The Armed Forces Institute of Pathology
Department of Veterinary Pathology
WEDNESDAY SLIDE CONFERENCE
2006-2007

CONFERENCE 1
6 September 2006

Conference Moderator: COL Dale Dunn, DVM, Diplomate ACVP
Department of Veterinary Pathology
Armed Forces Institute of Pathology
Washington, DC 20306

CASE I – 0600288 (AFIP 3024111).

Signalment: 9.5 year old black, neutered male domestic short-haired cat.

History: Shadow was euthanized after a 2-3 week history of breathing difficulty. The respiratory distress was not responsive to antibiotics and there was suspicion of widely disseminated metastatic neoplasia. There were multiple masses on the upper and lower left eyelids.

Gross Pathology: A mildly autolyzed adult gray neutered male cat has body weight 4.65 and is in good body condition. Mild autolysis is present. Multiple, 1-2 mm diameter circular masses are visible on the upper and lower right eyelids. When incised, these nodules have yellow-tan, soft centers. A larger 5 mm diameter, well defined, dark red, abraded mass is present in the upper eyelid of the left eye. Mucoid, reddish yellow serous fluid is present in the trachea. The lung lobes fail to collapse, are generally dark red, and firm. They contain 2-5 mm diameter disseminated yellow tan nodules, similar to those seen in the eyelids. The nodules continue throughout the underlying parenchyma. Lung sections sink in formalin. The heart weighs 0.27% body weight, within normal reference range. Both kidneys contain numerous disseminated tan to white raised nodules throughout the cortex. No other gross lesions were detected.

Laboratory Results: *Blastomyces dermatitidis* was isolated from a lung swab prior to necropsy.

Contributor's Morphologic Diagnosis: Multifocal granulomatous chorioretinitis, and anterior uveitis, with intralesional yeasts and retinal detachment.

Contributor's Comment: Not all ocular elements are present on all slides, and the focal nature of the lesions may result in a more limited distribution of inflammation. The animal also has granulomatous inflammation in the lung, kidney and eyelid caused by Blastomyces. Pulmonary disease was thought related to centrilobular degeneration in the liver due to hypoxia.

Blastomyces infection is much less common in cats than in dogs but can produce lethal multi-organ granulomas.

Blastomycosis is caused by the dimorphic fungus *Blastomyces dermatitidis*, found in the Ohio, Missouri, and Mississippi river valleys, Virginia, the Carolinas, and Georgia.[1] Severe pyogranulomatous uveitis is the most common histopathologic finding in feline blastomycosis. Blindness can result from ocular or central nervous system involvement. The posterior segment of the eye is more commonly affected than the anterior segment. A distribution of lesions in the ciliary body, choroid and tapetum has been previously noted.[2] As in other systemic mycoses, intraocular inflammation occurs in the presence of organisms in the eye, not as a secondary inflammatory phenomenon. The general character of the inflammation is similar to that seen in dogs, including necrosis, but organisms are quite numerous compared to many canine cases.[3,4]

Blastomyces can infect and cause ocular disease in a variety of species. Ocular disease is most often seen in a setting of multi-systemic disease,[5] and this patient was presented for its respiratory distress rather than blindness.[6] Ocular involvement occurred in 2 of 5 cats in that series, while others have reported 18%.[7] The overall prevalence of this infection is much less in the feline than canine population. Forty one percent of canine cases have ocular involvement.[8]

AFIP Diagnosis: Eye: Uveitis, pyogranulomatous, multifocal, moderate, with retinitis, retinal detachment, and numerous yeasts, etiology consistent with *Blastomyces dermatitidis*, domestic shorthair, feline.

Conference Comment: The contributor provides an excellent overview of Blastomycosis. Deep mycotic infections are rare in cats and are not always associated with immunosuppressive conditions.[7] The most common feline disseminated fungal infection is cryptococcosis.[3]

Conference attendees briefly reviewed the anatomy of the eye and discussed how to differentiate the systemic mycoses. Below is a chart to help identify the common systemic mycoses.

