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CONFERENCE 18

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<u>CASE I –</u> 419101 (AFIP 2938297).

Signalment: 10-year-old, intact female, cocker spaniel, *Canis familiaris*, dog.

History: Not available.

Gross Pathology: A 2.0 x 1.5 x 0.5 cm ellipse of haired skin has been removed from the lateral thorax caudal to the left humerus. The ellipse of haired skin has a firm, well circumscribed, expansile mass in the hypodermis.

Histopathologic Description: Within the hypodermis, there is an unencapsulated, expansile, well circumscribed and minimally invasive nodular mass that abuts and compresses preexistent hypodermal connective tissue and underlying skeletal muscle bundles. The mass is densely cellular and composed of tightly packed pleomorphic polygonal mononuclear cells that are arranged in confluent small clusters and supported by a delicate pervasive fibrovascular stroma. Individual neoplastic cells have a round to oval, occasionally indented or reniform euchromatic nucleus, single to frequently, multiple prominent nucleoli, and an abundant, variably eosinophilic, vesicular cytoplasm. Many neoplastic cells contain empty, sharply defined, variably sized cytoplasmic vacuoles. There are frequent binucleated and multinucleated cells, and there are a moderate number of cells that display anisokaryosis. Karyomegalic nuclei and nuclear "molding" are often seen in many microscopic fields. Mitoses average 1 to 3 per HPF. The neoplastic cells exhibit intense, diffuse cytoplasmic immunopositivity for vimentin; they are not labeled by an antibody to pancytokeratin.

Contributor's Morphologic Diagnosis: Haired skin with attached skeletal muscle: Liposarcoma, pleomorphic

Contributor's Comment: Liposarcomas are relatively rare mesenchymal neoplasms that are typically found in the subcutis of domestic animals. In dogs, liposarcomas are usually cutaneous but can be found in other anatomic locations, including the abdominal cavity and other extracutaneous sites.¹ There is no breed or sex predilection reported for liposarcomas, and they most often affect older dogs. Metastasis of liposarcomas is reported as infrequent; when it occurs, metastatic foci usually are observed in the lung, liver or bone.^{1,2} There are three distinct subtypes of liposarcomas that occur in dogs, namely well-differentiated, pleomorphic and myxoid.^{1,2} Diagnosis is usually straightforward based on these subtypes, although the pleomorphic variant can sometimes be confused with malignant fibrous histiocytoma.² In human medicine, liposarcomas typically involve the retroperitoneum, central body sites or thigh, occur in middle-aged to older people and have been reported to metastasize to the lungs, liver and bone.³

AFIP Diagnosis: Haired skin and subcutis: Liposarcoma, pleomorphic, Cocker Spaniel (*Canis familiaris*), canine.

Conference Comment: Liposarcomas are malignant tumors of lipocytes with variable pleomorphism and little or no collagenous stroma. Ultrastructural evaluation suggests that liposarcomas arise from precursor cells of white or unilocular adipose tissue. The etiology of canine liposarcomas is unknown; however, some strains of feline sarcoma virus have been associated with the development of liposarcomas in kittens.^{4,5}

As mentioned by the contributor, there are three distinct subtypes of liposarcomas that occur in dogs. Additionally, a fourth subtype, atypical lipoma, is included in <u>Skin Diseases of the Dog and Cat</u>. Atypical lipomas are composed primarily of well-differentiated lipocytes admixed with low numbers of smaller individual or clustered lipoblasts with large, centrally located nuclei and few cytoplasmic vacuoles. Mild pleomorphism, nuclear hyperchromatism, and rare mitotic figures are occasionally observed within lipoblasts. The presence of lipoblasts with occasional atypia is considered an indicator of early transition to a more aggressive behavior and, in the authors' opinion, atypical lipomas are best considered low-grade liposarcomas.⁵

