Joint Pathology Center
Veterinary Pathology Services

WEDNESDAY SLIDE CONFERENCE 2017-2018

Conference 11

6 December 2017

CASE I: SQ (JPC 4048071).

Signalment: Adult, female, eastern fox squirrel, *Sciurus niger*, squirrel.

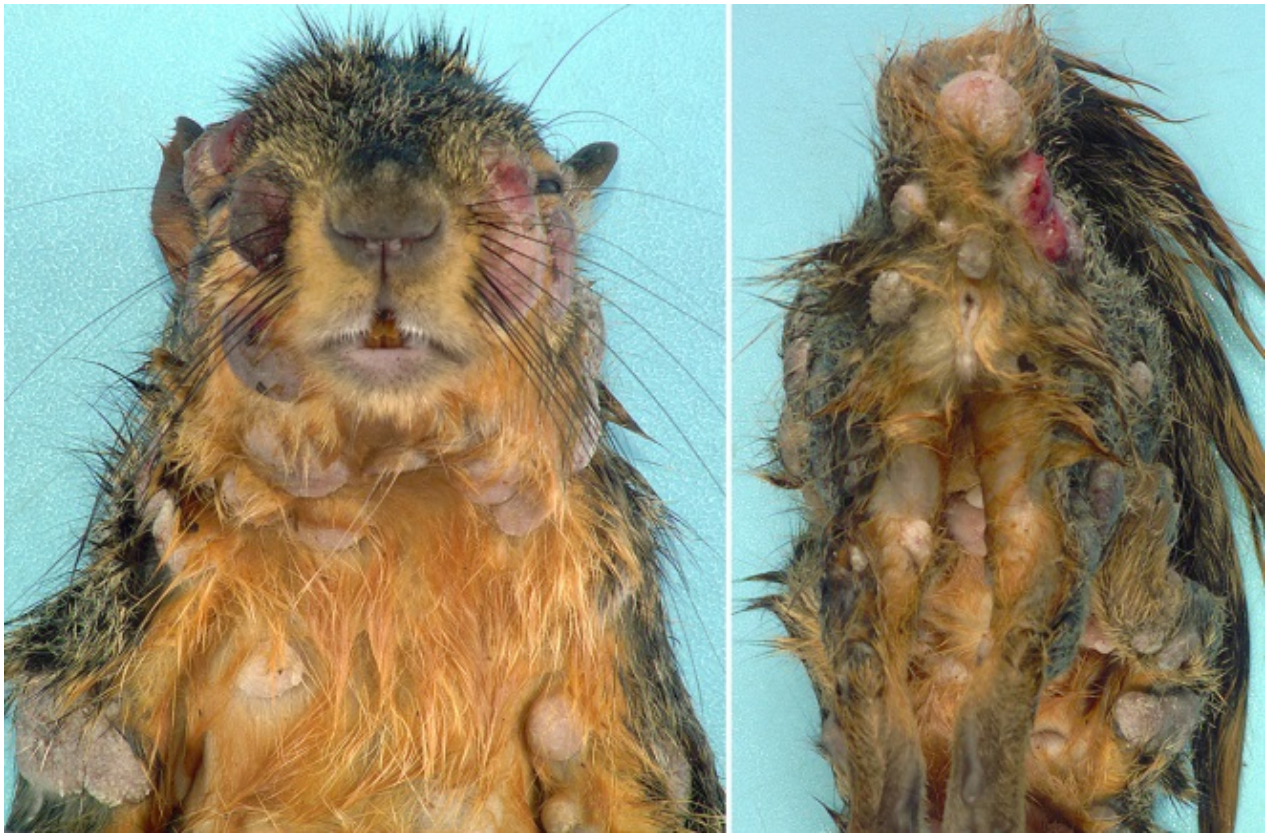
History: This squirrel was found being bitten by a dog. The squirrel died after extrication and the dog's owner presented the squirrel for necropsy due to its unusual external appearance.

Gross Pathology: Distributed throughout the skin, there were numerous (approximately 100), well-demarcated, ovoid to circular, raised nodules ranging from approximately 3 to 35 mm in diameter. The nodules were alopecic, tan to gray, and irregularly smooth surfaced, to variably eroded and ulcerated. On cut section, the nodules consisted of white to tan proliferative soft tissue expanding the dermis. The palpebral fissure of the right eye was narrowed by nodular expansion of the upper eyelid.

The thoracic cavity was filled with blood (hemothorax) and the right thoracic wall had two penetrating, blood-rimmed, tracts (dog bite wounds).

Laboratory results:
PCR using primers targeting the poxviral DNA polymerase and subsequent sequencing had 99% identity with GenBank squirrel fibroma virus isolates.

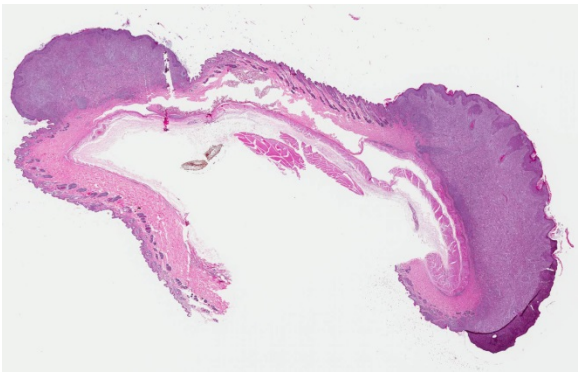
Microscopic Description: Haired skin: The cutaneous nodular lesions were fairly well-demarcated, broad-based, and raised, consisting of nonencapsulated proliferations of spindloid mesenchymal cells expanding and mildly infiltrating the superficial to deep dermis, with regionally moderate epidermal and follicular epithelial hyperplasia. The epidermis had prominent acanthosis, mild irregular granulosis, and mild laminar orthokeratosis, as well as low numbers of multifocally desquamating devitalized superficial keratinocytes. Some sections had mild multifocal superficial erosion associated with focal parakeratosis and sero-cellular crusting, and other sections (not submitted) had regionally extensive ulceration with dense surface crusting and interspersed coccoid bacteria. Moderate numbers of individualized keratinocytes, mainly in the stratum spinosum, had prominent cytoplasmic swelling and pallor (hydropic change, ballooning degeneration), and some of these keratinocytes also contained single to multiple variably sized,



Haired skin, squirrel. Head and neck (cranioventral view) and perineum (caudoventral view with hind limbs retracted toward bottom of image), Squirrel: Numerous raised, alopecic, and variously eroded to ulcerated, cutaneous nodules are distributed throughout the skin. The right upper eyelid is notably markedly enlarged by one of the nodular expansions. (Photo courtesy of: Michigan State University, Diagnostic Center for Population and Animal Health, www.animalhealth.msu.edu))

eosinophilic, globular cytoplasmic poxviral inclusions (approximately 8 to 20 micrometers in diameter). The proliferative spindloid cells were arranged in dense, interweaving, bundles amidst fine collagenous supporting stroma. These cells had small to moderate quantities of eosinophilic cytoplasm, indistinct cell borders, ovoid nuclei, finely stippled chromatin, and 1 to 2, small, indistinct nucleoli. Low to moderate numbers of the cells contained smaller (approximately 6-12 micrometer diameter), paler eosinophilic, cytoplasmic viral inclusions. Anisocytosis and anisokaryosis were mild to moderate, and mitotic cells were rare. Low to moderate numbers of lymphocytes and plasma cells were mixed with the dermal mesenchymal cell proliferation, especially at the deep margin, where they extended perivascularly into the adjacent dermis and hypodermis. In some regions, the superficial dermis also contained few interspersed neutrophils, free erythrocytes (hemorrhage), and scattered shrunken cells with pyknotic and karyorrhectic nuclei.

Contributor's Morphologic Diagnosis:
Haired skin: Multifocal dermal fibromas, with moderate epidermal hyperplasia, ballooning degeneration, intraepithelial and intramesenchymal cell cytoplasmic poxviral inclusions, and mild lymphoplasmacytic dermatitis.



