Joint Pathology Center
Veterinary Pathology Services

WEDNESDAY SLIDE CONFERENCE 2022-2023

Conference #10 9 November 2022

CASE I:

Signalment:
Unknown gestational age*, intact female, aborted dairy goat fetus (*Capra aegagrus hircus*)

*The animal appears to be nearly full-term on gross examination and measures 46 cm from crown to rump.

History:
None provided with the submission. This animal was submitted with a male twin. No placenta was submitted with the fetuses.

Gross Pathology:
The female twin was grossly unremarkable. The lungs of the male twin had hundreds of disseminated, smooth, white, and flat pinpoint to 2.0 mm nodules within the lung parenchyma and on the pleural surfaces. Lung sections from both twins sank in formalin.

Laboratory Results:
An in-house real time reverse transcriptase multiplex rRT-PCR test using pooled liver had the following result: infectious bovine rhinotracheitis (IBR) was suspect positive, with a Ct of 38; tissues were negative for bovine respiratory syncytial virus (BRSV) and parainfluenza-3 (PI3). Aerobic bacterial culture of lung yielded no growth of pathogens.

Caprine herpesvirus (CapHV-1) PCR testing of a lung sample at Colorado State University Veterinary Diagnostic Laboratory detected nucleic acids (positive).

The viral inclusions did not stain using bovine herpesvirus-1 (infectious bovine rhinotracheitis) antibody (immunohistochemistry).

Figure 1-1. Presentation, twin goats. Two twin goats were submitted for examination. Lesions were seen only in the male twin (top).(Photo courtesy of: University of Illinois at Urbana-Champaign, Veterinary Diagnostic Laboratory, http://vetmed.illinois.edu/vet-resources/veterinary-diagnostic-laboratory/)

Microscopic Description:
Lung: Multiple random foci of necrosis that measure up to 1 mm wide disrupt the pulmonary parenchyma. The alveolar septa are markedly expanded by flocculent pink cell debris, karyorrhectic material and fibrin (coagulative necrosis). Few macrophages, neutrophils, and erythrocytes are admixed. Alveoli are filled with fine pink fibrillar material (fibrin) and pale pink fluid. At the periphery of these foci are degenerating cells with usually a single, eosinophilic intranuclear inclusion that measures approximately 5 um and peripheralizes the chromatin.

Liver: Multiple random foci of hepatic necrosis disrupt the parenchyma and are composed of globular hypereosinophilic cell fragments and karyorrhectic debris admixed with small numbers of macrophages. Hepatocytes along the periphery often have eosinophilic intranuclear inclusions that peripheralize chromatin. Macrophages in and around these nodules have small amounts of globular, dark brown, intracytoplasmic pigment (presumably hemosiderin)

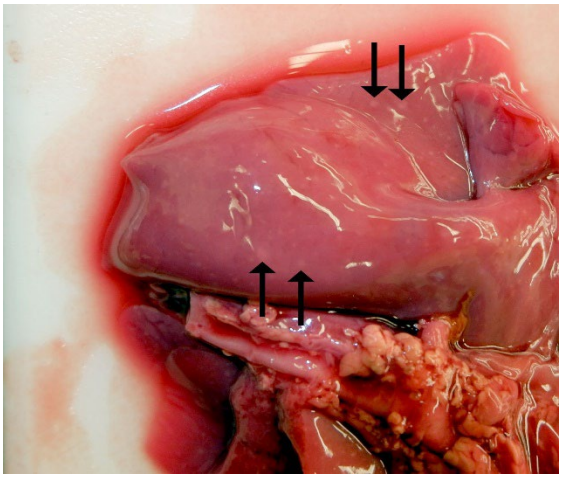

Figure 1-2. Lung, goat kid. There are multiple areas of necrosis scattered through the lungs (arrows). Photo courtesy of: University of Illinois at Urbana-Champaign, Veterinary Diagnostic Laboratory, http://vetmed.illinois.edu/vet-resources/veterinary-diagnostic-laboratory/)

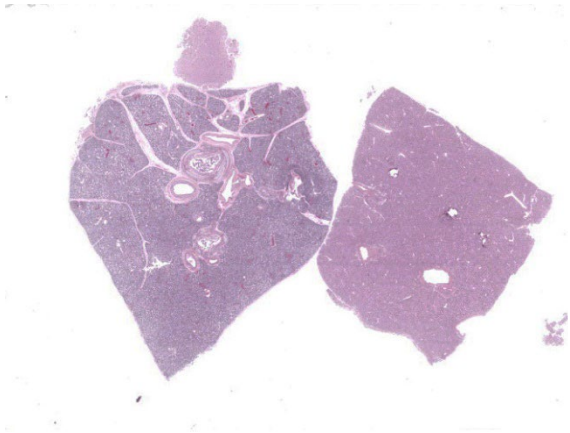

Figure 1-3. Lung, liver, goat kid. One section of lung (left) and liver (right) are submitted for examination. There are no visible lesions at subgross magnification.

Contributor's Morphologic Diagnoses:
1. Lung: multifocal, random, moderate, necrotizing pneumonia with intranuclear viral inclusion bodies
2. Liver: multifocal, random, mild, necrotizing hepatitis with intranuclear viral inclusion bodies

Contributor's Comment:
Caprine herpesvirus 1 (CpHV-1) is globally distributed alphaherpesvirus that occasionally causes disease and is less-commonly implicated as a cause of infectious abortion.[2,6,7,10,11] Clinical manifestation of disease depends on the age of the infected animal. In 1- to 2-week-old kids, a generalized disease with severe gastrointestinal lesions predominates.[1,3,4,6] In contrast, infected adults are often clinically silent or have genital tract infections characterized by vulvovaginitis or balanoposthitis; more rarely do respiratory tract infections and abortions occur. [2,6,7,10,11] Typically, does that abort are subclinically infected; the only manifestation of infection can be late term abortions, stillbirths, or even abortion storms at a herd level. [2,7,10,11] Transmission is thought to be from direct contact during coitus.[10] The source of infection can be challenging to determine, as alphaherpesviruses can remain latent in the trigeminal ganglia or other tissues.[2]

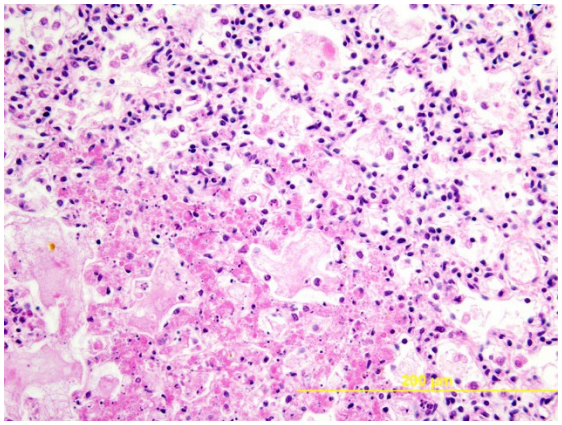

Figure 1-4. Lung, goat kid. There are areas of lytic necrosis scattered throughout the lung. (HE 400X) (Photo courtesy of: University of Illinois at Urbana-Champaign, Veterinary Diagnostic Laboratory, http://vetmed.illinois.edu/vet-resources/veterinary-diagnostic-laboratory/).

