Joint Pathology Center
Veterinary Pathology Services

WEDNESDAY SLIDE CONFERENCE
2021-2022

Conference 2

25 August, 2021

Joint Pathology Center
Silver Spring, Maryland

CASE I: 1512649 (JPC 4083340-00)

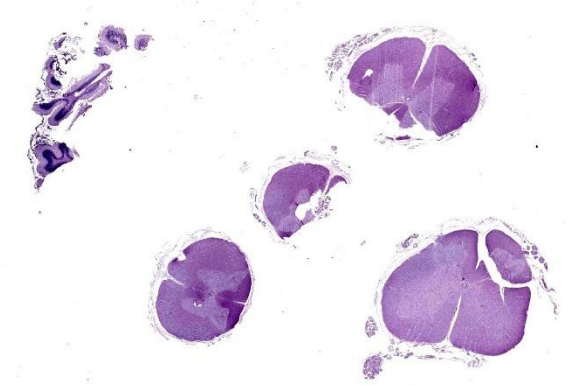

Figure 1-1. ***Spinal cord, goat: Multiple sections of spinal cord and cerebellum are submitted for examination. There is no significant lesion at subgross magnification. (HE, 4x)***

Signalment:
3.5-month-old, male, goat (*Capra aegagrus hircus*).

History:
The goat had been examined by the submitting veterinarian, with an initial complaint of ataxia in its rear limbs by the owner. By the time of clinical evaluation, the kid was recumbent, blind and grinding its teeth. The owner of the flock reported that 4 additional young kids had a clinically similar disease during in spring 2015.

The kid was euthanized and presented for necropsy examination.

Gross Pathology:
No gross lesions were observed.

Laboratory Results:
The goat was deficient in copper (approximately one tenth the normal levels), with molybdenum concentrations over the normal range. Liver copper was measured at 2.6 ppm (Normal 25-150 ppm).

Microscopic Description:
The spinal cord contained swollen, chromatolytic neurons that had lost Nissl substance, affecting Clarke's column and ventral horn neurons throughout the length of the cord. Pyknotic nuclei were rare. Similar changes were observed in cell bodies in the red and vestibular nuclei.

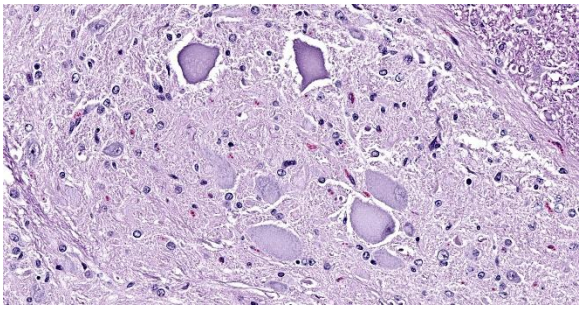

Figure 1-2. ***Spinal cord, goat: Neurons of the ventral horns are swollen and chromatolytic. (HE, 380X)***

These neurons retained cell-body phosphorylated neurofilaments. Spinal cord white matter degeneration was most severe in the lateral columns (spinocerebellar and spinomedullary tracts) and along the ventral median fissure, but was not easily visualized by myelin or neurofilament stains. The degree of tissue disturbance was more clearly demarcated with stains for microglia. CNPase did not demonstrate a reduction in oligodendrocyte numbers.

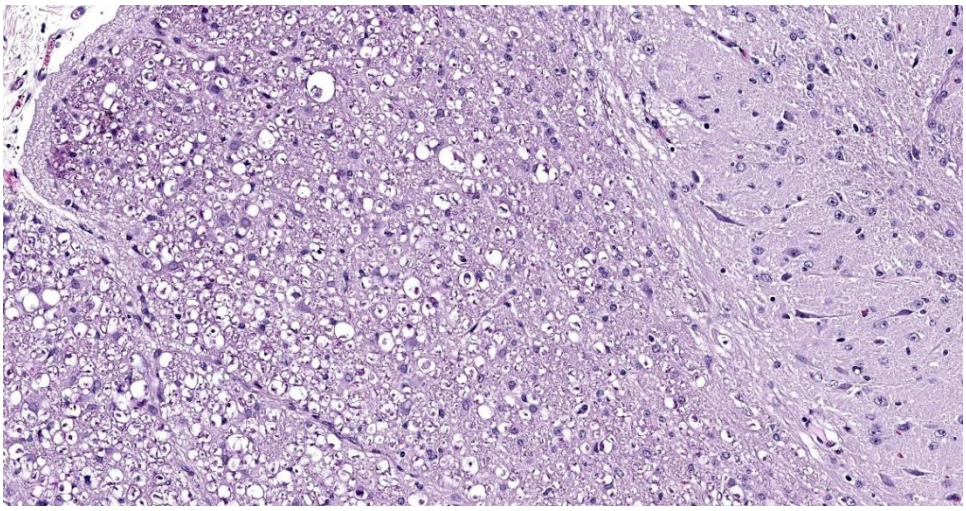

Figure 1-3. ***Spinal cord, goat: Within the dorsal aspects of the lateral funiculi and medial aspects of the ventral funiculi, there are numerous dilated myelin sheaths containing dilated axons, axonal debris, or Gitter cells. (HE, 30X)***

The kid had segmentally severe loss of cerebellar Purkinje and internal granular neurons in all folia, and occasional degenerating neurons were apparent with HE stain. Segmental cell loss was strikingly evident with calbindin immunohistochemistry. Some calbindin positive cells (Purkinje neurons) had dilated axons in the folial white matter near the cell body.

Contributor's Morphologic Diagnoses:
1. Purkinje cell degeneration and loss (abiotrophy) with axonal swellings.

2. Neuronal degeneration, spinal cord.

Contributor's comment:
Copper is a metabolic cofactor of several enzymes, including mitochondrial cytochrome oxidase and superoxide dismutase in the central nervous system.[4] Copper deficiency has a spectrum is microscopic lesions depending on timing and severity of disease. Ruminants are at particular risk, due to the potential of dietary copper binding to thiomolybdate complexes in the rumen. In one study, copper deficiency accounted for spinal ataxia in 13/23 goats.[1] Most affected animals were less than 6 months of age, but other studies suggest goats up to 18 months of age can be affected.[1,3]

Lesions of copper deficiency are recognized world-wide in small ruminants, including goats.[1,2,3,5] Number of cases varies widely between years, with variably severe clinical signs. In newborns, lesions consist of symmetrical necrosis of the cerebral white matter, sparing U fibers (swayback). Spinal cord changes of lateral white matter, termed demyelination in the literature, are described as concurrent axonal and myelin loss (axonopathy).

Cerebellar lesions are much more common in goats.[3]

"Swayback" has been recently reported in people, mostly women 50-70 years old who consumed excessive dietary zinc.[4]

Contributing Institution:
University of Missouri
Veterinary Medical Diagnostic Laboratory
vmdl.missouri.edu

JPC Diagnosis:
1. Spinal cord: Neuroaxonal degeneration, bilaterally symmetrical, moderate, with neuronal chromatolysis.

