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Case Report

Toxic myopathy following monensin exposure: a case report with 12 year follow-up

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Abstract: Toxic myopathy following monensin exposure, including histochemical examination of skeletal muscle biopsy, has not yet been published. In this paper, we report a 52-year old man with weakness and pain in both legs, and dark-red urine discharge. His occupational experience, clinical features, laboratory findings, and outcomes were collected and diagnozed as monensin toxicity. Muscle biopsy findings showed degenerating and necrotic fibers undergoing phagocytosis by infiltrating macrophages, in which the main lesion was necrosis. In lesion areas, the abundance of B lymphocytes were infiltrated in perivascular distributions, while a few T lymphocytes were located in perimysial distributions. The biopsy results were different from polymyositis in the type and location of lymphocytes, and the alteration of health muscle fibers. These pathological differences represent the fundamental distinction of muscular inflammatory response between secondary phenomenon following necrosis and primary immune-mediated pathological changes. The patient was followed up for 12 years. The content of CK and LDH were measured every year. Mild toxic myopathy of monensin intoxication seemed to have a self-limiting or reversible tendency.

Keywords: Monensin intoxicity, toxic myopathy, polymyositis, muscle fibre, follow-up

Introduction

Toxic myopathies are a clinical and pathological variety of diseases that may be caused by a variety of treatments used in clinical practice, as well as a variety of venoms and other biotoxins [1]. Mass production and life of drugs can lead to necrotizing myopathy, and the most severe form can produce fatal acute rhabdomyolysis and myoglobinuria. Other drugs can lead to various types of fibrosis. The pathogenesis of drug-induced myopathy is also diverse [2].

Monensin, a polyether antibiotic discovered in 1967, is a highly sodium-selective carboxylic ionophore enhancing the transmembrane exchange of sodium for other protons. It was discovered as a growth promotant in cattle via changing the rumen microbial population, increasing the ratio of propionate to acetate and butyrate, and decreasing methane and protein degradation [3-5]. Monensin is safe and effective for target animals receiving recommended dosage levels [6], and has been widely used in the poultry and livestock industries. Experimental and accidental animal studies have shown monensin toxicity episodes in many animal species owing to overdosage or misuse situations for decades [7]. Caldeira et al. have reported a 17-year-old boy that ingested monensin, died with irreversible cardiopulmonary arrest, which was the first report of monensin intoxication in humans. No other cases have been described thereafter [8]. Therefore, little is known about the toxicity following monensin exposure in humans.

Case report

A 52-year-old man was admitted to our hospital in August, 2001 because of weakness and pain in both legs, and dark-red urine discharge lasting for 7 days. Previously, he felt hypodynamia and breathlessness after exercise but this was relieved after rest. There was no dizziness, headache, and other complications. He had an occupational exposure to monensin for about 3 weeks before illness. There was no family history of other neuromuscular or metabolic diseases.

