

**The Armed Forces Institute of Pathology
Department of Veterinary Pathology
Wednesday Slide Conference
2009-2010
Conference 20
7 April 2010**

Conference Moderator:

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CASE I: AFIP Case 2 (AFIP 3066307).

Signalment: 12-year-old, female, Quarterhorse mare (*Equus caballus*); placental tissues retrieved at 310 days of gestation.

History: Placental tissues submitted were from a 12-year-old, multiparous, Quarterhorse mare. The mare produced a live foal in 2006. The mare was pregnant in 2007 with a thickened placenta detected by ultrasound at 290 days of gestation. The animal was treated medically for placentitis and delivered a live foal naturally at 310 days of gestation. The placenta was submitted for laboratory analysis.

Gross Pathology: Gross examination revealed a large region of placentitis on the dorsal chorionic surface near the cervical star. The placentitis was characterized by a markedly thickened placenta that was discolored brown and covered with a “mucoid-type” film. Gross morphologic diagnosis: Placentitis, cervical star region of the body.

Laboratory Results: Aerobic bacterial culture: Trace numbers of *Delftia acidovorans*, *Acinetobacter lwoffii* and *Staphylococcus epidermidis*. Fungal culture: *Bipolaris* sp.

Histopathologic Description: Histopathology revealed focally severe inflammation (suppurative and pyogranulomatous) along the chorionic surface with small bacterial rods, fungal hyphae and cellular debris. On H&E stains, the fungi (depending on the section) are inconspicuous. Of those present, few are pigmented. On GMS, the numbers and morphology of fungi are evident. The fungi are characterized by hyphae exhibiting non-parallel walls, 3-7 µm in width with occasional septa and branching. Branching occurs at both right and acute angles.

Contributor’s Morphologic Diagnosis: 1. Placenta: Marked pyogranulomatous placentitis, chronic with necrosis and squamous metaplasia.
2. Amnion: Membrane hyperplasia with moderate funisitis.

Contributor’s Comment: Placentitis is an important cause of equine reproductive loss with some variations in etiologies based upon the geographic distribution of the mares. *Streptococcus zooepidemicus*, *Escherichia coli*, *Pseudomonas aeruginosa*, *S. equisimilis*, *Enterobacter* sp. and *Klebsiella pneumonia* are bacterial agents most frequently isolated.(1) The distribution of the placentitis has important implications for the etiopathogenesis.(1,2) A diffusely distributed placentitis is more often found in early reproductive losses (mid-gestation or earlier), whereas focal placentitis, particularly at/or near the cervical star, is most frequently found in late gestational losses. Diffuse placentitis is the result of hematogenous infection; focal placentitis is associated with an ascending infection through the cervix.

Though recognized less often than bacterial placentitis, mycotic placentitis is still an important cause of reproductive loss. Mycotic placental infections are typically characterized by brown, thickened “leathery” lesions at the cervical star that indicates (as above) an ascending route of infection. Ascending mycotic infections can result in lesions restricted to the placenta only. Historically, this was hypothesized to be the reason for the delay in recognizing the importance of fungal abortions as well as the reason for the plea to submit fetal membranes along with the fetus for an accurate diagnostic work-up.(3) Certainly, the mycotic lesions can spread to the amnion and the fetus as well.

This horse was part of a group of horses that was under continual gestational monitoring and the placentitis was recognized and treated. The mare entered an uncomplicated parturition and the foal was born alive and healthy and as of this writing (4 months later) remains healthy. Unfortunate outcomes include fetal loss due to separation of the placenta or placental insufficiency or perinatal loss as an extension of either placental insufficiency (hypoxia) or infection of the fetus with the microorganisms causing the placentitis. In this case, there were trace numbers of bacteria and a dematiaceous fungus (*Bipolaris* sp.) isolated from the fetal membranes. Teeming numbers of fungi were seen associated with the placental lesion on GMS stains; however, on H&E stains, only a minority of the fungal hyphae seen was pigmented. As *Bipolaris* sp. exhibits rapid “take-over” growth in vitro, it is possible that a second fungal isolate was obscured. Otherwise, the inconspicuous nature of the pigmentation seen on H&E may be related to the age of the fungal growth within the lesion (intensity of pigmentation increases with time).

