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Department of Veterinary Pathology
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Conference Moderator: Dr. Matthew Starost, DVM, PhD, DACVP
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CASE I – 04-3248 (AFIP 2937763)

Signalment: Two-year-old, male, Golden Retriever.

History: The dog presented with weakness, fever, weight loss, and muscle atrophy. He was treated with multiple antibiotics for an undiagnosed condition. The patient was euthanized due to severe emaciation and failure to respond to treatment.

Gross Pathology: A necropsy performed by the referring clinician revealed generalized muscle atrophy and slight bilateral enlargement of the kidneys.

Contributor's Morphologic Diagnoses:
1. Multifocal pyogranulomatous myocarditis with intralesional "zoites" and random meronts and merozoites.
2. Diffuse lymphoplasmacytic enteritis with neutrophils, intralesional sporozoites, blunting and fusion of villi, crypt abscesses, and mild lymphangiectasia.

Contributor's Comment: American canine hepatozoonosis (ACH) is distinctly different from "Old World" canine hepatozoonosis and the two entities have recently been compared in excellent reviews.[1,2] ACH is an emerging tick-borne disease caused by *Hepatozoon americanum* and transmitted by *Amblyomma maculatum* (Gulf Coast tick). The life cycle, route of infection, and pathogenesis are unique and require that the dog ingest an infected tick rather than being bitten by the tick. Sporozoites released from tick oocysts penetrate the intestine, enter the circulation and are carried to muscle and other tissues where they undergo asexual reproduction. A Gulf Coast tick feeding on a dog with circulating gamonts becomes infected and they undergo sexual reproduction. The necropsy and histological findings in a series of naturally-occurring and experimental cases have

been reported.[3-5] Antemortem diagnosis is best made from muscle biopsies from the biceps femoris or semitendinosus muscles because detection of gamonts in neutrophils on peripheral blood smears is rare. Pelvic radiographs reveal periosteal proliferation at muscle attachments to bone. An ELISA test has been developed. Marked leukocytosis is a consistent finding.

The tissues in this case were selected because they contain rarely seen sporozoites in the tips of villi (Image 2), a developing meront (Image 1) and merozoites "zoites"/gamonts (Image 3) in pyogranulomas in heart muscle in addition to the commonly seen cysts. The persistence of schizonts in the intestinal tract in the terminal stages of the infection raises the question of whether this represents re-infection from a tick, delayed/retarded migration of the schizonts, or possible reproduction in the intestine. Re-infection by asexual stages has been shown to persist for >9 months.[5] Severe cachexia has been attributed primarily to muscle pain and weakness. Intestinal, as well as splenic (Image 5 – granuloma with zoites also present), amyloidosis has been reported and was also present in this case. Intestinal amyloidosis can lead to malabsorption and protein loss. In the intestinal section of this case, the lacteals were severely dilated, even though the amyloid deposits were minimal and stained poorly. Mesangioproliferative glomerulonephritis has been reported in cases of ACH. Proteinuria is common in chronic cases and nephrotic syndrome can develop. In this case, glomerular lesions were dramatic with focal accumulations of large foam cells. Many glomeruli were partially effaced and adhesions were noted (Image 4). A major veterinary pathology text states that glomerular lipidosis has no functional significance.

This case originated in rural Georgia and ACH is reported primarily from the Southeastern United States. A seasonal occurrence corresponding with the prevalence of ticks (Apr-Oct) has been seen. Most cases occur in young adults and this may be related to their increased physical activity. Heavily infected dogs have a guarded prognosis and the mortality rate is high. Treatment with a combination of trimethoprim sulfa, pyrimethamine, and clindamycin has relieved clinical signs and prolonged treatment with decoquinate has reduced relapses and prolonged survival time.

AFIP Diagnoses: 1. Heart: Myocarditis and epicarditis, pyogranulomatous, multifocal, mild, with numerous protozoal cysts and merozoites, etiology consistent with *Hepatozoon americanum*, Golden Retriever, canine.
2. Small intestine: Enteritis, subacute, diffuse, mild, with villar blunting and fusion, and few sporozoites.

