Diagnostic exercise From The Latin Comparative Pathology Group and the Davis-Thompson Foundation: Chronic copper poisoning in a sheep
Braz J Vet Pathol, 2022, 15(2), 118 – 120
DOI: 10.24070/bjvp.1983-0246.v15i2p118-120

BJVP
Brazilian Journal of Veterinary Pathology
ISSN 1983-0246

Diagnostic Exercise
From The Latin Comparative Pathology Group*

Chronic copper poisoning in a sheep

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Clinical History:

A one-year-old female Texel sheep had anorexia and jaundice. After one day, the clinical condition progressed to lethargy, lateral recumbency, and death within hours. The sheep was part of a flock of 20 housed indoors and received an increasing amount of feed (specific for sheep) for the last two months.

Gross Findings:

The sheep was in excellent body condition. The carcass was discolored by marked icterus (Fig. 1). In the subcutaneous tissue, there was multifocal petechiae and ecchymosis. The kidneys had a deep red-brown discoloration. The urinary bladder was distended and filled with dark red to black urine (Fig. 1). The liver was slightly soft and swollen, with a deep orange hue. The gallbladder was distended and filled with dark grumous bile.

Follow-up questions:

- *Cause?*
- *Pathogenesis?*

**The Diagnostic Exercises are an initiative of the Latin Comparative Pathology Group (LCPG), the Latin American subdivision of The Davis-Thompson Foundation and published in cooperation with the Brazilian Journal of Veterinary Pathology. These exercises are contributed by members and non-members from any country of residence. Consider submitting an exercise! A final document containing this material with answers and a brief discussion will be posted on the CL Davis website: https://davisthompsonfoundation.org/diagnostic-exercise/*

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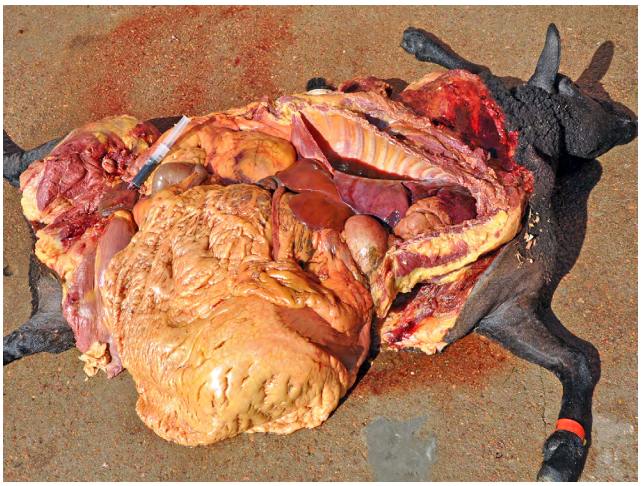

Figure 1. Subcutaneous tissue and abdominal fatare severely and diffusely yellow. The liver is diffusely deep orange. The urinary bladder is filled with dark red urine (as shown by the content within the syringe). Moderate amount of red fluid is evident in the thorax.

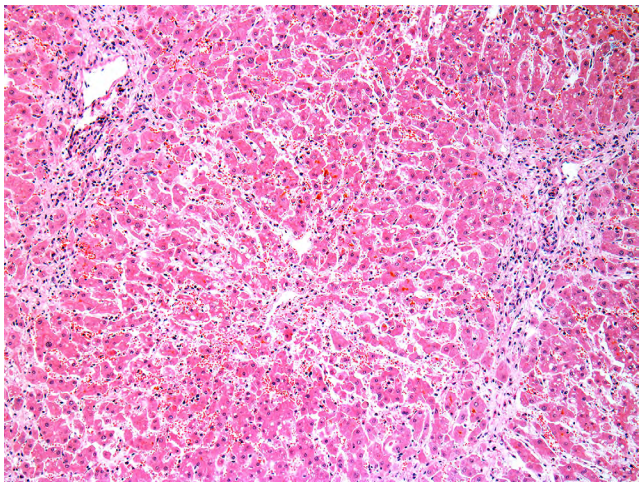

Figure 2. Liver histology. There is marked disorganization of hepatocyte cords mainly within the centrilobular regions. In periportal areas, mild fibrous tissue and mononuclear infiltrate are evident.

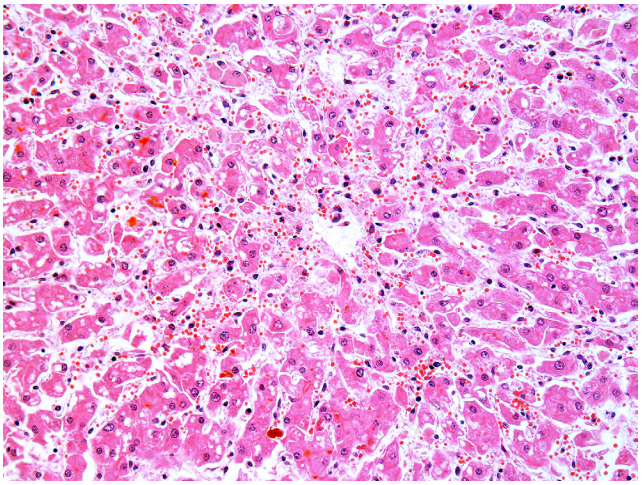

Figure 3. Liver histology. In centrilobular areas, there is individual hepatocyte necrosis, while the remaining adjacent hepatocytes show moderate amounts of granular yellow-brown pigment deposits within biliary canaliculi, as well as mild degenerative cytoplasmic changes within hepatocytes.

