

The Armed Forces Institute of Pathology
Department of Veterinary Pathology
WEDNESDAY SLIDE CONFERENCE
2004-2005

CONFERENCE 15
9 February 2005

Conference Moderator: Dr. Yvonne Schulman, Diplomate ACVP
Department of Veterinary Pathology
The Armed Forces Institute of Pathology
Washington, DC

CASE I – A040870057 (AFIP 2940514)

Signalment: Five year-old, female, mixed breed farm dog (*Canis domesticus*) weighing approximately 23 kg.

History: Over a period of several weeks, the dog developed progressive rear leg ataxia that worsened on exercise and then extended to the front legs. The dog also had a head tilt to the left and would stumble and fall to the left. During the course of the illness, the dog was alert, but unable to rise at times (astasia). The owner elected euthanasia, as the dog did not respond to treatment.

Gross Pathology: No overt gross findings were present on gross examination except for slight congestion of meningeal vessels.

Laboratory Results: Fluorescent antibody testing for rabies was negative. Immunohistochemistry using polyclonal antibody against both *Toxoplasma gondii* and *Neospora caninum* was positive.

Contributor's Morphologic Diagnosis: Brain, cerebrum at the level of hippocampus; meningoencephalitis, necrogranulomatous and eosinophilic, multifocally extensive, chronic, moderate to severe with intralesional protozoan cysts and tachyzoites.

Contributor's Comment: Several, smooth and thin-walled, nonseptate cysts (containing 1-2 μm bradyzoites) varying in size from 15-40 μm in diameter and individual tachyzoites are scattered in the vicinity of necrotic foci and inflamed leptomeningeal vessels. Meninges and Virchow-Robin spaces are moderately expanded by infiltration of moderate to large numbers of eosinophils, macrophages,

lymphocytes and plasma cells. Glial cells including microglia and astrocytes surround the necrotic foci and vacuolated neuropil.

Naturally occurring or experimental disease caused by *Neospora caninum* or a Neospora-like coccidian has been recognized in a variety of animals including the dog, cat, cattle, sheep, and horse as well as laboratory rodents. The dog has been recently identified as the definitive host for the organism but other hosts may exist. The organism has some features similar to *Toxoplasma gondii*, including division of tachyzoites by endodyogeny and has both a proliferative (tachyzoite) and tissue cyst (bradyzoite) phase.¹ Although there are morphologic differences between the organisms (*N. caninum* has a thicker cyst wall), differentiation based on light microscopy is problematic and definitive diagnosis necessitates immunohistochemistry or electron microscopy. *N. caninum* does not develop within a parasitophorous vacuole as does *T. gondii*. Tachyzoite multiplication in both infections results in focal necrosis, followed by inflammation. Postnatal neosporosis is less common than toxoplasmosis. Felids (both domestic and wild) are the only definitive hosts for *T. gondii*. Toxoplasma can be transmitted to intermediate hosts via oocysts in feline feces, via cysts in host tissue (meat), and via tachyzoites transplacentally (vertical transmission).^{2,3}

AFIP Diagnosis: Brainstem and cerebrum, at the level of the hippocampus: Meningoencephalitis, lymphoplasmacytic and eosinophilic, multifocal, moderate, with protozoal cysts and tachyzoites, mixed breed, canine.

Conference Comment: Dr. J.P. Dubey, USDA, Animal Parasitic Diseases Laboratory, performed immunohistochemistry using monoclonal antibody against both *Toxoplasma gondii* and *Neospora caninum*. The organisms in this case are positive for *N. caninum* and negative for *T. gondii*.

Neospora caninum is a recently recognized apicomplexan and until 1998, was misdiagnosed as *Toxoplasma gondii*.² *N. caninum* is a major pathogen for cattle and dogs, and occasionally causes clinical infections in goats, sheep, horses, and deer. Domestic dogs can be both the intermediate and the definitive host; they are the only known definitive host.⁴

N. caninum has three infectious stages: tachyzoites, tissue cysts, and oocysts. The tachyzoites and tissue cysts are intracellular and found in the intermediate hosts. Tachyzoites are approximately 6 x 2 μm , while cysts are round to oval, up to 107 μm wide, and found primarily in the central nervous system. The tissue cyst wall is up to 4 μm thick and the enclosed bradyzoites are 8 x 2 μm .