AFIP Diagnosis: Chorioallantois: Placentitis, fibrinonecrotizing, diffuse, marked, with fibrin thrombi, edema, reactive allantoic epithelial hypertrophy, and fungal hyphae.

Conference Comment: We thank the contributor for generously providing the additional GMS-stained slides for distribution to all WSC participants. There is considerable slide variation in the H&E-stained slides and in the conspicuousness of the fungal hyphae. The GMS method reveals myriad fungal hyphae, underscoring the utility of special histochemical stains for inflammatory lesions of suspected mycotic etiology.

In addition to the microscopic lesions described by the contributor, participants noted that the allantoic epithelium is diffusely cuboidal to columnar (i.e. reactive), in contrast to the squamous epithelium typical of the normal equine allantoic membrane. The histologic finding of reactive allantoic epithelium may be of particular diagnostic utility in cases with suboptimal sampling of the affected chorion, such as in cases with only focal or multifocal placentitis where inflammation is not present in the microscopic sections, because it usually occurs as a diffuse change and suggests inflammation somewhere in the placenta. The large size of the equine allantois as a proportion of the entire fetal membranes renders the finding of reactive allantoic epithelium a useful microscopic “sentinel” for inflammation elsewhere in the placenta. This is well-illustrated by the finding in this case that both severely and minimally affected areas of chorion are present in most sections, but the allantoic epithelium is diffusely reactive. Additionally, participants noted foci of coagulative necrosis in the chorion; these are interpreted as areas of ischemia secondary to thrombosis, as substantiated by the presence of variable numbers of vascular thrombi in the section.

In both mares and cows with mycotic placentitis, *Aspergillus fumigatus* is the most frequent isolate; however, significant species differences in distribution reflect a fundamental disparity in pathogenesis. In mares, fungi usually ascend through a patent cervix, resulting in a chronic, focally extensive placentitis in the region of the cervical star. In cattle, by contrast, lesions initially develop in placentomes, reflecting hematogenous arrival from rumen or pulmonary infections.(4)

Prior to the conference, the moderator reviewed comparative placentation with conference participants, emphasizing equine placentation and placental pathology. As discussed by the contributor, lesion distribution is of tremendous diagnostic significance for elucidating the etiopathogenesis of equine placentitis. As described above, many infectious agents ascend through the cervix to cause a focally extensive placentitis that originates near the cervical star. One exception is *Leptospira* spp., which characteristically produce a diffuse placentitis with numerous spirochetes demonstrated with special silver stains, particularly in the stroma.(1) A second exception is nocardiaform placentitis, caused by several genera of gram-positive, branching, filamentous actinomycetes (i.e. *Crossiella equi*, *Streptomycin* sp., *Amycolatopsis* sp.), which is typically localized to the cranial uterine body and entrance to the uterine horns and does not communicate with the cervical star.(4)

Finally, the conference moderator noted that syncytia and focal areas of mineralization are normal findings in the equine chorioallantois, but may increase in pathologic conditions. Other normal components of the equine placenta that may be confused with lesions were reviewed, including amniotic plaques, hippomanes, chorioallantoic pouches, allantoic pouches, and the yolk sac remnant.

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CASE II: 09-30175 (AFIP 3139936).

Signalment: 3-month-old, male, Clydesdale horse (*Equus caballus*).

History: Not reported.

Gross Pathology: The parenchyma of both testes is diffusely dark brown to black. Within one testis is an approximately 1 cm diameter, well circumscribed, white to tan, firm mass.

