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Department of Veterinary Pathology
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CASE I – S3177-98 (AFIP 2789175)

Signalment: 18-year-old, spayed female, Maine Coon, feline

History: Referred to The Animal Medical Center with a diagnosis of cutaneous lymphoma. A one-centimeter diameter mass was present in the skin for 120 days. The mass reoccurred following surgical resection.

Gross Pathology: Recurrent one-centimeter lesion in the dorso-lateral cervical skin with an enlarged prescapular lymph node.

Laboratory Results: Not significant.

Contributor's Morphologic Diagnosis: Neuroendocrine carcinoma, skin (Merkel cell) in a cat.

Contributor's Comment: The neuroendocrine carcinoma (Merkel cell) had similar morphologic, immunohistochemical, and electron microscopic features compared with similar tumors in humans. Unlike most Merkel cell carcinomas described in the dog, this tumor in the cat was malignant like the human Merkel cell carcinoma.

AFIP Diagnosis: Haired skin: Neuroendocrine carcinoma compatible with Merkel cell tumor, Maine Coon, feline.

Conference Comment: Merkel cells are neuroendocrine cells of the epidermis, cutaneous adnexa, and oral mucosa. They are derived from undifferentiated epidermal cells, thought to function as mechanoreceptors, and have been described in mammals, fish, amphibians and reptiles.

As demonstrated in this case, characteristic histologic features of neuroendocrine carcinomas include a trabecular pattern, ribbons, formation of rosette-like structures, and palisading along the stroma. Neoplastic cells are polygonal, have variably distinct cell borders, and centrally placed, often hyperchromatic nuclei. Infiltrative growth, high mitotic rate and atypia indicate malignancy. By immunohistochemistry performed at the AFIP, neoplastic cells were strongly positive for cytokeratin and lightly positive for neuron specific enolase, providing additional support for the diagnosis of neuroendocrine carcinoma.

Although the histomorphology and immunohistochemical findings in this case (see Vet Pathol **38**:553-555) are compatible with a neuroendocrine carcinoma, the diagnosis of a Merkel cell carcinoma depends on excluding the possibility of cutaneous metastasis from a neuroendocrine carcinoma in another location. Based upon this animal's history, the available evidence supports the conclusion that this neoplasm arose in the skin, and thus, represents a Merkel cell carcinoma.

In the mid to late 1980s, there were some reports of Merkel cell tumors in the skin and oral mucosa of dogs. Unlike this feline case, the canine tumors did not closely resemble human Merkel cell tumors morphologically or behaviorally. The photographs of the tumors in these articles appear to represent cutaneous and oral plasmacytomas. A more recent report of a canine Merkel cell tumor is more convincing.

Contributor: The Animal Medical Center, New York, NY 10021

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CASE II – 1999-513 (AFIP 2790159)

Signalment: 8-year-old captive-born male beluga whale (*Delphinapterus leucas*)

History: The whale had chronic intermittent bouts of caseous dermatitis, lethargy, anorexia, and depression for a year and a half prior to death. There had also been a

chronic regurgitation and anemia intermittently for 2.5 to 3.5 years before death. Low levels of lead (< 2.5 - 20 ug/dl, usually <10 ug/dl) were observed in the blood for 3 years before death. Repeated endoscopies were negative, but at necropsy a lead foreign body was found in the stomach. For the last 1.5 years before death, there were occasional bouts of anorexia and depression associated with leukopenia or leukocytosis with a left shift (band neutrophils, myelocytes, metamyelocytes) and elevations of ESR and fibrinogen. The fatal illness lasted about 6 weeks. Over the course of the last illness, treatments included: itraconazole; nystatin; miconazole; Silvadene; ciprofloxacin; Clavamox; amoxicillin; clindamycin; amikacin; levamisole; folic acid; supplemental vitamins E, C, and B complex; viokase; carafate; omeprazole; biolyte electrolyte solutions; prednisone; and MGA. He had previously been treated with fluoxetine too.

Antemortem cultures (blowhole, skin, blood, fecal) were never positive for Nocardia.

Gross Pathology: 1. Lung: Bronchopneumonia, multifocal to coalescing, chronic, severe
2. Lymph node: Lymphadenitis, diffuse, chronic, severe
3. Multiple organs: Disseminated abscesses (kidney, spleen, liver)
4. Thoracic cavity: Effusion
5. Stomach: Foreign bodies

Laboratory Results: Cultures at necropsy of the pleural fluid isolated pure and many *Nocardia spp*. In addition, *Nocardia* was isolated from synovial fluid.