Conference Comment: The contributor provides a thorough overview of *Hepatozoon americanum*. Besides the differences in regional distribution, between *H. americanum* (United States, and possibly Central and South America) and *H. canis* (India, Africa, Asia, South America, the Middle East, and southern Europe), there are a few key distinctions between these apicomplexan protozoa. First, *H. canis* appears to be adapted to dogs and therefore often results in subclinical disease or mild clinical signs. Moderate to severe clinical signs are only seen in immunosuppressed dogs. In contrast, *H. americanum* is poorly adapted to dogs and results in a more severe illness even in immunocompetent dogs. Secondly, the vectors differ, with the brown dog tick, *Rhipicephalus sanguineus* serving as the vector for *H. canis* and the Gulf Coast tick, *Amblyomma maculatum* serving as the vector for *H. americanum*. Lastly, the clinical presentation, pathology, and prognosis differ. *H. canis* causes anemia, and rarely an extreme leukocytosis. Radiographic bone lesions and significant histologic lesions within the muscle are absent. Meronts are found primarily in the spleen, bone marrow, and lymph nodes; they are rarely found in muscle and exhibit a wheel-spoke arrangement of merorozoites. The prognosis for dogs infected with *H. canis* is good. In contrast, *H. americanum* causes anemia, an extreme leukocytosis, and periosteal proliferation visible with radiography. Histologically, there are typical "onion-skin" cysts within muscle, meronts, and pyogranulomatous myositis. The prognosis for dogs infected with *H. americanum* is guarded.[1,7]

The sporozoite stage of *H. americanum* has not been well described in the literature. The contributor noted rare sporozoites within the villar tips. Although it seems logical that the organisms identified in the small intestine are sporozoites of *H. americanum*, they are very likely *Sarcocystis* oocysts containing multiple sporozoites. This case was reviewed in consultation with Dr. Chris Gardiner, AFIP consultant in veterinary parasitology, and Dr. J.P. Dubey. Dr. Dubey further described these organisms as having an oocyst wall, with two oval to elongate sporocysts, each containing two sporozoites. These characteristics are consistent with *Sarcocystis* sp. in the carnivore definitive host. In contrast, dogs are the intermediate host of *H. americanum*. Dogs become infected with *H. americanum* through ingestion of an adult tick containing oocysts. These oocysts are broken down in the intestinal lumen and the individual sporozoites then penetrate the intestinal wall.[6,7]

Contributor: University of Georgia-Tifton, Tifton Veterinary Diagnostic & Investigational Lab, P.O. Box 1389, 43 Brighton Road, Tifton, GA

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CASE II – MK04-1836 (AFIP 2937351)

Signalment: 47-month-old male rhesus macaque, (*Macaca mulatta*).

History: This macaque was on a clinical trial to test the effectiveness of monoclonal antibody therapy to prolong renal graft survival after renal transplantation. Pre-transplant treatment consisted of daily injections of an anti-CD154 antibody, IDEC131, for three days preceding surgery. Post-transplant therapy was limited to weekly treatments of IDEC131 for eight weeks, after which, the animal did not receive additional immunosuppressive therapy. Renal biopsies were performed periodically to assess the character of renal graft inflammation. Monitoring also consisted of regular evaluation for increases in serum creatinine and blood urea nitrogen, and for the presence of anti-donor antibodies. There was no intervention after the graft started to fail. The animal lived 533 days post-transplant, the longest post-transplant period of any animal on this particular clinical trial.

Gross Pathology: The animal was in thin body condition with mild subcutaneous edema and pericardial effusion. The lungs were moderately pale. There were multifocal mild hemorrhages on the capsular surface of the transplanted kidney and the kidney was pale. No lesions were noted in the heart, lungs, liver, spleen, or gastrointestinal tract.

