Joint Pathology Center
Veterinary Pathology Services

WEDNESDAY SLIDE CONFERENCE 2014-2015

Conference 12

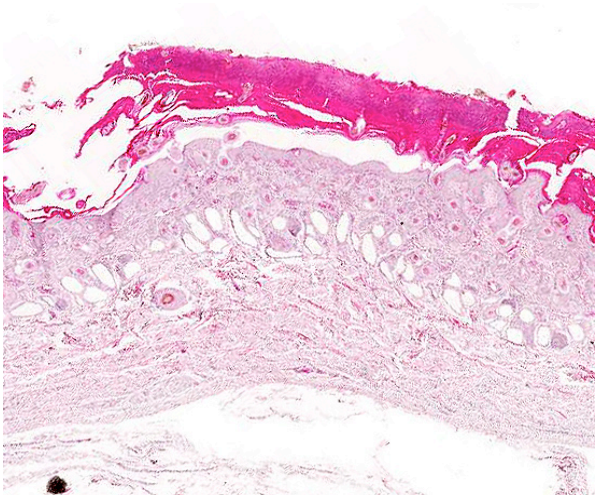
10 December 2014

CASE I: 1734-10 (JPC 4003079).

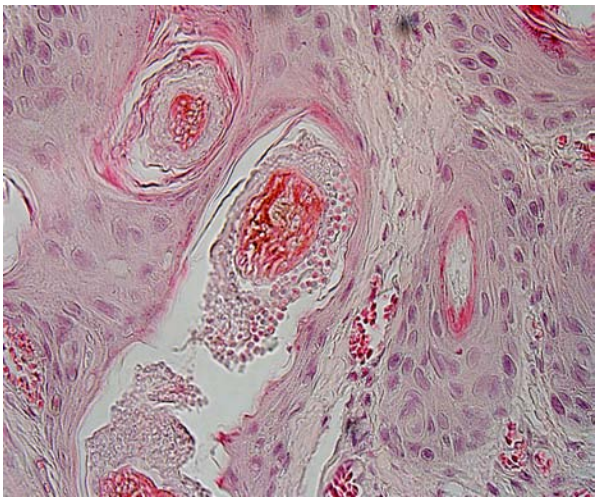
Signalment: 3-month-old female Holstein-Friesian calf, *Bos Taurus*.

History: In the flock there was a history of diarrhea, emaciation and pneumonia. This calf died and was submitted for necropsy.

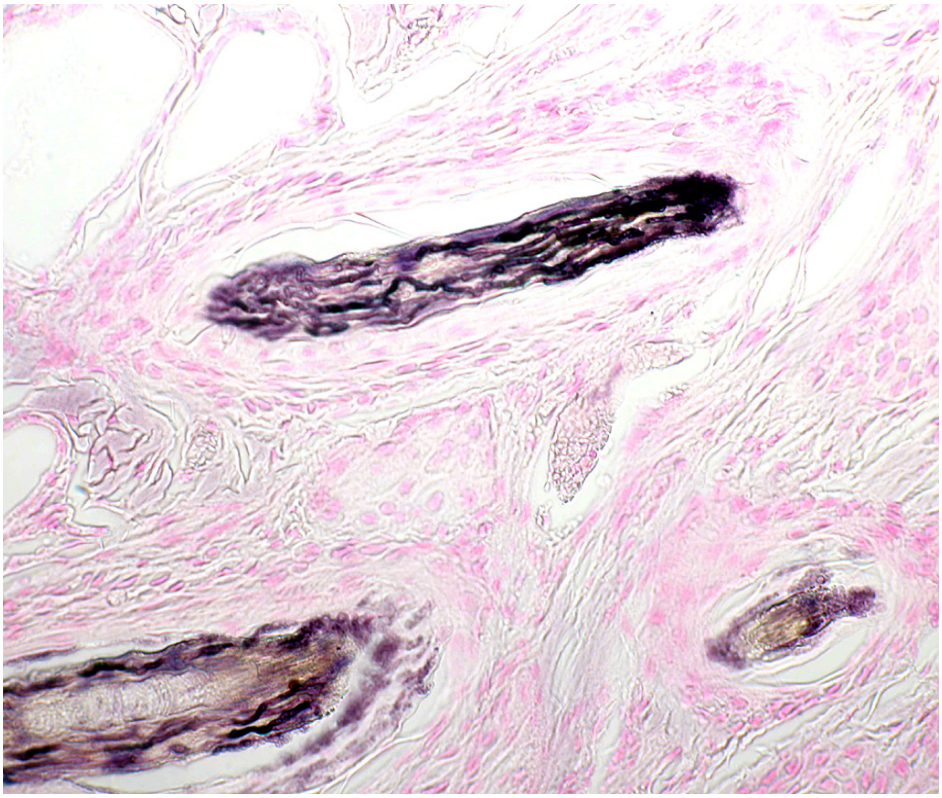
Gross Pathologic Findings: The calf was emaciated (weight 37.5 kg), with serous atrophy of the pericardial adipose tissue. There were multiple gingival ulcers located where the teeth had contact with the buccal mucosa, an acute diffuse purulent rhinitis and a marked bronchopneumonia of the cranioventral lung areas. Predominantly at the head and neck, the skin showed multifocal well demarcated areas characterized by alopecia, crusts and thickened epidermis.



1-1. Haired skin, calf: There is a thick serocellular crust covering a focally extensive area of the epidermis. (HE 6X)



1-2. Haired skin, calf: There are numerous 2-3 µ m arthrospores surrounding the hair shaft and hyphae within the medulla of the hair shaft itself, seen primarily in negative relief. (HE 400X)



1-3. Haired skin, calf: A silver stain demonstrates the fungal hyphae within the hair shafts. (Photo courtesy of: Institut fuer Veterinaer-Pathologie, Justus-Liebig-Universitaet Giessen, Frankfurter Str. 96, 35392 Giessen, Germany http://www.uni-giessen.de/cms/fbz/fb10/institute_klinikum/institute/pathologie) (Grocott, 400X)

Laboratory Results: No specific pathogens were identified. Skin was not examined microbiologically.

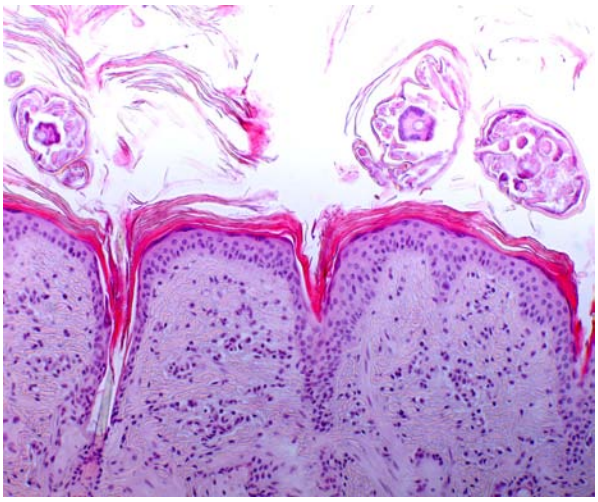
Histopathologic Description: Haired skin: Multifocally affecting the epidermis and dermis, there is an eosinophilic inflammation. The epidermis is covered by thick serocellular crusts composed of lamellated eosinophilic material (keratin), karyorrhectic and cellular debris (degenerated eosinophils and neutrophils) and an eosinophilic homogenous material (exudate). The epidermis is mildly thickened (hyperplasia) and shows an orthokeratotic hyperkeratosis. On the epidermal surface and between the keratin lamellae of the stratum corneum, there are multiple cross and tangential sections of adult arthropod parasites measuring up to 1 mm in diameter. They are round to oval, have a chitinous exoskeleton with occasional spines, striated musculature and jointed appendages (scab mites).

