Joint Pathology Center
Veterinary Pathology Services

WEDNESDAY SLIDE CONFERENCE 2025-2026

Conference #14 07 January 2026

CASE I:

Signalment:
9-year-old American Quarter Horse gelding (*Equus caballus*)

History:
This horse was acutely recumbent and depressed with severe colic, muscle fasciculations, and hyperhidrosis. A second horse from the same group had similar, more mild clinical signs, including depression and patchy sweating. A mule from the same pasture was found dead.

Gross Pathology:
Crown-rump length was 48.5 cm. No obvious gross abnormalities were seen within the examined organs.

Figure 1-1. Liver, horse: Stomach contents from the affected individual. (Photo courtesy of: University of Wyoming, Wyoming State Veterinary Laboratory).

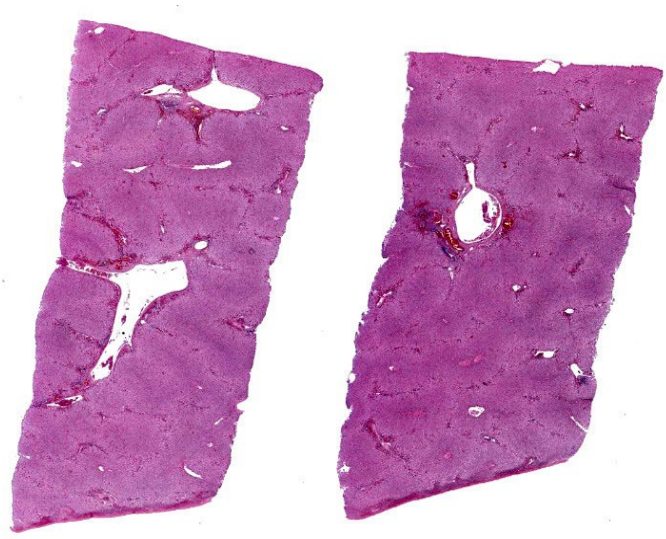

Figure 1-2. Liver, horse: Two sections of liver are submitted for examination. (HE, 10X).

Laboratory Results:
Phosphine gas was detected in the gastric contents of this horse and 3 of the 7 other horses in the same group.

Microscopic Description:
Liver: Diffusely, hepatocytes are moderately swollen and contain numerous small (~1µm) discrete to coalescing cytoplasmic vacuoles (microvesicular hepatopathy). Nuclei remain centrally located. Within the centrilobular interstitium, hepatocytes are occasionally individualized, rounded, shrunken, and/or hypereosinophilic with karyolysis (necrosis). There is mild, patchy periportal hemorrhage.

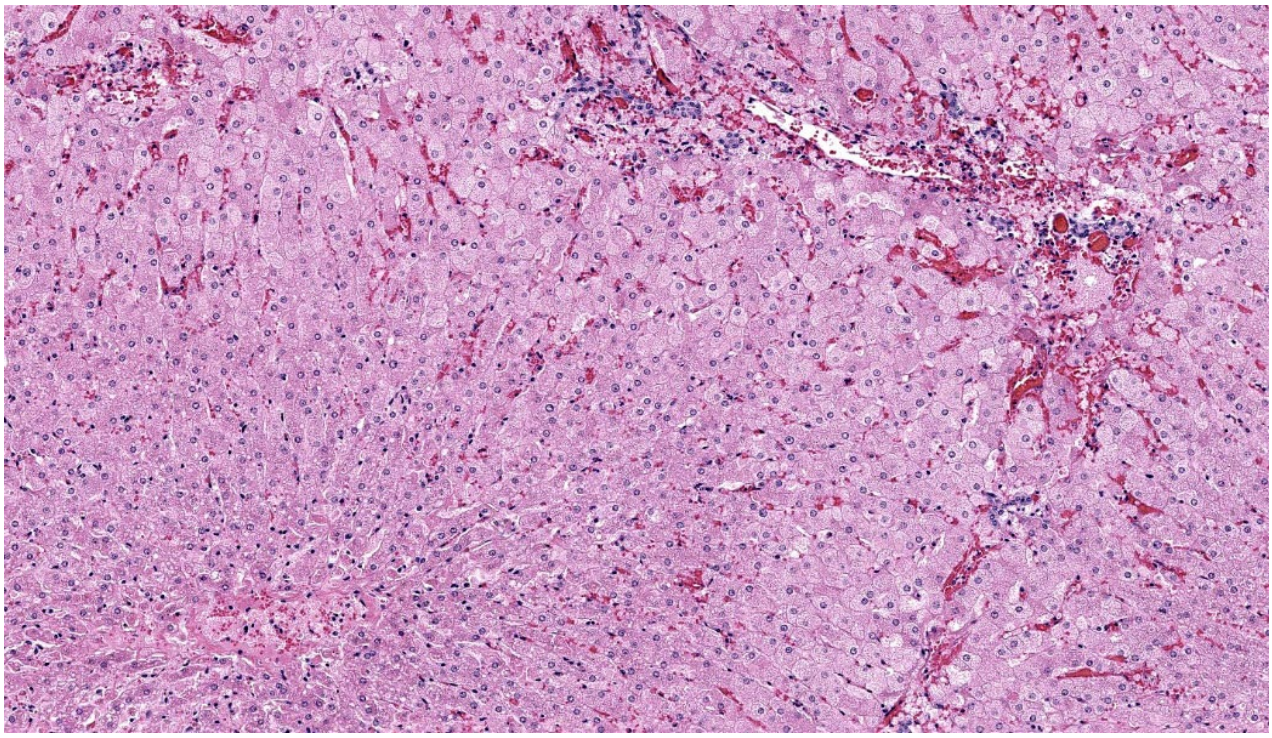

Figure 1-3. Liver, horse: Hepatocytes are diffusely swollen (and compress sinusoids) in all regions of the hepatic lobule by an accumulation of discrete lipid vacuoles. There is multifocal periportal hemorrhage. There is multifocal necrosis and loss of centrilobular hepatocytes. (HE, 195X)

Special stains:

- Osmium tetroxide post-fixation revealed prominent staining of microvesicular lesions, confirming the vacuoles as lipid droplets.
- Oil Red O revealed prominent staining of microvesicular lesions, again confirming the vacuoles as lipid droplets.

Contributor's Morphologic Diagnoses:
Liver: Microvesicular hepatopathy, moderate, acute, diffuse, with mild centrilobular hepatocellular necrosis.

Contributor's Comment:
Phosphine toxicosis was suspected based on recent use of grain-based zinc phosphide rodenticide to control a colony of black-tailed prairie dogs on a 200-hectare pasture. This suspicion was confirmed by the presence of phosphine gas in the stomach contents of this horse and 3 additional horses in the same group. Phosphine gas is a toxic metabolite of metallic phosphides, including zinc phosphide rodenticide and aluminum phosphide insecticide. It is readily produced in the acidic environment of the stomach and inhibits cytochrome C oxidase, thereby blocking mitochondrial oxidative phosphorylation and resulting in rapid energy depletion.[1] Metallic phosphides pose a threat to a wide variety of non-target mammalian and avian species, and are particularly dangerous to horses and other equids which cannot vomit.

Documented lesions of phosphine toxicosis are largely nonspecific and include disseminated congestion and hemorrhage, pulmonary edema, inconsistent myocardial, renal, and/or CNS pathology and recently described microvesicular hepatic steatosis.[2,3,4,5] Macrovesicular steatosis is seen in equine cases of

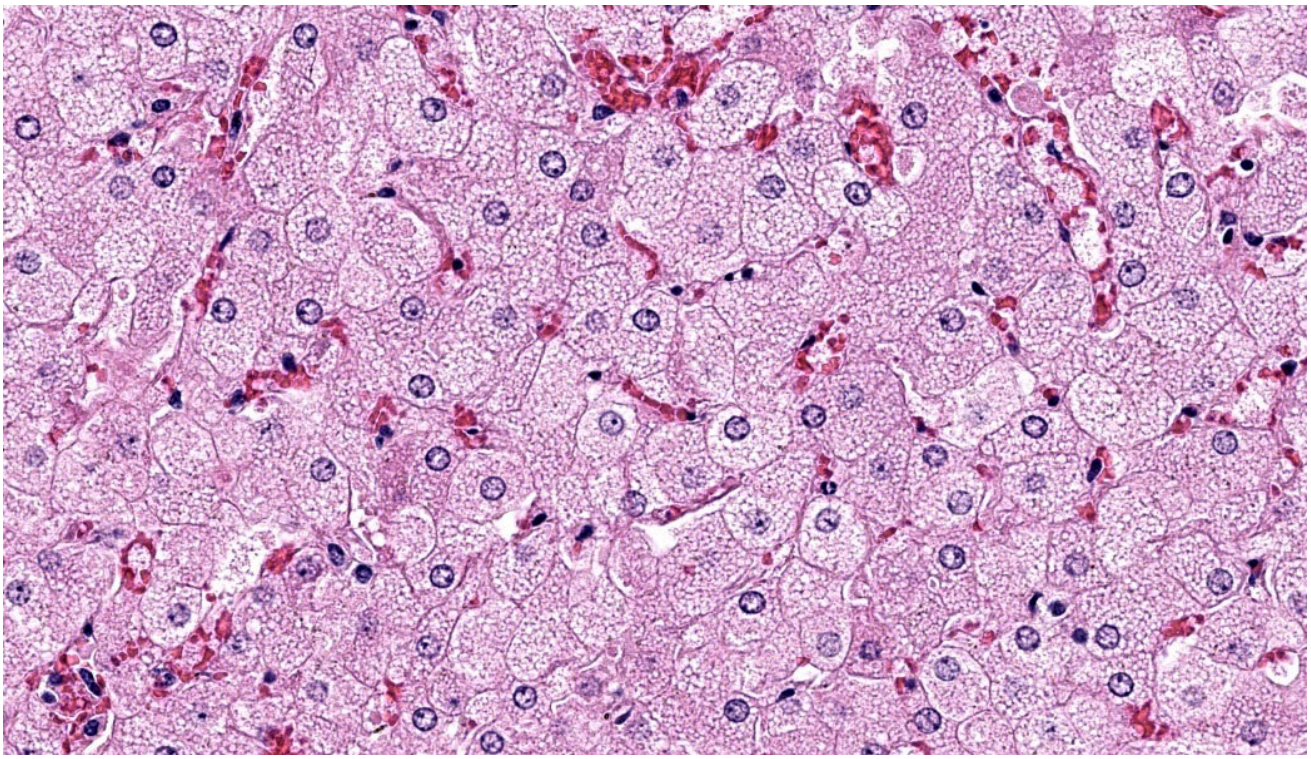

Figure 1-4. Liver, horse: High magnification of affected hepatocytes with numerous lipid vacuoles in their cytoplasm (HE, 705X).

