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Department of Veterinary Pathology
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CASE I – 02-12465 (AFIP 2886652)

Signalment: Adult, pigeon (free-ranging), female.

History: Animal control wardens reported a "dramatic" increase in the number of dead pigeons in an Illinois city (population 81,860). In addition to collecting dead birds, the wardens also collected several birds that were mentally dull and unable to fly. Pigeons appeared to be the only avian species affected.

Two dead pigeons and 1 live pigeon were submitted to the Veterinary Diagnostic Laboratory for necropsy examination.

Gross Pathology: One bird was in poor body condition, with moderate skeletal muscle atrophy and no visible body fat reserves. The crop was markedly distended (10 x 10 cm), thin-walled, and filled with a large number of corn kernels. There was a focal perforation of the crop associated with necrotizing ingluvitis and surrounding cellulitis.

Laboratory Results:
Aerobic culture of heart blood - no growth

Gastric (ventriculus) contents, liver, and kidney - drugs, organic compounds, and pesticides were not detected by Toxilab

Kidney - 381 ppm lead

Liver - 14.4 ppm lead

Contributor's Morphologic Diagnosis: Kidney, proximal renal tubular epithelium: Myriad acid-fast intranuclear inclusion bodies consistent with lead toxicosis.

Contributor's Comment: Lead toxicosis is not uncommon in avian species, particularly in migratory waterfowl in the United States. In metropolitan areas, pigeons have been used to monitor environmental exposure to lead contamination. Both chronic and acute effects of lead ingestion have been evaluated in pigeons. In chronic, dose-controlled studies using lead acetate, it has been shown that a dose of 6.25 mg/kg resulted in only marginal behavioral effects and a dose of 12.5 mg/kg resulted in moderate to marked behavioral effects without producing either ataxia or gross lesions of lead toxicosis[1]. However, a dose of 25 mg/kg had pronounced effects on behavior and produced gross lesions of toxicity[1]. Acute lead poisoning has also been experimentally produced in pigeons by a single intra-peritoneal (IP) administration of lead acetate[3]. The primary signs of acute toxicosis following IP dosing included weight loss, anemia, and death. Interestingly, the per os (PO) administration of lead acetate has been shown to induce crop dysfunction (stasis, dilatation, feed impaction, and regurgitation of crop contents) and lead-induced ataxia[2]. The exact mechanism of the crop dysfunction is not fully known, although possible explanations include an indirect effect on crop activity following a primary action on the cerebellum or semicircular canals of the inner ears. Since the intramuscular injection (breast muscle) of lead also induces crop stasis, it does not appear to require direct, local contact with the crop.

In the present case, the pigeon presented in poor body condition with a markedly dilated crop. Since the bird died prior to presentation, it is unknown if neurologic deficits were also present. Aside from ingluvitis and cellulitis associated with crop rupture, the histologic changes in this case were restricted to the kidney and consisted of numerous acid-fast, intranuclear inclusion bodies in the proximal renal tubular epithelium. Based on studies in mourning doves, the presence of intranuclear inclusion bodies suggests that the bird was exposed to lead at least 4 or 5 days previously. In mourning doves which were experimentally dosed PO with lead shot, the renal epithelial inclusion bodies were primarily intracytoplasmic at day 4 post-exposure, while they were primarily intranuclear at day 9 post-exposure[4]. It was suggested that the presence of intracytoplasmic inclusions may represent the early cytoplasmic transport of lead, before final deposition in the nucleus, and may be an indicator of duration of exposure.

Lead toxicosis was confirmed by the toxicologic analysis of the kidney (381 ppm Pb) and liver (14.4 ppm Pb).

AFIP Diagnosis: Kidney, tubular epithelium: Degeneration, multifocal, minimal, with numerous intranuclear inclusion bodies, pigeon, avian.

Conference Comment: Anemia is a consistent clinicopathologic finding in animals with lead intoxication. Lead inhibits the enzymes delta-aminolevulinic acid synthetase and ferrochelatase that are involved in hemoglobin synthesis. The inability to synthesize hemoglobin results in anemia. In addition, inhibition of nucleotidase causes increased fragility of red blood cells that also contributes to the anemia. Basophilic stippling is a

morphologic change in erythrocytes characterized by aggregation of residual RNA. When basophilic stippling is accompanied by metarubricytosis with minimal polychromasia, indicating an inappropriate response, lead toxicosis is a likely cause.[5,6]

Grossly, a "lead line" may been seen as a blue discoloration in the gingiva adjacent to the teeth as a result of precipitation of lead sulfide. This change, however, is more frequently observed in humans and nonhuman primates. Radiographically, a linear metaphyseal density (lead line) may be present in young animals as a result of impaired osteoclast resorptive activity causing a band of mineralized cartilage.[6]

Ultrastructurally, lead inclusions have a discrete electron dense central core surrounded by an outer zone of fibrillar structures[6], giving its borders an indistinct, hazy appearance.

Contributor: University of Illinois at Urbana-Champaign, Veterinary Diagnostic Laboratory & Department of Veterinary Pathobiology

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CASE II - 024-03-1 (AFIP 2888659)

Signalment: Pastured adult, female, Gelbvieh bovine.

History: On March 23, three Gelbvieh cows were discovered dead in their pasture at the morning feeding. Of the remaining 51 cattle, only a handful ran up to the feed truck in their usual manner. Clinical signs in affected cows included ataxia, “star-gazing”, lassitude, recumbency and brief, agonal convulsions. Gross post-mortem examination by the referring veterinarian did not reveal any remarkable abnormalities beyond a few

thistle-like seed heads in the rumen. Six animals were treated empirically with activated charcoal and mineral oil to no effect. By the following morning, another 6 cattle were dead. By the end of two weeks, a total of 42 died.

Gross Pathology: A second, recumbent, cow was admitted to the CSU College of Veterinary Medicine Teaching Hospital and died a few hours later. Lesions included subcutaneous edema and hemorrhage and a pronounced lobular pattern in the liver.

Laboratory Results: Tissues submitted to the Wyoming State Veterinary Laboratory (WSVL) were initially analyzed with normal results for cholinesterase, nitrate and toxic metals (As, Ba, Cd, Co, Cr, Cu, Fe, Hg, Mn, Mo, Ni, Pb, Se, Tl, V and Zn). Rumen pH was 7.0 and aqueous humor cations (Ca, Mg) were within normal limits. Brain sodium was elevated (2396 ppm, normal <1600) but aqueous humor was not. A serum chemistry panel revealed moderately elevated alanine aminotransferase and markedly elevated lactate dehydrogenase. A complete blood count revealed neutrophilia with a left shift and serum chemistry demonstrated severe hypoglycemia, hyperbilirubinemia, hypernatremia, hypokalemia, elevated creatine kinase, aspartate aminotransferase and gamma-glutamyl transferase, and decreased sorbitol dehydrogenase activity.

The kidney was analyzed for aflatoxin with negative results. Samples of the hay being fed were extracted with MeOH or water and bioassayed in mice, also with negative results. Post mortem samples and hay were submitted for mycotoxin analysis, herbicide screens, ethylene dibromide, dibromochloropropane, volatile and halogenated hydrocarbons, alkaloids, phenols and PCB's with negative results.

Liver and rumen from the index case were found to contain approximately 15 ppb microcystin by ELISA, a result later confirmed by mass spectrometry.

Contributor's Morphologic Diagnosis: Liver: necrosis, severe, diffuse acute periacinar to massive with vacuolar degeneration, Gelbvieh, bovine.

Etiologic Diagnosis: Toxic hepatic necrosis

Etiology: Microcystin

Contributor's Comment: Liver lesions from tissues examined at CSU and WVSL are similar. Section of liver with multifocal to massive hepatocyte loss with severe disruption of hepatic cords, primarily centrilobular and paracentral often with extension to the limiting plate of the portal areas. The hepatocyte necrosis is coagulative to lytic and individualization of hepatocytes is a notable feature. Nuclei are often swollen and there is margination of chromatin, with karyorrhexis and pyknosis found. Additionally, there is rarefaction of hepatocyte cytoplasm with increased vacuolization and cell swelling. No mitotic figures are identified nor evidence of reactive change. There is flooding of the sinusoids with blood. There is a mild accumulation of lymphocytes and plasma cells in the portal areas, with an occasional neutrophil identified. Large rod-

shaped bacteria, sometimes in chains, are encountered particularly within the portal areas and also within the expanded sinusoids (post-mortem putrefaction).

