in many different breeds. In these breeds, the disease is most commonly unilateral, although bilateral cases are reported. Few studies in these breeds suggest that the abnormal pigmented cells are melanophages.

Prognosis is considered good for general health, although recently, a paper described intraorbital presence of histologically benign pigmented cells.

References


III. Uveitis and inflammation within the globe

- There is a difference in the clinical vs. histopathology definition of uveitis. Histologically, the presence of inflammatory cells within the uvea is necessary for this diagnosis.

- Terminology:
  - **Uveitis**: inflammation of the uvea
  - **Anterior uveitis/iridocyclitis**: inflammation of the iris and ciliary body
  - **Posterior uveitis/choroiditis**: inflammation of the choroid.
  - **Endophthalmitis**: inflammation of the uvea and inner chambers of the globe
  - **Panophthalmitis**: inflammation of all the tunics of the globe.

a. Non-infectious uveitis

**Feline lymphoplasmacytic uveitis**

This is one of the most common histologic diagnoses in feline non-neoplastic submissions, and one of the main causes of glaucoma in felines. The cause and pathogenesis of this entity is unknown, and it is unclear if it is an end-stage manifestation of multiple causes of intraocular inflammation in cats (Toxoplasma spp., Bartonella spp., FIV, FeLV, etc.) or an immune-mediated response to an unidentified stimulus.
Grossly, there may be lens subluxation or luxation, and the vitreous is typically liquefied.

Histologically, one can see lymphocytes and plasma cells, mainly in the anterior uvea, and frequently forming lymphoid follicle-like structures. There are lymphocytes found within the non-pigmented ciliary body epithelium. The anterior vitreous is condensed in eosinophilic strands and cell-poor membranes seen in the posterior aspect of the lens or anterior vitreal face. There may be granular hypereosinophilic protein behind the lens, presumed to be of lens origin, although a break in the capsule is not always identified (leakage). In some cases there is lymphoplasmacytic perivascular inflammation in the retina.

Glaucoma develops secondary to the presence of inflammatory cells in the iridocorneal angle, presence of preiridal fibrovascular membranes, lens luxation or anterior vitreous prolapse.

**Equine recurrent uveitis (ERU)**

ERU cases are received by the pathologist when the eyes are blind and painful because of secondary glaucoma. Not all cases of uveitis in horses are due to ERU, and there are important histologic features that help identify this entity.

Grossly, changes are non-specific, and may be subtle. The globe may be phthisical, there may be cataract, and a pale tan floccular membrane may be deposited over the ciliary processes.

Microscopically, the distinctive features include:

- A lymphoplasmacytic infiltrate in the uvea, which frequently invades the non-pigmented ciliary body epithelium and occasionally forms follicle-like structures.
- Eosinophilic linear inclusions within the cytoplasm of the non-pigmented ciliary body epithelial cells. Electron microscopy shows that these inclusions are crystalline arrays of protein. These inclusions are occasionally seen in the optic nerve head.
- Deposition of a cell-poor hyaline membrane over the inner surface of the ciliary body processes. This membrane stains positive with Congo red (typical of amyloid) and shows green birefringence when viewed under polarized light. This has recently been characterized as AA amyloid.

Other microscopic findings are not specific of ERU, but can also be seen: fibrovascular membranes (preiridal, anterior or posterior synechiae, retrocorneal membranes), cataract, retinal detachment and/or degeneration, optic nerve inflammation. Typically there are signs of glaucoma (inner retinal atrophy and optic nerve head gliosis and degeneration).

**References**


**Canine uveo-dermatologic syndrome or Vogt-Koyanagi-Harada-like syndrome**

Although Akitas and Northern dog breeds are overrepresented, this entity can be diagnosed in many breeds. The disease is bilateral and, typically very symmetrical, so that many times both eyes from the same animal are received at the same time, or within few days.

It is interesting to note that not all dogs show dermal disease by the time the eyes are affected, so in these cases eyes are key to the diagnosis.

Grossly, there may be thickening of the uvea, which can vary among cases (in some cases the iris and ciliary body are thickened, whereas in others the choroid is markedly thickened), but this is very symmetric between eyes of the same dog.

Histologically, there is a granulomatous inflammation diffusely involving the entire uvea (the choroid is always affected), with fewer lymphocytes and plasma cells. The macrophages contain abundant melanin
granules within their cytoplasm. Although there may be retinal detachment (and glaucoma, by the time the globes are enucleated), the rest of the tissues of the eye are relatively unaffected (vitreous, retina, aqueous, cornea, sclera).

**The spectrum of lens-associated uveitis**

There is a range of inflammatory responses associated with lens disease, the understanding of which is evolving as the morphologic features are described. Although the pathogenesis is not fully understood, hopefully the histopathologic syndromes associated with these responses will be helpful in elucidating the mechanisms.

Histologically we see various syndromes associated with lens disease:

1. **Phacolytic uveitis (lens-induced uveitis)**

   This inflammatory process is presumed to be the response to the chronic leakage of lens protein through an intact lens capsule. To make this diagnosis from the pathologist perspective, various criteria must be met:
   - Grossly and histologically, a mature, hypermature or intumescent cataract must be present. Typically, when enucleated, cataracts will be hypermature with lens capsule wrinkling and partial collapse.
   - Histologically, a mild to moderate lymphoplasmacytic infiltrate is present within the anterior uvea. Since this inflammatory response is highly non-specific, other features must be seen to diagnose phacolytic uveitis, and features of other diseases must be ruled out.
   - Typically, in enucleated globes, glaucoma will be established, and pre-iridal fibrovascular membranes, anterior and/or posterior synechiae and iris bombé may be present. Again, these changes are not specific.

2. **Phacoclastic uveitis**

   Lens capsule rupture leads to intraocular inflammation presumably resulting from the release of lens protein into the intraocular environment. Diverse patterns can be seen histologically:
   - **Sterile phacoclastic uveitis/bland phacophagocytic inflammation:**
     - Grossly, there may be haziness to the ocular media surrounding the lens, and lens size may be increased, decreased or normal.
     - Histologically, there is lens capsule rupture and a moderate to marked inflammatory response surrounding the liberated lens fibers composed of bland macrophages and multinucleated giant cells.
   - **Asymmetric uveitis – Non-diabetic:**
     - This occurs most commonly in small breed dogs, with Poodles overrepresented.
     - Females may be overrepresented.
     - Grossly, the features are that of endophthalmitis, with ocular media showing haziness to whitish exudates. Characteristically, there is a white tissue carpeting the inner surfaces of the globe.
     - Histologically, there is a severe pyogranulomatous inflammatory exudate, with a characteristic macrophage-rich carpet lining the inner aspect of the uvea, cornea, lens and/or retina.
     - There may be histologic features that suggest a penetrating injury, including lens capsule rupture, scleral defect, sepsis or a foreign body.
     - The importance of this histopathological pattern of inflammation is that, when it is seen in an enucleated globe, the fellow eye is at risk of developing uveitis/endophthalmitis with similar morphological features. The time lapse between the enucleation of the first eye and development of disease in the contralateral eye ranges from almost immediately to 4 years.
   - **Asymmetric uveitis – diabetic variant:**
     - Similar histopathological features as described for the non-diabetic variant, but usually both globes are affected symmetrically (and may be received at the same time by the pathologist), and miniature Schnauzers are overrepresented.
3. **Septic implantation syndrome**

This syndrome occurs in dogs and cats and consists of a phacocentric suppurative endophthalmitis with lens capsule rupture. The features of this disease include:

- A history of a traumatic event is reported in 39% of dogs and 20% of cats; when the nature of the traumatic event is known, a cat scratch is most frequently reported. Male cats are overrepresented.
- Duration of clinical signs prior to enucleation ranges from 1 week to 1 year.
- Grossly, a whitish to light tan exudate is seen surrounding the lens. There is broad posterior synechia and the posterior segment of the globe (excluding the anterior vitreous in some case) is devoid of inflammation.
- Histologically, there is lens capsule rupture and inflammation is found surrounding and within the lens and has a suppurative nature (lenticular abscess or “phakitis”), with evidence of cataractous changes. Bacteria are found within the lens in 65% of dogs and 70% of cats, with gram-positive cocci most frequently found (occasionally, fungi are present). Typically, infectious organisms are embedded within the lens substance and away from the inflammatory infiltrates.
- Corneal or scleral rupture is rarely sampled in vertically sectioned globes.

Although this syndrome may have been previously included within phacoclastic uveitis, the inflammatory response in these cases suggests that the trigger is the infectious organisms implanted in the lens, and not the released lens proteins. This syndrome also has different morphologic features than fulminant septic endophthalmitides with foreign body and/or infectious organisms present.

4. **Encephalitozoon cuniculi** *(phacoclastic uveitis in rabbits)*

This is a particular case of lens capsule rupture in which *E. cuniculi* leads to cataract formation and lens capsule rupture with associated inflammation. It is seen in rabbits and Dwarf rabbits are overrepresented. It is believed that vertical transmission occurs, with lens infection occurring during embryonal development and inflammation bursting when the capsule is ruptured.

Grossly, there is a white nodule adhered to the anterior lens where the capsule is ruptured, extending into the anterior uvea and anterior chamber.

Histologically, there is a granulomatous to pyogranulomatous inflammation in the area of lens capsule rupture, within the lens and extending into the posterior and anterior chamber. The inflammation is highly localized to these areas. *E. cuniculi* is frequently not found, although special stains (Giemsa, Gram – positive – or Ziehl Neelsen stains) can be used to find them.

*E. cuniculi* has also been detected within the cataractous lenses of cats.

**References**


b. **Infectious uveitis/endophthalmitis/panophthalmitis**

Many infectious and parasitic diseases can have ocular manifestations and, relatively often, these will be the presenting complaint. Not all these diseases have specific histopathologic features and, for example, intraocular disease associated with rickettsiae and ehrlichiae, *Borrelia* spp., *Bartonella* spp., *Brucella* spp. and *Leptospira* spp. show non-specific inflammation and hemorrhage. Hence, they may be underdiagnosed in a pathology collection.

Other infectious organisms cause particular inflammatory changes or are associated with the presence of the organism within the lesion, and hence, can be diagnosed in a histological section.
**Suppurative endophthalmitis/panophthalmitis**

This is the most common consequence in globes that have suffered a penetrating injury.

In dogs, brachycephalic, and particularly Shih-tzus, are overrepresented, although large-breed dogs with outdoor lifestyles are also frequently affected.

Grossly, there are prominent light tan to yellow exudates are noted throughout the globe. Lens may be displaced or ruptured. The inflammation may extend into the fibrous tunic.