Common Systemic (Deep) Mycoses

Yeast	Size	Wall or Capsule	Reproduction
Blastomyces dermatitidis	5-25 µm in diameter	double-contoured, refractile	Broad-base budding
Cryptococcus neoformans	5-20 µm in diameter	2-8 µm thick mucopolysaccharide carminophilic capsule	Narrow-base budding
Histoplasma capsulatum	*var. capsulatum* 2-5 µm in diameter *var. duboisii* 8-15 µm in diameter	thin cell wall; no capsule	Narrow-base budding
Coccidioides immitis	Spherules 20-200 µm in diameter	double-contoured, refractile	Endosporulation

Discussion was directed at the eye as an immunologically privileged site with no resident lymphocytes, antigen presenting cells, or draining lymphatics and the presence of the blood-eye barrier. [10] The two major components of the blood-eye barrier are the blood-retinal barrier and the blood-aqueous barrier. These barriers prevent inward and outward movement of proteins and low molecular-weight solutes.[9] The blood-retinal barrier is composed of the endothelium of retinal capillaries and the retinal pigment epithelium. This barrier separates the choroidal and retinal tissue fluids. The blood-aqueous barrier is primarily maintained by the tight junctions between the nonpigmented ciliary body epithelium.[9] Discussion about this case was concluded with a review of the four types of hypersensitivity reactions. A table created directly from Robbins and Cotran has been included below to help residents remember the immune mechanisms and pathologic lesions associated with each type of hypersensitivity reaction.

Mechanisms of Immunologically Mediated Diseases

Type	Prototype Disorder	Immune Mechanisms	Pathologic Lesions
Immediate (type I)	Anaphylaxis; allergies; bronchial asthma (atopic forms)	Production of IgE antibody → immediate release of vasoactive amines and other mediators from mast cells; recruitment of inflammatory cells (late-phase reaction)	Vascular dilation, edema, smooth muscle contraction, mucus production, inflammation
Antibody-mediated (type II)	Autoimmune hemolytic anemia; Goodpasture syndrome	Production of IgG, IgM → binds to antigen on target cell or tissue → phagocytosis or lysis of target cell by activated complement or Fc receptors; recruitment of leukocytes	Cell lysis; inflammation
Immune complex-mediated (type III)	Systemic lupus erythematosus; some forms of glomerulonephritis; serum sickness; Arthus reaction	Deposition of antigen-antibody complexes → complement activation → recruitment of leukocytes by complement products and Fc receptors → release of enzymes or other toxic molecules	Necrotizing vasculitis (fibrinoid necrosis); inflammation
Cell-mediated (type IV)	Contact dermatitis; multiple sclerosis; type I diabetes; transplant rejection; tuberculosis	Activated T lymphocytes → i) release of cytokines and macrophage activation; ii) T-cell mediated cytotoxicity	Perivascular cellular infiltrates; edema; cell destruction; granuloma formation

Contributor: Veterinary Medical Diagnostic Laboratory and Department of Veterinary Pathobiology, University of Missouri, www.cvm.missouri.edu/vpbio/index.html

References:

1. A.M. Legendre: Blastomycosis. In: Infectious Diseases of the Dog and Cat, ed. Greene CE, 2nd ed., pp. 371–377. WB Saunders, Philadelphia, PA,1998
2. Alden CL, Mohan R: Ocular blastomycosis in a cat. J Amer Vet Med Assoc 164:527-528, 1974
3. Gionfreddo JR: Feline systemic fungal infections. Vet Clin North Am Small Anim Pract 30:1029-1050, 2000
4. Krohne SG: Canine systemic fungal infections. Vet Clin North Am Small Anim Pract 30:1063-1090, 2000
5. Nasisse MP, Van Ee RT, Wright B: Ocular changes in a cat with disseminated blastomycosis. J Amer Vet Med Assoc 187:628-631, 1985
6. Breider MA, Walker TL, Legrende AM, VanEe RT: Blastomycosis in cats: five cases (1979-1986). J Am Vet Med Assoc **193:**570–572, 1988
7. Davies C, Troy GC: Deep mycotic infections of cats. J Am Anim Hosp Assoc 32:381-391, 1996
8. Legendre AM, Walker M, Buyukmihci N, Stevens R: Canine blastomycosis: a review of 47 clinical cases. J Am Vet Med Assoc 178:1163–1168, 1981
9. Gum GG, Gelatt KN, Ofri R: Physiology of the Eye. *In* Veterinary Ophthalmology, ed. Gelatt KN, 3rd ed., pp. 161-162, Lippincott Williams and Wilkins, Baltimore, MD, 1999
10. Wilcock BP: The Eye and Ear. *In* Pathology of Domestic Animals, Volume 1, eds. Jubb KVF, Kennedy PC, Palmer N, 4th ed., p. 477, Academic Press, Inc., San Diego, CA, 1993
11. Abbas AK: Diseases of Immunity. *In* Robbins and Cotran Pathologic Basis of Disease, eds. Abbas AK, Fausto N, Kumar V, 7th ed., p. 206, Elsevier Saunders, Philadelphia, PA, 2005

CASE II - 04-5029 (AFIP 2944785).

Signalment: 9-month-old, female, Rag knockout mouse (*Mus musculus)*.

History: 20 out of 26 mice in a breeding colony died over the course of 2 days.

Gross Pathology: At necropsy, the mouse examined had a firm, red-tan liver with a diffusely pitted surface.

Laboratory Results: PCR performed on internal organs and feces was positive for mouse hepatitis virus (MHV).

Contributor's Morphologic Diagnosis: Massive hepatocellular necrosis with syncytia – liver, murine.

Contributor's Comment: MHV is the most important virus that infects laboratory mouse colonies. A coronavirus, MHV is ubiquitous and highly contagious. It is also highly mutable, with many strains, and variable organotropism. Infection with MHV is dependent upon the virulence of the specific strain, as well as many host factors – age, genotype, and immune status.[1] Though most infections are subclinical, very young mice (less than 2 weeks of age), genetically susceptible mice, and immunocompromised mice are vulnerable to MHV, with high mortality.[1] Virulent strains can be problematic even for adult mice with normal immune system function.

Strains of MHV have tropism for either enteric or respiratory mucosa. Viral tropism is believed to be mediated by the spike (S) protein, a gylcoprotein of the viral envelope.[2] Enteric strains, which are currently the most commonly isolated,[3] have a predilection for the intestinal mucosal epithelium, causing villus attenuation, mucosal necrosis, and syncytia. Severity of infection is very much age-dependent, with young mice being most susceptible.[4] Polytropic strains, which were more prevalent in the 1950s and 1960s[3], replicate in nasal mucosa, and then disseminate and replicate in the endothelium and parenchyma of other organs, including liver, brain, and lymphoid organs. The virus causes necrosis with syncytia formation in these sites.

In the case presented, the most severe lesions are present in the liver, but necrosis with syncytia is also present in the spleen, and there are some syncytia present in the small intestinal mucosa. Some strains of MHV affect both liver and intestine.[3] In some of the sections of liver provided, there are foci of extramedullary hematopoiesis.

AFIP Diagnosis: Liver: Necrosis, multifocal to coalescing, with syncytia, etiology consistent with murine coronavirus, Rag knockout mouse (*Mus musculus*), rodent.

