The Armed Forces Institute of Pathology
Department of Veterinary Pathology
WEDNESDAY SLIDE CONFERENCE
2002-2003

CONFERENCE 24
2 April 2003

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CASE I - 02-03 (AFIP 2838852)

Signalment: 1-year-old male Lewis rat, *Rattus norvegicus*

History: This rat was intracranially infected with Lymphocytic Choriomeningitis Virus (LCMV) four days after birth. It had been housed in standard caging with PMI rodent diet 5001 and water *ad libidum*. It reached an experimental endpoint at one year of age and was euthanized and perfusion fixed by the lab. The lab noticed a large mass in the abdomen and asked the pathology service to evaluate the mass.

Gross Pathology: The lab had already opened the abdomen, the rat had been decapitated, and the tissues were fixed. The bladder was very distended, about five times normal size, and contained about 150-200 small uroliths, most approximately 0.5 mm in diameter. In total, they weighed 26.01 g upon removal from the bladder. The kidneys and ureters were grossly normal. The rest of the organs were grossly normal.

Laboratory Results: The stones were 100% Magnesium Ammonium Phosphate.

Contributor's Morphologic Diagnosis: Nephritis and cystitis with squamous metaplasia secondary to urolithiasis.

Contributor's Comment: A high incidence of chronic renal disease and urolithiasis occurred in a group of Lewis rats in our facility. All rats were involved in an intracranial Lymphocytic Choriomeningitis Virus (LCMV) study, although not all rats were infected. Over three years, 52 rats were necropsied. Struvite uroliths were found in 12 (23%) rats and chronic renal disease was found in 30 (58%). Rats infected with LCMV had a higher relative risk for developing uroliths (RR=15.9, p<.002). However, LCMV infection did not correlate with chronic renal disease (RR=1.2, p=0.545) or cystitis (RR=2.1, p=0.244). Necropsies of other strains of rats housed in similar conditions and fed the same diet did not reveal urinary tract abnormalities, suggesting a potential strain predisposition. Struvite uroliths have been associated with bacterial infection, and

bacterial isolates were cultured from vulva (7/7), urine (6/12) and kidney (3/5). *Proteus mirabilis* was the most common species recovered. In preceding years, rats on this study had been housed in sterile conditions and had not shown signs of urinary tract disease. Housing Lewis rats in non-sterile conditions may increase the risk of developing ascending urinary tract infections and concomitant renal disease, and LCMV infection greatly increases the risk of subsequently developing urinary calculi.

AFIP Diagnoses: 1. Urinary bladder: Cystitis, chronic-active, diffuse, moderate, with urothelial hyperplasia and squamous metaplasia, Lewis rat, rodent.
2. Kidney: Pyelonephritis, chronic-active, diffuse, moderate, with urothelial hyperplasia, tubular ectasia, cellular casts, and intrapelvic coccobacilli.

Conference Comment: Urolithiasis occurs infrequently in the renal pelvis or urinary bladder of rats. In domestic animals, uroliths (calculi) form in the renal pelvis, ureter, or any part of the lower urinary tract, and more commonly cause obstruction in male animals because of their long, narrow urethra. Calculi may be composed of many types of crystals, including magnesium ammonium phosphate (struvite/triple phosphate), calcium oxalate, calcium phosphate, calcium carbonate, silica, apatite, urate, cystine, and xanthine. Uroliths develop from precipitation of salts or other materials in the urine, usually associated with an organic matrix (bacterial colonies, exfoliated epithelium, leukocytes) that serves as a nidus. The precipitation of crystals is dependent on pH, crystal concentration, urine temperature and degree of solubility.

In urinary tract infections, *Proteus* sp. are commonly implicated as predisposing factors to urolithiasis because of their capability to split urea through urease, which catalyzes the formation of ammonia from urea, lowers urine pH, and favors the formation of calcium phosphate and struvite uroliths. Urolithiasis may result in urinary tract obstruction, hydronephrosis, and urothelial trauma. Necropsy findings in urinary tract obstruction include marked distention, turgor, or rupture of the urinary bladder; renal pelvis and ureter dilation; thinning of the bladder wall with mucosal ulceration and necrosis, and hemorrhage of the lamina propria.

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CASE II - Case II 2B (AFIP 2852802)

Signalment: 16-month-old female Sprague-Dawley rat

History: Rat was found dead on day 267 of a 2-year gavage toxicity/carcinogenicity study.

Gross Pathology: At necropsy there was 20 ml of red fluid in the abdominal cavity and 10 ml of red fluid in the thoracic cavity. Diffuse pale nodules from 1x1x1 mm to 4x3x3 mm were present in the liver.

Laboratory Results: Not available.

