Joint Pathology Center
Veterinary Pathology Services

WEDNESDAY SLIDE CONFERENCE 2011-2012

Conference 12

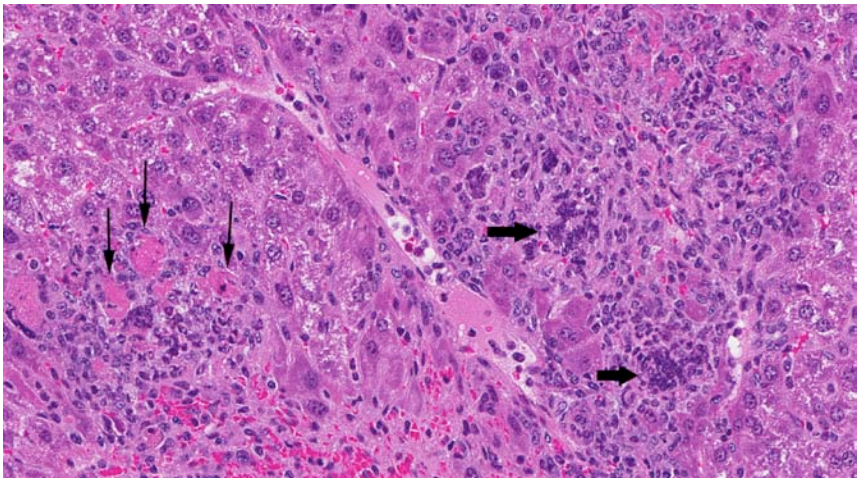
11 January 2012

CASE I: CRL-1 (JPC 3167482).

Signalment: 16-week-old female nude (NU-Foxn1nu) mouse (*Mus musculus*).

History: Submitted for routine health monitoring.

Gross Pathology: The liver was enlarged, with rounded margins and adhesions to the pancreas, intestines and right kidney.



1-1. Liver, mouse. Multifocally and randomly there are small foci of necrotic hepatocytes (thin arrows) admixed with infiltrating neutrophils, and histiocytes. There are also multinucleated giant cells (viral syncitia). (HE 320X)

Laboratory Results: MFIA and IFA positive for mouse hepatitis virus and murine norovirus (serology performed on an immunocompetent cagemate).

Contributor's Histopathologic Description: The liver has multiple foci of degeneration/necrosis and hemorrhage, with inflammatory cell infiltrates comprising neutrophils, histiocytes and lymphocytes. There are many syncytial cells characterized by large degenerate cells at the periphery of foci of necrosis which contain multiple deeply basophilic nuclei and nuclear remnants. There is multifocal extramedullary hematopoiesis. Depending on the section, there is variable capsular fibrosis and inflammation, with some fibrin admixed, and adhesions to the pancreas, with chronic suppurative dochitis and syncytial cells.

Contributor's Morphologic Diagnosis: Liver: Hepatitis, chronic, necrosuppurative, multifocal, marked, with syncytial cells.

Etiology: Mouse hepatitis virus.

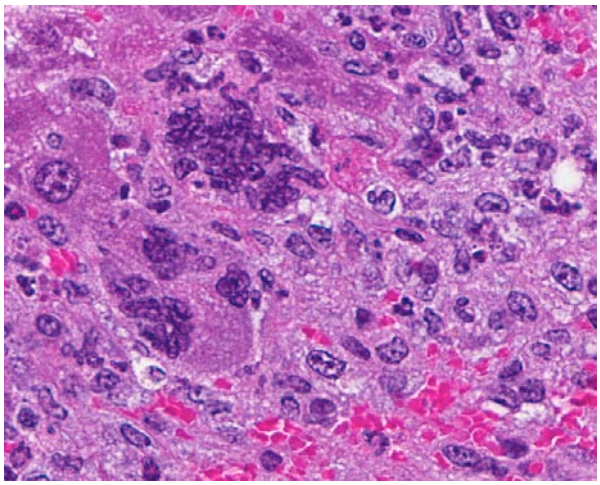
Contributor's Comment: Mouse hepatitis virus (MHV) is a coronavirus that infects mice, although the virus shares

antigenic cross reactivity with Group 2 coronaviruses, including rat coronavirus and bovine coronavirus.[5] Infant rats can be experimentally infected.[1] Susceptibility to MHV varies with host and viral factors, such as genotype, age, strain of virus, route of inoculation, immune status, diet, and concurrent infections. MHV can be loosely classified into two groups according to the primary target organ; enterotropic and respiratory strains. Enterotropic strains selectively infect intestinal mucosa with little, if any, dissemination to other tissues in immunocompetent mice. Respiratory strains are considered polytropic, replicating in the nasal mucosa followed by secondary dissemination to multiple organs. Although improved husbandry has markedly reduced the prevalence of MHV in laboratory mice, the rate of MHV seropositive samples received at a major commercial rodent diagnostic laboratory was reported to be 1.6% (commercial vendor mice excluded).[6] Diagnosis of MHV infection is typically accomplished with serology and histopathology on sick animals.

The pathogenesis of infection with a respiratory MHV strain begins with replication in the nasal epithelium, followed by dissemination via the blood stream to other tissues including liver, vascular endothelium, lymphoreticular tissues and brain, depending on host susceptibility. Pulmonary involvement is restricted to vascular endothelium and does not involve respiratory mucosa. The route of dissemination of infection to the brain is age-dependent. In adult mice, infection tends to occur by extension of virus along the olfactory neural pathway. Microscopic findings are multifocal necrosis with syncytia in multiple organs, commonly including liver, spleen, lymph nodes and other lymphoid tissue.[5] Hallmark syncytia of MHV infection are characterized by large degenerating cells at the periphery of necrotic foci, containing dense basophilic nuclei and nuclear remnants. Syncytia are more common and more well-developed in immunocompromised mice, as in this case.

