CASE I – 12-62868 (AFIP 2841154)

Signalment: 1.5-year-old, male, domestic ferret (*Mustela putorius furo*)

History: Blood donor noted to have a systolic murmur on routine examination. Echocardiogram performed and an apparent valvular defect noted. Animal humanely euthanized.

Gross Pathology: A 15 mm in diameter, round, well-encapsulated, reddish/black, firm mass replaces the left adrenal gland. On cut surface, the mass consists of a fleshy reddish-brown 1-4 mm thick capsule surrounding a central core of blackish/gray fibrillar material resembling hair that is compacted into a tight ball. Within the mass are several 2-3 mm in diameter areas of bony tissue. The left kidney is not involved in the mass. The right adrenal gland is within normal limits. The left ventricle of the heart is markedly dilated and rounded, although the left atrium is relatively normal sized. The septal leaflet of the mitral valve has a 6 mm in diameter opening through the body of the leaflet. Edges of the defect are smoothly rounded with only a slight uniform increase in valve thickness at the edges. There are no endocardial lesions in the left atrium.

Laboratory Results: N/A

Contributor’s Morphologic Diagnosis: Left adrenal gland: Teratoma.

Contributor’s Comment: A well-circumscribed mass of mixed fat, muscle, nervous tissue, sebaceous glands, hair shafts, follicles, and large cysts filled with hair shafts and abundant degenerate keratin compresses the surrounding thin layer of adrenal cortical tissue, leaving only a 10-30 cell layer thick rim. Moderate amounts of dense fibrous connective tissue, loose connective tissue and small nodules of bone with marrow elements are interwoven throughout the mass. Cysts are lined by a thin layer of stratified squamous epithelium with some areas of hyperplasia and exfoliation of squamous cells. Hair follicles, some hyperplastic, and sebaceous glands open into
these cysts. Scattered cystic structures are lined with ciliated respiratory epithelium and do not contain keratin. Small numbers of lymphocytes, neutrophils, macrophages and multinucleated giant cells infiltrate throughout the mass. Macrophages and multinucleated giant cells contain large amounts of granular, dark brown material.

Teratomas have been reported in humans, primates, the dog, cat, horse, sheep, ox, rabbits, swine, laboratory rodents, ferrets, poultry, a blue heron, frogs, hares, squirrels, and a spot-necked otter. These neoplasms consist of tissues from multiple germ cell lines, including ectoderm (nervous tissue, linings of the oral and nasal cavities, and epidermal structures of the skin, including adnexal structures), mesoderm (connective tissue, muscle, bone, cartilage, and urogenital and cardiovascular system structures), and endoderm (gastrointestinal and respiratory epithelium, including glandular structures). In the human and laboratory rodents, these are often malignant, with metastasis to other organs. In other domestic species, teratomas are more commonly benign.

The most common site of occurrence for teratomas in all species is in the gonads (comprising over 10% of all ovarian tumors in dogs, yet less than 1% of all tumors), presumably due to development from either diploid premeiotic or haploid postmeiotic germ cells. Extragonadal teratomas, while rare, have been reported in humans, an ox, a kitten, a sheep, a calf, rabbits, rats, ducks, ferrets, and a blue heron. Adrenal teratomas in particular have been reported in humans, an ox, a rat, and, most recently, in ferrets. These extragonadal teratomas are presumed to have developed from pluripotent cells that have not undergone embryonal organization during development and migration.

Teratomas have been referred to by a variety of terms due to the widely variable and complex histologic appearance of these neoplasms. The term “dermoid cyst” is often used to refer to a teratoma evidencing only 2 out of the 3 germ cell lines, specifically the ectodermal and mesodermal lines. In teratomas of this type, the mass is comprised of a central core of keratin surrounded by stratified squamous epithelium, adnexal structures, and connective tissues. A dermoid cyst carries with it the implication that the tumor is found in either the subcutis or the cornea, being a congenital or trauma-induced cystic lesion of the epidermis and associated adnexal structures. The term “germ cell tumor” is used when the teratoma is thought to have arisen from premeiotic diploid germ cells or postmeiotic haploid germ cells within the gonad. An “immature teratoma” is one in which there are not only elements of the three germ cell lines, but also nests of poorly differentiated mesenchymal tissue.

