

## **Chronic copper poisoning in sheep from Northern Paraná, Brazil: case report**

## **Intoxicação crônica por cobre em ovinos no norte do Paraná, Brasil: relato de caso**

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### **Abstract**

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Chronic copper poisoning (CCP) in sheep is a severe disease that occurs worldwide. This paper describes the pathological lesions of CCP that occurred in a flock of sheep from Northern Paraná, Southern Brazil. Seven, cross-breed Merino sheep, out of a flock of 14 were affected. Most of these animals demonstrated muscular tremors, nervous symptoms, difficult breathing, and died within 24-48 after the onset of clinical signs. Gross lesions were characterized by generalized icterus, hemoglobinuria, dark colored kidneys, and a softened spleen. Histological findings included tubular renal necrosis, centrilobular hepatic necrosis, and status spongiosis of the white matter of the brain; toxicological evaluation of the liver confirmed CCP.

**Key words:** Intoxication, pathology, sheep, copper, liver

### **Resumo**

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Intoxicação crônica por cobre (ICC) é uma doença severa de ocorrência mundial. Este artigo descreve as alterações patológicas de ICC que ocorreram em um rebanho de ovinos no norte do Paraná, Brasil. Sete ovinos, cruzados Merino, de um rebanho de quatorze foram afetados. A maioria dos animais demonstrou tremores musculares, manifestações neurológicas, dificuldade respiratória e morreu dentro de 24-48 horas após o início das manifestações clínicas. As alterações macroscópicas foram caracterizadas por icterícia generalizada, hemoglobinúria, rins enegrecidos e o amolecimento do baço. As alterações histológicas incluíram necrose tubular renal, necrose centrolobular do fígado e estatus esponjoso do encéfalo; avaliação toxicológica do fígado confirmou a intoxicação.

**Palavras-chave:** Intoxicação, patologia, ovino, cobre, fígado

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## Introduction

Chronic copper poisoning (CCP) in sheep is characterized by hemolysis, anemia, icterus, and hemoglobinuria (KIMBERLING, 1988; KELLY, 1993; ANGUS, 2000). 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 (KIMBERLING, 1988). The intoxication results in severe economic losses due to death of affected sheep and the implantation of control measures (KIMBERLING, 1988; RADOSTITS et al., 2002). All ovine breeds are considered highly susceptible to Cu poisoning, but some breeds (North Ronaldsay, Charollais, Texel, and Suffolk) are more predisposed than others (ANGUS, 2000); however other authors have considered the Mutton Merino and Suffolk cross-breeds resistant to copper intoxication (HUMANN-ZIEHANK et al., 2001). There is no apparent sex or age predisposition of sheep to Cu poisoning (ANGUS, 2000), but mature British ewes may develop the disease more frequently than other categories of animals (KIMBERLING, 1988).

Copper intoxication occurs in principal sheep-producing countries such as Australia, New Zealand, USA, Great Britain, and South Africa (KIMBERLING, 1988). There are few descriptions of CCP from Brazil; most cases were described in the sheep-producing regions of Rio Grande do Sul State (ILHA et al., 2001; RIET-CORREA et al., 1989; RIBEIRO et al., 1995). However, reports of this intoxication from Brazil are not frequently described in areas where sheep production is not the principal economic activity; there is one description from the State of São Paulo (MAIORKA et al., 1998). This paper describes the pathological and toxicological findings of an outbreak of chronic copper poisoning in a flock of sheep from Maringá, Northern Paraná, Brazil.

## Case report

The subsistence farm affected was located in Northern Paraná, Southern Brazil, and consisted of a

mixture of cattle and sheep rearing. Cattle ( $n = 50$ ) and Merino cross-breed sheep ( $n = 14$ ) were maintained on the same pastures, which were predominantly of African star grass (*Cynodon nlemfuensis*). Additional nutrition for all animals was obtained from a mineral supplement that was administered since early 2004 and contained 500 mg of Cu (as identified by the manufacturer's label). Water, obtained from a nearby stream, and the salt mixture were administered *ad libitum*. All sheep were maintained on pasture during the day and housed at night.

