The Armed Forces Institute of Pathology
Department of Veterinary Pathology

Conference Coordinator:
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WEDNESDAY SLIDE CONFERENCE 2008-2009

Conference 9

12 November 2008

Conference Moderator:

Dr. Michelle Fleetwood, DVM, Diplomate ACVP

CASE I – SDSU-1 (AFIP 3105831)

Signalment: 7 to 8-week-old pig (*Sus scrofa*)

History: Skin rash

Gross Pathology: Multifocal to coalescing skin lesions with mild to severe crusting were present over the entire body surface. Lesions were slightly raised. Periocular crusting was so severe the eyes appeared permanently closed. Generalized moderate lymphadenopathy was also present. This pig also had a large, reducible umbilical hernia.

Histopathologic Description: Within sections of skin, there is multifocal subcorneal pustular dermatitis with mild to moderate epidermal acanthosis and hyperkeratosis **(Fig. 1-1)**. Many cocci bacteria are present **(Fig. 1-2)**. Multifocal epidermal ulceration and suppurative folliculitis are evident in some areas (not present in every slide). Within the superficial dermis there is congestion, edema and multifocal hemorrhage. There is also mild perivascular to interstitial infiltration of the superficial dermis by lymphocytes. The dermal inflammation is more pronounced in areas of epidermal ulceration.

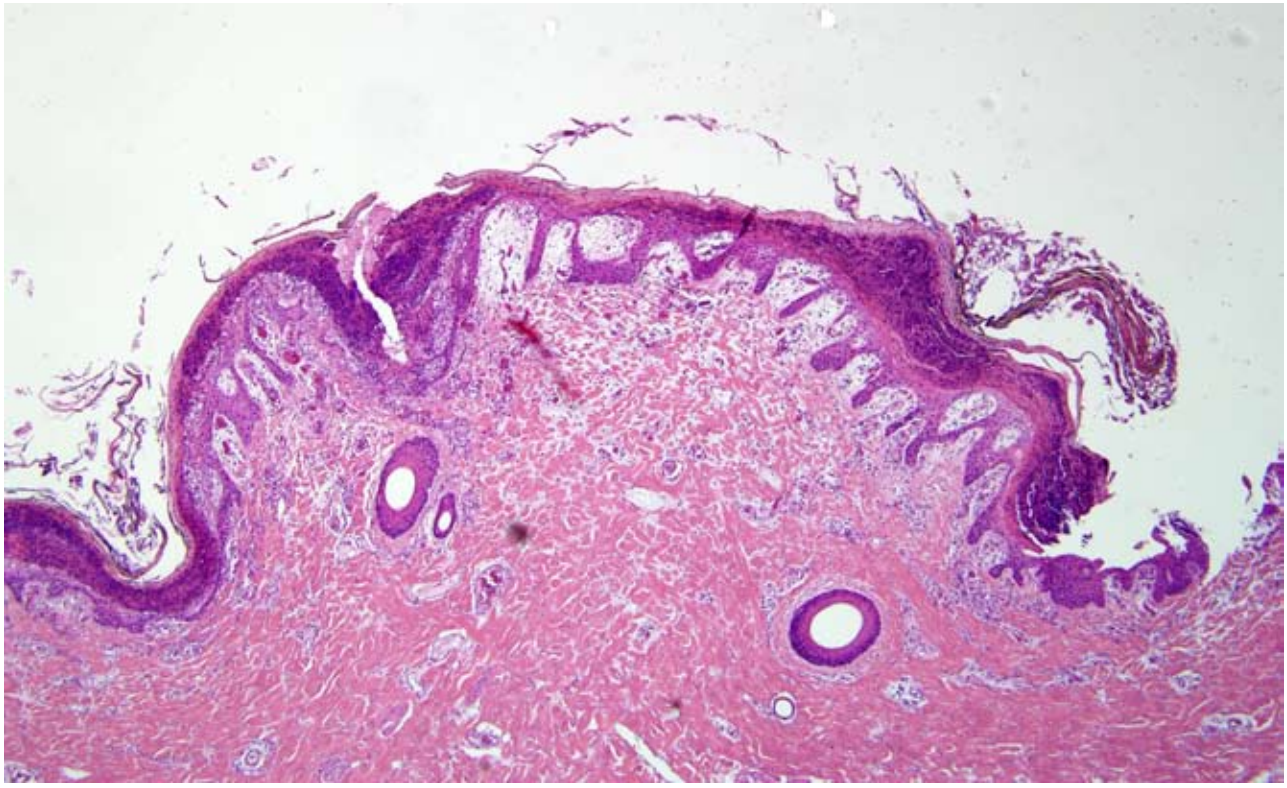
Contributor's Morphologic Diagnosis: Haired skin: Dermatitis, subcorneal, pustular and proliferative, acute to subacute, multifocal, mild to severe, with multifocal ulceration, and multifocal folliculitis due to *Staphlococcus hyicus*

