Joint Pathology Center
Veterinary Pathology Services

WEDNESDAY SLIDE CONFERENCE 2011-2012

Conference 22

18 April 2012

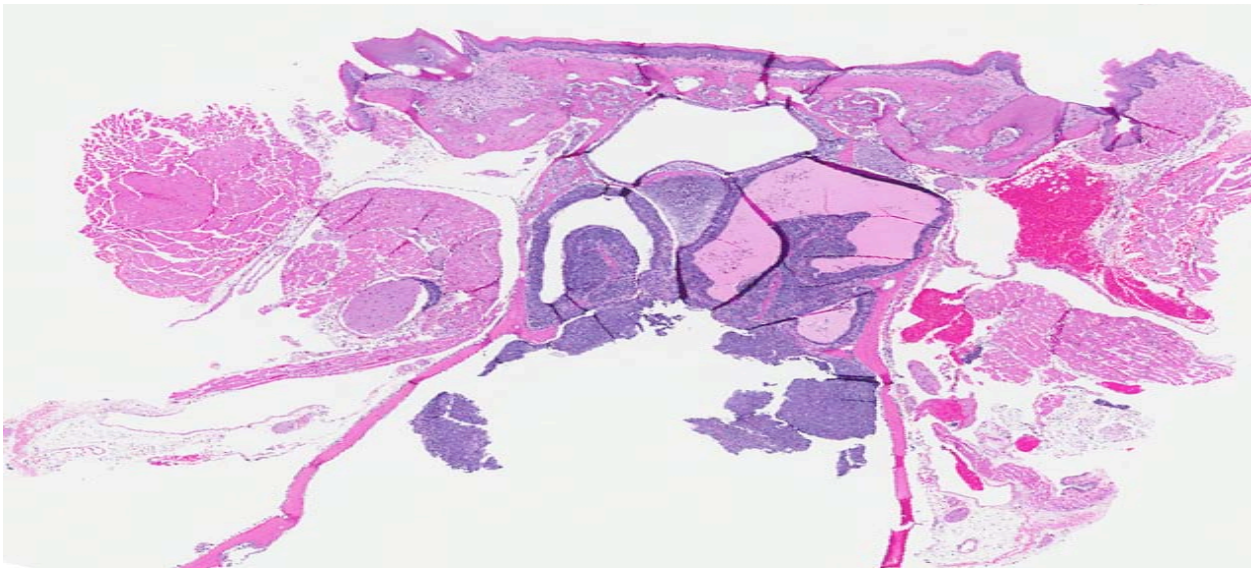
CASE I: 0801727 (JPC 3121674).

Signalment: Mouse (*Mus musculus*) heterozygous F1 p53(+/-) transgenic (C3H/HeNTac female inbred x C57BL/6-Trp53tml Brd het N12 male inbred F_1) approx 45 weeks age female.

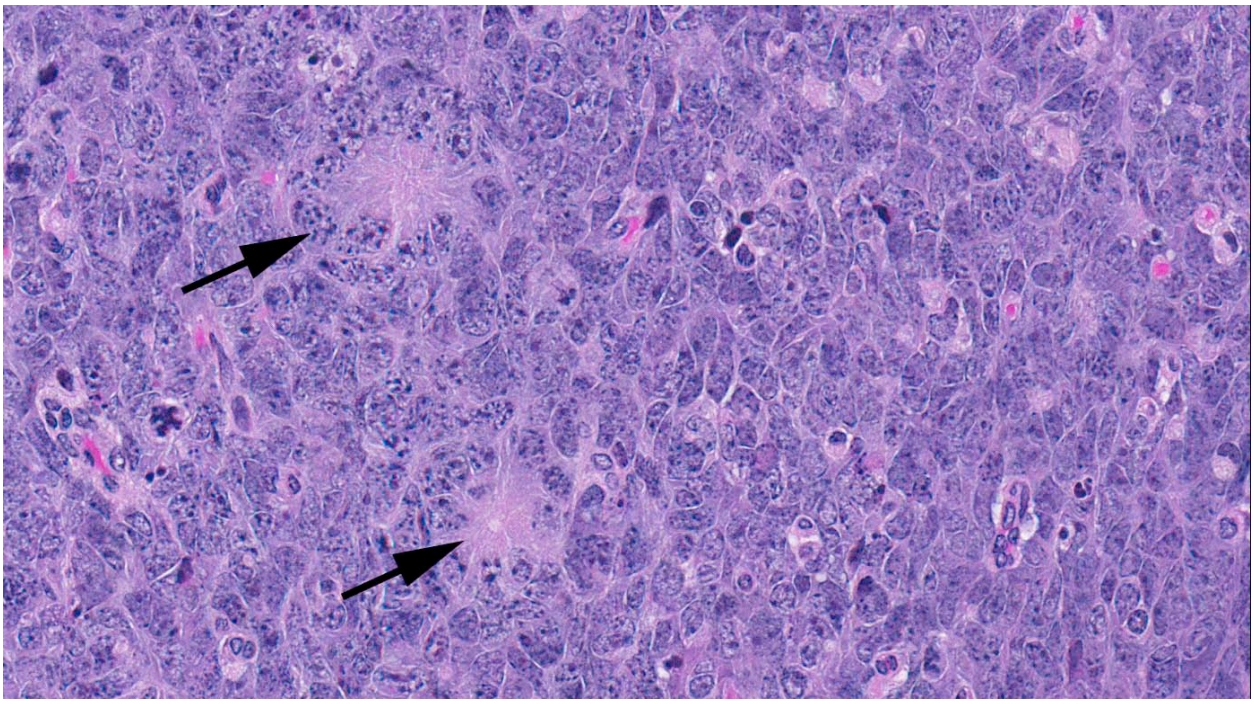
History: Mouse survived to terminal sacrifice in a 39-week study, with no clinical abnormalities noted.

