The Armed Forces Institute of Pathology
Department of Veterinary Pathology

WEDNESDAY SLIDE CONFERENCE 2007-2008

Conference 3

19 September 2007

Moderator:

Dr. Matthew Starost, DVM, PhD, Diplomate ACVP

CASE I – CRL#1 (AFIP 2936452).

Signalment: Female, approximately 6 months of age, *nu/+* mouse, congenic with BALB/c mouse (*Mus musculus*)

History: Routine submission from gnotobiotic colony for colony health monitoring

Gross Pathology: Firm anterior ventral cervical mass

Contributor's Morpho logic Di agnosis: Myoepithelioma, submandibular salivary gland

Contributor's Comment: Salivary gland tumors are generally rare in mice. An exception is myoepitheliomas in female BALB/c mice, where an incidence of 16.1/100,000 was reported in a large breeding colony at The Jackson Laboratories and 36/5090 in control groups in chronic studies.[1,5] The lower incidence at Jax probably reflects the fact that breeding mice are rarely kept past 6-8 months of age, with most animals leaving the colony at 4-6 weeks of age. Myoepitheliomas are rarely observed in male BALB/c mice or in mice of other strains.

Myoepitheliomas in mice can vary from solid to having numerous large cavities resulting from necrosis of tumor cells. This tumor was more solid than most we see, with only small cystic areas embedded in a tumor consisting of sheets and swirls of epithelioid to spindle cells. This histologic pattern and location are considered sufficient for diagnosis, with the key differentials being a complex adenoma and carcinosarcoma. Tumors with extensive squamous differentiation can also be confused with squamous cell carcinomas.

Although not apparent in most of these sections, mouse myoepitheliomas are invasive. They can also metastasize to the lungs, although this is seen infrequently in the diagnostic health monitoring laboratory setting, where subgeriatric mice are killed for other reasons or when tumors first become apparent.

AFIP Diagn osis: Submandibular salivary gland: Myoepithelioma, mouse (*Mus musculus*), rodent.

Conference Com ment: The myoepithelial cell is a modified epithelial cell that is located between the epithelial cell and the basement membrane. They contain long cytoplasmic processes that contract upon sympathetic or parasympathetic stimulation. Although myoepitheliomas can occur in any tissue, they most commonly arise from the **submaxillary** and **parotid s alivary glands** , mammary tissue, and sweat glands.[3] Neoplastic cells are positive for cytokeratin, actin, calponin and myosin.[2] Salivary myoepithelial neoplasms are rare in domestic animal

species.[2]

Contributor: Charles River Laboratories, Pathology Department, 251 Ballardvale St., Wilmington, MA 01887 www.criver.com

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CASE II – 05-999 (AFIP 3031552).

Signalment: Male, intact, INS-GAS mouse (*Mus musculus*) on an FVB background, adult, approximately 35-weeks-old

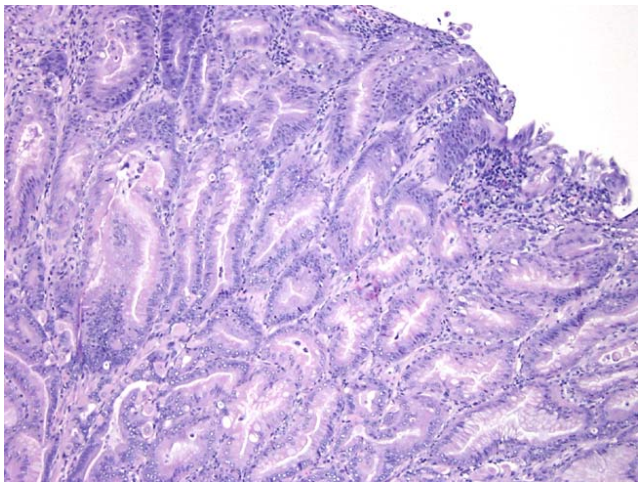
History: These three mice were experimentally infected with *Helicobacter pylori* (SS1) strain at 6 weeks old.

Laboratory Results: Serology was negative for a standard panel of murine infectious pathogens.

