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Unusual Subarachnoid Hemorrhage with Neurotoxicity after Consumption of Pufferfish: A Rare Case Report

Mohammed R Al-Tamimi, MD, Rashid M Khan, MD*

Department of Anesthesia & ICU, Khoula Hospital, Al Fahal St, Muscat, Oman

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***Corresponding author:** Dr. Rashid M Khan

Abstract **Case Report**

Ingestion of pufferfish can be extremely dangerous due to its poison. Victims may present with wide range of neurological and gastrointestinal symptoms. Manifestation may include nausea, vomiting, abdominal pain, numbness to perioral area, tongue and face, as well as muscle weakness and respiratory paralysis. In severe toxicity, cardiovascular system can be affected as well. In addition to severe hypotension, bradycardia and arrhythmias, patients may suffer convulsion and enter into deep coma. In this case report we describe a 40 years old male who ate puffer fish and went on to develop an extensive subarachnoid hemorrhage. The patient was transferred to our medical center on a ventilator. External ventricular drain was inserted for hydrocephalus. Intracranial pressure was kept within normal range. Digital subtraction angiography performed in our center excluded vascular pathology. During intensive care unit stay, the patient consistently spiked temperatures to 39 Celsius and above. The patient could be extubated 2 weeks later with a Glasgow coma scale of 13-14. External ventricular drain could also be removed but he soon became irritable, highly febrile, tachycardic and tachypneic with distended abdomen. Patient was re-intubated but progressed to fixed dilated pupils and sustained a cardiac c arrest from which he could not be resuscitated.

Keywords: Pufferfish; tetrodotoxin; subarachnoid hemorrhage.

INTRODUCTION

Pufferfish, also known as Albuqm in Oman, Fugu in Japan or Bok in Korea, is a very toxic fish. It is the second most poisonous animal in the world after the Golden Poison Frog [1]. Late in 17th century, Captain James Cook reported that he and two of his crew fell ill after eating a fish with a description of pufferfish [2]. In his book "A voyage towards the South Port and around the world" the captain described some symptoms of toxicity from the fish. The fish gain and accumulate toxins through food chain that begins from marine bacteria, which produce a neurotoxin known as tetrodotoxin (TTX) [3]. The toxin is more deadly than cyanide and cannot be degraded by cooking or freezing of fish flesh [4]. TTX binds to fast voltage-gated sodium channel and results in a temporary inhibition of nerve action potentials. This leads to both sensory and motor paralysis [5]. If not treated, the poison can kill more than a half of the victims. The survivors usually fully recover after 24 hours. Better outcome was noted among those who seek medical help early [6]. The main cause of death after pufferfish toxicity is respiratory failure [7]. There are also reports of death after cardiovascular collapse due to severe bradycardia resistant to anticholinergic and inotropic treatment [8]. Literatures have not yet described intracranial bleeding among these cases. We report a case of extensive subarachnoid hemorrhage (SAH) following TTX poisoning from puffer fish.

CASE REPORT

We present a case of 40 years old male patient who was not known to have any medical issues before, was referred to our hospital with intracranial bleed. The patient and his 5 co-workers gave history of eating puffer fish that was bought raw and fresh from a local fish seller. Few hours after consumption of fish and its eggs, all the 6 persons developed various gastrointestinal and neurological symptoms including nausea, vomiting, body numbness, and some had mild body weakness. Our patient's condition deteriorated into respiratory paralysis and his consciousness dropped into a Glasgow Coma Scale (GCS) of 6/15. He was intubated and mechanically ventilated in another hospital. Computed Tomography (CT) of the brain showed Subarachnoid Hemorrhage (SAH) mainly in pre-mesencephalic region and foramen magnum with intraventricular extension. In addition, there was