The lack of any sort of clinical signs indicative of adrenal disease in this animal suggests that the presence of this tumor was not a significant detriment to the overall adrenal function of the animal. The degree of compression of the left adrenal gland may have compromised the hormonal function of that adrenal, but the normal right adrenal gland seems to have maintained normal systemic hormonal function, at least from a clinical standpoint. This is similar to the normal adrenal function observed in ferrets with either leiomyomas or leiomyosarcomas of the adrenal gland.

Adrenal tumors are quite common in domestic ferrets (16.7% of all neoplasms). Although these are usually adrenocortical in origin, smooth muscle tumors are also reported, as are pheochromocytomas. The previous report of four adrenal teratomas in
ferrets, together with this case, suggests that teratomas should be added to the list of differentials for adrenal masses.

**AFIP Diagnosis:** Adrenal gland, left (per contributor): Teratoma, mature, ferret (*Mustela putorius furo*), mustelid.

**Conference Comment:** The contributor has provided a superb review of teratomas. We prefer to use the term mature when the germ layer components of the teratoma are uniformly well-differentiated. Neoplasms of the ferret adrenal gland that are more common than teratoma, include adrenocortical adenomas and carcinomas, and leiomyosarcomas. The adrenocortical neoplasms are often estrogen secreting, resulting in characteristic cutaneous, behavioral and reproductive clinical signs that are designated adrenal-associated endocrinopathy.

**Contributor:** Colorado State University, Department of Microbiology, Immunology, & Pathology, 1628B Campus Delivery, Fort Collins, CO 80523-1682

**References:**

**CASE II - 95-1872 (AFIP 2839453)**

**Signalment:** Two and one half week old, female, Hereford calf

**History:** The calf was orphaned at one and one half weeks of age. She was presented to the hospital emaciated and depressed and would not suckle. After some improvement the calf developed a fever and deteriorated and was euthanatized.
**Gross Pathology:** The rumen contained milk, corn and hay. Both the rumen and reticulum had marked proliferation of the mucosa with hyperkeratosis producing a corrugated surface. Ulcers were present on the rumen pillars and scattered through the rumen and reticulum.

**Laboratory Results:** N/A

**Contributor’s Morphologic Diagnoses:** Reticulitis, proliferative, pustular, diffuse, severe, bovine

**Contributor’s Comment:** This reticulum has marked epithelial hyperplasia with edema and vesicle formation. Artifactual separation of the upper epithelium is evident. There is severe purulent inflammation of the epithelium and within the lumen with microabscess formation. Large numbers of bacilli are on the luminal surface along with a few yeast organisms consistent with *Candida*.

This lesion is typical of that produced in lactic acidosis due to grain overload. In this calf on a milk diet the lesion is caused by excessive milk entering the rumen and producing lactic acidosis. This can be caused by consumption of excessive amounts of milk, reticular groove dysfunction, or tube feeding of milk. The disease is not usually fatal but can result in weight loss and poor condition.

**AFIP Diagnosis:** Reticulum: Reticulitis, acute, diffuse, moderate, with multifocal ulceration, Hereford, bovine.

**Conference Comment:** The pathogenesis of ruminal lactic acidosis usually begins with the abrupt engorgement of highly fermentable carbohydrates (cereal grains, fruits, root crops). Without adequate time for rumen microbial adaptation to such foods, the ingested carbohydrates promote the overgrowth of *Streptococcus bovis* and *Lactobacillus* sp. These bacteria produce sufficient lactic acid to lower the rumen pH to below 5. In the early stages of acidic fermentation, abundant volatile fatty acids (VFAs) are also produced and contribute to lowering the ruminal pH. The resultant acidity destroys the normal rumen microflora, damages the mucosa, and drives VFAs to their nondissociated state. Increased amounts of the latter are absorbed through the rumen wall and induce ruminal stasis. Death can result from dehydration that is secondary to increased ruminal osmolality, hemoconcentration, systemic acidosis and circulatory collapse. The gross lesions of ruminal lactic acidosis include acute rumenitis with sloughing of the mucosa. Secondary bacterial or mycotic invaders can complicate the rumenitis.