2. Cerebellum, Purkinje and granular cell neurons: Necrosis and loss, multifocal.

JPC Comment:
The contributor provides a concise review of copper deficiency, also known as hypocupremia, in ruminants.

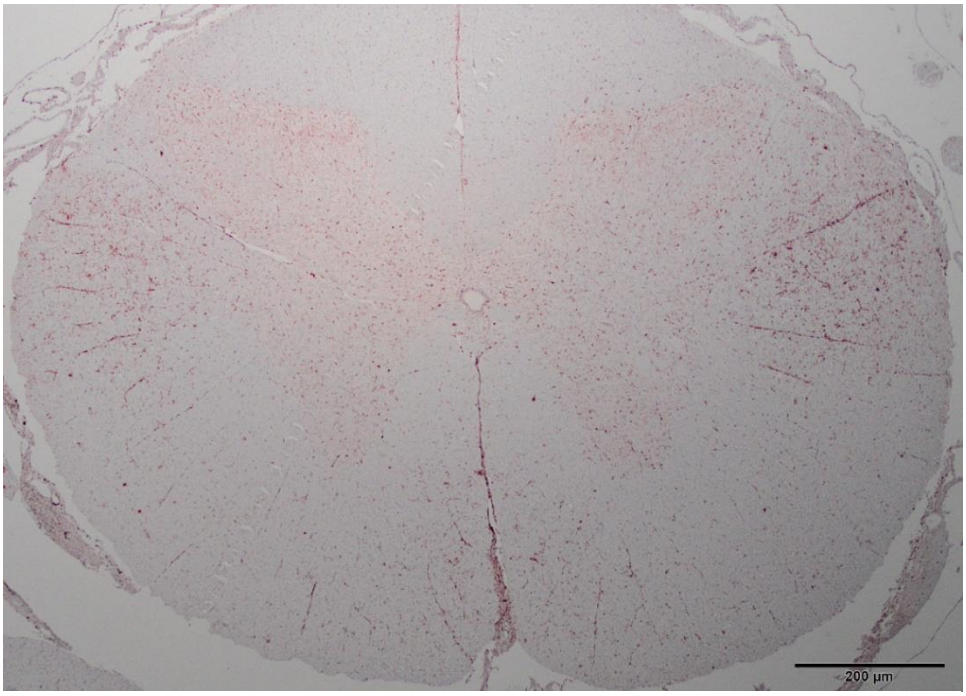

Figure 1-4. ***Spinal cord, goat: A stain for IBA-1 demonstrates enhanced staining in areas of axonal damage. (anti IBA-1, 40X) (Photo courtesy of: Veterinary Medical Diagnostic Laboratory, University of Missouri; vmdl.missouri.edu)***

Swayback and enzootic ataxia are two similar small ruminant central nervous system (CNS) diseases that occur as a result of a copper deficiency and are predominantly observed in small ruminants. Swayback is the term applied to the congenital form of disease which is primarily seen in neonatal lambs and rarely in kids. In contrast, enzootic ataxia has a delayed onset of clinical signs which typically manifest between one week and six months of age and affects both lambs and kids. Neonates with swayback are often stillborn, weak, unable to stand, or are ataxic while juveniles that develop enzootic ataxia are normal at birth but subsequently develop signs of disease characterized by incoordination, ataxia, and posterior paresis.[2]

Both forms of disease are due to insufficient dietary copper uptake, either by the dam while the fetus is in utero (swayback) or by the neonate following parturition (enzootic ataxia). Copper absorption from the diet is determined by the type of food, the mineral composition of the foodstuff, and the interactions between the food type and mineral composition. Copper is best absorbed from diets low in fiber, such as cereals, while fresh roughage is a poor source of copper. Due to the poor availability of copper in grass, primary copper deficiency most commonly affects grazing animals.[3] In addition, elevations of dietary molybdenum, cadmium, sulfates, and other minerals or substances can interfere with copper absorption and utilization, resulting in secondary copper deficiency.[1,2]

As described by the contributor, copper is an essential cofactor utilized by multiple enzymes key to the function and development of the CNS, including the mitochondrial enzyme cytochrome oxidase. Dysfunction of this enzyme has been described in sheep and goats with swayback, resulting in decreased energy production and disruption of homeostasis within motor neurons.[5]

Both enzootic ataxia and swayback result in bilaterally symmetrical lesions of the grey and white matter within the cerebellum, brainstem, and spinal cord of both lambs and kids. Cerebral lesions are also observed in cases of swayback.[5]

Affected neurons are frequently swollen with chromatolysis, ranging from central chromatolysis with an eccentric nucleus to complete disappearance of Nissl substance with disruption and loss of nuclei (ghost cells). Other neurons are variably dense pink, and homogenous to fibrillar cytoplasm (due to accumulation of neurofilaments), have eccentric nuclei, and are variably necrotic.[5] In cases of

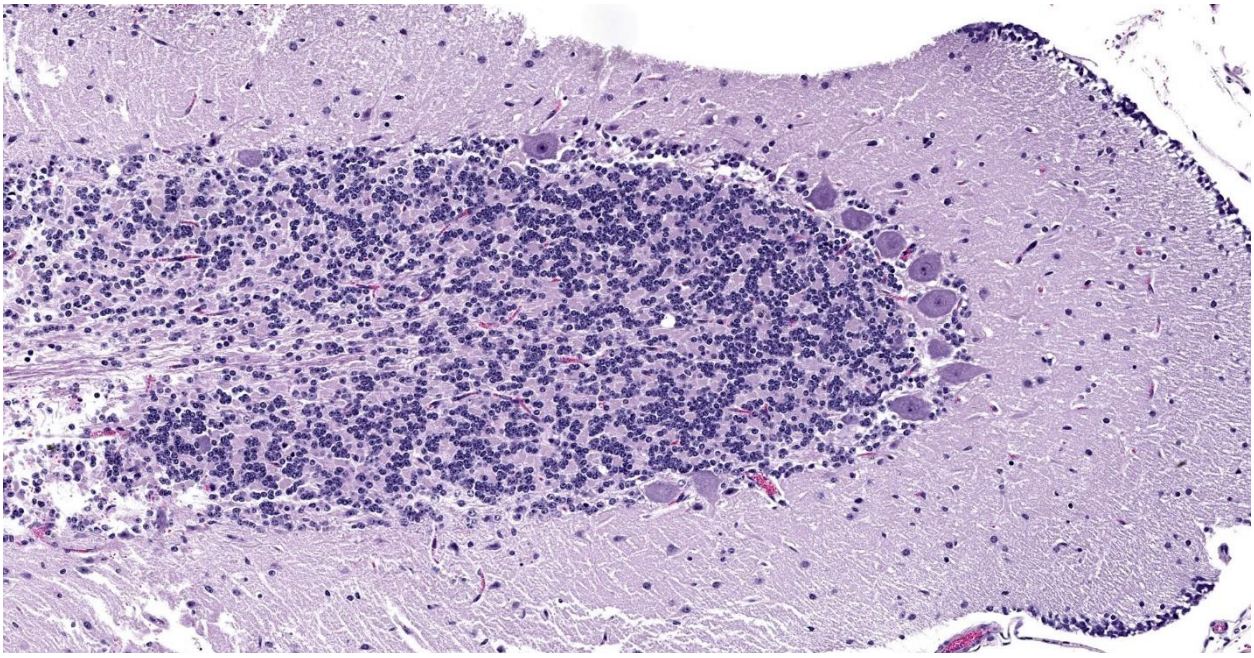

Figure 1-5. ***Cerebellum, goat. Cerebellar folia are decreased in size, and there are large stretches in which Purkinje cells are loss and an overall loss of nuclei in the granular layer. (HE, 159X)***

