Joint Pathology Center
Veterinary Pathology Services

WEDNESDAY SLIDE CONFERENCE 2015-2016

Conference 1

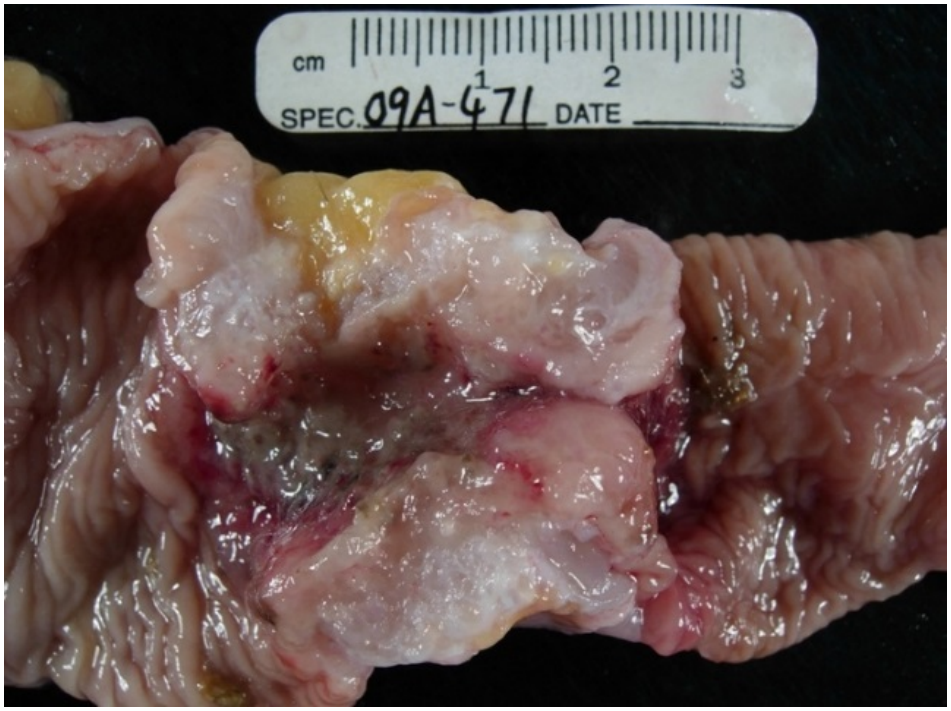
9 September 2015

CASE I: 09-A-471 (JPC 3167631).

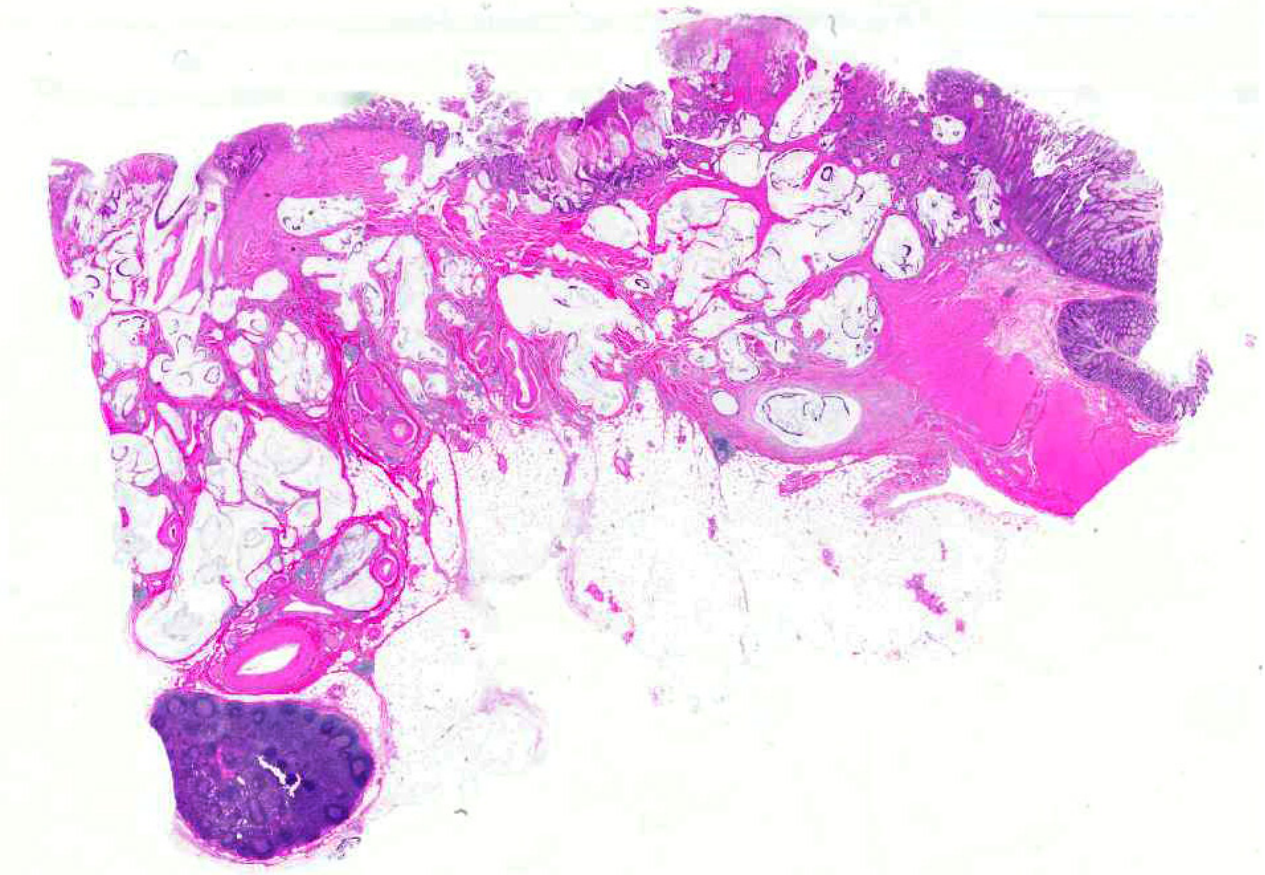
Signalment: 26 year old intact male rhesus macaque (*Macaca mulatta*).

History: This animal was born at Oregon National Primate Research Center (ONPRC). A cardiac murmur and mild to moderate cardiomegaly were noted approximately one year prior to necropsy. Four months prior to necropsy, weight loss was reported and thickening of the cecocolic junction was noted on abdominal palpation. Hematology results demonstrated an iron deficiency anemia.

Gross Pathology: At necropsy, the animal was in good nutritional condition. The apex of the heart was rounded. The left atrium was pale and enlarged twice normal size. The left atrioventricular valve was multifocally thickened with smooth, shiny, white nodules (endocardiosis). The endocardial surface of the left atrium was opaque, white and leathery. A pendulous red cystic mass was attached to the serosal surface of the jejunum and contained approximately 10 ml of blood. A white irregular mass was seen inside the cyst near



1-1. Circumferential thickening of intestinal wall by colonic adenocarcinoma resulted in narrowing of lumen. Note the mucosal ulceration and hemorrhage. (Photo courtesy of: Oregon National Primate Research Center http://onprc.ohsu.edu)



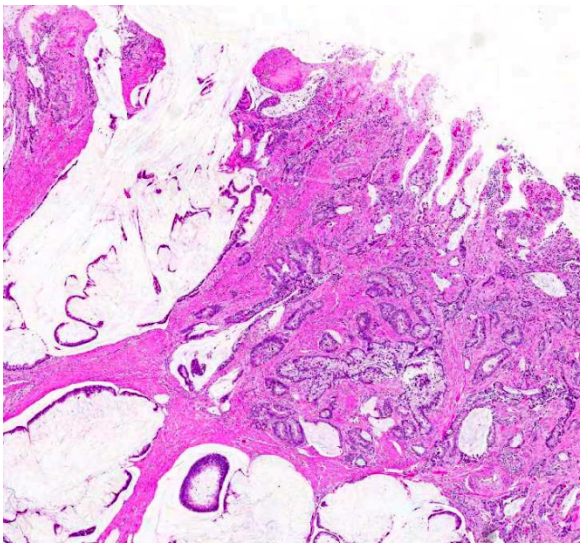
1-2 Colon, rhesus monkey. The colon is transmurally infiltrated by a multicystic epithelial neoplasm. (HE, 4X)

the point of attachment to the intestinal wall. A neoplasm measuring 2.5 cm in greatest dimension was present within the ascending colon. It narrowed the lumen and expanded the wall circumferentially and segmentally. The mucosa was multifocally ulcerated and hemorrhagic

Laboratory Results:

	Value	Ref. Interval
WBC	6.5 x 10^3/µL	3.8 – 12.6 x 10^3/µL
RBC	5.34 x10^6/µL	4.5-6.4 x 10^6/µL
MCV	60 fL	67-77 fL
MCH	18.4 pg	22.1- 25.84 pg
MCHC	30.6 g/dl	32.2 – 34.0 g/dl

Contributors Histopathologic Description: Disrupting the mucosal epithelium, expanding and transmurally infiltrating the intestinal wall is an unencapsulated, poorly circumscribed modestly cellular neoplasm. It is composed of epithelial cells arranged in tubules surrounded by a moderate reactive stroma (desmoplasia). Many neoplastic



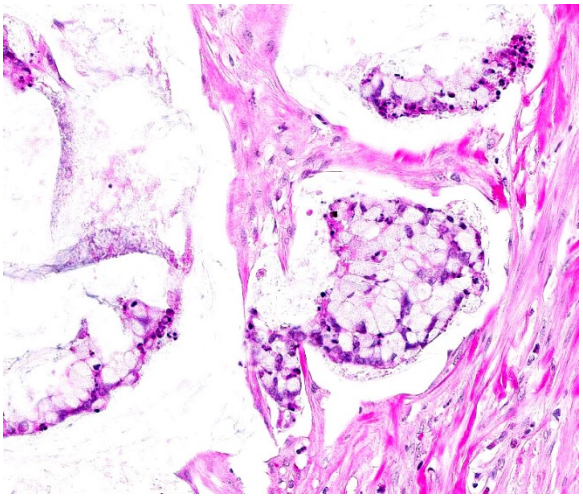
1-2 Colon, rhesus monkey. Neoplastic glands which contain abundant mucus multifocally efface the disorganized and ulcerated mucosa. (HE, 35X)

tubules are disrupted and appear as attenuated ribbons amid large lakes of mucin. The neoplastic cells exhibit marked anisocytosis and anisokaryosis, have distinct cells borders and a moderate amount of granular, eosinophilic cytoplasm. Nuclei are irregularly round to oval and vesiculate with one or two distinct nucleoli. The mitotic rate ranges from 1-3/HPF. There is extensive single cell necrosis of the neoplastic cells. An inflammatory infiltrate composed of lymphocytes, plasma cells, eosinophils and fewer neutrophils is associated with the neoplasm. The overlying mucosa is focally ulcerated. The mucosa adjacent to the neoplasm is proliferative with goblet cell hyperplasia. Multifocally crypts are dilated and contain moderate numbers of neutrophils.