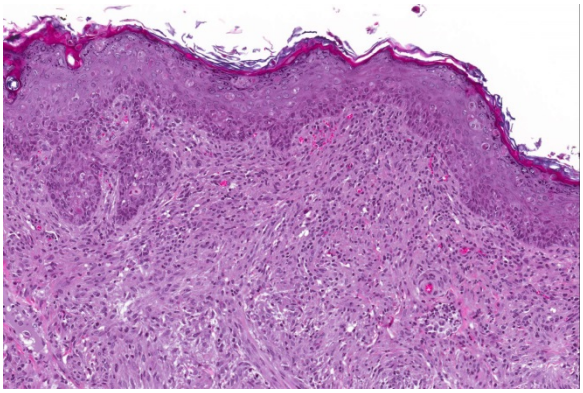
Haired skin, squirrel. There are two dome shaped neoplasms expanding the dermis of the submitted section of haired skin. (HE, 6X)

Contributor's Comment: Squirrel fibromatosis results from infection by squirrel fibroma virus, a poxvirus in the *Leporipoxvirus* genus, closely related to rabbit fibroma virus. The disease has been reported in North American eastern gray, western gray, red, and fox squirrels, and is generally sporadic in occurrence, with rare epizootics.[1] The gross lesions are considerably distinctive, consisting of single to multiple, alopecic, dermal soft tissue nodules that often occur on the face, trunk, limbs, and genital region.[1,9] Involvement of the eyelids has been reported as a common finding[9] (as in Image 1), and nodular lesions in internal organs are less common.[1,7]

Histologically, cutaneous squirrel fibromatosis lesions consist of a combination of typical poxviral epidermal changes and underlying dermal mesenchymal fibroblast-like cell proliferation.[1,9] The epidermal changes are characterized by epithelial hyperplasia, keratinocyte ballooning changes, and eosinophilic intracytoplasmic poxviral inclusions. The proliferative dermal spindle cells have mild cellular pleomorphism and fewer, smaller, intracytoplasmic viral inclusions. Mixed dermal inflammation (consisting of lymphocytes, neutrophils, and macrophages), as well as epidermal erosion, ulceration, and crusting are variable.[1,9] In fewer cases, widespread mesenchymal and epithelial proliferations with intra-cytoplasmic viral inclusions have also been reported to occur at extracutaneous sites, including the lungs, liver, kidney, and lymph nodes.[1,7]

The cutaneous lesions of squirrel fibromatosis are reported to often regress spontaneously, but mortality can occur with debilitation and/or systemic disease. Immunocompetence may play a role in disease susceptibility and the severity of lesions.[1,9] Routes of viral transmission are thought to include biting insects and direct contact, and multifocal lesions may arise from viremia and/or additive cutaneous exposures.[1,9]

Other species-selective poxviral infections of tree squirrels are squirrelpox virus (also previously termed "squirrel parapoxvirus") and the newly described Canadian squirrelpox virus.[1,2,5] In contrast to squirrel fibromatosis, the squirrelpox diseases are characterized by exudative and ulcerative dermatitis lacking nodular dermal mesenchymal proliferations. Furthermore, the squirrelpox diseases have a fatal clinical course (albeit the Canadian disease is limited to a single case report), and the



Haired skin, squirrel. The neoplasms are composed of short interlacing streams and bundles of proliferating fibroblasts. (HE, 140X)

causative poxviruses are distinct from the currently named poxviral genera.[1,2,3,5] Although serologic findings support exposure of North American eastern gray squirrels to the squirrelpox virus of the United Kingdom/Ireland, the gray squirrels do not develop clinical disease. Evidence suggests that the virus was introduced to the UK with the eastern gray squirrels and it now threatens the survival of European red squirrels.[4,5]

Table 1. Relevant details of squirrel-selective poxviral infections[1,2,3,5]

Disease Name	**Virus (Viral Genus)**	**Main Host(s) [Geography]**	**Clinical Outcome**	**Gross Lesions**	**Histologic Features**
Squirrel fibromatosis (SQFV)	Squirrel fibroma virus [*Leporipoxvirus*]	Eastern gray squirrels, also western gray, red, and fox squirrels [Eastern North America]	Lesions often regress, occasional mortality	Cutaneous and lesser visceral nodules	Epithelial hyperplasia and mesenchymal (fibroblast) proliferation; ballooning keratinocyte degeneration; ICIB in proliferative epithelial and mesenchymal cells
Squirrelpox (SQPV)	UK squirrelpox virus [*Novel genus within chordopoxvirinae, not yet named*]	European red squirrel (Gray squirrels clinically resistant) [United Kingdom and Ireland]	Fatal	Exudative dermatitis	Epidermal hyperplasia with ulceration, crusting, and necrsuppurative dermatitis; ballooning degeneration and ICIB in keratinocytes
	Canadian squirrelpox virus *[unassigned, most closely related to parapoxviruses]*	North American red squirrel (only 1 case) [Canada, Yukon territory]	Fatal	Exudative dermatitis (more like SQPV than SQFV)	(As above for SQPV) [more like SQPV than SQFV; virus identified only in epithelial cells]

Poxviruses are enveloped DNA viruses that are prominently epitheliotropic and commonly induce epithelial hyperplasia (acanthosis), epithelial cell swelling (ballooning degeneration), and intracytoplasmic inclusion bodies. Grossly, the archetypal cutaneous lesions progress through macule, papule, vesicle, pustule, crust and scar phases.[11] Ultrastructurally, poxviral particules are brick-shaped, enveloped, smooth-surfaced, electron-dense virions (approximately 200-300 nm), with a biconcave (dumb-bell shaped) nucleocapsid core and adjacent lateral bodies.[1] The family *Poxviridae* is classified into two subfamilies: *Entomopoxvirinae*, which infect insects, and *Chordopoxvirinae*, which infect a wide range of vertebrates. Poxviruses that induce cutaneous tumors include squirrel fibroma virus, rabbit fibroma virus, rabbit myxoma virus, yaba monkey tumor virus, lumpy skin disease virus, and sheeppox virus.

Table 2. *Chordopoxvirinae* genera, major viruses, and some notable features[11,JPC archives]

Genus	Major Viruses
Avipoxvirus	Fowlpox virus, Canarypox virus, Pigeonpox virus, Quailpox virus, Turkeypox virus - Characteristic histologic intracytoplasmic inclusion bodies: "Bollinger bodies"
Capripoxvirus	Sheeppox virus, Goatpox virus, Lumpy skin disease virus - All cause systemic disease, mortality/economic loss can be high, especially with sheeppox - "Sheeppox cells" accumulate in lesions: mononuclear cells (macrophages/monocytes, fibroblasts) with vacuolated nuclei/marginated chromatin and ICIB
Cervidpoxvirus	Deerpox virus
Crocodylidpoxvirus	Nile crocodilepox virus
Leporipoxvirus	Rabbit (Shope) fibroma virus, Rabbit myxoma virus, Squirrel fibroma virus - Rabbit (Shope) fibroma virus: causes rabbit fibromatosis (like squirrel fibroma virus) o Atypical dermal mesenchymal proliferation, epidermal hyperplasia, ballooning degeneration, ICIB in epithelium and mesenchymal cells o Benign, self-limiting disease - Rabbit myxoma virus: causes cutaneous myxomatosis ("bighead") o Atypical myxomatous mesenchymal proliferation, epidermal hyperplasia, ballooning degeneration, ICIB in epithelial cells only o Local/benign lesion in American rabbits, but systemic/severe in European rabbits
Molluscipoxvirus	Molluscum contagiosum virus - Infects horses, donkeys, kangaroos, etc.; large ICIB: "molluscum bodies"
Orthopoxvirus	Cowpox virus, Ectromelia (mousepox) virus, Monkeypox virus, Rabbitpox virus, Horsepox virus, Camelpox virus, Vaccinia virus, Variola (smallpox)

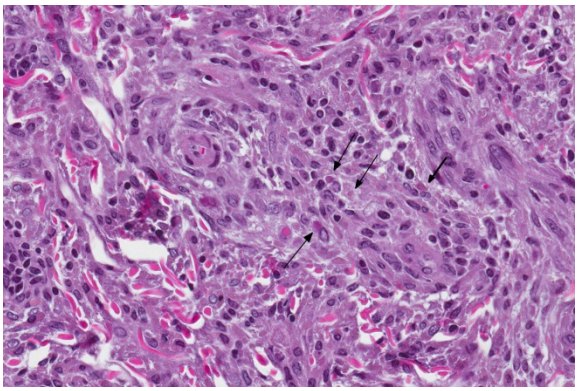
	virus
	- Cowpox virus: teat/udder lesions in cows, but not common; infects others including cats
	- Monkeypox virus: systemic disease in monkeys and rodents
	- Ectromelia virus: also causes splenic and hepatic necrosis
	  o A-type inclusions (Marchal bodies): eosinophilic, occur late in disease, common in epidermis (not liver)
	  o B-type inclusions (Guarnieri bodies): basophilic, occur early in disease, present in all infected cells
	- Rabbitpox: only been reported in laboratory populations
	- Vaccinia virus: used in vaccines to eradicate smallpox; no disease in domestic animals

Parapoxvirus	Ovine parapoxvirus (contagious ecthyma, contagious pustular dermatitis, Orf, sore mouth), Pseudocowpox virus, Bovine popular stomatitis virus - Ovine parapoxvirus: sheep, goats, cattle, less commonly others; zoonotic o Inclusions only briefly detected in vesicular stage - Pseudocowpox virus: lesions in milking cows, zoonotic to humans: "Milker's nodules" - Bovine popular stomatitis virus: lesions more often mouth/muzzle, transmission to humans looks comparable to "milker's nodules"
Suipoxvirus	Swinepox virus - Host specific, sucking louse (*Haematopinus suis*) contributes to mechanical transmission
Yatapoxvirus	Yaba monkey tumor virus, Tanapox virus - Yabapoxviral dermatitis: benign, dermal tumor, regress; previously termed "histiocytomas"; ICIB in proliferating dermal mesenchymal cells - Tanapox virus: causes "benign epidermal monkey pox"; ICIB in keratinocytes

JPC Diagnosis: Haired skin: Viral fibropapillomas, multiple, eastern fox squirrel (*Sciurus niger)*, squirrel.