enzootic ataxia, affected neurons include the reticular formation in addition to the red and vestibular nuclei within the brainstem; the ventral, lateral, and less commonly the dorsal horns of the spinal cord; and Purkinjie cells within the cerebellum, which is also characterized by thinning of the granule cell layer and hypertrophic Bergmann glial cell processes within the molecular layer.[5] In addition, Wallerian type degeneration is frequently observed in ventral spinal nerve rootlets and peripheral nerves.[5] Respiratory stridor, likely due to degeneration of the recurrent laryngeal nerve may also be clinically observed.[5]

Affected regions of white matter are characterized by areas of pallor due to degeneration of myelinated axons. Specific regions of affected white matter affected by enzootic ataxia include the spinocerebellar tracts extending into the middle cerebellar peduncles and the lateral and ventral funiculi of the spinal cord.[5]

While the above described lesions are characteristic, demonstration of low concentrations of copper in liver samples is diagnostic.[1]

References:

1. Allen AL, Goupil BA, Valentine BA. A retrospective study of spinal cord lesions of goats submitted to 3 veterinary diagnostic laboratories. *Can Vet J*. 2012;53:639-642.
2. Cordy DR, Knight, HD. California goat kids with a disease resembling enzootic ataxia or swayback. *Vet Pathol*. 1978;15:179-185.
3. Banton M, Lozano-Alcarcon F, Nicholson SS, et al. Enzootic ataxia in Louisiana goat kids. *J Vet Diagn Invest.* 1990;2:70-73.
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CASE II: 18-6787 (JPC 4116588-00)

Figure 2-1. ***Uterus, goat: A section of uterus (mesometrium to left) is submitted for examination. The uterine wall is diffusely, transmurally, and asymmetrically expanded up to 8mm and the architecture is effaced by an infiltrative neoplasm. (HE, 4X)***

Signalment:
15-year-old, female, Nigerian dwarf goat (*Capra aegagrus hircus).*

History:
One month history of hematuria, stranguria, polakiuria. By CT there was thickening of the reproductive tract causing compression of the ureters and secondary hyrdoureter and hydronephrosis. Multiple lung nodules bilaterally.

Gross Pathology:
A 26kg Nigerian Dwarf ewe in good body (BCS 3/5) and excellent postmortem condition is necropsied. Conjuctiva and oral mucous membranes are white. The metaphyseal bone marrow from the right femur is white with two small red areas (~3mm) on the lateral aspects. There is a ~5x3cm cystic mass embedded in the fascia between ventral cervical muscles near the thoracic inlet. Both thyroids contain numerous small cysts (~2-3mm in diameter). The lungs contain multifocal semifluctuant white nodules (~1-3cm in diameter) randomly distributed throughout the lung lobes; these nodules contain central areas of necrosis on sectioning. A similar nodular change effaced a tracheobronchial lymph node. The liver contains multifocal firm white areas with irregular margins (~1-3cm in diameter); these foci are solid white on sectioning.

The body of the uterus is firm with multifocal tan, slightly raised nodules on the serosal surface; on cross section, there is annular thickening with necrotic areas and red, mucoid material in the lumen. Both uterine horns contain inspissated pus (pyometra). There are fibrous adhesions between the dorsal aspect of the uterine body and the ventral aspect of the urinary bladder which is moderately distended with clear, yellow urine. The mesovarium and mesometrium is moderately edematous.

The urethra is entrapped in the fibrous adhesions between the bladder and uterus. Both kidneys have moderately dilated pelvises (hydronephrosis).

The right adrenal cortex has a small (~5mm) cyst filled with clear, yellow fluid.

The forestomach is full of fibrous feed. The small intestines contain liquid dark green ingesta. There are formed feces in the distal colon.

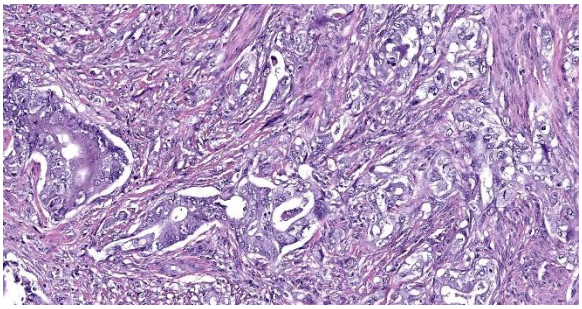

Figure 2-2. Uterus, goat. The neoplasm is composed of neoplastic epithelium forming glands and acini within a moderate fibrous stroma. (HE, 270X)

Laboratory Results:
None.

Microscopic Description:
Uterine body - The submucosa-lamina propria is circumferentially infiltrated by neoplastic epithelium forming broad trabeculae and sometimes forming tubular structures surrounded by dense, highly cellular fibrous tissue (desmoplastic response). Neoplastic epithelium exhibits marked anisocytosis and anisokaryosis with regular karyomegaly. They contain round to

ovoid, vesiculated nuclei and a small amount of basophilic cytoplasm. In more differentiated areas with tubular formation, the epithelial cells attain a cuboidal to columnar morphology while in less differentiated areas they are rather pleomorphic, ranging from polygonal to spindloid. There are 25 mitotic figures in 10 high power fields. Scattered within the neoplastic population is another cell population that exhibits more pleomorphism, contains a single, large deeply basophilic nucleus with coarsely-clumped chromatin and a small amount of eosinophilic cytoplasm (syncytiotrophoblasts); these cells can also be seen scattered without the surrounding desmoplastic stroma. Neoplastic epithelium and its accompanying desmoplastic response extends through the myometrium and abut the surrounding serosa, enveloping peripheral nerves. Vascular tumor emboli are present at the periphery. There are multifocal areas of lytic necrosis throughout the neoplasm (comprising ~20%) and scattered apoptotic cells within viable tissue. There is mild necrosis of surrounding adipose tissue.