Gross Pathology: All mice exhibited similar changes to the stomach; only the fundus exhibited diffusely thickened gastric folds. One mouse had gastric hemorrhage.

Contributor's Morphologic Diagnosis:
Stomach. Gastric intraepithelial neoplasia (GIN)

Contributor's Comment: Only one of the three mice is on each given slide, with 3 sections from one mouse. All mice exhibited similar histologic changes: gastric mucosal and submucosa inflammation, epithelial **hyperplasia, metaplasia, and dysplasia (fig. 2-1)**. Dysplastic changes supportive of a diagnosis of GIN include severe loss of gland organization and columnar orientation, intraglandular folding, papillary and ductular projections, elongated branched and tortuous glands, and pseudostratification up to several cells deep. Moderate to marked cellular pleomorphism, cellular atypia, visible mitoses, and occasional bizarre mitotic figures are present. Within dysplastic foci are single apoptotic cells characterized by diffusely granular to hyaline eosinophilic cytoplasm, karryorhexis, and nuclear pyknosis.



2-1 Stomach, INS-GAS mouse. The gastric mucosa is thickened and gastric glands are frequently tortuous, elongated, lack normal orientation and are lined by piled up epithelium. (H&E 100X)

Phagocytosed apoptotic cells or their remnants were common in cytoplasmic vacuoles in neighboring epithelial cells. Transition zones from normal to hyperplastic to dysplastic epithelium were usually discernible and occurred in a wave of decreasing severity aborally from the cardia such that lesions were invariably most severe adjacent to the cardia. There is severe chief cell atrophy and loss of up to 50-70% of parietal cells. Parietal cells, sometimes in large numbers, exhibit small vacuolar to foamy metaplasia. Frequently there is cystic dilation of glands, often with crypt abscesses, surface epithelial "tattering" as well as small surface erosions. There are multifocal areas of mineralization within dilated glands.

The insulin gastrin (INS-GAS) mouse is a transgenic mouse bearing the transgene that overexpresses amidated gastrin, the main biologically active form of gastrin. The transgene targets expression of human gastrin to the pancreatic islets. In adult mammals, gastrin is expressed mainly in the antral G cells of the stomach where it con-

trols the acid secretion and stimulates mucosal proliferation. The INS-GAS mice spontaneously develop gastric cancer, but this requires the virtual lifetime of the animal (1-2 years). However, when male INS-GAS mice are infected with *H. pylori*, they uniformly developed atrophy, intestinal metaplasia, and dysplasia by 6 weeks and carcinoma by 24 weeks.

Gastric carcinoma is the most common of malignant tumors of the stomach in people. It is the second most common tumor in the world. It exhibits a male-to-female ratio of about 2:1. The major factors thought to affect the genesis of gastric cancer include environmental factors, host factors and genetic factors. One environmental factor, infection by *H. pylori*, present in most cases of intestinal-type carcinoma. Chronic infection with *H. pylori* generally increases the risk for developing gastric carcinoma by five-to six-fold. The bacterial infection causes chronic gastritis, followed by atrophy, intestinal metaplasia, dysplasia and carcinoma. One host determinant that may influence the development of gastric cancer is gastrin. Hypergastrinemia occurs early in the course of human *H. pylori* infection, precedes the development of atrophic gastritis, and often resolves after eradication. In addition, *in vitro* gastrin stimulates gastric epithelial cell proliferation.

In addition to host factors, bacterial determinants also contribute to gastric carcinogenesis. One virulence-associated *H. pylori* constituent is the *CagA* (cytotoxin associated gene A) pathogenicity island, which is present in approximately 60% of United States strains, and carriage of a *Cag*+/- strain augments the risk for atrophic gastritis and distal gastric adenocarcinoma compared with that incurred by *Cag* -/- strains. Several *cag* genes encode products that possess homology to components of type IV secretion systems, and, following *H. pylori* adherence to epithelial cells in vitro, the product of the terminal gene in the island (*CagA*) is translocated into the host cell, in which it undergoes Src-dependent phosphorylation and activates a phosphatase (SHP-2), leading to cellular morphologic changes. Loss of *CagE* temporally retards but does not abrogate pathologic progression.

