**The Armed Forces Institute of Pathology**
**Department of Veterinary Pathology**

**WEDNESDAY SLIDE CONFERENCE 2007-2008**

# Conference 15

**30 January 2008**

*Moderator*:

Dr. Elizabeth Mauldin, DVM, DACVP, DACVD

**CASE I – N06-274 (AFIP 3074696).**

**Signalment:** Mature, female spayed, Miniature Schnauzer

**History:** The animal presented with a two day history of generalized skin erythema. This rapidly progressed to skin thickening, which began around the ears, head and neck, and soon involved the whole body. Severe depression and dehydration ensued (8% dehydrated), with vomiting and foul smelling diarrhea. Extreme pain was noted all over the body. There was prominent pitting edema which was most pronounced over the abdomen, base of the ears, sternum and vulva. Gentle manipulation of the skin revealed detachment from the underlying tissues (Nikolsky's sign). Blood biochemistry and hematology results are detailed below. Attempts at supportive therapy were unsuccessful and the owners elected for euthanasia on humane grounds.

**Gross Pathology:** Gross necropsy revealed generalized, moderate cutaneous erythema; the epidermis was easily detached from the underlying dermis on gentle manipulation (Nikolsky's sign). There were no other significant findings in other organs.

**Laboratory Results:** Provided in **table 1-1**.

**Histopathologic Description:** Haired skin: Diffusely, keratinocytes within all layers of the epidermis are hypereosinophilic with pyknotic to karyorrhectic nuclei (cell death). Frequently, this extends into the follicular infundibulum. Randomly scattered throughout the dermis, there are small to moderate numbers of lymphocytes, admixed with plasma cells, neutrophils, macrophages and numerous melanin-laden macrophages (pigmentary incontinence). Lymphocytes are occasionally present within the epidermis, however this is variable. In places, there is clefting between the epidermis and dermis, both beneath the basement membrane within the suprabasilar epithelium (this differs between sections). Superficial dermal vessels are prominent and lymphatics occasionally contain moderate numbers of neutrophils.

**Contributor's Morphologic Diagnosis:** Haired skin: Severe, diffuse, sub-acute epidermal necrosis with mild lymphoplasmacytic dermatitis and pigmentary incontinence (consistent with Toxic Epidermal Necrolysis)

**Contributor's Comment:** Toxic epidermal necrolysis (TEN) is a rare, and often life-threatening skin disease.[1,3,4,5,11] The distinction between this, erythema multiforme (EM) and Stevens-Johnson syndrome (SJS) remains a source of controversy. This partly stems from

Routine Blood Chemistry
Sodium: 148 mEq/L (142-151)
Potassium: 3.1 mEq/L (3.9-5.3)
Chloride: 115 mEq/L (107-117)
Bicarb: 19 mEq/L (15-25)
Anion gap: 17 mEq/L (13-25)
Na:K: 48
Urea: 40mg/dL (8-30)
Creat: 1.7mg/dL (0.5-1.3)
Calcium: 9.1 mg/dL (9.3-11.6)
Phosphate: 6.4 mg/dL (2.8-5.3)
Magnes: 2.8 mEq/L (1.4-2)
Tot Prot: 4.3 g/dL (5.6-7.1)
Alb: 2.1 g/dL (3.1-4.1)
Glob: 2.2 g/dL (1.9-3.6)
A/G: 0.95
Glucose: 183 mg/dL (60-120)
ALT/P5P: 85 U/L (25-106)
AST/P5P: 120 U/L (16-50)
Alk Phos: 348 U/L (12-122)
GGT: <3 U/L (0-10)
TotBili: 5 mg/dL (0-0.3)
Dir Bili: 4 mg/dL (0-0.1)
Ind Bili: 1 mg/dL (0-0.3)
Amylase: 934 U/L (286-1124)
Cholesterol: 269 mg/dL (124-335)
CK: 3633 U/L (58-241)
Iron: 93 ug/dL (98-220)
TIBC: 213 ug/dL (249-496)
%SAT: 44% (28-62)

