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Philadelphia, PA 19104

CASE I – PN11/01 (AFIP 2784724)

Signalment: 15-year-old, female-spayed, domestic shorthair, *Felis catus*, feline

History: The cat had a two months history of depression and anorexia with occasional episodes of fever and progressive dehydration. The cat developed an exfoliative dermatitis in the periocular area that extended progressively to the head and neck. The lesions generalized progressively to dorsal, flank and inguinal regions and were non-pruritic. All the affected skin was characterized by generalized scaling and focal crusting. Symmetrical erosions developed in the periocular area and in the left lateral thorax. The cat did not respond to antibiotic and steroid therapy and died spontaneously two months and 12 days after the initial clinical symptoms.

Gross Pathology: A full necropsy was performed. The cat was severely dehydrated and emaciated. The skin was unelastic, hard, dry and characterized by linear fractures. Severe thickening and crusting were present in the frontal region, ventral neck and dorsum. The hair epilated easily and on simple traction the epidermis detached from the underlying dermis. Areas of erosion were present in the periocular region and in the left lateral thorax. Grossly normal skin was present only on the tip of the tail and the tip of the ears. In the abdominal cavity both kidneys were pale, shrunken with capsular adhesions and cortical thickness was reduced on cut surface. In the cranial mediastinum, a 2x3 cm cystic mass was found. The cut surface of the mass was characterized by areas of hemorrhage with fluid filled cysts. No other gross findings were evident.

Laboratory Results: Skin scrapings did not reveal ectoparasites and fungal cultures were negative. FIV and FeLV serological tests were negative. Ultrasound or X-ray investigations were refused.

Abnormal hematologic values were HCT 19%, RBC $3.2x10^6$/ul, Reticulocytes 0% (non-regenerative anemia). The serum chemistry was characterized by elevated BUN (290mg/dl) and creatinine (4.4mg/d). Total serum protein was 3.3g/dl. Severe renal insufficiency was suspected.

Immunohistochemical analysis performed on formalin-fixed tissue sections with anti-CD79-a (B cells) and anti-CD3 (T cells) identified the lymphocytes in the epidermis and the follicular epithelium as CD3 positive T cells.

Contributor's Morphologic Diagnoses: Haired skin: 1) Severe, diffuse, chronic, lymphocytic interface dermatitis with severe, diffuse orthokeratotic hyperkeratosis; mild to moderate, diffuse acanthosis and focal parakeratosis.
2) Severe, multifocal, chronic, lymphocytic mural folliculitis with follicular keratosis.
3) Mild to moderate, chronic, perivascular lymphoplasmacytic dermatitis. Feline, DSH, 15 years old.

Contributor's Comment: In this cat, cutaneous gross and microscopic lesions paralleled previously reported cases of feline thymoma associated dermatitis. This hypothesis was confirmed by the finding of a tumor in the cranial mediastinum. The lesion contained cystic spaces and was composed of a mixture of neoplastic epithelial cells and a prevalence of small, mature lymphocytes. All these features were consistent with a cystic thymoma.

Thymoma is an uncommon neoplasm in cats that has been associated with two paraneoplastic syndromes: *myasthenia gravis* and an exfoliative dermatitis. The correlation between cutaneous disease and thymoma has been strongly suggested by regression of skin lesions after surgical excision of the concurrent thymoma.

Thymoma associated cutaneous disease is characterized by severe, diffuse orthokeratotic hyperkeratosis, focal parakeratosis, acanthosis and lymphocyte exocytosis with features of a cell-poor interface dermatitis. These lesions parallel microscopic features of erythema multiforme and differentiating between the two disease entities is based on the clinical behavior and the finding of thymoma. Thymoma associated exfoliative dermatitis and *myasthenia gravis* have been interpreted as paraneoplastic syndromes. An autoimmune pathogenesis in which thymic-derived lymphocytes may play a yet poorly defined role has been suggested for *myasthenia gravis*. In this cat, the finding of CD3 positive T-cells in the basal epidermis and follicular epithelium with an interface pattern suggests a T-cell immune-mediated mechanism most likely associated with abnormal antigen presentation by neoplastic thymic epithelial cells.