Conference Comment: Squirrel fibroma virus belongs to the *Leporipoxvirus* genus of the *Poxviridae* family of viruses and is related to rabbit (shope) fibroma virus and rabbit myxoma virus. The different poxvirus genera are concisely described by the contributor above. Of historical interest, Richard Edwin Shope was an American virologist and physician who identified Shope papillomavirus in 1933 which was the first human virus discovered[6]. This discovery assisted later researchers in linking papillomaviruses to warts and cervical cancer[8]. Among other pathologies, he identified *Influenzavirus* A in pigs (1931) and cultured it from a human in 1933 later identifying it as the virus that circulated in the 1918 pandemic[10]. Interestingly, his son, Robert Shope, was also a virologist that specialized in arthropod-borne viruses[6].

As is always the case when leporipox-driven entities appear in the Wednesday Slide Conference, vigorous debate surrounded the morphologic diagnosis. Emboldened by the recent identification of the neoplastic cells



Haired skin, squirrel. Proliferating fibroblasts occasionally contain a single 4-10um intracytoplasmic round viral inclusion. (HE, 400X)

within the dermis as fibroblasts[12], the staff of the Joint Pathology Center threw off the yoke of conservatism exemplified by its longstanding diagnosis of "atypical mesenchymal hyperplasia" and, noting the presence of viral inclusions in both the epidermis and dermis, unanimously endorsed that of "viral fibropapilloma".

Contributing Institution:
Michigan State University
Diagnostic Center for Population and Animal Health
www.animalhealth.msu.edu

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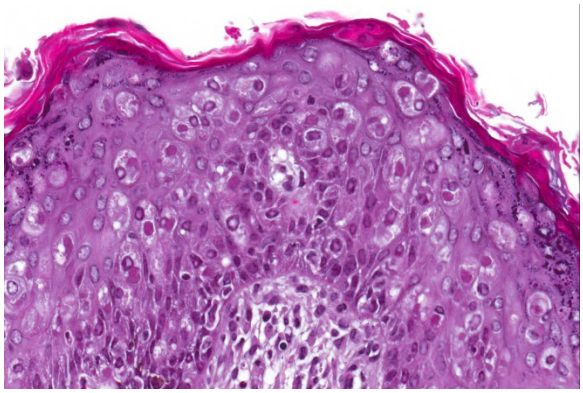

Intestine, ox. The overlying epithelium is hyperplastic, and the cells of the stratum spinosum exhibit ballooning degeneration with one or more 4-10um intracytoplasmic viral inclusions. There is mild orthokeratotic hyperkeratosis. (HE, 1 56X)

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CASE II: 14/160 (JPC 4048228).

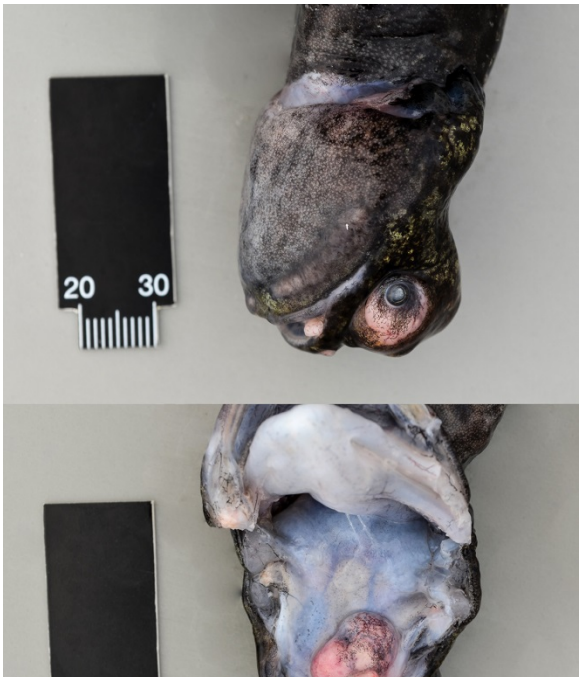
Signalment: Unknown age, adult, female, *Ambystoma mexicanum*, axolotl.

History: The animal was euthanized because of exophthalmia and poor condition due to a mass in the head which extends to the oral cavity.

Gross Pathology: On the head, between the eyes is a firm mass of about 2 x 2 x 1 cm in diameter, which reaches the oral cavity and has a multinodular appearance. The cut surface of the mass is firm, well-delineated and white. The right eye is exophthalmic.

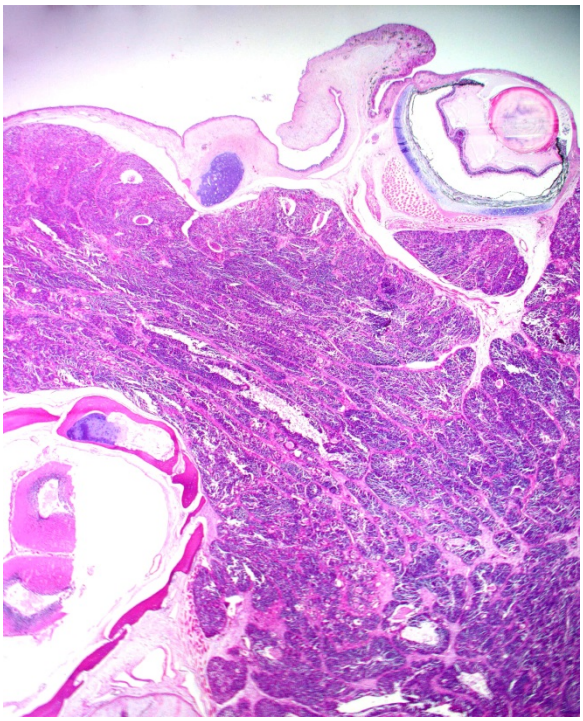
Laboratory results:
None submitted.

Microscopic Description: From the superficial dermis, extending to the cut borders, there is a poorly demarcated, nonencapsulated, infiltratively growing, cell rich neoplastic mass. The cells are polygonal to elongated, arranged in rosettes (Flexner-Wintersteiner-like rosettes), nests and packets and are supported by moderate amount of delicate septa of fibrovascular stroma. The neoplastic cells are 10-15 µm in diameter, have variably less distinct cell borders, moderate amount of eosinophilic, granular cytoplasm and a round to elongated nucleus with finely stippled chromatin and up to 4 nucleoli. The anisocytosis and anisokaryosis are moderate and there are 3-4 mitoses per 400X high power fields. Multifocal in the neoplasia necrosis is present. The surrounding dermis is edematous.



Skin, axolotl. A poorly pigmented neoplasm extends from between the eyes oral cavity. (Photo courtesy of: Vetsuisse Faculty, University of Bern, Institute of Animal Pathology, Laenggassstrasse 122, PF 8466, 3001 Bern Switzerland, http://www.itpa.vetsuisse.unibe.ch/content/index_eng.html)

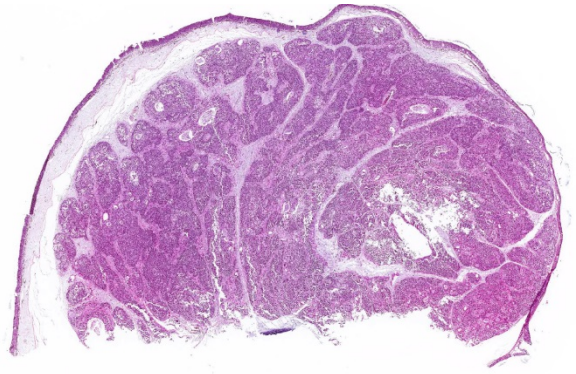
Contributor's Morphologic Diagnosis:
Head: Neuromastoma (Neuroepithelioma).



