CASE I: AP08-2649 (AFIP 3142086).

Signalment: 9-year-old, spayed female, mixed-breed canine (*Canis familiaris*).

History: This dog presented to the North Carolina State University, College of Veterinary Medicine Emergency Service for evaluation of cyanotic mucous membranes and tachypnea. Additional findings included diffuse pitting edema in the right hind limb. Right hind limb edema was first noted 4 years ago and was initially localized to the paw region. At the time of initiation, the dog held its leg up, but there was no associated traumatic event. Hind limb edema occurred intermittently over the next four years, but progressively worsened. Treatment with doxycycline and carprofen initially relieved the swelling and was administered for three recurrent episodes; however, after treatment for an episode in 2008, approximately three weeks prior to presentation to the veterinary school, she experienced vomiting and diarrhea. Carprofen was discontinued and treatment with prednisolone, ranitidine, and sucralfate was initiated. The leg continued to swell up to 5 times the normal size at which point all medications were discontinued. Labored breathing was first noted approximately one week prior to presentation along with trembling and shivering. Limited response to oxygen therapy and supportive care following admission, combined with a poor prognosis, resulted in the owner’s decision to humanely euthanize the dog.

Gross Pathology: At necropsy, subcutaneous tissues of the right hind limb were diffusely thickened by gelatinous edema fluid and multifocal hemorrhages. Lesions were most severe surrounding the metatarsus. Several sections through the leg did not reveal a mass.

The lungs were mottled pink-red, semi-firm, and markedly congested and edematous. Numerous (>20) pink-tan nodules ranging from 3 mm to 1 cm in diameter were distributed throughout the lungs. The liver was enlarged (5.4% total body weight), had rounded edges, and contained numerous tan, soft to firm, raised nodules that ranged from 1 mm to 4 cm in diameter. On cut surface, hepatic nodules were tan to mottled tan-brown. Larger nodules contained necrotic centers that oozed thick, dark brown exudate. The entire gastrointestinal tract was transmurally thickened. The pancreas was moderately enlarged, firm, and tan.

Laboratory Results: Immunohistochemistry - Endothelial cells lining the abnormal lymphatic channels had the following intracytoplasmic labeling:

- Greater than 90% of the cells had strong, nearly diffuse labeling with Factor VIII-related antigen (von Willebrand’s factor).
- 100% of the cells had strong, diffuse labelling with vimentin (mesenchymal marker).
- Approximately 60-70% of the cells had weak to strong, multifocal labeling with LYVE-1 (lymphatic vessel endothelial receptor 1).

Histopathologic Description: Skin, right hind limb (submitted tissue): Numerous anastamosing lymphatic channels dissect between deep dermal collagen bundles and extend into the subcutis and superficial dermis. The channels are lined by single layers of attenuated to mildly plump endothelial cells that separate variably sized islands of collagen and adipocytes. Individual cells are fusiform to spindloid, contain elongate to irregular hyperchromatic nuclei, and have scant, pale basophilic cytoplasm. Cell borders are variably distinct, and anisocytosis and anisokaryosis are minimal. Mitotic figures are not observed. Mild numbers of lymphocytes and plasma cells often
form small discrete aggregates around blood vessels with mild, multifocal infiltration into the surrounding dermis and panniculus. The dermis and subcutis are moderately expanded by clear edema fluid.

Lung, liver, pancreas, gastrointestinal tract (tissues not included on the submitted slide): The lung, liver, pancreas, and gastrointestinal tract contained multiple masses composed of neoplastic epithelial cells consistent with metastatic cholangiocarcinoma.

**Contributor’s Morphologic Diagnosis:** Right hind limb: Subcutaneous lymphangiomatosis with marked edema and multifocal, mild, lymphoplasmacytic dermatitis and panniculitis

**Contributor’s Comment:** The cause of progressive respiratory distress that was unresponsive to therapy is attributed to pulmonary cholangiocarcinoma metastasis. Sections of cholangiocarcinoma were not included in this submission.