All experiments were approved by the Committee on Animal care at Massachusetts Institute of Technology.

AFIP Di agnosis: 1. Stomach, glandular: Epithelial hyperplasia and dysplasia, diffuse, marked, with lymphoplasmacytic and neutrophilic gastritis (gastrointestinal intraepithelial neoplasia), INS-GAS mouse (*Mus musculus*), rodent.
2. Duodenum; pancreas: No significant lesions.

Conference Comment: Gastrointestinal intraepithelial neoplasia (GIN) is a term used to represent putative preinvasive neoplastic lesions not grossly visible. GIN is synonymous with atypical hyperplasia, atypia, microadenoma, carcinoma in situ, and dysplasia.[1]

Conference participants reviewed the primary cell types and functions of cells located within the stomach, such as parietal cells, chief cells, G cells, D cells, enterochromaffin-like cells, and mucous neck cells.

In the INS-GAS mouse, human heptadecapeptide gastrin is produced by the islet β cells and secreted into circulation. This gastrin release in turn causes an initial stimulation of gastric acid secretion (2-3 months of age), increasing the number of parietal and enterochromaffin-like cells. However, mice older than 5 months have a decline in acid secretion until 20 months of age when there is virtually no secretion at all, which coincides with decreasing numbers of parietal and enterochromaffin-like cells.[8]
Helicobacter spp. are Gram-negative spirochetes, approximately 3μm in length with 4-6 flagellae. Several species may contain ureases, catalases, oxidases, prote-

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Helicobacter sp. in various animal species:

Mouse[5]	*H. bilis*, *H. hepaticus*, *H. muridarum, H. rodentium, H. typhlonius, H. ganmani, H. rappini, H. mastomyrinus, H. muricola* (Korean wild mice)
Rat[5]	*H. bilis*, *H. muridarum, H. rodentium, H. trogontum, H. typhlonius*
Ferret[2]	*H. mustelae*
Hamster[5,6]	*H. aurati*, *H. cineadi, H. mesocricetorum, H. cholecystus*
Gerbil[5]	*H. hepaticus, H. bilis*
Dog[2]	*H. felis*, *H. heilmannii*
Cat[2]	*H. felis, H. pylori*, *H. heilmannii*
Pig[2]	*H. heilmannii*

ases, and phospholipases. *Helicobacter* spp. have been implicated in gastric lymphoma and carcinoma in ferrets and humans. *Helicobacter hepaticus* can cause an acute focal, non-suppurative necrotizing hepatitis in mice.

In this case, despite experimental inoculation, no *Helicobacter* sp. were noted with Warthin-Starry or Steiner's stains performed at AFIP.

Contributor: Division of Comparative Medicine, Massachusetts Institute of Technology, Cambridge, MA 02139.

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CASE III – CP03-0248 (AFIP 2938291).

Signalment: 6-month-old, male, Ptc +/- Background strain: C56BL/6;129SJ, mouse

History: The mouse was hunched, lethargic and had a rough hair coat.

Gross Pathology: A soft tissue mass was present in the cranial vault. The mass was attached to the cerebellum and compressed the adjacent brain parenchyma.

Contributor's Morphologic Diagnosis: Brain: Medulloblastoma

Contributor's Comment: A densely cellular mass is present in the cranium. The mass arises from the cerebellum and compresses the entire brain. The cells are arranged in densely packed sheets with occasional rosette formation. Neoplastic cells have elongated carrot shaped nuclei with dense chromatin and moderate pale eosinophilic cytoplasm with indistinct cell borders. Anisokaryosis and anisocytosis are minimal. Mitotic figures are rare.