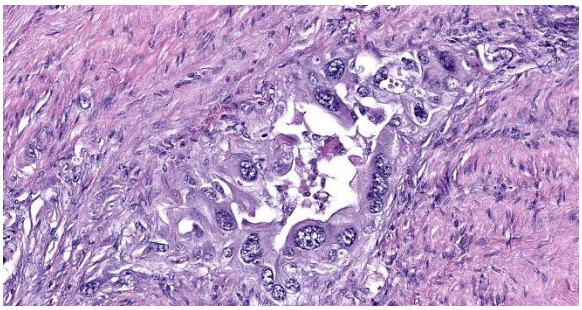

Figure 2-3. Uterus, goat. There is marked anisokaryosis and anisocytosis of neoplastic glandular epithelium. (HE, 360X)

Contributor's Morphologic Diagnosis: Uterine ductal carcinoma, transmural, with vascular invasion and intratumoral syncytiotrophoblasts (consistent with choriocarcinomatous differentiation).

Other lesions (not submitted):
1. Hepatic and pulmonary metastases.
2. Renal interstitial fibrosis with protein, hyaline and cellular casts.
3. Cystic thymoma (suspect).

Contributor's Comment:
Histopathology confirms the presence of uterine carcinoma, with a tubular pattern predominating. In general, neoplasia is uncommon in goats, with one large case series finding an incidence of 8.7%.[6] With regard to the uterus, leiomyomas were most common though case reports of leiomyosarcoma and adenocarcinoma have been documented.[1]

The striking variance in cellular morphology may reflect transition into what is known as choriocarcinomatous differentiation, which has been documented in both humans and an aged goat.[5] In these tumors, there are two distinct neoplastic populations, one which attains the typical ductal epithelium and another which resembles syncytiotrophoblast-like multinucleated giant cells mixed with highly pleomorphic cytotrophoblast-like cells. The former morphology is more consistently found within metastatic lesions in these neoplasms as was seen in this case (metastatic lesions not submitted). The prognostic significance of this type of differentiation is uncertain in caprine species, though expression of embryonic proteins may indicate a more primitive/anaplastic transformation has occurred which potentially behave more aggressively. To confirm this variant we would need to have IHC performed on uterine sections to prove production of chorionic origin antigens, such as chorionic gonadotrophins, within the more pleomorphic cell population.

Other domestic species including rabbits and pigs have been reported to develop choriocarcinomas, neoplasms of trophoblastic origin, without an endometrial component.[3,4] These can be subdivided into gestational (i.e. derives from placental tissue during pregnancy) and nongestational (i.e. derives from germ cells within ovarian tissue). Ovarian/nongestational choriocarcinomas have also been documented in non-human primates such as rhesus macaques[2] and a cynomolgus monkey.[8]

Contributing Institution:
Oregon Veterinary Diagnostic Laboratory
Oregon State University
Carlson College of Veterinary Medicine
30th and Washington Way
Corvallis, Oregon 97331.
https://vetmed.oregonstate.edu/diagnostic

JPC Diagnosis:
Uterus: Uterine adenocarcinoma.

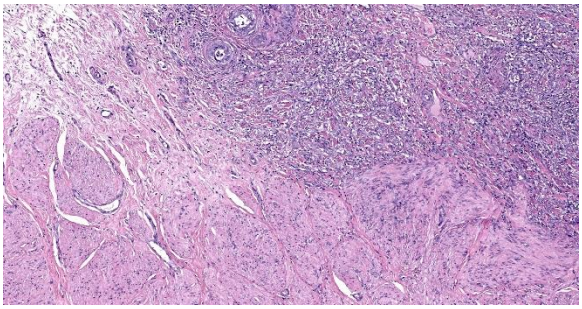

Figure 2-4. Uterus, goat. The neoplasm transmurally effaced the wall of the uterus; in this section, the neoplasm is infiltrating the last remaining area of smooth muscle. (HE, 120X)

JPC Comment:
Conference attendees were in agreement with the contributor in regard to the diagnosis of uterine adenocarcinoma. Confirmation of choriocarcinomatous differentiation was attempted using a battery of immunohistochemical stains, including human chorionic gonadotrophin (hCG), α-inhibin, and human placental alkaline phosphatase (hPLAP). Unfortunately, immunohistochemical stains for hCG, α-inhibin, hPLAP were non-contributory and choriocarcinomatous differentiation could not be confirmed.

Epithelial neoplasms of the caprine reproductive tract are relatively uncommon. In one study, there were only two reports of uterine adenocarcinoma following a retrospective review of 100 goats with 102 tumors.[6] Furthermore, the presentation of uterine adenocarcinoma with pleomorphic cells suggestive of choriocarcinomatous differentiation in this case is exceedingly rare, although a similar case of endometrial adenocarcinoma with choriocarcinomatous differentiation was confirmed in an aged goat, as noted by the contributor.[5]

Choriocarcinoma is a spontaneously occurring, highly malignant, biphasic trophoblastic tumor composed of cytotrophoblastic and syncytiotrophoblastic cellular components and is very rare in both animals and humans.[3] As described by the contributor, nongestational choriocarcinomas typically arise within the ovaries; however, nongestational choriocarcinomas can rarely arise from trophoblastic differentiation within poorly differentiated carcinomas, including endometrial carciomas.[3] Three hypotheses have been proposed in regard to choriocarcinomatous differentiation in endometrioid adenocarcinoma and are as follows: (1) dedifferentiation of epithelial cells into choriocarcinoma, (2) germ cells that fail to complete migration to the gonads, and (3) multidirectional tumor differentiation from a common stem cell.[5]

Participants noted the presence of neoplastic cells within not only lymphatics but also nerve ganglia, a feature consistent with perineural invasion. Physically, epineurial, perineurial, and endoneurial spaces of the neuronal sheath are loose connective tissues that can be exploited as low-resistance channels that allow for the rapid migration of neoplastic cells. In humans, perineural invasion has been shown to be a negative prognostic indicator in cases of endocervical adenocarcinoma in addition to other neoplasms.[7]

References:

1. Dockweiler JC, Cossic B, McDonough SP, et al. Tumor collision of uterine adenocarcinoma and leiomyosarcoma in a goat. *J Vet Diagn Invest* 2017;29(5):696-699.
2. Farman CA, Benirshcke K, Horner M, Lappin P. Ovarian choriocarcinoma in a Rhesus monkey associated with elevated serum chorionic gonadotropin levels. *Vet Pathol*. 2005;42(2):226-225.
3. Hirata A, Miyazaki A, Sakai H, et al. Choriocarcinoma-like tumor in a potbellied pig (*Sus scrofa*). *J Vet Diagn Invest*. 2014;26(1):163-166.
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rabbit (*Oryctolagus cuniculi*). *Vet Pathol*. 2008;45(1):77-79.
5. Kawashima M, Segawa R, Toshinori Y, et al. Endometrial adenocarcinoma with choriocarcinomatous differentiation in the uterus of a goat. *J Vet Med Sci*. 2017;79(6):1091-1095.
6. Lohr CV. One hundred and two tumors in 100 goats (1987-2011). *Vet Pathol*. 2012;50(4):668-675.
7. Wang W, Song G, Lin J, et al. Study of the revisited, revised, and expanded Silva pattern system for Chinese endocervical adenocarcinoma patients. *Hum Pathol*. 2019;84:35-43.
8. Yokouchi Y, Imaoka M, Syama A, Sanbuissho A. Mixed germ cell tumor with embryonal carcinoma, choriocarcinoma and epitheloid trophoplastic tumor in the ovary of a Cynomolgus monkey. *Toxicol Pathol*. 2011;39(3):553-558.

