The Armed Forces Institute of Pathology
Department of Veterinary Pathology

Conference Coordinator:
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WEDNESDAY SLIDE CONFERENCE 2009-2010

Conference 3

23 September 2009

Conference Moderator:

Dr. Marc E. Mattix, DVM, MSS, Diplomate ACVP

CASE I: 3383-08 (AFIP 3103744).

Signalment: Placenta from an aborted meat goat fetus (*Capra hircus*).

History: Increased late-term abortions were reported in the herd. We received a placenta only on the first submission and 2 fetuses with placentas later.

Gross Pathology: The fetal tissues were unremarkable and the placentas had diffuse rough thickening of the cotyledons and multifocal to coalescing pale, slightly raised foci and plaques on the intercotyledonary membranes (**fig. 1-1**).

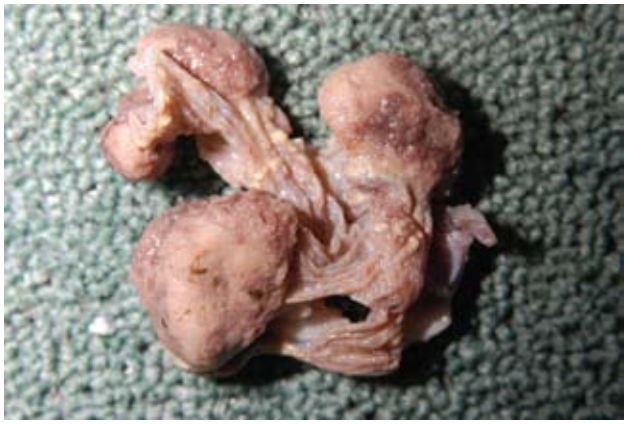
Laboratory Results: **Culture**: No *Brucella* sp. or other significant bacteria from the placenta or fetus (4+ alpha *Streptococcus* sp. and 4+ *E. coli* in the abomasal fluid and placenta). ***Leptospira* F.A.:** Negative on fetal kidneys. ***Chlamydia* (*Chlamydophila*) PCR:** Negative. ***Coxiella burnetii* immunohistochemistry:** Positive (done at UC Davis).

Histopathologic Description: There is diffuse cotyledonary necrosis with intralesional, intracellular (intratrophoblastic) minute, basophilic organisms and multifocal intercotyledonary necrotizing placentitis (**fig. 1-2**). Intact trophoblasts laden with the numerous intracytoplasmic bacteria are somewhat more evident on the intercotyledonary placenta (**fig. 1-3**).

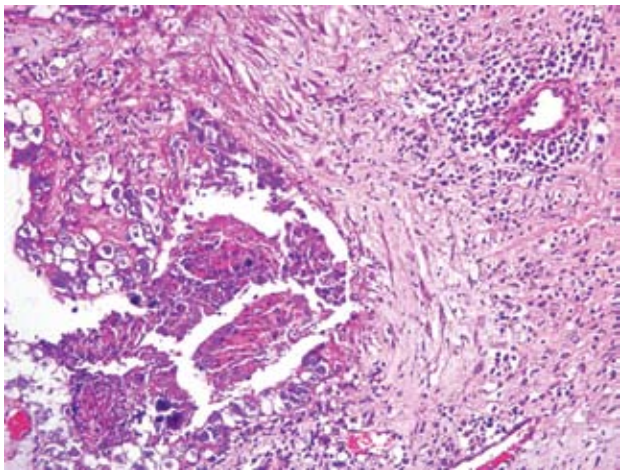
Contributor's Morphologic Diagnosis: Necrotizing placentitis, due to *Coxiella burnetii* (Q Fever).

Contributor's Comment: Myriad intracellular minute bacteria are in the surface trophoblasts of the cotyledons and on the intercotyledonary chorion with essentially diffuse necrosis that spares only limited sections of the intercotyledonary chorion. Ruminants, especially sheep and goats, are susceptible to *Coxiella burnetti* placentitis and abortion and humans are very susceptible to infection. The organisms are acid-fast,[8] as were ours, with a diffuse granular red staining of the infected trophoblast cytoplasm (**fig. 1-4**). They also stain with Gimenez as intracellular clusters of coccobacilli or thin rods, whereas *Chlamydophila* are uniformly round.[7,8] Our Giemsa stain also demonstrated that the swollen trophoblasts were filled with granular organisms. Toxoplasmosis was ruled out by

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



1-1. Placenta, goat. The cotyledons are diffusely thickened and rough, and there are multifocal to coalescing pale raised foci and plaques on the intercotyledonary membranes. Photograph courtesy of Livestock and Poultry Commission, P.O. Box 8505, Little Rock, AR 72215, jbritt@alpc.ar.gov



1-2. Placenta, goat. The placenta is diffusely edematous, with multifocal necrosis of the cytotrophoblasts and perivascular infiltrates of lymphocytes and plasma cells. (HE 200X)

the minute size of the organisms and lack of involvement of the brain and other internal fetal tissues and lack of reaction with PAS. Fetal lesions are generally lacking with Q fever, although the agent can be found in the fetal tissues by PCR [10] and about 10% of the fetuses may have multifocal subacute or histiocytic inflammation.[7] *Chlamydophila* would be the main consideration, and our PCR for it was negative. The causative agent for that has been renamed from *Chlamydia psittaci* serotype 1 to *Chlamydophila abortus*.