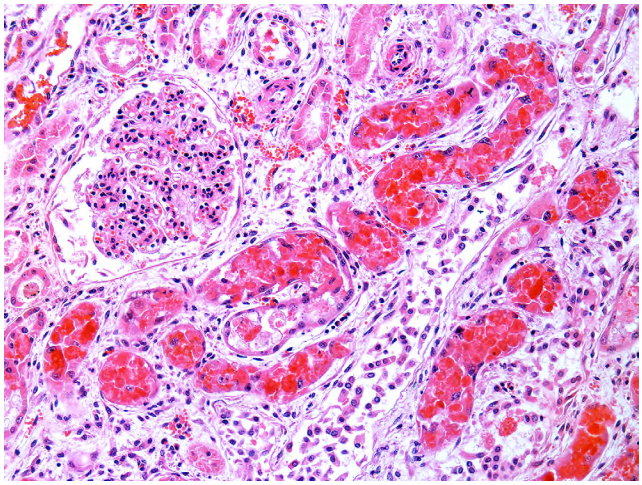

Figure 4. Renal tubular epithelial cells are severely attenuated. Renal tubules are filled with flocculent to eosinophilic dark-red granular casts.

Histological Description:

Liver: Moderate disorganization of hepatocytes cords in the centrilobular region, associated with multifocal hepatocyte swelling and individual necrosis (Fig. 2). The periportal areas showed moderate proliferation of fibrovascular tissue associated with mild lymphocytes and plasma cell infiltrate. Within biliary canaliculi, there was a moderate amount of yellow-brown pigment deposits (consistent with intrahepatic cholestasis) (Fig. 3). Diffusely, a mild vacuolar degeneration of hepatocytes was observed. In the kidneys, cortical renal tubules contain flocculent to eosinophilic dark-red granular casts. Renal tubular epithelial cells are attenuated, coagulated, and pyknotic or absent (epithelial degeneration and necrosis) (Fig. 4).

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- **Cause:** Chronic copper poisoning.

- **Pathogenesis:** Elevated dietary copper intake > copper sequestration in hepatocellular lysosomes > production of reactive oxygen species > destructive lipid peroxidation > loss of lysosomal membrane integrity and damage to mitochondria > hepatocellular apoptosis > elevated free copper ions > oxidation of hemoglobin in erythrocytes > intravascular hemolysis > anemia.

Comments:

Chronic copper poisoning results from the accumulation of copper in hepatic tissues over a few weeks to more than a year and can occur without any clinical manifestation (1,4). Sheep are intoxicated due to the gradual accumulation of large amounts of copper (Cu) in the liver and its sudden release into the circulatory system, resulting in a hemolytic crisis (4). The hemolytic crisis may be precipitated by many factors, including transportation, handling, weather conditions, pregnancy, lactation, strenuous exercise, or a deteriorating plane of nutrition (3). Hepatic copper toxicosis can result from a primary metabolic defect in hepatic copper metabolism, altered hepatic biliary excretion of copper (presence of other hepatotoxins, e.g., pyrrolizidine alkaloids), or excess dietary intake of the element (1). Sheep are especially prone to copper poisoning because of the reduced biliary excretion of copper (1). The gross lesions of fatal chronic copper poisoning include the mucosa and subcutaneous tissue discolored by severe jaundice. The kidneys are deep red-brown, and the urine is deep red (consistent with hemoglobinuria). The liver is often slightly soft, swollen, and deep orange (1). Histologically, the liver lesion varies with chronicity of exposure, from non specific acute centrilobular necrosis to cholangiohepatitis with periportal fibrosis (1). Our pathological findings were very similar to those described in the literature for the condition. The determination of the source of copper excess is essential for the diagnosis. Several sources are described in the literature, including feeding excessive grains to sheep, as seen in our case; feeding sheep with food compounded destined for other species (cattle); the use of grape subproducts in sheep diet (3,7). To conclude, the diagnosis of copper poisoning is necessary to determine the copper levels in the liver of the affected sheep (4). In our case, the copper determination was 1,063 μg/g (normal concentration up to 349 μg/g) (6).

Concentrations of Cu in the liver greater than 1000 mg/kg are diagnostic of copper intoxication (4,6). The diagnosis of copper poisoning and its differential diagnosis is often based on the animal's signalment, supportive historical information, clinical signs, and gross findings at necropsy (1). Differential diagnoses for the hemolytic crisis in sheep are scarce. In young lambs, the alpha-toxin generated by *Clostridium perfringens* type A can cause hemolysis, leading to "yellow lamb disease" (8). As copper poisoning and yellow lamb disease present similar signs and gross and microscopic findings, ancillary tests are necessary to obtain a final diagnosis. Yellow lamb disease affects only young lambs, and direct smears of the intestinal lining may reveal large numbers of gram-positive rods (8). Other intoxications related to hepatic failure and jaundice, such as *Crotalaria retusa*, *Brachiaria brizantha*, and *Brachiaria decumbens* plant poisoning, were described in sheep (2,5). The differentiation between these conditions and copper poisoning is mainly obtained through anamnesis and pathological findings. In addition, intravascular hemolytic anemia-related lesions are absent in these plant intoxications.

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