Within dilated hair follicles and around free hair shafts in epidermal crusts are numerous 2-3 µm sized basophilic arthrospores and hyphae with thin parallel walls and indistinct branching and septation (*Trichophyton sp.*). Often, hair follicles are additionally mildly expanded by clumped keratin (infundibular hyperkeratosis). Around blood vessels in the upper dermis is a mild inflammatory infiltrate composed of eosinophils, of lymphocytes and as well as of lesser neutrophils and macrophages. Sweat glands are mildly dilated.

Contributor's Morphologic Diagnosis: Haired skin: Dermatitis, perivascular, eosinophilic, mild, with superficial crusting, epidermal and follicular hyperkeratosis with dermatophytes and mites, etiology consistent with *Trichophyton verrucosum* and *Psoroptes ovis*. (Dermatophytosis and psoroptic mange)

Contributor's Comment: In the bovine, predominantly *Trichophyton verrucosum* causes ringworm. Other isolates (*T. mentagrophytes, T. equinum, Microsporum gypseum, M. canis, M. nanum*) may also play a role in bovine skin disease. Outbreaks are often associated with crowding with a seasonal increase of cases in fall and winter. Lesions have a typical anatomical distribution: the skin of head and neck. Clinical signs are pruritic and alopecic well-demarcated thickened skin lesions with scales and crusts.[1,3,4]

Transmission occurs through contact while arthrospores may survive in the environment for more than a year. Dermatophytes colonize the superficial dermis and hair follicles and they are adapted to digesting keratin.[4,5] Histologically, dermatophytes are more easily detectable using PAS method or Grocott stain. Septated hyphae are detectable between the keratin of the stratum corneum and within the hair shafts. There is



1-4. Haired skin, calf: Cross-sections of several arthropod parasties (consistent with mites) are present superficially to adjacent, less affected skin. Unfortunately, it is not possible to speciate the mite in tissue section. (Photo courtesy of: Institut fuer Veterinaer-Pathologie, Justus-Liebig-Universitaet Giessen, Frankfurter Str. 96, 35392 Giessen, Germany http://www.uni-giessen.de/cms/fbz/fb10/institute_klinikum/institute/pathologie) (Grocott, 400X)

regularly a mild acanthosis and hyperkeratosis. Inflammatory changes are often mild.[1] Vaccination is effective for prophylaxis and treatment of bovine ringworm.[6]

Scab mites cause a highly pruritic dermatitis and psoroptic mange is like demodicosis of high economic importance in bovine species. In some countries it is a reportable disease.[1,3] *Psoroptes ovis* is the assumed species of mites responsible for psoroptic mange in cattle.[8] Mites can survive for about 7-12 weeks outside the host. Transmission results directly by contact or indirectly by vectors (e.g. bedding, contaminated objects like feed fences or cow brushes). Psoroptes mites complete their life cycle on the skin. In contrast to *Sarcoptes sp.*, they do not invade the epidermis.[7]

Lesions in cattle can be detected at the skin of the head, neck, back, inguinal and sacral areas and may become generalized. They are characterized by alopecia, crusts, scales and exudation. Due to severe pruritus, excoriations and secondary bacterial infections may blur the picture. In more severe cases the skin shows increased thickness with diffuse alopecia and deep folds.[1,3,7]

In accordance with the clinical symptoms, histologically there is superficial perivascular dermatitis with eosinophils, lymphocytes, macrophages and mast cells. Due to an assumed hypersensitivity reaction there is often spongiosis and marked dermal edema. In chronic cases, hyperplasia of the epidermis can be observed.[1] Mites could be identified microscopically within skin scrapings or biopsies, but not with certainty.[7]

Sarcoptic mange is a differential diagnosis for the lesions in the present case. However, in the present case, the mites are detectable on the surface and between superficial keratin lamellae whereas *Sarcoptes* mites dig deeper. On the other hand there were no burrows filled with eggs and/or larvae within the layers of the epidermis, which are typical for *Sarcoptes* but not seen in *Psoroptes* infestation.[1]

In the present case, a combined infection with dermatophytes and mites occurred. The nutritional stage and concurrent debilitating diseases may have influenced the development of both infections. Both diseases, mange and dermatophytosis, are differentials for each other, and it has to be considered, that dermatophytosis is a zoonotic disease. In contrast to *Sarcoptes* mites *Psoroptes* mites are believed to be non-pathogenic for humans.[1]

JPC Diagnosis: Haired skin: Hyperplasia, epidermal, diffuse, moderate, with diffuse hyperkeratosis, serocellular crusts and numerous intrafollicular dermatophyte arthrospores, hyphae, and rare extraepidermal adult mites and eggs.

Conference Comment: Conference participants debated whether the rare mites observed in this case were associated with any of the identified lesions. As noted by the contributor, they are located superficially, sometimes exterior to the stratum corneum, are at a distance from the crust formation, and no burrows or larvae are present in the slides examined. We eventually elected to include the presence of mites within one diagnosis which implies their association with the cutaneous lesion, however, we cannot definitively prove their causality.

Dermatophytosis is more common in young animals and often associated with immunosuppression, which is supported in this case by the simultaneous symptoms of respiratory disease and oral ulcers. Notably, other than the neutrophils within the crusts, there is minimal inflammation present despite the fungal proliferation within nearly every hair shaft. Avoiding immune detection and subsequent

provocation of an inflammatory response is instrumental to survival for these pathogens. The arthrospores are always along the periphery of the hair while hyphae are confined within the hair shaft.[3] The organisms never penetrate Adamson's fringe into the mitotic region of the follicle, and fungal growth is terminated along with growth of the hair. Dead telogen hairs, known as "club hairs", are resistant to infection. Resolution of clinical signs typically occurs spontaneously within a few months.[3] This is in contrast to other fungal infections which invade the subcutaneous tissue, incite a tremendous inflammatory response, and often necessitate surgical excision such as pseudomycetomas, phaeohyphomycosis and sporotrichosis.[2]

Contributing Institution: Institut fuer Veterinaer-Pathologie, Justus-Liebig-Universitaet Giessen**,** Frankfurter Str. 96, 35392 Giessen, Germany**,** http://www.uni-giessen.de/cms/fbz/fb10/institute_klinikum/institute/pathologie

References:

1. Ginn PE, Mansell JEKL, Rakich PM. Skin and appendages. In: Maxie MG, ed. *Jubb, Kennedy, and Palmer's Pathology of Domestic Animals.* 5th ed. Vol 1. Philadelphia, PA: Elsevier Limited; 2007:553-781.
2. Hargis AM, Ginn PE. The integument. In: Zachary JF, McGavin MD, eds. *Pathologic Basis of Veterinary Disease*. 5th ed. St. Louis, MO: Elsevier Mosby; 2012:1038-1039.
3. Scott DW. *Large Animal Dermatology*. Philadelphia, PA: WB Saunders Company; 1988:174-182.
4. Chermette R, Ferreiro L, Guillot J. Dermatophytoses in animals. *Mycopathologia.* 2008;166(5-6):385-405.
5. Bond R. Superficial veterinary mycoses. *Clin Dermatol*. 2010;28(2):226-236.
6. Lund A, Deboer DJ. Immunoprophylaxis of dermatophytosis in animals. Mycopathologia. 2008;166(5-6):407-424.
7. Rommel M, Eckert J, Kutzer E, Körting W, Schnieder T. Veterinärmedizinische Parasitologie. 5th ed. Berlin: Parey; 2000.
8. Bates PG. Inter- and intra-specific variation within the genus Psoroptes (Acari: Psoroptidae). *Vet Parasitol.* 1999;83(3-4):201-217.

CASE II: 05-2655A/B (JPC 3139939).

Signalment: 3-month and 14-month-old unknown gender Nigerian dwarf goats, *Capra hircus*.

History: In a herd of 30 Nigerian dwarf goats, 10 have had bilateral crusty skin lesions on the face, perineum and distal limbs for up to 7 months.

Gross Pathologic Findings: The skin around the eyes and mouth of both goats is symmetrically alopecic, erythematous and covered by scales and dry crusts.