longer duration, along with variable centrilobular hepatocellular necrosis.[3] While macrovesicular hepatic steatosis is a relatively common and nonspecific lesion, microvesicular steatosis has a shorter list of differentials. Defined as multiple lipid vacuoles smaller in size than hepatocyte nuclei[6], microvesicular steatosis is a feature of toxicants that inhibit fatty acid oxidation, including tetracycline, salicylates, hypoglycin A, and valporic acid, in addition to metallic phosphides.[6]

Phosphine gas is toxic to humans and poses a risk to medical professionals treating intoxicated patients.[7] The smell of decaying fish in gastrointestinal contents, either due to phosphine gas itself or contaminants in the pesticide, should raise suspicion on postmortem examination; importantly, pathologists should take care not to inhale the odor in attempt to distinguish the gas. Detection of phosphine gas in gastric contents can be accomplished via reaction with sulfuric acid, which produces a color change that signals a positive result as a rapid, qualitative diagnostic assay.[3] Gas-chromatography-mass spectrometry can be employed for confirmation.[8]

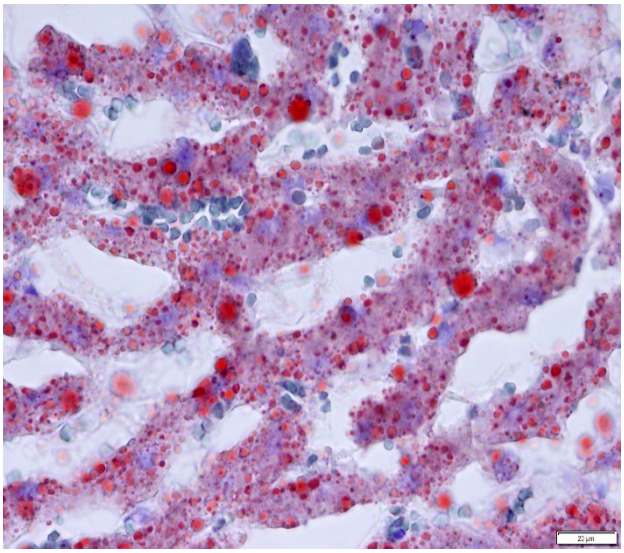

Figure 1-5. Liver, horse: An Oil Red O stain demonstrates lipid within hepatocellular cytoplasm. (Oil Red O, 400X). (Photo courtesy of: University of Wyoming, Wyoming State Veterinary Laboratory).

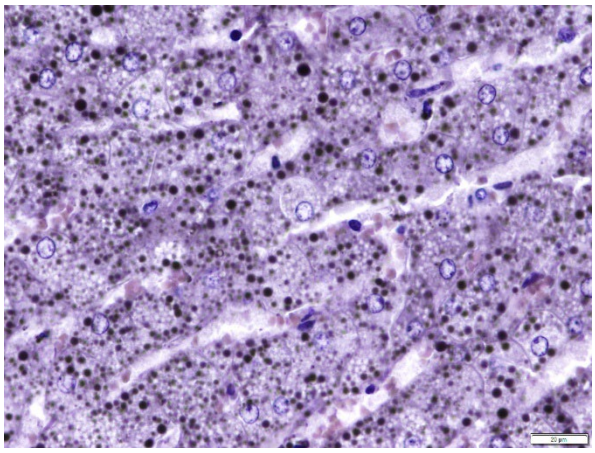

Figure 1-6. Liver, horse: An osmium tetraoxide stain demonstrates lipid within hepatocellular cytoplasm. (Osmium tetraoxide, 400X). (Photo courtesy of: University of Wyoming, Wyoming State Veterinary Laboratory).

Contributing Institution:
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JPC Diagnoses:

Liver: Hepatocellular lipidosis, microvesicular, acute, diffuse, severe.

JPC Comment:
Welcome to the second half of WSC 2025-2026! This fourteenth conference was moderated by one of our treasured regulars: Dr. Julie Engiles from the University of Pennsylvania's New Bolton Center! Although Dr. Engiles specializes in equine orthopedic pathology, the JPC is currently lacking equine bone cases for the WSC (the team is not-secretly hoping for more orthopedic case submissions for next year, hint, hint). As such, she led participants through an excellent equine-focused, "squishy tissue" conference.

Discussion of this first case, never seen before in the WSC, covered the ins and outs of phosphine gas poisoning and other potential differentials for acute hepatotoxins in horses. The pattern of lesion distribution in this case was, unlike most toxins that whack the liver, not focused predominantly on centrilobular hepatocytes. Many hepatotoxins are metabolized to their toxic forms by CP450 in centrilobular regions, hence why those cells end up predominantly affected. Centrilobular hepatocytes are already living on the razor's edge of hypoxia as it is, they don't need much to be pushed over that edge. Few toxins, however, such as phosphorus, microcystin, and phosphine gas, do not need to be metabolized to cause serious damage. Instead, they are so directly toxic that they affect whatever they come across first. In the liver, this is the periportal areas, as those are the sites of first contact in the liver for products from systemic circulation.

Other differentials for acute hepatic necrosis in horses include equine parvovirus (Theiler's disease) and the newly described equine hepacivirus. This flavivrus is closely related to human hepatitis C virus and is currently being looked at as a potential model for Hep C studies.[9]

There are two main forms of phosphides that are globally available and commonly used as pesticides: aluminum phosphide (AlP) and zinc phosphide (ZnP). AlP is generally considered the more volatile of the two. It reacts violently and exothermically with any moisture/acid it comes into contact with to create highly toxic, flammable, and often spontaneously igniting phosphine gas (PH_3).[6] This reaction is what makes it such a potent fumigant, but also makes it extremely hazardous. It is most commonly utilized in pellet form for grain fumigation, stored food protection, and large-scale pest control. Despite its risks, it is still the most widely utilized fumigant for stored grains.[1] Ingestion is the most common method of exposure in humans and animals,

followed by inhalation and absorption, respectively.[6] Most case reports of phosphine poisoning are from India, with many reports also from Iran, Sri Lanka, Morocco, and numerous "developed" countries.[6] As recently as 2022, there was an incident of accidental phosphine gas poisoning in Delhi, where two persons died of phosphine gas exposure after sleeping in a warehouse containing AlP.[12]

ZnP, on the other hand, primarily reacts with acids rather than just any form of moisture like AlP does, enabling its use as a common bait rodenticide. As with any other form of bait rodenticide, it is not uncommon for other animals that are not the intended target to ingest the poison and end up dead. Upon ingestion by an animal, the ZnP reacts with hydrochloric acid in the stomach to produce lethal phosphine gas that is rapidly absorbed through the gastrointestinal tract, leading to systemic toxic effects that can manifest as acute, severe cardiac arrhythmias, shock, acidosis, hepatic lipidosis (as in this case), seizures, and/or pulmonary edema.[1,6]

In addition to directly corrosive actions, phosphine is a potent metabolic poison that functions similarly to cyanide, disrupting cellular energy production by targeting mitochondria and inhibiting cytochrome C oxidase.[1,2,6] The electron transport chain, the major producer of ATP via oxidative phosphorylation and a process in which cytochrome C oxidase is a key player, occurs on the inner mitochondrial membrane. Following their production via the Kreb's cycle, NADH molecules enter the transport chain and donate electrons to NADH dehydrogenase (also known as complex I). From here, the electrons are passed down a series of subsequent complexes like a relay race that ultimately produce a proton gradient across the mitochondrial membrane. Once an electron reaches complex IV (also known as cytochrome C oxidase), it is combined with an oxygen molecule and protons to form water, making oxygen the final electron acceptor and enabling the continued flow of the transport chain. The resultant proton gradient powers ATP synthase which, as protons flow back into the mitochondrial matrix, converts ADP to ATP in large quantities for use in energy-driven cellular functions. Basically, if cytochrome C oxidase is unable to do its job, electrons can't reach oxygen, which causes the chain to back up with "stuck" electrons, halting proton pumping, stopping ATP synthesis, and severely depleting cellular energy, which eventually leads to cell death. This effect is particularly potent in high-energy organs like the heart, lungs, liver, and brain.

As noted by the contributor, a "rotting fish" or "garlic" smell may accompany phosphine gas at autopsy. While pure PH_3 gas is odorless, the fishy smell associated with phosphine gas results from common contaminants in the gas, primarily diphosphane (P_2H_4) or other organic phosphine compounds. Either way, sniffing dead bodies to try and figure out, "What's that smell?" is strongly ill-advised.

References:

1. Alzahrani SM, Ebert PR. Pesticidal Toxicity of Phosphine and Its Interaction with Other Pest Control Treatments. *Current Issues in Molecular Biology*. 2023;45(3):2461-2473
2. Bumbrah GS, Krishan K, Kanchan T, Sharma M, Sodhi GS. Phosphide poisoning: a review of literature. Forensic science international. 2012 Jan 10;214(1-3):1-6.
3. Cullen JM, Stalker MJ. Liver and biliary system. In: Maxie MG, ed. Jubb, Kennedy, and Palmer's Pathology of Domestic Animals.6th ed. Vol. 2. Philadelphia, PA: Elsevier, 2016:273–278.

4. Drolet R, Laverty S, Braselton WE, Lord N. Zinc phosphide poisoning in a horse. *Equine Veterinary Journal.* 1996;28(2):161-2.
5. Fox JH, Porter BF, Easterwood L, Hildenbrand JR, Hélie P, Smylie J, O'Toole D. Acute hepatic steatosis: a helpful diagnostic feature in metallic phosphide–poisoned horses. *JVDI*. 2018;30(2):280-5.
6. Gurjar M, Baronia AK, Azim A, Sharma K. Managing aluminum phosphide poisonings. *J Emerg Trauma Shock*. 2011;4(3):378-84.
7. Nagy AL, Bolfa P, Mihaiu M, Catoi C, Oros A, Taulescu M, Tabaran F. Intentional fatal metallic phosphide poisoning in a dog—a case report. *BMC Veterinary Research.* 2015;11(1):158.
8. Olivares CP, Martínez RR, Daba MM, Thomsen JL. Zinc phosphide poisoning in a mare. *Veterinaria México.* 2002;33(3):343-6.
9. Pacchiarotti G, Nardini R, Scicluna MT. Equine Hepacivirus: A Systematic Review and a Meta-Analysis of Serological and Biomolecular Prevalence and a Phylogenetic Update. *Animals (Basel).* 2022;12(19):2486.
10. Plumlee KH. Pesticide toxicosis in the horse. *Vet Clin North Am Equine Pract*. 2001;17:491–500.
11. Robison WH, Hilton HW. Gas chromatography of phosphine derived from zinc phosphide in sugarcane. *J Agric Food Chem.* 1971;19:875–878.
12. Singh R, et al. Mysterious death due to accidental inhalation of phosphine – A unique case study. *Forensic Science International: Reports*. 2022;5:100264.