Tissue submitted was from the skin and subcutis of the right hind limb. Histologic lesions in this tissue were consistent with lymphangiomatosis. Lymphangiomatosis is a rare disorder characterized by increased numbers of lymphatic endothelial cells forming irregular, anastomosing, vascular clefts and empty channels. Tumors of lymphatic origin typically occur in the skin and subcutis with the caudal ventral abdomen and inguinal regions predisposed. Additional reported locations include the head, neck, cranial trunk, axilla, bone, and extremities. Lesions present as intermittent, fluctuant swellings with a variably protracted clinical course and have reportedly affected an entire limb. Lesions often form ulcers and draining tracts with leakage of fluid resulting in cutaneous vesiculation. Smaller discrete lesions should be referred to as lymphangioma, whereas lymphangiomatosis has been described as lymphangioma affecting soft tissues and/or parenchymal organs in a diffuse or multifocal manner. Lymphangioma, lymphangiomatosis, and lymphangiosarcoma tend to occur in younger animals; however, lymphangiosarcoma has been reported in dogs ranging from 8 weeks to 13 years of age.

A single case of lymphangiosarcoma has been described in a cow and two cases have been described in horses. Immunohistochemistry may be used to confirm endothelial origin of proliferative lymphatic conditions using factor VIII-related antigen, CD31, vimentin, and LYVE-1. For this case, the abnormal endothelial cells had strong, nearly diffuse intracytoplasmic immunoreactivity for factor VIII-related antigen and vimentin, and moderate, multifocal immunoreactivity for LYVE-1.

If metastatic disease is not present, distinguishing lymphangiosarcoma from lymphangiomatosis based on clinical and histological features may be difficult. It has been suggested that some of the previously described cases of non-metastatic lymphangiosarcomas with well-differentiated endothelial cells may have represented lymphangiomatosis, particularly when these lesions were found in young dogs. Lymphangiomatosis, although histologically benign, is often recurrent and progressive. Surgical resection, chemotherapy, and radiotherapy have been used to treat both lymphangiomatosis and lymphangiosarcoma.

**AFIP Diagnosis:** Haired skin and subcutis, right hind limb (per contributor): Lymphangioma (lymphangiomatosis).

**Conference Comment:** Extensive discussion occurred among conference participants and the moderator regarding the best nomenclature for this interesting lesion, i.e. lymphangiomatosis and lymphangioma. In the absence of clinical information, all participants agreed the histologic findings represent a poorly demarcated proliferation of lymphatic endothelial cells that dissect dermal and subcutaneous collagen, with minimal cellular and nuclear atypia. The moderator favored the diagnosis of lymphangioma based on the biologic behavior of these lesions and the lack of a consensus in veterinary medicine as to the precise definition for lymphangiomatosis. This was case also studied in consultation with the subspecialty physician pathologists from the AFIP Department of Soft Tissue Pathology; they favored the diagnosis of lymphangiomatosis based on the diffuse, extensive infiltrative process with poor tumor demarcation. In human pathology, the diagnosis of lymphangioma is reserved for well-defined masses.

In humans there is a form of lymphangioma referred to as progressive lymphangioma which occurs in adults, most commonly on the limbs, and is characterized grossly as a red cutaneous macule that enlarges with age. Histologically, there is a proliferation of thin-walled lymphatic channels that dissect between dermal collagen bundles and forms horizontal clefts; lesions may extend into the subcutis. Cutaneous lymphangiomatosis occurs as a diffuse, benign lymphatic proliferation affecting multiple tissue planes over a large area, most commonly in young children; interestingly, the lesion tends to regress when the child stops growing. Lymphangiomatosis is characterized histologically as many variably dilated lymphatic channels which dissect between all normal
structures, resulting in islands of normal tissue that appear to be “hanging in the air.” A distinguishing feature between these two entities is the presence of cutaneous vesicles in lymphangiomatosis, a feature which is lacking in lymphangiomas.¹⁰