N. caninum can be transmitted transplacentally in several hosts and transplacental is the main mode of transmission in cattle. Carnivores can acquire infection by ingestion of infected tissues. Domestic dogs will shed unsporulated oocysts in the feces, which sporulate and become infective outside of the host. Sporulated oocysts can be found in the soil, water, or food and are subsequently ingested by the intermediate host (cattle, sheep, goats, horses, and dogs). Upon ingestion, sporozoites excyst, multiply, spread to many tissues as tachyzoites, and eventually encyst as bradyzoites.⁴

N. caninum is a major pathogen of cattle, causing abortion and neonatal mortality. *T. gondii* is a major pathogen in sheep and humans, and not of cattle. In dogs, the most severe cases of neosporosis occur in young, congenitally infected pups. The disease may be localized or generalized and virtually all organs may be involved, including the skin. Neurologic signs depend on the site parasitized, but often the hind limbs are more severely affected and often in rigid extension. Subclinically infected bitches can transmit the parasite to their fetuses, and successive litters from the same bitch may be born infected.⁴

Another differential diagnosis considered by conference attendees was *Sarcocystis canis*, a related protozoan known to cause systemic illness in dogs. *S. canis* has been documented in fatal visceral and neural disease in dogs. Although there are subtle histomorphological differences between *N. caninum*, *T. gondii*, and *S. canis*, electron microscopy or immunohistochemistry should be employed to positively identify the organism.⁵

Contributor: Texas Veterinary Medical Diagnostic Laboratory, Texas A & M University, 6610 Amarillo Blvd. West, Amarillo, Texas

References:

1. Storts RW, Montgomery DL: The nervous system. *In*: Thomson's Special Veterinary Pathology, eds. McGavin MD, Carlton WW, Zachary JF, 3rd ed., pp. 439- 440. Mosby, St. Louis, MO, 2001
2. Gardiner GH, Fayer R, Dubey JP: An Atlas of Protozoan Parasites in Animal Tissues, 2nd ed., pp. 53-60. Armed Forces Institute of Pathology, American Registry of Pathology, Washington, DC, 1998
3. Summers BA, Cummings JF, De Lahunta: Veterinary neuropathology, pp. 163-169. Mosby, St. Louis, MO, 1995
4. Dubey JP: Review of Neospora caninum and neosporosis in animals. The Korean J of Parasitology **41**(1):1-16, 2003
5. Trasti SL, Dubey JP, Webb DM, Blanchard TW, Britt J, Fritz D, Lewis RM: Fatal visceral and neural sarcocystosis in dogs. J Comp Path **121**:179-184, 1999

CASE II – CASE 1 (AFIP 2942328)

Signalment: 2.5 year old, white and brown, male Boer goat (*Capra hircus*)

History: A 2.5 year old buck presented with a 4-month history of multifocal proliferative, ulcerative and exudative epidermal lesions that were most severe on the right hind limb. Initial physical exam revealed a slightly thin, mildly dehydrated goat that was bright, alert and responsive. Orf, with a secondary bacterial infection, was considered the most likely diagnosis. Attempted treatments included systemic antibiotics, pain medications as well as topical antibiotics and antivirals applied to the skin lesions. No improvement was noted over several weeks and the owner elected humane euthanasia.

Gross Pathology: The main lesions were confined to the skin on the limbs and trunk. The skin on these areas displayed numerous and extensive proliferative epidermal lesions that consisted of firm, irregular, raised, gray, verrucous plaques or nodules with extensive superficial crusting, frequent ulceration and occasional purulent exudation. The lesions were limited to the epidermis and dermis and did not involve the subcutaneous tissues.

Other findings at postmortem examination include:

Focal spondylosis at the level of tenth thoracic vertebral body.

Mild diffuse pulmonary edema.

Multifocal moderate peripheral lymphadenopathy.

