



WEDNESDAY SLIDE CONFERENCE 2019-2020

Conference 11

4 December 2019

Conference Moderator:

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CASE I: S17-1101 (JPC 4116937).

Signalment: 4-year-old spayed female Bernese mountain dog (*Canis familiaris*).

History: The animal had a one year history of skin changes including multifocal alopecia, crust formation and discolorations, whose underlying cause could not be identified. The animal had been treated with high doses of dexadreson and cyclosporine, resulting in a mild and slow improvement of the skin lesions. Two weeks before death the animal started limping and a rupture of the cruciate ligament was suspected. The animal was euthanized because of the questionable prognosis of the skin lesions in combination with the cruciate rupture and recurrent episodes of fever of unknown origin (temperature >39.8°C).



Haired skin, dog. Around the bridge of the nose, the mouth and eyes, there are multiple sharply circumscribed partially hairless areas with severe crust formation. (Photo courtesy of: Institute of Veterinary Pathology, Vetsuisse Faculty (University of Z Zurich), Winterthurerstrasse 258, CH-8057 Zurich, Fax number +41 44 635 89 34, <http://www.vetpathology.uzh.ch>)

Gross Pathology: On both sides of the trunk extending to the axillas and groin, on the nasal bridge, on the ears, and around the



Haired skin, dog. Around the bridge of the nose, the mouth and eyes, there are multiple sharply circumscribed partially hairless areas with severe crust formation. (Photo courtesy of: Institute of Veterinary Pathology, Vetsuisse Faculty (University of Z Zurich), Winterthurerstrasse 258, CH-8057 Zurich, Fax number +41 44 635 89 34, <http://www.vetpathology.uzh.ch>)

eyes and mouth, there were multiple, sharply demarcated, hairless or partially hairless areas of skin with brown to grey discoloration and crust formation. Around these hairless areas, the fur was clotted with crusty, brown material. Bilaterally adjacent to the caudal aspect of the tongue, there were red, papillary masses of soft tissue and approximately 1 x 2 x 0.5 cm observed (histologically identified as chronic-active necrotizing and suppurative inflammation with granulation tissue formation). On the left cheek, there was a pale yellow, soft mass in the subcutis (lipoma). On the right knee joint the drawer test was positive with increased mobility of the joint. The joint was filled with turbid, slightly flocculent synovial fluid and both anterior and posterior cruciate ligaments were ruptured (right sided complete cruciate ligament rupture with secondary chronic multifocal gonitis on the right side with follicle formation). The liver was markedly enlarged and displayed round edges (diagnosed histologically as steroid induced hepatopathy).

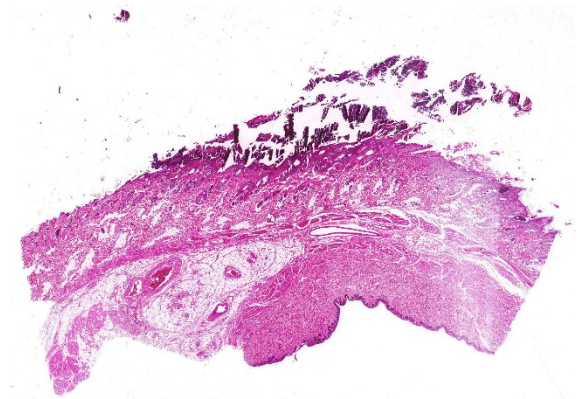
In the right cranial lobe of the lung, there was a firm, poorly demarcated structure palpable in the parenchyma. On the serosal surface of the left middle lobe, there were multiple plaque-like, sharply circumscribed, brown depositions of material observed (histologically identified as multifocal calcifications of pulmonary basal membranes with reactive histiocytic inflammation).

Laboratory results:

Ultrasound and radiography: no abnormalities detected. Hematology/blood chemistry: no abnormalities detected

Microscopic Description:

All layers of the epidermis and also the follicular infundibular epithelium contain rounded, hypereosinophilic keratinocytes with pyknotic nuclei (apoptosis). Multifocally, apoptotic keratinocytes are surrounded by lymphocytic infiltrations (satellitosis). Within the epidermis there are multifocal accumulations of neutrophils, separating the superficial from the deeper

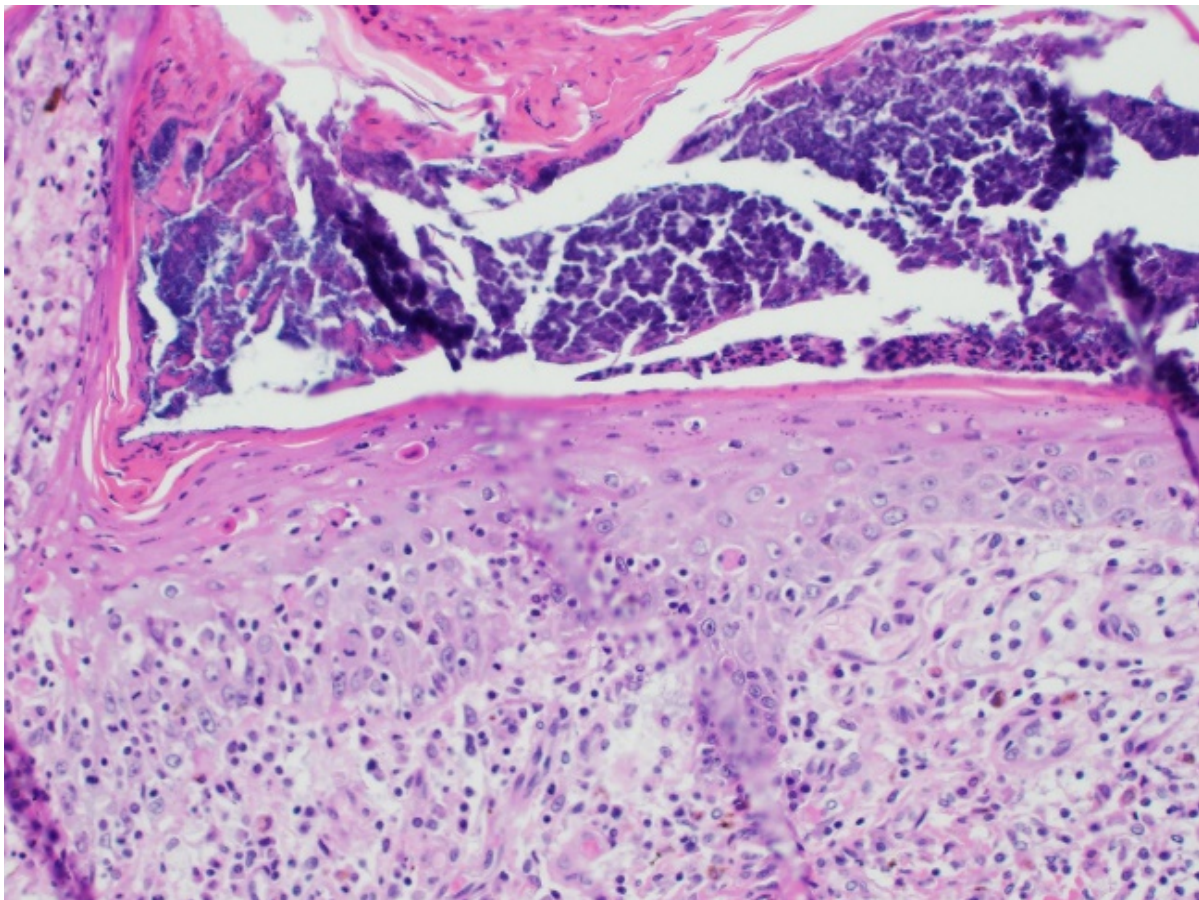


Haired skin, dog. The submitted section of haired skin contains a focally thickened area of epidermis with a hypercellular area of suppurative dermatitis. (HE, 7X).

epidermal layers (interpreted as pustule formation). The superficial dermis and the dermo-epidermal junction show ribbon-like, severe infiltrations of lymphocytes, plasma cells and fewer macrophages, separating the dermo-epidermal junction into areas which are variably clearly visible or severely obscured. Lymphoid infiltrates are observed in the basal layer and macrophages containing brown pigment (melanin) are visible in the dermis (melanin incontinence). Multifocally the stratified layer is thickened and multifocally nuclei can be observed also in the superficial keratinocytes (parakeratotic and orthokeratotic hyperkeratosis). Furthermore, the epidermal surface is covered by serocellular crusts and

accumulations of (partially degenerate) neutrophils. In the superficial areas, low numbers of thick-walled, round structures with a clear center and approximately 5- 10 μm in diameter (interpreted as *Candida* spores) are observed. The neutrophilic infiltrates extend multifocally deep into the dermis or into the hair follicles (secondary suppurative pyoderma and folliculitis).

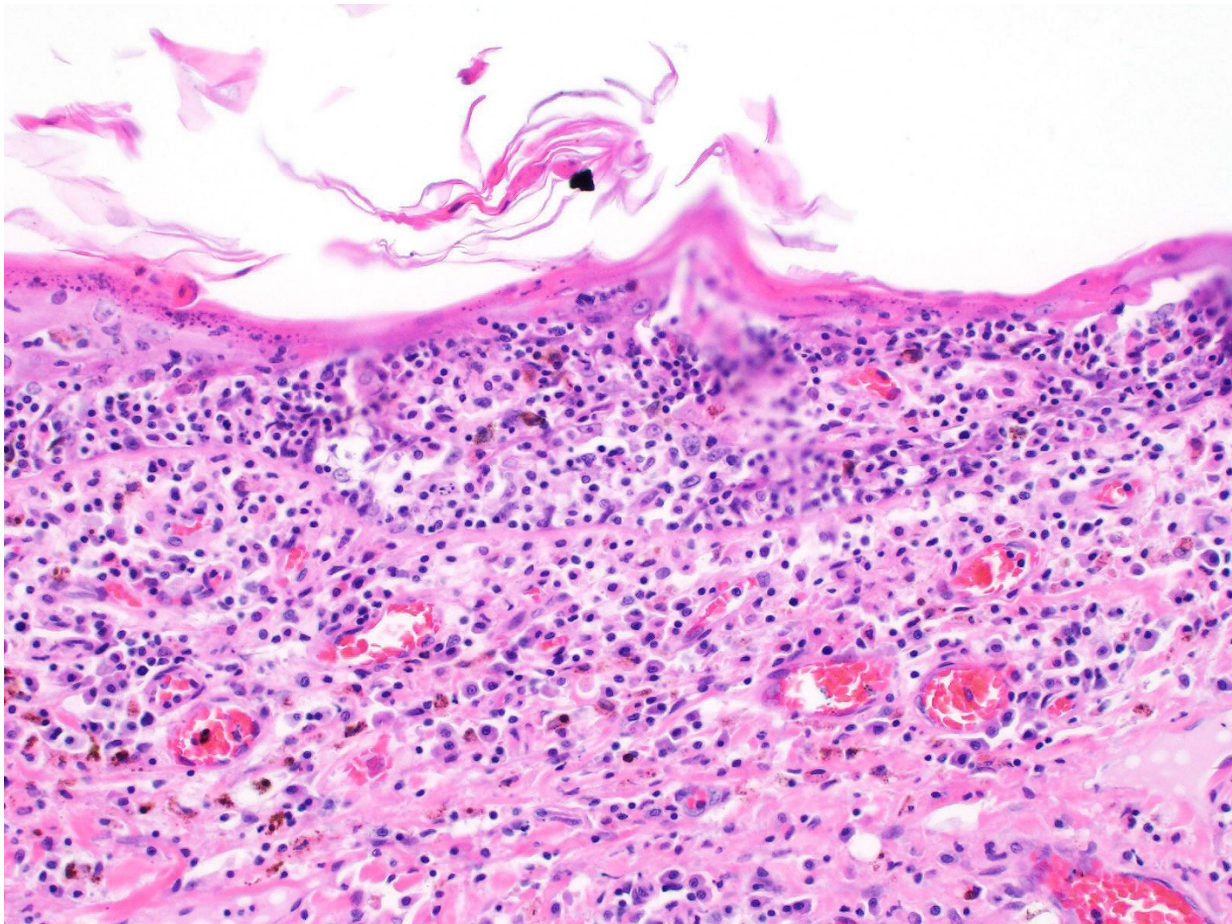
Contributor's Morphologic Diagnosis: Skin, chronic multifocal to coalescing interface dermatitis, with apoptotic keratinocytes, lymphocytic satellitosis and with secondary crust formation, parakeratotic hyperkeratosis, suppurative pyoderma and folliculitis (consistent with erythema multiforme)