Well-differentiated liposarcomas are the most common histopathologic subtype of liposarcoma in which the majority of cells resemble normal adipocytes with a single clear fat vacuole and a peripheral nucleus. Other cells have variable numbers of intracytoplasmic lipid droplets or resemble lipoblasts. Mitotic activity is low; however, most of the mitoses are atypical.^{2,4,5}

Myxoid liposarcomas are characterized by scattered lipoblasts, lipocytes, spindle cells, and stellate cells within a "bubbly" mucinous stroma. Occasional multinucleated cells may be present.^{2,4,5}

Pleomorphic liposarcomas are composed of anaplastic cells with large bizarre multinucleated giant cells. The cells have abundant eosinophilic glassy or foamy cytoplasm. Distinct lipid vacuoles are only present in a few cells. There is marked variability in nuclear size, shape, and chromatin pattern. Nuclear hyperchromatism is common and nucleoli are prominent. Many mitoses are present, and atypical mitoses are common.^{2,4,5}

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<u>CASE II –</u> 06-8313 (AFIP 3026722).

Signalment: 3-year-old, female spayed, Bassett Hound, *Canis lupus familiaris*. **History:** The owner noticed multiple ulcerated nodules on the bridge of the nose in the last 24 to 48 hours that increased in size. Biopsy specimens from the margins of four lesions were submitted for evaluation. **Histopathologic Description:** All four biopsy specimens had similar lesions. The epidermis was moderately acanthotic with decreased pigmentation. The superficial dermis was edematous with severely dilated vessels lined by swollen endothelial cells. Leukocytes were marginated in several vessels. Perivascular cuffs of predominantly eosinophils ranged from one to a few cells in thickness. Dermal macrophages laden with melanin indicated mild pigmentary incontinence. At the outer margin of the biopsy specimen, the inferior segment and isthmus portion of several hair follicles were extensively destroyed by infiltrates of eosinophils. Along the lesion margin some follicles were completely effaced. Fragments of hair shafts, keratin debris, and adnexal structures were often surrounded by eosinophilic exudate. Deep dermal fibrosis, edema, and perivascular infiltrates of inflammatory cells were noted. Small aggregates of degranulated eosinophils were present around a few collagen fibers in one section. Flame figures were not present. Special stains revealed no bacteria or fungi.

Contributor's Morphologic Diagnosis: Subacute eosinophilic folliculitis and furunculosis.

Contributor's Comment: The clinical and histopathological findings are consistent with canine eosinophilic furunculosis of the face.^{2,5} Although the face and especially the muzzle is the most common site for lesion development, lesions can also occur on other parts of the body. The disease is usually seen in young, active dogs with or without access to the outdoors. Lesions are often multifocal and, as in this case, they develop rapidly and frequently ulcerate. Most cases are diagnosed during the summer months. This case was received in late February.

Hypersensitivity reactions to envenomation by arthropods or stinging insects such as wasps, bees, and hornets are the most commonly listed causes of this lesion.^{2,5} Arthropoda is the largest animal phylum and includes a diverse group of taxa such as insects, crustaceans, spiders, scorpions, and centipedes. Without definitive knowledge of the causative agent, it is difficult to propose a pathogenesis. Regardless of whether it is multiple wasp, bee, or spider stings/bites, the role of insect or spider may be four fold: (1) insect parts and secretions act as irritants; (2) initiation of immediate and delayed hypersensitivity reactions; (3) cytotoxic and other effects of the venom components e.g. histamine and mellitin; and (4) vectors for secondary invaders.⁴ Once recruited by activated mast cells, eosinophils appear to play a significant role with infiltration and degranulation in the hair follicle sheaths with resultant destruction of the follicle. Eosinophil derived major basic protein and eosinophil cationic proteins are toxic to epithelial cells.¹ They also have the ability to amplify the hypersensitivity reaction. Eosinophil destruction of hair follicles is not unique to insect envenomation. It may be seen with dermatophyte infections, immune-mediated disease (pemphigus foliaceus), idiopathic skin disease (sterile eosinophilic pustulosis) and even in transplant rejection.^{2,3}

Kerion and sterile eosinophilic pustulosis should be considered in a list of differential diagnoses for eosinophilic folliculitis and furunculosis.² Kerion because of the low numbers of dermatophyte hyphae and spores can present a diagnostic challenge. The spores and hyphae can often be seen in H&E stained sections. Examination of multiple sections and fungal stains are helpful in establishing or ruling out the diagnosis. Sterile eosinophilic pustulosis has subcorneal pustules and less severe eosinophilic folliculitis and furunculosis.

