CASE I – PN375/02 (AFIP 2895485)

Signalment: 12 year old, male neutered, Persian, *Felis domesticus*, cat.

History: The cat developed progressive, diffuse, symmetrical alopecia of the neck, abdominal, axillary, inguinal regions and extremities. The skin was thin, greasy and glistening (Fig. 1). The footpads were fissured (Fig. 2). The cat was in poor body condition, lethargic and had severe abdominal distension.

Abdominal ultrasound identified a hypoechoic mass in the pancreatic region and multiple, hepatic focal areas characterized by peripheral hypoechoic and central hyperechoic features. Based on the ultrasound findings and on the owner’s request the cat was euthanized.

Gross Pathology: A full necropsy was performed. In the abdominal cavity a 1 cm in diameter pancreatic mass was observed. Multiple, round, umbilicated, variably sized (0.5 to 3 cm in diameter) hepatic masses were evident. Hepatic and renal lipidosis were observed. Multiple small white nodules were found in the mesenterial fat. Small nodules were disseminated throughout the lungs.

Laboratory Results: Routine haematology and serum biochemistry were unremarkable. T3 and T4 and cortisol levels were in the normal range. Feline leukemia virus and feline immunodeficiency virus tests were negative. Skin scrapings revealed the presence of elevated numbers of budding yeasts with the typical morphology of *Malassezia* sp. No mites were observed. Wood’s lamp examination and dermatophyte cultures were negative.
Contributor’s Morphologic Diagnoses:
Haired skin (neck):
1. Severe, diffuse, follicular telogenization with follicular miniaturization.
2. Minimal to mild, chronic lymphoplasmacytic and neutrophilic perivascular dermatitis with mild acanthosis and multifocal parakeratosis with loss of granular cell layer.

Contributor’s Comment: The epidermis of most areas evaluated was characterized by multifocal to diffuse parakeratosis with loss of normal superficial keratin layers, loss of granular cell layer and mild, diffuse, irregular acanthosis extending to the follicular infundibulum. In some sections a focal erosion can be seen. Occasionally (in few sections) mild keratinocyte basal and suprabasal dysplasia is present. The major finding is the presence of hair follicles in telogen phase and complete absence of anagen follicles. Moreover, most follicles are reduced in size (follicular miniaturization) and in some area of the mid-dermis, residual follicles have a thickened fibrous sheath. Sebaceous glands are normal in number and in size or mildly hyperplastic. Occasional sweat gland dilation and stasis is present. The dermal collagen was characterized by increased fragility.

The additional histopathological findings of the tissue examined were consistent with pancreatic exocrine adenocarcinoma with secondary hepatic, mesenteric and pulmonary metastases. The cutaneous findings were interpreted as paraneoplastic alopecia associated with pancreatic adenocarcinoma.

In cats, paraneoplastic alopecia has been associated with pancreatic exocrine adenocarcinoma or biliary duct adenocarcinoma. The association of pancreatic and hepatic malignancies with this dermatosis is not clear. Several metabolic imbalances such as hypoproteinemia or deficiencies in biotin, zinc, fatty acids have been proposed.

The glistening appearance of the skin is considered a characteristic feature of feline paraneoplastic alopecia. This feature is interpreted as secondary to the loss of the stratum corneum that is not related to trauma or excessive grooming. Also, no abnormal production of insulin, glucagon, somatostatin or adrenocorticotropic hormone has been detected. Both loss of stratum corneum and follicular atrophy have been hypothesized to originate from the release of circulating products from the tumor.

The differential diagnosis of bilaterally symmetrical alopecia in cats needs to include demodicosis, dermatophytosis, endocrine, immune mediated and neoplastic disease. In most cases, demodicosis and dermatophytosis are excluded by skin scrapings and cultures, as it was in this case.
In feline hyperadrenocorticism, clinical findings of polyuria, polydipsia, insulin resistant diabetes and increased skin fragility are typical. In cases of paraneoplastic alopecia no skin fragility has been reported and the glistening appearance is characteristic. Histopathology in the two diseases has some similarities, however in cases of paraneoplastic alopecia a normal or mildly acanthotic epidermis and follicular miniaturization with no prominent follicular keratosis are distinctive\textsuperscript{2}.