Laboratory Results: None.

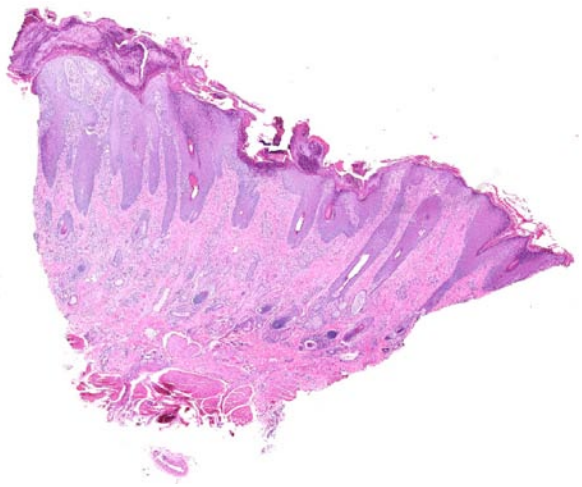
Histopathologic Description: Examined is one section of a punch biopsy of haired skin. The surface and follicular epidermis is acanthotic and hypergranular with areas of spongiosis and superficial erosions. The stratum corneum is diffusely thickened with parakeratosis and orthokeratosis layered with degenerative neutrophils admixed with amphophilic amorphous material (serum). Multifocal epidermal papillations are covered by parakeratotic caps expanded by intracorneal lakes of serum admixed with degenerative neutrophils. In some sections the surface or follicular epithelium is focally infiltrated by well-demarcated, intraepithelial aggregates of neutrophils surrounded by macrophages. In the superficial to deep dermis, abundant vascular profiles are lined by plump endothelial cells and surrounded by moderate to high numbers of eosinophils, lymphocytes and plasma cells, which extend into the interstitium. Lymphocytes exocytose through the surface of follicular epithelium. Follicular lumens occasionally contain small clusters of neutrophils and eosinophils.

Periodic acid-Schiff and Gomori methenamine silver stains revealed no fungi.

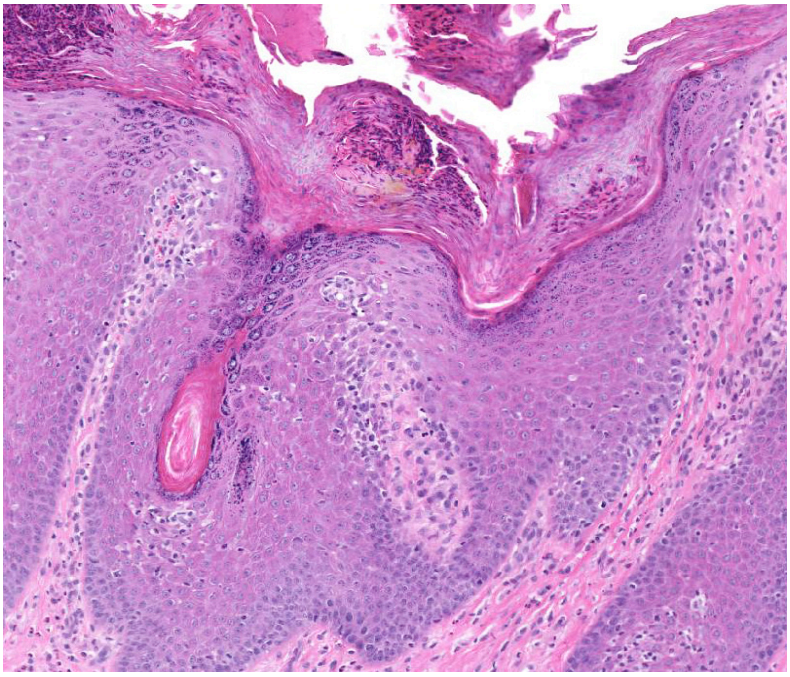
Contributor's Morphologic Diagnosis: Skin: Hyperkeratosis, parakeratotic and orthokeratotic, severe, diffuse with acanthosis and spongiosis; Dermatitis, perivascular to interstitial, eosinophilic and lymphoplasmacytic, multifocal to coalescing, moderate, chronic with transmural folliculitis, lymphocytic exocytosis and intraepithelial eosinophilic pustules, consistent with zinc responsive dermatosis.

Contributor's Comment: The section examined exemplifies the histological lesions of zinc-responsive dermatosis, which are similar in all ruminants, and include hyperkeratosis, predominantly parakeratotic, that extends into the follicular ostia and forms parakeratotic spires, epidermal hyperplasia, perivascular eosinophilic infiltrates and lymphocytic exocytosis. Inflammation and pustular dermatitis (not represented on all slides) reflect a secondary bacterial disease, self-trauma and, possibly, *Malassezia* infection. Staphylococcal dermatitis has been a reported complication of zinc responsive dermatosis in goats.[5] Zinc-responsive dermatosis in production animals is usually caused by excess dietary calcium or copper, which causes zinc malabsorption.[7] Zinc regulates apoptosis and DNA repair through activation of p53 gene, nuclear factor κβ and activator protein.[3] Zinc also reduces oxidative damage and regulates caspase activity by maintaining intracellular metalloprotease concentrations. Tissues with high cell turnover, like the skin, lymphoid and reproductive organs are most susceptible to disease due to zinc deficiency.[2]

Gross lesions of zinc-responsive dermatosis are similar in all species and include hyperkeratosis, alopecia and erythema. The distribution is generally, but not always, symmetrical and can involve the periocular and perioral skin, the pinnae and the nasal planum. In large animals the distal legs and coronary bands may develop crusts and fissures. In pigs, the ventral abdomen may be



2-1. Haired skin, goat: At subgross, there is marked epidermal hyperplasia with formation of thick, anastomosing rete ridges. There is a thick serocellular crust overlying the hyperplastic epidermis, and moderate perivascular inflammation within the underlying dermis. (HE 6.3X)



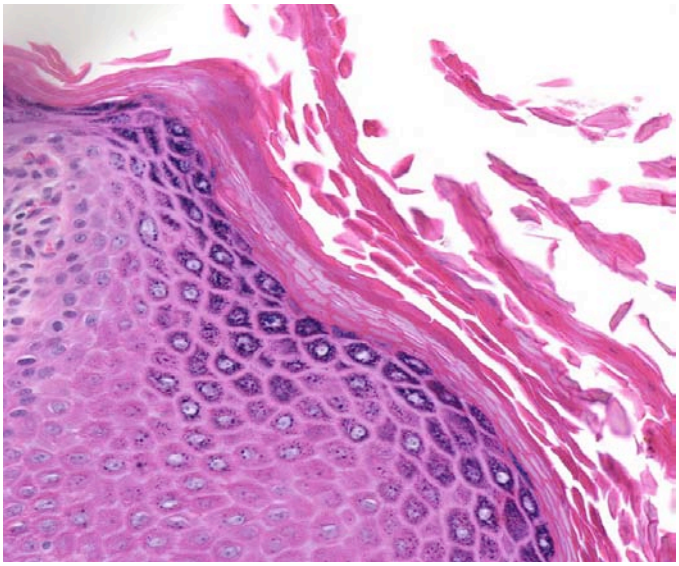
2-2. Haired skin, goat: The serocellular crust is composed of a combination of para- and orthokeratotic hyperkeratosis which extends into the follicular ostia, as well as focal pustules. (HE 112X)

affected. Low or low normal serum alkaline phosphatase levels have been described in ruminants, and serum zinc levels, as a rule, do not correlate with gross or histological lesions.[7]

Zinc deficiency in domestic animals is classified as hereditary or dietary. Hereditary zinc deficiency occurs in three forms: 1) lethal trait A46 in Black Pied Danish and Friesian calves; 2) lethal acrodermatitis in bull terriers (hypothetically due to zinc deficiency); and 3) inherited zinc responsive dermatosis in Northern breed dogs. Lethal acrodermatitis in bull terriers is not responsive to zinc supplementation, and its association with zinc deficiency is based largely on clinical similarities to inherited zinc deficient dermatoses in cattle and humans. Dietary zinc deficiency is the predominant form in production animals and large breed puppies.