AFIP Diagnosis: Haired skin: Dermatitis, folliculitis and furunculosis, eosinophilic, subacute, focally extensive, marked, with mucin and mild epidermal hyperplasia, Bassett Hound (*Canis familiaris*), canine.

Conference Comment: The contributor provides a concise overview of canine eosinophilic furunculosis of the face. Grossly, the lesions appear as severely erythematous or hemorrhagic pustules, papules as well as edematous nodules and plaques that frequently ulcerate forming a hemorrhagic crust. The lesions are most often localized to the dorsal and lateral muzzle and periorbital areas. Peripheral blood eosinophilia is present in most cases. Key histomorphologic features include intense, predominantly eosinophilic, destructive folliculocentric dermatitis; severe dermal edema/mucin deposition; and variable, sometimes severe, hemorrhage. Explosive follicular rupture is characteristic when present. Flame figures – brightly eosinophilic, granular to amorphous material bordering collagen fibers and somewhat obscuring fiber detail – may be present. The contributor explains how to differentiate kerion and sterile eosinophilic pustulosis from eosinophilic furunculosis of the face. Additionally, pemphigus foliaceus should feature more acantholysis and typically develops gradually from subtle initial lesions.^{2,5,6}

Canine eosinophilic furunculosis of the face exhibits very similar clinical and histopathologic lesions as feline mosquito bite hypersensitivity. The syndrome is characterized by lesions that develop in the summer and regress during fall predominantly occurring in outdoor cats. Lesions vary from a partially symmetrical, erythematous facial eruption with papules and crusting to bilaterally symmetric facial swelling, alopecia, erosion, ulceration, and fistulation. The planum nasale, periorbital region, and pinnae may be affected. Histologically, there is severe eosinophilic dermatitis with degranulated eosinophils forming flame figures. The epidermis is acanthotic with variable erosion, ulceration, and exudation. The intact epidermis and superficial hair follicles are spongiotic and acanthotic. Differential diagnoses include feline herpesvirus ulcerative dermatitis, eosinophilic plaque, and eosinophilic indolent ulcer. If herpesviral inclusions cannot be identified, herpesvirus ulcerative dermatitis may be indistinguishable from mosquito bite hypersensitivity. Eosinophilic plaques typically display more profound spongiosis and mucinosis of the intact epidermis and superficial hair follicles while indolent ulcers have eosinophilic granulation in or subjacent to the ulcerated epithelium.²

Insect hypersensitivity is the most common allergic skin disease of the horse caused by hypersensitivity to the bites of *Culicoides* (gnats), *Simulium* (black flies), *Stomoxys calcitrans* (stable fly), and, possibly, *Haematobia irritans* (horn fly). Histologically, a superficial and deep perivascular to interstitial eosinophilic dermatitis with focal areas of infiltrative to necrotizing eosinophilic mural folliculitis is seen. Focal eosinophilic granulomas may be present. Variable epidermal hyperplasia, hyperkeratosis, spongiosis, erosion, ulceration, dermal edema, and fibrosis may be seen. Hypersensitivity is also thought to be involved in the pathogenesis of cutaneous habronemiasis, which is believed to be a reaction to the larval stages of *Habronema muscae*, *H. majus*, and *Draschia megastoma*.⁷

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CASE III – B4903/06 (AFIP 3031852).

Signalment: 10-year-old, male, Tollare, canine, dog.

History: Large tumors in the skin/subcutis adjacent to the tuber ischii of the pelvic bones on both sides could be palpated. The tumors had developed during 1 month. One was sent for microscopic examination.