A review of veterinary pathology reference texts⁵,⁶,⁷,¹⁴ reveals discordance over the preferred nomenclature for this proliferative lymphatic lesion. Based on descriptions in humans, there are features of both lymphangioma and lymphangiomatosis in the case of this dog. The most recent WHO fascicle for soft tissue tumors of veterinary species only describes lymphangioma, which occurs most commonly in young animals and is believed to represent congenital malformation.⁷ The moderator commented that in the cases he has evaluated, the lesions are difficult to fully resect owing to the lack of a “mass effect” making palpation of the edges of the lesion difficult, resulting in incomplete surgical resection. The lesions are progressive, a feature also described in the reference texts, exhibit characteristic pitting edema, and occur most commonly on the abdomen, ventral neck, inguinal area and prepuce. The moderator further commented that in his experience, lymphangiomatosis involves many parts of the body, is histologically characterized by multiple dilated lymphatics, and contains a myxoid stroma.

In the case of this dog, the signalment and clinical history (e.g. older animal with a lesion is located on the limb) and the histologic findings of thin-walled lymphatic channels that dissect dermal collagen with formation of horizontal clefs with extension into the subcutis support a diagnosis of lymphangioma. However, the findings of diffuse lymphatic proliferation affecting multiple tissue planes over a large area and islands of tissue “hanging in the air” are more consistent with the classification of lymphangiomatosis, demonstrating the complexity of this lesion. One important fact for which the references agree is the progressive nature of both lymphangioma and lymphangiomatosis, a clinical feature that may be more relevant than the histologic classification from a prognostic standpoint.⁵,⁶,⁷,¹⁴

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References:
CASE II: 10-05194 (AFIP 3164900).

**Signalment:** 12-year 10-month-old, castrated male, Cocker Spaniel, canine (*Canis familiaris*).

**History:** This was a mass on the left front digit present for four months. The mass had not changed since first noticed. The left prescapular lymph node was enlarged and there were multiple other pedunculated skin masses. A mass was removed from the right front paw one year prior but not biopsied. The dog had chronic severe dental disease, severe chronic bilateral ear infections, keratoconjunctivitis sicca bilaterally, and hyperpigmentation and lichenification of the groin. The dog had been on long-term metronidazole, rimadyl, tacrolimis, and clindamycin.

**Gross Pathology:** The mass markedly enlarged the digit but did not grossly invade the bone.

**Histopathologic Description:** Haired skin, left front foot (per contributor): The deep dermis contains an unencapsulated, poorly demarcated, highly cellular, invasive neoplastic mass which effaces and surrounds the adnexal structures. The mass is composed of cuboidal epithelial cells arranged in tubules and acini that are often palisading and are supported by a small to large amount of collagensous stroma (desmoplasia) that multifocally contains many plasma cells and lymphocytes. The epithelial cells have a small amount of pale eosinophilic cytoplasm with distinct cell borders. The central or basally located nuclei are large and round, with finely stippled chromatin and 1 small nucleolus. Anisocytosis and anisokaryosis are marked. Mitotic figures range from 0-15 per 400x field, with an average of 5 per 400x field. Multifocally the neoplastic cells demonstrate piling upon one another, with occasional protrusion and blebbing into the acinar or tubular lumina, some of which also contain few sloughed or necrotic cells, proteinaceous material, or mild hemorrhage. Many follicles and glands are surrounded by numerous lymphocytes and plasma cells, fewer macrophages, and rare mast cells. Multiple follicles are mildly dilated, filled with laminated keratin, and contain 0-12 cross and/or tangential sections of arthropods that are up to 50 microns in diameter and 300 microns long. The arthropods have a thin eosinophilic chitinous exoskeleton, blunt jointed appendages, skeletal muscle, and digestive or reproductive tracts. The overlying epidermis is minimally hyperplastic with orthokeratotic hyperkeratosis. There is moderate pigmentary incontinence as well as scattered macrophages that contain a pale grey-tan pigment consistent with lipofuscin.

