CASE I – S9700095 A1 (AFIP 3024109).

**Signalment:**
S9700002B  Holstein cow, 2-year-old
S9700002D  Holstein cow, 3-year-old
S9700095A  Holstein cow, 4-year-old

**History:** The three animals were part of a group of approximately 20 cows which were corralled for hoof trimming treatment for lameness (a routine weekly procedure), on two 1000-cow drylot Holstein dairies in southern California. Both herds were involved by endemic papillomatous digital dermatitis (PDD; digital dermatitis; footwarts). Gross lesions of PDD were selected for transmission studies because of their high activity. They were surgically excised from the feet of the three cows and portions were placed in formalin.

**Gross Pathology:** The lesions were singular, oval to circular, 2 to 3 cm across, slightly raised and well-demarcated. Each lesion involved the skin of a heel of a hind leg adjacent to the interdigital cleft (S9700002B and D) or pastern (S9700095A). Their surfaces were non-crusted except around the edges, moist with serous exudates, red-blue, raw-appearing, very painful to touch and prone to bleed, and tufted by grey/yellow/black filiform papillae of varying lengths (approximately 1 to 20 mm). No digital swelling or interdigital lesions were present.

**Laboratory Results:** Darkfield microscopy of saline suspensions of homogenized superficial scrapings of the lesions revealed profuse numbers of singular and matted, highly motile, slender, spiral organisms (SSO) admixed with small numbers
of non motile, long, straight filaments with pointed ends. The motility, which was characterized by vigorous axial spinning and end-to-end flexing, was best observed in specimens stored in plain vials on wet ice and examined within 4 hours of biopsy. Motility diminished to zero by 8 hours post collection. Gram stain revealed numerous Gram negative filaments and rods and sparse gram positive diphtheroids. Victoria Blue and Steiner silver stains revealed profuse SSO’s resembling spirochetes (Fig. 1).

Aerobic and anaerobic bacteriologic cultures were performed on similar gross lesions on other cows in other dairies. Three novel molecular phylotypes of spirochetes were isolated and identified: most closely resembling, Treponema denticola (Type 1), phagendinis (Type 2) and medium/vincentii (Type 3). Other anaerobes regularly isolated were Porphyromonas levii and an unidentified Gram negative filamentous rod. Aerobic growth was inconsistent and slight. A Mycoplasma sp. of an unidentified serotype was regularly isolated.

**Histopathologic Description:** Findings were similar in each biopsy. Epidermis and dermis is well represented. Junctional borders with normal skin are not present.

Skin is raised and convex due to a combination of the bulk-effects of a markedly thickened epidermis and increased vascularity of deep dermis. Stratum corneum is, for the most part, transformed into a thick ragged, papillated, discontinuous layer of hyperkeratosis. The hyperkeratosis is extensively parakerotic and focally orthokeratotic. The parakeratosis is poorly cornified in some areas and has multifocal microcavities containing fibrin, proteinaceous fluid, red cells and/or neutrophils. The continuity of the stratum corneum is interrupted by ulceration of the tips of multiple dermal papillae. It is also focally to extensively involved by dense mats of pale, basophilic fibrillary material. In one biopsy, stratum corneum is mostly absent, not through artifact but by failure of the stratum spinosum to cornify. Stratum granulosum is absent except for beneath the focal areas of orthokeratotic stratum corneum. Stratum spinosum is markedly thickened by excessive numbers of hypertrophic keratinocytes (acanthosis). These are architecturally arranged in a broad band of uniformly thick (3-4 mm), interconnected columns, The columns are interdigitated by long, thin dermal papillae. In sections perpendicular to the surface of the lesion, the columns tended perpendicular also. Some columns are continuous with the papillae. Borders of the columns are spongiotic and lined by primitive-appearing basal cells, some of which are in mitosis. No breach of basement membrane is seen. Superficial stratum spinosum is focally to extensively involved by neutrophil infiltration and presence of the basophilic fibrillary material, often outlining keratinocytes. Dermal papillae are hyperemic, infiltrated by small numbers of neutrophils and plasma cells. Superficially they are involved by hemorrhage, capillary thrombosis, suppuration and invasion by the basophilic fibrillary material. Deep dermis is involved by
increased numbers of arterioles, most of which are hypertrophied, slight to moderate diffuse to perivascular infiltrations of neutrophils and plasma cells and presence atretic hair follicles. No granulation tissue, fibromatous change or inclusion bodies are present. Specially stained preparations reveal that the basophilic fibrillary material consisted almost entirely of dense mats of long (10-15 um) slender spiral organisms. These were blue with Giemsa, red with Gram’s method, black with Steiner silver, grey with Methenamine silver and pale blue with PAS.

