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

CONFERENCE 13
8 January 2003

Conference Moderator: LTC Mark Mense, DVM, PhD, Diplomate ACVP, ABT
Chief, Research and Education Division
Armed Forces Institute of Pathology
Washington, DC 20306-6000

CASE I – N01-279 (AFIP 2839959)

Signalment: Six-month-old, 500 lb., Beefmaster cow

History: This cow was one of two animals presented for necropsy examination. The animal showed neurological signs, would not eat or drink and became progressively dehydrated prior to death. Both had severe diarrhea of two days duration. They were from a group of five animals, three of which were found dead. The owner believed that recently purchased pelleted feed was responsible for the deaths.

Gross Pathology: At necropsy, the carcass was found to be in good condition. Examination of external orifices revealed pale oral mucous membranes, marked congestion of conjunctiva and nasal mucosa, and watery greenish feces around the anus. Approximately 5 –10 liters of serosanquinous fluid was present in the abdominal cavity. The abomasum was devoid of ingesta and contained blood-tinged mucus. The mucosa was markedly congested and showed areas of hemorrhage and edema. The upper 1/3 of the jejunum was markedly congested and edematous. Pale grey streaks were present in the renal cortex of both kidneys. The liver was enlarged and bulged slightly on the cut surface. Subepicardial and subendocardial petechia to ecchymoses were present in the heart. No other significant gross findings were observed. Similar lesions were found in the second animal presented for necropsy. Affected tissues of both animals were taken for histopathological examination and samples of rumen content, kidney and liver were submitted for toxicological examination.

Laboratory Results: Samples of liver, kidney and rumen contents from both animals were found to be positive for arsenic at levels of 14 and 18 ppm, 18 and 19 ppm, and 480 and 520 ppm, respectively.

Contributor's Morphologic Diagnosis: Toxic tubular necrosis, segmental, acute, severe, kidney, bovine, due to arsenic poisoning.

Contributor's Comment: Microscopic examination of the kidney revealed severe necrosis of the proximal straight tubules primarily of the outer stripe of the outer medulla. This localization appears to be related to metabolism of various metals. Some sections may contain clusters of rod shaped bacilli (postmortem). Centrilobular necrosis of the liver as well as severe gastroenteritis was observed.

An extensive examination of the pasture and other areas in which the cattle had access revealed an ash pile in which fence posts had been burned. The owner later admitted that he had observed cattle eating the ash but thought nothing of it. Samples of fence posts, burn pile ash, and soil at the bottom of burn pile were submitted for heavy metal analysis and found to be positive for arsenic levels at 16,000 ppm, 35,000 ppm and 60,000 ppm, respectively. Samples of pond water and feed samples were negative for arsenic.

Chromated-copper-arsenate is widely used as a wood preservative to prevent insect infestation. Fencing posts are often burned on farm premises, thus concentrating the pesticide in the ash. Burning copper-chrome-arsenate (an arsenic pentoxide) reduces it to the more toxic trivalent form. Because arsenic is a carcinogen, the Environmental Protection Agency has ordered a phase out of the production of chromated-copper-arsenate treated wood in decks, playgrounds structures and fences.

AFIP Diagnosis: Kidney, proximal tubules: Necrosis, segmental and medullary, acute, diffuse, moderate to severe, with granular casts, Beefmaster, bovine.

Conference Comment: Arsenic is the second most common heavy metal poisoning in domestic animals after lead. Toxicity is variable, dependent on formulation, species, amount, route, and length of exposure. Animals are usually exposed via ingestion; however, it may be absorbed percutaneously or inhaled. Arsenic occurs in organic and inorganic formulations. Arsenate is the natural, inorganic, pentavalent form, while commercial preparations of inorganic arsenite is trivalent. Arsenite's primary mechanism of action is to bind to sulfhydryl groups, which inhibits pyruvate dehydrogenase and alpha-ketoglutarate enzymes necessary for cellular metabolism. Additionally, arsenite inhibits sulfur containing amino acids, resulting in hepatic fatty infiltration. Arsenate's mechanism of action is to substitute for phosphorus in the glycolytic pathway, uncoupling oxidative phosphorylation. Clinically, in peracute cases, animals may present as a sudden death, or in acute or subacute cases, with diarrhea that is often hemorrhagic, anorexia, dehydration, weakness, colic and agalactia. Grossly, there is gastrointestinal hemorrhage, erosions, and edema. Histopathologic exam reveals multifocal hepatic and renal necrosis. Diagnosis of arsenic toxicosis is based on the history of potential exposure, clinical signs, gross and histologic lesions, and detection of the toxic levels in tissues (including kidney and liver) or rumen contents. Normal arsenic levels should be less than 0.5 ppm. Retrospective diagnosis of toxicity is made through analysis of arsenic in hair, where it is persistent.

