

**The Armed Forces Institute of Pathology**  
**Department of Veterinary Pathology**  
**Wednesday Slide Conference**  
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**Conference 13**  
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**Conference Moderator:**

Dr. Elizabeth A. Mauldin, DVM, Diplomate ACVP, Diplomate ACVD

**CASE I: 5221 (AFIP 2941533).**

**Signalment:** 11-year-old, castrated male, chinchilla longhair cat (*Felis catus*).

**History:** Presented with skin disease, weight loss, and polydipsia. Ultrasound revealed an abnormal pancreas, a nodular liver and congenital absence of the right kidney.

**Gross Pathology:** The cat was in poor condition and weighed 3.6 kg. Extensive alopecia was noted over the muzzle and periorbital areas, all four limbs, the thorax, on the ventrum and in the axillary and inguinal regions. Over the axillary and inguinal regions and plantar aspects of the carpus, metacarpus, tarsus and metatarsus, there were focally extensive erosions. Hyperpigmentation was present in the alopecic areas of the muzzle and periorbital. A paucity of subcutaneous and intra-abdominal fat was noted.

Diffusely the lungs were dark, red and heavy. The cut surface was similar and 100% of the lung was involved. The pericardial sac contained 10 mL of red fluid and diffusely there was minimal nodular thickening of the left atrioventricular valve.

Multifocally on the capsular and cut surface of the liver were numerous (approximately 10) raised, well-demarcated, yellow-white, soft, round nodules that were variably sized, ranging from 0.5 to 2 cm in diameter. Diffusely the pancreas was mottled dull grey-red and contained numerous raised, firm, round nodules that were up to 0.5 cm in diameter. Focally at the body of the pancreas, there was a larger, raised, poorly demarcated, yellow-white, firm, nodular mass that was 2 cm in diameter. The left kidney measured 42 x 30 x 20 mm and appeared normal. The right kidney and ureter were not present.

**Laboratory Results:** Bacterial culture of the liver revealed no significant growth.

**Contributor's Morphologic Diagnosis:** Skin: Dermatitis/cellulitis, chronic-active, diffuse, moderate with hair follicle and sebaceous gland atrophy and moderate epidermal hypoplasia and hypokeratosis.

**Contributor's Comment:** A diagnosis of feline paraneoplastic alopecia (FPA) was reached after postmortem diagnosis and histopathology revealed a pancreatic exocrine adenocarcinoma, which had metastasized to the liver. Changes in the hair follicles and dermis are characteristic of those reported for FPA. Feline paraneoplastic alopecia usually starts on the ventral neck, thorax or abdomen, the changes grossly apparent as a non-pruritic, progressive, symmetrical alopecia. Hairs are easily epilated and the skin is thin, shiny and inelastic. Footpad involvement has also been reported, with varying presentations from dry and cracked to moist, erythematous pads. These are usually painful. The cause of the alopecia is not fully understood and it is non-responsive to corticosteroid treatment. When the carcinoma was surgically excised the condition resolved in one case, although it did recur at the time of metastatic tumour recurrence.(4) Most affected cats are reported to groom excessively, and it has been postulated that the shiny appearance of the skin arises from the resulting exfoliation of the stratum corneum.(3) Affected animals range in age from 7-16 years (median 13 years), with no apparent breed predilection.(5) Skin lesions are often accompanied by other systemic clinical signs, such as weight loss, vomiting, diarrhea, anorexia and lethargy. This disease has been reported with pancreatic carcinoma in 12 cats and biliary carcinoma in two cats.(5)

Histopathological examination of the skin consistently shows a non-scarring alopecia with characteristic marked follicular telogenization, miniaturization and atrophy, with similar adnexal atrophy. Other findings include mild epidermal acanthosis and hyperplasia with a hypo- or non-keratinized epidermis, and a mild, mixed, perivascular inflammatory infiltrate of the dermis, consisting of lymphocytes, macrophages and neutrophils.(3,4) In a recent report of feline skin biopsies complicated by *Malassezia* spp., histopathology from 7 of 15 cases was consistent with FPA. Although pancreatic carcinoma was confirmed in only four of these cats, it is possible that an indication of internal malignancy could be made when *Malassezia* spp. are detected in histopathology of cats with generalized skin disease.(2)

Neoplastic diseases of the exocrine pancreas and biliary tree are rare in the cat. The prognosis for these is generally poor since at the time of diagnosis the disease has often metastasized to distant sites, such as the liver, lymph nodes and lungs, as well as possibly local seeding to intraperitoneal sites. Twelve of the fourteen cats reported in the literature died or were euthanized within 8 weeks of onset of clinical signs.