Histologically, there are myriad neutrophils, mostly degenerate, within all chambers and tissues of the globe, and may extend into the orbital tissues. There is typically lens capsule rupture. The retina may be necrotic and embedded within the suppurative exudates. Bacterial organisms may be found, most commonly in the vitreous. There may be fragments of foreign body, most commonly plant material.

The site of penetration may be sampled, and it can be in the cornea or sclera.

- **Corneal perforation**: it is difficult to impossible to discern histologically if a suppurative endophthalmitis is the result of a penetrating injury through the cornea or results from a progressive keratitis that leads to perforation.

Scleral perforation: a perforation that can be localized to the superior aspect suggests an injury related to an attack or plant material. If the perforation can be localized to the inferior aspect, an oral foreign body or plant material from below is suspected. In some cases, a visit to the dentist is reported prior to development of ophthalmic signs. The point of scleral penetration is not frequently sampled.

**Feline infectious peritonitis**

Caused by a mutated feline coronavirus, this disease is most commonly, but not exclusively, encountered in cats and other felines younger than 3 years.

Ocular involvement is most commonly seen in the non-effusive or “dry” form of the disease (vs. the “wet”, effusive form), which is characterized by a generalized pyogranulomatous inflammation in various organs, including the kidney, liver, lung, brain, etc. Occasionally, there will be involvement of the brain and eyes without any other organs being involved.

Grossly, the eye will show translucent to opaque media, and the aqueous and vitreous may be solidified due to the high protein content of the exudate present.

Histologically, it can be challenging to make the diagnosis, especially if the eye is submitted as a biopsy. Some of the features that can be used to make the diagnosis include:

- Mixed inflammation in the uvea (iris, ciliary body and choroid), retina and optic nerve and its meninges.
- Areas of plasma cell-rich inflammation.
- Macrophages may predominate in some areas, and these may show some atypical features (cleaved nuclei, prominent nucleoli, etc).
- Neutrophils may predominate regionally.
- Vasculitis is very helpful in making the diagnosis, but not always found.

**Mycotic uveitis**

Many of these diseases are regionally restricted so their diagnosis depends on the area where the animal comes from or has traveled to. In many of these diseases, the posterior segment is mostly involved, so that a pyogranulomatous chorioretinitis will be most commonly diagnosed. PAS or silver stains may help in the recognition of these fungi.
**Blastomycosis (Blastomyces dermatitidis)**

Blastomycosis is a systemic disease most commonly seen in dogs than in cats. It is endemic in the Mississippi, Ohio and Missouri River valleys, although it occurs in highly localized hot beds of infection within these areas.

Animals are infected by inhaling the spores from the soil or by direct implantation into an open wound. The lung is the most commonly affected organ, although skin, eye, lymph nodes and bone are also frequently involved.

Grossly, there is a light tan viscous exudate within the choroid and retina, extending into the subretinal space and vitreous, with variable involvement of the anterior segment.

Histologically, the inflammation is pyogranulomatous, and centered on the posterior segment, forming nodular or diffuse lesions, but with discrete pyogranulomas being rarely found. Yeasts can be seen with routine stains or, if sparse, with special stains (PAS or silver stains). These organisms are found, 10-15 microns in diameter with a refractile wall and granular protoplasm in the center. They show broad-based budding and frequently they are surrounded by Splendore-Hoeppli material. Hence, the typical diagnosis is pyogranulomatous chorioretinitis or endophthalmitis.

**Cryptococcosis (Cryptococcus neoformans)**

Much more frequent in cats than in dogs; in cats it is the most common disseminated mycotic infection. This yeast has a worldwide distribution.

Infection is by inhalation of spores from infectious soil, especially in areas where pigeon droppings are found.

The respiratory tract, central nervous system, lymph nodes, skin and eyes are the most commonly affected sites.

Grossly, a pyogranulomatous chorioretinitis and endophthalmitis is found, which can have a gelatinous appearance.

Histologically, a granulomatous to pyogranulomatous chorioretinitis, evolving to endophthalmitis, is frequently found, with what has been called a “soap bubble” appearance. The orbit may be affected. Occasionally the inflammatory infiltrate is minimal, and organisms abound (it is believed there is an inverse relationship between the severity of inflammation and the amount of organisms seen). The yeast is 5-8 microns in diameter and has a thick (1-30 microns) polysaccharide capsule that does not stain with routine stains. Alcian blue and/or PAS or mucicarmine highlight that capsule. Narrow-based budding can occasionally be seen. This yeast can form short pseudohyphae and budding is not seen.

**Histoplasmosis (Histoplasma capsulatum)**

Histoplasmosis in the eye is more commonly diagnosed in cats than in dogs. This fungus has a worldwide distribution, but it is frequently found in the Mississippi and Ohio River valleys.

The fungus is found as spores in the soil, especially if rich in bird or bat droppings.

Lesions are most commonly found in the lungs, intestine, lymph nodes, skeleton, skin and eyes.

Histologically, the eyes display a pyogranulomatous chorioretinitis, but any structure may be affected. The organism is 3-5 microns, found within the cytoplasm of macrophages, and can be stained with PAS or silver stains. Budding is not seen. Organisms may be few or nonexistent in the eye.

In cats there is a manifestation similar to the “Presumed ocular histoplasmosis syndrome” of humans, where organisms are few to not found and a thick spindle cell layer is found internal to the choroid and there is proliferation of RPE.

**Coccidioidomycosis (Coccidioides immitis)**

Coccidioidomycosis is more commonly diagnosed in dogs than in cats. It is typical of the South-West regions of the US and other parts of Central and South America. The infection is acquired by inhalation of
spores from the desert soil. Immunosuppressed and outdoor animals show higher risk of disseminated disease.

Most commonly affected tissues include lungs, bones and eyes.

Histologically, there is a pyogranulomatous chorioretinitis, which can evolve to endophthalmitis. The yeast is usually seen in low numbers, but its large size makes it easily recognizable (25-85 microns in diameter). The spherules have a thick refractile outer wall with numerous endospores inside.

**Aspergillosis (Aspergillus spp.)**

This is a systemic disease of dogs that carries a poor prognosis, although the eye may be the first site to be detected. Aspergillus spp. has a world-wide distribution. German Shepherd are overrepresented, and an aberrant immune response is thought to play a role in the disease.

Grossly, there is an endophthalmitis that is mostly centered on the vitreous, so a light tan thick exudate is noted in the vitreous, especially adjacent to the retina.

Histologically, there is a pyogranulomatous vitreitis to endophthalmitis with numerous hyphae typical of *Aspergillus* spp. noted, especially at the vitreous/retina interface. Organisms may be noted within the lens capsule and there may be lens capsule rupture.

**Algal infections – Protothecosis (Prototheca zopfii)**

Infection is rare, but can occasionally involve the eyes in dogs. Prototheca spp. has a world-wide distribution. Ocular disease is typically bilateral and occurs with systemic involvement, in which gastrointestinal signs predominate. Prognosis is poor.

Clinically, ocular signs are non-specific, with retinal detachment and blindness being the most common presenting signs.

Grossly, there is complete retinal detachment, with a light tan exudate surrounding the detached retina and extending into the vitreous and subretinal space.

Histologically, there is a granulomatous to pyogranulomatous endophthalmitis centered on the detached retina and inner choroid. Algal organisms are found intrahistiocytic and extracellularly, and are round to ovoid, 5-10 microns in diameter with a refractile cell wall and sporangiospores that stain poorly with routine stains. A PAS may be used to highlight the organisms.

**Protozoal infections**

**Leishmaniosis**

Leishmaniosis is a zoonotic disease caused by *Leishmania* spp. The disease is highly prevalent in the Mediterranean shore and Central America, but in the past years it has spread north in Europe and has been diagnosed in the south-west USA.

Ocular disease in dogs with leishmaniosis is highly prevalent, and can be found in approximately 30% of dogs. The anterior uvea is most commonly affected than the choroid, which is different from other infectious uveitides.

Grossly, an exudative uveitis is seen, with diffuse thickening of the anterior uvea, and proteinaceous exudates in the chambers and vitreous are variably present.

Histologically, a granulomatous infiltrate, which is most frequently diffuse but occasionally may form discrete granulomas, is found in the iris and ciliary body; only rarely is the choroid affected. Variable numbers of neutrophils, lymphocytes and plasma cells are also found. *Leishmania* amastigotes are identified in the cytoplasm of macrophages, but immunohistochemistry may be needed, since numbers may be low. Besides involving the uvea, leishmaniosis can cause blepharitis, primary conjunctivitis, episcleritis/scleritis, keratitis and lacrimal adenitis.
Leishmaniosis can occur in cats, which can have ocular involvement, but is a disease typical of immunocompromised animals.

References


PATHOLOGY OF THE LENS
Carol Naranjo Freixa

I. Congenital conditions

One has to remember that the lens is formed by surface ectoderm. Many of these abnormalities are typically seen in association with abnormalities of the anterior segment of the globe, although occasionally these can be seen in isolation.

- **Aphakia**: congenital absence of the lens (extremely rare).
- **Microphakia**: abnormally small lens.
- **Lens coloboma**: defect at the lens equator (notch) resulting in an abnormally shaped lens. Caused by a focal lack of zonular tension at the lens equator.
- **Spherophakia**: abnormally shaped lens, which is rounded. Caused by a diffuse lack of zonular tension at the lens equator.
- **Posterior lenticonus/lentiglobus**: axial elongation and increased curvature of the posterior lens, which has a conical or spherical protrusion at its posterior aspect.

**Congenital cataract**

Some morphologic features can be seen in congenital cataract:

- Abnormal position of the nucleus or lysis of the nucleus.
- Dysplastic changes in the lens capsule such as duplication or wrinkling.
- Posterior migration of lens epithelial cells.
- Associated vascular anomalies of the fetal vasculature.

II. Cataract

A cataract is any opacification of the lens. Similar to the clinical situation, a cataract can be categorized by etiology, extension of lens involvement or location within the lens. For smaller cataracts, the extent of involvement is best assessed clinically, since in a histologic section only a section through the lens is examined and not its entirety. And, in general, the correlation of clinical vs pathological diagnosis of cataract can be suboptimal, because of this two-dimensional observation histologically and because of the multiple artifacts associated with lens processing.

There are multiple etiologies described for cataracts, including inherited, senile, traumatic, dietary, diabetic, toxic or secondary to a variety of intraocular diseases, including inflammation (uveitis/endophthalmitis), retinal degeneration, glaucoma or neoplasia.