Between January to June 2005, there was a gradual loss of sheep resulting to 50% (7/14) of the flock; all cattle remained unaffected. The owner reported that most animals demonstrated muscular tremors, nervous symptoms, difficult breathing, and died within 24-48 after the onset of clinical signs; three of these were opened on the farm by the farming personnel, who described yellow discoloration of eyelids and subcutaneous tissue and the extremely darkened color of the kidneys. A visit to the establishment did not reveal any hepatotoxic plants.

One 2-yr-old moribund female sheep, from the same flock, was sacrificed and submitted for routine necropsy; selected tissues (brain, kidney, liver, lungs, and intestines) were fixed in 10% formalin solution and processed for routine histopathological evaluation. Frozen liver samples were sent to the Laboratory of Chemical Analyses (Lachem), Universidade Federal de Santa Maria (UFSM), RS, Brazil, for toxicological evaluation.

At necropsy widespread and severe icterus was observed at the oral and ocular membranes, subcutaneous tissues, abdominal and thoracic body fat, omentum, and the serous membrane of the gastrointestinal tract (Fig. 1A). Both kidneys were extremely black and slightly enlarged (Fig. 1B). The liver was remarkably icteric, slightly enlarged and with marked evidence of the lobular pattern (Fig. 1C); the gall bladder was marked distended by darkened granular bile. There was marked distension of the urinary bladder (Fig. 1D) by dark-colored urine (hemoglobinuria). Pleural pulmonary and parietal

surfaces were marked icteric; lungs were icteric, non-collapsible, and rubbery in nature; the spleen was slightly enlarged and soft. There was also an

accumulation of blood-tinged fluid within the pericardic sac and moderate petechial hemorrhage on the subepicardial surface.

