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Conference Moderator: LTC Keith Steele, DVM, PhD, Diplomate ACVP
Walter Reed Army Institute of Research
503 Robert Grant Avenue
Silver Spring, MD 20910

CASE I –D-04-0312 (AFIP 2936453)

Signalment: Two month old, female, large white-cross, pig.

History: A pig farm has had chronic problems for two years involving respiratory signs in young pigs. Symptoms exhibited by this weaner were typical of affected animals, and included labored breathing, mucoid nasal discharge and poor growth.

Gross Pathology: There was a diffuse lesion throughout the lungs, with all lobes discolored and consolidated. The cut surface was effusive and showed multiple white spots that appeared to be material in airways, but there was no pus. The thoracic and mesenteric lymph nodes were enlarged.

Laboratory Results: Microbiology results showed no significant bacterial growth on routine aerobic culture from the lungs, liver, or large intestine.

PCR test results were negative for porcine reproductive and respiratory syndrome virus (PRRSV) from lung tissue and a clotted blood sample. Virus culture on MARC cells showed cytopathic effect, and the culture medium was PCR-positive for PRRSV (US strain). The lung tissue was also PCR-positive for porcine circovirus 1 (PCV1), but the lymph nodes were negative. Lungs and lymph nodes were negative for PCV2.

Contributor's Morphologic Diagnosis: 1. Lungs: Pneumonia, interstitial and proliferative, severe, non-suppurative, subacute to chronic, coalescing lesions, with marked proliferation of type II epithelial cells.
2. Bronchioles: Bronchiolitis, severe, necro-suppurative, subacute, coalescing lesions, with caseating material present in airways.

Contributor's Comment: Porcine reproductive and respiratory syndrome (PRRS) has become a world-wide problem for pig producers since slightly differing syndromes (North America in 1987 and Europe in the 1990s) were united into one syndrome caused by genetic relatives of the Lelystad virus, now referred to as PRRSV.[1] The American and European isolates have been found to have marked genotypic and phenotypic differences, and variants of each have arisen even within their respective continents. The widely varying syndromes involve late-term abortion, stillborn and weak pigs, lowered farrowing rates, high death rates of neonates and weaned pigs, and delayed returns to estrus.[2]

Infection and disease associated with PRRSV are common in Hong Kong pig farms, and many cases are complicated by co-infection with porcine circovirus 2 (PCV2). This case was negative for PCV2, so the interstitial pneumonia was demonstrative of uncomplicated PRRSV infection. The pulmonary and bronchiolar lesions were given distinct morphological diagnoses because of the likelihood that secondary bacteria were involved in the bronchial lesion. The bacterial and mycoplasma culture results from this laboratory were negative, but the bronchial lesion is more consistent with secondary bacterial involvement than with pure PRRS, and many pigs in Hong Kong receive prophylactic antibiotics in the feed. The experimental disease in the lungs associated with uncomplicated PRRSV is limited to an interstitial pneumonia, is non-suppurative and dominated by mononuclear reaction.[2] Additional airway disease with neutrophils is usually attributed to bacteria or *Mycoplasma* spp..

The lymph nodes of this pig also showed severe diffuse changes, including a general loss of follicular architecture and replacement by histiocytes, lymphocytes and plasma cells. The overall appearance of the lymph nodes was of diffuse granulomatous lymphadenitis. The periphery of the lymph nodes showed areas of necrosis. The brain and meninges showed very mild perivascular cuffing, but this was not considered significant enough to have contributed to the pig's symptoms. The heart was normal but there were a few foci of monocytic infiltration in the liver.

Unfortunately it was not possible to obtain a more detailed history from the farm as to whether there were additional reproductive problems or other manifestations of PRRS disease. Records are not kept at many traditional farms and there are often multiple problems interacting at once.

AFIP Diagnosis: Lung: Pneumonia, bronchointerstitial, subacute, diffuse, moderate, with multifocal type II pneumocyte hyperplasia, cross-bred pig, porcine.

