Case Report

Death due to Ichthyotoxicosis: A Report of Death Following Consumption of Pufferfish

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ABSTRACT

Inadvertent consumption of toxic varieties of fish mistaken to be edible, results in the development of toxic signs and symptoms and fatality, and this phenomenon of toxicity by poisonous fish is referred to as ichthyotoxicosis. Pufferfish is a variety of poisonous fish, which contains a potent toxin called "tetrodotoxin," which is a neurotoxin. This case report deals with a case of poisoning following inadvertent consumption of pufferfish by a child. The child developed vomiting, altered sensorium and respiratory depression and was declared dead on arrival at the casualty despite emergency management. Histopathological examination revealed congestion and haemorrhages in the viscera, and blood culture showed growth of *Aeromonas hydrophila*.

Key Words: Ichthyotoxicosis; Pufferfish; Tetrodotoxin; *Aeromonas hydrophila*

INTRODUCTION

Accidental poisoning, including numerous deaths, have been reported from all over the world due to consumption of pufferfish. The majority of reported cases have occurred in Southeastern Asia, especially Malaysia, Taiwan, Hong Kong, and Korea.[1] Pufferfish is the second most poisonous vertebrate in the world, the first being the "golden poison frog."[2] Pufferfish contains a powerful and complex neurotoxin called tetrodotoxin (TTX). Tetrodotoxin (TTX) is a non-protein organic compound (aminoperhydroquinazoline), and one of the strongest marine paralytic toxins known today. TTX is named after the order of fish from which it is most commonly associated, the Tetradontiformes (*tetras* - *four* and *odontos* - *tooth*), or the tetraodon pufferfish. The liver, gonads, intestines, and skin of these fish contain tetrodotoxin, which is heat stable and can cause death in approximately 60% of persons who ingest it. The toxin has only occasionally been detected in the muscles of these fishes. If cleaned and dressed properly, the puffer flesh or musculature is edible and considered a delicacy by some persons in Japan.[1] In India, incidence of poisoning due to consumption of this type of fish is not very common.

The Case: The victim was a 14-year-old boy. The father stated that the family had gone fishing in the estuarine area of a river, and brought home a few "different types" of fish, which they had never consumed before, among the other regularly consumed ones. One of these "different-looking" fish was cooked and one of the remaining uncooked fish of the same type were shown to us and were identified as "pufferfish." Of all the family members, only the boy consumed the whole of this fish at dinner at around 9 pm and went to bed. About 2 hrs later, he woke up with tingling and numbness in the face, headache, vomiting, abdominal pain, marked weakness and altered sensorium. The victim was brought to the Casualty of Goa Medical College at about 12.50 am.

On examination, the pulse rate was 80/min, and the BP was 130/90 mmHg. The boy was hypoventilating with depressed respiratory rate of 7/min, and had cyanosis with paralysis of limbs. A CT scan was done to rule out head injury and was reported to be normal. At 1.15 am,

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after the scan, no breath sounds were present, the patient was deeply cyanotic, pulseless, and BP was unrecordable, and the victim was declared dead.

The body was subjected to autopsy. Examination revealed cyanosis the nail beds and lips. Marked cerebral congestion and oedema were present. Marked pulmonary congestion and oedema were also observed. Liver, spleen, and kidneys were also congested. A few masticated food particles were visible in the stomach. Significant portions of the consumed fish were not visible in the stomach, as most likely they had been vomited out by the child, as there was positive history of vomiting.

Histopathological examination revealed marked congestion and a few areas of haemorrhage in the brain. Lungs showed pulmonary oedema, congestion and a few areas of haemorrhage. Liver showed dilatation and congestion of sinusoids, increase in inflammatory infiltrate comprising neutrophils, lymphocytes and histiocytes in portal tracts. Kidneys and spleen showed congestion and areas of haemorrhages. Myocardium was also congested.

Blood culture revealed growth of *Aeromonas hydrophila* (**Fig 1**), which was confirmed by biochemical tests. This microorganism is a rod-shaped, non-spore forming, oxidase-positive, glucose-fermenting, facultative anaerobic, gram-negative bacterium that inhabits aquatic environments (**Fig 2**). Antibiotic sensitivity tests showed resistance to amoxycillin + clavulanic acid, tetracycline, roxithromycin, chloramphenicol, carbenicillin, nalidixic acid, tazobactam + piperacillin, and sensitivity to trimethoprim + sulfamethoxazole, amikacin, gentamycin, cefuroxime, cefoperazone, ceftriaxone, cefotaxime, ceftazidime, norfloxacin, ciprofloxacin, ticarcillin, cloxacillin and lomefloxacin.

The cause of death was opined as "death due to acute toxicity consequent to consumption of poisonous fish."