The animal was repeatedly negative on serology for a panel of morbilliviruses and fungi.

Contributor's Morphologic Diagnosis: Thoracic aorta: Aortitis, multifocal to coalescing, necrotizing to chronic, severe with hemorrhage, thrombi and filamentous bacteria

Contributor's Comment: Histopathologically, the tunica adventitia of the thoracic aorta is variably thickened by multifocal to coalescing nodular plaques. The plaques are composed of varying numbers of degenerate neutrophils, lymphocytes, plasma cells, and macrophages admixed with large amounts of necrotic cellular debris, fibrin, edema, and colonies of filamentous bacteria. In some sections, hemorrhage is a prominent feature. Occasional adventitial vessels contain thrombi. In less affected areas, vessels are congested and surrounded by low to moderate numbers of lymphocytes with fewer plasma cells.

Nocardia spp. are mostly soil saprophytes classified in the order Actinomycetales. Of the listed species of *Nocardia*, the most frequently implicated

in disease processes are *N. asteroides*, *N. brasiliensis* and *N. caviae*. In veterinary medicine, nocardial infections are most frequently reported in dogs and cattle but have occasionally been described in other species.

Infections with *Nocardia spp*. produce a variety of clinical manifestations depending of the route of exposure and the organ systems affected. Infections can occur as localized lesions or become systemic. Entry of the organism occurs through wounds, inhalation, or ingestion.

Nocardia spp. are branched slender filaments that can be difficult to demonstrate in H&E stained sections. They are Gram positive, silver positive and some are partially acid fast positive when stained with modified acid-fast technique (such as Fite Faraco).

Nocardial infections have been described in captive cetaceans. Infections have been recorded in a pilot whale, bottlenose dolphins, a harbor porpoise, a false killer whale, a spinner dolphin, killer whales, and beluga whales. Infections in cetaceans were most frequently the pulmonary and extrapulmonary forms. Infection is speculated to occur via inhalation.

AFIP Diagnosis: Aorta: Periaortitis, pyogranulomatous, chronic, focally extensive, severe, with fibrosis, hemorrhage, and numerous filamentous bacilli, beluga whale (*Delphinapterus leucas*), cetacean.

Conference Comment: Nocardiae are aerobic organisms that are widespread in the environment and are commonly found in soil, organic matter, and water. It has been hypothesized that infections in cetaceans can be initiated secondary to dust-spreading weather patterns. After initial pulmonary infection, erosion of a blood vessel can lead to dissemination.

Detection of the organism can be difficult in hematoxylin and eosin-stained sections. In this case, careful examination reveals discernible filamentous bacteria. Special stains performed at the AFIP demonstrated numerous Gram positive and GMS positive, branching, filamentous bacilli that were diffusely distributed within the zones of inflammation. A modified acid-fast technique (Fite-Faraco in this case) stained many of the bacilli red.

Although *Actinomyces* sp. and *Nocardia* sp. are morphologically similar and both cause pyogranulomatous inflammation, the two organisms and their associated diseases differ in several ways. Because treatments differ, accurate identification is important. *Actinomyces* sp. are facultative anaerobic organisms found in the oral cavity and gastrointestinal tract. Cases of actinomycosis have an association with the natural habitat of the organism. For example, grass awns contaminated with *Actinomyces* sp. and other saprophytes in the oropharynx may

then migrate in tissues and cause infection, as occurs fairly frequently in hunting dogs. In cats, bite wound abscesses may be caused by *Actinomyces* sp. In nocardiosis, acid fastness with modified acid-fast stains, general diffuse distribution within lesions, and a tendency to cause lesions at noncontiguous sites because of hematogenous spread contrasts with the lack of acid fastness, formation of "grains" or "sulfur granules", heavy fibrous encapsulation, and tendency to spread only to adjacent structures as seen in actinomycosis.

Contributor: Wildlife Conservation Society, Department of Pathology, Bronx, NY 10460.

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CASE III – 0019167 (AFIP 2788019)

Signalment: 16-month-old, female, Bernese mountain dog, canine

History: This dog had a 1-week history of lethargy, anorexia, weight loss, diarrhea and vomiting. Clinical examination revealed dehydration, hyperthermia, dyspnea and bilateral conjunctivitis. Thoracic radiographs revealed abnormal pulmonary opacities, a pneumothorax and a megaesophagus.

