Joint Pathology Center
Veterinary Pathology Services

WEDNESDAY SLIDE CONFERENCE 2023-2024

Conference #7 — 04 October 2023

CASE I:

Signalment:
9-year-old, male neutered mixed breed dog, canine (*Canis familiaris*)

History:
This patient developed skin nodules primarily affecting the distal forelimbs. The nodules were pruritic, alopecic, and erythematous, with minimal hemorrhagic exudate. Prior treatments included antibiotics, ivermectin, and lime sulfur dips.

The patient is a raccoon hunting dog who lives in an outdoor kennel with a concrete floor and no bedding. The dog has not traveled since the lesions began. Approximately 6 months after the nodules developed, multiple punch biopsies were collected from the right elbow and metacarpus and submitted for examination.

Laboratory Results:
A deep skin scraping revealed suspected larval nematodes as well as inflammatory cells and mixed bacteria.

A bacterial culture of the skin grew *Staphylococcus pseudintermedius*.

Microscopic Description:
Diffusely, follicles are large and distended with keratin and occasional nematode larvae that are 20-30 microns in diameter with double lateral alae and a rhabditiform esophagus.

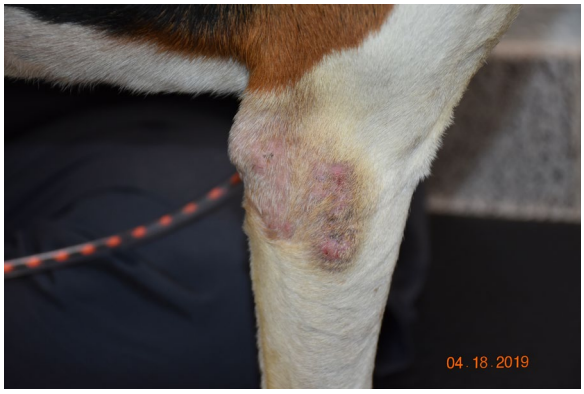

Figure 1-1. Haired skin, dog. There are pruritic, alopecic, and erythematous nodules within the skin. (*Photo courtesy of:* University of Tennessee, College of Veterinary Medicine, Department of Biomedical and Diagnostic Sciences http://www.vet.utk.edu/departments/path/index.php)

There is hyperplasia of the follicular epithelium. Adnexa are surrounded by plasma cells and fewer lymphocytes. There are multifocal aggregates of macrophages, neutrophils, and eosinophils with fewer multinucleated giant cells which tend to be at the base of follicles. In some sections, this inflammation is associated with follicular rupture with release of free keratin, and presumably nematodes, into the periadnexal dermis. There are varying degrees of hemorrhage and fibrosis around the ruptured follicles. Some follicles also contain bacterial cocci. There is diffuse mild epidermal hyperplasia with ortho-keratotic hyperkeratosis.

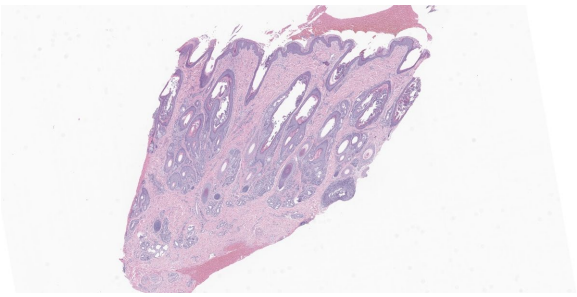

Figure 1-2. Haired skin, dog. A single biopsy of haired skin is submitted for examination. There is diffuse epidermal and follicular epithelial hyperplasia, and hair follicles are dilated. (HE, 5X)

Contributor's Morphologic Diagnosis:
Haired skin: Widespread periadnexal plasmacytic dermatitis with intrafollicular larval nematodes and multifocal follicular rupture with pyogranulomatous dermatitis.

Contributor's Comment:
The clinical, cytologic, and histologic findings are consistent with follicular *Pelodera strongyloides* infection. *P. strongyloides* is a free-living rhabditid nematode that lives in decaying organic matter. Infections are rare, and most infections in the United States have been reported in the Midwestern states.[5] Infections are often associated with dirty environments or the use of damp straw for bedding.[1,5] Cattle, swine, dogs, horses, rodents, sheep, and humans are infected by exposure to infested organic matter.[1,2,5] Lesions occur at sites of contact with contaminated materials, which, in dogs, are primarily the ventrum, paws, distal limbs, perineum, and tail. Short-coated dogs may be more easily parasitized.[5] Removal of the animal from infected bedding may clear the infection, although treatment with anti-parasitics is also warranted.[6] Fittingly, this dog is a short-haired hound dog mix whose lesions were primarily on the distal forelimbs.

Clinically, an erythematous maculopapular rash with variable alopecia is reported. The lesions are extremely pruritic, so there may be associated self-trauma.[5] Histologically, there is epidermal hyperplasia with hyperkeratosis and follicular keratosis. The nematodes can be found in hair follicles and in the superficial keratin.[5] Follicular nematode larvae can penetrate the follicular infundibula, inciting folliculitis that can progress to furunculosis and pyogranulomatous dermatitis.[2] Adnexa are surrounded by mixed inflammatory cells, including eosinophils, lymphocytes, plasma cells, macrophages, and mast cells.[5]

The nematodes are recognized by their small size, double (or paired) lateral alae, rhabditiform esophagus, platymyarian musculature, and intestine lined by uninucleated cells.[3,4] Given the small size of these nematodes, identification of some of these structures on histologic examination is challenging.

Lesions in this dog initially persisted despite appropriate antibiotic therapy, cleaning the environment, and ivermectin treatment. Lesions eventually improved and skin scrapes were negative following treatment with the antibiotic Simplicef (cefpodoxime proxetil)

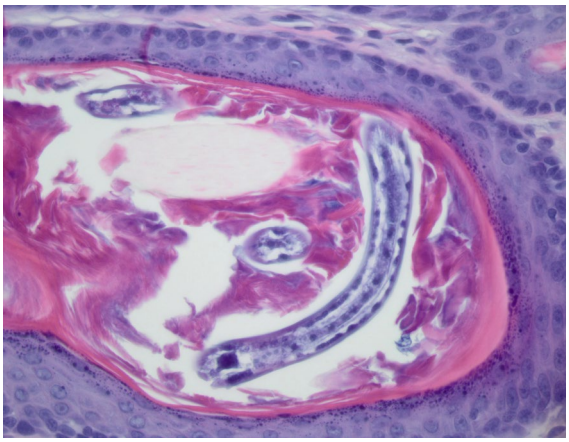

Figure 1-3. Haired skin, dog. Follicles are ectatic and contain keratin debris and numerous nematode larvae. (HE, 400X) (*Photo courtesy of:* University of Tennessee, College of Veterinary Medicine, Department of Biomedical and Diagnostic Sciences)

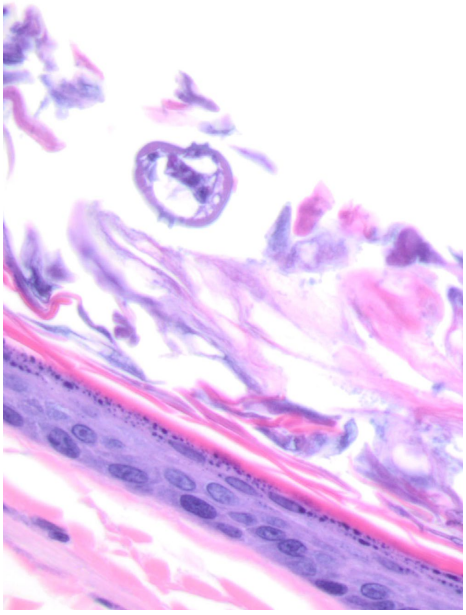

Figure 1-4. Haired skin, dog. Larvae have double lateral alae. (HE, 400X) (*Photo courtesy of:* University of Tennessee, College of Veterinary Medicine, Department of Biomedical and Diagnostic Sciences)

and the broad-spectrum anti-parasitic Advantage Multi (imidacloprid and moxidectin).

