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CASE I - 00-238 (AFIP 2738736)

Signalment: 3 year old, male, foxhound mix.

History: The dog was from a kennel of 120 dogs in New York. Twenty of the dogs were sick or had died recently. This dog presented with fever, generalized lymphadenopathy, multiple subcutaneous masses and multifocal facial and periocular alopecia. (This case was submitted in July 2000).

Gross Pathology: The dog exhibited marked muscle wasting and depleted fat stores. There were multiple patches of alopecia on the face and ears. There were three soft, tan subcutaneous nodules over the thorax. The liver, spleen and multiple peripheral and mesenteric lymph nodes were enlarged. The carpal, stifle and tarsal joints had a moderate amount of brown exudate.

Laboratory Results: None reported.

Contributor's Morphologic Diagnosis: Spleen: Histiocytic and lymphoplasmacytic splenitis, with numerous intrahistiocytic protozoa, consistent with *Leishmania* sp., lymphoid involution and extramedullary hematopoiesis.

Contributor's Comment: *Leishmania* sp. are intracellular, kinetoplastid protozoan parasites from the family *Trypanosomatidae* that parasitize cells of the mononuclear phagocytic system. Leishmania amastigotes have also been reported within fibroblasts, which may represent a survival mechanism to evade the immune system. Leishmania is endemic in many parts of the world. In some areas, dogs are a reservoir and therefore have a role in zoonotic transmission. Leishmania is spread by sandflies (*Lutzomyia* - new world, *Phlebotomus* - old world). Other biting

insects such as *Stomoxys* and *Rhipicephalus* may act as mechanical vectors. Leishmania are phagocytized by macrophages. Within the phagolysosome, the organism transforms into a round amastigote that lacks a flagella but contains a single, large mitochondrian-like structure (kinetoplast). A proton-transporting ATPase protects the amastigotes from the acidic environment and maintains an intracellular parasite pH of 6.5. Two additional virulence factors on the surface include lipophosphoglycans and gp63. Lipophosphoglycans bind C3b or iC3b. Organisms resist lysis by complement C5-C9, and are phagocytized by macrophages via complement receptors CR1 (LFA-1) and CR3 (MAC-1 integrin). Lipophosphoglycans may also scavenge oxygen radicals and inhibit lysosomal enzymes. Gp63 cleaves complement and some lysosomal antimicrobial enzymes. Amastigotes multiply by binary fission, which leads to mechanical rupture of the macrophage. The extent of lesions depends on the cell-mediated immune response. Parasite specific CD4+ helper T lymphocytes secrete interferon gamma and macrophages secrete TNF alpha, which activate phagocytes to kill toxic parasites via toxic metabolites of oxygen and/or nitric oxide. TNF alpha acts in an autocrine fashion to induce nitric oxide production. Nitric oxide is toxic to amastigotes by interfering with iron dependent enzymes responsible for DNA replication, the citric acid cycle and mitochondrial respiration. Parasite specific helper T cells secrete IL-4 which inhibits macrophage activation by interferon gamma and inhibits the secretion of TNF alpha, thereby depressing the immune response. Demodicosis is common in dogs with Leishmaniasis, and provides evidence of suppressed cell mediated immunity. There are three major forms of Leishmania, and they are each associated with a specific species of the organism: cutaneous, mucocutaneous and visceral. Dogs may develop concurrent cutaneous and visceral manifestations, while they are single entities in humans. Clinical signs include chronic wasting, generalized lymphadenopathy, cutaneous lesions ranging from alopecia to ulcers, hepatomegaly and splenomegaly. In the later stages, there is chronic renal failure secondary to immune mediated glomerulonephritis. Clinical pathology abnormalities typically include normocytic, normochromic anemia, hyperproteinemia, hypergammaglobinemia, hypoalbuminemia, thrombocytopenia, leukopenia and azotemia. Additional histologic lesions in this case are representative of described cases of canine Leishmaniasis and include proliferation of macrophages and plasma cells within the lymph nodes, kidneys, bladder, bone marrow, conjunctiva, skin, subcutaneous tissue and joint capsules, with varying numbers of intrahistiocytic protozoa. There are also infiltrates of varying numbers of macrophages and plasma cells within the myocardium, alveolar septa, testes, small intestine and colon. Other lesions include membranoproliferative glomerulonephritis, and depletion of the T-cell dependent areas in the spleen and lymph node. Histologic differential diagnoses include: 1) *Trypanosoma cruzi* (amastigotes are usually within pseudocysts in cardiac fibers, and are larger than *Leishmania*, with a larger more basophilic kinetoplast that is parallel to the nucleus),

2) *Histoplasma capsulatum* (lacks a kinetoplast, PAS +, GMS +), and 3) *Toxoplasma gondii* (PAS + cyst wall and GMS -).