**Contributor’s Morphologic Diagnosis:** 1. Adenocarcinoma, apocrine or eccrine origin, left front paw.
2. Intrafollicular mites (*Demodex* spp.)

**Contributor’s Comment:** Sweat glands are divided into two types: apocrine and merocrine (eccrine). Apocrine gland secretion consists of release of a large secretory granule that is surrounded by a small amount of cytoplasm and cell membrane, and is microscopically apparent as apical blebbing. In merocrine secretion, the contents of the secretory granules is released by fusion of the granule with the cell membrane. Apocrine glands are the most abundant in domestic animals, and consists of saccular tubular glands with a coiled secretory portion and a straight duct that is lined by two layers of epithelium and typically opens into the hair follicle. Merocrine glands are limited to the non-haired areas of the footpad of dogs and cats, the frog of ungulates, planum rostrale and the carpals glands of pigs, and the planum nasolabiale of cows. Myoepithelial cells are specialized smooth muscle cells that aid in emptying both apocrine and merocrine glands of secretion.

Apocrine gland carcinomas include solid, cystic, and tubular types. The tubular type is the most common and typically has marked desmoplasia. Apocrine carcinomas are locally aggressive, extending through the dermis, subcutis, and underlying skeletal muscle. Lymphatic invasion and spread to the regional lymph nodes and lungs is common. Apocrine carcinomas also occur as ductal, compound, and mixed types, similar to mammary gland tumors.

Tumors of eccrine glands are extremely rare but do occur as adenomas or carcinomas of the footpad of dogs and cats. Eccrine carcinomas are morphologically similar to apocrine gland carcinomas and are very difficult to differentiate by light microscopy. There is no reliable immunohistochemical antibodies that can separate eccrine carcinoma from apocrine carcinoma. Differentiation is based on proving that the tumor arises from the footpad,
rather than the adjacent haired skin, or by observing the apical blebbing that occurs when apocrine glands are in their secretory state. Both tumors types stain positively with antibody to carcinoembryonic antigen, which can help differentiate them from other tumor types.

Demodex mites are obligate parasites that are normal inhabitants of the hair follicles and sebaceous glands of dogs and most other domestic animals and humans. The exception is Demodex cati, which is found in the superficial stratum corneum. Disruption of the host-parasite equilibrium can result in overgrowth of the mites and lesions of demodecosis. Demodex has been found in association with several dermatologic conditions in humans and animals.

Juvenile-onset demodecosis is often familial, and is thought to be due to a genetic cell-mediated immunity disorder. In adult-onset demodecosis, the overgrowth of the mites is often associated with hyperadrenocorticism, corticosteroid administration, hypothyroidism, chemotherapy, or other serious diseases. Demodex is not typically associated with tumors in animals, but a significant increase in the prevalence and density of Demodex has been found in eyelid basal cell carcinomas in people, and is postulated to be a triggering factor for carcinogenesis due to chronic irritation. Demodecosis lesions in dogs are often generalized but are more severe on the face and paws, and in some may be confined to the paws. In this case, the patient had congestive heart failure, chronic severely infected gums, hypothyroidism, and had indications of pituitary-dependent hyperadrenocorticism in addition to a locally aggressive neoplasm in the area of mite overgrowth. The dog had hyperpigmentation and lichenification, which can be found in chronic cases of both generalized demodicosis and hyperadrenocorticism.

Histologically, demodecosis can range from early lesions of lymphocytic mural interface dermatitis, perifollicular pigmentary incontinence, and follicular hyperkeratosis, to suppurative folliculitis and pyogranulomatous furunculosis due to development of secondary bacterial infections. Rupture of the follicles results in release of mites into the dermis, and fragments of mites have occasionally been found in the draining lymph nodes.

**AFIP Diagnosis:** 1. Haired skin and subcutis: Apocrine adenocarcinoma. 2. Haired skin: Follicular ectasia, hyperkeratosis and hyperplasia, focally extensive, mild with histiocytic and lymphoplasmacytic dermatitis, pigmenatry incontinence, and intrafollicular arthropod parasites (Demodex spp.) 3. Haired skin, subcutis, vessels: Smooth muscle hypertrophy and hyperplasia, multifocal, with occasional luminal occlusion.

**Conference Comment:** Participants agreed with the diagnosis of adenocarcinoma, with most favoring apocrine origin based on the observation of occasional decapitation-type secretion (apical blebbing), location of the tumor in haired skin, and the extreme rarity of eccrine carcinoma in veterinary species. Another unique feature of apocrine adenocarcinomas noted by the moderator, and not found with eccrine carcinoma, is extension of neoplastic cells into the overlying epidermis with associated epidermal ulceration.

Participants also discussed the various histologic variants of apocrine adenocarcinoma mentioned above by the contributor. Several raised the possibility of apocrine ductal carcinoma; the moderator pointed out that there should be foci of squamous differentiation in addition to a double-layer of neoplastic epithelial cells, both of which are lacking in this specimen. In dogs and cats, eccrine carcinomas occur in the footpads, whereas apocrine adenocarcinomas and apocrine ductal carcinomas generally arise on the legs of dogs and on the head, legs and abdomen of cats.

Participants discussed the significance of finding Demodex spp. in this, as well as other, biopsy specimens. The finding of demodecosis must be communicated to the submitting clinician, regardless of the severity or apparent insignificance since treatment with steroids will worsen the condition. The moderator commented that follicular epithelial hyperplasia, melanin within basal cells, and perivascular lymphoplasmacytic dermatitis is highly suggestive of demodecosis and should prompt the reviewing pathologist to thoroughly search hair follicles for the presence of Demodex spp.

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**References:**


**CASE III:** 4096-10 (AFIP 3165075).

**Signalment:** 8-year-old, Rhodesian Ridgeback, canine (*Canis familiaris*).

**History:** Five skin punch biopsies were submitted from the nasal planum and lips. The clinician reported a one-month duration of crusting, scaling and depigmentation of the affected areas with some vesicles.

**Gross Pathology:** None.

**Histopathologic Description:** Haired skin: The epidermis is thickened (acanthotic) and there is a broad zone of plasma cells with some lymphocytes in the superficial dermis and occasionally infiltrating into the basal layer of the epidermis (interface lichenoid inflammation). Many scattered dermal macrophages contain somewhat coarsely granular melanin pigment (pigmentary incontinence). Scattered individual eosinophilic, shrunken, basal cells (apoptotic cells) are present and suggestive of an autoimmune condition.

**Contributor’s Morphologic Diagnosis:** Discoid lupus erythematosus (DLE).

**Contributor’s Comment:** This is probably the most common autoimmune disease we see in our submissions and is most common in Collies and Shetland sheepdogs. Typically, it involves the nose, lips, and periorbital skin but may involve the trunk, distal limbs, footpads, genitals and perianal area. Systemic lupus (SLE) is similar or identical microscopically but is usually more widespread and may have more apoptotic basal cells but less of the lichenoid inflammation than DLE. SLE should have a positive anti-nuclear-antibody serology as well and it may be associated with systemic illness. Vogt-Koyangi-Harada-like syndrome of melanin autoimmunity has more dermal macrophages with finer melanin clumps in them and it is most common in Akitas, Siberian Huskies, Alaskan Malamutes, Chow Chows, and their mixes; it is also limited to the face, but with uveitis. Mucocutaneous pyoderma of the lips also has heavy lichenoid plasma cell dermatitis with pigmentary incontinence; it may have neutrophils as well, and the apoptotic cells are more superficial keratinocytes rather than basal cells.