Contributor's Comment: Exudative epidermitis (greasy pig disease) is caused by *Staphlococcus hyicus* and is most common in pigs 5–35 days of age.[1,2] Although *S. hyicus* is a member of the normal skin flora of healthy pigs, trauma resulting in a breach of the skin barrier may predispose pigs to developing skin lesions.[1,2] *S. hyicus* produces exotoxins which cause intra-epidermal cleavage, resulting in separation of epidermal cells and lesions typical of exudative epidermitis.[1]

The presence of cocci bacteria in the epidermal pustules of pigs affected by exudative epidermitis makes this condition similar to human bullous impetigo. Human bullous impetigo is an infection caused by staphylococcal exotoxins and characterized by epidermal pustules which contain many cocci bacteria.[1]

AFIP Diagnosis: Skin: Epidermitis, exudative and proliferative, multifocal, moderate with ulceration and mild superficial dermatitis and intracorneal cocci

***Sponsored by the American Veterinary Medical Association, the American College of Veterinary Pathologists, and the C. L. Davis Foundation.**

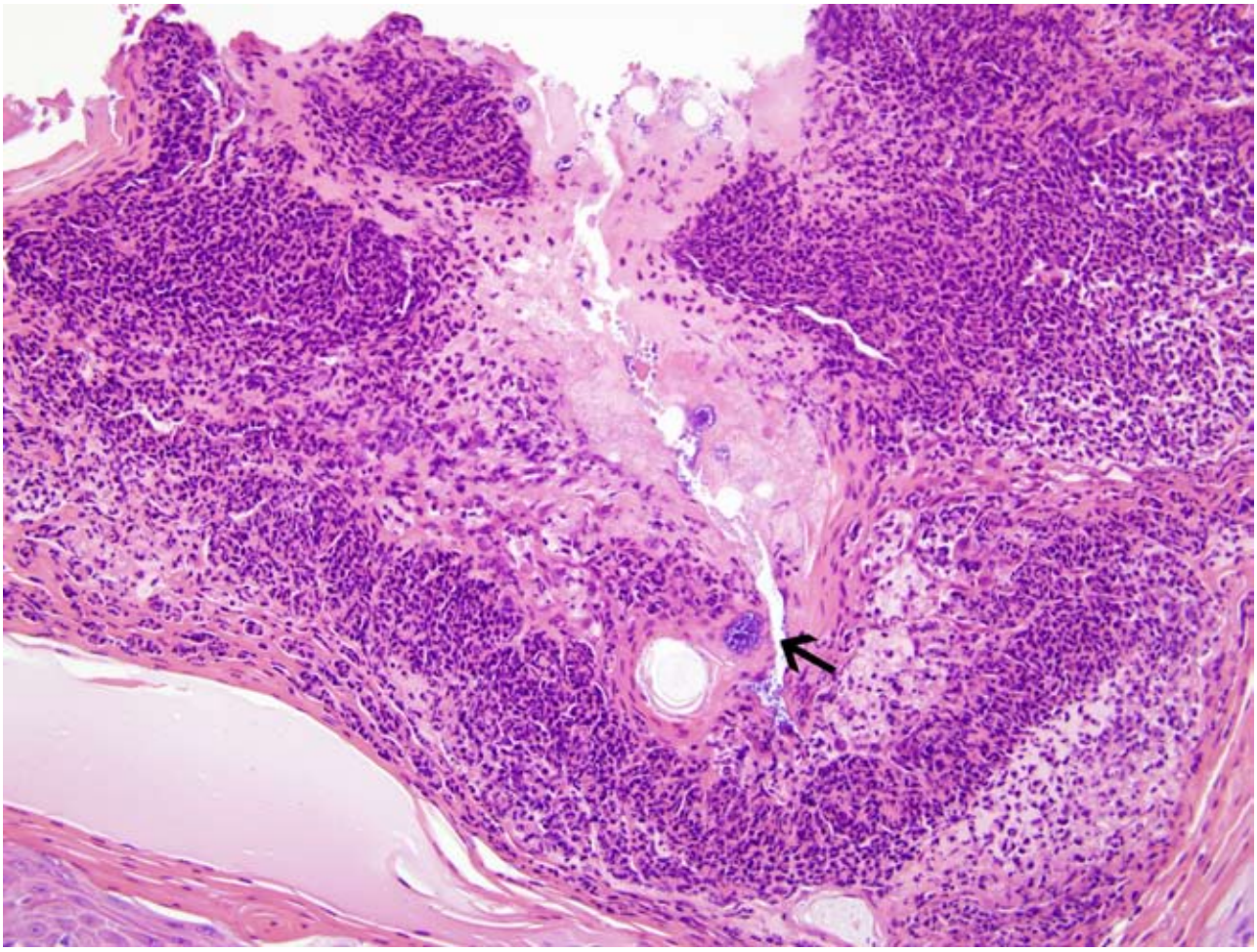


1-1. Pig, haired skin. Multifocal to coalescing intracorneal pustules, epidermal hyperplasia, and mild perivascular lymphoplasmacytic infiltrate. (HE 40 X)