Contributor's Morphologic Diagnoses: 1. Liver: Hyperplasia, regenerative, diffuse, marked.
2. Liver, bile duct: Hyperplasia, multifocal mild to moderate with biliary epithelial hypertrophy and periportal fibrosis.
3. Liver: Hyperplasia, regenerative, atypical, multifocal.

Contributor's Comment: The hepatic architecture is diffusely effaced. Hepatocytes are atypical and throughout the section are arranged in variably sized clusters and frequently appear to form glandular structures or pseudoglands. Frequently, the central hepatocytes appear degenerate. The hepatocytes are pleomorphic and vary tinctorially from mostly granular eosinophilic in central portions of the cell to pale and foamy with vacuolation at the periphery. Nuclei are round, vesicular, variably sized and contain one to three prominent nucleoli. There is multifocal, mild to moderate periportal fibrosis (at times bridging) accompanied by mild to moderate bile duct proliferation and biliary epithelial cell hypertrophy, and variable infiltrates of lymphocytes and macrophages. Randomly distributed throughout the section are multiple, variably sized, nodular areas composed of greatly enlarged pleomorphic atypical hepatocytes that have abundant pale eosinophilic often vacuolated cytoplasm and round vesicular nuclei with one to three nucleoli. Within these nodular areas there is multifocal cell degeneration and cell loss. Portal vessels are congested and frequently contain individual and clusters of macrophages and occasional atypical hepatocytes. Mitotic figures are rare.

The hepatic lesions observed in this rat were from one study of group of eight two-year gavage studies of structurally related chemicals. The lesions occurred in the

two highest dose groups and in the stop-study in which the animals were administered the chemical for thirty weeks and held two years. These chemicals all induced a dose related-toxic hepatopathy characterized by hepatocellular degeneration (sometimes cystic), necrosis, regeneration and hypertrophy, multinucleated hepatocytes, chronic inflammation, bile duct and oval cell hyperplasia, portal fibrosis and fatty change.

Cholangiofibrosis and cholangiocarcinomas occurred in two of the studies. The hepatic changes induced by this chemical were unique in the magnitude and character of what we consider to be an exaggerated atypical regenerative response.

AFIP Diagnoses: 1. Liver: Hyperplasia, nodular, regenerative, diffuse, marked, with cellular atypia, Sprague-Dawley rat, rodent.
2. Liver: Fibrosis, multifocal, moderate, with biliary hyperplasia.

Conference Comment: Focal or multifocal regenerative hyperplasia is a normal response of the liver to various acute injuries, including hepatotoxins and trauma. Following injury, hepatocytes divide to restore hepatic mass and oval cells may proliferate and develop into new hepatocytes or bile duct epithelium. Long-term or repeated hepatic injury typically results in nodular regenerative hyperplasia.

In the rat, the gross appearance of nodular regenerative hyperplasia includes enlargement or reduction of liver size, with multiple, well-demarcated nodules that may distort the liver lobes in severe cases. Histologically, hepatocytes within regenerative nodules typically lack characteristics of neoplasia, hepatic plate architecture is retained but often distorted, and there can be supportive evidence (inflammation, degeneration, necrosis, atrophy, fibrosis) of previous or concurrent hepatic damage. Additional histologic changes may include compression of adjacent hepatocytes, enlarged hepatocytes, increased mitoses, oval cell proliferation, and biliary hyperplasia.

Biliary hyperplasia can also result from injuries to the liver, especially those that target the portal triads, including toxins and physical obstruction of the bile duct. It is a common old age lesion in rats that is often associated with peribiliary fibrosis microscopically. Gross lesions are not recognized.

Conference participants discussed this intriguing case in detail, and considered neoplasia in their differential diagnosis. The AFIP's Departments of Hepatic & Gastrointestinal and Environmental & Toxicologic Pathology reviewed this case. These reviewers agree that markedly atypical nodular regenerative hyperplasia best describes the features of this unusual case. We are grateful for their assistance.

Contributor: National Institute of Environmental Health Sciences, Research Triangle Park, NC, 27709

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CASE III - A021360109 (AFIP 2839300)

Signalment: 5 months of age, castrated male, crossbreed, *Sus scrofa* (domestic swine)

History: This was one of two affected pigs in a group of 1000. The pig had multiple purple round slightly raised lesions on the lateral and ventral aspects. There was coalescence of the lesions in the perineum that extended down the hind limbs.

Gross Pathology: Small sections of tissue were submitted to the laboratory. The skin had multifocal irregular-shaped red to purple macules. The kidneys had multifocal white nodules (1-2 mm in diameter) on the external and cut surfaces. No lesions were present in the liver or spleen.

Laboratory Results: Cultures for bacteria were negative on the internal organs and low numbers of *Staphylococcus epidermidis* and alpha hemolytic *Streptococcus* spp (both considered contaminants) were isolated from the skin.