CASE III: 20-23 (JPC 4118594-00)

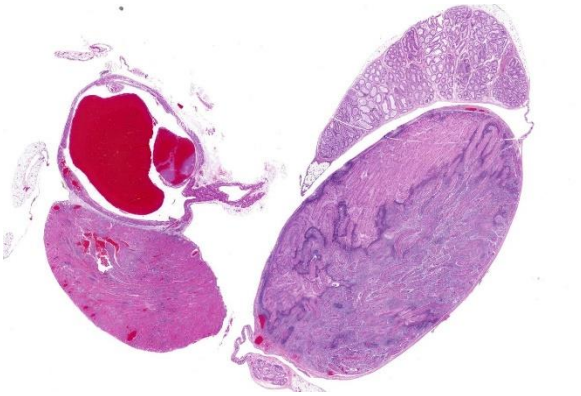

Figure 3-1. Heart, and testis, rat. At subgross magnification, there is marked atrial dilatation on the sagittal section of heart and areas of hypercellularity in the myocardium. There is diffuse loss of tubular architecture in the testis, and a large infarct outlined by a dense hypercellular band. (HE, 5X)

Signalment:

4-month-old, male, F344-*Il2rg/Rag2*^{em1Iexas} rat (*Rattus norvegicus domestica).*

History:

A cohort of 9 adult rats were received in order to expand a breeding colony for transplant research.

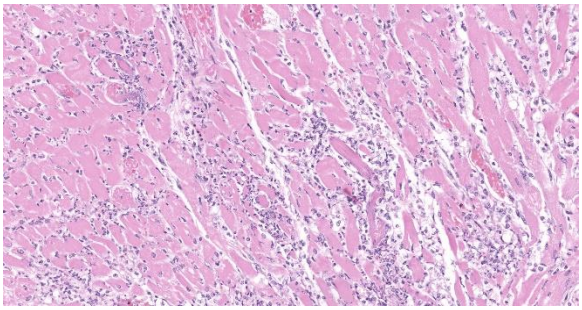

Figure 3-2. Heart, rat: There are large, coalescing areas of cardiomyocyte necrosis with infiltration by large numbers of viable and necrotic neutrophils. (HE, 400X)

Within 2 months, all animals aside from 1 female had either died or were euthanized in moribund condition. Clinical symptoms in rats that had them included hunching, weight loss, ataxia, and swollen limbs. Other animals were found dead with no previous clinical symptoms.

Gross Pathology:

Some animals had no gross lesions while others had white foci in various organs, most often the heart, kidneys, and livers. This animal also had enlarged, white-tan testes.

Laboratory Results:

Streptococcus suis was isolated from the blood via bacterial culture/sensitivity at necropsy.

Microscopic Description:

Heart: Throughout the myocardium, there are multifocal to coalescing aggregates of neutrophils and fibrin which separate, surround, and replace cardiomyocytes. Remaining cardiomyocytes in these areas either swollen with vacuolated sarcoplasm (degenerate), or shrunken with hypereosinophilic sarcoplasm, loss of cross striations, and pyknotic nuclei (necrotic). Multifocally, blood vessels contain adherent fibrin thrombi that contain enmeshed neutrophils and colonies of bacterial cocci.

Testis: Diffusely within the interstitium, separating and surrounding seminiferous tubules are aggregates of neutrophils (often degenerate), fibrin, macrophages, and colonies of bacterial cocci. Intravascular fibrin thrombi and necrosis of blood vessel walls are frequently observed as are areas of lytic and/or coagulative necrosis. Seminiferous tubules are degenerative to completely necrotic (degree varies based on

slide) with Sertoli cell vacuolation, spermatocyte necrosis, giant spermatids, and disorganization/loss of germ cells.

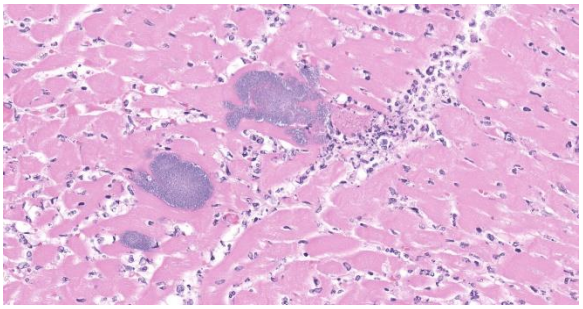

Figure 3-3. ***Heart, rat: There are numerous large colonies of cocci scattered throughout areas of necrotic myocardium. (HE, 380X)***

Contributor's Morphologic Diagnosis:
1. Heart: Myocarditis, suppurative, severe, multifocal to coalescing, with vascular thrombi and intralesional bacterial cocci

2. Testis: Orchitis, necrosuppurative, severe, diffuse with vascular thrombi and intralesional bacterial cocci

Contributor's Comment:
The F344-*Il2rg/Rag2* ^{em1Iexas} rat strain shows severe combined immunodeficiency caused by 5-bp deletion in *Il2rg* gene on the X chromosome and 1-bp insertion in *Rag2* gene on chromosome 3.[4] Like their mouse counterparts, these rats have high immunocompromised symptoms due to the simultaneous absence of mature T-cells, B-cells, and NK cells as well as defective macrophage activity and reduced dendritic cell function.[5] This model is ideal for studies involving implantation of human tissue; however, they are also extremely susceptible to secondary infections, particularly at the time of transport. Necrosuppurative lesions were also found in other organs including kidneys, meninges, joints (one animal), and liver. The testicular lesions were only noted in a single animal, and both testes were affected.

Streptococcus suis causes well-defined streptococcal septicemia in swine. The organism is carried in the palatine tonsils of pigs, and infection is likely spread via the respiratory route. Although outbreaks may occur, sporadic and isolated disease is more common. Lesions most frequently include purulent meningitis and polyserositis. Additional lesions that can be seen include purulent arthritis, fibrinopurulent pericarditis, endocarditis, or hemorrhagic, necrotizing myocarditis. Serotype 2 is the most commonly isolated serotype isolated from pigs and humans and is the most pathogenic serotype.[1]

S. suis is a significant human pathogen, particularly in southeast Asia, posing a challenge to public health.[1,2] Human disease most frequently can include meningitis, septicemia, and pneumonia with arthritis, endocarditis, streptococcal toxic shock-like syndrome (STSLS) occurring less commonly.[2]

An interesting feature of this case is the severity of the lesion in the testis. This is not a commonly described feature of *S. suis* in any species. There is a case report in a human from Thailand experiencing acute pyogenic arthritis with orchitis also described, though details of the testicular lesions are not detailed.[4]