Although the gross appearance of the lesions may be similar, clinical signs in this cat were not consistent with hyperthyroidism and T3 and T4 basal levels were normal. Other differential diagnoses need to include self-induced alopecia and telogen and anagen defluxion. However, clinical and histopathological findings allow the exclusion of these disorders.

*Malassezia* sp. infection is rare in cats. However, the association of *Malassezia pachydermatis* dermatitis with paraneoplastic alopecia and internal malignancies has been documented in cats\textsuperscript{5,6}. Thus, in cats *Malassezia* sp. generalized infection is considered indicative of internal disease. Frequently, as it was in this case, in cats with paraneoplastic alopecia no specific histopathologic changes associated with *Malassezia* overgrowth have been detected\textsuperscript{5}.

AFIP Diagnosis: Haired skin: Follicular atrophy, diffuse, severe, with epidermal hyperplasia and minimal lymphocytic perivascular inflammation, Persian, feline.

Conference Comment: The contributor gives a thorough review, with differential diagnosis, for paraneoplastic alopecia in cats. As mentioned, the features of complete follicular atrophy on the ventrum and the characteristic smooth, glistening gross appearance of the alopecic skin are diagnostic for this syndrome. Reports of successful surgical excision of the neoplasm resulted in regrowth of hair.\textsuperscript{8,9}

Rare *Malassezia* sp. were present in the stratum corneum in some sections. Finding *Malassezia* on histopathology is difficult because the organisms in the stratum corneum are often lost during processing. Generalized *Malassezia* dermatitis in cats is rare and their presence is considered a poor prognostic sign, as they are often associated with an internal malignancy or immune suppression.\textsuperscript{6}

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References:

CASE II – 1548-03 (AFIP 2888029)

Signalment: 13-year-old male, canine, Shetland sheepdog.

History: Lip biopsy from a dog with thickened, inflamed lips, and mild inflammation on the nose.

Gross Pathology: Not applicable.

Laboratory Results: None reported.

Contributor’s Morphologic Diagnosis: Discoid lupus erythematosus.

Contributor’s Comment: This section shows the junction of the normal lip haired skin and the inflamed glabrous skin, with heavy upper dermal, interface, plasma cell-rich, mononuclear cell inflammation in the upper dermis and sometimes

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migrating into the basal epithelium. There is marked basal layer melanosis and many melanophages are in the upper dermis (pigmentary incontinence). Hypereosinophilic, separating, acanthocytes (“Civatte bodies”) are occasionally seen in the epidermis, within and near small intraepidermal microabscesses. This dog is doing very well two months later with steroid therapy.

The lip margin is the most common site in our biopsy submissions of discoid lupus, but the lesions also occur on the nasal planum as “Collie nose”. Besides Collies and Shelties, German Shepherds and Siberian Huskies have a breed predilection.

AFIP Diagnosis: Mucocutaneous junction (per contributor): Dermatitis and cheilitis, superficial, lymphoplasmacytic, diffuse, moderate, with numerous intracorneal pustules, Shetland sheepdog, canine.

Conference Comment: There was marked variation in submitted slides, with two distinct presentations in the slides presented in conference.

The first presentation is that of dermatitis and cheilitis with intracorneal pustules, rare intraspinosus pustules, and acantholytic keratinocytes. The differential diagnosis discussed included pemphigus erythematosus, as it represents a crossover syndrome of pemphigus and lupus erythematosus, and pemphigus foliaceus, since pemphigus erythematosus is also described as a variant of pemphigus foliaceus. Both syndromes are characterized by subcorneal pustules and acantholysis. Lesions of pemphigus erythematosus are usually confined to the face and often have lichenoid inflammation. Pemphigus foliaceus may involve the dorsal muzzle, planum nasale, pinnae, periorbital skin, footpads, or trunk, although facial lesions of this syndrome are indistinguishable from pemphigus erythematosus. These two conditions may be differentiated using immunofluorescent or immunohistochemical testing. Immunoglobulins are found in the intercellular spaces of the epidermis in pemphigus foliaceous, whereas they are found both in intercellular spaces of the epidermis and along the basement membrane in pemphigus erythematosus.1,3