Contributor's Morphologic Diagnoses: 1. Glomerulonephritis, necrotizing, multifocal, severe, kidney.
2. Dermatitis, superficial, necrotizing, and leukoclastic vaculitis, multifocal, severe, skin.

Contributor's Comment: These lesions are consistent with porcine dermatitis and nephropathy syndrome. Several mechanisms have been proposed including vascular damage by an immune-mediated reaction or by direct damage caused by infectious agents. Immunoglobulins have been demonstrated in the vessels of the skin in similar cases and epidemiological, immunohistochemical, and PCR assay studies suggest possible involvement of porcine reproductive and respiratory syndrome virus and porcine circovirus in the pathogenesis.

AFIP Diagnoses: 1. Haired skin: Vasculitis, necrotizing, suppurative, diffuse, moderate, with multifocal dermal and epidermal necrosis (infarcts), crossbreed pig, porcine.

2. Kidney: Glomerulitis, fibrinous and necrotizing, suppurative, diffuse, severe, with multifocal vasculitis, tubulointerstitial nephritis and proteinosis.

Conference Comment: Porcine dermatitis and nephropathy syndrome is an often fatal disease of uncertain etiopathogenesis affecting piglets aged 1.5 to 4 months. Consistently, gross and microscopic lesions involve the skin and kidneys, although other organs may be involved. Grossly, acute skin lesions are described as round to irregular, multifocal to coalescing, erythematous macules, papules and plaques, which may progress in chronic cases to superficial crusts and ulceration. The skin lesions are distributed over the perineum, hindlegs, ventral thorax and abdomen, and ear margins. Microscopically, cutaneous lesions are characterized by severe necrotizing dermal and subcutaneous vasculitis, with epidermal necrosis, ulceration and dermal hemorrhage. Grossly, the kidneys are enlarged, pale and have superficial petechiae; histologic changes include exudative glomerulonephritis, interstitial nephritis, and necrotizing arteritis. The cutaneous lesions may be confused with infection by *Erysipelothrix rhusiopathiae*.

Contributor: Texas Veterinary Medical Diagnostic Laboratory, Amarillo, TX, 79116-3200

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CASE IV - 20197 (AFIP 2841137)

Signalment: 8-week-old, male/female, *Mus musculus*

History: A group of six young adult BALB/c *Rag2* knockout mice of both sexes was submitted by an investigator. The mice had been intravenously injected with CD45RB(high) lymphocytes from normal BALB/c donor mice to induce colitis as a model of inflammatory bowel disease, which usually requires about eight to ten weeks to develop. However, these mice became ill within two weeks after treatment. All six mice were lethargic and had rough coats, hunched posture, and rapid, deep respiratory efforts.

Gross Pathology: The lungs of all six mice were diffusely gray-purple, did not collapse completely when removed, and were difficult to infuse with fixative.

Microscopic Findings: This section contains left and right lungs. (Some sections also have mediastinal brown fat, lymph node, thymus, and/or esophagus.) In the lungs, there is extensive coalescent patchy to diffuse alveolitis, characterized primarily by macrophages. Epithelioid macrophages are common, and in some areas there are multinucleate giant cells with either centrally or peripherally located nuclei. In some areas, lymphocytes also are present within the lumina and the septa. Some are large, with prominent basophilic cytoplasm and oddly shaped nuclei with prominent nucleoli. Some alveoli contain collections of neutrophils. In some areas there is prominent proteinic material in alveoli, which contains multiple, uniform, tiny basophilic dots within small clear spaces. The proportions of the various cells and the proteinic material vary considerably throughout the section. Many vessels and airways have surrounding cuffs of mononuclear cells, mostly lymphoid cells as in the alveoli. The airways contain small amounts of mucus and cellular debris. In sections in which lymph node and/or thymus are present, the lymph node is populated with lymphoid cells of various sizes similar to those in the lungs, but lacks cortex, medulla, and other lymph node structure. The thymus is composed mostly of stroma and vessels, with very few lymphocytes.

Laboratory Results: Not available.

Contributor's Morphologic Diagnoses: 1. Diffuse granulomatous pneumonia with intra-alveolar organisms consistent with *Pneumocystis* sp.
2. Thymic and lymph node hypoplasia.

Contributor's Comment: Findings were identical in all six mice. In GMS stained sections, small black vesicular bodies characteristic of *Pneumocystis* were evident in areas corresponding to the small clear spaces within intra-alveolar proteinic material.

Genetic analysis indicates that *Pneumocystis* spp. are unusual fungi related to ascomycetes, with different species and strains characteristic of different host species. Cross infection experiments have shown that *P. carinii* isolated from one host species cannot infect another host species. Pneumocystis pneumonia is common in nude, SCID, and other severely immunodeficient mice, in which the inflammatory response usually is minimal or mild. This case is unusual in the simultaneous development of Pneumocystis pneumonia in all of the treated mice and in the intensity and character of the inflammatory response, which probably is related to the experimental procedure.