Cyanobacteria or blue-green algae constitute a large group of prokaryotic organisms characterized by the presence of chlorophyll a[14]. A variety of cyanobacterial species are capable of producing substances toxic to vertebrates. These substances are referred to as cyanotoxins and can be classified broadly into 3 structural groups: cyclic peptides (microcystins, nodularins) that target hepatic function; alkaloids (anatoxins, saxitoxins) that target the nervous system; and lipopolysaccharides that are potential irritants and are produced by all cyanobacterial species[14].

Microcystins are naturally occurring protein phosphatase inhibitors and potent hepatotoxins[6] with microcystin-LR being the most commonly occurring and at the same time most toxic congener[15], defined as having the highest capacity for protein phosphatase-1 and -2A inhibition[11]. Microcystin-LR is produced by the cyanobacteria *Microcystis aeruginosa*[7]. Globally it appears that blooms of microcystin-containing hepatotoxic species are a greater threat to health than the other groups and have been responsible for numerous incidents of acute animal poisoning episodes[10,12]. There are more than 60 different structural variants of microcystin identified with LD50's ranging from 50-800 ug/kg. Microcystins have also been associated with human toxicity resulting in acute sickness and death in dialysis patients in Brazil[10]. Moreover, it has also been suggested that microcystins play a role in the high incidence of hepatocellular carcinoma present in China[12]. Supporting this theory is laboratory data that incriminates microcystin-LR as an initiator in the promotion of liver tumor formation, hepatic neoplastic nodules and preneoplastic tumor growth[16].

The toxicity of microcystin-LR in mammals is characterized by fulminant intrahepatic hemorrhage, followed by hypovolemic shock[1], secondary to massive hepatocellular necrosis and collapse of hepatic parenchyma, and death[8,2,3,4]. Microcystin-LR is hydrophilic and does not readily cross lipid membranes[9]. Microcystins reabsorbed from the GI tract are taken up from the blood via a multispecific, rifampicin-sensitive, energy-dependent bile acid transport system of hepatocytes[7,12]. Rounding of hepatocytes occurs concurrently with the loss of normal hepatic architecture and is considered to result from the cytosolic interaction of microcystin-LR with serine/threonine phosphatases-1 and -2A[4,5], which are essential for maintaining the monomerization/polymerization equilibrium of cytoskeletal intermediate filaments. Through microcystin-mediated inactivation of these protein phosphatases, this equilibrium is shifted towards monomerization with resultant dissociation of the hepatocyte cytoskeleton[4]. Laboratory data have shown that within 10 minutes post-exposure to microcystin-LR a mild widening of centrilobular hepatocyte intercellular spaces can be identified[8]. Within minutes, plasma membrane invaginations occur with formation of intracytoplasmic vacuoles, loss of microvilli along the sinusoidal face, and widespread pronounced hepatocyte separation. This is followed by a marked widening of the space of Disse and of the centrilobular areas containing necrotic cells and apparently intact, isolated organelles intermingled with erythrocytes and platelets[8].

In the past, microcystin diagnosis was sufficiently cumbersome that it was seldom attempted in any but the most typical cases. However, with the advent of sensitive methods capable of detecting the toxin in tissue, microcystin poisoning should be included in the differential diagnosis for any case of severe, acute massive necrosis in outdoor animals. This case is unusual in that blue green algae toxicoses are commonly held to be a warm-weather problem, however there are precedents in the scientific literature for cyanotoxin production in cold weather. In this case, the onset of signs was preceded by several years of drought, and several days of unusually warm, windy weather leading to a sudden snowmelt runoff that flooded the pasture, leaving puddles of warm stagnant water. We hypothesize that either a mat of a benthic cyanophyte such as *Oscillatoria* was dislodged and washed into the pasture via the irrigation system, or that the unseasonably warm weather permitted a bloom to occur in standing water in the pasture.