Conference Comment: *Staphylococcus hyicus* causes a fatal generalized exudative epidermitis in neonatal pigs. The exotoxins produced by *S. hyicus* are metalloproteases that target the stratum granulosum, causing cleavage between the stratum corneum and stratum granulosum. In addition to the cutaneous lesions, piglets can have conjunctivitis, oral lesions and renal lesions. Renal lesions range from epithelial vacuolation, degeneration and exfoliatin of the cells lining the renal pelvis and collecting ducts that can lead to uretheral occlusion to suppurative pyelonephritis. Older pigs may develop subcutaneous abscesses, polyarthritis, necrosis of the ears and tail, abortion and mastitis. *S. hyicus* is the proposed cause of flank-biting and necrotic ear syndrome of pigs, which results in large ulcerated and crusty lesions in early weaned pigs. [2]

Exudative epidermitis of pigs is similar to two human conditions: staphylococcal scalded skin disease and bullous impetigo. Both of these conditions have exfoliotoxins that cause separation between the stratum spinosum and stratum granulosum. However, in bullous impetigo the cocci are present within the intact pustules like in exudative epidermitis, whereas in scalded skin syndrome the cocci are located at a distant often extracutaneous site.[2] *Staphylococcus intermedius* exfoliotoxins cause impetigo, bullous impetigo and superficial spreading pyoderma in dogs.[3]

Review of this slide led to a discussion of various cutaneous lesions in swine. *Sarcoptes scabiei* causes erythematous allergic dermatitis with secondary self trauma and crusting. Lesions are primarily located on the rump, flank and abdomen.[2] Zinc-responsive dermatosis in swine occurs in 2-4 month old growing pigs, and causes thick, dry scales and crusts that can produce deep fissures. Roughly symmetrical lesions are often found on the lower limbs, around the eyes, ears, snout, scrotum and tail. The microscopic lesion is marked hyperplastic dermatitis with parakeratotic hyperkeratosis.[2] Dermatosis vegetans is an inherited disorder in Landrace pigs that results in vegetating skin lesions, hoof malformations and giant cell pneumonia. Skin lesions range from brown-black plaques with a raised border and depressed center to dry-horny papillomatous lesions. The head is typically spared.[2] *Erysipelothrix rhusiopathiae* causes septicemia with cutaneous vasculitis and rhomboidal dermal infarcts, and is also known as “diamond back skin



1-2. Pig, haired skin. Colonies of cocci within the intracorneal pustules (arrows), admixed with numerous degenerate neutrophils. (HE 200X)

disease." Additional lesions in acute cases include fibrinoid glomerular necrosis, renal intracapsular hemorrhage and fibrinous polyarthritis. The most common lesions in chronic cases include vegetative valvular endocarditis, chronic proliferative arthritis and diskospondylitis.[6] Blue discoloration of the ears, tail and snout are due to venous thrombosis most commonly caused by *Salmonella cholerasuis*, but also other septicemic and viral infections such as *Erysipelothrix rhusiopathiae*, porcine pestivirus (Classical swine fever) and porcine asfarvirus (African swine fever).[1] Porcine dermatitis and nephropathy syndrome causes a systemic necrotizing vasculitis with hemorrhagic dermal infarcts, exudative glomerulonephritis and interstitial nephritis in feeder pigs. Skin lesions typically occur on the perineal area of the hindquarters, limbs, dependent areas of the abdomen and thorax, and ear margins. The condition has been associated with Porcine circovirus-2 and Porcine reproductive and respiratory syndrome virus (PRRS).5 Porcine juvenile pustular psoriasiform dermatitis is most common in weaned Landrace pigs, and causes erythematous serpigenous plaques on the ventral abdomen and inner thighs. Histological lesions include eosinophilic perivascular inflammation, spongiform pustules and psoriasiform hyperplasia.[2] Swinepox is caused by suipoxvirus. Typical poxviral lesions include proliferative and necrotizing skin lesions with large eosinophilic intracytoplasmic inclusions. Lesions primarily occur on the ventral and lateral abdomen, lateral thorax and medial legs of young, growing pigs. Mucosal surfaces are rarely affected. *Hematopinus suis*, the sucking louse, acts as a mechanical vector.[2] Melanomas are often congenital in the Duroc, Sinclair minipig and in Hormel crosses.[2]

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CASE II – 3777-3 (AFIP 3107686)

Signalment: Juvenile, weaned harbor seal (*Phoca vitulina*)

History: Over the course of the last 10 years, 20 apparently healthy neonatal and juvenile harbor seals presented to local rehabilitation facilities having either died peracutely with no overt premonitory signs, or had an acute onset of lethargy, depression and dehydration, that rapidly progressed to death.

