Joint Pathology Center
Veterinary Pathology Services

WEDNESDAY SLIDE CONFERENCE 2012-2013

Conference 13

30 January 2013

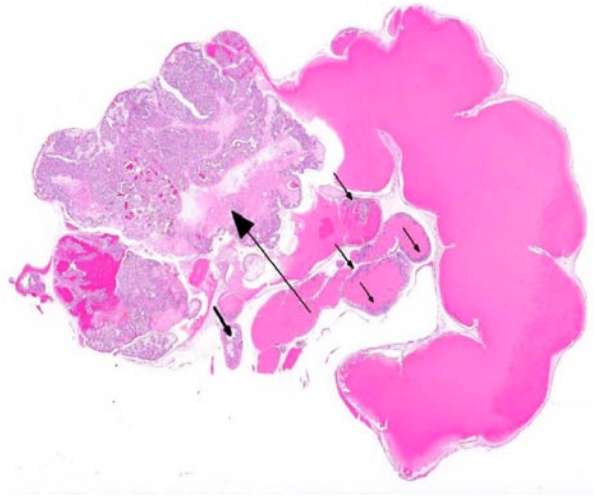
CASE I: Case 1 AVD-SV2 (JPC 3174956).

Signalment: Nine-month-old, male mouse/ C57BL\6/TRAMP.

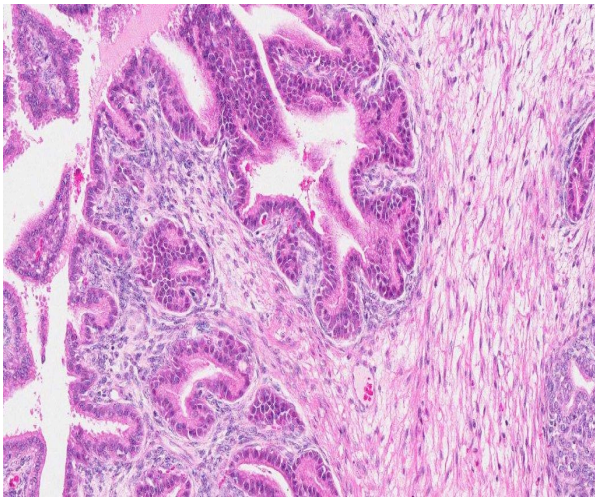
History: Breeding animal for TRAMP mouse colony. Did not receive any treatments.

Gross Pathologic Findings: Seminal vesicle – enlarged, lobulated, firm, white, and pink.

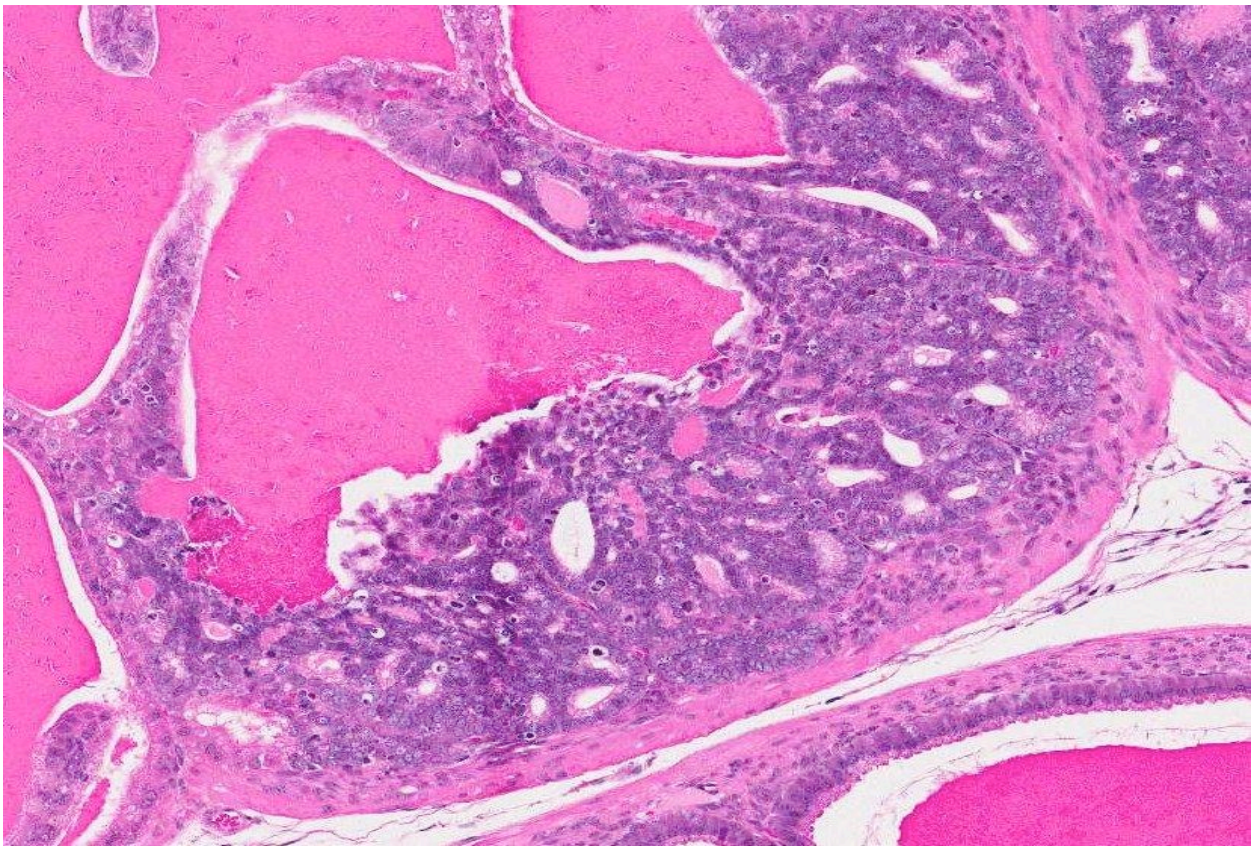
Histopathologic Description: Focally, approximately 45% of the lining glandular epithelium of the seminal vesicle projects into the lumen as a neoplastic mass characterized by extensive arborizing, multiple, often coalescing, long and short, papillary projections overlying a



1-1. Seminal vesicle, TRAMP mouse: The mucosa of the seminal vesicle contains multiple proliferative lesions including a large biphasic tumor (large arrow) and multiple foci of epithelial hyperplasia (small arrows). (HE 6.3X)