Laboratory Results: CBC and chemistry panel showed moderate anemia with severely decreased albumin levels. Aerobic bacterial culture resulted in isolation of *Proteus mirabilis* and *Pseudomonas aeruginosa*. Anaerobic bacterial culture resulted in isolation of *Fusobacterium necrophorum* and *Bacteroides* spp.. Tissues were submitted to Dr. A. Dela Concha at Texas A&M and viral isolation and PCR identified parapoxvirus (orf).

Contributor's Morphologic Diagnosis: Skin: Locally extensive epidermal hyperplasia and intraepidermal vesiculo-pustular proliferative dermatitis with severe superficial perivascular to diffuse lymphoplasmacytic, histiocytic and suppurative dermatitis and dermal edema.

Contributor's Comment: The section consists of large, exophytic, papillary projections covered by thick serocellular crusts within which there are numerous degenerate neutrophils, red blood cells and colonies of coccoid bacteria. The epidermis is irregularly thickened with marked parakeratosis, occasional pustules and ballooning degeneration of numerous keratinocytes. Individual keratinocyte necrosis and occasional intracytoplasmic, eosinophilic inclusion bodies are present.

Elongation of rete pegs is evident. The connective tissue core within papillary projections is loose, edematous, hemorrhagic and contains numerous small capillaries. It is heavily infiltrated by lymphocytes, plasma cells, macrophages and neutrophils.

Contagious ecthyma is also known as contagious pustular dermatitis, infectious labial dermatitis, scabby mouth, soremouth, lippengrind and orf (Old English for "rough").² It is a contagious viral skin disease of sheep and goats caused by a parapoxvirus related to those causing pseudocowpox and bovine papular stomatitis. It can be transmitted to humans.⁴ The disease is usually more severe in goats than in sheep, where it affects primarily the lips of young animals.^{1,2}

Typical contagious ecthyma lesions heal spontaneously over 3-4 weeks, and infection results in partial immunity to reinfection. Atypical contagious ecthyma infections have been described and the lesions are extremely severe and generalized and do not spontaneously regress.^{1,2,3} These atypical cases have been described in Boer or Boer-crossed goats. The virus isolated from these cases was orf virus-San Angelo 2000 (OV-SA00). This is the same type of virus isolated from this case (Dr. Dela Concha, personal communication).

It has not been elucidated if Boer goats have a particular susceptibility to the virus or if they are immunosuppressed in some way.² However, the lesions described in the initial report include lymph node depletion.⁵ In this case, lymph nodes were moderately enlarged with variable sized white to pale tan areas on cut section. Microscopically, the pale areas corresponded to large accumulations of amyloid, partially effacing normal lymphoid follicles (lymphoid depletion).

AFIP Diagnosis: Haired skin: Dermatitis, proliferative, lymphoplasmacytic and neutrophilic, chronic, diffuse, severe, with hyperkeratosis, intracorneal pustules, epidermal intracellular edema, and epidermal intracytoplasmic eosinophilic inclusion bodies, Boer goat, caprine.

Conference Comment: Ovine parapoxvirus, the cause of contagious ecthyma, belongs to the family *Poxviridae*, and genus *Parapoxvirus*. Contagious ecthyma is an important disease of sheep and goats causing high morbidity and low mortality. Transmission occurs through direct contact or indirectly through fomites. It is zoonotic; however, lesions in humans are usually circumscribed, solitary, and confined to the hands. Parapoxviruses infect a wide range of species, generally causing only localized lesions. Infections of cattle, goats, sheep, and camels can be of economic importance. Parapoxviruses also infect several terrestrial and marine wildlife species (chamois, red deer, seals).⁶

In animals, gross lesions of typical ovine parapoxvirus consist of papules, pustules, and thick crusts that occur primarily on the muzzle and mouth. However, lesions may appear in the oral cavity, and on the eyelids, feet, or teats. Orf may prevent lambs from suckling and severely affected animals may lose weight and be predisposed to secondary infections.⁶ Histologically, the pathognomonic changes include marked proliferation of keratinocytes, extreme cell swelling resulting in ballooning degeneration, nuclear shrinkage, and eosinophilic cytoplasmic inclusions. The virus is highly keratinolytic, and inclusions appear to be floating in the fluid remains of the cytoplasm. Virions average 320 x 125 nm, but vary in size and shape. Small cytoplasmic inclusions must be differentiated from deeply basophilic keratohyaline granules and moderately eosinophilic, larger, intracellular keratin bodies.⁷