Skin, axolotl. The neoplasm extends beneath the right eye and infiltrates underlying cranium. (Photo courtesy of: Vetsuisse Faculty, University of Bern, Institute of Animal Pathology, Laenggassstrasse 122, PF 8466, 3001 Bern Switzerland, http://www.itpa.vetsuisse.unibe.ch/content/index_eng.html) (HE, 2X)

Contributor's Comment: Neoplastic disorders in amphibians are rare and limited to specific species [orders: Anura (frogs and toads), Urodela (salamander), Gymnophiona (caecilians)].[7] The axolotl belongs to the Urodela and has become popular in cancer research, regenerative biology and immunology.[6] Spontaneous tumors described in axolotl are melanophoroma, epithelioma, neuroepithelioma, lymphangiosarcoma, mast cell tumor, fibropapilloma, sertoli cell tumor and teratoma.[4,6,7]

In our case, the axolotl had a mass on the head between the eyes reaching to the oral cavity. Histologically, the neoplastic cells formed rosettes which lead to the suspicion of a neuroendocrine tumor. In a previous report from an axolotl, a mass with the same distribution and similar histological pattern was described and referred to as a neuromastoma.[4] Neuromastoma (neuroepithelioma) is a neoplasia originating from neuromast cells.[4] These cells are distributed on the head and body and are the end organs of the lateral line system, which is a sensory system in all fishes and permanently aquatic amphibians.[2] On the head of axolotl, tumors like fibropapilloma, mast cell tumor and olfactory neuroblastoma can occur.[4,6,7] These are macroscopical differential diagnoses in our case. Fibropapillomas are common in urodeles[6], but in the histologic examination, fibropapilloma was excluded due to lack of the distinctive histological pattern of proliferative neoplastic fibroblasts. Mast cell tumors are common

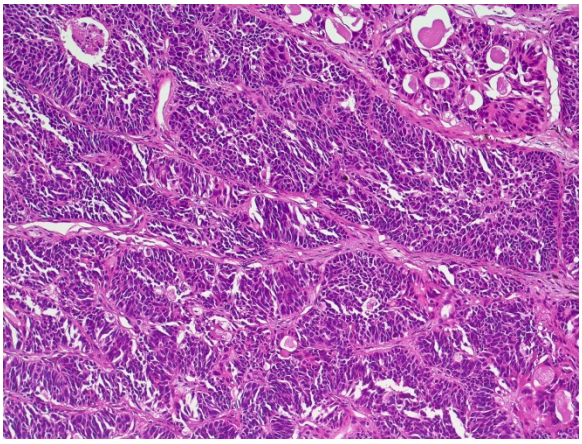


Skin, axolotl. The submitted section of skin shows a multilobular neoplasm within the deep dermis. There are large areas of necrosis and dropout scattered throughout. (HE, 6X)

neoplasias on the head of *A. mexicanum*, often with ulceration of the overlying epidermis.[4] In our histological examination, there was no indication of mast cells in the toluidine blue staining. Olfactory neuroblastoma and neuromastoma may have similar neuroectodermal origin, share similar histological and immunohistochemical features and are not easily distinguished from each other.[4,6] Considering the similar location and histological features of the previous report

of neuromastoma[4], we diagnosed the tumor in our case was diagnosed as a neuro-mastoma.
Only few cases of neuromastoma have been reported and only in Laurenti`s alpine newt and axolotl.[4] It has a prolonged course and the tumor localization impacts the health status of the animal.[7]

Amphibians share the same cell types as other animals, and any cell type can develop neoplastic changes.[7] The knowledge about neoplasia in wild amphibians is incomplete and inconsistent due to insufficient diagnoses and misdiagnoses and difficulty to interpret the neoplasias.[7] The best known amphibian neoplasm is the Lucké renal adenocarcinoma caused by ranid herpesvirus-1 (Lucké`s herpesvirus) and is endemic in the northern leopard frog (*Rana pipiens*) population.[4,7] Interestingly, some anuran species possess anticancer secretory products and cytoprotective capabilities which make them relatively resistant to carcinogens, and the regenerative capacity of urodels is hypothesized to explain the low tumor rate in these amphibians.[7]



Skin, axolotl. Neoplastic cells are separated into distinct lobules, and are pyramidal, often palisading along the outer edge of each lobule. (HE, 40X) (Photo courtesy of: Vetsuisse Faculty, University of Bern,

Table 1. Spontaneous neoplasias in amphibians: from Stacy et. al 2004

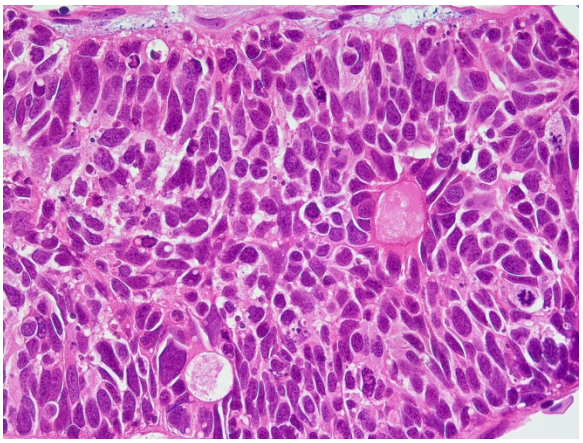
Organ system	Tumor type	Species
Integument and soft tissues	Epidermal papilloma	Urodele species
	Squamous cell carcinoma	Northern leopard frog (*R. pipiens*)
	Dermal gland tumors	Grass frogs (*R. temporaria*) Pond frogs (*R. ridibunda*)
	Melanophoroma	Urodele and anura species
	Fibropapilloma, Fibrosarcoma	Western tiger salamander (*A. mavortium*)
	Neuroepithelial tumors	Axolotl (*A. mexicanum*) Alpine newt (*T. alpestris*)
	Mast cell tumor	Urodele species

Hemolymphatic system	Lymphoma Granulocytic leukemia	African clawed frog (*X. laevis*) Axolotl (*A. mexicanum*) Toads (*Bufo* sp.)
Hepatobiliary system	Hepatocellular adenoma	Barking tree frog (*H. gratiosa*)
Alimentary system	Gastric adenocarcinoma Intestinal adenocarcinoma	African clawed frog (*X. laevis*) Marine toad (*B. marinus*)
Urogenital system	Lucké renal adenocarcinoma Nephroblastoma Renal carcinoma Sertoli cell tumor Cystadenocarcinoma Granulosa cell tumor Ovarian teratoma	Northern leopard frog (*R. pipiens*) Urodele and anura species Urodele and anura species Urodele and anura species Northern leopard frog (*R. pipiens*) Ornate horn frog (*C. ornata*) Northern leopard frog (*R. pipiens*)
Endocrine system	Pancreatic carcinoma	African clawed frog (*X. laevis*) *Rana* species

JPC Diagnosis: Oral mucosa: Neuroepithelioma (neuromastoma), *Ambystoma mexicanum*, axolotl.

Conference Comment: Amystomatidae, or mole salamanders, is a family of North American amphibians that contain approximately 30 species. The axolotl, *Ambystoma mexicanum*, is the most common aquatic species kept in captivity and has been used for many years in biomedical research. Axolotls exhibit a distinguishing feature termed "neoteny" which is the retention of juvenile characteristics. The Anderson's axolotl (*Amystoma andersoni)* are also neotenic and are common zoo residents. The Mexican axolotl is considered endangered due to habitat loss, pollution, and the introduction of fish into their habitats that predate larval axolotls[4].

Neuromastomata, aptly described above, have historically been transplanted successfully, and induced experimentally by numerous carcinogens.[3,4] Sensory cells of the lateral line system are found on the head, body, and tail of larval and adult aquatic amphibians. Specific cells in ampullary organs of the head in *A. mexicanum* contain similar cells that are called electroreceptors. It is not currently possible to distinguish olfactory, neuromastic, or electroreceptor cells from one another and neoplasms are often diagnosed as neuroepitheliomas. The lateral line and pit organs function as mechanoreceptors, while the ampullary organs are electroreceptors. The pit and ampullary organs are located only on head



Skin, axolotl. Higher magnification of neoplastic cells. Neoplastic cells occasionally form rosettes around a lumen filled with homogenous to fibrillar proteinaceous material. Neoplastic cells (HE, 40X) (Photo courtesy of: Vetsuisse Faculty, University of Bern, Institute of Animal Pathology, Laenggassstrasse 122, PF 8466, 3001 Bern Switzerland, http://www.itpa.vetsuisse.unibe.ch/content/index_eng.html)

and the lateral line usually extends from head to tail on each side of the body. In the axolotl, specifically, there are three pairs of lateral lines (similar to the northern leopard frog, *Rana pipens*) and only the middle pair extend all the way to the tail.[4] Oral neuroepitheliomas (neuromastomas) were first described in axolotls by Drs. Brunst and Roque in 1967 and there have been few reports since[1].