Coxiella, Brucella, and *Chlamydophila* infections in sheep and goats cause both cotyledonary and intercotyledonary necrosis [3,4,8] and all 3 agents target the intracellular fetal trophoblast cells.[10] *Campylobacter* infection causes similar lesions with necrotic inflammation also being in the fetal tissues.[4,5] Campylobacteriosis only affects the cotyledons in cows.[3]

One survey in France [8] found that infected or carrier cows and goats generally shed Coxiella in their milk and sheep mostly in vaginal secretions and feces. Since human infection is generally by aerosol, this might explain why humans are at greater risk from contact with sheep. This study did not find a correlation between recent parturition and shedding of organisms.

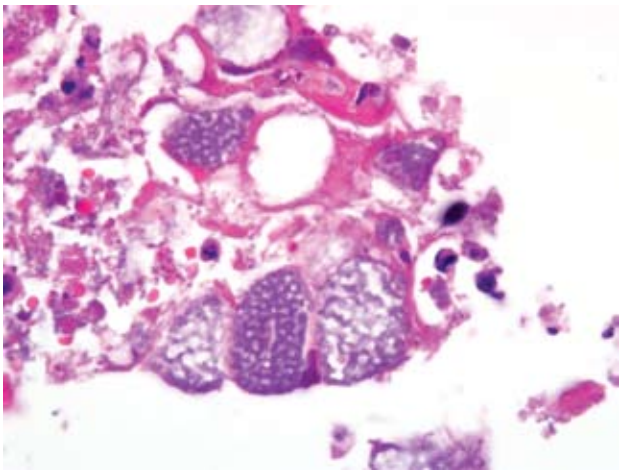
A PCR survey [5] of milk goat abortions on the island of Sardinia found 82.7% negative for an infectious agent and 16.3% positive with the results as below from 23 caprine fetuses and 8 placentas:

- *Toxoplasma*: 13% / 25% (fetus / placenta)
- *Salmonella abortusovis*: 0% / 0%
- *C. burnetti*: 0% / 12.5%
- *Chlamydophila abortus*: 0% / 12.5%
- *Neospora caninum*: 8.6% / 0%

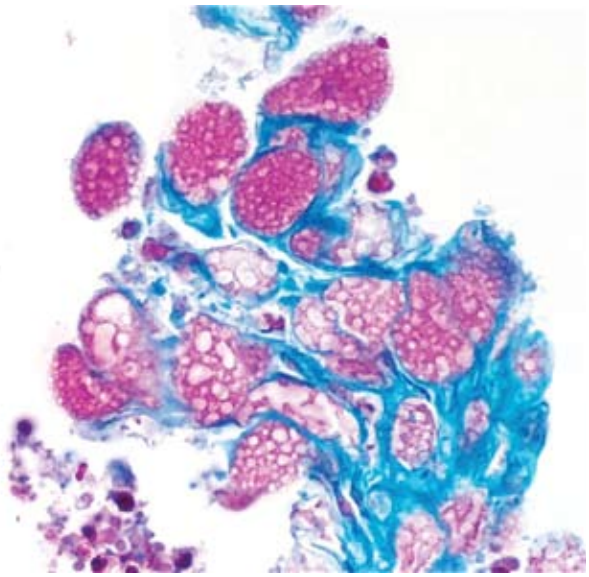
Goats may abort with *Coxiella* infection in 2 consecutive pregnancies although they have antibodies, so there may not be protective immunity after the first infection and a carrier state is possible.[1] Another survey found 9% of the goat abortions being due to Coxiella infection, but lesions were usually limited to the placenta and many submissions did not have the placenta.[7]

AFIP Diagnosis: Chorioallantois: Placentitis, necrotizing and suppurative, subacute, multifocal, marked, with vasculitis and intratrophoblastic coccobacilli.

Conference Comment: The contributor provides a succinct review of this entity and the differential diagnosis. Conference participants noted the foamy appearance of cells containing the *Coxiella burnetti* organism in this case, which is characteristic. Both *Coxiella burnetti* and *Chlamydophila abortus* stain positively with the modified acid fast stain or by the Gimenez method, which differentiates them from *Brucella abortus* and *Campylobacter* species. *Coxiella burnetti* and *Chlamydophila abortus* are morphologically distinct; the former are thin, pleomorphic, rod-shaped structures, while the elementary bodies in *Chlamydophila abortus* infection are round and smaller.[4] The pleomorphism of the *Coxiella* organism is attributed to the fact that when it replicates by binary fission, three distinct developmental forms result: spore, small cell variant, and large cell variant.[2]



1-3. Placenta, goat. Multifocally intercotyledonary cytotrophoblasts are swollen with numerous intracytoplasmic basophilic organisms. (HE 1000X)



1-4. Placenta, goat. Diffusely, intratrophoblastic organisms are acid-fast. Modified acid-fast photomicrograph courtesy of Livestock and Poultry Commission, P.O. Box 8505, Little Rock, AR 72215, jbritt@alpc.ar.gov

While both organisms can cause both cotyledonary and intercotyledonary necrosis, the gross lesions of *Chlamydophila* infection affect the cotlyledons and intercotyledonary regions in roughly equal proportions, while the placental lesions in *Coxiella burnetti* infection are most prominent in the intercotyledonary region. Both organisms can cause vasculitis in the placenta, although it is characteristically more marked in *Chlamydophila* abortion.[4]

Contributor: Arkansas Livestock and Poultry Commission, 1 Natural Resources Dr., Little Rock, AR 72205 http://www.arlpc.org/

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CASE II: 976/08 (AFIP 3134294).

Signalment: Adult, female banded mongoose (*Mungos mungo*).

History: The whole population of 8 banded mongooses (*Mungos mungo*) of a zoological park was affected and died within 11 days. Animals were housed in an outdoor enclosure. Some animals showed anorexia, lethargy and staggering gait. Severe dyspnea and swelling of the intermandibular region were regularly observed. Therapy with prednisolone and antibiotics was unsuccessful. There was no previous animal transfer in the population. Similar fatalities in other animal species did not occur. The animal keepers were healthy and free of any skin lesion. Mongooses died about two days after onset of disease. Four mongooses were submitted to our institute for pathomorphological examination.

Gross Pathology: Animals were in good nutritional condition. There were multiple inconspicuous skin lesions predominately at the head and ventral trunk, measuring up to 0.5 cm in diameter. Some lesions appeared as small papules or vesicles, others as pustules. Single skin lesions were covered by crusts. There was a small ulcer on the tongue in one animal. Retropharyngeal tissue (including lymph nodes) was replaced by a firm whitish mass compressing the larynx. Within liver and spleen there were miliary white foci of necrosis and multiple petechiae.

Laboratory Results: Orthopoxvirus was detected virologically and identified as cowpoxvirus (negative staining, transmission electron microscopy, cell culture, PCR, sequencing).

Histopathologic Description: Liver: Multifocally to coalescing there are randomly distributed foci of hepatocellular degeneration and necrosis, characterized by hypereosinophilia, loss of cellular detail, cellular debris, and pyknotic as well as karyorrhectic nuclei (coagulative necrosis). Foci vary in size from 40 to 200 µm; in some locations only single hepatocytes are affected. In less affected areas, hepatocytes are swollen, have pale eosinophilic cytoplasm and swollen nuclei (degeneration). Centrally in the necrotic zone there is extravasation of blood cells (acute hemorrhage) admixed with fibrin and degenerated inflammatory cells. Within the cytoplasm of necrotic cells, degenerating cells and unaltered hepatocytes there are up to five, oval or round, bright eosinophilic inclusion bodies ranging in 5-10 µm in size (**figs. 2-1 and 2-2**). Additionally, there is mild portal fibrosis and bile duct proliferation. There is a mild portal infiltration of lymphocytes and plasma cells. Single hepatocytes show cytoplasmic vacuolization (fatty change) and there is a mild intracanalicular cholestasis. **Spleen and lymph node** lesions (slides not submitted) were characterized by necrotizing inflammation, and cytoplasmic inclusion bodies were detectable occasionally. **Skin** lesions (slides not submitted) showed hyperplasia and degeneration of epithelial cells (ballooning degeneration) with acantholysis. Within the subcutaneous tissue of the neck there was marked edema and necrosuppurative cellulitis and necrotizing lymphadenitis of retropharyngeal lymph nodes.

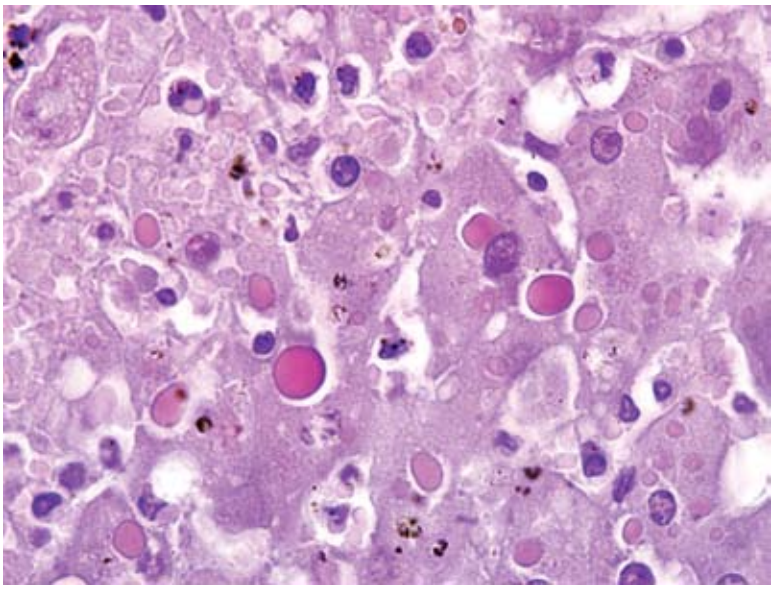
Contributor's Morphologic Diagnosis: Liver: Hepatitis, necrotizing, multifocal to coalescing, random, subacute, severe, with intralesional hemorrhage and numerous intracytoplasmic inclusion bodies, banded mongoose, *Mungos mungo*. Etiology: Consistent with systemic cowpoxvirus infection.

Contributor's Comment: Poxvirus infections in nonnative hosts are a focus of epidemiological studies and there is an obvious zoonotic potential.[7,11,13,14] The most common sources of human infection are infected cats.[1] Recently, cases of cowpoxvirus infection in humans have been described in France and Germany after transmission from pet rats.[2,9] Wild rodents are suspected as reservoir hosts.[3] There are several reports on cowpox virus infection in zoo animals. Reports of lethal poxvirus infections in elephants [4] and fatal cases in felids [1,8] can be found in the literature. Felids usually develop a mild dermal or a fatal pulmonary course of the disease. Necrotizing hepatitis due to cowpox virus is rare in felids; however, cases have been described in lions and cheetahs.[8]