**Contributor:** College of Veterinary Medicine, Virginia Tech, Blacksburg, VA 24061

**References:**
CASE III – 02-439 PCLV (AFIP 2839774)

Signalment: 4-year-old, female, neutered, Rottweiler, Canis familiaris

History: Two draining skin masses removed from right and left flanks. There are many similar lesions in various locations. Lesions first noticed two months ago.

Gross Pathology: N/A

Laboratory Results: N/A

Contributor’s Morphologic Diagnosis: Dermal and subcutaneous perivascular round cell tumor (T cell lymphosarcoma) with lymphohistiocytic vasculitis, perivasculitis, subcutaneous necrosis and invasion of skeletal muscle.

Contributor’s Comment: Greater than 50% of the cellular infiltrate was positive for CD3 antigen as determined by immunohistochemistry performed at the University of California, Davis, and had only faint staining for lysozyme. The predominance of T-cells and perivascular distribution is characteristic of lymphomatoid granulomatosis. The animal died two months after the initial biopsy and a necropsy was not performed.

Lymphomatoid granulomatosis is an angiocentric, angiodestructive, granulomatous disease affecting primarily the lungs. T cell lymphoma can develop as was present in this case. Bizarre multinucleated cells, and eosinophils can also be observed. Eosinophils do not appear to be a significant component of skin lesions. In addition to the skin and lungs, other organs such as the kidneys, liver, and brain can be affected. A few cases in humans have been associated with B cell markers and in some canine cases with typical histologic lesions, a predominant T cell origin for the infiltrating cells cannot be confirmed. The cutaneous lesions can wax and wane before the onset of pulmonary disease and some may regress without treatment. The majority of canine cases reported thus far lack cutaneous lesions. Early skin lesions may lack cellular pleomorphism and resemble non-neoplastic inflammatory diseases. This suggests that the disease may progress from an inflammatory disease to malignant transformation of proliferating lymphocytic elements. The factors involved in such transformation remain undefined.

The disease may be confused with malignant histiocytosis if multiple organs are involved or with allergic or parasitic lung disease since eosinophils are usually prominent in pulmonary lesions. Concurrent heartworm disease has been present in some cases. The angiocentric and angioinvasiveness of the lesions distinguishes lymphomatoid granulomatosis.
AFIP Diagnosis: Haired skin: Malignant lymphoma, angioinvasive, Rottweiler, canine.

Conference Comment: The interesting and controversial subject of lymphomatoid granulomatosis sparked the most discussion both during and after the conference. Participants considered a variety differential diagnoses, including injection site reaction, atypical histiocytic proliferation, lymphohistiocytic inflammation, histiocytic sarcoma, and malignant histiocytosis. We prefer the World Health Organization (WHO) classification for lymphomas that have vascular tropism. Lymphomatoid granulomatosis is now considered a form of angiotropic lymphoma, and the WHO subclassifies angiotropic lymphoma as angiocentric or angioinvasive, based on the degree of vascular involvement. Angiocentric lymphoma is characterized by malignant lymphoid cells that form perivascular cuffs of small arteries and veins and occlude lumina with minimal mural invasion. Alternatively, angioinvasive lymphoma is characterized by focally extensive invasion of vessel walls and occlusion of lumina by malignant lymphoid cells, causing ischemic infarction, and usually occurs in the skin of dogs or cats. In this case, atypical lymphoid cells center around small muscular arteries, with multifocal mural invasion, and extensive areas of infarction, which supports a diagnosis of angioinvasive malignant lymphoma.

Contributor: Phoenix Central Laboratory for Veterinarians, 11620 Airport Road, Everett, WA 98204

References:

CASE IV - 02-10575 (AFIP 2840052)

Signalment: 7-year-old, castrated male, Quarterhorse, Equus caballus, equine

History: The horse rapidly developed clinical signs of hypermetria of all four limbs, facial twitching, bruxism, and extreme hyperesthesia. Due to the rapid progression of clinical signs and the poor prognosis, the horse was euthanized. The horse was vaccinated for rabies virus a year prior to clinical signs and euthanasia.
**Gross Pathology:** The cervical spinal cord was the only portion of the spinal cord examined. There were multifocal, dark red to black, areas of hemorrhage and malacia in the gray matter. There were multifocal hemorrhages within the meninges.