In this case, the animal had presented to rehabilitation as a neonate in late August, 2007, had been apparently normal for 4 weeks, and fed a herring-based formula. The animal presented acutely moribund, inappetant, unresponsive, and died.

Gross Pathology: On necropsy, this animal featured segmental to diffuse hemorrhagic enterocolitis characterized by dark red to pink mucoid intestinal contents that were frequently admixed with variable amounts of fibrin. In more severely affected segments of bowel, the mucosa was diffusely dark red, friable, and frequently featured miliary punctuate foci of acute hemorrhage. Mesenteric lymph nodes were enlarged, grey black, and glistening on sectioned surfaces.

Laboratory Results: NA

Histopathologic Description: Along varying levels of bowel revealed superficial to near full thickness necrosis of the mucosa with segmental to diffuse fibrin pseudomembrane formation. The lamina propria had variable congestion with multifocal hemorrhage and occasional scattered neutrophils.

Contributor's Morphologic Diagnosis:
Intestine: Enteritis, fibrinous and erosive, marked, multifocal to segmental, presumptively due to *Clostridium difficile*

Contributor's Comment: In this case, aerobic and anaerobic culture of multiple levels of bowel yielded mixed growth of *Escherichia coli, Enterococcus* spp, and *Pseudomonas* spp. Culture with selective media isolated *Clostridium difficile*, and ingesta was positive for *Clostridium difficile* toxin A and B (ELISA, Premier TM Meridian Bioscience, Inc., Cincinnati, OH). Microscopically, these enteric lesions are consistent with a variety of bacterial pathogens, including *Salmonella* spp, *Clostridium perfringens, Clostridium difficile*, and strains of *Escherichia coli*, possibly exacerbated by agonal shock (peracute ischemia may present with similar mucosal changes). In human and veterinary medicine, many clostridial infections are polymicrobial and it is difficult to resolve their contribution to the pathogenesis of the lesions. Further microscopic characterization and possible in vitro studies or use of ligated bowel may assist in resolving the role of this pathogen in clinical disease.

Members of the genus *Clostridium* are considered ubiquitous within the environment, often associated with detritus, soil, ocean sediment, and as a component of the gastrointestinal tract flora of humans and other vertebrates. Many infections are considered endogenous. In humans, foals and piglets, this pathogen is associated with antibiotic associated diarrhea and pseudomembranous colitis and infection may be mild and self limiting or fatal due to enterocolitis. It is important to note that toxin positive animals may not exhibit signs or lesions and lab results should be correlated clinically and pathologically.

Even if this is not considered a significant pathogen from the host perspective, harbor seals in rehabilitation facilities may function as multiplying species for a potential zoonotic pathogen and staff should be appropriately educated about hygienic practices. The culture from this animal, and

isolates from 4 other post mortem cases were forwarded to the CDC, Atlanta, Georgia and the more virulent form of this bacteria, strain 027, was not detected by molecular screening.

AFIP Diagnosis: Small intestine, villi: Necrosis, acute, diffuse, with myriad bacilli

Conference Comment: *Clostridium difficile* causes pseudomembranous colitis in primates, and enteritis and/or colitis in many other species. Disease is usually associated with an imbalance in the intestinal flora and clostridial overgrowth secondary to antibiotics, stress or a change in feed.[1] In horses, *C. difficile* causes proximal enteritis and hemorrhagic enteritis in foals, and colitis in horses of all ages. Colitis X is an acute colitis in horses that is often attributed to *Clostridium perfringens* type A, or less commonly *C. difficile*.[1] In neonatal pigs, *C. difficile* causes fibrinous typhlocolitis with volcanic ulcers, and scrotal edema, hydrothorax and edema of the mesocolon similar to seen with Edema disease.[1] *C. difficile* causes disease in a variety of laboratory animals, but is most significant in the guinea pig where it results in antibiotic-associated dysbacteriosis. Although *C. difficile* can cause diarrhea in rabbits, the most common clostridial pathogen associated with the enteritis complex in juvenile rabbits is *Clostridium spiroforme*.[3]

C. difficile produces two major toxins: toxin A and toxin B. Toxin A is an enterotoxin that stimulates chemokine production, which attracts leukocytes. Toxin B is a cytotoxin that modulates cellular signaling pathways, induces cytokine production and causes apoptosis.[4,6]