Other parapoxviruses of ruminants include bovine parapoxvirus (bovine papular stomatitis) and pseudocowpox virus. Bovine papular stomatitis (BPS) is a disease of calves characterized by proliferative lesions in the oral cavity and esophagus, with little to no systemic disease. BPS is transmissible to humans and results in lesions resembling those of orf. Pseudocowpox virus causes pox lesions on the teats of cattle and is the agent of milkers' nodules in humans.⁷

Contributor: Department of Biomedical Sciences, Section of Anatomic Pathology, College of Veterinary Medicine, Cornell University, Ithaca, New York
www.vet.cornell.edu

References:

1. de la Concha-Bermejillo A, Guo J, Zhang Z, Waldron D: Severe persistent orf in young goats. *J Vet Diag Invest* **15**(5):423-31, 2003
2. Guo J, Zhang Z, Edwards JF, Ermel RW, Taylor C Jr, de la Concha-Bermejillo A: Characterization of a North American orf virus isolated from a goat with persistent, proliferative dermatitis. *Virus Res* **93**(2):169-79, 2003
3. Moriello KA, Cooley J: Difficult dermatologic diagnosis. Contagious viral pustular dermatitis (orf), goatpox, dermatophilosis, dermatophytosis, bacterial pyoderma, and mange. *J Am Vet Med Assoc* **218**(1):19-20, 2001
4. Buttner M, Rziha HJ: Parapoxviruses: from the lesion to the viral genome. *J Vet Med B Infect Dis Vet Public Health* **49**(1):7-16, 2002
5. Smith GW, Scherba G, Constable PD, Hsiao V, Behr MJ, Morin DE: Atypical parapoxvirus infection in sheep. *J Vet Intern Med* **16**(3):287-92, 2002
6. Murphy FA, Gibbs EPJ, Horzinek MC, Studdert MJ: Poxviridae. *In: Veterinary Virology*, 3rd ed., pp. 289-291. Academic Press, San Diego, CA, 1999
7. Cheville NF: Cytopathology of viral diseases. *In: Ultrastructural Pathology An Introduction to Interpretation*. pp. 497. Iowa State Press, Ames, IA, 1994

CASE III – PM03-90 (AFIP 293750)

Signalment: 4 year old, neutered female, English springer spaniel (*Canis familiaris*).

History: Variety of bizarre neurological and behavioral signs. These included stumbling and a periodic tremor. She was also reported to tire quickly. MRI showed changes suggestive of fucosidosis including swelling of the trigeminal nerve. Following laboratory investigations she was euthanized and submitted for full necropsy.

Gross Pathology: The cadaver weighed 19 kg. No gross abnormality of the brain was present but the trigeminal ganglia were twice the expected size. The vagosympathetic trunk and vagus nerves were also enlarged along with the cervical dorsal root ganglia. No other gross abnormalities were noted.

Laboratory Results: PCR screening on genomic DNA confirmed the animal was homozygous for the mutant gene producing alpha-L-fucosidase deficiency (Animal Health Trust, Newmarket, Suffolk, England).

Contributor's Morphologic Diagnosis: Trigeminal ganglion/Dorsal root ganglion. Neuronal degeneration with cytoplasmic vacuolation. Ganglionopathy, canine fucosidosis.

Contributor's Comment: Canine fucosidosis is a lysosomal storage disease which affects English springer spaniels. It occurs as a result of a frameshift mutation involving a 14 base pair deletion of exon 1 of the canine fucosidase gene.^{1,2} The disease is inherited recessively. There is deficiency of the enzyme, which is present in plasma, leukocytes and other tissues including brain, which results in defective degradation of water-soluble glycoproteins containing fucose. Homozygotes have less than 5% of normal enzyme activity. Heterozygotes have intermediate activity.³

Clinical signs include behavioral changes as well as motor abnormalities such as wide-based stance and hypermetria. Male dogs may be infertile. Visual impairment has also been reported. The onset is usually around 6 months of age and is progressive. Affected individuals rarely survive beyond 4 years.