evidence of hydrocephalus (Fig-1). CT angiography of head and neck did not reveal abnormal vessels like aneurism or arteriovenous malformation. The patient was transferred to our neurosurgical center and treated for spontaneous SAH as per hospital guidelines. He was not investigated for the toxin as the investigation was not available in our hospital. External Ventricular Drain (EVD) was inserted for hydrocephalus. Intracranial pressure (ICP) was kept within normal range. Digital Subtraction Angiography (DSA) performed in our center also excluded vascular pathology. During Intensive Care Unit (ICU) stay, the patient consistently spiked temperatures to 39 Celsius and above. Antibiotics were started and then upgraded empirically to higher doses as ventriculitis secondary to EVD insertion was suspected. Multiple cerebrospinal Fluid (CSF) cultures reported negative. Apart from high-grade fever, the patient's condition remained stable over the following days. Ten days later the EVD was removed and the patient was extubated the day after. GCS remained 13-14 (confused but obeying commands). Follow up CT brain after 24hrs of EVD removal showed resolution of the bleeding with mild hydrocephalus (Fig-2). Two days after extubation the patient was noted to be irritable, highly febrile, tachycardic and tachypneic with distended abdomen. He was re-intubated and sedated. Urgent CT abdomen and pelvis was done but was reported to be normal. Pulmonary embolism was also excluded by CT pulmonary angiogram. Investigations revealed marked elevation of white blood counts (35.25/mcL), mostly neutrophils 10.30/mcL). Liver function test also showed high alanine aminotransferase and alanine phosphatase (344 U/L and 258 U/L respectively). Electrolytes were within normal range. Patient was noted to have dilated and fixed pupils. CT brain was not repeated due to cardiovascular instability that hindered patient's transfer for head imaging. The patient died later that day after cardiac arrest.

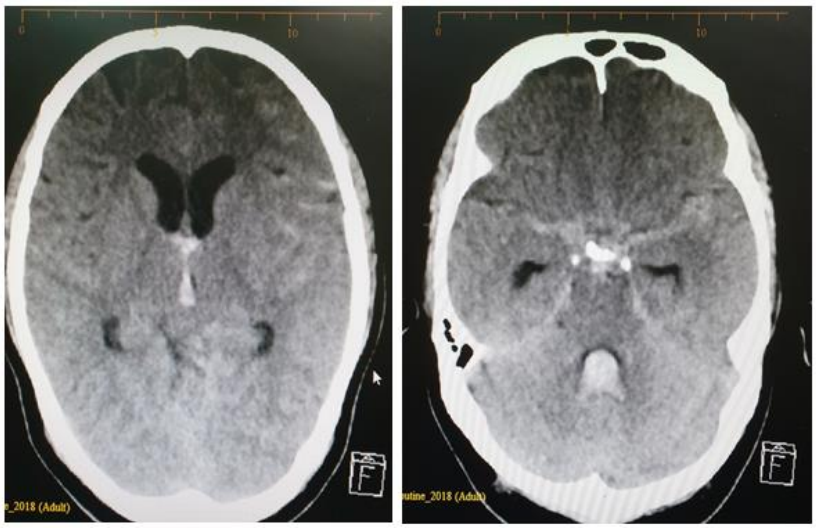

Fig-1: CT brain of the patient showing extensive SAH

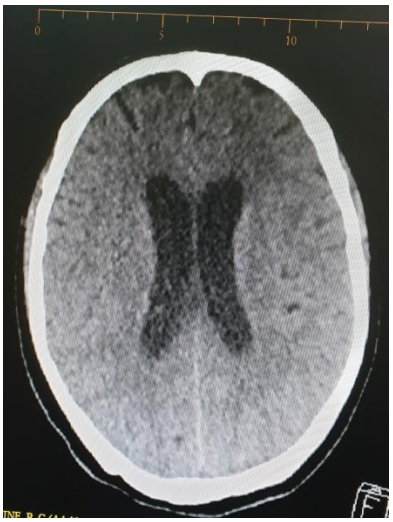

Fig-2: CT brain showing resolution of SAH and mild hydrocephalus

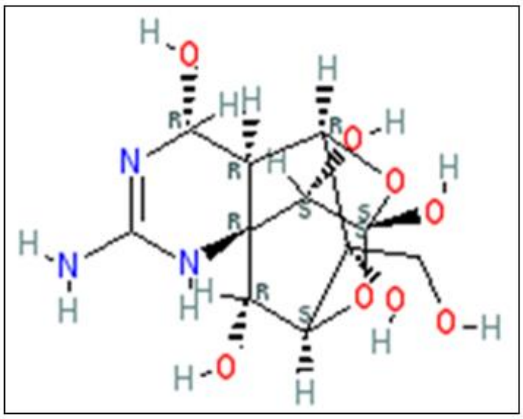

Fig-3: Chemical structure of Tetradotoxin

Table-1: Clinical Grading System for Tetrodotoxin toxicity

Clinical Grading System for Tetrodotoxin toxicity by Fuguda and Tani	
Grade	**Symptoms**
First	Oral numbness and paraesthesia, sometimes accompanied by gastrointestinal symptoms (nausea)
Second	Numbness of face and other areas, advanced paraesthesia, motor paralysis of extremities, incoordination, slurred speech, but still normal reflexes
Third	Gross muscular incoordination, aphonia, dysphagia, dyspnoea, cyanosis, drop in blood pressure, fixed/dilated pupils, precordial pain, but victims are still conscious
Forth	Severe respiratory failure and hypoxia, severe hypotension, bradycardia, cardiac arrhythmia, heart continues to pulsate for a short period