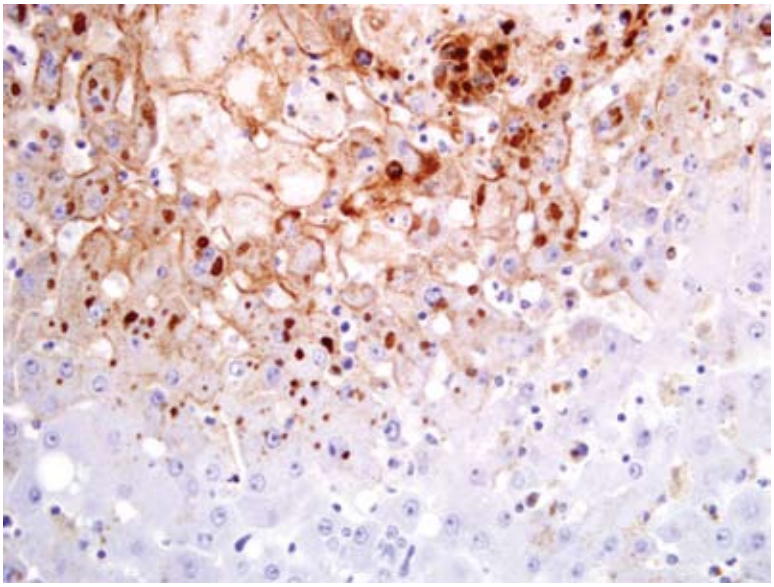
In the banded mongooses the most severe lesions were necrotizing hepatitis, splenitis and lymphadenitis with occurrence of characteristic eosinophilic cytoplasmic inclusion bodies. In contrast to cases of cowpox virus in other members of the suborder Feliformia, the lungs were unaltered. The etiologic diagnosis was confirmed by cell culture, electron microscopy, PCR and sequencing. Wild rodents may have served as reservoir and vector in our cases. This hypothesis was supported by observation of poxvirus lesions in a captured rat in the surrounding of the outdoor enclosure.

AFIP Diagnosis: Liver: Hepatitis, necrotizing, multifocal to coalescing, random, severe, with numerous intracytoplasmic eosinophilic inclusion bodies.

Conference Comment: Despite its name, cowpox virus infection is neither endemic nor common in cattle.[2,14] The contributor's review provides due emphasis on the



2-1. Liver, mongoose. Multifocal random areas of hepatocellular lytic necrosis, with degenerate hepatocytes containing one to five, round to oval, brightly eosinophilic, cytoplasmic inclusion bodies. (HE 1000X)



2-2. Liver, mongoose. Affected hepatocytes, have positive strong cytoplasmic immunoreactivity for cowpox viral antibody. (400X)

role of cats in zoonotic cowpox virus infection. Many attribute an apparent increase in human infections with cowpox virus to waning immunity to orthopoxviruses in general, associated with the cessation of immunization with Vaccinia virus for smallpox.[2,14]

While many members of the Poxviridae family cause only localized cutaneous disease, the following characteristically produce systemic disease, which may be severe: Sheeppox virus, Ectromelia virus, Monkeypox virus, and Variola virus.[5] Conference participants discussed these and other poxviruses of veterinary importance, which are summarized by genus as follows:

- Avipoxvirus: 10 species, including Fowlpox virus
- Capripoxvirus: Goatpox virus, Lumpy skin disease virus, Sheeppox virus
- Cervidpoxvirus: Deerpox virus W-848-83
- Leporipoxvirus: Myxoma virus, Rabbit (Shope) fibroma virus, Squirrel fibroma virus
- Molluscipoxvirus: Molluscum contagiosum virus
- Orthopoxvirus: Camelpox virus; Cowpox virus; Ectromelia virus; Monkeypox virus; Vaccinia virus (buffalopox virus, rabbit pox virus); Variola virus
- Parapoxvirus: Bovine papular stomatitis virus; Orf virus; Parapoxvirus of red deer in New Zealand; Pseudocowpox virus

- Suipoxvirus: Swinepox virus
- Yatapoxvirus: Tanapox virus; Yaba monkey tumor virus
- Unassigned: Squirrel poxvirus [5,6]

Typical poxviral lesions are both proliferative and necrotizing. As poxviruses are epitheliotropic, replication within cells causes degeneration (i.e. "ballooning degeneration") and necrosis, which is further exacerbated by ischemia when the virus replicates in endothelial cells and causes vascular damage. Several virulence factors may account for the ability of poxviruses to induce proliferation, including a gene whose product resembles epidermal growth factor.[5]

Unlike other DNA viruses, poxviruses produce intracytoplasmic, rather than intranuclear inclusion bodies. All poxviruses produce small, basophilic, intracytoplasmic inclusion bodies, designated *type B* or Guarnieri's bodies, early in the replication cycle. These represent the actual sites of virus replication. The numerous, large, prominent, eosinophilic, intracytoplasmic inclusion bodies noted in this case are designated *type A* or acidophilic-type inclusions (ATI), and they are produced later in the replication cycle. In humans, type A inclusions are diagnostically useful, because they are only associated with certain poxviruses (e.g. Cowpox and Ectromelia virus, but not Monkeypox, Variola, or Vaccinia virus). Capripoxviruses generally produce *type A* inclusions; the large inclusions in Avipoxvirus infections are known as Bollinger bodies and they contain smaller Borrel bodies representing virus particles.[12]

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http://www.uni-giessen.de/cms/fbz/fb10/institute_klinikum/institute/pathologie/

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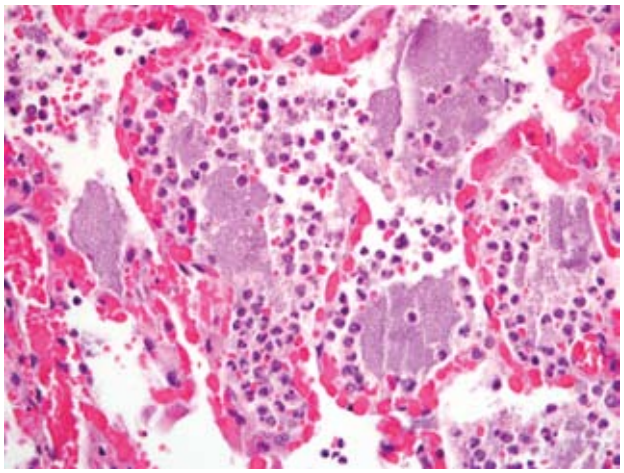
CASE III: 0418271 (AFIP 2991560).