A complete blood count identified consistent leukopenia of unknown cause, so concurrent immunosuppression may have contributed to the infection and delayed response to treatment.

Contributing Institution:
University of Tennessee
College of Veterinary Medicine
Dept. of Biomedical and Biological Sciences
http://www.vet.utk.edu/departments/path/index.php

JPC Diagnosis:
Haired skin: Dermatitis and folliculitis, lymphoplasmacytic, moderate, with furunculosis and numerous intrafollicular nematode larvae and adults.

JPC Comment:
Pelodera is an uncommon cause of canine dermatitis that receives only rare mention in veterinary literature. The contributor provides an excellent summary of this condition.

One of the main differentials for canine *Pelodera* dermatitis is hookworm dermatitis caused by *Ancylostoma caninum*, *Ancylostoma braziliense*, *Ancylostoma ceylanicum*, or *Uncinaria stenocephala*.[7] Similar to *Pelodera* dermatitis, hookworm dermatitis occurs on areas of the body in frequent contact with the ground, including the distal limbs and feet, ventrum, and tail. The third-stage hookworm larvae that invade the skin are generally not host-specific, leading to possible cutaneous larval migrans in many aberrant hosts, such as humans.[7] Clinical signs can include secondary pyoderma and paronychia and epidermal hyperplasia; histologic lesions include eosinophilic, neutrophilic, and histiocytic perivascular dermatitis with degenerate leukocytes lining cutaneous migration paths.[7] In addition to *Pelodera*, *Ancylostoma*, and *Uncinaria*, other helminth genera that can cause cutaneous larval migrans include *Necator*, *Strongyloides*, *Gnathostoma*, and *Bunostoma*.[7]

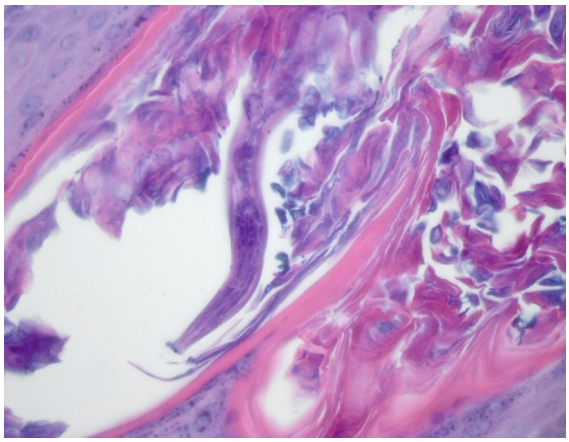

Figure 1-5. Haired skin, dog. Larvae have a rhabditiform esophagus. (HE, 400X)(*Photo courtesy of:* University of Tennessee, College of Veterinary Medicine, Department of Biomedical and Diagnostic Sciences)

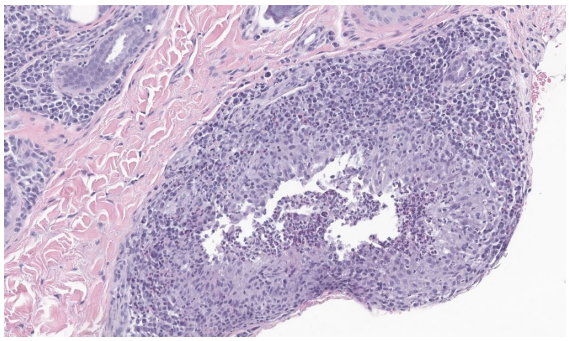

Figure 1-6. Haired skin, dog. There is a ruptured hair follicle which is replaced by pyogranulomatous inflammation. (HE, 300X)

The week's conference was moderated by Dr. Charles Bradley, Assistant Professor of Pathobiology at the University of Pennsylvania School of Veterinary Medicine. Dr. Bradley discussed several cutaneous nematodiases in various species. Examples included *Onchocerca cervicalis*, associated with equine bursitis (delightfully named "fistulous withers" and "poll evil," depending on location), and the ventral midline filarial dermatitis caused by *Stephanofilaria stilesi* in cattle. In the cutaneous nematode universe, however, only *Pelodera* invades the hair follicle and causes folliculitis and furunculosis, making for a straight-forward, if uncommon, diagnosis.

Dr. Bradley also discussed carefully curating morphologic diagnoses by including only histologic features essential to the diagnosis; histologic features that are nonspecific, incidental, or not prominent are better left to the description. To that end, the JPC morphologic diagnosis was ruthlessly pruned to highlight the essentials of this condition: the intrafollicular parasites and associated follicular inflammation.

References:

1. Bowman DD. Helminths. In: Bowman DD, ed. *Georgi's Parasitology for Veterinarians*. 10th ed. Elsevier; 2014:191-194.
2. Capitan RGM, Noli C. Trichoscopic diagnosis of cutaneous *Pelodera strongyloides* infestation in a dog. *Vet Dermatol.* 2017;28(4):413-e100.
3. Eberhard ML. Histopathologic Diagnosis. In: Bowman DD, ed. *Georgi's Parasitology for Veterinarians*. 10th ed. Elsevier;2014:418.
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5. Gross TL. Pustular and nodular disease with adnexal destruction. In: *Skin Diseases of the Dog and Cat*. 2nd ed. Blackwell;2005:449-450.
6. Mauldin EA, Peters-Kennedy J. Integumentary System. In: Maxie MG, ed. *Jubb, Kennedy, and Palmer's Pathology of Domestic Animals*. 6th ed. Vol 1. Elsevier; 2016:689.
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CASE II:

Signalment:
6-year-old, male neutered American pit bull terrier, canine (*Canis familiaris*)

History:
The patient had chronically pruritic, erythematous, and hyperplastic skin with numerous comedones. A prior history of intermittent superficial and deep pyoderma was reported.

Gross Pathology:
Lesions were predominantly on the ventral abdomen, inner thighs, and cranial hind limbs, but were also present over the dorsum and top of the head.