Gross Pathology: The brain had a mass. No lesion was recorded grossly in the nasal cavities.

Contributor's Histopathologic Description: The nasal submucosa is greatly expanded by nests of tumor cells sometimes forming rosettes along a basement membrane. The rosettes in some cases have a distinct lumen; others contain fibrillar cytoplasmic processes suggestive of microvilli. Nests of cells also extend under the olfactory and respiratory epithelium and in



1-1. Nasal cavity, turbinate bones, mouse: Filling the nasal cavity and infiltrating the nasal septum and turbinates is an unencapsulated, densely cellular neoplasm. (HE 4X)



1-2. Nasal cavity, turbinate bones, mouse: Neoplastic cells are polygonal and arranged in nests and packets, with a mitotic rate of up to 8 per 400X field. Multifocally, neoplastic cells are arranged in true rosettes (arrows). (HE 400X)

between Steno's and Bowman's glands along the turbinates and nasal septum. Tumor cells and nests extend through the cribriform plate into the olfactory bulb, across the nasal septum, and into the maxilla and periodontal space. Many tumor cells do not appear to rest upon a basement membrane. In several areas tumor cells appear contiguous with olfactory epithelium and then extend beneath it. There is scant fibrovascular stroma.

Tumor cells are pleomorphic: those in rosettes tend to be elongate to triangular, with a wider base and scant cytoplasm; apical processes are sometimes present. The nuclei are basal, round to ellipsoid, with coarsely clumped chromatin or multiple nucleoli. There is a second population of tumor cells that is smaller and rounder, with very scant cytoplasm and multiple nucleoli; these are most often outside of the rosettes. The mitotic index is high (up to 25 mitotic figures per 0.238 mm^2 high power field).

Adjacent to the main tumor mass, the architecture of many submucosal (Bowman's) glands is disorganized, with loss of cellular polarity and no apparent lumen. In some areas the cells are piled into more than one layer or even extend away from the basement membrane. These cells are enlarged and basophilic, with nuclei containing multiple nucleoli or coarsely clumped chromatin. Although not nearly as common as in the main tumor mass, mitotic figures are not rare in these glands.

Cells in the overlying epithelium range from normal to containing eosinophilic granules, pyknotic nuclei or nuclear remnants, and lacking microvilli. There are intact neutrophils and nuclear remnants within the eosinophilic material (fluid) within the nasal cavities.

Contributor's Morphologic Diagnosis: Neuroepithelial carcinoma (Esthesioneuroblastoma).

Contributor's Comment: The study pathologist received the brain sections before the nasal sections (since the latter required time to decalcify) and made a tentative diagnosis of ependymoma (based upon the rosettes), although the tumor morphology was not a "good fit". On receipt of the nasal sections it became obvious the lesion in the brain was an extension of a nasal esthesioneuroblastoma. This case illustrates the importance of keeping in mind esthesioneuroblastoma (and other tumors of nasal origin) as a differential for large brain tumors that may appear to originate in the rostral brain.

This tumor in the nasal sections is a good example of an esthesioneuroblastoma[1], with occasional true rosettes (Flexner-Wintersteiner rosettes) and more common pseudorosettes (Homer-Wright rosettes). This is an exceedingly rare tumor in mice, as in all mammals[2], and is likely present here in part because the strain is heterozygous for p53 gene knockout. The diagnosis in the brain was made more difficult as there the tumor adopted a solid sheet-type architecture, with

only rare rosettes, a situation apparently typical of esthesioneuroblastomas in animals other than humans.[2]

JPC Diagnosis: Olfactory bulb and nasal turbinates: Esthesioneuroblastoma.

