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Case Report

A Special Case of Fatal Chronic Poisoning by an Agricultural Pesticide of Freely Available Copper Sulphate Powder

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ABSTRACT

The present case study illustrates the fatal consequences of chronic copper poisoning with an additional sulphur consumption as a chronic self-administration. These two elements were consumed with the goal of self-treatment of a presumed chronic *Candida* infection. The patient exposed himself for over eight years, which led to liver failure, weight loss, ascites and gastrointestinal bleeding. The patient was treated with D-penicillamine for chelation of copper without effectiveness. Despite intensive care, the patient succumbed to multi-organ failure. The autopsy revealed cirrhosis of the liver, oesophageal varices and a 'blackberry jam spleen'. Histological examination confirmed the presence of copper deposits in both the liver and kidney. Copper determination by mass spectrometry showed elevated levels in several organs, but particularly in the liver. The present case highlights the dangers inherent in the consumption of copper with sulphur and underlines the toxicological implications of copper and sulphur exposure.

Keywords: Copper; Poisoning; Agricultural pesticide; Sulphur; Shikata's orcein; ICP-MS

INTRODUCTION

Copper (Cu) is an essential trace element in the human body and is vital for certain metabolic processes and for the function of many enzymes [1]. It ranks third in abundance among micronutrients [2], with recommended daily intake ranging from 0.6 to 1.6 mg [1]. Copper is a prosthetic group of several enzymes involved in the SOD1, CCO, CP, LOX and tyrosinase enzymes [3]. Deficiency reduces enzyme activity, while excessive intake leads to the development of Wilson's disease [4]. Acute copper toxicity typically results from ingestion of 1 g, with a lethal dose estimated at 10-20 g [5,6]. Copper poisoning can also occur through different administration routes [7], and copper sulphate poisoning can range from mild to severe [8]. Chronic copper poisoning can lead to liver and kidney damage, gastrointestinal problems and neurological disorders [7].

Sulphur plays a significant role in metabolic processes, serves as a building block for proteins and enzymes, and regulates oxidative stress [9]. Sulphites are food preservatives that are sometimes ingested by individuals with suspected *Candida* infections because of their antifungal properties, as seen in this case of severe copper ingestion.

CASE PRESENTATION

Anamnestic data and clinical findings

One month before death, the deceased experienced constipation and a 6 kg weight loss, with massive leg oedema and emaciated upper limbs. Blood was observed in stool after a forceful enema for constipation. For about a decade, the deceased self-treated for *Candida* with antifungal preparations and around 1 kg of copper sulphate annually, also using elemental sulphur on vegetables and in wine. His laboratory parameters are depicted in Table 1 [10-16]. Laboratory results showed severe liver and kidney involvement, indicative of cirrhosis and kidney failure risk. Psychiatric consultation diagnosed somatic paranoid disorder. Treatment involved various medications and dietary supplements. Despite inconclusive imaging, advanced cirrhosis was suggested by other findings. Liver transplantation feasibility was uncertain. Treatment included monitoring, hepatorenal syndrome therapy, antibiotics, ascites drainage, and D-penicillamine administration for copper excretion. Unfortunately, the patient's condition deteriorated, leading to multi-organ failure and death.

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Table 1: Copper levels were assessed in different samples obtained during the post-mortem examination of the patient suffering from chronic copper poisoning. The concentrations of copper were determined using Inductively Coupled Plasma Mass Spectrometry (ICP-MS). Elevated copper content was observed in whole blood, plasma, urine, and the liver, while levels in the brain and hair fell within the normal range. NA= not available.

Sample	Cu content	Wilson's disease	Normal value
Full blood (ng/ml)	2.766	370-870 [10]	63-81 [10]
Plasma (ng/ml)	3.53	3.690 [11]	590 ± 30 [12]
Urine (ng/ml)	6.212/11.200	4-178 [10]	17-38 [10]
Hair (ng/g)	38.087	5.500-86.500 [13]	5.400-72.000 [13]
Nail (ng/g)	359.187	NA	NA
Liver (ng/g)	918	5.400-410.000 [14]	<10.000 [14]
Brain (ng/g)	17.9	41.000 ± 18.600 [15]	10.000-37.000 [16]

Autopsy findings

The corpse measures 171 cm tall, with a medium build and generally pale, light yellow skin. Rigor mortis has dissolved in all extremities. External examination reveals several 0.1 cm-0.3 cm diameters, sometimes confluent, bright reddish skin haemorrhages on the lower limbs in front, on the chest, and on the shoulders. Additionally, some needle marks are visible on the body consistent with medical interventions. The eye slits are closed, with swollen eyelids, and oedema is diagnosed. The sclera appears light yellow, but no Kayser-Fleischner rings were seen.

In the brain (1260 g), general oedema is observed. Examination reveals lacunar infarctions, each measuring 0.1 cm-0.3 cm in diameter, in the left side of the cerebral grey nuclei, indicating evidence of an older form of ischemic stroke. Diffuse nodular scarring is visible in the myocardium.

In the lungs, congestion, oedema, emphysema, and soot deposits are observed. The abdominal cavity contains 70 ml of cloudy ascites. The liver is larger than average (1600 g), with an irregular and lumpy surface. The incisal surface of the liver shows nodularity due to the formation of fibrous tissue.

The spleen is larger (410 g) than normal (splenomegaly), with a wrinkled capsule and a dark red cut surface with a significant amount of scrape-off, resembling a "blackberry jam spleen" (Figure 1). In the gastric cavity, there are 200 ml of coffee-juice-like, acidic-haematinic contents. Examination of the stomach wall reveals that the gastric mucosa is detached along the great curvature in the stomach wall in an area of 14 × 6 cm, and erosion is observed here. Oesophageal varices were identified (Figure 1). The intestinal wall of the duodenum and jejunum is reddish discoloured, with sloughing off of the intestinal mucosa. The prostate gland is enlarged, with several nodules of 0.3 cm-0.5 cm in diameter.

Histological examination was conducted on liver, kidney, and brain specimens, stained with Haematoxylin-Eosin (HE) and Shikata's Orcein (SO). Microscopic analysis of the kidneys shows crystal deposits and damage in the epithelium of the canaliculi. Generally, shock can be diagnosed from the kidneys. Orcein-positive pigment granules were detected in the cytoplasm of hepatocytes and epithelial cells of kidney tubules (Figure 2). However, no copper deposition was observed in the brain. There were no significant changes in other organs.

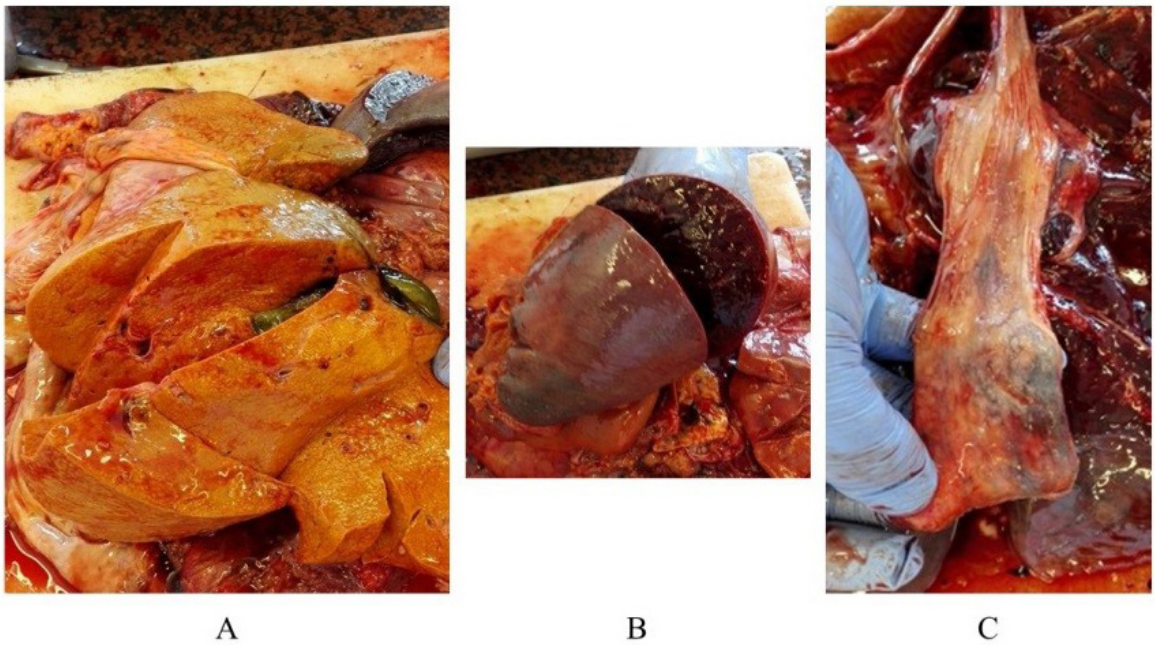

Figure 1: (A) During the autopsy, findings indicated an enlarged liver weighing 1600 g, displaying an irregular and lumpy surface. Nodularity on the incisal surface was evident due to the enlargement of fibrous connective tissue; (B) The spleen exhibited splenomegaly, weighing 410 g, characterized by a wrinkled surface and a cut surface displaying dark colouration with significant scrapings, resembling a "blackberry jam spleen"; (C) Varices were identified in the oesophagus.