CASE II:

Signalment:

9-year-old male Arabian horse (*Equus ferus caballus)*

History:

A 9-year-old male Arabian horse from Lagoa Santa (State of Minas Gerais, Brazil), was admitted to the veterinary hospital of the Universidade Federal de Minas Gerais (UFMG) with history of acute ataxia, depression, incoordination and reluctance to move. The horse belonged to a riding school, where no other horses showed any neurological signs, and was dewormed with Ivermectin. Therapy with steroidal and non-steroidal anti-inflammatory drugs was instituted (unknow drugs and dosages) at the horse training site, and the animal was anesthetized with detomidine and ketamine for the transport to UFMG. At admission, the horse was still anesthetized. When no longer anesthetized, the horse made several unproductive attempts to stand. Neurological signs progressed over the next 24 hours to bilateral ventromedial strabismus and reduction of threat response.

Physical exam revealed hypothermia (36.1°C), dry mucous membranes, increased

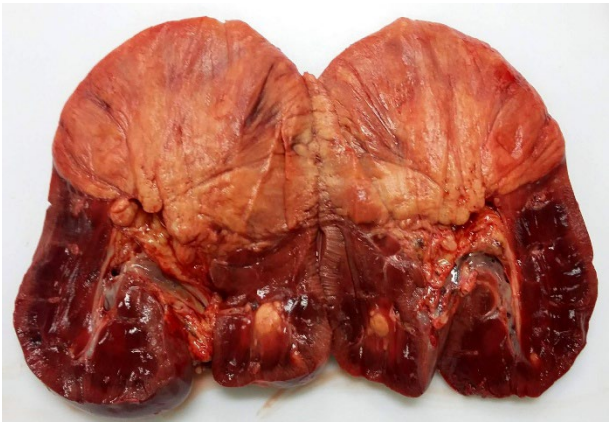

Figure 2-1. Kidney, horse: Gross appearance of the kidney with multifocal nodules, elevated, white-yellowish in the center, red on the edges and firm. (Photo courtesy of: Escola de Veterinária, Universidade Federal de Minas Gerais – www.vet.ufmg.br).

capillary refill time, skin ulcers secondary to decubitus in the tuber coxae, head and limbs, as well as a superficial wound in the atlanto-occipital region, probably due to previous fall.

At the veterinary hospital, intravenous (IV) fluid therapy with 7.2% hypertonic saline solution, followed by Ringer's lactate solution dimethyl sulfoxide (IV), ceftiofur, and dexamethasone therapy was initiated. Skull radiograph showed no significant abnormalities. Due to poor prognosis and lack of response to therapy the horse was euthanized and subject to necropsy.

Gross Pathology:
The kidneys had multifocal nodules, ranging from 2 to 15 cm in diameter, elevated, white-yellowish in the center, red on the edges, and firm. In the right kidney the lesion replaced, approximately, fifty percent of the renal parenchyma, whereas in the left kidney there were multiple nodules ranging from 1 to 3 cm in diameter. Renal and internal iliac lymph nodes were moderately enlarged and firm, with undefined cortico-medullary distinction. Meninges and brain parenchyma were moderately hyperemic.

Laboratory Results:
Cerebrospinal fluid (CSF) revealed no change in color (clear), protein (34.02 mg / dL) and glucose (61.5 mg / dL). A mild increase in nucleated cells were observed (20 cells / µL, reference value: 5 cells / µL). No erythrocytes, eosinophils or parasitic structures were observed.

Microscopic Description:
Kidneys: Multifocal to coalescent areas of loss of normal parenchyma with replacement by severe lymphohistioplasmocytic inflammatory infiltrate, with epithelioid macrophages, multinucleated giant cells, and large numbers of intralesional nematodes. Parasites were elongated, with aproximately 80 to 90 µm long (most of them fragmented), cylindrical, with

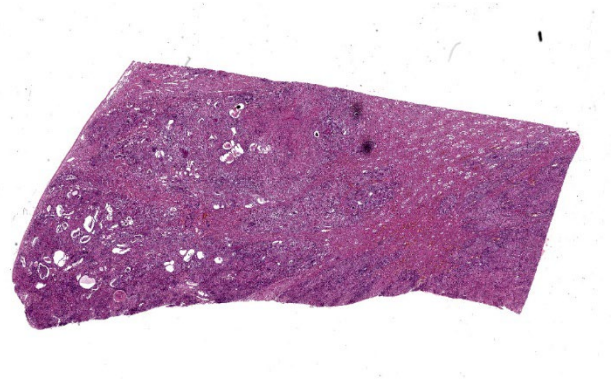

Figure 2-2. Kidney, horse. Within the submitted section of kidney, approximately 66% of the section is effaced by inflammatory changes. At subgross magnification, numerous severely ectatic tubules are present. (HE, 10X).

sharp ends, covered by smooth cuticle, platimiarian musculature and an evident elongated and central rhabditiform esophagus, occupying the initial third of the body (morphology consistent with *Halicephalobus gingivalis*). Associated with these lesions there were also fibroplasia, necrosis, vasculitis and the remaining renal tubules were dilated and filled with macrophages, neutrophils, cellular debris, and numerous sections of *H. gingivalis*.

Contributor's Morphologic Diagnoses:
Kidneys: multifocal to coalescent, severe, chronic, granulomatous nephritis associated to intralesional nematodes compatible with *Halicephalobus gingivalis* and multifocal, severe, vasculitis, horse.

Contributor's Comment:
H. gingivalis is a nematode, genus *Halicephalobus*, order Rhabditida, superfamily Rhabditoidea and family Rhabditidae that have a smooth and thin cuticle, with transverse striations, conical tail ending in fine point, elongated buccal cavity and a rhabditiform esophagus.[2] It is a free-living nematode, usually found in the soil and organic matter, but its life cycle and pathogenesis are still unknown. Apparently, skin or mucosal lesions are the port of entry from where the parasite spreads by

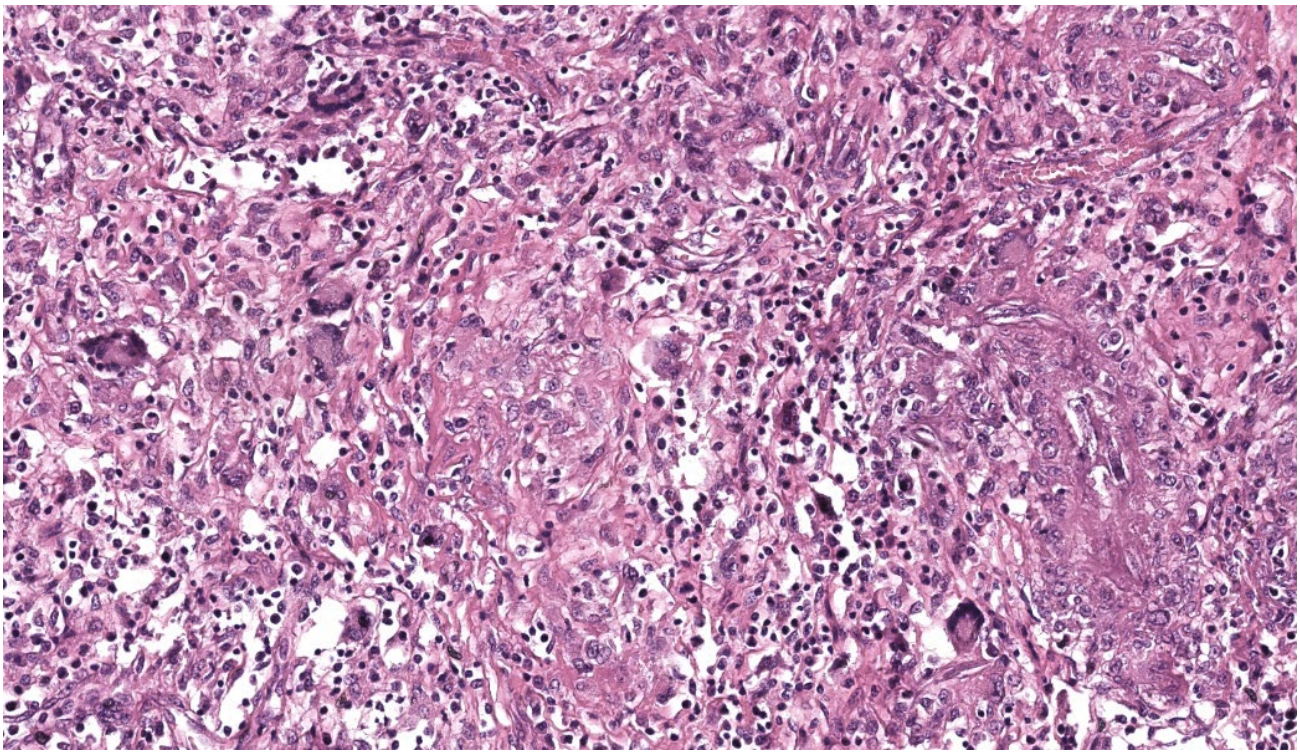

Figure 2-3. Kidney, horse. The renal parenchyma is effaced by granulomatoeus inflammation containing numerous epithelioid macrophages, multinucleated foreign body-type macrophages, fibrosis and cross and tangential sections of larval rhabditoid nematodes. (HE, 318X).

hematogenous or lymphatic route. Other possible ways of dissemination in organs are through the optic or trigeminal nerves, and the lacrimal duct.[3,7,9,10]

H. gingivalis often infects horses. However, there are reported infections affecting zebra, calves, and humans.[5,6,8] Most of the human and equine reported cases were from Europe, North America, and Northeast of Asia. Brazil have just three previously reported cases in horses, two of them with brain infection and one with granulomatous myocarditis.[4,11,13] Clinical signs in infected animals reflect the distribution and intensity of the lesions. The lesions observed on the organs of this horse are compatible with other reports.[6,11,13]

