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Conference Moderator:
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CASE I: 089-65832 (AFIP 3134358).

Signalment: Adult male striped skunk (*Mephitis mephitis*).

History: An adult male striped skunk was submitted to the Colorado State University Diagnostic Laboratory with a history of being found dead and suspected poisoning. No other history was provided.

Gross Pathology: The skunk was in fair body condition, with minimal autolysis. Gross findings included nasal and ocular discharge, diarrhea staining of the perineum, thickened and alopecic skin over the shoulders, neck, and head, and a moderate load of subcutaneous nematodes grossly consistent with *Dracunculus insignis* over the lower limbs, thorax, and abdomen. The right ventricle contained a single, pale focus 2 mm in diameter with indistinct borders, consistent with focal myocardial necrosis.

Laboratory Results: Fluorescent antibody testing of the brain for canine distemper virus was positive. Fluorescent antibody testing of the brain for rabies virus was negative.

Histopathologic Description: Haired Skin: Diffusely, there is marked orthokeratotic hyperkeratosis of the skin surface and mild to moderate acanthosis of the epidermis. Within the cells of the stratum spinosum, there is frequent cytoplasmic vacuolar degeneration, and occasional single cell necrosis characterized by shrunken cells with hypereosinophilic cytoplasm and nuclear pyknosis. Cells of the stratum spinosum also frequently contain one or more variably-sized, intracytoplasmic, glassy eosinophilic inclusions. Similar inclusions are occasionally present within nuclei of the stratum spinosum. The changes affecting the epidermis and skin surface extend to involve hair follicles. The superficial dermis is moderately expanded by fibroblasts, with mild infiltration by lymphocytes, plasma cells, and neutrophils. Some sections submitted also contain multifocal serocellular crusting of the skin surface with multiple intralesional cross sections of thick-shelled, embryonated eggs approximately 30 µm in diameter.

Contributor's Morphologic Diagnosis: 1. Haired skin: Hyperkeratosis, orthokeratotic, marked, with acanthosis and intracytoplasmic and intranuclear inclusions consistent with canine distemper virus infection.
2. Haired skin: Multifocal serocellular crusting of the skin surface with intralesional nematode embryonated eggs consistent with *Dracunculus insignis* (only in some slides).

Contributor's Comment: Canine distemper virus (CDV), of the genus *Morbillivirus* and family *Paramyxoviridae*, is a common and important pathogen encountered in a wide range of wild carnivores including, but not limited to coyotes, raccoons, skunks, wolves, foxes, black-footed ferrets, bears, and javelin.(8) Clinical signs of CDV are variable and reflect tropism of the virus for epithelial tissues and brain. Clinical signs include respiratory disease, enteric disease, and neurologic disease that can ultimately be fatal.(2)

Histologic lesions of CDV include lymphoid atrophy and necrosis, bronchointerstitial pneumonia, non-suppurative encephalomyelitis, demyelination of white matter tracts, enamel hypoplasia, conjunctivitis, keratitis, retinitis, optic neuritis, hyperkeratosis, persistence of primary spongiosa of bones, and myocardial necrosis. Viral inclusions are most prominent in the brain and epithelial tissues. Intracytoplasmic inclusions tend to be more common in epithelial cells, while intranuclear inclusions are more common in the brain.(2)

Skin lesions of CDV are most commonly found on the foot pads, nose, eyelids, lips, and anus,(8) although the haired skin can also be affected.(2,5) Histologic findings in the epidermis of haired or non-haired skin include hyperkeratosis and/or parakeratosis, acanthosis, rete ridge formation, epidermal syncytial cells, cytoplasmic and nuclear inclusions, pustular dermatitis secondary to hyperkeratosis, and periadnexal and perivascular mononuclear inflammation.(2) Immunohistochemistry and viral inclusions visible on H&E-stained slides demonstrate that viral particles are primarily located within the stratum spinosum and stratum granulosum.(5) The pathogenesis of hyperkeratosis in CDV is suggested to be due to defective differentiation of infected keratinocytes.(5)

In the case presented here, the infected skunk demonstrated multiple gross and histologic features of systemic infection by CDV, including oculonasal discharge, interstitial pneumonia, evidence of diarrhea, focal myocardial necrosis, and the submitted lesion of hyperkeratosis of the haired skin overlying the shoulders, neck, and head. Interestingly, the epidermis of the foot pads was not noticeably thickened in this case. Fluorescent antibody testing of the brain confirmed infection with CDV.

The additional finding in some slides of multifocal serocellular crusting of the skin surface with intralesional cross sections of nematode eggs is consistent with the gross finding of subcutaneous nematodes suggestive of *Dracunculus insignis* infection. Definitive identification of the parasite was pending at the time of case submission. *Dracunculus insignis* is a member of the spirurid group of nematodes and is commonly found in wild mammals (predominantly raccoons), but can also be transmitted to domestic mammals including dogs and cats.(1) For this parasite to reproduce, the female uterus is prolapsed through an ulcer in the skin to release larvae. The larvae are then ingested by *Cyclops* spp. (an aquatic copepod) where they develop to infective third stage larvae. The copepod is ingested either directly by the definitive host, or can be ingested first by a paratenic host such as a frog. Once ingested by the definitive host, the copepod dies, the infective stage is released, and the larvae penetrate the host's stomach and intestinal wall to mature and reproduce. Once fertilized, the female parasites migrate to the subcutaneous tissues, typically of the lower limbs, to expel ova.(1)

AFIP Diagnosis: 1. Haired skin and subcutis: Epidermal hyperplasia, diffuse, marked, with epidermal and follicular orthokeratotic hyperkeratosis, intracorneal pustules, and few embryonated filarid nematode eggs, etiology consistent with *Filaria taxideae*.
2. Haired skin and subcutis, epidermis, hair follicles, and apocrine glands: Epithelial degeneration, multifocal, mild, with rare intracellular edema and numerous intracellular eosinophilic viral inclusion bodies, etiology consistent with canine distemper virus.