According to the location within the lens, cataracts can be classified histologically:

- **Subcapsular**:
  - **Anterior**: one can see proliferation of the lens epithelium and/or lens epithelium fibrous metaplasia. These cells can be surrounded by collagen membranes, which can be the only thing left when the spindle cells are lost. Mineralization of these areas can also be seen.
  - **Posterior**: migration of the lens epithelium to carpet the inner aspect of the posterior lens capsule with any of the changes described for anterior subcapsular cataracts.

- **Cortical**:
  - **Early/incipient**: not always detected histologically, mild swelling of lens fibers is typically seen.
  - **Mature**:
    - Bladder cells: swollen and rounded lens fibers that still contain a nucleus.
    - Morgagnian globules: swollen and rounded lens fibers without a nucleus.
  - **Intumescent**: a type of cataract in which there is lens swelling (increased axial thickness) with abundant morgagnian globules present circumferentially in the cortex.
  - **Hypermature**:
- Lens swelling (increased axial thickness)
- Mineralization: mineral deposits in the lens cortex.
- Liquefaction of part or the entire cortex.
- Lens capsule wrinkling
  - **Morgagnian**: subtype of hypermature cataract that occurs when the lens cortex is completely liquefied and only the nucleus remains within a wrinkled to partially collapsed capsule. The axial thickness of the lens is decreased.
- **Nuclear**: there is protein degeneration in the nucleus but most commonly changes cannot be detected histologically.

**Special types of cataract**

- **Diabetic**: typically intumescent cataracts with swelling of the lens (increase in its axial thickness) and prominent morgagnian globules circumferentially around the cortex.
- **Traumatic**: there are various changes seen in the lens after a traumatic event, from lens capsule rupture with intralenticular inflammation in penetrating trauma to the changes seen in blunt trauma:
  - **Cataract**: anterior or posterior subcapsular cataract or cortical cataract.
  - **Lens capsule rupture**: to distinguish pathological from artifactual lens capsule rupture, various features can be searched for, from most to least reliable:
    - Presence of intralenticular cells: macrophages, neutrophils, erythrocytes, fibroblasts or blood vessels within the lens capsule.
    - Changes at the severed margins of the lens capsule: presence of proliferating lens epithelial cells entrapping the edges of the capsule or spindle cells associated with synchiae or frayed capsule edges with inflammatory cells.
    - Scrolling of the edges of lens capsule.
  - **Inflammation associated with the lens capsule rupture (phacoclastic uveitis)**: there will be a bland granulomatous foreign body reaction surrounding the liberated lens fibers. This is typically accompanied by a lymphoplasmacytic uveitis.
  - **Spindle cell metaplasia, proliferation and migration of lens epithelium**: these metaplastic cells express vimentin and smooth muscle actin (similar to myofibroblasts), so they will have contractile ability. These cells can also produce basement membranes reminiscent of lens capsule. These cells have the tendency to migrate and line the intraocular structures (outer surface of lens capsule, inner surfaces of the iris and ciliary body, surfaces of the detached retina and the inner choroid).
  - **Lens luxation**: the trauma has to be severe to cause lens luxation.

### III. Lens luxation

Lens luxation occurs when there is separation of the lens from its zonular ligament attachment. The lens may subluxate (partial dislocation) or can move anteriorly or posteriorly into anterior chamber or vitreous, respectively.

Lens luxation may be primary (zonular ligament dysplasia, Marfan syndrome) or secondary (uveitis, trauma, glaucoma, hypermature cataract, senile).

Lens luxation may be tricky to diagnose in a pathology setting, and certainly clinical assessment is the most accurate way to diagnose it. Lens may luxate during trimming and during histologic processing of the globe. Pathologist’s ways to diagnose luxation include, from most to least accurate:

- Observation at the time of trimming the globe. Besides lens displacement there may be vitreous liquefaction.
- Distorted angle of the iris leaflet (“dogleg”), which is bent posteriorly.
- Attenuation of the corneal endothelium, especially axially.
- Atrophy of the ciliary processes.
- Position of the lens on the histo slide is a very poor way to assess lens luxation.

Other histologic, non-specific, changes that may be seen in eyes with lens luxation include:
- Consequences of the attenuation and loss of endothelial cells: Corneal edema and possibly bullous keratopathy and corneal ulceration, queratitis or collagenolysis.
- Retrocorneal membranes.
- Retinal detachment.
- Glaucoma: various mechanisms have been proposed:
  - Entrapment of the lens in the anterior chamber (angle closure and/or pupillary block).
  - PIFM.
  - Posterior synechiae with iris bombé (pupillary block).
  - Anterior vitreous prolapse (pupillary block).
  - Inflammation within the anterior segment of the globe (unstable lens → low grade trauma to the posterior iris and ciliary body → release of melanin from these structures → inflammation → glaucoma).

Zonular ligament dysplasia (ZLD)

This is the morphologic/histologic change seen in certain dog breeds with primary lens luxation, including Terrier breeds (especially the Jack Russell terriers) and other non-terrier breeds, such as the Chinese crested dog, Shar Pei and Australian blue Heelers (Morris and Dubielzig, 2005). Dogs with lens luxation and whose eyes are sent for histopathology and that show this microscopic abnormality are typically younger than other dogs with lens luxation.

Zonular fibers are composed of microfibrils, whose primary components are the glycoproteins fibrillin-1 (not collagen). Fibrillins are also found in the elastin molecule.

Microscopically, in the previously mentioned breeds, a thick lamellar eosinophilic membrane showing a cross-hatching pattern is found carpeting the inner aspect of the ciliary processes, adherent to the non-pigmented ciliary body epithelium. This membrane is seen intermittently, so careful search throughout the section is warranted.

Besides this characteristic microscopic appearance on routine stains, a combination of special stains can be used to assess this protein membrane:

- Normal zonular fibers are PAS-positive and stain positive with Verhoeff’s elastin stain, whereas with Masson’s trichrome, most of the fibers stain red (indicating there is no collagen present).
- Zonular fibers in dogs with ZLD still stain magenta with PAS, but show a blue staining with Masson’s trichrome (indicating there is collagen within the fibers) and lack black staining with Verhoeff’s stain (indicating there is no elastin).

Finding these changes in an eye that has been enucleated or eviscerated due to lens luxation should be considered a risk factor for primary lens luxation (especially important for the second eye).

A recent study (Alario et al., 2013) has suggested that in dogs with primary lens luxation and secondary glaucoma there is a strong correlation with presence of inflammation and pigmentary changes in the anterior segment (base of the iris and ciliary processes and uveal trabecular meshwork). This inflammation was mostly mononuclear, although neutrophils can also be seen. There is also melanophage deposition and pigment dispersion, all of which can contribute to the development of glaucoma.

This same study identified hypertrophy and hyperplasia of the posterior iris epithelium, most prominently in the mid-iris. In contrast, the pupillary portion of the posterior iris epithelium was thinner, with epithelial cell loss and replacement by pigment-incorporating fibrocytes.

References


Pathology of the Vitreous

Phil Labelle

General Considerations The vitreous is difficult to evaluate histologically. Liquefied vitreous may not or only partially survive processing.

Asteroid Hyalosis is mostly seen in dogs but can be seen in otherspecies. It represents one form of vitreal degeneration. It can be an age related or secondary to disease. It is often seen with neoplasms (iridociliary neoplasms, melanocytic neoplasms). The asteroid bodies consists of lipid-calcium complexes. The exact composition of asteroid bodies varies between studies (Wang et al, Mol Vis 2006; Kador et al, Eye, 2008; Labruyere et al, Vet Radiol Ultrasound 2008)

Vitreal Hemorrhage can occur as a consequence of damage to normal vessels (trauma, uveitis), immature vessels (fibrovascular membranes, neoplasia), or abnormal vessels (hypertension, PHPV/PTVL). Blood disorders (coagulopathies) are a less common cause of vitreal hemorrhage. The response to vitreal hemorrhage is unique and differs from that in other organs. The purpose of this measured response may be to maintain ocular immune privilege and ocular function by avoiding a marked response leading to granulation tissue formation. The response is characterized by rapid fibrin clot and slow fibrinolysis; hemolysis of red blood cells; limited cell infiltration low turnover of macrophages, few hemosiderophages.

Canine Ocular Gliovascular Syndrome is a condition characterized by intraocular hemorrhage, retinal detachment fibrovascular proliferation and glaucoma. Histologically there are aggregates of glial (GFAP positive) cells in the vitreous. There is also neovascular proliferation extending into the vitreous from the retina or optic nerve head with hyalin collagen. See Treadwell et al, VO 2015, Naranjo et al, ACVO 2006; Zeiss et al, VO, 2004.

Shih Tzu Vitreoretinopathy is a condition characterized by retinal detachment, retinal tears, fibrovascular proliferation and glaucoma. Histologically there is cell poor collagen deposition in the vitreous. Some of the cells in the vitreous are myofibroblasts (contraction?). See Papaioannou et al, J Comp Path 2013.
Pathology of the Retina and Optic Nerve

Phil Labelle

General Considerations: Glaucoma related changes discussed elsewhere.

**Retinal detachment** is a frequent finding in enucleated globes. Potential causes include trauma, inflammation, neoplasia, vasculopathies, traction, congenital lesions, retinal degeneration, glaucoma/buphthalmos. In one database (PL database, 100 cases) the causes of canine retinal detachment diagnosed histologically were: Neoplasia 21%; Inflammation/trauma 34%; Vasculopathies/systemic hypertension 9%; Undetermined 36%. Case is classified as inflammation/trauma included: 4 VKH, 3 granulomatous scleritis and 2 diabetic cataract/granulomatous endophthalmitis. 13 cases are endophthalmitis from penetrating trauma, fungal, asymmetric uveitis. 12 cases had findings/ history of trauma w/o endophthalmitis.23/36 undetermined cases had severe intraocular hemorrhage and fibrovascular proliferation with the retinal detachment (“idiopathic retinal detachment”). In the other 13 cases, the significance of the retinal detachment was unclear. In the same database (PL database 50 cases), the causes of Feline retinal detachment diagnosed histologically were: Neoplasia 50%; Inflammation/trauma 32%; Vasculopathies/systemic hypertension 6%; Undetermined 12%. the cases of inflammation/trauma included: 18% with findings/ history of trauma where inflammation was not a significant component and 14% with severe inflammation (penetrating trauma, fungal, etc).