Haired skin, dog. The submitted section of haired skin contains a focally thickened area of epidermis with a hypercellular area of suppurative dermatitis. (HE, 7X)

Contributor's Comment: Erythema multiforme is a rare skin disease in dogs and cats and has also been described in horses, cattle, swine, ferrets and anecdotally in goats.^{3,6,7} The nomenclature and definitions of erythema multiforme (EM), Stevens-Johnson syndrome (SJS) and toxic epidermal necrosis (TEN) in veterinary literature are conflicting and therefore confusing.^{7,8} In human medicine, EM, SJS and TEN were considered to be different severities of the same disease. Nowadays it is accepted that EM and SJS/TEN represent separate conditions.⁸

The pathogenesis of erythema multiforme in animals is still poorly understood.^{3,6,7,8} Possible etiologies include adverse drug reactions (CADR), e.g. against sulphonamides, other antibiotics, and levamisole. Neoplasia, food (including commercial dog food and beef/soy diet), nutraceutical products and infections are reported triggers for erythema multiforme in canine patients.^{3,4,6,7,8} However, proven causalities by re-challenge are rare and a multicentric study revealed that only 19% of the canine EM cases were drug related.⁵ The histological characteristics and pattern indicate a misdirected immune response against keratinocytes, which is lymphocyte-



Haired skin, dog. The epidermis is infiltrated by large numbers of lymphocytes and macrophages. (HE, 400X).

mediated with direct cytotoxicity of target cells.^{6,8}

Clinical lesions

In dogs, lesions are normally bilateral and involve the trunk, groin and axilla and also the inner pinna, footpads and mucocutaneous junctions.^{3,8} Canine and feline lesions consist of erythematous macules, papules and plaques. Lesion borders are indurated and lesion centers are clear with discolorations to cyanotic or purpuric. Central crusting of lesions is common, but in canine patients this may extend to heavily crusted and/or scaly plaques.^{7,8}

Histology – typical lesions

Microscopic lesions in canine erythema multiforme are similar to those in human patients.^{3,8} Classic lesions include interface dermatitis, with cell death occurring in all epidermal (suprabasilar and basal) layers, accompanied by satellitosis (lymphoid infiltrates around apoptotic keratinocytes).^{3,6,7,8} Intraepidermal mononuclear cells are mainly lymphoid, but Langerhans cells have also been identified.^{3,8} In canine patients the follicular infundibular epithelium is regularly affected and hyperkeratosis and parakeratosis are common, which is not the case in human patients.^{3,7,8} Yager et al. further suggest that hydropic degeneration of the basal layer may not be such a prominent feature in canine patients compared to humans.⁸

Diagnosis and differential diagnoses

Erythema multiforme in the dog includes a wide range of clinical lesions, leading to a long list of differential diagnoses such as urticaria, demodicosis, dermatophytosis, bacterial folliculitis, superficial spreading pyoderma and bullous autoimmune skin diseases.^{3,7,8} The presence of scaling-crusting lesions additionally includes superficial necrolytic dermatitis, zinc-responsive dermatoses or other cornification disorders as possible differential diagnoses.^{3,8} Diagnosis of canine erythema multiforme therefore is often based on a combination of anamnesis, gross, and histological findings.^{3,6} Yager et al. emphasize the importance of taking the anamnesis and gross lesions into consideration when giving a diagnosis of erythema multiforme.⁸

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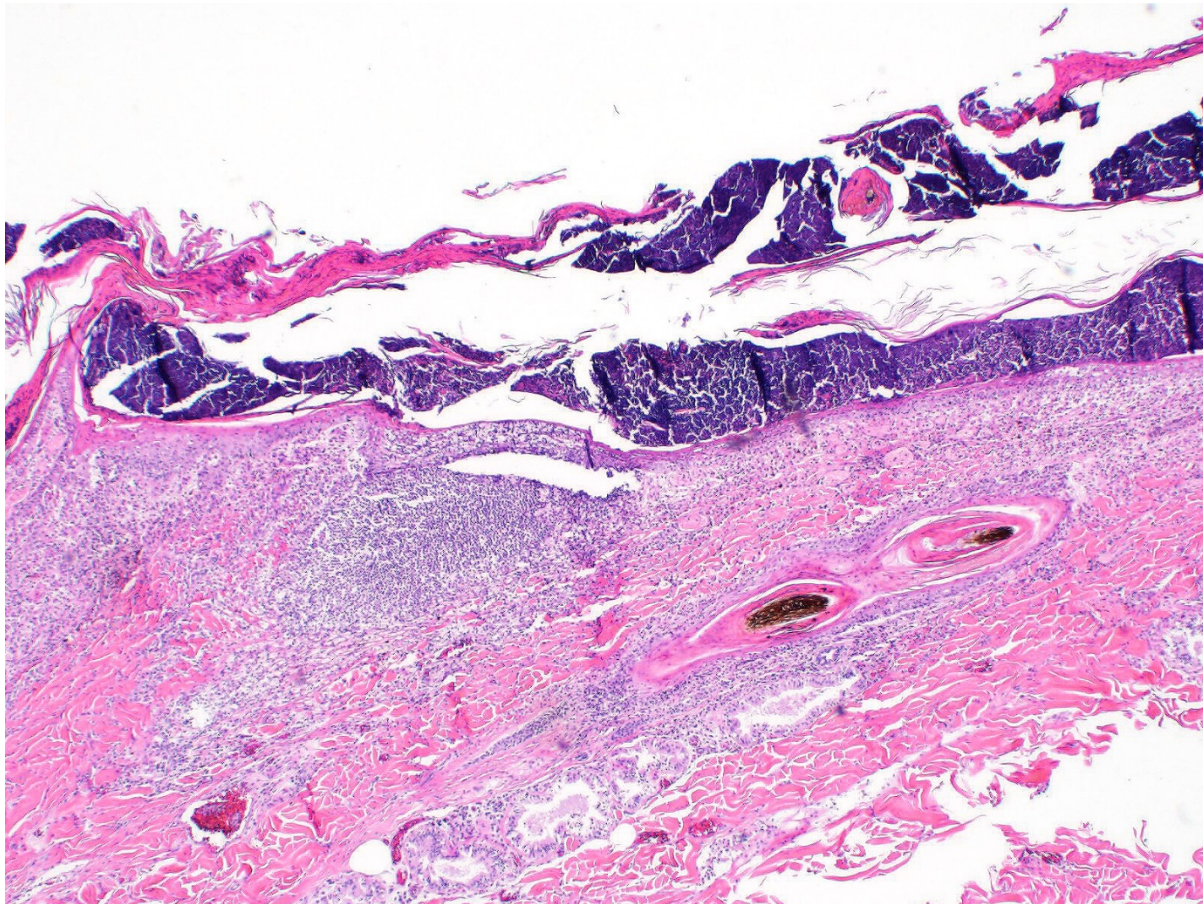
- JPC Diagnosis:** 1. Haired skin: Dermatitis, interface, lymphohistiocytic, diffuse, moderate, with transepidermal and follicular keratinocyte apoptosis.
2. Haired skin: Dermatitis, suppurative, multifocal to coalescing, severe, with diffuse moderate ortho- and parakeratotic hyperkeratosis and bacterial cocci.

JPC Comment: The contributor has compiled an excellent overview of the three entities of erythema multiforme, Stevens-Johnson syndrome (SJS) and toxic epidermal necrosis (TEN), syndromes about which there remains to this day a lot of disagreement in the veterinary literature. Comparison with the human disease has advanced knowledge in these chronic and occasionally fatal syndromes and provided an excellent starting point, but the differences in the human disease and its veterinary counterpart are profound as well. Moreover, the literature lacks a critical number of well-documented cases of these diseases, and many of the cases in the older literature may, upon further review in light of more recent advances in veterinary

dermatology, may have been incorrectly diagnosed.

In spite of significant disagreement in the veterinary literature from the last decade on these uncommon diseases, there are considerable points of agreement (many already mentioned by the contributor, but worthy of mentioning again):

1. Erythema multiforme (EM) and STS/TEN represent independent and different diseases, rather than opposite poles of a spectrum of immune-mediated disease.
2. Both EM and STS/TEN are mediated at least in part (STS/TEN) or in toto by cytotoxic lymphocytes directed against altered keratocyte antigens.



Haired skin, dog. The epidermis is infiltrated by large numbers of lymphocytes and macrophages. (HE, 400X).

3. There is considerable overlap in the histologic diagnosis of these diseases, and these findings must be closely correlated with clinical findings and history for a definitive diagnosis.
4. The histologic diagnosis of erythema multiforme is not a straightforward diagnosis and bears a number of differential diagnoses that should be considered before this diagnosis is rendered.

The reliable diagnosis of EM via STS/TEN has been confusing in both human and veterinary medicine for years. Early attempts at classification of these diseases⁵ were based on human schema and proposed classification on five categories: type of skin lesions, distribution, mucosal involvement, systemic signs, and precipitating factors. Areas of significant variation include types of lesions (in which epidermal detachment is useful for identifying STS/TEN) and mucosal involvement (in which an absence of mucosal involvement is seen only with EM. It may, however be seen with EM, so its presence is not of diagnostic utility). On a purely academic note, one of the few differentiating factors between Stevens-Johnson syndrome (STS) and toxic epidermal necrolysis (TEN) (and likely the reason that they are so often lumped together) is that STS should have <10% epidermal detachment) and TEN >30%. Regarding mucosal involvement, several classifications have tried to characterize mucosal involvement, either due to severity or the number of mucosal sites affected, but this criteria is still under evaluation.^{1,8} Significant overlap occurs in the remaining categories.

