

The Armed Forces Institute of Pathology
Department of Veterinary Pathology
WEDNESDAY SLIDE CONFERENCE
2002-2003

CONFERENCE 6
23 October 2002

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CASE I – 01B0449 (AFIP 2840167)

Signalment: 8-year-old, male, American Paint, Equine

History: This horse had lived in New York and Arkansas, and at the time of presentation was being stabled in Nevada. During a six year period, this animal had intermittent generalized swelling of the right hind leg associated with multiple ulcerative coalescing dermal and subcutaneous nodules that ranged in size from 0.1 to 5 cm in diameter. The nodules began as firm swellings that enlarged, ulcerated and drained a thick, yellow exudate that formed a crust. The cutaneous lesions were managed with regular cleaning and antibiotics, but were generally unresponsive. There were no clinical signs of systemic illness.

Gross Pathology: Multiple punch biopsies of lightly haired skin were submitted for histologic evaluation. The surface epithelium was thick and covered with a lightly adherent crust. The dermo-epidermal junction was obscured and the deep dermis and subcutis were firm and tan.

Laboratory Results: Complete blood count revealed a leukocytosis with neutrophilia, monocytosis and eosinophilia.

WBC	17,900/ul	(5,000-11,600)
Neutrophils	12,709/ul (71%)	(2,600-6,800)
Lymphocytes	4,117/ul (23%)	(1,600-5,800)
Monocytes	716/ul (4%)	(0-500)
Eosinophils	358/ul (2%)	(0-200)

Fungal culture (skin): *Sporothrix schenckii*

Direct smear of cutaneous exudate: No organisms seen

Aerobic culture (skin): Very small numbers of *Streptococcus zooepidemicus*,
Pasteurella caballi, and *Escherichia coli*

Anaerobic culture (skin): Very small numbers of *Fusobacterium necrophorum*

Synergistic hemolysis inhibition (SHI test): negative for *Corynebacterium pseudotuberculosis*

Contributor's Morphologic Diagnosis: Skin: Severe, diffuse, chronic pyogranulomatous dermatitis and lymphangitis with epithelial hyperplasia and intralesional yeast (etiology: *Sporothrix schenckii*)

Contributor's Comment: In these sections of skin, there is a dense pleocellular inflammatory infiltrate within the dermis that is arranged in multiple coalescing nodules that blend with markedly hyperplastic surface and follicular epithelium. The inflammatory infiltrate is composed of large numbers of histiocytes, neutrophils, lymphocytes, and plasma cells admixed with frequent multinucleated giant cells and dense granulation tissue. The multinucleated giant cells contain rare intracytoplasmic, well-demarcated, 2-6 um in diameter yeast. Neutrophils extend into the overlying hyperplastic epithelium and form intraepidermal pustules. The infiltrate disrupts the affected follicles and there is often a dense accumulation of degenerate inflammatory cells and sloughed epithelial cells within the follicular lumens. The hyperplastic epithelium is thrown into broad branching and anastomosing rete pegs and often there are isolated islands of keratinocytes in the superficial dermis. The deep dermis and subcutaneous tissues are replaced by dense mature granulation tissue, and the vessels in this region are surrounded by small numbers of lymphocytes and plasma cells. The surface epithelium is covered by a thin serocellular crust. Using special stains for infectious agents (Periodic Acid Schiff and Grocott's Methenamine Silver), as well as immunohistochemistry with anti-bacillus Calmette-Guerin (BCG) antibodies, rare intracellular and extracellular, 2-6 um, round yeast forms were identified. Rare budding yeast forms are present.