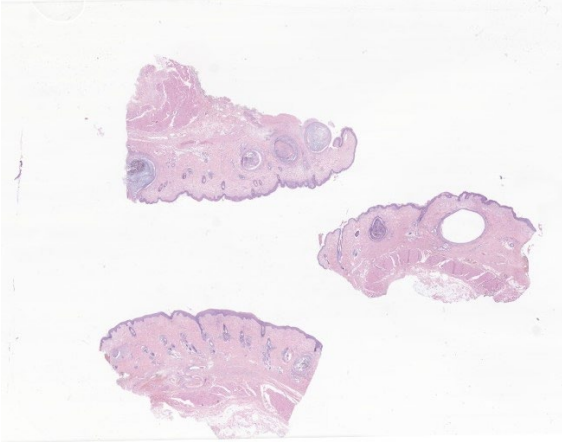

Figure 2-1. Haired skin, dog. Three sections of haired skin are submitted for examination. At low magnification, there are several large comedones within the submitted tissue. (HE, 5X)

Laboratory Results:
Superficial and deep skin scraping was performed and was negative for ectoparasites.

Surface cytology was performed and was reported as pyogranulomatous inflammation with the presence of cocci.

Aerobic culture and sensitivity of the skin surface was performed and *Staphylococcus pseudintermedius* sensitive to most antimicrobials was cultured.

Microscopic Description:
The epidermis is moderately hyperplastic with occasional dysplastic keratinocytes (increased nuclear to cytoplasmic ratio in the stratum spinosum) with suprabasal mitoses, and infrequent hypergranulosis. There are rare suprabasilar apoptotic keratinocytes (sunburn cells). There is multifocal parakeratotic hyperkeratosis. Follicular infundibula are markedly expanded by keratin (comedones) and surrounded by a rim of fibrosis. The superficial dermis has numerous wavy basophilic fibers (solar elastosis) and superficial fibrosis. There is a mild perivascular and perifollicular infiltrate of lymphocytes, plasma cells, and histiocytes with multifocal edema. There is a small focus of free keratin surrounded by macrophages adjacent to one of the comedones. The other sample (not submitted) demonstrated comedone rupture with pyogranulomatous dermatitis.

Contributor's Morphologic Diagnosis:
Haired skin: Epidermal dysplasia with solar elastosis, comedones, and mild dermatitis (actinic dermatosis).

Contributor's Comment:
This case exhibits classic features of actinic dermatosis, also called solar dermatosis or actinic keratosis. Exposure to ultraviolet radiation (most often sunlight) leads to epidermal hyperplasia and dysplasia with scattered suprabasilar mitoses and apoptotic keratinocytes ("sunburn cells"). The stratum corneum often exhibits parakeratotic hyperkeratosis.

In the dermis, elastin fibers are degenerate and appear as thick, wavy, basophilic strands (solar elastosis). Laminar fibrosis occurs in the superficial dermis and extends around follicular infundibula, which dilate to form comedones. There may also be a layer of pale, smudgy collagen fibers in the superficial dermis. There is often a superficial perivascular infiltrate of lymphocytes, plasma cells, and fewer macrophages, neutrophils, and occasionally eosinophils. Comedones may rupture, leading to furunculosis, and lesions can also become secondarily infected. Some cases may exhibit vasculopathy or proliferation of superficial dermal vessels.[2] The epidermis may exhibit hyperpigmentation, though this change is not observed in this patient's nonpigmented skin.[4]

Because exposure to sunlight is the initial step in the pathogenesis of actinic dermatosis,

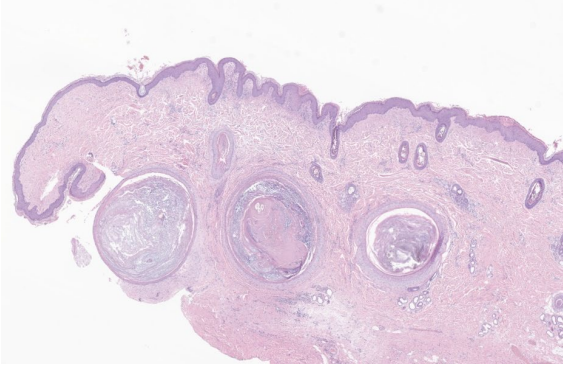

Figure 2-2. Haired skin, dog. There is mild to moderate epidermal hyperplasia and several large comedones. There is mild multifocal perivascular inflammation. (HE, 18X)

affected dogs are often known sunbathers and may live at low latitudes or high altitudes. Lesions are most common on sparsely haired areas, such as the ventral abdomen, inguinum, axilla, dorsal muzzle, and periorbital regions. Non-pigmented areas are also more commonly affected. Predisposed dog breeds include short-haired dogs such as pit bulls, boxers, whippets, Dalmatians, greyhounds and Italian greyhounds, beagles, and basset hounds.[2]

Actinic dermatosis is also commonly observed in cats, horses, cattle, and humans. In cats, predisposed locations include the face and pinnae. In horses and cattle, lesions are often found on the eyelids (including third eyelid), conjunctiva, and perineum.[7] Grossly, actinic dermatosis appears as patchy erythema, crusts, macules, and papules, progressing to plaques and nodules that may be ulcerated. Comedones may be grossly visible as dark foci or small nodules. Multiple lesions are often present, as solar exposure occurs over a large area of the patient. [2]

Several of the changes described above are protective mechanisms of the epidermis against damage caused by UV radiation. Melanin blocks UV radiation and absorbs free radicals.[1,4] Hyperpigmentation of the epidermis occurs via an immediate redistribution of existing melanin or more chronically via increased melanin synthesis by melanocytes and increased transfer of melanin to keratinocytes, which appears histologically as "hats" over the keratinocyte nuclei.[4] Epidermal hyperplasia and hyperkeratosis, stimulated by epidermal growth factors released after UV exposure, provides an increased physical barrier. [1]

If protective mechanisms fail, the epidermal dysplasia of actinic dermatosis can progress to *in situ* and then frank squamous cell carcinoma (SCC). Dogs with solar-induced SCC may have a longer median survival time than dogs with SCC without evidence of solar damage.[8] UV light causes cross-linking of pyrimidine nucleosides into pyrimidine dimers, which distort the structure of the DNA double helix, leading to DNA replication failure and cell death or transformation. [4] Additionally, investigation into the molecular basis for actinic dermatosis and carcinogenesis in humans demonstrates similar genetic dysregulation between actinic dermatosis and SCC and implicates UV-induced mutations in p53.[5,6] Other solar radiation-induced neoplasms, such as hemangioma/hemangiosarcoma, may occur concurrently in animals with solar exposure.[2,4] Basal cell carcinomas and squamous cell carcinomas in humans are both linked to UV exposure, and p53 mutations are commonly found in these tumors.[3]

Contributing Institution:
University of Pennsylvania
School of Veterinary Medicine
https://www.vet.upenn.edu/veterinary-hospitals/ryan-veterinary-hospital/services/diagnostic-laboratories

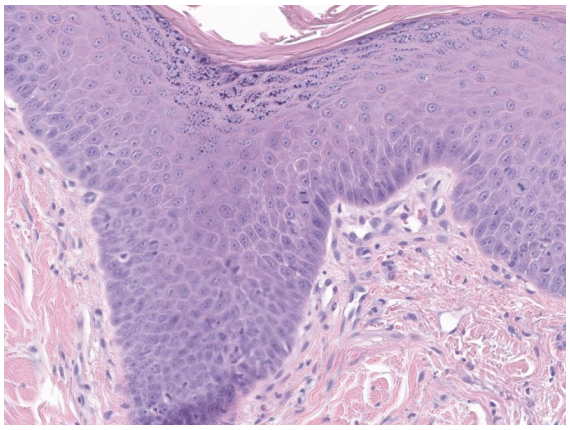

Figure 2-3. Haired skin, dog. There are numerous mitotic figures in the hyperplastic epidermis, and some above the basal layer. (HE, 229X)

JPC Diagnosis:
Haired skin: Epidermal dysplasia, mild to moderate, with keratinocyte apoptosis, solar elastosis, and comedones.