Conference Comment: This case was studied in consultation with Dr. Christopher Gardiner, Consulting Parasitologist to the AFIP Department of Veterinary Pathology; he opined that because adult females of the genus *Dracunculus* expel intact larvae as detailed by the contributor, the thick-shelled, embryonated eggs in the serocellular crust in this case are unlikely to be those of *Dracunculus* sp.(1) Rather, the eggs are interpreted as being most consistent morphologically with those of the primitive filarial nematode *Filaria taxidae*, which has been reported as a cause of filarial dermatitis in the American badger (*Taxidea taxus*),(4,6) striped skunk (*Mephitis mephitis*)(7) and lesser panda (*Ailurus fulgens*).(3) A high prevalence of infection has also been reported in raccoons (*Procyon lotor*) in Texas, but without associated lesions. The life cycle of *F. taxideae* is incompletely described; tabanid flies have been suggested as possible intermediate hosts.(6)

Two surveys of badgers in Wyoming found *F. taxideae* in 81%(6) and 39%(4) of badgers examined, respectively, and an apparent seasonal occurrence of associated dermatitis, with active lesions peaking during the summer. In badgers, gross lesions are most pronounced in the inguinal area, proximal thigh, and ventral abdomen and are characterized by blood-tinged fluid-filled vesicles and/or areas of serocellular crusting and ulceration.(6) In the single published report of filarial dermatitis attributed to *F. taxideae* in a striped skunk, the lesions consisted of large confluent areas of alopecia and marked thickening of the skin overlying the head, thoracolumbar region, and tail base; the description of the lesions in the case report bear striking resemblance to those depicted in the image submitted by the contributor for this case.(7)

Adult filarids are white, often tightly coiled, nematodes ranging from 122-131 mm (males) to 285-420 mm (females) in length; they are readily visualized in the subcutis and fascia, where they elicit little inflammatory response. Lesions result when gravid females deposit eggs in the upper dermis or between the epidermis and cutaneous basement membrane. Early microscopic findings in badgers consist of subepidermal vesiculobullous dermatitis extending into follicular infundibulae, with numerous embryonated filarid eggs occupying vesicles; lesions progress to ulceration and dermatitis, with orthokeratotic hyperkeratosis and acanthosis in the adjacent epidermis.(6) In

skunks, reported lesions include marked epidermal hyperplasia with orthokeratotic hyperkeratosis, and numerous dermoepidermal pustules containing larvated eggs.(7)

Conference participants attributed much of the acanthosis and hyperkeratosis observed in the submitted case to filarial dermatitis, rather than CDV infection, but acknowledged that the CDV inclusions in the epidermis, follicular epithelium, and apocrine glands are numerous and prominent. Infection with CDV may have predisposed this skunk to nematode infection; in addition to the microscopic lesions described by the contributor, several participants' slides contained few pigmented fungal hyphae in the superficial layers of the epidermis, interpreted as opportunistic dematiaceous fungi.

The contributor provides a useful synopsis of CDV infection, which participants reviewed in conference. Attendees briefly reviewed other noteworthy morbilliviruses of importance in veterinary medicine, including measles virus, rinderpest virus, peste-des-petits-ruminants virus, phocine distemper virus, and cetacean morbillivirus.

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CASE II: SP-08-8399 (AFIP 3134511).

Signalment: 12-year-old, female, spayed Toy Poodle dog (*Canis familiaris*).

History: The history provided by the referring veterinarian indicated that the right eye suddenly proptosed and ruptured. The dog had a history of cataracts. In the last few weeks, the dog had developed a purulent discharge from the right eye and had been rubbing its eye.

Gross Pathology: The received sample consisted of a globe with intact inferior and superior palpebrae and third eyelid. The base of the third eyelid was expanded by a well circumscribed, 1.0x1.3x1.0 cm, firm, pale white mass that had central areas of necrosis and hemorrhage. The cornea of the eye adjacent to this mass was indented and the anterior chamber of the globe was moderately collapsed. There were anterior and posterior synechiae between the iris and posterior cornea and the iris and anterior aspect of the lens, respectively.

Histopathologic Description: Sections of globe and periorbital tissue including superior and inferior palpebrae and third eyelid are submitted. The posterior aspect of the base of the third eyelid is expanded by a highly cellular, fairly circumscribed, partially encapsulated, slightly lobulated mass that replaces portions of the gland of the third eyelid. This mass is composed of varying populations of neoplastic epithelial cells and myoepithelial cells. Neoplastic epithelial cells are arranged in tubules, acini, nests, and sheets. Tubules and acini are generally lined by a single densely packed layer of neoplastic epithelial cells. Lumens of these structures often contain variable amounts of blood, eosinophilic to amphophilic secretory product, and few macrophages and/or neutrophils. Neoplastic

epithelial cells are cuboidal to attenuated with mild to moderate amounts of eosinophilic cytoplasm and indistinct cell borders. In some portions of the mass, the cytoplasm of neoplastic cells is obliterated by few sharply defined, open vacuoles. Nuclei are round to ovoid, finely stippled to vesiculated, and generally contain a single prominent nucleolus. Anisokaryosis is moderate. Mitotic figures are uncommon with 4-5 observed per ten high power fields. Neoplastic epithelial cells are supported by variable amounts of fibrovascular stroma containing myoepithelial cells. In some areas, this stroma is characterized by a fine fibrovascular meshwork separating the neoplastic tubules and nests. In other areas, the supporting stroma is composed of moderate bands of dense fibrous tissue. Significant proportions of some lobules are composed of highly cellular populations of spindle shaped myoepithelial cells that are surrounded by dense haphazardly arranged collagenous stroma. Myoepithelial cells have scant to mild amounts of eosinophilic cytoplasm, indistinct cell borders, and round to ovoid, finely stippled nuclei. Vast central areas of the mass are replaced by pools of hemorrhage, organizing mats of fibrin, and amorphous to flocculent proteinaceous fluid containing moderate numbers of hemosiderin and hematoidin laden macrophages and few neutrophils. Such central pools are bordered by dense bands of fibrosis that are often covered by a thin layer of neoplastic epithelial cells. There are few small aggregates of hemosiderin laden macrophages also within the stroma of the mass surrounding central areas of hemorrhage.