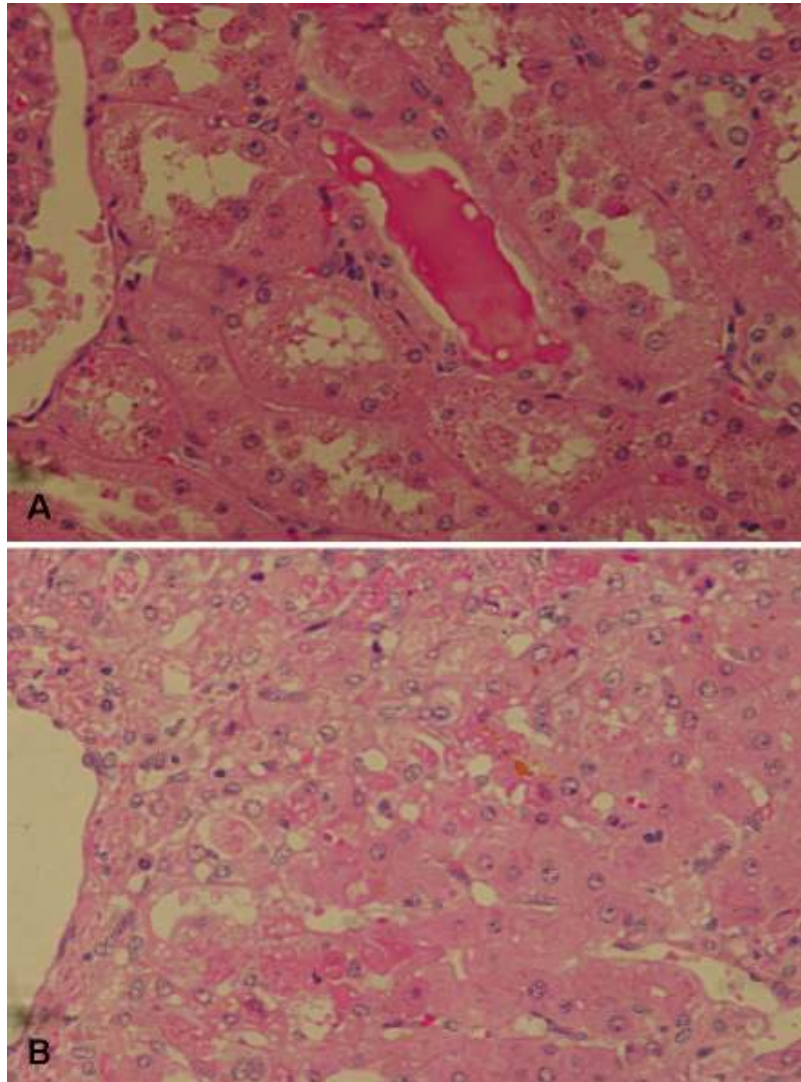


**Figure 1.** Mixed breed sheep; gross images of chronic copper poisoning. There is wide spread icterus of body fat within the abdominal and thoracic cavity (A). Note the severely dark colored kidney (B), the diffusely icteric liver (C), and the unusual color of the urine (D).

Significant histological lesions were restricted to the kidneys, liver, spleen, brain, and lungs. Renal lesions were characterized by multifocal tubular necrosis, intratubular hyaline casts with discrete to moderate areas of hemorrhage (Fig. 2A). There was discrete centrilobular hepatic necrosis, necrosis of individual hepatocytes, discrete to moderate fatty degeneration of hepatocytes, discrete proliferation of epithelial cells of bile ducts, and moderate accumulation of bile pigment within bile canaliculi (Fig. 2B). Moderate multifocal hemosiderosis was seen in the spleen. Multifocal discrete status spongiosis was observed in the white matter of the cerebellum and cerebrum. Mild pulmonary lesions

were characterized by proliferation of type II pneumocytes that resulted in moderate thickening of alveolar linings, moderate proliferation of smooth muscle of bronchioles and moderate hemosiderosis.

Toxicological analysis of the liver determined by the atomic absorption spectrometric method, with an initial acidic digestion, revealed  $1314.42 \pm 2\%$  mg/kg dry matter (DM) of Cu obtained from three different regions of the sample, realized in triplicate at Lachem, UFSC, RS, Brazil. According to the toxicological report, the value represented the average obtained from the three regions and the standard deviation indicated that the distribution of Cu was relatively uniform within the submitted liver sample.



**Figure 2.** Mixed breed sheep; photomicrography of chronic copper poisoning. Kidney; observe hyaline cast within the lumen of renal tubule, moderate accumulation of bile pigments in epithelial tubular cells and discrete tubular necrosis (A). Liver; there is individual necrosis of hepatocytes and accumulation of bile pigment within canaliculi at the centrilobular zone (B). (H & E; Obj. 40x).

## Discussion

A diagnosis of primary chronic copper poisoning (CCP) in this case was made due to the gross lesions and histological findings that are consistent with this intoxication (KELLY, 1993; ANGUS, 2000), and was confirmed by the elevated concentration of Cu (1314.42 mg/kg DM) within the liver by toxicological determination. Concentrations of Cu in the liver greater than 1000 mg/kg DM are diagnostic of this intoxication (KIMBERLING, 1988; ANGUS, 2000; RADOSTITS et al., 2002). Elevated liver copper

concentrations confirm excessive exposure to copper but do not necessarily confirm clinical copper toxicity. Therefore, liver copper concentrations reflect the copper status of the sheep, and once overloaded at the point of crisis copper concentrations may decline rapidly.