**Laboratory Results:** Fluorescent antibody testing of central nervous system tissue was positive for rabies virus.

**Contributor’s Morphologic Diagnoses:** 1. Trigeminal ganglion. Ganglionitis, nonsuppurative, perivascular and multifocal to coalescing, moderate, subacute with neuronal degeneration, satellitosis, neuronophagia, and rare intraneuronal cytoplasmic inclusion bodies.  
2. Cervical spinal cord. Poliomyelitis, nonsuppurative, perivascular and multifocal to coalescing, moderate, subacute with hemorrhage, neuronal degeneration, satellitosis, neuronophagia, and rare intraneuronal cytoplasmic inclusion bodies.

**Contributor’s Comment:** Within the gray matter of the spinal cord there are perivascular and multifocal to coalescing infiltrates of moderate numbers of lymphocytes with lesser numbers of macrophages and plasma cells and increased numbers of glial cells. Increased numbers of glial cells and inflammatory cells surround occasional neurons. Phagocytosis of occasional neurons by satellite cells, glial cells and macrophages is present, accompanied by neuronal cell debris. A few neurons are degenerate and are characterized by pale staining to hypereosinophilic, central and diffuse chromatolysis, and vacuolization. There are rare intraneuronal eosinophilic cytoplasmic inclusion bodies (Negri bodies). Variable numbers of neurons contain lipofuscin pigment. The gray matter of the spinal cord is vacuolated and has perivascular hemorrhage and edema. Lymphocytes, macrophages and plasma cells surround occasional venules within the white matter and meninges. Not all slides contain all of these lesions. Within the trigeminal ganglion, there are increased numbers of satellite cells and perivascular, perineuronal and multifocal inflammatory cells. There is mild nonsuppurative inflammation in the brain stem and cerebrum, mainly adjacent to the hippocampus. (Tissues not submitted).

Etiologies for nonsuppurative encephalomyelitis in horses within North America include rabies virus, eastern equine encephalomyelitis (EEE) virus, western equine encephalomyelitis (WEE) virus, Venezuelan equine encephalomyelitis (VEE) virus, West Nile virus, equine herpesvirus type 1 (EHV-1), *Sarcocystis neurona* (equine protozoal encephalomyelitis (EPM)), and occasionally equine infectious anemia virus. The clinical signs, macroscopic pathology, and microscopic pathology of all of these agents can be similar, and definitive diagnosis is often made with ancillary testing (i.e., virus isolation, fluorescent antibody testing, or immunohistochemistry). Microscopically, rabies virus causes nonsuppurative, mainly lymphocytic, polioencephalomyelitis and ganglionitis (initially craniospinal ganglia progressing to ganglia throughout the body) with mild neuronal degeneration and neuronophagia. Cytoplasmic inclusion bodies (Negri bodies) are often not present in neurons, but are in neurons that appear healthy when they do occur. The number of Negri bodies is reportedly inversely proportional to the amount of inflammation. EEE, WEE, and VEE virus infection is also characterized...
by nonsuppurative polioencephalomyelitis, but there is suppurative and mononuclear inflammation early in the infection, which progresses to mainly nonsuppurative inflammation. In VEE and EEE, there can also be necrotizing vasculitis, thrombosis, and cerebrocortical necrosis. The lesions are mainly in the gray matter of the cerebral cortex, but can involve the spinal cord gray matter. The trigeminal ganglia are reportedly not affected. West Nile virus infection in horses also causes polioencephalomyelitis with lymphocytes, macrophages, glial nodules, neutrophils and occasional neuronophagia. The characteristic lesion of EHV-1 infection is vasculitis, with thrombosis and infarction. The lesions of EPM are characterized by necrosis, axonal swelling, and hemorrhage, with infiltrates of lymphocytes, macrophages, neutrophils, eosinophils, and occasional multinucleated cells. Intracellular and extracellular organisms may or may not be present. Inflammation can be perivascular or within the neuropil. Lesions of EPM can occur anywhere in the neuroaxis, but are most prominent in the cervical and lumbar intumescences of the spinal cord. Occasionally equine infectious anemia virus causes nonsuppurative to granulomatous encephalomyelitis, which is centered on the ventricular system, and leptomeningitis.