The remaining portions of the gland of the third eyelid located adjacent to the mass are compressed and markedly infiltrated by varying numbers and combinations of lymphocytes, plasma cells, histiocytes, hemosiderin laden macrophages, and neutrophils. Lymphocytes form dense sheets and few lymphofollicular aggregates that separate glandular structures. Glandular structures are often tortuous and are occasionally hyperplastic, with hypertrophied plump cuboidal epithelium lining. Glandular structures are variably distended by variable amounts of eosinophilic to amphophilic proteinaceous fluid and occasional neutrophils. Severely distended glandular structures are lined by markedly attenuated epithelium. Occasionally, glandular tubules are surrounded by thin rings of fibrosis. Blood vessels within the gland and the surrounding stroma are prominently congested.

The conjunctival epithelium overlying the mass is variably eroded and ulcerated. There is prominent exocytosis of neutrophils through areas of intact epithelium. In areas of severe erosion, the epithelium is reduced to a thin layer of attenuated cells. In areas of ulceration, there is mild hemorrhage and prominent exudation of fibrin and neutrophils into the conjunctival sac. There is segmental squamous metaplasia of the mucosal epithelium lining the remainder of the conjunctiva, with focal erosion and ulceration. The normal pseudostratified columnar conjunctival epithelium in this area is variably replaced by thick nonkeratinizing squamous epithelium. Goblet cells are rare. In many areas, the superficial surface of the squamous epithelium is eroded and tattered. There is prominent exocytosis of neutrophils through the epithelium, with neutrophils rarely forming small aggregates in the superficial epithelial layers. A variably thick band of primarily lymphocytes and plasma cells, and fewer neutrophils and histiocytes parallels the junction of the mucosal epithelium and the underlying substantia propria of the third eyelid, the palpebrae, and the globe. Blood vessels in the superficial substantia propria of the entire conjunctiva are prominently congested.

The corneal epithelium of the globe is diffusely hyperplastic. The basal border of the epithelium is irregularly undulated with the epithelium rarely forming short thick rete pegs that extend into the underlying stroma. Rare basal epithelial cells contain finely granular, intracytoplasmic, dark brown pigment consistent with melanin. Exocytosis of neutrophils and, to a lesser degree, lymphocytes through the corneal epithelium is focally prominent. The corneal stroma contains small blood vessels lined by plump endothelial cells that are often surrounded by infiltrates of lymphocytes and neutrophils. Ingrowth of blood vessels is most prominent in the superficial corneal stroma, but is also present in the mid and deep stroma. The normal regularly arranged, pale staining corneal stroma is superficially replaced by dense, more haphazardly arranged collagenous stroma. Blood vessels at the limbus are surrounded by aggregates of lymphocytes and plasma cells.

The anterior chamber of the globe is moderately collapsed and contains scant amounts of fibrin and proteinaceous flocculent material. There is widespread synechiation between the axial posterior cornea, the iris, the ciliary body and the lens. In this region, there is focally extensive loss of the corneal endothelium, and the pupillary margins of the iris and the anterior capsule of the lens are adhered to Descemet's membrane by a thick band of fibrosis containing occasional melanin-containing round to spindle cells. This band of fibrosis is continuous with a thin periridal fibrovascular membrane composed of fibroblasts, small blood vessels, and scant collagenous stroma. In some sections, a dense retrocorneal band of fibrosis extends from areas of synechiation over the inferior portions of Descemet's membrane. The pupillary margins of the iris are reflected into the posterior chamber of the anterior compartment by bands of fibrovascular stroma that extend onto the posterior aspect of the iris creating entropion uveae. The pigmented epithelium that normally lines the posterior iris is widely lost and there are numerous loosely

arranged fibrous adhesions between the posterior iris, the pars plicata of the ciliary body, and the lens capsule. The superior aspect of the iris is bowed into the anterior chamber (iris bombé) and the associated ciliary cleft is collapsed. The anterior uvea (iris and ciliary body) is moderately infiltrated by lymphocytes, plasma cells and fewer histiocytes that aggregate around blood vessels. The stroma of the pars plicata of the ciliary body is expanded by edematous, myxomatous matrix containing melanin-laden round cells. A band of dense fibrovascular stroma extending from the ciliary body lines the posterior lens capsule. Within this cyclitic membrane, there are few variably sized, spherical, dull gray bodies consistent with asteroid hyalosis, and many melanin-laden cells.

There is severe cataractous change of the lens. Lens epithelial cells are widely lost. There is marked liquefaction of cortical lens material. Amorphous, eosinophilic pools of liquefied lens material contain numerous granular foci of dense mineralization. There are occasional granular to globular foci of mineralization distributed throughout the remaining lens fibers. The posterior lens capsule is focally wrinkled. There is marked plasmoid degeneration of the vitreous characterized by replacement of normal vitreous with pale eosinophilic flocculent material admixed with dependent aggregates of neutrophils, scant hemorrhage, and occasional pigment-laden cells.