Microscopic diagnoses of tissues not submitted:

Jejunum: Leiomyoma.

Heart:
1. Endocardiosis, right and left atrioventricular valves.
2. Myocardial necrosis, degeneration, mineralization, fibrosis.
3. Atrial subendocardial fibroelastosis, bilateral with jet lesion.



1-4. Colon, rhesus monkey. Neoplastic glands are lined by or contain a single layer of columnar epithelium admixed with abundant mucus and cellular debris. (HE, 256X)

Contributor's Morphologic Diagnosis:

Colon:
1. Adenocarcinoma, mucinous.
2. Colitis, proliferative, lymphoplasmacytic, eosinophilic, multifocal, marked with goblet cell hyperplasia and crypt abscesses.

Contributor's Comment: The primary findings in this case were mucinous colonic adenocarcinoma, jejunal leiomyoma and fibrosing myocardial necrosis. The hypochromic, microcytic anemia noted clinically was attributed to the hemorrhage in the ulcerated mucosa overlying the neoplastic mass.

The intestinal adenocarcinomas are classified according to histological features and include:

1. Papillary adenocarcinoma
2. Tubular adenocarcinoma
3. Mucinous adenocarcinoma
4. Signet ring cell adenocarcinoma

Intestinal adenocarcinoma is the most frequently diagnosed tumor of older macaques.[4,5,11,12,15] A high prevalence of intestinal tumors at the ileocecal junction in aged animals (over 20 years) has been documented.[11,12,13,14]

Intestinal neoplasms are rare in large animal species. Intestinal adenocarcinomas in dogs are seen in the proximal small intestine and large intestine. Regional metastasis to mesenteric lymph nodes may occur. Distant metastasis to the liver, spleen and lungs occurs less frequently. Boxers, collies, poodles and German shepherds are predisposed.[2]

In cats, intestinal adenocarcinoma is less common than lymphosarcoma. In sheep, the occurrence of intestinal adenocarcinomas is associated with ingestion of bracken fern and certain weeds. In cattle, intestinal adenocarcinoma is associated with bracken

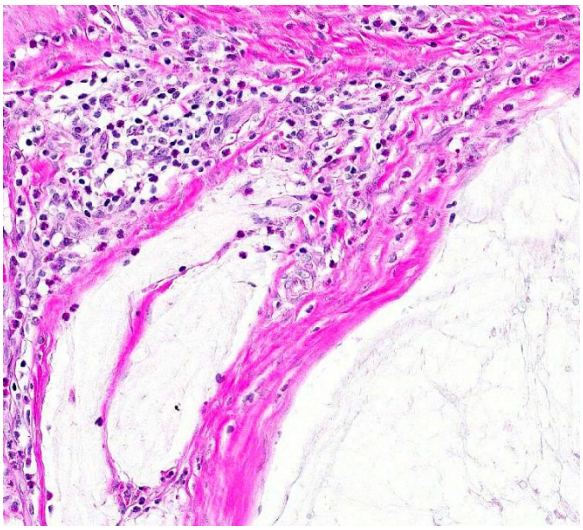
fern ingestion and bovine papillomavirus-4 infection and frequently metastasize to liver, lung, kidney, uterus and ovaries.[2] In contrast to other simian species, colonic carcinomas are frequently seen in cotton-top tamarins[1,8] and has been linked to the high prevalence of chronic colitis in these animals.[9]

Although, the tumorigenesis has not been completely studied in non-human primates, long term feeding of a high-fat, low-fiber diet has been shown to cause pre-malignant alterations in African green monkeys.[11] A novel *Helicobacter* sp. has been isolated from inflamed colons of cotton-top tamarins, which are predisposed to developing inflammatory bowel disease (IBD) and colon cancer.[13] Also, the colonic adenocarcinoma in rhesus monkeys has been linked to *Helicobacter macacae*.[9] Mutation in *K-ras* has been observed in approximately 40 % of colonic adenocarcinoma of humans; however, no such mutations were recorded in macaques with intestinal adenocarcinoma.[11]

JPC Diagnosis: Colon: Mucinous adenocarcinoma.

Conference Comment: Conference participants agreed that the histologic appearance of this neoplasm is distinctive, due in part to the presence of large lakes of mucin, and does not lend itself to a long differential diagnosis list; however, two candidate conditions for consideration include endometriosis and simian retrovirus induced peritoneal fibromatosis. Detailed features of the neoplastic cells were discussed with special mention of the basally located nuclei and prominent apical globules present within the cytoplasm. In addition to the description of the neoplastic cells, conference participants described the numerous secondary changes present within the colon including extensive goblet cell hyperplasia, inflammatory infiltrates within the colonic mucosa, as well as areas of ulceration and the presence of crypt abscesses.

Large intestine (LI) adenocarcinomas share many characteristics with their human counterparts and a recent study characterized the immunohistochemical profile of these tumors in the rhesus macaque. LI adenocarcinomas demonstrated a modification in the expression of one or more of the following markers: CD10, β-catenin, sirtuin 1, cytokeratin 17, and p53. Additionally, this study described the histologic characteristics of LI adenocarcinoma as having abundant mucin deposition, transmural spread and lymphatic invasion, the first two of which



1-5. Colon, rhesus monkey. Neoplastic glands are lined by or contain a single layer of columnar epithelium admixed with abundant mucus and cellular debris. (HE, 256X)

were described in this case.[4]

Participants also discussed the classic gross description of intestinal adenocarcinoma as having a “napkin ring-like” appearance due to constriction caused by the desmoplastic response elicited by the neoplasm, which is present in the excellent gross image provided by the contributor. The desmoplastic response is related to the interaction of tumor cells with the surrounding stroma via many types of mediators including cytokines and growth factors. One such mediator is platelet derived growth factor (PDGF), which stimulates fibroblasts and results in excessive production of collagen,[7] often referred to as a scirrhous response. Tumor cells can have

various effects on stromal fibroblasts including causing them to differentiate into other types of mesenchymal cells, such as myofibroblasts, and inducing the production of cytokines that stimulate tumor growth, as well as stimulating them to de-differentiate and produce abnormal extracellular matrix. Growth factors are also sequestered within the stroma, and the actions of tumor cells can control their release.[7] Intestinal adenocarcinoma is described in humans[12] and domestic animal species[2] as having a similar gross appearance, and the mucinous variant is indicative of a poorer prognosis due the mucinous excretions facilitating invasion through the intestine wall.[12]

As mentioned by the contributor, intestinal adenocarcinoma in sheep is thought to be at least partially related to the ingestion of bracken fern, or may be related to the application of fertilizers or herbicides.[2,6] Bracken fern affects grazing animals throughout the world and causes a variety of syndromes ranging from neurologic and cardiac conditions in horses and pigs to enzootic hematuria in cattle and sheep. Bracken fern-induced neoplasia is most commonly associated with the urinary bladder and upper alimentary tract and is most often described in cattle, where it may also be associated with bovine papillomavirus-2. All parts of the plant are considered toxic and contain multiple toxins, including a thiaminase as well as multiple carcinogens, ptaquiloside being the most common.[10] There is also a recent report of intestinal adenocarcinoma in farmed sika deer where bracken fern may have played a role, in combination with other factors.[6] Intestinal carcinomas in sheep are more commonly located in the small intestine, and less commonly in the colon, and they are also associated with luminal constriction and a marked desmoplastic response. Intestinal adenocarcinomas in large domestic species other than sheep, and other than those associated with bracken fern or papillomavirus, are uncommon.[2]

Contributing Institution:
Oregon National Primate Research Center
http://onprc.ohsu.edu

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CASE II: 15-0022 (JPC 4066309).

Signalment: Two-year-old, intact male African green monkey (*Cercopithecus aethiops*).

History: The animal was wild caught on St. Kitts. It was part of a group of 22 African green monkeys brought to the institution on 12/17/2014. Health records from vendor indicated heavy growth of *Klebsiella pneumoniae.* All were treated with enrofloxacin at the vendor. The first quarantine exam on 12/22/14 was unremarkable. Decreased appetite was noted on 12/30/14, and it continued to decrease with marked weight loss. Physical examination on 1/2/14 revealed a large, firm mass in the right cranial abdomen. Abdominal fluoroscopy and CT scan revealed a loss of serosal detail mid-abdomen, with a mass effect with intestines displaced cranially and caudally.