Conference Comment: Esthesioneuroblastomas, or olfactory neuroblastomas (ONB), arise from olfactory neuroepithelium, residual neural crest cells, or local components of the dispersed neuroendocrine system and are most often reported in dogs and cats. The olfactory epithelium contains three cell types, which can be histologically identified in the tumor: basal cells, olfactory neurosensory cells, and supporting sustentacular cells. They arise in the ethmoturbinate region and may penetrate the cribriform plate and infiltrate the cerebral cortex. ONBs may be confused with lymphoma or undifferentiated carcinoma if important diagnostic features such as palisades around blood vessels and rosette or pseudorosette formation are not present. ONBs are positive for synaptophysin, chromogranin, CD56, neuron specific enolase (NSE), neural fibrillary protein (NFP) and S-100 protein.[4]

Ultrastructural features include cytoplasmic membrane-bound dense core neurosecretory granules which contain neurotubules and neurofilaments. Olfactory differentiation with olfactory vesicles and microvilli or apical cilia on apical borders may be seen in Flexner-Wintersteiner rosettes. The fibrillary stroma corresponds to the immature nerve processes, and Schwann-like cells are uncommonly encountered.[4,5]

The differential diagnosis of ONB includes the group of "small round blue cell" malignant neoplasms that can occur in the sinonasal tract, such as sinonasal undifferentiated carcinoma, extranodal NK/T cell lymphoma, rhabdomyosarcoma, Ewing/primitive neuroectodermal tumor (PNET), mucosal melanoma and neuroendocrine carcinomas (NEC).[4] Other tumors considered in the differential diagnosis are paraganglioma, extramedullary plasmacytoma, pituitary adenoma, extracranial meningioma, mesenchymal chondrosarcoma, and granulocytic sarcoma. In cats, feline leukemia virus has been identified in association with olfactory neuroblastoma, but a causal role has not been established.[3]

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CASE II: 2010 628 (JPC 4003044).

Signalment: 9-year-old, female, intact Kuhl's black-eared marmoset (*Callithrix kuhlii*).

History: Euthanized due to progressive lethargy with weight loss and diarrhea.

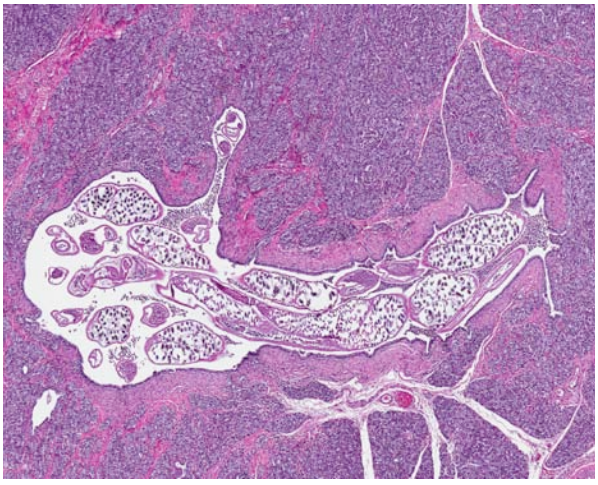
Gross Pathology: The animal was in markedly thin body condition at the time of death. The small and large intestines were distended with gas, and the contents were diffusely sparse, pasty and tan to slightly green. The intestinal wall varied segmentally from thin and flaccid to irregularly thickened and corrugated. The mesenteric and colonic lymph nodes were uniformly enlarged.

Contributor's Histopathologic Description: Pancreas: The lobular architecture of the exocrine pancreas is distorted by confluent deposits of mature collagenous connective tissue that separate, infiltrate and accentuate the preexistent lobular architecture and expand the periductal connective tissue stroma. There is diffuse atrophy of the exocrine secretory acini and many of the interlobular ducts are ectatic and contain one or more cross- and oblique sections of spirurid nematodes that measure up to 150 µm in diameter. Intraductular spirurids are characterized by a 10-15 µm thick cuticle with sharp spicules, polymyarian-coelomyarian somatic musculature, prominent lateral cords, each containing an excretory canal. The intestinal tract is composed of cuboidal to columnar uninucleated cells that are often finely vacuolated and exhibit a prominent eosinophilic brush border. Female nematodes have uteri containing thick-shelled, 50 µm x 25 µm, embryonated eggs and males display ductus deferens with intralumenal spermatozoa. Associated with the nematodes are intralumenal aggregates of eosinophils, macrophages and fewer neutrophils. Overall, the pancreatic lobules are composed of small groups of disorganized acini with lightly eosinophilic, vacuolated cytoplasm, abundant intralobular duct profiles and increased exocrine to endocrine tissue ratio (exocrine pancreatic atrophy) as well as low number of lymphocytes and plasma cells. Isolated pancreatic lobules have low to moderate numbers of interstitial and intralumenal neutrophils (not present in all sections).