Patched (Ptc) controls growth and pattern formation in early neural development and adult cerebellum. Ptc gene encodes a Sonic hedgehog (Shh) receptor and a tumor suppressor protein. Shh binds to Ptc, activates smoothened which leads to over expression of Gli-1 and some Wnt and TGF-ß gene families. Without Hh signaling, Ptc represses transcription of these target genes and itself. [2-4] Absence of Ptc causes derepression of target genes. Hedgehog (Hh) protein induces a high level of Ptc transcription through inhibition of Ptc function. While many aspects of signaling remain obscure it is clear that balance between Hh protein and Ptc is critical for normal development. Ptc expression is reduced by up to 50% in Ptc heterozygous mice. This causes ectopic expression of Shh target genes and uncontrolled cell proliferation. In Ptc heterozyogous mice, medulloblastomas have been reported as early as 5 weeks in 8.3% of mice.[3] Tumor incidence increases with age in Ptc heterozygous mice with an incidence of about 30% at six months of age. Ptc mutation has been associated with basal cell carcinoma, fibroma, medulloblastoma and rhabdomyosarcoma in man.[4]

Medulloblastomas arise from primitive neuroectodermal cells. Some cells may express neurofilament protein or synaptophysisn. However, the majority of the cells will be undifferentiated. During fetal development, cerebellar granular cells develop in the external granular layer then migrate past Purkinje cells to form the granule cell layer.

Remnants of the fetal external granular layer in the form of proliferative rests are thought to be the source of medulloblastoma cells.[5] Medulloblastomas occur with some frequency in young cattle and dogs and sporadically in pigs and cats.[7]

AFIP Diagnosis: Cerebellum: Medulloblastoma, mouse (*Mus musculus*), rodent.

Conference Comment: The contributor gives an excellent explanation of the functions of Ptc in cell growth regulation. Activation of the hedgehog pathway is shown to influence the growth of several neoplasms including medulloblastomas. Hedgehog effectors Gli1 and *Bcl*II are increased in areas of decreased apoptosis within medulloblastomas.[1]

Medulloblastomas are a subset of the primitive neuroectodermal tumors (PNETs). Medulloblastomas are derived from a germinal neuroepithelial cell and presumably arise from the matrix cells of the external granular layer.[6] Typical light microscopic findings can include palisading of neoplastic cells and rosette formation, polygonal to elongate ("carrot shaped") nuclei, and frequent mitoses. Immunohistochemical reactivity for various neural markers can vary according to the degree of differentiation.

In this case, there is extension into the inner ear in some sections.

Contributor: St. Jude Children's Research Hospital, Department of Pathology, Memphis, TN, 38105-2794

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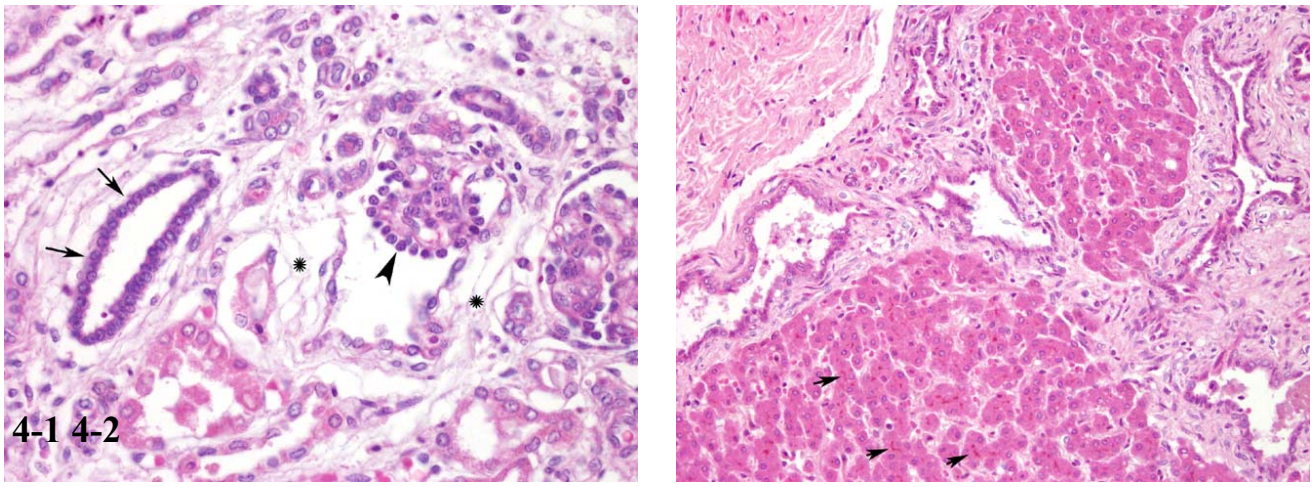
CASE IV - 02A499 (AFIP 3065784).