Hematology
HCT: 34% (42-57)
HB: 11.5 g/dL (14.6-19.7)
RBC: 4.6 mill/uL(6.1-8.5)
MCV: 73 fL (63-74)
MCH: 25 pg (21-26)
MCHC: 34 g/dL (32-37)
RDW: 12.8% (11.3-14)
Retic: 0.4% (0.2-1.1)
Retic-abs: 18.4 thou/ul (10.1-75.9)
Nucl RBC: 1/100WBC (0-1/100WBC)
WBC: 24.8 thou/ul (6.2-14.4)
Seg Neuts: 19.1 thou/ul (3.4-9.7)
Band Neuts: 2.5 thou/ul (0-0.1)
Lymph: 0.5 thou/ul (1.2-4.7)
Mono: 0.7 thou/ul (0.1-1)
Eosin: 2 thou/ul (0.1-2)
Baso: 0 thou/ul (0-0.1)
Plat smear: Low
Plat: 67 thou/ul (179-483)
MPV: 12.3 fL (8.4-13.2)
TP: 6.6 g/dL (5.9-7.8)
RBC Morphology: No significant abnormalities
WBC Exam: Toxic changes in neutrophils (moderate)
Plasma appearance: Icterus (moderate)

Coagulation Panel
Activated Partial Thromboplastin Time: 21.5s (10-17)
Antithrombin 3: 48% (75-120)
D-dimer: 250-500 ng/ml (<250)
Fibrinogen: 1414 mg/dL (150-480)
Protein C: 70%
Prothrombin Time: 17s (14-18)
Thrombin Clotting Time: 5s (5-9)

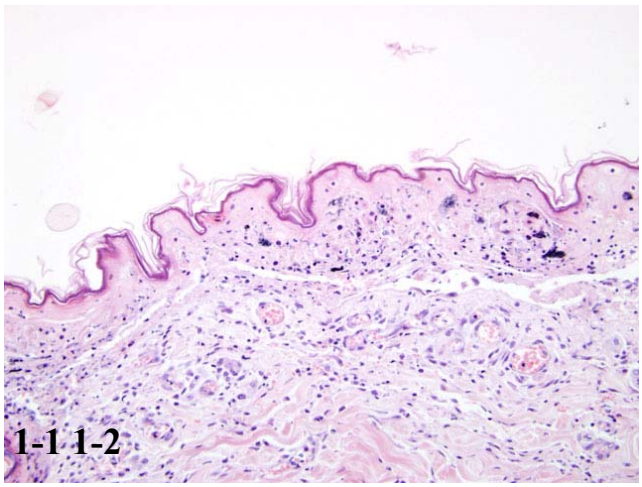
Ancillary Tests
Antinuclear antibody test: Negative

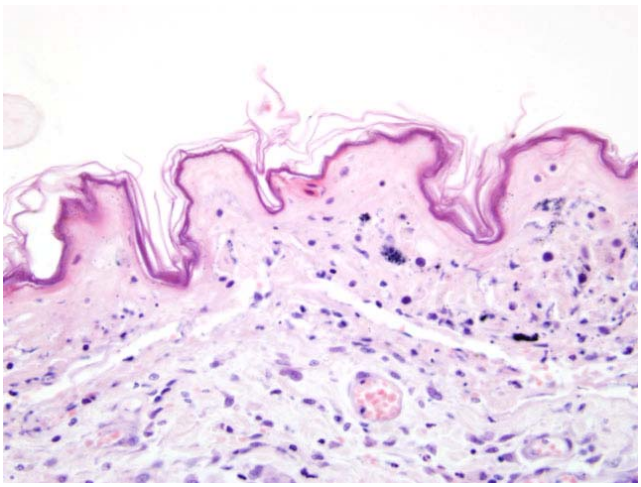
*Table 1-1. Laboratory Values, Case 1.*

the criteria applied to the different conditions, which for some time, was poorly defined. In dogs, Hinn *et al* divided the clinical lesions into five categories: EM-minor, EM-major, SJS, SJS-TEN 'overlap', and TEN.[5]

Clinically, TEN represents the most severe of the three syndromes.[3,4,11] This distinctive clinical presentation has led many to believe this is a pathologically distinct entity from EM.[3,4,11] Microscopically, TEN is characterized by extensive, full thickness, **epidermal cell de ath (fig. 1-1, 1-2).** In the classical sense, this is associated with little to no inflammation. However more advanced cases can develop a degree of inflammation, particularly following dermal-epidermal detachment.[3] SJS bears similarity to TEN, though has less extensive epidermal detachment.[5]

Many authors now consider EM to be clinically and histologically distinct from SJS and TEN.[3,4] Classically,



*1-1. Haired skin, Miniature Schnauzer. Diffuse epidermal necrosis at all levels of the epidermis. H&E X400*
*1-2. Haired skin, Miniature Schnauzer. Higher magnification of keratinocyte necrosis. H&E X100*

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EM is characterized by multiple 'target' lesions (present in 15.9% of cases)[11], and these affect less than 50% of the body. The severity of disease can be variable, but removal of the inciting causes usually produces a clinical resolution within three weeks.[11] Histologically, EM is characterized by multi-level, single cell-death surrounded by lymphocytes or macrophages (satellitosis). Severe cases of EM (EM-major) can develop to transepidermal necrosis, whereby lesions may resemble those of TEN.