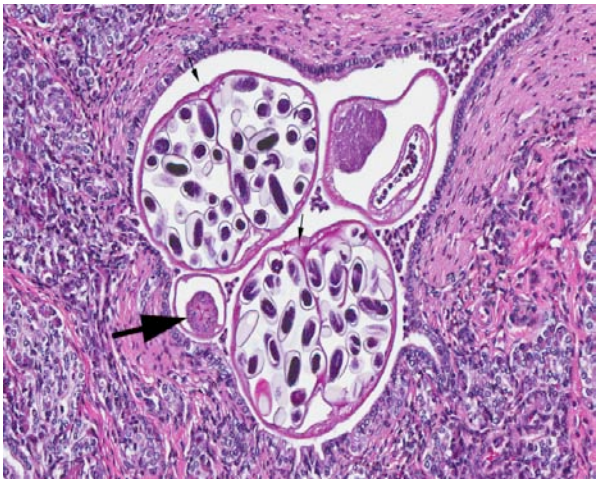
Arterioles, pancreaticoduodenal ligament: The walls of arterioles are multifocally expanded by irregular plaques of mineralized to hyalinized connective tissue that efface the tunica media, interrupt the elastic lamina, elevate the endothelium and impinge on the vascular lumina (arteriosclerosis).

Duodenum: Multifocally throughout the mucosa, villi are blunted and fused, enterocytes are attenuated and crypts are lined by hyperplastic epithelial cells. Expanding the lamina propria in the villous tips and effacing multiple glands in the submucosa is a lightly eosinophilic, acellular matrix (amyloid) that is mildly infiltrated by low numbers of neutrophils and contains karyorrhectic debris. Moderate numbers of lymphocytes, plasma cells and neutrophils are scattered throughout the muscularis mucosa.

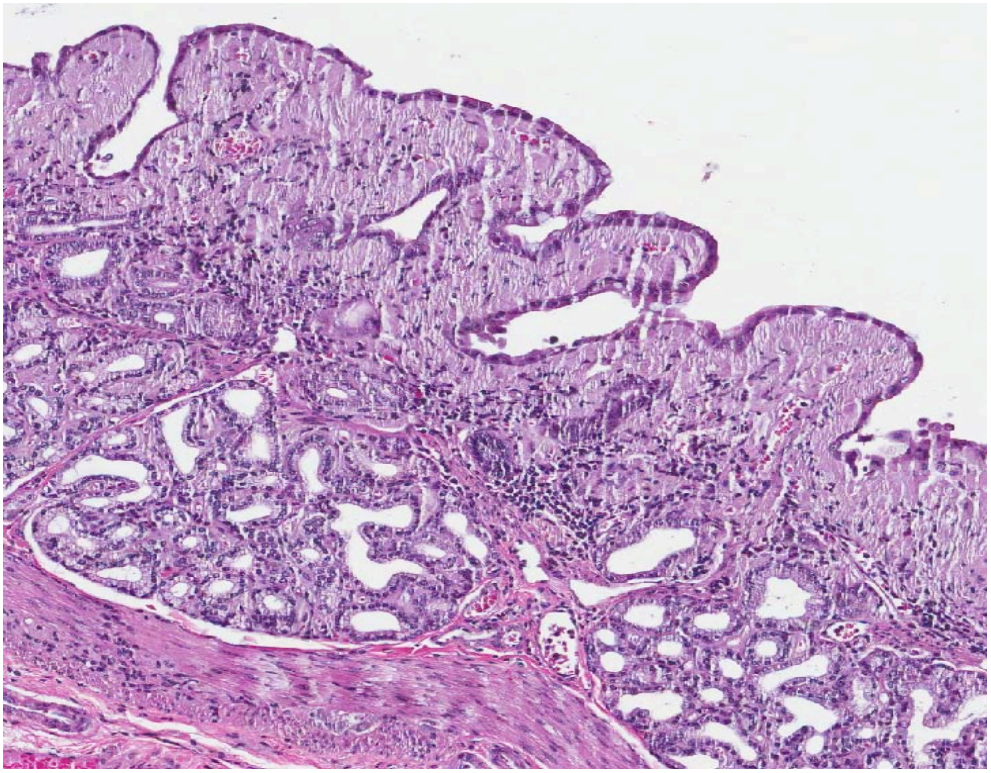
Special stains:
Congo Red: Congophilic, birefringent (green under polarized light) material, consistent with amyloid, was abundant in the tips of duodenal villi and around



2-1. Pancreas, marmoset: Throughout the section, pancreatic ducts are ectatic and contain cross sections of expanded by the presence of numerous adult spirurid nematodes. (HE 35X)



2-2. Pancreas, marmoset: Adult nematodes have a 5µm thick, smooth cuticle, a pseudocoelom, lateral cords (small arrows), a prominent triradiate esophagus (arrow), and numerous larvated eggs within the uterus. The surrounding pancreatic exocrine tissue (representative of the entire pancreas) is diffusely atrophic, characterized by smaller cell size, loss of zymogen granules, and a subjective increase in interlobular fibrous connective tissue. ***(HE 144X)***



2-3. Duodenum, marmoset: Villi are diffusely blunted and fused, and their lamina propria is effaced by a homogenous amphophilic material (amyloid). (HE 100X)

Brunner's glands. Amyloid deposits were also present in the liver, kidney and spleen.

Contributor's Morphologic Diagnosis: Pancreas:
1) Atrophy, acinar cell, chronic, severe with dissecting and periductular fibrosis, lymphoplasmacytic and eosinophilic infiltrates, ductular ectasia and intralumenal nematodes (morphology consistent with *Spirurid* spp.).
2) Pancreatitis, neutrophilic, subacute, mild (not present in all sections).

