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CASE I – X-96-235728 (AFIP 2839466)

Signalment: 19-year-old female Cynomolgus macaque (*Macaca fascicularis*)

History: This female monkey arrived at Wake Forest University School of Medicine on February 1, 1997, from the Institute Pertanian Bogor in Indonesia. The animal was ovariectomized in July 1997, for use in a cardiovascular study evaluating the long-term effects of various hormonal agents in post-menopausal women. She had received oral conjugated equine estrogens (CEE) daily at a dose equivalent to that used for estrogen replacement therapy (0.042 mg/kg). Lesions were noted on routine histologic examination of the reproductive tract at necropsy.

Gross Pathology: None

Laboratory Results: None

Contributor's Morphologic Diagnoses: 1. Intraepithelial carcinoma *in situ*, multifocal, ectocervix and vagina.
2. Invasive squamous cell carcinoma, cervical os.
3. Vaginitis and cervicitis, lymphoplasmacytic, multifocal, chronic, mild.
4. Hyperkeratosis, parakeratotic, diffuse, chronic, moderate, vagina and ectocervix.

Contributor's Comment: Midsagittal sections of a segment of the reproductive tract are provided extending from the vaginal canal to the glandular cervix. The primary neoplastic lesions are focused at the cervical os and fornix, with varying degrees of dysplasia and atypia along the vaginal wall, ectocervix and squamous endocervix. Morphologic features include multifocal vaginal and cervical epithelial dysplasia with marked nuclear atypia, expansion of the basal epithelium, and multifocal perinuclear

vacuolation (koilocytosis). The epithelium contains an increased mitotic index with atypical mitoses and mitotic figures above the basal layer. Epithelial invasion of the underlying stroma is present multifocally with disruption of the basement membrane and submucosal aggregates of densely packed, disorganized, hyperchromatic basal epithelial cells. Varying degrees of submucosal invasion are present depending on the given slide. Immunohistochemical staining of this lesion confirmed the presence of papillomavirus proteins (Wood et al. 2001).

Histologic changes represented in this case are characteristic of human cervical carcinomas, currently the second leading cancer of women worldwide. The major risk factor for development of cervical cancer in women is infection with human papillomavirus (HPV). Papillomaviruses (Family: Papovaviridae) comprise a diverse group of small double-stranded DNA viruses, best known for causing benign papillomas on skin and mucosal surfaces. However, among the 100+ HPV types now identified, certain high-risk types (particularly HPV 16, 18, 35, and 41) may induce malignant changes in the human reproductive tract. High-risk HPV DNA has been found in greater than 90% of precancerous cervical lesions and close to 100% of invasive cervical carcinomas in women (Wallboomers et al 1999). Oncogenic papillomaviruses induce cellular transformation through production of E6 and E7 oncoproteins, which inhibit tumor-suppressor gene products p53 and retinoblastoma (Rb). E6 binds p53 and accelerates its ubiquitin-mediated proteolysis, while E7 binds and inactivates members of the Rb family, deregulating the G1/S checkpoint of the cell cycle (for review see Stanley et al 2001). Pre-malignant and invasive cervical intraepithelial neoplasms should be distinguished from genital warts (condylomata acuminata), which are benign exophytic verrucous genital lesions associated with non-malignant or low-risk papillomavirus types, and from cervical clear cell adenocarcinomas induced by *in utero* exposure to the potent synthetic estrogen, diethylstilbestrol (DES).

In the veterinary literature, naturally occurring papillomaviruses have been described in numerous species, including several species of non-human primates. However, reports of papillomavirus-associated genital malignancies are rare. Most notably, Ostrow and colleagues (1990, 1995) have provided histopathologic and molecular evidence for cervical and vaginal dysplasias associated with papillomaviruses in rhesus macaques (*Macaca mulatta*). Additionally, Chan et al (1997) have genetically characterized 12 types of genital rhesus papillomaviruses and one papillomavirus in a cynomolgus macaque from random cytologic sampling. The lesion represented in this case, along with similar lesions described recently in cynomolgus macaques (Wood et al 2001), suggest that macaques may provide a useful animal model for the study of cervical carcinogenesis.