A diagnosis of EM, with confluent areas of epidermal necrosis, was considered as a differential in this case. However, we feel that the clinical and histologic findings differ from EM on a number of levels. Importantly, the clinical disease in this animal was severe and rapidly progressive: dermatologic lesions affected large areas of the body (significantly greater than 50%) and there were large areas of epidermal detachment. This was accompanied by profound depression and lethargy, with vomiting and diarrhea. Blood biochemistry and hematology also revealed electrolyte abnormalities; a coagulation panel revealed late stage changes consistent with Disseminated Intravascular Coagulation. Although animals with EM can also be systemically unwell, the extent of antemortem lesions would favor a diagnosis of TEN. From a histologic perspective, the lymphocytes could represent a more chronic change, and possibly a sequel to the extensive epidermal changes.

All of the above syndromes have been associated with an immune reaction against a hematogenous antigen. Drug administration appears to be an important predisposing factor, particularly in cases of TEN where there was a temporal association in over 80% of human cases.[4,11] A similar association seems to exist in the dog.[5] Medication has also been associated with EM and SJS: however the study by Hinn *et al*. found that unlike TEN, the majority of EM cases were not associated with previous drug administration. Other antigens such as infections, vaccination, food, and neoplasms are therefore thought to account for disease in animals.[11] The remaining cases are thought to be idiopathic.

Given the infrequency of the disease in veterinary species, recent studies regarding pathogenesis are largely derived from the human literature. It is generally agreed that the disease represents massive, immune mediated apoptosis of epidermal keratinocytes; however the mechanism by which this occurs is controversial. A number of different theories have been proposed. Some papers have suggested a primary role for both T-cells and NK cells in the development of disease.[2,8,10] Part of the basis for this is the presence of CD8+ lymphocytes within blister fluid and the epidermis in the early stages of disease. Blister fluid is also found to contain high levels of soluble IL-2 receptor, indicative of activated T-cells.[10] Other cytokines and chemokines may also play a role in human cases of SJS and TEN.[2,8,10] In particular, over expression of TNF-α has been shown in many cases of SJS/TEN.[10] IL-5, IL-13 and IFN-g, may also contribute to the inflammation.[2]

A primary role of apoptotic mechanisms has also been proposed.[1,7,12,13] The activation of Fas (CD95), through binding of FasL, may be fundamental to the development of disease. Viard *et al*. showed that blocking Fas/FasL

interactions, through the antibodies in pooled human sera, could prevent keratinocyte death *in vitro*.[13] In one report, a single dog with SJS was successfully treated with human immunoglobulin, and the authors attributed this to the same mechanism.[9] Initial studies suggested that FasL was translocated to the surface of affected keratinocytes. However subsequent publication have failed to consistently demonstrate surface expression of FasL in affected patients.[1] One study found increased levels of soluble Fas ligand (sFasL) in the peripheral blood of patients with SJS-TEN, and this was derived form peripheral blood mononuclear cells(PBMCs).[1] In this same study, keratinocyte apoptosis could be induced *in vitro* , following treatment with serum from SJS and TEN patients. Single nucleotide polymorphisms in Fas and FasL have been suggested to confer susceptibility to these diseases in humans.[7]

Following the appropriate stimulation, apoptosis may occur via activation of death receptors, of which Fas is the most widely studied.[6] In the Fas pathway, binding with FasL (from either autocrine, paracrine or endocrine route) induces receptor triimerization. This facilitates binding of a Fas-associated death domain (FADD), leading to conversion of procaspase 8 and subsequent caspase activation. Other potential mechanisms of apoptosis include activation of TNF-related apoptosis-inducing ligand (TRAIL), which may be important given the high concentrations of TNF-α in lesions.[10] Activated cytotoxic T-cells may also induce apoptosis by perforin/ granzyme B.[10] The contribution of these various pathways is unclear, however there is evidence to suggest that multiple pathways may be involved.

**AFIP Diagnosis:** Haired skin: Epidermal necrosis, diffuse with subepidermal clefting, mild subacute dermatitis, dermal edema, and congestion, Miniature Schnauzer (*Canis familiaris*), canine.

**Conference Comment** : The contributor gives an excellent review of toxic epidermal necrolysis (TEN), the controversy over its association with erythema multiforme (EM) and Stevens-Johnson syndrome (SJS), and the proposed mechanism of epidermal cell death.