Gross Pathology: One ulcerated, firm tumor, 3 cm in diameter, was submitted.

Histopathologic Description: An inflammatory reaction in the deep dermis and subcutis with severe diffuse cell infiltrates is present. A diffuse granulomatous inflammation is mostly seen, with multiple granulomas, sometimes discrete but often confluent. The granulomas are characterized by central collagen necrosis with macrophages in a radiated palisading pattern around collagen fibers. Marked infiltrates of plasma cells are found throughout the lesion. The plasma cells are predominantly seen in the periphery of the granulomas, perivascularly and diffusely in the adjacent connective tissue. A mild mixture of lymphocytes and neutrophils is noted focally in the plasma cell infiltrates.

In some sections the epidermis/dermis is present. The overlying dermis and epidermis show mild epidermal hyperplasia and a diffuse to perivascular infiltration of mostly plasma cells in the dermis.

Contributor's Morphologic Diagnosis: Granuloma, palisading, skin, dog.

Contributor's Comment: Palisading granulomas are described in the literature as solitary nodules, occasionally seen in dogs, usually located over pressure points.¹ It is macroscopically seen as a discrete nodule of the dermis or tongue. The localization in dermis is noted at the zygomatic arch, hip or lips, which has lead to suggest blunt trauma as the cause. The present case developed bilateral lesions. One lesion was surgically removed, but the other one decreased in size after treatment with corticosteroids, systemically.

There are no case reports of palisading granuloma in the dog, except for the description in the book <u>Skin Diseases of the Dog and Cat</u>.¹ Granulomas with a similar morphology have been reported in man as cutaneous extravascular necrotizing granuloma.^{2,3} In these cases, it was associated with systemic immunoreactive or autoimmune disease.

The present case, with bilateral lesions and the good response to corticosteroids may indicate that this canine palisading granuloma was associated with an immunoreactive disease.

The microscopic differential diagnoses for this type of granuloma are reported to be sterile granuloma and pyogranuloma syndrome, cutaneous sarcoidosis and reactive fibrohistocytic nodules. The typical palisading arrangement of the macrophages adjacent to the necrotic collagen, found in the present case, is not found in these three syndromes. The clinical features also differ; however, the reported solitary lesion of palisading granuloma can be questioned.

AFIP Diagnosis: Haired skin and subcutis: Panniculitis, granulomatous and palisading, marked, with lymphoplasmacytic inflammation, Tollare (*Canis familiaris*), canine.

Conference Comment: Palisading granulomas typically present as solitary nodules composed of distinct, discrete granulomas centered on supposed ischemically altered, degenerate or devitalized collagen fibers. Histologically, the nodules are composed of a central core of brightly eosinophilic, fragmented, smudged and occasionally mineralized (basophilic) collagen fibers admixed with few neutrophils surrounded by a zone of pale, eosinophilic, amorphous material further bounded by epithelioid macrophages that palisade along the fibers. The palisading pattern can be striking in some lesions creating a "starburst" pattern. Lymphoplasmacytic inflammation variably separates the granulomas. Additionally, necrotic foci may obliterate parts of the lesion and mucin may be present in some cases. The lesions may be present in the dermis, panniculus and subcutis.¹

The moderator emphasized that this case was atypical in the degree of lymphoplasmacytic inflammation present. Although lymphoplasmacytic inflammation can be seen in palisading granulomas, it is usually not this severe. Additionally, the moderator also emphasized that this case is not an extravascular necrotizing granuloma which is multicentric, neutrophilic and leucocytoclastic.

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CASE IV - 05-2007 (AFIP 2984011).

Signalment: 2-year-old Quarter Horse stallion.

History: This horse was reported to have extremely pliable skin over the lumbar region and withers.