1-2. Seminal vesicle, TRAMP mouse: The large biphasic neoplasm is composed of two populations of neoplastic cells, proliferative spindled cells which with the overlying covering of epithelial cells (which occasionally form glands deeper inside the neoplasm, for papillary fronds supported by dense fibrous connective tissue. (HE 175X)



1-3. Seminal vesicle, TRAMP mouse: Multifocally, the remainder of the mucosal epithelium lining the seminal vesicle is markedly hyperplastic, often forming a cribriform pattern. (HE 175X)

sparsely cellular neoplastic mesenchymal stroma, supported by compact, dense smooth muscle matrix. The lining glandular epithelium is comprised of cuboidal to columnar epithelium often with piling of layers. Individual cells of the lining epithelium reveal basal, round to oval nuclei with coarsely stippled chromatin, indistinct nucleoli, and abundant eosinophilic cytoplasm. The mitotic index is ~ 0-1 PHF (400x). There is mild anisocytosis and anisokaryosis. The underlying mesenchymal stroma is often myxomatous, sparsely cellular and comprised of loosely arranged cells with indistinct borders; loose, wispy, eosinophilic vacuolated cytoplasm; spindle-shaped to angular and stellate nuclei with stippled chromatin, and indistinct nucleoli. Mitotic figures are numerous in the mesenchymal stromal cell population ranging between ~ 4-12 PHF (400x). There is moderate to marked anisokaryosis of the mesenchymal stroma. No unequivocal evidence of malignancy, such as invasion or metastases was noted.

The lumen and ducts are often variably ectatic, lined by attenuated epithelium, and contain homogeneous, brightly eosinophilic, proteinaceous material/colloid with occasional hemorrhage. Multifocally, occasional foci of necrotic debris are noted within the stroma associated with breaching of the lining epithelium into the lumen admixed with eosinophilic debris and hemosiderin-laden macrophages.

Multifocally, other areas of the lining epithelium of the seminal vesicle extend as nodular, papillary proliferations into the lumen and have piling of the epithelial cells, and mildly expanded supporting stroma with increased mitoses.

Contributor's Morphologic Diagnosis: Seminal vesicle: Focal papillary adenoma with epithelial stromal differentiation.

Contributor's Comment: **TR**ansgenic **A**denocarcinoma **M**ouse **P**rostate (TRAMP) mice are a well-studied animal model for human prostate cancer.[3,5,8] TRAMP mice are genetically engineered to harbor a transgene composed of SV 40 Large T/ small-t antigen promoted by the rat probasin gene.

Species	Seminal Vesicles	Prostate		Bulbourethral (Cowper's)
		Body	Disseminate	
Bull	++	+	+	+
Ram	+	-	+	++
Boar	+++	+	+	+++
Stallion	+++	++	-(+)	+
Dog	-	++	-	-
Cat	-	++	-	++
Rodent	+++	++	-	++
Human	+	++	-	+

Typically, lesions noted in TRAMP mice include the prostate, for which lesions may be assessed using a well-characterized grading scheme.[6] In addition to prostate neoplasms, tumors are also noted in the seminal vesicles.[7]

The normal luminal surface of seminal vesicles in mice is lined by an anastomosing glandular epithelium lined by cuboidal to tall columnar cells forming an intricate arrangement of primary, secondary and tertiary folds. These folds are normally present and should not be confused with hyperplastic changes. Brightly eosinophilic luminal secretions expand the seminal vesicles, resulting in an extended vesicular wall lined by short epithelial papillae, a scanty submucosal layer, and a thin smooth muscle layer.

As in the present case, seminal vesicle tumors in TRAMP mice typically exhibit features of biphasic organization. Although stromal cells proliferate rapidly, they are always lined by a single-layered epithelial component and do not form solid stromal masses such as those seen in uterine stromal tumors. Also, compared to prostatic tumors in TRAMP mice, seminal vesicle tumors display prominent proliferation of stromal cells with frequent mitotic figures lined by bland epithelium, whereas prostatic tumors display epithelial tumor cell proliferation with scant stromal components.[7]

Although the tumors of TRAMP seminal vesicles resemble epithelial–stromal tumors found in the breast, prostate, and seminal vesicles in humans, no reports of this type of tumor in any other rodents exist, and these tumors are considered to be TRAMP mouse-specific lesions.

JPC Diagnosis: Seminal vesicle: Papillary adenoma.

Conference Comment: The contributor provides a very good description of both normal and neoplastic changes in TRAMP mouse seminal vesicles. When the moderator emphasized the importance of describing the biphasic population of cells when characterizing this tumor, a question arose as to the cell of origin in the spindle cell population, specifically whether these cells are myoepithelial or mesenchymal. In an attempt to answer this question, immunohistochemistry was performed. The stromal cells showed multifocal positive cytoplasmic immunoreactivity to desmin; however, other stains (calponin, vimentin, pancytokeratin, p63 and CD10) were noncontributory, precluding a definitive determination as to the cell of origin of the spindle cell population.

Accessory genital glands, found along the length of the pelvic urethra in males, have two purposes: providing nutrition and a transport medium for spermatoazoa.[1] There are four main male accessory genital glands: the ampullae, seminal vesicles (vesicular glands), prostate and bulbourethral glands (Cowper's glands). Their presence, size, type and number vary among species. The ampullae are paired glands located on the dorsal neck of the bladder. They are composed of secretory alveoli lined by cuboidal to columnar pseudostratified epithelial cells with few basal cells. The seminal vesicles are paired saccular glands that are located between the prostate gland and the ampulla.[1,4] Seminal vesicles consist of lobules of tubuloalveolar glands with pseudostratified epithelium with sparse basal cells, divided by interlobular septa that contains either abundant smooth muscle (in ruminants) or connective tissue with little smooth muscle (stallions and boars).[1] The prostate, which has a higher proportion of connective tissue than the seminal vesicles, originates at the urinary bladder and surrounds the urethra.[4] The prostate is composed of either the corpus (body) of compact prostatic tissue located external to the urethra, and/or the disseminated prostate, characterized by diffuse prostatic tissue found along the length of the pelvic urthera.[4] Prostatic glands are classified as compound tubuloacinar glands, and are lined predominantly by pseudostratified and occasionally low cuboidal or squamous epithelium. Bulbourethral glands are paired, dense glands containing abundant fibrous connective tissue located below the prostate and are composed of compound tubuloalveolar glands.[4]

The moderator provides the included chart summarizing the presence and relative size of accessory genital glands in various species.