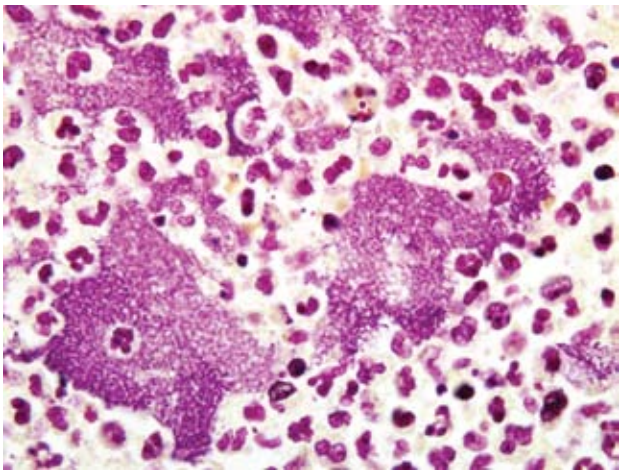
Signalment: 7-year-old, spayed female, domestic shorthair cat (*Felis catus*).

History: This cat was presented with general lethargy and responded initially to anti-inflammatory therapy (Rimadyl) for 24 hours. Marked swelling of the left cervical lymph node and tongue occurred after hospitalization. The animal's condition worsened, with respiratory signs (rales, rapid and open mouth breathing, dyspnea). The animal eventually was unable to stand, and was euthanized.

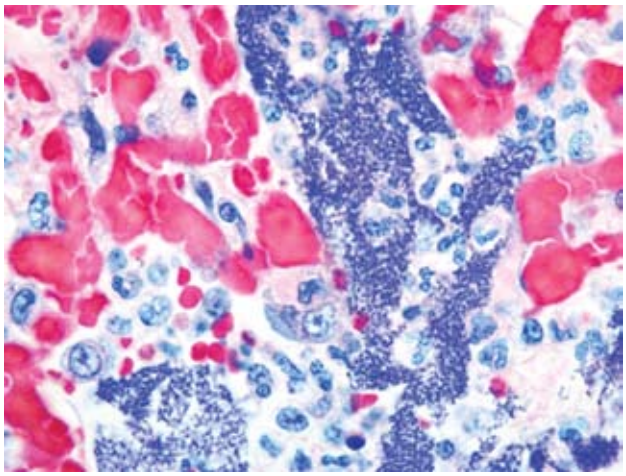
Gross Pathology: This cat had enlarged cervical lymph nodes with a draining lesion of the left cervical



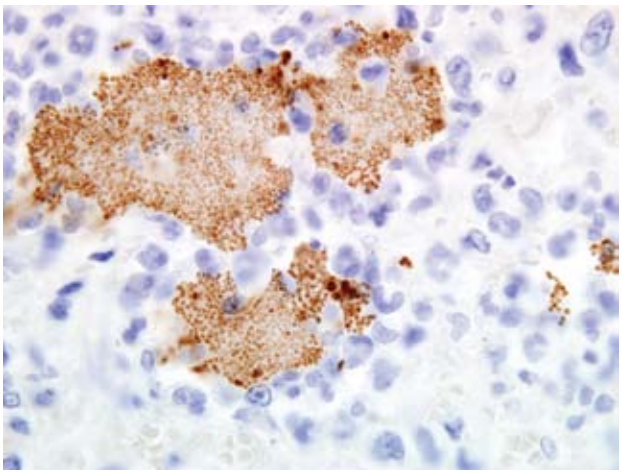
3-1. Lung, cat. Multifocally flooding alveoli are many viable and degenerate neutrophils and fewer alveolar macrophages centered upon large colonies of 1x3um bacilli. (HE 1000X)



3-2. Lung, cat. Intraalveolar organisms are diffusely gram negative. (Brown and Hopps 1000X)



3-3. Lung, cat. Intraalveolar organisms are diffusely Giemsa positive, occasionally exhibiting bipolar staining. (1000X)



3-4. Lung, cat. Intraalveolar organisms have strong immunoreactivity for Yersinia antibody. (1000X)

node. The left tonsil was enlarged, and there was a large area of swelling and reddening under the tongue. A pseudomembrane was over a portion of this area. All lobes of lung were markedly congested, deep reddish-purple, and just barely floated in formalin.

Laboratory Results: Bacteriology: *Yersinia pestis* was isolated from lung. Lung was also positive on FA testing of lung swab smears for *Y. pestis*.

Histopathologic Description: In the lung, there are multifocal to coalescing areas of necrosis that obliterate the normal architecture. In the affected areas, the bronchioles and alveoli are filled with numerous bacteria, intact and degenerate neutrophils, fewer macrophages, fibrin, and edema fluid (**fig. 3-1**). Alveolar macrophages sometimes contain phagocytosed erythrocytes, necrotic cellular debris, and bacteria. The alveolar capillaries are engorged with RBCs and the necrotic foci occasionally contain fibrin thrombi.