**AFIP Diagnosis:** Haired skin and subcutis: Follicular atrophy, diffuse, marked, with mild, multifocal, lymphoplasmacytic and histiocytic dermatitis.

**Conference Comment:** The sections of haired skin from this cat contain the histologic features of FPA, including profound follicular atrophy with sparing of the sebaceous glands and acanthosis. Additionally, the presence of a pancreatic adenocarcinoma supports a diagnosis of FPA. However, the moderator and several conference participants identified other histologic features not typical of FPA, including: small areas of epidermal necrosis and/or individual cell necrosis in the epithelium in some slides; subepidermal clefting; congested small blood vessels in the superficial dermis; and ulceration in a few sections. Conference participants debated whether the subepidermal clefting was real or artifact, and suggested that additional history may be helpful in identifying other factors to explain the clefting and epithelial necrosis.

Differentiation between FPA and feline hyperglucocorticoidism (FHG) was discussed. Follicular atrophy is present in both conditions, but it is more striking in FPA and hair follicles in FHG have increased tricholemmal keratinization (bright eosinophilic core in an atrophic follicle) and follicular hyperkeratosis. Sebaceous glands may be atrophied in FHG, but are usually normal in FPA. The most striking feature of FHG is profound dermal atrophy, whereas the dermis is normal in FPA. FPA is also characterized by acanthosis with parakeratotic hyperkeratosis.(1)

In addition to FPA, other paraneoplastic skin lesions include feline thymoma-associated exfoliative dermatitis, nodular dermatofibrosis, feminization syndrome associated with Sertoli cell tumors, superficial necrolytic dermatitis and paraneoplastic pemphigus, all of which are described in an excellent review article.(5) Nodular dermatofibrosis occurs primarily in the German Shepherd Dog and is associated with renal cystadenomas or cystadenocarcinomas and uterine leiomyomas.(5) Superficial necrolytic dermatitis occurs more commonly due to hepatopathy or diabetes mellitus, but it has also been associated with a glucagonoma.(5) Paraneoplastic pemphigus is extremely rare.

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**CASE II:** 06-26654-3 (AFIP 3134295).

**Signalment:** 10-year-old, castrated male, border collie cross dog (*Canis familiaris*).

**History:** One-month history of a mass on the ventral abdomen. The mass had doubled in size over the last few weeks. It was freely moveable within the subcutaneous layers of the skin and measured approximately 3 x 3 cm at the time of removal.

**Gross Pathology:** Received a 3 x 2.5 cm ellipse of haired skin containing a firm, pale 2 cm diameter subcutaneous mass.

**Histopathologic Description:** Haired skin: Beneath the superficial dermis is an unencapsulated, well demarcated, moderately cellular, focally infiltrative neoplastic mass. Neoplastic cells are arranged in thin streams dissecting between large thick bundles of well defined eosinophilic homogenous (hyalinized) birefringent material (collagen) within a fine fibrovascular stroma. In one location, neoplastic cells form interlacing bundles and streams with small embedded collagen bundles. Cells are spindloid with indistinct cell borders, a scant amount of finely fibrillar eosinophilic cytoplasm with an elongate central nucleus with finely stippled chromatin and indistinct nucleoli. There is three-fold anisocytosis and anisokaryosis. The mitotic rate is low with an average of 0.1 mitotic figures per 400x HPF. Neoplastic cells extend to one margin of the biopsy. Small areas of hemorrhage are scattered throughout the tumor and around the tumor base. Small numbers of lymphocytes and plasma cells surround small vessels around the margins of the tumor.

**Contributor's Morphologic Diagnosis:** Keloid fibrosarcoma.

**Contributor's Comment:** Keloid fibrosarcomas are an uncommon variant of fibrosarcomas, distinct from the other forms of fibrosarcoma and other collagen-rich masses due to the presence of thick bands of hyalinized collagen.(3) These bands of hyalinized collagen can also be seen in cytologic preparations.(2) Keloidal tumors are infrequently reported in dogs and have not been reported in other domestic animal species. They appear somewhat similar histologically to keloids, hypertrophic scars and keloid dermatofibromas in humans.(2) The one published retrospective study of keloidal tumors in dogs suggests that the presence of macrophages within the tumors may indicate that these tumors are reactive inflammatory lesions, rather than true neoplasms.(3)

Differentiation of keloid fibromas from keloidal fibromas is based on the presence of portions of the tumors that are composed largely of thickly packed neoplastic cells with only a small amount of fibrovascular stroma and small numbers of hyalinized fibers.(3) These areas are reportedly more common in the deeper margins of the tumors as is the case in this example. It was suggested that keloidal fibrosarcomas may represent a malignant transformation of keloid fibromas; however, no difference in prognosis has been demonstrated between keloid fibromas or keloid fibrosarcomas.