The dog was euthanized at the owner's request.

Gross Pathology: Postmortem examination revealed dehydration, megaesophagus, tracheal collapse with congestive tracheitis, and diffuse congestion of the whole digestive tract. The spleen was slightly hypertrophied. In the lungs multiple, poorly defined, firm grayish nodules were disseminated throughout left and right lobes. Other organs were unremarkable.

Laboratory Results: Routine hematological examination revealed leucocytosis with regenerative neutrophilia and monocytosis.

Cytologic examinations of Cytopunctions of the lung and of the spleen showed the following results:

Lungs : presence of numerous macrophages
Spleen : discrete plasmocytosis

Contributor's Morphologic Diagnosis: Lung, lymphomatoid granulomatosis.

Contributor's Comment: Microscopically, the lesion was composed of multinodular to coalescent infiltration of the lung parenchyma by a pleomorphic cellular population. Most lesions were organized around blood vessels (angiocentric) and infiltrated the wall of the vessels. The cellular infiltrate consisted of a pleomorphic population of cells including large cells with abundant cytoplasm and clear nucleus, smaller cells exhibiting a dense nucleus like lymphocytes, and neutrophils. Large bizarre cells were also remarkable which sometimes were bi- or multinucleated. In some regions, necrosis was seen associated with a ring of well-preserved cells just around a vessel wall. Eosinophils and mitotic figures are rare in these lesions. Congestion was also visible in the slides. These pulmonary lesions are consistent with a diagnosis of lymphomatoid granulomatosis. No significant histological lesions were observed in other organs.

Lymphomatoid granulomatosis is a rare, slowly progressive lymphohistiocytic proliferative disorder recognized in man, dog, and the cat involving most commonly the lungs but also other organs like the skin, kidneys, liver, and brain. In this case, only the lungs were affected. An explanation of this fact could be that this dog was euthanized early during the course of the disease.

The classical histological lesions of this entity include an angiocentric infiltration of affected tissues by a population of large histiocytic cells accompanied by variable number of lymphocytes, plasma cells, neutrophils and eosinophils. Bizarre, giant, multinucleated cells were also described in these lesions. Mitotic figures were frequent and many were abnormal.

By immunohistochemistry, cells involved in lymphomatoid granulomatosis are negative for antibodies labelling the macrophages like lysozyme and alpha-1-antitrypsin. However, some cells are positive for CD3 antibodies indicating that this entity could be considered as an angiocentric form of T-cell lymphoma.

This lesion must be differentiated from malignant histiocytosis that was reported primarily in Bernese mountain dog. Malignant histiocytosis is characterized histologically by a proliferation of histiocytic cells with marked atypia and erythrophagocytosis.

AFIP Diagnosis: Lung: Angiocentric, angioinvasive, histiocytic and lymphocytic infiltrate, favor systemic histiocytosis, Bernese mountain dog, canine.

Conference Comment: As indicated by the contributor, the lesion is morphologically compatible with lymphomatoid granulomatosis (LG). The differential diagnosis for this lesion was noted to include malignant histiocytosis of Bernese mountain dogs but systemic histiocytosis (SH) of the same breed was not mentioned. SH is an angiocentric, angioinvasive, histiocytic proliferative disorder; lesser numbers of lymphocytes are also present, as may be neutrophils and eosinophils. There may also be a small component of multinucleate histiocytic cells. The mitotic rate is low. Skin and lymph nodes are primarily affected, but lesions may be found in many tissues including lung. By immunohistochemistry performed at the AFIP, the uninucleate and multinucleate histiocytic appearing cells were diffusely positive for lysozyme, which is compatible with histiocytes. Unfortunately, CD3 (a T-lymphocyte marker) and CD79a (a B-lymphocyte marker) did not work properly; no cells were stained. The cases of LG reported in dogs indicate the presence of frequent mitoses and prominent atypia, features not present in this case. Cases of low-grade LG have been described in humans.

Consultation was obtained from Dr. Peter Moore, the author of a number of articles on histiocytic diseases of dogs, including the initial report of SH in Bernese mountain dogs. Dr. Moore favored SH in this case. He commented that the history of conjunctivitis was interesting and noted that orbital and nasal mucosal involvement is a common feature of SH in Bernese mountain dogs. He has presented evidence that histiocytes in SH of Bernese mountain dogs and other breeds have the immunophenotype of activated dendritic antigen presenting cells. On this basis, he has classified systemic histiocytosis as a reactive histiocytic proliferation that probably results from immune dysregulation.