Diagnosis of *H. gingivalis* infection based on direct detection of larvae by CSF analysis has been previously reported.[1] However, there are no studies demonstrating a correlation between larval detection in CFS and the brain lesions. Detection of larvae in the urine of infected horses has been also reported, suggesting that it can be a route of elimination to the environment, which is compatible with the abundant amount of nematode inside renal tubules found in the histopathology of this horse.[7,12] This horse was dewormed with Ivermectin. Some reports suggest that this drug or the recommended dose to treat gastrointestinal parasites are not effective against *H. gingivalis,* and no other chemical therapies have been described for this infection.[3,9,11]

Contributing Institution:
Escola de Veterinária, Universidade Federal de Minas Gerais – www.vet.ufmg.br

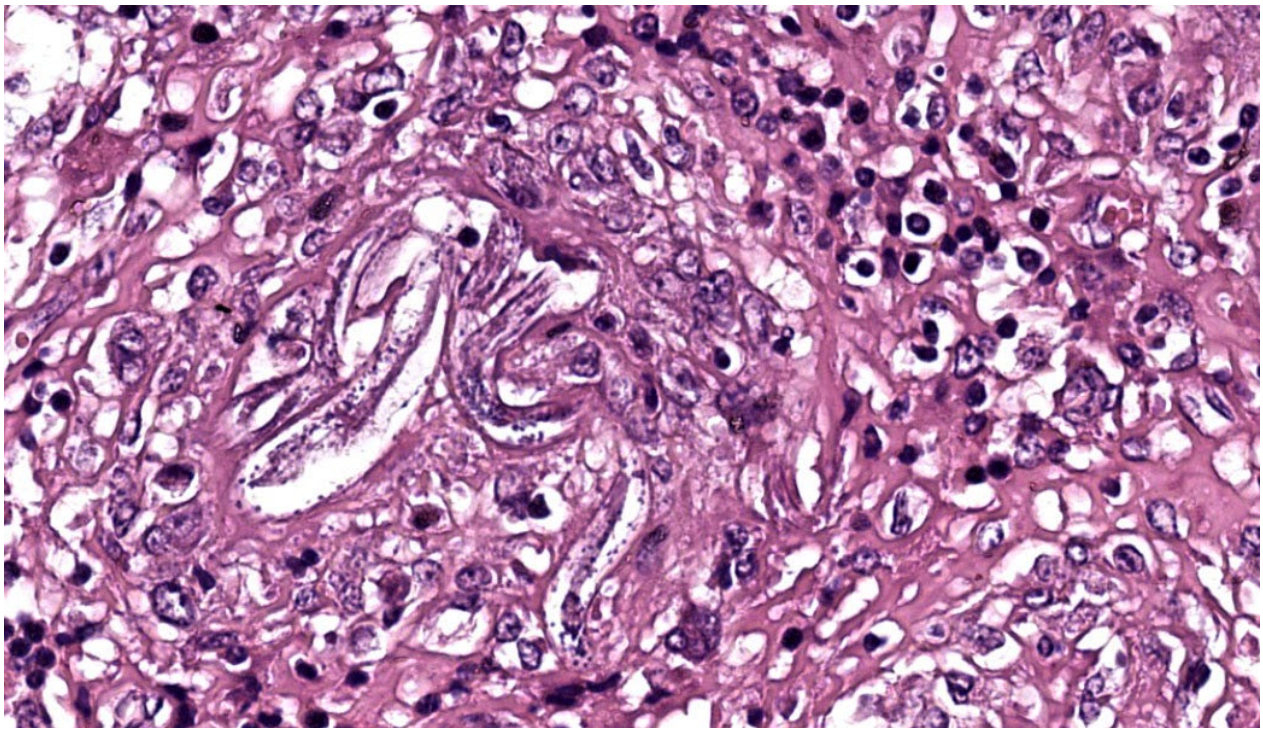

Figure 2-4. Kidney, horse. Higher magnification of larval rhabditoid nematodes embedded within an inflammatory focus. (HE, 1120X).

JPC Diagnoses:
Kidney: Nephritis, granulomatous, chronic-active, multifocal to coalescing, severe, with adult and larval rhabditid nematodes and eggs.

JPC Comment:
This is a great example of a classic entity in horses. The contributor's comment covers most of what was discussed regarding *H. gingivalis*. A few points of note from this conversation are that, as a reminder, the neutrophils most of our routine large animal species (equines and bovines, especially) are more eosinophilic that in small animals and can be mistaken for eosinophils. Remember, in horses, their eosinophils are prominent and look like raspberries! Additionally, *H. gingivalis*, although commonly associated with the oral cavity, facial bones, kidneys, and brain, can cause lesions anywhere throughout the body. Dr. Engiles told participants of a recent case she had of *H. gingivalis* infection in the cannon bone of a horse where the parasites had migrated into the bone hematogenously. The horse's presenting complaint was just "lameness." This was an important lesson in not pigeonholing oneself and remaining open-minded about possible diagnoses.

The genus *Halicephalobus* is derived from the Greek roots "*hyalinos*", "*kephalon*", and "*lobos*", meaning "transparent head lobe". This apparently refers to the clear, lobed head structure of the adult nematode seen on stereomicroscopy. You'll have to ask the parasitologists on that one. For *H. gingiavlis*, the specific species epithet originates from its initial identification in the oral cavity of a horse. Stefanski was the first person to describe the nematode in 1954 when he found worms in a gingival granuloma in a horse in Poland.[9] *H. gingivalis* has also been referred to as *Micronema deletrix* or *H. deletrix* over the years.[2,9]

In all cases of *H. gingivalis* in both humans and animals, only parasitic female adults, larvae, and eggs have been isolated from hosts. This strongly suggests that *H. gingivalis* can reproduce parthenogenetically, which is

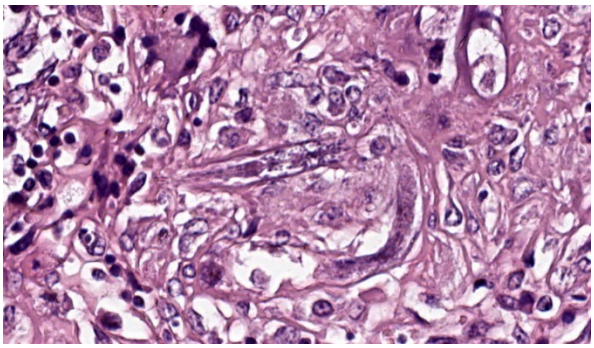

Figure 2-5. Kidney, horse. Higher magnification of the characteristic rhabditoid esophagus)corpus, isthmus, and buld) within a larval nematode. larval rhabditoid nematodes embedded within an inflammatory focus. (HE, 1120X)

known to occur in other rhabditid nematodes. *H. gingivalis* is primarily considered a pathogen of horses and other equids but is also known to affect humans and was recently reported in ruminants.[5,9] Transmammary infection from mare to foal has also been reported once.[9]

References:

1. Adedeji AO, Borjesson DL, Kozikowski-Nicholas TA, Cartoceti AN, Prutton J, Aleman M. What is your diagnosis? Cerebrospinal fluid from a horse. *Vet Clin Pathol.* 2015; 44(1):171-2.
2. Anderson RC, Under KE, Peregrine AS. *Halicephalobus gingivalis* (Stefanski, 1954) from a fatal infection in a horse in Ontario, Canada with comments on the validity of *H. deletrix* and a review of the genus. *Parasite*.1998; 5:255-61.
3. Brojer JT, Parsons DA, Linder KE, Peregrine AS, Dobson H. *Halicephalobus gingivalis* encephalomyelitis in a horse. *Can Vet J.* 2000;41:559-61.
4. Cunha BM, França TN, Miranda IC, Santos AM, Seixas JN, Pires APC, Santos BBN, Peixoto PV. Miocardite granulomatosa em cavalo por *Halicephalobus gingivalis* (*H. deletrix*) - Relato de caso. *Rev Braz Med Vet.* 2016;38(2):113-16.
5. Enemark HL, Hansen MS, Jensen TK, Larsen G, Al-Sabi MNS. An outbreak of bovine meningoencephalomyelitis with identification of *Halicephalobus gingivalis*. *Vet Parasitol.* 2016;218:82-6.
6. Isaza R, Schiller CA, Stover J, Smith PJ, Greiner EC. *Halicephalobus gingivalis* (nematoda) infection in a grevy's zebra (*Equus grevyi*). *J Zoo Wild Med.* 2000;31(1):77-81.
7. Kinde H, Mathews M, Ash L, Leger JSt. *Halicephalobus Gingivalis* (*H. Deletrix*) infection in two horses in southern California. *J Vet Diagn Invest*. 2000;12(2):162–5.
8. Lim CK, Crawford A, Moore CV, Gasser RB, Nelson R, Koehler AV, Bradbury RS, Speare R, Dhatrak D, Weldhagen GF. First human case of fatal *Halicephalobus gingivalis* meningoencephalitis in Australia. *J Clin Microbiol.* 2015;53:1768-74.
9. Onyiche TE, Okute TO, Oseni OS, Okoro DO, Biu AA, Mbaya AW. Parasitic and zoonotic meningoencephalitis in humans and equids: Current knowledge and the role of *Halicephalobus gingivalis*. Parasite Epidemiol Control. 2017 Dec 29;3(1):36-42.
10. Pearce SG, Bouré LP, Taylor JA, Peregrine AS. Treatment of a granuloma caused by *Halicephalobus gingivalis* in a horse. *J Am Vet Med Assoc.* 2001;219(12):1735-8.
11. Rames DS, Miller DK, Barthel R, Craig TM, Dziezyc J, Helman RG, Meale R. Ocular *Halicephalobus* (syn. *Micronema*) *deletrix* in a horse. *Vet Pathol.* 1995;32(5):540-2.
12. Sant'Ana FJF, Júnior JAF, Costa YL, Resende RM, Barros CSL. Granulomatous meningoencephalitis due to *Halicephalobus gingivalis* in a horse. *Braz J Vet Pathol.* 2012;5(1):12-5.
13. Taulescu MA, Ionicã AM, Diugan E, Pavaloiu A, Cora R, Amorim I, Catoi C, Roccabianca P. First report of fatal systemic *Halicephalobus gingivalis* infection in two Lipizzaner horses from Romania: clinical, pathological, and molecular characterization. *Parasitol Res.* 2015;115(3):1907-2103.
14. Vasconcelos RO, Lemos KR, Moraes JRE, Borges VP. *Halicephalobus gingivalis* (*H. deletrix*) in the brain of a horse. *Cienc Rural.* 2007;37(4):1185-7.