In general the separation of these disease entities depends on the clinical as well as the histological criteria. **Table 1-2** lists general characteristics of EM, SJS, and TEN.[4]

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*Table 1 –2.*

| Condition | Location | Characteristics |
|---|---|---|
| **EM, Minor** | No signs of systemic illness<br>At least 1 mucosal surface affected<br>< 10% of body surface | Lymphohistiocytic, perivascular and interface<br>Lymphocytic sattelitosis |
| **EM, Major** | Signs of systemic illness<br>>1 mucosal surface affected<br>10-50% of body surface<br><10% epithelial detachment | High degree of epidermal inflammation, vesiculobullous lesions |
| **Steven-Johnson Syndrome** | 50% of body surface<br>10-30% epithelial detachment | Severe epithelial necrosis |
| **TEN** | Generalized disease<br>More than 30% epithelial detachment | None, or minimal except when ulcerated |

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**CASE II – 22923-05 (AFIP 3066306).**

**Signalment**: Adult, female, spayed, domestic shorthaired, cat, *Felis catus*

**History:** The cat had initially presented with multiple cutaneous and subcutaneous nodular swellings on the paws. Over a 2 year period, these nodules slowly increased in size, coalesced and the overlying skin often ulcerated and developed crusts. Similar, large nodular, firm, coalescing, often ulcerated lesions also developed on the head, deforming the face and along the trunk. There was no response to several courses of antibiotic treatment. The cat was eventually euthanized.

**Gross Pathologic Findings:** The cat was in good body condition having moderate visceral fat stores. Large, 4-5 cm in greatest diameter areas of the dorsal skin surface of both metatarsals were ulcerated and the skin was markedly thickened measuring up to 2.5-3 cm thick due to the presence of coalescing tan-colored nodules. A similar, thickened tan colored, fleshy, ulcerated nodule measuring 3.5 cm in greatest diameter was present on the dorsal surface of the left front metacarpals (**Fig. 2-1**). The skin extending medially and proximally to this area was alopecia and also mildly thickened. Multifocal to coalescing 5-10 mm in greatest diameter firm, nodules expanded the skin below the eyes. The bridge of the nose was ulcerated and the skin was markedly thickened, multinodular and firm (**Fig. 2-2**). A large, 9 cm in greatest diameter and 2 cm thick, flattened, oval, ulcerated, nodule expanded the dermis and subcutis on the left flank (**Fig. 2-3**). These lesions, with the exception of those on the bridge of the nose were freely moveable and on cut surface, were all pale, tan and had a homogenous texture. On the nose, this homogenous tissue extended into and partially effaced the underlying cartilage of the rostral, bridge of the nose and the nasal planum. In the area of the left popliteal lymph node, there was a pale, tan, 4-5 cm in greatest diameter tan nodule. The overlying skin was alopecic. There were several, freely movable, 3-4 cm in greatest diameter, subcutaneous, soft nodules in the mid to caudal ventral abdomen. The visceral organs were grossly unremarkable.

**Laboratory Results:** At postmortem, samples of skin and enlarged regional lymph nodes were sampled. Aerobic and anaerobic culture did not reveal significant pathogens.

**Histopathologic Description:** Sections of skin from lesions from the face, flank, left front and hind feet were examined. Sections of enlarged subcutaneous lymph node were included in some sections. Lesions were all


*2-1. Tan-colored, fleshy mass measuring 3.5 cm in greatest diameter was present on the dorsal surface of the left metacarpals.*
*2-2. Multifocal to coalescing firm nodules expanded the skin below the eyes. The bridge of the nose was ulcerated and the skin was markedly thickened, multinodular and firm.*
*2-3. A large, 9 cm in greatest diameter and 2 cm thick, flattened, oval, ulcerated, nodule expanded the dermis and subcutis on the left flank.*

*Photographs courtesy of Department of Pathology/Microbiology, Atlantic Veterinary College, University of Prince Edward Island, www.upei.ca*