The most severe inherited forms are lethal trait A 46 or bovine hereditary zinc deficiency in Black Pied Danish and Freisian calves and lethal acrodermatitis in bull terrier pups. These diseases are clinically similar to acrodermatitis enteropathica in humans, caused by a defect in the SLC39A4 gene that encodes the Zip4 protein, a zinc transporter protein distributed along the apical border of duodenal and jejunal enterocytes. Similar mutations in the bovine ortholog of SLC39A4 have been identified in affected calves.[7] In bull terriers the disease is not genetically characterized, but the pathogenesis of the disease has recently been attributed to increased oxidative stress secondary to hepatocelluar metabolic dysfunction. Symptoms begin in the first few weeks of life, and can include acrodermatitis, generalized alopecia, growth retardation, diarrhea, small or absent thymus, defective T-lymphocyte function, and chronic infections. Without treatment affected humans and animals invariably succumb to secondary infection. Humans and calves are responsive to oral zinc supplementation. The disease is currently untreatable in bull terriers.[10]

Northern breed dogs, Siberian huskies and Alaskan malamutes, are genetically predisposed to a more benign inherited zinc responsive dermatosis, known as syndrome I. Onset of symptoms can occur in dogs of any age, but most commonly affects juveniles.[9] Lesions are distributed most commonly on the periorbital skin, pinna and nasal planum and are histologically similar to those reported in other inherited zinc dermatopathies, though less severe.



2-3. Haired skin, goat: Areas in which there is a stratum granulosum are covered by orthokeratotic hyperkeratosis, recapitulating normal epidermal maturation. (HE 220X)

A dietary form of zinc responsive dermatosis, known as Syndrome II, occurs in growing large breed puppies with increase metabolic demands.[1]

Zinc deficiency in production animals is generally attributed to high dietary concentrations of calcium and copper, which block zinc absorption. Cereal grains contain high concentrations of phytates and phytic acids (inositol hexaphosphate) which chelate zinc; however, this mechanism of zinc deficiency is considered less important in ruminants due to production of phytases by rumen microflora. Excessive levels of oxalates, cadmium, iron, molybdenum and orthophosphates in the diet have also implicated zinc malabsorption. Conversely, zinc availability is enhanced by vitamin C, lactose and citrate.[5,8]

Despite the etiogenesis, histologic lesions of zinc-responsive dermatosis are similar in most species, allowing for moderate variations in severity. The differentials commonly include dermatophytosis, demodicosis, pemphigus foliaceus (dogs, cats, horses, goats) and other nutritional dermatopathies.

JPC Diagnosis: Haired skin: Hyperplasia, epidermal, diffuse, moderate, with acanthosis and hyperkeratosis, lymphocytic and neutrophilic dermatitis, and intracorneal pustules.

Conference Comment: The histopathology and clinical history are suggestive of zinc-responsive dermatosis in this case; however, the conference moderator noted that in the absence of serum or hair zinc levels, response to therapy must be demonstrated for definitive causation. Serum or hair zinc levels can be diagnostic when decreased; however, studies have demonstrated similar zinc concentrations between clinical animals and healthy animals from nearby farms.[7] Additionally, comparing metallothionein immunoreactivity of squamous epithelial cells to normal controls may be indicative of low zinc levels and possibly helpful in obtaining a definitive diagnosis.[6] Besides zinc deficiency, typical differential diagnoses for parakeratotic hyperkeratosis include thallium toxicity, hepatocutaneous syndrome, glucagonoma, autoimmune diseases, dermatophytosis, demodicosis, and superficial bacterial infections.

The contributor elaborates on the various manifestations of zinc-responsive dermatoses, including both hereditary and dietary. The pathogenic mechanisms underlying the development of cutaneous lesions in zinc deficiency is largely unclear. Zinc has a prominent role in the influence of molecular conformation, stability and activity in addition to its antioxidant effects which support the hypothesis of oxidative stress inducing these cutaneous lesions.[6] The heat shock protein 72 (Hsp72) is synthesized in response to damaged cellular proteins and functions to prevent their aggregration. It is found at increased concentrations in the nucleus of keratinocytes in canine zinc-responsive dermatoses[6], further demonstrating the increased susceptibility to protein damage of squamous epithelial cells when zinc levels are low.

Contributing Institution: Cornell University**,** College of Veterinary Medicine**,** Department of Biomedical Sciences**,** Division of Anatomic Pathology**,** S2118 Schurman Hall**,** Ithaca, NY 18453-6401

References:

1. Colombini S, Dunstan RW. Zinc-responsive dermatosis in northern-breed dogs: 17 cases (1990-1996). *J Am Vet Med Assoc*. 1997;211:451-453.
2. Cummings JE, Kovacic JP. The ubiquitous role of zinc in health and disease. *J Vet Emerg Crit Care. 2009;*19:215-240.
3. Grider A, Mouat MF, Mauldin EA, Casal ML. Analysis of the liver soluble proteome from bull terriers affected with inherited lethal acrodermatitis. *Molecular Genetics and Metabolism*. 2007;92:249-257.
4. Krametter-Froetscher R, Hauser S, Baumgartner W. Zinc-responsive dermatosis in goats suggestive of hereditary malabsorption: two field cases. *Vet Dermatol*. 2005;16:269-275.
5. Nelson DR, Wolff WA, Blodgett DJ, Luecke B, Ely RW, Zachary JF. Zinc deficiency in sheep and goats: three field cases. *J Am Vet Med Assoc*. 1984;184:1480-1485.
6. Romanucci M, Bongiovanni L, Russo A. Oxidative stress in the pathogenesis of canine zinc-responsive dermatosis. *Vet Dermatol*. 2010;22(1):31-38.
7. Scott, DW. *Large Animal Dermatology*. Philadelphia, PA: W.B. Saunders Company; 1988:487.
8. Singer LJ, Herron A, Altman N. Zinc responsive dermatopathy in goats: two field cases. *Contemp Top Lab Anim Sci*. 2000;39:32-35.

9. White SD, Bourdeau P, Rosychuk RA, Cohen B, Bonenberger T, Fieseler KV, et al. Zinc-responsive dermatosis in dogs: 41 cases and literature review. *Vet Dermatol*. 2001;12:101-109.

10. Yuzbasiyan-Gurkan V, Bartlett E. Identification of a unique splice site variant in SLC39A4 in bovine hereditary zinc deficiency, lethal trait A46: An animal model of acrodermatitis enteropathica. *Genomics*. 2006;88:521-6.

CASE III: 13-1614/6 (JPC 4048849).

Signalment: 3-year-old adult female bovine limousine breed, *Bos Taurus.*

History: A 3-year-old female limousine was referred to the Veterinary School of Lyon for clinical signs of 1 month duration. Cow shows persistent severe hyperthermia, bilateral keratitis, conjunctivitis, mucopurulent nasal discharge, ulcerative lesions on muzzle and in oral cavity, hooves and horn junctions, and emaciation. There are also sheep on the farm.