Differential diagnoses for acute centrilobular hepatic necrosis in ruminants includes numerous plant toxins including *Cestrum parqui*, *Helichrysum blandowskianum*, cocklebur (*Xanthium strumarium*)[17] and *Trema aspera* ("poison peach"). In cattle, Rift Valley fever and acute poisoning with aflatoxin should also be considered as differentials.

AFIP Diagnosis: Liver: Necrosis, centrilobular and midzonal, diffuse, with hemorrhage and hepatocellular dissociation, Gelbvieh, bovine.

Conference Comment: The contributor gives a thorough overview of microcystin toxicosis.

Differential diagnoses for acute hepatic necrosis discussed during the conference and by the contributor may be differentiated from microcystin toxicity based on additional histopathologic features. The toxic plants *Cestrum parqui*, *Helichrysum blandowskianum*, *Xanthium strumarium*, and *Trema aspera* usually cause acute periacinar necrosis. Aflatoxicosis may be differentiated based on the presence of bile duct proliferation and megalocytosis. Rift Valley fever, caused by an arthropod-borne bunyavirus, is characterized by randomly distributed foci of hepatocellular necrosis that progresses to massive hepatic necrosis, and the occasional presence of elongated, eosinophilic intranuclear inclusion bodies within degenerate hepatocytes.[18]

Contributor: Colorado State University, Veterinary Diagnostic Laboratory, Ft. Collins, Colorado

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CASE III – 2003-02 (AFIP 2888032)

Signalment: 12-week-old, male, Sprague-Dawley rats.

History: Rats were treated with 10 mg/kg cisplatin as a single dose administered via intraperitoneal injection then sacrificed on Day 4.

Gross Pathology: None.

Laboratory Results: Increases were observed in blood urea nitrogen (2.9x-3.1x controls) and creatinine (2.9x-5x controls) on Days 3 and 4 post treatment.

Contributor's Morphologic Diagnosis: Kidney, corticomedullary tubules (proximal and distal): Epithelial cell necrosis, acute, multifocal, moderate with vacuolar degeneration and tubular ectasia, multifocal, mild to moderate.

Contributor's Comment: Cisplatin represents a class of platinum coordination compounds with potent antitumor activity[1]. The adverse effects of cisplatin include renal impairment, intestinal toxicity, and myelosuppression, of which renal toxicity is the most serious dose-limiting factor clinically. The kidney is known to retain platinum at the highest tissue concentration among various organs examined and the renal accumulation of platinum most likely involves the excretory function of the kidney, since cisplatin and/or its metabolites are eliminated in the urine[1].

Tubular lesions associated with acute cisplatin nephropathy include cytoplasmic vacuolation and swelling of tubular epithelial cells with subsequent necrosis and sloughing of necrotic epithelial cells resulting in cast formation and tubular ectasia[1]. A single intraperitoneal dose of cisplatin (6 mg/kg) in the rat has been shown to induce marked acute tubular necrosis in the proximal and distal tubules with a maximum lesion on day 7[1]. One of the characteristic features of acute cisplatin nephropathy is that tubular lesions are primarily localized in the corticomedullary region, involving both the proximal and distal tubules. In contrast, nephrotoxicity of other heavy metal compounds usually causes epithelial damage in the proximal tubules in the cortex. The toxic injury of cisplatin in the corticomedullary region is likely a result of the large accumulation of platinum in that particular region[1].

Impairment of renal function is manifested as elevated serum levels of blood urea nitrogen and creatinine post exposure. Following a single injection of cisplatin (6 mg/kg IP) to rats, serum levels of BUN and creatinine have been observed to rise to a peak of 12- and 11-fold, respectively, above controls on day 5[1].

AFIP Diagnosis: Kidney, corticomedullary tubular epithelium: Degeneration and necrosis, acute, multifocal to coalescing, Sprague-Dawley, rodent.