The histologic features in this section of skin and the morphology of the yeast are consistent with *Sporothrix schenckii*, which was confirmed by fungal culture. *S. schenckii* is a dimorphic saprophyte that is widely distributed in the environment. Infection is commonly initiated via cutaneous wounds resulting in suppurative and granulomatous dermatitis and lymphangitis. Several factors are believed to contribute to the development of sporotrichosis, including the size of the initial fungal inoculum, the host immune status, the virulence of the fungi, the depth of inoculation, and the thermal tolerance of the fungal strain. Three main clinical manifestations are recognized: lymphocutaneous, fixed-cutaneous and disseminated. The lymphocutaneous form begins as an indurated papule that slowly enlarges, becomes nodular and frequently ulcerates. The nodules tend to spread along lymphatic channels. The lymphocutaneous form is the most common form described in the horse, in which there is a predilection for the extremities. Dogs and cats generally present with lesions on the head or distal extremities. Multiple verrucous plaques and ulcers, without lymphatic involvement characterize the fixed-cutaneous form. The systemic form involves a wide range of tissues and it is believed to arise as a result of hematogenous spread from the primary inoculation site, or possibly following inhalation of conidia. Cats are most prone to developing the systemic form.

Virulence factors of *S. schenckii* have not been entirely elucidated, but some have been suggested. These factors include the production of extracellular proteases, the ability to bind to type II collagen, fibronectin and laminin, a high rhamnose content of

the cell wall, the presence of melanin, and the ability to grow at biological temperatures (37°C). Immunosuppressed animals are believed to be at a higher risk of disease, and T lymphocyte mediated immunity is crucial for host defense.

Sporotrichosis affects a wide variety of species, including humans, dogs, cats, horses, mules, cattle, buffalo, mice, pigs, rats, camels, foxes, goats and chickens. Humans with an increased risk include rose gardeners, masonry workers and Christmas tree farmers. Typical histologic features of cutaneous sporotrichosis include marked epithelial hyperplasia or ulceration, pyogranulomatous dermatitis with multinucleated giant cells, intraepidermal pustules and marked dermal and subcutaneous fibrosis. Evidence of lymphangitis will accompany the cutaneous lesions in the lymphocutaneous form. The yeast forms are 2-6 um in diameter, round, oval or 'cigar-shaped' and predominantly solitary with rare budding forms. The 'cigar-shape' is considered a hallmark for identification. In addition, the yeast forms are occasionally surrounded by the Splendore-Hoeppli reaction, but this is not specific. In most species, the yeast forms are rare and special stains are required (GMS and PAS) for detection. In contrast, sporotrichosis in the cat is associated with large numbers of yeast forms, which facilitates the diagnosis in this species.

Antibodies directed against *Mycobacterium bovis* (Bacillus Calmette-Guerin, BCG) are highly sensitive in detecting bacteria, mycobacteria and fungi, whereas spirochetes, viruses and protozoa fail to stain. Therefore, BCG immunohistochemistry is a highly sensitive, but non-specific test. In this respect, this immunohistochemical stain is a useful screening method to identify the presence of certain infectious organisms and can help direct further diagnostic procedures. For the diagnosis of *S. schenckii*, fungal culture is considered the gold standard.

AFIP Diagnosis: Haired skin: Dermatitis, pyogranulomatous, diffuse, severe, with pseudocarcinomatous hyperplasia, intra-epidermal microabscesses, and rare yeast, etiology consistent with *Sporothrix schenckii*, American paint, equine.

Conference Comment: The contributor has provided a concise summary of sporotrichosis. The differential diagnosis discussed by conference participants included: 1) equine cutaneous lymphangitis, caused by *Burkholderia mallei* (glanders/equine farcy) and *Burkholderia pseudomallei* (melioidosis/pseudoglanders); 2) equine ulcerative lymphangitis caused by *Corynebacterium pseudotuberculosis*; and 3) equine epizootic lymphangitis caused by *Histoplasma farciminosi*.

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CASE II - S885.02 (AFIP 2841663)

Signalment: 2.5-month-old, female Chow Chow dog.

History: A 2.5-month-old, brown female Chow Chow dog presented with bilateral, periorbital, periocular and perinasal alopecia, as well as, bilateral purulent conjunctivitis, complete closure of the pupils and total blindness. This animal was euthanized and presented for necropsy.