The cervicovaginal hyperkeratinization is a drug-induced response to estrogen treatment, and is considered to be unrelated to the cervical neoplasm.

AFIP Diagnoses: 1. Cervix: Squamous cell carcinoma, Cynomolgus macaque (*Macaca fascicularis*), nonhuman primate.

2. Cervix and vagina: Squamous metaplasia, diffuse, moderate.
3. Cervix: Cervicitis, lymphoplasmacytic, chronic, diffuse, moderate.

Conference Comment: Conference participants discussed the similarity between this case and cervical carcinoma in women. The World Health Organization (WHO) classifies cervical squamous intraepithelial lesions in women as cervical intraepithelial neoplasia (CIN) of three grades. CIN typically forms at the transformation zone of the cervix, and is graded CIN I (mild dysplasia), CIN II (moderate dysplasia) or CIN III (severe dysplasia/carcinoma in situ). The transformation zone is the region of the cervix in which the endocervical glandular epithelium undergoes metaplastic transformation to squamous epithelium. This metaplastic squamous epithelium is a permanent and important change, as it relates to the development of cervical neoplasia. In women, CIN III is most often associated with progression to invasive cervical carcinoma.

Squamous cell carcinoma of the cervix is subdivided by the WHO into two categories, microinvasive (limited invasion of the stroma) and frankly invasive (invasion beyond depth limits defined by microinvasive). There are three gross presentations of invasive squamous cell carcinoma: exophytic (most common); ulcerated; and infiltrative. Also, squamous cell carcinoma can be keratinizing or nonkeratinizing.

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CASE II – H98-2111A/98-0567 (AFIP 2834338)

Signalment: 10-year-old female neutered German Shepherd Dog (*Canis familiaris*)

History: A 10-year-old German Shepherd Dog was referred to the Murdoch University Veterinary Hospital with a 3-month history of intermittent vulval bleeding that occurred for weeks at a time. The bitch had been spayed at less than one year of age. The source of the bleeding was identified as trans-cervical by vaginoscopy and urinalysis. Abdominal ultrasound demonstrated a thickened, irregular uterine stump visible from mid bladder to within the pelvic canal.

Gross Pathology: Exploratory laparotomy identified a spherical mass approximately 1.5 cm in diameter in the region of the right ovarian pedicle and a thickened irregular uterine stump attached to the bladder by many adhesions.

Laboratory Results: Urinalysis: No abnormalities detected.

Contributor's Morphologic Diagnoses: 1. Luteinised gonadal stromal tumor (luteoma, luteinised granulosa cell tumor)
2. Marked, diffuse cystic endometrial hyperplasia and multifocal adenomyosis

Contributor's Comment: The spherical mass from the right ovarian pedicle was composed of a densely cellular, nodular, circumscribed population of neoplastic epithelioid cells, surrounded by a wide band of mature fibrous connective tissue. Within the fibrous capsule were scattered tubular structures lined by cuboidal epithelium (rete ovarii). The neoplastic cells were arranged in solid lobules and cords by mature fibrovascular connective tissue septae. There was moderate cellular pleomorphism. Cells ranged from 15 to 50 um in diameter with polyhedral or infrequently spindleoid to columnar morphology and an abundant, foamy eosinophilic cytoplasm. The lobules of large polyhedral cells resembled lutein cells whereas the more elongate, columnar to spindleoid cells arranged in cords resembled sertoli cells. Nuclei were generally ovoid, with stippled basophilic chromatin and a single basophilic nucleolus. There were occasional atypical cells with large, irregular basophilic nuclei, prominent nucleoli and abundant foamy eosinophilic cytoplasm. Mitoses were not observed.