In humans, LG was initially characterized as an angiocentric and angiodestructive process of lymphoreticular cells. Lesions are typically composed of mixtures of small lymphocytes, plasma cells, histiocytes (which may form granulomas), and atypical lymphoid cells. Early studies suggested that the condition was essentially a T-cell lymphoma. Recently, however, it has been shown that many cases of typical human LG are T-cell-rich, B-cell lymphomas with Epstein-Barr virus (EBV) infection of the B-cells. Molecular studies have shown an association with EBV in at least half to three fourths of cases. Molecular examination of canine cases for evidence of herpesvirus infection would be of interest.

While we cannot exclude the diagnosis of LG in this case, we favor systemic histiocytosis based on our opinion that the lesion resembles the reported canine cases of that disorder more closely than the reported canine cases of LG.

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CASE IV – 1995-469 (AFIP 2790084)

Signalment: 25-month-old, female, beluga whale (*Delphinapterus leucas*)

History: Three weeks prior to death, this animal was very thin and in poor condition. Physical examination was otherwise unremarkable. This animal had never eaten solid food on her own and when force-fed fish, she would vomit (an animal this age would normally consume 15 pounds of fish per day). She was force-fed water and 3 pounds of fish daily and had a peduncle catheter present for a week prior to death.

Gross Pathology: This beluga whale presented in very thin body condition. The pericardium and ventral mediastinum were moderately to markedly thickened by glistening, translucent, pale yellow gelatinous material (edema and serous atrophy). The pleural cavity contained approximately 1.5-2.0 liters of clear to slightly opaque, pale yellow-red fluid that clotted readily on exposure to air (fibrin). The mucosa of

the second compartment of the stomach had numerous pinpoint dark red foci. Additional findings include small foci of pale yellow, mucoid material in the kidneys.

Laboratory Results: Blood work showed mild anemia and leukopenia with a severe lymphopenia and hypoglobulinemia; no specific organ dysfunction was discerned.

Pleural fluid: Specific gravity: 1.024, Total protein: 3.1

Transmission electron microscopy of adrenal gland: consistent with Herpesvirus

Frozen adrenal tissue was not available for virus isolation. PCR was attempted on paraffin embedded adrenal tissue but was unsuccessful. As a known herpesvirus positive control material also failed to produce visible bands on the PCR product gel for either the DNA polymerase or DNA terminase gene primer sets, the results of the PCR testing are considered inconclusive (R. Garber, personal communication)

Aerobic culture: Pleural fluid: no growth
Kidney: many *Vibrio alginolyticus* and *Alteromonas putrefaciens*

Contributor's Morphologic Diagnosis: Adrenal gland, cortex: Adrenalitis, necrotizing, acute to subacute, multifocal, moderate with intralesional eosinophilic intranuclear inclusion bodies consistent with herpesvirus infection.

Contributor's Comment: Randomly within the adrenal cortex, there are multiple, variably sized, discrete foci of necrosis often accompanied by small to moderate numbers of neutrophils and rare to occasional lymphocytes and plasma cells admixed with abundant karyorrhectic cellular debris. Small to moderate numbers of cortical cells, primarily at the margins of the necrotic foci, have single, 4-6 um, round to slightly oval, eosinophilic intranuclear inclusion bodies that are sometimes surrounded by an amphophilic to clear space. Additionally, within some sections necrotic foci are associated with mild to moderate hemorrhage. Many sections also have multifocal, mild lymphoplasmacytic infiltrates at the corticomedullary junction. Throughout the cortex in most sections, there are single to multiple, coalescing clear spaces containing tufts of loosely arranged amorphous to fibrillar, lightly basophilic material (significance unknown).

Similar intranuclear inclusions are also present within small numbers of respiratory epithelial cells but are not associated with necrosis or inflammation. Transmission electron microscopy of adrenal gland demonstrated numerous capsids, nucleocapsids and enveloped virions consistent with herpesviruses.

Herpesviruses and herpes-like viruses have been detected in several cetacean species including beluga whales, harbor porpoises, dusky dolphins and, recently, in Atlantic bottlenose dolphins. In belugas and dusky dolphins, lesions with typical herpesviral inclusion bodies were restricted to the skin. In a harbor porpoise,

herpesviral lesions occurred only in the penile mucosa. Herpesviral encephalitis has also been seen in harbor porpoises. Fatal disseminated herpesviral infection was documented in two Atlantic bottlenose dolphins; the herpesviruses in these dolphins were determined to be related but distinct alphaherpesviruses.