Contributor: Tuskegee University, College of Veterinary Medicine, Nursing and Allied Health, Department of Pathobiology, Tuskegee, AL 63088

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CASE II - 02041617 (AFIP 2841648)

Signalment: Tissues from an 18-month-old, intact female Holstein bovine weighing approximately 409 kg were presented for histological evaluation.

History: Two Holstein heifers were found dead on the morning of April 19, 2002 with no signs of struggle or bloat. A herd-check the night before revealed no premonitory clinical signs. Heifers were grazing in a grassy paddock that was watered by a creek. Inspection of the pasture revealed cocklebur growing along side the creek. Heifers have been grazed in this lot prior to the deaths of the two reported without any problems.

Gross Pathology: A field necropsy was performed. The liver was reported to be swollen and pale. No other gross lesions were observed.

Laboratory Results: Results not provided.

Contributor's Morphologic Diagnoses: 1. Liver, centrilobular coagulative necrosis, diffuse, severe, acute, Holstein-Freisian, bovine.
2. Heart, subepicardial and myocardial hemorrhage, multifocal, moderate, acute, Holstein-Freisian, bovine.

Contributor's Comment: Cocklebur (*Xanthium spp.*) has a worldwide distribution. This herbaceous annual grows best along side pond and river/creek banks. Toxicosis from this plant has been reported in sheep, cattle, swine, and poultry. The poisonous

agent in cockleburs (carboxyatractyloside) is found in highest concentration in the seeds; however, poisonings most commonly occur when the cotyledonary stage is consumed. Carboxyatractyloside's mechanism of action is to inhibit oxidative phosphorylation and binding of adenine nucleotides across mitochondrial membranes.

Clinical signs associated with cocklebur toxicosis include nausea, ataxia, weakness, prostration, depression, dyspnea, hypothermia, opisthotonos, blindness, hypersensitivity, spasmodic contraction of limbs and neck, convulsions, and acute death.

Gross lesions reported with cocklebur toxicosis include gastrointestinal, hepatic and renal congestion, hepatic centrilobular accentuation, and ascites.

In this case, the typical histological lesion of *Xanthium* spp. (diffuse, centrilobular coagulative necrosis) was present. Additionally, multifocal hemorrhages were observed microscopically in the sections of heart examined. These lesions, in addition to the clinical history and presence of *Xanthium spp.* on the premise support a diagnosis of Cocklebur toxicosis.

Differentials for acute centrilobular hepatic necrosis in this case include toxic plants such as *Cestrum parqui*, *Helichrysum blandowskianum*, and *Trema aspera*. Algae blooms on water sources include *Microcystis aeruginosa* and blue-green algae. Poisoning from these plants result in acute death and periacinar to massive distribution of necrosis. Infectious diseases in cattle that would cause severe, centrilobular necrosis include Rift Valley fever.

AFIP Diagnosis: Liver: Necrosis, centrilobular to midzonal, diffuse, with congestion and hemorrhage, Holstein, bovine.

Conference Comment: Pattern recognition is important in cases of zonal hepatic necrosis. Centrilobular (periacinar) necrosis is more common than midzonal or periportal. Centrilobular hepatocytes are more vulnerable to toxic insult because these cells are most distant from sources of oxygenated blood and contain the highest concentrations of mixed-function oxidases that transform exogenous compounds into toxic metabolites. An example is the conversion by p450, of the hepatic smooth endoplasmic reticulum, of carbon tetrachloride to $CCl_3^{\cdot}$, the toxic free radical metabolite. Alternatively, massive hepatic necrosis refers to necrosis of an entire hepatic lobule (acinus) including hepatocytes of the periportal limiting plate. An example is hepatosis dietetica of swine.