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CASE II: 2009913311 (JPC 3165094).

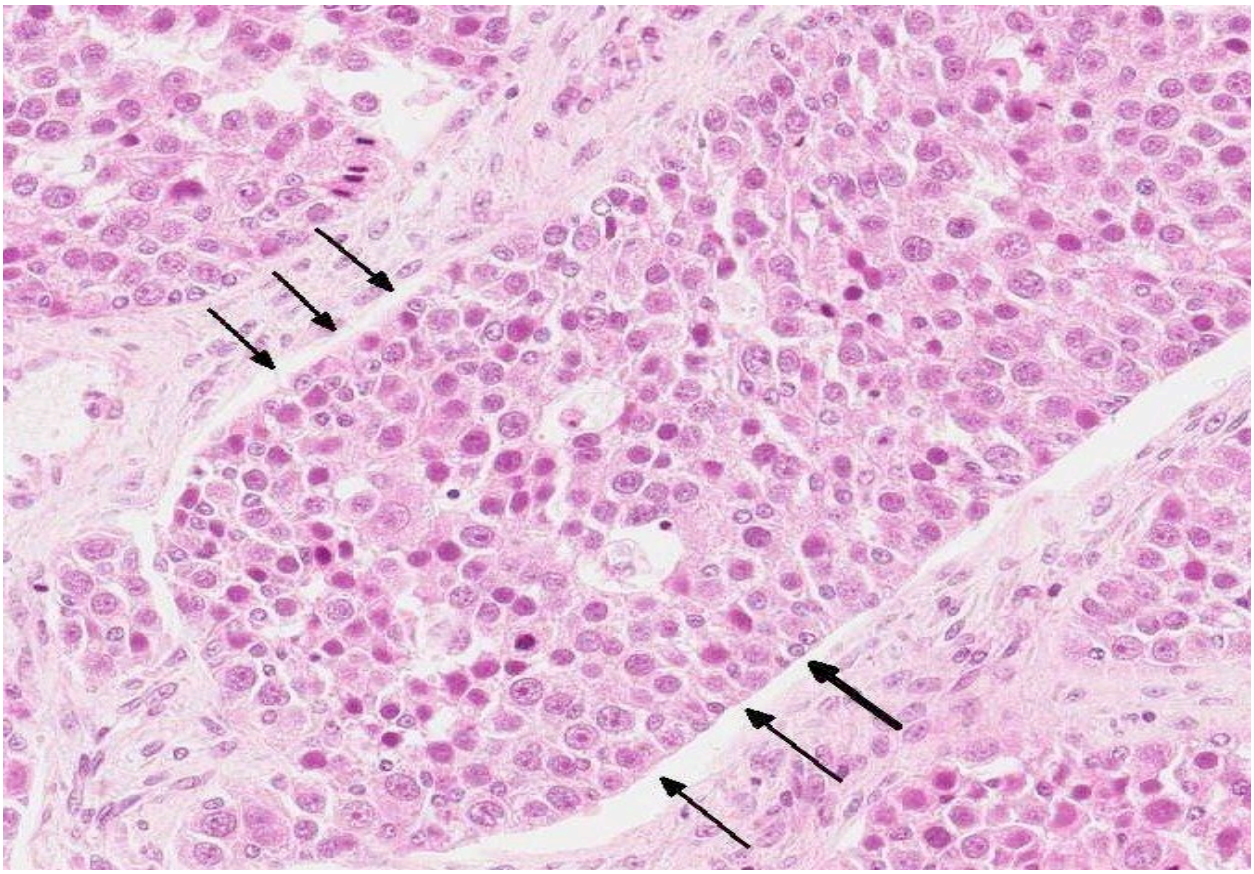
Signalment: 11-year-old, female, mixed breed, dog (*Canis familiaris*).

History: The dog showed clinical signs suggestive of endometritis or pyometra and underwent ovariohysterectomy.

Gross Pathologic Findings: An approximately 4 cm diameter mass of the right ovary was surgically resected and sent to our laboratory for histopathologic examination with the uterine tissue. The mass was soft with a milky-white, smooth surface. The cut surface was solid and homogeneous. No abnormal change was detected in the left ovary.

Histopathologic Description: The tumor mass is formed in the ovary, so stretched ovarian tissue is detected on the surface of the mass. The tumor mass consists of solid or trabecular cellular nests surrounded by thin connective tissue stroma. Irregularly-sized cysts filled with eosinophilic homogeneous fluid are sometimes formed in the nests. The tumor mass has an appearance similar to granulosa-theca cell tumor, but nuclear size varies among the cells. The tumor cells are irregular to spindle shaped, having an elongated or oval nucleus of medium to smaller size, and resembling neoplastic cells of granulosa-theca cell tumor. However, large round to polygonal cells similar to germ cells are mingled with smaller cells at various rates in the nest. The granulosa-theca cell-like tumor cells have a hyperchromatic nucleus and prominent nucleolus. The cytoplasm of these cells is relatively scanty and eosinophilic. In contrast, large tumor cells similar to germ cells have large round nuclei with scattered chromatin, and one or a few large nucleoli with abundant pale eosinophilic or clear cytoplasm. Mitotic figures are seen more frequently among the large cells similar to germ cells than other tumor cells. Structures resembling to Call-Exner bodies with or without central calcification are not observed.

Immunohistochemically, the large round cells are positive for one of the germ cell markers, PLAP



2-1. Ovary: The ovary is effaced by a multilobular neoplasm composed of tubules containing two populations of cells – columnar stromal cells palisading along the basement membranes (small arrows), and centrally, round, mildly anisokaryotic germ cells.

(placental alkaline phosphatase) and are negative for granulosa cell markers such as WT-1 and vimentin. In contrast, small spindle cells are positive for WT-1 and vimentin, and are negative for PLAP. Some tumor cells of middle-sized nuclei are positive for all three markers.

Contributor's Morphologic Diagnosis: Ovary: Ovarian mixed germ cell sex cord-stromal tumor, canine.

Contributor's Comment: Mixed germ cell sex cord-stromal tumors have been rarely reported in human ovaries and testes and in canine testes;[4,5] however, this tumor is extremely rare in female dogs and was not included as an ovarian tumor in the second series of WHO classification in domestic animals.[3] Among the ovarian tumors in dogs, granulosa cell tumors and epithelial tumors are the most common.