Gross Pathology: Apart from alopecia and conjunctivitis, no specific gross changes were observed at necropsy. Both the eyes were removed and fixed in 10 % buffered formalin.

Laboratory Results: None.

Contributor's Morphologic Diagnoses:

1. Skin: Diffuse mild hyperkeratosis, diffuse moderate parakeratosis, with mild diffuse vacuolation of epidermal cells in all layers. Marked pigmentary incontinence of basal cells. Moderate multifocal to coalescing subepidermal infiltration of mononuclear leukocytes and large macrophages, some of which contain granular, phagocytosed melanin.
2. Eye: Severe diffuse granulomatous uveitis, with extension and involvement of sclera and retina. The granulomatous infiltrate contains numerous large macrophages with finely granular phagocytosed melanin.

Contributor's Comment: The history, clinical signs, macroscopic and histopathological changes correspond to the descriptions of VKH-like syndrome which may be seen in certain dog breeds such as the Chow Chow. The cutaneous and ocular lesions may be present simultaneously, and are usually characterized by symmetric facial, genital, perianal and pedal leukoderma, which may be complicated by acute

exudative dermatitis. Leukotrichia and alopecia may also be present and may become generalized. Although the facial cutaneous changes appear more prominent, the ophthalmic lesions are more important and may result in blindness.

Cutaneous histopathological changes are characterized by acanthosis with a localized or generalized decrease in epidermal melanocytes, as well as a dermal infiltration of variable numbers of mononuclear leukocytes and plasma cells, with fine granular melanin particles in the cytoplasm of macrophages. The presence of granulomatous uveitis, with plasma cells and similarly pigmented macrophages in the eye serve as further confirmation of the diagnosis. Vogt-Koyanagi-Harada-like syndrome must be differentiated from cutaneous diseases of the facial area such as discoid and systemic lupus erythematosus, pemphigus foliaceus, pemphigus vulgaris and vitiligo. Positive histopathology on biopsy specimens from areas of recent erythema, scaling and depigmentation, as well as the presence of uveitis on ophthalmic and histopathological examination are indicative of VKH-like syndrome.

The morphologic changes are compatible with the cutaneous and ocular lesions described in humans with VKH-like syndrome. This is a rare suspected autoimmune condition with a type-IV hypersensitivity to melanin in humans also accompanied by deafness and suspected meningeal involvement.

AFIP Diagnoses: 1. Eye: Uveitis, granulomatous and neutrophilic, multifocal to coalescing, moderate, with intrahistiocytic melanin pigment, and adjacent mild scleritis, Chow Chow, canine.

2. Haired skin: Dermatitis, superficial and periadnexal, histiocytic and lymphoplasmacytic, multifocal, moderate, with marked pigmentary incontinence.

Conference Comment: Vogt-Koyanagi-Harada-like (uveodermatologic) syndrome is a rare canine disease with a likely autoimmune etiology. Dogs present with bilateral granulomatous panuveitis, poliosis, and vitiligo. The dog breeds most often reported in VKH-like syndrome include the Akita, Siberian Husky, Alaskan Malamute, Chow Chow and Samoyed.

In humans, there are three phases of VKH: 1) meningoencephalitic, 2) ophthalmic, and 3) dermatologic. The proposed pathogenesis of VKH syndrome in humans involves antimelanin and antiretinal autoantibodies, and cytotoxic T cell (Type IV) hypersensitivity to melanin and melanocytes of the uvea and epidermis.

The submitted sections vary and along with the eye and haired skin, may include conjunctiva, and periocular muscle with eosinophilic myositis.