Contributing Institution:
Vetsuisse Faculty, University of Bern
Institute of Animal Pathology
Laenggassstrasse 122
PF 8466
3001 Bern Switzerland
http://www.itpa.vetsuisse.unibe.ch/content/index_eng.html

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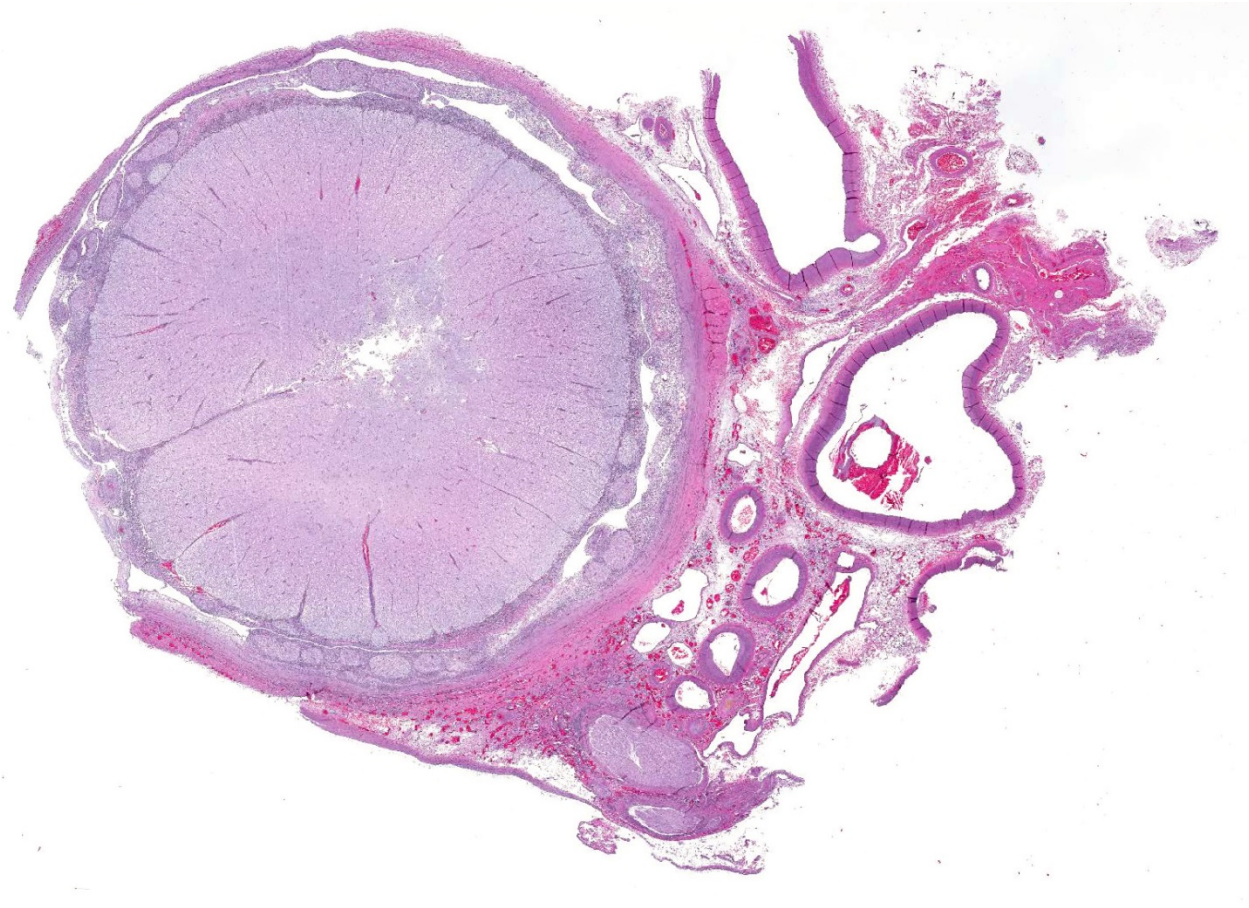
CASE III: 17-1539 (JPC 4102429).

Signalment: Adult,male, *Stenella coeruleoalba*, dolphin.

History: An adult male dolphin (*Stenella coeruleoalba*) was found dead on the beach with multiple signs of trauma and sent to Oregon State University for necropsy.

Gross Pathology: The animal was in good body condition and had numerous full thickness lacerations throughout the skin.

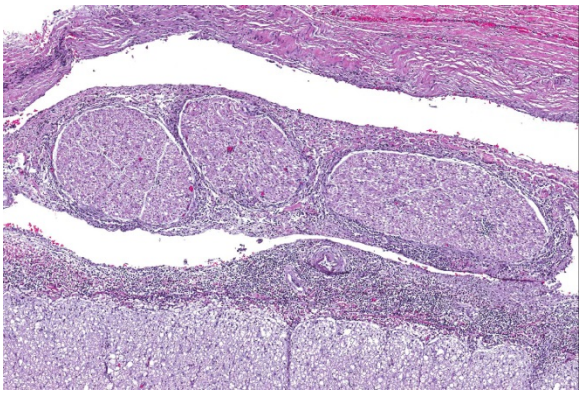


Spinal cord, dolphin. At subgross magnification, the leptomeninges and inner half of the dura is expanded by a prominent cellular infiltrate. There is a large area of cavitation within the grey matter. Within the vertebral canal, the walls of adjacent arteries are thickened. (HE, 6X)

Adjacent to both testes, there was a 3cm diameter abscess. The animal's rectum contained dozens of well circumscribed, firm parasitic nodules.

Laboratory results:
Brucella ceti was isolated from brain tissue.

Microscopic Description: Spinal cord: All tissues represented by the slide are affected by variable degrees of inflammation, necrosis and degenerative changes. Diffusely, submeningeal spaces are markedly expanded and disrupted by dense infiltrates composed of copious amounts of lymphocytes admixed with fewer macrophages and plasma cells admixed with fibrin. Mononuclear infiltrates extend into the dura and surround nerve roots and blood vessels (perivascular cuffs). In the spinal cord, most blood vessels throughout the white and gray matter are surrounded by inflammatory cells. In many slides, the central region of gray matter is rarefied and, in severe cases, undergoes liquefactive necrosis. The dorsal root ganglion (displayed on some slides) has multifocal areas of satellitosis associated with chromatolysis and neuronophagia. Multifocally, blood vessels within the vascular plexus are completely occluded by subintimal proliferations of spindle cells, hematoidin deposits or fibrinous thrombi. Throughout the section, numerous blood vessels undergo fibrinoid necrosis.



Spinal cord, dolphin. The inflammatory infiltrate expands the leptomeninges as well as surrounds the adjacent spinal nerves. There is some infiltration of the spinal nerves as well. (HE, 74X)

Contributor's Morphologic Diagnosis:
Spinal cord: Severe, diffuse, chronic-active lymphocytic meningomyelitis with poly-radiculoneuritis, pachymeningitis, vasculitis, and myelomalacia.

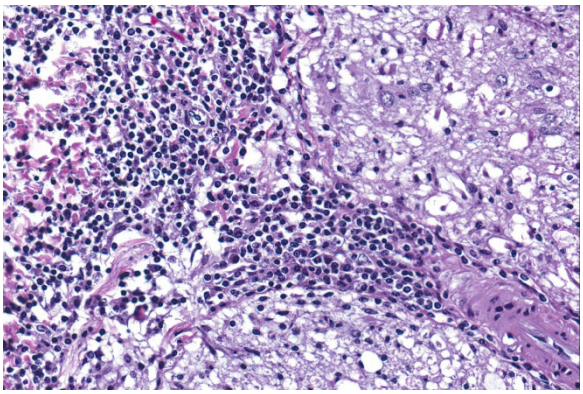
Contributor's Comment: Brucellosis is a zoonotic and endemic disease that affects a diverse array of land and aquatic mammals in many world regions including the Middle East, Asia, Africa, and North and South America. Domestic and wildlife species can become chronically infected, thus playing an important role disseminating the disease and acting as reservoirs[4,12].

Brucella are nonmotile, un-encapsulated, facultative intracellular, gram-negative coccobacilli. Taxonomically, the *Brucella* genus is divided into ten species according to their host specificity. Four out the ten, *Brucella* abortus, *B. melitensis*, *B. suis*, and *B. canis* are pathogenic to humans[4].

Their lifecycle contains three phases: incubation, acute and chronic infection. The bacterium enters the host via contact with mucosal surfaces and is phagocytized by macrophages and dendritic cells that reach the lymphatic system. Systemic infection follows replication in peripheral and visceral lymph nodes[6]. Once in the host phagocytic cell, the bacterium forms the *Brucella*-containing vacuole (BCV). Derived from the endoplasmic reticulum; the BCV permits the bacteria to evade the immune response, allowing it to survive and replicate with consequent progression to the acute phase where the bacterium infects non-phagocytic cells[13].