Figures 2-5, illustrate colonization of stratum corneum and invasion of stratum spinosum by spirochetes by use of Steiner silver stain, electron microscopy and immunohistochemistry in PDD lesions of similar histologic character to those supplied in this case. Ultrastructurally, the slender spiral organisms were identified as spirochetes by the presence of a periplasmic membrane enclosing axial filaments at each extremity and an axial protoplasmic body.

**Contributor’s Morphologic Diagnosis:** Skin: Chronic-active, diffuse ulceroproliferative dermatitis with papillary epidermal hyperplasia, parakeratotic hyperkeratosis, ulceration of dermal papillae and superficial colonization and invasion by spirochete-dominant bacterial mat, heel, hind leg, Holstein cow, bovine.

**Contributor’s Comment:** Papillomatous digital dermatitis (PDD), also known as “footwarts” or “hairy heel warts” in the US, is a world-wide, contagious, painful, wart-like disease of the feet of cattle. It was first reported in 1974 in Italy by Cheli and Mortellaro. In Europe it is commonly known as Mortellaro’s disease or digital dermatitis (DD). In North America, the disease was first reported in 1980 in New York where it was known as interdigital papillomatosis (IP). We reported a similar disease in California in 1992 associated with invasive spirochetes. It is now generally believed that all three entities are the same disease. This is supported by a comparative histopathologic and immunohistochemical study of lesions of PDD and DD from 18 countries which found that the pathologic character and immunoreactivity of the spirochetes in the three entities were identical.

The gross appearance of PDD varies markedly. In our studies, in which we observed the spontaneous progression/remission of natural and experimental lesions, the appearance depended on the wetness/dryness of the foot environment, whether or not the lesion was recently treated by antibacterials/footbaths, age of the lesion and/or anatomic location. The sections in this case had gross features of high activity lesions, namely, moist, red/grey raw-appearing surfaces. These lesions were not photographed but are typically represented in photographs of lesions in other cows that had wet foot environments (Figs. 6-9). Typically, these lesions have ulceration and dense mats of invasive spirochetes. However, if foot environment becomes dry or if footbaths are introduced, lesion surfaces
become water resistant, brown, rubbery and non-painful in a matter of a few days.\textsuperscript{3,5} They still appear grossly “warty” but the histologic diagnosis become presumptive because the spirochetes disintegrate, the ulcers heal and the stratum corneum becomes intact.\textsuperscript{7} Papillomatous change (Figs. 8 and 9) is probably an indication of maturity but its relationship to age is not clear-cut because papillae were observed to occur in only 40% of large lesions.\textsuperscript{5} My estimate of the ages of the lesions in figures 6-9 are: 3-4 weeks (Fig. 6), 2-3 months (Fig. 7 and 8) and 3-6 months (Fig. 9). The anatomic site seems to influence the gross appearance of PDD because papillae have not been observed in lesions involving the interdigital skin.\textsuperscript{5,9}

The sections nicely illustrate the diagnostic criteria of PDD: parakeratotic hyperkeratosis, epidermal acanthotic hyperplasia, ulceration of tips of dermal papillae; and, colonization of stratum corneum and invasion of stratum spinosum and dermal papillae by spirochete-dominant mats.\textsuperscript{9}

PDD differs pathologically from other ulcerative/proliferative conditions of the bovine foot. Interdigital necrobacillosis (Footrot) is characterized by deep fissuring and caseation necrosis of dermis with extensive cellulitis.\textsuperscript{10} Bovine papillomavirus-induced lesions rarely involve the feet of cattle, the granular layer is prominent and cytoplasm of keratinocytes in the stratum spinosum is basophilic.\textsuperscript{11} Traumatic laceration of skin, or deep ulceration from any cause, heals by granulation tissue formation, a rare finding in PDD. Granulomatous inflammation, or presence of fungal elements, foreign bodies, \textit{Dermatophilus}, parasites or inclusion bodies have not been observed.\textsuperscript{9}