Endemic infections are usually subclinical, sustained by continued arrival of naive susceptible animals (newborns), as there is generally no carrier state.[1]

Immunocompromised mice infected with either respiratory or enterotropic strains of MHV may develop progressively fatal, multi-systemic infections with severe necrotizing lesions in nasal epithelium, vascular endothelium, brain, liver, bone marrow, lymphoid tissue and other sites.[2] Virulent MHV strains kill these mice rapidly, but disease can be chronic with wasting in mice exposed to natural, avirulent strains of virus. Immunocompromised mice with only B cell defects infected with enterotropic MHV may develop enteric infections which are chronic but may not manifest overt clinical disease.[2] High morbidity and mortality can develop with enterotropic MHV infection in neonatal mice in naive mouse colonies.[5]



1-2. Liver, mouse. Closer view of multinucleated giant cells (viral syncitia) are present, often at the periphery of necrotic foci. (HE 400X)

JPC Diagnosis: 1. Liver: Hepatitis, necrotizing, multifocal and random, with hepatic and endothelial viral syncitia, and capsular fibrosis.
2. Pancreas: Dochitis, necrotizing, diffuse, minimal.

Conference Comment: The mouse strains most susceptible to the polytropic strain of mouse hepatitis virus (MHV) are C57BL, DBA/2, nude mice, SCID mice, and BALB/c. C3H is a partially susceptible strain, and A/J and SLJ mice are resistant. All strains are susceptible to the enterotropic strains. Tumor necrosis factor (TNF) -/- and transgenic mice persistently infected with MHV can transmit infection for months and infect susceptible mice and immunocompetent sentinel mice.[5] Co-infection of MHV with bacteria (i.e. *Helicobacter hepaticus*) decreases the severity of acute lesions but exacerbates hepatitis and meningitis in chronic infections.[3]

Despite the name "mouse hepatitis virus", polytropic MHV is not always hepatotropic. In addition to hepatic necrosis, common gross lesions include lymphoid tissue involution, ascites, hemorrhagic peritoneal exudate, necrotizing enterocolitis, thickened bowel segments in weanlings and adults, and mucosal proliferation or hyperplasia of the ascending colon and ileocecal junction in older mice. Microscopic lesions seen in other organs include intraepithelial eosinophilic intracytoplasmic viral inclusion bodies, necrotizing enterocolitis, segmental to diffuse villus blunting and atrophy at the ileocecal junction and ascending colon, and necrosis and syncytial giant cells of the splenic red pulp, lymphoid tissue, and hematopoietic tissues. In mice susceptible to neurotropic effects, there is necrotizing meningoencephalitis with spongiosis,

demyelination, and syncytial giant cells in the central nervous system.[5]

The differential diagnosis in mice for hepatitis and enteritis include:

a) Tyzzer's disease caused by *Clostridium piliformis* with intracytoplasmic bacilli and no giant cells
b) salmonellosis
c) mouse pox caused by ectromelia virus, an orthopoxvirus characterized by splenic necrosis ("tiger striping") and skin lesions with intracytoplasmic eosinophilic viral inclusion bodies
d) epizootic diarrhea of infant mice (EDIM) caused by a rotavirus with less severe disease in neonatal mice with epithelial vacuolar degeneration in the ileum and jejunum, and epithelial eosinophilic intracytoplasmic viral inclusion bodies and no multinucleated giant cells or endothelial changes
e) reovirus-3, an orthoreovirus which causes foci of hepatic necrosis, CNS lesions, myocardial necrosis and pulmonary hemorrhage
f) adenovirus, which presents with intranuclear viral inclusion bodies
g) *Helicobacter hepaticus,* which causes proliferative colitis and rectal prolapse.[3,5]

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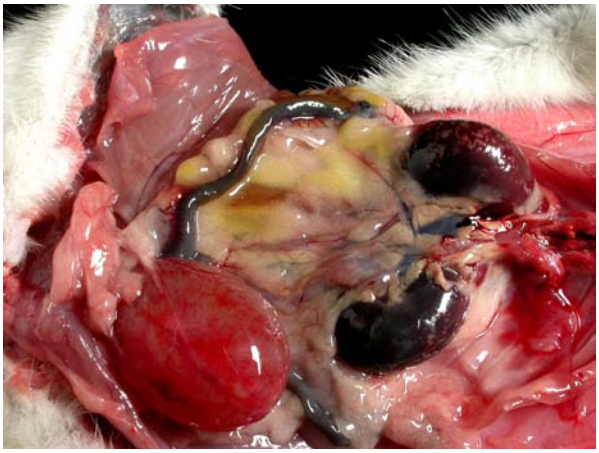
CASE II: 42100-A (JPC 4001557).

Signalment: 5-month-old female Sprague-Dawley rat (*Rattus norvegicus*).

History: Tissues are from three rats that were part of a group of 60 rats receiving a trial diet that contained a single protein source. Rats within the group did not gain weight as rapidly as expected.

Gross Pathology: Rats were in a poor state of nutrition and weighed less than would be predicted for their age. Examination of the urinary system revealed pitted kidneys with white streaks within the cortex.

Laboratory Results: A pure growth of *Escherichia coli* was cultured from a sample of kidney from one of the rats.



2-1. Kidney, rat. The kidneys are pitted with white streaks. Photograph courtesy of Institute of Veterinary, Animal, and Biomedical Sciences, Massey University, www.massey.ac.nz

Contributor's Histopathologic Description: Lesion severity is variable within the sections. The predominant lesion is visible within the renal pelvis. Here, mild to marked dilation of the pelvis is visible. Inflammation is visible surrounding the pelvis. This inflammation consists predominantly of lymphocytes and plasma cells with some sections also containing significant numbers of neutrophils. Small foci of mineralization are visible surrounding the pelvis in some sections. The transitional epithelium within the renal pelvis has undergone squamous metaplasia. Inflammation and necrosis is visible extending from the renal pelvis into the cortex. Tubules that are dilated by neutrophils are visible within the sections. Areas of fibrosis indicate previous episodes of nephritis within the cortex.

Contributor's Morphologic Diagnosis: Kidney. Pyelonephritis, moderate, subacute, neutrophilic, with marked squamous metaplasia of the transitional epithelium.