Within the uterine stump there was effacement of the lumen and marked expansion of the endometrium by diffuse, irregular, cystic hyperplasia of the endometrial glands. Many of the cystic glands contained proteinaceous material within their lumen and there was irregular extension of the endometrial glands into the underlying myometrium.

Gonadal stromal cell tumors are the most commonly reported form of ovarian neoplasm in all species except the sow (Yamini B et al 1997). They differ from other ovarian neoplasms by their capacity to form hormonally active steroids (Nielson SW and Kennedy PC 1990). Classification of these tumors into specific subtypes is difficult

because of the tendency for these tumors to have a mixed histological pattern and inconsistency in terminology within the veterinary literature and between human and veterinary literature. Although the tumor in this case largely resembled lutein cells, the term luteoma in human pathology generally refers to single or multiple aggregates of large lutein cells that develop during pregnancy and regress thereafter. In the veterinary literature, the ability of granulosa cell tumors to undergo luteinisation, and demonstrate a tubular pattern similar to Sertoli cell tumors is recognized (Kennedy PC and Miller RB 1993). Because these features were demonstrated by this case it was finally classified as a luteinised granulosa cell tumor (Sivacolundhu RK, O'Hara AJ & Read RA 2001).

Steroidogenesis by gonadal stromal tumors can induce variable clinical signs including anestrus, nymphomania, masculinization and hyperadrenocorticism (Yamini B et al 1997). In this case the clinical presentation was suggestive of pro-estrus/ oestral bleeding (despite ovariohysterectomy at less than 1-year-old) and identification of marked cystic endometrial hyperplasia and multifocal adenomyosis within the uterine stump was consistent with excessive and prolonged estrogenic stimulation. These changes suggest the tumor was predominately producing estrogenic hormones.

Professor Don Schlafer (Cornell University) is gratefully acknowledged for his comments on the histological classification of the tumor and pathogenesis of the changes in the uterine stump.

AFIP Diagnosis: Ovary, right (per contributor): Sex-cord stromal (gonadostromal) tumor, luteinized, with Sertoli cell features, German Shepherd Dog, canine.

Conference Comment: Tumors of the ovary are divided into three categories, based on embryological origin: epithelial, germ cell, and ovarian stroma. Most epithelial tumors of the canine ovary arise from subsurface epithelial structures (SES), which are unique to the bitch among the domestic species. Their growth patterns are often papillary (papillary adenoma, papillary adenocarcinoma) or cystic (cystadenoma, cystadenocarcinoma). Germ cell tumors include dysgerminoma, teratoma and embryonal carcinoma. Sex-cord stromal tumors are composed of neoplastic cells that resemble the normal hormone secreting apparatus of the ovary, and include granulosa cell tumor, thecoma, and interstitial cell tumor (luteoma).

Conference participants experienced some difficulty in identifying the tissue of origin (ovary) in this case. Histologic features supporting ovarian origin include: 1) neoplastic cell morphology - polygonal cells with abundant eosinophilic granular to vacuolated cytoplasm arranged in multiple lobules and follicles (sex-cord stromal cells), 2) presence of surrounding adipose tissue (ovarian bursal fat), and 3) epithelial lined structures in the rim of dense collagenous tissue. Admixed with the polygonal cells are multifocal nests and short cords of palisading spindle cells that resemble Sertoli cells of the testis. In addition, the capsular tubular structures are diffusely strongly positive for cytokeratin, confirming their epithelial origin.

As an alternative to ovary, a few participants considered adrenal gland origin for this neoplasm, because of the lack of recognizable ovarian stroma or follicles.

However, the presence of keratin-positive epithelial structures is not consistent with adrenal gland origin.

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CASE III – E02-475 (AFIP 2843557)

Signalment: Approximately 10 month gestational age, 34 kg, male Standardbred fetus, equine

History: The 8-year-old mare was purchased pregnant last November and aborted in January, at approximately 10 months of gestation. There is no history of sickness prior to or after the abortion. She was rebred successfully in May.