CASE III:

Signalment:
33-year-old, female intact donkey (jenny), *Equus asinus*)

History:
1-week history of weight loss. There was an acute decline over 24 hours with depression and anorexia. Physical exam revealed a heart rate of 88bpm, ileus, and delayed capillary refill time. ICU care was offered but, due to the poor prognosis, the owners opted to euthanize.

Gross Pathology:
Externally the animal was emaciated. There was 24.5L of red watery peritoneal fluid, and 500ml of red watery pleural fluid. There were multifocal to coalescing exophytic, papillary, white nodules ranging from pinpoint to 5x5x2cm on the abdominal and thoracic body walls, the diaphragm, the omentum, the mesentery, the lung, the liver, the spleen, the perirenal adipose tissue, and the ovary. The nodules were frequently associated with multifocal to coalescing hemorrhages.

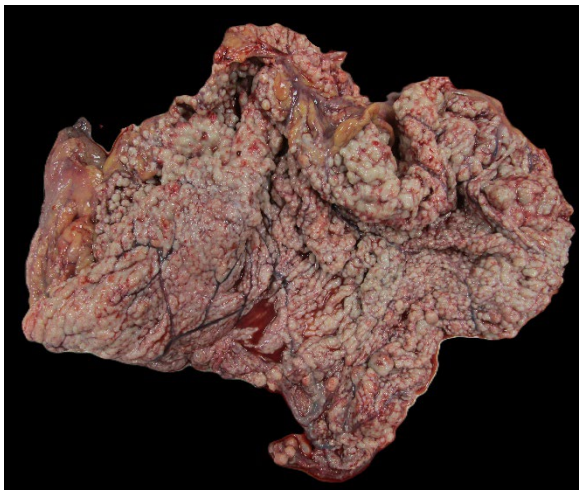

Figure 3-1. Omentum, donkey: The omentum is covered by multifocal to coalescing exophytic, papillary, white nodules ranging from pinpoint to 5x5x2cm in diameter. (Photo courtesy of: University of Nottingham, https://www.nottingham.ac.uk/vet/service-for-business/veterinary-pathology-service/index.aspx).

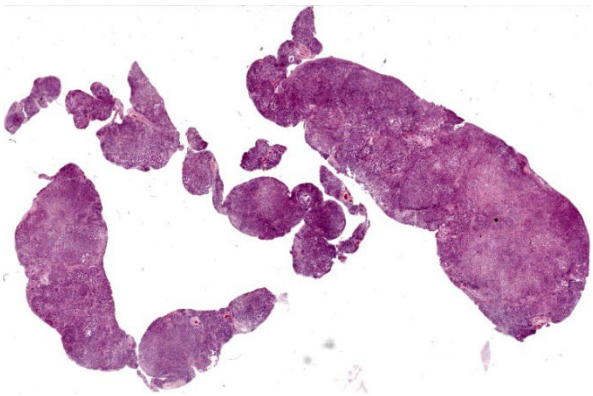

Figure 3-2. Omentum, donkey: One section of omentum is submitted for examination. The omental architecture is effaced by an infiltrative neoplasm. (HE, 6X).

Laboratory Results:
N/A

Microscopic Description:
Extending from and infiltrating the omentum is an unencapsulated, poorly demarcated, moderately cellular neoplasm composed of cuboidal to polygonal cells arranged in acini, tubules and nests, and more rarely micropapillary projections, on a moderate fibrovascular stroma. Neoplastic cells have variably distinct cell borders, an abundant amount of granular, eosinophilic and occasionally indistinctly vacuolated cytoplasm, and a pleomorphic, centrally placed nucleus with finely stippled to marginated chromatin and up to 3, occasionally very large distinct magenta nucleoli. There is marked anisocytosis and anisokaryosis, and 21 mitotic figures in 2.37mm2 – equivalent of 10 high power fields (40x obj); these are occasionally bizarre. There are occasional multinucleated neoplastic cells with up to 3 nuclei which occasionally compress and occasional apoptotic bodies are seen. Multifocally, neoplastic stroma contains minimal extravasations of erythrocytes (haemorrhage), and there are multifocal mild infiltrations of deform adjacent nuclei (nuclear molding).

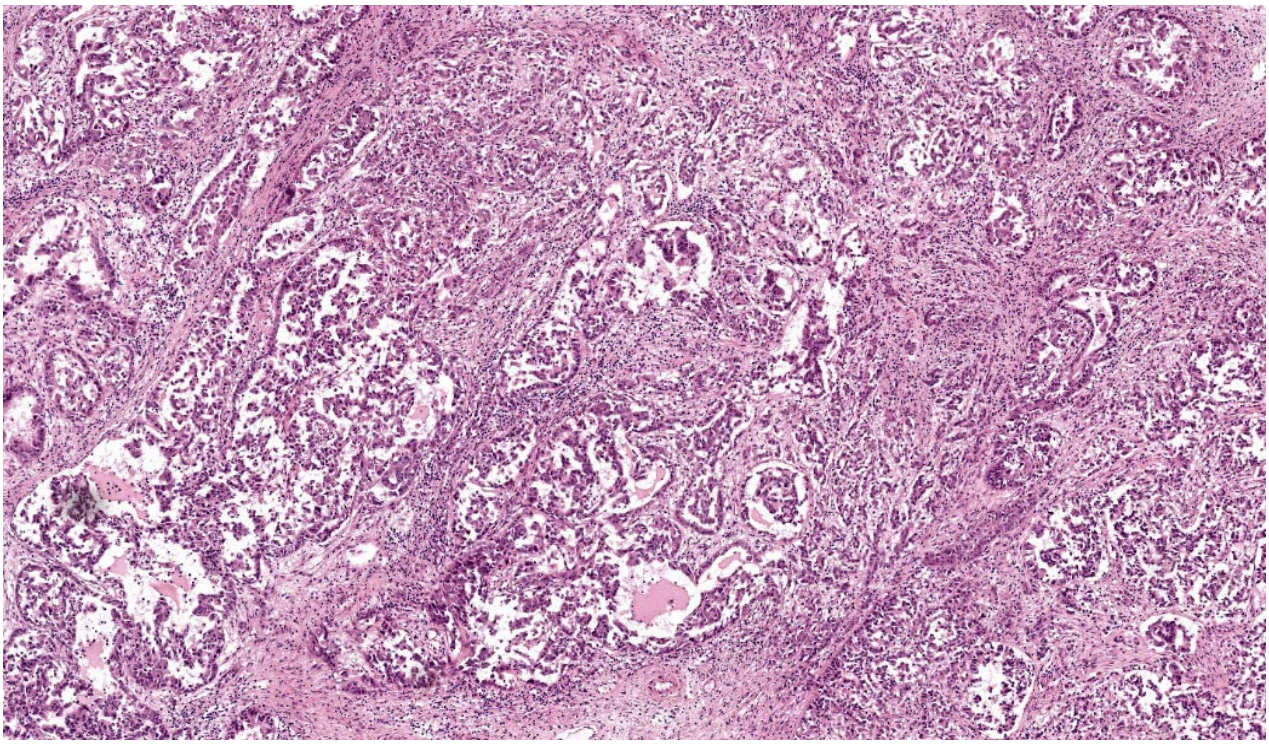

Figure 3-3. Omentum, donkey: The omentum is effaced by mesothelial cells forming large cystic spaces containing epithelioid mesothelial cells forming papillary and micropapillary projections on a dense fibrous stroma. (HE, 98X).

There is occasional single cell necrosis, and-mainly mature small lymphocytes, some plasma cells, and fewer neutrophils. Blood vessels are multifocally moderately congested and are often lined by plump (reactive) endothelium.

Immunohistochemistry: Neoplastic cells are diffusely strongly positive for vimentin. The majority of neoplastic cells are moderately positive for cytokeratin.

Contributor's Morphologic Diagnoses:
Pleural and peritoneal cavities: Mesothelioma, epithelioid subtype.

Contributor's Comment:
Postmortem examination revealed the presence of a neoplastic process within the pleural and peritoneal cavity, which on histopathology had a morphology most likely consistent with a mesothelioma.[3,12] Additionally, the immunopositivity of both cytokeratin and vimentin, is consistent with a mesothelial origin, although rarely this dual positivity can be present in metastatic ovarian or renal carcinomas, which were not identified in this case.[12]

Mesotheliomas are considered rare and affect many animal species; they are most commonly reported in cattle, which have a congenital form, and in canines.[4,8,9,17] They have also been reported in goats, cats, sheep, horses, jaguars, skunks, and amazon parrots.[5,6,11,13-15] They should be differentiated from mesothelial hyperplasia using the features in Table 1, taken from Husain et al., 2018.[3] This case displays a moderate amount of fibrovascular stroma with invasion, contains complex tubular and micropapillary structures with disorganized growth, and only a mild inflammation which is consistent with mesothelioma.[3]

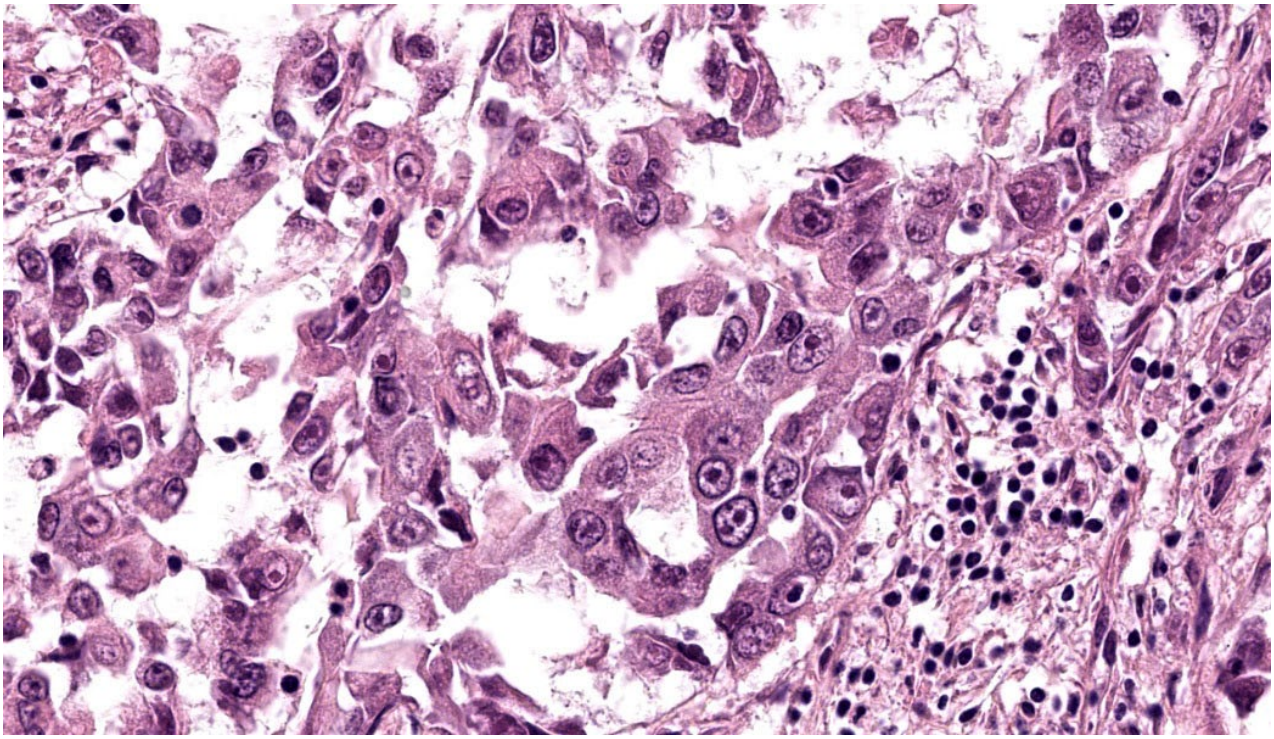

Figure 3-4. Omentum, donkey: Neoplastic mesothelial cells are moderately pleomorphic. (HE, 686X).