Contributor's Comment: The high mortality within the group of rats receiving this experimental diet suggested a dietary toxin or deficiency. In addition to the renal pelvis, squamous metaplasia of the transitional epithelium was also visible within the ureters and bladder suggesting vitamin A deficiency. Subsequent analysis revealed that the experimental diet that these rats were receiving contained an inadequate concentration of vitamin A. Overall within the 60 rats, 27% had visible uroliths and 5% had nephroliths. Bilateral pyelonephritis was detected histologically in 43% of rats and unilateral pyelonephritis in 25%.

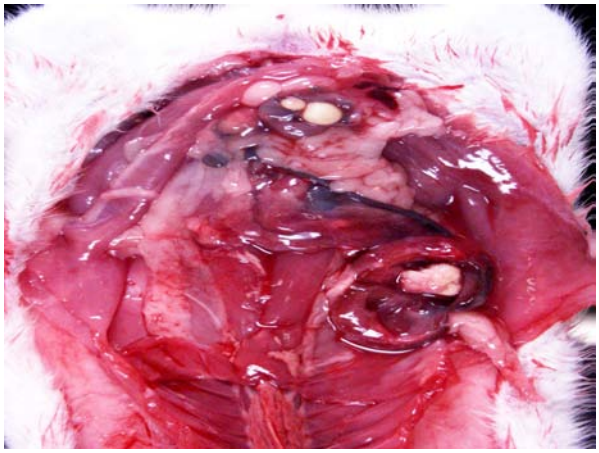
Vitamin A regulates epithelial cell growth and differentiation, enables production of visual pigment, is necessary for normal function of the immune system, and influences skeletal development.[8] When rats are fed diets that contain no vitamin A, the most commonly reported clinical signs of deficiency are weight loss, corneal keratinization and ulceration, respiratory or skin disease, and salivary gland enlargement.[1] An 80% mortality rate due to inanition or bacterial infection of the skin or respiratory tract is expected after 15 weeks.[1] In the present case, the rats received some vitamin A, albeit in inadequate quantities. The restriction of the lesions to the transitional epithelium in these rats suggests that the transitional epithelium is the most susceptible to squamous metaplasia due to moderate vitamin deficiency.[6] The squamous metaplasia of the transitional epithelium then predisposed to the development of ascending bacterial infections and urolith and nephrolith formation.

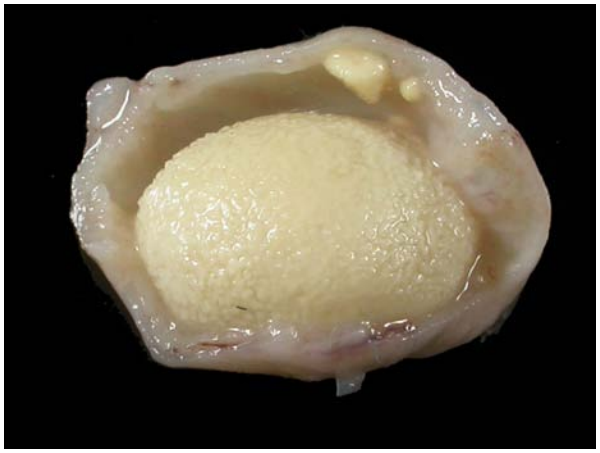
While squamous metaplasia of the transitional epithelium lining the renal pelvis can occur secondary to bacterial infection, the metaplasia visible within the present case was considered an excessive reaction to an ascending bacterial pyelonephritis.

JPC Diagnosis: Kidney: Pyelonephritis, neutrophilic and lymphohistiocytic, diffuse, marked, with urothelial squamous metaplasia and coccobacilli.

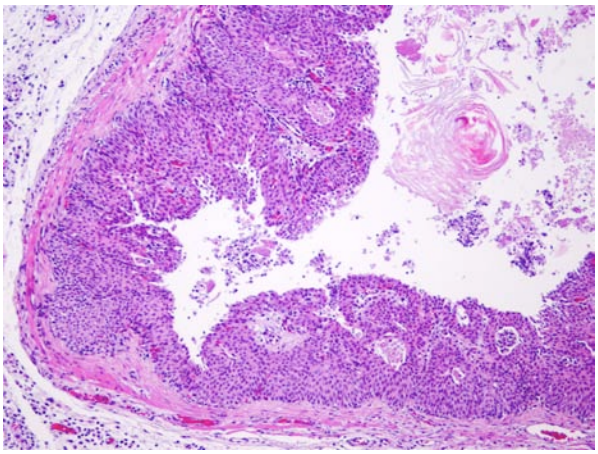
Conference Comment: Vitamin A is one of four fat soluble vitamins, along with vitamins D, E and K, and has multiple functions. Vitamin A as retinoic acid functions in morphogenesis during embryonic development, maintenance of epithelial cells, bone growth, reproduction, immunostimulation, and may also have antioxidant effects.[3]

Vitamin A deficiency leads to impaired epithelial differentiation through an unknown mechanism, and leads to reduction in mucus-secreting cells, squamous metaplasia of the respiratory and genitourinary





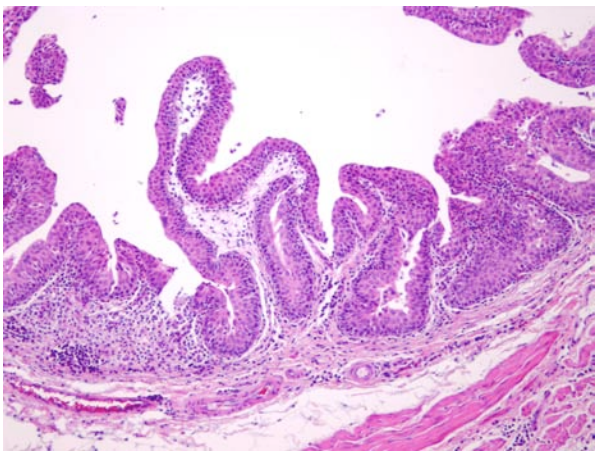
2-2, 2-3, 2-4. Kidneys, urinary bladder, rat. Nephroliths and uroliths were present in 5 and 27%, respectively, of examined rats. Photographs courtesy of Institute of Veterinary, Animal, and Biomedical Sciences, Massey University, www.massey.ac.nz