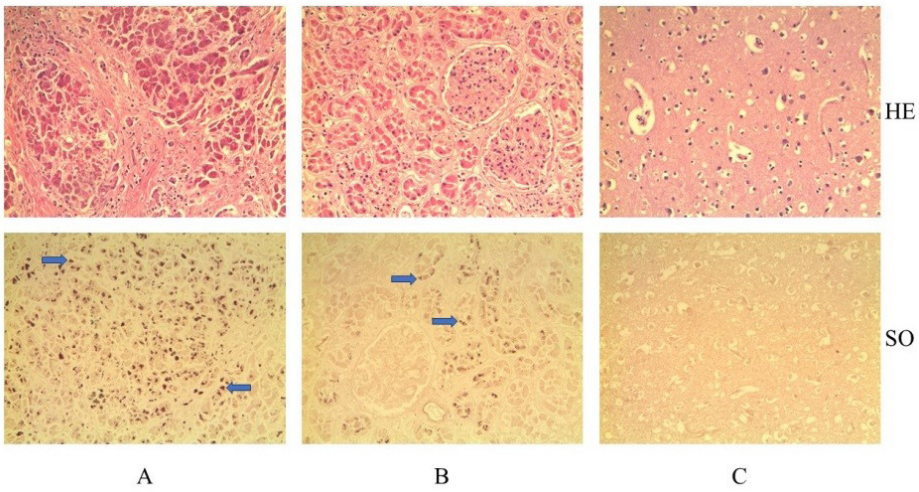

Figure 2: Post-mortem histological analysis of the (A) liver; (B) kidney; (C) brain of the deceased individual suffering from chronic copper poisoning was conducted using Haematoxylin-Eosin (HE) and Shikata's-Orcein (SO) stains. Copper accumulation is evident in the liver and in the tubular cells of the kidney, as indicated by arrows in the images obtained through SO staining. The magnification used was 10,000X.

Measurement of tissue copper content

Copper content was assessed using Inductively Coupled Plasma Mass Spectrometry (ICP-MS), a method with low detection limits for analysing multiple elements. Samples underwent microwave-assisted digestion prior to analysis. The Thermo Scientific X-Series 2 ICP-MS was used, verifying accuracy with certified reference material. Elevated copper concentrations were found in all organs tested, especially in the liver, serum, and plasma. Hair copper levels were normal, while nails showed a notable increase. Urinary copper content was low. See Table 2, for organ copper contents.

Table 2: The blood chemistry findings were obtained five days prior to the patient's demise from copper poisoning. The table displays the measured values, the corresponding normal values, and the variance between them. (L=Low; H=High).

Parameter	Value	Dimension	Normal value	Change
Sodium	128	mmol/L	133-146	L
Potassium	2.7	mmol/L	3.5-5.3	L
Chloride	78	mmol/L	99-111	L
Urea	20.9	mmol/L	2.8-8.0	H
Creatinine	208	µmol/L	62-106	H
Total Bilirubin	75.4	µmol/L	<20	H
CK	445	U/L	24-195	H
AST (SGOT)	433	U/L	<40	H
LDH	401	U/L	135-220	H
ALT (SGPT)	55	U/L	<40	H
GGT	224	U/L	18445	H
ALP	32	U/L	40-115	L
WBC	13.34	Giga/L	4.5-10.8	H
RBC	2.72	Tera/L	4.7-6.1	L
Albumin	23	g/L	35-52	L
Fibrinogen	1.05	g/L	1.5-4.0	L
GFR (EPI)	28	ml/min/1.73 m^2	>90	L

RESULTS AND DISCUSSION

We present a case involving the chronic self-administration of copper sulphate and sulphur over an extended period (approximately 8 years), resulting in the demise of the subject. To our knowledge, this case represents the initial instance in published literature detailing the lethal consequences of chronic copper and sulphur poisoning spanning multiple years in an adult.