Microscopically there is neuronal swelling with cytoplasmic vacuolation. The vacuoles are large, single and displace the Nissl substance. Some are empty. Others contain fine floccular material. Similar changes were present throughout the CNS. In the springer spaniel, most symptoms are related to CNS pathology. It was first described in this breed in 1982.

Fucosidosis also occurs in humans. Mental retardation is a common sign. Twelve different mutations have been described in people and there is more widespread involvement of organs. The condition in dogs most resembles the intermediate form of the human disease and has been used as an experimental model for the CNS pathology. In addition to the neuronal changes in dogs, vacuolated macrophages are found in the meninges, perivascularly in the CNS, and in thickened peripheral nerves.⁴

Bone marrow transplantation has been shown to limit the severity and progression of the disease. Enzyme activity levels rise in a range of tissues including the CNS. If symptoms are already manifested, transplant is less effective.⁵ Age at marrow transplantation has been shown to be important for survival, disease progression and the level of enzyme activity attained.⁶ Gene therapy and recombinant enzymes have also been proposed as treatment modalities for humans.

AFIP Diagnosis: Ganglion: Vacuolar change, neuronal, multifocal, marked, with multifocal mild lymphoplasmacytic ganglionitis, English Springer Spaniel, canine.

Conference Comment: The contributor provides a thorough overview of fucosidosis, which is a lysosomal storage disease of complex carbohydrates, specifically a defect in the gene encoding the alpha-L-fucosidase enzyme, resulting in accumulation of fucose-containing sphingolipids and glycoprotein fragments.

Lysosomes are key components of the “intracellular digestive tract” and contain many hydrolytic enzymes that function as the acid milieu of the lysosomes. These lysosomal enzymes (acid hydrolases) are synthesized in the endoplasmic reticulum and then uniquely processed in the Golgi apparatus. Within the Golgi complex, these enzymes undergo post-translation modification, which involves the addition of terminal mannose-6-phosphate groups to some of the oligosaccharide side chains. This is an “address label” that is recognized by specific receptors found on the inner surface of the Golgi membrane. Lysosomal enzymes bind to these receptors, are segregated from other secretory proteins, and are delivered to lysosomes in transport vesicles.⁷

Lysosomal acid hydrolases catalyze the breakdown of a variety of complex macromolecules, from both metabolic turnover of intracellular organelles (autophagy) and from phagocytosis (heterophagy). With an inherited deficiency of a functional lysosomal enzyme, catabolism of its substrate remains incomplete, leading to accumulation of the partially degraded insoluble metabolite within the lysosomes. As this accumulation progresses, organelles increase in number and become enlarged, eventually interfering with normal cell functions.⁷

Lysosomal storage diseases may result from the lack of any protein essential for the normal function of lysosomes. Defects may include reduced synthesis of lysosomal enzymes, synthesis of a catalytically inactive protein that cross-reacts with the normal enzyme, defects in post-translational processing of the enzyme protein, lack of an enzyme activator, lack of a substrate activator protein, or lack of a transport protein.⁷

In general, the distribution of the organs affected is determined by two factors: the tissue where most of the material to be degraded is found; and, the cells or location where most of the degradation normally occurs. Lysosomal storage diseases can be divided into categories based on the biochemical nature of the accumulated metabolite:⁷

Disease	Enzyme Deficiency	Accumulating Metabolites
Glycogenosis		
Type 2—Pompe disease	alpha-1,4-glucosidase	Glycogen
Sphingolipidoses		
GM1 gangliosidosis	GM1 ganglioside β -galactosidase	GM1 ganglioside, Galactose-containing oligosaccharides
GM2 gangliosidosis		
Tay-Sachs disease	Hexosaminidase-alpha subunit	GM2 ganglioside
Sandhoff disease	Hexosaminidase-beta subunit	GM2 ganglioside, globoside
Variant AB	Ganglioside activator protein	BM2 ganglioside
Sulfatidoses		
Metachromatic leukodystrophy	Arylsulfatase A	Sulfatide
Krabbe disease	Galactosylceramidase	Galactocerebroside
(Globoid cell leukodystrophy)		
Gaucher disease	Glucocerebrosidase	Glucocerebroside
Niemann-Pick disease	Sphingomyelinase	Sphingomyelin
Mucopolysaccharidoses (MPS)		
MPH I H (Hurler)	alpha-L-Iduronidase	Dermatan sulfate, heparan sulfate
MPH II (Hunter)	L-Iduronosulfate sulfatase	
Mucopolipidoses (ML)		
I-cell disease (ML II)	Deficiency of phosphorylating enzymes essential for the formation of mannose-6-phosphate recognition marker	Mucopolysaccharide, glycolipid