The tapetal (superior) retina is widely detached. Peripheral portions of the tapetal retina are markedly atrophied showing marked loss of neurons throughout all layers, vesiculation of plexiform layers, blending of the inner and outer nuclear layers, and loss of photoreceptors. More centrally within this portion of retina, ganglion cells and inner nuclear layer neurons remain intact, but many neurons in the outer nuclear layer and nearly all photoreceptors are lost. There are rare foci of interretinal hemorrhage. The subretinal space contains mild accumulation of flocculent basophilic material and scant hemorrhage. Retinal pigmented epithelial cells in the superior fundus are markedly hypertrophied, creating rounding and tomb-stoning of the apical border of these cells. The nontapetal (inferior) retina is nondetached, but is severely atrophied. Atrophy within this portion of the retina is often diffuse, but is generally most severe within the inner most retinal layers. In the most severely affected areas, the retina is reduced to a thin layer of glial cells that contains occasional round to spindle shaped pigmented cells. In segmental areas of the nontapetal fundus, there is loss of retinal pigmented epithelial cells with adherence of the atrophied retina to Bruch's membrane. In one area, the nontapetal retina is torn and the anterior portion of the torn retina is detached (not present in all sections). The free end of the torn retina is rounded while the end that remains adherent to the RPE is attenuated. There is mild accumulation of hemorrhage in the subretinal space. Vessels in the choroid and retina are lined by plump endothelial cells and often contain prominent numbers of neutrophils. The neuropil of the optic nerve is mildly vesiculated.

Contributor's Morphologic Diagnosis:

1. Third eyelid:
    - Complex adenocarcinoma of the gland of the third eyelid
    - Chronic lymphoplasmacytic adenitis of the gland of the third eyelid
2. Third eyelid and palpebrae: Severe chronic lymphoplasmacytic and suppurative conjunctivitis with squamous metaplasia and multifocal ulceration
3. Eye:
    - Severe chronic superficial keratitis with corneal epidermalization
    - Retrocorneal fibrous membrane
    - Preiridal fibrovascular membrane
    - Anterior and posterior synechiae, lenticular-corneal synechia, and iridocyclitic synechia
    - Retrolenticular cyclitic membrane
    - Entropion uveae and mild iris bombé
    - Moderate chronic lymphoplasmacytic anterior uveitis
    - Mature cataract (loss of lens epithelium, lens fiber liquefaction, and mineralization)
    - Plasmoid degeneration of the vitreous and asteroid hyalosis
    - Chronic diffuse tapetal retinal detachment with moderate outer retinal atrophy
    - Severe diffuse nontapetal inner retinal atrophy with focal retinal tear and detachment

Contributor's Comment: While this case may not be a diagnostic challenge, as there is an obvious glandular epithelial neoplasm in the region of the gland of the third eyelid, it does present a challenge from a descriptive standpoint, as there are numerous other changes within the adjacent globe and periorbital tissue.

A diagnosis of adenocarcinoma rather than adenoma was based on the moderate cellular atypia of neoplastic epithelial cells and the focal infiltration of neoplastic cells into the partial capsule. Carcinomas of the gland of the

third eyelid may be locally invasive, but metastasis is generally considered rare. In a report by Wilcock and Peiffer, local recurrence occurred in three of four dogs in which a carcinoma of the gland of the third eyelid was excised.(4)

In our case, the neoplastic mass was diagnosed as a complex adenocarcinoma based on the prominence of myoepithelial cells within the mass. On immunohistochemistry, the prominent spindle cell populations within some areas of the mass were immunoreactive for muscle specific actin and a pancytokeratin marker (MNF116), but were not labeled for vimentin. This pattern of immunoreactivity supports the designation of these cells as myoepithelial cells. To our knowledge, complex adenocarcinoma of the gland of the third eyelid has not previously been reported. In the report by Wilcock and Peiffer, spindle-cell and squamous metaplasia was described in a proportion of the tumors.(3) It is possible that the spindle-cell metaplasia described by Wilcock and Peiffer actually represented myoepithelium, but was not addressed as such in their report.

There was marked inflammation within the remaining portion of the gland of the third eyelid and throughout the conjunctiva. Such inflammation may be secondary to the mass itself and local irritation, but a secondary bacterial infection cannot be ruled out. The changes within the globe are numerous, and all are likely secondary to the presence of the mass in the third eyelid and associated trauma.

Corneal epidermalization (cutaneous metaplasia) is an adaptive change to chronic superficial irritation/trauma. Such change in this case was characterized by epithelial hyperplasia with mild rete peg formation, rare epithelial pigmentation, and superficial stromal fibrosis and vascularization. Keratinization of the corneal epithelium is another feature that is commonly seen with corneal epidermalization, but it was not prominent in this case.

Chronic uveitis likely led to the formation of a preiridal fibrovascular membrane, a retrocorneal fibrous membrane, a retrocorneal cyclitic membrane, and multiple synechiae between the cornea, iris, lens and ciliary body. The widespread synechiae between the iris, lens, and cornea resulted in obstruction of the pupil and glaucoma. Changes consistent with glaucoma are most prominent in the nontapetal retina. There is some degree of sparing of the detached tapetal retina in terms of atrophy in comparison to other segments of the retina. Such differences between the degree of atrophy between the tapetal and nontapetal retina and between detached and nondetached portions of the retina are common. The pathophysiology explaining the differences in susceptibility between various segments of the retina is unclear.

The cataractous changes within the lens may have occurred secondary to uveitis and the proliferation of fibrovascular stroma surrounding the lens or may be a degenerative age related change as cataracts were reported in both eyes of this dog. Clear evidence of the reported prolapse of the eye and rupture was not observed in the examined sections.

AFIP Diagnosis: 1. Eye, lacrimal gland: Epithelial-myoepithelial carcinoma of lacrimal gland (low-grade complex adenocarcinoma of the lacrimal gland).
2. Eye, conjunctiva, third eyelid and palpebrae: Conjunctivitis, lymphoplasmacytic and neutrophilic, chronic, diffuse, severe, with squamous metaplasia.
3. Eye, cornea: Keratitis, superficial, diffuse, chronic, severe, with epidermalization.
4. Eye, uvea: Anterior uveitis, lymphoplasmacytic, moderate, diffuse, with anterior and posterior syncehiae, lenticular-corneal synechia, iridocyclitic synechia, and preiridal fibrovascular membrane formation.
5. Eye, lens: Lens fiber degeneration and liquefaction, diffuse, severe, with mineralization (mature cataract) and retrolenticular cyclitic membrane formation.
6. Eye, retina: Detachment, focally extensive, with marked atrophy.