Gross Pathology: In a locally extensive area, measuring approximately 10 cm by 8 cm, on the chorionic surface of the gravid horn, there is a raised, irregular pale gray plaque, which is covered by abundant friable pale yellow granular material. The corresponding surface of the allantois is thickened and irregularly folded. The body and non-gravid horn of the fetal membranes as well as the fetus are grossly normal.

Laboratory Results: The Animal Health Diagnostic Laboratory microbiological culture of the placenta and fetal lung revealed a positive culture for *Candida lusitaniae.*

Contributor's Morphologic Diagnosis: Chorioallantois: Severe locally-extensive subacute necrosuppurative placentitis with myriad intralesional yeasts and pseudohyphae (compatible with *Candida* spp.)

Contributor's Comment: There is a locally extensive area of necrosis throughout the chorionic epithelium, with accumulation of small numbers of degenerated neutrophils predominantly around large vessels and extending into the chorionic mesenchyme. The majority of trophoblasts are distended by a large number of yeast cells. Occasional trophoblast cells have ruptured and yeast bodies are free and mixed with the necrotic debris. Round to oval budding yeasts measuring 3-5 microns in diameter are seen on the surface and within the epithelium. Occasional yeast organisms are elongated and forming pseudohyphae. The stroma of the villous tips is infiltrated by large numbers of neutrophils and a lesser number of lymphocytes. There are small multifocal areas of mineralization. Similar yeast organisms are within the alveolar spaces of the fetal lung. The lung has a mild diffuse acute neutrophilic bronchopneumonia.

The genus *Candida* is composed of an extremely heterogeneous group of organisms that grow as yeasts. Most members of the genus also produce a filamentous type of growth (pseudohyphae). Pseudohyphae can be differentiated from hyphae by the pattern of growth. Pseudohyphae form from yeast cells or from hyphae by budding, but the new cell remains attached to the parent cell and elongates, resulting in filaments with constrictions at the cell-cell junctions of the filaments. True hyphae form from yeast cells or as branches of existing hyphae. Classification of fungi is confusing and based on several criteria including formation of hyphae, pseudohyphae, or yeast forms. Another feature important in classification is the presence of a sexual stage of reproduction (teleomorph stage) or absence of sexual reproduction (anamorphous stage).

The kingdom of Fungi is classified in six phyla. The pathogenic fungi belong to only four (numbered II, III, IV, and V on below chart) of the six phyla.

					Species (examples)
I	Chytridiomycota		Chytridiomycetes		
II	Zygomycota	Non-septate hyphae	Zygomycetes	Perfect fungi Sexual spores = ZYGOSPORES	*Mucor,Rhizopus Absidia Mortierella*
III	Ascomycota	Septate hyphae	Ascomycetes	Perfect fungi Sexual spores = ASCOSPORES	*Histoplasma, Blastomyces. Pichia*
IV	Basidiomycota	Septate hyphae,	Basidiomycetes	Perfect fungi Sexual spores = BASIDIOSPORES	*Cryptococcus*
V	Deuteromycota	Yeast, septate hyphae and/or pseudohyphae.	Imperfect fungi	Imperfect fungi No sexual spores	*Candida, Coccidiodes,Aspergillus, Malassezia, Pneumocystis*
VI	Mycophycophyta	Slime molds	Myxomecetes	no pathogens known	

The genus *Candida* includes around 154 species. Among these, it is well established that only a small number are pathogens. Six are most frequently isolated in human infections. While *Candida albicans* is the most abundant and significant species, *Candida tropicalis*, *Candida glabrata*, *Candida parapsilosis*, *Candida krusei*, and *Candida lusitaniae* are also isolated as causative agents of *Candida* infections. *Candida* spp. are opportunistic fungi, occurring as normal inhabitants of the digestive tract, oral cavity and vagina of humans and other domestic animals.