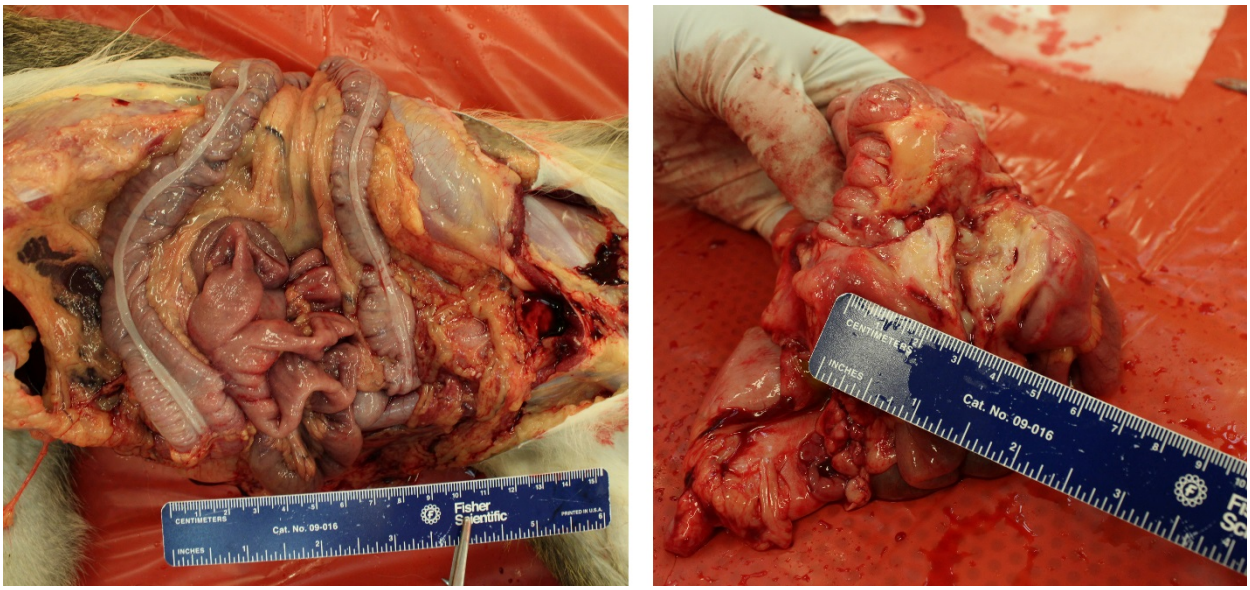
Gross Pathology: A 4.5 x 3.5 x 2.2 cm firm, tan, irregular mass was present in the mesentery and involved the ileocecocolic junction. Loops of duodenum, jejunum and colon were adhered to the mass and to themselves multifocally. The serosa of the intestinal loops was roughened, with multifocally light red discolorations. On cut section, 80% of the mass was firm, and tan to yellow. Multifocally, there were half a dozen irregular cavitations, which varied in size from 3-8mm in diameter. These were filled with mucoid white to yellow material. On the left medial lobe of the liver, along the diaphragmatic surface, there was a focal, 15x5 mm pale tan, irregular, flat and friable area.

A 4.5 cm x 1 mm tan nematode was present free within the stomach (*Physaloptera* sp, presumptive).

Embedded within the mucosa of the cecum were half a dozen tan nematodes, 4.5-5cm x0.5mm diameter with anterior filamentous ends (consistent with *Trichuris* sp).

Laboratory Results: The CBC was within normal limits with the exception of moderate numbers of reactive lymphocytes and moderate numbers of neutrophils with basophilic cytoplasm. The chemistry panel was within normal limits. Urinalysis revealed moderate blood, ketonuria, mild proteinuria, and large numbers of calcium oxalate crystals.

Hypermucoviscosity (HMV) variant of *Klebsiella pneumoniae* was isolated from the abscess and rectal and oropharyngeal swabs.



2-1. Peritoneal mass, African green monkey. A 4.5 x 3.5 x 2.2 cm firm, tan, irregular mass was present in the mesentery and involved the ileoceco-colic junction. Loops of duodenum, jejunum and colon were adhered to the mass (left). At right is a closer view of the excised mass. (*Photo courtesy of:* Laboratory of Comparative Pathology, Memorial Sloan-Kettering Cancer Center (www.mskcc.org/research-areas/programs-centers/comparative-medicine-pathology)).

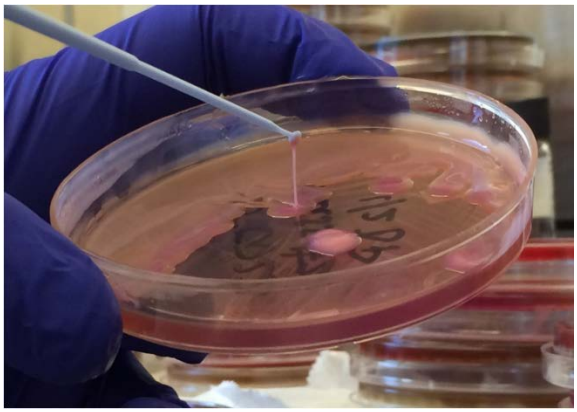
Histopathologic Description: Abdominal mass: The muscularis and serosa of the intestinal sections and adjoining mesenteric fat are obliterated and expanded by large areas of liquefaction necrosis, infiltrates of large numbers of degenerate neutrophils, macrophages, foamy macrophages, moderate numbers of lymphocytes and plasma cells admixed with eosinophilic proteinaceous material, fibrin, necrotic debris, and occasional hemorrhage and dissecting fibrosis. Many arteriolar walls in the mesentery are expanded by fibrillar eosinophilic material (fibrinoid necrosis). There are multifocal areas of liquefaction necrosis in the mesenteric lymph node, with infiltrates of large numbers of foamy macrophages and neutrophils (abscess), and proliferation of fibrous connective tissue that extend to the mesentery. Within the cytoplasm of macrophages and freely within the necrotic debris, there are large numbers of bacterial rods with a clear thick capsule.

The intestinal mucosa is multifocally infiltrated by moderate numbers of lymphocytes and plasma cells, with fewer eosinophils.

Contributor's Morphologic Diagnosis: Abdominal mass: Severe, locally extensive, chronic necrosuppurative and histiocytic mesenteritis, lymphadenitis and enterocolitis with abscess formation and myriad intrahistiocytic and extracellular encapsulated rod-shaped bacteria.

Contributor's Comment: Gross and microscopic examination revealed a locally extensive chronic abscess involving the mesenteric lymph nodes, small and large intestines and mesentery with large numbers of intrahistiocytic and free bacterial rods containing a thick capsule. Hypermucoviscosity (HMV) variant of *Klebsiella pneumoniae* was isolated from the abscess and rectal and oropharyngeal swabs. The invasive HMV phenotype of Klebsiella pneumoniae has been associated with multisystemic abscesses, and especially abdominal abscess in African green monkeys.[10, 1]

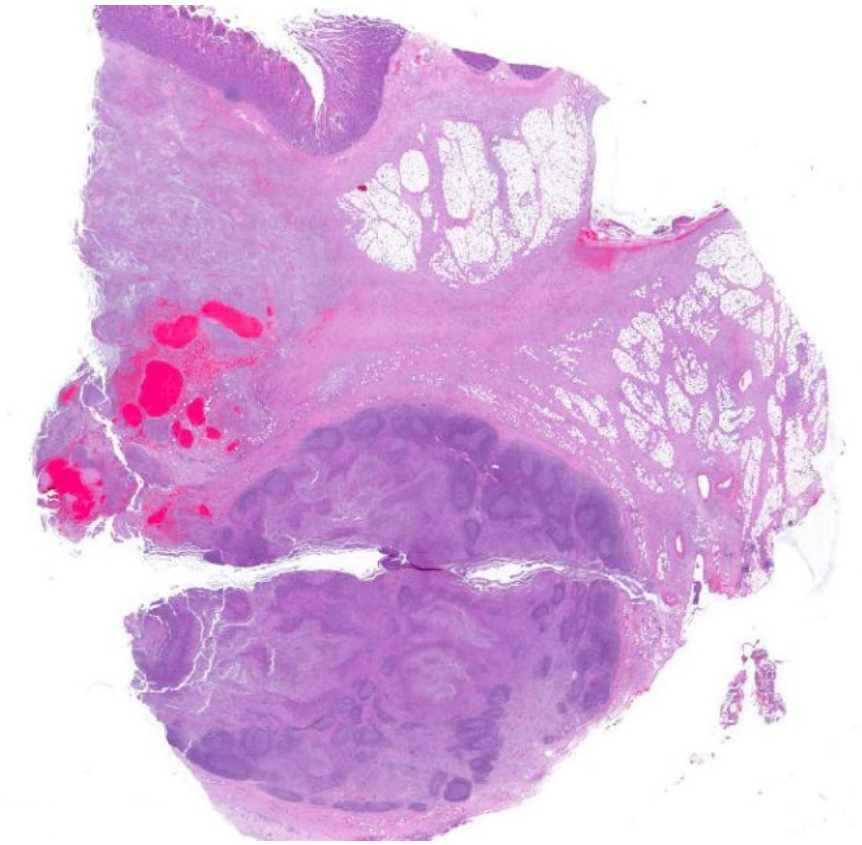
Klebsiella pneumoniae is a gram-negative, aerobic, nonmotile bacillus and is a common



2-2 Bacterial culture, African green monkey. Demonstrating the "string test" associated with the hypermucoviscosity (HMV) variant of Klebsiella pneumoniae. (Photo courtesy of: Laboratory of Comparative Pathology, Memorial Sloan-Kettering Cancer Cent Cancer Center (www.mskcc.org/research-areas/programs-centers/comparative-medicine-pathology)).

cause of a wide range of infections in humans and animals. In Old and New World monkeys, infection with *K. pneumoniae* causes pneumonia, meningitis, peritonitis, cystitis, and septicemia.[8] *K. pneumoniae* also constitutes normal fecal and oral flora in many nonhuman primates. In the past 2 decades, a new type of invasive *K. pneumoniae* disease has emerged in humans in Taiwan and other Asian countries, and more recently from non-Asian countries, including the USA.[4] Fatal human infections with invasive strains of *K. pneumoniae* involve pulmonary emboli or abscess, meningitis, endophthalmitis, osteomyelitis, or brain abscess.[4] Recently, a highly invasive *K. pneumoniae* causing primary liver abscesses in humans has also been reported.[5] These invasive, abscess-forming strains of *K. pneumoniae* are associated with the so-called hypermucoviscosity (HMV) phenotype, a bacterial colony trait identified by a positive string test (>5mm string length).[3] These *Klebsiella* spp. generally develop prominent polysaccharide capsules which increase virulence by protecting the bacteria from phagocytosis and preventing destruction by bactericidal serum factors.