Conference Comment: The proximal tubule is a common site of toxicant-induced injury. Three discrete segments of the proximal tubule are described: S_1 is the pars convoluta, S_2 is the transition between the pars convoluta and the pars recta, and S_3 is the pars recta. The S_3 segment, or the distal portion of the proximal segment, is the site-selective target of cisplatin in the rat.[2] As noted by the contributor, platinum accumulates in the corticomedullary region and induces injury in this area.

The exact mechanism of toxicity is not known, but it may involve the metabolites of cisplatin and not the platinum atom itself. *In vitro* studies have shown that inhibition of DNA synthesis is the mechanism of action by which cisplatin exerts its nephrotoxic effects.[2]

Contributor: Pfizer Global Research and Development, Groton, CT 06340
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CASE IV - 46822 (AFIP 2888627)

Signalment: Adult, male, C57BL6 mouse, *mus musculus*, rodent.

History: These animals had surgically-placed intraabdominal telemetric implants and were administered 300 mg/kg of acetaminophen PO pre- and post-operatively. There was a 10% mortality rate of the population within one week post-surgery.

Gross Pathology: The livers of the animals examined at necropsy were diffusely mottled red and tan.

Laboratory Results:
ALT 1638 U/L (10-35)
AST 1122 U/L (10-45)
BUN 504 mg/dL (9-30)
Creatinine 3.6 mg/dL (0.4-1)
Phosphorus 27.3 mg/dL (4.2-8.5)

Contributor's Morphologic Diagnosis: Liver, hepatocellular necrosis, centrilobular, diffuse, severe, acute with hemorrhage and mineralization.

Contributor's Comment: Acetaminophen is a widely used analgesic and antipyretic agent. Toxic levels of acetaminophen have been associated with massive liver cell necrosis, usually 3 to 5 days after the ingestion of the toxic doses.[1] Central lobular necrosis is the most frequent form of hepatocellular necrosis in animals exposed acutely to many hepatotoxic agents. Hepatocytes in this region of the lobule are highly susceptible to such agents because of their relatively high levels of cytochrome P450 and associated enzymes that metabolize and therefore activate xenobiotics. Many of these agents are not intrinsically toxic but become toxic once metabolized by the target organ.[2] Centrilobular hepatocytes also receive the blood with lower oxygen concentration further increasing their susceptibility to toxic injury.[3]

The toxic effects of acetaminophen are a result of increased production of a reactive intermediate, N-acetly-p-benzoquinone imine (NAPQI). The liver normally uses reduced glutathione to neutralize NAPQI, which can then be excreted in the urine. Further exposure to acetaminophen can eventually deplete glutathione stores and permit build-up of NAPQI. The excess NAPQI is then free to react with hepatic proteins, more specifically, mitochondrial proteins, causing morphologic changes and inhibition of mitochondrial respiration. Another hypothesis cites oxidative stress as the mechanism of hepatocellular damage. NAPQI depletes the cell of glutathione, which is normally protective against oxidative stress. This stress to erythrocytes causes methemoglobinemia and Heinz body formation, which is the most common manifestation of acetaminophen toxicity in cats.[4]

AFIP Diagnosis: Liver, hepatocytes: Necrosis, centrilobular, diffuse, with hemorrhage and mineralization, C57BL6 mouse, rodent.

Conference Comment: The contributor gives a concise overview of the toxic principle of acetaminophen toxicity. Acetaminophen is metabolized via three pathways in the liver. The first is the pathway described above, whereby NAPQI is formed from oxidation of acetaminophen by the P-450 pathway. Acetaminophen may also conjugate to a sulfate compound or conjugate to a glucuronide compound by glucuronosyltransferase.[4]

In cats, the major pathway for acetaminophen conjugation is through the sulfate pathway because cats have very little glucuronosyltransferase activity. Cats, however, have limited amounts of sulfate so this pathway becomes quickly overwhelmed, forcing metabolism via the P-450 pathway and increased formation of NAPQI.[4]

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