Conference Comment: The contributor provides a thorough review of MHV. Variation in morphologic diagnoses prompted a discussion about the definition of massive hepatic necrosis. Robbins and Cotran defines necrosis of entire lobules as submassive and of most of the liver as massive; whereas, Thomson's defines

massive necrosis as that of an entire hepatic lobule or contiguous lobules without reference to a submassive pattern.[5,6]

Further discussion was directed at the variability in the susceptibility and clinical outcome associated with the polytropic (respiratory) and enteroptropic strains, respectively, depending on the age and immune status of affected mice. Infection with polytropic MHV in neonatal, genetically susceptible, or immunocompromised mice results in viremia and dissemination of the virus with viral replication in the endothelium and parenchyma of multiple tissues throughout the body to include the brain, liver, lymphoid organs, bone marrow, and other sites. The virus is cleared without persistence or a carrier state by 3-4 weeks post-infection. Infection of post-weaning age mice is usually subclinical. Nude or SCID mice cannot clear the virus and develop severe multisystemic disease. In contrast, enterotropic strains tend to infect only the intestinal mucosa with minimal or no dissemination to other organs, even in immunocompromised mice. Mice of all ages are susceptible to disease; however, the development of disease is age related. Neonatal mice infected with enterotropic MHV develop a severe necrotizing enterocolitis with high mortality. With advancing age, lesion severity and mortality progressively decrease. Infected adult mice develop minimal lesions, including adult SCID and nude mice. This prompted discussion about what determines the severity of infection in entertropic strains. The moderator emphasized that severity of intestinal disease is associated with the age-related rapid turn over of intestinal epithelial mucosal cells rather than immune-related susceptibility accounting for the severe infection in neonatal mice.[1]

Differential diagnoses for random hepatic necrosis in the mouse include Tyzzer's disease (*Clostridium piliforme*), salmonellosis, and mousepox (ectromelia virus). Tyzzer's disease and salmonellosis do not have syncytial cells as a characteristic microscopic finding. If present in sections, salmonella organisms may be demonstrated by tissue Gram stains as short, Gram-negative, bacilli. Necrosis of Peyer's patches frequently occurs with enteric salmonellosis. Silver stains, such as the Warthin-Starry, best demonstrate the filamentous bacilli within hepatocytes at the periphery of necrotic areas, typical of Tyzzer's disease. In the liver lesions of mousepox, intracytoplasmic inclusions are evident in hepatocytes at the periphery of necrotic foci, and syncytial cells are not present. Cutaneous lesions, splenic necrosis, and necrosis of lymph nodes and Peyer's patches are often present in cases of mousepox.

The gallbladder is present in some sections.

Contributor: Department of pathology and toxicology, University of Pennsylvania School of Veterinary Medicine, 3800 Spruce Street, Philadelphia, PA 19104 www.vet.upenn.edu

References:
1. Percy DH, Barthold SW: Pathology of Laboratory Rodents and Rabbits, 2nd ed., pp 28-31. Iowa State University Press, Ames, Iowa, 2001
2. Homberger FR: Enterotropic mouse hepatitis virus. Lab Animals **31**, 97-115, 1997
3. Homberger FR, Zhang L, Barthold SW: Prevalence of enterotropic and polytropic mouse hepatitis virus in enzootically infected mouse colonies. Lab Animal Science **48**(1): 50-54, 1998
4. Barthold SW, Beck DS, Smith AL: Enterotropic coronavirus (mouse hepatitis virus) in mice: influence of host age and strain on infection and disease. Lab Animal Science **43**(4): 276-284, 1993
5. Crawford JM: Liver and biliary tract. *In* Robbins and Cotran Pathologic Basis of Disease, eds. Abbas AK, Fausto N, Kumar V, 7th ed., p. 877-936, Elsevier Saunders, Philadelphia, PA, 2005
6. Cullen MJ, MacLachlan JN. Liver and biliary system, and exocrine pancreas. *In* Thomson's Special Veterinary Pathology, eds. McGavin MD, Carlton WW, Zachary JF, 3rd ed., pp. 81-124, Mosby, St. Louis, MO, 2001

CASE III –06-17282 (AFIP 3026714).

Signalment: 1.5 year-old, female, Yorkshire, *Sus scrofa*.