Laboratory Results:
Day 29 post-transplant: renal biopsy, moderate tubulointerstitial nephritis.
Immunohistochemistry of the interstitial infiltrate revealed $CD3^+$ cells.
Day 469: anti-donor antibodies detected in the serum
Day 533: BUN: 217 mg/dl Creatinine: 3.7 mg/dl

Contributor's Morphologic Diagnosis: Kidney: Mesangioproliferative glomerulonephritis, generalized, diffuse, moderate to marked, with periglomerular fibrosis, synechia formation and glomerular obsolescence; tubular degeneration, atrophy and loss and tubular proteinosis; interstitial nephritis; vascular smooth muscle hyperplasia and fibrosis with multifocal vasculitis and fibrinoid degeneration and medullary edema.

Contributor's Comment: The microscopic appearance of rejection in renal allografts generally is divided into three categories: hyperacute, acute and chronic. Hyperacute rejection occurs shortly after transplantation of non-HLA cross-matched organs or transplantation into patients who have been sensitized by previous allografts or pregnancy. Histologically, the reaction is characterized by collections of neutrophils in arterioles, glomeruli, and peritubular capillaries as well as thrombi. This reaction is antibody mediated and the endothelium of the donor graft, along which antigen-antibody complexes are deposited, is the target of the immune response. Acute rejection may occur months to years later after transplantation and immunosuppressive therapy and it is mediated by cellular and humoral processes. Histologic changes suggestive of cellular rejection are: interstitial accumulation of mononuclear cells, edema, and interstitial hemorrhage.[1] The primary lesion associated with humoral rejection is vasculitis. Chronic rejection is characterized by disruption of vascular elastic lamina, interstitial fibrosis, and tubule loss.[2]

The Banff Working Classification of Renal Allograft Pathology has been developed by an international consortium of pathologists, clinicians, and investigators to serve as a definitive resource by which inflammatory changes in renal allografts are scored. The scoring system quantifies tubular, vascular, glomerular, and interstitial changes seen in acute rejection and chronic allograft nephropathy. The histological changes are then correlated with the severity of renal function deterioration seen clinically. This classification is revised periodically and is used by pathologists to standardize the diagnosis of renal allograft rejection, by clinicians to guide therapy for patients, and by investigators to evaluate clinical trial results. Acute or active rejection is characterized by tubulitis, tubulointerstitial inflammation, arteritis, and vasculitis. Mild, acute changes are thought to be primarily T-cell mediated but more severe acute changes are likely to involve an antibody mediated component.[2] Changes suggestive of an antibody mediated component include vasculitis with fibrinoid change, glomerular and small vessel thrombosis, infarction, glomerulitis

and margination of polymorphonuclear leukocytes across peritubular capillaries and the presence of C4d, a component of the complement cascade, in peritubular capillaries and circulating anti-donor antibody.[3] Chronic changes due to immune reaction against renal allografts include interstitial fibrosis and tubular atrophy and loss. Deposition of basement membrane-like material to form "double contours" within capillary loops of glomeruli is a specific change associated with chronic transplant glomerulopathy. Additional chronic changes seen in allografts may be due to renal ischemia, hypertension, drug effects, infection, increased ureteral pressure, and nonimmune inflammation.[2] The changes seen in this case had many lesions similar to those seen in human acute and chronic allograft rejection, although interstitial fibrosis was not a significant finding.