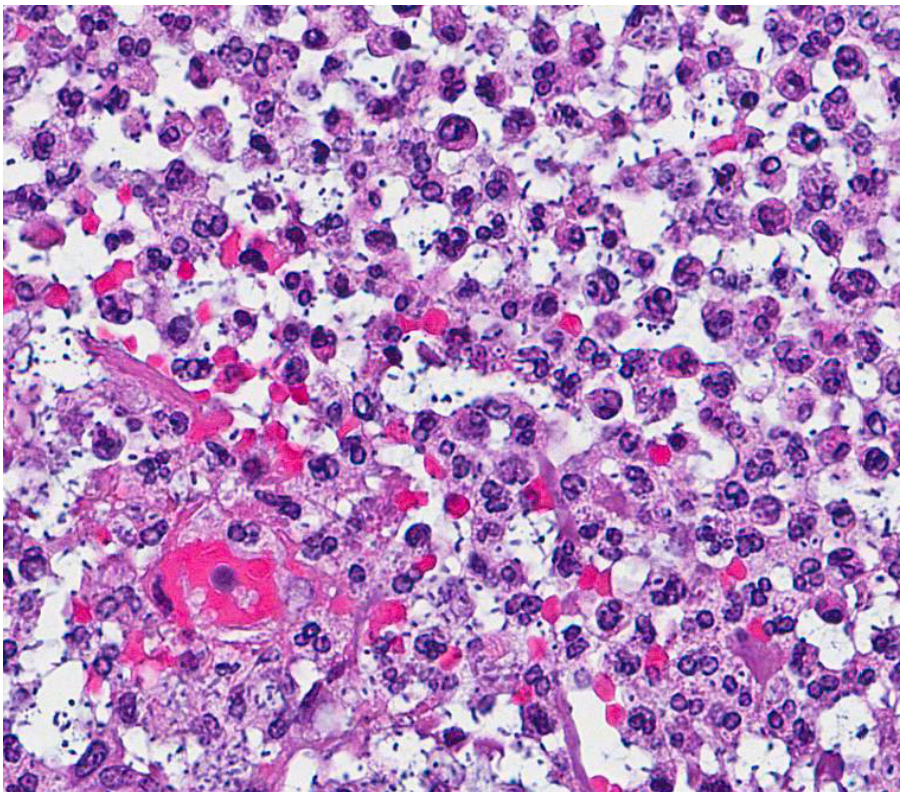
The HMV phenotype is seen in *K. pneumoniae* expressing either the capsular serotypes K1 or K2. K1 serotypes of *K. pneumoniae* have 2 potentially important genes, rmpA, a transcriptional activator of colanic acid biosynthesis, and magA, which encodes a 43-kD outer membrane protein. K2 serotypes of *K. pneumoniae* also have rmpA but do not have magA. Capsular serotypes K1 and K2 are reported to play an important role in the invasive ability of HMV *K. pneumoniae*. The role of rmpA and magA in the pathogenesis of invasive *K. pneumonia*, however, seems less certain.[11]



2-3. Peritoneal mass, African green monkey. A large adhesion incorporating the jejunum (top), mesentery, and mesenteric lymph node (bottom). There are multiple areas of necrosis and inflammation within the mesentery and lymph node (arrows.) (HE, 4X).

JPC Diagnosis: Intestine, lymph node, mesentery: Enterocolitis, lymphadenitis, peritonitis, pyogranulomatous and necro-, tizing, chronic-active, multifocal, marked with myriad intra and extracellular bacilli.

Conference Comment: Conference participants commented on slide variability with some slides containing a section of large intestine and others having small intestine. This is consistent with the excellent gross images provided by the contributor, consisting of overlapping sections of small and large intestine enmeshed within a focally extensive abscess. A gram stain was viewed during the conference, revealing histiocytes with abundant intracellular gram negative rods and a prominent capsule; however, in many cases similar features were readily visible on H&E. Participants discussed other stains which would facilitate visualization of the bacterial capsule, including mucicarmine. There was agreement the appearance of a gram negative bacillus with a large clear capsule is distinctive for *Klebsiella* sp.; however, one differential diagnosis mentioned for this lesion was melioidosis. Melioidosis, caused by the gram negative bacterium *Burkholderia pseudomallei,* afflicts humans and many animal species including non-human primates, resulting in a wide range of disease manifestations. It is uncommon in North America, but has been associated with primates imported from endemic areas. Clinical and pathologic findings are often non-specific, resembling a bacterial septicemia, but abscesses can be seen in multiple tissues.[9]



2-4. Mesentery, African green monkey. Areas of pyogranulomatous inflammation contain large numbers of bacilli which are surrounded by a thick capsule. Bacilli have been phagocytized by both neutrophils and macrophages. (HE, 400X).

Two conference participants (co-authors on the Twenhafel et al. manuscript) referenced below, discussed in detail the events surrounding the cases described in that publication. At the time of that report, African green monkeys presenting initially with extensive mid-abdominal abscessation (and less commonly in other body systems), caused by hypermuco-viscosity *K. pneumoniae* was a novel finding.[10] Since, work has been done to characterize the hypermucoviscosity variant of *K. pneumoniae* as discussed in the contributor's comment. The source of infection remains unclear and requires further epidemiologic studies. However, in at least one report in co-housed infected rhesus and cynomolgus macaques, transmission was thought to be fecal-oral and not from environmental contamination.[1] Like the source, the pathogenesis is still debatable particularly in light of extensive abscess formation in the mid-abdominal cavity in many cases. Participants dis-

cussed possible pathways to include septicemia or other methods of bacterial translocation from the intestine lumen. Regardless, the hypermucoid variant of *K. pneumoniae* is better able to resist innate immune defenses, including oxidative killing, and is more cytotoxic to blood monocytes in African green monkeys, compared to the non-hypermucoid variant, likely playing an important role in the pathogenesis.[2]

Conference participants also discussed infections caused by non-hypermucoviscosity *K. pneumoniae* in different animal species to include: Neonatal septicemia and pneumonia in foals and, abortion and stillbirth in mares;[6] mastitis in cattle; urinary tract infections in dogs; bronchopneumonia and polyserositis in guinea pigs; enterotyphlitis in rabbits; bacteremia, liver and kidney abscesses, pneumonia and myocarditis in mice; and abscesses in multiple locations in rats.[7]

Contributing Institution:
Laboratory of comparative pathology, Memorial Sloan-Kettering cancer center
https://www.mskcc.org/research-areas/programs-centers/comparative-medicine-pathology

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CASE III: 14-144 (JPC 4065942)

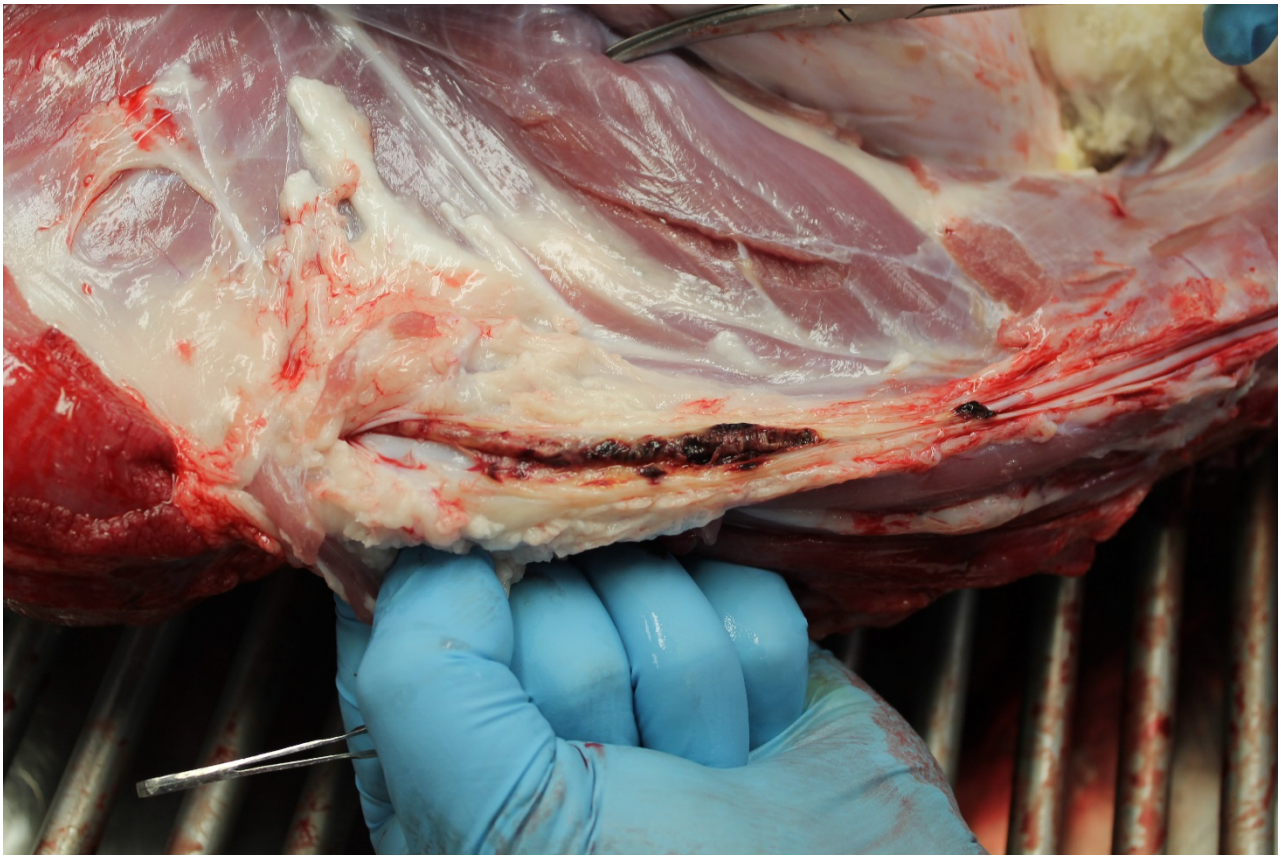
Signalment: 4 month old Dorset cross ewe (O*vis aries)*

History: As part of an IACUC-approved experimental protocol, this lamb had a long term IV catheter in the right jugular vein. Catheter care included frequent bandage changes and cleaning of the catheter site with a chlorhexidine based solution. The catheter was replaced several times during the study, with aerobic bacterial cultures of the catheter tip when removed.