2-5, 2-6. Ureter, urinary bladder, rat. Urothelium is hyperplastic, piling up several layers deep, and the superficial layers are composed of flattened squamous epithelium (squamous metaplasia). The ureter (1-5) contains abundant keratin debris and sloughed epithelium. Photographs courtesy of Institute of Veterinary, Animal, and Biomedical Sciences, Massey University, www.massey.ac.nz

epithelium, and hyperkeratosis.[4] Hypovitaminosis A also leads to retarded osteoclastic resorption of endosteal bone, and lesions are varied depending on species affected, stage of growth, and severity of the deficiency.[7] Vitamin A deficiency also leads to the arrest of spermatogenesis at the spermatid phase in all species, especially in cattle, rats, and chickens, and causes abnormal estrous cycles, congenital anomalies, and fetal resorption. Hypovitaminosis A affects immune function, as vitamin A is thought to stimulate T-cells directly through 14-hydroxyretinol. During infection, synthesis of the negative acute phase protein, retinol-binding protein, is down-regulated, decreasing availability of vitamin A.[4]

In dogs, vitamin A deficiency results in hyperkeratosis of sebaceous gland ducts; vitamin A-responsive dermatosis in cocker spaniels is characterized by marked follicular keratosis of the chest and abdomen.[2] In male calves, vitamin A deficiency results in stenosis of the optic foramen and atrophy of the optic nerve,



leading to blindness. Squamous metaplasia of the parotid gland is a pathognomonic lesion of hypovitaminosis A in cattle.[9] In guinea pigs and rats, vitamin A deficiency results in inadequate differentiation and organization of odontoblasts,

leading to irregular dentin formation and enamel hypoplasia.[5]

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CASE III: S111/11 (JPC 4003457).

Signalment: 6-week-old male BALB/c mouse (*Mus musculus*).

History: The mouse was infected by intracerebral inoculation with a lethal dose of rabies virus (genotype 1).

Gross Pathology: No gross lesions were observed.

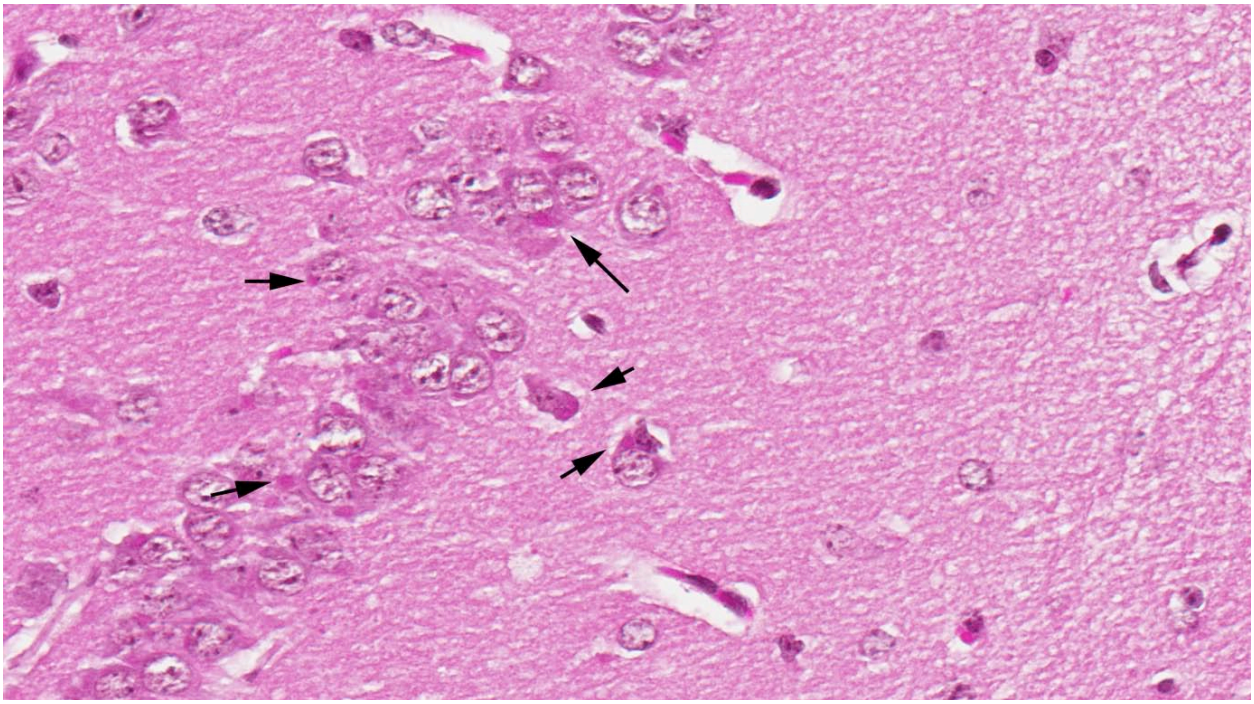
Laboratory Results: Further laboratory investigations were not performed.

Contributor's Histopathologic Description: Cerebrum: Within the gray matter of the cortex, thalamus, hippocampus and hypothalamus regions (these sections were submitted to the conference) there is low to moderate numbers of neurons with shrunken cell bodies, and hypereosinophilic cytoplasm frequently accompanied by karryorhexis or karyolysis (neuronal degeneration and necrosis). Occasionally in these cells, but significantly more often in normal appearing neurons, especially within the hippocampus, there are one to several intracytoplasmic, pale eosinophilic inclusion bodies up to 7 µm in diameter (Negri bodies). Some affected neurons are surrounded by lymphocytes and glial cells (neuronophagia). Focally distributed throughout the neuropil, aggregates of glial cells and lymphocytes are present (glial nodules). Perivascularly, there is a slight lymphocytic and histiocytic infiltration (perivascular cuffing) and few lymphocytes and histiocytes are found in submeningeal regions. In some sections, ventricles contain low amounts of lymphocytes and histiocytes.