Since all sheep that died demonstrated similar gross lesions and were subjected to the same feeding practice it is reasonable to assume that death was associated with CCP, due to the chronic ingestion of a commercially prepared mineral supplement destined

for cattle; a similar case was described in São Paulo (MAIORKA et al., 1998). Feedstuff especially prepared for sheep contain low levels of Cu, while those designed for other farm animals normally have levels of Cu that are toxic for sheep (ANGUS, 2000; RADOSTITS et al., 2002), as was this case. Additionally, this outbreak occurred in a region where sheep production is not intensified (INSTITUTO BRASILEIRO DE GEOGRAFIA E ESTATÍSTICA - IBGE, 2006), which favor this intoxication probably due to the lack of information relative to the consequences of furnishing a cattle based mineral supplement to sheep. The State of Paraná and the Northern Paraná region contributes with 3.24% (488,142/15,057,838) and 0.34% (50,794/15,057,838) respectively, of the Brazilian sheep herd (IBGE, 2006). Moreover, in the State of Paraná sheep are raised principally for internal consumption. Sheep production is concentrated within the semiarid Northeast (57.86%) and temperate South (30%) of Brazil; in the South, the State of Rio Grande do Sul is responsible for 25.41% of the national herd (IBGE, 2006).

During this outbreak the animals received the mineral supplement for almost one year before the first case was observed and all sheep died acutely after the onset of clinical signs. On the other hand, sheep experimentally intoxicated did not demonstrate clinical signs consistent with CCP more than 2.5 yr after the first administration of daily doses of Cu (HUMANN-ZIEHANK et al., 2001). The hepatic accumulation of Cu may take weeks or more than a year to occur without any corresponding clinical manifestation, after which a sudden release of Cu into the circulatory system initiates clinical signs typical of CCP (ISHMAEL; GOPINATH; HOWELL, 1971; KIMBERLING, 1988). The abrupt liberation of Cu from the liver is related to death of hepatocytes (KIMBERLING, 1988; KELLY, 1993). Simultaneous stress situations (such as deworming, transportation, starvation or food withdrawal) can accelerate Cu toxicosis in susceptible sheep (ANGUS, 2000; RADOSTITS et al., 2002).

Ovine breed resistance/susceptibility directly affects Cu poisoning, but the available information is not clear. In this case of CCP, all sheep affected were Merino cross breeds. However, it was suggested that this breed may be somewhat resistant to CCP (HUMANN-ZIEHANK et al., 2001). These authors did not observe clinical signs consistent with CCP, nor variations of haematocrit, haemoglobin or leucocytes values, or any hemolytic crisis in Merino and Suffolk cross breeds. In another experiment Merino sheep demonstrated signs of CCP, with and without the addition of Heliotrope to their diets (HOWELL et al., 1991). All sheep breeds are considered highly susceptible to Cu poisoning (ANGUS, 2000), although there may be tolerance differences between certain breeds (KELLY, 1993; ANGUS, 2000; RADOSTITS et al., 2002). Additionally, the North Ronaldsay, Charollais, Texel, and Suffolk breeds are considered more apt to CCP than the Scottish Blackface (ANGUS, 2000). Further, the Texel and Finnish Landrace breeds are probably more resistant than Ronaldsay and Orkney breeds (RADOSTITS et al., 2002). Therefore, ovine breed susceptibility to CCP should be thoroughly investigated, as this phenomenon could be extremely preventative particularly in regions where sheep production is the main economic activity. Further, why this tolerant breed was intoxicated was not entirely elucidated and the possible level of copper in the pasture is also unknown. Maybe the animals were previously exposed to a liver toxin which accelerated copper toxicosis, since liver degeneration will affect the ability of the liver to store copper and may therefore predispose to clinical copper toxicosis.

Copper intoxication is a serious problem that affects the sheep industry worldwide. Affected sheep normally demonstrate characteristic clinical manifestations that are associated with hepatic and renal dysfunctions. Intoxication can be confirmed by the evaluation of hepatic and renal accumulations of copper by specific laboratorial methods. Ovine-breed resistance/susceptibility to copper intoxication may be the key feature to reduce economic losses in modern sheep production.

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