Duodenum:
1) Amyloidosis, mucosal and interstitial, multifocal, severe with villous blunting, atrophy and fusion, attenuation of enterocytes, crypt hyperplasia, gland loss.
2) Enteritis, lymphoplasmacytic to neutrophilic, chronic, generalized, mild.

Arterioles (mesenteric, not present in all sections):
Medial arteriosclerosis, hyaline-type, chronic, multifocal, mild with mineralization.

Contributor's Comment: Nematodes in the pancreatic ducts were associated with lobular atrophy, periductular fibrosis and mild inflammation. The nematodes exhibit morphologic features consistent with *Trichospirura leptostoma*, a spirurid that inhabits the pancreatic duct of certain species of calltrichids (members of the New World primate family, *Callitrichidae*) including marmosets, tamarins, squirrel monkeys and owl monkeys.[1] Transmission occurs through ingestion of the intermediate host, the common cockroach. Trichospiruriasis is usually considered asymptomatic in marmosets; however, chronic wasting syndrome and exocrine pancreatic insufficiency have been associated with a heavy parasitic burden.[2] Morphologically, the severity of pancreatic lesions are associated with parasite load and progress from pancreatitis to pancreatic fibrosis with atrophy of exocrine pancreatic tissue and, rarely, to obstructive cholestasis.[1,3]

Unique histomorphological features of *T. leptostoma* include their location in interlobular pancreatic ducts, small cross-sectional diameter, long muscular esophagus, excretory pores in the lateral cords and primitive somatic musculature.[4] Based on the changes in the section presented, trichospiruriasis likely contributed to pancreatic insufficiency and secondary malnutrition.

A complicating disease in this animal that is also exceedingly common in captive calltrichids is chronic inflammatory bowel disease (IBD) characterized by diffuse, mucosal atrophy, lymphoplasmacytic inflammation and areas of mucosal ulceration. Typically, callitrichid IBD is most severe in the colon, but lesions were diffuse in this case and were complicated by intestinal amyloidosis. This condition is presently enigmatic, but multiple contributory factors have been implicated including various bacterial infections (*Helicobacter sp.*, *Campylobacter jejuni*, and enteropathogenic *Escherichia coli*), immune dysfunction, genetic predisposition and stress.[5,6,7,8] Cotton top-tamarins (*Saguinus oedipus*) have been previously used as a primate model of colitis-

associated colonic carcinogenesis because of the high propensity for spontaneous colitis that often progresses to adenocarcinomas in this species.[9]

Chronic systemic inflammation caused by the parasitic infestation and enterocolitis likely induced systemic AA amyloidosis due to elevated levels of the SAA amyloidogenic precursor molecule. In addition to the intestinal tract, amyloidosis was also present in the liver, spleen and kidneys. Ingestion of 'amyloid enhancing factors' and hereditary predisposition have been implicated as contributory to the development of systemic AA amyloidosis in colonies of captive marmosets.[10]

JPC Diagnosis: 1. Pancreas, exocrine tissue: Atrophy, diffuse, severe.
2. Pancreatic ducts: Numerous male and female adult spirurid nematodes with mild intraductal neutrophilic exudates.
3. Duodenum, mucosa: Amyloid, diffuse, moderate with marked villar blunting and fusion.
4. Mesentery, adipose tissue: Atrophy, diffuse, severe.
5. Large muscular artery: Mineralization, medial, mural, multifocal, marked.

Conference Comment: Although marmosets are popular as a laboratory primate species for a number of reasons, in captivity the animals are very susceptible to a not fully understood condition known as wasting marmoset syndrome (WMS). WMS is characterized by failure to thrive and generalized weakness which often progresses to death. Characteristics commonly associated with WMS are poor weight gain, weight loss, muscle atrophy, alopecia, diarrhea, and colitis. Histologic features include thin, atrophic intestinal mucosa and chronic lymphoplasmacytic enteritis usually in the distal jejunum and ileum. Other lesions include ulcerative typhlocolitis and bone fragility due to decreased intestinal vitamin D absorbtion. WMS is perhaps the most important and poorly understood disease syndrome of callitrichids.[14,15,16]

The etiology of WMS is not known; however, malnutrition, alterations in intestinal microflora, parasitic infestations, and malabsorption have been suggested as the possible primary or contributing causes. Conference participants discussed several possible underlying etiologies, such as pancreatic spirurid infestation as in this case; bile duct fibrosis and obstruction by fluke migration; and immune-mediated enteropathic disease due to antibodies to gliadin, a glycoprotein found in wheat and other cereals, which is common in humans with celiac disease. In the moderator's experience, pancreatic trichospirurids are often incidental and associated with no pathologic effects. Conference participants attributed the prominent fibrous connective tissue separating and surrounding exocrine pancreatic lobules as due to pancreatic atrophy from WMS and not fibrosis from the trichospirurids, and the loss of exocrine pancreatic zymogen granules as due to depletion.[14,15,16]

The predominant clinical pathologic alterations in marmosets with WMS include mild macrocytic normochromic anemia, thrombocytosis, hypoproteinemia, hypoalbuminemia, and elevated alkaline phosphatase levels due to colonic inflammation. Most of these changes have been attributed to protein-calorie malnutrition and muscle wasting. Thrombocytosis in these marmosets probably represents a nonspecific response of the bone marrow to the chronic wasting and enteric inflammation. Thrombocytosis is mediated by cytokines released during chronic inflammation, and include thrombopoietin (TPO) and interleukin 6 (IL-6), which is commonly increased in inflammatory conditions.[1]

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CASE III: 11-0394 (JPC 4004300).

Signalment: Adult male African green monkey (*Cercopithecus aethiops*).

History: This single-housed nonhuman primate was on a research protocol but had not been exposed to an agent. The monkey had not been eating well for several days. One morning, caretakers noted the monkey had dark tarry feces and respiratory difficulty. Moist rales were auscultated bilaterally. Radiographs were taken and showed a gas-filled stomach and intestines and a cloudy hemithorax. Rule outs were gastric dilatation and intestinal intussusception. The monkey was treated by passing an orogastric tube to relieve the gas and giving IV fluids, furosemide, and enrofloxacin. Barium was also administered via the orogastric tube for further radiographs. The animal was found dead in the cage a couple of hours after treatment began.

Gross Pathology: The monkey was in thin body condition (body condition score of 2/5) with small amounts of subcutaneous and abdominal fat and severe dehydration. There was a self-bite wound on the left lateral aspect of the cranial tongue. The nasal passages were mildly edematous and there was a small amount of clear mucus present. There was focally extensive subcutaneous and muscular bruising over the right cranial skull and mild subcutaneous edema of the ventral neck. The lungs were non-collapsed and consolidated with extensive multifocal to coalescing dark red to pale firm areas and multifocal pleural adhesions to the thoracic wall and the diaphragm. The pericardium was moderately thickened. The liver was diffusely dark and congested with multifocal pitting over all lobes. The gallbladder was markedly distended by clotted blood, fibrin, and bile. The stomach was moderately distended by white fluid (barium) and gas. The upper half of the small intestine contained a moderate amount of barium-stained digesta and the lower half contained a moderate amount of dark green fluid digesta. The cecum contained abundant dark green soft material. The colon was empty except for a small amount of gas. There were no significant gross findings in any of the other organs observed.

Laboratory Results: *Bordetella bronchiseptica* was cultured from the lung.

Contributor's Histopathologic Description: Diffusely affecting the section of lung, bronchi, bronchioles, and alveoli are filled by an exudate composed of abundant fibrin, neutrophils that are often degenerate, hemorrhage, and eosinophilic proteinaceous edema fluid and fewer macrophages. Normal tissue architecture is disrupted and displace by distinct multifocal to coalescing abscesses composed of abundant necrotic debris, degenerate neutrophils, fibrin, and hemorrhage. Multifocally the bronchial and bronchiolar epithelium is hyperplastic. There is multifocal mild to moderate perivascular edema, fibrin, and hemorrhage with occasional neutrophils. The pleura is expanded multifocally by fibrin, hemorrhage, and hyperplastic mesothelial cells. Numerous cilia-associated gram-negative coccobacilli are noted with the Brown-Hopps stain.

Contributor's Morphologic Diagnosis: Lung: Bronchopneumonia, fibrinosuppurative and necrohemorrhagic, diffuse, severe, with fibrinous pleuritis and gram-negative cilia-associated coccobacilli.

Contributor's Comment: Other notable histopathologic findings in this animal included a severe hemorrhagic and fibrinosuppurative cholecystitis, a diffuse moderate subacute periportal

hepatitis with bile stasis, a mild acute tracheitis, and numerous cecocolic oxyurids (pinworms) with minimal granulomatous typhlitis and colitis.

Bordetella bronchiseptica is a small gram-negative coccobacillus of the respiratory tract in numerous animal species. Along with other factors, it is the cause of nonprogressive atrophic rhinitis in pigs as well as bronchopneumonia and is considered the primary cause of infectious tracheobronchitis in dogs.[1] It is also considered a major cause of respiratory disease in guinea pigs.[2] *Bordetella bronchiseptica* is an occasional opportunistic respiratory pathogen causing suppurative bronchopneumonias in several other species including rabbits, rats, foals, cats, and sea otters.[1-3] In nonhuman primates, *Bordetella bronchiseptica* has been documented as a cause of pneumonia and upper respiratory infections in prosimians (bushbabies), new world primates (marmosets and squirrel monkeys), and old world primates (African green monkeys and rhesus macaques).[4-5] Nonhuman primates can be naturally infected with *Bordetella pertussis* and develop whooping cough-like disease also.[5]

