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ACUTE NECROTIZING MYOPATHY AND PODOPHYLLIN TOXICITY

REPORT OF A FATAL CASE

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ABSTRACT - A 21 year old male ingested podophyllin in a suicide attempt. The disorder was marked by seizures, coma, peripheral neuropathy, renal failure and acute necrotizing myopathy, an unusual finding. The coma and systemic disturbances resolved within three weeks. The myopathy resolved in 7 weeks, demonstrating a high capacity of muscle recuperation. The sensorimotor peripheral neuropathy persisted until the patient's death 9 weeks after the ingestion, due to septicemia. This report confirms the transient central neurotoxicity of podophyllin and persistent peripheral neurotoxicity of podophyllin, and describes a reversible necrotizing myopathy associated to mitochondrial abnormalities, a still unreported feature of podophyllin toxicity.

KEY WORDS: podophyllin, acute toxicity, myopathy.

Miopatia necrotizante aguda e toxicidade por podofilina: relato de caso fatal

RESUMO - Paciente de 21 anos, sexo masculino, ingeriu 20 mL de podofilina a 25% como tentativa de suicídio. O quadro clínico caracterizou-se por crises convulsivas, coma, neuropatia periférica, insuficiência renal e miopatia necrotizante aguda. O estado de coma e os distúrbios sistêmicos resolveram-se em 3 semanas. A miopatia resolveu-se em 7 semanas, demonstrando uma alta capacidade de recuperação muscular. A neuropatia periférica sensitivo-motora persistiu até o óbito do paciente, por septicemia, 9 semanas após a ingestão da podofilina. Esta descrição confirma os achados de literatura com alterações transitórias do sistema nervoso central e persistentes do nervo periférico relacionadas à podofilina, e descreve uma miopatia necrotizante associada com anormalidades mitocondriais, mas de caráter reversível, característica até então não reportada de toxicidade pela podofilina.

PALAVRAS-CHAVE: podofilina, toxicidade aguda, miopatia.

Podophyllin peltatum (Mayapple plant) is a source of podophyllotoxin, an antimicrotubule agent, and is a constituent of herbal preparations used in some parts of the world as cathartics and in treatment of inflammation[6]. Podophyllin is now a resin commonly used in the topical treatment of warts and condylomata. Systemic toxicity may result from either topical exposure[4,20-22] or ingestion[3,5,7,12,16,17,23] of this alkaloid. Systemic manifestations of toxicity include nausea, vomiting, and diarrhea[3-5,8,10,12,16-23], followed by marrow suppression[4,13,20,21,23], renal[3,23] and hepatic[13,18,20,21,23] failure. Neurotoxic effects may involve the central and peripheral nervous system, with impairment of consciousness[3,5,7,8,12,13,19,22], seizures[2,10], and sensory, motor, and autonomic neuropathy[4,7,8,13,16,19,20,22,23]. The clinical course is sometimes fatal[3,7,12,22,23].

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We report a patient with podophyllin intoxication who exhibited many of these manifestations, and who displayed an acute and reversible necrotizing myopathy, a feature not previously reported.