The etiology of PDD is unknown because Koch’s postulates have not been demonstrated. However, several lines of evidence have shed light on its pathogenesis. A viral association was investigated by electron microscopy, immunohistochemistry for generic papillomavirus, DNA probes for bovine papillomavirus types 1-6 and inoculation of laboratory animals.\textsuperscript{12,13} No virus was detected. The marked sensitivity of the lesion to parenteral antibiotics (without manipulating the lesion) in association with the consistent finding of invasive spirochetes provided evidence that bacteria may play a major role.\textsuperscript{3,5,9} Sequential ultrastructural examination of experimental lesions revealed that spirochetal invasion was both primary and dominant; other bacteria rarely invaded viable tissue, even in full-blown lesions. No viral particles were observed.\textsuperscript{14} Isolation of spirochetes and detection of significant increases in humoral antibody responses to PDD-associated \textit{Treponema spp}. in cows with natural PDD indicated that the spirochetes isolated were invasive, not mere commensals colonizing non-viable parakeratotic debris.\textsuperscript{15,16} Experimental proof that hydropic maceration of digital skin (by constant moisture for 7-14 days) was an essential prerequisite for successful transmission indicated that the pathogenesis of PDD was multifactorial with
infectious and environmental factors. Finally, the histologic similarity of PDD to yaws, a papillomatous ulcerative condition of the feet of people living in the tropics caused by Treponema pallidum subsp. pertenue, also adds support to the notion that Treponema sp. may play a major role in the genesis of PDD.

**AFIP Diagnosis:** Glabrous skin: Epidermal hyperplasia, papillated, diffuse, marked with orthokeratotic and parakeratotic hyperkeratosis, superficial necrosis, mild chronic-active dermatitis, and intracorneal bacteria, Holstein, bovine.

**Conference Comment:** The contributor provides a thorough overview of papillomatous digital dermatitis as well as how to differentiate PDD from other ulcerative/proliferative conditions of the bovine foot. Below is a table from Pathologic Basis of Veterinary Disease summarizing the digital infections of ruminants.

**Digital Infections of Ruminants**

<table>
<thead>
<tr>
<th>Species</th>
<th>Disorder</th>
<th>Predisposing Factors</th>
<th>Bacteria Involved</th>
<th>Severity</th>
<th>Contagious</th>
</tr>
</thead>
<tbody>
<tr>
<td>Sheep</td>
<td>Contagious foot rot, virulent form</td>
<td>Moisture &amp; trauma</td>
<td><em>Dichelobacter nodosus</em> plus <em>Fusobacterium necrophorum</em> and other bacteria</td>
<td>Severe; virulent strains of <em>D. nodosus</em> produce more proteolytic enzymes</td>
<td>Yes</td>
</tr>
<tr>
<td>Sheep</td>
<td>Contagious foot rot, benign form (foot scald)</td>
<td>Moisture &amp; trauma</td>
<td><em>Dichelobacter nodosus</em> <em>Fusobacterium necrophorum</em></td>
<td>Mild; less virulent strains of <em>D. nodosus</em> produce fewer proteolytic enzymes and are less pathogenic</td>
<td>Yes</td>
</tr>
<tr>
<td>Sheep</td>
<td>Necrobacillosis of the foot</td>
<td>Wet seasons Heavy adult sheep</td>
<td><em>Fusobacterium necrophorum</em> Other bacteria, but no <em>Dichelobacter nodosus</em> <em>Fusobacterium necrophorum</em> <em>Arcanobacterium pyogenes</em></td>
<td>Can cause severe lameness with permanent foot deformity</td>
<td>No</td>
</tr>
<tr>
<td>Sheep</td>
<td>I. Ovine interdigital Dermatitis</td>
<td>Heavy adult sheep</td>
<td><em>Dichelobacter nodosus</em> <em>Fusobacterium necrophorum</em> <em>Arcanobacterium pyogenes</em></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Sheep</td>
<td>II. Foot abscesses</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>A. Heel abscesses (infective bulbar necrosis)</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>B. Toe abscesses (lamellar abscesses)</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Cattle</td>
<td>Foot rot</td>
<td>Trauma &amp; moisture</td>
<td><em>Dichelobacter nodosus</em> <em>Fusobacterium necrophorum</em> Other bacteria</td>
<td>Mild; similar to benign foot rot in sheep</td>
<td>Yes</td>
</tr>
<tr>
<td>Cattle</td>
<td>Necrobacillosis of the foot (foul-in-the-foot)</td>
<td>Trauma</td>
<td><em>Fusobacterium Necrophorum Bacteroides melaninogenicus</em></td>
<td>Can be severe with cellulitis involving tendons, joints, and bone</td>
<td>No</td>
</tr>
<tr>
<td>Cattle</td>
<td>Papillomatous digital dermatitis (foot warts; hairy heel warts)</td>
<td>Prolonged wet conditions</td>
<td>Probably <em>Treponema</em> sp. spirochete</td>
<td>Moderate to severe lameness</td>
<td>Yes</td>
</tr>
</tbody>
</table>
Contributor: California Animal Health and Food Safety Laboratory System, San Bernardino Branch, University of California – Davis, School of Veterinary Medicine, 105 W. Central Avenue, San Bernardino, CA 92408, www.cahfs.ucdavis.edu

References:

CASE II – 06-1098 (AFIP 3027583).

