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Case Report

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Cholinergic Mushroom Poisoning With a Detection of Muscarine Toxin in Urine

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Abstract

We report an uncommon case of cholinergic poisoning following an ingestion of wild mushrooms. Two middle-aged patients presented to the emergency unit with acute gastrointestinal symptoms including epigastric pain, vomiting and diarrhea, followed by miosis, palpitations and diaphoresis which were compatible with a cholinergic toxidrome. The patients volunteered a history of taking two tablespoons of cooked wild mushrooms collected in a country park. Mildly elevated liver transaminase was noted in one female patient. Mushroom specimens were sent to a mycologist for identification using morphological analysis. Muscarine, a cholinergic toxin found in mushrooms such as *Inocybe* and *Clitocybe* species, was subsequently extracted from and identified in the urine specimens of both patients, using a liquid-chromatography tandem mass spectrometry method. In this report, the variable clinical presentation of cholinergic mushroom poisoning is discussed. Key issues in the management of these cases were presented. In addition to conventional mushroom identification methods, this report also highlights the use of toxicology tests on different biological and non-biological specimens for diagnosis, prognosis and surveillance purposes.

Keywords: Cholinergic toxidrome; Gastrointestinal toxicity; Muscarine; Mushroom poisoning

Introduction

Every year, thousands of mushroom poisoning cases are reported worldwide [1-3]. There are regional differences in the incidence of mushroom poisoning globally, but high-quality epidemiological data are lacking. The average annual incidences were estimated to be 1.7 cases per 100,000 in the United States [4] and 5.0 cases per 100,000 in Switzerland [5]. Poisoning caused by muscarinic mushrooms is considerably rarer: an average of one to two cases yearly were reported by poison centers in Northern Italy [6], Israel [7], and Hong Kong [8]. Only isolated cases were reported in the literature [9-14], but the exact incidence worldwide is unknown.

Muscarine is most commonly found in mushrooms such as *Inocybe* and *Clitocybe* species [2]. It was first identified in *Amanita muscaria* [15] and subsequently it was also isolated in *Entoloma, Mycena, Boletus, Hygrocybe, Lactarius* and *Russula* species [16, 17]. Examples of muscarine-containing wild mushrooms are shown in Figure 1.

When muscarinic mushrooms are ingested, muscarine stimulates postganglionic cholinergic receptors in the autonomic nervous system, causing a cholinergic toxidrome that may include symptoms such as diarrhea, urinary frequency, miosis, bradycardia, bronchorrhea, vomiting, lacrimation, lethargy and hypersalivation [2, 18]. Clinical manifestations of muscarine poisoning are usually mild and self-limiting [2], but fatal cases due to parasympathetic overdrive causing severe hemodynamic compromise have been reported [9, 10].

Here we report two cases of cholinergic poisoning with exposure to muscarinic mushrooms in Hong Kong. The clinical and biochemical features are described and compared with reported cases in the literature.

Case Report

Investigations

A 49-year-old woman and a 37-year-old man presented to the emergency unit with an acute onset of gastrointestinal symptoms including epigastric pain, vomiting and diarrhea; this was followed by salivation, palpitations and diaphoresis approximately 1 h after the ingestion of two tablespoons of cooked wild mushrooms picked from a local country park. The clinical presentations were compatible with a cholinergic toxidrome. The patients also complained of lower limb numbness and drowsiness. There was no hallucination, chest pain or shortness of breath.

The patients were normotensive and had stable vital signs. Physical examination of the patients revealed miosis (bilateral equal pupil size 2 mm) with an otherwise unremarkable neu-