Mycotic abortion is very common in the bovine species. It was reported for the first time in 1920. Bovine abortions due to *Candida* are sporadic and have been reported in many countries. However, in horses *Candida* has been associated with pyometra, panophthalmitis, glossitis, esophagitis, and systemic neonatal infection. Mycotic abortions in mares have been diagnosed in only 1.7 % of the cases in a 1993 review from the University of Kentucky. Of sixty-one cases of mycotic abortion, thirty-eight were caused by *Aspergillus spp*, thirteen by zygomycetes, seven by *Histoplasma capsulatum*, one case by *Candida spp*. and two with unidentified yeasts.

The classification of many species of *Candida* groups them as Deuteromyctes or imperfect fungi, because they lack a teleomorph stage. However, more recently, the teleomorph stages of several pathogenic *Candida* species have been described. The classification is confusing at present because the asexual (anamorph) stage may be identified as different species from the teleomorphic stage of the same yeast. Unfortunately, at present, there are no rules or international agreements governing the creation of organized classification schemes.

AFIP Diagnosis: Atlantochorion: Placentitis, lymphoplasmacytic and neutrophilic, chronic-active, focally extensive, moderate, with villous necrosis, and intratrophoblastic yeast, hyphae, and pseudohyphae, Standardbred, equine.

Conference Comment: The contributor has concisely summarized candidiasis as a causative agent of mycotic abortion. The placentae of the various domestic species are classified based on gross and microscopic anatomy, degree of implantation, and the number of layers of tissue that separate the fetal and maternal circulation. The gross types of mammalian placentae are diffuse, cotyledonary, zonary and discoidal. The microscopic types are villous, folded and labyrinthine. The nondeciduate placenta describes both the absence of invasion by the trophoblasts into the endometrium, and the lack of maternal tissue loss at parturition. Alternatively, in the deciduate placenta, there is invasion and destruction of the superficial endometrium by trophoblasts and formation of decidual cells with shedding of maternal tissue at parturition. Finally, the four categories based on the fetal to maternal circulation are epitheliochorial, syndesmochorial, endotheliochorial, and hemochorial. A summary of the comparative placentation of the domestic and laboratory animal species follows:

1) mare - diffuse, (microcotyledonary) villous, nondeciduate, epitheliochorial
2) ruminant - cotyledonary, villous, nondeciduate, epitheliochorial
3) sow - diffusely folded, nondeciduate, epitheliochorial
4) carnivore - zonary, labyrinthine, deciduate, endotheliochorial
5) primate - discoid, villous, deciduate, hemochorial

6) rodent - discoid, labyrinthine, deciduate, hemochorial.

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CASE IV – UK LDDC 2 5850 (AFIP 2839785)

Signalment: Adult (age not indicated), female, Thoroughbred, *Equus caballus*, equine

History: A placenta was submitted. The foal was alive but was thin and weak. There had been no obvious problems with the pregnancy and the foal was full term.

Gross Pathology: The placenta was complete. The allantochorion weighed 13 pounds and the amnion weighed 6 pounds. The umbilical cord was 98 cm in length. There was a circumscribed lesion approximately 40 cm in diameter on the chorionic surface. The lesion was located at the base of the horns, in the cranial aspect of the body of the allantochorion. This area was covered by thick, tenacious brownish-tan material and the underlying chorion was thin with loss of villi. There was no involvement of or communication with the cervical aspect of the allantochorion and no other gross lesions were observed in the placental membranes.

Laboratory Results: Culture of the allantochorion produced numerous Gram-positive branching bacilli.

Contributor's Morphologic Diagnosis: Allantochorion: Placentitis, necrotizing, lymphocytic, neutrophilic, focally extensive, severe, with branching filamentous bacteria, Thoroughbred placenta, equine.

Contributor's Comment: The placenta is characterized by necrosis of the chorionic villi with areas of chorionic epithelial hyperplasia and metaplasia. The stroma and villi are infiltrated by lymphocytes, neutrophils, and macrophages. Blood vessels are congested. The chorionic surface is covered by exudate containing necrotic leukocytes, epithelial cells, and filamentous bacteria. There is mild cystic hyperplasia of the allantoic surface.