The observed herpetic inclusions are consistent with typical Cowdry type A inclusions, which are characterized by large, intranuclear, and eosinophilic to amphophilic inclusions that marginalize the chromatin.[2,3,7] With CpHV-1, inclusions are often at the periphery of necrotic foci.[7] The adrenal glands, liver, lungs, and kidneys are the organs that most commonly contain inclusions.[7] With advanced autolysis, inclusions can be challenging to identify; however, examination of the adrenal gland appears to be a reliable site of inclusion identification.[12] In this case, inclusions were found in the lung, liver, thymus, and adrenal glands but were most numerous within the lung and liver, as submitted.

The other distinguishing histopathologic feature for this infectious abortigenic agent is widespread necrotic foci that are most common within the lungs, adrenal gland, and thymus.[2,7,12] Other affected organs can include the kidney, intestine, lymph nodes, and spleen.[7,12] Thymic necrosis is associated with clusters of macrophages containing the typical Cowdry type A inclusion bodies, which, interestingly, is similar to what is observed in infected neonatal kids.[3,11]

The pathogenesis has yet to be completely elucidated, but it is thought to be associated with viremia of the dam after respiratory or genital colonization.[2,11,12] This results in leukocyte trafficking or hematogenous spread to the uterus where placental endothelium, mesenchyme, and trophoblasts become infected.[12] Death is due to tissue destruction within the fetus and placenta.[12] Viremic potential varies with individual strain, which may further contribute to the rarity of these abortions.[11,12]

Other, more common, causes of caprine abortion should be considered first when presented with a late term caprine abortion, including: *Chlamydophila abortus*, *Coxiella burnetii*, *Toxoplasma gondii*, and *Listeria monocytogenes*.[2,7] In this case, however, these agents were not identified via histologic examination or ancillary testing.

The "suspect" result of the rtPCR for infectious bovine rhinotracheitis suggests that this causative virus has genetic homology with bovine herpes virus-1 (BHV-1). It has been previously shown that CpHV-1 and BHV-1 are closely related and often antibodies will often cross-react on fluorescent antibody or

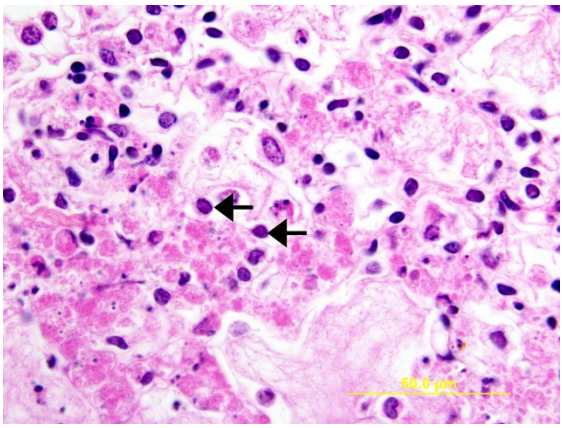

Figure 1-5. Lung, goat kid. Cells at the edge of the areas of necrosis contain intranuclear viral inclusions. (HE 400X) (Photo courtesy of: University of Illinois at Urbana-Champaign, Veterinary Diagnostic Laboratory, http://vetmed.illinois.edu/vet-resources/veterinary-diagnostic-laboratory/)

immunohistochemical assays.[2,6,7] Furthermore, goats can seroconvert against bovine herpesvirus 1, although no BHV-1 induced abortions have been identified in goats, to the author's knowledge.[12] The fetal lesions of CpHV-1 and BHV-1 are essentially identical.[12] Bovine herpesvirus-1 abortions tend to consistently have a necrotizing vasculitis within small vessels of the placental villi.[12] Unfortunately, the placenta was not submitted with this case for evaluation.

The male twin had histologically similar lesions in the lungs, adrenal glands, and thymus.

Contributing Institution:
University of Illinois at Urbana-Champaign, Veterinary Diagnostic Laboratory

JPC Diagnosis:
1. Lung: Pneumonia, necrotizing, multifocal, mild to moderate, with intranuclear viral inclusions.
2. Liver: Hepatitis, necrotizing, multifocal, mild to moderate, with intranuclear viral inclusions.

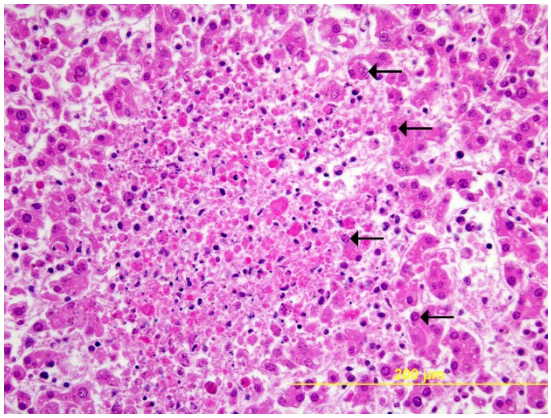

Figure 1-6. Liver, goat kid. There are multifocal areas of necrosis within the liver; hepatocytes at the edges of necrosis contain eosinophilic intranuclear viral inclusions (arrows). (HE 400X) (Photo courtesy of: University of Illinois at Urbana-Champaign, Veterinary Diagnostic Laboratory, http://vetmed.illinois.edu/vet-resources/veterinary-diagnostic-laboratory/)

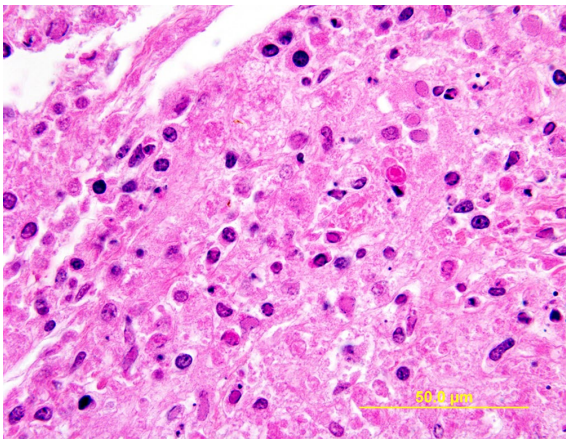

Figure 1-7. Adrenal gland, goat kid. Necrotic cells within the adrenal cortex contain eosinophilic intranuclear viral inclusions (arrows). (HE 400X) (Photo courtesy of: University of Illinois at Urbana-Champaign, Veterinary Diagnostic Laboratory, http://vetmed.illinois.edu/vet-resources/veterinary-diagnostic-laboratory/)

JPC Comment:
This week's moderator, LTC Joseph Anderson, described a few of the histologic features which can indicate that lung samples originated from fetal or neonatal animals. In neonatal rats, the terminal bronchiolar epithelial cells are vacuolated due to intracytoplasmic glycogen accumulations, a feature which was also present in this case.[5] Additionally, developing lung in the saccular stage has thickened airway walls with a large amount of stroma.[5] In this case, there are also squamous epithelial cells within the alveolar lumina which were introduced by amniotic fluid.