Contributor's Morphologic Diagnosis: Encephalitis, nonsuppurative, minimal, with neuronal degeneration and necrosis and neuronal eosinophilic intracytoplasmic inclusion bodies, mouse, etiology consistent with rabies virus infection.

Contributor's Comment: Rabies virus (RV) belongs to the genus *Lyssavirus* in the *Rhabdoviridae* family of the order *Mononegavirales*. The characterization of the rabies virus isolates based on monoclonal antibodies grouped the rabies-associated viruses into four serogroups, with classical rabies forming serogroup 1, the African lyssaviruses forming serogroup 2 (Lagos bat virus), serogroup 3 (Mokola virus), and serogroup 4 (Duvenhage virus). DNA sequencing was used to further distinguish the members of each serogroup, which in turn became genotypes (see table).[21] The European bat lyssaviruses were classified into two groups (EBLV-1 and EBLV-2) and designated genotypes 5 and 6.[14] A further genotype has been identified in Australia, Australian bat lyssavirus.[11]

The genome of RV comprises five genes encoding the viral proteins nucleoprotein, phosphoprotein, matrix protein, glycoprotein and the viral RNA polymerase. The replication of RV proceeds in the presence of the host immune response, including the antiviral type I



3-1. Brain, hippocampus, mouse. Many neurons contain 2-7 micron bright eosinophilic intracytoplasmic inclusion bodies (Negri bodies). (HE 400X)

interferon (IFN) system. RV is known for its IFN-sensitivity and therefore must encode mechanisms that prevent IFN expression.[5] It is hypothesized that the viral phosphoprotein is involved in this mechanism.[1]

Rabies occurs in more than 150 countries and territories worldwide. Dogs are the source of infection in all of the estimated 55,000 human rabies deaths annually in Asia and Africa. Bats are the source of most human rabies deaths in the United States of America and Canada. Bat rabies has also recently emerged as a public health threat in Australia, Latin America and Western Europe. Infections due to contact to rabid foxes, raccoons, skunks, jackals, mongooses and other wild carnivore are very rare. Human-to-human transmission by bite has never been confirmed.[23]

RV is the causative agent of the classical rabies and is responsible for the vast majority of all human rabies cases. The transmission occurs via the bite of rabid animals shedding virus within their saliva, or direct contact of infectious material (i.e. saliva, cerebrospinal liquid, nerve tissue) to mucous membranes or skin lesions. The virus cannot penetrate intact skin. Rabies virus replicates in striated muscle cells or infects nerve cells, followed by a retrograde transport of virions to the central nervous system (CNS). Within the CNS, virus replication induces pathologic effects on nerve cell physiology. The anterograde transport of virus to secretory tissues of salivary glands leads to viral shedding via saliva.[24]

In animals, RV infection brings out neurological signs which might differ slightly depending on the species and the time point infected. The incubation period for rabies is typically 1–3 months, but may vary from <1 week to >1 year.[23] After this so-called prodromal stage, the onset of clinical symptoms follows, which lasts for about 1-3 days with aggressiveness, daytime activities in nocturnal animals or abnormalities in appetite. Potentially, the prodromal stage is followed by the excitative phase with severe agitation and aggressiveness. Further, in the paralytic phase, the infected animals are unable to swallow, leading to a typical sign of foaming saliva around the mouth. A complete paralysis occurs and is followed by death.[24]

Many neurotropic viruses use apoptosis as a mechanism of neuropathogenicity.[16] The induction of apoptosis by rabies virus has been a controversial topic, but increasing evidence indicates that pathogenic rabies virus strains do not induce apoptosis.[8]

In natural rabies, pyknotic chromatolytic neurons are seen throughout the CNS most frequently in the brainstem, and periaqueductal gray matter, cervical spinal cord, thalamus and less frequently the cerebral cortex.[4] In general, these degenerated neurons do not harbor Negri bodies but are positive for viral antigen and may be accompanied by inflammatory reaction.[6] As in other viral encephalitides, neuronophagia and glial nodules are seen often in areas where neuronal degeneration and inflammatory cell infiltration are conspicuous. Topographic dissociation between location of inflammatory reactions and of Negri body has been reported in an autopsy study of 49 cases. Inflammatory changes were most frequently found in medulla, pons and spinal cord followed by thalamus and less frequently in cerebellum and hippocampus. Negri body bearing neurons were rare where inflammation was dense.[10] Perivascular infiltrates are composed of lymphocytes and monocytes intermingled with small numbers of granulocytes and plasma cells, depending on the stage and severity of infection.[7]

Two different mechanisms have been proposed for the transport of rabies virus through the axon to the cell body: transport of either the rabies virus capsid alone or transport of the whole virion. A recent study showed that the whole virion is transported to the cell body in an endosomal vesicle, although the exact mechanism by which this occurs remains unclear.[12] The rabies virus glycoprotein mediates the entry of the virion into the vesicle. However, as the rabies virus glycoprotein is inside the vesicle, it should not be able to interact directly with a specific transporter complex. Based on these observations, it is speculated that entry into the vesicle determines the direction and provides the driving force of rabies virus transport. This indicates that the nature of the vesicle formed dictates the transport method that follows.[19]

In cases of human rabies, the patients die with absence of protective antibodies. The immune privileged status of the CNS and the blood–brain barrier might explain the delayed development of a protective immune response and the poor survival rate.[10] Remarkably, there is one report of a human survivor of rabies. The patient had detectable antibody and the treatment applied was aimed to allow the humoral immune response to develop. High IgG titres developed and might have contributed to the survival of this patient.[24]

The influence of the immune privileged status of the CNS on the antibody response is controversial. In contrast to RV, Herpes viruses and Borna disease virus can infect the brain, but are effectively controlled by the immune system. Several other factors are discussed, as for example that the infectious dose transmitted with a bite is too small to trigger immune responses and further enable the virus to infect sensory nerves. A final explanation for the lack of antibody could result from immunosuppression induced by the virus. It is known that the viral phosphoprotein inhibits interferon response. However, RV infection is

associated with the increase in gene transcripts for interferon-inducible genes. It is speculated that interferon inhibition is transitory and provides a short delay in the host response.[10]