The dog was treated with short term prednisolone and doxycycline and long-term niacinamide (all 3 are presumed immunosuppressors used to treat DLE and SLE) and the dog was normal in about one month.
**AFIP Diagnosis:** Haired skin: Dermatitis, lichenoid interface, lymphoplasmacytic, neutrophilic and histiocytic, diffuse, marked with epidermal acanthosis, spongiosis, parakeratosis, and rare apoptotic basal cells.

**Conference Comment:** Participants and the moderator were hesitant to assign the specific diagnosis of discoid lupus erythematosus (DLE) in this case due to the variation in specimen quality and the presence of only rare basal cell apoptosis. Many conference participants experienced difficulty in separating tissue processing artifact from pathological changes. Participants agreed with the contributor that several histologic features are suggestive for DLE, although the basal cell apoptosis is not as conspicuous in this dog as would be expected for most animals with the condition. The additional history of clinical response to immunomodulatory treatment supports an underlying autoimmune process, such as DLE.

The moderator commented that the differential diagnosis for superficial lymphoplasmacytic dermatitis with neutrophilic inflammation includes lupus (systemic lupus erythematosus or discoid lupus erythematosus) and mucocutaneous pyoderma (MP). A retrospective study by Weimelt et. al. demonstrated the difficulty in differentiating these two conditions, as the histopathological features of both frequently overlap making treatment modality and clinical response difficult to determine and predict. Whereas mucocutaneous pyoderma responds well to antibiotics, treatment of lupus involves immunomodulatory drugs.

Since DLE and SLE are nearly indistinguishable histologically, it is worthwhile to briefly review the pathogenesis of SLE. Lymphopenia and an overall decrease in the numbers of T-lymphocytes occurs, and there is an imbalance in the ratio of CD4+;CD8+ T-lymphocytes, with an increase up to 6 to 1 (in healthy dogs the ratio is 2.3 to 1); this favors B-cell stimulation and antibody production. In addition to the imbalance in T-cell populations, there is loss of self-tolerance in both B-cells and T-cells. After massive cell death due to exogenous (e.g. ultraviolet light, environmental) insults or endogenous (metabolic, hormonal, genetic) triggers, there is defective clearance of cellular debris, resulting in increased amounts of nuclear antigen. The altered B-cells are stimulated by the released nuclear antigens to produce anti-nuclear antibodies. The anti-nuclear antibodies then bind additional antigen, and the resulting antigen-antibody complexes then bind to Fc receptors on B-cells and antigen-presenting cells (APC). The stimulated APC's secrete type 1 interferon, which is autostimulatory (including for other B-cells).

Antinuclear antibodies have been shown to bind to one of four nuclear components: DNA, histones, non-histone proteins bound to RNA, and nuclear antigens. Generalized tissue damage ensues as part of a Type III hypersensitivity reaction whereby antigen-antibody complexes deposit in the kidney, skin, blood vessels etc. The antibody-antigen complexes lodge beneath the basement membrane of the epidermis.

As part of the continuous review and study of the complex pathology of DLE, some authors recommend referring to the lesion as photosensitive nasal dermatitis, suggesting the nomenclature of this entity should change as the pathogenesis is further elucidated. In the skin, DLE and SLE are both photoresponsive, and ultraviolet (UV) light aggravates the autoimmune condition by causing translocation of intracellular antigens (frequently nuclear antigens) to the keratinocyte cell membrane. Autoantibodies then bind the translocated cell membrane antigens, and the keratinocytes are subsequently killed by T-cells or monocytes (antibody dependent cellular cytotoxicity). Injured and necrotic keratinocytes release cytokines (IL-1, IL-2, IL-6, and TNF-β), which then recruit and activate B-cells and histiocytes to the sites of injury.

The use of mouse models for human SLE has been recently reviewed and readers are encouraged to consult the article for a thorough discussion of the pathogenesis of SLE.