Caprine herpesvirus-1 is a double-stranded DNA virus that was first isolated in California and Switzerland in the 1970s and has subsequently achieved a world-wide distribution.[9] Serologic testing for CpHV-1 involves measuring BoHV gB and gE ELISA reactivity; positive gB and negative gE results indicate CpHV-1 infection.[1,13] Serologic studies have elucidated risk factors for CpHV-1 infection, which include large herd size, meat or mixed production breeds, older age, and caprine arthritis-encephalitis viral co-infection.[1] A separate study in France confirmed

that larger herds were more likely to be seropositive, and in these herds, up to 51% of animals were seropositive.[13] The correlation of older age with seropositivity suggestive of prolonged exposure and viral re-circulation within the herd.[1,13]

CpHV-1 has been the subject of recent research on therapeutic oncolytic viruses, which can replicate in and destroy neoplastic cells without harming normal cells. A few viruses, such as adenoviruses, herpesviruses, and reoviruses, have been investigated for their oncolytic properties.[4] Oncolytic herpes simplex virus 1 (oHSV-1) is the first approved oncolytic virus and targets advanced stage, non-resectable melanomas in humans.[4] As it is based on a naturally-occurring human virus, oSHV-1 can cause disease in non-neoplastic tissue as well; thus there is interest in using wild-type viruses that do not normally infect humans. Additionally, humans do not have pre-existing immunity to this virus and thus may be more susceptible to therapeutic infection.[4] Several alpha herpesviruses, including BoHV-1, equine herpesvirus 1, and now CpHV-1 have demonstrated oncolytic properties.[8] CpHV-1 can replicate in and increase apoptosis in several human cancer cell lines.[8] CpHV-1 has promising effects in the treatment of mesothelioma, which has an average survival time of less than 12 months in humans.[4] A recent study showed that the virus induced apoptosis in neoplastic cell cultures, halted cell cycle progression, and had synergistic effects with cisplatin, the current chemotherapeutic of choice for mesothelioma, with minimal effects on normal mesothelial cells.[4]

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CASE II:

Signalment:
5-year-9-month-old neutered female Domestic Shorthair cat, *Felis catus*

History:
A 5-year-old neutered female Domestic Shorthair cat was presented to our institution following a two-week history of pollakiuria and urinating in the house, which progressed to ataxia and tetraparesis. Neurologic examination localized the clinical signs to multiple spinal cord segments and an MRI of the spinal cord revealed multifocal intramedullary lesions. The cat was euthanised due to the acute onset, progressive clinical signs and was submitted for necropsy.

Gross Pathology:
Gross examination revealed multifocal, intramedullary, grey-beige areas throughout the spinal cord. The brain was grossly unremarkable. The only other findings were those of splenic congestion and pulmonary reddening (congestion), which were attributed to barbiturate euthanasia.

Laboratory Results:
One year prior to presentation, the submitted cat was tested for FIV, FeLV and *Toxoplasma spp.* (testing method not provided) and was revealed to be positive for FIV and negative for FeLV and *Toxoplasma spp.* At the time of presentation, serology for *Toxoplasma spp.* revealed a high IgG titre (equal to or greater than 800, which is consistent with, though does not confirm active infection) and an IgM titre of <20.

Microscopic Description:
Cervical spinal cord:
Unilaterally, the grey and white matter are focally extensively replaced by large numbers of infiltrating lymphocytes, plasma cells, and fewer macrophages. Neurons in this area are lost and there is amorphous eosinophilic material (necrosis). Within this area are multiple variably sized, approximately 30-60 µm diameter, eosinophilic protozoal cysts bordered by a thin (0.5 µm) capsule and containing numerous 1 µm elongate basophilic bradyzoites (presumptive *Toxoplasma gondii* cysts). Multifocally, there are bands of eosinophilic, fibrillar material (glial scars) and increased numbers of glial cells including gemistocytic astrocytes characterized by large, swollen, eosinophilic cytoplasm, and peripheral round nuclei and gitter cells with foamy cytoplasm and pyknotic nuclei. The adjacent white matter is rarefied and degenerate with distended axon sheaths, occasionally containing swollen, rounded and eosinophilic axons (spheroids) or associated with gitter cells (ellipsoids). Endothelial cells are lined by prominent (reactive) nuclei and Virchow-Robin

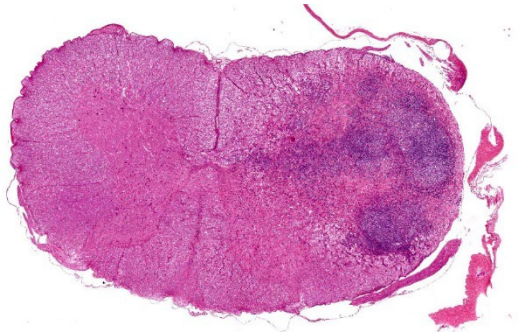

Figure 2-1. Spinal cord, cat. A section of the cervical spinal cord is submitted for examination. There is a large unilateral focus of necrosis, and cellular infiltration at subgross magnification. (HE, 6X)

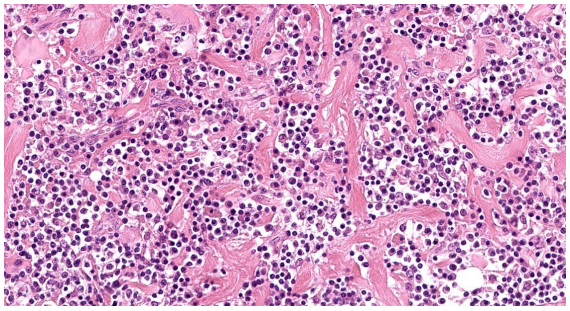

Figure 2-2. Spinal cord, cat. The neuropil (in this case, the white matter) is effaced by innumerable inflammatory cells, with lymphocytes predominating, but there are also large numbers of neutrophils, histiocytes, and plasma cells. (HE, 381X)

spaces are expanded by lymphocytes and plasma cells (perivascular cuffing).

Contributor's Morphologic Diagnoses:
Spinal cord, cervical; focally extensive necrotizing and lymphoplasmacytic myelitis with protozoal cysts (*Toxoplasma gondii*)

Contributor's Comment:
The histologic features in this case are consistent with protozoal necrotizing myelitis due to *Toxoplasma spp.*

Toxoplasma spp. are protozoan parasites able to infect a diverse range of species including humans, nonhuman primates, birds and a large number of mammals[12]. Domestic and non-domestic cats are the definitive host of *Toxoplasma spp.* and become infected following ingestion of asexual stages in tissue or oocysts, or less frequently, congenitally[12]. Organisms then undergo asexual development in intestinal epithelium and can disseminate to a range of other tissues, including the lungs, liver, heart, and nervous system as free organisms or via leukocyte trafficking in lymphocytes or macrophages[11]. Tachyzoites are responsible for the acute presentation of toxoplasmosis and can continue to replicate indefinitely[12].

Typical histologic changes in the central nervous system of cats with active toxoplasmosis include non-suppurative meningoencephalitis and necrosis. Infection in utero can cause placentitis, myocardial injury or systemic inflammation, which in turn lead to necrosis in the brainstem and cerebrocortical white matter[12]. Cell necrosis also occurs directly as a result of intracellular replication of tachyzoites in target cells and subsequent cell lysis or as a consequence of the host immune response. T-cell lymphocytes kill infected cells directly or via interferon-gamma-mediated activation of microglia and astrocytes[11].

Chronic toxoplasmosis is characterized by a dormant stage in which bradyzoites are enclosed within cyst walls and divide slowly. Such bradyzoite-containing cysts are typically found in the brain, skeletal muscle, and myocardium in chronically infected cats[12]. Cyst walls are poorly immunogenic and protect bradyzoites from the host's immune system, allowing them to remain dormant. Thus, there is usually little, if any, associated inflammation. However, in this case, areas of necrosis and inflammation in the spinal cord were associated with bradyzoite-containing cysts.