One of the major obstacles facing successful organ transplantation is overcoming the recipient's immune response against alloantigens. Most post-transplant therapies focus on regulating the recipient's immune system by lifelong suppression, usually with a combination of a calcineurin inhibitor (cyclosporin or tacrolimus), steroids, and an antiproliferative agent, (mycophenolate, mofetil or azathioprine).[4] Calcineurin inhibitors specifically suppress T-cell activity. Calcineurin is a key signaling enzyme in T-lymphocyte activation.[5] Calcineurin inhibitors have improved short-term outcomes and reduced rates of acute rejection in renal transplant recipients; however, these drugs are nephrotoxic, and their use over a prolonged period of time contributes to chronic allograft nephropathy.[6] Antiproliferative agents non-selectively inhibit cell proliferation and can cause bone marrow suppression and hepatoxicity. Steroids inhibit T-lymphocytes but also cause systemic immunosuppression.[7] Additional undesirable side effects of these immunosuppressive drugs include hypertension, hyperlipidemia, osteoporosis, and chronic allograft nephropathy.[4] In addition to chronic kidney damage by therapeutic agents and the undesirable effects of these agents, an allograft recipient receiving immunosuppressive therapy is predisposed to infection by adventitial microorganisms and to developing neoplastic disease.[4]

In order to decrease the use of immunosuppressive drugs with their attendant detrimental side effects, monoclonal antibodies are being developed to target cell surface molecules on the cells associated with rejection. By targeting a specific pathway, monoclonal antibodies may provide an adjunct to traditional therapy by rendering the recipient tolerant to donor tissue while incurring minimal systemic immunosuppression and, ultimately, leading to prolonged graft survival.[4]

The animal in this case was treated with 'costimulation blockade' monoclonal antibody therapy, which inhibits one of the two main signals necessary for T-cell activation. The first signal in T-cell activation is the presentation of antigen to T-cells in association with MHC-I or MHC-II molecules. Costimulatory molecules are the second immunological signal required for the activation of T-lymphocytes.[4,8,9]

These molecules may activate or suppress T-cell response to an antigen. Monoclonal antibodies against costimulatory molecules are used at the time of transplantation when the recipient encounters foreign antigens from the graft for the first time. In theory, T-cells that are presented with novel antigens, such as those found on an allograft, without costimulation are rendered anergic or undergo apoptosis, removing the cells that potentially could mount an immune response against the graft.[4]

Monoclonal antibodies to CD-154 have been used to induce long term (years) renal allograft survival in nonhuman primates. CD-154 is found on the surface of T-cells and its expression is increased in activated T-cells. Interaction of CD-154 with CD40 found on antigen presenting cells (APCs) increases APC expression of B7 and MHC molecules and increases production of cytokines. The relationship between inhibition of CD-154:CD-40 binding and altered T-cell function has not been characterized completely. Use of anti-CD-154 agents in humans has not been as successful as predicted by studies in nonhuman primates. Some of these agents have had the undesirable side affect of predisposing the recipient to thrombi formation.[4]

There are several centers in the United States that now offer kidney transplantation for the treatment of end-stage renal disease in companion animals. While immunosuppressive regimes are similar between feline and human graft recipients, histological patterns of renal rejection differ between the two species. In a recent issue of *Veterinary Pathology*, the authors attempted to classify histologic changes in feline renal transplants using the Banff 1997 Guidelines. However, the scoring system did not accurately reflect the severity of lesions based on serum creatinine and BUN levels. Criteria for acute rejection in humans, tubulitis, lymphocytic glomerulitis, and vasculitis were seen rarely in cats. Additionally, subcapsular and interlobular phlebitis were seen in this series of cats but have been reported rarely in man.[10]

The classification and treatment of allograft rejection continues to be an ongoing challenge. New therapies, such as monoclonal antibodies targeted against effectors of the immune response, may alleviate the need for multiple transplants by inducing life-long tolerance in organ recipients. However, at the present time, there is still no effective and definitive treatment or group of treatments to prevent the main cause of late graft loss, chronic rejection. An even more urgent problem than chronic allograft rejection is the tremendous demand for donated organs. In the United States, 52,000 people wait for a kidney each year.[6] The waiting period for a kidney is in excess of 800 days, and people often die waiting for a donor.[8] It may come to pass that, in refining our knowledge of the mechanisms of allograft rejection, we may be able to understand the causes of, and to develop effective treatments for, renal disease before transplantation becomes the only treatment option.