This is an example of a typical case of nocardioform placentitis. A single area of placentitis on the chorionic surface in the cranial body at the base of the horns of the placenta characterizes this condition. The lesion can be small but often is extensive and can involve portions of the horns. The surface is covered with thick brown mucoid material. The underlying allantochorion is thin with loss of the velvety appearance of the chorionic villi. The margins are moderately demarcated and are more reactive and inflamed. Microscopically, the central portions exhibit chronic changes with lymphoid infiltrates and loss of villi. The peripheral areas often have more active inflammation with necrosis of villi, chorionic epithelial hyperplasia/metaplasia, and infiltration by a mixed population of inflammatory cells. The surface exudate contains amorphous proteinaceous material, leukocytes, sloughed epithelial cells and branching filamentous bacteria. The bacteria are only isolated from the chorionic surface and extension of the infection to the fetal tissues and fluids is not seen. Except for fetal malnutrition, no lesions are seen in the fetal organs. This condition appears to be a relatively chronic placentitis caused by bacteria of low pathogenicity. Harm to the fetus appears to be the result of placental insufficiency causing malnutrition and possibly abortion. Mares affected with nocardioform placentitis can abort in late gestation, produce weak premature or term foals, or have normal foals with the placentitis being an incidental finding. The mare may exhibit premature mammary gland development and lactate, but often shows no manifestation of problems. Since there is no involvement of the cervical area of the placenta, vaginal discharge is not seen. This condition can sometimes be diagnosed in the mare using trans-abdominal ultrasound examination that reveals placental thickening and separation and the voluminous exudate. Trans-rectal ultrasound, used to diagnose typical ascending placentitis, is not diagnostic in cases of nocardioform placentitis. The pathogenesis of nocardioform placentitis is unknown.

This unique form of equine placentitis was first recognized in the mid-1980's and was referred to as "nocardioform" placentitis since the unclassified bacteria that were isolated fit into the broad category of nocardioform actinomycetes. The University of Kentucky Livestock Disease Diagnostic Center receives an average of 30 cases of this condition annually. In 1998 and 1999, for undetermined reasons, the number of cases exceeded 100 each year. Rare cases of nocardioform placentitis have been diagnosed in other areas of the United States, as well as, in several foreign countries. Several different species of unclassified Gram-positive filamentous bacteria cause nocardioform placentitis. The most common causative bacterium has recently been characterized and phylogenetically determined to be a new species of *Crossiella* for which the name *Crossiella equi* has been proposed.

AFIP Diagnosis: Allantochorion: Placentitis, necrosuppurative, chronic-active, diffuse, severe, with branching filamentous bacteria, Thoroughbred, equine.

Conference Comment: The contributor has provided a concise review of the emerging problem of nocardioform placentitis caused by *Crossiella equi* and similar unclassified bacteria. Common causes of equine placentitis and abortion include bacterial, fungal and viral etiologies. Bacterial pathogens include primarily *Streptococcus zooepidemicus*, but also *E. coli*, *Leptospira* spp., *Pseudomonas aeruginosa*, and *Klebsiella pneumoniae*. *Aspergillus fumigatus* is the most common fungal cause of equine abortion. Other fungal causes of abortion include the phycomycetes (*Absidia, Mucor*, *Rhizopus*), *Candida* sp. and *Histoplasma* sp. Viral causes of equine abortion include equine herpesvirus 1 and equine arteritis virus.

Poor perineal conformation of the mare may contribute to an ascending infection of bacterial and fungal placentitis. Some sections had mild adenomatous hyperplasia of the allantoic epithelium. Although the cause is not known, it may represent a reactive lesion in response to chronic placentitis. Lesions ranged from not grossly visible to large, nodular cystic masses near the insertion site of the umbilical vessels. Histologically, there is hyperplasia and hypertrophy of the allantoic epithelium often with formation of glands and cystic structures within the epithelium and underlying stroma.

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