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CASE III – 01-726 (AFIP 2840296)

Signalment: 11.5-year-old, spayed female, domestic short hair, *Felis catus*, feline

History: The cat presented originally in May of 2000 with a history of chronic renal failure. A renal transplant was performed and the cat was placed on immunosuppressive therapy consisting of 2.5 mg of Prednisolone twice daily and oral Cyclosporine once daily. In December of 2001 the cat presented for a two-month history of weight loss and inappetence with a recent onset of vomiting, diarrhea and blood in the stool. Abdominal radiographs revealed possible mesenteric lymphadenopathy and peritoneal effusion. An ultrasound-guided biopsy of the mesenteric lymph nodes was performed and severe granulomatous inflammation (of presumptive lymph node tissue) with innumerable intrahistiocytic acid fast positive bacilli was found. The cat was euthanized.

Gross Pathology: At necropsy, there was a moderate amount of straw colored effusion within the abdomen. Both native kidneys were extremely small, shrunken, firm and irregular. The renal allograft was sutured to the left body wall and the transplanted ureter entered into the apex of the bladder. Within the mesentery was a large (6.5x3.5x1.5cm), soft, bright yellow mass in the region of the ileocolic lymph nodes. On

cut section, no normal nodal architecture was detected. Plaques of similar, bright yellow material surrounded the attachment site of the donor kidney to the body wall and a focal adhesion of the stomach to the body wall. The liver was enlarged, mottled yellow-red and friable. A sample of the mesenteric mass (mesenteric lymph node, presumptive) was submitted for mycobacterial culture and species identification.

Laboratory Results:

Complete blood count: nonregenerative anemia (PCV: 18%); neutrophilic leukocytosis (27,000 neutrophils/ul); lymphopenia (280 cells/ul); monocytosis (1100 cells/ul)

Chemistry screen: BUN: 77 mg/dL; creatinine: 1.9 mg/dL; phosphorous: 8.3 mg/dL; potassium: 4.9 mmol/L; alanine transferase: 542 U/L; aspartate transferase: 952 U/L

Microbiology: *Mycobacterium avium* was cultured and identified.

Contributor's Morphologic Diagnoses:

1. Small intestine: Moderate, diffuse, chronic, granulomatous enteritis with intrahistiocytic acid fast bacilli.
2. Liver: Mild, chronic, portal and multifocal, random, granulomatous hepatitis with intrahistiocytic acid fast bacteria. Severe acute bridging centrilobular to midzonal hepatocellular necrosis.

Contributor's Comment: On histopathology, granulomatous inflammation was present within the mesenteric mass (mesenteric lymph node), spleen, liver, small intestine, large intestine and lungs. This inflammation was most severe within the lymph node, spleen and small intestine. Similar inflammation was present along the capsule of the donor kidney at the abdominal wall attachment site and at the gastric adhesion site. Scattered clusters of epithelioid macrophages were present within the bone marrow.

The majority of affected organs examined (spleen, mesenteric lymph node, small intestine, large intestine) were diffusely infiltrated by large, epithelioid macrophages with abundant, blue-gray, granular cytoplasm. Smaller numbers of neutrophils and lymphocytes were admixed amongst the macrophages. The inflammation typically expanded and replaced the normal architecture. In the sample of small intestine, the lamina propria and submucosa were expanded by a diffuse infiltrate of epithelioid macrophages. Many of the intestinal villi were thickened and blunted. The intestinal crypts were moderately separated.

Within the liver, the infiltrate of epithelioid macrophages was focused primarily within the portal areas. Small foci of similar cells were randomly distributed throughout the rest of the hepatic parenchyma. Additionally, there was severe coagulation necrosis of the centrilobular to midzonal hepatocytes with multifocal hemorrhage and congestion of the central veins. We believe this necrosis may be secondary to the hypoxemia resulting from the chronic anemia and granulomatous pulmonary disease.