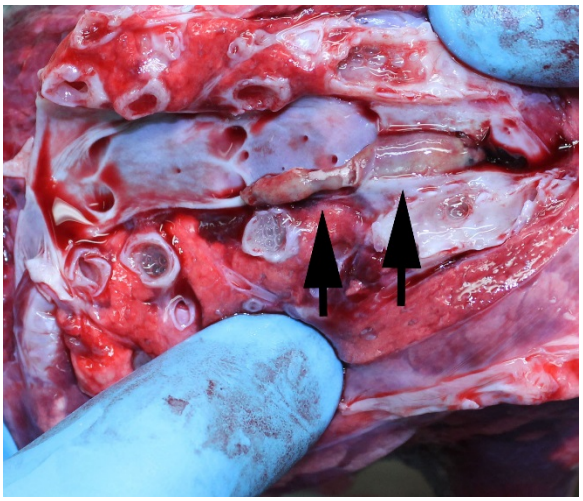
Gross Pathology: At necropsy, the right jugular catheter was encased in a thick coat of fibrin with enmeshed erythrocytes, which merged into the jugular wall (thrombophlebitis, figure 3-1). In the right caudal lung lobe, an adherent fusiform shiny tan thromboembolus, approximately 4 x 4 x 30 mm, largely occluded the lumen of the large pulmonary artery (figure 3-2).

Laboratory Results: There were multiple negative blood cultures and catheter cultures during the study (duration approximately 90 days). Two weeks prior to necropsy, the removed catheter grew a heavy pure culture of *Pseudomonas aeruginosa.* Additional cultures of blood surfaces at necropsy were positive for heavy pure growth of *P. aeruginosa.*

Histopathologic Description: Submitted tissue is right jugular vein (cross-section, opened longitudinally) and adjacent soft tissues. Adherent to the intima are two large nodular organizing septic thrombi, one with a central ovoid defect (catheter sheath). The two thrombi occlude >50% of the lumen. The thrombi contain large numbers of predominantly degenerate neutrophils and



3-1. Right jugular vein, sheep. The right jugular vein contains an indwelling cathether encase in a thick coat of fibrin. (Photo courtesy of: Department of Comparative Medicine, Penn State College of Medicine, Penn State Hershey Medical Center, http://www.hmc.psu.edu/comparativemedicine/)

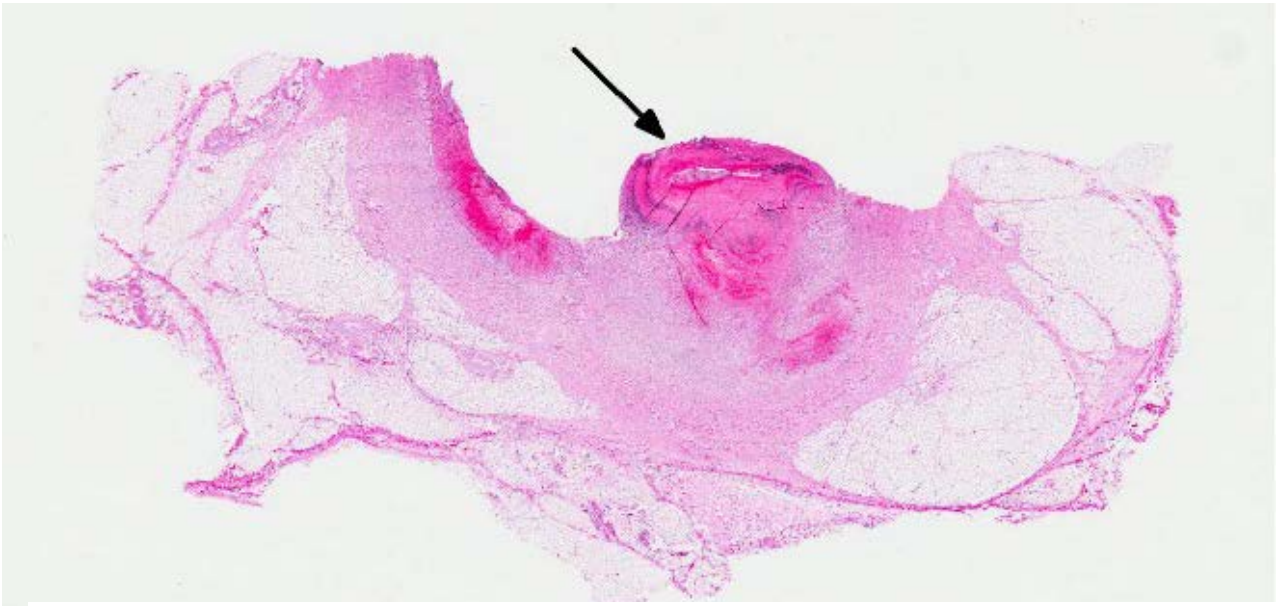


3-2. Lung, sheep. A large thrombus (arrow), occludes the pulmonary artery within the right caudal lung lobe. (Photo courtesy of: Department of Comparative Medicine, Penn State College of Medicine, Penn State Hershey Medical Center, http://www.hmc.psu.edu/comparativemedicine/)

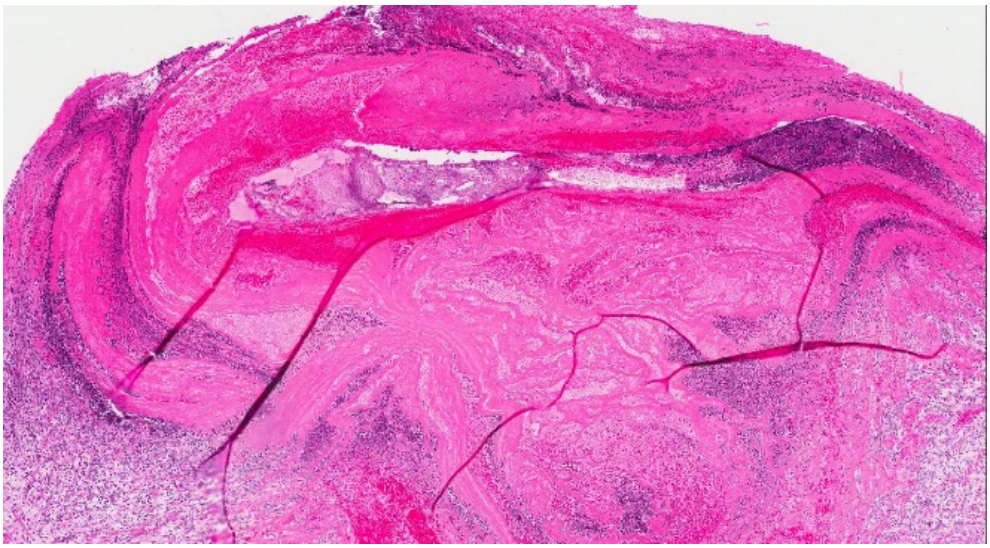
karyorrhectic debris as well as bacterial rods, often forming discrete lamellations separated by fibrin with abundant enmeshed erythrocytes. A Brown and Hopps tissue Gram stain identifies the rods as gram-negative, and they are often present in very large numbers. At the peripheral margins of both thrombi there is ingrowth of plump fibroblasts with scant immature collagenous matrix as well as new small caliber blood vessels lined by plump endothelium (angiogenesis). There is partial and incomplete re-endothelialization of both thrombi. The venous wall is largely effaced by fibroplasia, with extension into adjacent adnexa. In some sections there is focally extensive recent hemorrhage in the venous media. Histology of the pulmonary artery thromboembolus (not submitted) was similar, including central canal.

Contributor's Morphologic Diagnosis: Jugular vein: Thrombophlebitis, chronic-active, focally extensive, severe with Gram negative rods.