The CDC identified the isolates as *Leishmania donovani*. It still remains a mystery how the foxhounds contracted the Leishmania. Wildlife, horses, humans and pets in the surrounding area are negative. The dogs have an extensive travel history throughout the east coast, including to southern areas where the vector is present. Additional cases of Leishmania in foxhounds in other areas have occurred recently. As a result, the American Foxhound Association has cancelled all of their spring/summer shows. The reason for the high incidence in foxhounds is unclear. Some clinicians involved in this outbreak feel that Leishmania may not be a new problem for the foxhounds, but has just been under diagnosed.

AFIP Diagnosis: Spleen: Splenitis, histiocytic and plasmacytic, diffuse, moderate, with numerous intrahistiocytic amastigotes, etiology consistent with *Leishmania* sp., foxhound mix, canine.

Conference Comment: The contributor provides a thorough review of the pathogenesis and host immune response in animals with leishmaniasis.

Since visceral leishmaniasis was detected in foxhounds from a hunt club in New York in 2000, seropositive dogs have been detected in 60 foxhound kennels in 22 states and two Canadian provinces. Other breeds, to include wild canids living in close proximity to the infected foxhounds, have been sampled and none have generated positive titers. So far, data indicate that direct transmission between dogs, as well as a possible sand fly vector may be important means of transmission in foxhounds. There are species of sand flies in the United States capable of transmitting *Leishmania* sp., particularly *Lutzomyia shannoni* (a possible vector of *Leishmania mexicana* which is endemic in Texas and Mexico). No infected sand flies have been identified in association with this outbreak. A group of Beagles and Bassett Hounds that were housed with seropositive foxhounds, and traveled to the southeastern United States with them (where they presumably would have been exposed to the same vector, if present), were seronegative. It is not known why foxhounds are more susceptible than other breeds.[7-10]

Although no human disease has been detected in association with these cases of canine visceral leishmaniasis, this is an important consideration since dogs are reservoir hosts for human visceral leishmaniasis, a significant concern in immunosuppressed individuals.[8,10]

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CASE II - S1138.03 (AFIP 2890233)

Signalment: Thirteen-month-old breeder hens (*Gallus domesticus*).

History: Severe dyspnoea and mortality in breeder hens in an intensive production system.

Gross Pathology: Severe, diffuse, acute caseous necrotic laryngo-tracheitis.

Laboratory Results: On histopathological examination there was severe diffuse epithelial hyperplasia and necrosis with infiltration of colonies of coccoid bacterial organisms. There was also severe multifocal to coalescing degeneration of epithelial cells with accumulation of eosinophilic intracytoplasmic and amphophilic intranuclear inclusion bodies as well as the infiltration of numerous heterophils, plasma cells and mononuclear leucocytes into the mucosa and submucosa.

On electronmicroscopic examination of uranyl acetate and lead citrate-stained sections of affected tracheal mucosa, numerous large (250 x 254 nm) brick-shaped to biconcave intracytoplasmic virus particles with dense cores as well as smaller (80-100 nm in diameter) intranuclear virus particles with dense cores and a vague icosahedral symmetry, could be observed (Figures 1 and 2 - see arrows).

Contributor's Morphologic Diagnosis: Severe multifocal to coalescing chronic active and necrotic laryngotracheitis with intracytoplasmic and intranuclear viral inclusion bodies.

Contributor's Comment: The intracytoplasmic and intranuclear inclusions are morphologically compatible with Avian pox virus and Infectious Laryngotracheitis virus (ILTV-Herpes virus) infections respectively, which represents a dual infection. Avian poxviruses (fowl, turkey, pigeon, canary, junco, quail, sparrow and starling) are members of the genus *Avipoxvirus* of the family *Poxviridae.* Psittacine poxvirus and mynah poxvirus probably represent different members of the genus. Fowl poxvirus represents the type species of the genus[1,3]. Avian poxviruses affect a wide range of birds of various families by naturally or artificially occurring infection. A substantial degree of host specificity exists among some avian species, especially those that infect wild birds. Both skin and respiratory epithelium may become infected with respiratory infections being the most severe with mortalities rising as high as 50% in chickens and turkeys. Infectious laryngotracheitis virus is classified as a member of the family *Herpesviridae* in the subfamily *Alphaherpesvirinae* and is taxonomically identified as Gallid herpesvirus[2]. Virus particles are also similar in shape to herpes simplex [2,4]. The chicken is the primary natural host of ILTV, and although the virus affects all ages, the most characteristic signs are observed in adult birds. Viral multiplication is limited to respiratory tissues with little evidence of viraemia. Severe epizootics of the disease cause high morbidity and variable mortality of 5-70%. Milder enzootic forms of the disease also occur. Gross lesions may be found throughout the respiratory tract, but they are most consistently found in the larynx and trachea.[2] Although ILT is routinely diagnosed by histopathology, a specific PCR test has been introduced recently and would appear to render more specific diagnoses in cases of suspected ILTV infection[5].