AFIP Diagnosis: Kidney: Glomerulonephritis, membranoproliferative, global, diffuse, chronic, moderate, with lymphoplasmacytic interstitial nephritis, and arteritis with intimal fibromuscular proliferation, rhesus macaque (*Macaca mulatta*), primate.

Conference Comment: As the contributor discussed, one of the most important goals of immunologic research is successful transplantation of tissues in humans without rejection. Although the surgical techniques for transplantation of many tissues, including kidneys, skin, heart, lungs, liver, spleen, bone marrow, and endocrine organs are well refined, the ability to confer permanent acceptance of foreign grafts is still out of reach. The basis of graft rejection involves differences in HLA proteins that are expressed on cells. HLA genes are highly polymorphic and any two individuals, other than identical twins, will express some HLA proteins that are different. Therefore all individuals will recognize some difference in HLA molecules as foreign and mount an immune response to them. Conference attendees discussed, in detail, the two types of hypersensitivity, cell-mediated (Type IV hypersensitivity) and antibody-mediated (Type II hypersensitivity) that are fundamental to transplant rejection. [11]

Type II hypersensitivity is mediated by antibodies directed toward antigens present on cell surfaces. In the case of transplant rejection, these antigens are the HLA proteins of the donor organ. This process is called humoral rejection and can take two forms: hyperacute and acute. Hyperacute rejection occurs when the recipient has preformed antidonor antibodies in circulation. These can develop in multiparous women who receive grafts from their husband, children, or unrelated individuals who share HLA alleles with the husband; people who have received prior blood transfusions; and, people who have already rejected a kidney transplant. The rejection is immediate, with circulating antibodies reacting to graft endothelium, inducing complement fixation, and resulting in thrombosis of graft vasculature. The acute humoral rejection occurs in recipients who are not previously sensitized. The antibodies formed cause injury via complement-dependent cytotoxicity, inflammation, and antibody-dependent cell-mediated cytotoxicity, targeting the graft vasculature. [11]

Type IV hypersensitivity is T-cell mediated, is called cellular rejection, and is induced by two mechanisms: CD8+ cytotoxic T-lymphocyte (CTL) mediated destruction of graft cells, and CD4+ helper T-cell mediated delayed hypersensitivity. The direct pathway, mediated by the CD8+ CTLs occurs when the T-cells of the recipient recognize donor HLA (MHC) molecules on the surface of antigen presenting cells (APCs) in the graft. However, both CD8+ and CD4+ T-cells are activated and differentiate into mature CTLs and Th1 cells, respectively.

Mature CTLs mediate cell destruction by either perforin-granzyme-dependent killing or Fas-Fas ligand-dependent killing. Th1 cells secrete cytokines that increase vascular permeability, are chemotactic for lymphocytes and macrophages, and activate macrophages, resulting in graft injury.[11]

Contributor: National Institutes of Health, Diagnostic & Research Services Branch, Division of Veterinary Resources, 28 Service Road West, Bldg 28A--Room 115, Bethesda, MD

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CASE III – 04-14567 (AFIP 2938299)

Signalment: 4-week-old, female, Golden Retriever-cross (*Canis familiaris*).

History: This individual was one of two puppies from a litter of seven that died suddenly. The puppy had been nursing and then became cyanotic, dyspneic and died.

Gross Pathology: The carcass was mildly autolyzed and was in good nutritional condition. The thoracic cavity contained a few milliliters of watery yellow fluid and the lungs were diffusely edematous and had a rubbery consistency. There was marked pallor of the left ventricle. Gastrointestinal contents were sparse and the urinary bladder was contracted.

Laboratory Results: Abundant canine parvovirus antigen was detected in the myocardium by immunohistochemistry.

Contributor's Morphologic Diagnosis: Heart: Myocarditis, lymphohistiocytic with cardiomyocyte degeneration, necrosis and loss and intranuclear inclusion bodies.