Signalment: Female mountain goat.

History: An old, adult female mountain goat was found dead near a hot springs in central Idaho.

Gross Pathology: The submitter reported an emaciated, partially scavenged carcass with severe dental disease. Two “chicken egg-sized cysts” were present in the lungs. The gross specimen submitted was a piece of lung with a discrete, 5 x 4.5 x 4.5 cm cyst filled with clear fluid and having a finely granular lining (figs. 1 and 2)

Histopathologic Description: In a section of lung, alveoli are compressed by a cyst that is composed of a peripheral rim of collagenous tissue (host tissue) lined by a prominent, slightly lamellar layer of finely granular, lightly basophilic, acellular material (fig. 3). Internally, the cyst is further lined by a thin, eosinophilic layer with numerous, round to ovoid, lightly eosinophilic structures (calcareous corpuscles), (fig 4). From this extends a discontinuous layer of numerous, spherical, thin-walled structures (brood capsules) up to 460 μm diameter and containing groupings of 2 -14 protoscolices with prominent refractive hooks and containing calcareous corpuscles (fig. 5).

Contributor’s Morphologic Diagnosis: Pulmonary unilocular hydatid cyst (typical of Echinococcus granulosus)
Contributor’s Comment: The hydatid cyst found in the aged mountain goat was thought to be an incidental finding unrelated to the cause of death (likely due to emaciation related to poor dental condition).

The cestode genus *Echinococcus* includes 2 major species, *E. granulosus* and *E. multilocularis*. Both species are parasites of canids (dog, coyote, wolf and dingo), although there is a lion-adapted strain in Africa. The parasite has world wide distribution, and the range of *E. granulosus* and *E. multilocularis* overlap in North America. The intermediate hosts for the larval stages of *Echinococcus* include sheep, swine, cattle, wild cervids (primarily moose and caribou) and other species such as kangaroos in Australia and a variety of prey species in Africa. The sylvatic cycle between wild canids and wild cervids can overlap into a pastoral cycle between domestic dogs (and occasionally cats) and domestic ungulates. Man may become infected as an intermediate host primarily through contact with domestic dogs. Cystic echinococcosis in people in North America occurs throughout Canada and Alaska due to the practice of feeding wild cervid entrails to domestic dogs. A nidus of infection in the 1970s occurred among shepherders in the western US (primarily California and Utah) presumably because of similar practices. A few cases continue to be diagnosed among Native Americans in New Mexico. Recombinant vaccines have been developed for *E. granulosus* intermediate stages in cattle and sheep.

The intermediate or larval stage of *E. granulosus* is called the unilocular hydatid cyst. This stage begins as a small cyst and slowly grows, usually reaching a size of a few centimeters in cattle and sheep. Longer lived hosts such as human beings (and, in this case, an aged mountain goat) cysts may grow to several centimeters. Generally, unilocular hydatid cysts do not cause clinical disease, although they may inhibit organ function by compression in some human patients. This is in contrast to the alveolar hydatid cyst, intermediate stage of *E. multilocularis*, which grows by infiltration of surrounding tissue and is often fatal.

Unilocular hydatid cyst has a typical gross and histological appearance as seen in this case. The smooth wall of the cyst is made up of a layer of host connective tissue adjacent to the hyalinized cyst wall. Numerous small scolices, termed protoscolices are clustered in brood capsules. The “hydatid sand” is made up of scolices that break free and float in the hydatid fluid. Calcareous corpuscles, characteristic of cestodes, are present in the cyst lining.

Cystic echinococcosis has not previously been reported in wild ungulates in Idaho; this parasite may have arrived with re-introduced wolf populations from Canada.
AFIP Diagnoses: Lung: Hydatid cyst, with mild interstitial fibrosis, mountain goat, caprine.

Conference Comment: The contributor provides a concise summary of Echinococcosis. While both *E. granulosus* and *E. multilocularis* form hydatid cysts composed of a bladder with myriad protoscolices that are often clustered into brood capsules, *E. granulosus* forms unilocular hydatid cysts and *E. multilocularis* forms multilocular hydatid cysts. Other cystic larval cestodes include the following:5

1. **Cysticercoids** – very small larvae, with a tiny bladder and a scolex that is surrounded by parenchymous arms
2. **Cysticercus** – bladder with a single inverted neck and scolex; scolex may be armed, and always has four suckers
3. **Coenurus** – resembles Cysticercus but has more than one scolex

Solid-bodied cestode larvae include the following:5

1. **Plerocercoid** – lacks suckers
2. **Tetrathyridium** – has suckers

Below is a useful chart from Veterinary Pathology summarizing the features of some important tapeworms.6