Contributor's Comment: Inflammation or infection of the venous wall (phlebitis) is frequently complicated by thrombosis. Thrombosis results from antemortem intravascular coagulation, and must be differentiated from post-mortem clotting.[2,5] Predisposing factors are described by the classic Virchow's triad of endothelial damage, turbulence or stasis of flow, and hypercoagulability. In this case, the presence of the catheter may potentially cause endothelial damage by direct physical injury, as well as turbulence by interrupting laminar flow. Both inflammation as well as endotoxin from gram-negative bacteria may



3-3 Right jugular vein, sheep. A large lamellated thrombus (arrow) is attached to the wall of the markedly thickened vein. (HE, 6X)



3-4. Right jugular vein, sheep. Higher magnification of the attached thrombus, showing lines of Zahn, as well as the central empty space where the catheter was located. There is extensive fibrin attaching this thrombus to the underlying wall of the vessel, and the endothelial lining is diffusely lost. (HE, 28X)

activate the coagulation cascade. Resolution of thromboemboli can occur by thrombolysis, organization (fibrosis and contracture) with re-endothelialization, and/or re-canalization.[2]

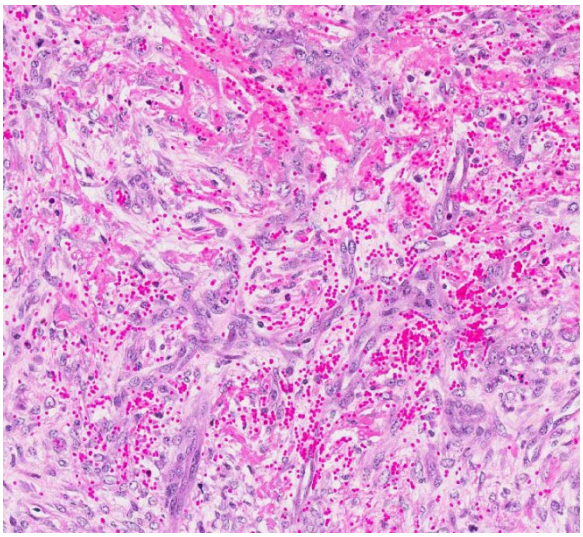
Jugular thrombophlebitis can be a significant problem in ruminants, both related to catheterization as well as perivascular administration of irritating solutions (such as 5% dextrose for ketosis or calcium gluconate for milk fever). Broken off fragments from the jugular site were able to travel to the right heart before lodging in a pulmonary artery (thromboembolism). The distinction between bland and septic thromboemboli can be of critical importance, as the latter may give rise to additional foci of infection, including embolic pneumonia or nephritis.

The inherent resistance of *Pseudomonas aeruginosa* to chlorhexidine-based disinfectants is well-documented.[3,4] *Pseudomonas aeruginosa* is a normal inhabitant of water systems, and is therefore nearly ubiquitous in distribution. The organism is a significant cause of hospital acquired infections, often with a poor prognosis related both to the resistance of the organism to treatment as well as co-morbidities in the patients. *Pseudomonas aeruginosa* colonization of medical devices is facilitated by pili and fimbriae as well as biofilm formation, the latter making antibiotic treatment unrewarding.[1] Single blood cultures are frequently negative in cases of bacteremia, and frequent repeated large volume blood cultures have the best success.

JPC Diagnosis: Jugular vein: Thrombophlebitis, fibrinosuppurative, chronic-active, focally extensive, with marked mural granulation tissue.

Conference Comment: Conference participants were impressed by the level of detail within the organizing thrombus, including the presence of lines of Zahn. These are more characteristically present in arterial thrombi and refer to the laminated appearance of the thrombus due to alternating layers of platelets and fibrin with enmeshed erythrocytes and leukocytes.[2] Most participants misinterpreted the vessel as an artery due to the thickness of the wall. Although they did not see an internal elastic lamina to confirm the vessel as an artery, most believed the vessel wall was too expanded by mural granulation tissue to allow its visualization. Participants described the clear area within the center of the larger thrombus but did not readily associate it with a catheter, and most agreed that while they considered the possibility of bacteria within the lesion, the abundant karyorrhectic debris made identification of microorganisms exceedingly difficult.

Hemostasis was reviewed in detail during the conference including a discussion of initiating events. While turbulent blood flow, a component of Virchow's triad, is clearly present with the placement of an intraluminal catheter, endothelial injury is also a very important factor in the formation of a thrombus. Endothelial injury results in the exposure of tissue factor, and other subendothelial components such as collagen, resulting in platelet aggregation and the initiation of coagulation. The release of tissue factor, located within the plasma membrane of activated endothelium, results in the initiation of the extrinsic coagulation



3-5. Right jugular vein, sheep. The wall of the jugular vein is diffusely thickened by granulation tissue. (HE, 240X)

pathway; the intrinsic pathway is initiated by collagen and other subendothelial components coming into contact with prekallikrein, high molecular weight kininogen and factors XII and XI (contact group of coagulation factors). [2] When tissue factor comes into contact with factor VII, it forms a complex which along with calcium, activates factor X to initiate the common pathway. While conceptually it is easier to learn and discuss the coagulation cascade as two separate pathways which combine to form the common pathway, the in vivo process is more commonly considered a single intertwined set of events that begins with the exposure of tissue factor. [2]

Participants reviewed the basic steps in the hemostatic process starting with vasoconstriction and formation of a platelet plug, followed by coagulation and formation of a fibrin meshwork, followed by fibrinolysis and finally tissue repair, and the role of platelets in this process was discussed. Platelets adhere to exposed subendothelial collagen and von Willebrands factor is released by local activated endothelium, which provides a more secure connection between the collagen and platelets via platelet receptor GPIb. Platelets then release the contents of their α-granules and produce other mediators which continue to promote hemostasis. The release of adenosine diphosphate (ADP) results in the binding of fibrinogen to platelet receptor GPIIb-IIIa, and the fibrinogen forms a scaffold as the platelets aggregate, eventually covering the defect. Factors released from the aggregated platelets, such as platelet derived growth factor, stimulate fibroblast recruitment which can eventually result in fibrosis at the thrombus location, as occurred in this case. [2]

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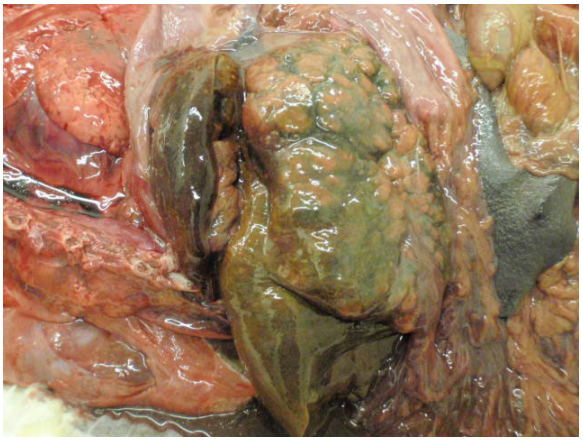
CASE IV: D12-33071 (JPC 4049056)

Signalment: 4 year-old, spayed female, Labrador retriever dog (*Canis lupis familiaris)*



4-1. Liver, dog. The liver was 2-3 times normal size and contained numerous cysts ranging up to 15cm within the hepatic parenchyma. (Photo courtesy of: Prairie Diagnostic Services (PDS) and Department of Veterinary Pathology, Western College of Veterinary M Medicine, 52 Campus Drive, University of Saskatchewan, Saskatoon, Saskatchewan,S7N,5B4,CAN www.usask.ca/wcvm/vetpath)

History: The dog presented to its primary care veterinarian for a two-month history of gradual, progressive weight loss and inappetence. In the two weeks prior to presentation, the owner had noted marked abdominal distention. On physical examination by the primary care veterinarian, the dog was reasonably bright but very thin, with severe muscle wasting. The abdomen was markedly distended and a fluid wave could be ballotted. In-house routine bloodwork revealed a mild anemia and hypoalbuminemia. Abdominal ultrasonography revealed an intra-abdominal mass of mixed echogenicity that appeared to occupy several areas within the liver. Ultrasound-guided fine needle aspiration (FNA) cytology of the suspect hepatic lesion was attempted twice and yielded only necrotic debris. The primary care veterinarian was highly suspicious of a hepatic malignancy and referred the dog to a veterinary specialty center for further evaluation and probable exploratory laparotomy.

At the referral center, the dog was again noted to be thin (BCS 2/9) with severe muscle wasting. The abdomen was markedly distended by free fluid and there was a palpable fluid wave. The degree of abdominal distension hampered abdominal palpation for organomegaly. Three-view thoracic radiographs revealed mild lymphadenomegaly of the sternal lymph nodes. Presurgical routine blood work was performed (see results under 'Laboratory Results'). A coagulation profile was unremarkable.

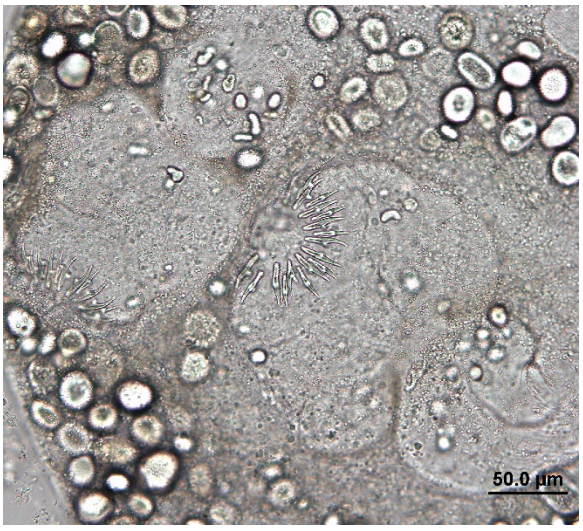
An exploratory laparotomy was performed through a ventral midline incision and 3.5 liters of a red-tinged abdominal fluid was removed. The liver was two to three times the normal size; firm to friable; and mottled red-brown and

4-2 Liver, dog. Fluid aspirated from the hepatic cysts. (Photo courtesy of: Prairie Diagnostic Services (PDS) and Department of Veterinary Pathology, Western College of Veterinary Medicine, 52 Campus Drive, University of Saskatchewan, Saskatoon, Saskatchewan,S7N,5B4,CAN www.usask.ca/wcvm/vetpath)

tan. Multiple, variably sized, often raised nodules were present on the hepatic surface and extended into the hepatic parenchyma. The largest nodule was approximately 15.0 cm in diameter and involved almost the entirety of the right lateral liver lobe. A partial lobectomy was performed on the left lateral liver lobe. Not all of the abnormal hepatic tissue could be removed. Multiple, small, white nodules were present in the omentum, and the wall of proximal duodenum was thickened. A hepatic biopsy; the excised portion of the left lateral liver lobe; a section of omentum; and a full-thickness duodenal biopsy were submitted for histopathologic examination.

The dog recovered uneventfully from surgery and was discharged four days after the surgery to the primary care veterinarian for continued supportive therapy and monitoring.

Following the histopathologic diagnosis of alveolar echinococcosis, a fecal sample from the patient was submitted for fecal flotation examination. Parasite eggs were not identified.



4-3 Liver, dog. A wet mount prep of material aspirated from the cysts revealed protoscolices with an armed rostellum as well as aggregates of mineralized material (calciferous bodies) (400X)

The dog received a single treatment of albendazole after it returned to the primary care veterinarian. Unfortunately the dog's condition continued to decline and it died nine days after it was discharged. The owners gave their consent for a full postmortem examination.

Strict safety precautions were observed during the whole necropsy procedure. On gross examination, the body condition of the dog was poor with marked generalized muscle wasting; accentuation of all boney prominences (i.e. zygomatic arch, spine of scapula, ribs, tuber coxae); and depletion of subcutaneous and visceral adipose stores.

Gross Pathology: The gastrointestinal tract was removed after gross external examination and was frozen at -70° for three weeks to inactivate *Echinococcus* spp. eggs. It was thawed, dissected and the intestinal contents were examined for *Echinococcus* spp. Adult cestodes were not seen.

There was approximately one litre of serosanguinous fluid in the abdomen and small amounts of fibrin on the serosal surface of the intestines. Approximately 75% of the liver was replaced by multifocal to coalescing, variably raised, firm, yellow to brown masses that on cut section effaced the parenchyma, were occasionally cystic, and exuded moderate amounts pale yellow viscous fluid with white sand-like material (interpreted to be 'hydatid sand'; see mages 4-1 and 4-2). The hepatic lymph nodes, pancreas, and the adjacent mesentery contained numerous, small (approximately 4-mm in diameter) translucent cysts. The sternal, tracheobronchial, hepatic and mesenteric lymph nodes were moderately enlarged and dark black in color

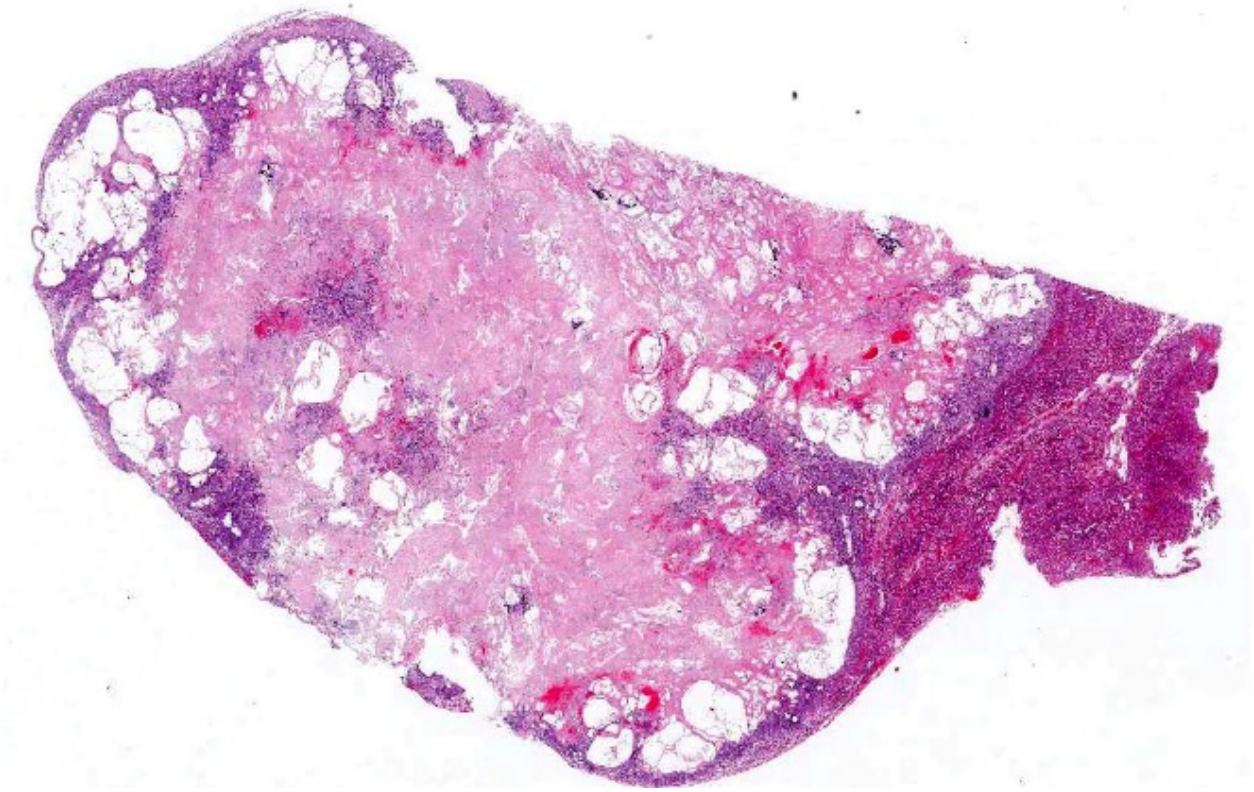
Laboratory Results: A wet mount preparation of the viscous fluid from one of the cysts was examined microscopically and revealed metacestode larva and aggregates of mineralized material (calciferous bodies).

The cyst contents and abdominal fluid were submitted for PCR. Based on the band size, PCR for both of these samples was considered positive for *Echinococcus multilocularis.* PCR amplification and sequencing was performed on liver tissue using in-house primers developed by Dr. Karen Gesy for the *cob*, *cox1* and *nad2* mitochondrial genes; the alveolar hydatid cyst of *Echinococcus multilocularis* found in this dog grouped with European-type strains of the cestode.

Histopathologic Description:

Liver: Effacing and replacing approximately 70-90% of the examined sections were optically vacant areas with multiple hydatid cysts that were lined by a thin bladder wall and contained numerous calciferous bodies and metacestode protoscoleces that had a parenchymatous body, calcareous corpuscles, and rostellar hooks which were variably surrounded by large numbers of epithelioid macrophages, foreign body and Langhans-type giant cells, neutrophils, hemorrhage, necrotic hepatocytes, and extensive areas of fibrosis. Multifocally, large numbers of degenerate neutrophils and necrotic cellular debris surrounded the hydatid cysts and occasional cysts were mineralized. In the surrounding parenchyma, hepatocytes frequently contained granular and globular intracytoplasmic, gold-brown material (interpreted to be hemosiderin and/or bile, respectively), clear vacuoles (vacuolar degeneration) and were separated and individualized by bands of fibrous connective tissue (fibrosis) and foamy and streaming eosinophilic material admixed with postmortem bacteria (autolysis artifact).

Lymph node (hepatic): Approximately 50-70% of the cortex and medulla in the examined sections were replaced and distorted by large optically vacant areas with small numbers of hydatid cysts containing metacestode protoscoleces and were surrounded by fibroblasts and collagen. There were marked numbers of hemosiderophages



4-4. Liver, dog. Approximately 80% of the section is replaced by a degenerate multilocular cyst characteristic of Echinococcus multilocularis. (HE, 4X)

in the subcapsular sinus and throughout the trabecular and medullary sinuses.

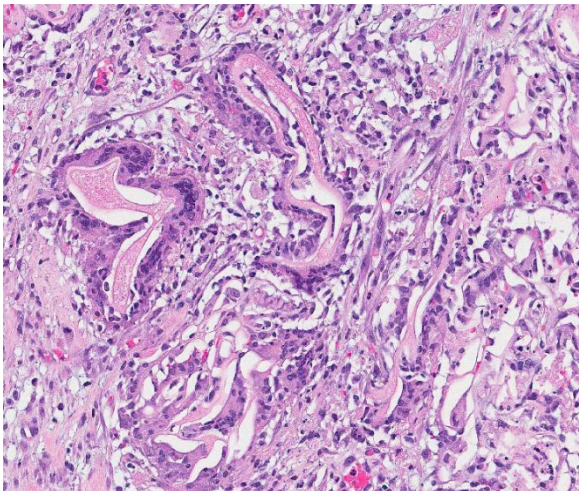
Mesentery: Multifocally, there were small numbers of collapsed hydatid cysts associated with extensive areas that were infiltrated by large numbers of fibroblasts, macrophages, giant cells, neutrophils, and fewer lymphocytes and plasma cells.

Pancreas: There were large optically vacant spaces and small numbers of protoscoleces were seen in these spaces.

Contributor's Morphologic Diagnosis: Left lateral liver lobe and liver biopsy: Multiple, intrahepatic, multilocular cysts with rare metacestode larva of *Echinococcus* spp. and accompanying macrophagic to mixed inflammation, necrosis and fibrosis.