Rabies virus is a neurotropic virus of the genus *Lyssavirus*, family Rhabdoviridae. It is most often transmitted by the bite of an infected animal. All mammals are thought to be susceptible. Rabies virus is maintained in wildlife with extension into the domestic animal population and occasionally humans. However, with specific geographic areas, rabies usually involves a unique virus variant that is transmitted predominately within a single species. In the United States, the common variants are the raccoon variant in raccoons along the East Coast, the skunk variants in skunks within the Midwest, portions of the Southwest, and California, and the bat variants in bats. A single bat species may have its own variant of rabies virus. Recently, there has been an increase in human rabies cases caused by the bat variant. Because bat bites are small and often go undetected, this has raised some question about the mode of transmission of the bat variant viruses. The prevailing theory is that people are unknowingly bitten by a bat. However, aerosol transmission (exposure of spelunkers in caves heavily laden with bat urine and guano) and a second host that after being bitten by a bat, transmits the virus to humans, have been proposed as mechanisms of transmission.

Following inoculation, rabies virus replicates within myocytes. The virus then invades the axon terminals of motor neurons and the neuromuscular and neurotendinous spindles, to allow access to sensory axon terminals. After entry into the axon, rabies virus moves by retrograde axoplasmic flow to the spinal cord ventral horn or to the brain stem nuclei via motor neurons or to the craniospinal ganglia via sensory neurons, to gain access to the central nervous system (CNS). In the CNS, the virus continues to move by axonal transport from neuron to neuron via synapses. Rabies virus disseminates widely in the brain and spinal cord. Centrifugal spread along visceral nerves results in rabies virus infection of the main viscera, skin, eyes, brown fat, and salivary glands. The virus buds into the lumen of the salivary gland acini after replicating within the epithelium. The presence of rabies virus in the saliva along with aggressiveness results in an excellent chance of viral transmission from an infected to a susceptible host.
AFIP Diagnoses: 1. Ganglion, trigeminal (per contributor): Ganglionitis, nonsuppurative, diffuse, moderate, with neuronal degeneration, necrosis, satellitosis, neuronophagia, and rare intracytoplasmic eosinophilic inclusion (Negri) bodies, Quarterhorse, equine.  
2. Spinal cord: Poliomyelitis, nonsuppurative, multifocal, mild, with neuronal degeneration and necrosis, rare intracytoplasmic eosinophilic inclusion (Negri) bodies, and hemorrhage.

Conference Comment: The contributor has provided a succinct review of the differential diagnosis for equine nonsuppurative encephalomyelitis. The family Rhabdoviridae includes more than 175 viruses which infect many species; the notable animal pathogens include rabies virus, vesicular stomatitis virus, bovine ephemeral fever virus, and several fish rhabdoviruses. Rhabdovirus virions are classically bullet- or conical-shaped, enveloped, and measure 70 nm in diameter and 170 nm in length. The genome is composed of a single molecule of linear, negative-sense, single-stranded RNA. The severity and extent of nonsuppurative encephalomyelitis and ganglioneuritis with rabies infection varies among species, and is typically most severe in dogs. The horse and dog may have significant neuronal degeneration; however, neuronal changes are usually minimal in cattle. In skunks, foxes, cattle, horses, cats and sheep, rabies virus may manifest as a spongiform change of the neuropil of the gray matter. In carnivores, Negri bodies are classically recognized in the hippocampal neurons, while in ruminants, Negri bodies are found in the Purkinje neurons of the cerebellar cortex. Spinal cord hemorrhage, as in this case, can occasionally be severe in horses and cattle infected by rabies virus and be grossly evident. Additionally, the neuronal changes in this case are more evident in the ganglion, while there is little evidence of neuronal lesions and Negri bodies in the spinal cord.

Contributor: Department of Diagnostic, Medicine, Pathobiology, Kansas State University, 1800 Denison Avenue, Manhattan, KS 66502

References:

Kathleen A. Ryan, DVM
Major, Veterinary Corps, U.S. Army
Wednesday Slide Conference Coordinator
Department of Veterinary Pathology
Armed Forces Institute of Pathology
Registry of Veterinary Pathology*

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