There is also significant disagreement and uncertainty yet remaining in the exact pathogenesis of the lesions in EM and STS/TEN. EM is characterized by lymphocytic targeting of individual keratinocytes, which SJS/TEN lesions are lymphocyte poor, with extensive areas of epidermal necrosis and lifting. Early SJS/TEN lesions resemble the pattern seen in EM, while later lesions with large confluent areas of necrosis suggest a progression to either waves of apoptosis,⁸ soluble mediators of inflammation such as reactive oxygen species, granulysin, and soluble Fas ligand or programmed cell death (necroptosis) A recent publication established the death of keratinocytes in TEN to be an apoptotic event, as seen in its human counterpart², but this does not explain the complete pathogenesis of this disease.

As complex as the diagnosis of STS/TEN may be, the correct diagnosis of erythema multiforme may be even more complex due to the variable histologic presentation and potential differential diagnosis. Lymphocytic-driven keratinocyte apoptosis at all levels of the epidermis and indeed, full-thickness epidermal necrosis may also be seen in EM lesions. The potential for hyperkeratosis in EM cases (also known as “hyperkeratotic” or “old dog” EM also brings cornification or clinical scaling disorders into the differential diagnosis.⁸ Moreover, cases complicated by other secondary bacterial diseases or opportunistic infectious agents (as illustrated by this particular case) pose an additional diagnostic challenge.

The moderator stressed the importance of a good history as well as an optimal sample (often from the center of the lesion in which devitalization and lesion development in the differentiation of EM/SJS/TEM on surgical biopsy. As these three lesions may also resemble each other on a single biopsy sample, in the absence of a good history and clinical distribution of lesions, the prudent surgical pathology may withdraw to a conclusion that the biopsy likely is within the EM/SJS/TEM spectrum, but refrain from the desire to place it in one of the three categories. In the cat, exfoliative dermatitis associated with thymoma (and even a few without) may also present as a cytotoxic dermatitis which resembles EM.

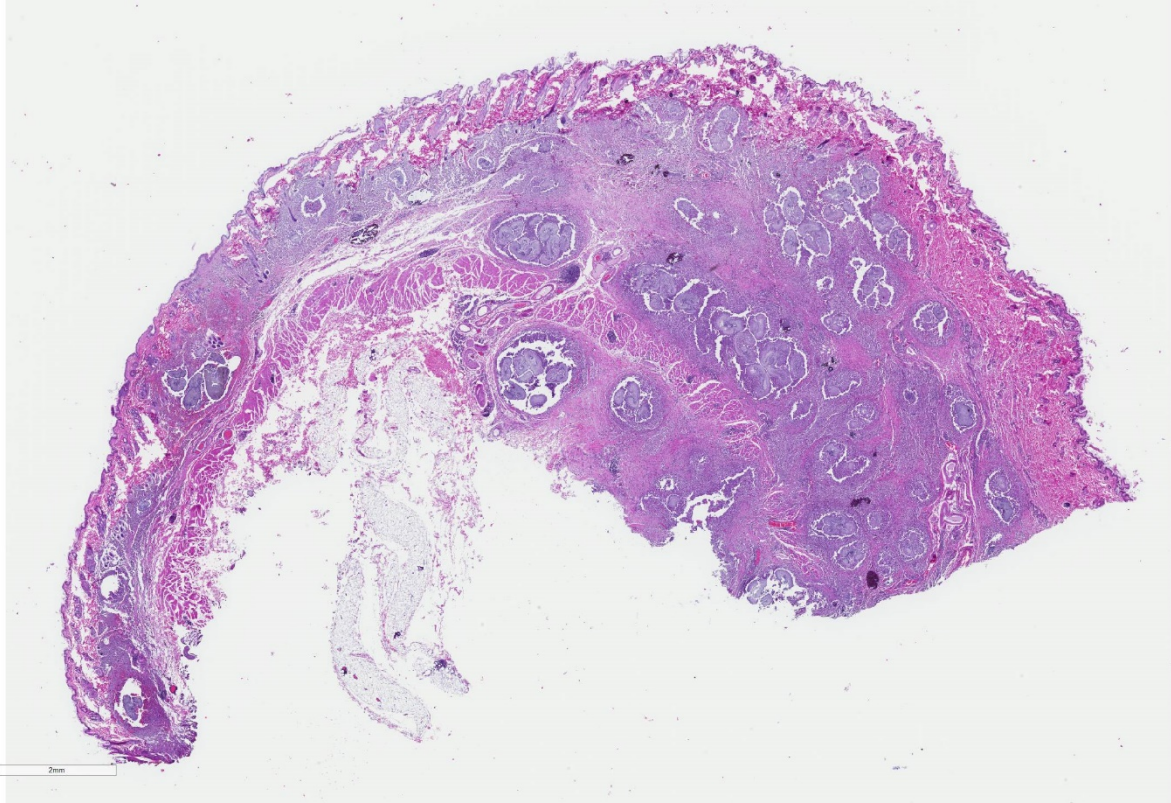
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CASE II: WSC-SC-2 (JPC 4114031).

Signalment: 7 year old, male neutered Munchkin, *Felis catus*



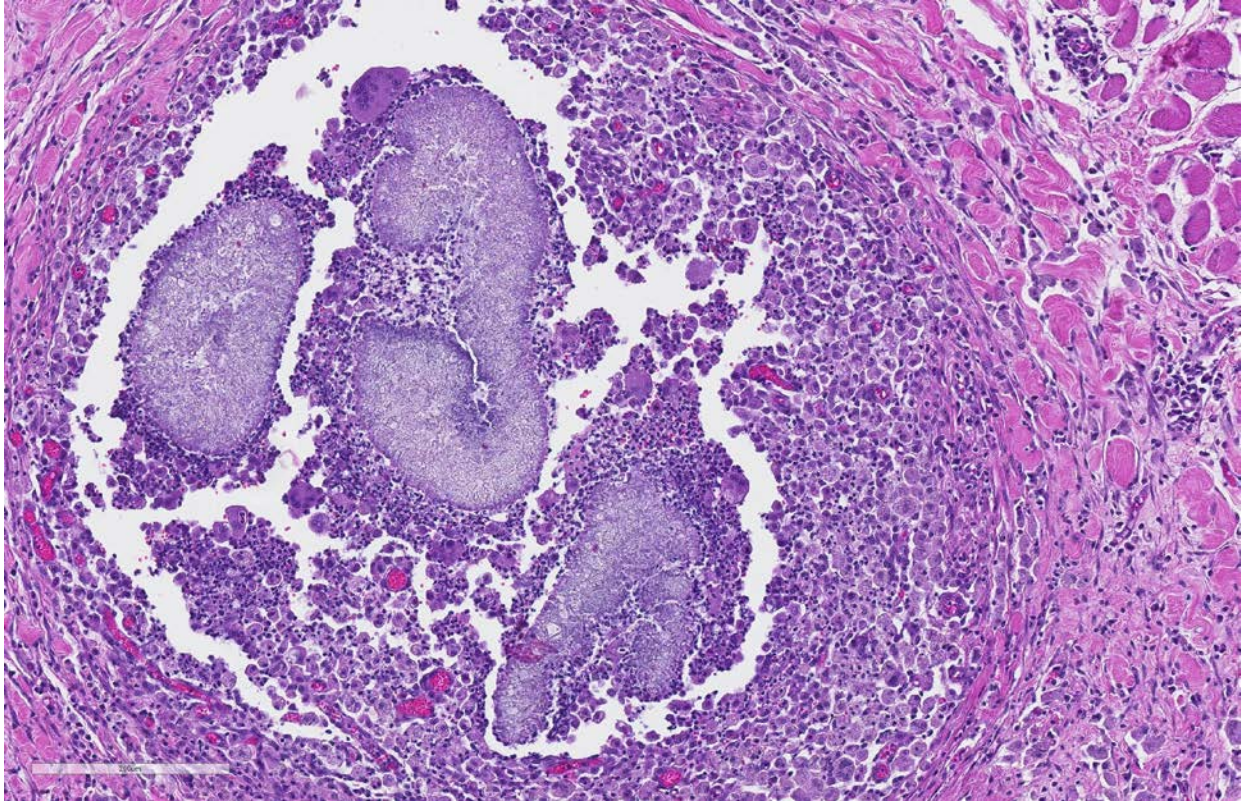
Haired skin and subcutis, cat. The superficial and deep dermis is expanded with large grains surrounded by a rim of inflammatory cells and fibrous connective tissue (HE, 7X)

History: Since birth, the patient has suffered from chronic dermatophytosis, which was diagnosed on histopathology when the cat was approximately 1 year old. The cat was treated with ketoconazole and lime sulfur dips. Since then, the cat intermittently developed raised, alopecic skin lesions that would wax and wane without treatment. Four months prior to the current submission, the cat had lost 40% of his body weight and had intermittent vomiting. Physical examination revealed multiple mammary nodules. A complete left chain mastectomy was performed and submitted for histopathologic examination.

Gross Pathology: Two sections of formalin fixed pigmented haired skin with subcutis and mammae. The dermis and subcutis was markedly thickened and nodular around the teats. When sectioned, the tissue was firm and mottled light tan and brown.

Laboratory results:

Bloodwork and cytology was performed by the referring veterinarian. Bloodwork



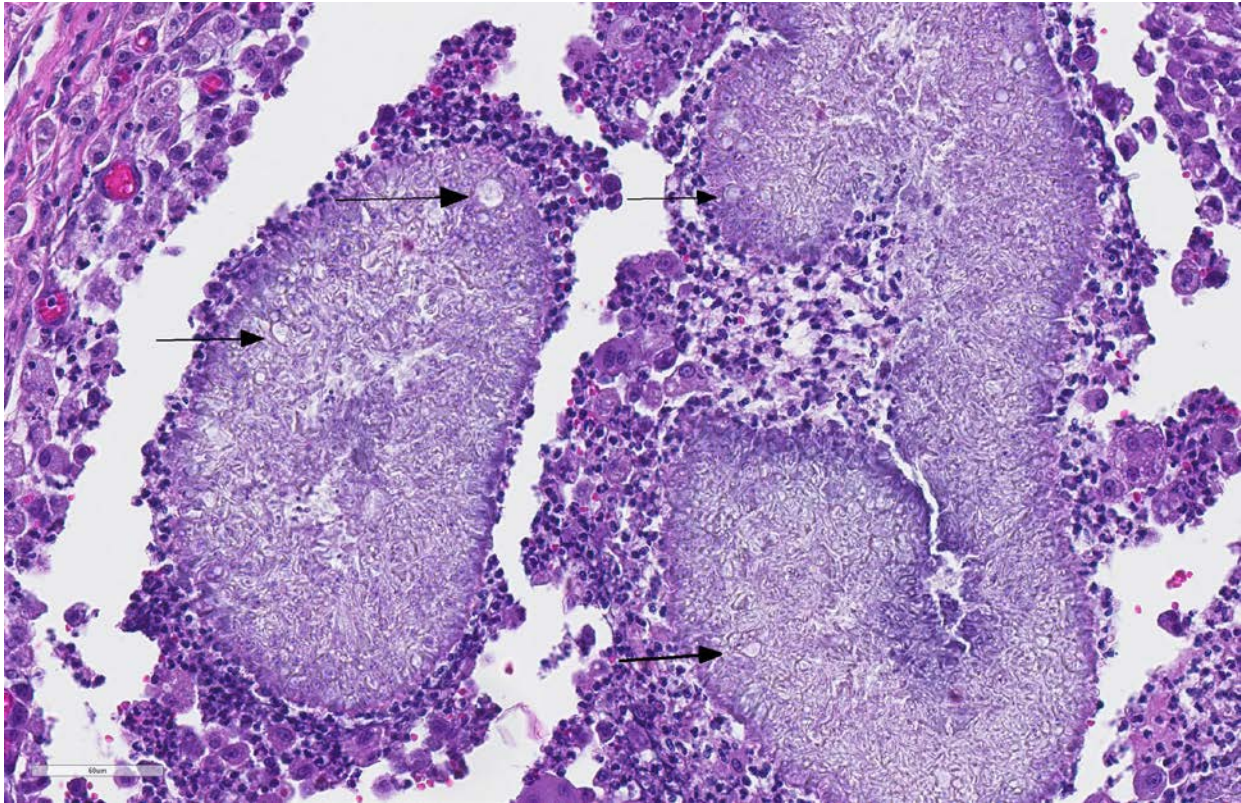
Haired skin and subcutis, cat. Higher magnification of “grains” (fungal hyphae enmeshed in antigen-antibody complexes), and surrounded by macrophages, neutrophils, and rare giant cells. (HE, 180X)

revealed elevated liver values. Cytology of a mammary nodule was suggestive of adenocarcinoma.

Microscopic Description:

The sections of lightly pigmented, haired skin have intense nodular and diffuse infiltrates extending from the deep dermis into the subcutis that often efface the dermis and subcutis. The nodules are composed of large mats of hyphae embedded in granular eosinophilic material that is slightly radiating and forms irregularly-shaped tissue grains (Splendore-Hoeppli material). The hyphae are often tangled and irregularly

arranged, are approximately 5-7 micrometers in diameter, have parallel walls with frequent bulbous dilations, are septate and have rare acute-angle branching. The mats of hyphae and Splendore-Hoeppli material are surrounded by many foamy and epithelioid macrophages, Langhans and foreign body-type multinucleated giant cells and neutrophils. Some large nodules have a thin peripheral rim of fibrous tissue containing moderate numbers of fibroblasts. Many macrophages and multinucleated giant cells are moderately to markedly distended with abundant amorphous to globular material that stains intensely eosinophilic with a PAS histochemical stain and black with GMS histochemical staining (presumptive dermatophyte remnants). On H&E sections this phagocytized material is



Haired skin and subcutis, cat. Higher magnification previous field, demonstrating a better view of aggregated fungal hyphae and dilated terminal swellings (arrows). (HE, 400X)

clear with pale eosinophilic hyphal margins. Within lower numbers of macrophages and multinucleated giant cells there are fragments of hyphae with parallel walls, bulbous dilations, and septae. Also within the nodular to diffuse infiltrate there are often small moderate-sized aggregates of mineralized material that contain abundant, similar hyphae. Areas of mineralization are most common within the superficial margins of the infiltrate. Within tissue that is not effaced, there are nodules composed of many lymphocytes and few plasma cells and macrophages surrounding blood vessels in the deep dermis and subcutis. There is a clear line of demarcation between the nodular to diffuse infiltrate within the deep dermis and superficial dermis. Within the superficial dermis there are perivascular and

interstitial infiltrates composed of lower numbers of lymphocytes, plasma cells, mast cells and few neutrophils. The overlying epidermis has an irregular, papillated appearance and there is mild to marked basket-weave and compact orthokeratotic hyperkeratosis. PAS and GMS histochemical stains do not reveal hyphae along the epidermal surface or within follicles.

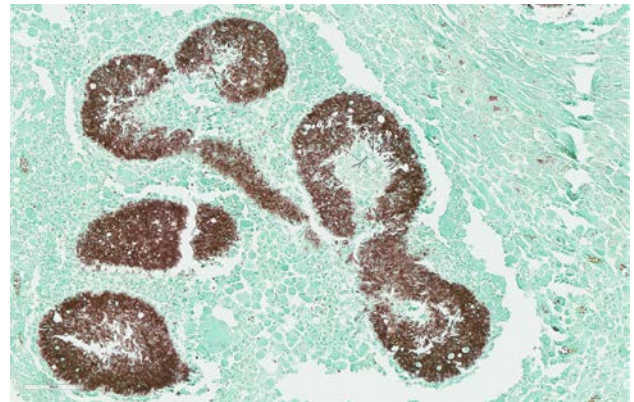
Contributor's Morphologic Diagnosis:

Dermatitis, pyogranulomatous, multifocal and focally extensive, chronic, severe, with myriad fungal hyphae embedded within Splendore-Hoeppli material, deep dermis and subcutis of the ventral abdomen.

Contributor's Comment: The histologic findings were most consistent with dermatophytic pseudomycetoma. Dermatophytic pseudomycetomas are deep dermal to subcutaneous atypical dermatophyte infections with nodules that frequently ulcerate and form draining tracts. Pseudomycetomas have been reported to range from 1-8 cm in diameter and can mimic neoplasia, as in this case.^{4,5,7} Initially, the nodules are small and non-painful, so disease is often chronic before detections, particularly in long-haired cats. Dermatophytic pseudomycetoma is most commonly caused by *Microsporum canis* and has almost exclusively been reported in Persian cats and to lesser extent Himalayan cats.^{5,7,9} The lesions have been reported to occur with or without a history of skin trauma and occur more commonly on the head, neck, dorsum, tail, flanks or limbs,^{5,7} and lesions on the ventral abdomen are uncommonly reported.⁵ The granules present within the tissue and fistulous tracts have been described as white, yellow, or light brown.⁵

The histomorphology of hyphae in tissue alone is an inaccurate method to identify fungi/dermatophytes and culture and/or PCR are needed for definitive diagnosis. Unfortunately in this case, fresh tissue was not obtained at the time of surgery, as neoplasia was suspected, and an infectious etiology was not on the referring veterinarian's differential list because of the clinical presentation and fine needle aspirate results. We did submit formalin fixed paraffin embedded (FFPE) tissue for pan-fungal PCR, and despite the large numbers of hyphae within the lesions, PCR failed to

identify the organisms. In a case report of four cats with dermatophytic pseudomycetomas, PCR performed using FFPE tissue failed to identify the dermatophytes one of the two cases in which *Microsporum canis* was confirmed with culture, and in two of the cases that had characteristic lesions, but in which tissue was not submitted for culture.⁵



Haired skin and subcutis, cat. Dermatophyte hyphae stain strongly with a Grocott's methenamine silver (GMS, 271X)

Dermatophytic pseudomycetomas are very similar to true eumycotic mycetomas as the organisms are present in tissue as grains or granules, however there is a difference in the formation of the granules in that there is less amorphous eosinophilic material (cement-like substance) within the grains in mycetomas, and more Splendore-Hoeppli material is present in pseudomycetomas.^{7,9} Pseudomycetomas are formed by dermatophytes and bacteria that are not members of the Actinomycetales order.⁹

The pathogenesis of dermatophytic pseudomycetoma is unclear, and most reported cases lack the history of trauma preceding the development of the lesions. It is believed that furunculosis resulting from

typical dermatophyte infections may lead to the migration of dermatophyte hyphae into the deep dermis and subcutis, followed by development of pseudomycetomas.^{5,6} An underlying immunosuppression or a selective immunodeficiency is thought to underlie the susceptibility of Persian cats to conventional dermatophytosis and dermatophytic pseudomycetoma.^{5,7} Others have hypothesized that long-haired cat breeds, such as Himalayan and Persian cats may be more susceptible due to incomplete grooming of the hair coat and long hair, which may predispose to more chronic dermatophytosis and furunculosis.^{5,6} In this case, although there was a chronic history of dermatophytosis in this cat, there was no histologic evidence of dermatophytosis in the dermis, epidermis and hair follicles. There has been one case report, of intra-abdominal dermatophytic granulomatous peritonitis in a Persian cat.⁴ The authors in this case report hypothesized that generalized dermatophytosis at the time the cat was spayed may have led the inoculation of dermatophyte hyphae in to the abdomen, despite the surgery occurring several years prior to diagnosis. The significant weight loss, vomiting, and increasing liver values in his cat, raises the possibility of systemic involvement. One thought we had was that the body confirmation of this cat breed with very short legs could have been a predisposing factor for the development of these pseudomycetomas, possibly due to traumatic furunculosis that could be more common in a Munchkin cat with chronic dermatophytosis, due to an increased likelihood of contact to the ventral abdomen

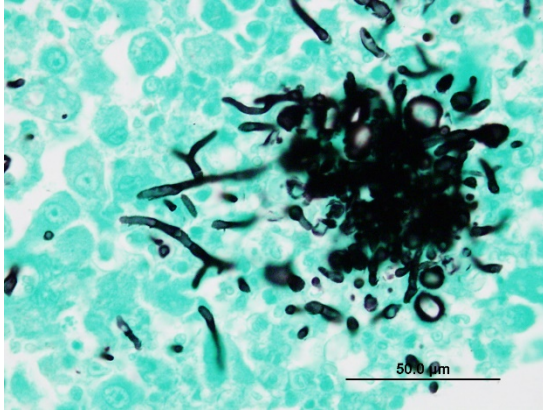
against contact surfaces during play, etc due to the short stature of the breed.

Treatment of dermatophyte pseudomycetomas in cats is difficult with variable responses to anti-fungal medications alone.^{4,5,6,10} It has been suggested that wide surgical excision and concurrent treatment with oral itraconazole prior to and after wide surgical excision are beneficial in the treatment of dermatophytic pseudomycetoma with results ranging from long-term disease free interval prior to recurrence to presumptive clinical cure of up to 2 years and 8 months at the time of publication.⁵ In another paper the use of oral terbinafine resulted in resolutions of dermatophytic mycetomas in two cats. One cat's (Persian) clinical signs require continual pulse therapy of the drug as the lesions recurred after complete discontinuation. The other cat had no recurrence for 28 months after discontinuation of the medication at the time of publication.² Dermatophytic pseudomycetoma has been rarely been reported in dogs, with reported cases occurring in a Manchester Terrier, two Yorkshire Terriers, and a Chow Chow.^{1,7}

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JPC Diagnosis: Haired skin and subcutis: Pyogranulomas, multiple, with dermal fibrosis, Splendore-Hoeppli material,



Haired skin and subcutis, cat. Higher magnification of the argentaaffinic fungal hyphae, demonstrating parallel walls, dichotomous branching, septation, and terminal bulbous swellings. (GMS, 1000X) (Photo courtesy of: University of Florida, College of Veterinary Medicine, Department of Comparative, Diagnostic, and Population Medicine, <http://cdpm.vetmed.ufl.edu/>)

and numerous intradermal fungal hyphae (pseudomycetoma).