Histopathologic Description: Within the testis and compressing the adjacent parenchyma is an approximately 2 x 1.5 cm expansile, unencapsulated mass composed of large nodules of cartilage surrounded by a mix of adipose tissue, neural tissue, often lined by ependymal epithelium, myxomatous mesenchymal tissue, mature connective tissue with occasional glandular structures lined by cuboidal to columnar epithelial cells, and small foci of smooth muscle and skeletal muscle. The seminiferous tubules are small and hypocellular and present within an abundant, mesenchymal matrix. A large number of polygonal cells containing abundant, globular, intracytoplasmic, golden-brown pigment (lipochrome) are present within the interstitium surrounding most of the seminiferous tubules. A similar smaller mass is present within the contralateral testis. Note that not all sections of teratoma show all the features listed above.

Contributor's Morphologic Diagnosis: Testes: Bilateral teratomas.

Contributor's Comment: A teratoma is a benign germ cell tumor in which the cells have undergone somatic differentiation, producing mature but disorganized tissues of two or more embryonic layers.(1) They are thought to be parthenogenic tumors derived from a single germ cell that has completed its first meiotic division, but not its second.(6) This case was unusual in that the teratomas occurred in such a young, non-cryptorchid foal, and that they were bilateral.

Teratomas of the testis are the most frequently reported testicular tumor in young horses and are more commonly found in cryptorchid testes.(1) To the contributor's knowledge, there are two published reports in horses less than a year old, one in a cryptorchid, neonatal 3 day old foal(5) and the other a cryptorchid 4-day-old foal,(4) in which the spermatic cord entrapped the small colon resulting in signs of abdominal pain. It is thought that testicular teratomas may be congenital(4) and that their presence in a fetal testis may prevent normal descent,(1,4) although this may depend on the size of the tumor relative to the size of the inguinal canal at the time of testicular descent.(4) There have been no reports, to the contributor's knowledge, of bilateral testicular teratomas in horses.

Grossly, teratomas may be single or multiple and often have a cystic or multilobular structure. Hair and mucoid or sebaceous-like secretions are often seen on cut section (and these are sometimes referred to as "dermoid cysts") as well as yellow-white masses with fibrous, adipose, cartilaginous, and bony tissue.(1) Histologically, teratomas are composed of structures derived from all embryonic germ layers, including ectodermal, neuroectodermal, endodermal, or mesodermal.(1) The presence of nervous and adipose tissue is very common.

The remainder of the testicular parenchyma in this foal is normal for the age of the horse. The seminiferous tubules are immature, as spermatogenesis is not initiated until approximately 2 years of age.(2) From a fetal gestational age of 155 days to 1 year old, the seminiferous epithelium consists of gonocytes and Sertoli cells. Another interesting feature of these testes was the dark-brown discoloration grossly, and the abundant pigmented interstitial cells present around immature seminiferous tubules histologically. This is also a normal feature for testes from a foal of this age (3 months). These pigmented cells are not present between fetal gestational ages 155 days to 248 days, but are

present in large numbers in the neonatal 3-day-old testis. They increase to reach a maximum number at 2 months of age, and then gradually diminish and disappear by 3 years of age.(2) A morphologic study on these pigmented cells of the horse testis found that ultrastructurally, they were characterized by the presence of abundant residual bodies consisting of secondary lysosomes, having variable internal structures, and an eccentrically located nucleus.(3) In combination with histochemical staining, it was suggested that the pigmented granules found within the pigmented cells have some characteristics of ceroid. It is hypothesized that these pigmented cells may be derived from macrophages which are phagocytizing the degenerating fetal type of interstitial cells, and that they gradually increase in volume by storing digested materials as ceroid-like pigment.(2,3)

AFIP Diagnosis: Testis: Teratoma.

Conference Comment: As mentioned by the contributor, there is substantial slide variation in this case. On the surface, this is an apparently undemanding example of a teratoma of the young horse. However, several findings in this case are particularly intriguing. Foremost is the highly unusual bilateral occurrence. Furthermore, the neoplasm is more common in cryptorchid testes, in which it may prevent testicular descent. Finally, the conference moderator noted that the absence of skin and hair in equine teratoma is fairly atypical.