Conference Comment: Porcine pneumonias are a major problem faced by the contemporary swine industry. The incidence, prevalence, and mortality rates of pneumonias in pigs are linked to many interdependent factors, including: the host (age, genetic makeup, immune status), infectious agents (viruses, bacteria, mycoplasmas), environmental conditions (humidity, temperature, ammonia concentrations), and management practices (crowding, mixing of animals, air quality, nutrition, stress).[3]

Porcine reproductive and respiratory syndrome (PRRS) is endemic in many swine producing countries and is a major cause of late-term abortions, stillbirths and respiratory disease in young pigs. PRRS is caused by PRRS virus (PRRSV), an enveloped single stranded RNA virus in the family *Arteriviridae*, genus *Arterivirus*. Other arteriviruses include equine arterivirus (EAV) and simian hemorrhagic fever virus (SHFV).[4]

PRRSV is transmitted by direct contact between infected and naïve pigs, although the exact route of transmission (aerosol, body fluids, fecal) has not been proven experimentally. The virus replicates in alveolar macrophages and glial cells. However, the virus antigen or RNA has been identified in macrophages of multiple tissues, monocytes, endothelial cells, smooth muscle cells, and fibroblasts. PRRSV infection has been limited to domestic swine, with a single report of PRRSV infection in Mallard ducks.[4]

The clinical presentation of PRRSV infection depends on the age, pregnancy status, and trimester of gestation of the infected pig. Clinical presentation on a farm varies from sporadic abortions to abortion storms. Individual animals may present with late-term abortion, premature farrowing with stillborn fetuses, partially autolyzed fetuses, or mummified fetuses. Clinical signs in infected sows or gilts vary from none to anorexia, fever, lethargy, pneumonia, agalactia, cyanosis of the ears and vulva, edema, delayed return to estrus, and less commonly, death.[4]

Gross lesions associated with PRRSV infection vary widely from none to diffuse tan consolidation of the lungs, and are commonly complicated by lesions resulting from concurrent bacterial infection. Lymph nodes may be markedly enlarged and vary from solid to polycystic. Fetuses from PRRSV abortions are late term and the body condition ranges from fresh to autolyzed.[4]

Light microscopic lesions most commonly involve the lung and lymphoid tissue. However, other lesions include vasculitis, myocarditis, and encephalitis. Lung lesions are characterized by septal thickening by macrophages, type II pneumocyte hyperplasia, necrotic debris, macrophages and syncytial cells within alveoli, peribronchial lymphoid hyperplasia, and lymphoplasmacytic perivascular cuffing. Lymphoid tissue exhibits lymphoid hyperplasia and necrosis.[4]

Other infectious causes of pneumonia in swine are listed below[3]

Viral

Swine influenza virus
Porcine circovirus (Postweaning multisystemic wasting syndrome, PMWS)
Porcine respiratory coronavirus (PRCV)

Bacterial

Mycoplasma hyopneumoniae (Porcine enzootic pneumonia)
Actinobacillus pleuropneumoniae (Porcine pleuropneumonia)
Haemophilus parasuis (Glasser's disease)
Pasteurella multocida
Streptococcus suis type II
Mycobacterium spp. (*M. avium*, *M. bovis*, *M. tuberculosis*)
Salmonella spp. (*S. choleraesuis*, *S. typhisuis*)

Parasitic

Metastrongylus spp. (*M. apri*, *M. salmi*, *M. pudendotectus*)
Ascaris suum

Contributor: Tai Lung Veterinary Laboratory, Agriculture, Fisheries and Conservation Department, Lin Tong Mei, Sheung Shui, NT, Hong Kong SAR of China
http://www.afcd.gov.hk

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CASE II – 15303 6a or 15303 6e (AFIP 2946723)

Signalment: Adult, female, intact, rabbit (*Oryctolagus cuniculus*).

History: This rabbit received intrahepatic inoculation of VX2 carcinoma cells in the development of a tumor model to assess the response to treatment by various gene therapy agents. One week post inoculation, the rabbit developed anorexia and was noted to be losing weight and condition. After 2 days of supportive therapy with no clinical improvement, the animal was euthanized.

Gross Pathology: The rabbit was thin with scant body fat. Abdominal organs, including the liver and kidney, contained multiple tumor masses composed of pale, yellow-white, soft tissue. There was palpable thickening of the pyloric region of the stomach, with pale transmural tumor-like masses noted on cut section.