Contributor: Department of Veterinary Pathobiology, College of Veterinary Medicine, Oklahoma State University, Stillwater, OK 74078

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CASE III – UFSM 1 (AFIP 2841064)

Signalment: 5-year-old, female, Holstein, bovine (*Bos taurus*)

History: Fifty adult Holstein cows were set on a pasture consisting of approximately 70% of *Vicia villosa*, 20% of *V. sativa* and 10% of oat + rye grass, since June 2001 (beginning of winter). In August-September of the same year (late winter-early spring) five cows became ill, four of which died spontaneously after a 2-week clinical course and another one was euthanatized. Clinical signs in these five cows included dramatic drop in milk yield (80% in the case of the cow of this report), fever (40°-41°C), pruritus, diarrhea, loss of weight, serous nasal and ocular discharges, and multifocal areas of alopecia. Skin lesions affected both pigmented and non-pigmented areas and usually involved the head, neck, trunk, tail base escutcheon and udder; they started as multiple small areas (10 mm in diameter) of exudation and matting of the overlying hair which progressed to irregular areas and confluent areas of alopecia with thickening and wrinkling of the skin.

Gross Pathology: The necropsy findings described herein belong to the cow of this report but are closely similar to the changes found in the other four affected cows. Besides the skin lesions already described with the clinical signs there were multifocal to coalescing, soft to slightly firm gray to gray-yellow nodules which infiltrated multiple organs but were particularly prominent in the myocardium, lymph nodes, spleen, adrenal glands and renal cortex. These lesions resulted in enlargement and disruption of normal architecture of most of the affected organs.

Laboratory Results: Hemogram performed one week prior to death revealed mild leukocytosis due to monocytosis (12,800 leukocytes/mm^3 of blood being 11% monocytes, i.e., 1,408/mm^3). Both the red blood cell and platelet counts were within normal limits.

Contributor's Morphologic Diagnosis: Myocardium, granulomatous and eosinophilic myocarditis, multifocal to coalescing, with multinucleated giant cells, with cardiomyocyte degeneration and loss, chronic, severe.

Etiologic diagnosis: Toxic myocarditis.
Etiology: *Vicia villosa* (hairy vetch) poisoning.

Contributor's Comment: Granulomatous inflammation similar to the one observed in the myocardium represented in the glass slides submitted were found in the kidneys, adrenal glands, lymph nodes, spleen, periportal areas of the liver, mammary gland, thyroid gland, ovaries, uterus, lungs and in leptomeninges and perivascular spaces of the encephalon in the cow of this report. Microscopically, this polysystemic granulomatous inflammation consisted of variable proportions of epithelioid macrophages, lymphocytes, plasma cells, multinucleated giant cells and large numbers of eosinophils. The inflammatory infiltrate caused degeneration and loss of parenchymal cells of affected organs. Microscopically, the skin lesions consisted of mild to moderate orthokeratotic hyperkeratosis, mild mononuclear and eosinophilic perivascular and periadnexal cellular infiltrates and dilatation of the ducts of apocrine glands.

Poisoning by the ingestion of the legume *Vicia* spp. has been reported in domestic mammals and human beings. The seeds and vegetative portion of several *Vicia* spp. have been reported to contain cyanogenic glycosides as well as substances that induce toxic hepatitis and photosensitization. In Mediterranean people with inherited deficiency of glucose 6-phosphate dehydrogenase the ingestion of the beans or aspiration of the pollen of *V. faba* may induce acute hemolytic anemia.

In cattle, the ingestion of *Vicia* species has been associated with three clinical manifestations. There is one clinical form associated with acute neurological signs compatible with the cyanogenic glycosides poisoning mentioned above. The second form has a fatal outcome after 12 to 15 days of clinical signs that include subcutaneous swellings of the head, neck and body and herpetiform eruptions in the oral mucous membranes, purulent nasal discharge, rales, cough, congestion and cyanosis of mucous membranes, alopecia, weakness and loss of appetite.

The third form of *V. villosa* (and to a lesser extent other *Vicia* species) poisoning in cattle is the best studied and documented of the three forms and is known in the United States since 1955. This form is characterized by dermatitis (with alopecia) and systemic granulomatous inflammation (SGI). The vetch-associated SGI is the one represented by the cow of this report. Most outbreaks of vetch-associated SGI occur in Holstein and Aberdeen cattle consuming *V. villosa* (hairy vetch) athough a few cases have been reported in Limousine, Murray Grey, Guernsey and Hereford breeds of cattle in association with the ingestion of hairy vetch or other *Vicia* species, such as *V. benghalensis*; a hybrid *V. villosa* x *V. dasycarpa*; and *V. villosa* subsp. *dasycarpa*. Outside of the USA, the vetch-associated SGI has been described in cattle from South Africa, Australia, Argentina and Brazil. A similar disease has been reported in horses from Pennsylvania and California associated with the ingestion of *V. villosa* and *V. benghalensis* respectively.