Contributor's Morphologic Diagnosis: Lung: Pneumonia, necrotizing, suppurative, acute, multifocal to coalescing, moderate with intralesional bacteria colonies of *Yersinia pestis.*

Contributor's Comment: Plague is a zoonotic infection caused by *Yersinia pestis* affecting rats, mice,

ground squirrels, prairie dogs, kangaroo rats, bobcats, cats, rabbits, and chipmunks. The disease has also been described in ferrets, llamas, camels, mule deer, and goats. In New Mexico, it is occasionally also seen in dogs, although most of the literature cites that dogs are resistant. In our experience, we would modify that statement to "most dogs are resistant". *Yersinia pestis* is a pleomorphic, non-motile, non-spore forming, facultative anaerobe, gram negative, bipolar staining coccobacillus of the family *Enterobacteriaceae* (**figs. 3-2, 3-3 and 3-4**). The organism is now more accurately classified as a subspecies of *Y. pseudotuberculosis* based upon DNA-DNA pairing. It is a disease of antiquity, decimating human populations at various stages in history. Plague continues to be a problem today in many parts of the world, particularly in the western United States. In the Southwest, it is seen primarily in northern New Mexico and northeastern Arizona. In New Mexico, plague is most commonly found at elevations where piñon and juniper trees flourish. The main reservoirs are rock squirrels and prairie dogs, as well as deer mice and kangaroo rats. The principal mode of transmission of *Y. pestis* in mammals is via flea bite. A less common mode of transmission is ingestion of, or exposure to another animal infected with *Y. pestis*. Inhalation of aerosolized bacteria from animal with pneumonic plaque is a rare but effective mode of transmission also.

Cats (and dogs) acquire the disease most commonly following predation on infected rodents and lagomorphs or by bites from the prey's plague-infected fleas. The "season" for plague in New Mexico begins in mid-May, and peaks in August, tailing off in October. However, cases occur at any time with proper conditions. In New Mexico, plague cases increase after unusually wet winter and spring weather; these conditions are conducive to increase in the rodent (and subsequently, flea) population.

The lesions seen in *Y. pestis*-infected animals vary according to the mode of transmission of the organism and susceptibility of the host. The three classic clinical manifestations of *Y. pestis* infection include bubonic, pneumonic and septicemic plague and are seen primarily in susceptible non-rodent species. Cats submitted to our laboratory typically have some type of enlargement of tonsils, cervical lymph nodes, or both. These may or may not present as draining lesions. Exudate produced is typically mucoid, grey, and contains large numbers of bacteria. When the disease has progressed to the lungs, all lobes of both lungs will typically be deep reddish-purple, very congested, and often will sink (or just barely float) in formalin. When presented with a suspect plague case (either clinically or in the laboratory), it is important to take proper precautions with the animal. Intense and immediate flea control is paramount with these cases; in our laboratory, suspect cases are routinely sprayed liberally with an appropriate pyrethrin based insecticide prior to any examination or handling.

Clinically, these animals usually present with some type of oral lesion, salivating, gagging, respiratory difficulty or distress, and lymph node enlargement accompanied by a high temperature. There may be a draining lesion from the cervical lymph node region or tonsils. When diagnosed early, these animals respond readily to appropriate antibiotic therapy. The disease is so common in Santa Fe County in the summer months as to commonly be one of the differentials in ADR (i.e. "ain't doing right") cats. This disease is of importance as a public health risk, and as one of the select agents of bioterrorism.

AFIP Diagnosis: Lung: Pneumonia, necrosuppurative, multifocal to coalescing, severe, with myriad extracellular coccobacilli.

Conference Comment: Pneumonic plague has killed more people than any other bacterial pathogen in recorded history[1], and the contributor appropriately emphasized the importance of 1) having a high index of suspicion for plague based on geographical location and clinical and gross findings, and 2) using appropriate personal protective equipment when handling suspect cases in a clinical or diagnostic setting.

The virulence of *Yersinia* sp. depends on its ability to invade the host and evade host immune responses. This begins in the gut of the infected flea, where *Y. pestis* forms a biofilm that obstructs the gut; the flea then must regurgitate before feeding, and thus infects the host that it bites. Via an elaborate gene complex, the Yop virulon, *Yersinia* spp. form proteins that assemble into a type III secretion system, a hollow tube that projects from the bacterial surface, binds to host cells, and injects the bacterial toxins, known as *Yersinia* outercoat proteins (Yops). YopE, YopH, and YopT interfere with actin polymerization inside the host cell, thus blocking phagocytosis of the bacterium. YopJ inhibits the production of inflammatory cytokines by inhibiting the signaling pathways that are activated by lipopolysaccharide.[9]

While natural *Y. pestis* infections still occur in humans, large outbreaks have been prevented by improved sanitation and prompt, successful antibiotic treatment of patients with the bubonic form of the disease. However, it is now apparent that that *Y. pestis* can acquire multidrug resistance via plasmids that are readily horizontally transmitted, and in 1995, two fatal cases of bubonic plague were caused by multidrug resistant *Y. pestis*. As a result, the threat of *Y.*

pestis emergence as a deadly, multidrug resistant epidemic has prompted renewed interest in vaccination as a best line of defense against resurgent plague.[1]

Because whole cell vaccines are considered potentially unsafe and unreliable, vaccine research has focused on two antigens, F1 and LcrV. The F1 protein is a bacterial surface antigen that aids *Y. pestis* in evading recognition by the innate immune system; it is not essential for virulence, however, and is therefore not considered sufficient as a sole vaccine antigen. The LcrV protein is essential for virulence, and mediates insertion of a translocation pore, assembled via the type III secretion system, in the host cell membrane. Vaccines which combine both LcrV and F1 show promise against bubonic and pneumonic plague in animal models. The Brown Norway rat has emerged as a model for both human bubonic and pneumonic plague.[1]

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CASE IV: 1484/03 (AFIP 2940307).