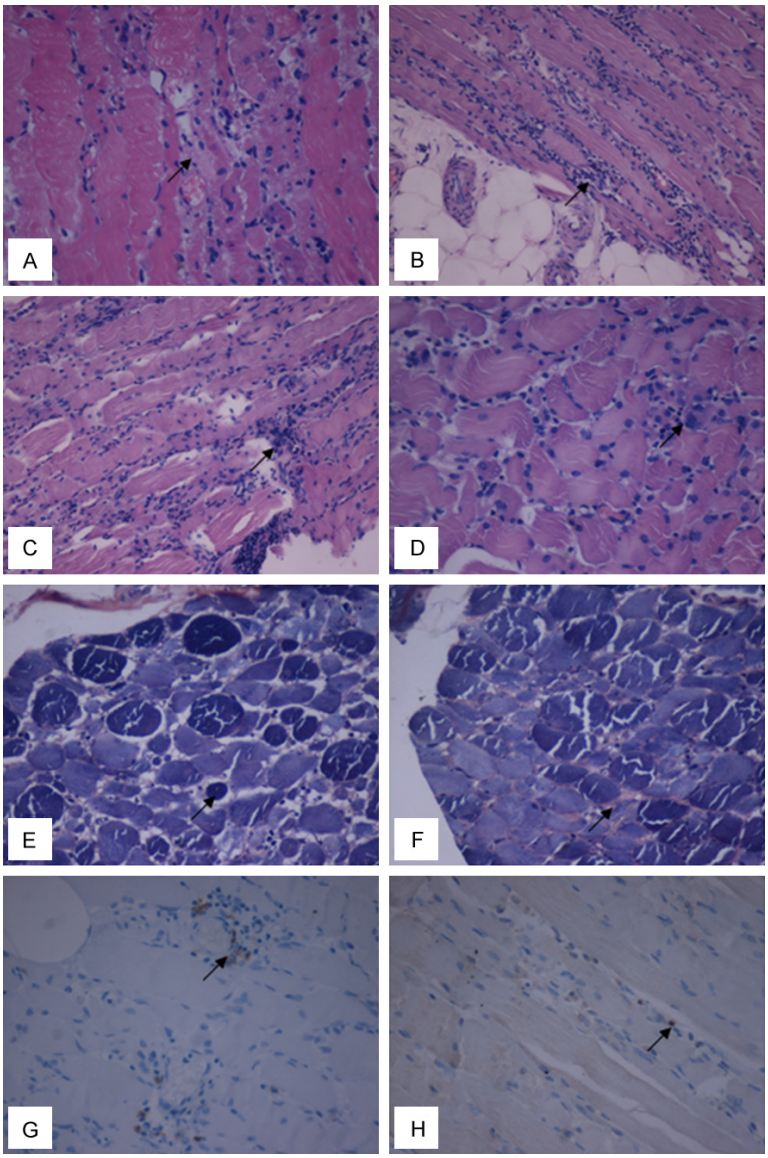

Figure 1. Hematoxylin-eosin (×100) showing the tissue had multifocal degeneration and (A) necrotic muscle fibers surrounding by infiltration of (B, C) lymphocytes and (D) macrophages. (E) PATH staining (×100) showing type 2 muscle fiber atrophy. (F) Masson staining (×100) showing a loose meshwork of fine eosinophilic fibres which stained positively for collagen. (G, H) Immunohistochemical studies (×400) showing most infiltrating lymphocytes expressed CD20 around blood vessels in the perimysium and some expressed CD3 against the necrosis muscle fiber.

Neurological examinations revealed that the muscle strength in the iliopsoas muscle and biceps femoris muscles was graded as II-III and V respectively, with discharge in knee jerk and negative pyramidal signs. There was mild muscle pain in the lower limbs when squeezing. Electromyogram showed myogenic abnormality.

Laboratory results revealed serum CK, CK-MB fraction and LDH levels peaked at means of 25702 U/L, 16876 U/L and 2939 U/L, respectively. Myohemoglobin in routine urine sample was detected accompanying with slightly increased serum of BUN and Cr. Urine routine also indicated occult blood was strongly positive and urine protein was weakly positive. The results of hepatic and renal function, as well as blood electrolyte value, were within normal range.

Gastrocnemius muscle biopsy was done and the histopathological changes showed both the fibrous and interstitial changes. The former included multifocal degenerating and necrotic muscle fibers (**Figure 1A**) separated by healthy muscle fibers. Atrophy, stained by PATH (**Figure 1E**), mainly affected type 2 fibers. Eosinophilic inclusion or rimmed vacuole was not detected. The interstitial changes included lymphocyte (**Figure 1B**, **1C**) and macrophage (**Figure 1D**) infiltration. The abundance of lymphocytes that infiltrated in the lesion areas had perivascular and perimysial distributions. Collagen fibers which stained positively by Masson could be found in between muscle (**Figure 1F**). Microvessels were occasionally proliferative and congested.

Immunohistochemical studies were done on paraffin-embedded sections with antibodies against CD20 (clone L26 1/100; DakoCytomation), CD3 (clone 1801 1/75; Maixin.Bio), CD68 (clone KP1 1/100; DakoCytomation). The results showed in lesion areas, an abundance of B lymphocytes had infiltrated with perivascular distributions and they also expressed CD20 (**Figure 1G**). A few T lymphocytes in perimysial distribu-

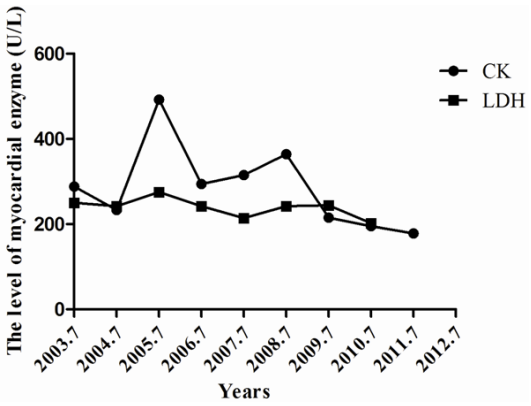

Figure 2. The change of CK and LDH in the past ten years. CK Normal range 25-190 U/L; LDH Normal range 114-240 U/L.

tions which expressed CD3 (**Figure 1H**). Some CD68-positive cells were macrophages.