Laboratory Results: None

Contributor's Morphologic Diagnosis: Stomach: Carcinoma, invasive, transmural, intravascular, compatible with VX2 carcinoma, rabbit, *Oryctolagus cuniculus.*

Contributor's Comment: The wall of the stomach is thickened by multiple unencapsulated, poorly circumscribed and highly infiltrative, multilobular masses that expand the submucosa and tunica muscularis, and extend into the serosa and mucosa. Lobules of various sizes and shapes separate muscle bundles, connective tissue and structural elements, and are supported on a fine to coarse fibrovascular stroma. Coalescing areas of coagulative and liquefactive necrosis occupy 10-40% of tumor area, depending on the section, and sometimes are associated with intravascular thrombi and hemorrhage (infarction). Within lobules, neoplastic cells form cords and packets supported on a fine fibrovascular stroma. The cells are polygonal with variably distinct borders, and moderate amounts of pale eosinophilic and vacuolated cytoplasm, a round vesiculate nucleus with dispersed chromatin and 1 to 3 small nucleoli. There are 3 to 8 mitoses per high power field (HPF) with numerous bizarre mitotic figures. There are scattered large karyomegalic and multinucleated atypical cells. Vascular invasion seems to be primarily within thin-walled lymphatic vessels, but also sometimes in blood vessels. There is mild to marked submucosal edema, depending on the section. There is mild to moderate lymphoplasmacytic infiltration of the mucosa and submucosa.

VX2 carcinoma was established from a carcinoma induced in a rabbit by the Shope cottontail rabbit papillomavirus (CRPV) in 1940.[1] Papillomaviruses induce benign and malignant tumors in humans and animals. VX2 tumor cells contain multiple copies of CRPV genome integrated into their cellular DNA as tandem repeats. VX2 tumor is considered to be an anaplastic carcinoma, composed of poorly

differentiated keratinocytes that do not keratinize (cornify). VX2 cells grow rapidly in adult allogenic recipients, frequently metastasizing to the lungs. They are known for having extremely aggressive behavior in vivo, and are used to model various types of aggressive epithelial cancers including liver tumors and lung tumors.[1] Auricular VX2 carcinoma of the New Zealand White rabbit is an animal model for human squamous cell carcinomas of the head and neck region (HNSCC), since both tumors tend to metastasize lymphatically, leading to early lymph node and subsequent distant metastasis.[3] It has also been used as a model of tumor-induced hypercalcemia.[4]

AFIP Diagnosis: Stomach: Carcinoma, with intravascular tumor emboli, rabbit, lagomorph.

Conference Comment: Without the above history, an obvious differential is metastatic uterine adenocarcinoma, as it is the most common spontaneous neoplasm of rabbits. The incidence is relatively low, approximately 4%, in younger does (2-3 years old) and much higher, approximately 80%, in older does (5-6 years old). Grossly the tumors are nodular, often multicentric, and usually involve both horns. On cut surface, they are firm, often with a cauliflower-like surface and central ulcerations. Carcinomatosis and/or metastasis to the lung and liver may occur. Histologically, cells invade the underlying muscular tunics and form acinar and tubular structures.[6]

Conference attendees also discussed the multistep model of carcinogenesis, which involves the sequential stages of initiation and promotion. Initiation causes permanent DNA damage (mutations), is rapid and irreversible. However, initiation alone is not sufficient for tumor formation. On the other hand, promoters can induce tumors in initiated cells, but are nontumorigenic by themselves. In contrast to the effects of initiators, the cellular changes resulting from promoters do not affect DNA directly and are reversible. Promoters enhance the proliferation of initiated cells, which may lead to additional mutations.[7]

Initiation involves nonlethal genetic damage that may be acquired by the action of environmental agents, such as chemicals, radiation, or viruses, or it may be inherited in the germ line. There are four classes of normal regulatory genes that are the principal targets of genetic damage: the growth-promoting protooncogenes, the growth-inhibiting tumor suppressor genes, genes that regulate programmed cell death (apoptosis), and genes involved in DNA repair.[7]

Carcinogenesis is a multistep process at both the phenotypic and genetic levels. Characteristics such as excessive growth, local invasiveness, and the ability to

form distant metastases are phenotypic attributes that are acquired sequentially, a process known as tumor progression. At the molecular level, progression is a result of cumulative genetic damage that may be favored by defects in DNA repair.[7]

There are eight fundamental changes in cell physiology that together determine malignancy. They include the following: self-sufficiency in growth signals, insensitivity to growth-inhibitory signals, evasion of apoptosis, defects in DNA repair, limitless replicative potential, sustained angiogenesis, ability to invade and metastasize, and the ability to evade the immune system. Mutations in genes that regulate these cellular traits are seen in every cancer.[7]

Contributor: Baylor College of Medicine, Center for Comparative Medicine, 600D, One Baylor Plaza, MS BCM 145, Houston, TX
www.bcm.tmc.edu

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CASE III – 04-11575 (AFIP 2937341)

Signalment: 1 month old, female, Spotted Saddle Horse (*Equus caballus*).