AFIP Diagnosis: Haired skin: Hyperkeratosis, diffuse, moderate to marked, with moderate acanthosis, mild to moderate lymphoplasmacytic interface dermatitis, and focally extensive necrotizing epidermitis, Domestic Shorthair, feline.

Conference Comment: This cat had an exfoliative dermatitis. The differential diagnosis discussed in conference included epitheliotropic lymphoma, erythema multiforme, thymoma-associated dermatitis and other immune-mediated processes. The clinical history of an exfoliative dermatitis that began on the head and became generalized in an old cat, histologic features that include a cell-poor mononuclear interface dermatitis with marked hyperkeratosis, and gross findings of a thymic mass are compatible with thymoma-associated dermatitis. However, other diagnoses were considered because: not all sections have marked hyperkeratosis; there are relatively few apoptotic epithelial cells; there is extensive ulceration in the gross photograph; and it was not possible to demonstrate regression of the skin lesions after removal of the thymic mass.

Conference participants noted areas of necrotizing epidermitis. These areas, which were not present in all slides, contained epithelial cells with possible intranuclear inclusions. This lead to a discussion of possible herpesviral dermatitis. Feline herpesvirus 1 dermatitis is an uncommon necrotizing dermatitis that primarily involves the face. Herpesviral dermatitis is usually associated with eosinophilic inflammation and is typically not as generalized as the lesions in this case. Stress, immunosuppression, and other infections are regarded as predisposing factors that lead to what is most likely reactivation of a latent infection. Immunohistochemistry performed at the AFIP for herpes simplex virus, Ebstein Barr virus, and cytomegalovirus was negative.

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CASE II – 01-14173 (AFIP 2790164)

Signalment: 14-year-old, male intact, Mixed-breed, Canine

History: Owner noticed difficulty in eating, swallowing and excessive salivation.

Gross Pathology: 3cm x 1cm mass found on dorsal surface of the tongue. Surgically excised using laser surgery.

Laboratory Results: None.

Contributor's Morphologic Diagnosis: Oral lymphosarcoma – nodular and epitheliotrophic – tongue - Canine

Contributor's Comment: Tissue is a portion of the lingual mass with one natural border and 3 cut borders.

The oral mucosa is intact. At one surgical margin, where the lingual papillae can be identified, the epithelial cells are distorted and are elongated due to the use of electrocautery to remove the mass. Within the lingual epithelium, confined to the basal and lower spinous layer are aggregates of neoplastic lymphoid cells forming Pautrier's microabscesses. There is minimal to no involvement of the superficial submucosal tissue by the neoplastic lymphoid cells, with a broad zone of unaffected superficial submucosa at one edge and a narrow zone at the opposite edge. The neoplastic cells within the epithelium have ovoid, vesicular nuclei. A few cells have a reniform or more convoluted appearance to their nuclei. Individual cells have little cytoplasm. There is little cellular pleomorphism and mitotic figures average less than 1 per 200x field.

The submucosal mass consists of sheets of neoplastic cells and the remnants of the lingual muscle fibers that are atrophic. The majority of the neoplastic cells have round to ovoid vesicular nuclei and some cells have clumped chromatin at the rim of the nucleus. A small amount of lightly eosinophilic cytoplasm is present with indistinct cell borders. These cells exhibit moderate nuclear pleomorphism and there are from 2 to 6 mitotic figures per 200x field. Interspersed among these cells are cells with giant nuclei and multilobated nuclei.

The presence of intraepithelial lymphoid aggregates is very characteristic for mucosal and mucocutaneous lymphosarcoma. What is unusual and confusing are the cells with giant nuclei and multilobated giant nuclei, a feature more commonly associated with Oral Plasmacytoma, which is a common tumor of the tongue.

Immunohistochemistry showed the following:

CD3 (Dako) – T and NK cells – All submucosal and intraepithelial cells including the cells with giant nuclei stained positive

CD79a (Dako) – Plasma and B cells – submucosal and intraepithelial cells including the cells with giant nuclei did not stain

BLA36 – B cells - submucosal and intraepithelial cells including the cells with giant nuclei did not stain

S100a (Dako) – Melanoma - submucosal and intraepithelial cells including the cells with giant nuclei did not stain

In our laboratory most Plasmacytomas stain with CD79a.