AFIP Diagnosis: Larynx and trachea: Laryngotracheitis, necrotizing, proliferative, heterophilic, lymphoplasmacytic, and histiocytic, diffuse, severe, with ulceration, abundant caseonecrotic exudate, epithelial eosinophilic intracytoplasmic and intranuclear inclusion bodies, and myriad luminal bacteria, etiologies consistent with avian poxvirus and gallid herpesvirus-1, chicken, avian.

Conference Comment: As mentioned by the contributor, avian poxvirus may affect both skin and respiratory epithelium. There are two forms of fowl pox: dry (cutaneous) and wet (diphtheritic). The dry form is more common, with nodular proliferative lesions on unfeathered skin of the head, neck, legs, and feet. Fibrinonecrotic lesions of wet pox often occur in the mouth, esophagus, trachea, pharynx, and larynx. These lesions begin as small white nodules and progress to form coalescing raised plaques with a diphtheritic membrane. Large (15-30um) eosinophilic, intracytoplasmic inclusion bodies, also known as Bollinger bodies, within epithelial cells are characteristic for fowl pox.[1,6]

Important differential diagnosis for lesions resembling wet pox includes hypovitaminosis A, trichomoniasis, and candidiasis. Vitamin A deficiency is characterized by small white nodules, often with a central depression, in the nasal passages, mouth, esophagus, and pharynx. These lesions are the result of squamous metaplasia and subsequent blockage of mucous glands and their ducts by necrotic debris and secretions. *Trichomonas gallinae* causes caseous, proliferative lesions, which may be surrounded by a zone of hyperemia, in the buccal cavity, pharynx, esophagus, and crop. In pigeons, this condition is known as "canker". *Candida albicans* causes gray-white pseudomembranous patches in the mouth, pharynx, esophagus, and, most frequently, the crop.[7]

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CASE III - 139-03 (AFIP 2887157)

Signalment: 11 year old, female spayed, mixed breed (Spaniel/Terrier) canine.

History: This otherwise healthy dog presented to our referral hospital for surgical resection of an oral mass that had been identified by the referring veterinarian during a routine physical examination appointment.

Gross Pathology: A 3 X 1 X 1 cm raised firm tan non-pigmented gingival mass from the buccal surface of the right cranial mandible was submitted in 10% buffered formalin. The mass caused distortion of the first premolar and canine tooth. On cut section, the mass was expansile, gelatinous and pale tan with gritty white foci throughout.

Laboratory Results: Elevations were seen in the following blood parameters: WBC - 17.0 (4-15.5), Absolute Polymorphs 13430 (2060-10600), and Absolute Monocytes 1020 (0-840). Clinical Chemistry revealed elevations in all of the following: Glucose 144 (70-138), BUN 30 (0-25), Total protein 9 (5-7.4), Phosphorus 6.3 (2.5-6.0), Sodium 165 (139-154), Potassium 5.7 (3.6-5.5), Chloride 129 (102-120), and Globulin 5.1 (1.6-3.6). Chest radiographs were within normal limits.

Contributor's Morphologic Diagnoses:
1. Oral Malignant Melanoma with Chondroid Metaplasia.
2. Severe Focally Extensive Subacute Ulcerative, Suppurative and Lymphoplasmacellular Gingivitis.

Contributor's Comment: Malignant melanoma can have desmoplastic, neurotropic or osteochondrogenic differentiation.[1] Osteochondroid differentiation is an extremely rare feature of malignant melanoma in humans and dogs.[1] Chondroid formation has been seen in some canine dermal malignant melanomas.[2] In veterinary medicine, a single canine osteoid-producing variant of melanoma was described in the gingiva of a 12 year old miniature Dachshund and three chondroid-

producing variants have been reported, one involving the lip commissure in an 11 year old FS cocker spaniel and the others within the gingiva of two unknown breeds.[1,3,4] Only rare combined osteochondroid variants of melanoma have been described in people - 3 with osteoid and bone, 3 with osteoid, bone and cartilage and 4 with osteoid and cartilage.[1] Generally, these variant tumors can be distinguished from osteosarcoma or chondrosarcoma because of junctional activity, the presence of melanin and positive melanin A staining. Surprisingly, Melanin A staining of the tumor, including regions of prominent junctional activity, was negative. This does not rule out melanoma as a small percentage of canine oral melanomas will be melanin A negative.[4]

The origin of these matrices are not well determined but may result from pseudosarcomatous differentiation of neoplastic melanocytes or from metaplasia of the surrounding stroma during invasion by the melanoma.[1] Some authors strongly support the contention that the chondroid formation is a result of melanocytic histiogenesis.[1] By far the most prominent matrix component in this tumor is chondroid and as pigmented and pleomorphic spindle cells are seen interspersed within this matrix it is thought to be a direct differentiation product of the malignant melanocytes.

It is of interest in this case that there are proliferative changes in several other gingival elements that may have resulted from induction of the periodontal ligament and resembled benign canine epulidides.[5] There were focal regions where squamous epithelial clusters and aggregates of hypereosinophilic matrix product (not seen in every section) were interspersed throughout a loose fibrous connective tissue. Special stains of the matrix (blue with Alcian blue and Masson's trichrome and weakly congophilic with Congo red but without birefringence under polarized light) suggested this was possibly of dental origin (i.e. dentin) and was not consistent with amyloid or osteoid. The possibility that malignant melanocytes induced epulis-like changes by induction of the periodontal ligament needs to be considered in this case.

AFIP Diagnosis: Gingiva (per contributor): Malignant melanoma with osseous and cartilaginous metaplasia, spaniel/terrier cross, canine.

Conference Comment: Melanocytic neoplasms vary among sites and among species. In dogs, a large majority of melanocytic neoplasms of the skin and eye are benign, whereas digital and oral melanocytic neoplasms are frequently malignant. Benign and malignant cutaneous melanocytic neoplasms occur with nearly equal frequency in cats but are uncommon tumors in this species.[6,7,8]

Gray or white horses often present with a melanocytic neoplasm of the perineum, base of the tail, or external genitalia. Although melanomas are possible in any breed or color of horse, they are clinically detectable in 80% of gray horses over 15 years of age. Some authors believe that all gray horses will develop melanomas if they live long enough. Three growth patterns of equine melanocytic tumors are described. The first pattern are those that grow slowly over many years and do not metastasize, whereas the second pattern are those that present as a benign growth but suddenly begin to grow rapidly and assume malignant characteristics. The third pattern are those that grow rapidly and are malignant from the onset.[6,9]

Pigs are frequently used in melanoma research. Sinclair miniature pigs, used as models for human cutaneous melanoma, and Duroc pigs are genetically predisposed to develop these tumors. Melanomas are unique in pigs in that up to 90% spontaneously regress, making pigs a valuable animal model for studying immunopathogenesis.[6]

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CASE IV - N688/01 (AFIP 2890236)

Signalment: Presumed 15 years old, female, bottlenose dolphin, *Tursiops truncatus*.

History: The animal had a history of cutaneous traumatic lesions caused by fighting with a male of the same species. The last report of a lesion on the caudal fin was a month before time of the death. The animal died suddenly after one day of acute symptoms and signs characterized by abdominal contractions and vomit; acute, severe, green-yellowish diarrhea and a bilateral, diffuse, moderate subcutaneous swelling behind the blowhole. A clostridial infection was suspected. Antibiotics, cortisone and fluid therapy was carried out with no positive results.

Gross Pathology: At necropsy, a bilateral, diffuse, moderate to severe subcutaneous swelling was observed just behind the blowhole (Fig. 1). Removing the skin and the blubber, in the corresponding area, severe and diffuse subcutaneous hemorrhages, edema and emphysema and slight multifocal necrosis of the blubber were present (Fig. 2). The superficial muscular fascial planes and the skeletal muscles were characterized by diffuse, severe superficial edema, hemorrhages and emphysema and deep severe, multifocal to coalescent, hemorrhagic muscular necrosis. Moreover severe periocular hemorrhages and bilateral mucopurulent conjunctivitis was found. The lungs showed moderate to severe, diffuse hyperemia and slight, bilateral, diffuse pulmonary edema. Mild superficial enteritis and multifocal superficial hyperemic gastric erosions were observed.