Fig 1: *Aeromonas hydrophila* (on culture)

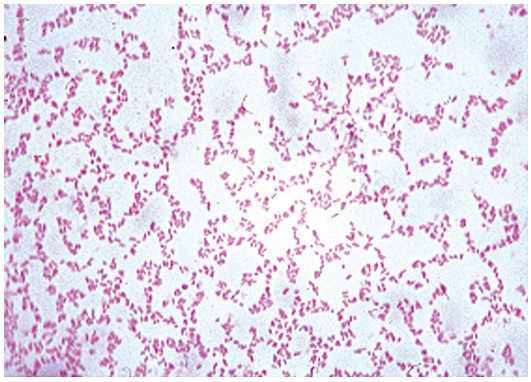

Fig 2: *Aeromonas hydrophila* (under microscope)

DISCUSSION

Pufferfish: Tetraodontidae is a family of primarily marine and estuarine fish of the order Tetraodontiformes. The family includes many familiar species, which are variously called pufferfish, puffers, balloonfish, blowfish, bubblefish, globefish, swellfish, toadfish, toadies, honey toads, sugar toads, and sea squab. They are named after their habit of inflating themselves with water or air when threatened, making it difficult for a predator to swallow them. They are most diverse in the tropics and relatively uncommon in the temperate zone and completely absent from cold waters.[1] There are 189 species of pufferfish and 28 genera in the family Tetraodontidae. In this case, the species involved was *Tetraodon nigroviridis* (green spotted pufferfish) (**Fig 3**).

Tetraodon nigroviridis or green spotted pufferfish reaches a typical maximum length of about 15 cm (5.9 in), with reports of up to 17 cm. It is found across South and Southeast Asia in coastal freshwater and brackish water habitats. It is greenish in colour with black spots. Its belly is white and its fins/tail are light green.[3,4]

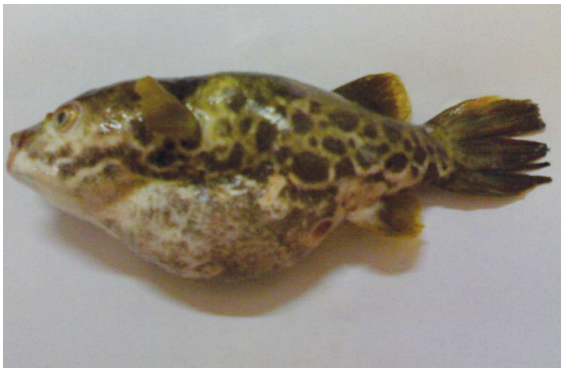

Fig 3: *Tetraodon nigroviridis* (green spotted pufferfish)

Tetrodotoxin: The chemical name is octahydro-12-(hydroxymethyl)-2-imino-5,9:7,10a-dimethano-10aH-[1,3]dioxocino[6,5-d]pyrimidine-4,7,10,11,12-pentol. The molecular formula is C11H17N3O8. Tetrodotoxin is not an alkaloid, steroid or carbohydrate, and it is not like any conventional amino acid. It is a low molecular weight, small molecule with a unique cage structure. Tetrodotoxin exists in an equilibrium mixture of its ortho ester, anhydride and lactone forms.[5]

This neurotoxin is found primarily in the ovaries and liver, although smaller amounts exist in the intestines and skin, as well as trace amounts in muscle. Tetrodotoxin blocks action potentials in nerves by binding to the voltage-gated, fast sodium channels in nerve cell membranes, essentially preventing any affected nerve cells from firing by blocking the channels used in the process. The binding site of this toxin is located at the pore opening of the voltage-gated Na^+ channel.[6]

Although tetrodotoxin was discovered in pufferfish and found also in several other animals (e.g., blue-ringed octopus, rough-skinned newt), it is actually produced by certain symbiotic bacteria, such as *Aeromonas, Pseudoalteromonas*, certain species of *Pseudomonas* and *Vibrio*, *Pasteurella*, *Alteromonas*; *Escherichia,* etc.[7,8] The comparative toxicity was summarized by William H Light who said, weight for weight, tetrodotoxin is ten times as deadly as the venom of many-banded krait of Southeast Asia.[5] It is 10–100 times as lethal as black widow spider venom (depending on the species) and more than 1000 times deadlier than potassium cyanide. In humans, the lethal dose of tetrodotoxin is around 1–2 mg, and the minimum dose necessary to cause symptoms has been estimated to be 0.2 mg.[9,10]

Tetrodotoxin (TTX) binds specifically to sodium channels by mimicking the hydrated Na^+ ion, denying entry to Na^+ ions. It is considered as an irreversible inhibitor. It has been proposed that the binding between TTX and the Na channel results from the interaction between the positively charged guanidino group of TTX and the negatively charged carboxylate groups on the side chains at the mouth of the channels. Being much larger than the Na^+ ions, the bulk of the molecule blocks the entrance to the Na channel, preventing the flow of Na^+ ions until it slowly diffuses off. In addition, TTX has a tenacious hold on the Na channel, demonstrated by its occupancy time. Hydrated Na^+ ions bind reversibly to the channel on a timescale of nanoseconds. Comparatively, TTX binds and remains at the Na channel in the order of tens of seconds. As a consequence of TTX blockage, sodium ion movement is effectively shut down and the propagation of action potential ceases. The central and peripheral nervous systems are impaired, resulting in paralysis and death.[5]

Symptomatology: The first symptoms occur 15 min to several hours postingestion of tetrodotoxin-containing food. A recent report on toxicity found that initial symptoms may occur up to 20 hrs after ingestion. These include lip and tongue paraesthesias, followed by facial and extremity paraesthesias and numbness. Salivation, nausea, vomiting, and diarrhoea with abdominal pain develop early. Motor dysfunction with weakness, hypoventilation, and speech difficulties then develop. A rapidly progressing paralysis occurs over 4–24 hrs. Extremity paralysis precedes bulbar paralysis, which is followed by respiratory muscle paralysis. Deep tendon reflexes are preserved early in the course of paralysis. Finally, cardiac dysfunction with hypotension and dysrhythmias (bradycardia), central nervous system (CNS) dysfunction (e.g., coma), and seizures develop. Patients with severe toxicity may have deep coma, fixed nonreactive pupils, apnoea, and loss of all brain stem reflexes. Loss of sensory and motor neuron function is a prominent finding. Cyanosis occurs with respiratory failure. Hypotension can occur with myocardial dysfunction. Cardiac rhythm disturbances, especially bradycardia, atrioventricular (AV) nodal block, and bundle-branch block, can be life threatening.[11] Death can occur within 4–6 hrs. Typically, death occurs from respiratory muscle paralysis and respiratory failure.

DIAGNOSIS AND TREATMENT

No specific laboratory test that confirms tetrodotoxin ingestion exists; thus, dietary history is key for diagnosis. Mouse bioassays for paralytic shellfish toxin (i.e., saxitoxin) exist that are positive with tetrodotoxin. There are research chromatography techniques for tetrodotoxin as well, but neither is available in the acute clinical situation. Analogues of tetrodotoxin have been identified by a combination of liquid chromatography and electrospray ionization mass spectrometry. Tetrodotoxin also may be detected by fluorescent spectrometry. Measurement of routine serum electrolytes, calcium, magnesium, and ABGs is to be done to rule out metabolic causes of diffuse sensory and motor neuron dysfunction.

Prehospital care is to be provided with careful attention to the airway, breathing, and circulation (ABCs).

Patients may require endotracheal intubation for oxygenation and airway protection in the setting of muscle weakness and respiratory failure, which can occur soon after ingestion of the tetrodotoxin. Cardiac dysfunction may require IV intervention with fluids, pressors, and antiarrhythmics.

Severely poisoned patients may be very weak, have difficulty speaking, and be unable to provide a history. Thus, clues from the environment and bystanders are very important. The toxin is to be removed from the intestinal tract by the usual toxicologic modalities. The use of nasogastric or orogastric lavage is theoretically beneficial but can be complicated by aspiration and damage to the oesophagus. If vomiting has occurred, gastric lavage is not indicated.

The administration of activated charcoal (with or without a cathartic) is recommended for all symptomatic patients. Activated charcoal is empirically used to minimize systemic absorption of the toxin. It may only benefit if administered within 1–2 hrs of ingestion. Careful monitoring of vital signs and oxygenation is important, because patients can decompensate suddenly. All alterations in vital signs are to be treated aggressively. Further treatment should focus on supporting cardiovascular function until the toxin is eliminated from the body.[11]

No specific antidote has been tested in humans. An animal study using monoclonal antibodies against TTX has been done.[12] Monoclonal antibodies were shown to be life saving in mice treated both before and after the ingestion of a lethal dose of TTX. Further studies are needed to document the efficacy in humans. In another animal study, 4-aminopyridine (a potassium channel blocker) was used in guinea pigs intoxicated with tetrodotoxin or saxitoxin. A dramatic improvement in respiratory, cardiac, and CNS status occurred after administration of the drug.[13] It acts by blocking potassium channels, prolonging action potentials and thereby increasing neurotransmitter release at the neuromuscular junction.[14] However, its effectiveness as an antidote in humans for TTX poisoning has not yet been established.[11] The anticholinesterase drug neostigmine has been proposed as a treatment option but has not been tested adequately. It may be useful in reversing the neurological complications of the venom; however, it should not be a substitute for airway management. Although not clinically proven, neostigmine has been used anecdotally to restore motor strength. It inhibits destruction of acetylcholine by acetylcholinesterase, which facilitates transmission of impulses across myoneural junction. Repeat doses are to be given based on patient's response.[11]

Mortality rates are difficult to establish; however, anecdotal reports suggest 50–60% mortality, even with good supportive care. Symptoms may last several days, even in nonlethal ingestions. Prognosis is good if the patient survives the first 24 hrs.[11]

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