The Armed Forces Institute of Pathology
Department of Veterinary Pathology
WEDNESDAY SLIDE CONFERENCE
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CONFERENCE 10
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Conference Moderator: Captain Georgina Miller, DVM, Diplomate, ACVP
National Institutes of Health
Bethesda, MD 20892

CASE I - 01N271 (AFIP 2840305)

Signalment: Three-month-old, male, Wistar-Hanover, *Rattus norvegicus*, rat

History: This rat was not yet on study and had begun to produce bloody urine. A large red-blue mass was visible and palpable beneath the skin over the right abdomen. The rat was subsequently euthanized and a necropsy performed.

Gross Pathology: The right kidney was one large mass, 50 gm, 5.0x5.0x3.0 cm^3 with clotted blood beneath the renal capsule. The surface was lobular, tan, with no gross trace of normal kidney. The left kidney was normal, however the bladder was filled with blood. The spleen had rounded edges.

Laboratory Results: None.

Contributor's Morphologic Diagnosis: Embryonal nephroma (Wilm's tumor), right kidney.

Contributor's Comment: Nephroblastoma (Wilm's tumor) is the most common primary renal tumor of pigs and chickens. Nephroblastomas occur far less in calves and in dogs are very uncommon in other species. They are usually seen in young animals and sometimes in fetuses, but also mature sows, and are more common in adult dogs than in pups. In rats, various carcinogens, including dimethlynitrosamine, can induce tumor formation of nephroblastomas and other tumors. Spontaneous occurrence of this tumor in rats is rare.

Grossly, nephroblastomas may attain a huge size and cause abdominal enlargement. They are often multiple in the affected kidney, growing expansively and compressing the adjacent parenchyma. Histologically, the characteristic features are primitive glomeruli with primitive Bowman's spaces, abortive tubules, and loose spindle cell stroma, which may show some differentiation to a variety of mesenchymal tissues, including striated muscle, collagen, cartilage, bone, and adipose tissue.

This particular tumor histologically resembles disorganized embryonal kidney with tubules of moderate-sized cuboidal epithelial cells. Smaller darkly staining cells in some fields form fetal-type glomeruli.

AFIP Diagnosis: Kidney: Nephroblastoma, Wistar-Hanover rat (*Rattus norvegicus*), rodent.

Conference Comment: Nephroblastoma has been reported in humans, dogs, cats, horses, cattle, sheep, swine, chickens, rabbits and rats. The differential diagnosis in rats includes renal cell carcinoma and renal mesenchymal tumor. Renal cell carcinoma is predominantly cortical, and is composed of atypical, pleomorphic epithelial cells arranged in tubules, islands, nests, or papillary projections - which can resemble primitive glomeruli - supported by variable amounts of stroma. Renal mesenchymal tumor is composed of fibroblastic spindle cells that proliferate between and around tubules and there are less cellular areas of stellate cells that resemble embryonic mesenchyme or myxomatous tissue.

During the conference, the participants discussed the three developmental stages of the fetal kidney: pronephros, mesonephros and metanephros (definitive kidney). The mesonephros is present when the genital tubular system, external genitalia and gonad are developing. The mullerian (paramesonephric) and wolffian (mesonephric) ducts are present initially in both sexes. In the male, mullerian inhibiting factor is produced by the rete testes, resulting in mullerian duct regression, while testosterone acts to maintain the wolffian duct. The wolffian duct develops into the epididymis and part of the vas deferens. In the female, the wolffian duct regresses in the absence of testosterone, and the mullerian duct develops into the oviduct, uterus, cervix and vagina.

Contributor: Georgetown University, Division of Comparative Medicine, Washington, DC 20057-1435

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CASE II - 12544 (AFIP 2843559)

Signalment: 8-month-old, female, Syrian golden hamster, *Mesocricetus auratus*

History: This animal was involved in a study of SV40 induced lymphoma in hamsters, and had received an intraperitoneal inoculation of SV40 virus, at 3 weeks of age. Some inoculated hamsters, including this one, developed abdominal distention due to ascites, 4-8 months post inoculation.