The second presentation has furunculosis and intraepithelial pustules containing bacteria, but acantholytic keratinocytes are not present. The differential diagnosis discussed for this second presentation included mucocutaneous pyoderma and discoid lupus erythematosus (DLE). Both of these affect the nasal planum and mucous membranes and have similar clinical and histopathologic features. Plasma cells often predominate in mucocutaneous pyoderma, whereas lymphocytes and macrophages predominate in DLE. Features of DLE include lichenoid interface
dermatitis, hydropic degeneration of basal cells, thickened basement membrane zone, apoptotic keratinocytes, and marked mononuclear periadnexal and perivascular dermal infiltrate. Basal cell degeneration is not a feature of mucocutaneous pyoderma.\textsuperscript{1,2,3}

Conference attendees discussed the clinical importance of these two different presentations within the same lesion and the limitations of evaluating a single section. If only one tissue section from this dog was evaluated, indicated therapy or prognosis could significantly differ, depending on which section was evaluated.

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**References:**

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**CASE III – G6535/7 or G6542/9 (AFIP 2892541)**

**Signalment:** Tissue from a 1 year-old male tamarin (*Saguinus fuscicollis*).

**History:** The animal had nonspecific clinical signs. In the course of a febrile disease the animal exhibited severe sero-mucous nasal discharge and single hemorrhagic to papular skin lesions.

**Gross Pathology:** At necropsy skin lesions were distributed randomly over the body, but preferentially on the face, scrotal regions and on the soles and palms. The skin lesions presented as hemorrhagic lesions. Some developed into erythematous papules, and single papular lesions became crusted. The oral mucous membranes had severe necro-ulcerative inflammation. Notable facial oedema was evident. Peripheral lymphadenopathy was marked and involved submandibular and axillary lymph nodes.

**Laboratory Results:**

Histology: A spectrum of different focal epithelial lesions became obvious. These patterns were categorized as severe epidermal hemorrhage and vesiculation, epidermal acanthosis and acantholysis as well as full thickness epidermal necrosis and ulceration. In some locations hair follicles and sebaceous glands were involved. The histopathologic pattern depended on the stage of development, degree of severity and superimposed bacterial infections. Eosinophilic granular intracytoplasmic inclusion bodies were found in degenerate keratinocytes within single locations of epidermal origin.

Electron microscopy revealed virus particles with orthopox-like morphology within intracytoplasmic inclusions. Ultrastructurally, mature viral particles measured 140 x 260 nm. The enveloped viral particles were ovoid to brick-shaped with a pale central zone, presenting characteristic pox-like ultrastructural features.

Real time PCR: DNA from different tissues was analyzed with a set of orthopox specific real time PCR assays. The presence of orthopox virus was confirmed, excluding at the same time variola virus. Virus could be detected in different organs among them liver, spleen, lung, intestine, skin and mucosa.

Contributor’s Morphologic Diagnosis: Skin: Dermatitis, vesicular, multifocal, severe, subacute, with epithelial ballooning degeneration, epithelial syncytia and eosinophilic variably sized intracytoplasmic inclusion bodies (Guarnieri bodies).