**Contributor:** Arkansas Livestock and Poultry Commission Lab
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**References:**
CASE IV: 109087E (AFIP 3167325).

Signalment: 7-year-old, female, Thoroughbred, equine (*Equus caballus*).

History: The horse was referred with a two-month history of multiple papules, round elevated cutaneous lesions with central crusts on the trunk and limbs, and associated scaling and crusting on the head and neck. The lesions were secondarily pruritic. The animal had also reluctance to move associated with distal limb edema. No parasite, bacteria or fungus was identified on skin scrapings, and cytology of the crust revealed the presence of many acantholytic cells and numerous filamentous bacteria consistent with *Dermatophilus congolensis*. The cutaneous lesion quickly spread to the whole body and the animal was euthanized due to progressive loss of body condition and hindlimb pain.

Gross Pathology: The mare had generalized chronic severe crusting, scaling and exfoliative dermatitis except in the pasterns, associated with emaciation and pitting edema of the hindlimbs.

Histopathologic Description: Haired skin: Sections of skin are characterized by multiple foci within the superficial epidermis, especially the granular layer, consisting in detachment of keratinocytes with loss of cellular bridges, round and well-defined cell borders and abundant deeply eosinophilic cytoplasm with a viable nucleus characteristic of acantholytic cells. In advanced foci, the acantholysis leads to formation of large subcorneal and intraepidermal clefts of about 300 µm filled with many acantholytic cells admixed with well-preserved neutrophils (acantholytic pustules and vesicles). Acantholytic pustules are also observed in the outer follicular sheats. Ruptured pustules form numerous thick laminated crusts at the surface of the epidermis where acantholytic cells and non-suppurative neutrophils predominate. The superficial dermis is diffusely thickened by a mild perivascular infiltrate composed of neutrophils and few plasma cells and lymphocytes, associated with moderate capillary congestion and mild superficial edema.

Contributor's Morphologic Diagnosis: Skin: Subcorneal acantholytic vesiculo-pustular dermatitis, chronic severe, characteristic of pemphigus foliaceus in a horse, *Equus caballus*.

Contributor's Comment: Pemphigus foliaceus (PF) is the most common autoimmune skin disease in horses, first described in this species in 1981. Pemphigus foliaceus has also been reported in the dog, cat and goat. There is a lack of breed or sex predilection in horses, even if one case study suggested Appaloosas to be predisposed. The disease can occur at any age from few months-old foals to aging horses up to 25 years old. A higher risk in winter and fall have been observed in one case study, but this seasonal pattern was not confirmed in a second one. Lesions are generalized crusting, scaling and alopecia first affecting the face, neck, trunk and extremities but often spreading in a few months to involve the whole body. Equine PF can be painful and pruritic. The lower extremities and ventral abdomen often develop edema; the exact pathogenesis of this remains unknown. Systemic signs such as weight loss, anorexia, fever, anemia, neutrophilia and hypoalbuminemia have been reported. The primary lesion consists of fragile and transient intraepidermal and follicular vesicles evolving into crusting so that the lack of intact pustules in some cases can be a diagnostic challenge.

Diagnosis of PF in horse is based on histologic features and by ruling out differential diagnoses, such as dermatophytosis in the horse. This fungal infection caused by *Trichophyton* spp. has been reported to cause generalized pustular and crusting exfoliative dermatitis with the presence of many acantholytic cells. Acantholysis is thought to be mediated by fungal proteolytic enzymes. A PAS stain can help to exclude such infection from cases of pemphigus foliaceus lacking characteristic subcorneal pustules. Deposition of IgG at epidermal intercellular bridges can be demonstrated by immunofluorescence (IF) or immunohistochemistry (IHC) but is not specific of PF.
“Pemphigus” encompasses a group of blistering skin diseases caused by a type II hypersensitivity response involving production of circulating autoantibodies directed against cellular adhesion proteins of desmosomes. Different forms of pemphigus are recognized based on the level at which the acantholysis occurs within the epidermis according to the location of target antigen (cf. Table I). In human beings, PF autoantibodies target the desmosomal protein desmoglein 1 (Dsg1) which is expressed more intensely in the upper layer, explaining the formation of superficial epidermal cleft. Autoantibodies against desmoglein 1 have been reported only in few cases of canine PF where others antibodies are involved. In domestic animals PF seems to be an immunologically heterogenous disease.