JPC Comment:
As the contributor notes, DNA damage due to sunlight exposure is the inciting cause of actinic dermatosis and the malignant transformation of keratinocytes that may occur with prolonged exposure. Sunlight contains three types of ultraviolet radiation that reach the earth's surface: long wavelength UVA radiation in the 400-315 nm spectrum, UVB radiation (315 to 280 nm), and short-wave UVC radiation (280 to 100 nm).[9] The vast majority of UV radiation that reaches the skin of humans and animals is UVA radiation, as all but approximately 5% of UVB radiation, and all UVC radiation, is absorbed by atmospheric ozone.[1,9] Once UV light reaches the skin, host factors such as amount and type of hair and melanin pigmentation within the skin, as well as environmental factors, ultimately determine the amount of UV exposure received by the skin of a particular animal.[9]

UV radiation is considered a "complete carcinogen" in that it is both a mutagen, due to its direct effects on DNA, and a non-specific damaging agent, giving it properties of both a tumor initiator and a tumor promoter.[1] In the skin, UVA penetrates deeply into the dermis and is efficient at generating reactive oxygen species that damage DNA via indirect photosensitizing reactions.[1] In contrast, UVB is almost completely absorbed by the epidermis, where it is directly absorbed by DNA within keratinocytes, leading to molecular rearrangements, such as covalent bonds between adjacent thymine or cytosine bases ("pyrimidine dimers").[1,9] Most pyrimidine dimers are removed by DNA repair mechanism; however, some pyrimidine dimers escape this process and cause cells either to undergo apoptosis, leading to the "sunburn cells" seen in actinic keratosis, or to accumulate DNA mutations during subsequent replication, leading to neoplasia.[1,9]

The lesions of actinic dermatosis described by the contributor and well-illustrated in this case, are a result of chronic exposure to UVB and UVA radiation. At the outset, lesions appear grossly as areas of erythema with scaling and crusting, followed by the appearance of papular or plaque-like foci of thick, lichenified, erythematous crusted patches and plaques.[4,9] Progression to *in situ* carcinoma, squamous cell carcinoma, or basal cell tumors may occur in areas of preneoplastic actinic dermatosis.[9]

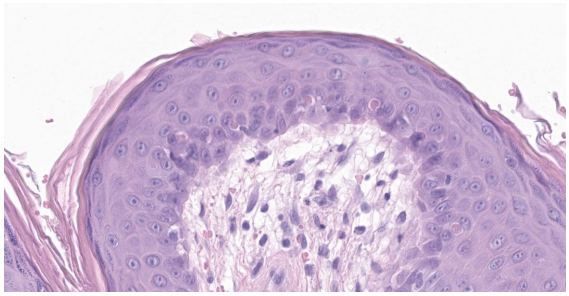

Figure 2-4. Haired skin, dog. There are occasional necrotic keratinocytes scattered throughout the stratum spongiosum ("sunburn cells")(HE, 386X)

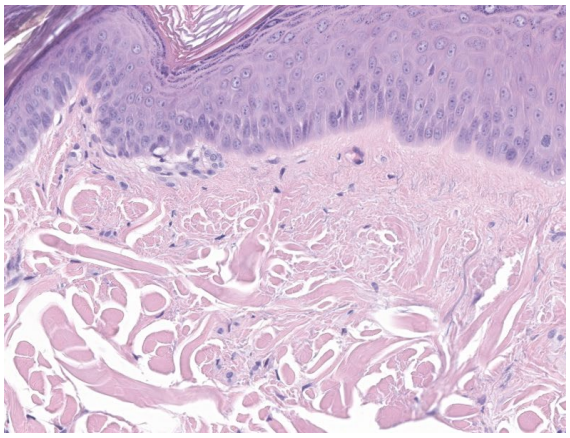

Figure 2-5. Haired skin, dog. There is fibrillation of the superficial dermal elastic fibers (solar elastosis). (HE, 244X)

Exposure to UV radiation can also damage skin through photosensitization. Photosensitization is skin damage due to the interaction of UV radiation and photodynamic chemicals within the skin.[9] When UV radiation interacts with photodynamic chemicals, the released energy produces a range of reactive oxygen species that damage cell membranes, DNA, proteins, and organelles, causing cell activation, degeneration, and/or death.[9]

Photosensitization injury is classified into four types based on the origin of the photodynamic substance. In type I (primary) photosensitization, the photodynamic substance is ingested by the animal, usually in the form of plants or drugs, and then absorbed systemically and deposited into the skin. Type II photosensitization occurs via accumulation of endogenous hematoporphyrins due to the inability to properly metabolize heme pigments. Type III photosensitization occurs when phylloerythrin, a chlorophyll degradation product, accumulates in the skin; this is also known as hepatogenous photosensitization since deposition in the skin is due to the inability of the liver to disposing of phylloerythrin normally. Finally, type IV photosensitization refers to photosensitization for which the pathogenesis is unknown.[4]

A final way that UV radiation can damage skin is through photoallergy. Photoallergy is distinct from photosensitization and occurs when an exogenous photodynamic substance functions as an antigen.[4,9] Gross and histologic pathology is typically due either to an immediate, Type I hypersensitivity reaction or a delayed, Type IV cell-mediated hypersensitivity reaction in which the photoactivated substance acts either as a hapten or an allergen.[9]

Conference participants appreciated the impressive comedones in the examined section. Actinic comedones such as these can be distinguished from regular comedones by their concentric, peripheral fibrosis and the lack of attenuation of the outer root sheath. Inflammation resulting from the rupture of an actinic comedone is sometimes called solar furunculosis.

The moderator also pointed out the substantial dysplastic changes evident within the epithelium, including suprabasilar mitotic activity, irregularly piling up of keratinocytes, and the formation and elongation of rete ridges. In human medicine, these changes might be enough for a diagnosis of *in situ* squamous cell carcinoma; however, veterinary medicine tends to be more cautious of making this leap. The moderator noted that the epithelium appeared to be well on its way to malignant transformation.

Finally, the moderator discussed the importance of differentiating feline actinic dermatosis from Bowenoid in situ carcinoma (BISC), which can exhibit more aggressive and invasive biological behavior. Compared to actinic dermatosis, in BISC, keratinocytes in all layers of the epidermis typically appear more basaloid, rete ridges tend to be more bulbous and extend farther into the dermis, and dysplastic changes extend to the follicular outer root sheath.