The histologic findings that support a diagnosis of retinal attachment include material in the subretinal space (hemorrhage, inflammation, proteinaceous, vitreous), hypertrophy +/- hyperplasia of the retinal pigment epithelium, outer retinal atrophy, and retinal tears. Retinal tears can be identified by the presence of interrupted retinal segments with rounded edges with gliosis. RPE hypertrophy/”tomb-stoning” is often described as the hallmark of retinal detachment. Its presence is diagnostic but its absence does not exclude retinal detachment. The change may be absent in cases with subretinal material or very chronic retinal detachment. Of note, while inner retinal atrophy suggests glaucoma, retinal detachment prior to the development of glaucoma can have a sparring effect on the inner retina (ie clinical glaucoma without inner retinal atrophy)

It is not possible to accurately determine the age of the RD. Proliferative and hypertrophic changes to the RPE can be detected 24h after RD (1-3 days), photoreceptor atrophy/degeneration after 1-3 days. Early changes to the ONL are present within a few days. More severe atrophy implies chronicity (few days-1 week or more). In some cases RPE hypertrophy may decrease with chronic RD. The severity, cause, nature of subretinal material, etc. all likely affect the development of retinal changes. See Anderson IOVS 1981; Anderson IOVS 1983

**Progressive Retinal Atrophy** is mostly seen in dogs but also in cats. It is likely that in many conditions with different pathogenesis are included under the PRA name. These conditions are inherited or presumed inherited. Clinical evaluation required for the diagnosis and the condition is typically seen in globes removed for other diseases. Histologic evaluation has limited value; the molecular work done in numerous breeds does not translate the specific histologic findings. Histologically the lesions are recognized as outer retinal atrophy which will initially be focal-multifocal. Ganglion cells may “drop” in the blended nuclear layers. Eventually the lesion progresses to full-thickness atrophy. Secondary findings may include retinal detachment and cataract. From a histologic standpoint, SARDS, Retinal detachment, toxic/nutritional retinal injury maybe considered as differential diagnoses. PRA can be suggested as a dx when there is outer retinal atrophy, especially if early and multifocal; once there is full thickness atrophy, there are no specific features to suggest SARDS. Furthermore cases with retinal detachment will not have features that allow a histologic dx of preceding PRA.

**Sudden Acquired Retinal Degeneration Syndrome** is a canine disease. Clinical evaluation required for the diagnosis. The lesion is usually only seen in globes removed for other diseases. As with PRA histologic evaluation has limited value. Most cases present with a previous clinical diagnosis of SARDS. From a histologic standpoint PRA, Retinal detachment, toxic/nutritional retinal injury are differential diagnoses. Histologically the lesions are recognized outer retinal atrophy that is diffuse in early stages. The lesion progresses to full-thickness atrophy. Lymphoplasmacytic inflammation has been described in some studies, but it is histologically minimal. Once there is full thickness atrophy, there are no specific features to suggest SARDS. Histologic evaluation offers no insight on the possible association with
systemic/hormonal disease. See Keller et al. VO 2006; Carter et al. JAAHA 2009; Stuckey et al JAVMA 2013; Komaromy AM et al, VO 2015 [Epub]; Heller AR et al, VO 2016 [Epub].

**Fluoroquinolone-Induced Retinal Toxicity** is an acute condition seen in cats. It is rare and cases are unlikely to be examined histologically. The lesions do not occur at recommended doses in normal cats. This last lesion consists of photoreceptor loss. See Gelatt KN et al, VO 2001; Weibe V et al, JAVMA 2002; Ramirez Pharmacogenet Genomics 2011; Rampal S et al Hum Exp Toxicol 2008 (ofloxacin rabbits).

**Systemic Hypertension** can cause vascular lesions that can be recognized histologically. The lesions are usually bilateral, but may be asymmetrical. The lesions can be found in the vessels of the retina, choroid, and rarely iris. The arterioles have hyalin thickened walls and narrowed lumen (“fibrinoid necrosis”). Special staining with PAS can help visualize the vascular changes. Most cases diagnosed histologically also present with retinal detachment, hemorrhage and necrosis. The retinal injury leads to intraocular hemorrhage, fibrovascular proliferation, and glaucoma.

**Diabetic Retinopathy** is rarely diagnosed in clinical cases, but represents a potential cause of ocular disease. The lesion consists of loss of pericytes with thickening of the basement membrane of vessels. There may be retinal hemorrhages. Glycemic control may protect against ganglion cell loss in dogs. The proliferative component in humans is not seen in dogs. See Herring IP et al, JVIM 2014; Howell SJ et al, Mol Vis 2013.

**Retinal Inflammation:** Infectious diseases that target the retina are rare and often cause more significant lesions elsewhere. Infectious retinitis may be caused by infection with canine distemper, Toxocara canis, Haemophilus somnus, Bovine Viral Diarrhea, Toxoplasma gondii, West Nile Virus; usually as part of systemic disease. Extension of uveitis/endophthalmitis (trauma, bacterial, fungal, Prototheca, etc) is a common cause of retinitis. Perivascular lymphoplasmacytic retinitis can be seen with lymphoplasmacytic uveitis; the retinal lesions does not provide insight on a possible cause.

**Tapetal Sparing** occurs in both bases but is most frequent and most prominent in dogs. Tapetal sparing describes the fact that the dorsal retina tends to be less affected by glaucomatous change. The presence of a tapetum is not necessary as the changes also seen in atapetal globes. The change likely represents increased susceptibility of the ventral retina rather than increased resistance of the dorsal/tapetal retina. See Beamer G et al. Vet Clin North Am Small Anim Pract 2015.

**Retrograde atrophy** (“dieback”) describes the loss of ganglion cells secondary to optic nerve injury. It is most commonly seen with canine orbital meningiomas. Its significance lies in that it must be differentiated from inner retinal atrophy/glaucoma.

**Peripheral Retinal Cysts** and also termed peripheral cystoid degeneration. It is a age-related change in dogs. Pathologic examination of globes does not support the suggestion (G4) that these cysts may be clinically significant as part of retinal detachment. Similar cystic degeneration is seen in cats and horses in the ciliary pars plana (not the retina).

**Optic nerve**

**General Considerations:** Glaucoma related changes discussed elsewhere

**Trauma** is a common cause of optic nerve injury. It is often seen with proptosis. In those instances the lesions consist of necrosis/malacia, hemorrhage, atrophy, gliosis and fibrosis with chronicity. In the horses the lesion includes necrosis with infiltration of Gitter cells. Gitter cells may extend in the vitreous (exudative optic neuropathy). Atrophy and fibrosis are features of chronic injury.

**Ischemic Optic Neuropathy** is a condition of horses that follows acute hypovolemia. It can be seen with surgical occlusion of ext/int carotid arteries (guttural pouch mycosis). Histologically the lesion consists of edema and hemorrhage in chronic cases may include atrophy and fibrosis. There can be retinal hemorrhage and degeneration.

**Optic Neuritis** is mostly a canine disease in most cases are idiopathic. Canine distemper, granulomatous meningoencephalitis and tick-borne encephalitis virus are possible infectious causes. These cases are unlikely to be examined histologically pre-mortem, or at all in the case of idiopathic optic neuritis.
Proliferative Optic Neuropathy is a condition of older horses. It is a benign lesion consisting of the proliferation of macrophages and glial cells. See Saunders Vet path 1972.

**Schnabel’s Atrophy** is seen in dogs with glaucoma and consists of extension of the vitreous in the optic nerve forming cavitations.

“**Optic neuroma**” is also seen and often associated with glaucoma. The lesion consists of nodular proliferation of peripheral nerve adjacent to the optic nerve. The lesions are typically not recognize clinically and are of unclear significance.
The Glaucomas

Chris Reilly

Abbreviations Guide
• GD – Goniodysgenesis
• PIFM – Preiridal fibrovascular membrane
• PAS – Peripheral anterior synechia
• RD – Retinal detachment
• TM – Trabecular meshwork
• ICA – Iridocorneal angle
• AC – anterior chamber; PC – posterior chamber
• IOP – Intraocular pressure
• ON/ONH – Optic nerve/optic nerve head

Definition
• Characteristic optic neuropathy, most often due to elevated IOP
  – Normal tension much more common in humans
• Many causes, most are secondary
  – Pathogenesis of “primary” glaucoma in dogs enigmatic

Histologic Approach
• Thorough clinical history key
  – Clinical assessment often more precise
  – Signalment to increase suspicion of breed-related disease
  – Assessment of 1º v. 2º changes
• Lack of history significant source of histologic discrepancy (when it occurs)

Histologic Approach
• ALWAYS examine subgross
  – Best overall look at globe
• BUPHTHALMIA – oft overlooked in reports
• Masses, RD, lens lux, ruptures, exudates, hemorrhage
• ICA and retinal changes in severe cases

Key Low Power Features
• Buphthalmia – Dogs/cats > horses > primates, others?
  - young animals > older animals
• Sharp (or curved!) ICA
• Compressed/collapsed, inapparent TM
• Obvious retinal atrophy (dogs >> others)
• Optic nerve head flattening/cupping

Glaucoma progression
• Studies in dogs have demonstrated fairly orderly sequence of events
• Progressive lesions in ICA/TM, retina, and optic nerve
• Superficial keratitis
  – Haab’s striae
• Lens luxation (1º v. 2º)
• Ciliary body atrophy
  – Chronic cases (2º to lens lux, too!)
• Beware the peripheral retina – can atrophy with age
• End stage phthisis

So, you’ve “diagnosed” glaucoma…..
• Now the search for a cause…..
• Often fairly obvious at subgross
  – Neoplasia
  – Thick PIFMs/iris bómbé/neovascular
Species Differences

Dog
- Most varied causes of glaucoma
  - Selection bias? – most submissions
- In most spontaneous settings, retinal atrophy is rapid and segmentally severe
- Tapetal retina = inner retinal atrophy
  - Like other species
- Non-tapetal (dependent) retina often worst affected – “tapetal sparing”
  - Less often in lens luxation?