### Features of some important tapeworms

<table>
<thead>
<tr>
<th>Name of adult tapeworm</th>
<th>Definitive host</th>
<th>Intermediate stage Name/type of larval cestode</th>
<th>Intermediate hosts</th>
<th>Anatomic Site</th>
</tr>
</thead>
<tbody>
<tr>
<td><em>Taenia saginata</em></td>
<td>Humans</td>
<td>Cysticercus (bovis)</td>
<td>Cattle</td>
<td>Heart, skeletal muscle</td>
</tr>
<tr>
<td><em>T. solium</em></td>
<td>Humans</td>
<td>Cysticercus (cellulosae)</td>
<td>Swine</td>
<td>Muscle, heart, viscera</td>
</tr>
<tr>
<td><em>Echinococcus granulosus</em></td>
<td>Humans, dog, fox, wolf, jackal</td>
<td>Echinococcus (granulosus)</td>
<td>Humans, cattle, swine, sheep, deer, horse, moose, etc.</td>
<td>Liver, lungs, other viscera</td>
</tr>
<tr>
<td><em>E. multilocularis</em></td>
<td>Humans, dog, fox, wolf, jackal</td>
<td>Echinococcus (multilocularis)</td>
<td>Humans, cattle, swine, sheep, deer, horse, moose, etc.</td>
<td>Liver, lungs, other viscera</td>
</tr>
<tr>
<td><em>Taenia hydatigena</em></td>
<td>Dog</td>
<td>Cysticercus (tenuicollis)</td>
<td>Squirrels, cattle, wild ruminants, sheep, goats, swine</td>
<td>Peritoneal cavity</td>
</tr>
<tr>
<td><em>T. ovis</em></td>
<td>Dog, fox, wolf, coyote</td>
<td>Cysticercus (ovis)</td>
<td>Sheep, goats</td>
<td>Muscles</td>
</tr>
<tr>
<td><em>T. pisiformis</em></td>
<td>Dog, cat, fox, wolf</td>
<td>Cysticercus (pisiformis)</td>
<td>Rabbit, squirrel, other small rodents</td>
<td>Liver capsule, peritoneum</td>
</tr>
<tr>
<td><em>T. taeniaeformis</em></td>
<td>Cat, dog, fox</td>
<td>Cysticercus (fasciolaris)</td>
<td>Rats, mice, rabbits</td>
<td>Liver</td>
</tr>
<tr>
<td>(syn.: <em>T. crassicolis</em>)</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td><em>T. Multiceps</em></td>
<td>Dog</td>
<td>Coenurus (cerebralis)</td>
<td>Sheep, goats</td>
<td>Brain, spinal cord</td>
</tr>
<tr>
<td><em>multiceps</em></td>
<td></td>
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<td></td>
</tr>
<tr>
<td>Organism</td>
<td>Hosts</td>
<td>Life Cycle Stages</td>
<td>Organ</td>
<td>Comments</td>
</tr>
<tr>
<td>----------</td>
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</tr>
<tr>
<td><em>T. serialis</em></td>
<td>Dog, other carnivores</td>
<td>Coenurus (serialis)</td>
<td>Rabbit</td>
<td>Subcutis</td>
</tr>
<tr>
<td><em>Diphyllobothrium latum</em></td>
<td>Humans, bear, dog, cat, pig, fox</td>
<td>Proceroid and plerocercoid</td>
<td>Microcrustacea, freshwater fish</td>
<td>Muscles</td>
</tr>
<tr>
<td><em>Spirometra (Diphyllobothrium) mansonioides</em></td>
<td>Dog, cat</td>
<td>Proceroid and plerocercoid (sparganum)</td>
<td>Snakes, humans, monkeys, dog</td>
<td>Peritoneal cavity</td>
</tr>
<tr>
<td><em>Mesocestoides corti</em>, <em>M. lineatus</em></td>
<td>Dog, cat, wild carnivore, humans</td>
<td>Tetrathridium</td>
<td>Mites and wild rodents, dogs, cat, other mammals, reptiles</td>
<td>Peritoneal and pleural cavities, liver, lung, other organs</td>
</tr>
<tr>
<td><em>Dipylidium caninum</em></td>
<td>Dog, cat</td>
<td>Cysticercoid</td>
<td>Dog flea, biting lice</td>
<td></td>
</tr>
<tr>
<td><em>Moniezia expansa</em></td>
<td>Sheep, goats, cattle</td>
<td>Cysticercoid</td>
<td>Mites: Galumna, Scherloribates, Scutovertex minutus</td>
<td></td>
</tr>
<tr>
<td><em>M. benedeni</em></td>
<td>Sheep, goats, cattle</td>
<td>Cysticercoid</td>
<td></td>
<td></td>
</tr>
<tr>
<td><em>Anoplocephala magna</em></td>
<td>Equines</td>
<td>Cysticercoid</td>
<td>Mites of family Oribatidae</td>
<td></td>
</tr>
<tr>
<td><em>A. perfoliata</em></td>
<td>Equines</td>
<td>Cysticercoid</td>
<td>Oribatidae</td>
<td>Intestinal tract</td>
</tr>
<tr>
<td><em>Paranoplocephala mammillana</em></td>
<td>Equines</td>
<td>Cysticercoid</td>
<td>Oribatidae</td>
<td></td>
</tr>
<tr>
<td><em>Thysanosoma actinioides</em></td>
<td>Sheep, cattle, goats, deer</td>
<td>Cysticercoid</td>
<td>Oribatidae</td>
<td></td>
</tr>
<tr>
<td><em>Spirometra mansonioides</em></td>
<td>Cat</td>
<td>Sparganum</td>
<td>Snakes, rodents</td>
<td>Connective tissue</td>
</tr>
</tbody>
</table>