Table: Current classification of the Lyssavirus genus, host species and geographical distribution.[11]

[a] Species from which the virus is predominantly isolated.
[b] Single isolations have been made.

numbers in salivary epithelial cells of carnivores, and the virus can be detected in chromaffin cells of the adrenal medulla, basal epithelial cells of the nasal mucosa, cornea, epidermis, and external root sheath of hair follicles. Infection of these sites is by peripheral nerves.[2]

Australian bat lyssavirus, mentioned by the contributor, is a virus closely related to rabies that was discovered in Australia in 1996. It occurs in various species of flying foxes and occasionally in other

Virus and Genotype (I-VII)	**Host[a]**	**Geographical distribution**
Classical rabies virus (RABV), I	Numerous chiropteran and carnivoran species	Worldwide
Lagos bat virus (LBV), II	*Epomophorus wahlbergi* (Wahleberg's epauletted fruit bat)	Africa
Mokola virus (MOKV), III	Unknown	Africa
Duvenhage virus (DUVV), IV	*Miniopterus* species (?)	Southern Africa
European bat lyssavirus type 1 (EBLV-1), V	*Eptesicus serotinus* (Serotine bat)	Europe
European bat lyssavirus type 2 (EBLV-2), VI	*Myotis daubentonii* (Daubenton's bat)	Western Europe
Australian bat lyssavirus (ABLV), VII	Australian mega- and microchiropteran species	Australia
Aravan	*Myotis blythi* (lesser mouse-eared bat)[b]	Kyrgistan
Khujand	*Myotis mystacinus* (whiskered bat)[b]	Kyrgistan
Irkut	*Murina leucogaster* (greater tube-nosed bat)[b]	Eastern Siberia
West Caucasian bat virus (WCBV)	*Miniopterus schreibersi* (common bent-winged bat)[b]	Western Caucasus Mountains

JPC Diagnosis: Brain, cerebrum: Neuronal necrosis, with minimal lymphoplasmacytic perivasculitis and numerous neuronal intracytoplasmic viral inclusion (Negri) bodies.

Conference Comment: The contributor provided a very thorough overview of rabies virus. Following invasion and replication in rhabdomyocytes, virions enter the extracellular space of the neuromuscular junction and neurotendinal sensory stretch receptors, and enter the neurons via the acetylcholine receptor at the neural synapses. Once in the central nervous system, the virus concentrates in the limbic system and generally spares the neocortex, which is the cause of the furious stage of infection. Once in the central nervous system, virions can bud from the neuronal cell body and process plasma membranes and directly infect neighboring neurons. Negri bodies are found in greatest concentration in large neurons, such as in the pyramidal cells of the hippocampus, ganglionic neurons of the pontine nuclei, and cerebellar Purkinje cells. Negri bodies represent the accumulation of rabies virus nucleocapsids in cells due to the defective assembly of virions. Negri bodies are found in large

species of bats and is responsible for a few human fatalities. Lesions are similar to rabies and consist of nonsuppurative meningoencephalomyelitis and ganglioneuritis with Negri bodies.[6]

Pseudo-Negri bodies, which may be confused with rabies and are a reason that rabies diagnosis should not be based solely on the presence of Negri bodies, are found in cats, skunks, and dogs and are nonspecific, 1.5 µm, homogenous inclusions in the pyramidal cells of the hippocampus. They present in cats as nonspecific inclusions in the lateral geniculate neurons; in dogs as cytoplasmic lamellar bodies in the thalamic neurons and Purkinje cells; in aged sheep and cattle as nonspecific 1 µm, brightly eosinophilic, angulated inclusions in the large neurons of the medulla and spinal cord; in Japanese brown beef cattle; in mice as hippocampal inclusions; and in woodchucks as inclusions in the brainstem.[3,15,17,18,20,22]

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CASE IV: VS11 (JPC 4003034).

Signalment: 8-year-old male Rhesus macaque (*Macaca mulatta*).

History: Clinical History: This monkey developed intermittent antibiotic unresponsive hematuria, and ultrasonography showed a rounded, misshapen right kidney with a loss of architecture in the renal pelvis. ACT scan revealed a mass occupying the caudal 2/3 of the kidney and proximal ureter, consistent with a neoplasm. Unilateral nephrectomy was performed and the specimen was submitted as a biopsy.

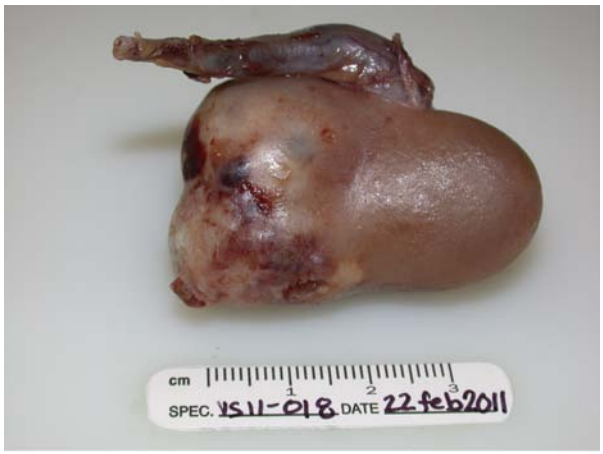
Experimental History: This monkey received a single 7.55 Gy dose of whole-body irradiation at 3 years of age.

Gross Pathology: The entire right kidney, with attached capsule and 4.5cm segment of ureter was submitted in 10% neutral buffered formalin. An irregularly-shaped, 3.8x3x2cm firm, tan mass with scattered hemorrhages on cut surface replaced the caudal two-thirds of the kidney. A 5mm diameter x 4mm nodule protruded from the surface, underneath the capsule. The renal capsule was easily removed except for a 3mm diameter area, where it was firmly attached. The ureter measured 5mm in diameter where it exited the renal pelvis and was of normal diameter at the distal end of the specimen.