While gonadal teratomas are uncommon, still rarer are the extragonadal teratomas, the most common form of which is the dentigerous cyst, usually found at the base of the ear in horses. Extragonadal teratomas are well-documented in humans, and sporadically reported in other domestic, wild, and laboratory species. Specifically, adrenal teratomas have been reported in humans, ferrets, an ox, and a rat. Interestingly, extragonadal teratomas are thought to arise from diploid pluripotent progenitor cells that escape embryonal organizers during maturation, in divergence from the histogenesis of gonadal teratomas described by the contributor.(7)

Of equal or perhaps greater interest are the pigmented interstitial cells, which garnered the bulk of the discussion during the conference, and remain fairly enigmatic. What little is known about these cells is well-summarized by the contributor; from a diagnostic standpoint, it is important to recognize them as normal structures in the neonatal foal testis.

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CASE III: W9332754 (AFIP 3134193).

Signalment: 8-year-old, intact, female Great Dane (*Canis familiaris*).

History: This dog had intermittent abdominal pain for the last 4 weeks. An exploratory laparotomy revealed the presence of a 9 cm diameter mass coming from the left ovary.

Gross Pathology: Not reported.

Histopathologic Description: Ovary: Sections are largely effaced by sheets of neoplastic round cells that exhibit mild to moderate anisocytosis and anisokaryosis. Rarely, these sheets are separated by a fine stroma. Neoplastic cells completely efface the architecture and have round euchromatic nuclei with single prominent nucleoli. Mitotic figures are present in moderate numbers (2-4 per 40x HPF). Neoplastic cells (17-25 µm) have moderate amounts of amphophilic cytoplasm and large round nuclei (12-17 µm) with 1-2 prominent nucleoli. Rare aggregates of 2-5 small lymphocytes are present amid the neoplastic cells. Immunohistochemistry: Approximately 50% of the neoplastic cells stain positively for vimentin and negatively for CD18, synaptophysin and pancytokeratin.

Contributor's Morphologic Diagnosis: Ovary: Dysgerminoma.

Contributor's Comment: The primary ovarian neoplasms are classified into 3 categories according to their histogenic origin: tumors of the surface coelomic epithelium, tumors of the gonadal stroma, and tumors of germ cells. Germ cell neoplasms of the ovary include dysgerminomas and teratomas.(2,4) Dysgerminomas are rare neoplasms that are considered to be the counterpart of the more common seminoma of the testicle in gross and microscopic features. They are extremely rare in all species but most cases have been reported in the bitch and mare.(1,2) They are usually unilateral and have a low potential for local and distant metastasis. The neoplastic cells stain positively for vimentin and alkaline phosphatase and negatively for cytokeratin.(1) The differential diagnosis in the current case included lymphoma, neuroendocrine carcinoma, pheochromocytoma and histiocytic sarcoma. The diagnosis of dysgerminoma was confirmed using immunohistochemistry, wherein, the neoplastic cells stained positively for vimentin and stained negatively for CD18, pancytokeratin, and synaptophysin.

AFIP Diagnosis: Ovary: Dysgerminoma.

Conference Comment: In addition to the morphologic features described by the contributor, conference participants noted frequent individual cell necrosis among the neoplastic cells. Moreover, many sections contain abundant hemorrhage; in the absence of evidence for chronicity (e.g. hemosiderin-laden macrophages), participants interpreted the finding as likely representing acute, surgical induced hemorrhage associated with ovariectomy. The moderator also commented that reproductive tissues are very sensitive to surgical manipulation and susceptible to hemorrhage. The conference moderator further reminded participants that it is not uncommon to find two or more different neoplasms in a single gonad.