Dr. Chris Gardiner adds, “This is a good case. All the characteristics we would want to see of the organism are present. The laminated cyst wall is well represented, the germinal membrane, the protoscolices, the calcareous corpuscles, the hooklets are all present…another interesting fact is that the hooklets are acid fast and sometimes when the cysts are old and ruptured you can find the hooklets out in the tissue and when you do an acid fast stain they are nice and red!”

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**References:**
CASE III – A06-18116 (AFIP 3030466).

Signalment: 3-month-old, female, pug-cross, *Canis lupus familiaris*.

History: Depression, nasal discharge and dyspnea

Gross Pathology: An 11-week-old female Pug puppy with a history of depression, nasal discharge, and dyspnea was submitted for necropsy in good body condition with a moderate amount of cloudy white, partially crusting exudate along the nares and the eyelid conjunctiva. Autolysis was minimal. The lungs were diffusely heavy and wet, and remained inflated. All four foot pads were markedly thickened with crusts.

Laboratory Results:
Fluorescent Antibody Tests:
1. Canine Distemper: Positive
2. PI3: Negative

Histopathologic Description: The following tissues were examined microscopically: cerebrum, hippocampus, cerebellum with brain stem, nasal mucosa and turbinates, trachea, lung, liver, kidneys, urinary bladder, spleen, mesenteric lymph node, heart, jejunum, stomach, and footpads (all four feet).

Foot pads (all four feet): There is marked compact orthokeratotic hyperkeratosis. Multifocally and predominantly within the superficial layers of the stratum spinosum, numerous keratinocytes exhibit varying degrees of ballooning degeneration/spongiosis, with 1-3 round to ovoid, 2-4 um-wide brightly eosinophilic intracytoplasmic viral inclusion bodies. Rarely keratinocytic syncytial cells with multiple nuclei are present (Note: Not observed in all slides submitted). Occasionally, similar viral inclusion bodies are present in basal cells. There is mild to moderate irregular acanthosis with thickened rete ridges extending into superficial dermis. Within superficial dermis, there is mild perivascular inflammatory cellular infiltrate chiefly consisting of lymphocytes and macrophage.
Contributor’s Morphologic Diagnoses:
Distemper virus infection, with:
- Necrotizing encephalitis, multifocal, severe, with gitter cells and I/C viral inclusion bodies.
- Necrotizing bronchopneumonia, lymphohistiocytic, subacute, severe, multifocal, with I/C viral inclusion bodies.
- Mild multifocal necrotizing enteritis with I/C viral inclusion bodies.
- Orthokeratotic hyperkeratosis of foot pads, moderate, quadrilateral, with keratinocytic ballooning degeneration, rare syncytia and I/C viral inclusion bodies.
- Nasal thrush

Contributor’s Comment: Canine Distemper is a disease of certain species of terrestrial carnivores. In recent years the host range of this disease appears to have widened which includes wild felids like cheetahs and lions. Similarly, the disease outbreaks have been reported in seals, weasels and ferrets. In a typical disease outbreak, the virus spreads through aerosol and localizes in lymphoid organs (tonsils, bronchial lymph nodes, thymus, spleen and retropharyngeal lymph nodes). Within a week followed by aerosol exposure, viremia is established and mononuclear cells of blood can carry virus into multiple organs. Poor humoral response by the host predisposes for severe multisystemic disease. Mild or inapparent disease and recovery is seen in animals with adequate humoral response.¹