Disease	Enzyme Deficiency	Accumulating Metabolites
Other Disease of Complex Carbohydrates		
Fucosidosis	alpha-fucosidase	Fucose-containing sphingolipids and glycoprotein fragments
Mannosidosis	alpha-mannosidase	Mannose-containing oligosaccharides
	beta-mannosidase	Mannose-containing oligosaccharides
Other Lysosomal Storage Diseases		
Wolman disease	Acid lipase	Cholesterol esters, triglycerides
Neuronal Ceroid-Lipofuscinosis	Unknown	Unknown

Contributor: University of Liverpool, Department of Veterinary Pathology, Crown Street, Liverpool, England
www.liv.ac.uk

References:

1. Skelly BJ, Sargan DR, Herrtage ME, Winchester BG: The molecular defect underlying canine fucosidosis. *J Med Genet* **33** (4):284-288, 1996
2. Occhiodoro T, Anson DS: Isolation of the canine alpha-L-fucosidase cDNA and definition of the fucosidosis mutation in English Springer Spaniels. *Mammalian Genome* **7**:271-274, 1996
3. Keller CB, Lamarre J: Inherited lysosomal storage disease in an English Springer Spaniel. *J Am Vet Med Assoc* **200**:194-5, 1992
4. Jubb KVF, Huxtable CR: The Nervous System. *In: Pathology of Domestic Animals*, eds Jubb KVF, Kennedy PC, Palmer N, 4th ed., pp. 314-315. Academic Press, San Diego, CA 1993
5. Taylor RM, Farrow BR, Stewart GJ: Amelioration of clinical disease following bone marrow transplantation in fucosidase-deficient dogs. *Am J Med Genet* **42**(4): 628-632, 1992
6. Ferrara ML, Taylor RM, Stewart GJ: Age at marrow transplantation is critical for successful treatment of canine fucosidosis. *Transplantation Proceedings* **24**:2282-2283, 1992
7. Kumar V, Abbas AK, Fausto N: Genetic disorders. *In: Robbins and Cotran Pathologic Basis of Disease*, 7th ed., pp. 158-161. Elsevier Saunders, Philadelphia, PA, 2005

CASE IV – P04-5855 (AFIP 2956372)

Signalment: 5 year-old, castrated male, European domestic shorthair cat (*Felis domesticus*).

History: A 5 year-old, European domestic shorthair, castrated, male cat was presented at a veterinary clinic in The Netherlands with progressive abnormal behavior, anorexia and loss of weight, ataxia, ocular mydriasis and nystagmus. The cat deteriorated over the next 2 months, was euthanized, and admitted to the Pathobiology Department of the Veterinary Faculty in Utrecht, The Netherlands.

Gross Pathology: At necropsy, gross pathologic findings were limited to the central nervous system (CNS). Between both cerebral hemispheres there was a large mass (3 x 1.5 cm diameter). This process was well demarcated and had a yellowish aspect with some empty spaces in it.

Laboratory Results: Earlier PCV, blood chemistry and FIV/FelV tests showed no specific remarks.

Contributor's Histopathologic Description: Microscopically, between both hemispheres, there is a well demarcated, expansive growth that is partly encapsulated. This mass contains many cholesterol clefts and a large amount of foamy macrophages filled with lipophilic material. Many multinucleated giant cells with the same appearance are seen particularly surrounding the cholesterol clefts. Between these cells there are some fibrous strands and areas of mineralization. Multifocally, in the margins of the process, some lymphocytes and plasma cells are present. The nervous tissue around this mass is moderately compressed. Locally the process is continuous with the meninges.

Contributor's morphologic diagnosis: Brain: Xanthomatous meningioma, European domestic shorthair, (*Felis domesticus*).