CASE REPORT

This 21 year old man drank about 20 mL of 25% podophyllin resin solution in ethyl alcohol in a suicide attempt. Later that day he had mild headache, nausea and diarrhea. On the next day he was drowsy. In the ensuing three days he became disoriented and confused and progressed into a coma. There was no history of previous psychiatric disorder, head trauma, drug or alcohol abuse, or other toxin exposure. Upon admission his pulse was 70/min, blood pressure 130/80, respiration rate 22/min, and axillary temperature 40° C. There was no response to verbal stimuli and minimal response to pain in all 4 extremities. There was no attempt to withdraw the limb from the painful stimulus. Tone was diminished and deep tendon reflexes were absent. No muscle atrophy or fasciculations were detected. Plantar responses were flexor. Cranial nerve examination was unremarkable and ocular fundi were normal. Minutes later the patient had a tonic-clonic generalized seizure. Initial laboratory studies included, hemoglobin 15.8 g/dL, hematocrit 48%, WBC 23200/mm^3 (98% polymorphonuclears, 1% lymphocytes, 1% eosinophils) platelets 300 000/mm^3, sedimation rate 5 mm/h, urea 31 mg/dL, creatinine 1 mg/dL, Na 139 mEq/dL, K 3.6 mEq/dL, SGOT 450 units (normal range 7-40), SGPT 200 units (normal range 0-16), CK 5 810 U/dL (normal up to 50 U), LDH 1 127 U/L (normal range 90-250). Urinalysis was normal. Serum and standard toxicology screens, urinary porphyrin, and heavy metal screens were negative. A lumbar puncture revealed a CSF opening pressure of 120 mm H_2O with 2 red cells/mm^3, 2 white cells/mm^3, protein 30 mg/dL and glucose 68 mg/dL. An initial CT brain scan was normal. By the 3rd hospital day the patient became progressively more responsive, and by the 10th day he was completely alert, with well preserved cortical functions. However, the muscle weakness continued to deteriorate and by the 10th day he had a flaccid, areflexic quadriplegia with distal muscle atrophy in the 4 limbs. There was loss of superficial sensibility in the extremities of the limbs. His serum enzymes started to drop and went back to normal by the 30th day. At this time he experienced some improvement in muscle power. On the 46th days he could barely lift his arms and legs against gravity.

The patient's clinical course worsened on the 3rd day with hypertension (220/110 mm/Hg), and tachycardia (120/min), on the 11th day with hyperhemic esophagitis and upper gastrointestinal bleeding, on the 12th day with kidney failure, pneumonia and pulmonary insufficiency leading to mechanical ventilation and antibiotic therapy. On the 15th day he had cardiac failure that was interpreted as myocarditis. Dialysis was not needed. During the course of his illness, disturbances in serum electrolytes were not detected. On the 69th day he died. Post mortem examination showed septicemia. Unfortunately no muscle, peripheral nerve or root was examined. No abnormalities could be evidenced in the liver, heart or kidney.

Muscle biopsies. Muscle biopsies from deltoid were performed on the 20th and 46th days and were processed according to standard criteria[11]. The first showed many necrotic muscle fibers in all fascicles, with few macrophages and lymphocytes, and marked mitochondrial abnormalities on trichrome (Fig 1) and SDH stainings. These findings were interpreted as an acute necrotizing myopathy associated to mitochondrial

Table 1. Findings of motor nerve conduction study.

	Latency (ms)	M.C.V. (m/s)	Amplitude (v)
right peroneal	6.6	32.8	400
left peroneal	7.6	40.3	500
right median	4.4	32.4	1800
right ulnar	3.0	43.1	10000
Normal values:	Peroneal	median	ulnar
distal latency	4.4 + 0.9	3.3 + 0.5	2.6 + 0.5
motor conduction velocity (MCV)	52.3 + 1.8	58.3 + 4.4	58.3 + 5.2
amplitude	15325 + 5283	23500 + 5889	18250 + 4241