Contributor's Comment: Multifocally, there are foci of cardiomyocyte degeneration and necrosis characterized by hypereosinophilia, loss of cross striations and fragmentation. The interstitium is mildly expanded by lymphocytes, macrophages and rare plasma cells. Within the cardiomyocyte nuclei, there are moderate numbers of 5-8 um, amphophilic to basophilic intranuclear inclusion bodies that often cause margination of the chromatin. Based on the lesion, this was suspected to be a case of parvoviral myocarditis and immunohistochemistry confirmed the presence of parvovirus antigen within cardiomyocytes.

The *Parvoviridae* are non-enveloped viral particles about 18-26 nm in diameter with a single-stranded DNA genome.[1] In the late 1970's, a new parvovirus emerged worldwide as the cause of severe enteritis and myocarditis in dogs. The agent was named canine parvovirus type 2 (CPV-2) to distinguish it from the less pathogenic canine parvovirus type 1 (Minute Virus of Canines) which is associated with mild diarrhea, fetal losses, myocarditis and fading puppy syndrome.[2] Historically, it was believed that CPV-2 evolved from the closely related feline panleukopenia virus; however, recent work suggests that a wild carnivore may have harbored the immediate ancestor of CPV-2.[3] Since its emergence in the 1970's, CPV-2 has been replaced by two antigenic variants CPV-2a and CPV-2b. Interestingly, CPV-2a and CPV-2b regained the ability to infect both domestic and large cats. It is believed that approximately 5% of parvovirus infections in cats are caused by either CPV-2a or CPV-2b.[4]

Parvoviruses may infect cells at any phase of the cell cycle but replication is dependent on cellular mechanisms functional only in the S phase prior to mitosis. For this reason, the effects of parvovirus infection are greatest in tissues with a high mitotic rate, including hematopoietic tissue, intestinal crypt epithelium and neonatal cardiomyocytes (<2 weeks of age).[1] In the original outbreaks of CPV-2 in naïve populations, myocarditis was a common finding. CPV-2 myocarditis is most often seen in puppies under 4 weeks of age and usually all pups in the litter are affected. Pups are often found dead or die after a brief period of dyspnea, crying and retching. Signs of cardiac dysfunction may be preceded by the enteric form of the disease or may occur suddenly without apparent previous illness.[2] The myocardial form of the disease has virtually disappeared as a result of population immunity. Virtually all bitches are immune and pass immunity to their pups via colostrum resulting in protection during the critical period when infection of the myocardium is possible.[5] Myocarditis is still occasionally found in pups born to isolated, unvaccinated bitches or in cases where adequate colostrum is not received.[2]

AFIP Diagnosis: Heart: Myocarditis, lymphohistiocytic, multifocal, minimal, with myocyte degeneration and necrosis, and basophilic intranuclear inclusion bodies, Golden Retriever-cross, canine.

Conference Comment: The contributor provides a thorough overview of canine parvovirus type 2 (CPV-2) and compares it to the less pathogenic canine parvovirus type one (CPV-1). Members of the genus *Parvovirus* infect many other species of laboratory and domestic animals, including cats, mink, calves, and swine.[1]

Canine parvovirus enteritis was first recognized in dogs because the gross and microscopic lesions were identical to feline parvoviral enteritis, caused by feline panleukopenia virus (FPV). FPV affects all members of the Felidae, as well as mink, raccoons, and some other members of the Procyonidae.[1] It is the cause of panleukopenia, also known as cat distemper, feline enteritis, and mink enteritis,[6] and is very similar to CPV-2. Panleukopenia virus is ubiquitous in environments frequented by cats; infection is common, but generally subclinical. Transmission is primarily through oronasal exposure and results in uptake of the virus by epithelium over the tonsils and Peyer's patches. The virus infects lymphoblasts and disseminates to other lymphoid organs (spleen, bone marrow, thymus, lymph nodes). Viral infection of these organs results in lymphocytolysis and viremia. Infection of the gastrointestinal epithelium is a secondary event and leads to destruction of the cells in the crypts of Lieberkuhn. If severe enough, this will result in focal or widespread villus atrophy, mucosal erosion or ulceration. Proliferating cells in the bone marrow are also affected during viremia, resulting in cytolysis and bone marrow depletion of both erythroid and myeloid elements. Infection of the fetus during late prenatal life by FPV results in cerebellar hypoplasia.