Gross Pathologic Findings: The main gross lesions at necropsy were:

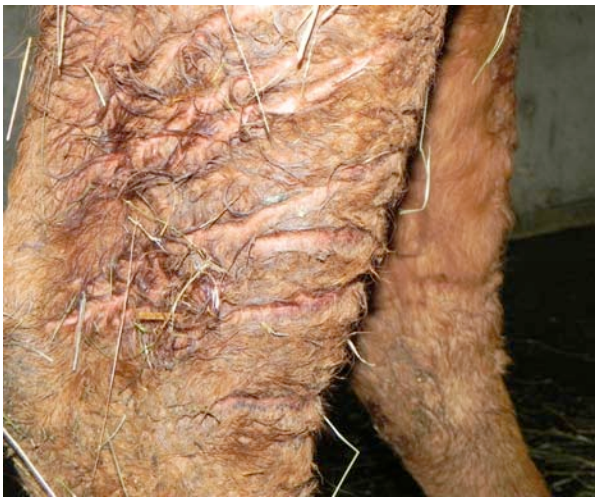
- Multifocal severe ulcerative dermatitis with crusts on muzzle, hooves and one horn
- Multifocal to diffuse exudative dermatitis with skin thickening and matted hairs
- Ulcerative gingivitis and loss of lingual papillae
- Numerous ulcers on esophageal mucosa
- Prescapular lymph node hypertrophy
- Bilateral mucopurulent rhinitis
- Marked congestive laryngitis

Laboratory Results: PCR: positive for Ovine herpes virus 2 (OvHv-2).

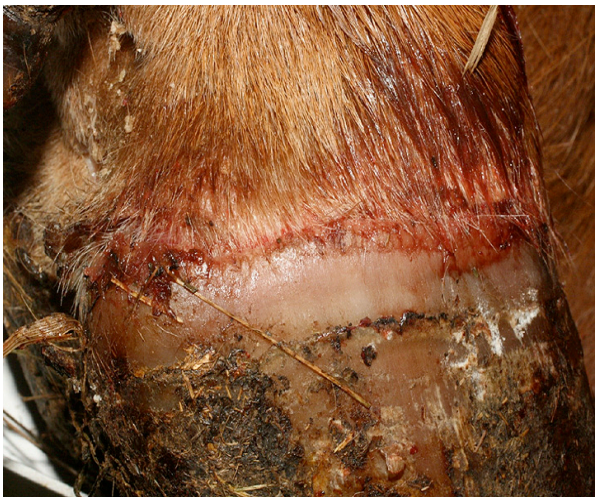
Histopathological Description: Haired skin: More than 90% of epidermis and superficial dermis is necrotic and replaced by crusts containing colonies of cocci and degenerate neutrophils. In viable adjacent epidermis (only in some slides) or in the follicular wall there are pustules containing necrotic or apoptotic keratinocytes and degenerate neutrophils. There are also hemorrhages and perivascular infiltration by numerous lymphoid cells admixed with plasma cells and viable and variable number of degenerate neutrophils. In the deep dermis, some vascular walls are expanded by fibrin, edema, and admixed with cellular and karyorrhectic debris (necrotizing vasculitis). Multifocally, vessel lumena were partially or completely occluded by fibrin thrombi.

Contributor's Morphological Diagnosis: Haired skin: Severe necrotizing and ulcerative dermatitis, necrotizing vasculitis with fibrin thrombi, lymphocytic périvasculitis and vasculitis, consistent with malignant catarrhal fever, limousine breed, bovine.

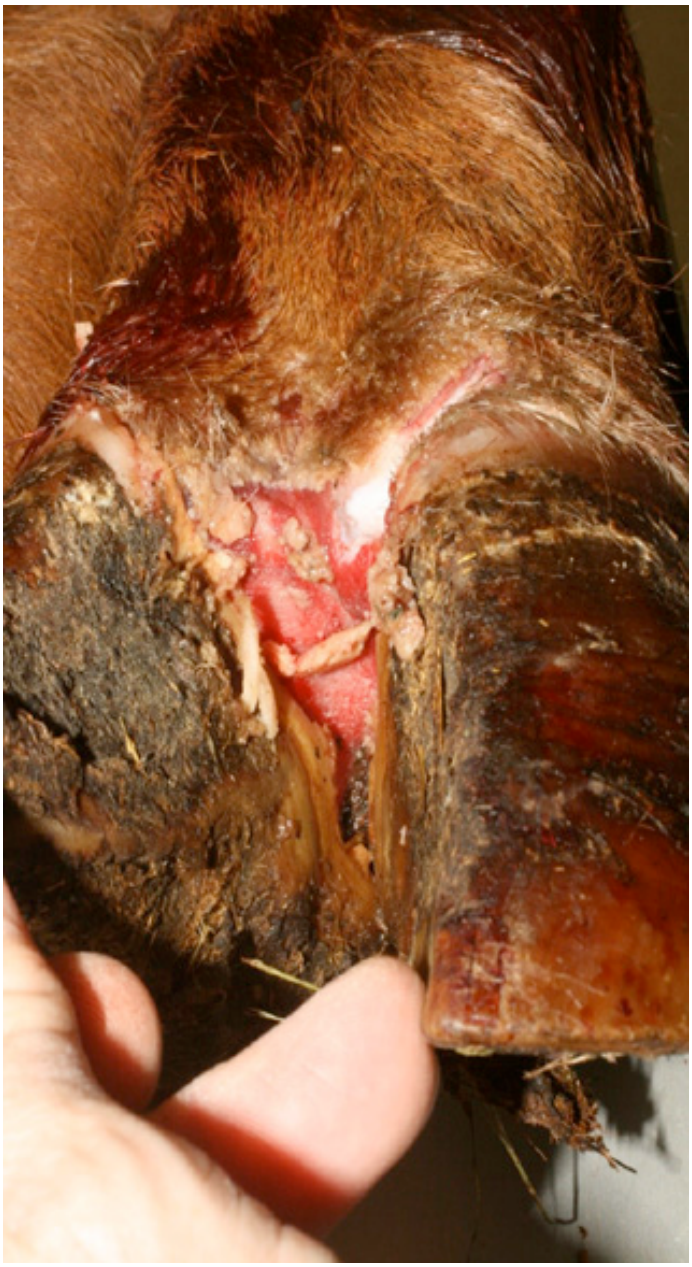
Contributor's Comment: Malignant catarrhal fever (MCF) is an infectious disease of domestic cattle, some wild ruminants and occasionally pigs. The disease is characterized by lymphoproliferation, vasculitis and erosive-ulcerative mucosal and cutaneous lesions. It is generally sporadic although severe herd outbreaks



3-1. Haired skin, ox: There are extensive areas of exudative dermatitis with thickening of the skin and matted hair. (Photo courtesy of: Anatomie Pathologique, Vetagro Sup, Campus veterinaire, 1, Avenue Bourgelat, 69280 Marcy l'etoile, France)



3-2. Haired skin, ox: The coronary band is ulcerated. (Photo courtesy of: Anatomie Pathologique, Vetagro Sup, Campus veterinaire, 1, Avenue Bourgelat, 69280 Marcy l'etoile, France)



3-3. Hoof, ox: There is sloughing of the hoof. (Photo courtesy of: Anatomie Pathologique, Vetagro Sup, Campus veterinaire, 1, Avenue Bourgelat, 69280 Marcy l'etoile, France)

have been reported. Mortality in susceptible species approaches 100%. MCF is caused by cross species infection with members of the MCF virus group of ruminant rhadinoviruses (genus *Rhadinovirus* subfamily Gammaherpesvirinae).[2] Economically important outbreaks of MCF are due to 2 of the 10 viruses of the MCF virus group: ovine herpesvirus 2 (OvHV-2 and alcelaphine herpes virus I (AIHV-I).[3]

The pathogenesis, clinical signs and lesions are similar whatever the agent inducing MCF. MCF is characterized by marked T lymphocyte hyperplasia. A population of large granular lymphocytes appears to be infected and transformed by rhadinovirus infection, and OHV-2 genome has been detected in CD8+ T cells. These cells are probably cytotoxic T lymphocytes or T-suppressor cells but the mechanism by which they mediate the lesions of MCF is unclear.