Conference participants reviewed the primary ovarian tumors of domestic species, among which the dysgerminoma is rare. As classified by the World Health Organization, these are summarized below:(3,4)

Primary Ovarian Tumors of Domestic Animals		
Category	Neoplasm	Notes
Tumors of the surface coelomic epithelium	Papillary adenoma; papillary cystadenoma	Common only in the bitch; arise from the coelomic mesothelium forming surface epithelium or subsurface epithelial structures (SES); form papillary projections covered by ciliated cuboidal to columnar cells, with or without glandular or cystic cavity formation
	Papillary adenocarcinoma	Common only in the bitch; malignant counterpart of papillary adenomas; larger and extends through ovarian bursa; fronds may dislodge and cause metastatic implantations (carcinomatosis) and ascites)
	Rete adenoma	Rare; reported only in the bitch; arise from the tubular network of rete; differentiate from papillary adenomas by location in the tubal extremity of the ovarian medulla (vs. surface epithelium for the latter)
Mesenchymal tumors	Hemangioma	Most common ovarian tumor of the sow; rare in the cow, mare, and bitch
	Leiomyoma	Rare; reported in the bitch, queen, and sow; arise from smooth muscle of the mesovarium

Sex cord-stromal (gonadostromal) tumors	Granulosa (granulosa-theca) cell tumor; thecoma (theca cell tumor); interstitial cell tumor (luteoma, lipid cell tumor, steroid cell tumor)	Most common ovarian tumor of the cow and mare; slightly less common than epithelial tumors of the ovary in the bitch; infrequent in the queen; arise from granulosa and theca interna cells (and their luteinized counterparts); may produce estrogens or androgens; produce inhibin in the mare with contralateral ovarian atrophy; rarely metastasize; distinctive Call-Exner bodies are present histologically
Germ cell tumors	Dysgerminoma	Uncommon; arise from germ cells before differentiation; may metastasize or spread locally but biological behavior largely unknown due to low incidence in domestic species; histologically indistinguishable from the much more common testicular seminoma
	Teratoma	Rare; arise from totipotential germ cells that have undergone somatic differentiation; consist of two or more of the three embryonic layers (i.e. endoderm, mesoderm, ectoderm); usually well-differentiated and benign
	Embryonal carcinoma	Arise from embryonic multipotential cells capable of further differentiation; variable histologic pattern

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CASE IV: 09030 WFUHS (AFIP 3134304).

Signalment: 31-year-old, female, rhesus macaque (*Macaca mulatta*).

History: This rhesus macaque developed vaginal bleeding 13 months prior to euthanasia. Pap smear revealed atypical epithelial cells with large, irregularly shaped, vesicular nuclei. Colposcopic examination was suggestive of cervical intraepithelial neoplasia at the cervico-vaginal junction. Surgical removal of the cervix was performed 1.5 months later, and a 2.0 x 1.5 x 0.6 cm, multilobular, unencapsulated, bright red, fleshy, mass was found at the external cervical os near the cervico-vaginal junction. Histological examination was consistent with cervical adenocarcinoma. Nearly a year later the animal became anorexic and constipated, and was euthanized.

Gross Pathology: At necropsy the distal colon was constricted and adhered to the urinary bladder, and a 7 x 5 x 5 mm, unencapsulated, reddish-brown mass infiltrated the vaginal mucosa adjacent to the cervical stump. Multifocal to coalescing, tan to milky white plaques were present on the serosa of the urinary bladder and colon. Gross morphologic diagnoses: Cervical adenocarcinoma with serosal metastasis to the colon and urinary bladder.

Laboratory Results: A PCR on Pap smear tissue using a rhesus papillomavirus D sequence was positive.

Histopathologic Description: Extensively infiltrating and replacing the vaginal wall is part of an unencapsulated, poorly demarcated, densely cellular epithelial neoplasm. The neoplastic cells are arranged in solid sheets, acini, and nests supported by a fine fibrovascular stroma. The cells are often irregularly multilayered, range from oval to polygonal or columnar, have indistinct cell borders, moderate to abundant pale eosinophilic, homogenous or finely vacuolated cytoplasm, and vesicular, oval nuclei with 1-2 basophilic nucleoli. Anisokaryosis and anisocytosis are moderate to marked, and mitoses range from 3-8 per 40x HPF. Invasion of the lymphatics, colonic serosa,

muscularis and submucosa is present multifocally, although it is not present in all sections. The surface of the neoplasm is variably covered by a 2 mm thick sheet of fibrin and necrotic debris admixed with degenerate neutrophils and small basophilic bacterial colonies.