The neoplastic cells in keloidal tumors of dogs are vimentin positive and smooth muscle actin negative and are interpreted to be fibroblasts in contradistinction to human keloidal tumors which are comprised of myofibroblasts.(3)

**AFIP Diagnosis:** Haired skin and subcutis: Fibrosarcoma, low grade (keloidal).

**Conference Comment:** The large bundles of hyalinized collagen are a distinctive histologic feature in this case, and in dogs are generally limited to keloidal fibromas and fibrosarcomas and mast cell tumors with keloidal change. (1) Differentiation between keloidal fibromas and keloidal fibrosarcomas is based on the presence of interlacing fascicles of neoplastic cells and/or infiltration in the malignant variant. Since keloidal fibrosarcomas may arise from keloidal fibromas, the malignant characteristics may be present only in a small portion of the tumor.(3) Keloidal fibrosarcomas also may contain cellular atypia and have an increased mitotic rate.(1) The differential diagnosis includes dermatofibroma and peripheral nerve sheath tumor (PNST). In dermatofibromas, and occasionally in PNSTs, the spindle cells are separated by enlarged, but non-hyalinized, collagen bundles. Additionally, dermatofibromas usually contain inflammation and overlying epithelial hyperplasia, while PNSTs have a neural pattern, demonstrate variation in cellularity, and frequently contain a myxomatous matrix.(1)

Conference participants also noted the presence of small capillaries within the large, hyalinized collagen fibers and areas of microhemorrhage; these changes have been described previously.(3)

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**CASE III: B08-24914 (AFIP 3136050).**

**Signalment:** 3-year-old, female spayed greyhound dog (*Canis familiaris*).

**History:** The dog developed two cutaneous nodules on the right and left dorsal ear pinnae two months prior to presentation.

**Gross Pathology:** The nodules on the right and left dorsal pinnae were alopecic, firm, focally ulcerated and measured 1 cm and 2 mm in diameter, respectively.

**Histopathologic Description:** Each sample has a well-demarcated, dense, nodular proliferation of inflammatory cells that expands the deep dermis and subcutis and elevates the overlying epidermis. Inflammatory cells consist predominantly of epithelioid macrophages with rare multinucleated giant cells admixed with lymphocytes, plasma cells and scattered aggregates of neutrophils. Discrete granuloma formation is not present. Between aggregates of inflammatory cells, there is a moderate collagenous stroma and blood vessels are lined by hypertrophied endothelial cells. Within the inflammatory lesion, there are few foci of acute hemorrhage and there are scattered melanophages. In the larger nodule, from the right pinna, there is a focal ulcer (present in some sections) covered by a fibrinocellular exudate.

In the adjacent dermis, there is clumping of melanin within hair follicles with multiple melanophages in the surrounding dermis and mild periadnexal infiltrates of lymphocytes and plasma cells.

Ziehl-Neelson acid fast stain: Low numbers of acid-fast-positive bacilli, measuring 1-2 um in length, are within the cytoplasm of epithelioid macrophages.

**Contributor's Morphologic Diagnosis:** 1. Haired skin (dorsal pinna): regional nodular granulomatous and lymphoplasmacytic dermatitis with focal ulcer and rare intrahistiocytic acid-fast bacilli (canine leproid granuloma syndrome).  
2. Haired skin (dorsal pinna): follicular melanin clumping with dermal melanophages (possible color dilution alopecia).

**Contributor's Comment:** Canine leproid granuloma syndrome is a mycobacterial skin disease characterized by single or multiple, well-circumscribed, firm, variably-sized (2 mm to 5 cm diameter) nodules within the skin or subcutis, predominantly affecting the ear pinna, head and occasionally the distal extremities.(2,6) Short-coated dog breeds, particularly boxer dogs and boxer crosses, are most commonly affected.(2,6) The nodules are thought to be non-pruritic and painless, and occasionally, particularly in the larger nodules, the overlying epidermis is ulcerated or alopecic.(2,6) The nodules have been reported to spontaneously regress without treatment and in some cases surgical excision is considered curative.(2,6) Other cases with a more persistent infection may require antimicrobial therapy.(7) The lesions are confined to the skin with no involvement of lymph nodes or internal organs.(2,6)