The finding of bradyzoite cysts within areas of inflammation and necrosis in feline spinal cords has been documented in several case reports of *Toxoplasma* or *Toxoplasma*-like

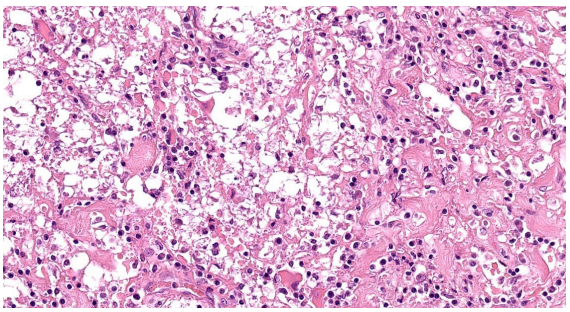

Figure 2-3. Spinal cord, cat. Within the affected white matter, there is necrosis, inflammation and edema (right), dilated myelin sheaths with spheroids (left), and gemistocytic astrocytes (bottom center). (HE, 381X)

infection.[1,6] It is thought that the inflammation in these reports was the result of cyst rupture and zoite release following reactivation of latent infection. From their findings, Lyndsay et al. suggest that when toxoplasmosis in cats manifests as neurologic signs alone, without concurrent systemic signs, it is more frequently due to reactivation than acute infection.[10]

Reactivation of *Toxoplasma* has been reported in immunodeficient or immunosuppressed cats infected with Feline Immunodeficiency Virus (FIV) (as in this case) or receiving immunosuppressive therapy.[2] However, the relationship between concurrent FIV infection and toxoplasmosis is not clear. A recent study by Dubey et al. did not find a correlation between naturally infected cats that were seropositive for FIV and *T. gondii*.[8]

Contributing Institution:
Pathobiology and Population Sciences
Royal Veterinary College
Hawkshead Lane, North Mymms
Hertfordshire
AL9 7TA
United Kingdom

JPC Diagnosis:
Cervical spinal cord: Myelitis, histiocytic and lymphoplasmacytic, unilateral, focally extensive, severe, with gliosis and intracellular protozoal cysts.

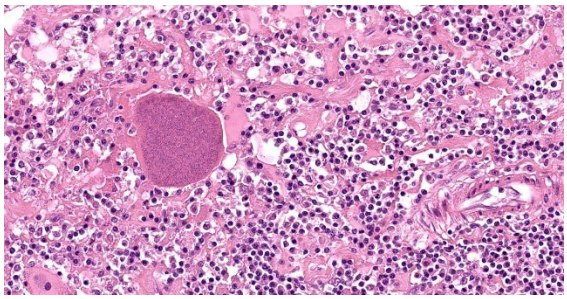

Figure 2-4. Spinal cord, cat. The grey matter is similarly effaced by necrosis and inflammation. Scattered throughout the grey matter are few large protozoal cysts. (HE, 381X)

JPC Comment:
Toxoplasma gondii was first described in 1908 by researchers investigating *Leishmania* in gundis, a type of rodent native to Tunisia.[5] The name was derived from the words *Toxo-*, which means arc and refers to the crescentic shape of zoites; *-plasma*, meaning life; and *gondii*, referring to the species it was first identified in.[5] The first congenital case of *T. gondii* was described in 1938 in a human neonate who died after developing encephalitis and retinitis, and the first case of infection in a cat was diagnosed in 1942.[4,5] In the 1950s, it was discovered to be the causative agent of abortion in ewes in New Zealand (referred to as "type II abortions").[5] Around this time, researchers also discovered links between *T. gondii* infection and the consumption of raw meat and exposure to cat feces, but it wasn't until 1970 that the key to *T. gondii* spread was uncovered: sexual reproduction and shedding of oocysts by felids.[4]

Our knowledge of *T. gondii* has expanded drastically since its initial discovery, and the protozoa is now known to have a worldwide distribution and a wide host range.[5] Felids, both domestic and wild, are the definitive hosts and become infected after ingesting meat infected with bradyzoite-laden cysts.[4] Cats can also be infected by ingesting infected oocytes in feces, but this is less common.[4] There are a wide range of intermediate hosts with significant inter-species variability in morbidity. Australian marsupials and New World monkeys are particularly susceptible to infection, while horses, cattle, and rats seem resistent.[4,11] Other species which can be infected include other mammals, birds. fish, amphibians, and reptiles.[11] Outbreaks in humans have been linked to drinking contaminated water, and it has been speculated that runoff may be the cause of recent infections documented in marine mammals.[8,11]

In cats, acute systemic infections most commonly result in pulmonary, nervous, hepatic, cardiac, and ocular lesions, and, as the contributor mentions, reactivated infections are more commonly restricted to the nervous or ophthalmic systems.[8] *Neospora caninum* and *Sarcocystis neurona* are less common causes of encephalitis and myeloencephalitis in cats.[3,7] These organisms are difficult to impossible to distinguish using light microscopy and should be considered as differential diagnoses in this case. PCR, immunohistochemistry, and serology (as conducted in this case) are generally used to differentiate between these protozoa.[13]

References:

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CASE III:

Signalment:
5.5 year old, Female, New Zealand White Rabbit (*Oryctolagus cuniculus*)

History:
2 month history of "red urine". Initial urinalysis was within normal limits, with no RBCs detected. Radiographs revealed urinary blad

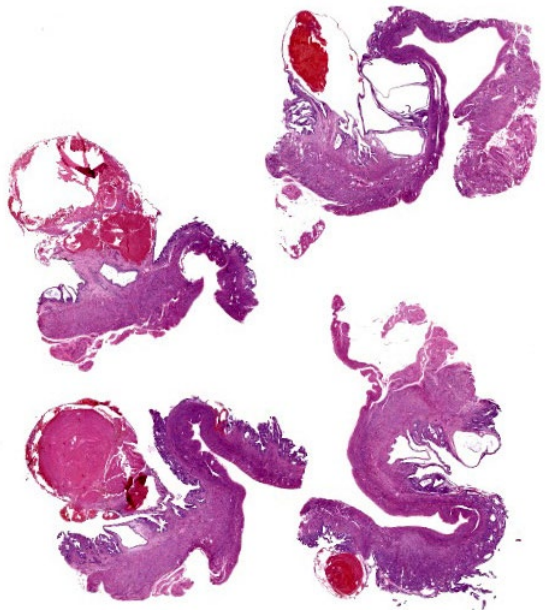

Figure 3-1. Uterus, rabbit. Multiple section of uterus are submitted for examination. A cross section of a large thrombosed endometrial vein and numerous endometrial cysts are evident at subgross magnification. (HE, 6X)

der sludge, which was resolved after subcutaneous fluids. The rabbit was then reported for "red urine" again one month later. Another free-catch urinalysis was submitted which came back positive for red blood cells (too numerous to count) with high protein (100mg/dL) and 1+ cocci. CBC/Chemistry was within normal limits. The rabbit was euthanized at endpoint (for an ocular study) and submitted for necropsy.

Gross Pathology:

An adult female New Zealand White rabbit presents for necropsy several hours post euthanasia via intravenous euthasol. The carcass is in good post-mortem and adequate body condition with adequate subcutaneous and mildly increased visceral adipose stores. Externally, there is an intravenous catheter present in the left ear. There is mild focal yellow staining of the fur surrounding the perineum (urine). The bladder contains a mild amount of thick, moist, white to yellow sediment. The uterus is mildly enlarged, and there are multifocal raised nodules along the uterine horns bilaterally. On cut section, these nodules correspond to semi firm, papillary to polyploid masses that protrude into the uterine lumen, ranging from 1-3 cm in length and 0.5-1.5 cm in diameter. The endometrial surface between the polyploid masses contains numerous variably sized cysts and occasional foci of loosely adhered dark red gelatinous material (clotted blood) ranging from 1-2.5 cm in length. There are no other significant lesions.