COPLOW Distribution - Dogs
- Neoplasia
- Goniodysgenesis – primary angle closure glaucoma
  - POAG?
- Unknown
- Neovascular
- Uveitis
- Lens luxation
- Hemorrhage
- RD/PIFM (neovascular)
- Post-operative
- Phacochlastic
- Phacolytic
- Melanosis
- Iridociliary cysts
- Less than 1 yo
- VKH
- Anterior segment collapse

Goniodysgenesis
Malformation of the iridocorneal angle
  - Failure of regression of ICA mesoderm
  - Aka mesodermal dysgenesis, PCAG, pectinate ligament dysplasia, others?
- Congenital/developmental defect WITHOUT congenital glaucoma
- Affects many breeds, as well as mixed breeds and ‘unexpecteds’

COPLOW distribution (N=233)
- Cocker – 84
- Bassett hound - 21
- Chow – 11
- Mixed – 10
- Labrador – 8
- Samoyed – 8
- Shih Tzu – 7
- Husky – 7
- Springer Spaniel – 6
- Unknown – 6
- Akita – 4
- Cockapoo – 4
- German Shepherd – 4
- Dachshund – 3
- Maltese – 3
- Shar pei – 3
- Beagle – 2
- Bichon – 2
- Briard – 2
- Collie – 2
- Dalmation – 2
• Lhasa apso – 2
• Malamute – 2
• Others - 30

Canine goniodysgenesis

• Only small % of dogs with GD → glaucoma
• The greater % of ICA affected, the higher the chances of glaucoma
• Think of like clock face
• Fellow eye at risk of glaucoma after 1st diagnosis
• Sudden onset of painful, red, often blind eye with high IOP
• Typically middle aged, female (2:1)
• Poor long term prognosis with most (all?) treatments
• Often leads to enucleation
  – Often more rapid decision in 2nd eye

Histopathologic observations

• Evidence of lens iris contact and loss of iris pigment epithelium
• Differential accumulation of pigment in the TM
  – Present to some degree at all timepoints
• Acute and chronic inflammation in the TM (and limbus), depending on stage
  – Neuts > in acute, LP in all stages
• Gradual TM atrophy/remodeling

• Preiridal membranes frequently present – role unknown

Canine POAG

• Heritable Glaucoma in Beagles is the only known animal model of primary open angle glaucoma.
• Inherited as an autosomal recessive trait
• Two groups of affected dogs:
  – Group 1. High IOP at young age
    (~ 40 mm Hg at 2 years); Blindness at ~ 4 years
  – Group 2. Gradual IOP increase
• Older animals (8-9 years) still visual
• The intraocular pressure increases at about 12 months in both groups.

POAG Beagles

• Iridocorneal angle and ciliary cleft normal throughout most of disease
As A Model
• Canine POAG better model for humans than dogs
  – Mutation in ADAMTS-10 recently identified
• Lesions in spontaneous glaucoma progress more rapidly
  – Both in ICA and retina/ON
• Leaves many ?’s about canine glaucoma unanswered

The preiridal membrane

• Common sequel to intraocular disease
  – Uveitis
  – Neoplasia
  – Retinal detachment
• Results from release of angiogenic factors and cytokines
  – Inflammatory cytokines
  – Angiogenic factors from growing neoplasia
  – Or from hypoxic, detached retina
• Aqueous environment = diffusion throughout eye
Neovascular glaucoma
• Peripheral anterior or posterior synechiae
• With or without intraocular hemorrhage
• Most common in dogs
  – Cat preiridal membranes seem less distinct

Lens luxation
• Can be primary or secondary in dogs, cats
  – Buphthalmia can lead to lens lux
  – Detailed history very helpful
• Frequent sectioning artifact – Look for
  – Malposition/orientation (i.e. backwards)
  – ‘Dog-legging’ of iris
  – Ciliary body atrophy
  – Retrocorneal membranes/segmental retinal atrophy
• Retinal atrophy more often symmetrical

Retinal detachment/PIFM
• Retinal detachment is a leading cause of PIFMs
  – Retinal hypoxia > VEGF/angiogenic factor release > aqueous environment > regionally unregulated angiogenesis
• Retinal detachment spares retina from glaucomatous changes
• Can be seen with or without hyphema
  – Reactive vessels are delicate

Iridocorneal Endothelial Syndrome/lens epithelial membranes
• Recent retrospective on preiridal membranes
• Divided fibrovascular and endothelial-like (single cell)
• Determined single cell NOT endothelial like
• A few anecdotal reports of ICE-like syndrome
  • Often trauma related (blunt), can be consequence, rather than cause, of glaucoma
• Difficult to distinguish lens epithelial membranes from endothelial like membranes (e.g. post-phaco enucleations)

Aqueous Misdirect
• Challenging histopathologic diagnosis
• Shallow anterior chamber
• Irregular, cavitated anterior vitreous
• “crowded”, anterior vitreous, forward shifted
• Pools of aqueous in vitreous

Feline Primary Glaucoma
• Open angle/ciliary cleft with posterior segment lesions of glaucoma
• No significant inflammation
• Diagnostic lesion is myxomatous matrix surrounding equatorial scleral veins
  • Post-trabecular glaucoma? Controversial

Equine Glaucoma
• Etiology reakdown less well known
  – Most cases uveitis/ERU, may be neovascular
• Similar retinal changes as cats
  – Inner retinal atrophy until very chronic
  – Can be very subtle
• Reminder that end stage of glaucoma (or any destructive ocular disease) is….
  PHTHISIS!!
General Considerations: Neoplasms can be separated based on the histogenesis. The distinction is helpful to evaluate growth patterns and morphologic features. Epithelial neoplasms form nests, glands, trabeculae and cords. Spindle cell neoplasms form streams and bundles. Round cell/leukocytic neoplasms typically form sheets. Any poorly differentiated neoplasm can form sheets. Neuroepithelium (from the neuroectoderm) often forms packets and usually has features similar to epithelium that is ectodermal in origin. The term “round cell” occasionally leads to confusion as it is use both for a category of cells (leukocytes) as well as a descriptor of cell shape. Well-differentiated epithelial cells are cuboidal, columnar or polygonal. They often have distinct borders, mature cells have abundant cytoplasm. Basal cells have less cytoplasm. Spindle cells are spindle with scant cytoplasm and round cells are round with scant cytoplasm. However, the eye is full of exceptions.

The rules for ocular neoplasia are similar to those in other organs, but there are many exceptions: Iris and ciliary epithelium (neuroectoderm) share some but not all features of epithelial (ectoderm) cells, Lens epithelium takes on a mesenchymal phenotype, Melanocytic neoplasia does not neatly fit in any category

Immunohistochemistry is used to target and visualized specific components of cells. It is most often used for cell identification as part of neoplasia, but can also be used for other purposes. It can be performed using polyclonal and monoclonal antibodies. Polyclonal antibodies tend to be more sensitive but less specific than monoclonal antibodies. The method of fixation and the duration of fixation can affect the results. Enzymatic antigen retrieval and heat-induced epitope retrieval are commonly used to facilitate exposure of the targeted antigen, especially when using antibodies intended for use in human tissues in veterinary samples. Almost all commonly used stains for diagnostic purposes use an indirect method; one antibody targets the antigen and a second marked antibody is used for visualization. Avidin-biotin method (ABC) and peroxidase-antiperoxidase method (PAP) are most commonly used detection systems. The chromagens 3,3’-diaminobenzidine tetrachloride (DAB) which produces a brown color and 3-Amino-9-ethylcarbazole (AEC) which produces a red color are the most commonly used for detection. Although most stains are read as positive vs negative, it is important to consider the distribution, localization, intensity of the immunohistochemical staining when evaluating the results. See Ramos-Vara JA. Vet Path 2005; Ramos-Vara JA et al. Vet Path 2014; Labelle P et al. Vet Path 2012.

Common antibodies used for diagnostic purposes include cytokeratin, vimentin, melanocytic markers (melan-A, PNL-2, TRP1-2), muscle markers (SMA, actin, desmin), neuro/neuroendocrine markers (S100, NSE, GFAP, SYN, PGP9.5), round/leukocytic markers (CD45, CD18, CD3, CD20/CD79a, Pax5, CD204, CD117).
Neoplasia of the Canine Eyelids and Conjunctiva

Phil Labelle

General Considerations for the eyelids: Any cutaneous neoplasm can affect the eyelid skin and eyelid predisposition is really predisposition to the head/neck region. See Labelle al et al VO 2013.

Trichoblastoma presents as a solitary, firm, alopecic, dome-shaped or polypoid mass. These were previously lumped under “basal cell tumor”. It is an epithelial neoplasm composed of small basal cells with scant cytoplasm. The cells form ribbons, nests, cords and trabeculae often in combination. There are many histologic subtypes. In catheter especially the cells may be more spindle.

Sebaceous Tumors include hyperplasia/adenoma, epithelioma and are mostly seen in middle aged to older dogs. Most present as dome-shaped or papillated masses which can be solitary or multiple. These are epithelial neoplasms composed of nests of well-differentiated sebaceous glands with ducts. Basal cell predominate in epitheliomas. The distinct between nodular hyperplasia and adenoma is sometimes made based on the presence of ducts and surrounding glands with normal orientation in hyperplasia. The masses may be pigmented.

Mast Cell Tumors typically presents as single or multiple masses that are alopecic, erythematous, edematous. The neoplastic cells form sheets within collagenous stroma. The cells are round with cytoplasmic granules that can be more easily visualized with giemsa and Toluidine blue stains. Variable numbers of eosinophils are usually admixed with the neoplastic cells. There are grading systems developed (Patnaik, 2-tier) for cutaneous/subcutaneous neoplasms that help predict behavior and response to treatment. See Patnaik Vet Path 1984; Romansik Vet path 2005; Kiupel Vet Path 2011; Thompson Vet Path 2011.

Lymphoma has a gross appearance of various considerably between cases. Most cases that affect the eyelids are epitheliotropic. Histologically the round cells with scant cytoplasm form sheets and variably extend in the surface and follicular epithelium. Almost all epitheliotropic lymphomas are of T cell origin (CD3 positive, CD79a/CD20 negative). Lymphomas can be typed by cell size and pattern. The mitotic index corresponds to grade.

Canine Cutaneous Histiocytoma usually presents as a button lesion, round, red +/- ulcerated. It is a round cell neoplasm composed of histiocytic-Langerhans cells. The cells form sheets and subepidermal cords, +/- epidermal invasion. The cells have round to reniform nuclei. Of note mitotic index highly variable and a high mitotic index is not suggestive of aggressive behavior. Most masses include a prominent lymphocytic infiltrate which can lead to regression. It is mostly, but not exclusively seen in young dogs. In one database (PL database, 150 cases): 48% are 3yo or younger, 65% are 4yo or younger; 35% 5yo or older. Those in older dogs are often sampled due to concern for malignant neoplasia. There is less spontaneously regression older dogs and histiocytoid lymphoma should be considered as a differential diagnosis in older dogs.

Granular Cell Tumor is a canine neoplasm typically affecting the medial canthus presenting as a solitary firm mass that is variably ulcerated. The lesion consists of sheets of large round cells with abundant granular cytoplasm. There is minimal pleomorphism and a low mitotic index. The cells show strong staining with PAS. Those of the medial canthus are histologically similar to sublingual GCT. See Lu JE et al. VO 2012.

Melanocytic Neoplasia typically presents as a solitary, dome-shaped, pink to brown to black mass. Most eyelid masses are benign melanocytomas. Histologically the cells our spindle to polygonal in form sheets, packets, bundles, whorls. There may be junctional activity. Most masses are heavily pigmented. Features that suggest a malignant neoplasm include mitotic index of 3 or more, nuclear atypia, deep extension and ki-67 of >15%. See Smedley R et al. Vet Path 2011.