Conference Comment: The submitted section of globe and periorbital tissues, studied in the context of the contributor's detailed, logical morphologic description, provides an eloquent tour through numerous microscopic lesions unique to ocular pathology. Conference participants appreciated the challenge of identifying, describing, and interpreting the numerous ancillary changes present, and in well-constructed comments, the contributor adeptly elaborates on the complex relationships among these lesions and with the neoplasm.

Histologically, the neoplasm resembles epithelial-myoepithelial carcinoma of salivary gland, i.e., well-circumscribed, partially encapsulated tumor of both luminal epithelium and myoepithelium, in which the myoepithelium predominantes and myoepithelial cells are multifocally polygonal with clear cytoplasm. Using the unstained serial histologic sections submitted with this case, immunohistochemistry was performed for cytokeratin AE1/AE3, vimentin, smooth muscle actin, and the myoepithelial markers calponin and p63. Most neoplastic cells

display strong cytoplasmic immunoreactivity for cytokeratin, and many – particularly the spindled neoplastic cells – are strongly immunoreactive for smooth muscle actin. Rare vimentin-positive cells are scattered throughout the tumor; these are interpreted as non-neoplastic supporting stromal cells. While neoplastic cells are negative for calponin by immunohistochemistry performed at the AFIP, over 80% of the neoplastic cells exhibit positive, specific nuclear immunohistochemical staining for p63, which is a sensitive and specific marker for myoepithelium in canine tissue.(2)

The immunohistochemistry results generally agree with those reported by the contributor, and support the presence of myoepithelial proliferation; and although not officially recognized in the current World Health Organization classification scheme, participants agreed with the contributor's diagnosis of complex adenocarcinoma. This case was also studied in consultation with the AFIP Department of Ophthalmic Pathology, which concurred with the diagnosis. Dubielzig and coworkers at the Comparative Ocular Pathology Laboratory of Wisconsin reportedly have collected 109 cases of epithelial tumors of the gland of the third eyelid in dogs, which includes adenocarcinoma, adenoma, and complex and mixed tumors that collectively represent 1.9% of canine tumor submissions to that laboratory.(1)

Conference participants briefly reviewed neoplasia in the nictitating membrane among animals, a rarity in the dog, a species more prone to the development of protrusion of the gland of the third eyelid ("cherry eye"). Squamous cell carcinoma is the most common neoplasm in domestic animal species, particularly in cattle and horses; its prevalence is correlated with high altitude and sunlight exposure. Conjunctival squamous cell carcinoma (SCC) develops via progression from precancerous changes to malignancy, akin to those described for cutaneous SCC: squamous plaque, squamous papilloma, squamous cell carcinoma in situ, and invasive SCC. Less common tumors of the nictitans include vascular tumors (e.g. hemangioma, hemangiosarcoma, and angiokeratoma), lymphoma, melanoma, and mast cell tumor.(3)

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CASE III: D-09-7312(18) (AFIP 3149836).

Signalment: 63-day-old, unknown gender, White Leghorn chicken (*Gallus gallus domesticus*).

History: This white leghorn chicken was hatched from specific-pathogen-free (SPF) eggs and grown up in a clean and non-infectious environment. It was part of a vaccination trial which was recently conducted by this laboratory. The birds were challenged intranasally with a highly pathogenic avian influenza H5N1 virus.

On day two post challenge, this vaccinated chicken was found to be quiet. It was lethargic and anorexic on day three post inoculation and dead on day four. Virus was isolated at day two, three and four days post inoculation from both upper respiratory and cloacal swabs. Post mortem examination was performed and organs submitted for histopathological examination.

Gross Pathology: At post mortem examination, the head region was swollen with an edematous cervicocephalic air sac. The lungs were mildly congested.

Histopathologic Description: Brain: Multifocally, the meninges are massively expanded by an infiltrate of large numbers of heterophils, macrophages, fewer lymphocytes along with abundant fibrin, proteinaceous fluid (edema) and necrotic cellular and karyorrhectic debris. The necrosis and inflammation extends multifocally into the underlying neuropil. Occasionally neuron cell bodies are hypereosinophilic and shrunken with pyknotic nuclei (neuronal necrosis). Neuronophagia is also evident rarely. There is a mild diffuse gliosis. Blood vessels diffusely in the meninges, grey matter, and white matter are lined by reactive endothelial cells and many are undergoing fibrinoid necrosis. Fibrin thrombi are seen multifocally. Perivascular cuffs are prominent and comprised of macrophages and lymphocytes.

Contributor's Morphologic Diagnosis: Brain: Meningoencephalitis, diffuse, severe, fibrinous, heterophilic and lymphohistiocytic with fibrinoid necrosis, vasculitis and thrombosis, white leghorn chicken, avian.

Contributor's Comment: Highly pathogenic avian influenza (HPAI) is caused by infection with influenza A viruses of the family Orthomyxoviridae.(5) The viral genome is composed of eight segments of single-stranded, negative-sense RNA that code for ten proteins.(6) Two of these proteins are hemagglutinin (HA) and neuraminidase (NA). All 16 HA and 9 NA influenza A subtypes have been isolated from avian species but HPAI viruses have been restricted to subtypes H5 and H7.(5)

The HA gene is the primary determinant of high pathogenicity in chickens, but a proper constellation of all eight gene segments is required for the maximal expression of virulence potential. The cleavage of the HA into the HA1 and HA2 proteins is essential for the virus to be infectious and produce multiple replication cycles. In moderately pathogenic AI viruses, trypsin-like proteases found in restricted anatomical sites, such as respiratory and intestinal epithelial cells or within secretions of the respiratory lumen, are required to cleave the HA and thereby produce infectious virus. However, in HPAI viruses the HA is cleaved by ubiquitous furin proteases present in many cells of numerous visceral organs, the nervous system and the cardiovascular system. Trypsin-like proteases will also cleave the HA of HPAI viruses.