Gross Pathology: This female hamster developed abdominal distention due to ascites, approximately 7 months post inoculation. At necropsy there were approximately 50 ml of clear abdominal fluid, a 1-1.5 cm in diameter, intrabdominal, pale soft tissue mass, attached to the body wall near the left flank, adhesions between abdominal viscera, and creamy white-yellow, frequently confluent, soft tissue masses on serosal surfaces of abdominal viscera, mesentery, peritoneal surfaces of body wall and diaphragm.

Laboratory Results: ND

Contributor's Morphologic Diagnoses: Intestine, mesentery, serosa, Neoplasm, multifocal, severe, non-encapsulated, invasive (Mesothelioma, peritoneal, diffuse, biphasic)

Contributor's Comment: The neoplasm involves and thickens most peritoneal/serosal surfaces and there is invasion of lymph nodes, pancreas and peritoneal or mesenteric fat in some sections. It is contiguous with peritoneal lining cells (mesothelium) on the gastrointestinal tract, pancreas, lymph nodes, uterus (some sections), and mesentery. It forms many exophytic papillary fronds that project from surfaces, as well as solidly cellular, non-encapsulated areas and nodules, with mild to marked infiltration/invasion of subjacent structures (e.g. mesenteric/peritoneal, fat, pancreas, lymph nodes). Projecting papillary fronds are supported on stalks or cores of eosinophilic elongate-spindle cells, and are covered/lined by one-several layers of pleomorphic polyhedral to columnar epithelioid cells with variably distinct cytoplasmic borders; scant to ample, pale to eosinophilic cytoplasm; rounded, generally euchromatic nuclei with dispersed chromatin and generally indistinct nucleoli, and occasional bizarre cells with marked karyomegaly or multiple nucleoli. Adjacent serosal surfaces are covered/lined by single to multiple layers of cells that vary in morphology from inconspicuous flattened cells (resembling normal mesothelium) to plump, bulging columnar cells and occasional large, bizarre cells. In solid areas, plump and elongate cells are arranged haphazardly in sheets (patternless pattern), sometimes in indistinct packets, and there are scattered

gland-like or tubule–like structures, supported in scant to ample, fine to coarse fibrovascular stroma. Here the cells have scant to ample, pale or eosinophilic cytoplasm that can be vacuolated. There is mild to marked atypia with multifocally marked anisocytosis, anisokaryosis, multinucleated cells, cytomegaly and karyomegaly. The mitotic index varies with up to 6 mitotic figures/high power field, and scattered bizarre mitotic figures. There was pulmonary metastasis and retroperitoneal invasion around the kidney (tissue not included).

The World Health Organization (WHO) recognizes three morphologic classifications of human malignant mesotheliomas: epithelioid, sarcomatoid and mixed (biphasic) forms, although histomorphologic diversity even within the same patient or on the same slide can be significant. The neoplasm in this case is most consistent with the biphasic form. Linear arrays of atypical mesothelial cells on peritoneal surfaces are prominent in some areas, and have been called 'mesothelioma in situ', however these should not be called malignant in the absence of unequivocal invasion.

In human patients, most mesotheliomas are pleural and there is a history of asbestos exposure. There is considerable circumstantial evidence implicating SV40 in human mesotheliomas, but some controversy remains.

Expected histochemistry findings in mesothelioma include:

+	PAS except after diastase
+	Alcian Blue (fades after hyaluronidase)
-	Mucin/mucicarmine

Malignant mesotheliomas exhibit diverse histologic patterns, and distinguishing mesothelioma from carcinomas and sarcomas can be challenging. Immunohistochemical expression of mesothelioma markers can vary even in the same section. Some immunohistochemistry (IHC) findings for mesothelioma include:

+	Calretinin (nuclear)
+	Thrombomodulin (focal membranous)
+	cytokeratin 5/6 (diffuse cytoplasmic)
++	keratins perinuclear > peripheral
+	vimentin
+	acid mucopolysaccharide (inhibited by hyaluroindase)
-	CEA etc epithelial glycoprotein antigens

Electron microscopic findings can vary substantially even between adjacent cells, with epithelial cells (microvilli, tight junctions, basement membranes) and mesenchymal (elongate nuclei, abundant RER) cells side by side. Features that should be sought include: long microvilli, abundant tonofilaments, desmosomes, absent microvillous rootlets, giant mitochondria, rough endoplasmic reticulum and lamellar bodies.