Confirmed cases are unreported in donkeys, however, there are suggested similarities in neoplastic diseases in donkeys and horses.[1] Most diagnoses are made postmortem.[12]
Mesotheliomas can be classified as:

- Epithelioid (most common, better prognosis): Small oval to cuboidal cells shape that connect often forming small tubular or papillary structures;
- Sarcomatoid or Fibrous: fusiform cells that do not connect or form structures and widely infiltrate surrounding tissue; or
- Mixed or Biphasic: contains at least 10% of each cell type (epithelioid and sarcomatoid cells).[3,12]

In humans and dogs further subclassification can be performed with 17 subtypes, and stroma can contain chondroid or osseous differentiation, due to the multipotency of mesothelial cells.[3,12] In humans, canines and bovines, mesothelioma has been associated with asbestos fiber inhalation.[2,4,8]

Calretinin, where commercially available, can be a useful addition to an immunohistochemistry panel for suspected mesothelioma in horses, and may be useful in the donkey, in addition to vimentin and cytokeratin.[16]

Looking at the ultrastructure may aid diagnosis, particularly where concern remains for malignant carcinomas. Neoplastic epithelioid

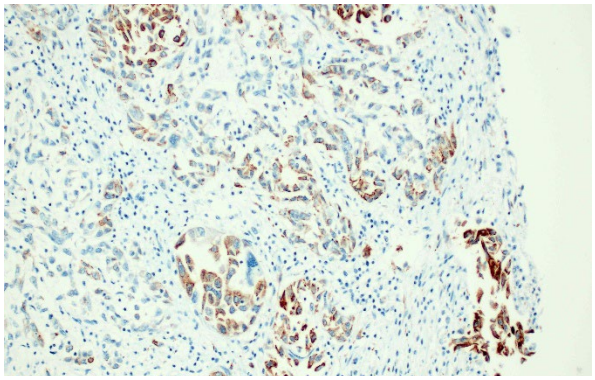

Figure 3-5. Omentum, donkey: Neoplastic mesothelial cells demonstrate moderate cytoplasmic immunoreactivity for cytokeratin. (anti-AE1/AE3, 400X) (Photo courtesy of: University of Nottingham, see weblink in Fig 3-1)

mesothelial cells have abundant, long, occasionally branching microvilli, and circumferential nuclear intermediate microfilaments.[3]

Table 1: Reactive Mesothelial Hyperplasia Versus Mesothelioma (taken from Husain et al., 2018)[3]

Mesothelial hyperplasia	**Mesothelioma**
Absence of stromal invasion (beware of entrapment and *en face* cuts)	Stromal invasion usually apparent (highlight with pancytokeratin staining)
Cellularity may be prominent but is confined to the mesothelial surface/ pleural space and is not in the stroma	Dense cellularity, including cells surrounded by stroma
Simple papillae, single cell layers	Complex papillae, tubules and cellular stratification
Loose sheets of cells without stroma	Cells surrounded by stroma (''bulky tumor'' may involve the mesothelial space without obvious invasion)
Necrosis rare	Necrosis present (occasionally)
Inflammation common	Inflammation usually minimal
Uniform growth (highlighted with cytokeratin staining)	Expansile nodules; disorganized growth (highlighted on cytokeratin staining)
Usually not useful	
Mitotic activity Mild to moderate cytology's atypia	

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JPC Diagnoses:
Omentum: Mesothelioma.

JPC Comment:
This third case was challenging due to the epithelioid nature of this mesothelioma. Most conference participants were readily able to reach a diagnosis of "carcinoma" or "adenocarcinoma" and many listed epithelioid mesothelioma as a differential. Tissue identification was challenging and only the most experienced participants felt confident calling it omentum based off the HE secttion. The features described by these participants that clued them in to "omentum" included a nodular "string of pearls" subgross appearance, the composition of a highly vascular fibroadipose tissue, and the wherewithal to remember that the omentum exists in the first place, which can be challenging in and of itself some days. The contributor provided a succinct, eloquent write-up on mesotheliomas and their classifications, which were covered during the conference discussion.

An interesting feature within the nuclei of some of the neoplastic cells caught the eye of a few of the participants. Infrequently, neoplastic mesothelial cells have what look like irregularly shaped, eosinophilic, intranuclear inclusion bodies (INIBs). This is an uncommon, but documented, feature of certain mesotheliomas in humans that can be seen both cytologically and histologically, particularly in adenomatoid and epithelioid forms.[5,6] INIBs have also been seen, albeit rarely, in laboratory hamsters and rats infected with SV40 that subsequently developed mesothelioma.[21] INIBs are reported, also rarely, in both cattle and dogs with mesothelioma associated with asbestos exposure, although the significance of those inclusions is unknown. Lastly, INIBs can be a rare feature of reactive mesothelial cells as well, making their presence challenging to interpret, but may prompt pathologists to assess for viral or asbestos-related causes.[21]

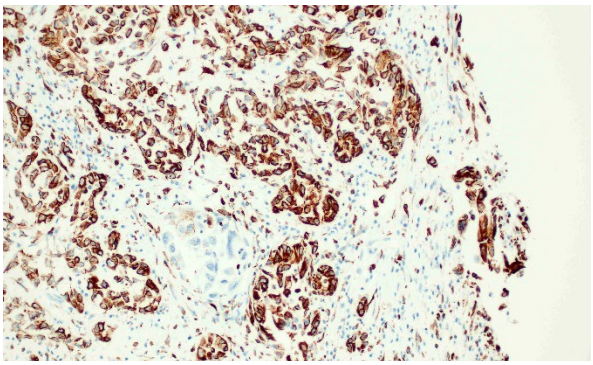

Figure 2-6. Omentum, donkey: Neoplastic mesothelial cells demonstrate strong cytoplasmic immunoreactivity for vimentin. (anti-vimentin, 400X) (Photo courtesy of: University of Nottingham, see weblink in Fig 3-1).

The last notable point in this case discussion focused on other possible differentials for this lesion in equids, which prompted a quick conversation on equine herpesvirus-5, the cause of equine multinodular pulmonary fibrosis in horses. In donkeys, asinine herpesvirus-5 causes a similar syndrome and, if this tissue had been from the lungs, this virus would have been a good differential to put on the list.

Mesothelioma was first described by Bichat in 1827. Mesothelial cells originate from the embryonic lateral plate mesoderm, forming a protective epithelial lining known as the mesothelium for the pleural, pericardial, and peritoneal spaces.[3] There are two layers to the lateral plate mesoderm that form during development. The dorsal layer, called the somatic mesoderm, is associated with the overlying ectoderm, while the ventral layer, termed the splanchnic mesoderm, is associated with the underlying endoderm.[3] The splanchnic mesoderm eventually forms the visceral mesothelium on organs, whereas the somatic mesoderm develops into the parietal mesothelium of the body wall.

Mesothelial cells are somewhat unique amongst cell types for their dual immunoreactivity to both pancytokeratin and vimentin. During development, mesothelial cells differentiate from their mesodermal precursors, developing features of both epithelial and mesenchymal cells. With certain stimuli, mesothelial cells can undergo epithelial-to-mesenchymal transition (EMT) into other cell types, such as myofibroblasts, smooth muscle cells, and/or endothelial cells.[3] This ability highlights their roles in repair and tissue formation following injury or inflammation.

While this immunohistochemistry (IHC) profile can be a useful feature for diagnosis, there are other neoplasms that can express dual positivity for pancytokeratin and vimentin when neoplastic cells undergo EMT. As mentioned by the contributor, this has been reported in metastases from both ovarian and renal carcinomas.[16] It has also been documented in melanomas and aggressive metaplastic mammary carcinomas in humans.[9] The absence of an additional primary neoplasm can help rule out other tumors, but there are other IHCs utilized in veterinary literature to assist in definitively diagnosing mesotheliomas. The JPC performed in-house calretinin and Wilms Tumor 1 (WT1) immunohistochemistry on this case post-conference, as both of these markers have been utilized in animal species to diagnose mesothelioma successfully.[20] Unfortunately, neither of these IHCs worked on the donkey tissue in this case.