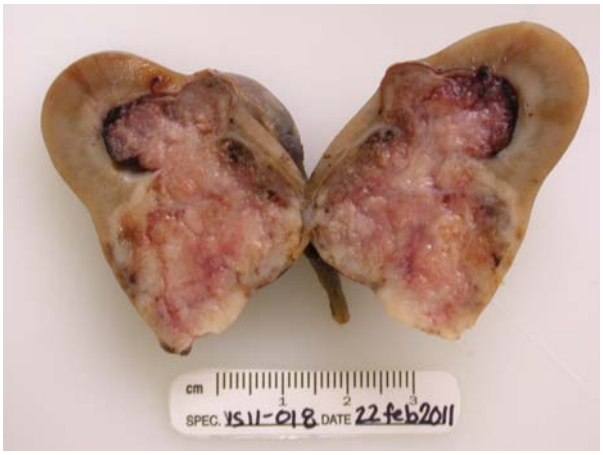
Laboratory Results:
Blood Chemistry:
BUN 13 mg/dL (13-27 mg/dL)
Creatinine 1.5 mg/dL (0.8-1.5 mg/dL)

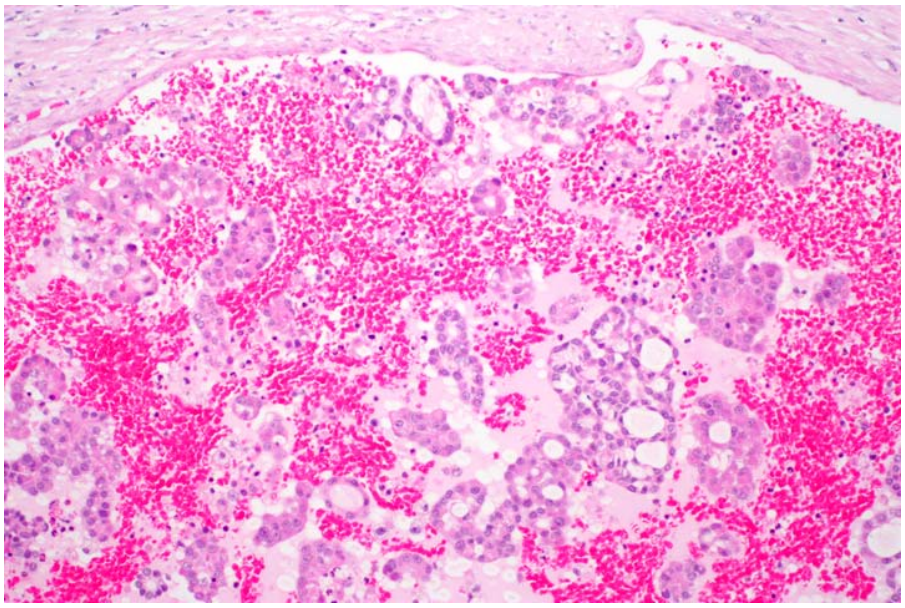
Urinalysis:
Specific Gravity 1.007
Blood 80 cells/mL
Protein: 2+ (100 mg/dL)
Bacteria: none
WBC: 6-10/HPF
RBC: 30-50/HPF

Contributor's Histopathologic Description: An infiltrative neoplasm, irregularly dissected by tracts of mature collagenous connective tissue, distends the proximal ureteral lumen, effaces the adjacent renal parenchyma (more prominent in some sections) and compresses normal renal cortical tissue. The neoplasm is composed of fronds of collagenous connective tissue lined by single to multiple layers of epithelial cells which have oval, 15x10 micron nuclei with finely stippled basophilic chromatin and single nucleoli. The cytoplasm is eosinophilic, sometimes with clear vacuoles, and cell borders are indistinct. Mitotic figures are rare, with up to only 1 per five 40X fields. Small accumulations of granular to clumped deeply basophilic material (mineral) are scattered throughout. Rafts of neoplastic cells are present in blood vessels at the margins in some sections. Lymphoplasmacytic infiltrates are scattered throughout the neoplasm. Immunohistochemical staining for uroplakin III is negative. An internal positive control is provided by normal urothelium of the ureter. The parenchyma adjacent to the renal cortex is atrophied, with loss of tubules and glomeruli, and interstitial lymphoplasmacytic inflammation. Glomeruli are often small, occasionally segmented and some are surrounded by variably thick fibrous connective tissue. Cystic structures, lined by flattened epithelium, are filled with pale pink amorphous material. Occasional renal tubular epithelial cells have undergone karyolysis, and others have abundant eosinophilic cytoplasm containing brown granular pigment. Sporadically, epithelial cells are present in the tubular lumina. Interstitial fibrous connective tissue is prominent in areas where tubules are less numerous.

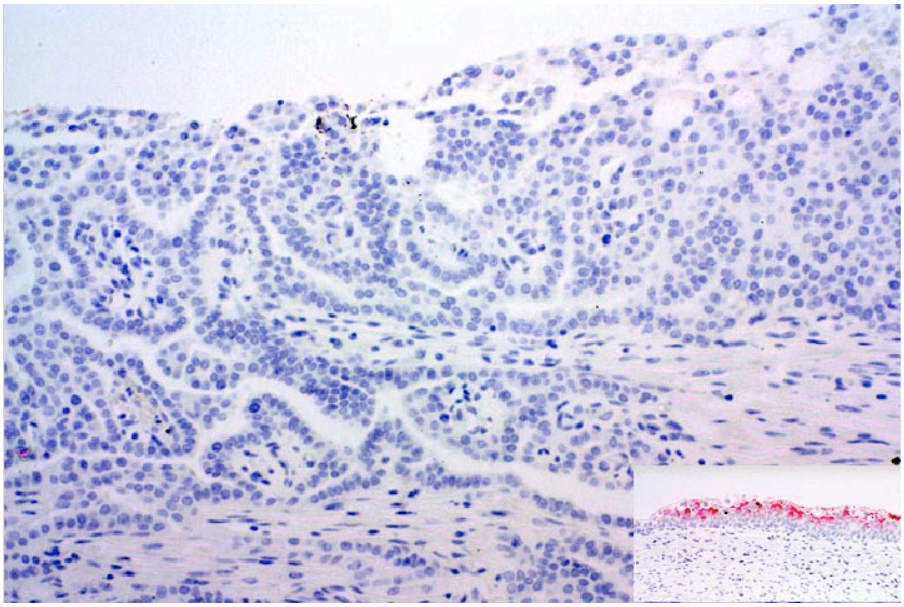


4-1, 4-2. Renal papillary carcinoma, Rhesus macaque. An irregular, firm, tan mass with scattered hemorrhages replaces the caudal kidney. Photographs courtesy of Wake Forest University Health Sciences, Animal Resources Program, http://www.wfubmc.edu/schoolofmedicine./





4-3. Renal papillary carcinoma, Rhesus macaque. A renal blood vessel contains numerous rafts of neoplastic epithelial cells. Photograph courtesy of Wake Forest University Health Sciences, Animal Resources Program, http://www.wfubmc.edu/schoolofmedicine.