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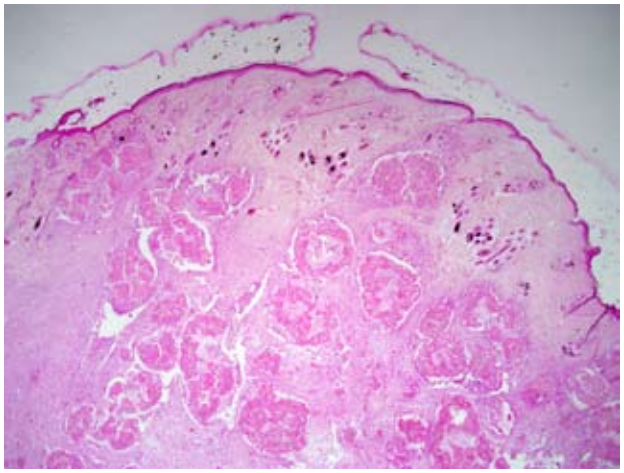
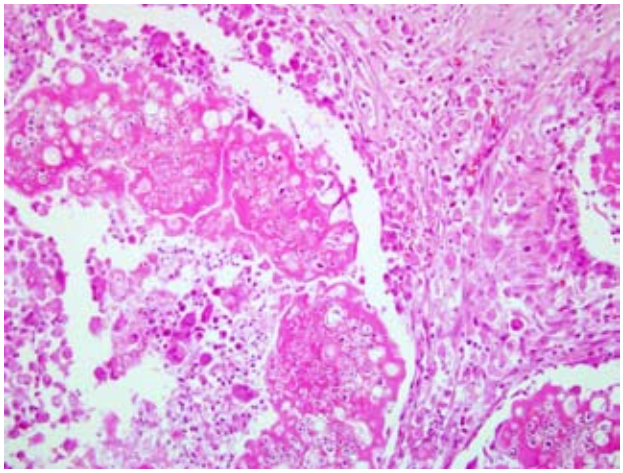


3-1. Cat, skin. Expanding the panniculus and deep dermis are numerous multifocal to coalescing variably sized nodules composed of a deeply eosinophilic material bounded by a cellular infiltrate and fibrosis. (HE 40X)



3-2. Cat, skin. Pyogranulomtous inflammation, homogenous eosinophilic material and numerous fungal hyphae and which often exhibit bulbous swelling. (HE 400X)

CASE III – 5512 (AFIP 3106280)

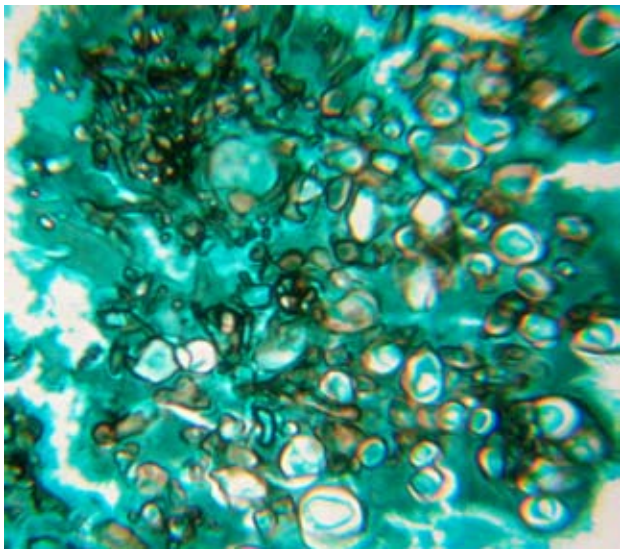
Signalment: 5-year-old, female, persa, *Felis catus*, feline

History: At the first examination the cat had numerous variably ulcerated dermal nodules at dorsal and mammary region, which drained purulent exudates with cement-like substances containing yellowish granules. The cat was treated with griseofulvin at 10 mg kg, orally twice a day. However, the size of the nodules increase after the fifth month of treatment and the cat showed progressive weight loss. Combination treatment of surgical excision with systemic antifungal therapy excision would be initiated, but the animal died during the surgical procedure.

Gross Pathology: External examination revealed numerous subcutaneous irregular shaped coalescing nodules (2.5–5.0 cm in size) at the back, mammary and inguinal regions. Fistulisation of the nodules was common. From the opened nodules drained an orange honey-like and finely granulous content. Skin on the nodules was alopecic, darkened with a blue or violaceous color and without erythema.

Laboratory Results: Microbiology of dermal lesions: Culture performed from nodules yielded dark yellow colonies consistent with *Microsporum canis*. No pathogenic bacteria were isolated.

