Rare case of Stevens-Johnson-TEN overlap syndrome caused by mycotoxins

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Abstract: Mushroom poisoning is rarely associated with skin involvement. Stevens-Johnson syndrome (SJS) and toxic epidermal necrolysis (TEN) are life-threatening mucocutaneous reactions, characterized by extensive necrosis. SJS/TEN overlap includes patients with skin exfoliation between 10 to 30 percent of the body surface area. We report the case of a patient that was assumed to have ingested one type of toxic mushroom within the twelve hours prior to the appearance of skin lesions typical for SJS/TEN overlap syndrome.

Keywords: Amatoxin, skin involvement, SJS/TEN overlap, MODS

INTRODUCTION

Picking wild mushrooms is a very popular activity in European countries, therefore mushroom poisoning is a constant and serious health issue [1-3]. More than fifty species of toxic mushrooms are known, which are usually very similar to edible mushrooms. [4,5]

The most severe cases of mushroom poisoning are mainly caused by ciclopeptides – toxins contained by Amanita mushrooms. [2,5,6] The most frequent cause of death in mushroom poisoned patients is Amanitaphalloides, also called “the death cap”. [5-8] Toxic effects of Amanitaph. are determined by phallatoxins and amatoxins.[6,9] Phallatoxins are heptapeptides with severe toxic systemic effects that cannot be absorbed from the digestive tract.[10] However these toxins can induce gastrointestinal symptoms through lesions of the enterocytes. [1]

α-amanitin, the most important amatoxin, is resistant to all gastrointestinal fluids and after absorption it mainly locates in the hepatocytes.[10,11] After reaching the liver cells, α-amanitin binds DNA-dependent ribonucleic acid (RNA) polymerase II, with high specificity, causing protein synthesis inhibition.[11,12] Its toxic effects are also increased through the enterohepatic circulation of this toxin.[1,11]

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Histopathological results of these effects are initially represented by nuclear lipid and carbohydrate deposits and finally by hepatic centrolobular necrosis.[1,12] α-amanitin also affects other metabolically active tissues like the kidney or the gastrointestinal tract.[7,12,13] No cases of skin involvement secondary to Amanita ph. poisoning have been reported so far except erythromelalgia – a disease that is characterized by erythema and pain especially in the extremities – that was sometimes associated with some species of mushroom intoxication, but never with Amanita ph. Poisoning.[14,15]

Steven-Johnson syndrome (SJS) and toxic epidermal necrolysis (TEN) are rare but highly severe disorders that can affect patients of all ages.[16,17]

Caused by a variety of drugs, infections and rarely by toxins, SJS and TEN are defined as a hypersensitive cutaneous reaction that produces dermato-bullous skin lesions.[16,18-20] Pathogenesis of these conditions is controversial and involves genetic susceptibility (haplotypes like HLA B*1502, HLA B12 etc.), immune cells (especially T lymphocytes CD 8+), cytokines and mediators of cell death.[16,19,21]

Although initially was thought that SJS and TEN are separate entities, today it is considered that they are varying degrees of severity of the same disease.[22] The difference between these two forms of disease is represented by the percentage of the affected body surface area (BSA) – SJS detachment of <10 % BSA and TEN detachment of >30% BSA.[17,22]

Overlapping SJS/TEN includes cases with detachment between 10-30% BSA.[22,23] Regardless of the size of the affected area erythematous and macular lesions may be associated.[17]

Apart from skin lesions, mucosal (respiratory, gastrointestinal, urinary) and other organs (liver, lungs and kidneys) involvement can occur.[20,24-26] Despite numerous attempts of identifying an effective curative therapy SJS/TEN has a mortality rate from 5 to 30%.[27]

Furthermore a variety of long-term sequelae can be encountered in surviving patients.[24]

**CASE PRESENTATION**

We present the case of a 49 year old female patient who was transferred to the Anesthesiology – Toxicology – Intensive Care Unit of the Clinical Emergency Hospital in Bucharest from a regional Hospital Unit. She was suspected to have ingested a sort of poisonous mushroom within the 12 hours prior to admission. She presented to the emergency room after mushroom consumption after picking them from a local forest. During the night the patient presented abdominal pain, nausea, vomiting and diarrhea, for which she administered no treatment. In the morning she decided to go to the emergency room, although clinical signs became milder. Her medical records revealed no pathological findings, except an untreated dyslipidemia. Clinical examination revealed a mediocre general condition, pale skin, gingivitis, tachycardia and mild abdominal pain. Furthermore she noticed appearance of cough and rhinorrhea in the last two hours. After volume and electrolyte rebalancing, she was transferred to our Department.

On admission the patient presented an altered general state, she was conscious and feverish (38.6°C). Apart from cough and rhinorrhea she also presented dysphagia, myalgia and arthralgia especially in the lower limbs. Physical examination revealed jaundice, diffuse erythema on hands and feet, tachypnea, tachycardia (HR=113bpm), hepatomegaly. Preliminary laboratory results indicated hepatic cytolysis (ALAT = 9,412 U/L, ASAT = 6,720 U/L), hyperbilirubinemia (4 mg/dl), decreased serum potassium (3.1), elevated creatinine level (2 mg/dl) and blood urea nitrogen (BUN = 49.4 mg/dl). Electrocardiography showed no abnormality, except the abovementioned tachycardia. Superior digestive endoscopy indicated diffuse erythematous lesions in the pharynx and esophagus.