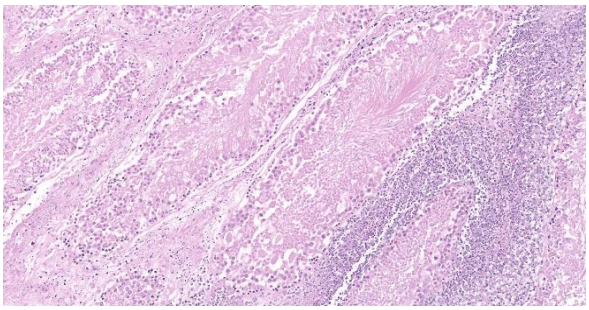

Figure 3-4. ***Testis, rat: Approximately 33% of the testis is exhibits coagulative necrosis, and is bounded by bands of necrotic neutrophils and cellular debris. (HE, 136X)***

Contributing Institution:
Division of Laboratory Animal Resources
University of Pittsburgh
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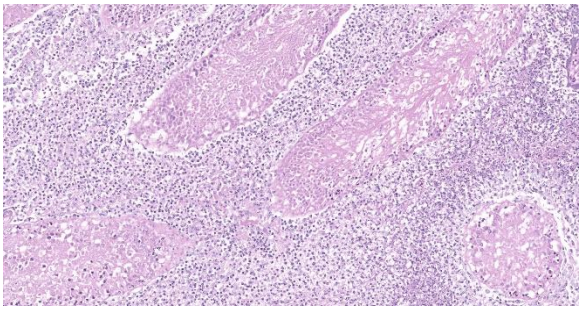

Figure 3-5. Testis, rat: The remainder of the testis is undergoing lytic necrosis. (HE, 140X).

JPC Diagnosis:
1. Heart: Myocarditis, necrotizing and suppurative, multifocal to coalescing, marked, with vasculitis and thrombosis, mural endocarditis, and large colonies of bacterial cocci.

2. Testis: Orchitis, necrotizing, diffuse, severe (infarct), with necrotizing arteritis and large colonies of bacterial cocci.

JPC Comment:
The contributor provides a concise overview of the spectrum swine and human lesions caused by *Streptococcus suis* in addition to the unique circumstances likely contributing to the lesions observed in this case.

S. suis is a gram-positive facultative anaerobe that is spherical to oval in shape and exists in pairs and short chains. When cultured on blood agar, a zone of green discoloration is formed around colonies (α-hemolysis).[2]

S. suis can be cultured from blood or CSF samples obtained from septicemic patients and/or those with meningitis via standard microbiological techniques; however, it is often misidentified or the infection goes undiagnosed. Based on one author's experience, *S. suis* is commonly misidentified and reported as *Streptococcus* species α-hemolyic or viridans streptococci, *Enterococcus faecalis*, *Aerococcus viridans*, and *S. pneumonia*.[6]

35 *S. suis* serotypes (1 to 34 and 1/2) were initially identified based on the antigenic composition of the bacterial capsule during early classification.[3] However, subsequent studies have demonstrated serotypes 32 and 34 belong to *Streptococcus orisratti* and analysis of 16S ribosomal RNA of serotypes 20, 22, and 26 revealed these serotypes are also genetically different, resulting in a new species coined *Streptococcus parasuis*. Therefore, *S. suis* is currently composed of 29 serotypes, with serotype 2 strains recognized as the most virulent and widely studied.[3]

In regard to zoonosis, *S. suis* is a worldwide threat due to its distribution, although the majority of reported human infections originate in Southeast Asia.[6] Studies in Vietnam and China have found occupational or household exposure occurring during the slaughtering and trimming process of pig carcasses and the handling and consumption of pork-derived products are significant risk factors for zoonotic transmission. In addition, farmers in these countries were found to be at increased risk due to the common practices of sharing accommodations with pigs and the slaughtering and consumption of diseased animals at home.[6]

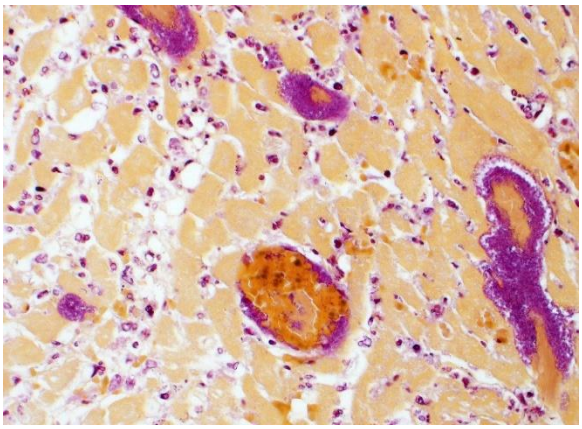

Figure 3-6. ***A Gram stain highlights the presence of large colonies of cocci within the lumen of small veins and the interstitium. (Brown-Brenn, 400X)***

A systematic survey of bacterial meningitis in Vietnamese adults recently suggested *S.* suis serotype 2 is the most common pathogen associated with human bacterial meningitis within that population. Although mortality was relatively low (2.6%), hearing loss was a common complication (66.4%).[2]

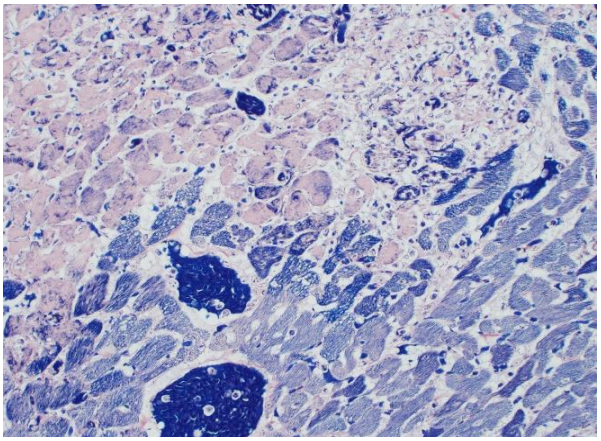

Figure 3-7. ***Heart, rat. The supravital staining provided by phosphotungstic acid hematin staining easily demonstrates the areas of recent necrosis of cardiac (upper left) and skeletal muscle. (PTAH, 200X)***

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CASE IV: 20-21 345 (JPC 4153945-00)

Signalment:
13-year-old, female, rhesus macaque (*Macaca mulatta*).

History:
This rhesus monkey has a two-year history of severe menses. The monkey would become pale, quiet, lethargic and hyporexic during these periods. Subcutaneous fluids and other supportive care were provided during these periods and ultimately the animal would recover over the course of a few weeks. During the monkey's last month, she began to rapidly decline, in the absence of menses, which was characterized by decreased activity/recumbency in her cage, and weight loss where she would no longer take treats from staff. Ultimately euthanasia was elected due to the clinical decline of the animal.