Animals probably encounter these viruses through inhalation and ingestion of fomites from oronasal-pharyngeal-ocular fluids from reservoirs animals that are actively shedding virus.[3]

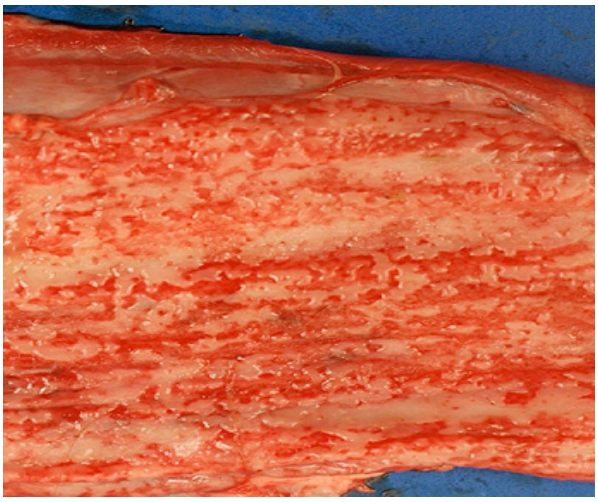
Disease is not contagious among affected cattle, which are thought to be dead end hosts

There is a great variation in the presenting clinical syndromes which are potentially pansystemic.[2]

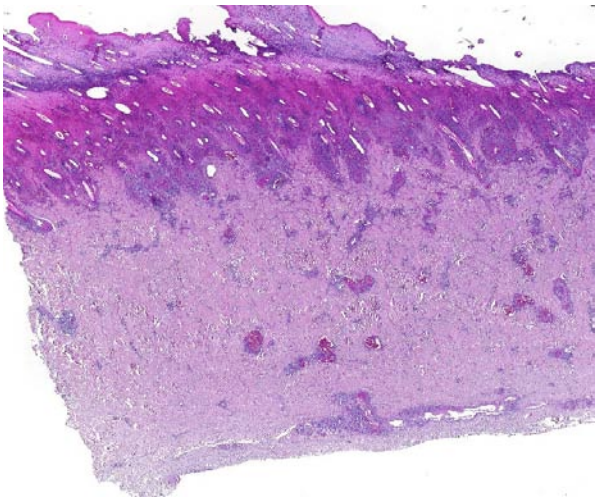
Gross cutaneous lesions especially in sheep-associated MCF are common. Affected areas include the thorax, abdomen inguinal regions, perineum, udder and occasionally the head. Sometimes the cutaneous changes begin in about the base of hooves and horn. In our cases, cutaneous lesions were severe in hooves and coronary band and the cow has lost all epidermal parts of one horn.

The characteristic histological changes are found in lymphoid tissue and in the adventitia and walls of medium sized vessels, especially arteries. They are characterized by perivascular accumulation of mainly mononuclear cells and fibrinoid necrotizing vasculitis. These changes may be focal or segmental and may involve the full thickness of the wall or be confined more or less to one layer.

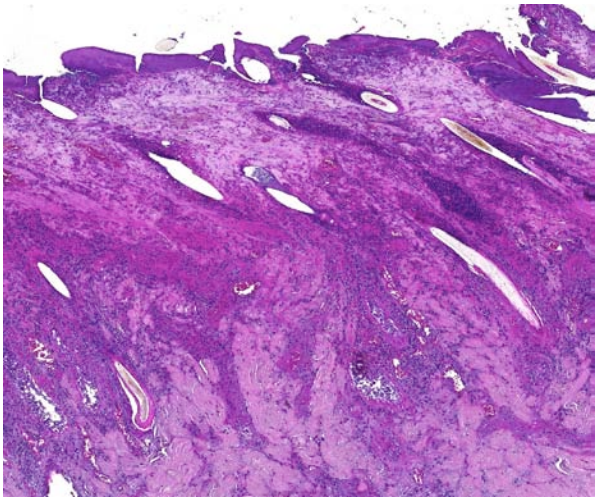
Differentiation of acute severe mucosal disease is sometimes difficult but MCF affects more organs and there is lymphoid hyperplasia whereas lymphoid tissue in BVDV infection is expected to be atrophic. Other differential diagnosis include: bluetongue, vesicular stomatitis, foot and mouth disease, and photosensitization.[3]



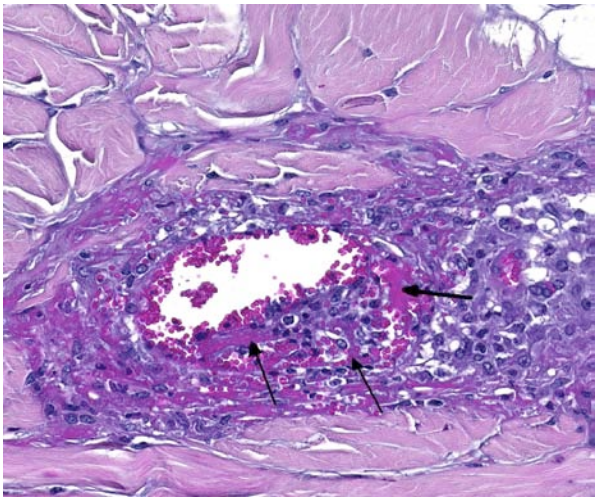
3-4. Esophagus, ox: There are extensive areas of ulceration on the esophageal mucosa. (Photo courtesy of: Anatomie Pathologique, Vetagro Sup, Campus veterinaire, 1, Avenue Bourgelat, 69280 Marcy l'etoile, France)



3-5. Haired skin, ox: There is diffuse severe necrosis of the epidermis, and vessels within the dermis are emphasized by an outlining cellular infiltrate and necrotic debris. (HE 2X)



3-6. Haired skin, ox: The epidermis is diffusely necrotic – hair follicles and adnexa are infiltrated by numerous degenerate neutrophils. There is not a single viable cell left in this whole field! (HE 38X)



3-7. Haired skin, dermis, ox: Vessel walls are expanded by numerous viable and degenerate lymphocytes and fewer neutrophils, edema, and extravasated brightly eosinophilic protein (arrows) (fibrinoid necrosis). Hemorrhage and protein-rich edema fluid, as well as moderate numbers of lymphocytes infiltrate the surrounding perivascular dermis. (HE 328X)

In our case definitive diagnosis was made by histology and positive OVHV-2 PCR results. This method is sensitive and specific.

Clinical MCF is divided into four variable and overlapping categories:[5]

·Peracute form: Severe oral and nasal mucosal inflammation, hemorrhagic gastroenteritis

·Intestinal form: Pyrexia, diarrhea, hyperemic oral and nasal mucosa with profuse catarrhal and mucopurulent discharge, generalized lymphadenopathy

·Head-and-eye form (most common): Pyrexia, copious serous to mucopurulent ocular and nasal secretions, encrusted muzzle with occluded nostrils, dyspnea and open-mouthed breathing, oral mucosal hyperemia with erosions, sloughed buccal mucosal tips; Ocular lesions: Ophthalmia, photophobia, palpebral conjunctival hyperemia and edema, corneal opacity, +/- hypopyon

·Mild form: mild oral and nasal mucosal erosions

JPC Diagnosis: Haired skin: Vasculitis, necrotizing, multifocal, severe, with thrombosis,

and diffuse epidermal and adnexal necrosis (infarct).

Conference Comment: This is a unique look at a disease more familiarly causing the gastrointestinal trifecta of arteritis, lymphoid proliferation and mucosal necrosis.[3] The degree of necrosis in this case is so dramatic, one conference participant accurately declared, "There is not a single living epithelial cell!" The hallmark of MCF in cattle is severe lymphocytic arteritis-periarteritis with necrosis of the tunica media[3] which is beautifully demonstrated in this example.