References:

1. Davis CR, Valentine BA, Gordon E, McDonough SP, Schaffer PA, Allen AL, & Pesavento P. Neoplasia in 125 donkeys (*Equus asinus*): literature review and a survey of five veterinary schools in the United States and Canada. *JVDI*. 2016;28(6):662–670.
2. Glickman LT, Domanski LM, Mawire TG, Dumxzig RR, & Churgs A. Mesothelioma in Pet Dogs Associated with Exposure of Their Owners to Asbestos. *Environmental Research.* 1983;32.
3. Hiriart E, Deepe R, Wessels A. Mesothelium and Malignant Mesothelioma. *Journal of Developmental Biology*. 2019;7(2):7

4. Husain AN, et al. Guidelines for pathologic diagnosis of Malignant Mesothelioma: 2017 Update of the consensus statement from the International Mesothelioma Interest Group. *Archives of Pathology and Laboratory Medicine.* 2018;142(1):89–108)
5. Kadota K, Suzuki K, Colovos C, Sima CS, Rusch VW, Travis WD, Adusumilli PS. A nuclear grading system is a strong predictor of survival in epitheloid diffuse malignant pleural mesothelioma. *Mod Pathol.* 2012;25(2):260-71.
6. Kawai T, Kawashima K, Serizawa H, Miura H, Kyeongil K. Adenomatoid mesothelioma with intranuclear inclusion bodies: a case report with cytological and histological findings. *Diagn Cytopathol.* 2014;42(5):436-40.
7. Kim SM, Oh Y, Oh SH, & Han JH. Primary diffuse malignant peritoneal mesothelioma in a striped skunk (*Mephitis mephitis*). *Journal of Veterinary Medical Science.* 2016;78(3):485–487
8. Krametter R, Bago Z, Floeck M, Baumgartner W. Abdominal mesothelioma in a goat. *N Z Vet J.* 2004;52(5):293-6.
9. Kuburich NA, Kiselka JM, den Hollander P, Karam AA, Mani SA. The cancer chimera: Impact of vimentin and cytokeratin co-expression in hybrid epithelial/mesenchymal cancer cells on tumor plasticity and metastasis. *Cancers (Basel).* 2024;16(24):4158.
10. Lopez A, et al. Respiratory system, Thoracic Cavities, Mediastinum, and Pleurae. In: Zachary JF, ed. Pathologic Basis of Veterinary Disease. 6th ed. St. Louis, MO: Mosby Elsevier; 2016: 597-598.
11. McCleery B, Jones MP, Manasse J, Johns S, Gompf RE, Newman S. Pericardial Mesothelioma in a Yellow-naped Amazon Parrot (*Amazona auropalliata*). *J Avian Med Surg*. 2015;29(1):55-62.
12. Misdorp W. Congenital tumours and tumour-like lesions in domestic animals. 1. Cattle. A review. *Vet Q.* 2002;24(1):1-11.
13. Misdorp W. Tumours in calves: comparative aspects. *J Comp Pathol.* 2002;127(2-3):96-105
14. Moberg HL, Gramer I, Schofield I, Blackwood L, Killick D, Priestnall SL, Guillén A. Clinical presentation, treatment and outcome of canine malignant mesothelioma: A retrospective study of 34 cases. *Vet Comp Oncol*. 2022;20(1):304-312.
15. Movassaghi AR, Maleki M, & Khanzadi S. Primary pericardial mesothelioma in a sheep. *Comparative Clinical Pathology.* 2009;18(4):459–461.
16. Munday JS, Löhr CV, and Kiupel M. Tumors of the Alimentary tract - Tumors of the peritoneum and retroperitoneum. In: Meuten DJ, ed. Tumors in Domestic Animal, 5th Ames, IA: John Wiley and Sons Inc; 2017:592-595.
17. Passantino G, Sassi E, Filippi I, Serata V, Tinelli A, Zizzo N. Thoracic and Abdominal Mesothelioma in an Older Horse in Lazio Region. *Animals (Basel).* 2022;12(19):2560.
18. Schlueter AH, Dehghanpir SD, Boudreaux B, Robinson C, Menk P Lima JC, Langohr IM. Feline mesothelioma: case report and review of cytologic, immunocytochemical, histopathologic, and immunohistochemical findings. *J Vet Diagn Invest.* 2021;33(4):753-757.
19. Souza Fde A, de Carvalho CJ, de Almeida HM, Pires LV, Silva Ldos S, Costa FA, Silva SM. Peritoneal mesothelioma in a jaguar (*Panthera onca*). *J Zoo Wildl Med.* 2013;44(3):737-9.
20. Stoica G, Cohen N, Mendes O, Kim HT. Use of immunohistochemical marker calretinin in the diagnosis of a diffuse malignant metastatic mesothelioma in an equine. *J Vet Diagn Invest*. 2004;16(3):240-3.
21. Testa JR, Berns A. Preclinical Models of Malignant Mesothelioma. *Front Oncol.* 2020;10:101.
22. Uzal FA, Plattner BL, Hostetter JM. Alimentary system. In: Maxie MG, ed. Jubb, Kennedy, and Palmer's Pathology of Domestic Animals, Vol 2, 6th ed. St. Louis, MO: Elsevier; 2016:256-7.

CASE IV:

Signalment:
6 year-old female Merino sheep (*Ovis aries*)

History:
Six of 2,300 5-6 year old first cross ewes run on improved pastures in the Cowra district of NSW were noticed to be unusually thin in late October 2014. As ovine Johne's disease was considered a possibility, one of these ewes was euthanased and necropsied on the 26 November 2014.

Gross Pathology:
The serosa of the small intestine, caecum and colon was covered in miliary to focally extensive firm, white, raised plaques. In some areas, the plaques were as small as 1mm diameter, pinpoint lesions, whereas in others as much as 90 percent of the serosal surface was covered.

Laboratory Results:
N/A.

Microscopic Description:
Colon: The lamina propria, submucosa, muscularis mucosa and serosa are markedly expanded by a poorly demarcated, non-encapsulated, infiltrative neoplasm composed of two populations of neoplastic epithelial cells. The neoplastic cells occur singly and in loose packets, lobules and cords, and are supported by variable fibrous stroma containing fibrocytes, fibroblasts and a light basophilic matrix. The predominant neoplastic cell is round to ovoid, 20–50 µm in diameter, with distinct cell borders, abundant finely granular basophilic cytoplasm, peripherally located oval nuclei with lightly stippled pale chromatin and single nucleoli. The secondary type of neoplastic cell is round to oval; 15-30 µm in diameter; with distinct cell borders; moderate amounts of cytoplasm containing small eosinophilic granules; single, peripherally located, large nuclei with coarse chromatin and single nucleoli. Both sub-populations of neoplastic cells exhibit moderate anisocytosis and anisokaryosis. Mitoses are rare (< 1 per HPF). There is moderate expansion of the adventitia of large vessels with neoplastic cells. The lamina propria propria is diffusely expanded by moderate numbers of lymphocytes, plasma cells, occasional macrophages and rare eosinophils. Crypts are often ectatic, lined with attenuated epithelium and containing non-degenerate neutrophils, rare macrophages and lymphocytes (crypt abscess).

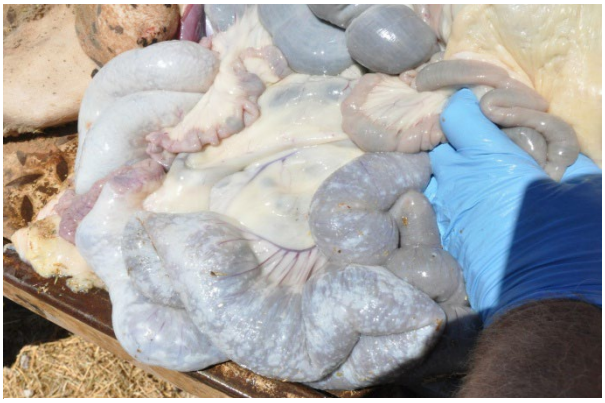

Figure 4-1. Sheep, jejunum: The serosa of the small intestine, caecum, and colon is covered in military to focally extensive firm, white, raised, plaques. (Photo courtesy of: Elizabeth Macarthur Agricultural Institute, Menangle, New South Wales.)

Figure 3-2. Sheep, jejunum: Plaques are white, and slightly raised. Lymphatics are mildly dilated. (Photo courtesy of: Elizabeth Macarthur Agricultural Institute, Menangle, New South Wales.)

Contributor's Morphologic Diagnoses:
1. Large intestine, colon: Intestinal adenocarcinoma, sheep (Ovis aries), ruminant.

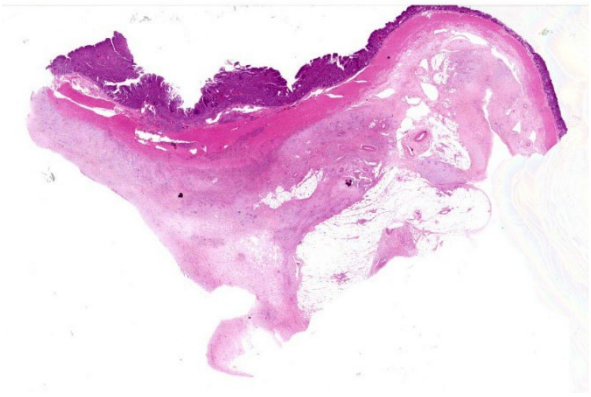

Figure 4-3. Sheep, ileocecal junction: One section of jejunum is submitted for examination. Centrally, there is an area of architectural loss within the mucosa, and an infiltrative neoplasm extending transmurally to the markedly fibrotic serosa. (HE, 7X).

2. Large intestine: Colitis, lymphoplasmacytic, chronic, diffuse, mild, with multifocal crypt abscesses.

Contributor's Comment:

Intestinal adenocarcinoma is a common gastrointestinal tumour of older sheep.[4,11] A wide range of neoplasms have been described in sheep, adenocarcinoma of the small intestine is reported to be the most common of these by far (Table 1).[2] Most are usually discovered at slaughter as incidental findings; if clinical signs are present, weight loss and occasionally ascites are usually the only signs. In an early report of the disease, Ross (1980) reported an overall prevalence of 0.272 percent in sheep examined at abattoirs in southern NSW, and McDonald and Leaver (1965) found that 0.4 percent of all sheep on a single property and 2 percent of sheep over 5 years of age had lesions consistent with intestinal adenocarcinoma.[5,12]

To date, only a limited number of studies have investigated factors associated with intestinal adenocarcinoma in sheep. According to Simpson (1972), intestinal adenocarcinoma in New Zealand is more common in British breeds than in "fine wool" breeds, and is associated with increased stocking density.[13] Ross (1980) reported that regional prevalence in NSW varied between 0.2 to 1.5 percent, however Simpson (1972) found that geographic variation in the prevalence of intestinal adenocarcinoma was not statistically significant.[12,13] Munday et al. (2009) found no association between intestinal adenocarcinoma and herpesviruses, *Helicobacter* spp., or *Mycobacterium avium* subspecies *paratuberculosis* in sheep in New Zealand.[9]

Intestinal adenocarcinomas have been reported in a wide range of animal species. [3] Ovine intestinal adenocarcinomas appear histologically similar to human colonic adenocarcinomas, although there are differences in site of primary growth, development of polyps, and site of metastasis.[6] Neoplastic ovine intestinal adenocarcinoma cells grown in vitro do not express fibronectin, and have altered expression of beta-catenin, E-cadherin, cycloxygenase-2, and p53 protein.[7,10] Mismatch repair protein defects do not appear to be associated with tumorigenesis.[8] Other differential diagnoses for chronic ill-thrift in sheep include ovine Johne's disease (OJD), malnutrition, balanoposthitis, cutaneous myiasis, peritonitis and pneumonia. [11] From a