Signalment: Newborn, female, pigtailed macaque (*Macaca nemestrina*)

History: This animal belongs to the breeding colony from Tulane National Primate Research Center (TNPRC). This newborn macaque was found dead.

Gross Pathology: This macaque was in poor body condition, emaciated and dehydrated. One kidney was pale, firm, extremely enlarged (3 X the normal size) and slightly irregular.

Histopathologic Description: The submitted specimen consists of a section of kidney and liver. Grossly the kidney is surrounded by a thick capsule of connective tissue with numerous incomplete radial bands of connective tissue producing an abnormal lobar organization. Throughout the kidney renal corpuscles are small **(fetal glomeruli) (fig. 4-1)** predominantly in the outer cortex. There is expansion of both the cortical and medullary interstitium by abundant mesenchymal tissue. In the medulla there are multiple immature ductular structures lined by low columnar to flattened epithelial cells with prominent and hyperchromatic **nuclei** surrounded by poorly differentiated (immature) **mesenchymal tissue (fig. 4-1)**. There are also multiple cysts containing granular and fibrillar eosinophilic exudation lined by the flattened epithelial cells, islands of undifferentiated mesenchyme (cartilage matrix), and immature collecting ducts lined by psudoestratified columnar epithelial cells representing persistent metanephric ducts. The histological examination of the liver revealed hyperplasia of the intrahepatic bile ducts with multiple cystic or saccular dilata-



4-1 Kidney, pigtailed macaque. Renal dysplasia characterized by primitive mesenchyme (stars), fetal glomeruli (arrowhead) and primitive tubules (arrows). (H&E 400X)
4-2 Liver, pigtailed macaque. Portal areas are markedly expanded by increased numbers of bile duct profiles and abundant fibrous connective tissue. Hepatocytic cytoplasm and bile canaliculi often contain amber-brown globular pigment interpreted as bile (arrows) (H&E 200X)

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tions lined by low cuboidal epithelial cells and overgrowth of **portal connective tissue (fig. 4-2)**.

Contributor's Morpho logic Di agnosis: 1. Kidney: Cystic renal dysplasia
2. Liver: Bile duct ectasia and hyperplasia associated with portal fibrosis

Contributor's Comment: Cystic diseases of the kidney are a heterogeneous group comprising hereditary, developmental but nonhereditary, and acquired disorders. A useful classification of renal cysts is as follows:[2]

1. Cystic renal dysplasia
2. Polycystic kidney disease
    a. Autosomal-dominant (adult) polycystic disease
    b. Autosomal-recessive (childhood) polycystic disease
3. Medullary cystic disease
    a. Medullary sponge kidney
    b. Nephronophthisis
4. Acquired (dialysis-associated) cystic disease
5. Localized (simple) renal cysts
6. Renal cysts in hereditary malformation syndromes (e.g., tuberous sclerosis)
7. Glomerulocystic disease
8. Extraparenchymal renal cysts (pyelocalyceal cysts, hilar lymphangitic cysts)

Renal dysplasia is defined as disorganized development of renal parenchyma due to abnormal differentiation. This disease refers to a developmental disorder of renal parenchyma due to imperfect inductive interaction between the mesonephric duct and the matanephric blastema.[2]

In human beings renal dysplasia can be unilateral or bilateral and is almost always cystic. The abnormalities in the collecting system are common. In gross appearance, the kidney is usually enlarged, extremely irregular, and multicystic. The cysts vary in size from microscopic structures to some that are several centimeters in diameter.[11]