JPC Comment: The contributor has done an outstanding job on describing this uncommon finding in cats, and even more rare in other veterinary species. The terminology of this condition continues to be confusing, with mycetoma, eumycotic mycetoma, actinomycotic mycetoma, bacterial mycetoma, and pseudomycetoma all floating around in the literature.

A mycetoma contains three distinguishing features: 1) the formation of a nodular fibrotic inflammatory lesion, 2) formation of draining tracts, and 3) the grossly visible presence of fungal or bacterial grains.^{3,4} When bacteria are at the center of the grains, the term bacterial mycetoma may be applied.¹¹ More specific bacterial terms may be utilized, such as “actinomycotic mycetoma” in cases of subcutaneous infection with *Actinomyces*, *Nocardia*, and *Actinmadura* spp.² Eumycotic mycetomas

are caused by species of true fungi (non-dermatophyte), which are enmeshed in “grain cement” which contains melanin, proteins, and lipids.²

The usage of the term pseudomycetoma is somewhat less well-defined. In humans, pseudomycetomas are smaller, do not form draining tracts, and are often on parts of the body other than the feet.³ Bacterial cultures are usually negative. The material that binds the hyphae into grains is Splendore-Hoeppli material, which may be composed of antigen-antibody complexes, major basic protein, or both.³ In the veterinary literature, the term pseudomycetoma is used to describe mycetomas resulting from dermatophyte infection of subcutaneous tissue, while in other publications the term is used to describe fungal species that have been traumatically implanted (most of which are dermatophytes as well). Many authors now prefer the term “dermatophytic pseudomycetoma” which provides both agent and method of traumatic implantation to deep tissues.^{6,7,8} It should be pointed out that dermatophytic pseudomycetoma is a separate (and disparate) disease from superficial dermatophytic infection.³

In humans, mycetomas are considered endemic in certain parts of the world within the so-called “mycetoma belt” which included India, Sudan, and Mexico.² These forms of deep fungal infection are true mycetomas, without representation from dermatophytes. The mycetomas in question are most often seen in the feet, with disfiguring lesions, multiple draining sinuses, and variably colored and shaped

grains. Deep surgical excision of of grains under aseptic conditions is important in diagnosis, as direct visualization and culture of fungal hyphae within the grains is paramount.² Grains that wash out through draining tracts are not considered appropriate for diagnosis. Serodiagnostic test have proved valuable in certain instances, and PCR testing of grains shows great promise in parts of the “mycetoma belt” where they have been employed.²

The moderator also noted the bulbous swellings on the end of the hyphae within the deep dermis. While usually seen in dermatophytic mycelia, these "chlamydiospore-like" structures are also seen in pseudomycetomas for unknown reasons. In vary rare cases, in Persian cats, the sexual stage of *Microsporium canis*, *Arthrosporum canis*, has been isolated.

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Presentation, cat. The cat is cachectic, and the skin of the abdomen, ventral thorax, flanks and legs, is thin, smooth, and reddened. (Photo courtesy of: Unité d'Histologie et d'Anatomie pathologique, BioPôle Alfort, Département des Sciences Biologiques et Pharmaceutiques, Ecole Nationale Vétérinaire d'Alfort).

CASE III: H18-0008-92 (JPC 4122525).

Signalment: Unknown age (adult), european, male neutered, cat (*Felis catus*).

History: This cat was found dead in the street by a passerby and brought to the *Centre Hospitalier Universitaire Vétérinaire d'Alfort* (ChuvA) of the *Ecole Nationale Vétérinaire d'Alfort* (EnvA). We were unable to find and contact the owner despite the presence of a microchip. As a consequence, no information regarding the medical history was available. A necropsy was performed for pedagogic purpose.

Gross Pathology: The animal was severely cachectic and dehydrated. The skin of the ventral abdomen, ventral thorax, ventral neck, flanks and all legs was alopecic, thin, smooth and focally erythematous. Remaining hairs could be easily removed. The pawpads were smooth, erythematous and sometimes shiny. A 2-cm-diameter, unencapsulated but rather well-demarcated, lobulated, firm, white mass was found at the extremity of the left pancreatic lobe. On cut section, the mass was cystic. The pancreatic lymph node was slightly enlarged, firm and

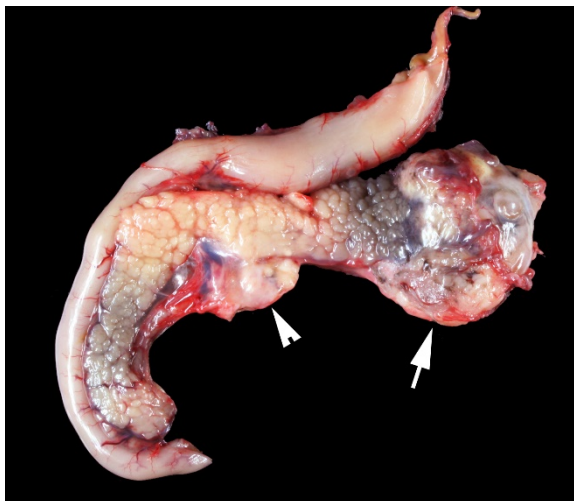
white. Numerous firm, ill-demarcated, 1-3-cm in diameter, often umbilicated, white masses were found in the liver and on the abdominal side of the diaphragm.

Laboratory results: None.

Microscopic Description: SKIN: The main dermatopathologic pattern was non-inflammatory adnexal atrophy.

The epidermis was slightly and diffusely acanthotic. The *stratum corneum* was diffusely thin, compact and orthokeratotic, with focally areas of parakeratosis. There was diffuse and severe follicular atrophy of hairless telogen type. Hair follicles were reduced to thin and tortuous epithelial cords surrounded by a thick, homogenous and glassy sheath of collagen. Sebaceous and apocrine glands were present and only minimally atrophic.

There was a slight increase in the number of dermal mast cells. The hypodermis was diffusely and severely atrophic with only few and small remaining adipocytes.



Pancreas, cat. A 2-cm-diameter, unencapsulated but rather well-demarcated, lobulated, firm, white mass was found at the extremity of the left pancreatic lobe (arrow). The pancreatic lymph node was enlarged (arrowhead) (Photo courtesy of: Unité d'Histologie et d'Anatomie pathologique, BioPôle Alfort, Département des Sciences Biologiques et Pharmaceutiques, Ecole Nationale Vétérinaire d'Alfort).

PANCREAS: A rather well-circumscribed but infiltrating and only partially encapsulated, highly cellular neoplasm developed in the pancreas. Neoplastic epithelial cells formed cords and nests supported by a moderately abundant fibrovascular stroma. Cells were polygonal to cuboidal, had a high nucleocytoplasmic ratio, a scant brightly eosinophilic cytoplasm and a central to paracentral round nucleus with a prominent eosinophilic nucleolus and coarse chromatin. Cytonuclear atypias were marked with anisocytosis and anisokaryosis, occasional binucleation, hyperchromatic nuclei. The mitotic count was moderate (7 mitoses per 10 high-power 0,237-mm²-fields). A large central area of necrosis was present. No lymphovascular emboli were found but several images of perineural invasion were present at the periphery.

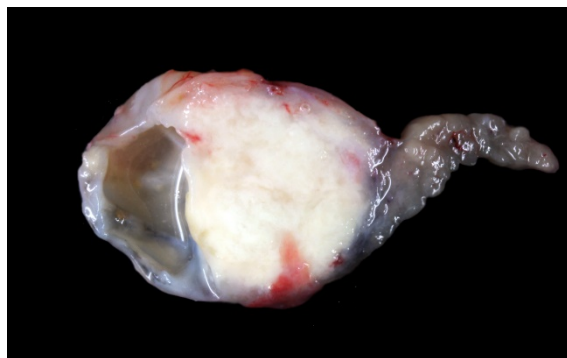
In the remaining pancreatic parenchyma, the lobulation was prominent due to a moderate to marked thickening of interlobular septa by fibrosis and multifocal lymphoplasmacytic infiltrates. Affected lobules often had rounded borders. Some pancreatic ducts were dilated and/or filled with degenerated neutrophils. There were also multiple foci of exocrine lobular hyperplasia.

Contributor's Morphologic Diagnosis:

SKIN: Follicular atrophy, severe, diffuse, with telogen hairless follicles and diffuse slight epidermal acanthosis and compact *stratum corneum*, findings consistent with feline paraneoplastic alopecia.

PANCREAS:

1. Pancreatic adenocarcinoma.
2. Pancreatitis, neutrophilic and lymphoplasmacytic, chronic-active, multifocal, moderate with interstitial fibrosis (chronic interstitial pancreatitis).
3. Exocrine nodular hyperplasia.



Upon dissection, the pancreatic nodule was cystic as a result of central necrosis. (Photo courtesy of: Unité d'Histologie et d'Anatomie pathologique, BioPôle Alfort, Département des Sciences Biologiques et Pharmaceutiques, Ecole Nationale Vétérinaire d'Alfort)

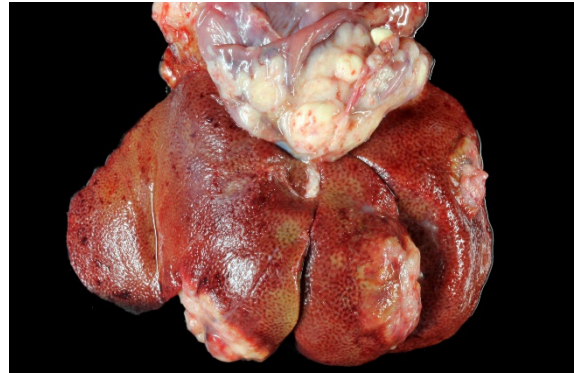
Name of the disease: Feline paraneoplastic alopecia.

Contributor's Comment: Paraneoplastic syndromes (PNS) are non-neoplastic but neoplasm-associated disorders that cannot be readily explained neither by the location of the primary tumor or its metastases, nor by the elaboration of hormones indigenous to the tissue from which the tumor arose.^{7,11,14} PNS can be associated to both benign or malignant tumors and some PNS are highly specific of particular tumors.^{7,11} PNS are important to recognise because they can be the first sign of a tumor, can be used as a marker of the disease (as such, they may indicate recurrence) or because they can cause significant clinical problems.⁶ If the tumor is removed, resolution of the PNS usually occurs. Recurrence or persistence of a PNS may indicate tumor recurrence, incomplete excision and/or metastases.

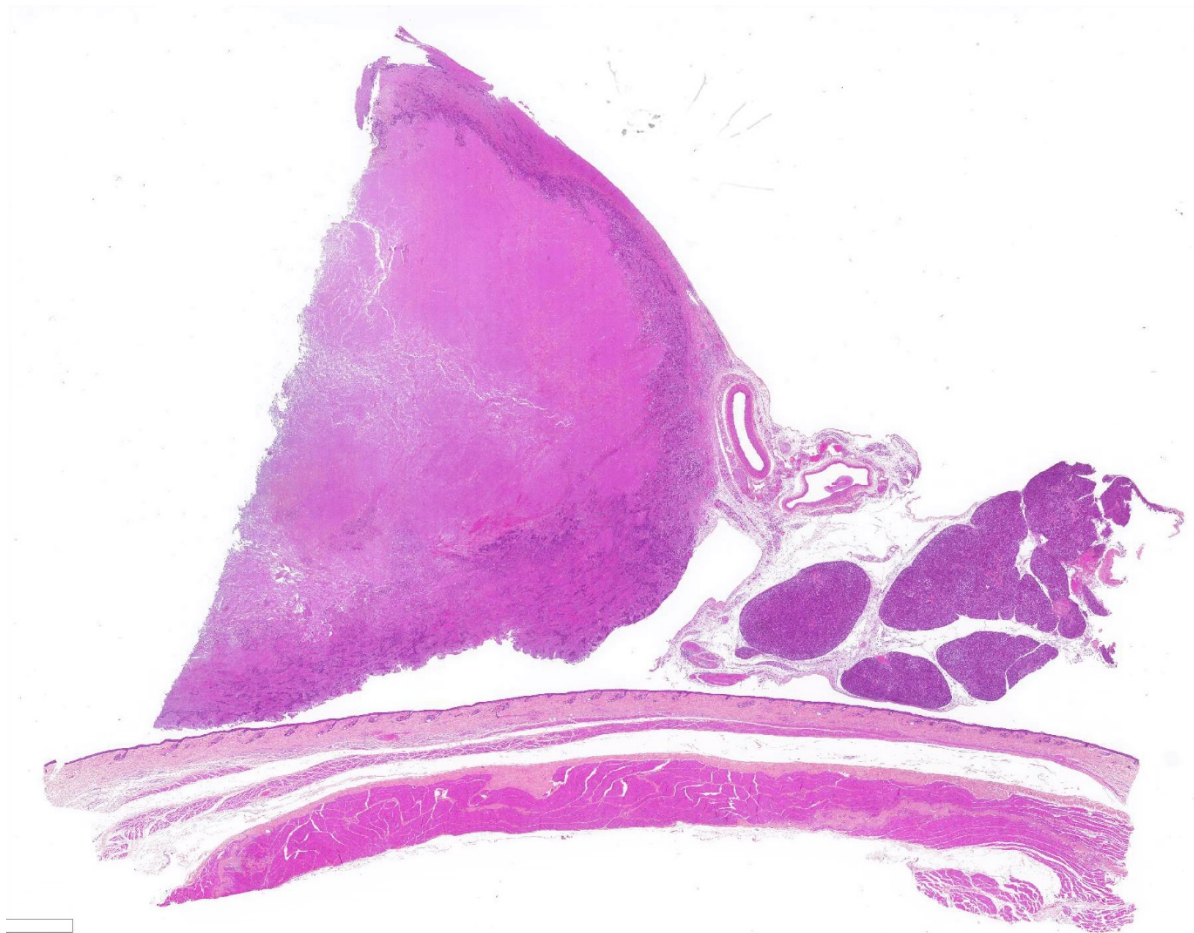
In people, it is expected that 10-50% of patients with a malignancy will experience at some point a PNS.^{7,14} In veterinary medicine, the exact frequency of PNS is unknown but several cutaneous PNS of internal tumors (mainly cancers) have been described and are summarized in table 1. More cutaneous PNS are described in humans.¹⁴

In many veterinary textbooks and papers, we found that nodular dermatofibrosis associated with renal cystadenocarcinoma in dogs is often described as a cutaneous PNS.^{9,11,14} We believe that this disease should be regarded as a genetic tumor syndrome in which dermatofibromas represent markers of the disease rather than PNS. Indeed, dermatofibromas usually precede, rather than

follow, renal cystadenocarcinomas and thus appear to develop independently from them.^{3,14} Furthermore, there are evidence that dermatofibromas develop first because they reflect haploinsufficiency in dermal



Diaphragm, liver cat. Numerous 1-3 cm white neoplastic nodules are present on the abdominal side of the diaphragm (above) and within the liver (below). (Photo courtesy of: Unité d'Histologie et d'Anatomie pathologique, BioPôle Alfort, Département des Sciences Biologiques et Pharmaceutiques, Ecole Nationale Vétérinaire d'Alfort)



Pancreas, haired skin, cat. A largely necrotic section of the pancreatic nodule (above, left), and a section of haired skin (below) is submitted for examination. (HE, 7X).

fibroblasts whereas renal cystadenocarcinomas develop later because they require a second-hit mutation (loss of heterozygosity) in the Birt–Hogg–Dubé gene. This resembles fibrofolliculomas associated with renal cancers in Birt–Hogg–Dubé syndrome in humans.³

Feline paraneoplastic alopecia has been associated with pancreatic adenocarcinoma, bile duct carcinoma, hepatocellular carcinoma, neuroendocrine pancreatic carcinoma, intestinal adenocarcinoma and

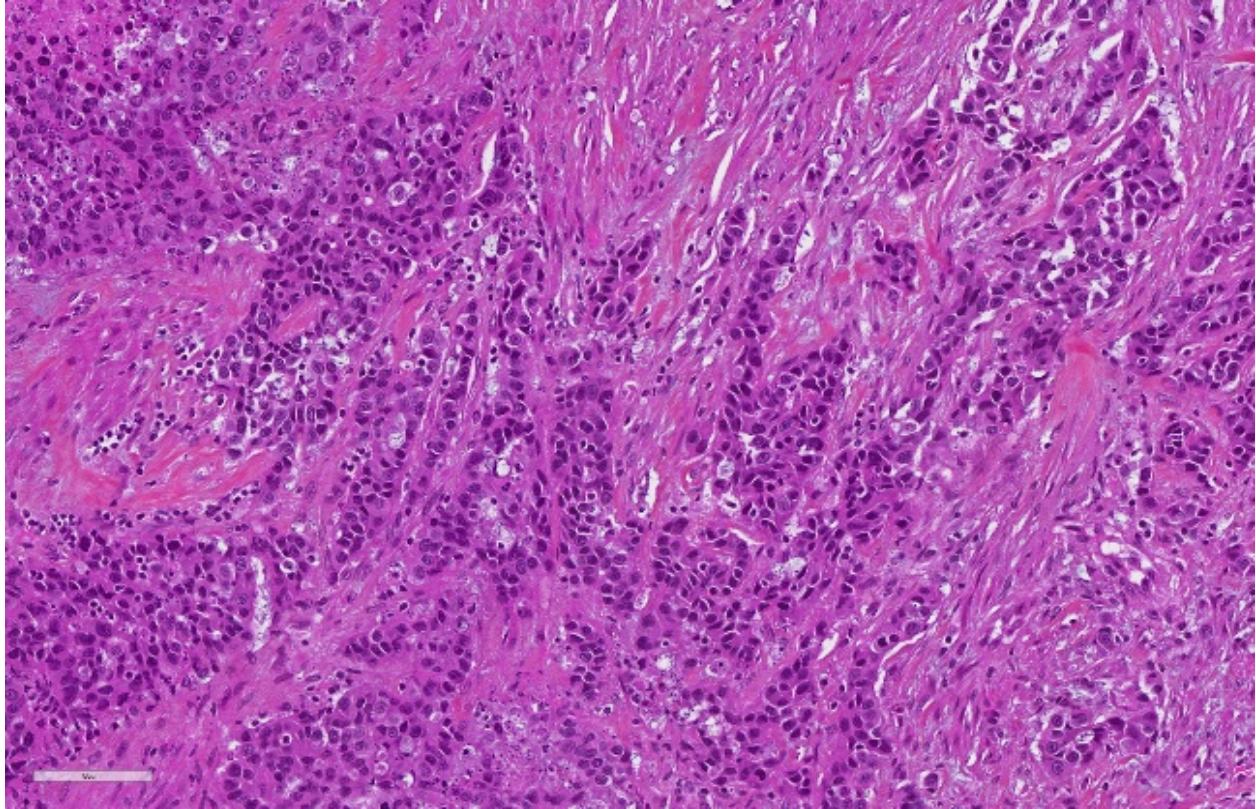
hepatosplenic plasma cell tumor, the first one being the most frequent cause.^{1,4,9,14} In most cases, paraneoplastic alopecia is recognized in advanced stages of the disease and affected cats are usually euthanized due to an extremely poor prognosis. The mechanism underlying feline paraneoplastic alopecia has not been elucidated. In the rare cases in which excision of the primary tumor was performed, hair regrowth was observed but alopecia then returned when metastases developed.⁴ Interestingly, alopecia has been described in a woman with a bile duct

| PNS | Most common associated tumor | Main dermatologic features | Main cutaneous histopathological features | Comments |
|---|---|--|---|---|
| Feline <u>paraneoplastic alopecia</u> | Pancreatic or biliary carcinoma | Progressive alopecia, easily epilated hair, glistening skin, sometimes footpad involvement | <u>Nonscarring alopecia</u> with follicular <u>telogenization</u> , miniaturization and atrophy | Also weight loss. Late in the course of malignancy. Possible secondary infections (<u>Malassezia spp.</u>) |
| Feline <u>thymoma-associated exfoliative dermatitis</u> | <u>Thymoma</u> | Progressive erythema and scaling, alopecia, waxy debris between digits and in nail beds | Cell-poor hydropic interface dermatitis with hyperkeratosis. Sebaceous gland often absent. | Assumed to be immune-mediated (resembles graft-versus-host reaction) |
| Feminization syndrome | Testicular tumors, in particular <u>Sertoli cell tumors</u> | Bilateral symmetrical alopecia, linear preputial dermatosis, gynecomastia, pendulous prepuce | Epidermal thinning, follicular keratosis and atrophy, sebaceous gland atrophy | Also myelosuppression and behavioral changes. Believed to be related to sex hormone aberration (<u>hyperestrogenism</u> and/or <u>testosterone:oestrogen imbalance</u>) |
| Superficial <u>necrolytic dermatitis</u> | <u>Glucagonoma</u> | Foot pad hyperkeratosis, alopecia and erosions with crusts on pressure points, mucocutaneous junctions, the muzzle, perineal area and feet | Parakeratosis, <u>keratinocytic edema/necrosis</u> and basal cell hyperplasia (French flag or red, white and blue epidermal appearance) | Also found in cases of <u>hepatocutaneous syndrome</u> which is more frequent. |
| Para-neoplastic pemphigus | Lymphoma, splenic sarcoma (other?) | Erythematous <u>vesiculobullous</u> lesions of head, trunk and limbs | <u>Suprabasal cleft-forming acantholysis</u> , <u>dyskeratotic</u> or necrotic keratinocytes at all epidermal levels, basal vacuolization, intense epidermal exocytosis of inflammatory cells | Also severe, erosive stomatitis with involvement of upper digestive and respiratory tracts. One reported case in a dog associated with mediastinal lymphoma |