Bordetella is transmitted by aerosolization or fomites and the bacteria adhere to the ciliated epithelium of the upper respiratory tract. Interspecies transmission can occur. The bacteria evade the immune defenses via several virulence factors (hemolysin, lipooligosaccharide, and tracheal cytotoxin) and replicate among the cilia. Ciliostasis with decreased mucociliary clearance and host cell death occurs.[1] Bronchopneumonia typically occurs in animals with weakened pulmonary defenses due to age, stress, viruses or other infectious agents, or other predisposing factors.[5] Once the defenses are breached, the bacteria can enter the lung and the inflammatory process begins centered on the bronchioles, then spreads upward into the bronchi and downward into the alveoli. The inflammatory exudate collects in the airways and tends to spread centrifugally and exudate can be coughed up and aspirated into other lobules, continuing the process. The cytokines released from pulmonary injury cause rapid recruitment of neutrophils and alveolar macrophages and cause increased vascular permeability resulting in leakage of edema fluid, fibrin, and sometimes hemorrhage.[6]

Other ruleouts considered at necropsy for the bronchopneumonia in this case included *Streptococcus pneumoniae* or other *Streptococcus* spp, *Klebsiella pneumoniae*, *Mycoplasma* spp, *Pasteurella* spp, and viruses such as influenza, measles, and cytomegalovirus. An interesting finding in this animal was the hemorrhagic and fibrinosuppurative cholecystitis, which is typically associated with gram-negative agents like *Salmonella* or *E. coli*. It is possible the cholecystitis was caused by the *Bordetella* infection but since cultures were not taken of the gallbladder, this cannot be definitively proven.

JPC Diagnosis: Lung: Pneumonia, bronchointerstitial, fibrinosuppurative and necrotizing, diffuse, severe, with hemorrhage and numerous cilia-associated coccobacilli.

Conference Comment: The typical gross appearance of pulmonary bordetellosis in primates is a purulent bronchopneumonia with severe pulmonary consolidation and fibrinopurulent pleuritis and pericarditis. Other reported gross findings include mucopurulent exudate within the nares, nasal passages, trachea and often tympanic bullae; middle ear infection; and meningitis.[5]

As mentioned by the contributor, *Bordetella* spp. have several important virulence factors. Adenylate cyclase toxin, known as hemolysin, is a member of the RTX (repeats in toxin) family of toxins and is secreted by the bacteria. The RTX domain forms ion-permeable pores in host cell membranes and allow the transfer of the adenylate cyclase domain. Increased cAMP production occurs after entry of the toxin into leukocytes, which greatly inhibits phagocytosis and the oxidative burst. Tracheal cytotoxin is secreted by the bacteria and stimulates host cells to secrete nitric oxide which induces ciliostasis and apoptosis of ciliated epithelial cells. Dermonecrotic toxin (DNT) is an intracellular toxin that is vasoconstrictive and cytotoxic and is released upon bacterial lysis; it shares structural and functional homology with cytotoxic necrotizing factor 1 (CNF1) of *E. coli*.

Filamentous Hemagglutinin (FHA), pertactin and fimbriae are adhesive proteins that allow attachment of the bacteria to ciliated epithelial cells. Lipooligosaccharide is a lipopolysaccharide with endotoxin activity found in the bacterial cell wall. The *Bordetella* virulence gene (Bvg) operon regulates the expression of most of these virulence factors.[1,6]

Although *Bordetella* is usually a co-pathogen in pigs, cattle, dogs and cats, it is the primary agent in several important veterinary diseases. *Bordetella bronchiseptica,* as a primary agent, can cause severe pneumonia in guinea pigs.[2] *B. avium* is the primary agent of turkey coryza. *B. avium* can also infect several species of fowl, psittacines, ratites, finches and domestic songbirds, and in cockatiels it has been associated with lockjaw syndrome, which is a respiratory disease with temporomandibular rigidity.[8] *B. hinzii*, a commensal organism in the upper respiratory tract of poultry and an opportunistic pathogen in immunocompromised humans, has been

identified as the causative agent of rhinitis, tracheitis, and bronchopneumonia in a rabbit and a B6 mouse.[7]

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CASE IV: CVD 11-4 (JPC 4006049).

Signalment: Eight year-old female baboon (*Papio* sp.).

History: Multiple ulcerated skin lesions were noted on the limbs, tail, and sex skin of an 8 year-old female baboon from the Southwest National Primate Research Center at the Texas Biomedical Research Institute. Impression smears were taken and submitted for cytology. The animal was euthanized following the identification of organisms and evidence of extensive infection.

Gross Pathology: The animal was thin with decreased body fat. Multiple irregular-shaped, slightly raised, firm and frequently ulcerated skin lesions were present on all four limbs, feet, sex skin, and the tail, ranging in size from <0.5 cm to >4 cm. On section the dermis was expanded by pink-tan nodules.