An issue separate from HA cleavability is receptor binding between the receptor-binding site of the HA and the receptor on the host cells. This is a poorly understood phenomenon but impacts both host specificity (host-adaptation) and cell or tissue tropism within the host. This may restrict virus replication to specific cells, tissues and organs. Changes in the receptor-binding site of the HA have been shown to change the host range of an influenza virus. Both the virus and the host impact receptor binding.

Avian influenza viruses exert pathological effects on avian cells by two mechanisms: necrosis and apoptosis. Necrosis has been associated with intense virus replication and demonstration of abundant AI viral nucleoprotein in the nucleus and cytoplasm. Apoptotic cell death has been demonstrated in various cell culture systems. In chicken embryos, apoptosis and necrosis may share similar biochemical features and their differentiation is neither always easy nor clear.

Typically, histological lesions consist of multi-organ necrosis and/or inflammation. The most consistently and severely affected tissues are the brain, heart, lung, pancreas and primary and secondary lymphoid organs. Lymphocytic meningoencephalitis with focal gliosis, neuronal necrosis and neuronophagia are common, but edema and hemorrhage may be seen. Lesions in the brain have abundant associated influenza virus proteins in neurons.(6) In our case, immunoperoxidase staining revealed antigen in a variety of cells in the brain including endothelial cells, neurons, perivascular cuffs, ependymal cells as well as inflammatory cells in the meninges. Lesions were present in most organs including the lung, heart, kidney, spleen, ventriculus, small and large intestines, and pancreas.

In most cases involving chickens, HPAI is fulminating with some birds being found dead prior to observance of any clinical signs. If the disease is less fulminating and birds survive for 3-7 days, as in our case, individual birds may exhibit nervous disorders such as tremors of the head and neck, inability to stand, torticollis, opisthotonos and other unusual positions of head and appendages. Respiratory signs are less prominent than with less pathogenic AI viruses, but can include rales, sneezing and coughing.

The virus is transmitted by direct contact between infected and susceptible birds or indirect contact through aerosol droplets or exposure to virus-contaminated fomites. Aerosol generation from the respiratory tract is a significant mode of transmission because of high virus concentrations in the respiratory tract, but the large volume of lower concentration AI virus in infected feces makes fomites a major mode of transport.(6)

The importance of the human health implications of AI infections were revealed during the 1997 Hong Kong outbreak, in which the H5N1 virus was shown to have infected 18 people, six of whom died.(1) This virus, which is panzootic in poultry, continues to spread and pose a major challenge to animal and human health. While the H5N1 virus transmits zoonotically from infected poultry to humans, often with fatal consequences, such transmission remains inefficient. Although the virus replicates efficiently in diseased humans, it has not yet adapted to efficient human-to-human transmission. The H5N1 virus therefore continues to challenge our understanding of interspecies transmission of influenza viruses.(4)

AFIP Diagnosis: Brain: Meningoencephalitis, necrotizing, acute, diffuse, severe, with multifocal neuronal necrosis, gliosis and vasculitis.

Conference Comment: We thank the contributor for the timely provision of this relevant case, which features an etiology with tremendous global economic and public health implications. Without having the elevated index of suspicion afforded by knowing the history or age of this chicken, most conference participants considered several other etiologies much more likely than HPAI (fowl plague) in the differential diagnosis, including nutritional encephalomalacia (e.g. vitamin E deficiency), fungal encephalitis, or bacterial infection with septicemia, among others.

Vitamin E deficiency affects chicks, causing encephalomalacia, exudative diathesis, and nutritional myopathy. Encephalomalacia usually manifests clinically between days 15 and 30 of life as ataxia or paresis, and grossly, hemorrhages are often noted on the cerebellar surface. Microscopic lesions include ischemic necrosis, demyelination, and neuronal degeneration, most prominently in the cerebellum, striatal hemispheres, medulla oblongata, and mesencephalon.(3) The submitted case is characterized by more severe inflammation than would be expected in nutritional encephalomalacia.

Fungal encephalitis of young chickens, turkey poults, and quail chicks is caused by the dematiaceous thermophilic fungus *Ochroconis gallopavum* (*Dactylaria constricta* var. *gallopava*). Gross lesions may involve both the cerebellum and cerebrum, and range from hard, gray, well-circumscribed foci to focally extensive areas of red discoloration. Histologic lesions include infiltration by numerous heterophils, macrophages, and multinucleated giant cells centering on areas of necrosis with numerous readily-apparent dematiaceous fungal hyphae, which are conspicuously absent in this case.(2)

The contributor provides a succinct review of AI in general, and H5N1 HPAI specifically, which since 2003 has produced natural infection in a number of species, including humans, domestic pigs, dogs, cats, tigers, leopards, stone martins, and civets. Migratory aquatic birds, particularly those belonging to the orders Anseriformes and Charadriiformes, are the reservoirs of all AI viruses, and typically do not develop disease due to infection. In poultry, as described by the contributor, clinical signs and pathology depend not only on the pathotype of AI virus (i.e. low pathogenicity [LP] or high pathogenicity [HP]), but also on host species, age, sex, immune status and environmental factors, among others. The gross and histologic lesions of HPAI listed by the contributor are nonspecific, and the differential diagnosis includes velogenic Newcastle disease virus, septicemic fowl cholera (*Pasteurella multocida*), heat exhaustion, water deprivation, and several toxins. For LPAI, which affects the respiratory tract and causes reduced egg production, the differential diagnosis is long, and includes lentogenic Newcastle disease virus, avian pneumovirus and other paramyxoviruses, infectious laryngotracheitis (gallid herpesvirus 1), infectious bronchitis (avian coronavirus), chlamydiosis and mycoplasmosis, among others. As such, the diagnosis of AI infection requires the employment of virologic and serologic methods.(5)