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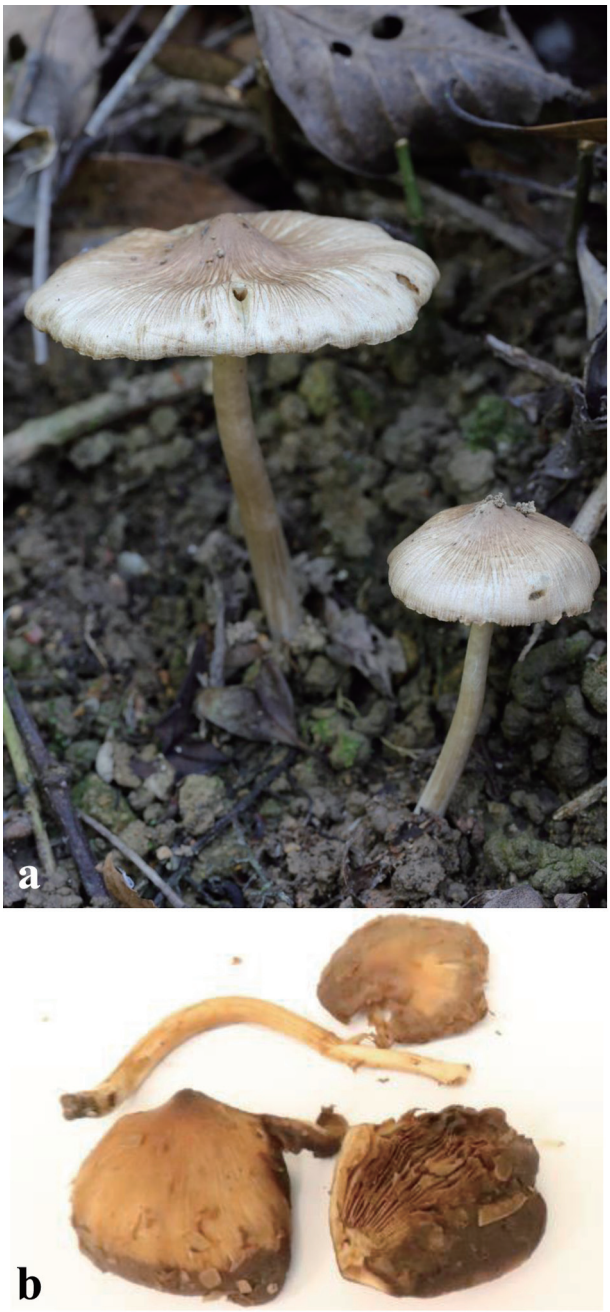

Figure 1. Examples of muscarine-containing mushrooms. (a) An *Inocybe rimosa* mushroom picked from a country park. (b) An Inosperma species collected by hikers from a mountain.

rological examination. Their Glasgow Coma Scale score was 15/15. There was no muscle power deficit with normal tendon reflexes and intact sensation. Electrocardiogram showed sinus rhythm with normal heart rate. Biochemical tests revealed that the female patient had mildly elevated liver enzymes (alanine transaminase 50 IU/L; alkaline phosphatase 114 IU/L) and a normal total bilirubin of 9 µmol/L. The other patient had normal liver function test results. The complete blood counts, serum amylase and glucose were all unremarkable.

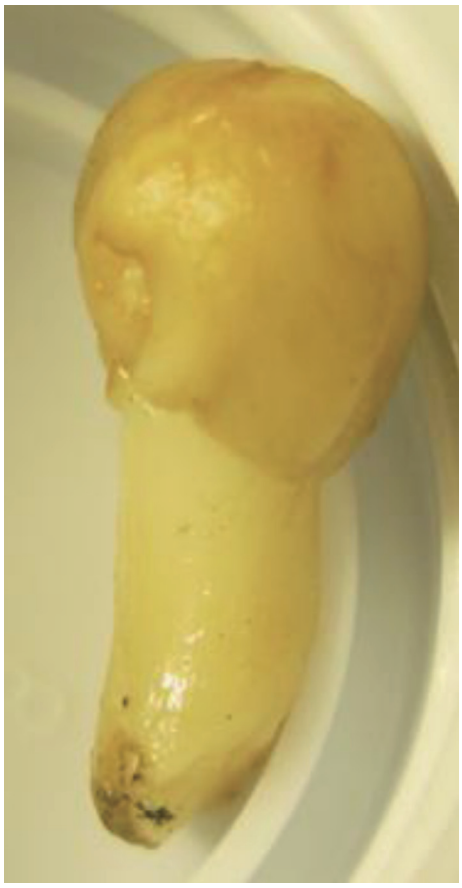

Figure 2. A small (1.5 cm in length) piece of cooked mushroom saved by the patients for morphological identification.