Clinical signs and organs affected depend on strain of the virus, environmental conditions, age and immune status of the animal. It is interesting to note that puppies with vesicular and pustular dermatitis rarely develop CNS lesions. On the contrary, dogs with nasal and digital hyperkeratosis usually have neurologic lesions as it has been observed in the present case submission.¹

Digital hyperkeratosis (hard pad disease) is an uncommon manifestation of the disease process. It is characterized by severe orthokeratotic hyperkeratosis with eosinophilic intracytoplasmic viral inclusion bodies in footpad epithelium.¹ Disease mechanism of hyperkeratosis in CDV is poorly understood. However, a recent study involving naturally infected dogs with CDV indicated that selective infection of keratinocytes in the stratum spinosum might be the key event in development of hard pad disease. Furthermore, this report also indicated that presence of CDV specific-inclusion bodies and ballooning degeneration in footpad epidermis may not be present in hard pad disease.² Conversely, in dogs with experimental inoculation of virulent CDV strains can exhibit CDV antigen and viral specific mRNA in all layers of footpad epidermis.³ Findings in another experimental study concluded that accelerated proliferation of keratinocytes in hard pad disease may be due to
interference of CDV in reducing translocation of p65 (a component of nuclear factor (NF)-kappa B transcription factor) into nucleus.\textsuperscript{4}


\textbf{AFIP Diagnosis:} Footpad: Epidermal hyperplasia, diffuse, moderate, with orthokeratotic and parakeratotic hyperkeratosis, rare syncytia and numerous epithelial eosinophilic intracytoplasmic inclusion bodies, Pug, canine.

\textbf{Conference Comment:} Canine distemper virus (CDV) is a member of the genus Morbillivirus in the Paramyxoviridae family. This family is composed of large (100-300 nm), pleomorphic, single-stranded RNA viruses. Members of the genus Morbillivirus include measles virus, rinderpest virus, peste-des-petits-ruminants virus, phocine morbillivirus, and cetacean morbillivirus.\textsuperscript{5,6,7}

Canine morbillivirus infects a wide range of species including Canidae (eg., dog, dingo, fox, coyote, wolf, jackal), Procyonidae (e.g., raccoon, coati, kinkajou, panda), Mustelidae (eg., ferret, mink, badger, weasel, otter), Viveridae (Binturong), marine mammals, and wild Felidae.\textsuperscript{5,6,7}

CDV is pantropic, preferentially infecting lymphoid, epithelial, and nervous cells, and can cause a variety of clinical signs in dogs with an inadequate antibody response. In addition to digital hyperkeratosis, CDV can target the lungs directly causing a viral pneumonia or indirectly render the lungs susceptible to secondary bacterial infections (eg. \textit{Bordetella bronchiseptica}, mycoplasma) due to its immunosuppressive effects.\textsuperscript{6,8} Viral infection of ameloblasts during enamel formation results in segmental enamel hypoplasia.\textsuperscript{6,9} Dogs that survive the disease may develop late complications such as demyelinating encephalomyelitis and hyperkeratosis of the footpads (“hard pad” disease) and nose. Other complications include systemic toxoplasmosis and sarcocystosis.\textsuperscript{6}

Microscopically, eosinophilic intranuclear and/or intracytoplasmic inclusion bodies can be seen in epithelial cells of many tissues, but are most prominent in epithelium of the urinary bladder, renal pelvis, stomach, and lung.\textsuperscript{6}

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\textbf{References:}
2. Koutinas AF, Baumgartner W, Tontis D, Polizopoulos Z, Saridomichelakis MN,
CASE IV – S0507399 (AFIP 3024118).

Signalment: 12-year-old, female, Paso Fino, Equus caballus, domestic horse.

History: Horse was euthanized for chronic laminitis.

Gross Pathology: A 0.8 cm diameter, fluctuant, tan, exophytic mass, with multifocal hemorrhagic areas was present within the anterior pituitary gland.

Histopathologic Description: Within the pars distalis is an expansile, nonencapsulated, well-demarcated, ovoid mass, which compresses the adjacent normal parenchyma. The neoplastic cells are arranged in a sheet of closely-packed, polygonal cells supported by scant fibrovascular stroma. Cells have abundant cytoplasm, distinct cell borders and contain large numbers of densely packed eosinophilic granules. Nuclei are singular, round to ovoid, usually with coarsely clumped chromatin. Occasional agranular cells of uncertain histogenesis are
present. No mitotic activity, vascular/lymphatic invasion or local metastases are present.