History: Two of ten non-bred sows recently moved to a pasture developed diarrhea, lost body weight, and died.

Gross Pathology: The sow was thin with a body condition score of 2. The stomach contained forage and a small amount of ground feed. The mucosa of the pyloric region was congested with mild hemorrhage. Intestinal contents in the duodenum and jejunum were grayish brown and had normal consistency. Segmental congestion was noted on the serosa of the ileum. The ileum was not rigid or thickened. The mucosa of the ileum was necrotic and hemorrhagic with a ragged appearance (Fig. 1). No lesions were observed in the cecum or colon.

Laboratory Results: No pathogens were isolated by aerobic culture of the small and large intestine, lung, liver, and kidney.

Histopathologic Description: The villi were denuded and covered by a thick layer of exudate composed of cellular debris, thick-walled oocysts, mucus, and myriads of bacteria. The villi were necrotic and expanded by proliferation of numerous coccidia organisms to include schizonts, gamonts, and oocysts. The oocysts were ellipsoidal with a rough, golden wall. They were approximately 50 by 35 microns. Many

degenerate gamonts and oocysts were surrounded by exudate and bacteria. Blood vessels in the lamina propria often contained poorly-formed fibrin clots. Necrotic mucosal tissue with degenerate gamonts and oocysts was herniated into a few partially depleted foci of gut associated lymphoid tissue (Peyer's patches). Some of the degenerate oocysts were surrounded by multinucleated giant cells.

Contributor's Morphologic Diagnosis: Subacute severe necrotizing ileitis with numerous intralesional protozoa (*Eimeria spp.)* and bacteria.

Contributor's Comment: Although many species of *Eimeria* have been identified in swine, most are considered nonpathogenic.[5] Reports of disease in swine are rare. *Eimeria* was considered the primary pathogen in this case and a previously diagnosed and reported case from our laboratory.[1] Both cases involved animals maintained on pasture or dirt lots with sandy soils. Attempts to experimentally reproduce the disease in confinement produces minimal or no significant lesions.[3] In naturally-occurring cases, the animals are likely exposed to heavily contaminated soil with the opportunity for repeated exposure to the organism.

The size of the oocyst is one parameter used to determine the species of *Eimeria.* A mixed population of *Eimeria* was isolated in the other case diagnosed at our laboratory. Another report involved lesions associated with *E. spinosum.*[4] This species has smaller oocyst (20.4 by 14.2) with spiny walls. The size of the oocyst in this case is larger than the size reported for *E. scabra* (31.9 by 22.5 microns)*.*[6] *E.* scabra has the largest oocysts of the coccidia associated with swine.

Silver stained sections of intestine in this case and the other case diagnosed at our laboratory revealed no intracellular organisms with morphologic features consistent with *Lawsonia intracellularis*. Numerous mixed bacteria were observed in this case. Some of the bacteria were slender long bacilli arranged in sheaves suggestive of *Fusobacterium spp.* Damage to the mucosal epithelium by coccidia provides a portal of entry for the numerous bacteria present in the lower GI tract.[2] The bacteria may have been synergistic or secondary opportunists. Bacterial toxins may have been a factor in lesion promotion and death.

AFIP Diagnosis: Ileum: Ileitis, subacute, diffuse, moderate, with myriad coccidia, etiology consistent with *Eimeria spp.*, Yorkshire pig (*Sus scrofa*), porcine.

Conference Comment: The Phylum Apicomplexa includes intracellular parasites characterized by a sporozoite stage with a typical apical complex of oraganelles. Genera include: *Eimeria*, *Isospora*, *Caryospora*, *Hammondia*, *Toxoplasma*, *Besnoitia*, *Sarcocystis*, *Cystoisospora*, *Frenkelia*, *Cryptosporidium*, *Neospora*,

Klossiella, *Haemogregarina*, *Hepatozoon*, *Calyptospora*, *Haemoproteus*, *Leucocytozoon*, *Hepatocystis*, *Plasmodium*, *Babesia*, *Theileria*, and *Cytauxzoon*.[7] The Family Eimeriidae includes *Eimeria* and *Isospora*. Coccidia of domestic animals are relatively host and tissue specific. A table listing the common *Eimeria* and *Isospora* species of animals and the tissues in which they are found has been included below for quick reference.