The histological appearance of canine ovarian granulosa cell tumors is variable; testicular Sertoli cell tumor-like appearance is observed along with the follicular (i.e., micro- and macro- follicular), insular, diffuse, and trabecular growth patterns.[1,3] Granulosa cell tumors in the human ovary are further classified into adult and juvenile types. Juvenile granulosa cell tumors have solid and follicular growth patterns of tumor cells with abundant (luteinized) cytoplasm. Solid or follicular growth pattern of tumor cells with immature nuclei and abundant cytoplasm are thought to be important characteristics distinguishing juvenile from adult granulosa cell tumors.[8] The histological characteristic of the ovarian tumor in the present case is similar to the micro follicular pattern of canine granulosa cell tumors, but nuclear size varies among tumor cells and there are very large cells that appear similar to germ cells. According to the criteria for classification of human ovarian granular cell tumors, variation of nuclear size and the presence of very large nuclei, which may represent immature nuclei, suggest the diagnosis of juvenile granulosa cell. However, tumor cells characterized by large round nuclei and abundant cytoplasm in the present case are positive for PLAP (one of the germ cell markers), suggesting that these tumor cells are characteristic of germ cells rather than malignant neoplastic granulosa cells with immature nuclei. Although a majority of canine ovarian granulosa cell tumors are composed of multiple growth patterns in a single mass, the present tumor is composed of a single pattern throughout.[1,3] This growth pattern may be further evidence to rule out the diagnosis of granulosa cell tumor.

Patnaik and Mostofi first reported mixed germ cell-stromal tumors that were different from collision tumors of seminoma and Sertoli cell tumors in the testis of 16 dogs, whereas cellular components are identical in both tumors.[5] In their mixed germ cell-stromal tumors, the tumor is composed of uniform and close intermixing of two type cells: germ cells with a large round nucleus and Sertoli cells with a smaller elongated nucleus.[4] It is unlikely that the present tumor is a collision tumor of dysgerminoma and granulosa-theca cell tumor that originated in different sites of the ovary, because the histopathological features of the tumor were almost uniform throughout the mass.

Mixed germ cell sex cord-stromal tumors are further subdivided into two types: gonadoblastoma and mixed germ cell sex cord-stromal tumor. These two types of tumors are distinct clinicopathological and histopathological entities. In human cases, approximately 80 percent of gonadoblastomas occur in phenotypic female patients who have a Y chromosome (almost all have karyotypes of 46XY or 46XY/XO and dysgenetic gonads).[2,5,7] In contrast, mixed germ cell sex cord-stromal tumors develop in phenotypically and karyotypically normal females and males. Mixed germ cell sex cord-stromal tumors have been reported in male dogs with recognizable gonads.[2,4,5,7] Judging from normal development of the left ovary and other genital organs, the present dog was probably a genotypically normal female; however, an examination was not done on gene abnormality.

JPC Diagnosis: Ovary: Mixed germ cell sex cord-stromal tumor.

Conference Comment: This interesting case stimulated a great deal of discussion among conference participants, with some favoring the diagnosis of mixed germ cell sex-cord stromal tumor (MGCSCST) and others questioning the diagnosis, since, as the contributor noted, MGCSCSTs are not well-documented in canine ovaries. Like the contributor, conference participants considered a differential diagnosis that included juvenile granulosa cell tumor, gonadoblastoma and collision tumor. We reviewed this case in consultation with physician reproductive pathologists at the Joint Pathology Center, who favored a diagnosis of dysgerminoma; however, the majority of conference

participants agreed that the stromal component is a significant part of the neoplastic process, and therefore concurred with the contributor's diagnosis of MGCSCST. Participants agreed that a karyotype would be useful to rule out gonadoblastoma.

The conference moderator led a practical discussion of immunohistochemical markers in human ovarian germ cell and sex cord-stromal tumors based on a recent report in *Histopathology*. The authors describe the use of SALL4 (Sal-like protein 4) and PLAP (placental alkaline phosphatase) to mark germ cell differentiation; OCT4 (octamer-binding transcription factor 4), CD117 and D2-40 to mark dysgerminoma; α-fetoprotein and glypican-3 to mark yolk sac tumors; OCT4, CD30 and SOX2 (sex determining region Y-box 2) to mark embryonal carcinoma; calretinin, inhibin, SF-1 (splicing factor 1) and FOXL2 (forkhead box L2) to mark sex cord–stromal differentiation; and melan-A to mark steroid cell tumors.[6] The following is a summary of immunohistochemical stains used to differentiate human ovarian tumors as discussed in this article:

- PLAP is expressed in dysgerminomas, gonadoblastomas, embryonal carcoinomas, yolk sac tumors and choriocarcinomas.
- SALL4, a transcription factor required for development and maintenance of embryonic stem cell pluripotency, is more sensitive and specific than PLAP in identifying ovarian germ cell tumors; however, PLAP is more sensitive for choriocarcinomas.
- OCT4, a transcription factor required for maintaining embryonic stem cell pluripotency, is expressed in dysgerminomas, gonadoblastomas and embryonal carcinomas, whereas other germ cell tumors lack OCT4.
- CD-117 is a transmembrane tyrosine kinase growth factor receptor for stem cell factor (SCF) that shows strong membranous immunohistochemical staining in over 85% of dysgerminomas, and half of solid pattern yolk sac tumors. CD-117 is also overexpressed in other tumors, such as gastrointestinal stromal tumors and mast cell tumors; expression in these tumors is often cytoplasmic.
- D2-40, which marks the protein podoplanin, expressed in fetal germ cells, shows cytoplasmic and membranous expression in most dysgerminomas.
- NANOG is expressed in up to 83% of dysgerminomas and in the germ cell population of gonadoblastoma.
- SOX2 and CD30 expression is present in many embryonal carcinomas.
- Alpha-fetoprotein and glypican-3 is expressed in many yolk sac tumors.
- Glypican-3, a surface heparan sulphate proteoglycan that regulates cell growth during fetal development, is very specific for yolk sac tumors. Choriocarcinomas are also positive for glypican-3 but are usually easily differentiated from yolk sac tumors by histomorphology.
- HCG (human chorionic gonadotropin) is expressed by the syncytiotrophoblastic cells but not the mononuclear trophoblasts of an ovarian choriocarcinoma. Keratin, inhibin and glypican-3 are also expressed in choriocarcinomas.
- Inhibin is sensitive and specific for sex cord-stromal cell tumors.
- Calretinin, a maker of mesothelial differentiation, is more sensitive but less specific than inhibin for sex cord-stromal differentiation.
- SF-1, a transcription factor that regulates steroidogenesis, sexual differentiation and gonadal and adrenal gland development, is expressed in 100% of granulosa cell tumors.
- FOXL2, which encodes a transcription factor that is required for granulosa cell function and ovarian follicle development, is expressed in almost all granulosa cell tumors; it also appears to mark all types of sex cord-stromal tumors except for steroid cell tumors.
- WT-1 (Wilms tumor 1) is sensitive for sex cord-stromal differentiation.
- Steroid cell tumors express calretinin, inhibin, and SF-1and melan-A (also known as MART-1, or melanoma antigen recognized by T-cells 1).
- EMA (epithelial membrane antigen) is the best marker to exclude epithelial ovarian cancer.[6]