Signalment: 12 week-old, male castrated pig (*Sus scrofa*), body weight 27 kg.

History: Died after anorexia, depression and weight loss with multiple hemorrhagic and necrotic skin lesions.

Gross Pathology: Irregular, red to purple macules and papules, which tend to coalesce, located mainly on the hind limbs and perineal area; moderately enlarged lymph nodes all over the body; kidneys enlarged, edematous, and pale with petechial cortical hemorrhages.

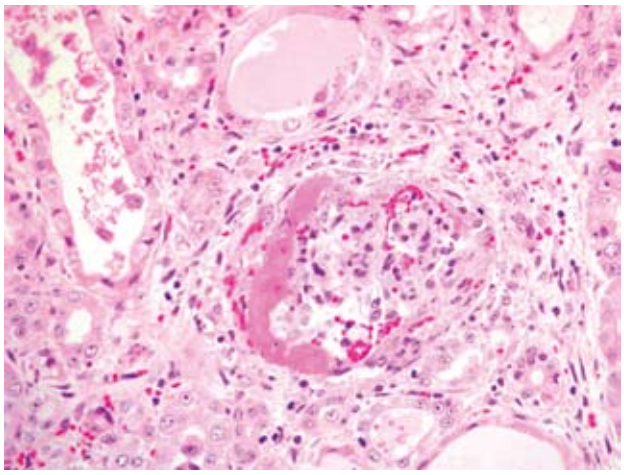
Laboratory Results: Porcine circovirus 2 positive.

Contributor's Morphologic Diagnosis: Severe, diffuse, segmental fibrinous glomerulonephritis with infiltration of neutrophilic leukocytes; sporadic glomerular sclerosis; interstitial nonsuppurative nephritis; proteinaceous casts and necrotizing vasculitis.

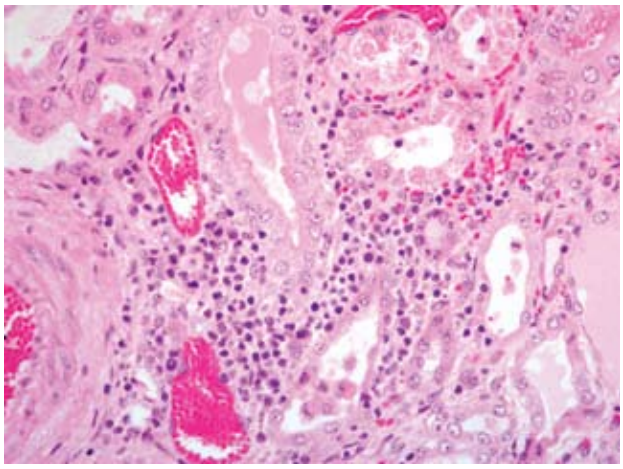
Contributor's Comment: Porcine Dermatitis and Neprhopathy Syndrome (PDNS) mainly affects growing pigs between 12 and 16 weeks of age, and less commonly older animals. The syndrome has been observed in herds of various genetic origin and health status.

The most striking clinical signs of PDNS are necrotizing skin lesions due to necrotizing vasculitis. At necropsy, other frequent findings are enlarged and pale kidneys with cortical petechiae. Microscopically, these renal lesions vary from acute necrotizing glomerulitis to chronic glomerular sclerosis. Besides the skin lesions, systemic necrotizing vasculitis in a variety of organs has been observed.[7] As a possible pathogenetic mechanism for this disease a type III hypersensitivity reaction due to microscopic features has been suggested.[7]

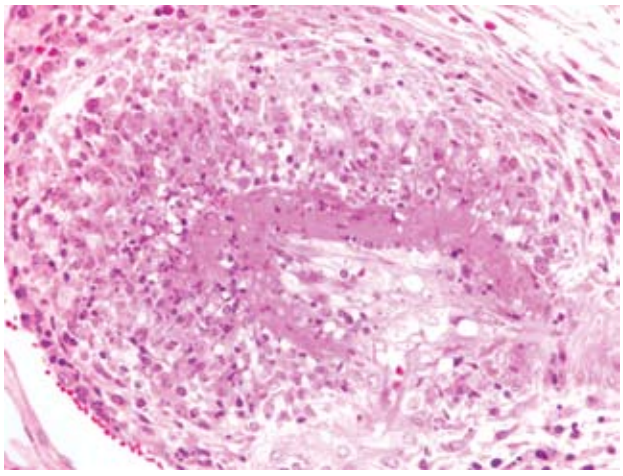
The etiology still remains unknown, but porcine circovirus 2 (PCV2) and porcine reproductive and respiratory syndrome virus (PRRSV) and *Pasteurella multocida* are discussed in the literature as possible contributing etiological agents.[8]



4-1. Kidney, pig. In the cortex, glomeruli are necrotic and expanded by abundant of fibrin, hemorrhage, and occasional macrophages. Multifocally tubules are degenerative or necrotic, and contain pink proteinaceous material and sloughed cellular debris. (HE 400X)



4-2. Kidney, pig. Multifocally the cortical interstitium is moderately expanded by many macrophages, lymphocytes, plasma cells, and edema. (HE 400X)



4-3. Kidney, pig. Within the renal pelvis, there is multifocal necrotizing vasculitis. (HE 400X)

PDNS was first described in the United Kingdom in 1993. Since then, several cases in Europe, North and South America and Africa have been described, suggesting a worldwide distribution.[7] This syndrome sometimes, but not always, occurs in commercial pig farms simultaneously with Postweaning Multisystemic Wasting Syndrome (PMWS). The relationship between the two syndromes is unclear.[7]

Differential diagnosis includes classical swine fever, African swine fever, swine erysipelas, and porcine stress syndrome. Bacterial diseases causing reddish discoloration of skin, petechiae, or cyanosis include infections by Actino*bacillus suis*, *Actinobacillus pleuropneumoniae*, *Streptococcus suis*, *Haemophilus parasuis*, and salmonellosis.