The herpesviruses reported from free-ranging and captive belugas and from the beluga case presented here have not been isolated or fully characterized (i.e., assigned to the alpha- beta- or gammaherpesvirus subfamily). In beluga whales, necrotizing herpesviral lesions have not been reported in organs other than the skin. There were no skin lesions associated with herpesvirus in our beluga case. Herpesviral inclusions were observed in lung and adrenal cortex and were associated with necrosis only in the adrenal gland. Although other tissues had more prominent histologic changes, one Atlantic bottlenose dolphin with disseminated alphaherpesvirus infection had foci of acute adrenal cortical necrosis associated with herpesviral inclusions. In young Pacific harbor seals infected with phocid herpesvirus type-1 (PhHV-1), an alphaherpesvirus showing greatest similarity to canine herpesvirus, the major lesion is adrenal cortical necrosis. Adrenal cortical necrosis with intranuclear inclusion bodies occurs in systemic infection of neonatal puppies with *Herpesvirus canis* and has been reported in experimental pseudorabies (*Herpesvirus suis*) in sheep, both of which are classified as alphaherpesviruses.

Little is known about the epidemiology of herpesvirus infections in cetaceans; it is thought that they probably increase with age and become latent similar to alphaherpesvirus infections in other species. This beluga was a young captive born individual that presented in very poor body condition presumably because at 25 months of age she was still not eating fish on her own. Most of the lesions seen at necropsy can be attributed to inanition and stress. Possibly, she was harboring a latent infection that was activated by an immunocompromised state and stress secondary to malnutrition. Alternatively, her condition could have predisposed her to infection with herpesvirus being shed by subclinically infected conspecifics.

Prior to death, this beluga whale had severe lymphopenia and hypoglobulinemia. Lymphoid depletion was observed in histologic examination of the spleen. In PhHV-1 infection in Pacific harbor seal pups, marked lymphopenia occurred just prior to death. These seals died with herpesvirus associated adrenal necrosis but death was not associated with adrenal insufficiency. The extent to which the herpesviral adrenal lesions compromised adrenal function in the beluga presented here is not known. Adrenal function testing was not performed.

Vibrio alginolyticus was isolated from the kidney. *Vibrio* spp. are commonly isolated from both healthy and diseased cetaceans. In this case, there was minimal multifocal lymphoplasmacytic nephritis.

AFIP Diagnosis: Adrenal gland: Necrosis, multifocal, with eosinophilic intranuclear inclusion bodies, etiology consistent with herpesvirus, beluga whale (*Delphinapterus leucas*), cetacean.

Conference Comment: Herpesviruses are double stranded DNA viruses and form characteristic hexagonal, unenveloped, intranuclear, virions that are approximately 100 nm in diameter. Cytoplasmic virions are enveloped and approximately 160 nm in diameter. The spectrum of herpesviral pathogenicity is very broad, ranging from subclinical infection to fatal disseminated disease. There are several possible mechanisms for the more severe manifestations of clinical disease. These include overwhelming infections in immunologically naive animals, recrudescence of latent infections following stress or other causes of immunosuppression, and infections of aberrant hosts.

During the conference, herpesviral diseases of pinnipeds also were discussed. As noted by the contributor, phocid herpesvirus type-1 (PhV-1), an alphaherpesvirus, is a cause of adrenal cortical necrosis in young Pacific harbor seals. Generalized infections have been described in neonatal harbor seals. Generalized infections also have been observed in adult seals concurrently infected with phocid distemper virus; morbillivirus-induced immunosuppression is presumed to be the cause of dissemination. PhV-1 infection of European harbor seals has been associated with signs of respiratory disease. Phocid herpesvirus type-2 (PhV-2), a gammaherpesvirus, has been isolated from harbor seals. Metastatic carcinomas of unknown origin are common in California sea lions. Recently, intraepithelial neoplasia of the genital tract was described in affected male and female sea lions and proposed to be the site of origin of the metastatic carcinomas. Intranuclear inclusion bodies and herpesviral particles were detected in both intraepithelial neoplasia and metastatic carcinoma. A novel gammaherpesvirus was detected in metastatic carcinomas by PCR and sequencing, and was proposed as a possible cause of the cancer.

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