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similar in appearance and consisted of poorly-defined, infiltrative, densely cellular, monomorphic populations of large, polygonal to plump, slightly spindloid cells (resembling fibrohistiocytic populations) which had large, oval to sometimes slightly bean-shaped, nuclei with coarse chromatin, often a single, prominent nucleoli and moderate amounts of variably well-defined, eosinophilic cytoplasm. Anisokaryosis within these cell populations was mild and mitotic figures are occasionally seen (1-2 per 6 HPF). These cellular populations were interspersed with small numbers of lymphocytes, plasma cells, mast cells, occasional small lymphoid follicles and were supported by small amounts of fine, collagenous stroma. These infiltrates extended from the dermoepidermal junction to the panniculus markedly expanding and often effacing the tissue. The overlying epidermis was mildly to moderately acanthotic and often extensively ulcerated. The left popliteal lymph node was markedly enlarged and adherent to the overlying skin. The normal nodal architecture was largely replaced by similar, dense infiltrates of mononuclear cells in which these fibrohistiocytic cellular proliferations predominated. Small residual cortical lymphoid nodules remained, as did the outline of the capsule in areas. There were multifocal large areas of pale lytic necrosis within the node. Subcutaneous nodules from the caudal abdominal or inguinal area represented similarly affected and enlarged lymph nodes. Modified acid-fast and PAS staining of sections of skin and lymph node do not reveal infectious agents. Toluidine blue staining did not reveal cytoplasmic, metachromatic granules. Immunohistochemistry was performed. The majority of mononuclear cell infiltrates were CD18 positive, MHC II positive and negative for T and B cell markers. These findings would be typical of a histiocytic cell population. Numerous CD3 positive T lymphocytes and rare single and clusters of CD45 B cells were also scattered within these infiltrates.

**Contributor's Morphologic Diagnosis:** Severe, multifocal to locally extensive, cutaneous, atypical histiocytic proliferation with ulceration and regional lymph node infiltration, skin of distal limbs, face, and flank

**Contributor's Comment**: The large ulcerated, nodular skin lesions that were so grossly prominent were composed of densely cellular infiltrates of histiocytes or macrophages-like cells interspersed with fewer lymphocytes. Special stains did not reveal infectious agents (such as mycobacterium or fungi) and these infiltrates did not form classic granulomas but instead were arranged in dense sheets. Regional lymph nodes were also multifocally enlarged due to prominent infiltrates of these same histiocytic populations which largely respected lymph node architecture. The postmortem findings, immunohistochemical results and the clinical history in this case are highly suggestive of a rare condition recently reported in cats called Feline Progressive Dendritic Cell Histiocytosis (FPDCH)[1,2]. Very few cases have been reported but the clinical features of those reported cats are very similar to those reported in this cat. Affected cats initially present with a solitary skin nodule, typically located on the head, neck or distal limbs. These lesions progress to multiple, non-painful nodules which may occur anywhere and which commonly become ulcerated. Nodules may

wax and wane but complete spontaneous regression has not been reported. In general, nodules progress in size and may coalesce to form large plaques. Regional lymph node involvement is common in chronic cases. The cause of this rare condition has not been determined. Immune dysregulation and proliferation of cutaneous dendritic cells, such as in Canine reactive histiocytosis, is one possible pathogenesis. However, unlike the canine cases, rare reported attempts to treat affected cats with immunomodulatory drugs has been unrewarding. FPDCH may represent a low grade neoplastic proliferation of dendritic cells which slowly progresses over time.

**AFIP Diagnosis:** 1. Haired skin and panniculus: Atypical histiocytic proliferation, diffuse, severe, with low to moderate numbers of lymphocytes, plasma cells and mast cells, domestic shorthair (*Felis catus*), feline.
2. Lymph node: Atypical histiocytic proliferation, severe (not included in all sections).

**Conference Comment**: Feline progressive dendritic cell histiocytosis (FPDCH) resembles Langerhans cell histiocytosis in humans and is divided into two subgroups, epitheliotropic and nonepitheliotropic.[1] In epitheliotropic form, the cellular infiltrate extends from the dermis up to the basement membrane, with single or clusters of cells located within the epidermis. In nonepitheliotropic form, the infiltrate extends within the dermis up to but not beyond the basement membrane.[1] The exact lineage of proliferating dendritic cells is not known.[1,2]

Histiocytic proliferative diseases may be reactive or neoplastic. Chronically, FPDCH clinically and morphologically resembles histiocytic sarcoma and may affect one or more internal organs.[1,2] This suggests that FPDCH should be considered an indolent, slowly progressive, cutaneous neoplasm that may disseminate to various organs.[2]

The etiology of FPDCH is currently unknown but it is thought to be related to chronic antigen stimulation, although animals do not respond to immunomodulatory therapy.[2]

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**CASE III – CPC07-043; H07-388A (AFIP 3063259).**

**Signalment:** A 6-year-old, female Labrador cross dog (*Canis familiaris*).

**History:** This dog has a ~3 year history of atopy which has been managed using allergen specific immunotherapy and symptomatic anti-pruritic therapy. At the time of biopsy the dog was receiving cyclosporin 30mg q 24hrs, ketoconazole 250mg q 24 hrs, prednisolone 6.25mg q 48hrs, and Episoothe® shampoo baths once a week.