SV40 is a polyomavirus that was discovered in 1960 as a contaminant of polio vaccines prepared from primary cultures of Rhesus monkey kidney cells, and distributed to millions of people from 1955 - 1963. Asian macaques are the natural hosts of SV40. In susceptible species (including rhesus and cynomolgus macaques and African green monkeys), SV40 establishes persistent renal infections with viremia and viruria. Infection of healthy monkeys is asymptomatic, but in SIV-infected or otherwise

compromised monkeys, it can become disseminated, and associated with disease. SV40 is an oncogenic DNA virus, and is used in research to model cellular transformation. The viral replication protein, large T antigen (T-ag), is also the viral oncoprotein. In transgenic mice, SV40 T-ag expression under the control of tissue specific promoters has been used to induce tumors in the targeted tissues. In humans SV40 has been implicated in progressive multifocal leukoencephalopathy, in mesothelioma, pulmonary carcinomas, osterosarcoma, pituitary and thryroid tumors, and in various brain tumors. SV40 inoculation of hamsters results in development of lymphoma, osteosarcoma, histiocytic sarcoma, anaplastic sarcomas and mesothelioma, depending on virus strain, site of inoculation, age and genetic background of hamster. SV40's T-ag has been implicated in inactivation of p53 in the pathogenesis of mesothelioma, and notable especially in the solid sarcoma-like areas of some tumors in these hamsters, is profound atypia, reminiscent of 'undifferentiated sarcomas' in p53 -/- mice.

AFIP Diagnosis: Multiple serosal surfaces; mesentery; pancreas; and lymph node: Mesothelioma, Syrian hamster (*Mesocricetus auratus*), rodent.

Conference Comment: The contributor has provided an excellent summary of mesothelioma and SV40 infection. SV40's large T antigen (Tag) is directly mutagenic by altering the number and stability of the infected cell's chromosomes. Tag can also bind and inactivate tumor-suppressor gene products, including p53 and retinoblastoma (pRb). The p53 protein acts in the nucleus to arrest the cell cycle and initiate DNA repair. It causes cell cycle arrest in the G_1 phase by inducing transcriptional up-regulation of the cyclin dependent kinase (CDK) inhibitor p21. The p21 protein inhibits cyclin/CDK complexes, thereby preventing phosphorylation of pRb necessary for cells to enter the S phase. Activation of p53 initiates DNA repair by up-regulating the GADD45 gene (growth arrest and DNA damage). If the p21 and GADD45 induced mechanisms fail to repair the DNA damage inflicted by SV40, p53 up-regulates the *bax* gene, which promotes apoptosis. Tag also induces expression of the insulin-like growth factor 1 (IGF-1) and its receptor, which directly promotes cellular growth of infected cells.

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CASE III - EX17AI (AFIP 2840046)

Signalment: Gestational day 18.5 homozygous embryo of a p63 knockout mouse.

History: A homozygous embryo of a p63 knockout mouse collected at gestational day 18.5 (E18.5).

Gross Pathology: Mating of heterozygotes produces litters composed of affected (homozygous) and unaffected (heterozygous & wildtype) viable embryos in the expected ratios. Homozygotes die shortly after birth and are grossly abnormal. They have a translucent and smooth skin through which internal organs and bones (e.g. ribs) can be seen. Superficial blood vessels are prominent. The hindlimbs are absent and the forelimbs are truncated with stumps evident in the shoulder region. In the head, teeth, eyelids and external ears are missing, the upper and lower jaws are relatively short, and the snout is pointed without a whiskers' pad and a well-defined nose.

Laboratory Results: None.

Contributor's Morphologic Diagnosis: Stratified squamous epithelium (skin and stomach): dysplasia with erosion and ulceration.