References:

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5. Nelson MA, Einspahr JG, Alberts DS, et al. Analysis of the p53 gene in human precancerous actinic keratosis lesions and squamous cell cancers. *Cancer Lett*. 1994: 85(1):23-9.
6. Padilla RS, Sebastian S, Jiang Z, et al. Gene expression patterns of normal human skin, actinic keratosis, and squamous cell carcinoma: a spectrum of disease progression. *Arch Dermatol*. 2010:146 (3):288-93.
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9. Welle MM, Linder KE. The Integument. In: Zachary JF, ed. *Pathologic Basis of Veterinary Disease*. 7th ed. Elsevier; 2022:1154-1156.

<u>CASE III</u>:

Signalment:
11-year-old, male neutered domestic short hair, feline (*Felis catus*)

History:
The patient is an outdoor cat with a completed vaccination protocol and no other animals live in the same household. The cat developed skin lesions due to dermatophytosis and was treated with itraconazol. There was partial remission of the skin lesions; however, approximately five months later, the skin lesions progressed despite therapy.

Gross Pathology:
Clinical examination of the skin showed severe diffuse exfoliation and crust formation. In addition, the skin presented with mild to moderate multifocal erythema and follicular casts. The ear canal was filled with dry and brown secretions.

Figure 3-1. Haired skin, cat. Four sections of haired skin are submitted for examination. At low magnification, a dense layer of hyperkeratosis is evident. (HE, 5X)

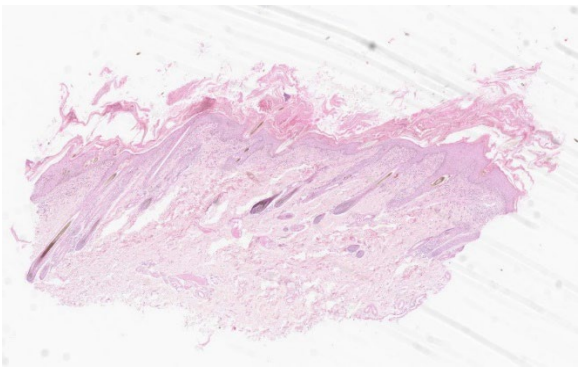

Figure 3-2. Haired skin, cat. A dense layer of hyperkeratosis covers a mildly hyperplastic epidermis. (HE, 16X)

Laboratory Results:
Cytological examination of the skin crusts revealed numerous neutrophils and bacterial cocci. Trichogram examination revealed the presence of follicular casts. A skin scraping was negative for ectoparasites. Wood lamp examination was negative for fungal microorganisms. Blood evaluation revealed mild thrombocytopenia and a mild increase in ALT.

Chest radiographs revealed a mass in the thymic region. Cytologic evaluation of an ultrasound guided fine needle aspirate of the mass was diagnosed as epithelial thymoma.

Microscopic Description:
Histological examination of the skin sections revealed a marked, diffuse predominantly orthokeratotic and, to a lesser degree, parakeratotic hyperkeratosis of the epidermis. Multifocally, small aggregates of neutrophils as well as extravasated erythrocytes (haemorrhage) and occasional small bacterial colonies (coccoid bacteria, not seen in all slides) can be seen. The epidermis and hair follicle infundibula are moderately thickened (acanthosis). The following changes are seen in the epidermis and, to a lesser degree, in hair follicles: disruption and vacuolation (interpreted as hydropic degeneration) of the basal keratinocytes; an infiltrate of small lymphocytes within the stratum basale and rarely within upper layers (exocytosis); scattered isolated deeply eosinophilic and rounded cells (apoptotic cells) with loss of cohesion from other keratinocytes in all epidermal layers; increased numbers of intraepidermal melanocytes; and increased numbers of keratinocytes with intracytoplasmic melanin (hyperpigmentation). A moderate band-like mononuclear infiltrate composed mainly of lymphocytes, plasma cells, occasional melanin-laden macrophages (interpreted as melanin incontinence), and mast cells is seen in the superficial dermis and around hair follicles. This infiltrate obscures the dermo-epidermal junction (interpreted as interface dermatitis). Sebaceous glands are absent.

Contributor's Morphologic Diagnosis:
Haired skin: Moderate to severe lymphocytic interface dermatitis with mild transepidermal apoptosis, moderate to severe parakeratotic hyperkeratosis, and severe atrophy of sebaceous glands.

Contributor's Comment:
Thymoma associated exfoliative dermatitis is a rare paraneoplastic syndrome which has been reported in middle-aged to older cats affected by a thymoma.[7,12] This condition has also been reported in rabbits and goats.[1,5] In cats, the exfoliative dermatitis regresses after thymectomy.[2,7,13] Other thymoma associated paraneoplastic syndromes include myasthenia gravis in cats and dogs, erythema multiforme in dogs, and granulocytopenia in cats.[4,13,15,16]

Affected cats present with alopecia, crusting, scaling, desquamation, and erythema usually starting from the head and progressing to the rest of the body.[2,6,12] Keratinaceous debris may build up in interdigital spaces and claw folds. Pruritis is usually absent unless there

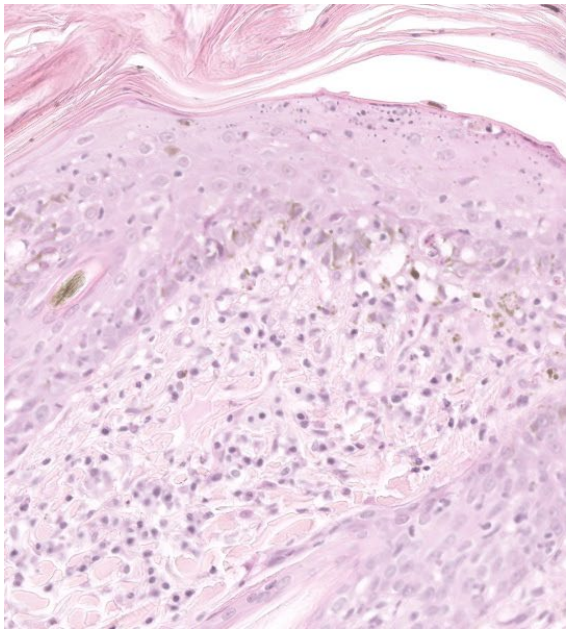

Figure 3-3. Haired skin, cat. A band of low numbers of lymphocytes is present at the dermoepidermal junction and infiltrates the overlying, often vacuolated basal epithelium. (HE, 305X)

are dermal lesions, namely alopecia and exfoliation, are reported in goats and rabbits.[1,5]

Typical histopathological lesions in cats include orthokeratotic and parakeratotic hyperkeratosis, extensive desquamation and transepidermal keratinocyte apoptosis, as well as apoptosis of keratinocytes in the follicular infundibula. In addition, there is hydropic degeneration of the basal keratinocytes and cell poor to cell rich CD3+ lymphocytic interface dermatitis. The infiltrative lymphocytes can lead to mural folliculitis with subsequent atrophy of sebaceous glands. Pigmentary incontinence and concurrent *Malasezzia* infections have also been reported.[7,12] Similar histologic lesions have been described in goats and rabbits.[1,5]

In humans, thymomas have been shown to produce autoantigen responsive CD4+ T cells. This has been shown to occur in paraneoplastic myasthenia gravis, erythema multiforme, and graft versus host disease. It is therefore proposed that the same occurs in thymoma associated exfoliative dermatitis in cats due to the occurrence of auto reactive T lymphocytes targeting keratinocytes.[12] Differential diagnoses of thymoma associated exfoliative dermatitis in cats according to histological features of the lesion include non-thymoma associated exfoliative dermatitis, systemic lupous erythematosus, erythema multiforme, and sebaceous adenitis.[7]

Nonthymoma associated exfoliative dermatitis is clinically and histologically indistinguishable from the thymoma associated exfoliative dermatitis.[3,10] The diagnosis is based on the demonstration of the absence of thymic neoplasia and the lesions usually resolve after administration of cyclosporine.[3,10,14]

Erythema multiforme has similar histologic lesions to thymoma-associated exfoliative dermatitis. The lesions in thymoma associated exfoliative dermatitis present with milder transepidermal apoptosis in comparison to erythema multiforme.[6,7,12] In addition, the clinical skin lesions differ and are mainly characterised by erythematous macules, papules or plaques over the dorsum and spreading peripherally.[7,8]

Lupus erythematosus is considered another differential due to histologic similarities. The difference is that in lupus erythematosus, there is usually a more prominent interface dermatitis and mild apoptosis restricted to the basal cells.[7] Gross lesions in lupus erythematosus include erosions and ulcerations on the face, particularly on the nose.[8]

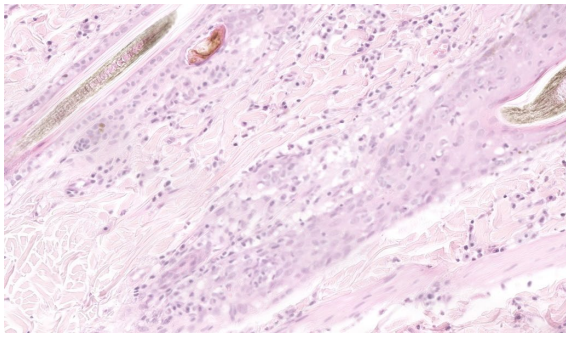

Figure 3-4. Haired skin, cat. There is effacement of sebaceous glands by lymphocytes and macrophages. (HE, 400X)

Feline sebaceous adenitis is considered a differential when the sebaceous glands are absent or reduced in number. However, the inflammation will be confined to the follicular isthmus and apoptosis is absent in sebaceous adenitis.[7] A final diagnosis of thymoma-associated exfoliative dermatitis is achieved by evaluation of skin biopsies and demonstration of simultaneously occurring thymic neoplasia.[1]

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JPC Diagnosis:
Haired skin: Dermatitis and mural folliculitis, lymphocytic, cytotoxic interface, moderate, with epidermal hyperplasia, parakeratotic hyperkeratosis, and sebaceous gland loss.

JPC Comment:
Thymomas are rare in dogs and cats and arise from the epithelium of the thymus. Curiously, thymomas are classified as benign or malignant based on their ability to be resected at surgery, and not based on histopathologic criteria.[13] Regardless of classification, metastasis is uncommon and recurrence after surgical resection is rare.[13]

Patients with thymomas may seek veterinary care due to respiratory symptoms from the primary tumor or for clinical signs referrable to any one of several reported paraneoplastic syndromes. As the contributor notes, the most common thymoma-associated paraneoplastic syndromes include exfoliative dermatitis, erythema multiforme, myasthenia gravis, granulocytopenia, and polymyositis. The association between thymoma and exfoliative dermatitis is poorly understood; however, immune-mediated injury is the current leading theory based on the characteristic presence of a T cell-rich cytotoxic interface dermatitis.[12]

In health, T cells are prevented from attacking self-antigens due to central and peripheral tolerance. Central tolerance begins during T cell development in the thymus, where rearrangement of T cell receptors generates a panoply of epitope receptors sufficient to recognize all possible antigens encountered during the life of the animal. In this generative process, T cell receptors are inadvertently created which have a high affinity for self-peptides. These T cells are screened in the thymic medulla and are either eliminated via apoptosis ("clonal deletion") or differentiated into thymically-derived T regulatory cells ("clonal diversion").[11]

Screening of self-reactive T lymphocytes is achieved through a remarkable process of so-called "promiscuous gene expression" by a subset of thymic epithelial cells called medullary thymic epithelial cells (mTECs).[11] These mTECs present self-antigens to developing T lymphocytes and expose maturing T lymphocytes to a nearly complete representation of the animal's protein coding genome.[11] T lymphocytes that pass this screening (i.e., have low binding affinity for self-peptides) are tolerant for most proteins in the animal's body.[11] A key player in this system is the

transcriptional regulator Autoimmune Regulator (AIRE) protein, which is highly expressed in mTECs where it promotes promiscuous gene expression of a wide array of tissue-specific antigens for presentation to the developing T lymphocytes.

The processes of central tolerance work well, but not perfectly; thus, occasionally self-reactive T lymphocytes slip through the thymic cracks and are released into systemic circulation. In addition, though the mTECs present developing T cells with an impressive array of self-peptides, they do present them with all possible self-peptides. The processes of peripheral tolerance, most notably anergy and deletion of self-reacting lymphocytes, acts as a second line of defense against mature lymphocytes that encounter self-peptide for the first time outside the context of the thymus.[11]

Given that the thymus is the key site for establishing immune tolerance, it is not surprising that thymic epithelial cell tumors may generate syndromes caused by perturbations of this system. In humans, myasthenia gravis is the most studied thymoma-associated neoplastic syndrome. Patients that develop myasthenia gravis have cortical thymomas with active thymopoiesis (i.e., they retain the ability to export mature T lymphocytes).[9] The neoplastic cells express lower levels of MHC Class II and AIRE when compared to normal thymic epithelium; thus, defective negative screening in the thymus, reduced levels of regulatory T cells, and export of autoreactive T lymphocytes are the key features associated with myasthenia gravis in human thymoma patients.[9] As the contributor notes, it is thought that a similar mechanism underlies the apparent auto-immune keratinocyte destruction characteristic of thymoma-associated exfoliative dermatitis in a animals.

Conference discussion focused on distinguishing exfoliative dermatitis from erythema multiforme, as often the histologic lesions can be extremely similar or even identical. The clinical picture in these two conditions is different, however, with erythema multiforme typically causing small multifocal lesions while exfoliative dermatitis tends to be more widespread throughout the body. Another differential considered, largely due to the loss of sebaceous glands, is sebaceous adenitis; however, involvement of the epidermis in the form of cytotoxic interface dermatitis in this case rules out a diagnosis of sebaceous adenitis, which is characterized by immune destruction of sebaceous units only. The loss of sebaceous units probably does contribute to the exfoliation in this condition, however, as the loss of sebum is a known cause of disordered desquamation. Conference participants discussed several other paraneoplastic syndromes, including paraneoplastic alopecia, nodular dermatofibrosis in German Shepherd dogs, paraneoplastic pemphigus, and superficial necrolytic dermatitis.

There was spirited discussion among conference participants surrounding the term “diffuse” when used to describe distribution in dermatopathologic lesions. The moderator prefers to avoid the term as “nodular to diffuse” dermatitis is one of the eight defined inflammatory reaction patterns in veterinary dermatopathology and its use in a broader-sense may be confusing. In this case, the moderator felt that the terms “dermatitis” and “mural folliculitis” are sufficient to convey the distribution of the lesions examined in conference.