Outbreaks of the vetch-associated SGI occur more frequently during the season of maximal vetch growth but sporadic cases can be seen throughout the year. Vetch-associated SGI is more prevalent and severe in cattle $\geq$ 3 years old. There is no sex predilection. On reviewing all the various reports of this disease in cattle, one finds

morbidity rates from 1 to 68% (but in most outbreaks is around 10%) and lethality rates from 20% to 100%.

Main clinical signs of vetch-associated SGI include dermatitis, pruritus, diarrhea, dehydration, weight loss, drop of milk yield, cough, dyspnea and conjunctivitis. The body temperature may be normal or markedly elevated. The interval between the appearance of clinical signs and death ranges from 3 days to 5 weeks, but is usually two weeks. The salient and basic lesion of the disease is a polysystemic, multifocal, confluent, granulomatous inflammation similar to the one described in the myocardium and in the various other organs of the cow of this report.

Although the compelling circumstantial evidence implicates the ingestion of *Vicia* spp. in the etiology of this disease, the experimental reproduction was achieved only once in a 7-year-old 432 kg Angus cow that had recovered from the natural disease one year earlier. This cow consumed 100 kg of hairy vetch before presenting with clinical signs of the toxicosis. The toxic principle of *Vicia* spp. is yet unknown. Based on the inflammatory morphological features of vetch-associated SGI, a type IV hypersensitivity reaction was proposed as part of the pathogenesis of the disease: constituents of the plant would be absorbed and act as antigens that sensitize lymphocytes and evoke the SGI that characterizes the disease; or a vetch lectin may directly activate T lymphocytes to initiate the cellular response. The fact that the vetch-associated SGI was reproduced in a cow that had recovered from the disease is claimed as further evidence to the hypersensitivity theory. A genetic predisposition is also suggested because vetch-associated SGI occurs mainly in Holstein and Angus cattle.

It is interesting to note that clinically and pathologically very similar (if not identical) diseases have been observed in cattle that have not had access to vetch. These diseases have been referred to as "vetch-like diseases." These include citrus pulp toxicosis that has been reported in England, Brazil and the United States in cattle (mainly dairy cattle); a syndrome referred to as “pyrexia with dermatitis” reported several times in Britain; and a disease reported in the Netherlands associated with the consumption of ration containing diureido-isobutane (DUIB). This latter syndrome was actually reproduced in cattle by feeding ration containing DUIB. Citrus pulp toxicosis was once thought of being caused by citrinin present in the citrus pulp. Experiments performed in our laboratory failed to confirm that either citrinin or another known mycotoxin is the cause of citrus pulp toxicosis. To the contrary, our results seem to rule out this hypothesis. Cases of "pyrexia with dermatitis” reported from Wales in 1978 associated the disease to the consumption of silage preserved with Sylade (a commercial silage additive consisting of a combination of formalin and sulphuric acid). Although some reports have incriminated infectious organisms (e.g. *Sporothrix schenkii*) in some of these vetch-like diseases, this was never properly confirmed and, in fact, the vast of majority of reports on vetch-like diseases and all of the reports on vetch-associated SGI rule out the participation of an infectious agent in the etiology.

In the cow of this report, although the myocardial lesion was severe, no observable signs of heart failure (e.g. dependant edema, nutmeg liver) was noted; neither detectable neurological clinical signs were present although the granulomatous reaction was present also in the brain.

AFIP Diagnoses: 1. Heart: Myocarditis, granulomatous and eosinophilic, multifocal to coalescing, severe, with myocardial degeneration and necrosis, Holstein, bovine.
2. Heart: Protozoal cysts, few, etiology consistent with *Sarcocystis* sp.

Conference Comment: The contributor has provided a complete summary of hairy vetch toxicosis.

Contributor: Departamento de Patologia, Universidade Federal de Santa Maria, 97105-900, Santa Maria, RS, Brazil

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CASE IV - 011634-3 (AFIP 2840707)

Signalment: 15-year-old, spayed female, pointer, *Canis familiaris*, dog.

History: A digital melanoma was removed in 1995. No metastasis or cardiac disturbances were detected. The dog received seven injections of adriblastin, during 5 months. Since 1999, the dog presented with ventricular extrasystole, irregular cardiac rhythm, sinus tachycardia with right branch block and was out of breath when exercising. It was treated with digoxine. Recently, incontinence and arthrosis led to euthanasia.