Histopathologic Description: Histological lesions were characterized by a pyogranulomatous



3-3. Cat, skin. Subcutaneous tissue contains myriad fungal hyphae with bulbous swellings. (GMS). Photomicrograph courtesy of Departamento de Patologia Animal Faculdade de Veterinária UFPel – Campus Universitário s/nº 96010-900 Pelotas-RS Brazil.

inflammation with giant cells, macrophages, neutrophils and lymphocytes surrounding oval to polyhedral, variable sized granule-like structures **(Fig. 3-1)**. Each of these granules was composed of fungal aggregates with markedly dilated bulbous spores and few vesicular septate hyphae **(Fig. 3-2)**. These fungal structures are embedded in abundant amorphous eosinophilic deposits characteristic of the Splendore-Hoeppli reaction. The periphery of the nodules was characterized by infiltration

of macrophages, lymphocytes and plasma cells, an intense fibroblastic reaction and angiogenesis. Overlying epidermis was ulcerated, or showed discrete acanthosis.

Organisms were strongly positive using periodic acid-Schiff stain. Mycelia was also evidenced with the Gomori's methenamine-silver stain **(Fig. 3-3)**. Both are used to demonstrate the fungal nature of the granules.

Contributor's Morphologic Diagnosis: Skin: Pseudomycetoma and granulomatous dermatitis focally extensive severe with fungal structures, *Felis catus*, feline

Contributor's Comment: Dermatophytic pseudomycetoma is a rare manifestation of *Microsporum canis* infection [11] and causes deep dermal/ subcutaneous infection of man and animals, with granulomatous/ pyogranulomatous reaction surrounding dermatophytic hyphal elements. The infection has been reported mostly in cats, in humans, rarely in dogs and horses.[7] Persian cats have a high incidence of pseudomycetoma formation, suggesting a heritable predisposition. Those cats may also show a concomitant typical dermatophytosis, but others were detected previously as asymptomatic carriers or can have no known history of previous ringworm.[2]

This type of dermatophytic infection differs from dermatophytosis, in which lesions are restricted to epidermal structures.[2] Pseudomycetomas must be distinguished from fungal mycetomas, or eumycotic mycetomas. True mycetoma is a nodular inflammation with fibrosis, fistulae draining from deep tissue, the presence of grain, and an indolent infection of certain fungi or higher bacteria inoculated into subcutaneous tissues.[4] In pseudomycetomas there are 1) multiple lesions, 2) lack of skin trauma history, 3) association with dermatophytes, most commonly *Microsporum canis* [1, 2, 7] histologically, lack of true cement material and a more abundant Splendore-Hoeppli reaction.[1,2,4] Additionally, in pseudogranules, there are fewer hyphal filaments than in true eumycotic granules. Pseudomycetoma granules have a sequential development, characterized by the presence of small to large clusters of mycelia elements.[4]

It is unclear why the cat developed a pseudo-mycetoma.[9] Several hypotheses on the pathogenesis of the disease have been proposed. In contrast to the supposed traumatic origin of a mycetoma, in pseudomycetoma some authors propose that mycelial elements escape from the hair follicle into the surrounding tissues [1, 7] where they aggregate and induce an immune response. The exact immunological mechanism responsible for the formation of the granules is much debated, as well as the predisposition of Persian cats to the disease.[1] There is a recent report of an intraabdominal pseudomycetoma in a Persian cat who had no suspicion of immunosuppression, no history of cutaneous ringworm infection, and no prior abdominal surgery. Possible sources of this infection include: ingestion of infected foreign material, secondary to prior castration, inoculation from rectal thermometer, or other penetrating wound.[9] A chronic evolution is the rule, and the prognosis is fair even with systemic antifungal therapy of long duration.[2]

A definitive diagnosis of pseudomycetoma involves a combination of histopathology and either identification of the causal organism by fresh tissue culture or by identification of the organism by immunohistochemical stains.[1,9]

The pathognomonic histologic lesion is the presence, deep in the dermis and subcutis, of aggregates of compact mycelia within a granulomatous tissue reaction. The fungi may be surrounded by amorphous eosinophilic material representing the Splendore-Hoeppli reaction. The overlying skin may show parasitized shafts in the absence of inflammation or the more typical folliculitis. Fungi in the superficial lesions have normal morphology. Invasion of hyphae through the external root sheath has been described.[11] Cytology is useful for making diagnosis of mycetomas in humans, but it can be difficult to perform.[9] A cytological diagnosis of pseudomycetoma should be suspected and is warranted if arthrospores and refractile septate hyphae are present in cytologic specimens from Persian cats with single or multiple dermal nodules, especially if pyogranulomatous inflammation is also present.[2]

Fungal culture represents by far the most reliable diagnostic evidence to ascertain the aetiological agent of these infections.[7] Microsporum canis is isolated in most cases, but colonies do not always have a typical appearance on primary cultures, and macroconidia are often lacking. Molecular tools have been used on histological sections for identification of dermatophytic mycetomas.[2] PCR seems to be a reliable and useful complementary method to identify the aetiological fungus from paraffin-embedded sections obtained from cases of dermatophytic pseudomycetoma in different animal species. Molecular biology could be a valid alternative identification method when 1) culture is unsuccessful; 2) in retrospective analysis, when only a stored histological section is available; 3) and in further studies on the aetiologic agents of Dermatophytic pseudomycetoma from biopsy confirmed pathological specimens.[7]