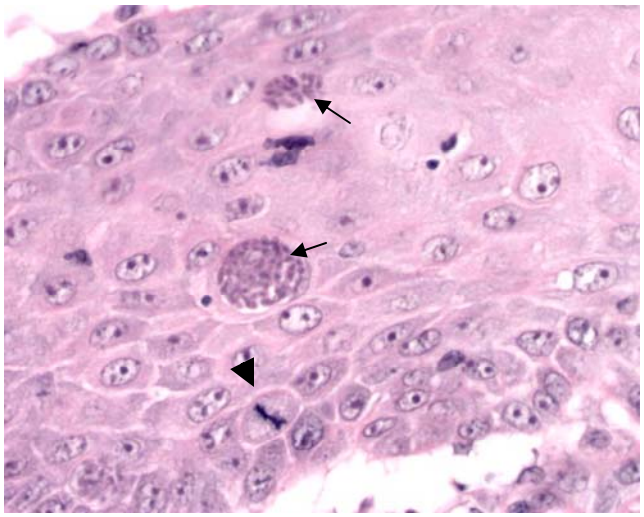
**Gross P athology:** On clinical examination, there were multiple erythemic dermal papular to nodular lesions located on the head, trunk and limbs ranging from 0.5cm to 4cm in diameter.

**Laboratory Results:**
Anti-*Toxoplasma* IgG Indirect Immunofluorescence (IFAT) $\geq$ 1:512
Anti-*Toxoplasma* IgM Indirect Immunofluorescence (IFAT) < 1:32

Anti-*Neospora* Indirect Immunofluorescence (IFAT) $\geq$ 1:25600
Indirect Immunohistochemistry: Anti-*Neospora* Antibody (monoclonal): Positive; Anti-*Toxoplasma* Antibody (polyclonal).
Microbiology: Negative for fungal and bacterial growth

The two samples from the skin of the dog were strongly positive for *Neospora ca ninum* with a *Neospora* qPCR and a nested *Neospora* PCR.

**Histopathologic D escription:** Ten tissue sections were examined from the biopsies submitted, only one was submitted as our Wednesday Slide Conference submission. In all sections there was moderate to marked hyperplasia of the epidermis and outer root sheath of the follicular infundibulum. Within basal and spinous layer keratinocytes of predominately the infundibulum, but also the epidermis were frequent, scattered protozoal pseudocysts containing numerous (~5 to 100) rectangular to banana-



*3-1. Haired skin, Labrador cross. Protozoal pseudocysts containing numerous zoites (arrows) within hyperplastic epidermis. Note mitotic figure in stratum basale (arrowhead) H&E X400.*

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shaped **zoites measuring ~2 x 5 microns (fig. 3- 1)**. There were occasional nodular aggregates of neutrophils and eosinophils within the follicular epithelium and epidermis associated with the protozoal pseudocysts. Follicular infundibulae were distended with keratin, aggregates of degenerate neutrophils and sheets of free protozoal zoites. There was also occasional follicular rupture. Within the dermis was a diffuse interstitial infiltrate of neutrophils, macrophages, lymphocytes and plasma cells. Associated with the inflammatory infiltrate were modest numbers of free and phagocytosed protozoal zoites, which in some areas may have been within vascular endothelium.

**Contributor's Morphologic Diagnoses:** Haired Skin:
1. Moderate to severe, chronic, follicular and epidermal hyperplasia and hyperkeratosis with intra-keratinocyte protozoal pseudocysts DDx: *Neospora*
2. Moderate to marked, diffuse, interstitial pyogranulomatous dermatitis with intrahistiocytic, intraendothelial and free protozoal zoites: DDx: *Neospora*
3. Moderate to marked, multifocal, neutrophilic folliculitis and pyogranulomatous furunculosis with numerous intrakeratinocyte and free protozoal zoites: DDx: *Neospora*

**Contributor's Com ment:** Although indirect immunohistochemistry was positive using a monoclonal primary antibody against *Neospora* and a polyclonal primary antibody against *Toxoplasma*, the very high anti-*Neospora* titre supports a diagnosis of cutaneous Neosporosis in this case. Further work using PCR to further discriminate between *Neospora* and *Toxoplasma* is underway.