On cytologic evaluation of fine-needle aspirates of the nodules, there are spindle-shaped macrophages with variable numbers of lymphocytes and plasma cells with fewer neutrophils and there are few to moderate numbers of negative-staining bacilli extracellularly or within macrophages.(1) On histopathology, there is dermal and/or subcutaneous granulomatous inflammation, with or without pyogranulomatous foci, and the inflammatory lesion consists mainly of epithelioid macrophages and neutrophils with lymphocytes, plasma cells, and rare multinucleated

giant cells.(1,2,6) In Ziehl-Neelson acid-fast-stained specimens, there are very low to low numbers of intracellular bacilli in the majority of cases.(1,2,6)

The cause is a saprophytic, as yet unnamed and uncultivated, species of *Mycobacterium*.(1,2,4,6) Culture is unsuccessful, but with 16s rRNA PCR-based gene analysis on fresh and formalin-fixed, paraffin-embedded tissue, a proposed novel mycobacterial sequence has been identified.(4) The closest relatives of this agent are *Mycobacterium tilburgii*, *M. simiae*, and *M. genavense*.(4) There are significant molecular similarities between the organisms identified in the United States and those in Australia and New Zealand.(2) The suggested mode of transmission of the etiologic agent in canine leproid granuloma syndrome is thought to be percutaneous inoculation via wounds or biting insects.(2,6)

In the present case, the follicular melanin clumping with dermal melanophages is suggestive of concurrent color dilution in this dog. Color dilution alopecia is a hereditary skin disease in dogs with “blue” or “fawn” color-diluted coats and has been reported in the greyhound.(3) This disease is typically characterized by atrophy, distortion and abnormal melanin pigmentation of hair follicles with variable alopecia. Large amounts of clumped melanin pigment are within the hair follicle and within melanophages in the dermis around the base of hair follicles.(3) Some of the features of color dilution alopecia, such as the melanin clumping, may be seen in color-dilute dogs without alopecia and are not of pathologic significance.(3) Without enough supporting clinical history in this case, the contributors cannot determine whether this dog was color-diluted or fits the criteria for color dilution alopecia.

**AFIP Diagnosis:** 1. Haired skin and subcutis: Dermatitis, pyogranulomatous, focally extensive, severe, with rare intrahistiocytic acid-fast bacilli.  
2. Haired skin and subcutis: Follicular melanin clumping, multifocal, mild, with perifollicular pigmentary incontinence.

**Conference Comment:** The contributor provides an excellent review of canine leproid granuloma. Conference participants considered histiocytoma, plasmacytoma, fungal dermatitis, atypical mycobacteriosis, and sterile granuloma and pyogranuloma syndrome in the differential diagnosis. This case lacks the typical histological features of histiocytoma, including epithelial hyperplasia, superficial dermal edema, occasional reniform nuclei and a moderate mitotic rate.(3) Plasmacytomas typically have few large nuclei and binucleated cells with differential staining of the chromatin pattern, vague packeting, and more differentiated plasma cells at the tumor periphery (3); additionally, small clusters of neutrophilic inflammation and scattered giant cells would be unusual histologic features for tumors of plasma cell origin. Opportunistic fungal infections could cause similar histologic lesions; however, fungal organisms are not observed. Atypical mycobacteriosis more commonly affects cats, and the histopathologic features consist of nodular pyogranulomatous dermatitis and panniculitis with draining tracts and rare acid-fast bacilli found within clear spaces in areas of inflammation.(2) Sterile granuloma and pygranuloma syndrome is an inflammatory condition of unknown cause that is responsive to glucocorticoid therapy; unlike leproid granuloma, lesions are more often multifocal and track hair follicles, and special stains do not reveal an etiological agent.(3) Due to the presence of epithelioid macrophages, giant cells and fibrosis, mycobacterial lesions can resemble sarcoma, and are therefore sometimes described as sarcomatoid.(5)

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**CASE IV: 22809/1 (AFIP 3138538).**