Histopathologic Description: The epidermis in some sections has mild orthokeratotic hyperkeratosis. The superficial dermis is infiltrated by minimal numbers of mast cells. Within the mid to deep dermis, collagen bundles are short, comma-shaped and arranged in clusters frequently separated by clear spaces. In the deep dermis, collagen bundles are small, packeted and separated by clear spaces. Hair follicles and other adnexal structures are within normal limits.

Contributor's Morphologic Diagnosis: Collagen dysplasia, compatible with hereditary equine regional dermal asthenia (HERDA).

Contributor's Comment: Hereditary equine regional dermal asthenia (HERDA), previously known as 'hyperelastosis cutis' is a hereditary collagen dysplasia affecting horses primarily of the Quarter Horse breed, although similar conditions have been reported in a few other breeds and in some cross bred horses.¹ A recent report indicates autosomal recessive as the most likely mode of inheritance.² Diagnosis of HERDA is made based upon a combination of clinical findings, histopathology and other ancillary tests, such as special stains and electron microscopy.

Horses often present at an early age with complaints of seromas or hematomas, non-healing wounds, sloughed skin or easily tented skin. A distinct regional distribution over the dorsum is characteristic. Areas affected in decreasing frequency are 1) withers and croup, 2) gluteal region, 3) neck, 4) lateral thorax and abdomen, 5) distal legs, 6) face and 7) coronary band.¹ Owners may report the onset of signs as coincident with saddle training.

Histopathology of skin biopsies is not pathognomonic, but is characteristic and suggestive if combined with clinical history. Collagen bundles in the mid to deep dermis are small, thin and often arranged in small packets separated by clear spaces. A clear cleft may be present in the deep dermis. Early reports indicated that trichrome stains would demonstrate abnormal collagen fibers with red cores; this has been found to be an inconsistent finding.^{1,3} Elastin abnormalities are also variable and non-diagnostic. Electron microscopy shows random orientation of collagen fibers, although this change is non-specific and may be seen in other skin

conditions.¹ Immunohistochemistry for types I and III collagens has failed to show a difference between affected and normal horses.

HERDA is one member of a heterogeneous group of inherited collagen dysplasias of man and animals.⁴ Ehlers-Danlos syndromes in humans include defects in various structural components of different collagen types or in enzymes which process those proteins to form collagen fibrils. Autosomal dominant, Ehlers-Danlos type syndromes have been described in the dog and cat. 'Dermatosparaxis' (literally 'torn skin') is a disease described in cattle, sheep and cats. It is an autosomal recessive genetic disease resulting from a defect in procollagen peptidase. Procollagen accumulates and cannot be packeted into normal collagen fibrils. The mutation responsible for HERDA has not been identified, nor is the type of collagen affected in HERDA known.

HERDA seems to be unique in having a distinct regional distribution of affected tissue. While dorsal midline lesions may be predisposed by rubbing from saddles, several reports have noted normal wound healing after castration of affected males and lack of lesions in the girth.^{1,3} These facts suggest there is an actual differential expression of this defect in horses.

Veterinary pathologists need to be aware of this clinical condition in horses, and should be prepared to corroborate clinical findings with compatible histologic lesions.

AFIP Diagnosis: Haired skin: Collagen dysplasia, diffuse, Quarter Horse (*Equus caballus*), equine.

Conference Comment: The contributor provides an excellent summary of hereditary equine regional dermal asthenia (HERDA). Collagen dysplasia (hyperelastosis cutis, dermatosparaxis, cutaneous asthenia) occurs in most domestic animals and is characterized by hyperextensible, loose skin that tears easily. Histologic features vary among the different types of collagen dysplasia syndromes, and in some can be histologically normal. Electron microscopy or biochemical analyses are sometimes necessary to reach a definitive diagnosis.⁵

An important histologic feature of cutaneous dermal asthenia is the subfollicular artifactual split that occurs during procurement or processing. As pointed out by the moderator, this is a useable artifact (after Stannard). Additionally, the dermis ends abruptly and granulation tissue is often present at the deep margin of biopsies of tears or lacerations indicating prior healing attempts where the skin was pulled up and snapped back.⁶

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