**Contributor’s Morphologic Diagnosis:** Pituitary gland, pars distalis: Acidophil adenoma

**Contributor’s Comment:** Acidophil adenomas are benign neoplasms derived from granulated acidophils within the pars distalis of the pituitary gland and have previously been described in the rat, dog, sheep, cat, rabbit, and goat. Acidophils can be divided functionally into somatotrophs (which produce growth hormone) and mammotrophs (which produce prolactin). Here, we report an acidophil adenoma in a Paso Fino horse.

In this case, the mare had grossly evident mammary enlargement in the absence of recent pregnancy or parturition, suggesting an endocrinopathy. Teat enlargement was reported in New Zealand White rabbits with prolactin-secreting acidophil adenomas. Udder enlargement and inappropriate lactation associated with acidophil adenoma was also reported in two goats. Interestingly, both goats also had concurrent pheochromocytoma and cystic endometrial hyperplasia. In cats, acidophil adenomas are often associated with hypersecretion of somatotropin, resulting in acromegaly. In the dog, hypersecretion of somatotropin resulting in diabetes mellitus was reported.

**AFIP Diagnosis:** Pituitary gland, pars distalis: Adenoma.

**Conference Comment:** This case is unusual in that the adenoma is within the pars distalis. Most equine pituitary gland adenomas occur in the pars intermedia of older female horses. They are often large neoplasms that extend out of the fossa hypophysialis and severely compress the overlying hypothalamus. The clinical syndrome in horses with adenomas of the pars intermedia is distinctly different from that of Cushing’s disease seen in dogs, cats, and humans, and is characterized by polyuria, polydipsia, polyphagia, muscle weakness, somnolence, intermittent hyperpyrexia, generalized hyperhidrosis, and hirsutism. Horses with larger neoplasms often have insulin-resistant hyperglycemia most likely due to down regulation of insulin receptors on target cells secondary to chronic excessive intake of feed and hyperinsulinemia. The hypothalamus is the primary homeostatic regulatory center for body temperature, appetite, and cyclic shedding of hair. The clinical syndrome is considered to be primarily due to deranged hypothalamic function secondary to compression by the neoplasm. Additionally, some adenomas of the pars intermedia are endocrinologically active.
In the dog, functional pituitary adenomas usually arise in the pars distalis, but can also arise in the pars intermedia, and are most likely derived from ACTH-secreting corticotrophs. Adult to aged boxers, Boston terriers, and dachshunds are predisposed. Bilateral adrenocortical hyperplasia and hyperfunction result in pituitary origin Cushing’s disease. Larger tumors may compress the posterior pituitary and infundibular stalk leading to diabetes insipidus.\textsuperscript{10,12}

Growth hormone secreting acidophil adenomas have been most frequently described in cats and have also been reported in sheep. In adults, whose epiphyses have closed, the bones grow heavier and thicker, producing large hands, feet, and skull bones (acromegaly). Acromegaly results from the production of somatomedins which stimulate cartilage formation. Excessive growth hormone secretion also leads to diabetes mellitus due to interference with tissue glucose uptake and insulin resistance.\textsuperscript{12}

Prolactin-producing pituitary adenomas in rabbits result in hormone-responsive dysplastic changes in the mammary glands. Microscopically, dilated cystic ducts are lined by flattened to cuboidal epithelium with papillary projections into cystic areas.\textsuperscript{13}

Pituitary adenomas commonly occur in aged male and female rats, especially in certain strains (e.g. Sprague-Dawley, Wistar). Prolactin-producing tumors are the most common type and most frequently arise in the pars distalis. Attempts have been made to correlate prolactin-producing pituitary tumors with an increased incidence of mammary fibroadenomas, but this had not been resolved to date.\textsuperscript{13}

Histologically, pituitary adenomas are composed of polygonal to spindle cells arranged in solidly cellular or sinusoidal patterns. Neoplastic cells have round to oval, vesiculate nuclei, one to two small nucleoli, and a moderate to abundant amount of granular cytoplasm. The mitotic rate is low. Neoplastic cells may be immunoreactive for ACTH, thyroid stimulating hormone (TSH), luteinizing hormone (LH), β-endorphin, and β-lipoproteins. In horses, cells stain strongly for (POMC), α- and β-melanocortin, β-lipoprotein and β-endorphin with a weak reactivity for ACTH and are presumably melanotrophs not corticotrophs.\textsuperscript{10,11,12}

Pituitary carcinomas are similar to pituitary adenomas; however, in contrast to pituitary adenomas, pituitary gland carcinomas are rare and exhibit extensive invasion along the base of the brain into the sphenoid bone, vascular invasion and/or metastasis. The mitotic index and cellular atypia are often greater in pituitary carcinomas than adenomas.\textsuperscript{10,11}

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