Disseminated mycobacterial infection by nontuberculous mycobacteria (NTM) is an infrequent occurrence in both domestic animals and humans. Infection can present as diffuse cutaneous disease, multifocal bone or joint disease, visceral infection or positive blood/bone marrow cultures. Seventy to 80% of human patients have underlying immunosuppression. In immunocompromised human patients, organisms in

the *Mycobacterium avium* complex (predominantly *M. avium*) group are the most common cause of disseminated infection. Dogs and cats are considered relatively resistant to *M. avium*. However, Bassett Hounds, Miniature Schnauzers and Siamese cats have an increased incidence of infection. Most NTM species are found ubiquitously in the environment, particularly in acidic soil, which contains a large amount of organic matter. Animal to animal and animal to human transmission have not been proven.

Among human transplant patients, disseminated mycobacterial infections are uncommon. However, infections in kidney, liver, and heart transplant recipients have all been reported. Again, *M. avium* is the most common agent of infection, which is most likely due to the combination of anti-rejection therapy and exposure to the agent in the environment.

There are very few reported cases of feline *Mycobacterium avium* complex infection in the literature. The majority of cats present with disseminated disease. The next most common presentation is with cutaneous infection. The predisposing factors for systemic infection are not noted in the majority of these reports. In a retrospective study of 66 cats that received renal transplants, death due to infection occurred in eight cats. Three of the eight suffered from systemic infections, including toxoplasmosis, actinobacillosis and one case of unspecified mycobacteriosis.

The cat in this case had undergone renal transplantation and was on immunosuppressive therapy for 18 months. Cyclosporine inhibits the activation and proliferation of T lymphocytes by interfering with interleukin-2 synthesis by inhibition of calcineurin. This likely resulted in decreased cell mediated immunity and increased susceptibility to mycobacterium, which resulted in disseminated infection.

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- AFIP Diagnoses:**
1. Intestine: Enteritis, histiocytic, multifocal, moderate, with myriad intrahistiocytic bacilli, Domestic Short Hair, feline.
 2. Mesentery: Peritonitis, histiocytic and neutrophilic, multifocal, mild, with myriad intrahistiocytic bacilli.
 3. Liver: Hepatitis, portal and random, histiocytic, multifocal, moderate, with myriad intrahistiocytic bacilli.
 4. Liver: Necrosis, coagulative, centrilobular to midzonal, diffuse.

Conference Comment: *Mycobacterium avium* is an obligate, intracellular, tubercle bacillus that is 0.5 um in width, Gram-positive and acid-fast. *M. avium* serovars 1, 2 and 3 are most commonly reported in animals. Cats are more susceptible to *M. bovis* than to *M. tuberculosis* and *M. avium*. Feline mycobacteriosis is usually acquired via ingestion of contaminated milk, and lesions are primarily in the alimentary tract. *M. avium* most commonly causes disease in birds and marsupials. Avian mycobacteriosis is acquired via ingestion, and disseminates to the liver, spleen, intestines and bone marrow, forming tubercular granulomas. Marsupial mycobacteriosis is proposed to be acquired via inhalation, resulting in pyogranulomatous and necrotic pulmonary lesions that may spread hematogenously. In pigs, *M. avium* is acquired via contact with feces of tuberculous fowl and wild birds, and it typically causes suppurative lymphadenitis of the cervical and mesenteric lymph nodes. In ruminants, *M. avium* subspecies *paratuberculosis* (Johne's disease) is acquired via ingestion or fetal infection. It results in chronic, segmental, corrugated thickening of the terminal small intestine, cecum, and

proximal colon with mesenteric lymph node enlargement. Conference participants experienced some difficulty in distinguishing small versus large intestine in the submitted sections.

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CASE IV - N02-173 (AFIP 2839007)

Signalment: 8-month-old, male, quarter horse

History: A horse presented with a 1-week history of fever, anorexia and diarrhea. At presentation, the horse was in hypovolemic shock (tachycardia, purple mucous membranes, increased capillary refill time and cold extremities). The horse developed colic, which was unresponsive to Xylazine and Butorphanol, and the animal was euthanized.

Gross Pathology: The changes in the intestinal tract were limited to the cecum and large colon. The mucosa was red/black with multifocally loosely adhered fibrin. The colon wall thickness was from 1.5 to 4 cm.