Contributor’s Comment: A putative cowpox virus, member of the genus orthopoxvirus, was identified as the causative agent for this fatal infection. Cowpox virus is a rodent virus that may infect cats, cows and zoo animals and, through contact to these, humans. Cowpox virus infections are endemic in cattle, although clinical cases in the European cattle population are rare. Field and experimental studies have indicated that cowpox has a broad host range and a wildlife reservoir in rodents and foxes. Furthermore, the virus is often isolated from domestic cats, which should be regarded as important vectors in urban areas. The orthopoxviruses are epitheliotropic. Typical lesions are characterized by vesicle formation and intracytoplasmic inclusion bodies. The presence of abundant co-infecting bacteria is a common sequela to poxviral ulceration. Lesions in humans can often be found on the hands, forearms, face and neck. Predisposition, such as immunosuppression, may lead to a more severe or fatal course of infection like in a case of a glucocorticoid treated asthma patient after contact with a cat. A careful evaluation of the epidemiology of cowpox virus infection suggests that cowpox has a low virulence and contagiousness for humans, although the situation for nonhuman primates is still unclear.
**AFIP Diagnosis:** Haired skin: Dermatitis, vesicular, acute, multifocal, marked, with superficial dermal hemorrhage, and keratinocyte and sebocyte syncytia and eosinophilic intracytoplasmic inclusion bodies, saddle-backed tamarin (*Sanguinus fuscicollis*), nonhuman primate.

**Conference Comment:** Conference attendees discussed the presence of very large syncytia and the presence of intracytoplasmic inclusion bodies in both keratinocytes and sebocytes.

Cowpox virus is found in Western Europe and Asia. Among the range of species infected by this virus, cats are important in the zoonotic transmission of this virus. Cowpox in cats has even been called “feline cowpox” or “catpox”. The disease in cats is presumably due to exposure to infected rodent hosts, as cases increase in the autumn when the rodent populations peak.\(^6,^8\)

Cats present with a single primary cutaneous lesion on the head or forelimbs, which is the site of direct contact with the infected rodent. The primary lesion is characterized by an ulcerated nodule with crusts. After 7-14 days, multiple secondary lesions develop anywhere on the body as ulcerated erythematous nodules that eventually scab over. Systemic signs are rare but may be present if the cat is immunosuppressed. Cats with cowpox and concurrent feline immunodeficiency virus (FIV) or feline leukemia virus (FeLV) infection have been reported to have fatal complications.\(^6,^7,^8,^9\) Histopathology reveals typical orthopoxviral lesions: hydropic degeneration of epithelial cells (ballooning degeneration) and eosinophilic, intracytoplasmic inclusion bodies. Immunohistochemistry, culture, PCR analysis, rising antibody titer, and electron microscopy may be used to confirm the diagnosis. Ultrastructurally, orthopox virions are brick-shaped, 250 x 200 nm and have an irregular arrangement of surface tubules.\(^7,^8,^9\)

Besides orthopoxviruses, only three other genera of poxvirus cause disease in humans: parapoxvirus, molluscipoxvirus, and yatapoxvirus. Parapoxviruses (orf, pseudocowpox, bovine papular stomatitis) cause erythematous papules on the hands, fingers, and forearms (“milker’s nodules”) in humans. Molluscipoxvirus causes molluscum contagiosum in humans, characterized by multiple discrete epidermal nodules that occur anywhere on the body except the soles and palms. Yatapoxviruses (Yabapox and tanapox) occur naturally in tropical regions. Yabapox produces large, benign tumors that regress in 2-3 months. Tanapox is a common skin infection in parts of Africa.\(^7,^9\)

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References:

CASE IV – 252/03 (AFIP 2899565)

Signalment: 2-year-old heifer, Ayrshire, Bos taurus, bovine.

History: Three heifers on a dairy farm had developed skin lesions during the winter. The lesions were pruritic, alopecic, circular, 2-3 cm in diameter, with moderate crust formation. The lesions were situated in the head and thorax region. There were also nodular skin lesions. Skin biopsies were sent for histologic examination.

Gross Pathology: See history.

Laboratory Results: None reported.
Contributor’s Morphologic Diagnosis: Haired skin: Dermatitis and folliculitis, lymphocytic and eosinophilic, chronic, focal, with mild hyperkeratosis. Within stratum corneum and hair, fungal structures (hyphae and arthrospores), consistent with *Trichophyton* sp. Dermatophytosis (ringworm)

Contributor’s Comment: Dermatophytosis is most commonly caused by zoophilic dermatophytes, *Trichophyton* and *Microsporum* in animals\(^2\). Bovine dermatophytosis is almost exclusively caused by *Trichophyton verrucosum*. Other dermatophytes that have been isolated from bovine dermatophytosis are, for example, *T. mentagrophytes*, *T. quinckeanum*, *T. rubrum*, *T. megninii* and *M. canis*\(^4\). The disease occurs worldwide. It is not fatal but it causes high economic losses in cattle farming and it is zoonotic\(^4,5\).