Contributor's Comment: The submitted slides are transverse sections of the abdomen at the level of the stomach of an E18.5 embryo. The epidermis and epidermal appendages are completely absent. The outermost cells in the skin are spindle shaped and interpreted as exposed dermis. [At this age in wildtype littermates, the epidermis is approximately 100 um thick and consists of 4-5 cell layers. Keratinocytes in the basal layer are columnar, in the superficial layers there are prominent keratohyaline granules and there is a robust layer of keratin. Developing hair follicles extend from the epidermis into the dermis at regular intervals]. In the stomach the mucosa of the squamous region is dysplastic and its height is irregular. Areas where the mucosa is reduced to 1-2 cell layers alternate with foci where keratinocytes form cellular clusters and tufts. The cells are disorganized and do not exhibit the usual orderly sequence of maturation. Numerous large intracellular (as well as probable intercellular) vacuoles are present and are especially frequent in the superficial mucosa. Dead cells with karyorrhectic debris are common. [In wild type littermates, the non-glandular portion of the stomach is lined by orderly stratified squamous epithelium]. The gastric lumen

contains sloughed necrotic cells admixed with neutrophils. Similar cellular debris is also present in the lumen of the intestinal tract.

The p63 gene is a homologue of the tumor suppressor p53. It is highly expressed in the basal layer of stratified epithelium throughout the body, where it is critical for maintenance of the progenitor-cell population. In its absence, the embryonic epidermis appears to undergo terminal non-regenerative differentiation leading to an absence of all squamous epithelia and their derivatives, including teeth, vibrissae and hair follicles, mammary, sebaceous, lacrimal and salivary glands, and limbs. Limb truncation is due to failure to maintain the apical ectodermal ridge, a stratified epithelium essential for limb development. Dysplastic changes similar to those in the stomach are also observed in the esophagus, vagina, cervix, and transitional epithelium of the urinary bladder.

In man, heterozygous mutations in the p63 gene cause the EEC syndrome (*E*ctrodactyly, *E*ctodermal dysplasia and *C*left lip). Patients with this autosomal dominant condition have a wide variety of abnormalities of the hands and feet ranging from syndactyly to split hand/split foot malformation. In addition, they may have sparse hair, dry skin, pilosebaceous gland dysplasia, lacrimal gland obstruction, oligodontia, and cleft lip with or without cleft palate

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AFIP Diagnoses: 1. Stomach, gastric epithelium: Dysplasia, segmental, p63 knockout mouse, rodent.
2. Skin: Epidermal hypoplasia, diffuse, with adnexal aplasia.

Conference Comment: According to Schofield and Cotran in the sixth edition of *Robbins Pathologic Basis of Disease*, aplasia is the complete absence of an organ due to failure of development; hypoplasia is the incomplete or underdevelopment of an organ with reduced number of cells; and dysplasia is the abnormal organization of individual cells. These three definitions and their applicability to the histomorphologic changes present in this case were discussed at length. Conference participants essentially agreed with the contributor's histologic description of the gastric epithelial changes and interpretation of these changes as dysplasia. Participants also agreed with the contributor's histologic description of the epidermis, but did not agree that these changes represent dysplasia. Most instead preferred the interpretation of epidermal hypoplasia with adnexal aplasia, citing the diminished epidermis with its lack of evidence of dysplasia and the absence of adnexa as justification. Immunohistochemistry for cytokeratin performed at the AFIP demonstrated an irregular thin layer of epidermal cells without demonstrable evidence of dysplastic change. The contributor provided excellent 2x2 photomicrographs comparing the gross appearance of this p63 knockout mouse to the wild type mouse; copies will be provided to all contributors with this conference report.

As an aside, the moderator introduced the fascinating topic of how to determine the gestational age of rodents. Mating of rodents is confirmed by checking the female mouse or the cage for a vaginal (copulatory) plug. The accessory sex glands of the male mouse form this plug post copulation. Therefore, the gestational age is counted as 0.5-days-old when a vaginal plug is detected, which allows for the assumption that mating occurred at midnight.

Contributor: The Weizmann Institute of Science, Department of Veterinary Resources, Rehobot 76100 Israel

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CASE IV - Abbott Labs 1 (AFIP 2840312)

Signalment: 9-month-old, female, Beagle, *Canis familiaris*

History: This beagle dog was in a 3-month toxicity study. During the study, the dog was observed to be ataxic, weak, and had ears that were warm to the touch (interpreted to be evidence of fever).

Gross Pathology: None.

Laboratory Results: Mild to moderate neutrophilia and minimal to mild lymphocytosis

Contributor's Morphologic Diagnosis: Cervical spinal cord: Meningitis and arteritis, marked, acute to subacute with fibrinoid necrosis, canine.

Contributor's Comment: The slide presented is from the cervical spinal cord. Cross and longitudinal sections are provided. The meninges are markedly expanded by a large accumulation of a mixture of neutrophils, lymphocytes, plasma cells, and macrophages along with neovascularization. The inflammation has a periarterial/periarteriole orientation. In some areas, the infiltrate is more limited to mononuclear cells. There are occasional arteries characterized by segmental hyalinization of the wall and loss of cellular structure (fibrinoid necrosis) with accumulation of large numbers of neutrophils. In occasional vessels, only the outer

media and adventitia appear to be affected. The inflammatory infiltrate extends along the meninges to surround small arterioles within the neuropil.

In addition to the findings in the spinal cord, this dog also had nonsuppurative inflammation throughout the meninges in the cerebrum, brainstem, cerebellum, optic nerve, and lumbar spinal cord. The changes were most severe in the cervical and lumbar spinal cord.

The changes are interpreted to be most consistent with Canine Juvenile Polyarteritis Syndrome (CJPS). This disease entity has been given a number of names including Beagle pain syndrome, necrotizing vasculitis, idiopathic polyarteritis, steroid-responsive meningitis-arteritis. Both references supplied provide a good general summary of what is known and unknown about this disease.

Although a well-known entity in laboratory beagles, the disease can be found in any dog breed. According to Tipold (Kirk's), Bernese mountain dogs and Boxers also are over-represented. Most commonly reported in young adult dogs, the condition generally has an acute onset followed by later relapses. Clinical signs most often reported include fever, ataxia, stiff gait, hyperesthesia, and cervical rigidity. Laboratory findings often include a leukocytosis with left shift and a decreased albumin to globulin ratio due to decreased albumin and increased globulins.

Histologically, the findings consist of vasculitis (arteritis)/perivasculitis in multiple organs. According to Snyder *et al*., (Vet Path 1995), the sites most consistently affected were small to medium-sized muscular arteries of the cervical spinal cord, heart, and cranial mediastinum. The changes can be acute to chronic depending on the time course of the disease and range from endothelial swelling and intimal/medial edema to fibrinoid necrosis of the wall to fibrosis. Thrombosis and wall disruption with hemorrhage have also been noted. In addition, the lesion within an artery can be segmental in distribution.

The etiology and pathogenesis of this disease entity remains unknown. However, most investigators suggest that it is an immune-mediated process and cite the following evidence: 1) response to steroid therapy, 2) vascular orientation and character of histologic lesions, 3) laboratory findings.

As a final note, given the predisposition of Beagle dogs, recognition of the condition can be particularly important for toxicologic pathologists where its presence can complicate the interpretation of toxicity studies when a high incidence is present in compound-treated groups. For any pathologist, it is important to keep in mind that diagnosis is in part based on exclusion of infectious, particularly bacterial agents.

AFIP Diagnosis: Spinal cord, cervical (per contributor): Meningitis, pyogranulomatous, diffuse, moderate, with fibrinonecrotic arteritis, and multifocal, mild, lymphoplasmacytic myelitis, Beagle, canine.

Conference Comment: Conference participants discussed the following differential diagnosis: canine juvenile polyarteritis (beagle pain syndrome) - which the contributor has concisely described - pug dog encephalitis, old dog encephalitis, and granulomatous meningoencephalomyelitis. Pug dog encephalitis is a chronic, nonsuppurative and necrotizing meningoencephalitis that predominantly affects the cerebral hemispheres. The brainstem, cerebellum, and spinal cord are mildly and less

commonly affected. Old dog encephalitis primarily is a disseminated, nonsuppurative encephalitis characterized by lymphoplasmacytic perivascular cuffing, microgliosis, astrogliosis, demyelination, and rare nuclear and cytoplasmic inclusion bodies. Leptomeningitis and neuronal degeneration are variable in old dog encephalitis. Granulomatous meningoencephalomyelitis is characterized by lymphoplasmacytic and histiocytic perivascular cuffing with nests of epithelioid macrophages in the cuffs, primarily in the white matter and leptomeninges.

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