A summary of parvoviruses that affect domestic and laboratory animals are listed below:[7,8]

Virus	**Disease**
Feline parvovirus	Panleukopenia, cerebellar hypoplasia, enteritis
Canine parvovirus-1	Mild diarrhea
Canine parvovirus-2	Enteritis, myocarditis, leukopenia
Porcine parvovirus	Stillbirth, mummification, abortion, embryonic death, infertility (SMAEDI)
Mink enteritis virus	Panleukopenia, enteritis
Aleutian disease virus of mink	Chronic immune complex disease, encephalopathy
Minute virus of mice	Lymphotrophic, erythrocyte-associated anemia
Mouse parvovirus	Lymphotrophic, immunomodulation
Kilham's rat virus	Multifocal hemorrhage (brain, liver, testes)
Toolan's H-1 virus of rats	Nonpathogenic
Rat parvovirus	Nonpathogenic
Hamster parvovirus	Domed calvaria, malformation of incisor teeth
Lapine parvovirus	Mild to moderate enteritis in rabbits
Goose parvovirus	Hepatitis, myocarditis
Duck parvovirus	Hepatitis, myocarditis

Contributor: Department of Veterinary Pathology/ Prairie Diagnostic Services Western College of Veterinary Medicine, University of Saskatchewan, 52 Campus Drive, Saskatoon, SK Website: www.usask.ca/wcvm/vetpath

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CASE IV – D-04-0229 (AFIP 2936454)

Signalment: Three-month-old, female, albino rat (*Rattus norvegicus*).

History: This was one of a group of 12 rats and mice imported from Los Angeles to Hong Kong four days previously. When examined subsequently they were showing upper respiratory tract disease signs and ruffled coats. Four younger rats appeared weak. They were all medicated with Baytril, but one rat died the next day (this case) and a second died 2 days later. The animals had been held in a warehouse for an extended period before departure and the flight was delayed in arriving at Hong Kong.

Gross Pathology: The submitted carcass was a 3-month-old white female rat in normal body condition, but dehydrated. The right cranial lung lobe was completely consolidated, dark red, and had a large amount of pale mucoid exudate in the bronchioles. The rest of the lungs were congested and edematous. The stomach contained no ingesta. The small intestine was distended with gas and the colon contained several fecal pellets.

Laboratory Results: A pure growth of *Streptococcus pneumoniae* was isolated from the rat's lung and liver.

Contributor's Morphologic Diagnosis: 1. Brain: Leptomeningitis, suppurative, diffuse, subacute, severe, and severe focal paraventricular encephalitis with numerous intralesional diplococcoid bacteria present.
2. Lung: Bronchopneumonia, suppurative, multifocal, severe, subacute with some alveolar septal destruction.

Contributor's Comment: This is a case of severe subacute suppurative meningoencephalitis and bronchopneumonia caused by *Streptococcus pneumoniae*. In addition to the lesions in lung and brain, the left ventricle of the heart had a focal area of severe myocarditis involving the endocardium and deeper myocardium with degenerate myocardiocytes and an infiltration of fibroblasts, macrophages and fewer lymphocytes. There was also a mild tracheitis with an infiltration of moderate numbers of degenerate neutrophils and macrophages in the lamina propria with exudation into the lumen. The tracheal mucosal epithelium showed squamous metaplasia and loss of mucous glands.