AFIP Diagnosis: 1. Kidney: Glomerulonephritis, exudative and membranoproliferative, diffuse, severe, with multifocal glomerular thrombosis and necrosis.
2. Kidney, arcuate arteries and branches: Arteritis, necrotizing and proliferative, diffuse, moderate to severe.
3. Kidney, pelvis: Epithelial hyperplasia and hypertrophy, diffuse, moderate, with marked cytoplasmic vacuolation.

Conference Comment: In the submitted sections of kidney, all levels of the nephron are affected. Diffusely, glomeruli exhibit one or more of the following changes (**fig. 4-1**): markedly dilated uriniferous space containing abundant fibrin with varying hemorrhage and necrotic debris; increased glomerular tuft cellularity with increased numbers of mesangial cells and thickened capillary basement membranes (membranoproliferative glomerulopathy); glomerular tuft thrombosis and necrosis; hypertrophy and hyperplasia of the parietal epithelium; attachment of the glomerular tuft to Bowman's capsule (synechia); and periglomerular fibrosis. Cortical tubules are ectatic and contain intraluminal hemorrhage, hematoidin, or hyaline casts. Multifocally, tubular epithelium is degenerate, necrotic, regenerative, or attenuated. Throughout the cortical interstitium, there are moderate numbers of histiocytes, lymphocytes, plasma cells, and rare hypertrophied fibroblasts (**fig. 4-2**). Multifocally, arcuate arteries and their branches at the corticomedullary junction are transmurally disrupted by neutrophils, macrophages, lymphocytes, plasma cells, and necrotic debris (**fig. 4-3**). The transitional epithelium

lining the renal pelvis is moderately hyperplastic and hypertrophied, and often contains one or more large, clear, intracytoplasmic vacuoles.

In the United States, the incidence of PCV2-associated disease (PCVAD) is increasing. Clinically, PCVAD is characterized by one or more of the following manifestations: PMWS, PDNS, respiratory disease, enteritis, reproductive disease, myocarditis, vasculitis, and exudative dermatitis.[2,5] The preponderance of evidence suggests that PCV2 is essential, but not sufficient, for PCVAD development. Therefore, PCVAD can best be thought of as multifactorial, with such factors as the virus, host, cofactors, and immune modulation playing important roles in disease pathogenesis.

Circoviridae are small, single-stranded, circular DNA viruses. The Circoviridae family consists of the following genera: Gyrovirus, which contains chicken anemia virus as its sole member; the recently-discovered Anellovirus; and Circovirus. Along with PCV1 and PCV2, the Circovirus genus includes several avian circoviruses: beak and feather disease virus (BFDV), canary circovirus, goose circovirus, pigeon circovirus, duck circovirus, finch circovirus, and gull circovirus.[5,6] PCV1, which was initially discovered in tissue culture, is distributed worldwide and is nonpathogenic. PCV2 is very stable in the environment and has been found in wild boar in Germany and Spain, suggesting that they may be a reservoir.[6] PCV2 persists in dendritic cells, which are thought to serve as a vehicle for transport throughout the host.[5]

This case was submitted in 2004, and while there has been much work in the interim to further elucidate the cause and pathogenesis of PDNS, the role of PCV2 in the disease remains enigmatic and controversial. Numerous other etiologies, including PRRSV and a variety of bacteria have been proposed.[5] In one study, a high anti-PCV2 antibody titer was significantly associated with the development of PDNS, and PCV2 DNA was present in all PDNS cases; PPV and PRRSV nucleic acids were absent in many of the cases.[10] However, PDNS has not been experimentally reproduced in using PCV2, and PCV2 proteins are not detected in the vascular and glomerular lesions of PDNS.[4]

In a recent study, inoculation of gnotobiotic 2- and 3-day-old pigs with either of the following produced PDNS: 1) pooled plasma from healthy feeder pigs in a herd that was in the initial phases of a respiratory disease outbreak, and 2) a combination of PRRSV and tissue homogenate containing genogroup 1 torque teno virus (g1-TTV). All pigs seroconverted to PRRSV and were PCR-negative for PCV2; this was the first report of experimental induction of PDNS renal and cutaneous lesions in swine, and the authors concluded that PDNS is a manifestation of disseminated intravascular coagulation.[4] Interestingly, g1-TTV was also shown to potentiate PMWS in gnotobiotic pigs when inoculated together with PCV2. Disease was not produced by g1-TTV or PCV2 alone, or when PCV2-infected pigs were later challenged with g1-TTV.[3]

In addition to those listed by the contributor, other diseases that may mimic the skin lesions of PDNS include exudative epidermitis and swine pox. For the described gross renal lesions, i.e. "turkey egg kidney", the differential diagnosis includes salmonellosis, African swine fever, and classical swine fever.[2] The cause and significance of the marked vacuolation of the epithelium lining the renal pelvis in this case is unclear.

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