Eimeria and _Isospora_ of Animals

Geese & ducks	*E. truncata*	Kidney
Sandhill whooping cranes	*E. reichenowi*	Disseminated
Parrots	*E. psittaculae*	Intestine
Chicken	*E. acervulina*	Duodenum
Chicken	*E. necatrix*	Mid-intestine
Chicken	*E. tenella*	Ceca
Cattle	*E. bovis*	Small intestine, cecum, colon
Sheep	*E. ashata*	Small intestine
	E. bakuensis	Small intestine
	E. ovinoidalis	Ileum, large intestine
Goats	*E. Christenseni*	Small intestine
	E. arlongi	Small intestine
	E. ninakohlyakimovea	Large intestine
Horses	*E. leukarti*	Small intestine
Swine	*I. suis*	Intestine
	E. debliecki	
	E. porci	
	E. scabra	
Dogs	*I. canis*	Ileum, cecum occasionally
Cats	*I. felis*	Small intestine, colon occasionally
Mice	*E. falciformis*	Colon
Rabbit	*E. stiedae*	Bile ducts
	E. intestinalis	Ileum, cecum
	E. flavescens	Ileum, cecum
Guinea pig	*E. caviae*	Large intestine
Ferret	*E. furonis*	Gallbladder, bile duct

Conference participants briefly reviewed the coccidian life cycle. Oocysts are shed in feces and sporulate. The oocysts of each species are morphologically distinct, but share similar features. The oocysts of *Eimeria* have four sporocysts, each with

two sporozoites, with a total of eight sporozoites in each oocyst. The oocysts of *Isopora* have two sporocysts, each with four sporozoites, with a total of eight sporozoites in each oocyst. Ingested sporozoites excyst in the intestine and invade epithelial cells where they round up and form trophozoites. Asexual replication or schizogeny follows forming schizonts containing merozoites. The schizonts rupture, releasing the merozoites, which infect other epithelial cells and continue to replicate. Merozoites eventually form sexual stages (male-microgamete, female-macrogamete) which unite to form oocysts.[8]

Conference attendees also reviewed the ultrastructural features of Apicomplexans specifically *Toxoplasma* to include the following: parasitophorous vacuole, rhoptries, micronemes, apical conoid, apicoplasts, and dense granules.

This case was reviewed in consultation with Dr. Chris Gardiner, AFIP consultant in veterinary parasitology. Dr. Gardiner adds, "There are myriads of macro- and microgametocytes throughout with associated oocysts. And, it (this case) shows the segmental nature of the infection, i.e., that the trophozoites would have been more proximal in the intestines. *Eimeria* is the only genus of coccidians I know to have the very large gametocytes and oocytes."

The contributor provides an overview of the *Eimeria* species infecting swine. We are grateful to Dr. Gardiner for his comments on this interesting case.

Contributor: UGA Tifton Veterinary Diagnostic and Investigational Laboratory
43 Brighton Rd, PO Box 1389, Tifton, GA 31793

References:

1. Hill, JE, Lomax LG, Lindsay DS, Lynn BS: Coccidiosis caused by *Eimeria scabra* in a finishing hog. JAVMA 186:981-983, 1985
2. Koudela B, Vitovec J, Stebra J: Concurrent Infection of Enterocytes with *Eimeria scabra* and other Enteropathogens in Swine. Veterinary Parasitology 35:71-77, 1990
3. Lindsay DS, Blagburn BL, Boosinger TS: Experimental *Eimeria dubliecki* Infections in Nursing and weaned Pigs. Veterinary Parasitology 25:39-45, 1987
4. Lindsay DS, Neiger R, Hildreth M: Porcine Enteritis Associated with *Eimeria spinosa* Henry, 1931 Infection. J Parasitol 88:1262-1263, 2002
5. Linsay DS, Dubey JP:Coccidia and Other Protozoa. *In* Diseases of Swine, eds. Straw BS, Zimmermann JJ, D'Allaire S, Taylor DJ, 9th ed., p. 865. Blackwell publishing, Ames, IA, 2006
6. Veterling JM, Coccidia (Protozoa: Eimeridae) of Swine. J Parasitol 75:172-173, 1965
7. Jones TC, Hunt RD, King NW: Diseases due to Protozoa. *In* Veterinary Pathology, 6th ed., pp. 549-567, Williams and Wilkins, Baltimore, MD, 1997

8. Gardiner CH, Fayer R, Dubey JP: An Atlas of Protozoan Parasites in Animal Tissues, 2nd ed., pp. 20, American Registry of Pathology, Washington, DC, 1998

CASE IV - E969/03 (AFIP 2940309).

Signalment: Four-year-old, female, canine (*Canis familiaris*), mixed-breed.

History: Two weeks after whelping, a severe persistent bloody vaginal discharge occurred suddenly. After clinical examination an ovariohysterectomy was performed.

Gross Pathology: The placental sites were enlarged and irregularly thick. The luminal surface was rough, grey to brown, and foci of hemorrhages were detectable. The interplacental endometrium was inconspicuous.

Laboratory Results: None reported.

Contributor's Morphologic Diagnosis: Subinvolution of placental sites (SIPS).

Contributor's Comment: The luminal epithelium of the placental sites was partly detached. The residual epithelial cells were mostly cuboidal but in some regions columnar with a vacuolated cytoplasm. Intraepithelial remnants of secretion and intraluminal projections were detectable. Large amounts of eosinophilic collagen masses in a lobular arrangement were found in the subepithelial layer. Numerous intact large polygonal cells with multiple nuclei and a foamy cytoplasm (so-called "trophoblast-like cells") lay within the collagen masses as well as inside the layers underneath. Multifocal hemorrhages accompanied by hemosiderophages and an accentuated periglandular mononuclear inflammatory reaction were recognized. The secretorically active endometrial glands showed a moderate to severe dilation with retention of mucus and cell detritus. Furthermore, a marked periglandular fibrosis was visible. The endometrium of the interplacental zones, the myometrium and perimetrium showed no obvious changes.

Although in literature subinvolution of placental sites (SIPS) is described at later stages of the puerperium, in the present case the alterations observed in the endometrium differ in their degree from normal postpartum involution[2] and correspond to those described in other reports on subinvolution.[1,3,4,5,7] Therefore, an involution abnormality is assumed in the present case, too. Subinvolution of placental sites occurred predominantly in younger bitches.[1,4,7] The etiology and pathogenesis of subinvolution are unknown as well as the fetal or maternal origin

of the prominent "trophoblast-like cells".[1,6] The relevance of these cells for the pathogenesis of SIPS is discussed.[1,8]

AFIP Diagnosis: Endometrium: Fibrosis, hemorrhage, and subacute inflammation, focally extensive, moderate, with trophoblast-like cells, consistent with placental site involution, mixed breed, canine.

Conference Comment: Thomson's defines subinvolution of placental sites (SIPS) as longer than normal persistence and deeper than normal penetration of trophoblast-like cells in the uterus after parturition.[9] In some cases, the trophoblast-like cells can perforate the uterine wall.[9-11]

Typical gross findings include multiple ellipsoidal enlargements of the endometrium that are visible from the serosal surface. The enlargements correspond with areas of previous placental attachment. The endometrial surface is characterized by hemorrhagic, irregularly thickened, rough, gray to brown plaques up to twice the size of a normal placental site form the same breed at the same stage after parturition. The endometrium between the enlarged sites is normal.[1,9-11]