*Trichophyton verrucosum* has been isolated from soil, dung and numerous fomites. The disease is commonly seen where the climatic conditions are optimal to fungi. Most cases appear in the winter among housed animals (crowding, contamination, high humidity and darkness in the buildings). It is transmitted by direct contact or by indirect contact by contaminated objects such as housing, fencing and grooming equipment. Latent carrier animals act as a reservoir of the infection. Young animals are more susceptible; they have not developed immunity against the disease and their skin physiology is different (alkaline pH). Other predisposing factors are poor condition and immunosuppression\(^1,2\).

Dermatophytosis is a superficial cutaneous mycosis. The infection involves the keratinized layers of the skin and the hair; dermatophytes do not invade living tissue. The fungi are keratinolytic. The infection with *Trichophyton* sp. may be initiated if the stratum corneum is altered by slight trauma or by continued moisture and maceration. The branching septate hyphae of the fungi colonize the surface stratum corneum, the follicular infundibulum and the hair shafts. The boring hyphae penetrate the hair cuticle and tunnel extensively through the cortex. The hyphae break up into round arthrospores within the hair (endothrix) or on its external surface (ectothrix). The dermatophyte produces disease by excreting irritant substances like trichophytin, causing an effect similar to irritant contact dermatitis. This results in increased epidermopoiesis in the surface epidermis and proximal external root sheet, histologically seen as hyperplasia and hyperkeratosis. Mononuclear cells and neutrophils infiltrate the dermis and epidermis. Later, subcorneal and intracorneal microabscesses are formed and significant numbers of eosinophils may be seen, especially in bovine and canine\(^3\). Secondary bacterial infections may occur.
The classic gross lesion in dermatophytosis is an annular area of alopecia, stubbled hairs, and scaling or crusting, and dermatitis. The predilection sites are the head, neck and pelvis. The lesions may be pruritic and painful.

The infection is usually self-limiting and the duration of the disease is usually 1-4 months. Reinfection is uncommon. Cell-mediated immunity is considered more important than humoral, antibody-mediated reactions, but it seems that the combination of both is needed for the elimination of the fungi. Efficient vaccines have been developed. Preventive measures consist of hygiene and vaccination of cattle.

AFIP Diagnosis: Haired skin: Dermatitis, perifollicular and perivascular, lymphocytic and eosinophilic, diffuse, moderate, with intracorneal pustules, epidermal hyperplasia, and intrafollicular hyphae and arthrospores, Ayrshire, bovine.

Conference Comment: The pathogenic genera of dermatophytes include Microsporum, Trichophyton, and Epidermophyton. Zoophilic dermatophytes (such as Microsporum canis and Trichophyton verrucosum) are animal pathogens. Anthropophilic dermatophytes (Epidermophyton) are adapted to human beings and rarely infect animals. Geophilic dermatophytes (such as Microsporum gypseum) are soil saprophytes and, under favorable conditions, may infect humans and animals.

The most important causes of dermatophytosis in dogs and cats are Microsporum canis, Trichophyton mentagrophytes, and Microsporum gypseum. Cats are natural hosts for M. canis and are often asymptomatic carriers. Lesions in cats vary from small areas of alopecia or broken hairs to nodular and ulcerated lesions. Dermatophytic pseudomycetoma is a rare manifestation of M. canis infection that occurs almost exclusively in Persian cats. Grossly, lesions are nodular with fistulous tracts. Histologically, granulomatous inflammation with aggregates of compact mycelia is present in the deep dermis and subcutis. The most frequently isolated species in dogs is M. canis, which causes alopecia with scaling, crusting, erythema, folliculitis and furunculosis. Microsporum gypseum causes a rare manifestation of dermatophytosis in dogs that produces discrete, solitary cutaneous nodules called kerion. These are areas of intense inflammation and furunculosis.

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