These markers have proven to be quite helpful in diagnosing ovarian germ cell tumors and sex cord-stromal tumors in humans; however, their efficacy in canine tumors has not been determined.

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CASE III: N1012728 (JPC 4006582).

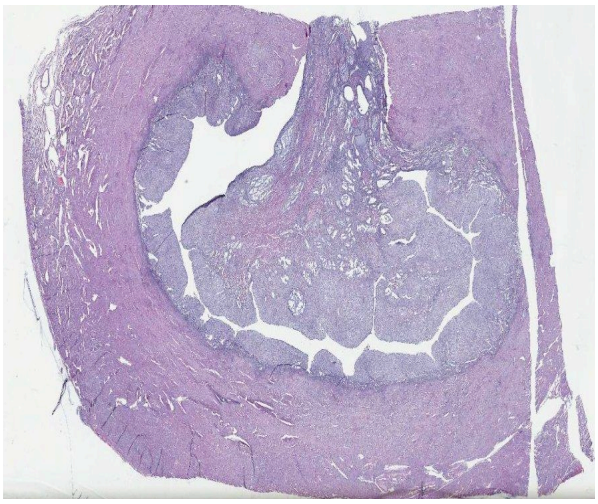
Signalment: 20-year-old, female, intact, nonhuman primate (NHP) *(Macaca mulatta).*

History: In February 2010, the NHP presented with heavy menstruation and a depressed attitude. A mid-abdominal mass, approximately 5 cm in diameter, was found on palpation, and confirmed by radiography. The NHP was used in psychotropic drug studies. Her past medical history included kyphosis and irritable bowel syndrome. The latter currently managed with bi-weekly injections of 1.2 mg dexamethasone. Past gynecological exams detected an enlarged uterus and cervix. Laboratory results (see below) included neutrophilia, hypoproteinemia and mild azotemia. A working diagnosis of endometriosis led to monthly administration of medroxyprogesterone injections (40 mg, IM). The NHP presented three months later with a dark, red mass protruding from the vulva. At the first surgery, three masses were removed. The vaginal mass was determined to be a hemangioma. The uterus was firm and enlarged with multiple red foci over the ovaries that were confirmed as endometriosis. The dorsal aspect of the cervix had a 2 cm, firm, whitish-pink mass confirmed as a leiomyoma. Post surgery, the uterus was opened and found to contain a firm, white, lobulated mass. A second surgery was performed to remove a large 6.5 cm omental mass and smaller 2-3 cm omental mass (not shown) similar in appearance to the large omental mass.

Gross Pathology: 1. Vaginal mass: 4.8 x 3.2 x 2 cm multilobular dark red/black mass. 2. Uterus and ovaries: serosa: multiple dark red/black foci. 3. Uterus Lumen. 1.9 x 2.8 x 1.9 white, firm polyploid intrauterine mass. 4. Omentum: 6.5 x 5.5 x 3 cm round mass with numerous fingerlike projections covered by a smooth surface found in the omentum. 5. Omentum: 2 cm smaller mass.

Laboratory Results:

Parameter	Normal range	Feb 2010	April 2010
WBC	5.5-19.0 x 10^3/mL	21.9	4.0
Total protein	7.8-9.6 g/dl	5.1	6.1
BUN	8-20 mg/dl	25	24
Albumin	3.1-5.3 g/dl	3.0	3.8
AST	14-30 U/L	22	40