Meibomian Adenoma/Epithelioma typically present as tan, pink, gray or black masses. They’re usually well-circumscribed and variably exophytic. Histologically the masses consist of lobules of sebaceous glands with ducts. Basal cell predominate in epitheliomas. Many masses are pigmented.
**Conjunctival Squamous Papillomas** are discrete, papillary lesions. Histologically there are no features of atypia and no viral cytopathic effects. Squamous papillomas must be differentiated from reactive papillary hyperplasia (“reactive papilloma”) and viral papillomas. See Beckwith-Cohen B et al. Vet Path 2015.

**Viral Papillomas** of the conjunctiva are exophytic, papillary masses composed of papillary fronds of hyperplastic, variably pigmented epithelium with a prominent granular layer and hyperkeratosis. Koilocytes (abundant pale cytoplasm, large or pyknotic nuclei) and intranuclear inclusions indicate viral origin. Viral inclusions are not however required for the diagnosis (and are less common than koilocytes).

**Third Eyelid Gland Adenocarcinomas** are pink, firm masses. Histologically these infiltrative masses are composed of nests and tubules; some may be almost completely solid. There can be squamous metaplasia/ductular differentiation. The mitotic index highly variable and is not predictive of behavior. Adenoma are much less common than adenocarcinomas. Third eyelid gland adenocarcinomas are more aggressive and metastasized more readily in cats than dogs See Wilcock B et al. JAVMA 1988; Dees DD et al. VO 2016.

**Vascular Neoplasms** usually present as smooth, raised, pink to red masses. Hemangiomas are well-circumscribed and composed of attenuated endothelial cells within mitoses. Hemangiosarcomas are composed of irregular channels, plump endothelium, +/- mitoses. Reported as mostly (2/3) benign, this may be a subjective overestimation as most conjunctival hemangiosarcomas are well differentiated. UV exposure may be a contributing factor See Pirie CG et al. VO 2006.

**Conjunctival Mast Cell Tumors** typically present as smooth, firm, subconjunctival masses. Most are well-circumscribed. Histologically the neoplasm consists of sheets of mast cells admixed with eosinophils. Edema is a common finding. The cytologic features of most conjunctival mast cell tumors are most often similar to those of Grade I-II (Patnaik system) or low grade (2-tier system) skin neoplasms. However, the significance of grading systems developed for cutaneous mast cell tumors has not been determined for conjunctival neoplasms. Similarly, prognostic markers used in cutaneous mast cell tumors (kit immuno, kit PCR, ki-67) have not been investigated in conjunctival mast cell tumors. Most respond to excision and cryotherapy. See Fife M et al. VO 2011.

**Conjunctival melanocytic Neoplasia** presents as pink to brown to black masses. Most conjunctival melanocytic neoplasm are malignant (MI>4). They are poorly circumscribed and may be multifocal. Histologically the neoplastic cells are spindle to polygonal to round end form sheets, packets, bundles, whorls. Most masses are mildly pigmented. Local recurrence is common even after aggressive surgical intervention. Metastasis has been described in 10-20% of cases. See Collins et al. Prog Vet Comp Ophthalmol 1993.

**Limbal Melanocytic Neoplasia** present as broad-based nodular brown to black masses. Almost all are benign melanocytomas. Limbal melanocytic neoplasms are presumed to arise from the melanocytes that demarcate the limbus at the junction of the corneal stroma and sclera. They expand along the planes of least resistance toward the conjunctiva readily and into the adjacent corneal stroma minimally. Histologically the masses are composed of discohesive heavily pigmented plump polyhedral cells often admixed with fewer pigmented spindle cells. There is no atypia; mitoses are rare to absent. Necrosis is present in approx. 20% of cases. Rare cases extend intraocularly. Rare histologically malignant limbal melanomas have been described, and some otherwise benign neoplasms may include areas with cells that are less pigmented or amelanotic and mitotically active.
Canine Uveal Melanocytic Neoplasia

Phil Labelle

Melanocytic neoplasms are the most common primary ocular neoplasms in dogs representing approximately 55% of all primary ocular neoplasia. They are typically seen in middle-aged to older dogs. The neoplasm skin form massess expanding the iris and extending into the anterior chamber or massess posterior to the iris that anteriorly displaces the iris face. There may be thinning of the sclera with a pigmented mass. See Labelle et al. VO 2013; Giuliano EA et al. VO 1999; Wilcock B et al. Vet Path 1986.

Uveal Melanocytoma is most common in the iris and ciliary body, typically affecting both (94% anterior, 6% choroidal). 75% of anterior melanocytic neoplasms are benign, 85% of choroidal melanocytic neoplasms are benign. The neoplasms readily efface the iridocorneal angle. Many expand along the corneoscleral meshwork which extends anterior to the termination of Descemet's membrane and blend with the deep peripheral corneal stroma. Scleral and extrascleral extension is common for both anterior uveal and choroidal melanocytomas and is not a feature that is indicative of malignancy. All melanocytomas have a similar histologic appearance independent of their origin (anterior vs choroid). The neoplasms are composed of variable proportions of heavily pigmented spindle cells and discohesive heavily pigmented plump polyhedral cells. The spindle cell population has indistinct cell borders, small to moderate amounts of pigmented cytoplasm, and oval nuclei often with one nucleolus. There is minimal anisokaryosis and anisocytosis. The plump polyhedral cells are large with distinct cell borders, abundant pigmented cytoplasm, and central to peripheralized round nuclei. There is severe anisocytosis but minimal anisokaryosis. Mitoses are not present in the plump polyhedral cells. Mitoses are rare to absent (<4 in 10 HPF). Individualized pigmented cells may be seen in the anterior and posterior chambers and vitreous. Necrosis and infiltration of melanophages are common. Intraocular hemorrhage, pre-iridal fibrovascular membrane, asteroid hyalosis, and glaucoma are frequent secondary findings. Retinal detachment is expected with choroidal melanocytomas.

Uveal malignant Melanoma it is most common in the iris and ciliary body, typically affecting both (97% anterior, 3% choroidal). 25% of anterior melanocytic neoplasms are malignant, 15% of choroidal melanocytic neoplasms are malignant. Unfortunately there are no histologic features can reliably predict metastasis. The neoplasms readily efface the iridocorneal angle. Many expand along the corneoscleral meshwork which extends anterior to the termination of Descemet's membrane and blend with the deep peripheral corneal stroma. Scleral and extrascleral extension is common for both anterior uveal and choroidal melanocytomas and is not a feature that is indicative of malignancy. All melanocytomas have a similar histologic appearance independent of their origin (anterior vs choroid). The neoplasm are composed of variably pigmented spindle cells to polygonal cells. Typically there is odrerate to severe pleomorphism with a mitotic index of 5 or more. Necrosis and infiltration of melanophages are common. Intraocular hemorrhage, pre-iridal fibrovascular membrane, asteroid hyalosis, and glaucoma are frequent secondary findings. Retinal detachment is expected with choroidal involvement.
Iridociliary epithelial neoplasia

Tumors originating from the ciliary body epithelium (pigmented or nonpigmented) and posterior iris epithelium are the second most common primary ocular neoplasms in dogs. These tumors occur in middle aged to older dogs, with a possible predisposition for Golden and Labrador retrievers and no gender predilection.

Current classification of these tumors includes adenoma, adenocarcinoma and pleomorphic adenocarcinoma, being defined by the invasiveness within the globe. In pleomorphic adenocarcinomas, a history of chronic intraocular disease (uveitis or glaucoma) is frequently reported (44% of the cases) and 25% of the cases have received an intraocular gentamicin injection.

Grossly, adenomas and adenocarcinomas are well delineated masses that partially fill the posterior chamber and cradle the lens (occasionally the tumors may be found within the anterior chamber and involve only the iris). Pleomorphic adenocarcinomas are much less defined and typically invade much of the structures of the globe, infiltrating through the sclera into the orbit.

Histologically, adenomas and adenocarcinomas form trabeculae, cords and acinar structures composed of polygonal cells, frequently with robust basement membrane-like material between these structures. Both adenomas and adenocarcinomas can be nonpigmented or may show varying degrees of pigmentation. Accompanying histologic features include asteroid hyalosis in the vitreous in 27% of the tumors and preiridal fibrovascular membranes.

- **Adenomas** can be non-invasive (entirely confined within the posterior and anterior chamber), uveo-invasive (the uveal stroma is infiltrated). This is the most common iridociliary neoplasm.
- **Adenocarcinomas** are defined by the presence of scleral invasion, and they typically show more anaplastic features.
- **Pleomorphic adenocarcinomas** are organized in irregular cords and nests, and neoplastic cells are highly anaplastic and atypical, although basement membrane material can also be seen between neoplastic cells. This is the least common iridociliary neoplasm.

PAS stain can be demonstrated to highlight the smooth, thick basement membranes that can be seen between cords of neoplastic cells, in approximately 60% of these tumors. With an Alcian Blue stain, hyaluronic acid can be demonstrated between neoplastic cells or within tubular or cystic structures.

Immunohistochemically, the more benign tumors are vimentin and NSE (neuron-specific enolase) positive. Staining with S100, GFAP and desmin is variably positive. Cytokeratin expression is negative in adenomas, and increases with increasing malignancy of the tumor. TERT (telomerase reverse transcriptase) has also been shown to increase with increasing aggressiveness. Conversely, staining with cytokeratin 20 decreases as tumor aggressiveness increases.

The prognosis of adenomas and adenocarcinomas is typically good, since enucleation is curative and they do not metastasize. Pleomorphic adenocarcinomas are frequently locally invasive, with both recurrence within the orbit and distant metastases reported (6/16 cases in COPLOW died with suspected or confirmed metastases, whereas 6/16 died of unknown reasons).

**References**


Medulloepithelioma and other primitive neuroectodermal tumors (PNET)

PNET is a generic name that is used for embryonal tumors that arise from the germinal epithelium of the neural tube (neuroectoderm). They include tumors such as neuroblastomas, ependymoblastomas, retinoblastomas and medulloepitheliomas.

In the eye, PNET can occur in the peripheral retina or in the area contiguous with the ciliary body.

Retinoblastoma cases in dogs reported in the literature are sparse. There are tumors with neural differentiation, but it is difficult for them to meet the histologic criteria defined for human retinoblastomas. Recently, 4 cases of retinoblastoma-like PNETs have been described in dogs. These dogs were younger than 2 years and had tumors in the retina or the ciliary body. Histologic features similar to those described in humans: single-layered rosettes and fleurettes. This was in contrast with medulloepitheliomas, which were seen in dogs older than 7 years and no such rosettes were seen. Retinoblastoma-like tumors were also immunohistochemically positive for IRBP, a protein that is only present in retinal photoreceptors. Medulloepitheliomas were negative for these tumors.