History: Apparently healthy filly became acutely ill and died overnight.

Gross Pathology: The liver was slightly swollen and icteric. The kidney was 20% swollen. The spleen was 3X normal size with petechial hemorrhages.

Laboratory Results: Replicate sections of liver stained with Steiner silver stain reveal clusters of long bacterial rods within adjacent hepatocytes. Low numbers of *Listeria monocytogenes* as well as *Salmonella typhimurium* were isolated from the liver of this foal. *Listeria monocytogenes* was also isolated from the kidney in slightly higher numbers. Replicate sections of liver stained with Brown and Brenn (tissue gram stain) reveal rare extracellular short bacterial rods, most of which are gram positive.

Contributor's Morphologic Diagnosis: Liver: Severe, acute, multifocal random, necrotizing hepatitis with intracellular bacteria.
Etiology: Tyzzer's disease **(***Clostridium piliformis***)** with concurrent *Listeria monocytogenes* and *Salmonella typhimurium* infection**.**

Contributor's Comment: Tyzzer's disease is a fatal necrotizing hepatitis caused by *Clostridium piliforme* (previously named *Bacillus pilliformis*). This disease is most commonly encountered in young foals[1,2] and laboratory rodents[3], but occasional cases in cats and dogs are observed.[2] The disease is characterized by multifocal to miliary hepatic necrosis with the adjacent hepatocytes containing intracellular 10 to 40 micron long, spore forming, gram-negative clostridial organisms[4] arranged into "match stick" bundles. The organism is difficult to culture and diagnosis is dependent upon demonstration of the organism within the lesions.[3,4,5] It is principally a disease of foals 1-5 weeks of age[1] and is characterized by sudden onset of fever, shock, terminal coma and death within a few hours to two days. Clinical symptoms include tachycardia, tachypnea, jaundice and severe diarrhea. Affected foals are usually leukopenic and have highly elevated liver enzymes.

Although clinical disease is rare, the prevalence of antibody in horses suggests that *Clostridium piliforme* infection is common. Why only certain foals are susceptible to fatal infections is not known. Adult inapparent carriers can infect newborn foals, which are normally coprophagous. Spores survive moderate heating, freezing and thawing. Contaminated litter remains infective for months.[6]

Salmonellosis and listeriosis are uncommon forms of septicemia in the horse.[7]

AFIP Diagnosis: Hepatitis, necrotizing, acute, random, severe, with intrahepatocytic bacilli, etiology consistent with *Clostridium piliforme*, Spotted Saddle Horse, equine.

Conference Comment: Tyzzer's disease was first reported in Japanese waltzing mice by Ernest Tyzzer in 1917. The organism is now recognized to produce disease in a wide variety of other species including rats, gerbils, hamsters, guinea pigs, rabbits, and horses, and rarely in cats, birds and humans with AIDS. The etiologic agent, *Clostridium piliforme*, is a gram-negative, spore-forming, filamentous, obligate intracellular bacterium that is difficult to isolate using standard bacteriologic techniques.[8,9]

The organism is shed in the feces and spores may persist in the environment for up to one year. Transmission is primarily through ingestion, although intrauterine infection has been produced experimentally in mice. Outbreaks of Tyzzer's disease are characterized by low morbidity and high mortality in affected animals. Animal strain, age, and immune status are important factors in susceptibility to the disease. Typically, the organism invades the intestinal mucosal epithelium and disseminates to other organs, particularly the liver and heart.[9]

Gross lesions include multifocal coagulative to suppurative hepatic necrosis, segmental necrotizing enteritis, primarily in the terminal ileum and cecum (except for the rabbit, in which the cecum and colon are the target organs),[10] and multifocal necrotizing myocarditis. Foci of necrosis may also be found in the mesenteric lymph nodes. Histologically, there are intracytoplasmic bundles of bacilli within enterocytes and hepatocytes adjacent to necrotic foci. The organisms are easily identified in Warthin-Starry 4.0 stained tissue sections.[9]

Contributor: C.E. Kord Animal Disease Diagnostic Laboratory, P.O. Box 40627, Melrose Station, Nashville, TN
http://www.state.tn.us/agriculture/regulate/labs/kordlab.html

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CASE IV – N03-912 (AFIP 2946701)

Signalment: 11 year old adult female cynomolgus monkey (*Macaca fascicularis*).