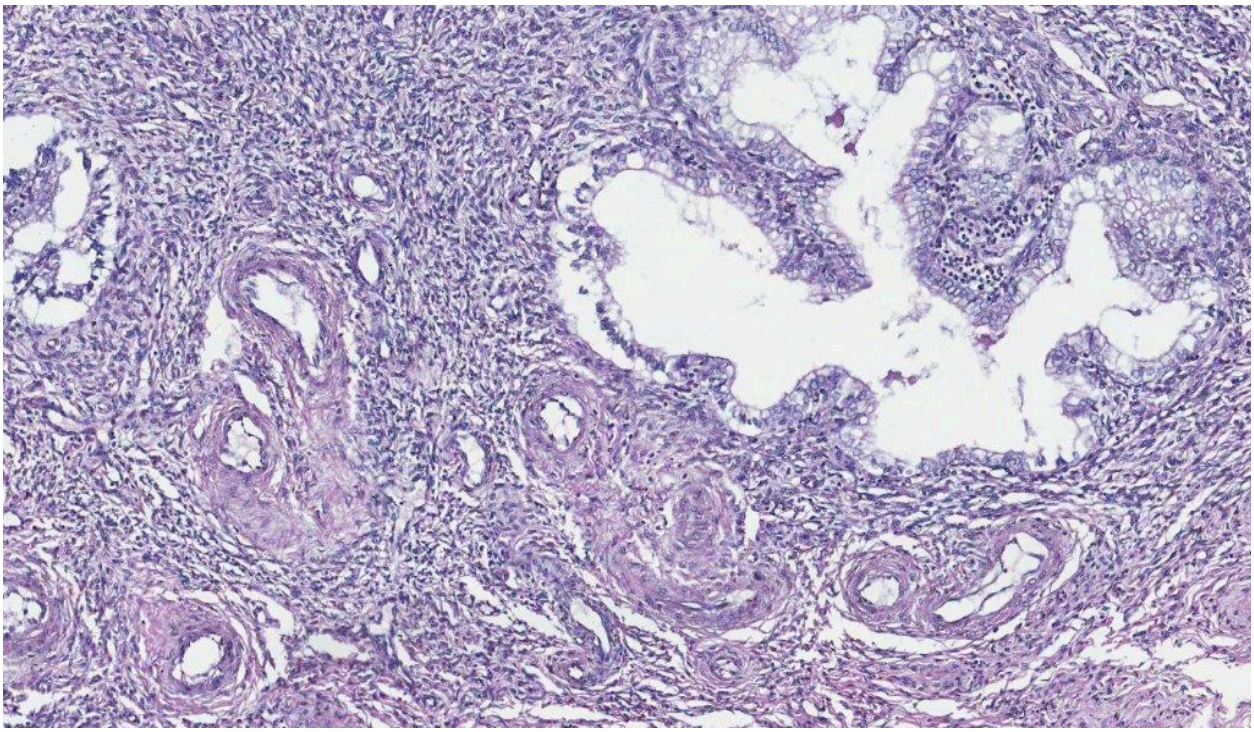


3-1. Uterus, macaque: A neoplasm circumferentially expands the endometrium and forms a polypoid mass that protrudes into the lumen. (HE 4X)

Histopathologic Description: The intrauterine mass was endometrial in origin and extended into the lumen. It was comprised of disorganized, predominantly spindle-shaped cells with one to two large, ovoid nuclei per cell. The cytoplasm was amphophilic to eosinophilic, with varied volume. There were frequent foci of glandular cells. Neoplastic stromal cells were frequently whorled around arterioles. Mitotic figures ranged from 0-3 per 40 power field. Tumor cells were variably positive for collagen (not shown) by Masson's trichrome and displayed variably positive immunohistochemistry (IHC) against CD10, and were uniformly negative against CD34 (not shown). The large omental mass had small foci of endometriosis, as well as neoplastic cells similar to the intrauterine mass. Scattered foci of necrosis, increased cellular atypia and frequent mitotic figures were present.

Contributor's Morphologic Diagnosis: 1. Intra-uterine mass, endometrial stromal sarcoma (ESS), high grade.
2. Omental masses, metastatic ESS.

Contributor's Comment: In humans, common uterine tumors include leiomyosarcoma, endometrial stromal tumors (ESS) and carcinosarcoma.[10] Uterine sarcomas may be from 3-7% of all uterine cancers.[8] In the NHP, endometrial stromal tumors are rare, while tumors of the uterine musculature are common.[4,5,20] Poorly differentiated, high-grade endometrial stromal tumors have not been reported in the NHP.[5] Endometrial stromal tumors have been



3-2. Uterus, macaque: Neoplastic spindle cells, which recapitulate endometrial stroma, surround and separate tortuous cystic endometrial glands and blood vessels. (HE 144X)

reported in a chimpanzee, rats, mice, African hedgehogs and in a cat.[1,10,3,11,15,17,19,13] The frequency of ESS has been reported as less than 1% in B6C3F1 mice.[13] ESS has also been reported in the Donryu and F344 rat strains, though at a much lower incidence compared to other uterine tumors.[17] Two studies of the F344 rat found a 0.9 % and 0.11 % occurrence of ESS.[11,13-15]

A uterine tumor in a 25-year-old chimpanzee, presented to necropsy for tuberculosis, was comprised of cells similar to proliferating endometrial stroma, and contained medium sized muscular arteries, as well as a fibrillar lattice around the cells.[20] The cells, arranged in cords, clumps and swirls, had lightly basophilic, ovoid to spindle-shaped nuclei with an indistinct nucleolus, and a moderate amount of eosinophilic cytoplasm.[20]

In the mouse, ESS is not uncommon. It is found within the wall or protruding into the lumen of the uterus. Murine ESS may arise within benign, endometrial stromal polyps.[13,15] These polyps may contain foci of greater malignancy, characterized by mitosis, cellular atypia, vascular deformation with hematoma or hemorrhage, and necrosis.[13] As in other species, ESS is arranged in sheets with whorls or fascicles of intersecting, spindle-shaped cells with indistinct borders and marked cellular pleomorphism.[15] Giant cells may be seen, though most cells are oval, fusiform cells with scanty basophilic cytoplasm and spherical nuclei with dispersed clumps of chromatin.[13] The neoplastic cells may be surrounded by a fibrillar and collagenous matrix.[3] Metastases may occur in the myometrium, cervix, and other abdominal structures.[15] ESS can be modeled *in vivo* using mice with mutations in p53 genes, which are treated with mutagens such as N-ethyl-N-nitrosurea (ENU).[9]

ESS has been reported in a 12-year-old, domestic shorthair queen presenting with depression, anorexia, panting, vomiting and a purulent vaginal discharge. A 3 x 10 cm solid mass was palpated in the abdomen, and radiographs demonstrated different sized masses less than 1.5 cm in the lungs.[19] The intra-abdominal mass showed both endometrial stromal and smooth muscle cells with focal tumor cell necrosis. The stromal cells had small, ovoid and spindle-shaped cells with scant cytoplasm, arranged in a diffuse pattern, with prominent vasculature.[19] The cells showed moderate nuclear pleomorphism and no mitotic figures. Neoplastic cells were also seen within blood and lymphatic vessels. Endometrial stromal cells stained positive with Vimentin.[19]

In captive African hedgehogs, *Atelerix albiventris*, submitted to IDEXX and Zoo/Pathology services for routine pathology, ESS was the second most commonly diagnosed uterine tumor, and was often found during hysterectomies.[16] Vaginal bleeding (13/15 animals), hematuria for two days to six months (11/15), as well as weight loss (5/12), were reported.[16] The ESS tumors were similar to adenosarcomas (the most common tumor), except they did not contain a tubular epithelial component. ESS tumors were dense, polyploid nodules of 1-15 mm in diameter, and often were locally invasive. The stromal cells contained mitotic figures, formed fascicles and whorls, and were supported by fibrovascular stroma.[16]