Contributor's Comment: Meningioma is the most common primary CNS tumor in the cat. It rises within the meninges, has a mesodermal character and is composed of arachnoid cap cells and occasionally pial cells.¹ Usually it is in close association with the dura, and grows expansively, compressing but seldom invading the brain. Malignant meningiomas, which invade the surrounding brain tissue or metastasize, are rare in cats.^{1,2} Meningiomas are seen more often in older cats (between 9 and 15 years old) and there is a slight predominance towards the male gender.³ Meningiomas are quite common incidental findings at autopsy in the aged feline.¹ In cats, meningiomas have the tendency to be multiple and often arise from the tela choroidea of the third ventricle. They can be soft or firm and may be gritty on cut surface. They grow slowly (except for the malignant variant) and the clinical signs associated with the tumor reflect the neuroanatomical location of the tumor and the severity of any secondary pathology, such as edema, hemorrhage, brain herniation or hydrocephalus.⁴

Meningiomas show a remarkable diversity in histopathology probably due to the fact that both the mesoderm and neural crest contribute to the formation of the meninges. The range of patterns recognized is: meningothelial, fibrous, transitional, psammomatous, angiomatous, papillary, granular cell, myxoid and anaplastic (malignant) meningioma. Most meningiomas exhibit vimentin, and less often cytokeratin and S-100 protein immunoreactivity.⁵

In cats most are meningothelial or psammomatous and many have cholesterol deposits.¹ In humans xanthomatous infiltration in meningiomas has been described as metaplastic changes and rarely xanthomatous meningiomas are documented.^{6,7,8} In 2004 a human case was presented with extensive xanthomatous change with focal lymphoplasmatoid infiltration and foci of necrosis with nuclear debris and cholesterol clefts. There were many epithelioid cells surrounding the areas of necrosis, forming granulomas. The xanthomatous change is often the result of lipid accumulation in meningeal cells, rather than infiltration by foam macrophages-lipid laden "xanthomatous" cells. They have been shown to be meningeal in nature by immunohistochemistry and electron micrography but they also demonstrated the presence of the macrophage marker CD68. In between the xanthomatous zones there was presence of typical meningioma areas and there was a gradual transition from areas of typical meningioma to xanthomatous zones.⁹ This suggests metaplastic changes are occurring in the meningothelial cells and that changes are not only from the entering of blood borne histiocytes from the bloodstream to ingest necrotic tumor cells.⁶

In this cat, next to the xanthomatous changes as could be found in a cholesterol granuloma, there are zones with evidence of neoplastic meningeal cells consistent with a meningioma. Those areas are positive in vimentin expression and negative for S100 protein, PAS and cytokeratin. Only three cases of a xanthomatous meningioma in a cat are documented: the case described here, in Veterinary Neuropathology and one case earlier described as a granular cell tumor, which in our opinion, is also a xanthomatous meningioma. It is remarkable that all three cases appear at the same site in the meninges.^{1,10}

AFIP Diagnosis: Brain, cerebrum and meninges: Cholesterol granuloma, focally extensive, European domestic shorthair, feline.

Conference Comment: Although we gave careful consideration to the contributor's diagnosis of meningioma, we interpret the lesion in the provided sections as a cholesterol granuloma. Many feline meningiomas contain cholesterol deposits,¹ but to our knowledge a meningioma with diffuse xanthomatous metaplasia has not been reported in the veterinary literature. When present in feline meningiomas,

xanthomatous/cholesterinic granulomatous inflammation is often located in areas of necrosis and hemorrhage. Although the lesion in this case is continuous with the meninges in some sections, transition of the xanthomatous /cholesterinic granulomatous inflammation to recognizable meningioma is not evident in the sections examined by the conference attendees. This case was reviewed by the Department of Neuropathology of the Armed Forces Institute of Pathology, which concurred with the diagnosis of cholesterol granuloma. Meningiomas usually affect cats significantly older than the one that had this lesion. Interestingly, meningiomas have been reported in young cats with mucopolysaccharidosis I.¹¹

In veterinary medicine, cholesterol granulomas, also known as cholesteatomas or cholesteatosis, are most commonly seen as incidental findings in aged horses. In horses, they frequently occur in the fourth ventricle; those that occur in the lateral ventricle may be very large, leading to obstruction and hydrocephalus, which results in dilation and pressure atrophy of the walls of the ventricles. Possible causes of cholesterol granulomas include necrosis and hemorrhage or hyperlipidemia.¹²

Cholesterol granulomas are also occasionally documented in other animals, including a great plated lizard,¹³ and meerkats,^{14,15} as well as in humans.