Brucella have a tropism for the reticuloendothelial system, bone marrow, reproductive organs, and mammary glands, but the central and peripherial nervous system can also be infected[6]. The pathophysiology behind the initial neurological infection is not completely elucidated. It is known that the inflammation associated with the initial infection is the key contributor to the lesions associated with neurobrucellosis. In the literature, a robust body of evidence shows that, in vivo and in-vitro, *Brucella*'s lipoproteins infect endothelial and glial cells activating the CNS innate immunity leading to secretion of matrix metalloproteases, nitric oxide, cytokines, and upregulation of Toll-like receptors exacerbating and promoting a severe inflammatory response[15].

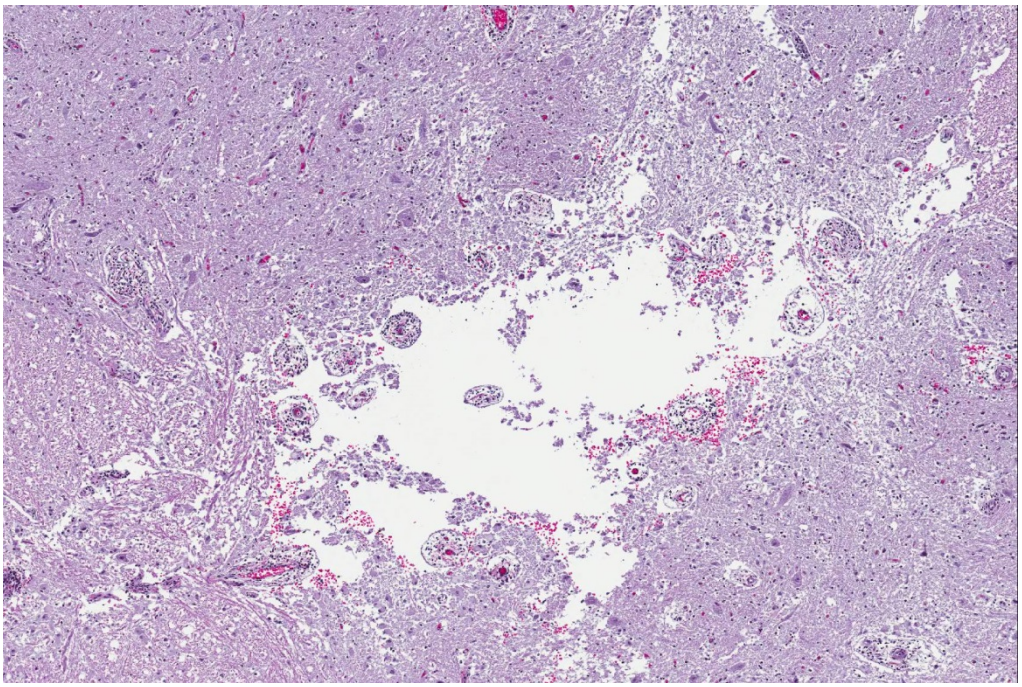
In marine mammals, *Brucella sp.* infections were initially reported in 1994, and since then, numerous reports associating



Spinal cord, dolphin. The inflammatory infiltrate, which extends downward along Virchow-Robin's spaces is composed of numerous lymphocytes and fewer histiocytes, neutrophils and plasma cells. (HE, 400X)

cetaceans' neurological lesions with *B. ceti* and *B. pinnipedialis* infection were widely documented[14].

In cetaceans, *Brucella* associated neurological lesions include meningo-encephalitis, meningitis, choroiditis, spinal discospondylitis, altered cerebrospinal fluid and remodeling of the occipital condyles[2,7,8,9,11].



Spinal cord, dolphin. There is a large area of cavitation (malacia) within the central area of the grey matter. (HE, 62X)

The incidence of neurological involvement in cetaceans with brucellosis is not known, we speculate that the large vascular plexus inside the cranial vault with anastomosing arteries and veins along the vertebrae and base of the skull, predispose these animals to develop neurobrucellosis. Worthy of note in this case particularly is the pattern of malacia with minimal inflammation in the gray matter. This lesion is broadly characteristic of vascular compromise and ischemia due to the exquisite sensitivity of the gray matter to hypoxia. The extensive vascular involvement observed in this lesion is highly consistent with the gray matter lesion.

The zoonotic potential of marine mammal *Brucella sp*. is still not clear. There are few reports which describe the isolation of marine mammal *Brucella sp* from humans exposed to the pathogen that further developed granulomatous lesions. However, characterization and comparison of *Brucella* sp. Strains from naturally infected marine mammals and isolates from exposed humans differed[10,16,18]. Therefore, more research is needed to characterize their true zoonotic potential.

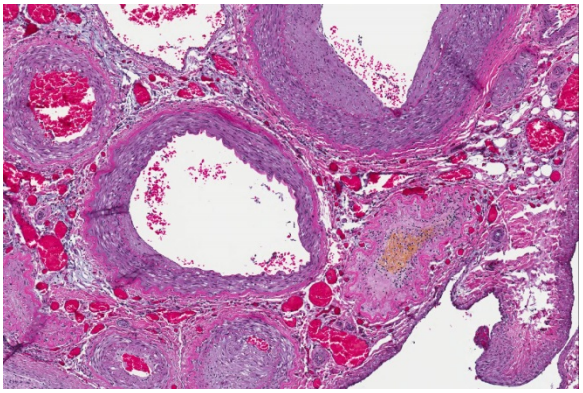
Although *Brucella* sp. is now a well-recognized etiological agent for cetacean's nonsuppurative neurological disease, other infectious agents are can also develop similar lesions such as *Herpesviruses*, *Toxoplasma gondii*, West Nile virus, and *Morbillivirus*.

JPC Diagnosis:

1. Spinal cord: Meningomyelitis, lymphohistiocytic, diffuse, severe with focal grey matter necrosis, lymphohistiocytic radiculoneuritis and fibrinoid vasculitis, *Stenella coeruleoalba*, dolphin.

2. Spinal canal: Arteriosclerosis, proliferative, multifocal, moderate to severe.

Conference Comment: A wide range of marine mammals are exposed to or infected with *Brucella* sp. The biovars of *Brucella sp.* that infect marine mammals are genetically distinct from those affecting terrestrial species; however, there have been reported cases of human brucellosis caused by marine mammal serovars[3]. Clinical disease in cetaceans is most common among marine mammals with pinnepeds being the most sensitive. In cetaceans, *Brucella ceti*, is the most common infectious culprit resulting in vertebral osteomyelitis and abortions particularly in bottlenose dolphins[2]. In these cases, atlanto-occipital joints were filled with inspissated, caseous material and there was a chronic, nonsuppurative meningo-encephalitis characterized by patchy congestion of meningeal blood vessels and mononuclear cell cuffing of blood vessels in the brain and meninges. A recent article described *Brucella* spp. Infections in endangered Hector's dolphins that are currently declining in population[1]. A total of 27 dolphins found dead on the New Zealand coastline were evaluation for lesions associated with brucellosis. Of note, *Brucella pinnipedialis* was the most common isolate and resulted in reproductive disease in affected animals which may be a contributing factor to the dwindling numbers in this species.



Spinal canal. There are extensive mural changes in arteries in the adjacent spinal canal include subintimal fibrosis (vessels at center and 2'oclock), occlusion and thrombosis with hematoidin deposition (4 o'clock), as well as smooth hyperplasia and recanalization (6 o'clock). (HE, 80X)

Conference participants had an energetic dialogue regarding the association of the grey matter necrosis, inflammatory meningoencephalitis, and the lesions in the adjacent arteries; even a temporal thread does not connect these acute, subacute, and chronic lesions, respectively. Athero-sclerosis has been reported in marine mammals, specifically aged dolphins, and is most likely an incidental finding in this case[17].

Contributing Institution:
Oregon Veterinary Diagnostic Laboratory-College of Veterinary Medicine
Oregon State University, Corvallis, Oregon
http://vetmed.oregonstate.edu/diagnostic

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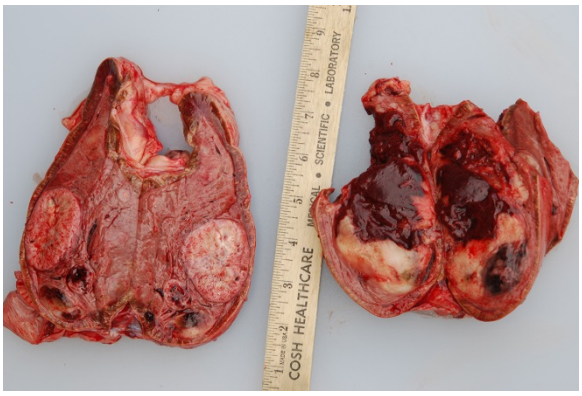
CASE IV: WSC 2017-2018 Rhinoceros (JPC 4101227).