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CASE IV:

Signalment:
8-year-old, female spayed boxer, canine (*Canis familiaris*).

History:
The patient was referred to Auburn University Dermatology specialty service for a disease affecting all claws of all four paws with a clinical duration of approximately six months. Affected claws were misshapen, fractured, and ranged from soft to brittle. No systemic abnormalities were reported at the time of admission.

Gross Pathology:
Multiple claws had moderate paronychia characterized by edema, erythema, congestion, and purulent to hemorrhagic exudate at the claw fold with keratinous debris around the claw. All claws had moderate to severe onychodystrophy characterized by onychorrhexis, onychomalacia, onycholysis, onychogryphosis, onychauxis, and onychoschizia. An onychobiopsy without onychectomy employing the technique described by

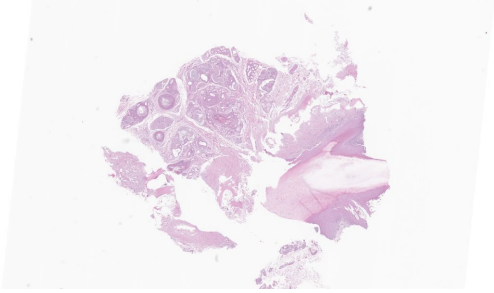

Figure 4-1. Haired skin and claw, dog. A single section of haired skin and fragments of the 3rd phalanx and claw are submitted for examination. (HE, 5X)

Mueller and Olivry (1999) was performed and samples were sent for histopathology and fungal culture.

Laboratory Results:
Claw tissue submitted for fungal culture was negative for dermatophytes.

Microscopic Description:
Affecting the claw bed, the dermo-epidermal junction is blurred by a band-like infiltrate composed of moderate numbers of lymphocytes, plasma cells, histiocytes, fewer neutrophils, and melanin-laden macrophages (pigmentary incontinence). At these segments and other less inflamed epidermal stretches, the basal epithelium is markedly vacuolated and interspersed with individualized, shrunken hypereosinophilic keratinocytes with pyknotic nuclei (apoptosis). The superficial dermis is minimally replaced by a smudgy collagenous matrix. Eccrine glands are mildly ectatic, filled with amphophilic product, and surrounded by mixtures of similar inflammatory infiltrates within increased concentric bands of fibrous tissue.

Contributor's Morphologic Diagnosis:
Claw to claw base/bed (digit unspecified): Dermatitis, interface and lichenoid, lymphoplasmacytic and histiocytic, moderate, with pigmentary incontinence, basal epithelial vacuolation, and apoptosis (consistent with symmetric lupoid onychodystrophy).

Contributor's Comment:
Symmetric lupoid onychodystrophy (SLO), also known as symmetric lupoid onychitis, is an uncommon primary ungual disease that has been described in dogs.[1,4,6] This condition may occur in dogs of all ages; however, young to middle-aged dogs appear to be more commonly affected.[4] Certain breeds seem to be predisposed, including German Shepherd and Gordon Setter; nevertheless, SLO has been reported in numerous breeds, and sex predisposition has not been described.[1,4,9]

SLO lesions are restricted to the claws and affected dogs are usually otherwise healthy with no systemic involvement.[1] Typically, the first clinical signs observed by owners are licking of the paws and lameness due to onychalgia or onychomadesis.[1,4] Paronychia with onycholysis of multiple claws is observed and, within weeks, several or all claws of all paws are affected.[1,3] After sloughing, regrown claws are commonly misshapen, brittle, dry, and discolored, and secondary bacterial infections are common.[1,4]

Term	Definition
Onychodystrophy	Abnormal claw formation
Paronychia	Inflammation or infection of the claw folds
Onychomalacia	Softening of the claws
Onycholysis	Separation of the claw from the underlying corium but with continuing proximal attachment
Onychogryphosis	Hypertrophy and abnormal curvature of the claws
Onychauxis	Hypertrophy of the claws
Onychoschizia	Splitting or lamination of claws, usually beginning distally
Onychalgia	Claw pain
Onychomadesis	Sloughing of the claws (claw shedding)

Table 4-1. A sampling of claw disorder terminology. Table adapted from Muller and Kirk's *Small Animal Dermatology*. 7th ed. 2012.

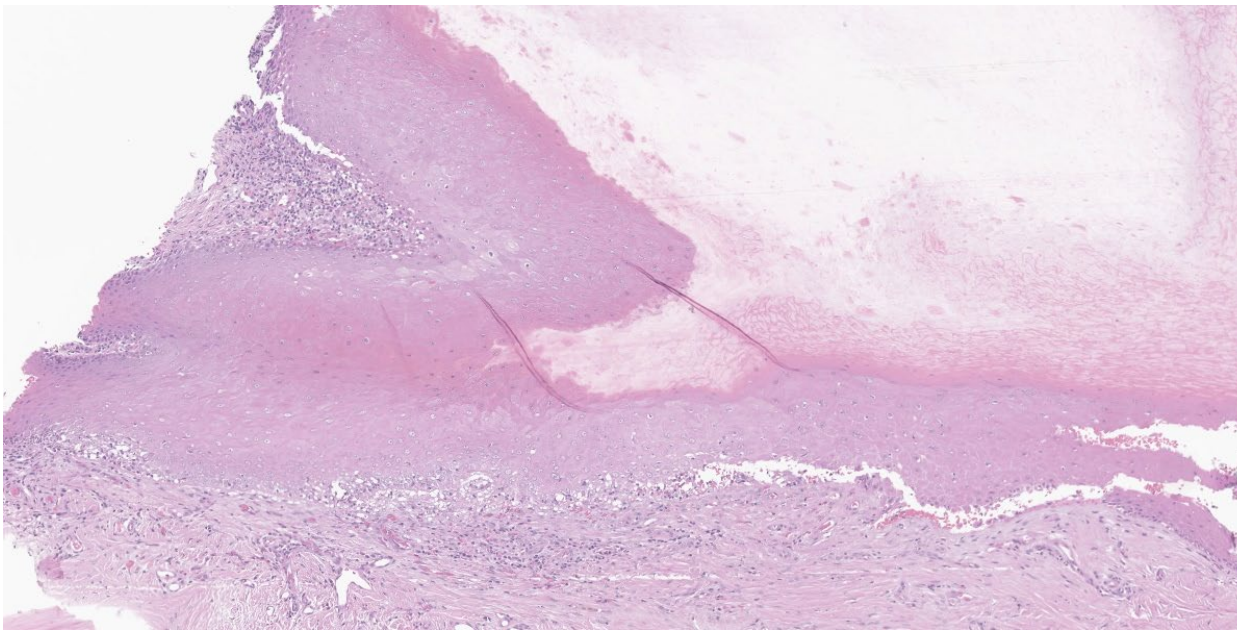

Figure 4-2. Nailbed, dog. There is a linear band of lymphocytes subjacent to the germinative epithelium of the nailbed. (HE, 92X)