Table 1: Main features of cutaneous PNS in dogs and cats.^{7,11}

carcinoma who presented a round alopecic area just on the top of the skull. A complete removal of the liver tumor allowed hair to grow back until metastases developed.²

In cats, differential diagnoses for acquired alopecia should include dermatophytosis, demodicosis due to *Demodex cati*, immune-mediated lymphocytic mural folliculitis, pseudopelade and vasculitis for primary alopecia. *Cheyletiella blakei*, *Notoedres cati*,



Pancreas, cat. Nests and cords of epithelial cells with small amount of granular eosinophilic cytoplasm infiltrate the capsule of the nodule at the edge of the large necrotic central focus. Many of these cells are undergoing necrosis as well. (HE, 267X)

Demodex gatoi, allergic disease, cutaneous infections with bacteria and/or fungi or fleas should be considered as a cause for secondary alopecia. Other causes such as *telogen effluvium*, hyperadrenocorticism and hypothyroidism occur very rarely in cats.^{1,4}

Interestingly, in this case, the remaining pancreatic parenchyma had lesions of chronic pancreatitis. Chronic inflammation is well known as a predisposing factor for cancer and

there are numerous examples: *Helicobacter pylori*-associated gastritis causing gastric lymphoma in humans, *Spirocerca lupi*-infestation causing esophageal sarcomas in dogs, etc.^{7,11} Many studies have found a link between chronic pancreatitis and pancreatic malignancy in humans.^{5,12,13,15,16} It is thus tempting to speculate that the chronic pancreatitis may have favored the development of a pancreatic adenocarcinoma in this case.

Contributing Institution:

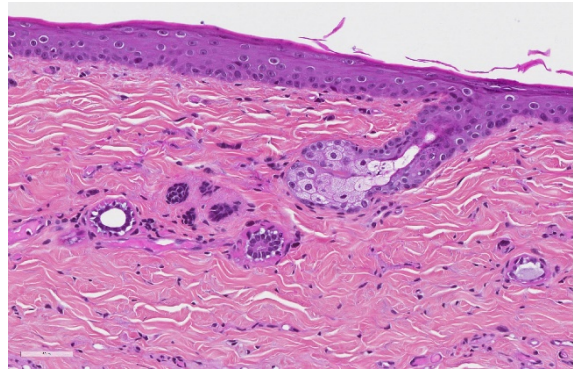
Unité d'Histologie et d'Anatomie pathologique, BioPôle Alfort, Département des Sciences Biologiques et Pharmaceutiques, Ecole Nationale Vétérinaire d'Alfort

JPC Diagnosis:

1. Pancreas: Pancreatic exocrine carcinoma.
2. Pancreas: Pancreatitis, interstitial, subacute, diffuse, mild, with acinar atrophy.
3. Pancreas, islets: Amyloidosis, diffuse, mild.
4. Haired skin: Follicular atrophy, diffuse, severe, with loss of hair shafts, and mild acanthosis.

JPC Comment: The contributor has provided an excellent review of feline paraneoplastic alopecias, and their speculation on the exclusion of nodular dermatofibrosis from the classification of paraneoplastic syndromes as well as on the potential inflammatory origin of the pancreatic neoplasm in this cat are logical and appear sound.

Pancreatic exocrine neoplasia is an uncommon entity in dogs and cats, although hyperplastic lesions of the exocrine pancreas is very common in older individuals. Subtypes of pancreatic exocrine carcinoma include ductal, acinar, and less common hyalinizing, clear cell, and undifferentiated.¹⁰ These neoplasms are subtyped by the primary discernable pattern of the neoplastic cells. In this particular case, as the majority of the neoplasm is necrotic, and only cells infiltrating the capsule are viable, a definitive pattern is not available, making



Pancreas, cat. There is diffuse severe atrophy of hair follicles which lack hair shafts. The apocrine glands are also atrophic with vacuolated epithelium. Sebaceous glands are normal. The Overlying epidermis is mildly acanthotic with a small amount of parakeratosis. (HE, 346X)

subtype of this neoplasm untenable in this particular case. A 2011 report suggested that loss of expression of tight junction protein claudin-4 might result in cellular detachment and invasion in poorly-differentiated neoplasm and was suggested as a marker of poorly differentiated tumors.⁶

In cats, this is a neoplasm of older animals (median 11.6 years).^{8,10} They progress rapidly with animals presenting with weight loss, and anorexia, occasionally vomiting, and a palpable abdominal mass.^{8,10} Involvement of the liver or bile duct by metastatic foci or explants may result in icterus or elevated liver enzymes. In the cat, these are usually solitary masses, but may also infiltrate and efface the pancreas as well.^{8,10} Untreated, the median survival time is 97 days, while animals receiving surgical treatment or chemotherapy survive an average of 165 days.⁸ One retrospective study identified diabetes mellitus in 15% of cats with pancreatic malignancies.¹⁰

In dogs, pancreatic adenocarcinomas present with similar signs, and may also

present either as solitary masses or infiltrate the pancreas. Unlike the cat, elevated levels of amylase and lipase may be seen as a result of pancreatitis.⁸ Metastasis, often to the liver and local lymph nodes is seen in the majority of cases. Hyalinizing pancreatic adenocarcinoma, a rare variant (WSC 2013-2014, Conference 2, Case 4), occasionally arises as a solitary mass in the right lobe of the pancreas. The nature of the hyalinized stroma in these tumors is not known, but it is not amyloid, as it does not stain with antibodies for serum amyloid A, light chains, amylin, or alpha-1-antitrypsin.

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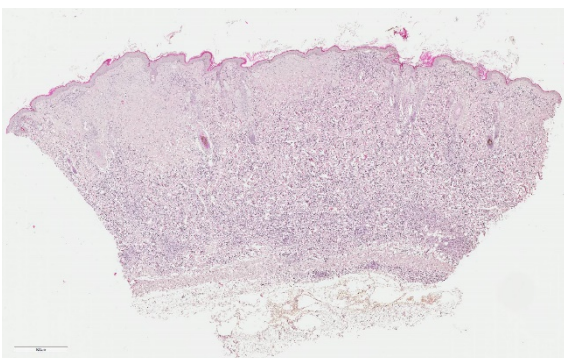
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CASE IV: 847/19 (JPC 4137402).

Signalment: 17-year-old, neutered female, Domestic Shorthair (*Felis catus*), feline

History: This cat was found dead in the street by a passerby and brought to the *Centre Hospitalier Universitaire Vétérinaire d'Alfort* (ChuvA) of the *Ecole Nationale Vétérinaire d'Alfort* (EnvA). We were unable to find and contact the owner despite the presence of a microchip. As a consequence, no information regarding the medical history was available. A necropsy was performed for pedagogic purpose.

Gross Pathology: Two skin biopsies from areas with alopecia and crusting measuring 0.8 x 0.7 x 0.4 cm and 0.8 x 0.6 x 0.4 cm respectively, were fixed in formalin and submitted.



Haired skin, cat The superficial and deep dermis are diffusely infiltrated with lymphocytes which appear more densely packed in the deep dermis and form multiple nodular aggregates. (HE, 30X)

Laboratory results:

Cytological examination of a superficial skin lesion identified few neutrophils but no evidence of bacterial or fungal structures. Microbiological and a fungal culture were negative, too.

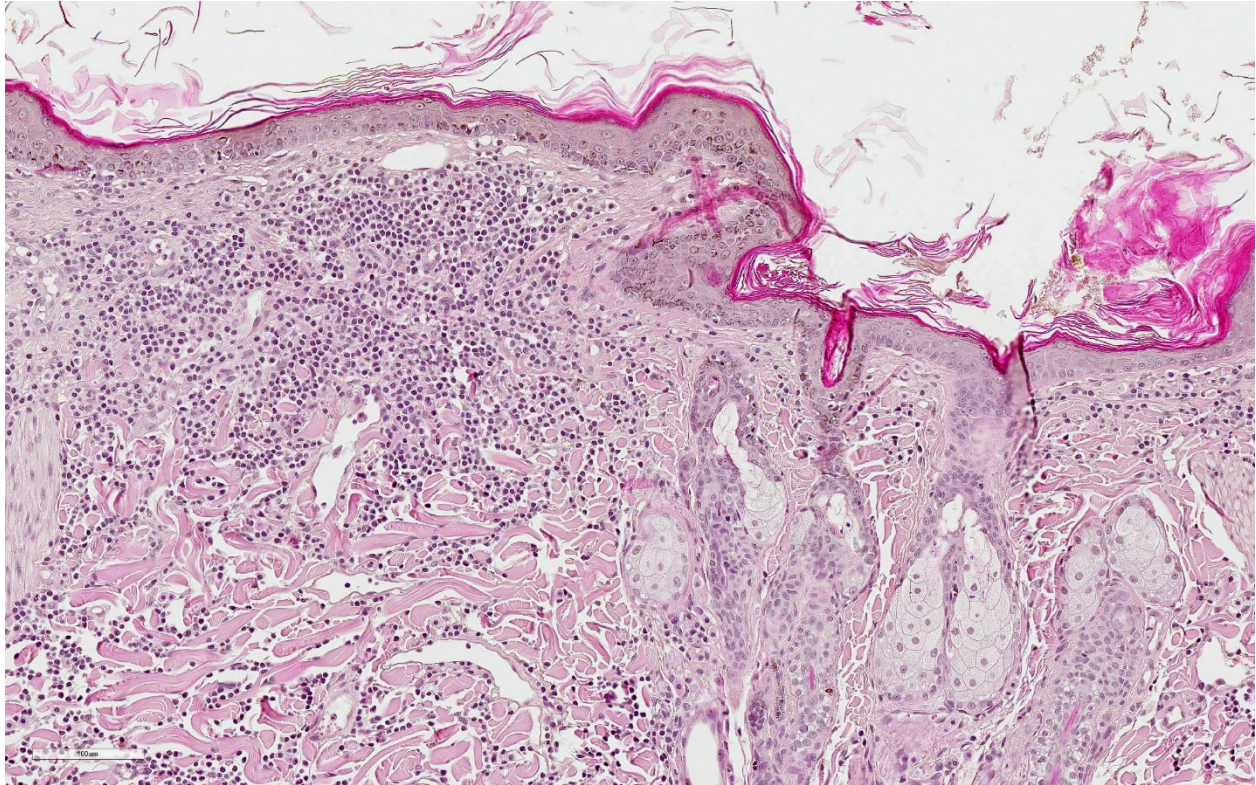
Microscopic Description:

Haired skin: Multifocally to coalescent the dermis is loosely infiltrated by mostly uniform, small round cells (Fig. 1) with scant or only minimal pale amphophilic cytoplasm and dark round to oval nuclei with condensed chromatin consistent with mature lymphocytes. The infiltrate abuts the epidermal and follicular epithelia but infiltrates them only occasionally (Fig. 2).