Cutaneous Neosporosis has been reported in dogs before, although it is more commonly recognized as a cause of neuromuscular disease in young dogs and abortion in cattle.[2] The predominately cutaneous manifestation of Neosporosis demonstrated in this case may be associated with the concurrent immunotherapy this dog was receiving. CD4+ T-cells have been shown to play an important role in mice in protecting them against *N. caninum* infection.[8] Although cyclosporine is recognized to be an effective treatment for canine atopy with minimal side effects[9], the combination of prednisolone and cyclosporine treatment in this dog would have had a suppressive effect upon cell mediated immunity which is important in protecting dogs against *N. caninum* infection.[8] Neosporosis has been previously reported in an adult dog receiving prednisone and azathioprine.[6]

**AFIP Di agnosis**: Haired skin: Dermatitis and furunculosis, pyogranulomatous, multifocal, moderate, with neutrophilic folliculitis, and intraepithelial intrahistiocytic and free protozoa, Labrador cross (*Canis familiaris*), canine.

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*Table 3-1. Ultrastructural features of Neospora and Toxoplasma.*

| | |
|---|---|
| *Neospora caninum* | Over 11 rhoptries<br>Tachyzoites often not within a parasitophorous vacuole<br>Tissue cysts are relatively uncommon |
| *Toxoplasma gondii* | Few rhoptries<br>Always found in membrane-bound vacuole in cytoplasm |

**Conference Com ment**: *Neospora c aninum* is an apicomplexan that up until 1988 was often misdiagnosed as *Toxoplasma g ondii*.[3] There are three infective stages: oocysts, tachyzoites, and tissue cysts. Canids, in addition to acting as an intermediate host, are considered the primary definitive host.[5] Oocysts are only found in and shed by the definitive host.[5] Tissue cysts, 110µm diameter with a 1-4µm thick cyst wall, are usually found in the brain, spinal cord, and rarely muscle, and contain numerous 2 X 8 µm bradyzoites.[1] Tachyzoites are 4-7µm X 1.5-5 µm and may be located within macrophages, keratinocytes, neutrophils, endothelial cells, or fibroblasts.[5]

Neosporosis affects a variety of species including sheep, goats, and deer, but most importantly, dogs and cattle.[4] It is reported to be one of the most important causes of bovine abortion, and transplacental transmission can occur.[4] In dogs, neurological disease in puppies is common, and cutaneous manifestations have been reported in immunosuppressed animals.[4] Histologically, cutaneous lesions are composed of pyogranulomatous and eosinophilic to necrotizing and hemorrhagic dermatitis.[7] Diagnosis primarily relies on serologic testing.[7]

*N. caninum* can be distinguished from *T. gondii* based on ultrastructural features **(table 3-1).**[1]

We thank Dr. C. H. Gardiner, PhD, veterinary parasitology consultant to the AFIP, for his review of this case.

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## CASE IV - Case #1 (AFIP 3065823).

**Signalment:** 6-year-old, male, neutered, mixed breed dog (*Canis familiaris*).

**History:** The animal had severe non-responsive skin lesions on the left hind leg.

**Gross Pathologic Findings:** The specimen was a formalin-fixed, excisional biopsy of a haired skin mass. The mass was firm, raised and measured 1.7 x 1.0 x 0.3 cm. On cut surface the mass was grey-white.

**Histopathologic D escription:** Expanding the dermis, elevating the overlying epidermis, which is ulcerated in some sections, and infiltrating the subcutis is an unencapsulated, highly cellular mass composed of round cells that infiltrate the superficial dermis and surround hair follicles and adnexa. The cells infiltrate the follicular and glandular epithelium in some foci. Individual cells have distinct cytoplasmic borders, scant to moderate eosinophilic cytoplasm, and irregularly round to indented nuclei with fine lacy chromatin and one or two nucleoli. Mitotic figures range from 1 to 4 per high power field. In some sections, the deeper dermis is infiltrated by neutrophils together with fibrin and edema. In one of the sections provided, there is ulceration of the epidermis and segments of exposed dermis are covered by lytic collagen, protein, necrotic cells (neutrophils) and cellular debris. Within the epidermis are small clusters of lymphocytes and individual round cells surrounded by clear ha-

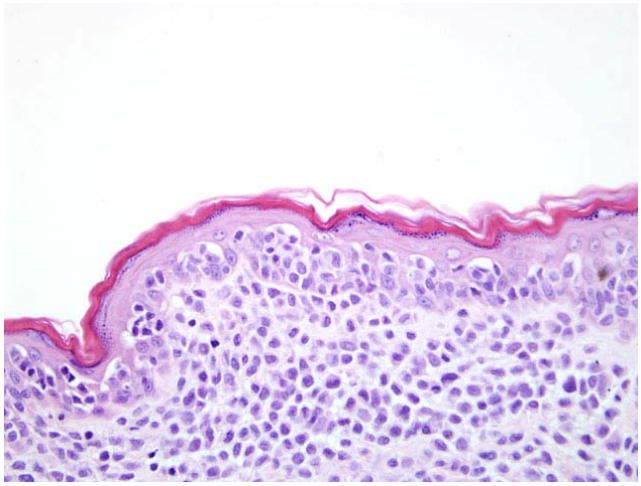
los. Small numbers of plasma cells and macrophages are dispersed throughout the round cell population.