$CD4^+$ T cells are indispensable in the resistance to the organism, but under certain circumstances, $CD4^+$ T cell-mediated inflammatory responses have deleterious effects on the host and significantly contribute to the *Pneumocystis carinii* pneumonia pathogenesis. *Pneumocystis carinii* infected SCID mice develop fatal pulmonary "hyperinflammation" when reconstituted with wild-type lymphocytes or sorted $CD4^+$ cells, but not $CD8^+$ cells.

The pathogenesis of inflammatory bowel disease (IBD) is complex and not well understood, but is thought to result from dysregulated immune and/or inflammatory

responses to normal bowel flora and/or as-yet-unrecognized enteric bacterial pathogens. Studies of the pathogenesis of IBD is now a major use of mice having mutations in various genes involved in induction and/or regulation of immune and inflammatory responses, such as IL-2, IL-10, various T cell receptor proteins, MHC II, and many others, as a result of spontaneous development of colitis in these mice, an unanticipated consequence of these induced mutations.

In one mouse IBD model, colitis is induced by transfer of CD45RB(high) T cells from immunocompetent, histocompatible donor mice to SCID or *Rag* knockout mice. CD45 (leukocyte common antigen) is a transmembrane tyrosine phosphatase expressed by all leukocytes, which in T cells activates tyrosine kinases downstream of the TCR and functions in regulation of T cell activation. Different CD45 isoforms are expressed to different degrees in different T cell subsets. High levels of CD45RB expression is characteristic of a subset of CD4+ cells that home to the intestine and, in the absence of normal regulation, induce colitis, in part as a result of production of pro-inflammatory Th1 cytokines, particularly TNF-alpha. Presence of bowel flora is required for T cell activation and induction of colitis, because colitis does not develop in germfree mice. This case suggests that CD45RB(high) cells also may home to the lung and become activated in response to *Pneumocystis.*

SCID mice are the result of a spontaneous mutation in *Prkdc* (protein kinase, DNA activated, catalytic polypeptide). Prkdc is a VDJ recombinase system component that joins immunoglobulin and T cell receptor variable region gene segments during lymphocyte differentiation, but the mutation does not totally block this step; thus, SCID mice are “leaky” and can spontaneously develop oligoclonal T and/or B cell responses. Loss of either recombinase activating gene 1 or 2 proteins (*Rag1, Rag2*), also VDJ recombinase components, prevents rearrangement of immunoglobulin and T cell receptor genes early in lymphocyte differentiation, and completely blocks B and T cell development. *Rag1* and *Rag2* knockout mice are thus phenotypically similar to SCID mice but are not “leaky.”

Another interesting aspect of this case is that although none of the mice had colitis, *Helicobacter bilis* was detected by PCR in samples from all six mice. The role of *Helicobacter* spp. in genetically altered mouse models of IBD remains controversial. *Helicobacter hepaticus* and *H. bilis* can alter development of IBD, and *H. hepaticus* can induce colitis when introduced into germfree immunodeficient mice engrafted with CD45RB(high) cells. *H. hepaticus*, *H. bilis*, and/or other *Helicobacter* spp. can induce colitis in IL-10 -/- mice, as well as TCR and *Rag* -/- mice and SCID mice. Thus, although T cell dependent responses and their regulation have been the major focus of IBD research in mouse models to date, the pathogenesis of helicobacter enteric disease must involve other mechanisms not dependent on T cells. Perhaps this is also true of IBD.

AFIP Diagnoses: 1. Lung: Pneumonia, granulomatous, multifocal to coalescing, moderate, with intralveolar fungal cysts, etiology consistent with *Pneumocystis* sp., BALB/c *Rag2* knockout mouse, rodent.
2. Lymph node and thymus: Lymphoid hypocellularity, diffuse, severe.

Conference Comment: *Pneumocystis carinii* is an opportunistic, atypical fungal pathogen of humans and many animals, which often causes fatal pneumonia in immunocompromised individuals. There are two tissue forms of *P. carinii:* trophozoites, and cysts containing sporozoites. In addition to histomorphology, Grocott's methenamine silver, toluidine blue, immunohistochemistry, and fluorescent in situ hybridization are techniques used to diagnose pneumocystosis. Conference participants noted the hypocellularity within the thymus and lymph node, which suggests that this mouse is immunocompromised. The contributor gave a concise overview of the *Rag2* knockout mouse as an animal model of inflammatory bowel disease.

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**Sponsored by the American Veterinary Medical Association, the American College of Veterinary Pathologists and the C. L. Davis Foundation.