History: This female cynomolgus presented to the clinician for marked lethargy, and with a previous history of seizures of unknown etiology. Examination and laboratory work-up revealed an inflammatory leukogram and low protein. The animal's condition did not respond over time to treatment and she was subsequently euthanized.

Gross Pathology: Gross postmortem examination revealed clear fluid in the thorax (hydrothorax).

Laboratory Results: None.

Contributor's Morphologic Diagnosis: Pancreas and adjacent fibrovascular connective tissue: Arteritis, necrotizing, subacute to chronic, multifocal.

Contributor's Comment: The full range of the severity and duration of the polyarteritis in this animal was not evident in all sections. Mildly affected arteries were characterized by mixed populations of inflammatory cells located primarily in the tunica adventitia. More severely affected vessels displayed transmural inflammation, intimal proliferation and fibrinoid necrosis within the tunica media. The disease in this animal involved multiple tissues including pancreas, heart, kidney and mesentery.

Polyarteritis nodosa (PAN) -like diseases have been described in several species including humans, dogs, cats, pigs and rodents, but only rarely in nonhuman primates. The contributor is aware of four cases of idiopathic PAN reported in cynomolgus macaques. The disease in humans is multisystemic and characterized by necrotizing lesions in small and medium-sized arteries. Other shared features of the disease as it is observed in both cynomolgus monkeys and people include

segmental distribution in affected vessels, predilection for areas of arterial branching, and coexistence of acute and chronic lesions. Although the pathogenesis of PAN is not well understood, it is generally thought to involve an immune-mediated disease process. Immune complex deposition with complement activation may play a role in initiating the disease, while cell-mediated immune interactions are likely to contribute to the progression of the lesion.

In rats, polyarteritis nodosa (polyangiitis, panarteritis) is a well-described entity and the incidence varies among different strains. Grossly, the disease typically presents as nodular lesions affecting the pancreatic, mesenteric and/or spermatic arteries. Depending on the chronicity of the lesion, microscopic features include fibrinoid necrosis of muscular arteries, mixed inflammatory cell infiltrate of vessels and surrounding tissue, and fibrosis. Spontaneous arterial diseases are also described in dogs including idiopathic necrotizing polyarteritis in Beagle dogs (Beagle pain syndrome) and idiopathic extramural coronary arteritis. Drug administration can be associated with both non-necrotizing (often hypersensitivity induced) and necrotizing inflammatory vascular lesions. Some examples of drug induced vascular injury include the mesenteric vasculitis in rats treated with phosphodiesterase III inhibitors and the coronary and systemic arteritis associated with endothelin A receptor antagonists in dogs and monkeys.

AFIP Diagnosis: Pancreas: Arteritis, histiocytic and lymphocytic, necrotizing, multifocal, with intimal fibromuscular proliferation, cynomolgus macaque (*Macaca fascicularis*), primate.

Conference Comment: As the contributor mentions, there is slide variability, with the full range of severity and duration of the polyarteritis not evident in all slides. Within all slides the pancreatic arteries are affected to varying degrees. Within some sections, islet capillaries are also affected and occasionally contain thrombi. The arteries in the peripancreatic adipose tissue of some slides are also affected.

In rats, the disease most frequently occurs in the Sprague-Dawley and spontaneous hypertensive rat (SHR) strains, and in rats with late-stage chronic nephropathy. Classically, at necropsy, vessels are enlarged and thickened in a segmental pattern, with marked tortuosity. The lesions occur most frequently in the pancreaticoduodenal artery and medium-sized arteries of the mesentery, pancreas, and testis. Histologically, there typically is fibrinoid degeneration and thickening of the tunica media, and infiltration by monocytes and fewer neutrophils. There is marked variation in the luminal size of affected vessels, which are often thrombosed, and occasionally recanalized.[5]

These features and the intimal proliferation are best appreciated with appropriate special stains and immunohistochemistry (IHC). The modified Movat's pentachrome method is very helpful as it stains elastic laminae black, collagen and reticular fibers yellow, ground substance and mucin blue, fibrin intense red, and muscle fibers red.[6] With the Movat's pentachrome method, the quantity of intimal proliferation is readily apparent as are disruptions of the elastic laminae. Other stains and IHC, such as Masson's trichrome and smooth muscle actin aid in differentiating increased amounts of intimal connective tissue from smooth muscle hyperplasia. Immunohistochemistry for CD68 confirms that most of the infiltrating leukocytes are macrophages.

Contributor: Southwest Foundation for Biomedical Research, PO Box 760549, San Antonio, TX 78245

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esday, 07 December, 2004 at 18:

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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