Medulloepitheliomas are tumors within the family of PNETs, which is a more generic term for tumors that do not meet the criteria to be more specifically diagnosed.

Medulloepitheliomas have features of iridociliary tumors (they also originate from neuroectoderm) and also share features with retinoblastomas in humans. These are uncommon tumors in dogs and can be diagnosed in dogs of any age.

Grossly, the tumors originate from the ciliary body in dogs, filling posterior chamber, and they can extend to infiltrate the retina. In horses, they typically originate from the optic nerve. Less commonly they can arise in the retina. They are light tan to white and can form papillary or botryoid projections into anterior chamber, forming small nodules.

Histologically, tumors may show a pattern of survival around blood vessels, with necrosis present away from them. The characteristic feature of medulloepitheliomas is the formation or rosettes, which can have multiple layers. Individual cells are elongate and show a long and hyperchromatic nucleus (“carrot-shaped”). Some tumors may exhibit cartilage, skeletal muscle or brain-like tumor formation, and then the term “teratoid medulloepithelioma” applies.

Immunohistochemically these tumors are positive for TERT, with limited positivity for vimentin and cytokeratin.

Behaviorally, these are locally invasive tumors, but metastases are very infrequent.

References


Uveal schwannoma of blue-eyed dogs

Formerly known as spindle cell tumor of blue-eyed dogs, this is an uncommon tumor that occurs in blue-eyed (or partially blue-eyed) dogs. Hence, breeds in which blue eyes are common are overrepresented, including Siberian Huskies, Border Collies, Catahoula hounds, etc. Dogs are typically middle-aged to old and there is no gender predilection.
Grossly, the anterior uvea is typically affected, mostly the iris, although there may be extension to the ciliary body. Rarely, the posterior uvea is involved. Although some tumors may form a discrete mass, many of them present as a diffuse thickening of the iris, and hence, they can go unnoticed clinically.

Histologically, the tumor is poorly delineated, causing swelling of the iris (plus or minus the ciliary body), although in some cases it may be forming a mass lesion. Neoplastic cells are spindle, ranging from slender and lacking anaplastic features to larger plump cells with numerous cytologic atypia. These cells are organized in bundles or whorls, forming highly cellular to loosely arranged areas (Antoni A and Antoni B patterns). In few cases, neoplastic cells invade the sclera.

Immunohistochemically, these tumors are positive for vimentin, S100 and, in most of the cases, GFAP positive. Besides labeling the astrocytes of the central nervous system, GFAP stains Schwann cells of nonmyelinated nerves of the iris stroma in normal blue eyes of dogs. Other markers that have been studied variably label the cells of this tumor.

Electron microscopy shows that the neoplastic cells have long interdigitating cytoplasmic processes and intermittent basal laminae at the plasma membrane, indicative of a peripheral nerve sheath origin.

Prognosis is guarded, since there may be recurrence within the orbit (or scleral shell in eviscerated specimens) and recently, a case in which metastases developed (lung, liver and mesenteric lymph nodes) has been described. Survival time has not been determined, since cases with confirmed metastatic disease are too few (in the published case, 17 months lapsed between enucleation and euthanasia. To date, no particular morphological or immunohistochemical characteristics have been linked to the development of metastases.

References


Metastatic tumors

There are specific patterns that can identify a tumor as metastatic in the eyes of dogs. Most frequent metastatic tumors in dogs are lymphoma and histiocytic sarcoma, followed by carcinoma, melanoma, hemangiosarcoma, osteosarcoma and others. Within epithelial tumors, mammary carcinomas are the most commonly diagnosed. Rare cases of primary extraskeletal osteosarcomas and chondrosarcomas are described in dogs, so exhaustive search for a primary tumor should be made before making these diagnoses.

Lymphoma can present as a discrete mass but most commonly forms a diffuse infiltrate in the uvea. Histiocytic sarcoma typically forms a mass-like lesion in the anterior uvea.

Other metastatic tumors manifest with the following histologic features:

- Metastases may be present in only one eye, but bilateral involvement is common.
- Anterior uvea is most commonly affected (than posterior uvea).
- Neoplastic cells are frequently identified within blood vessels.
- Two patterns of involvement are noted:
  o Discrete mass
  o Diffuse infiltrate without a mass-like lesion, typically lining the inner surfaces of the eye (most commonly uveal surfaces).
Canine posterior segment and orbital neoplasia
Chris Reilly

Ocular gliomas

- Optic nerve, nerve head, retina
- Can be astrocytic, oligodendroglial, or mixed
- Astrocytic – spindle cells with fibrillar cytoplasm and indistinct matrix
  - GFAP immunoreactive
- Oligodendroglial – small, rounds cells with pale/clear cytoplasm
  - Olig-2 immunoreactive (but can label some astrocytes)

Orbital neoplasia – General considerations

- Anything in/near orbit can be origin
- Meninges (meningioma)
- Skeletal muscle (Rhabdomyosarcoma)
- Bone (osteosarcoma, multilobular osteo)
- Fat (Prolapse, lipoma, liposarcoma, hibernoma)
- Blood vessels (hemangiosarcoma)
- Glands (lacrimal, nictitating andenocarinoma)
- Inflammatory cells (histiocytic sarcoma, lymphoma)

Orbital lobular adenoma

- Organized in tight lobules/acini; friable, botryoid gross appearance
- Bland, densely amphophilic and granular cytoplasm
- No ducts
- No metastatic risk, but can recur and require exenteration

Orbital meningioma

- From optic nerve meninges
  - Remember: The optic nerve is CNS
- Benign tumor in a bad place
  - Exophthalmos, exposure keratitis
  - Occasional retinal detachment
- Thought to arise from arachnoid cap cells, near the optic nerve insertion
  - Several subtypes
  - Often have:
    - meningothelial whorls
    - psammoma bodies
- bone
- cartilage

NOT IN PRESENTATION – NOTES FOR YOUR REVIEW

**Rhabdomyosarcoma**
- Skeletal muscle tumor
- Typically aggressive – local, mets
- Young dogs
- Often pleomorphic/embryonal
  
  IHC can be key to diagnosis – desmin, skeletal myosin, myoglobin, pan-muscle actin

**Orbital fat prolapse**
- Dogs, horses
- Fluctuant orbital/subconj swelling
- Histologically = mature adipose

**Liposarcoma**
- A malignant tumor of adipose
- Increased cellularity, atypia
  - Well-differentiated – close to lipoma
  - Myxoid – abundant myxoid matrix
- Some lipid vacuoles
  - Pleomorphic – increased atypia, mitoses
- Oil red O – frozen (fresh or fixed unprocessed)

**Orbital Hibernoma**
- Tumor of brown fat origin
- Characteristic IHC:
  - UCP-1 – Uncoupling protein-1
- Mitochondrial protein
- enables brown fat to store energy
  
  Variable for muscle antigens, like Myo-D, desmin
  Common origin with muscle; liposarcoma rarely reported to express muscle markers??

**Multilobular osteosarcoma**
• aka – multilobular tumor of bone
• Occurs in cranial and orbital bones
• Characteristic histologic pattern
• Less aggressive than appendicular OSAs
  – Malignant behavior reported

  Hence trend to call osteosarcoma
Equine Neoplasia

Chris Reilly

Equine Sarcoid

• Mass effect (with variable clinical appearance – nodular, flat/occult, verrucous, and fibroblastic subtypes)
• Spindle cell proliferation
• Bundles
• No significant pleomorphism, low mitotic index
• Thin rete pegs extend in the mass
• Bovine papillomavirus

Equine Squamous Cell Carcinoma

• UV induced, with genetic predisposition (Haflinger, +/- Appaloosa, paint, others
• Damage-specific DNA binding protein 2 (DDB2) mutation – decreased ability to repair UV damage to DNA
• Often in conjunction with other UV-damage lesions (e.g. elastosis)
• Preceded by hyperplasia, dysplasia, carcinoma in situ – spectrum of progression

Equine Hemangiosarcoma

• Often more inflamed than in other species
• UV-link less established
• Dense vascular channels in heavily inflamed, or lymphofollicular background
• Requires high index of suspicion, +/- IHC for confirmation
  • Factor VIII or CD31

Equine Conjunctival melanoma

• Often heavily pigmented
• Nests, sheets and clusters
• Histologic features correlate poorly with metastatic potential

Equine medulloepithelioma

• PNET, similar to canine features
• Densely cellular, Flexner-Wintersteiner rosettes
• Typically benign, but can cause severe ocular complications
Feline Conjunctival and eyelid neoplasia

Chris Reilly

General Considerations

• Any cutaneous neoplasm can affect the eyelid skin
• Eyelid predisposition is really predisposition to the head/neck region

Apocrine Adenoma

• Solitary, cystic
• Epithelial neoplasm
• Tubules and nests, solid areas
• Prominent ductular differentiation, ductular adenoma
• Can be pigmented

Peripheral Nerve Sheath Tumor

• Solitary, pink, firm
• Bundles, streams, whorls
• Antoni A/B

Mast Cell Tumor

• Smooth, pink, alopecic
• Sheets
• Round cells with cytoplasmic granules
• +/- eosinophils
• Often multiple, but rarely associated with systemic mastocytic disease or metastasis

Apocrine Hidrocystomas

• Masses are collections of cysts
• Not true neoplasm (misnomer)
• Often multifocal
• Cysts are lined by cuboidal to attenuated epithelium and contain secretions
• Secretion-laden macrophages may border the cysts
Third Eyelid Gland Adenocarcinoma
- Pink, firm
- Infiltrative – higher recurrence and metastatic rate in cats (v dogs)
- Nests and tubules, or solid

Squamous cell carcinoma
- Horses, bovine, feline, canine
- In situ (does not breach basement membrane)
- Loss of normal maturation, subtle dyskeratosis, pleomorphism, numerous mitoses not limited to basal cells
- Invasive
- Trabeculae and nests within fibrous stroma
- Dyskeratosis is variable

Mucoepidermoid carcinoma
- Often third eyelid, can be bulb
- Exophytic and infiltrative
- Papillary fronds, nests and glands

Vascular neoplasms
- Smooth, raised, pink to red
- Hemangiomas
- Well-circumscribed, attenuated endothelial cells, no mitoses
- Hemangiosarcomas
- Irregular channels, plump endothelium, +/- mitoses
- May be associated with other UV lesions (e.g. elastosis)