The cause and pathogenesis of SLO are controversial and have not been completely elucidated.[4] In a study with Gordon Setters, dog leukocyte antigen (DLA) class II alleles associated with the disease and negatively correlated with the disease were described, suggesting a genetic predisposition.[9] A case series reported the detection of antinuclear antibodies in 3/10 Gordon Setters with SLO, suggesting that SLO may be an auto-immune disease.[2] Nevertheless, some authors believe that the histopathological findings of SLO, characterized by lichenoid-interface dermatitis and basal cell vacuolation/damage affecting the claw represent a tissue response pattern to different conditions and not a separate entity.[4] For instance, lesions affecting the claws with similar histopathological findings to those of SLO have been reported in cases of leishmaniasis, even when amastigotes were not detected in the affected tissue.[3]

The diagnosis of SLO is usually based on the clinical presentation with the disease restricted to the claws/digits and typical histological findings.[4] Distal onychectomy (third phalanx [P3] amputation) has been considered the gold standard method to diagnose SLO. An alternative technique, onychobiopsy without onychectomy, was employed in this case.[5] Through this technique, only a portion of the lateral claw matrix is collected, and no amputation is necessary; however, some downsides include the fact that localized lesions may be missed.[5] Other systemic diseases may affect the claws, including systemic lupus erythematosus, hepatocutaneous syndrome, pemphigus vulgaris, and bullous pemphigoid, leading to potentially overlapping gross or microscopic findings; however, other cutaneous or systemic lesions are expected with these diseases.[4,7]

Several treatments for SLO have been reported with variable success, including supplementation with omega-3 and omega-6 essential fatty acids (EFA), as well as combinations of EFA with other therapies such as topical glucocorticoids, pentoxifylline, and tetracycline/niacinamide.[1,4,6] In this case, the

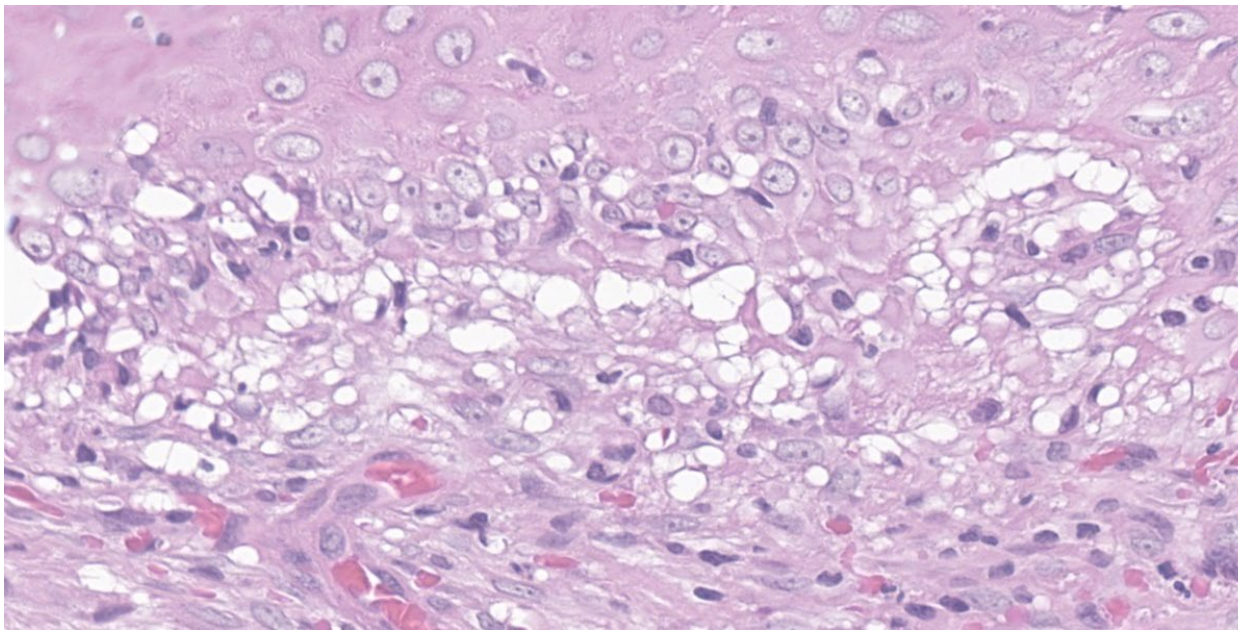

Figure 4-3. Nailbed, dog. There is loss of a discrete dermoepidermal junction and infiltration of the basal layers of the vacuolated germinative epithelium by lymphocytes (cytotoxic interface dermatitis). (HE, 695X)

patient showed significant clinical improvement after treatment with pentoxifylline, vitamin E, and omega EFAs.

Contributing Institution:
Auburn University
Department of Veterinary Pathobiology
https://www.vetmed.auburn.edu/academic-departments/dept-of-pathobiology/

JPC Diagnosis:
Nailbed: Onychitis, lymphocytic, cytotoxic interface, marked.

JPC Comment:
A clinical history of loss of one or more claws on multiple paws within 2 weeks to a few months after initial onset should suggest a diagnosis of SLO.[8] Regrown nails are typically misshapen and friable and will re-slough. The sequence of onychomadesis followed by onychodystrophy is required for an SLO diagnosis and differentiates this condition from idiopathic onychodystrophy of dogs, where there is no onychomadesis preceding onychodystrophy.[8] In addition, SLO lesions are restricted to the claw and no skin or mucosal lesions occur.[8]

The contributor provides an excellent overview of this uncommon condition, and the case presented here is characteristic of the disease. The examined slide exhibits the typical histologic features of SLO - lymphocytic interface dermatitis with basal cell vacuolation, apoptosis, and pigmentary incontinence – though the interface dermatitis can vary widely in severity.[8] Typical histologic findings may also be found in conjunction with superimposed bacterial infections and osteomyelitis.[8] These histologic findings are relatively non-specific and can be found in a variety of diseases of the canine claw, making clinical history paramount in the diagnosis of this condition.

The moderator began by reviewing claw anatomy and the specialized terminology used to describe nail pathology (see Table 4-

1). The moderator emphasized that SLO requires lesions in all paws and (almost) all claws; if a patient has the same clinical presentation but with only one affected nail, the moderator would prioritize onychomycosis as a differential diagnosis. The moderator uses a PAS stain to rule in or out onychomycosis as fungal elements are largely impossible to visualize on H&E sections of the claw.

Several participants questioned whether the clefting noted in the examined section is real or artifactual. While clefting can be an artifact caused during tissue collecting and processing, it can also be real and diagnostically helpful since clefting at the epidermal-dermal junction would be expected to occur in this condition. The moderator believes that the clefting present in this section is real due to the hemorrhage and cellular debris present within the cleft. The moderator also noted that the examined section is an exceptional example of cytotoxic interface dermatitis. The moderator showed more typical examples with less florid inflammatory infiltrates and less affected basilar epithelium.

The JPC morphologic diagnosis was once again whittled down to the essentials. While the original morphologic diagnosis contained many of the same histologic features enumerated in the contributor's diagnosis, conference participants felt that many of the terms, such as basilar cell vacuolation, apoptosis, and pigmentary incontinence, were subsumed within the term "cytotoxic interface onychitis." The resulting morphologic diagnosis is zippy, accurate, and mercilessly brief.

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