Laboratory Results:

CBC/Chemistry: Within normal limits.
Urinalysis (free catch from pan): Red blood cells TNTC; protein 100 mg/dL; 1+ cocci

Uterus: Moderately expanding the endometrium and projecting into the uterine lumen are multifocal dilated veins which contain circular concentric lamellations of red blood cells and fibrin with scattered admixed leukocytes and plump fibroblasts (thrombus). Adjacent endometrium contains macrophages with intracellular brown pigment (hemosiderin, presumptive), mildly dilated blood vessels (congestion), and increased clear space (edema). Endometrial glands are mildly to moderately ectatic and hyperplastic, with attenuated or hyperplastic columnar epithelium occasionally thrown into papillary

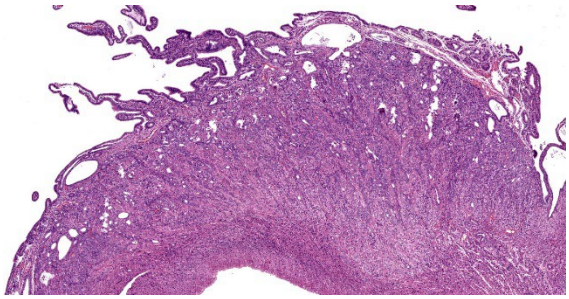

Figure 3-2. Uterus, rabbit. Neoplastic cells forming glands infiltrate the underlying smooth muscle. (HE, 45X)

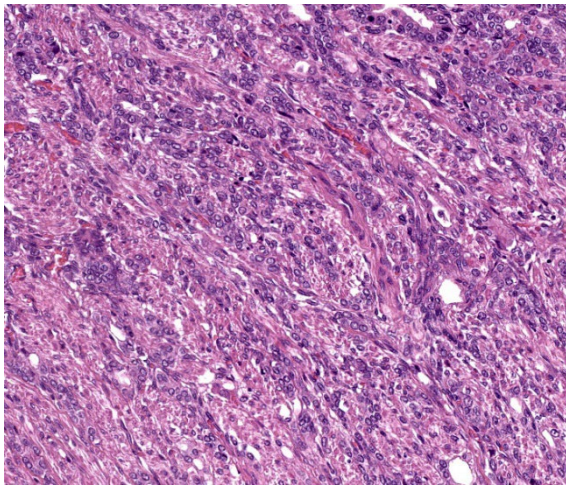

Figure 3-3. Uterus, rabbit. A neoplasm arising in the endometrium infiltrates the underlying uterine mural smooth muscle. (HE, 233X)

folds, and contain low numbers of histiocytes, erythrocytes, and basophilic acellular material. Dysplastic endometrial glands are also present with loss of nuclear polarity, angular glands projecting towards the myometrium, or intraluminal atypical endometrial cells. In other sections of uterus, multifocal uterine adenocarcinoma is present.

Contributor's Morphologic Diagnoses:
Uterus: Endometrial venous aneurysms.
Uterus: Papillary adenocarcinoma, multicentric, with mild multifocal necrosis.
Uterus: Mild multifocal cystic endometrial hyperplasia.

Contributor's Comment:
Hematuria in rabbits may be due to blood originating in the renal system or the reproductive system. Specific causes include neoplasia (uterine adenocarcinoma), uterine or bladder polyps, pyelonephritis or cystis, and urolithiasis.[4,5] An additional cause of hematuria that appears to be unique to lagomorphs is endometrial venous aneurysms. This condition has been reported in multiple species of rabbit, including New Zealand White rabbits and a Holland Lop rabbit.[4,7] The red urine in this case is reproductive in origin and associated with the uterine lesions. Histology of the lesion depicted on this slide was consistent with endometrial venous aneurysm. This rabbit also had multicentric uterine adenocarcinoma, which is not as well represented on this slide.

Grossly, endometrial aneurysms present as dark red, ovoid structures protruding into the uterine lumen from the endometrium, which corresponds microscopically to dilated venous structures containing blood or thrombi.[5] Endometrial venous aneurysms are thought to be a congenital lesion and are characterized by localized venous dilation which may be fusiform or saccular in shape.[7] In humans, congenital aneurysmal lesions of myometrial, cervical, and vaginal vessels but not endometrial veins have been reported.[7] It has also been proposed that prolonged pseudopregnancy, which is common in rabbits and results in prolonged exposure to estrogen and progesterone, may also pay a role in increased vascularity or other vascular changes of the rabbit uterus.[5] In a previous study, endometrial venous aneurysm was identified in 14/854 necropsy cases and 5/150 biopsy cases, with a median age of 32 months.[3]

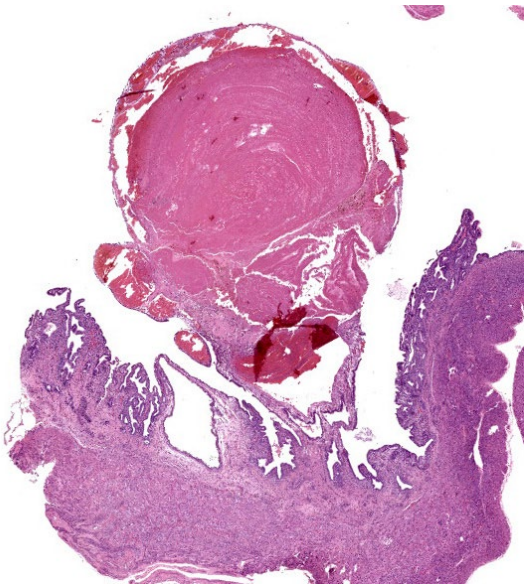

Figure 3-4. Uterus, rabbit. A large thrombosed thin-walled vein measuring 3mm in diameter extends from the endometrium into the uterine lumen. (HE, 45X)

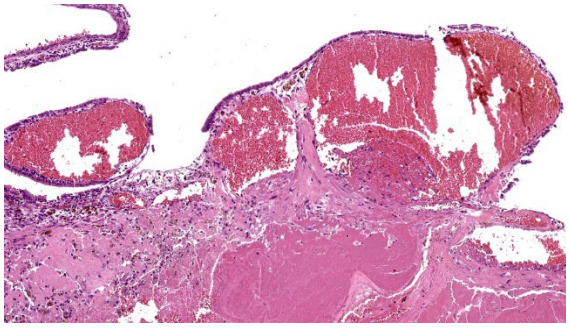

Figure 3-5. Uterus, rabbit. There are smaller vascular lumina at the periphery of the thrombosed vein. The thrombus is attached to the wall and there are siderophages scattered throughout the thrombus. (HE, 96X)

For rabbits that present with hematuria secondary to endometrial venous aneurysms, ovariohysterectomy is recommended because of the risk of life-threatening hemorrhage.[7] Ovariohysterectomy is curative in these cases.[7]

Contributing Institution:
University of Washington
Department of Comparative Medicine
Health Science Center
Seattle, WA 98105

JPC Diagnosis:
1. Uterus: Uterine adenocarcinoma.
2. Uterus: Endometrial venous aneurysms with thrombi.
3. Uterus: Cystic endometrial hyperplasia, diffuse, moderate.