Signalment: 48-year-old female, southern white (*Ceratotherium simum)*, rhinoceros.

History: This 48-year-old, female southern white rhinoceros was housed at a zoologic institution. The animal was humanely euthanized due to quality of life concerns including progressive right forelimb lameness that had become poorly responsive to medical management.

Gross Pathology: At necropsy, both adrenal medullas were markedly enlarged relative to the adrenal cortices (cortex: medulla thickness ratio approximately 1:8). The right adrenal medulla contained a well demarcated, 4cm diameter, slightly firm, round, tan to pink mass that focally compressed the adjacent cortex. Also



Adrenal glands, rhinoceros. Both adrenal medullas are markedly enlarged (cortex:medulla ratio approximately 1:8). There are multiple expansile nodules within both medullas which compress the adjacent medulla and cortex. (Photo courtesy of: Johns Hopkins University School of Medicine, Department of Molecular and Comparative Pathobiology, http://www.hopkinsmedicine.org/mcp/)

present within the right medulla, were two, well demarcated, 1-1.5cm diameter, soft, ovoid masses that were mottled light tan to dark red. Approximately 90% of normal tissue in the left adrenal medulla was replaced by an irregular, multilobulated, approximately 8cm diameter mass that was light tan and soft, with multiple areas that were dark red, shiny, and friable.

Additional gross findings in this animal included severe osteoarthritis affecting all appendicular joints examined, multiple uterine leiomyomas, sclerotic kidneys with numerous cysts, severe dental disease, and a pedunculated mesenteric lipoma.

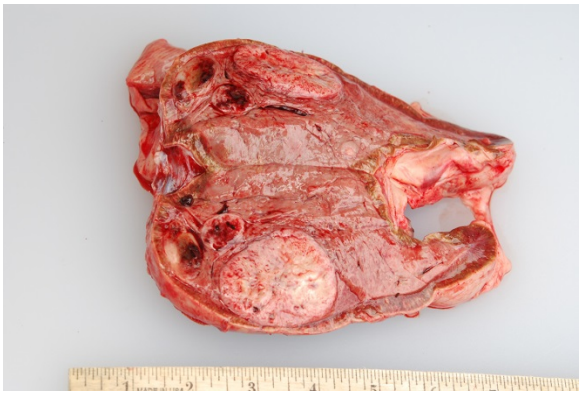
Laboratory results:
None submitted.

Microscopic Description: The tissue consists of a single section from the right adrenal gland. Within the medulla are two, distinct, neoplastic masses that are well-demarcated, partially encapsulated, and variably compress the adjacent parenchyma. One mass is composed of mature adipocytes and hematopoietic precursor cells arranged in sheets on a scant fibrovascular stroma. All three blood cell lineages (erythroid, myeloid, and lymphoid) are represented. There are also abundant mature red blood cells admixed with small amounts of eosinophilic proteinaceous fluid and scattered, golden to dark brown pigment-laden macrophages. Cellular atypia is minimal and mitotic figures are rare in this mass (<1 per 10 HPF). The second mass is composed of neoplastic cells arranged in nests and packets on a highly-vascularized fibrous stroma. Neoplastic cells frequently palisade around blood vessels (pseudorosette formation). Neoplastic cells are polygonal with distinct cell borders, abundant finely granular, basophilic cytoplasm, and round nuclei with finely stippled chromatin and one distinct nucleolus. There is minimal anisocytosis and anisokaryosis. Mitoses average less than 1 per 10 HPF. Affecting approximately 30% of the mass is an area of central coagulation necrosis and mineralization. Multiple medium-caliber arteries within the medulla contain intraluminal aggregates of neoplastic cells (vascular invasion).

Additional note: The large mass in the left adrenal medulla was histologically identical to the first mass described above, with areas of hematopoietic precursor cells and mature adipose tissue.

Contributor's Morphologic Diagnosis:

1. Adrenal gland, pheochromocytoma, unilateral, with necrosis and vascular invasion
2. Adrenal gland, myelolipoma, multifocal, bilateral
3. Adrenal gland, medullary hyperplasia, diffuse, unilateral, marked (gross diagnosis)



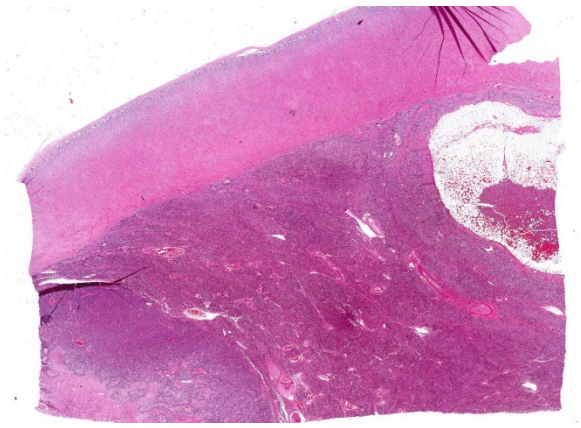
Right adrenal gland, rhinoceros. The right adrenal gland contains one 4cm mass and two smaller 1-1.5cm mass . (Photo courtesy of: Johns Hopkins University School of Medicine, Department of Molecular and Comparative Pathobiology, http://www.hopkinsmedicine.org/mcp/)

Contributor's Comment: This case documents the presence of bilateral adrenal myelolipoma with concurrent unilateral pheochromocytoma and adrenal medullary hyperplasia in a rare species.

Myelolipomas are benign, hormonally inactive, extra-marrow tumors composed of mature adipose tissue and hematopoietic elements. While myelolipomas are not uncommon in humans, they are relatively rare in veterinary species. Reports of myelolipomas in animals are limited to dogs,[20] domestic and non-domestic cats (most notably cheetahs),[2] rodents,[3,18] opossums,[13] and Old and New World monkeys.[9] In animals, they are most commonly reported in the liver, spleen, and adrenal cortex; additional sites include the subcutis (birds),[7] extradural space (dog),[11] and eye (dog).[21]

The etiology of adrenal myelolipomas remains unclear; however there are three proposed mechanisms of development: (1) distant seeding of bone marrow via hematogenous emboli, (2) maturation of embryonic mesenchymal rests, and (3) metaplasia of the adrenal cortex due to chronic hormonal imbalance or adrenocorticotropic hormone (ACTH) secretion.[5] Support for hypothesis #3 comes from controlled experiments in rats, which demonstrated that prolonged administration of testosterone and ACTH induced transformation of the inner zona fasciculata to tissue resembling bone marrow.[19] Additionally, myelolipomas frequently occur in people concurrently suffering from Cushing's disease, hypertension, diabetes and obesity, further suggesting a link with hormonal imbalance or chronic stress.[6] Myelolipomas are rarely reported in conjunction with pheochromocytomas in both people[22] and non-human primates.[10]

Pheochromocytomas are tumors of the chromaffin cells in the adrenal medulla; these are the cells which synthesize and secrete catecholamines (norepinephrine, epinephrine, and dopamine). They are the most common tumor of the adrenal medulla in animals, have been reported in a wide variety of mammals, and are best documented in humans, dogs, bulls, and rats.[15] There is a single previous report of pheochromocytoma a white rhinoceros.[1] While most pheochromocytomas in animals are reportedly non-functional,[14] functional tumors can be associated with hypertension



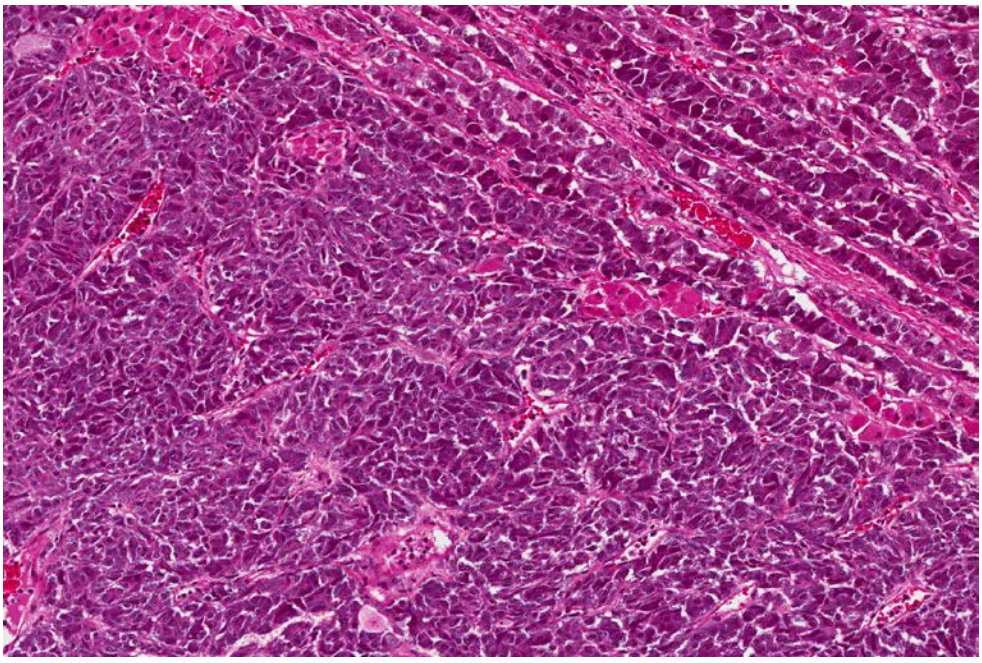
Right adrenal gland, rhinoceros. At low magnification, the submitted section contains two expansile masses (at left and right). (HE, 6X)