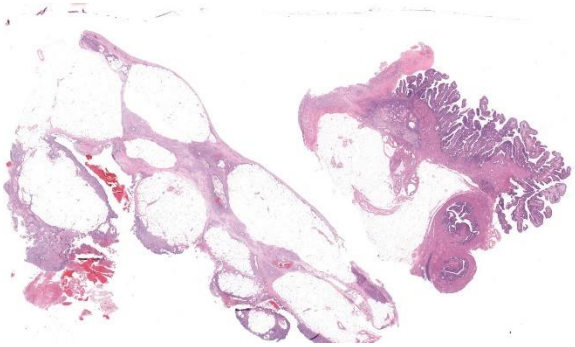

Figure 4-1. ***Oviduct, ovary, and mesentery, rhesus macaque. At subgross magnification, oviduct serosa is expanded by uterine glands and stroma, which also infiltrate the adjacent mesometrium and mesentery. Ovarian tissue is fused with the infundibulum of the oviduct. (HE, 5X)***

Gross Pathology:
No gross description or images were provided by the clinical veterinarians. Their working diagnosis was endometriosis and they submitted a sample of uterus and mesenteric mass for confirmation.

Laboratory Results:
Comprehensive CBC 6 months prior to euthanasia was consistent with a hypochromic and macrocytic regenerative anemia. Clinically this was attributed to iron deficiency affiliated with chronic blood loss.

CBC Parameters	
WBC (k/ul)	9.4[1]
RBC (M/uL)	3.30
HGB (g/dL)	9.6
HCT (%)	33.9
MCV (fL)	103
MCH (g/pg)	29.1
MCHC (g/dL)	28.3
Platelet Count (K/uL)	361
RBC Morphology	
Reticulocyte (%)	18.4
Absolute Reticulocyte (K/uL)	607
Nucleated RBC (/100 RBC)	25
Polychromasia	Moderate
Anisocytosis	Moderate
Poikilocytosis	Moderate
Heinz bodies	None seen
Differential Absolutes	
Neutrophils (/uL)	5358
Bands (/uL)	0
Lymphocytes (/uL)	2820
Monocytes (/uL)	1222
Eosinophils (/uL)	0
Basophils (/uL)	0
WBC corrected for the presence of nucleated RBC's[1]	

Microscopic Description:
Uterus: The myometrium is multifocally thickened by hyperplastic islands and focal aggregates of papillary fronds of endometrial glands and stromal elements (adenomyosis), which disrupt and replace smooth muscle bundles. Occasionally similar findings extend to the perimetrium and adjacent mesentery (endometriosis). Lumina of endometrial glands occasionally are ectatic containing variable amounts of eosinophilic homogenous material (secretory product) admixed with cellular debris and moderate numbers of neutrophils and macrophages. The myometrium occasionally contains dense aggregates of pigment laden histiocytes interpreted to represent hemosiderin (chronic hemorrhage). There are rare lymphocytes, plasma cells and neutrophils within the uterine stroma. The uterine lumen contains low numbers of erythrocytes, eosinophilic homogenous material, and neutrophils.

Mesentery: Expanding and effacing the mesentery are multiple, infiltrative islands of endometrial glands surrounded by abundant, densely cellular endometrial stroma. The endometrial glands are lined by simple to pseudostratified columnar epithelial cells with a moderate amount of clear to pale eosinophilic cytoplasm and prominent basilar vacuolation. Nuclei are anti-basilar and oval with finely stippled chromatin. Occasionally, glands contain moderate numbers of macrophages, neutrophils, erythrocytes, and exfoliated cellular debris.

Contributor's Morphologic Diagnoses:
1. Uterus: Adenomyosis and endometriosis

2. Peritoneum: Endometriosis

Contributor's Comment:
Endometriosis (endometrial glands or stroma explanted outside of the uterus-i.e., ovary, peritoneum) and adenomyosis (endometrial stroma and/or glands confined within the myometrium of the uterine wall) are non-neoplastic, estrogen-dependent, hyperplastic lesions of endometrial elements. In humans this condition has been reported to affect 10-15% of women in reproductive age, while prevalence in aged intact-female cynomologous macaques has been reported as high as 28.7%.[1,7] The menstrual cycle of rhesus monkeys (*Macaca mulatta*) is seasonal, while that of baboons (*Papio* spp.) and cynomolgus monkeys (*Macaca fascularis*) is similar to humans (~4-week menstrual cycle). Accordingly, the later two are considered more relevant spontaneous models of endometriosis.

Histologic components of adenomyosis and endometriosis are heterogenous and include variable ratios of endometrial epithelium and CD10 positive stromal cells with hemorrhage and inflammation, but also smooth muscle metaplasia and nerve fibers.[5,6]

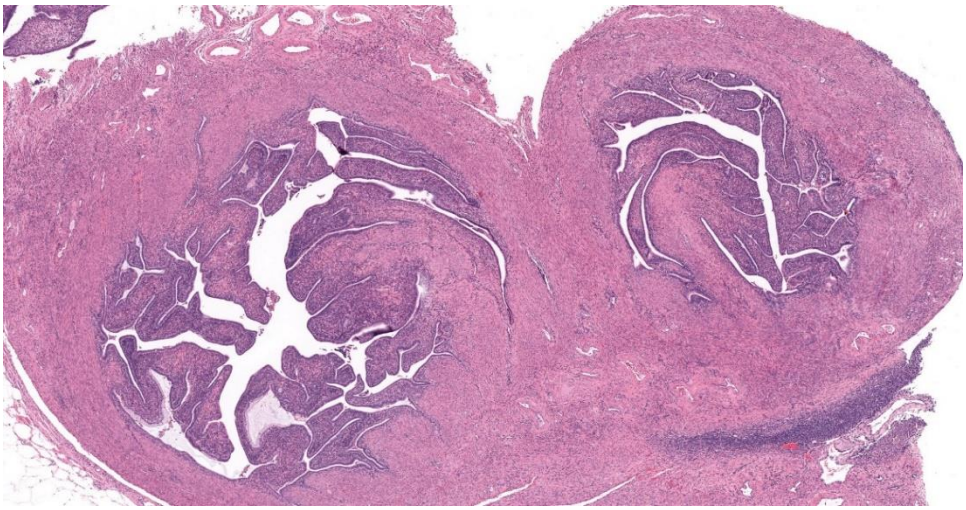

Figure 4-2. ***Oviduct, rhesus macaque. Oviduct serosa (bottom right) is infiltrated by uterine glands and stroma (endometriosis). (HE, 32X)***

Gross differential diagnosis such as carcinomatosis and mesothelium are readily ruled out microscopically, given both of these conditions display features of malignancy such as cellular pleomorphism and a high mitotic index that is not observed with adenomyosis and endometriosis.