Diagnosis

A mushroom specimen was collected from the patients, and this was sent to a mycologist for identification (Fig. 2). The small, cooked mushroom measuring 1.5 cm in length was identified by the mycologist to be *Psathyrella incerta.* The morphological identification result, however, could not explain the patients' clinical cholinergic toxidrome.

The apparent cholinergic toxidrome led to a suspicion of muscarine mushroom poisoning. A urine specimen was collected after admission to look for muscarine toxin, which was extracted and tested using a liquid-chromatography tandem mass spectrometry method.

To extract muscarine from urine specimens, different solid phase extraction (SPE) methods were tested to give the cleanest extract for analysis. As muscarine is a quaternary amine, which is known to be a very polar compound and a strong base, Waters HLB, MCX and WCX cartridges were chosen for optimization. The mixed-mode weak ion exchange SPE method using Waters WCX cartridge, which is a cation exchange sorbent, was shown to produce the best signals. Edrophonium was used as an internal standard as it shares similar chemical properties with muscarine. The sample was subjected to a liquid-chromatography using a hydrophilic interaction liquid

chromatography (HILIC) column for polar analytes and a tandem mass spectrometry method using SCIEX 5500Q operating in the multiple ion monitoring (MRM) mode. The MRM is obtained by infusing standard muscarine chloride hydrate into the system. The compound was monitored by three MRM transition pairs (174.1→57.1, 174.1→115.1 and 174.1→60.1). The percentage relative intensities of the three transition pairs were compared with and should correspond to that of the reference standard. A negative and two levels of urine positive quality control (QC) spiked at 6 and 10 ng/mL respectively were performed on each analysis.

The limit of detection of 2 ng/mL was obtained by spiking five level standards in 10 urine matrixes. The limit of quantification was not determined and no calibration curve was obtained as this was a qualitative test only. Ten patient urine specimens and 10 negative control specimens were obtained from individuals known to be free from muscarine exposure; no non-specificity was observed. The analytical results are reported qualitatively as detected or not detected. Muscarine was subsequently identified in patients' urine specimens, thus confirming muscarine exposure.

Treatment

The Poison Information Centre was consulted. The patients were given supportive treatment at the emergency department. Activated charcoal was given to the patients under close monitoring. Intravenous fluids were not used as there was no significant hypotension observed in these patients. Atropine was considered in view of the cholinergic toxidrome but it was not given to the patients as their cholinergic symptoms were self-limiting.

Follow-up and outcomes

The patients were subsequently transferred to medical wards for close observation for a further 24 h to look for any delayed presentations. Blood tests for liver and renal function tests were repeated and were unremarkable. Their gastrointestinal and cholinergic symptoms gradually subsided. After 3 days of hospital stay, they fully recovered. The patients were discharged with follow-up appointments scheduled 2 months after the admission.

Discussion

We reported two cases of cholinergic mushroom poisoning with classical signs and symptoms. Muscarine was detected in patients' urine specimens which confirmed the diagnosis.

Muscarinic mushroom poisoning cases typically have a mild clinical course and a rapid onset time within 30 to 120 min of exposure [7, 8, 13, 14]. An exception was reported in one Israeli patient who presented 5 h after consuming toxic mushrooms [7]. The symptoms usually subside within 24 h. Gastrointestinal symptoms are the most frequently reported with up to 90% of patients experienced symptoms mimicking gastroenteritis [7, 8]. Profuse sweating is the most useful clinical presentation in differentiating poisoning induced by cholinergic mushrooms and gastroenteritic mushrooms (personal communication, Dr. CK Chan). In our case, both patients reported profuse sweating, salivation and palpitations 40 min after ingesting wild mushrooms. They also complained of drowsiness, which was unexpected as muscarine is not known to cross the blood-brain barrier [2]. In a review of 14 cases by Lurie et al, none of the patients had central muscarinic effects which may include sedation, rigidity or convulsions [7]. The presentation and the severity of symptoms can vary among individuals from the same cluster of poisoning cases [7, 14].