OVHV-2 can be a contentiously complicating infectious disease for producers, as owners of sheep can move flocks in and out of a facility without consequence while an adjacent closed-herd of cattle or bison suffers severe outbreaks. In endemic areas, nearly all sheep are infected during their first year of life and rarely develop clinical disease; which is in stark contrast to infection in cattle where the clinical course typically ends in death or euthanasia. Even in cases where outbreaks of systemic vasculitis occur in a sheep flock and positive detection of viral antigen is confirmed, OVHV-2 can only be considered with suspicion. The detection of ORF25, a viral-encoded protein of OVHV-2, would be more persuasive in such instances.[3]

All gammaherpesviruses have a tropism for T or B lymphocytes, and members of the MCF viruses preferentially target T cells.[3] Infected CD8+ T lymphocytes spread the virus systemically and incite production and recruitment of proinflammatory cytokines which lead to the tremendous lesions observed.[4] In sheep, only aerosol challenges result in infection, where initial replication occurs within type II pneumocytes. Intravenous, intraperitoneal, and transplacental inoculations do not result in infection while infected colostrums may rarely result in infection.[3]

The contributor mentioned important differentials to consider in cases which present with acute mucosal disease. The endemicity of MCF, BVDV, and now bluetongue among cattle in Europe make obtaining a definitive diagnosis of special importance. Studies have characterized MCF and BVDV as being more clinically similar; however, cattle with bluetongue more often have a better appetite, demeanor and facial appearance and do not have bilateral lymph node enlargement.[1]

Contributing Institution: Anatomie Pathologique, Vetagro Sup, Campus vétérinaire, 1 Avenue Bourgelat, 69280 Marcy l'etoile, France

References:

1. Bexiga R, Guyot H, Saegerman C, et. al. Clinical differentiation of malignant catarrhal fever, mucosal disease and bluetongue. *Vet Rec*. 2007;161:858-859.
2. Brown CC, Baker DC and Barker IK. Alimentary system. In: Maxie MG, ed. *Jubb, Kennedy and Palmer's Pathology of Domestic Animals*. Vol 2. 5th ed. Philadelphia, PA: Elsevier Saunders; 2007:152-158.
3. O'Toole D, Li H. The pathology of malignant catarrhal fever with an emphasis on Ovine Herpesvirus 2. *Veterinary Pathology*. 2014;51(2): 437-452.
4. Zachary JF. Mechanisms of Microbial Infections in Pathologic Basis of Disease. Fifth edition. 2012:219.
5. Joint pathology VSPO U-V02 - Malignant catarrhal fever (MCF) - kidney, haired skin – steer.

CASE IV: RP19229 (JPC 4048505).

Signalment: Adult male wild house mouse, *Mus musculus*.

History: Found dead.

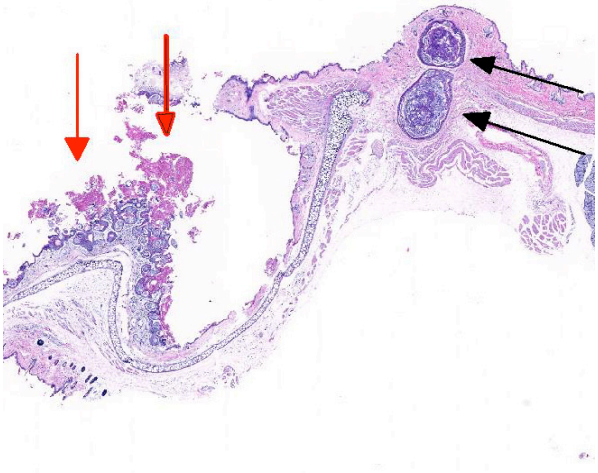
Gross Pathology: The mouse was 17.5 g and had minimal to no adipose stores. There were multiple hairless patches along the dorsum and face. Bilaterally, the margins of the pinnae were irregular and lacerated. The right pinna contained a 5 x 3 x 3 mm tan, multinodular skin mass. There were similar 1 mm diameter tan nodules within the hairless patches of the dorsum and face. The thoracic cavity contained a moderate amount of dark red hemorrhage.

Laboratory Results: None.

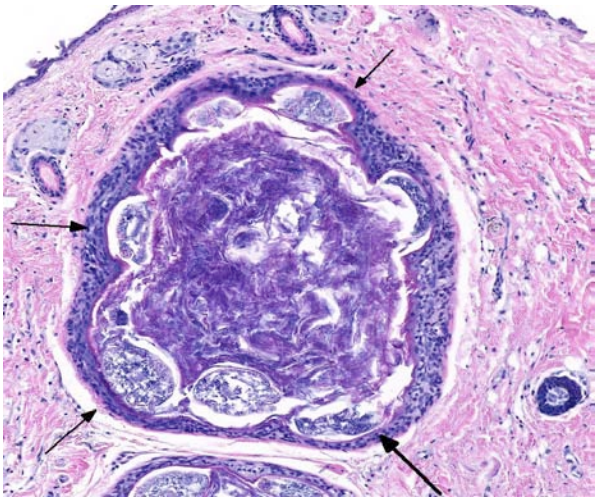
Histopathologic Description: Hair follicles of the face, pinnae, and dorsum are multifocally dilated and contain abundant arthropods (mites) embedded in hyperkeratotic and hyperplastic follicular epithelium. Arthropods are 80 - 110 microns in diameter with a chitinous exoskeleton, multiple jointed appendages, skeletal muscle, and a reproductive tract containing basophilic material. Similar mites are embedded in hyperkeratotic surface epithelium. There are multifocal 40 - 60 micron diameter basophilic eggs. Rare sections contain subcutaneous inflammation characterized by lymphocytes, plasma cells, and neutrophils and hemorrhage. Rarely, follicles also contain clusters of 3 - 5 micron round to oval structures that are periodic acid-Schiff positive (yeasts).

Contributor's Morphologic Diagnosis: Haired skin (face, pinnae, and dorsum): Severe follicular plugging, hyperkeratosis, and hyperplasia with intrafollicular and superficial epidermal mites (etiology: *Psorergates simplex*).

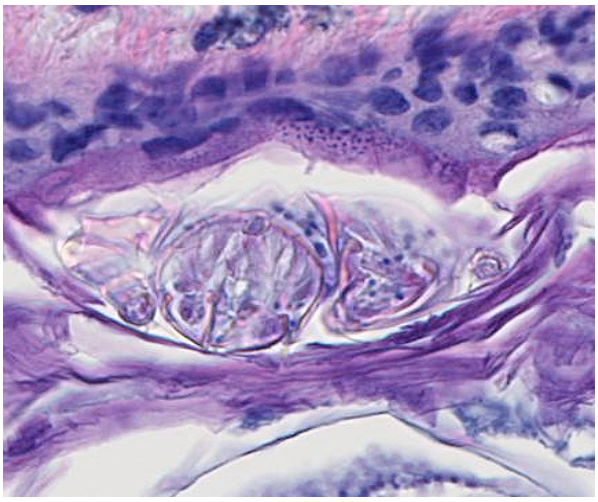
Contributor's Comment: The gross and histologic presentation in this case is typical of the follicular mite, *Psorergates simplex*. The characteristic gross lesion caused by this mite is numerous 2 mm tan to white cystic dermal nodules.[1,2,4,5] The nodules, also described as nests and pouches,[3] are most obvious when the skin is reflected back during postmortem examination.[1,2,4] Lesions most commonly occur in the loose skin of the neck, back, trunk, shoulders, and abdomen, but can occur anywhere, including the face and legs. The cysts resemble comedones and histologically are characterized by dilated follicles plugged with abundant mites and keratin debris.[1,5] Inflammation is usually minimal but will occur around ruptured follicles (furunculosis). The presence of mites in hair follicles of the pinnae, as was seen in this case, is a less common presentation.[1] Nodules can occur on either or both sides of the pinna and may need to be differentiated from notoedric ear mange,[1] in which the lesion tends to be more superficial and proliferative with mites embedded in the stratum corneum.[4] *Notoedres* sp. are also larger mites (250 - 400 microns long), whereas *P. simplex* are 90 - 150 microns long.[1]