In humans, common clinical signs and or symptoms include severe dysmenorrhea, chronic pelvic pain, diarrhea and constipation and infertility.[3] Fortunately in both humans and non-human primates, clinical progression is typically slow and for the most part stable over long periods of time. Complete resection of all visible foci of disease via surgery offers the best control of symptoms, however the possibility of achieving this goal both in humans and NHPs is limited by the difficulty of detecting all foci and the risks associated with radical surgical strategies, including additional seeding within laparotomy scars.[8]

Effective clinical screening for endometriosis in NHP colonies includes the observation of regular menstrual bleeding, serum Cancer antigen 125 (CA125) levels and palpation of the abdomen. Elevated serum CA125 levels are correlated with the presence of chocolate cysts in monkeys with endometriosis as well as humans.[4,6] Longitudinal MRI screening in at risk populations has received recent attention as a non-invasive method both in human clinics as well as NHP breeding colonies, but is logistically and financially restrictive.[9] Regardless of approaches, screening is recommended in rhesus and cynomolgus monkeys within the 11-20-year-old age group, which are at a greater frequency of menstrual bleeding and active ovarian function. Decreased food consumption has been indicated as a proposed terminal endpoint for endometriosis in NHPs knowing that this relates to severe pelvic pain and reduce quality of life.[6]

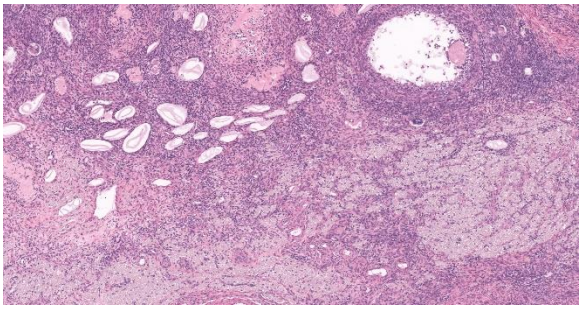

Figure 4-3. ***Ovary, rhesus macaque. Multifocal follicles of varying maturity in addition large aggregates of thecal cells with yellow-brown pigment (corpus luteum). (HE, 74X)***

Contributing Institution:
Department of Pathology and Laboratory Medicine
Boston University Medical Campus
http://www.bumc.bu.edu/busm-pathology/

JPC Diagnosis: Oviduct, serosa and mesentery: Endometriosis with ovarian adhesion.

JPC Comment:
The contributor provides an excellent overview of endometriosis in NHPs and humans.

Interestingly, diagnosis of endometriosis remains a difficult and often lengthy process despite the prevalence of this condition in both NHP and humans. On average, women 18-45 years old

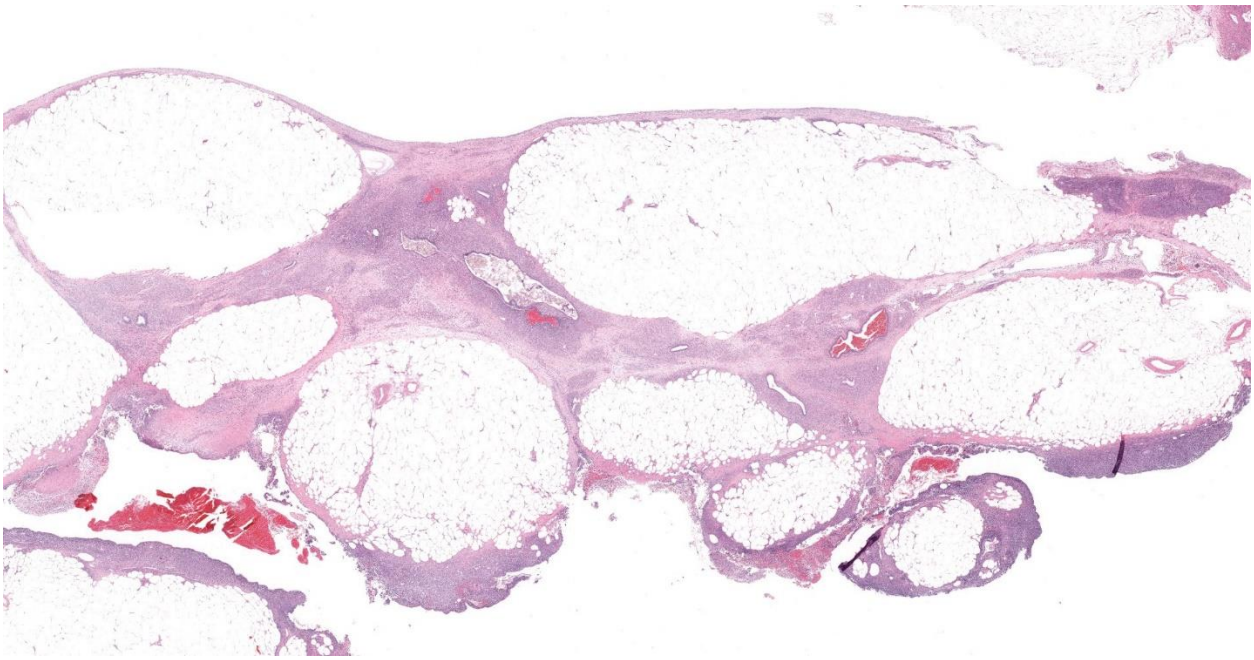

Figure 4-4. ***Mesentery, rhesus macaque. The mesentery is infiltrated and lobules of adipocytes are surrounded by infiltrating endometrial glands and uterine stroma, often in turn surrounded by dense fibrous connective tissue. (HE, 9X)***

with endometriosis symptoms are not diagnosed for 6.7 years.[7] Clinical history, physical exam, and testing for other common causes of pelvic pain often begin the diagnostic process, followed by transabdominal or transvaginal ultrasounds and occasionally MRI and CT.[7] Numerous biomarkers and assays have been evaluated as less invasive diagnostic tools, but thus far none have proven reliable.[7] Diagnosis and the development of minimally invasive testing is presumably complicated by a lack of clear pathogenesis for endometriosis.

Retrograde menstruation is the most evidentially supported hypothesis, during which endometrial fragments adhere to the mesothelium and in the absence of an appropriate immune response begin to grow, bleed cyclically, and eventually cause adhesions and fibrosis.[5] While this hypothesis has the most supporting evidence, additional research suggests alternative causes or contributing factors toward the development of endometriosis. This argument is partially based on the idea that retrograde menstruation is common in menstruating women, while the prevalence of endometriosis is low.[7] This mismatch of prevalence leads to the idea that other factors including hormones, inflammation, and immunologic status may also play a role in its development. In the face of these barriers, biopsy and histological confirmation remain gold standard for definitive diagnosis.[7]

Grossly, endometriosis is described in humans and NHPs as "chocolate cysts" that are brown, reddish, black, or blueberry in color and are found to be associated with the ovaries, uterus, and sometimes the surface of other organs or the peritoneal wall. Severe abdominal adhesions are also commonly described in both human and NHP with severe endometriosis.[5]

The unique histomorphologic features within the submitted section generated spirited discussion amongst conference participants in regard to tissue and lesion identification. The case was subsequently referred to our colleagues within the subspecialty of (human) reproductive pathology.

Following consultation and further discussion amongst the staff, there is consensus that regions of tissue described as adenomyosis are more consistent with oviduct and adhered atypical ovarian tissue.

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