Gross Pathology: There were abdominal (500 ml) and pericardic (200 ml) passive effusions. A chronic stasis of the liver was noted (hepatomegaly, fibrin covering lobe surfaces). Chronic stasis and edema of the lungs were observed. The heart presented with cardiomegaly and several, focal, well delineated, depressions in the myocardium (essentially in the right ventricle). There was no macroscopic metastasis of the malignant melanoma.

Laboratory Results: Not applicable.

Contributor's Morphologic Diagnosis: Heart: Myocarditis, multifocal to coalescent, necrotizing, non suppurative, chronic, mild to severe.

Contributor's Comment: The foci (1 to 4 mm in diameter) tend to be coalescent. Their center is composed of a mild lymphoplasmocytic infiltrate with a few activated macrophages and a conjunctivo-vascular tissue (due to post-necrotic fibrosis). Around these foci, there are hypereosinophilic myocardial fibers with pyknotic or lytic nuclei (coagulation necrosis). A lymphoplasmocytic infiltrate is also noted between the necrotic myocardial cells. The lesions were attributed to the cardiotoxicity of adriblastin.

Adriblastin and other anthracyclin antiobiotics are widely used antineoplastic agents in human and veterinary clinical practice. In veterinary oncology, the drug is used to treat animals with various soft tissue sarcomas, thyroid carcinomas and lymphoproliferative disorders. However, a consistent undesirable side effect of long-term administration of this compound is the development of delayed and progressive cardiotoxicosis. The risk of cardiomyopathy is higher when animals receive cumulative doses higher than 240 mg/m^2 (dogs) and higher than about 300 mg/m^2 (cats). In humans, usually doses higher than 400 to 550 mg/m^2 must be administered to produce cardiotoxicity. Dogs and cats are much more sensitive to the cardiotoxic effects.

Cardiotoxicity of adriblastin is manifested as arrhythmia, myocardial failure, or both. Cardiotoxicity is cumulative, dose dependant and irreversible. A cardiac dilatation is often noted and, less frequently, mural thrombosis. Lesions are primarily vacuolar degeneration of myocytes ("adria cells"). Ultrastructurally, these vacuoles are caused by distension of the sarcoplasmic reticulum. Myocytolysis, myofibril atrophy and varying degrees of interstitial edema and fibrosis can also be noted.

The major mechanism of action of anthracyclin against tumor cells is thought to involve the ability of these drugs to intercalate between strands of DNA double helix. This results in blocking DNA, RNA and protein synthesis. The pathogenesis of anthracyclin induced myocardial damage is controversial, but is probably not related to the drug's antitumor effects. The most likely hypothesis is a direct alteration of the function of cardiac cell membranes by the drug or drug induced free radical myocardial damage. Anthracyclin could cause changes in membrane electrolyte flux, potentially resulting in diminished myocardial contractility. Anthracyclin could also be metabolized into free radicals, superoxides and hydrogen peroxides, all of which cause damage to lipid membranes.

AFIP Diagnoses: 1. Heart: Myocarditis, necrotizing, subacute, multifocal to coalescing, moderate.
2. Heart, small arteries: Amyloid, intramural, multifocal, mild.

Conference Comment: Conference participants considered numerous causes of canine myocardial necrosis in their differential diagnosis, including nutritional deficiencies, chemical and plant toxicities, central nervous system injuries, metabolic disorders, and ischemia. Myocardial necrosis in puppies can be caused by canine morbillivirus (primarily degenerative changes), canine herpesvirus and canine parvovirus (also has inflammatory cell component) and vitamin E-selenium deficiency. Furthermore, ingestion of thallium-containing rodenticides or sodium fluoroacetate (compound 1080) by dogs may result in myocardial necrosis. The mechanism of action of fluoroacetate involves conversion to fluoroacetyl-coenzyme A, which when combined with oxaloacetic acid, forms fluorocitrate. The citric acid cycle is inhibited by

fluorocitrate, resulting in the formation of inadequate amounts of adenosine triphosphate.

In some sections, the walls of a few small coronary arteries are partially obscured by an eosinophilic homogenous material that was verified as amyloid through Congo red staining at the AFIP.

Contributor: Ecole Nationale Vétérinaire d'Alfort, Service d'Anatomie Pathologique, 7, avenue du Général de Gaulle, 94704 Maisons-Alfort cedex, France

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Kathleen A. Ryan, DVM
Major, Veterinary Corps, U.S. Army
Wednesday Slide Conference Coordinator
Department of Veterinary Pathology
Armed Forces Institute of Pathology
Registry of Veterinary Pathology*

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