Chronic copper toxicity, more common in livestock, poses a threat to cattle and sheep. An outbreak in Brazilian cattle was linked to excessive copper supplementation [17]. Clinical signs in cattle include jaundice and darkened urine, while diagnosing sheep is challenging due to slow symptoms [18]. Sheep may develop liver damage from copper injections [19]. Our case mirrors observations in animals, with symptoms appearing suddenly after years of copper consumption. Pasture sulphur may mitigate copper toxicity in sheep [20]. Blood parameters could aid in detecting silent copper buildup in animals [21,22].

Acute copper poisoning in humans typically manifests as gastrointestinal symptoms such as abdominal pain, diarrhoea, and vomiting [23]. In severe cases, it can lead to cardiac and renal failure, intravascular haemolysis, hepatic necrosis, encephalopathy, and even death [5]. However, our case involves chronic poisoning, as the deceased had been ingesting copper sulphate for approximately 8 years. Chronic copper poisoning cases are less common. Eife reported a unique case of chronic copper poisoning in newborns fed instant milk made from tap water contaminated with copper due to passage through copper pipes [24]. This resulted in liver cirrhosis and significant copper accumulation in the liver resembling "Indian Childhood Cirrhosis. This phenomenon is more likely to occur in regions where copper water plumbing is prevalent [25,26], highlighting a public health concern.

Complications of copper sulphate poisoning in humans, including hepatotoxicity, acute renal failure, and gastrointestinal bleeding, were described, clear on the diverse health effects of copper exposure [27]. The death of hepatocytes is attributed to copper-mediated oxidative damage, driven by copper's intrinsic ability to undergo redox cycling between Cu(II) and Cu(I) (Fenton reaction) [28,29]. Experimental studies in rats have demonstrated that copper induces structural and functional deficits in liver mitochondria,

including mitochondrial swelling and crosslinking of the outer and inner membranes [30,31]. These changes are associated with thiol modifications in key mitochondrial membrane proteins, such as Voltage-Dependent Anion Channel (VDAC), Adenine Nucleotide Translocase (ANT), and ATP synthase B, as well as reversible intermolecular thiol bridges between proteins anchored in the outer and inner membranes [32]. In the deceased individual, cirrhotic liver, renal failure, and gastrointestinal bleeding were identified. Additionally, histological examination revealed fibrosis and damaged mitochondria in the liver cells. However, it is essential to acknowledge that these changes may be obscured by signs of post-mortem decomposition.

In our case, D-penicillamine (β, β-dimethylcysteine) was administered as a specific chelating agent to detoxify the patient as a final rescue. However, the effectiveness of exogenous chelating agents like D-penicillamine relies on their ability to compete with endogenous ligands such as metallothionein for toxic copper ions [33,34]. Over time, the binding between toxic copper ions and endogenous ligands may strengthen, reducing the efficacy of chelation therapy. This limitation highlights the challenge of long-term effectiveness in chelation therapy, particularly in cases where the binding dynamics between metal ions and endogenous ligands change over time. This could explain the limited effectiveness of D-penicillamine treatment in our case.

Copper sulphate is extensively used in agriculture for various purposes, including controlling algae, parasites, and bacteria in aquatic environments, acting as a fungicide, soil amendment, seed treatment, and food preservative. It exists as hydrates with varying formulas, with the pentahydrate being the most common. Widely employed in chemical experiments and viticulture, copper sulphate, designated with the ATC code V03AB20, is readily available without special permissions. In our case, the deceased consumed 1 kg annually, far exceeding the established upper limit. It is worthy to mention that we discovered no evidence of the Kayser-Fleischner rings due to copper deposition in the Descemet membrane of the cornea, which are characteristic of Wilson's disease. This was not observed during his clinical stay either. Even a pseudo-Kayser-Fleischner ring can be observed in patients with a high bilirubin concentration (>85.5 μmol/l) [35]. Our patient had a total bilirubin concentration of 75.4 μmol/l, but this did not lead to the appearance of even pseudo-Kayser-Fleischner rings.

CONCLUSION

In conclusion, the presented case underscores the serious consequences of chronic self-administration of copper sulphate and sulphur over an extended period, resulting in multi-organ failure and ultimately death. This instance, while rare in published literature concerning adults, parallels observations of chronic copper toxicity in livestock. The case highlights the limitations of chelation therapy in addressing long-standing copper toxicity. Moreover, it raises concerns about the accessibility and unregulated use of copper sulphate in various domains, including agriculture and viticulture, warranting greater awareness and regulatory measures to mitigate potential health hazards associated with its misuse.

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