DISCUSSION

Tetraodontidae (refers to the 4 strong large teeth in their upper and lower jaws, tetra=four, odous=tooth) are family of many species of order Tetraodontiformes. There are more than 120 species of pufferfish worldwide with various level of toxicity in their bodies. They have various names including pufferfish, balloon fish, blowfish, bubble fish, swell fish, toad fish, honey toads and sea squab [9]. In Oman they are known as Albuqm or Alfigl. Mostly they are found in tropical and subtropical areas of Indian, Atlantic and Pacific sea [10]. Pufferfish contain the deadly poison TTX, which is believed to be 1200 times more poisonous than cyanide [11]. The toxin concentration remains higher in their livers throughout the year. However, during reproductive period, the females accumulate more toxin in the reproductive system and eggs. This is probably a defensive mechanism to protect their eggs from predators [3]. The puffer fish accumulate toxin through food chain that begins from marine bacteria such as Vibrio agenolyticus, Pseudoalteromonas that produce TTX.

TTX is an aminoperhydroquinazoline poison that was first isolated from pufferfish by Yokoo [12] in 1950 with a molecular formula $C_{11}H_{17}N_3O_8$ and weight of 319.27 g/mol (Fig-3). The dose of 1-4mg is fatal to a human. TTX is mainly a neurotoxin that binds to the extracellular pore opening of the fast-gated sodium channel causing temporary inhibition of nerve action potential. The interference in neuromuscular conduction results in paresthesia and paralysis of the victim [5]. Although TTX targets nervous system in the first place, cardiovascular and gastrointestinal systems are frequently affected. Diagnosis is usually clinical along with history of consumption of the poisonous fish [13]. Victims may present with wide range of symptoms including perioral paresthesia, numbness to face and extremities, body weakness, ascending paralysis within 24 hours, which may involve respiratory muscles at the later stage. In severe toxicity patient may develop seizures, inter into deep coma and lose all brainstem reflexes [7]. There are four clinical stages of the disease progression described by Tani and Fuguda (Table 1) [14]. So far, there is no antidote available and treatment is basically supportive [13]. This may include mechanical ventilation, volume expansion and gastric lavage. Muscle relaxant reversal by anticholinesterases may be helpful. A case reported by Kheifets et al from Israel showed a dramatic improvement of conscious level and muscle weakness in a victim with deep coma and dense muscle paralysis after treatment with neostigmine [15]. The mechanism may be due to increase in amount of acetylcholine in the nerve endplate that enhance neuromuscular reversal and boots nerve conduction. Our patient presented with both gastrointestinal and neurological symptoms that evolved into respiratory paralysis and deterioration of GCS. The drop of consciousness most probably was due to intracranial bleeding. Head trauma is the most common cause of SAH, while ruptured aneurysms cause around 80% of spontaneous bleeds [16]. CT angiogram followed by DSA brain and neck few days later did not show vascular pathology. Despite the absence of history of hypertension in this patient, a transient undocumented high BP could be the cause of bleeding. However other rare causes cannot be excluded. Coma lasting for several days following poisoning from the fish was also described [9], but it is not clear if that was related with intracranial pathology or bleed. Status epilepticus, post ictal period, or subclinical seizures could be the cause of the reported coma, yet intracranial bleeding is a possibility. Our patient was treated for CNS infection that was possibly secondary to CSF shunt insertion. Two days later after successful extubation, the patient's condition deteriorated suddenly and died. Cardiac issues and sepsis may be the cause of death in this patient.

CONCLUSION

This is to highlight the presentation of subarachnoid hemorrhage in a patient after ingestion of pufferfish. Neurological deterioration following pufferfish intoxication must be investigated thoroughly and brain imaging should be obtained to exclude intracranial hemorrhage. Early recognition and treatment of SAH may improve outcome in those patient who may otherwise go undiagnosed. SAH may be one of the causes of prolonged coma or death following severe toxicity from pufferfish.

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