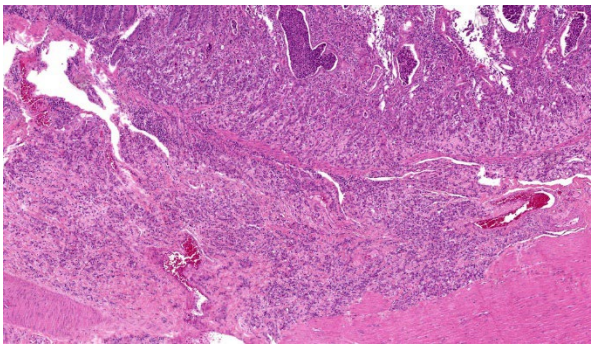

Figure 4-4. Sheep, ileocecal junction: The neoplasm extends from the overlying disordered mucosa through the muscularis mucosa into the submucosa. In the overlying mucosa, remnant crypts are markedly ectatic and filled with neutrophils and cellular debris. (HE, 105X).

production and biosecurity perspective, OJD is of the most concern. The two diseases appear markedly different grossly and histologically, although the simultaneous occurrence of both diseases has been reported by Bush et al. (2006).[1]

Table 1: Neoplasms in sheep described at the Ruakura Animal Health Laboratory from 1955 to 1968. Adapted from Cordes and Shortridge (1971)[2]

Site of neoplasm	No. of cases	Diagnosis
Small intestine	143	Mucous-gland adenocarcinoma
Liver	12	Hepatoma
	2	Adenocarcinoma - possibly primary in genitalia
Liver and/or pancreas	15	Ductal adenocarcinoma
Adrenal	1	Cortical adenoma
Pituitary	1	Adenocarcinoma of pars intermedia
Ovary	3	Granulosa tumour
Testicle	2	Seminoma
	1	Sertoli cell tumour
Kidney	1	Renal adenocarcinoma
	3	Embryonal nephroma
Epidermis	4	Papilloma of skin
	2	Squamous carcinoma of mouth
	1	Metastatic squamous carcinoma in liver and colon
	1	Squamous carcinoma of ear
Reticuloendothelial system	32	Lymphosarcoma - lymphoid
	7	Lymphosarcoma - reticulum cell
of	1	Thymoma
Blood vessel	8	Angiosarcoma of:
		brain (1)
		liver (5)
		stifle joint (1)
		hock joint (1)
Nerve	1	Neurofibroma of wall of thorax
Striated muscle	3	Rhabdomyoma of heart
Brain	1	Astrocytoma
Other connective tissues	4	Fibrosarcoma
	3	Myxosarcoma
	2	Osteogenic sarcoma
	1	Liposarcoma
	1	Synovioma

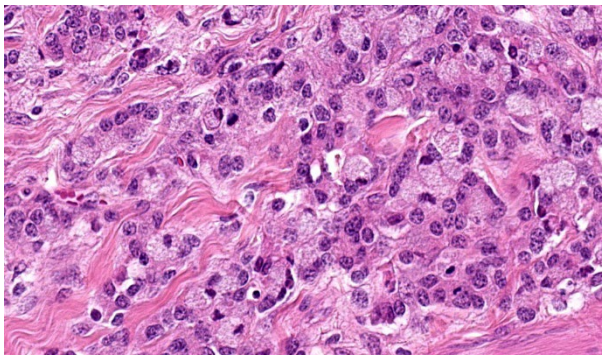

Figure 4-5. Sheep, ileocecal junction: High magnification of neoplastic cells. (HE, 1051X).

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JPC Diagnoses:

Ileocecal junction: Intestinal adenocarcinoma.

JPC Comment:

This last case is a classic! Many thanks to the contributor for a great submission and write-up. Most participants were readily able to reach a diagnosis of intestinal adenocarcinoma in this case due to the high mitotic rate, degree of invasion the neoplasm into abluminal tis-

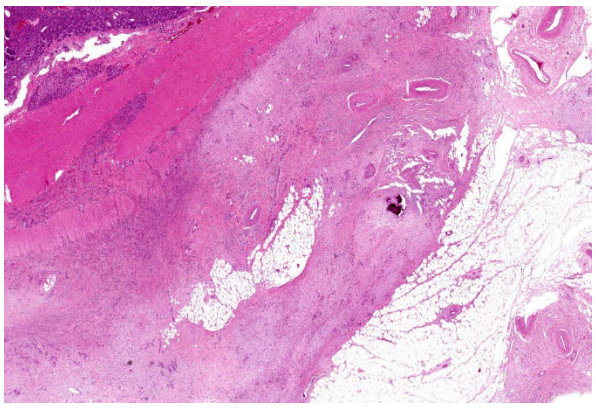

Figure 4-6. Sheep, ileocecal junction: The neoplasm extends through the markedly fibrotic serosa into the adjacent mesentery. (HE, 23X).

sue layers, and the striking desmoplastic response. The deep infiltration from the mucosa outwards allows for a strong argument of a primary intestinal adenocarcinoma rather than a metastatic carcinoma. Intestinal adenocarcinomas tend to invade from the mucosa deep into and run laterally through the submucosa and subsequent layers.

In sheep, the primary ruleout would be metastatic uterine adenocarcinoma, but this would more likely present on the serosal surface due to direct seeding of the abdomen (carcinomatosis) or via lymphatic spread rather than invading from the mucosa. Additionally, intestines are not a primary site for lymphatic metastases for uterine adenocarcinoma in most species; the lungs, liver, and mesentery, however, are.[3] Although generally considered an incidental finding at slaughter, previous studies have demonstrated an increased incidence of intestinal adenocarcinoma in sheep in New Zealand following exposure to feedstuffs sprayed with phenoxy and picolinic acid herbicides.[10]

Despite being able to reach a diagnosis, most participants struggled with the specific anatomic location for this tissue. After much back and forth, the consensus amongst conference-goers was that this is likely representative of the ileocecal junction or close to it, since there are features of both small and large intestine on opposite ends of the H&E slide. While there are crypts, mucus glands, and subcutaneous fat consistent with large intestine visible on one side, there are also villi on the other, most clearly seen associated with and around the neoplasm.

Lastly, there are notable mucosal erosions with regional neoplasia-associated architecture disruption that most participants felt was likely the cause of the inflammation present in the slide rather than an additional primary enteritis. As such, this is reflected in the JPC morphologic diagnosis, which focuses solely on the neoplasm and considers the other changes to be secondary.

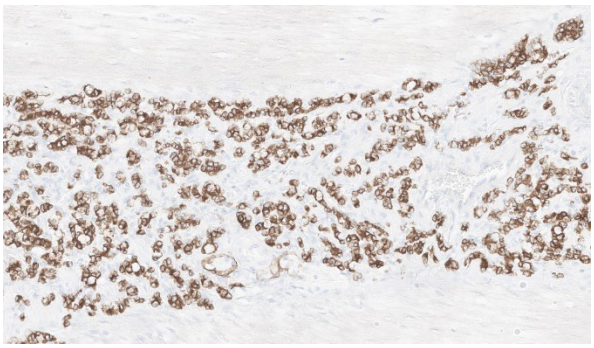

Figure 4-7. Sheep, ileocecal junction: Neoplastic cells demonstrate strong cytoplasmic immunoreactivity for cytokeratin. (anti-AE1/AE3, 321X).

References:

1. Bush RD, Toribio JA, Windsor PA: The impact of malnutrition and other causes of losses of adult sheep in 12 flocks during drought. *Aust Vet J.* 2006:84(7)**:**254-260.
2. Cordes D, Shortridge E: Neoplasms of sheep: a survey of 256 cases recorded at Ruakura Animal Health Laboratory. *NZ Vet J.* 1971:19(4)**:**55-64.
3. Hananeh WM, Ismail ZB, Daradka MH. Tumors of the reproductive tract of sheep and goats: A review of the current literature and a report of vaginal fibroma in an Awassi ewe. *Vet World.* 2019;12(6):778-782.
4. Lingeman CH, Garner F: Comparative study of intestinal adenocarcinomas of animals and man. *Journal of the National Cancer Institute.* 1972:48(2)**:**325-346.
5. Maxie G: Jubb, Kennedy & Palmer's Pathology of Domestic Animals: 3-Volume Set: Elsevier Health Sciences; 2007.
6. McDonald JW, Leaver DD: Adenocarcinoma of the small intestine of Merino sheep. *Australian Veterinary Journal.* 1965:41(9)**:**269-271.
7. Munday JS, Brennan MM, Jaber AM, Kiupel M: Ovine intestinal adenocarcinomas: histologic and phenotypic comparison with human

colon cancer. *Comp Med.* 2006:56(2)**:**136-141.
8. Munday JS, Brennan MM, Kiupel M: Altered expression of beta-catenin, E-cadherin, cycloxygenase-2, and p53 protein by ovine intestinal adenocarcinoma cells. *Vet Pathol.* 2006:43(5)**:**613-621.
9. Munday JS, Frizelle FA, Whitehead MR: Mismatch repair protein expression in ovine intestinal adenocarcinomas. *Vet Pathol.* 2008:45(1)**:**3-6.
10. Munday JS, Keenan JI, Beaugie CR, Sugiarto H: Ovine small intestinal adenocarcinomas are not associated with infection by herpesviruses, *Helicobacter* species or *Mycobacterium avium* subspecies *paratuberculosis. J Comp Pathol.* 2009:140(2-3)**:**177-181.
11. Newell KW, Ross AD, Renner RM. Phenoxy and picolinic acid herbicides and small-intestinal adenocarcinoma in sheep. *Lancet*. 1984;2(8415):1301-5.
12. Norval M, Head K, Else R, Hart H, Neill W: Growth in culture of adenocarcinoma cells from the small intestine of sheep. *British journal of experimental pathology.* 1981:62(3)**:**270.
13. Radostits OM, Gay CC, Hinchcliff KW, Constable PD: Diseases caused by bacteria *Veterinary Medicine: A Textbook of the Diseases of Cattle, Sheep, Pigs, Goats, and Horses*: Elsevier Saunders; 2007:920.
14. Ross AD: Small intestinal carcinoma in sheep. *Aust Vet J.* 1980:56(1)**:**25-33.
15. Simpson BH: The geographic distribution of carcinomas of the small intestine in New Zealand sheep. *New Zealand Veterinary Journal.* 1972:20(3)**:**24-28.