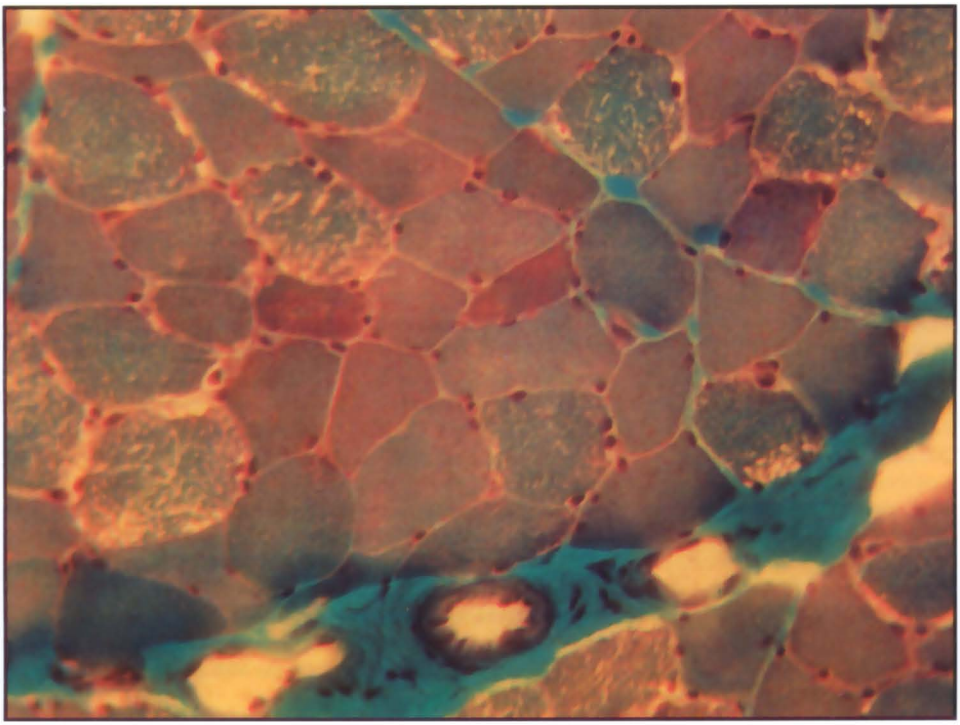

Fig 1. Degenerative necrotic changes in many muscle fibers and marked mitochondrial abnormalities on trichrome staining (fibers stained in red) (Modified Gomori X 125).

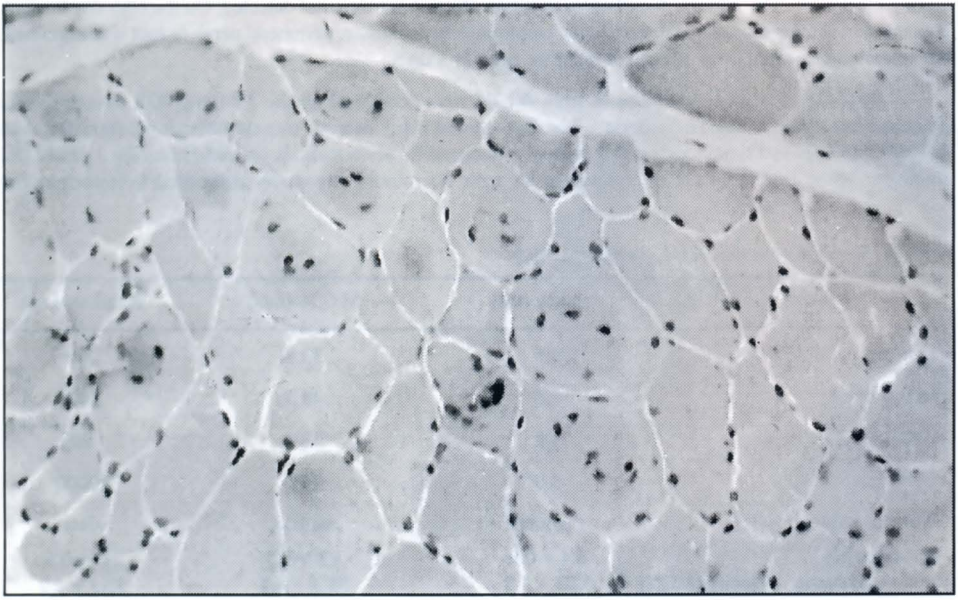

Fig 2. Few scattered atrophic muscle fibers, and nuclei centralization (HE X 125).

dysfunction. The second biopsy showed the presence of few scattered atrophic muscle fibers, nucleus centralization (Fig 2) and fiber type-grouping, signs of a neurogenic process. No more necrotic fibers were seen and the mitochondrial abnormalities were still present, but less intense.