JPC Comment:
The contributor mentions several potential causes of hematuria originating from the reproductive tract in rabbits, including adenocarcinomas and endometrial hyperplasia. Several large-scale studies of neoplasms and uterine lesions in rabbits have demonstrated the relative frequency that these occur. According to several studies, uterine adenocarcinomas are the most frequently diagnosed uterine lesion in rabbits and the third most common neoplasm in rabbits in general, with only mammary carcinomas (20.2% of submissions) and trichoblastomas (18%) occurring with higher frequency in a study of 1238 rabbits.[2,6,9] Most rabbits with uterine adenocarcinoma present with hematuria or serosanguinous vaginal discharge; anorexia is a less common clinical sign.[9] The neoplasm is typically multicentric and nodular and may involve both uterine horns.[1] The average age for diagnosis is 5-6 years of age, and the neoplasm tends to metastasize within 1-2 years to the lungs, liver, bone, or brain.[9]

Endometrial hyperplasia is the second most commonly diagnosed lesion of the rabbit uterus and outnumbers adenocarcinomas in some smaller scale studies.[2,6,8,9,10] Endometrial hyperplasia occurred in 44% of 1928 rabbits with uterine lesions, and the most common clinical signs were similar to adenocarcinoma, with approximately half having hematuria or serosanguinous vaginal discharge and fewer having anorexia. The median age for endometrial hyperplasia is slightly younger, around 4 years.[9,10] Additionally, it is common for adenocarcinoma to develop within areas of endometrial hyperplasia in rabbits, as was described in this case.[2]

In rabbits, hematuria must be differentiated from pigmented urine due to nonpathogenic

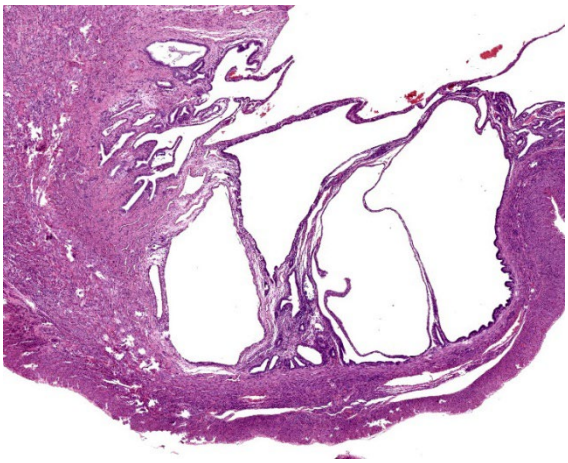

Figure 3-6. Uterus, rabbit. There is marked cystic endometrial hyperplasia of the endometrium. (HE, 26X)

crystals, porphyrins, or bilirubin by conducting a urinalysis, as was done in this case.[1]

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CASE IV:

Signalment:
A 3-year-old female (intact) Mastiff dog (*Canis familiaris*)

History:
The dog presented with a two-day history of lethargy, inappetence, pyrexia, coughing and a brown/red vaginal discharge. She had been previously diagnosed with a steroid-responsive cough (one year prior to current presentation).

On clinical presentation, the dog was dehydrated, pyrexic and had a thick vaginal discharge. Digital examination of the reproductive tract revealed an open cervix. Abdominal radiographs and ultrasonography showed a fetus with no heartbeat in the uterus. Abortion and pyometra were diagnosed, and an ovariohysterectomy was performed. To further investigate the respiratory disease, thoracic radiographs and bronchoalveolar lavage (BAL) were performed. Radiographs revealed a bronchointerstitial pattern with bronchiectasis and BAL showed a differential count of 40-45% eosinophils, 40-45%

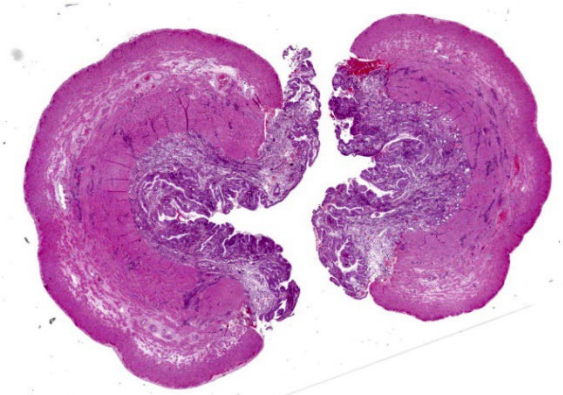

Figure 4-1. Uterus, dog. Two sections of uterus with hyperplastic endometrium are submitted for examination. At subgross, there is a prominent cellular infiltrate. (HE, 5X)

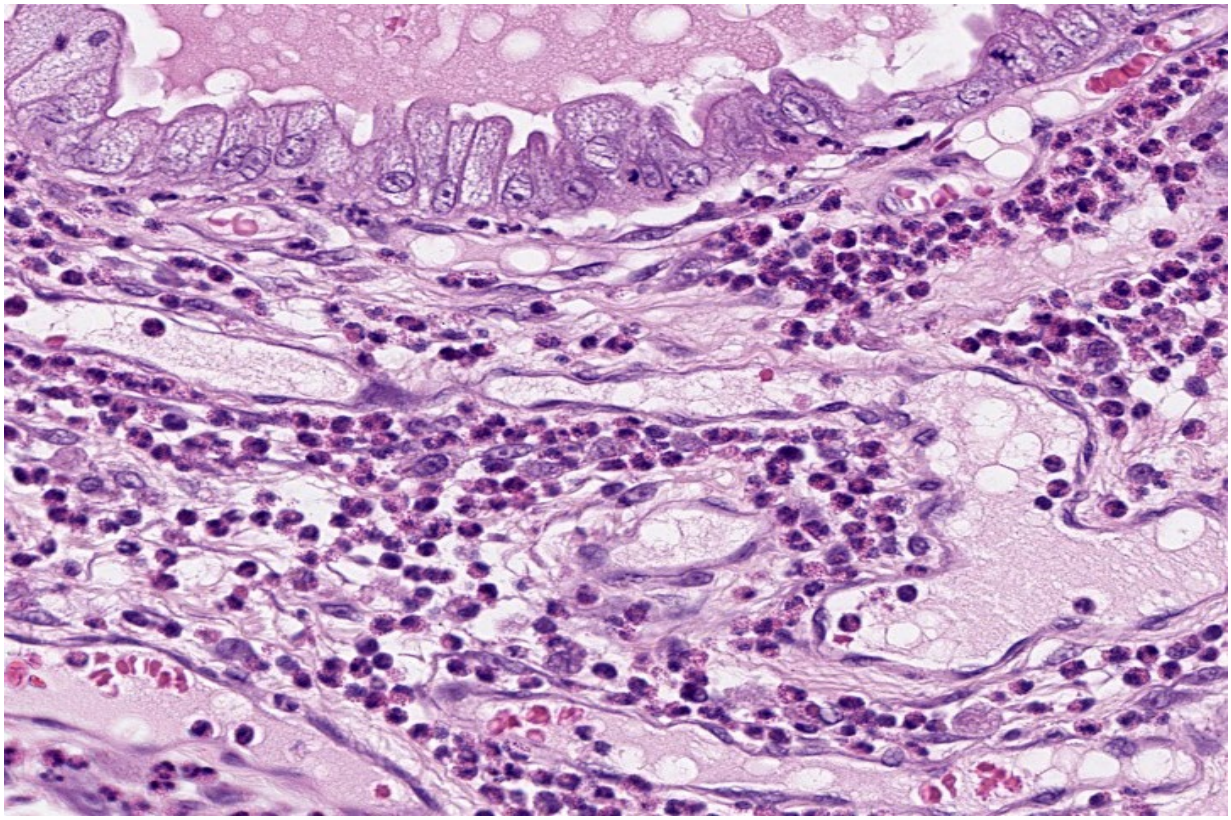

Figure 4-2. Uterus, dog. The edematous stroma is expanded by an infiltrate of large number of eosinophils and fewer foamy macrophages. The endometrial epithelium contains numerous cytoplasmic vacuoles (progesterone change). (HE, 380X)

neutrophils, 10-15% macrophages, and rare lymphocytes in a lightly mucinous background.