Laboratory Results: An hour prior to euthanasia, a complete blood count revealed severe leukopenia ($0.76 \times 10^3/\text{ul}$; normal range $5.2\text{-}13.9 \times 10^3/\text{ul}$). A biochemical profile revealed azotemia (BUN=66mg/dl; normal range 10-23mg/dl), panhypoproteinemia (Albumin 1.5g/dl; normal range 2.8-4.3g/dl; Globulin = 1.7g/dl; normal range 2.5-5.0 g/dl), hyponatremia (117mEq/l; normal range 137-146mEq/l), and hypochloremia (80mEq/l; normal range 95-106mEq/l).

Contributor's Morphologic Diagnosis: Severe diffuse subacute fibrinonecrotic colitis with myriad intralesional cyathostome larvae, large colon, equine.

Contributor's Comment: While a rare cause of death in the horse, severe diarrhea and death can occur when large numbers of hypobiotic cyathostomes leave the mucosa and enter the intestinal lumen. This emergence of developing larvae causes loss of mucosal integrity leading to hypoproteinemia and electrolyte imbalances.

There are over 40 species of small strongyles (cyathostomes) that parasitize the large intestine of horses. Eggs from luminal adults are passed in the feces and develop in stages to L3 infective larvae. When ingested, these larvae lose the outer protective sheath (the L2 cuticle which was retained) and enter the mucosa of the cecum and colon where they become surrounded by a thin fibrous capsule. Inflammatory responses to these hypobiotic larvae are usually mild and there is no associated clinical disease.

It is believed that a trigger for synchronized release of larvae to the lumen is an associated loss of the adult luminal cyathostomes, as might occur with deworming. Ivermectin® has excellent efficacy on adult cyathostomes with limited efficacy on the encysted larvae. Case reports of fatal diarrhea secondary to intestinal cyathostomiasis usually record a history of deworming. In the submitted case, deworming protocols followed were more frequent than required, and involved multiple drug classes. Resistance of cyathostomes to anthelmintics has been reported; the role of resistance in this case is unknown.

The most common presentation of larval cyathostomiasis is a young (<2 year old) horse with weight loss and a sudden onset of diarrhea. The clinical pathology changes in this animal are slightly different than reported; most horses have a neutrophilia and no hypoglobulinemia. While a fecal floatation was not performed, most of these cases are not shedding ova in the feces. This may be due to timing. The loss of the adult worms is followed by excysting of the larvae that must develop to adults prior to shedding ova.

AFIP Diagnoses: 1. Large intestine: Colitis, lymphoplasmacytic, diffuse, mild, with numerous strongyle larvae, Quarter horse, equine.
2. Large intestine: Colitis, neutrophilic and histiocytic, diffuse, severe, with lymphangitis, hemorrhage, edema, and myriad intracellular and extracellular bacilli.
3. Lymph node: Lymphadenitis, histiocytic and neutrophilic, multifocal, mild, with myriad bacilli.

4. Serosa, mesentery: Peritonitis, histiocytic and neutrophilic, multifocal, mild, with myriad bacilli.

Conference Comment: Histologic exam of the large intestine reveals numerous strongyle larvae characterized by a pseudocoelom, platymyarian meromyarian musculature with lateral chords, a chitinized buccal cavity, intestines composed of few, multinucleate cells, and lacking mature gonads. A few larvae are surrounded by sections of cuticle, interpreted as molting. Conference participants discussed the presence of fewer numbers of larvae, which have intestines that contain granular material. This led to the hypothesis that there may be a co-infection of two small strongyle larvae, or the same larvae in different stages. Typical small strongyle adults are 7-25 mm in length, white to dark red, and visible on close exam of large intestinal mucosa. The eggs are 90 x 50 um, ellipsoid, with a smooth surface. Gram stains of the intestine revealed myriad Gram-negative bacilli that were associated with colitis, hemorrhage and edema. Endotoxic shock was likely a cofactor in this horse's illness.

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