It is estimated that the mushroom toxins remained unidentified in more than 90% of cases [18]. Currently, morphological examination remains the gold standard for identifying toxic mushrooms. In our report, the unknown mushroom was identified to be *Psathyrella incerta*. From the literature, *Psathyrella incerta* has a clear yellowish, convex cap and non-distinctive odour and taste [19]. However, it was neither known to contain muscarine nor associated with cholinergic toxidromes upon ingestion. Morphological identification is laborious and requires experts with local mycological knowledge. Microscopic examination of intact mushroom is seldom possible in the emergency setting where clinical samples are often incomplete and may come in the form of leftovers from a cooked dish, vomitus or gastric lavages. Contrary to common misconceptions, muscarine is a thermostable compound and is not destroyed by cooking [18]. Biochemical detection of muscarine helps to determine patients' prognosis and treatment options.

Treatment of cholinergic mushroom poisoning is mainly supportive [2, 14, 18]. In our case, gastric decontamination using activated charcoal was given. Repeated doses of activated charcoal were shown to enhance the excretion of amatoxin [17], but its role in excreting muscarine remains controversial [7, 14]. In cases with hypotension and severe symptoms associated with muscarine overstimulation, intravenous atropine may be considered [17]. In a case series reported by Lurie et al, five out of 14 patients required low-dose atropine [7], whereas two out of five patients from the same family in Malaysia required atropine treatment [14]. Fluid resuscitation should be provided to correct any volume depletion or electrolyte imbalance. In our case, one patient was noted to have elevated liver transaminases. In a small case series, Chew et al also reported two patients from the same family with deranged liver function tests [14], whereas Lurie et al reported one middle-aged female with mild renal impairment, probably caused by fluid depletion from recurrent vomiting and diarrhea [7]. These patients should be closely monitored for any liver or renal impairment. Cholinergic mushroom poisoning is mostly self-limiting and only on rare occasions fatal cases were reported [9, 10]. In the United States, none of the fatal cases reported in a retrospective review was induced by cholinergic mushrooms [20].

Muscarinic mushrooms, often with appearances mimicking edible mushrooms [7], tend to fruit in urban area [21]. In our case, the mushrooms were picked in a country park. With the discovery of more diverse muscarine-containing species [7, 9, 13], it is important for medical professionals to be aware of these mushrooms being the culprits of such toxidromes.

In conclusion, we have reported two cases of cholinergic mushroom poisoning. The clinical features and mushroom species associated with cholinergic toxicity are likely under-reported and under-diagnosed. The course of illness is usually mild and self-limiting with the management mainly being supportive. Muscarine testing may be advantageous for the early confirmation of the diagnosis and to uncover cases of poisoning induced by muscarinic mushrooms.

Learning points

Cholinergic mushroom poisoning is uncommon - only a limited number of cases were reported in the literature. Clinical presentations of profuse sweating, salivation and palpitation, as well as gastrointestinal symptoms, are experienced by patients with a rapid time of onset. Together with a history of consuming wild mushrooms, poisoning by muscarine-containing fungi needs to be considered. Muscarine testing in the urine or other biological specimens would be particularly useful in confirming the diagnosis in cases with ambiguous presentations. It would also serve as an important tool for prognostication purposes and clinical surveillance.

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Conflict of Interest

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Informed Consent

Verbal consent was obtained. Data were anonymized and written informed consent was waived by an ethics committee because minimal patient data have been included in the manuscript.

Author Contributions

Study conception and design: TYC Chan, CK Chan, HHC Lee, TWL Mak; data collection: TYC Chan, SW Ng, CK Chan; analysis and interpretation of results: TYC Chan, SW Ng, CK Chan, HHC Lee; draft manuscript preparation: TYC Chan, SW Ng, CK Chan, HHC Lee, TWL Mak. All authors reviewed the results and approved the final version of the manuscript.

Data Availability

The authors declare that data supporting the findings of this study are available within the article.

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