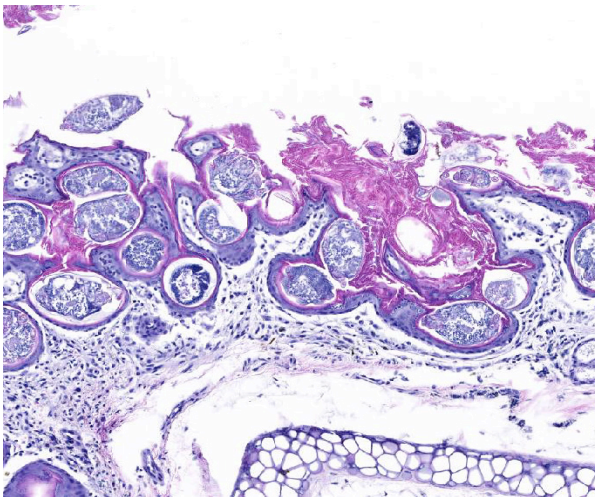
4-1. Haired skin and ear canal, mouse: There are two large dilated hair follicles containing abundant keratin debris (comedones) (black arrows) subjacent to the base of the ear, and a marked area of crusting within the external ear canal (red arrows). (HE 7X)



4-2. Haired skin, mouse: There are numerous cross sections of arthropod parasites (mites) lining the wall of the comedone. (HE 7X)



4-3. Haired skin, mouse: The cross sections of the mites contain a chitinous exoskeleton, obvious jointed appendages, and striated muscle. (HE 400X)

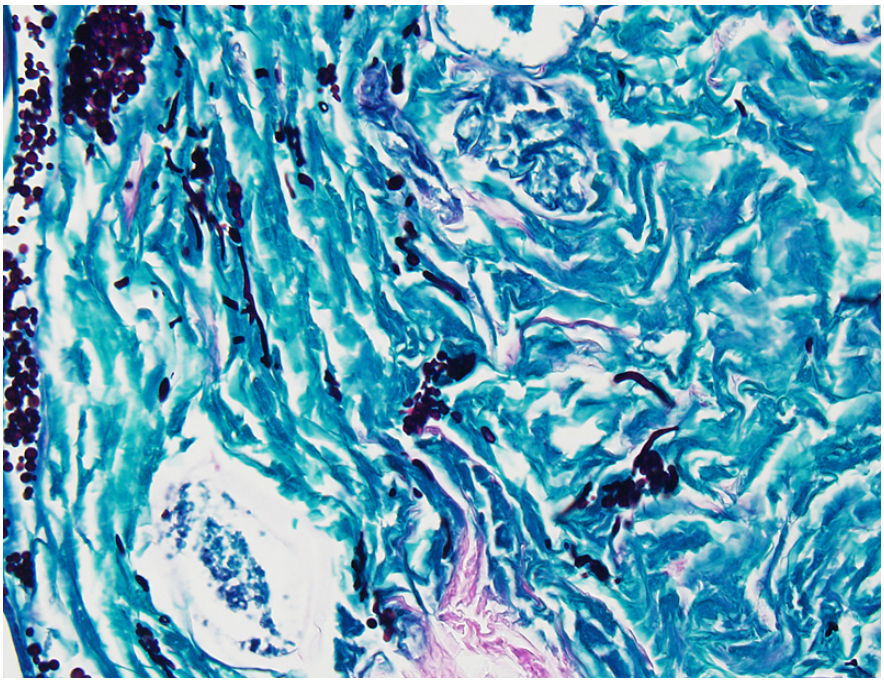


4-4. External ear canal, mouse: There is a focal area of epidermal hyperplasia and hyperkeratosis within the dorsal ear canal with numerous intraepithelial and intrafollicular mites. (HE 125X)

Infection with *P. simplex* is uncommon in wild and pet mice and rare to absent in laboratory mice. The complete life cycle of *P. simplex* is unknown.[1,5] The mites are transmitted by direct contact[1] and gravid females enter the hair follicles to form nests which expand the follicles by internal pressure.[1,2] All stages of the mite life cycle (eggs, larvae, nymphs, and adults) can be found within hair follicles.[1,5]

Death of this wild house mouse was attributed to a suspected traumatic event which caused dermal hemorrhage and hemothorax. The mites were an incidental finding. We receive few wild mice at our laboratory but in our experience *P. simplex* is uncommon. Rare yeasts in the follicles are most consistent with *Malassezia* sp. and most likely represent a secondary infection.

JPC Diagnosis: 1. Haired skin: Comedones, multiple, with infundibular adult mites and eggs. 2. Haired skin: Infundibular fungal arthrospores (presumptive) and hyphae. 3. Pinna: Otitis externa, hyperkeratotic and lymphohistiocytic, diffuse, moderate, with infundibular adult mites and eggs.



4-5. Hair follicles, mouse: Centrally within the comedones, there are moderate numbers of yeasts and hyphae, which are likely incidental. (Periodic acid-Schiff, 400X)

Conference Comment: For an institution with thousands of animals comprising hundreds of different species, this case serves as a reminder of the importance in monitoring the health of wildlife pests in addition to exhibit animal population. *Psorergates simplex* mites were once prevalent in laboratory mice but are now only readily recognized among wild and pet mice.[5] While little is

known regarding its pathogenesis, most skin mites of mice are directly transmissible which may pose a risk to some zoo inhabitants. Conference participants discussed the finding of some sections of mites which appeared to be larger (200-300 µ m) and found superficial to the epidermis in some slides. These larger mites often had a striated cuticle not observed among the intrafollicular mite sections, leading many to speculate on the presence of a second species. Several species of mites are relatively common in mice, including *Myobia musculi, Myocoptes musculinis*, and *Radfordia affinis*.[5] Additionally, the contributor mentions *Notoedres* sp. which are much larger and more superficial in histologic sections. Any of these are a possibility, as all lack distinguishing morphologic characteristics. In fact, of all genres of mites, only *Sarcoptes* sp. (with dorsal cuticular spines) and *Demodex* sp. (with elongated abdomen and closely apposed appendages) can be readily identified on histologic section by their morphology alone.[3] *Myobia* sp. are the most clinically significant mites which cause a hypersensitivity reaction while *Myocoptes* sp. is most common.[5]

We also observed the 3-5 µm spores present often in conjunction with mites in dilated follicles. These are PAS- and GMS-positive, which also revealed few fungal hyphae in the same location. Upon histochemical staining, we are unable to determine the specific species of this fungus though we do not believe this morphology is consistent with *Malassezia* sp.; their location within the follicles as well as hyphal formation is consistent with a dermatophyte. The lack of inflammation associated with the dilated follicles was curious, as neither the mites nor fungi seemed to elicit a response from the host. In some slides, sections of ear pinna were identified which appeared to be the only area where lymphocytes and macrophages were recruited. We elected to include a third diagnosis for this location, though it is worth mentioning the mites seemed to be concentrated in larger numbers in these sections.

Contributing Institution: Wildlife Disease Laboratories, Institute for Conservation Research, San Diego Zoo Global: http://www.sandiegozooglobal.org

References:

1. Baker DG. Parasites of Rats and Mice. In: *Flynn's Parasites of Laboratory Animals*. 2nd ed. Ames, IA: Blackwell Publishing Professional: 2007:366-367.
2. Flynn RJ, Jaroslow BN. Nidification of a mite (*Psorergates simplex* Tyrell, 1883: Myobiidae) in the skin of mice. *J Parasitology*. 1956;42:49-52.
3. Gardiner CH, Poynton SL. *An Atlas of Metazoan Parasites in Animal Tissues*. Washington, DC: Armed Forces Institute of Pathology; 1999:56-58.
4. Izdebska JN, Fryderyk S. New for the fauna of Poland species of *Psorergates* spp. with the data of occurrence of mites from Psorergatidae family (Acari, Prostigmata) in native mammals. *Annals Parasitology*. 2012;58:19-22.
5. Percy DH, Barthold SW. Mouse. In: *Pathology of Laboratory Rodents and Rabbits*. 3rd ed. Ames, IA: Blackwell Publishing Professional: 2008:85-87.