Contributor: University of Utrecht, Faculty of Veterinary Medicine, Department of Pathobiology, Pathology Division, Yalelaan 1, 3508 TD Utrecht, The Netherlands

References:

1. Summers BA, Cummings JF & De Lahunta A: Tumors of the central nervous system. *In: Veterinary Neuropathology*, 1st ed, pp. 355-362. Mosby, St Louis, MO 1995
2. Jubb KV, Huxtable CR: The nervous system. *In: Pathology of Domestic animals*, eds. Jubb KVF, Kennedy PC, Palmer N, 4th ed., vol 1, pp. 430-432. Academic Press, San Diego, CA, 1993
3. Troxel MT, Vite CH, Van Winkle TJ, et al: Feline intracranial neoplasia: Retrospective review of 160 cases (1985-2001). *J Vet Intern Med* **17**:850-859, 2003
4. Lu D, Pocknell A, Lamb CR, Targett MP: Concurrent benign and malignant multiple meningiomas in a cat: clinical, MRI and pathological findings. *Vet Rec* **152**:780-782, 2003
5. Koestner A, et al: Tumors of the meninges. *In: Histological classification of tumors of the nervous system of domestic animals*, 2nd ed, pp. 27-30. Armed Forces Institute of Pathology, Washington, DC, 1999
6. Germano A, Galatioto S, La Rosa G, et al: Xanthomatous posterior pyramid meningioma in a 2-year-old girl. *Child's Nerv Syst* **13**:406-411, 1997

7. Ijiri R, Tanaka Y, Hara M, Sekida K: Radiation-associated xanthomatous meningioma in a child. *Child's Nerv Syst* **16**:304-308, 2000
8. Kepes JJ: Lipidized meningothelial tumor cells in "xanthomatous" meningioma express macrophage antigen. *J Neuropathol Exp Neurol* **53**:384-388, 1994
9. Vlodaysky E, Konstantinesku M, Pery-Eran A, Zaaroor M: Meningioma with extensive necrotizing granulomatous changes: possible mimic of inflammatory dural lesion. *Histopathology* **44**:406-408, 2004
10. Mandara MT, Ricci G, Sforza M: Cerebral granular cell tumour in a cat. *In*: Abstract from the 22nd meeting of the European society of veterinary pathology, 1st ed, pp.137, University of Warmia and Mazury, Olsztyn, 2004
11. Haskins M, McGrath J. Meningiomas in young cats with mucopolysaccharidosis I. *J Neuropathol Exp Neurol*. **42**:664-70, 1983
12. Jubb KVF, Huxtable CR: The nervous system. *In*: Pathology of Domestic Animals, eds. Jubb KVF, Kennedy PC, Palmer N, 4th ed., vol. 1, pp. 334-335. Academic Press, San Diego, CA, 1993
13. Gyimesi ZS, Stedman NL, Crossett VR: Cholesterol granulomas in a Great Plated Lizard *Gerrhosaurus major*. *J Herpet Med Surg* **12**(3):36-39, 2002
14. Sladky KK, Dalldorf FG, Steinberg H, Wright JF, Loomis MR: Cholesterol granulomas in three meerkats (*Suricata suricatta*). *Vet Pathol* **37**:684-686, 2000
15. Blanchard TW, Lipscomb TP, Inskeep W: Department of Veterinary Pathology, Wednesday Slide Conference 1997-1998, Conference 2, Case III, Microslide #7, pp.15-17. The Armed Forces Institute of Pathology, Washington, DC, 1998

Signature Authenticated by Approve
 Approved by: Shelley P Honnold,
 Wednesday, 02 March, 2005 at 7:2

Shelley P. Honnold, DVM
 Major, 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.