Conference participants briefly discussed several salient properties of influenza viruses in general. Ultrastructurally, virions are spherical to pleomorphic and range from 80 to 120 nm in diameter, although filamentous forms may be much longer.(5) Germane to any review of influenza virus epidemiology is mention of the two mechanisms by which new variants of the virus emerge, forcing the continual need for vaccine reformulation to maintain population immunity: antigenic drift, accomplished through point mutations; and antigenic shift, resulting from genomic segment reassortment when two influenza viruses infect the same cell. Notably, both human and avian influenza viruses have established stable infections in pigs, which is attributed to the presence of receptors for both types of viruses on porcine epithelium; accordingly, pigs are regarded as a potential “mixing vessel” for the generation of pandemic influenza virus through reassortment.(4)

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http://www.afcd.gov.hk

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CASE IV: C9775-08 (AFIP 3149913).

Signalment: 2.5-year-old, male American pit bull terrier (*Canis familiaris*).

History: A young pit bull dog presented to a veterinary clinic with a 5-day history of lethargy and vomiting. Initial blood work revealed the following: BUN 76 mg/dl (7-25), creatinine 5.3 mg/dl (0.5-1.4), phosphorus 10 mg/dl (9-10.8), calcium 9 mg/dl (9-10.8), total protein 8.1 g/dl (5.4-7.1), albumin 2.4 g/dl (2.5-3.6), globulin 5.7 g/dl (2.4-3.6) and amylase 1,056 U/L (510-1,864); other values were within normal limits. The owner's initial concern was that the dog had been poisoned and the veterinarian's presumptive diagnosis was ethylene glycol toxicity. Some treatment was attempted, but the dog was euthanized shortly after presentation.

Gross Pathology: The dog was in good body condition. Mucous membranes were pale with occasional random petechiae. The kidneys were bilaterally swollen and had prominent hyperemia of capsular vasculature. The subcapsular surface of the kidney and the corresponding cut surface of the cortex were pale tan and had numerous, disseminated, slightly raised, tan to white, pinpoint to 0.2 cm foci. A raised, fairly well-delineated, irregular, 0.2-0.5 cm band of similar coalescing nodular foci followed the corticomedullary junction; occasional sometimes discontinuous similar bands were in the adjacent outer medulla. A wider dark reddish purple medullary band that was up to 1.2 cm wide extended from the renal crest into the medulla. The renal pelvis was dilated. Some pale tan streaks radiated from the capsular surface into the medulla. The urinary bladder was distended with pale yellow urine. The lungs were red and some frothy fluid was present on the cut surface.

Laboratory Results: Serology (Texas VMDL) revealed the following titers:

- *L. pomona* 12,800
- *L. grippotyphosa* 12,800
- *L. bratislava* 12,800
- *L. hardjo* 3,200
- *L. icterohaemorrhagiae* 3,200
- *L. canicola* 3,200

PCR of kidney and urine for *Leptospira* sp. (Texas VMDL) was positive.

Histopathologic Description: An intense predominantly mononuclear interstitial inflammatory infiltrate was within the cortex and outer medulla, although similar filtrates occurred in the inner medulla. Lymphocytes, plasma cells and macrophages predominated, although neutrophils were intermingled in multiple foci. These infiltrates often separated and effaced tubules within the cortex. Intermittent tubules had attenuation or irregularity of the tubular epithelial lining and luminal necrotic debris. The inner medulla along the renal crest had extensive necrosis and hemorrhage. Warthin Starry stain revealed clumps of black argyrophilic material within tubular lumina and in the apical cytoplasm of tubular epithelial cells. No discrete leptospires were identified. However, the argyrophilic material corresponded with discrete positive staining by immunohistochemistry (Purdue ADDL). The staining could be identified both within proximal convoluted tubules and collecting ducts.

Contributor's Morphologic Diagnosis: Tubulointerstitial nephritis, lymphoplasmacytic, with necrosis, subacute, diffuse, severe. Etiology: *Leptospira* sp.

Contributor's Comment: Leptospirosis is a ubiquitous and important bacterial infection resulting in significant disease in food animals, dogs and humans. Part of the enigma and mystery of leptospirosis is a consequence of cycling of infection in wildlife species resulting in sporadic spillover into domestic animals and humans. Although lately the presumed reemergence of leptospirosis has fallen into the opportunism of blaming global warming, a more likely explanation of the increased awareness is improved methods of detection. The organism has unique niche requirements and does not multiply outside of a host species, although it can survive quite well in wet soil, and, particularly, stagnant surface water. Transmission is typically by direct contact with infected urine or discharges subsequent to abortion; such contact may occur indirectly from water contaminated with the urine of wildlife carriers.

Classically, hosts for leptospirosis have been subdivided into primary versus incidental or accidental. Therefore, dogs are regarded as the primary host for *Leptospira canicola* and accidental hosts for *Leptospira icterohaemorrhagiae* (primary host, rat). In the last 12 years or so, multiple outbreaks of leptospirosis have been attributed to non-canine serovars such as *Leptospira grippotyphosa* (primary host, vole), *Leptospira pomona* (primary host, cattle and pig) and *Leptospira bratislava* (primary reservoir, pig and horse). The dog in the case submitted had high serologic titers to all of the atypical canine serovars. Although it is fun to speculate that *Leptospira grippotyphosa* is the primary infection and that the other serovars are cross reactions, this is always arrogant speculation and not evidence-based science.