Laboratory Results:
Hematology (same day of clinical signs and death):
WBC 1.00 (10/mm)
Creatine kinase 5.000 (mg/dl)
K 6.54 (mEq/l)

CYTOLOGY of the subcutaneous effusion behind the blowhole revealed numerous bacterial cocci, either isolated or in chains, associated with occasional neutrophils and macrophages and abundant slightly stained proteinaceous material and vacuoles referable to adipose tissue (Fig. 3).

MICROBIOLOGY on sterile swabs from subcutaneous lesions: isolation and identification of *Streptococcus agalactiae.*

Contributor's Morphologic Diagnosis: Muscles, thorax/head, anterior, dorsal: myositis, hemorrhagic-necrotizing, purulent, severe, coalescent associated with numerous Gram-positive bacterial cocci and with thrombi formation.
Etiology: *Streptococcus agalactiae*
Additional histology reveals:
Skin and superficial muscles, thorax - head, anterior, dorsal: cellulitis and fasciitis, diffuse, moderate associated with numerous Gram-positive bacterial cocci.
Superficial lymph nodes: reactive hyperplastic lymphadenitis and diffuse severe hemorrhages and hyperemia.
Stomach: muscular part - superficial diffuse erosion and moderate superficial diffuse chronic gastritis.
Mesenteric lymph nodes: chronic, diffuse, moderate, lymphoplasmacytic enteritis; diffuse lymphocytic depletion, diffuse moderate histiocytosis of the sinuses and follicular hyalinosis moderate diffuse.
Liver: hydropic degeneration, severe, diffuse and slight diffuse biliary stasis.
Kidney: tubular degeneration, diffuse, moderate, associated with occasional tubular pigmentation.
Lungs: severe, diffuse hyperemia, associated with moderate, diffuse emphysema and diffuse bronchiolar epithelial erosion with disseminated dystrophic mineralization.

Contributor's Comment: The severe localized subcutaneous and muscular lesions associated with a severe *Streptococcus agalactiae* infection were considered responsible for a toxic-shock syndrome responsible for hypotension and septic-toxic multiple organ failure and consequential death of the subject.

In veterinary medicine *Streptococcus agalactiae* is one of the most important organisms in bovine mastitis; nevertheless its role in invasive cutaneous infections is well documented in man[1]. Particularly, after *Clostridium* sp., streptococci (mainly group A and group G) play an important role in the pathogenesis of necrotizing fasciitis (NF), a well-known soft tissue infection, primarily affecting the superficial fascial planes and often associated with cellulitis and myositis[2,3]. Few cases of NF have been associated with isolation of *S. agalactiae*[4,5].

Severe fascial and muscular necrotizing lesions, referred to as NF, have been recently recognized in veterinary medicine particularly associated with *Streptococcus canis.*[6] Therefore, the specific lesions we report could be considered a case of NF in a marine mammal associated, in this case, with *S. agalactiae*.

Necrotizing fasciitis is often secondary to traumatic / post surgical wounds in compromised patients (stressed, immune-depressed)[7,1]. In this subject the history of cutaneous lesions and eventual stress for its captive condition cannot be ruled out as presumptive predisposing factors. The eye lesions might also have represented the portal of entry for the pathogen.

AFIP Diagnosis: Skeletal muscle: Myositis, necrotizing, fibrinosuppurative, diffuse, severe, with hemorrhage and myriad cocci, bottlenose dolphin (*Tursiops truncatus*), cetacean.

Conference Comment: Classification of streptococci is based on numerous factors, including carbohydrate and protein antigen composition and hemolytic properties. The Lancefield system (groups A-H and K-V) uses antigenic differences in the cell wall carbohydrates for classification. Bacterial action on erythrocytes in culture media is another defining characteristic. Alpha hemolysis is characterized by a greenish-colored zone associated with partially digested erythrocytes and reduction of hemoglobin. Beta hemolysis is characterized by complete lysis of erythrocytes and a halo of clearing around the colonies. Some strains are nonhemolytic (gamma hemolysis). Beta hemolytic strains are typically the most pathogenic, while alpha hemolytic and nonhemolytic strains are found on the skin and mucous membranes of healthy animals.[8]

Streptococcus agalactiae is the only member of Lancefield group B and is alpha hemolytic. The contributor mentions the significance of this organism in bovine mastitis. Infections with this strain are rare in dogs and cats, but have been reported to cause septicemia, endometritis, and fading puppy syndrome.[8]

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