and cardiomyopathy due to high circulating levels of catecholamines.[4,24] The previous report of pheochromocytoma in a rhinoceros documented increased serum epinephrine and norepinephrine, as well as histologic changes consistent with systemic hypertension.[1] Hormone levels were not tested in this animal, however medial hypertrophy of arteries and arterioles in multiple organs and a focally extensive area of myocardial fibrosis at the junction of the right and left ventricles, suggest that the pheochromocytoma may have been functional. Histologic grading of pheochromocytomas in humans is based on a scoring system (Pheochromocytoma of the Adrenal gland Scaled Score) in which points are assigned for characteristics including vascular invasion, capsular invasion, local invasion, necrosis, mitoses, and nuclear pleomorphism.[8] While vascular invasion and necrosis were observed in the present case, there was no evidence of local invasion or distant metastases.

Grossly, the right adrenal gland of this rhinoceros had a cortical to medullary thickness ratio of roughly 1:8, suggestive of generalized medullary hyperplasia and / or cortical atrophy. The ratio in the left adrenal gland was similar, but this may have been due to replacement and expansion of normal medullary tissue by the large myelolipoma. While normal ratios for white rhinos are not well established, a previous morphologic study reported that the medulla accounted for only 20% of the mass of the entire adrenal gland.[14] Medullary hyperplasia in veterinary species can be associated with pheochromocytoma and multiple endocrine neoplasia (MEN was not documented in this case).[12]

JPC Diagnosis:

1. Adrenal gland: Pheochromocytoma, Southern white (*Ceratotherium simum)*, rhinoceros.
2. Adrenal gland: Myelolipoma.



Right adrenal gland, rhinoceros. The nodule at left is composed of large nests of medullary epithelium morphologically similar to that present outside the compression capsule (consistent with a pheochromocytoma). (HE, 176X)

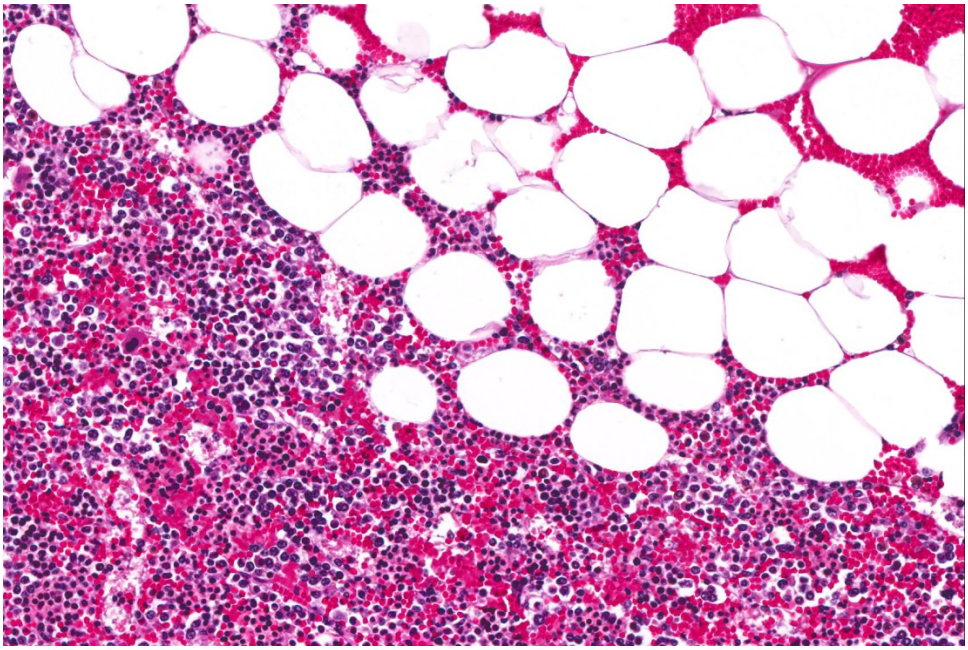
Conference Comment: In prehistoric times, rhinoceroses were the most common large herbivores in North America, and today, they are one of the most primitive of the world's large mammals. There are five species that exist in four genera: in Africa there are white (*Ceratotherium simum)* and black (*Dicero bicornis*) rhinos, in Asia there are Sumatran

(*Dicerorhinus sumatrensis*), Indian (*Rhinoceros unicornis*), and Javan (*Rhinoceros sondaicus*) rhinos. Of the five species, Sumatran are the most primitive and predate the wooly rhino (*Coelodonta antiqitatis*), now extinct, which inhabited northern Europe and Asia during the last Ice Age. In Africa, white rhinos prefer to live on flat terrain which short grasses and black rhinos live in areas with shrubs and young trees, these preferences are associated with their dietary requirements. Regardless, all species of rhino are hindgut fermenters with fast transit times who require regular access to water to cool off, keep their skin free of external parasites, and stay hydrated. Of the five species, white rhinos have the largest world population estimate at 20,143 (2012). The skin of a rhinoceros is extremely thick, with the white rhino's skin reaching a thickness of five centimeters.[11]

In rhinoceroses, neoplasia is fairly uncommon. There have been reported cases of squamous cell carcinoma in white, black, and Indian rhinos as well as cutaneous melanoma in black and Indian rhinos. Rare cases of thyroid carcinoma, hepatocellular carcinoma, and acute lymphoblastic leukemia have been reported in black rhinos.[11]

Myelolipomas are benign tumors that are most often encountered in the adrenal glands of cattle, nonhuman primates, and occasionally other species composed of aggregates of mature adipocytes, reactive fibroblasts, and myeloid and erythroid hematopoietic cells. Occasionally, fibroblasts undergo osseous differentiation and areas of osseous metaplasia occur within the tumor. These tumors are thought to originate from metaplastic transformation of adrenal cortical cells, although their exact origin in currently unknown.[16,23]

Pheochromocytomas are the most common neoplasm arising in the adrenal medulla of domestic animals, but are more frequent in cattle and dogs. Microscopically, they arise from the chromaffin cells of the adrenal medulla, are either unilateral or bilateral, and generally have abundant hemorrhage and necrosis. Macroscopically, the Henle chromaffin reaction can be used to detect the tumor using either potassium dichromate or iodate. When Zenker's solution is applied to a flat surface of freshly cut tumor, there is



Right adrenal gland, rhinoceros. The nodule at right is composed of adipocytes (right) and trilinear marrow elements (left) . (HE, 264)

oxidation of the catecholamines, and a dark brown pigment that forms within 20 minutes. Ultrastructurally, pheochromocytomas are composed of epinephrine secreting cells, norepinephrine secreting cells, or a combination of the two. The cells that secrete epinephrine have many low electron density granules with a narrow submembranous space. Conversely, the norepinephrine secreting cells have secretory granules with an eccentric electron dense core surrounded by a prominent submembranous space. With chronicity, tumor cells can grow into the caudal vena cava and form a neoplastic thrombus that can occlude drainage from caudal extremities. Metastasis occurs in about 50% of affected dogs to the liver, regional lymph nodes, spleen, and lungs. Since they are of endocrine origin, pheochromocytomas, when functional, can have serious systemic effects related to excessive catecholamine secretion such as: tachycardia, edema, cardiac hypertrophy, arteriolar sclerosis, and medial hyperplasia of arterioles.[16,17]

When discussing the adjacent "normal" adrenal medullary tissue, attendees reached an impasse. Some believed it to be truly hyperplastic, as evidenced by the gross images submitted by the contributor, while others believed that the thinned cortex was due to the mass of two neoplasms expanding the medulla and compressing and stretching the cortex. In short, it was difficult to make a definitive diagnosis of medullary hyperplasia with the single slide available to conference participants; however, if the contributor's other sections of the medulla revealed increased amounts of normal medullary tissue histologically, we support the contributor's gross diagnosis of medullary hyperplasia.

Contributing Institution:

Johns Hopkins University School of Medicine
Department of Molecular and Comparative Pathobiology
http://www.hopkinsmedicine.org/mcp/

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