Differential diagnosis with nodulous tumoral diseases

is necessary, and a dermatophytic origin would be suspected for all pseudo-tumoral masses observed on feline skin [2] and, especially in Persian cats, when poorly marginated intraabdominal mass were detected on imaging examinations.[9]

AFIP Diagnosis: Skin: Panniculitis and dermatitis, pyogranulomatous, nodular, focally extensive, severe with multiple aggregates of fungal hyphae

Conference Comment: The contributor provided an excellent overview of the entity. Pseudomycetomas are most common in Persian and Himalayan cats. Other conditions that are more common in Persian cats include polycystic kidney disease, alpha-mannosidosis, facial dermatitis (Himalayan cats included), and Chediak-Higashi Syndrome. Polycystic kidney disease (PKD) is inherited as an autosomal dominant trait, like the adult form of PKD in humans. Fibrosis and cysts also occur within the liver of many affected cats.[8] Alpha-mannosidosis is most common in cattle (Angus, Murray Grey and Galloway) and cats (Persian and domestic). There is deficient lysosomal alpha-mannosidase activity in almost every cell but hepatocytes, resulting in cytoplasmic vacuolation most evident in neurons and secretory epithelium.[6] Facial dermatitis of Persian and Himalayan cats is an uncommon, idiopathic facial dermatitis that causes a matting of the facial hair by dark, greasy sebaceous material in young cats.(3) Chediak-Higashi syndrome is an autosomal recessive condition that is reported most commonly in humans, cattle, Persian cats, beige mice, rats and Aleutian mink.[10] Affected animals have a defective LYST/CHS1 gene that regulates intracellular protein trafficking and vesicle fusion.[5] This defect causes enlarged granules in melanosomes, granulocytes and platelets which results in color dilution, bleeding tendencies and recurrent infections.[10]

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CASE IV – 0707051 (AFIP 3075498)

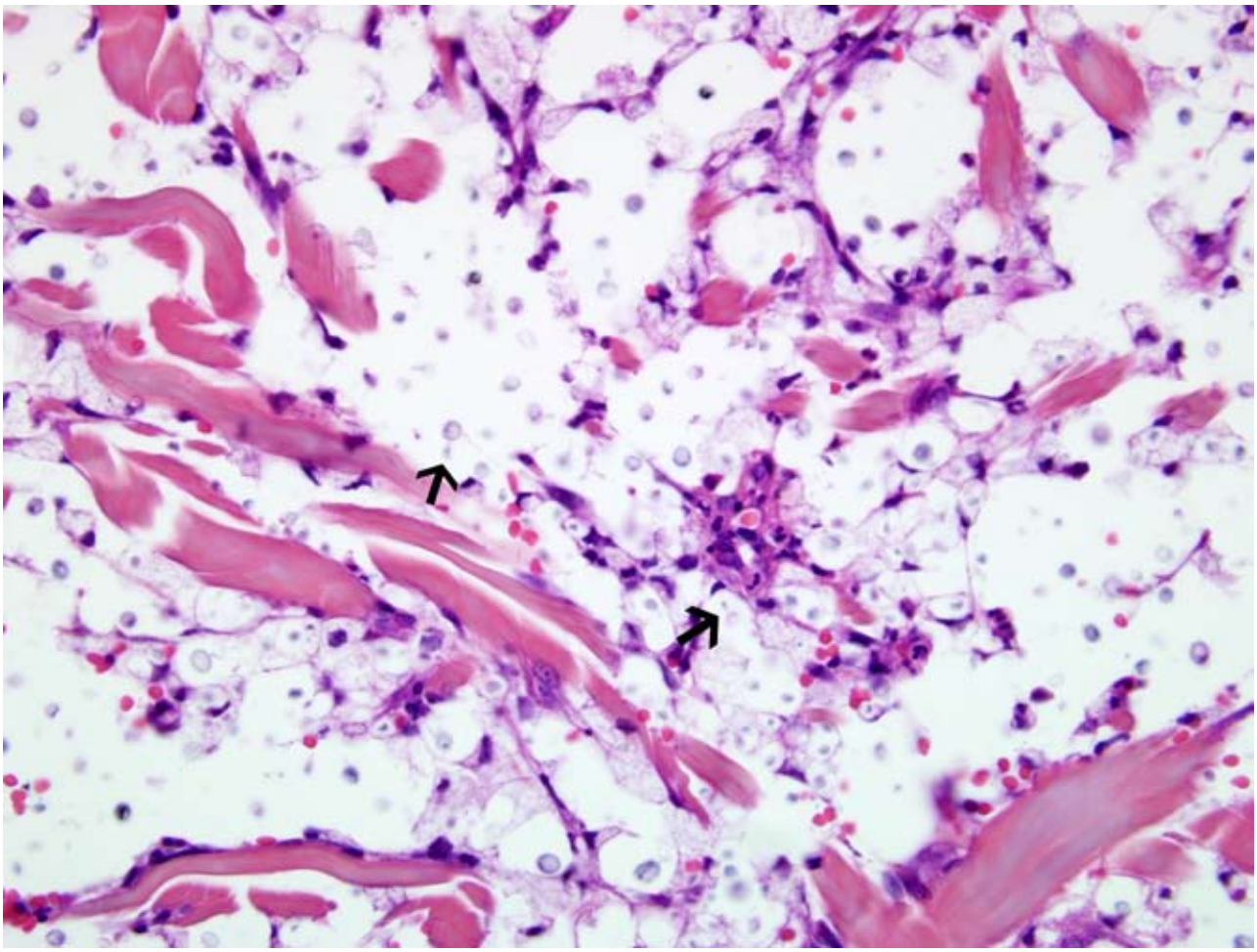
Signalment: Canine, 2-year-old, female, Husky-cross, *Canis lupus familiaris*

