Tremorgenic mycotoxin intoxication with penitrem A and roquefortine in two dogs

Kristin L. Young, DVM; David Villar, DVM, PhD; Thomas L. Carson, DVM, PhD, DABVT; Paula M. Imerman, PhD; Ronda A. Moore, BS; Michael R. Bottoff, DVM

An 11-year-old female Labrador Retriever was admitted to a veterinary clinic early in the morning because the owners noticed that the dog was vocalizing, appeared weak, and was panting heavily. At the time of admission, the dog was tachypneic, hyperexcitable, and tachycardic (190 beats/min). On palpation, the abdomen was tense and seemed painful, and the dog had striking generalized muscle fasciculations and hyperextension of all extremities. The dog also had blepharospasms.

Immediate treatment to control muscle fasciculations and hyperesthesia was instituted with 3 doses of diazepam (60 mg, IV, q 10 min) along with IV administration of fluid. At approximately 11 AM, the dog began to vomit and was assisted in an attempt to avoid aspiration. The vomit did not appear as typical from the ingestion of pelleted food, but instead consisted of black tarry lumps that were 3 to 4 mm in diameter with white flecks on a side; the vomit also had a putrid fishy odor. Because muscle fasciculations and hyperextension of all extremities. The dog also had blepharospasms.

The following morning, minor muscle tremors were still noticeable, and the dog had some agitation and exaggerated responses to noise and other stimuli. However, later that afternoon, clinical signs of hyperkinesia had completely resolved, and IV administration of fluid was stopped. The dog was still unable to walk completely and dropped its hind limbs when assisted for a walk but was able to wag its tail again. The next day, the dog was still ataxic on its hind limbs but was able to walk without assistance and was therefore discharged. The dog made a full recovery, and on a recheck examination the following week, the owners simply reported that the dog had slight lethargy.

A tentative diagnosis of strychnine poisoning had been made at the time of the initial admission. However, the owners reported that the dog got into the garbage the night before and that they had found a moldy cream cheese wrapper with a similar smell to the vomited material. The owners had thrown away 2 packages of cream cheese that were half full and had become completely overgrown with mold after being in the refrigerator for approximately 3 months. The moldy cream cheese foil wrapper obtained from the garbage was submitted to the Veterinary Diagnostic Laboratory at the Iowa State University for analysis of tremorgenic mycotoxins. Penitrem A and roquefortine C were identified by initial thin-layer chromatography and subsequently quantified by high-pressure liquid chromatography at 3.5 and 37 ppm (µg/g), respectively.²

³

A 3-year-old male yellow Labrador Retriever was admitted to a veterinary clinic shortly after 9:00 AM because the dog was in status epilepticus. According to the owners, the dog had ingested moldy macaroni and cheese at 7:00 AM, vomited 3 to 4 times by 8:30 AM, and was seizing at 9:00 AM. Upon arrival to the clinic, the dog received repeated doses of diazepam (60 mg, IV) to effect. Thiopental sodium was given to effect for sedation, and a gastric lavage followed by activated charcoal administration was performed. The dog was later referred to the Iowa State University Veterinary Teaching Hospital because of severe clinical signs of respiratory distress. Aspiration pneumonia was diagnosed on the basis of findings on thoracic radiographs and the results of arterial blood gas analysis. The dog eventually recovered following a week of intensive treatment with antimicrobials, oxygen administration,
nebulization with acetylcysteine, and supportive care. The offending moldy macaroni and cheese was analyzed at the Veterinary Diagnostic Laboratory at the Iowa State University, and penitrem A was detected at concentrations estimated to be between 20 and 50 ppm (µg/g) by a thin-layer chromatography method.7

Roquefortine and penitrem A are tremorgenic mycotoxins that should be suspected as differentials for acute onset of convulsive seizures similar to what might be expected with strychnine poisoning. There are not many reported instances of roquefortine toxicity in the literature, probably because they go largely underdiagnosed. Interestingly, some veterinary diagnostic laboratories routinely check for these tremorgenic mycotoxins in samples that have negative results for strychnine.7 To our knowledge, of the 2 toxins, penitrem A has been most commonly incriminated as a cause of intoxication in the literature7 and also identified previously at the Iowa State University Diagnostic Laboratory. Results of mycologic studies indicate that roquefortine and penitrem can be synthesized concurrently by Penicillium crustosum after growth and sporulation.7 However, the conditions that favor the relative production of each mycotoxin remain unclear. In the affected dogs of our report, roquefortine was the predominant mycotoxin present in the moldy cream cheese wrapper, and penitrem A was the only mycotoxin detected in the macaroni and cheese. Penitrem A has been previously found in overwintered, moldy walnuts where favorable conditions apparently develop for the growth of P crustosum.8

The exact mechanism of action of tremorgenic mycotoxins is unknown; however, results of in vitro studies indicate that penitrem A interferes with the spontaneous release of transmitter amino acids (ie, glutamate, aspartic acid, and γ-aminobutyric acid) in central and peripheral synapses, and there is indication that inhibition of glycine transmission in the inhibitory neurons may also play a role.9 This could in turn facilitate transmission of impulses across the motor end plate and result in loss of coordination of neural mechanisms controlling muscle action and brain stem reflexes. Results of pathologic studies in rats indicate that ingestion of penitrem A (3 mg/kg [1.4 mg/lb]) results in widespread necrosis and loss of Purkinje neurons in rats that make a complete recovery from the initial tremorgenic phases and are apparently clinically normal days to months after the exposure.9 Lesions were confined to the cerebellum and were typical of ischemic neuronal necrosis, which develops in response to unchecked excitotoxic neurotransmitters such as glutamate and aspartic acid. We are not aware of long-lasting effects attributed to penitrem A or roquefortine toxicosis in dogs, because affected dogs either succumb during the convulsive crisis or eventually make a full recovery.

Treatment of dogs with tremorgenic mycotoxin intoxication involves supportive care. Once the patient is receiving fluids IV, diazepam administration is usually recommended initially to control seizures. If this is insufficient to control excessive muscle fasciculations and hyperesthesia, methocarbamol (55 to 220 mg/kg [25 to 100 mg/lb], IV, to effect and at a rate of ≤ 2 mL/min) or barbiturates should be administered.10 Additional clinical signs of tremorgenic mycotoxin intoxication that can develop and may require treatment include hyperthermia, exhaustion, dehydration, metabolic acidosis, and rhabdomyolysis.10 To our knowledge, clinical signs of CNS involvement resolve within 24 to 48 hours following appropriate treatment. In another report of roquefortine toxicosis in 6 dogs, 4 had vomited and responded well to treatment, and the 2 other died despite barbiturate treatment.5 Of the 2 dead dogs, 1 had developed aspiration pneumonia from an attempted gastric lavage.3 In the second dog that died, it was unclear whether gastric lavage or the initial episodes of vomiting had caused the dog to develop aspiration pneumonia. Nevertheless, on the basis of the potential risk of aspiration, any attempts to remove the offending material and administer activated charcoal should be approached with extreme caution.

On the basis of findings in the dogs of our report, dog owners should be informed to dispose properly of moldy products such that they do not become accessible to dogs. Veterinarians should also be aware that clinical signs of CNS stimulation and vomiting following garbage ingestion might incriminate the ingestion of moldy dairy products.

References