**Contributor's Morp hologic Di agnosis:** Haired skin**:** Epitheliotropic lymphoma.

**Contributor's Comment:** Cutaneous epitheliotropic lymphoma (mycosis fungoides) is an uncommon, slowly progressive disease characterized by neoplastic infiltration of the epidermis and adnexal structures. It represents only 3-8 % of all canine lymphoma cases.[3] This disease has a T-cell origin and includes a wide spectrum of diseases such as mycosis fungoides, sezary syndrome, and pagetoid reticulosis.[4]

Two representative samples of the biopsy of the haired skin were submitted. In one section, there is marked epidermal ulceration with superficial bacterial colonization. The histopathologic lesions in each sample of the biopsy were characteristic of cutaneous **epitheliotrophic lymphoma (abnormal l ymphocytes loc alized in epidermis (fig. 4 -1)**.[4,5] This condition is thought to be analogous to mycosis fungoides (MF) in humans[1], except that in dogs, lymphocytic infiltrates consistently express CD3 and CD8, whereas in human cases, expression of CD 4 predominates.[9] This condition is commonly observed in older dogs; however, its etiology is unknown.[1,3]

In this case, immunohistochemical stains were performed on paraffin-embedded sections with antibodies to the T-cell marker CD3 and the B-cell and plasma cell marker CD 79a. The lymphocytes that compose the population within the dermis and infiltrating the epidermis were strongly positive for CD3 antigen but were negative for CD 79a, indicating that this tumor had a T-lymphoid lineage consistent with immunohistochemical staining patterns previously reported in dogs.[4]



*4-1. Haired skin, mixed breed, canine. Intraepidermal clusters of neoplastic ymphocytes (Pautrier's microabscesses). H&E X400*

The disease progresses from erythematous patches and plaques to nodules and tumors, which are initially localized to the skin and mucous membranes but eventually spread to lymph nodes and metastasize.[9] Due to the uncommon nature of the disease, diagnosis is often difficult. Differential diagnosis for skin lesions in canines include diseases like pemphigus vulgaris and discoid lupus or systemic lupus erythematosus lupus (immune-mediated diseases), histiocytoma, cutaneous histiocytosis and mastocytoma.[5]

This disease has a poor prognosis in the dog. Palliative treatment is often resorted to in order to prolong survival and maintain some reasonable quality of life for the animal.[3,8] Anti-neoplastic drugs may induce temporary remission but are accompanied by side effects like contact dermatitis or cutaneous neoplasia.[2,3,6] Radiotherapy is another option for treatment due to the radiosensitive nature of lymphoma cells.[6]

**AFIP Dia gnosis**: Haired skin: Lymphoma, epitheliotropic, mixed breed dog (*Canis familiaris*), canine.

**Conference Comment** : Cutaneous lymphoma is traditionally divided into epitheliotropic (mycosis fungoides) and nonepitheliotropic forms. The key histological feature of epitheliotropic lymphoma is the tropism of the neoplastic cells for the epidermal and adnexal structures, particularly that of the follicular epithelium and the sweat glands.[7] The neoplastic lymphocytes may be distributed within the epithelium diffusely or as aggregates termed 'Pautrier's microabscesses.'[7]

The epitheliotropic form is further subclassified in the human literature into 4 forms, and although these forms do not generally correlate well clinically, they have been adapted by veterinary literature for histopathological classification (**table 4-1**).[7]

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*Table 4-1.*

| | |
|---|---|
| Pagetoid reticulosis<br>Woringer-Kolopp (localized)<br>Ketron-Goodman (generalized) | Localized or generalized exfoliative erythroderma with scaling, alopecia, erosions or ulcerations without palpable masses<br>Generalized form usually predominates in dogs and cats |
| Classical mycosis fungoides | Most common form seen in dogs<br>Three stages (patch, plaque, and tumor)<br>Patch and plaque stage usually seen simultaneously<br>Progresses to tumor stage with spread to lymph nodes and other organs |
| d'emblée form | Tumor formation without a previous patch or plaque stage |
| Sézary syndrome | Circulating tumor cells in peripheral blood with epitheliotropic lymphoma and peripheral lymphadenopathy |

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