Following surgery, the dog presented twice (11 days and 2 months post-surgery) with a cough and labored breathing. On both occasions the dog responded to corticosteroid treatment. Thoracic radiographs taken at two months post-surgery revealed a bronchointerstitial pattern and a 3 cm opaque mass in the caudal lung lobe. Based on clinical and clinico-pathological findings a diagnosis of canine eosinophilic bronchopneumopathy (EBP) was proposed. Unfortunately, there was no repeat bloodwork and the dog was lost to follow up.

Gross Pathology:
The uterus, the placenta and the aborted fetus were submitted for microscopic examination. The uterine mucosa was pale tan to green, irregular and thickened.

Laboratory Results:
CBC showed a marked eosinophilia (11.86 x 10^9/L), neutrophilia (14.35 x 10^9/L), basophilia (1.01 x 10^9/L), and a mild regenerative anemia (HCT 37%). Biochemistry showed a mild increase in creatinine 166 µmol/L (range: 44-159 µmol/L). A Baermann test for lungworm larvae was negative.

Microscopic Description:
Uterus: The endometrium is circumferentially expanded by the presence of large numbers of eosinophils and lesser numbers of foamy macrophages that diffusely infiltrate the interstitium and separate endometrial glands. Multifocally, eosinophils and rare neutrophils are seen migrating through the endometrial epithelial lining. The endometrial glands are mildly dilated, occasionally

tortuous, and mostly lined by cuboidal epithelium. Rare granulocytes are present in the lumen of the glands. In the surface epithelium, cells are arranged in a single layer or are pseudostratified. Endometrial epithelial cells vary from low cuboidal, to tall columnar with eosinophilic foamy cytoplasm and vesiculate nuclei (progestational epithelium). Endometrial blood vessels are moderately congested and lymphatics are ectatic. There are multifocal areas where the endometrial stroma is distended with numerous clear spaces separating blood vessels and endometrial glands (edema). In the lumen of the uterus, there are scattered, multifocal aggregates of erythrocytes, eosinophils and neutrophils admixed with cellular debris. There is moderate to marked edema in the stratum vasculare causing separation of the inner and outer layers of the myometrium with multifocal, dense aggregates of eosinophils infiltrating and separating interconnecting bundles of smooth muscle and surrounding vessels.

Special stains: Luna and Congo red stains demonstrated bright orange to red granules in the cytoplasm of the numerous eosinophils present throughout the endometrium and myometrium.

Tissue autolysis prevented optimal examination of the fetus and the placenta.

Contributor's Morphologic Diagnoses:
Uterus: Eosinophilic endometritis and myometritis**.**

Contributor's Comment:
This case is unique in presenting with eosinophilic endometritis and myometritis, eosinophilic bronchopneumopathy (EBP), and peripheral blood eosinophilia. It is unclear whether the eosinophilic endometritis and myometritis, and the EBP are separate entities or whether these conditions may be part of the multisystemic disorder termed hypereosinophilic syndrome. An eosinophilic leukemia, characteristically presenting with a peripheral eosinophilia count greater than 25 to 30 eosinophils × 10^9/L,[16] was excluded based on a peripheral count of 11.86 x 10^9/L in this patient.

Eosinophilic endometritis and myometritis, representing an abundant eosinophilic infiltration of the endometrium and myometrium respectively, are occasionally reported in dogs. In a recent study, 7.3% of endometrial biopsies in subfertile dogs were classified with eosinophilic endometritis.[12] Despite the surprisingly common incidence of this condition, the pathogenesis and clinical significance remains poorly understood. A significant relationship between eosinophilic endometritis and fetal loss has been established. However, it is unclear if eosinophilic infiltrates result in fetal loss, or if eosinophils infiltrate secondarily to tissue responses associated with placental maturation and late pregnancy.[12] It has been previously reported that high numbers of eosinophils may be present in the uterus of healthy post-partum doges, whereas low numbers of eosinophils may be seen during pro-estrus, estrus, diestrus, early pregnancy and early to mid-anestrus post-partum.[27]

Eosinophilic endometritis has been reported in several other species including ferrets,[11] horses,[23] donkeys,[24] and elk.[4] In ferrets, eosinophilic endometritis was attributed to fetal death resulting from suspected "single kitten syndrome."[11] A similar entity termed "single pup syndrome" has been reported in dogs, where a single-fetus pregnancy results in failure of parturition.[19] It is believed that the single puppy produces insufficient cortisol and ACTH to initiate parturition, and if the birth process is not initiated, the placental supply of oxygen and nutrients diminishes leading to fetal death and mummification or maceration

in utero. A diagnosis of "single pup syndrome" could be potentially considered in the present case. In horses, a causal association between pneumovagina and pneumouterus leading to eosinophilic endometritis has been suggested.[23]

The failure of a single pup to initiate the onset of parturition on or around the expected date has been postulated to be due to the concentration of cortisol secreted by one pup being insufficient to adequately initiate luteolysis via prostaglandin release.

Eosinophilic bronchopneumopathy is a disease characterized by eosinophilic infiltration into the bronchi, terminal bronchioles, alveoli and blood vessels. Siberian Huskies and Alaskan Malamutes appear overrepresented. In some cases, blood peripheral eosinophilias are reported concurrently.[9] Affected dogs usually present with a corticosteroid responsive cough, similar to the patient from the case described here. Eosinophilic bronchopneumopathy is typically diagnosed by cyto logical examination of bronchoalveolar lavage fluid or histologic examination of the bronchial mucosa, combined with radiographic and bronchoscopic findings and exclusion of known causes of eosinophilic infiltration into the airways. In dogs, the most common causes of eosinophilic pneumonitis include heartworm disease caused by *Dirofilaria immitis* and migration of *Angiostrongylus vasorum* larvae through the pulmonary parenchyma.[6,17] *Dirofilaria immitis* is a reportable disease in New Zealand and there are no reports of canine infection with *A. vasorum*, and thus infection with these parasites was considered unlikely in the present case. Less commonly, *Oslerus osleri, Filaroides hirthi, Crenosoma vulpis, Paragonimus kellicotti* and neoplasia (lymphoma and mast cell tumors) have been implicated with pulmonary eosinophilic infiltrates in dogs.[7,18] Other possible causes have been described in the human literature (idiopathic pulmonary fibrosis, medications, mycobacteria or fungi) and could potentially cause this clinical syndrome in dogs, but no reported cases were found in the literature. While the etiology of EPB remains unclear, hypersensitivity to aeroallergens is suspected, however most cases are still considered idiopathic.[7]

Little is known about the cytokines and chemokines involved with EBP. Flow cytometric analysis of BAL samples from dogs with EPB demonstrated an increase of CD4+ T-cells and a decrease of CD8+ T-cells, and resolution of clinical signs with corticosteroid treatment normalized the CD4:CD8 ratio.[8] It was proposed that CD4+ T-cells are at least in part responsible for the infiltration of eosinophils, which has also been shown in asthmatic humans[21] and rodents.[15]

Alternatively, the underlying cause of the multi-organ eosinophilic infiltrates in the present case may be due to idiopathic hypereosinophilic syndrome (HES). This is a rare systemic illness of unknown cause and presents as a sustained peripheral eosinophilia ($>5\times10^9$/L) with multi-organ infiltration causing dysfunction.[16] In humans, peripheral eosinophilia must be present for at least 6 months to be considered HES.[5] Although the cause of HES is still considered idiopathic, it has been proposed that generalized immune