Contributor's Morphologic Diagnosis: Cervical adenocarcinoma with vaginal and colonic invasion.

Contributor's Comment: Papillomaviruses are a diverse group of epitheliotropic double-stranded DNA viruses, of which more than 75 have been identified in 20 species. The rhesus papillomavirus type D (RhPV-d) is the most common isolate associated with genital infections in macaques, and was associated with 60% of genital lesions diagnosed in rhesus macaques,(7) which include vaginal papillomas, varying stages of intraepithelial dysplasia, and invasive cervical carcinoma.(6) Infection requires the availability of epidermal or mucosal epithelial cells still able to proliferate (basal cells).(9) Histological characteristics include koilocytosis, epithelial atypia and loss of basal cell maturation.

Cervical adenocarcinoma associated with genital papillomaviruses has been well described in human medical literature and recently in macaques.(6-8) The normal cervix has two distinct epithelial zones, an ectocervix covered by squamous epithelium, and an endocervix lined by simple glandular epithelium. During adolescence, the endocervical epithelium undergoes squamous metaplasia and is replaced by immature squamous epithelial cells which later undergo maturation. This metaplastic region is called the transformation zone and is the most common site for the development of cervical cancer.(3) High grade lesions often occur at the squamo-columnar junction. In humans, nearly 80 percent of the population is infected by genital papillomaviruses, which are considered the most prevalent sexually transmitted oncogenic pathogens. Only rarely does infection lead to invasive cervical carcinoma which is characterized as squamous cell carcinoma (SCC) or adenocarcinoma (AC). Human papillomavirus (HPV) 16 is the most frequent isolate in SCC, while HPV 18 is detected more frequently in AC. In many human cases, the cervical lesions harbor multiple HPV types.(8)

Human papillomavirus integration into the genome leads to inactivation of the p53 and retinoblastoma (Rb) pathways by the action of primary papillomaviral oncoproteins E6 and E7. Viral E6 protein binds to and degrades p53, and viral E7 protein causes functional inactivation of the Rb protein. High-risk HPV infections are associated with increased expression of E6 and E7 genes in precancerous lesions.(2) E5 is another gene important in the early course of infection as it stimulates cell growth by binding the epidermal growth factor receptor, the platelet-derived growth factor- β receptor, and the colony-stimulating factor-1 receptor. Recently, E5 has also been shown to prevent apoptosis following DNA damage.(9)

AFIP Diagnosis: Cervicovaginal junction: Cervical adenocarcinoma.

Conference Comment: As one of very few suitable animal models for one of the leading causes of cancer mortality in women worldwide, this entity is extremely relevant and timely. Furthermore, the contributor provides a superb synopsis of its pathogenesis. Readers may recall a recent discussion of the role of oncoproteins E5, E6, and E7 in neoplastic transformation in bovine enzootic hematuria associated with bovine papillomaviruses 2 and 4 and bracken fern (see WSC 2009-2010, Conference 10, case IV). Not surprisingly, oncoproteins E5 and E7 are expressed in and have been implicated in the pathogenesis of equine sarcoid, a condition of which bovine papillomaviruses 1 and 2 are the suspected etiologies. The E5 oncoprotein binds the platelet-derived growth factor – beta receptor, which is also expressed in equine sarcoids.(1) In general, papillomaviruses characteristically exhibit marked species specificity, and equine sarcoid is one of the rare exceptions to this tendency. Recently, feline sarcoid-associated papillomavirus DNA sequences have been amplified from bovine skin, suggesting that cattle may be the reservoir host of this papillomavirus.(4) Finally, RhPV-d and RhPV-a, previously found only in rhesus macaques, recently were isolated from the genital tracts of female cynomolgus macaques.(6,7)

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