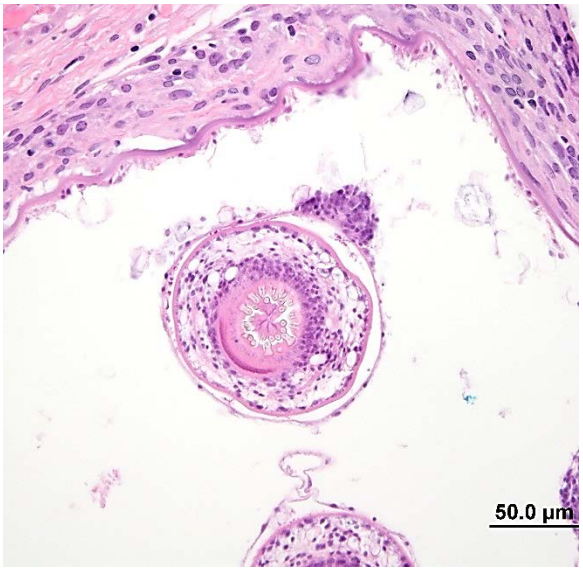
Contributor's Comment: *Echinococcus multilocularis* is a zoonotic tapeworm and the cause of alveolar hydatid disease (aka: Alveolar echinococcosis) in people, dogs and other abnormal hosts; includes domestic and wild pigs, horses, and monkeys.[5,7] *E. multilocularis* is found in Canada, the United States and Europe.[5,7] The worldwide importance of the parasite has increased due to global travel and trade as well as changes in climate, landscape and wildlife-human interactions.[5]

The life cycle of *E. multilocularis* involves wild canids and rodents.[7] The adult tapeworms live in the intestines of a carnivore (primarily foxes and to a lesser extent coyotes, wolves and wild felids) and produce eggs that are shed in the feces. Eggs passed in the feces of the definitive host are immediately infective for the intermediate hosts. Rodents (typically voles, lemmings and deer mice), the intermediate hosts, ingest the eggs which develop into a multilobed larval form (metacestode stage; hydatid cyst) in the liver and abdomen. The metacestode stage consists of aggregations of small vesicles (cysts) in which protoscoleces are produced by the germinal layer in natural intermediate hosts. The cyst aggregates form alveolar structures composed of numerous cysts of irregular shapes with dimensions between less than 1 and 10mm (in some hosts up to 20–30 mm). The cysts contain a highly variable number of protoscoleces or they may be sterile (no protoscolex formation) and partially calcified. Progressive budding and expansion of the cyst causes severe tissue damage and may result in the spread of metacestodes to other tissues, as present in this case, where the metacestode stage was found in the local lymph nodes, pancreas, and mesentery. The life cycle is completed when a carnivore ingests a rodent infected with the cyst stage of the parasite. Dogs, and less commonly cats, can be definitive hosts (i.e. adult tapeworm develops in the small intestine) when they ingest an infected rodent. Rarely, as in this case, the dog can act as an intermediate host (develop the metacestode larval stage) likely by ingesting eggs shed in the feces of wild carnivores, pets or even their own feces. People become infected with the larval stage when they ingest eggs in the soil; food or water contaminated with feces of wild carnivores or pets; or less commonly, through close association with infected animals.



4-5. Liver, dog. The hyaline wall of collapsed cysts are surrounded by multinucleated foreign body macrophages as well as numerous epithelioid macrophages. (HE, 196X)

Until 2009, *E. multilocularis* was considered to be endemic in wildlife in only two regions of Canada: the northern tundra zone of the Canadian territories and the southern Prairie Provinces, Manitoba, Saskatchewan and Alberta.[3,8,9] Cases involving domestic dogs had not been reported in Canada. In 2009, hepatic alveolar hydatid disease (HAD) was diagnosed in a 3-year-old dog that had lived only in the British Columbia.[8,9] In 2012, a second case of HAD was diagnosed in a 2-year-old dog that had resided in only two parts of southern Ontario.[2] This dog is the third case to be reported in a domestic dog in Canada. The dog was acquired from a breeder in north-eastern Alberta and lived most of its life in southern Alberta. The dog had brief visits to British Columbia (Vancouver Island) and Manitoba. At the time of its death the dog had been residing in southern Manitoba for a couple of months. While in southern Alberta the dog had plenty of opportunity to come in contact with the feces of wild carnivores. It is likely the dog acquired the infection while residing in southern Alberta.



4-6. Liver, dog. Rare viable cysts are lined by a 3-4um hyaline wall, germinal epithelium, and protoscolices containing an armed rostellum. (Photo courtesy of: Prairie Diagnostic Services (PDS) Department of Veterinary Pathology, Western College of Veterinary Medicine, 52 Campus Drive, University of Saskatchewan, Saskatoon, Saskatchewan, S7N 5B4, Canada www.usask.ca/wcvm/vetpath) (HE, 200X)

Genetic analysis of tissue from the dogs in British Columbia and Alberta grouped with strains of *E. multilocularis* from west-Central Europe. The origin of the European-type strains of *E. multilocularis* in these Canada dogs is unclear but appears to be associated either with the importation of domestic dogs into Canada from Europe, since cestode treatment at the time of importation is not required or the historic importation of red foxes into North America from Europe for hunting and the fur trade.[8]

In Canada, human cases of alveolar hydatid disease are rare with a single case being reported in Manitoba in the 1930`s. There is currently no evidence to suggest cases of alveolar hydatid disease are occurring in people in Canada. However, cases of alveolar hydatid disease in domestic dogs are not only of clinical interest, but also of epidemiological importance as they are indicators of environmental contamination with *E. multilocularis* eggs and likely represent the main infection route for humans in North America.[5, 7, 6]

The antemortem diagnosis of alveolar hydatid disease in dogs is difficult. Spontaneously excreted proglottids are very small and are only occasionally detected on the surface of fecal samples by the animal owner or at laboratory examination. By flotation techniques taeniid eggs may be detected in fecal samples, but morphological differentiation of the eggs of *E. multilocularis, E. granulosus* and the *Taenia* species inhabiting the intestine of domestic dogs and cats is not possible.[7] In routine practice, abdominal masses of unclear origin in dogs and other animals can be assessed by fine needle aspiration cytology for tumour identification or exclusion. In this case, ultrasound-guided fine needle aspiration cytology did not confirm a metacestode infection. Molecular diagnostics performed on fresh and formalin-fixed tissues, abdominal fluid and fluid samples from the

hepatic cysts did help to establish the diagnosis in this case and may be useful in establishing the antemortem diagnosis.

The post mortem diagnosis of alveolar hydatid disease in aberrant hosts is based on pathognomonic macroscopic and histopathologic findings, and in doubtful cases, on results of immunological and molecular tests. Although alveolar hydatid disease of the liver is rare in dogs, it should be considered as a possible differential diagnosis in cases of space-occupying lesions in the liver, even in a young dog.

JPC Diagnosis: Liver: Multilocular hydatid cysts, with granulomatous hepatitis and hepatocellular atrophy, Labrador retriever dog, canine.

Conference Comment: Conference participants mentioned the variability between slides, with only a few sections containing cysts with protoscolices. Most of the slides did have aggregates of germinal epithelium along the inner margin of the cyst wall, and there was speculation these structures represented parts of developing capsules which would contain protoscolices. Others considered the possibility that the cysts were sterile due to the dog being a non-traditional intermediate host for this cestode.

The differential diagnosis discussed by participants included cysticercosis, denoting the larval form of many *Taenia* genera cestodes, although most agreed the multiloculated nature of the cysts and the appearance of the laminated cyst wall was fairly distinctive for hydatid cysts despite the absence of protoscolices. Cysticerci (second stage taeniid larva) have a thick fluid filled bladder (hence the name "bladderworm"), one or more scolices which are usually inverted, and are often surrounded by a fibrous capsule formed by the intermediate host. The structure has a series of hooks and suckers that allow it to attach to host tissue.[1] See the table below for a list of taeniid tapeworms with larval stages commonly found in mammalian intermediate hosts.

Echinococcus granulosus typically parasitizes wild canids as the definitive host, but the intermediate host is usually a large domestic species, such as cattle, sheep and horses among others. Wild canids pass the proglottids in areas where these animals graze, and upon ingestion the embryos develop into hydatid cysts. The cysts are most commonly found in the liver and lungs, although other organs can be infected; they may never result in clinical disease, but can result in carcass condemnation at time of slaughter.[4] In contrast to *E. multilocularis*, hydatids of *E. granulosus* are unilocular in nature and do not infiltrate but rather expand and compress adjacent tissue as space occupying structures, and may rupture or leak fluid, causing a hypersensitivity reaction.[1] Hydatid sand refers to the cyst fluid containing free protoscolices from ruptured brood capsules, of which the contributor provides an excellent image.

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Cestodes of veterinary importance with gross and/or histologically identifiable larval stages (not comprehensive)				
ADULT CESTODE	**DEFINITIVE HOST**	**LARVAL STAGE**	**INTERMEDIATE HOST (IH)**	**COMMON SITE for IH**
Taenia saginata	humans	***Cysticercus bovis***	cattle	muscle
Taenia solium	humans	***Cysticercus cellulosae***	pig	muscle
Taenia*(*Multiceps*) *multiceps	canids	***Coenurus cerebralis***	sheep, cattle	CNS
Taenia hydatigena	canids	***Cysticercus tenuicollis***	sheep, cattle, pig	peritoneum
Taenia ovis	canids	***Cysticercus ovis***	sheep	muscle
Taenia pisiformis	canids	***Cysticercus pisiformis***	rabbit	peritoneum, liver
Taenia serialis	canids	***Coenurus serialis***	rabbit	Subcutis, connective tissue
Taenia taeniaeformis	cats	***Cysticercus fasciolaris*** **(strobilocercus)**	rodents	liver
Taenia krabbei	canids	***Cysticercus tarandi***	Reindeer, wild ruminants	muscle
Echinococcus granulosus	domestic and wild canids	***Unilocular hydatid cyst***	sheep, cattle, swine, horses	Liver, lung
Echinococcus multilocularis	domestic and wild canids	***Multilocular hydatid cyst***	Mice and rats	liver

Self-Assessment - WSC 2015-2016 Conference 1

1. Which of the following is a common site for development of intestinal adenocarcinoma in macaques?
    a. Gastrointestinal junction
    b. Papilla of Vater
    c. Ileocecal junction
    d. Appendix

2. Which of the following laboratory tests help to identify the hypermucoviscosity phenotype of *Klebsiella pneumonia*?
    a. Satellite phenomenon
    b. String test
    c. Mannitol fermentation
    d. Methylamine uptake

3. Which of the following has not been identified as a potential cause of jugular thrombosis in ruminants?
    a. Embolization of bacterial from rumenal abscesses
    b. Perivascular administration of 5% dextrose
    c. Jugular catheterization
    d. Perivascular administration of calcium gluconate

4. Which of the following is the definitive host for the cestode *Echinococcus multilocularis?*
    a. Ruminant
    b. Wild canid
    c. Rodent
    d. Human

5. Which of the following is most useful for the antemortem diagnosis of alveolar hydatid disease in dogs?
    a. Identification of characteristic eggs on fecal floatation
    b. Fine needle aspiration of abdominal masses
    c. Examination of excrete proglottids in the feces
    d. Molecular diagnostics on fresh and formalin fixed samples from hepatic cysts