The key histologic finding is the presence of syncytial masses of trophoblast-like cells with abundant vacuolated, eosinophilic cytoplasm in the endometrium, often surrounding blood vessels. These cells may invade the myometrium and perforate the serosa. Other characteristic light microscopic findings include a plaque (placental site) that protrudes into the uterine lumen composed of amorphous eosinophilic necrotic debris, fibrin, hemorrhage, and regenerating endometrium. Deeper within the plaque, there is collagen deposition and dilated endometrial glands.[1,9-11]

The contributor points out that SIPS is usually diagnosed at a later stage of the post-parturient period than the two weeks stated in the clinical history. Conference participants discussed the process of involution and the criteria required to make the diagnosis of SIPS. Given a 12-week involution interval, participants had difficulty accepting this case as an example of SIPS. Conferees agreed that the histological features were consistent with involution, but that two weeks postpartum was too early to make a definitive diagnosis.

This case was reviewed in consultation with Dr. Donald Schlafer, Cornell University College of Veterinary Medicine, who adds, "I couldn't tell a normal involution at two weeks from subinvolution of placental sites unless there was massive or marked deep invasion of trophoblast cells. I know of no accepted criteria for

making a distinction between the two." We are grateful to Dr. Schlafer for his comments on this thought provoking case.

Readers are encouraged to review reference number two below.

Contributor: Institute of Veterinary Pathology, Website: www.patho.vetmed.uni-muenchen.de

References:

1. Al-Bassam MA, Thomson, RG, O'Donnell L: Involution abnormalities in the postpartum uterus of the bitch. Vet Pathol **18**: 208-218, 1981
2. Al-Bassam MA, Thomson RG, O'Donnell L: Normal postpartum involution of the uterus in the dog. Can J Comp Med **45**: 217-232, 1981
3. Beck AM, McEntee K: Subinvolution of placental sites in a postpartum bitch. A case report. Cornell Vet **56** (2): 269-277, 1966
4. Burke TJ: Post-parturient problems in the bitch. Vet Clin North Am **7**: 693-698, 1977
5. Dickie MB, Arbeiter K: Diagnosis and therapy of the subinvolution of placental sites in the bitch. J Reprod Fert Suppl **47**: 471 – 475, 1993
6. Fernández PE, Portiansky EL, Barbeito CG, Gimeno EJ: Characterisation of cytotrophoblastic-like cells present in subinvolutioned placental sites of the bitch. Histol Histopathol **13**: 995 – 1000, 1998
7. Schall WD, Finco DR: Spontaneous recovery after subinvolution of placental sites in a bitch. J Am Vet Med Assoc **159** (12): 1780 – 1782, 1971
8. Wheeler SL: Subinvolution of placental sites in the bitch. In Current Therapy in Theriogenology II, pp. 513 – 515. Morrow and Saunders, Philadelphia, 1986
9. Acland HM: Reproductive System: Female. *In* Thomson's Special Veterinary Pathology, eds. McGavin MD, Carlton WW, Zachary JF, 3rd ed., p. 607, Mosby, St. Louis, MO, 2001
10. Kennedy PC, Miller RB: The Female Genital System. *In* Pathology of Domestic Animals, Volume 3, eds. Jubb KVF, Kennedy PC, Palmer N, 4th ed., pp. 444-445, Academic Press, Inc., San Diego, CA, 1993
11. Kennedy PC, Cullen JM, Edwards JF, Goldschmidt MH, Larsen S, Munson L, Nielsen S: Histological Classification of the Tumors of the Genital System of Domestic Animals, Second Series, Vol. IV, pp. 33-34. Armed Forces Institute of Pathology, Washington, DC, 1998

Michelle E. Thompson, DVM
Captain, Veterinary Corps, U.S. Army
Wednesday Slide Conference Coordinator
Department of Veterinary Pathology
Armed Forces Institute of Pathology
Registry of Veterinary Pathology*

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