History: A biopsy from the ear was submitted.

Gross Pathology: NA

Laboratory Results: NA

Histopathologic Description: A section of haired skin from the ear was submitted in which there is diffuse (and in other regions not included, multinodular foci of dense yeast-like organisms that extended from the superficial dermis to the deep dermis underlying a multifocally ulcerated epidermis with multifocal acanthosis and intraepidermal separation (just above the basal layer). There was associated neutrophilic inflammation and scattered foamy macrophages. Organisms were round



4-1. Dog, skin. Diffusely with the dermis there are myriad yeast characterized by an approximately 15-20 micron nucleus surrounded by thick up to 40 micron clear capsule; occasional yeast exhibit narrow-based budding (arrows).

to oval (3-20 microns) and refractile surrounded by a clear capsule (up to 40 microns). Some structures exhibit narrow-based budding **(Fig. 4-1)**.

Contributor's Morphologic Diagnosis: Dermatitis, multifocal ulcerative with intradermal yeast-like fungi (*Cryptococcus neoformans*); cutaneous cryptococcosis

Contributor's Comment: Cutaneous crypto-coccosis is apparently rare in dogs and more common in cats.[2] The organism is a ubiquitous saprophyte that is common in nitrogen-rich, alkaline soil and particularly associated with pigeon excrement. The disease is seen most frequently in humid climates and is unusual in climates such as Wyoming. Inhalation of airborne organisms is frequently followed by local upper respiratory tract infection and cutaneous infection is thought to be local extension. Concurrent immunosuppressive conditions such as diabetes and neoplasia may predispose to infection but this association is still inconclusive.[3] Rare reports of cryptococcosis in dogs include infection of the central nervous system and rare cutaneous infection results from disseminated systemic disease.

AFIP Diagnosis: Dermatitis and panniculitis, pyogranulomatous, diffuse, severe with numerous yeast, etiology consistent with *Cryptococcus neoformans*

Conference Comment: *Cryptococcus neoformans* (*C. neoformans* ssp. *neoformans*) is the most common systemic fungal infection in cats. The respiratory system is primarily infected; with hematogenous spread to other organs, most commonly the central nervous systems, skin and eyes. Cryptococcal mastitis in cows is an ascending, rather than hematogenous, infection. *Cryptococcus* sp. is the only pathogenic fungus with a capsule. The capsule

causes the gross lesions to appear gelatinous and the histological lesions to have a "soap bubble" appearance.[1] Mucicarmine stains the capsule.

The major virulence factors of *Cryptococcus* are the capsule and the production of antioxidants such as melanin. The capsule impairs phagocytosis, activates complement, and possibly suppresses T lymphocytes. The rare acapsular strains of *Cryptococcus* sp. incite abundant granulomatous inflammation and are readily phagocytized, making them much less pathogenic than the capsular strains. The acapsular strains of *Cryptococcus neoformans* resemble *Blastomyces dermatitidis* but can be distinguished by the presence of narrow-based budding in the former and broad-based budding in Blastomyces dermatitidis. Some strains are able to produce antioxidants such as melanin and phenoloxidase (laccase), which protect the organism from oxidative damage by leukocytes.[1]

Cryptococcus gattii (previously *C. neoformans* ssp. *gattii*) is primarily found in tropical and subtropical climates. It is associated with eucalyptus trees and infections in koalas. However, it has recently been reported in the temperate Pacific Northwest, primarily in British Columbia, where it has infected humans, dogs, cats, porpoises and ferrets. Unlike *Cryptococcus neoformans*, it often infects immunocompetent hosts.[4]

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