Table I: Autoimmune acantholytic dermatoses in animals

<table>
<thead>
<tr>
<th>Disease</th>
<th>Species</th>
<th>Distribution</th>
<th>Target</th>
<th>Location of vesicles</th>
</tr>
</thead>
<tbody>
<tr>
<td>Pemphigus foliaceus (PF)</td>
<td>Dog, Cat, Horse, Goat</td>
<td>Skin</td>
<td>Dsg 1 in human and dog (&lt;10%)</td>
<td>Subcorneal</td>
</tr>
<tr>
<td>Pemphigus vulgaris</td>
<td>Dog, Cat, Horse, Goat,</td>
<td>Oral mucosa, skin</td>
<td>Dsg 3</td>
<td>Suprabasal</td>
</tr>
<tr>
<td></td>
<td>Llama, Monkey</td>
<td></td>
<td></td>
<td></td>
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<tr>
<td>Paraneoplastic pemphigus</td>
<td>Dog</td>
<td>Oral mucosa, skin and non stratified squamous epithelia</td>
<td>Dsg 3 and plakins</td>
<td>Suprabasal</td>
</tr>
<tr>
<td>Pemphigus erythematous (variant of PF)</td>
<td>Dog, Cat</td>
<td>Skin (face and feet)</td>
<td>Subcorneal, lichenoid infiltrate</td>
<td></td>
</tr>
<tr>
<td>Panepidermal Pustular Pemphigus (PF subtype)</td>
<td>Dog</td>
<td>Oral mucosa, skin</td>
<td>All epidermal layers</td>
<td></td>
</tr>
<tr>
<td>Pemphigus vegetans</td>
<td>Dog (one case)</td>
<td>Skin, oral mucosa</td>
<td>Dsg 1</td>
<td>Suprabasal, exophytic hyperplasia</td>
</tr>
</tbody>
</table>

Acantholysis can result from mechanisms other than autoimmunity; mutations involving genes encoding desmosomal adhesion proteins (genetic acantholytic dermatoses) or infectious proteases produced by some strains of fungus or bacteria can cleave desmosomes (proteolytic acantholytic dermatoses). The following acantholytic dermatoses are described in various species: dermatophytosis caused by *Tricophyton* spp; some staphylococcal infections of dog and swine (such as exfoliative epidermitis caused by *Staphylococcus hyicus* in swine); and bullous impetigo in the dog caused by *Staphylococcus pseudointermedius*. This bacterium (which produces a circulating exfoliative toxin specific for desmoglein-1) induces blisters locally and at sites distant from primary infection. In human beings, a third group of acantholytic dermatoses is recognized as genetic diseases involving mutations in genes encoding desmosomal adhesion proteins. Such genetic acantholysis has rarely been described in the dog and cattle.

**AFIP Diagnosis:** Haired skin: Dermatitis, superficial, histiocytic and lymphoplasmacytic, diffuse, mild with intraepidermal pustules, acantholytic keratinocytes, acanthosis, parakeratosis, and pigmentary incontinence.

**Conference Comment:** The moderator and participants commented on the excellent quality of the specimen. The moderator noted that it is rare to observe such well developed pustules as seen in this case. Additionally, the large size of the biopsy specimen reduces the chances of tissue loss during processing. The contributor provides an excellent review of the pemphigus complex of diseases in veterinary species, with due attention to pathogenesis as well as the disease manifestation in horses.

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**References:**