Some sections have a small central area of mucosal ulceration but this does not preclude arriving at a definitive diagnosis.

AFIP Diagnosis: Tongue: Malignant lymphoma, epitheliotropic, mixed breed, canine.

Conference Comment: As described by the World Health Organization, cutaneous T-cell neoplasms are classified as epitheliotropic or nonepitheliotropic. Epitheliotropic lymphomas are further subclassified as mycosis fungoides type or pagetoid reticulosis type. Reported in cattle, dogs, cats, and horses, the mycosis fungoides type is composed of small lymphocytes of intermediate type. The lesion distribution is focal or multifocal. Neoplastic cells are present in the dermis, form intraepithelial nests, and are characterized by moderate amounts of clear cytoplasm and indented or cerebriform nuclei. In cattle the disease typically affects two to three year olds, waxes and wanes, and mimics ringworm in the early stages. In horses the condition is rare. If allowed to progress, animals may develop a leukemic phase referred to as Sezary syndrome in humans.

In the pagetoid reticulosis variant, malignant lymphocytes are predominantly distributed above the basement membrane. Histologically, the epidermis is initially hyperkeratotic eventually becoming ulcerated. Inflammation of the superficial dermis is often present.

Neoplastic cells in cutaneous nonepitheliotropic lymphoma occupy the deeper dermis. The epidermis and a thin zone of adjacent superficial dermis remain clear of neoplastic cells. Histologically, neoplastic cells resemble those of epitheliotropic lymphoma.

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CASE III – 01N 324 (AFIP 2790937)

Signalment: 16-year-old, male, mixed-breed dog

History: Three and a half-year history of multiple subcutaneous masses that began on the distal extremities and progressed to the entire extremities and ventrum.

Gross Pathology: Numerous firm, white homogenous nodules (ranging from 1-4 cm diameter and coalescing in some areas) are found throughout the subcutaneous tissues of the limbs and ventral abdomen. Skin covering nodules is intact and unaffected, with the exception of calluses around both hocks. Pinpoint to 1cm diameter white nodules are distributed throughout the peritoneal surface of the abdominal wall, pleural and peritoneal surfaces of diaphragm, serosal surfaces of all abdominal organs, and pericardium. There is a 5cm diameter, fluid-filled cyst at the cranial pole of the left kidney. The cranial pole of the right kidney has a 4 cm diameter firm, tan mass that extends through the cortex into the medulla.

Laboratory Results: None.

Contributor's Morphologic Diagnoses: 1. Skin, nodular dermatofibrosis

2. Kidney, renal cell adenoma

Contributor's Comment: The left kidney mass is comprised of well-differentiated epithelial cells forming numerous small tubules. The mass is well-encapsulated and compresses the surrounding renal parenchyma.

Skin lesions consist of multiple nodular accumulations of normal appearing collagen. Similar discrete accumulations of collagen were found in the ventral body wall, diaphragm, stomach, intestine, and myocardium. These lesions are consistent with nodular dermatofibrosis.

Nodular dermatofibrosis is considered a hereditary disease of German Shepherds with associated renal tumors. Skin lesions consist of subtle to discrete accumulations of normally arranged collagen in the dermis and subcutis. The presentation of this case is unusual in that nodular dermatofibrosis lesions generally do not involve underlying skeletal muscle and do not spread to the internal body surfaces and organs as in this case. Reported renal tumors with this condition are usually renal adenocarcinomas. The tumor in the right kidney of this dog is characterized as an adenoma due to the expansile growth pattern, relatively distinct fibrous tissue encapsulation, and lack of anaplasia in the comprising cell population. The distinction between renal adenocarcinoma and renal adenoma, however, is difficult and subjective since most malignant renal tumors fail to exhibit many traditional characteristics used to evaluate malignancy (infiltrative growth and metastasis). Solitary renal cysts, as seen in the left kidney, are generally considered incidental findings.

AFIP Diagnoses: 1. Haired skin and subcutis: Fibrosis, nodular, multifocal, moderate, mixed breed, canine.
2. Kidney: Renal cell neoplasm.

Conference Comment: We agree with the contributor that the distinction between adenoma and adenocarcinoma is often difficult, and in this case, the distinction is further hampered by poor tissue preservation. The case was studied in consultation with the Department of Genitourinary Pathology at the AFIP. After deliberation they favored the diagnosis of low-grade renal cell carcinoma based on mild atypia and binucleation of neoplastic cells. Most conference participants favored the less specific diagnosis of renal cell neoplasm.

The canine syndrome renal cystadenocarcinoma and nodular dermatofibrosis (RCND) has an autosomal dominant mode of inheritance and is localized to a defect in canine chromosome five. Histologic findings in the kidney are multifocal and nearly always bilateral. These include hyperplastic nodules, cysts, cystadenomas, or cystadenocarcinomas and may represent a continuum. Uterine leiomyomas

occur in most affected females. In contrast, renal neoplasms that are not associated with the syndrome are usually solitary and unilateral.

The exact pathogenesis of RCND is unknown. Theories include a common genetic abnormality (an unidentified tumor suppressor gene) resulting in both renal and skin lesions or a paraneoplastic syndrome where collagen-stimulating growth factors are produced by the renal tumor. In humans, several genes are associated with various renal neoplasms. These genes include WT1 (Wilm's tumor), NF1 (neurofibromatosis), VHL (von Hippel Lindau disease), and PKD1 and 2 (polycystic kidney disease).

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CASE IV – 99A9254 (AFIP 2678477)

Signalment: 13-year-old, neutered female, mixed-breed dog, *Canis familiaris*

History: This animal was presented to necropsy following a long history of pododermatitis and migratory erythema. The superficial layers of the footpads were sloughing. There was erythema and alopecia on the trunk. Most recently, the dog has experienced weight loss.

Gross Pathology: The animal was thin and there was a generalized loss of muscle mass. The epidermis over the footpads was markedly thickened due to multiple layers of keratin. Several nails were missing and there was partial thickness sloughing of the epidermis. There were multiple foci of alopecia characterized by pigmentation and crusting distributed along the skin of the trunk and abdomen. The liver was discolored dark-green and was small, firm and nodular.

Laboratory Results: Serum alkaline phosphatase and alanine aminotransferase were elevated.

Contributor's Morphologic Diagnoses: 1. Superficial necrolytic dermatitis with marked hyperkeratosis.
2. Severe diffuse hepatocellular vacuolar degeneration with macro and micronodular regeneration and portal arteriolar hyalinosis

Liver failure (Hepatocutaneous syndrome)

Contributor's Comment: In sections of skin from the edges of the footpads, there is marked parakeratosis and follicular keratosis. Spongiotic change, ballooning degeneration and coagulative necrosis are present in the granular layer of the epidermis.

Zones of parenchymal collapse and hepatocellular vacuolar degeneration separated by nodular hyperplasia alter the normal hepatic lobular architecture. There is mild biliary hyperplasia and Kupffer cells contain hemosiderin. Periportal fibrosis is mild and there is a modest periportal infiltration of neutrophils, macrophages, lymphocytes and plasma cells. Portal arterioles are characterized by marked hyaline thickening of the tunica media.

Superficial necrolytic dermatitis is an uncommon necrotizing dermatitis associated with metabolic disorders. In dogs, it is most commonly associated with severe vacuolar hepatopathy or diabetes mellitus. In humans, a similar syndrome is associated with glucagon-producing pancreatic tumors. Severe reduction in plasma amino acids has been proposed as a direct cause for the dermal lesions. The characteristic lesions include a thick superficial layer of parakeratosis overlying a subjacent zone of epidermal edema and keratinocytes degeneration with basilar hyperplasia forming rete pegs. Differential diagnoses for the skin lesions include idiopathic erythema multiforme, drug eruption, pemphigus foliaceus, systemic lupus erythematosus, thallium toxicity, and zinc responsive dermatoses. The cause for the hepatopathy in this dog was not determined.

AFIP Diagnoses: 1. Haired skin: Parakeratotic hyperkeratosis, diffuse, marked, with laminar epidermal edema and necrosis, basal cell hyperplasia, and mild superficial lymphoplasmacytic dermatitis, mixed breed, canine.
2. Liver: Hepatocellular vacuolar degeneration and loss, diffuse, severe, with multinodular regeneration and mild biliary hyperplasia.

Conference Comment: The contributor has provided a concise review of this entity.

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