Although according to the description of the ingested mushroom we suspected an Amanita ph. poisoning, rapid Meixner test could not be performed due to the lack of gastric material when endoscopy was performed. Therefore mushrooms leftovers from the meal were sent to a specialized laboratory.

Considering the high suspicion of developing Steven-Johnson syndrome and the liver insufficiency
secondary to mushroom poisoning, initial therapy management was carefully selected. Oxygen therapy, fluid replacement was initiated in combination with gastric protection, antiemetic and diuretic therapy. Vitamin supplementation, corticotherapy (prednisone 138 mg/day) and antioxidant therapy (N-acetyl-cysteine 1,800 mg/day and alpha lipoic acid 900 mg/day) were also added. We performed continuous digestive decontamination by administering 25 mg mannitol p.o, 20 g lactulose and Ricinus communis oil 15 mg. Moreover activated charcoal administration was started in order to interrupt mushroom toxins enterohepatic recirculation.

Twelve hours after admission the patient presented altered mental status, dyspnea, tachypnea and a peripheral oxygen saturation of 80% under oxygen mask. Because of that she was intubated and mechanically ventilated. Despite volume controlled ventilation hypoxemic index could not raise above 100. Furthermore over the erythematous areas of the feet and hands atypical irregular lesions with darker centers were observed. These lesions evolved within the next twenty four hours to vesicles and bullae (Nikolsky sign and Asboe-Hansen sign positive) (Figures 1 and 2).
Skin lesions extended in the next few hours on both forearms (Figure 3) and legs thus evaluating the affected body surface, this case was classified as Steven-Johnson – TEN overlap syndrome.

Gynecological exam also revealed vulvar bullae. In this conditions SCORTEN score indicated a mortality risk of 58.3%.

Four days from admission Amanita ph. toxins were identified in the laboratory.

Since Amanita ph. poisoning is not a specific cause of Steven-Johnson syndrome, other causes were thoroughly investigated.

Usually associated medication which is a trigger for Steven-Johnson was excluded through detailed anamnesis of the patient and her family. Viral and bacterial causes like HIV, Cytomegalovirus or Mycoplasma pneumoniae were excluded after the PCR and/or serological tests were negative.

Although liver insufficiency was remitted after one week of treatment the evolution of the patient was severe. Twelve days after admission the patient died with multisystem organ failure.

**DISCUSSION**

Numerous studies are dedicated to the toxic effects of mushroom poisoning. A considerable percentage of fatal mushroom poisoning cases occur after ingestion of Amanita ph.[1] Although amatoxins induce massive liver cell necrosis, not all patients develop fatal acute liver failure.[4]

Moreover, various treatment strategies proposed in the literature decreased the mortality rates in these patients.

Delayed onset of signs and the polymorphic symptoms due to amatoxin poisoning may aggravate liver toxicity, in the absence of early decontamination treatment.[2] Besides liver failure, amatoxin was associated with nephrotoxicity.[7] However there is no report in the literature about the amatoxin’s toxic effects on skin.

SJS/TEN is an acute severe mucocutaneous disease caused by a variety of drugs, infections or malignant comorbidities.[21] In the case presentation, the patient did not receive any medication potentially associated to SJS/TEN, neither in our unit nor in the regional hospital. Moreover she was not on any chronic treatment or suffered from any infectious or malignant disease. However, several serological tests were performed in order to exclude the most frequent infectious causes of SJS/TEN.

SJS/TEN is often preceded by a prodrome characterized by fever, headache and pharyngitis.[16,17] In this case report after the gastrointestinal phase of the amatoxin poisoning, the patient developed rhinorrhea, malaise, dysphagia and fever.

SJS/TEN may be associated with multisystem organ failure.[16] In addition to the hepatic failure caused by the amatoxin poisoning, soon after admission the
patient developed respiratory dysfunction, requiring mechanical ventilation. Secondary to the respiratory and hepatic dysfunction, neurological dysfunction developed. Despite adequate volume repletion, circulatory dysfunction appeared requiring continuous vasopressor therapy.

There are no recommendations regarding treatment of the acute phase of SJS/TEN.[16] Considering that there is no specific treatment for SJS/TEN, minimizing the risk of aggravation of SJS/TEN was trialed and corticotherapy was initiated. Despite the maximal supportive treatment and liver function improvement, the patient died from multisystem organ failure.

CONCLUSIONS
From our knowledge this is the first case report on Stevens-Johnson/TEN overlap syndrome induced by mushroom poisoning. This case presentation aims to highlight the polymorphic manifestations of severe amatoxin intoxication as well as the difficulties of managing such a patient. Clinicians should be aware of the systemic involvement in mushroom poisoning.

References:


