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Acute Hypoxemic Respiratory Failure With Hemoptysis in a Dog Exposed to Copper Sulfate Powder

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A 2-year-old male mongrel dog was presented because of the onset of dry cough. About 16 hours before, the dog had been exposed to the pesticide that the owner was spraying in the vineyard. Approximately 3 hours later an acute respiratory failure, with a rapid evolution, began. Hemoptysis and regenerative normocytic normochromic anemia arose within hours, and a pulmonary hemorrhage was diagnosed. Pulmonary hemorrhage fast led to pneumonia, as evidenced by the serial CXR findings and the developing of leukocytosis. The hypothesis that we believe more likely is that the dog inhaled an amount of copper sulfate powder enough to determine respiratory tree damage, extending from the trachea to the pulmonary alveoli. Oxygen supplementation, antibiotics, antioxidant, and gastroprotective medications had been administered. After 4 days of hospitalization the dog was discharged. After a follow-up of more than 2 years later, the dog is still alive and in good health. To the authors knowledge no evidences of acute pulmonary involvement after copper sulfate inhalation exist in any species. This report is a contribution to the knowledge of copper poisoning, scarcely mentioned both in human and veterinary literature, and which has never been described in companion animals.

Introduction

Copper is an essential trace element involved in complex enzymatic reactions. Both deficiency and excessive intake can lead to life-threatening complications.[1] Its high redox activity can be harmful to cells by inducing oxidative stress, which will finally lead to cell death.[2] Copper sulfate ($CuSO_4$) is commercially available as powder or water solution and it is widely used as pesticide.

Acute and chronic copper poisoning is well described in food animals.[3–5] In humans, it is more often chronic and accidental (occupation-related) but some voluntary poisonings have been described as a uncommon attempt of suicide[6,7] or abortion.[8] In companion animals there is a lack of information about copper toxicity. The only reference concerns to the use of copper sulfate to induce emesis.[9]

Although is well known that copper sulfate could induce mucosal lesions after ingestion, studies concerning its respiratory toxicity lack, both in human and veterinary literature. The so-called "Vineyard sprayer's lung"[10] and several adverse effects after exposition and inhalation of copper fumes in humans have been reported.[11] *In vitro* studies have demonstrated that copper-sulfides and copper oxide nanoparticles (CuO NPs) induce cytotoxicity and oxidative stress in cultivated human lung cells, up-regulating cellular reactive oxygen species (ROS) and causing cell death.[12,13] Antioxidant *N*-acetylcysteine reduced CuO NPs, which cause cytotoxicity, by lowering the production of intracellular ROS.[13] Some authors have shown that intratracheal instillation of CuO NPs induced oxidative stress, inflammation, and neoplastic lesions in rats.[14]

We report a case of cupric poisoning with acute respiratory failure in a young dog after exposure to a copper sulfate powder, used as anticryptogamic.

Case Description

A 2-year-old male mongrel dog was presented to our Veterinary Teaching Hospital because of the onset of a dry cough. Approximately 16 hours before, the dog was exposed to a copper sulfate pesticide (pentahydrate copper sulfate > 98%-99%; Solfato di rame, Manica S.p.a., Rovereto, TN, Italy) that the owner was spraying in the vineyard. The owner saw the dog sniffing in the bag of copper sulfate powder and, after that, he noticed blue powder spots on its nose. Until that moment, the dog had always enjoyed good health.

During the first physical examination, the dog was alert and no clinical abnormalities were found, except for a dry cough easily elicited on tracheal palpation. No alterations were found on chest auscultation. Hematological and serum biochemistry profiles, as well as urinalysis, were unremarkable.

Based on the effects of copper sulfate reported in literature, possible gastrointestinal and/or hematological involvements were

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suspected. Therefore, the dog was discharged with gastroprotective, detoxifying, and antioxidant preventive therapy.

Approximately 3 hours later, the dog was readmitted to the hospital because the owner noticed a small blood spot on the floor and because of a gradual loss of liveliness.

The dog was alert but not bright; at physical examination, tachycardia (HR = 112 bpm) and tachypnoea (RR = 36 breaths/min), prolonged capillary refill time of 3 seconds, pale mucous membranes, weak and fast pulse, and normal rectal temperature were found. Auscultation of the lungs was unremarkable.

Microhematocrit was slightly low (33%, laboratory range: 37%-55%), total solids, evaluated by refractometer, were within the physiological values (7, laboratory range: 6.5-7.5 g/dL), whereas the lactate, measured by means of a portable lactacidometer (Lactate Scout +, EKF Diagnostics), was slightly high (3.8, normal value = <2.5 mmol/L), suggesting inadequate tissue perfusion.

Fluid therapy with lactate Ringer's solution (Ringer lactate solution S.A.L.F. S.p.A., Cenate Sotto, BG, Italy) was started, at a rate of 10 mL/kg/h. After 15 minutes of infusion, an improvement in perfusion, with normalization of capillary refill time and reduction of the lactate (3.2 mmol/L), was observed. In contrast, the breathing became faster (RR = 52 breaths/min) and shallow, cough worsened and haemoptysis occurred. Chest auscultation revealed bilateral end-inspiratory crackles.

Fluid therapy was immediately stopped, supplemental oxygen (flow-by) was provided and a chest X-ray (CXR) was taken. This showed a radiating perihilar interstitial pattern and patchy alveolar infiltrates, indicative of pulmonary edema and/or hemorrhage, a luminal narrowing at the tracheal bifurcation, due to mediastinal lymphoadenopathy, mild peribronchial pattern. Adjacent lung fields appeared normal (Fig 1).

Arterial blood gas (ABG) analysis (Vet Scan, i-STAT Analyzer Abaxis) showed a mixed disorder characterized by normal pH, as the effect of slight metabolic acidosis and respiratory alkalosis, with hypocapnia and severe hypoxia (Table).

The hematological analysis showed normocytic normochromic anemia, leukocytosis, with neutrophilia, monocytosis and eosinopenia, and thrombocytopenia (Table). A blood sample was collected into tubes containing sodium citrate to evaluate clotting times.

Clinical examination and radiological, hematological, and blood gas findings supported the diagnosis of an acute hypoxemic respiratory failure (AHRF) probably due to pulmonary edema and hemorrhage. The etiological hypotheses considered in the differential diagnosis were as follows: aspiration pneumonia, pulmonary contusion, inhalation of hot or toxic gases, drug or toxin exposures (i.e., anticoagulant rodenticide poisoning), and other causes of acute respiratory distress syndrome (ARDS).[15]

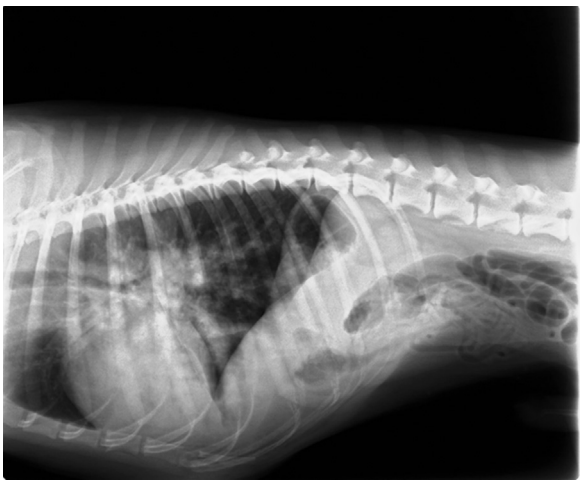

Fig. 1. Day 1 (afternoon). Chest X-ray: radiating perihilar interstitial pattern and patchy alveolar infiltrates, luminal narrowing at the tracheal bifurcation.

Table
Arterial Blood Gas Analysis, Lactate, and Hematological Findings Throughout Hospitalization

Parameter	Normal Values	Day 1	Day 1 (after 6 h)	Day 2	Day 4
pH	7.35-7.45	7.42	7.48	7.54	7.48
HCO_3^- (mmol/L)	22-27	18.7	14.7	21.4	27.5
$PaCO_2$ (mm Hg)	35-45	28.9	19.6	24.8	37.1
PaO_2 (mm Hg)	80-110	58	44	44	64
PaO_2/FiO_2 (mm Hg)	>300	276	≤209*	≤209*	304
Lactate (mmol/L)	<2.5	3.20	7.88	7.70	6.71
RBC ($\times 10^{12}$/L)	5.65-8.87	4.39	/	5.01	5.28
PCV (%)	37.3-61.7	29.4	29	33.5	35.1
Hemoglobin (g/L)	131-205	106	/	121	128
Reticulocytes ($\times 10^9$/L)	10-110	96.1	/	94.7	204.3
WBC ($\times 10^9$/L)	5.05-6.76	28.16	/	31.48	32.16
Neutrophils ($\times 10^9$/L)	2.95-11.64	24.11	/	26.68	24.64
Lymphocytes ($\times 10^9$/L)	1.05-5.10	1.97	/	2.48	3.22
Monocytes ($\times 10^9$/L)	0.16-1.12	2.05	/	2.31	4.20
Eosinophils ($\times 10^9$/L)	0.06-1.23	0.01	/	0.00	0.08
Basophils ($\times 10^9$/L)	0.00-0.10	0.02	/	0.01	0.02
Platelets ($\times 10^9$/L)	148-484	92	/	92	91

* In oxygen cage (oxygen > 21%).

To reduce respiratory distress, edema and pulmonary hemorrhage, methadone (0.1 mg/kg intramuscularly, IM; every 6 hours; Semfortan, Eurovet Animal Health B.V., Segrate, MI, Italy), furosemide (2 mg/kg intravenously, IV; twice a day, BID; Diuren, Teknofarma S.p.a., Turin, Italy) and tranexamic acid (15 mg/kg IV, BID; Ugurol, Rottapharm S.p.a., Monza e Brianza, Italy) were administered respectively.

The dog was hospitalized in an oxygen cage. The respiratory rate was constantly monitored and methadone was repeated every 6 hours.

To the initial therapy, the following drugs were added: ceftriaxone (50 mg/kg IV; once a day, SID; Ceftriaxone Hexal S.p.a., Agrate Brianza, Monza e Brianza, Italy) and doxycycline (10 mg/kg orally, OS; SID; Ronaxan, Merial Italia S.p.a., Noventa Padovana, PD, Italy), to control a probable bacterial pneumonia; *N*-acetylcysteine (140 mg/kg in bolus followed by 70 mg/kg IV; SID; Fluimucil, Zambon Italia s.r.l., Bresso, MI, Italy) and glutathione (33 mg/kg IV; SID; TAD, Biomedica Foscama Industria Chimico-Farmaceutica S.p.a., Ferentino, FR, Italy), for their antioxidant effects; cyanocobalamin/thiamine association (1/100 mg, IV; SID; Dobetin B1 10,000, Esteve S.p.a., Milan, Italy), as hepatoprotector/antianemic support; metoclopramide (0.2 mg/kg IV; BID; Vomend, Eurovet Animal Health B.V., Bladel, The Netherland) and ranitidine (1 mg/kg IV, BID; Zantadine, Ceva Salute Animale S.p.a., Agrate Brianza, Monza e Brianza, Italy), as gastroprotective therapy; phytomenadione (5 mg/kg IV; BID; Konakion, Roche S.p.a., Monza e Brianza, Italy), pending the results of coagulation tests, because the history could not exclude an anticoagulant rodenticide poisoning.

The ABG analysis performed after 6 hours showed a worsening in the results, with respiratory alkalosis, more severe hypoxia and metabolic acidosis due to hypoxic hyperlactatemia (Table). CXR confirmed the worsening with development into pneumonia (Fig 2).

The next morning, ABG and CXR were performed. The ABG showed a further increase in blood pH as the result of an improvement of both metabolic acidosis and respiratory alkalosis, likely due to the normalization of the respiratory rate. Despite the increase of the fraction of inspired oxygen (FiO_2), due to the oxygen-enriched air in the oxygen cage (approximately 40%), the arterial partial oxygen pressure (PaO_2) remained unchanged