**Signalment:** 3-year-old, female bloodhound dog (*Canis familiaris*).

**History:** The dog was caught in the countryside and no history was available.

**Gross Pathology:** Not reported.

**Histopathologic Description:** Haired skin and subcutis, posterior limb. Within the dermis and the hypodermis there is a nodular (approximately 1.5 cm), slightly exophytic, infiltrative, poorly demarcated, unencapsulated, densely cellular lesion that effaces the dermal collagen and displaces the adnexa. The population is predominantly composed by atypical discrete round cells with generally distinct cell borders and a small to moderate amount of eosinophilic cytoplasm. Nuclei (approximately 1.5-2 x RBC) are central irregularly round and occasionally indented, with finely stippled chromatin, and one generally indistinct nucleolus. Mitoses average 5 per high power field. The atypical cells show occasional epidermal and follicular epitheliotropism. In association there is a second cellular population composed of high numbers of disseminated protozoa-laden macrophages. Intrahistiocytic protozoal amastigotes are evident; they are 2-3 um in diameter with clear cytoplasmic halo, basophilic nucleus, and a smaller adjacent (perpendicular) kinetoplast (consistent with *Leishmania* spp. amastigotes). In addition, numerous plasma cells and Mott cells and occasional small lymphocytes are also disseminated within and around the lesion, and multifocally extend into the subcutis where they are predominantly focused around blood vessels. There is also multifocal ulceration associated with degenerate and non-degenerate neutrophils, necrotic debris, and collagen lysis. There is diffuse parakeratotic hyperkeratosis. The superficial dermis is multifocally mildly expanded by edema and ectatic lymphatics.

Immunohistochemistry for CD3, CD5, CD79a, CD20 was performed (not submitted). The predominant atypical population showed a moderate diffuse cytoplasmic staining for CD3. Staining for CD5, CD20, and CD79a was negative. A nonspecific nuclear staining was detected for CD79a.

**Contributor's Morphologic Diagnosis:** Haired skin and subcutis, posterior limb: Epitheliotropic lymphoma associated with histiocytic and lymphoplasmacytic dermatitis, severe, diffuse with myriad intrahistiocytic protozoal amastigotes, consistent with *Leishmania* spp., *Canis familiaris*, dog.

**Contributor's Comment:** Canine leishmaniasis (CL) is a systemic disease caused by different species of the genus *Leishmania* that is transmitted by blood sucking phlebotomine sandflies. The majority of affected dogs present with poor body condition, immunosuppression, lymphadenomegaly and excessive skin scaling. The disease is endemic in the Mediterranean area. In the dog, the cellular immune response against *Leishmania* is still not well defined, although in affected individuals capable of overcoming the disease characteristic immune responses of type Th1 have been shown. Cutaneous epitheliotropic T-cell lymphoma in the dog is a rare neoplastic condition with unknown etiology. In dogs, epitheliotropic T-cell lymphoma pursues a progressive course of disease with several months to 2 years before death. The neoplastic population is characterized by infiltration of neoplastic T lymphocytes with a specific tropism for the epidermis and the adnexal structures.(2)

From literature, prolonged antigenic stimulation and chronic immunosuppression plays a crucial role in the etiopathogenesis of T-cell lymphoma.(1) Persistent environmental antigens act as a stimulus for chronic T-cell activation and proliferation and progression to a clonal expansion has been suggested as a possible cause of epitheliotropic lymphoma in humans.(3) To our knowledge some reports are present describing association between skin lymphoma and atopic dermatitis or chronic skin allergic disease. Our dog could further confirm that chronic antigen stimulation may be an initiator of a clonal neoplastic T-cell population in the skin. Canine epitheliotropic lymphoma has been further subtyped as a tumor predominantly of CD8- $\gamma\delta$ -T cells. In the present case, a deeper investigation of the immunophenotype was not possible since monoclonal antibodies available for detection of CD4

and CD8 on formalin fixed tissue biopsies were not available. The cell population appeared to be CD3+ and therefore compatible with T-cell lymphoma.

**AFIP Diagnosis:** 1. Haired skin and subcutis: Lymphoma.

2. Haired skin and subcutis: Dermatitis, histiocytic and lymphoplasmacytic, diffuse, moderate, with focal ulceration and numerous intrahistiocytic protozoal amastigotes.

**Conference Comment:** While conference participants agreed with the histologic diagnosis of malignant lymphoma, neoplastic epitheliotropism was not observed in the slides examined during conference, suggesting this is a case of cutaneous nonepitheliotropic lymphoma. The majority of cutaneous nonepitheliotropic lymphomas in dogs and cats are of T-cell origin. Additionally, cutaneous lymphoma is more commonly epitheliotropic in dogs and nonepitheliotropic in cats.(4)

*Leishmania* sp. have several adaptations that allow their entry into and survival within macrophages.(5)

1. Lipophosphoglycans bind to C3b and iC3b and enhance phagocytosis, and protect organisms by scavenging oxygen free radicals and inhibiting lysosomal enzymes.
2. Gp63, a zinc-dependent proteinase, cleaves complement and some lysosomal antimicrobial enzymes.
3. Proton-transporting ATPase allows the amastigotes to survive in the phagolysosome's extremely acidic environment.

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