Melanocytic Neoplasia
- Pink to brown to black
- Most/all are malignant melanoma – cellular features poorly predictive
- Most on the bulbar conjunctiva
- Poorly circumscribed
• Sheets, packets
• Polygonal and spindle cells
• Variably pigmented
Feline Uveal Melanocytic Neoplasia

Chris Reilly

Feline diffuse iris melanoma - FDIM

• One of leading 1° feline ocular tumors
• Typically starts along anterior iris face
• Degree of involvement most prognostic
  o Choroidal involvement, extrascleral invasion
• Tumoral features
  o Intratumoral necrosis
  o Mitotic figures >/= 7 per 10 400x fields
• Accurate prognostication remains controversial
  o Lack of follow-up and anecdotal bias
  o Secondary glaucoma controversial prognostic indicator – depends on study

FDIM

• Key histologic features:
  – spindle, polygonal, and/or enlarged “Balloon cells”
  - Pigment (variable)
• Pheomelanin v eumelanin
  – Anisocytosis/anisokaryosis – karyomegaly and bizarre nuclei
  – Distribution almost always includes iris
  – Cytoplasmic invaginations into nucleus
• Express: MelanA, PNL-2, E-cadherin

Feline Atypical Melanoma

• Rare variant
• Unusual distribution
  – Multifocal within a globe
  – RPE involvement
  – Often distinctly SPARE the iris
• Bland, heavily pigmented cellular morphology
  – Maybe more commonly truly malignant
FELINE NEOPLASIA: NON-MELANOCYTIC AND ORBITAL NEOPLASIA

Carol Naranjo Freixa

Feline post-traumatic ocular sarcoma

This is the second most common primary ocular tumor in cats. These tumors arise within chronically inflamed globes, frequently after a traumatic event (reported in approximately 50% of the cases), with an average of 7 year latency period between said event and the diagnosis (range of 2 months to 10 years). Commonly, the history includes information referencing that the eye already looked abnormal when adopted (adult stray cat or kitten). So the tumors occur in older cats with no breed predilection, although a male predisposition has been suggested.

Three morphologic variants are distinguished:

Spindle cell variant

This is the most common variant, occurring in 70% of the cases. This variant is thought to originate from lens epithelial cells.

Grossly, this tumor tends to line the inner surface of the globe in the early stages, but progressively fills the globe, making it a solid, firm, light tan mass that destroys all the intraocular structures.

Histologically, neoplastic cells initially line the inner aspect of the globe and, in more advanced cases, invade and destroy all intraocular tissue, extending into the scleral tunic. This tumor ranges from fibrosarcoma, with deposition of collagen matrix, to anaplastic sarcoma, composed of plump spindle cells forming haphazard bundles, with prominent cytologic atypia, high mitotic rate and, in some tumors, presence of multinucleated cells. Almost all of these show lens capsule rupture.

With special stains, many tumors have localized areas in which there is a PAS-positive staining membrane, reminiscent of lens capsule.

Immunohistochemically, these tumors are positive for vimentin and variably positive for smooth muscle actin (20%), cytokeratin (15%) and alpha A crystallin (33% of cases, a protein only found in the lens). The PAS-positive membrane is immunolabeled with collagen type IV, which is a collagen found in basement membranes.

Prognosis is typically poor. Extension beyond the sclera and involvement of the optic nerve are both bad prognostic indicators. Tumor can recur within the orbit, extend along the optic nerve or peripheral nerves to the brain, or can metastasize to distant sites (lymph nodes), although the incidence of the latter is difficult to assess.

Evidence that this tumor originates from lens epithelium comes from the following:

- In early tumors, the neoplastic cells are only found around the lens.
- Lens capsule rupture is present in almost all of the cases, whereas in other intraocular neoplasms, even though if they are large, lens capsule is rarely disrupted.
- The PAS, collagen type IV-positive basement membranes are reminiscent of lens capsule, which is the basement membrane that lens epithelial cells produce.
- Some tumor label with alpha A crystallin, a protein only found in the lens.

It is important to note that even though these tumors have been sporadically described in other species (rabbit, dog, bird), no cases of neoplasia arising from the lens are found in the human medicine literature.

Round cell variant or post-traumatic lymphoma

This is the second most common variant, occurring in 24% of the cases.

Grossly, this tumor also tends to fill the globe, with a minor tendency to line the inner structures of the globe when compared to the spindle cell variant. The neoplastic infiltrate is light tan and soft.
Histologically, neoplastic cells are round and organize in solid sheets with scant vascularization present. There is a typical pattern of extensive coagulation necrosis with survival of neoplastic cells around blood vessels. Individual cells show a large nucleus to cytoplasm ratio and mitoses are abundant. Lens capsule rupture is frequently seen, although not in all cases. There may be areas of lymphoplasmacytic inflammation within the tumor.

The immunohistochemical profile of this tumor is highly variable, since some stain with B cell markers, others with T cell markers and some with both. Clonality studies indicate that most of the tumors are of B cell origin.

Different from classic lymphoma: extension within the globe, lens capsule rupture, extent of necrosis and history.

The prognosis is guarded to poor. No clear association is found between invasion of the sclera, optic nerve or peripheral nerve and development of additional complications in the orbit, brain or distant sites. Despite this, there is evidence of local recurrence and systemic spread in some cases.

**Osteosarcoma/Chondrosarcoma variant**

This is the least common variant, accounting for 6% of the post-traumatic sarcomas. The cell of origin of this tumor is currently unknown.

Grossly, these tumors infiltrate and fill the eye, making it a solid globe.

Histologically, features of osteosarcoma (mesenchymal spindle cells cells with production of neoplastic osteoid matrix), chondrosarcoma (mesenchymal cells with production of neoplastic osteoid matrix), or a combination of both are found. All cases show lens capsule rupture.

The prognosis is difficult to assess due to the paucity of cases reported.

**References**


**Feline iridociliary epithelial neoplasia**

These tumors are the third most common primary intraocular neoplasm in cats. Affected cats are middle-aged to older animals, with no breed or gender predilection.

Grossly, these tumors form a discrete light tan mass in the posterior chamber, cradling the lens and may infiltrate the iris, ciliary body and anterior chamber. The sclera is rarely involved. Similar to the canine counterpart, adenoma is diagnosed when the sclera is not involved (non-invasive or uveo-invasive), and adenocarcinoma when this structure is infiltrated. In some cases, there are cavitated areas within the tumor.

Histologically, neoplastic cells typically are arranged forming a solid sheet of fairly monomorphic and tightly-packed polygonal cells. There is a delicate fibrovascular stroma between neoplastic cells, which can be highlighted with a PAS stain. Tumors may contain osteoid matrix or metaplastic bone.

Immunohistochemically these tumors are NSE positive, most of them are vimentin positive, and show variable positivity to S100 and GFAP. Only few adenocarcinomas are positive for cytokeratin.

**References**
Feline restrictive orbital myofibroblastic sarcoma

This is an insidious neoplastic process that affects middle-aged to older cats, with no breed or gender predilection. Previously called orbital pseudotumor, or idiopathic sclerosing orbital pseudotumor, the name has been changed to clearly indicate that this is a malignant proliferation, since it is progressive, poorly responsive to treatment and frequently leads to euthanasia.

The neoplastic cells do not form a discrete mass and rather infiltrate the orbit, eyelids, lips and oral cavity and can spread through fascial planes to the contralateral orbit, so disease is frequently bilateral. These cells cause restriction of globe and eyelid movement, so the most common clinical findings include reduced retropropulsion of the globe, lagophthalmos, ulcerative keratitis and thickened eyelids. The globe itself may be exophthalmic, enophthalmic or in a normal position. The time between presentation for the first eye and presentation for clinical disease in the contralateral eye ranges from 0 to 8 months, whereas the time between presentation and development of oral lesions ranges from 0 to 14 months.

Grossly, the orbital tissue may be thickened, although no discrete masses are noted. The tissue filling the orbit may be light tan to white and resembles fibrous tissue. There may be thickening of the eyelids, interorbital dermis, palate, lips and maxillary gingiva.

Microscopically, the abnormal tissue is composed of poorly delineated and infiltrative bland spindle cells within a collagenous matrix that extends into the orbital tissue and shows low mitotic activity. The globe typically shows ulcerative keratitis (occasionally with perforation or sequestrum). The infiltration is typically densest in the substantia propria of the bulbar conjunctiva at the limbus or in the palpebral conjunctiva near the fornix. In the skin, the infiltration is more severe in the deep than in the superficial dermis. There is mild to moderate perivascular lymphoplasmacytic infiltration, typically at the edges between neoplastic foci and preexisting tissue. There may be lysis of the orbital bone due to neoplastic invasion.

Immunohistochemically, these tumors are vimentin and smooth muscle actin positive, which support the name of “myofibroblastic sarcoma”. There is moderate S100 staining and GFAP stains weakly some of the tumors, the latter being explained by the presence of fragments of peripheral nerves with nonmyelinating Schwann cells within the neoplasm. Melan A and CD18 are negative, ruling out melanocytic or leukocytic (histiocytic) origins.

It is obviously very important to differentiate this process from reactive fibroplasia or granulation tissue, which would have a similar appearance histologically, so history is crucial to make this diagnosis. A few considerations should be kept in mind when submitting these specimens:

- If the globe is submitted, do NOT trim away the eyelids or orbital periocular tissues, as is recommended for other cases.
- If only an incisional biopsy is submitted, then the best tissues include:
  - Orbit: anterior and superior aspect of the episclera.
  - Eyelid: thickened areas of the substantia propria of the palpebral conjunctiva near the fornix.
  - Skin: thickened areas including the deeper dermis/subcutis.

Prognosis is guarded to poor, since many cats develop bilateral disease and/or oral or facial lesions despite enucleation or exenteration, so euthanasia is a frequent outcome due to poor quality of life. Metastases have not been reported to date. Survival time is short, ranging from 3 to 15 months since first presented.
References


Metastatic tumors

Just like in dogs, metastatic tumors follow a particular pattern in cats. Lymphoma is the most common metastatic tumor in cats, which can present as a discrete mass or as a diffuse thickening of the uvea. Other common metastatic tumors in cats are pulmonary carcinomas (“lung-eye syndrome”), squamous cell carcinomas and fibrosarcomas.

Histologic features of metastatic tumors in cats include:

- Unilateral or bilateral involvement
- Choroid is more frequently involved than anterior uvea.
- If the anterior uvea is affected, neoplastic cells typically line the inner aspect of iris and ciliary body.
- Blood vessels are widely infiltrated, which typically causes extensive areas of choroidal infarction (wedge-shaped areas in which the tapetum is discolored and there is vascular attenuation).
- Orbit can be affected along with posterior segment involvement.