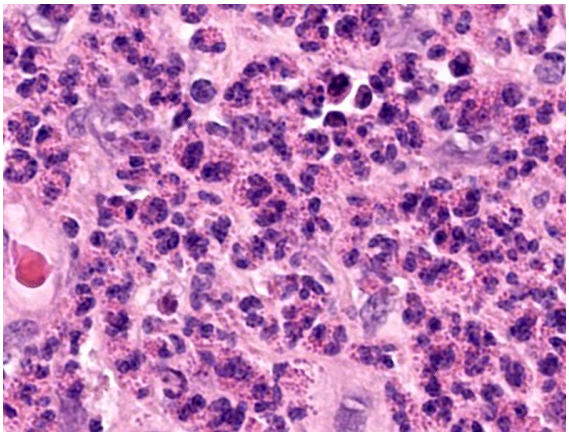

Figure 4-3. Uterus, dog. Higher magnification of the eosinophilic endometrial infiltrate. (HE, 1180X)

dysregulation may lead to increased maturation and recruitment of eosinophils from the bone marrow that enter the circulation and target tissues and organs. Several cytokines, particularly IL-5 and eotaxin, which prime, activate and enhance eosinophilic migration into tissues, have been implicated with HES.[16] In dogs, Rottweilers appear overrepresented,[25] and the condition has been reported in cats,[26] humans,[5] and an owl monkey.[13] In horses, multisystemic eosinophilic epitheliotropic disease is considered the equivalent to HES. Affected horses present with a peripheral eosinophilia of unknown primary origin with multi-organ infiltration.[22]

In dogs with HES, eosinophilic infiltrates have been reported in several organs including the liver, spleen, lung parenchyma, myocardium, lymph nodes, skeletal muscle and bone marrow.[1,14,20,25] Although pulmonary eosinophilic infiltrates are common in dogs with HES, the case presented here could be the first description of uterine infiltrates in an HES dog.

In the human literature, few reports of pregnant women with HES appeared to have minimal complications with no mention of eosinophilic uterine infiltrates. One baby was delivered with a transient hypereosinophilia and there was a single report of a premature twin delivery, however these and all other cases resulted ultimately in the delivery of healthy infants.[2,3]

In this case, the concurrent EBP, eosinophilic myometritis, endometritis and blood peripheral eosinophilia raise the question whether this case should be considered an unusual presentation of HES. A similar report of two Cavalier King Charles Spaniels presenting with eosinophilic stomatitis, peripheral eosinophilia and eosinophilic disease in other body systems also questioned if these cases

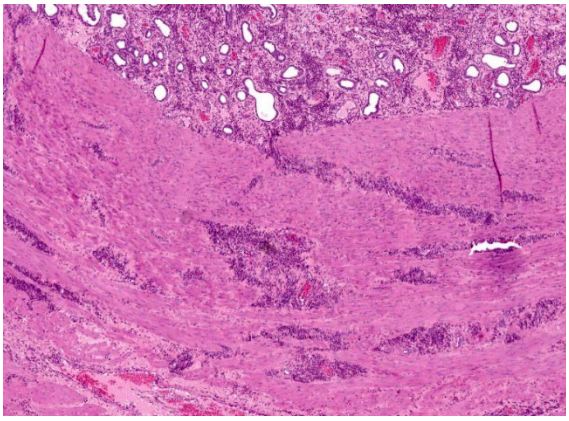

Figure 4-4. Uterus, dog. The eosinophilic infiltrate extends along perivascular connective tissue within the uterine smooth muscle. (HE, 35X)

were unusual presentations of HES.[10] Unfortunately, this case was lost to follow up and a definitive diagnosis could not be established. The persistence and worsening of a corticosteroid responsive cough following ovariohysterectomy, and the presence of similar clinical signs one year prior to presentation, suggests at least EBP. Alternatively, the likelihood of HES with pulmonary and uterine infiltrates is also equally considered.

Contributing Institution:
IVABS
Massey University
Palmerston North, New Zealand
http://www.massey.ac.nz

JPC Diagnosis:
1. Uterus: Endometritis, eosinophilic, diffuse, severe, with edema.
2. Uterus, endometrium: Hyperplasia, diffuse, moderate, with progestational change.

JPC Comment:
The contributor provides a great overview of eosinophilic bronchopneumopathy, eosinophilic endometritis, and the possible link with hypereosinophilic syndrome (HES) in this patient. As the contributor states, HES is a rare and life-threatening disease in dogs and information regarding pathogenesis and

treatment is extrapolated from the human literature.

One common sequela in humans with HES is a thromboembolic event.[17,21] In HES patients, several proteins, cytokines, and chemokines produced by eosinophils create a hypercoagulable state.[17,21] Major basic protein damages endothelial cells, causing endothelial cell and platelet activation, while eosinophil cationic protein activates factor XII (Hageman factor).[21] Eosinophils also release both tissue factor and plasminogen activator inhibitor 2 and separately inhibit fibrinolysis.[17] The net result is a hypercoagulable state, and in humans this manifests as microvascular thrombi in multiple organs and large thrombi within the heart.[17] A case of HES-induced thromboembolism was recently reported in a 3 year old boxer dog. The animal presented with respiratory distress, marked eosinophilia, and a thrombus in the left atrium visible on echocardiography.[17] Increased D-dimer levels and tissue-factor-activated thromboelastography confirmed that the dog was hypercoagulable, and the dog was euthanized after it developed acute aortic thromboembolism and paraplegia.[17] On necropsy, eosinophils infiltrated the lungs, liver, spleen, and lymph nodes and accounted for 90% of the myeloid cells in the bone marrow.[17] This was the first case to be thoroughly documented in a dog; however a similar case was reported in an 11 year old mixed breed dog with HES and a possible intracardiac thrombus on echocardiography.[21] This patient was unique in that it responded well to treatment with hydroxyurea and prednisolone, and the thrombus was not apparent 3 months later.[21] These case reports illustrate that hypercoagulability may be a consequence of HES in dogs, and thromboembolism may be prevented with rapid treatment and resolution of hypereosinophilia, as has been shown in human medicine.[17]

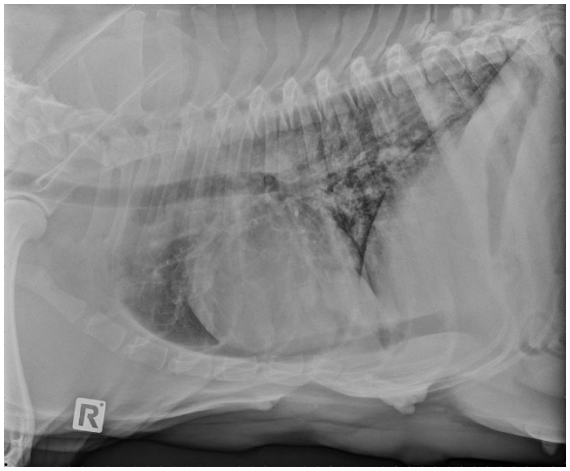

Figure 4-5. Thoracic radiograph, dog. There was a diffuse interstitial pattern and a single nodule within the caudodorsal lobe at presentation. (Photo courtesy of: IVABS, Massey University, Palmerston North, New Zealand, http://www.massey.ac.nz)

In addition to the differentials listed by the contributor, another differential diagnosis for hypereosinophilia is paraneoplastic syndrome. In dogs, cats, horses, and humans, lymphomas can rarely cause hypereosinophilia.[20] It is believed that lymphocytes elaborate products like IL-3, IL-5, and GM-CSF which inhibit eosinophil apoptosis and result in eosinophilia.[20]

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