Electromyographic and nerve conduction study. EMG was performed using a TECA TD-10 model, on the 46th hospital day, and disclosed fibrillations, positive sharp waves and almost no voluntary muscle potentials in all muscles examined in the 4 extremities. The nerve conduction study showed a severe and predominantly neuropathy. Sensory nerve potentials were unobtainable in the sural, median and ulnar nerves. Motor conduction velocity was decreased in the peroneal, median and ulnar nerves.

DISCUSSION

Podophyllin resin contains numerous compounds but the toxic agent is thought to be podophyllotoxin, a highly lipid-soluble b-d-glycoside molecule that crosses the cell membranes with ease. This substance and its derivatives have a colchicine-like effect, arresting the mitotic spindle[24]. Podophyllin is absorbed readily through the gastrointestinal tract. Topical application may result in significant systemic absorption, especially if it is applied to a large area allowed to remain in contact for a prologned period of time, is apllied to friable or recently biopsied condylomata, or if inadvertently administered to surrounding skin or mucous membranes[21]. The fatal dose of podophyllin resin for humans has been estimated to be 0.3g to 0.6g, or as little as one half teaspoon of 25% podophyllin resin in benzoin tincture[9].

Both systemic and neurological disturbances occur from severe podophyllin toxicity. The initial manifestations exhibited by our patient, headache, nausea, diarrhea, and altered sensorium are among those previously described[18,20]. Later in the course, our patient showed transient hypertension, tachycardia, renal failure, pulmonary insufficiency and cardiac abnormalities, all known complications of the toxicity[3,20,22]. The central nervous system toxicity is usually transient and reversible over a period of up to ten days[8,18], but deep coma leading to a fatal outcome[3,22] or severe encephalopathy characterized by irreversible cognitive dysfunction may also occur[5]. The peripheral neurotoxicity shows frequently a protracted course[13,20]. Both these features have been well exemplified by our patient.

Sensorimotor mixed neuropathy with tetraplegia, areflexia, hypotonia, and sensory and automatic disturbances shown here followed the same course described in other patients[4,7,13,16,18]. The course of the neuropathy is chronic and the recovery is delayed[16], sometimes with minimal improvement[20]. Sural nerve biopsies performed in the acute phase showed loss of myelinated fibers and signs of axonal degeneration[7,16]. The mechanism by which podophyllin produces an axonal neuropathy is related to its action on microtubular proteins and consequent inhibition of axoplasmic flow.

Our patient also exhibited an acute necrotizing myopathy, an aspect of podophyllin intoxication hitherto undescribed.

He showed important weakness and wasting in his limbs as early as the 3rd day post-intoxication accompanied by very high serum CK, and LDH. These features were suggestive of voluntary muscle destruction. The first muscle biopsy on the 20th day post-intoxication confirmed our suspicion showing a massive muscle necrosis. Associated we found marked abnormalities in the mitochondria. Experimental data available showing that podophyllin interferes with protein synthesis and aerobic respiration[14] could explain our histopathological findings in the muscle biopsy. Podophyllin appears to attach to cell proteins and its actions include increasing the incorporation of amino acids into protein, inhibition of purine synthesis, and inhibition of purine incorporation into RNA. It has also been found to have a direct effect on the mitochondria, being able to reduce the activity of cytochrome oxidase and succinoxidase[14]. Although podophyllin is known to act as a spindle poison, thereby blocking mitosis at metaphase[1,15], the second muscle biopsy, performed 26 days after the first one, showed important muscle regeneration. This is most probably explained by the short half-life of the drug in humans as exemplified by the transient altered sensorium and usually reversible systemic manifestations.

We wish to reinforce the potentially toxic side-effects of podophyllin and add a fatal case who displayed an acute necrotizing myopathy. The absence of previous descriptions of muscle involvement in that intoxication could be due to either a failure of recognition due to the accompanying severe manifestation of the PNS or to a dose-related phenomenon.

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