Streptococcus pneumoniae is a gram-positive, capsulated, non-motile, facultatively aerobic coccus that occurs singly, in pairs, or in short chains in its natural habitat, the upper respiratory tract of humans or other mammals.[1] In infected tissues and pus this bacterium commonly occurs as pairs of cocci which gave cause for its previous generic name of *Diplococcus*. It is an important pathogen in humans causing primarily lobar pneumonia (giving rise to the name pneumococcus), but also causing septicemia and meningitis.[2] In the past, this infection was recognized as a common problem in rodent colonies with clinically normal carrier animals maintaining infection in the nasoturbinates and tympanic bullae, but human carriers have also been implicated as a source of infection to laboratory rodents.[3] There are also reports of *S. pneumoniae* causing bovine mastitis, calf septicemia and septicemia and septic arthritis in cats.[4]

S. pneumoniae is alpha-hemolytic in culture on blood agar but can show some variation in colony type. Compared to other alpha-hemolytic streptococci, *S. pneumoniae* can be identified by rapid lysis in bile salts and optochin (ethylhydrocupreine hydrochloride) sensitivity.[2] There are over 84 serotypes of this bacterium, but most infections are caused by less than 10 serotypes.[4]

In lesions, pus, or blood smears *S. pneumoniae* has a distinctive polysaccharide capsule which enables it to resist phagocytosis by host cells.[2,3] *S. pneumoniae* is not known to produce soluble toxins but several serotypes produce tissue damage by activation of the alternate complement pathway.[3]

Other lesions that have occurred in outbreaks of this infection in rodent colonies have included fibrinopurulent polyserositis, suppurative rhinitis, otitis media and embolic suppurative lesions in organs such as liver, spleen and kidney.[3]

AFIP Diagnosis: 1. Lung: Bronchopneumonia, necrotizing, suppurative, subacute, moderate, rat, rodent.
2. Midbrain: Meningoencephalitis, suppurative, diffuse, moderate, with myriad bacterial diplococci.

Conference Comment: *Streptococcus pneumoniae* was previously a common problem in laboratory rats. Today, outbreaks of clinical disease are rare in barrier-maintained facilities. Clinical signs may include serosanguinous nasal discharge, rhinitis, sinusitis, conjunctivitis, and vestibular signs consistent with middle ear involvement. Asymptomatic animals may develop clinical disease when there is a concurrent infection or a change in environment. Gross lesions are varied depending on the organ system(s) involved and include: serous to mucopurulent exudates in the nasal passages and/or tympanic bullae, fibrinopurulent pleuritis, peritonitis, pericarditis, periorchitis, meninginitis, or polyserositis. Histologically, in the acute form of the disease, fibrinopurulent pleuritis and pericarditis are typical findings. Pulmonary lesions vary from localized suppurative bronchopneumonia to acute fibrinopurulent bronchopneumonia, with obliteration of normal architecture in the affected lobes. Fibrinopurulent lesions may be identified in any organ affected by *S. pneumoniae*. Embolic suppurative lesions have been identified in the liver, spleen, and kidney. Differential diagnoses for *S. pneumoniae* in a rat include corynebacteriosis, salmonellosis, pseudomoniasis, and pasteurellosis.[3]

Streptococcus pneumoniae is known to cause similar lesions in other animals, including guinea pigs, hamsters, and non-human primates.[3,5] Mice are resistant to *S. pneumoniae*[6] but can develop suppurative lesions when infected with beta-hemolytic streptococcal organisms. However, SCID mice may develop systemic disease with alpha-hemolytic streptococci.[3,6] Rabbits have developed acute diplococcal infections on rare occasions and streptococcal septemia has been reported in young rabbits.[3]

Contributor: Tai Lung Veterinary Laboratory, Agriculture, Fisheries and Conservation Department, Government of Hong Kong SAR, Lin Tong Mei, Sheung Shui, New Territories, Hong Kong SAR, China

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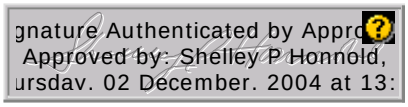

Shelley P. Honnold, DVM
Major, Veterinary Corps, U.S. Army
Wednesday Slide Conference Coordinator
Department of Veterinary Pathology
Armed Forces Institute of Pathology
Registry of Veterinary Pathology*

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