Contributor's Histopathologic Description: Skin: There is a focally extensive area of epidermal ulceration, hemorrhage and in some sections, overlying serocellular crust. The remaining epidermis is mildly to moderately thickened (acanthosis). The dermis is markedly expanded by granulation tissue and coalescing nodular aggregates of mixed inflammatory cells consisting of variable numbers of neutrophils, plump macrophages, multinucleated giant cells and fewer lymphocytes and eosinophils. Within the cytoplasm of many of the macrophages and multinucleated giant cells are numerous round to oval, pale staining organisms (yeast), which are 8-15 microns in diameter, with a clear, refractile, ~1-2 micron-thick cell wall, a 1-2 micron, basophilic nucleus, and rare narrow-based budding, morphologically consistent with *Histoplasma capsulatum* var. *duboisii*. Lymphohistiocytic perivascular cuffs are present at the periphery of the lesion.

Contributor's Morphologic Diagnosis: Haired skin: Dermatitis, granulomatous, nodular, multifocal, moderate, with ulceration, hemorrhage, epidermal hyperplasia, and numerous intrahistiocytic yeasts, baboon (*Papio* sp.), nonhuman primate.

Contributor's Comment: African histoplasmosis is a chronic progressive fungal infection endemic in Western and Central Africa and caused by *Histoplasma capsulatum* var. *duboisii*. Natural infection is rare and has been reported only in baboons and humans. In 1988, the first reported animal case in the United States was diagnosed in an adult red baboon at the Southwest Foundation for Biomedical Research (currently the Texas Biomedical Research Institute) in San Antonio, Texas. Imported from Senegal, this animal was in the United States for approximately 2 years prior to diagnosis.[2] In 1991 this same research institute experienced an epizootic of *H. capsulatum* var. *duboisii* involving over 20 cases in both wild-caught and native-born baboons.[3]

Although the ecology and pathogenesis of infection remain unclear, soil is believed to be the natural reservoir of *H. capsulatum* var. *duboisii,* with inhalation, ingestion, and possibly dermal contact the most likely methods of transmission. Inhalation and ingestion of the organism are thought to initially infect the lung or intestinal tract, with subsequent

hematogenous spread to the skin, for which the organism appears to have a predilection. Infected animals may remain asymptomatic for a year or more before clinical symptoms become apparent.[3,4]

Grossly, the lesions are typically nodular, ulcerated and/or exudative and commonly found on the face, ears, digits, tail, scrotum and buttocks.[3,4] Draining regional lymph nodes may become enlarged. Osteomyelitis caused by *H. capsulatum* var. *duboisii* has been reported, presumably by extension from skin to subjacent bone. Lesions have also been reported in nasal turbinates and testis.

Although *Histoplasma capsulatum* var. *duboisii*. stains well with Gomori's methenamine silver or Gridley's fungal stains, identification can usually be made from standard histology sections by its unique morphologic appearance which often includes organization in pairs and short chains, combined with the characteristic granulomatous inflammation.[6] The organism can be easily distinguished from the more common *Histoplasma capsulatum* var. *capsulatum* which presents as small oval yeast only 2-4 m in diameter. *Blastomyces dermatitidis* is similar in size and shape to *H. capsulatum* var. *duboisii*, but can be differentiated by its broad-based budding and lack of chain formation. *Cryptococcus neoformans* typically incites much less inflammation in tissues compared with *H. capsulatum* var. *duboisii,* and morphologically the yeast phase is slightly smaller with a thin cell wall and a wide, clear, unstained capsule that stains positive with mucicarmine. The immature or non-endosporulating spherules of *Coccidioides immitis* can be similar in shape but are often slightly larger (5-25 m) than *H. capsulatum* var. *duboisii*; and are accompanied by the presence of larger mature spherules containing endospores.[5,6]

The disease in humans is rare and generally limited to people in or from Africa. Epidemiologic data reveal the organism's predilection for lymph nodes, skin and bone. In humans, pulmonary involvement is more common in HIV-negative individuals while the incidence of disseminated disease is increased in HIV-positive patients.[5] It is unclear what role immunosuppression plays in the risk of infection. The reported incidence of disease remains very low despite the high incidence of HIV infection in endemic regions, and is much lower compared with reports of opportunistic infections with *Histoplasma capsulatum* var. *capsulatum* from the same areas.[5]

JPC Diagnosis: Glaborous skin: Dermatitis, pyogranulomatous, focally extensive, severe, with numerous intracytoplasmic yeasts.

Conference Comment: This is an excellent example of African histoplasmosis in a baboon and the contributor provides a thorough overview of the disease. Conference participants discussed the list of rule outs mentioned by the contributor, as well as *Lacazia loboi* and cutaneous *Paracoccidioides brasiliensis*, which have similar morphology. Lobo's disease has only been reported in humans and dolphins and is characterized morphologically by 10 m in diameter yeast which bud to form chains that resemble a string of pearls. Cutaneous paracoccidiomycosis is characterized by pyogranulomatous inflammation and multibudding yeast mother cells approximately 60 m in diameter with a 1 m thick refractile cell wall surrounded by 2-10 m spherical daughter cells.[1,4]

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