In dog the histologic features used to diagnose renal dysplasia include the prescence of 1) fetal or immature glomeruli, 2) fetal or immature tubules, 3) persistent metanephric ducts surrounded by primitive mesenchyma, 4) bone or cartilage in the parenchyma, and 5) anomalous presence of interstitial fibrous connective tissue.[6,13] Renal dysplasia has been reported in many breeds, such as the Golden Retriever, Labrador Retriever, Shih Tzu, Bull Mastiff, Boxer, and Finish Harrier [1,6,7,9,10,13-17] and human patients.[11]

In Rhesus macaque (*Macaca mul atta*) adult polycystic kidney disease and infantile polycystic kidney disease has been reported, and in Cynomolgus monkey (*Macaca fascicularis*) a case of spontaneous congenital polycystic kidney has been also described.[3,8,18]

In this case, the histological examination of the liver showed hyperplasia with cystic and saccular dilatations

of the intraepithelial bile ducts lined by low cuboidal epithelial cells associated with overgrowth of portal connective tissue.

In human being abnormalities of the biliary tree are an heterogeneous group of congenital lesions (von Meyemburg complexes, polycystic liver disease, congenital hepatic fibrosis, and Caroli disease) in which the primary abnormality is altered architecture of the intrahepatic biliary tree.[4]

The precursor of the intrahepatic biliary tree is a double-layered sleeve of cells know as the ductal plate (DP). The DP first arises from hepatocyte precursors surrounding hilar portal vein vessels, and more peripheral regions of the DP then develop sequentially. During the remainder of gestation, a process of DP remodeling occurs in which small areas of the double layer separate to form tubules, which join to form the intrahepatic biliary tree, while the remaining regions of the DP involute. Hepatic fibropolycystic diseases are thought to originate from failures in this process and are known collectively as DP malformations. However depending on the size of the bile ducts affected and the time during organogenesis, different syndromes, with marked overlap, can be differentiated. Caroli disease is a subcategory of these diseases, characterized by multiple cystic and segmental saccular dilations of the larger intrahepatic bile ducts.[4] Caroli syndrome involves malformations of smaller bile ducts and congenital hepatic fibrosis, marked by portal tract enlargement with irregular and broad bands of collagenous tissue, in which variable numbers of abnormally shape bile ducts are embedded.[4,5] Caroli syndrome is often associated with autosomal recessive polycystic kidney disease (ARPKD), and both the hepatic and renal processes reflect developmental process in the context of different organs. [4,5]

The present report described a congenital cystic renal dysplasia associated with bile ducts ectasia and prominent portal fibrosis in a new born Pigtailed macaque (*Macaca n emestrina*), a combination not previously reported in macaques.

The finding in our case of renal and bile duct dysplasia mimics previously reported cases in human and rat of Caroli syndrome.

AFIP Di agnosis: 1. Kidney: Renal dysplasia, characterized by fetal glomeruli, primitive mesenchyme, immature tubules, tubular ectasia and cysts, and interstitial and capsular fibrosis, with minimal lymphoplasmacytic interstitial nephritis and mineralization, pigtailed macaque (*Macaca nemestrina*), primate.

2. Liver: Biliary duct hyperplasia, diffuse, marked, with biliary duct ectasia, portal fibrosis, and cholestasis.

Conference Comment: The contributor gives a good review of the different forms of cystic kidney diseases with emphasis on renal dysplasia. There is debate in the literature on what features are necessary for the diagnosis of renal dysplasia. Although cartilaginous or osseous metaplasia is described in the human literature, it is rarely present in dysplastic kidneys of animals.[11]

Renal dysplasia has been associated with fetal infections of feline panleukopenia virus, canine herpesvirus, and bovine viral diarrhea virus, as well as hypovitaminosis A during gestation in swine.[11] There is not an apparent connection between the renal dysplasia and the biliary duct hyperplasia with congenital hepatic fibrosis (Caroli Syndrome) in the present case.

It is possible that the small cysts seen in this case are due to autosomal recessive polycystic kidney disease (ARPKD). It is important to make the distinction that although ARPKD is associated with Caroli syndrome, it is not a defining feature of the disease process.

Contributor: Tulane National Primate Research Center, Comparative Pathology Division, Covington, LA, 70433 http://www.tpc.tulane.edu/

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