In summary, ESS are formed from the glandular epithelium or connective tissue stroma.[5] The tumors are tan to grey, and extend by polyploid growth into the endometrial cavity, the myometrium and myometrial vessels.[1,8,12] The cells are small, resembling the proliferative phase of endometrial stroma.[1,5] They often encircle small and medium size muscular arteries.[5] ESS is usually aggressive, with local recurrence and metastases.[10] The current classification system states tumors previously called high-grade ESS are now called poorly differentiated or undifferentiated uterine sarcomas.[1] The undifferentiated tumors invade the myometrium, have severe nuclear pleomorphism, high mitotic activity and/or tumor cell necrosis.[8] Immunohistochemical staining has shown endometrial stromal sarcomas to be positive for CD 10 and uniformly negative for CD 34.[2,8] The tumors lack estrogen and progesterone receptors.[18]

The human literature reports early diagnosis is often a challenge, as no imaging modality is reliable preoperatively, although ultrasound and MRI may be more useful than CT.[1] After preoperative imaging for metastasis, bilateral salpingo-oorphorectomy and total hysterectomy are usually performed.[1,18] Lymphadenectomy is controversial as it may not produce a survival benefit.[1,18] Radiotherapy may decrease local recurrence.[10] Chemotherapy, as well as endocrine therapy options are also used.[10,18] JAZF1/JJAZ1, JAZF1/PHF1 and EPC1/PHF1 are cancer –specific fusion genes that are being studied as diagnostic and treatment targets.[1,12] Genetic testing of the tissues is planned at a future date.

Survival times vary from months to years, depending on the extent and classification of the tumor. Median recurrence time is usually less than two years.[7,10] In one retrospective study, the median survival time in humans for high grade sarcomas was one year, while the median survival time for lower grades ESS was 11 years.[8] The hedgehogs reported had a mean survival time of 303 days post-surgery.[16]

JPC Diagnosis: Uterine mass: Endometrial stromal cell sarcoma.

Conference Comment: The contributor provides an excellent review of ESS. In addition to the special stains and immunohistochemistry performed by the contributor, JPC performed AE1/AE3, desmin and smooth muscle actin (SMA) with the following results: Epithelial cells showed strong cytoplasmic immunoreactivity with AE1/AE3; desmin was negative; and there was moderate to strong positive cytoplasmic immunoreactivity with smooth muscle actin within the stromal component.

A recent study of gene expression signatures in uterine endometrial stromal sarcoma (ESS) and leiomyosarcoma (LMS) in humans found that genes overexpressed in ESS included *SLC7A10*, *EFNB3*, *CCND2*, *ECEL1*, *ITM2A*, *NPW*, *PLAG1* and *GCGR*; whereas, genes overexpressed in LMS included *CDKN2A*, *FABP3*, *TAGLN*, *JPH2*, *GEM*, *NAV2* and *RAB23*.[6] Many genes overexpressed in LMS included those that code for myosin light chain and caldesmon, but not the genes coding for desmin or actin. *CD10* was not overexpressed in ESS. Interestingly, although CD10 was once considered specific for ESS, it has been shown to be expressed in many adenosarcomas as well as LMS and 33% of undifferentiated endometrial or uterine sarcoma. Approximately a quarter of all ESS in this study were CD10 negative, thus raising the question of the usefulness of this marker in human uterine sarcomas.[6]

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CASE IV: CRL-1 (JPC 4019837).

Signalment: Female mouse (*Mus musculus*), age and strain not given.

History: Incidental finding at sentinel health monitoring.

Gross Pathology: The left ovary was enlarged and hemorrhagic.

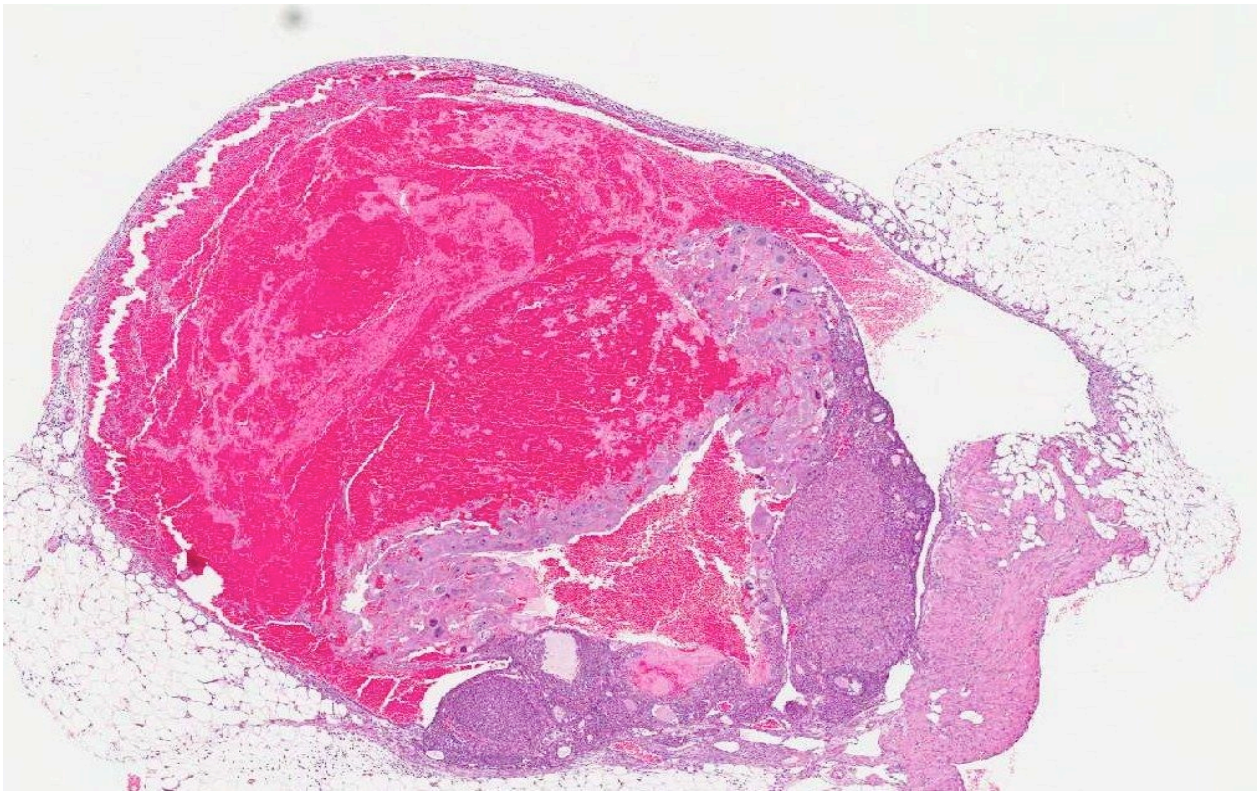
Histopathologic Description: The enlarged ovary contains a mass, characterized by sheets of large pleomorphic cells with abundant eosinophilic cytoplasm, in a large focus of hemorrhage within the ovarian bursa. The cells have a large round to oval, sometimes irregular, nucleus, with vesicular chromatin and multiple nucleoli, with occasional dark staining nuclei, and rare binucleate cells. Mitoses are rare.