The deep dermis contains perivascular to nodular aggregates of tightly packed mature lymphocytes with almost no cytoplasm and dense basophilic nuclei (Fig. 3). Mitotic figures were not seen.

Small numbers of mast cells, plasma cells and neutrophils are loosely intermingled. The epidermis shows mild to moderate epidermal hyperplasia and mild orthokeratotic hyperkeratosis.

Immunohistochemistry (Fig 4) identified almost all cells in the superficial and deep dermis as CD3-positive T cells. The small, tightly packed aggregates in the deep dermis consisted of PAX5-positive B cells.



Haired skin, cat. Lymphocytes within the superficial dermis with sparing of the mildly spongiotic epidermis, mild orthokeratotic hyperkeratosis, and mild superficial dermal edema. (HE, 200X)

Contributor’s Morphologic Diagnosis:

Haired skin: cutaneous lymphocytosis, moderate to severe, diffuse

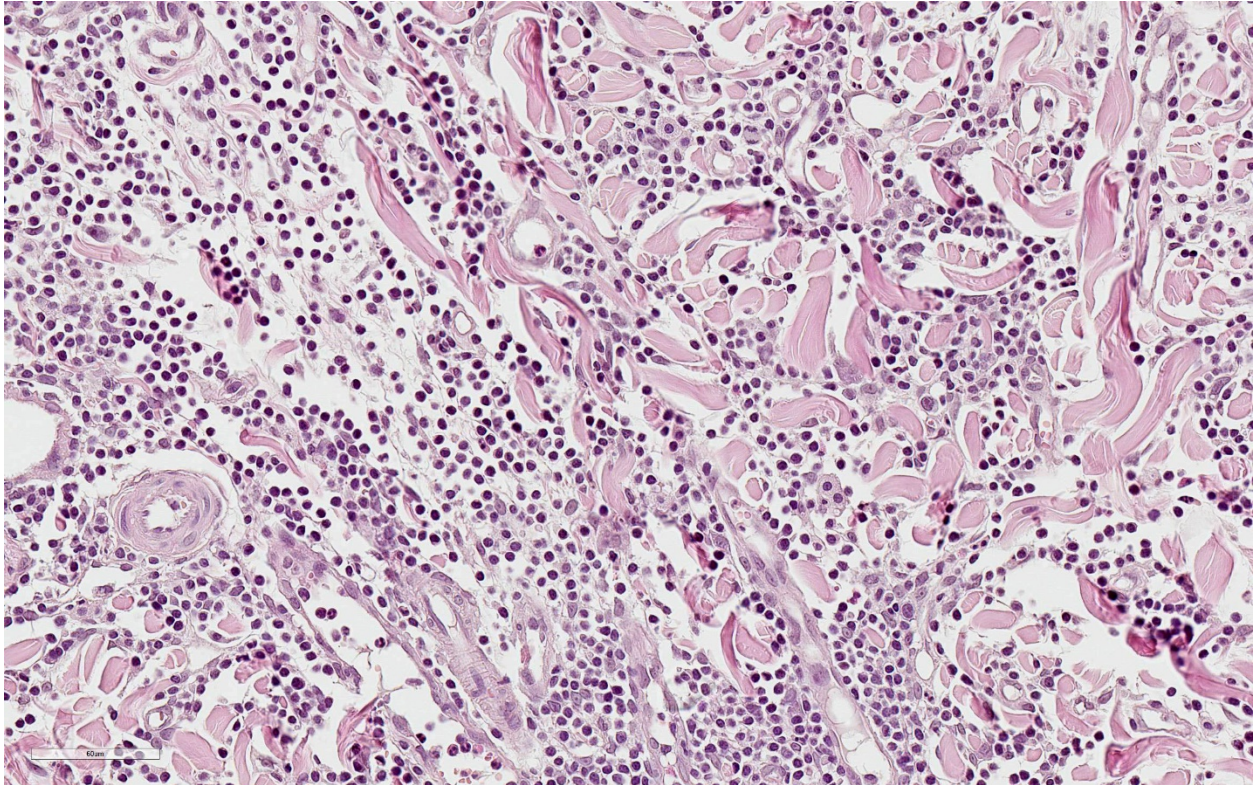
Contributor’s Comment: Cutaneous lymphocytosis is an uncommon disease and has been described in cats, dogs and humans ^{1,2,11}. The condition is most often seen in older cats, without a breed predisposition, but a slight predominance in females. The etiology is unknown.²

The typical clinical presentation is characterized by acute onset with slow progression.² Cutaneous lymphocytosis is mostly a solitary lesion showing alopecia, erythema and scaling, with or without crusting or ulceration. Pruritus can be seen in more than half of the cases, most commonly affecting the lateral thorax but also various other body sites (legs, pinnae, flank, neck, abdomen, hip, digit and planum nasale for instance).² It is a

relatively benign disease with rare occasions of systemic illness in some cats and dogs associated with anorexia, weight loss and well-differentiated T-cell infiltrates in internal organs.^{1,2} In most of the cases, treatment with glucocorticoids resulted in marked improvement of the clinical outcome.²

Cutaneous lymphocytosis in cats and dogs resembles cutaneous pseudolymphoma (lymphocytoma cutis, cutaneous lymphoid hyperplasia) in humans, a reactive proliferation of well-differentiated T- or B-cells in the skin of humans. In most cases, hypersensitivity reaction to various antigenic stimuli has been described (such as arthropod bites, vaccination, tattoo dyes, drugs and contactants).^{6,7,10}

In human cases, malignant transformation has been observed in some cases with systemic lymphoid involvement including enlarged mesenteric lymph nodes, infiltration of the liver, pancreas, stomach,



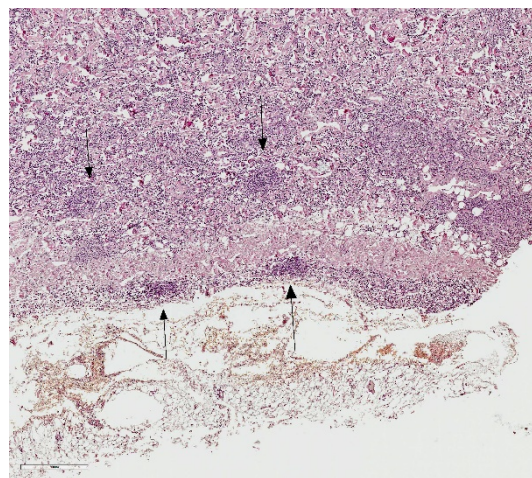
Haired skin, cat. Lymphocytes are small, bland, and diffusely expand the dermis. (HE, 400X)

kidney and heart by T lymphocytes and B cell infiltration of the small intestine.^{4,8,11}

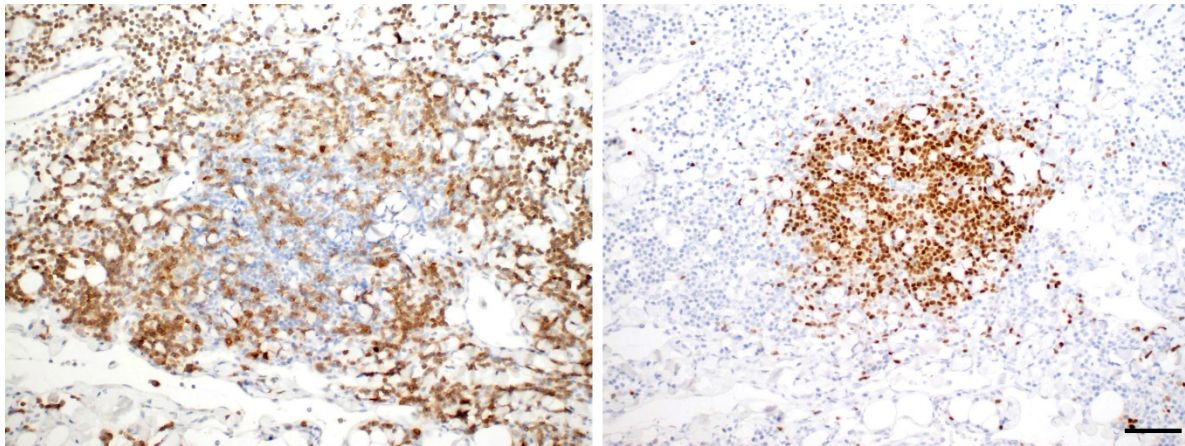
Histologically, cutaneous lymphocytosis in dogs and cats is characterized by proliferation of well differentiated CD3-positive T cells in the superficial and deep dermis and in most cases also nodular aggregates of CD79-positive B-cells in the dermis.^{2,4,11} In some cases, a T-cell receptor gamma gene rearrangement (TCR γ) can be verified suggesting that this condition is a low-grade or indolent T cell lymphoma.³

As a differential for cutaneous lymphocytosis, cutaneous T cell lymphoma must be considered. Cutaneous histiocytosis may be difficult to clinically or histologically differentiate from well-differentiated cutaneous malignant lymphoma with predominance of mature. However, histopathology of cutaneous T cell lymphomas often identifies epitheliotropic lymphoma characterized by a

diffuse superficial or follicular epitheliotropic infiltrates of medium sized to large lymphocytes / lymphoblasts and in some cases additional Pautrier's intraepidermal aggregates. In non-epitheliotropic lymphomas a deep dermal and subcutaneous infiltration of small to blastic lymphoid cells (bottom heavy configuration) with a variable mitotic activity can be seen.⁹



Haired skin, cat. Nodular aggregates of lymphocytes are present in the deep dermis (arrows). (HE, 400X)



Haired skin, cat. Immunohistochemistry of nodules in the deep dermis demonstrates the preponderance of diffusely arrayed CD 3-positive T-cells (similar to that in all levels of the dermis) at left, and a nodular aggregate of PAX-5 positive B cells at right. (Anti-CD#, and anti PAX-5, 400X) . (Photo courtesy of: Department of Veterinary Pathology, Freie Universität Berlin [http://www.vetmed.fu-](http://www.vetmed.fu-berlin.de/en/einrichtungen/institute/we12/index.html)

Contributing Institution:

Department of Veterinary Pathology,
Freie Universität Berlin
<http://www.vetmed.fu-berlin.de/en/einrichtungen/institute/we12/index.html>

JPC Diagnosis: Haired skin:
Lymphocytosis, diffuse, marked, with mild
acanthosis and orthokeratotic
hyperkeratosis.

JPC Comment: The contributor has provided an excellent review of this uncommon entity in the dog and cat. This particular specimen appears to very closely match descriptions in the veterinary literature. Immunohistochemical stains run at the JPC revealed the infiltrate to be overwhelmingly populated by CD-3 positive T-cells, with scattered aggregates of CD-20 and Pax-5 positive B cells in the deeper regions of the dermis.

In Gross et al, while the condition share most features in dogs and cats, cases in the dog often demonstrate a Grenz or lymphocyte-free zone in the superficial dermis at the dermo-epidermal junction.⁵

The attendees found it of note that a PubMed search for Dr. Nicolas Kluger⁷ (cited below)

yielded 77 publications on dermatologic conditions involving tattoos.

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