4-4. Renal papillary carcinoma, Rhesus macaque. Neoplastic cells are negative for uroplakin III. An internal positive control is provided by normal urothelium of the ureter (inset). Photograph courtesy of Wake Forest University Health Sciences, Animal Resources Program, http://www.wfubmc.edu/schoolofmedicine

Contributor's Morphologic Diagnosis: 1. Papillary carcinoma, kidney and ureter with vascular invasion. 2. Glomerulonephropathy, diffuse, subacute to chronic, mild, with interstitial fibrosis, glomerular atrophy, tubular loss and cyst formation.

Contributor's Comment: This submission provides a good example of what are considered to be radiation-induced lesions in the kidney. The kidney is one of the most radiosensitive organs[16] and is prone to secondary malignancies[2,3,5,13], as well as degenerative changes leading to renal dysfunction[6,16] following irradiation. Fifty percent of rhesus macaques that received whole body irradiation developed malignant neoplasms, 80% of which were renal carcinomas.[2,5] Humans undergoing radiation treatment for neoplasia have increased risk for developing renal neoplasms.[13] Although primary renal tumors are rare, greater than 65% in dogs[11], and more than 85% in humans are carcinomas[1], with the main differential diagnosis being urothelial (transitional cell) carcinomas. Primary tumors of the ureter are rare and often occur concurrently with neoplasms of the renal pelvis or urinary bladder[1,4,11]. Abnormalities were not detected in the urinary bladder during the CT scan or visible during the nephrectomy surgery in this animal. This combined with negative uroplakin III staining makes an urothelial carcinoma less likely. However, urothelial carcinomas in humans may not stain for uroplakin III, particularly those with invasive or metastatic behaviors.[15] In humans, renal carcinomas are further characterized based on morphology.[14,15]

Although mild, the nephropathy is likely secondary to irradiation. Irradiation-induced nephropathy is a significant long-term complication in rhesus macaques and humans.[6,16] The changes in rhesus macaques, 6-8 years after a single dose of irradiation (7.2-8.5 Gy) include glomerulopathy, ectatic capillaries, glomerulosclerosis, and periglomerular fibrosis.[16] About 25% of human patients receiving comparable doses of radiation (7-7.5 Gy) develop renal dysfunction.[6]

JPC Diagnosis: 1. Kidney: Renal papillary carcinoma.
2. Kidney: Glomerulonephropathy characterized by interstitial fibrosis, tubular degeneration and regeneration, proteinosis, and lymphoplasmacytic interstitial nephritis.

Conference Comment: Primary renal neoplasms are relatively uncommon in animals and humans; however, renal adenocarcinoma is the most common primary neoplasm affecting the kidneys of dogs, cats, cattle and horses, and occurrence is sporadic in sheep and pigs. The origin is most likely proximal convoluted tubular epithelial cells. Small, well-circumscribed neoplasms with no evidence of capsular invasion or metastasis are generally considered to be benign. Well-differentiated carcinomas may be very difficult to differentiate from adenomas, with cellular atypia, a high mitotic rate, local or vascular invasion, necrosis, and size (>2 cm) used as criteria for malignancy. Renal adenocarcinomas are reported more often in middle-aged male dogs with no breed predilection. In dogs, 50-60% of renal epithelial neoplasms metastasize, compared with 5% in the cow and 70% in the horse.[9,10,12]

Some renal adenocarcinomas in dogs have elevated expression of COX-2, suggesting COX-2 mediated prostaglandins may play a role in the modulation of neoplastic cell growth.[7] A notable paraneoplastic syndrome and common clinical pathology finding is secondary absolute polycythemia due to secretion of erythropoietin or erythropoietin-like peptide by the tumor.[12]

Grossly, renal adenocarcinomas appear as large (>2 cm), spherical to ovoid, well-demarcated masses that are usually unilateral and occupy one pole of the kidney. They usually arise in the cortex and compress adjacent renal parenchyma, and may occupy 80% or more of the kidney. They often present as light yellow to gray lobulated masses with areas of necrosis and hemorrhage. Common sites of metastasis are the lungs, regional lymph nodes, liver, and occasionally the skin. Invasion into the renal vein and posterior vena cava may can occur. Multiple and bilateral renal neoplasms, without evidence of metastasis to other organs, are considered to be of multicentric origin.[9,10,12]

Histologically, these neoplasms are often described by the predominant histologic type and further sub-classified by the predominant cytologic type, although there is no prognostic significance to histologic or cytologic type. Histologic types include papillary, tubular, and solid, and a mixture of all three patterns may be present in any one tumor. The tubular variant is most common in domestic animals, and often, the solid variant is usually poorly differentiated. There are several cytologic types, such as chromophobic, eosinophilic, and clear cell (with vacuolated cytoplasm).[9,10,12] The clear cell variant is more often seen in laboratory animals and they tend to be solid rather than tubular. Electron micrographs, may demonstrate abundant monoparticulate glycogen often within phago-lysosomes and few mitochondria or endoplasmic reticulum.[10] Uromodulin (Tamm-Horsfall glycoprotein), a unique protein produced by the kidney, is useful as an immunohistochemical marker.[9]

Differential diagnoses include oncocytoma, nephroblastoma and transitional cell carcinoma.[9,10,12]

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