Contributor's Morphologic Diagnosis: Ovary: choriocarcinoma.

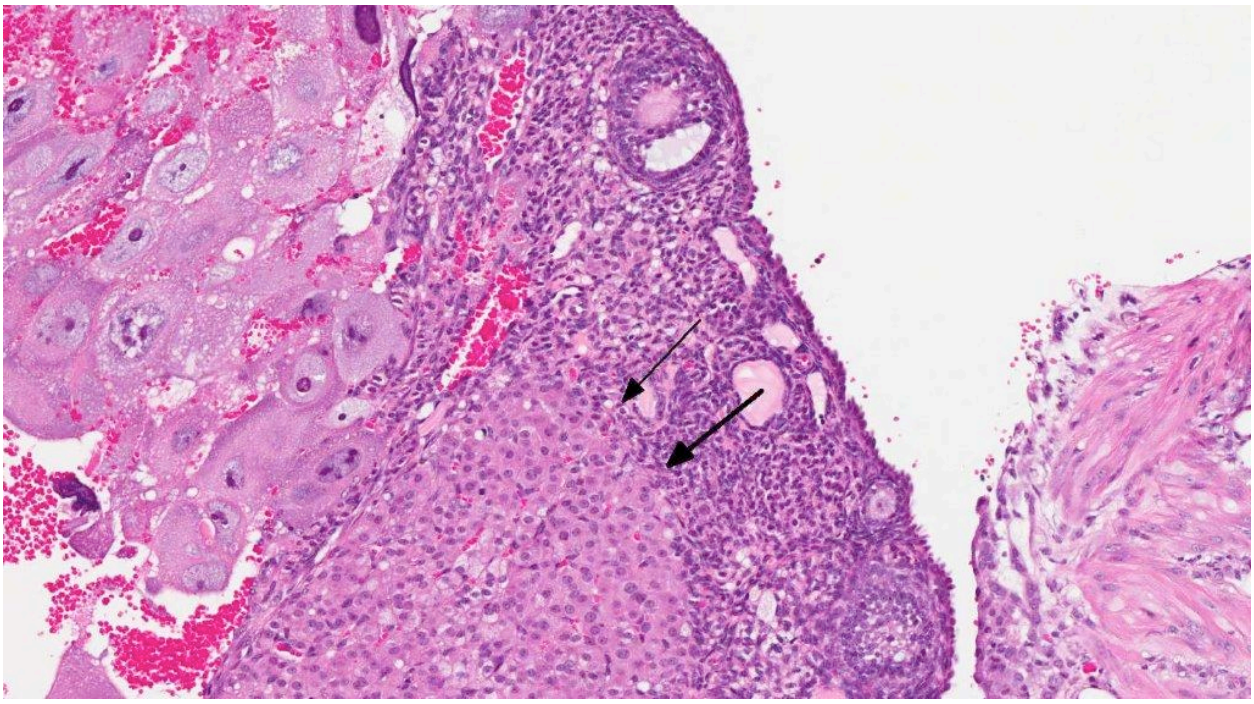
Contributor's Comment: Tumors of the ovary are divided into three groups based on the presumed tissue of origin: tumors of surface epithelium, including adenomas and carcinomas; germ cell tumors including teratomas, dysgerminomas, choriocarcinomas; and sex cord–stromal tumors including granulosa cell tumors, thecomas, fibromas.[1]

The choriocarcinoma is a malignant neoplasm of trophoblastic cells, which in women often has widespread metastases. Choriocarcinoma is one of the rarest ovarian tumors in women, estimated to occur in only 1 in 369,000 women.[3] Most choriocarcinomas in women occur in the uterus, post pregnancy. These tumors are also rare in animals, although they have been reported in rhesus and cynomolgus macaques, rabbits, a cow, dogs, mice and rats.[1,2,3,4,6,7] Choriocarcinomas may arise in the uterus, ovary or testis.

The incidence of ovarian tumors in mice varies with the strain.[2,4] Ovarian tumors are also more common in older mice (> 18 months of age). In mice, ovarian neoplasms are more common in the B6C3Fl mouse, but ovarian choriocarcinoma is only 1% of ovarian tumors.[4] The most common ovarian tumors in B6C3F1 mice are epithelial, granulosa cell tumors and teratomas.[1] In our laboratory, we have identified



4-1. Ovary, mouse: The ovary is expanded and largely effaced by a neoplasm. Hemorrhage within the neoplasm extends into the ovarian bursa. (HE 40X)



4-2. Ovary, mouse: Neoplastic cells, which resemble large trophoblasts, range up to 150 m. The neoplasm abuts a normal corpus luteum (arrows). (400X HE)

six ovarian choriocarcinomas in the last 10 years, all in sentinel mice as an incidental finding during health monitoring.

JPC Diagnosis: Ovary: Choriocarcinoma.

Conference Comment: Malignant trophoblastic tumor variants are classified as choriocarcinomas (CC), epithelioid trophoblastic tumors (ETT), or placental site trophoblastic tumors (PSTT). Trophoblastic tumors usually develop either during or following gestation, but have rarely been reported to develop from germ cells in the absence of pregnancy.[7] Choriocarcinomas, as seen in this case, are characterized by a bilaminar pattern composed of cytotrophoblasts and syncytiotrophoblasts often associated with prominent hemorrhage.[5] Although pure nongestational choriocarcinomas are extremely rare in humans, CC can be a component of a mixed germ cell tumor of the ovary.[7] ETTs are composed of a relatively uniform population of mononucleate trophoblastic cells with eosinophilic or clear cytoplasm; these cells are intermediate trophoblastic cells that resemble chorion laeve.[5] PSTTs originate from large, polygonal intermediate trophoblastic cells of the placental bed. Although nongestational trophoblastic tumors are rare in humans, several have been described in captive non-human primates, including CC and ETT. Additionally, a pure nongestational malignant PSTT of the ovary was recently reported in a young rhesus monkey.[7]

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