The *Leptospira* microscopic agglutination test (MAT) is ideally performed on paired sera 3-4 weeks apart, looking for a fourfold rise in antibody titer. This is likely more important with *Leptospira canicola*, particularly if a dog was previously vaccinated. The high levels seen in this case are more typical of an accidental host with a non-canine serovar. Antibodies are typically first detected 7-10 days after infection. Several other diagnostic techniques were pursued to confirm the diagnosis. PCR of kidney and urine was positive for *Leptospira* DNA (Texas VMDL). This is a genus-specific result only. Warthin-Starry silver staining was attempted to demonstrate leptospires in tubules and was unsuccessful. Immunohistochemistry was performed (Purdue ADDL) revealing convincing clumped *Leptospira* antigen in tubular epithelial cells and tubular lumina. This disparity was interpreted as a consequence of lack of viability of the leptospires due to the prolonged postmortem interval. Similarly, dark field microscopy of urine was inconclusive; this test also requires fresh urine to observe normal leptospires. Fluorescent anybody testing of centrifuged urine sediment also has the advantage of not requiring leptospires to be viable. Researchers at Mississippi State University have identified transcriptional regulator genes that are present in pathogenic *Leptospira* strains and absent in non-pathogenic strains. PCR primers have been developed that conceivably can easily separate pathogenic from nonpathogenic *Leptospira*.(4)

The stratified appearance of an intense white band in the inner cortex and zones of hemorrhage and necrosis in the medulla are a classic pattern of acute leptospirosis culminating in acute renal failure in dogs. A series of these cases was studied retrospectively and prospectively and determined to have a unique ultrasonographic pattern strongly suggestive of acute leptospirosis by Lisa Forrest and colleagues at the University of Wisconsin.(1) When dogs are presented in acute renal failure to veterinarians, initiation of appropriate antibiotic therapy requires timely decisions, and ultrasonography was determined to be a strongly suggestive finding for identifying leptospirosis due to atypical serovars. Otherwise, many of these dogs are euthanized with the presumption of chronic renal failure.

The classification of *Leptospira* has recently been changed.(3) Previously, one pathogenic species (*Leptospira interrogans*) and one nonpathogenic species (*Leptospira biflexa*) were recognized. These two species were subdivided into serovars—200 in *Leptospira interrogans* and around 60 in *Leptospira biflexa*. Based on DNA hybridization *Leptospira* has been reclassified into 13 genomospecies. Since both pathogenic and nonpathogenic species may occur in a single genomospecies, the utility of this scheme for veterinarians, microbiologists, pathologists and others dealing with the disease has not been clarified. Therefore, serovars and serogroups will likely persist in diagnostic reports.

AFIP Diagnosis: Kidney: Nephritis, tubulointerstitial, lymphoplasmacytic and neutrophilic, diffuse, severe, with tubular degeneration and necrosis and focally extensive medullary hemorrhage.

Conference Comment: The contributor provides an instructive example of this entity, the importance of which in both veterinary and human medicine is apparently ever-growing. In general, leptospirosis is characterized by any combination of septicemia, hepatitis, nephritis, and meningitis in humans and animals, and abortion and stillbirth in livestock. In maintenance hosts, which serve as the natural reservoir for the spirochete, the organism persists in the renal proximal convoluted tubules, and in some cases, the genital tract. As the contributor notes, recent taxonomic revisions have introduced tremendous complexity into the classification of *Leptospira* spp. Fortunately the serovar, which correlates most reasonably with epidemiology and disease, persists in the current nomenclature, and many circumvent the new taxonomy altogether by simply abbreviating to genus and serovar names, as in the contributor's comments. The bulk of the discussion during conference was devoted to comparative pathology of leptospirosis, as outlined in the table that follows:(2,5-9)

Leptospira Serovars, Maintenance Hosts, and Disease		
Serovar	**Maintenance host(s)**	**Significant Disease**
canicola	Dog	Dog: primarily renal disease; now rare due to vaccination
grippotyphosa	Raccoon, skunk, rodent	Dog: renal and hepatic disease; increasingly important
		Horse: abortion, premature foaling
icterohemorrhagiae	Rat	Dog: primarily hepatic disease; hyperacute disease in puppies; now rare due to vaccination
bratislava	Pig, horse, +/- dog	Dog: nephritis and abortion
		Pig: abortion, small litters of weak piglets
		Horse: abortion, premature foaling
pomona type kennewicki	Pig	Dog: renal and hepatic disease; increasingly important
		Pig: abortion, small litters of weak piglets
		Cattle: • Acute form (calves): hemoglobinuria, hematuria, fever, anemia, icterus, dyspnea, +/- meningitis • Acute form (adults): agalactia, abortion of decomposed fetus • Chronic form (adults): abortion, stillbirth, or premature weak calves
		Horse: • Chronic form: recurrent uveitis ("periodic ophthalmia"), abortion, premature foaling • Acute form (rare): fever, icterus
		Pinnipeds: abortions, hemorrhagic syndromes in fetuses and neonates, interstitial nephritis and glomerulonephritis, hepatic necrosis
autumnalis	Rodents	Dog: renal and hepatic disease; increasingly important
		Pig: infertility syndrome ("repeat breeder")
hardjo type hardjo-bovis (North America)	Cattle, sheep	Cattle: chronic form; abortion, stillbirth, or premature weak calves
		Sheep: • Lambs: acute form; similar to *pomona* in calves • Ewes: late-term abortion, stillbirth, weak lambs, agalactia
hardjo type hardjoprajitno (Europe)	Cattle	Cattle: • Subacute form: "milk drop syndrome," "flabby udder mastitis" • Chronic form: abortion, stillbirth, or premature weak calves
		Sheep: • Lambs: acute form; similar to *pomona* in calves • Ewes: late-term abortion, stillbirth, weak lambs, agalactia

ballum	Mouse	Hamster: severe hemolysis, icterus, hemoglobinuria, nephritis, hepatitis

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