The patient was treated to initiate therapy with methylprednisolone 1000 mg/d five days and 500 mg/d two days, and then tapered off gradually. In the following weeks he progressively improved and, at the time of discharge, two months after the onset, he was able to walk with assistance and the enzyme levels returned to normal concomitantly.

Twelve months after discharge (in November 2002), the patient could walk slowly without a cane, but had difficulty in arising from a squatting position or in climbing up-staircases. His upper limbs showed partial unsteadiness when holding a thermos bottle. The strength of the proximal muscle in the lower limbs was assessed as IV-bilaterally. The distal strength was normal as V. However, the patient had very mild muscle atrophy but no fasciculation in the lower part of thighs. The change of CK and LDH activitied were listed in **Figure 2**.

In April 2006, the patient could rise from a squatting position when putting hands on the knees, and do routine activities of daily life at home. But he was readmitted several times due to weakness and elevated enzyme levels during the period of past 41 months. Noticeably, the proximal upper limb strength had returned to V. No muscle atrophy was found.

Discussion

Monensin intoxication is a severe syndrome including skeletal muscle weakness, locomotor deficits, flaccid paralysis, ataxia, tachycardia, cardiac failure, dyspnea, myoglobinuria, acute renal failure, elevation of serum creatine kinase, aspartate aminotransferase, and high lethality rate. The main cause of death is multiple organ failure [9]. In this study, our patient worked at a monensin supplementary workshop and contacted it two or three days with a gap of 1 week to 4 months before getting ill. Clinical manifestation included myasthenia, myalgia, increasing of muscle enzyme, hemoglobinuria, and renal dysfunction. Monensin was not on the National Occupational Health and Safety Commission List of Designated Hazardous yet. The diagnosis of monensin intoxication in the present study was therefore on the basis of a history of monensin exposure and clinical symptoms. Not being measured in non-hospitalized subjects at the onset, the parameter of serum muscle enzymes was regarded as supplementary.

Muscle biopsy findings showed both fibrous and interstitial changes. The former include denaturation and necrosis. Denaturation was just a slight alteration. This case was mainly the multifocal necrosis of muscle fibres, which was more thorough. Atrophy mainly happened in the small, polygonal type 2 fibres. The interstitial changes include lymphocyte aned histiocyte infiltration and fibrosis. In lesion areas, the abundance of B lymphocytes was found infiltrated with perivascular distributions, and a few T lymphocytes were infiltrated with perimysial distributions. The surrounding healthy fibers had not been infiltrated at all. Collagenous fiber hyperplasia in between muscle could be found. The pathological features of toxic myopathy were differented from polymyositis. In polymyositis, normal muscle fibers were not only surrounded but also invaded by CD8-positive T lymphocytes located in the endomysium, which seemed to indicate immune-mediated mechanism [10, 11]. In contrast, inflammation in toxic myopathy was usually found to be associated with the necrotic areas and the predominant infiltrative cells were B lymphocytes located in perivascular distributions. These pathological differences represented the fundamental distinction of muscular inflammation response between secondary phenomenon following necrosis and primary immune-mediated pathologic changes [12]. The possible pathogenesis may be that monen-

sin induced significant production of lactate in intact muscles through increased glycolysis secondary to augmented activity of Na^+, K^+-ATPase. This production was largely prevented by ouabain and almost totally abolished when a sodium-free medium was used.

The outcome and prognosis were related to the severity of intoxication, and the prompt and proper treatments [13]. Mild monensin intoxication seemed to have a self-limiting or reversible tendency. Monensin contact reaction symptoms disappeared soon after the affected subjects stopped contacting with the pollutant, and muscular symptoms improve spontaneously in months. However, severe intoxication was lethal unless the patient could get prompt treatment. Obviously, due to the difference of severity, our patient was cured with large dose hormone treatment and without sequela by follow-up. However, the data of CK and LDH turned out to be normal until 2010 or 2011.

In conclusion, the diagnosis of monensin intoxication in the present study was on the basis of a history of monensin exposure and clinical symptoms. Muscle biopsy findings showed multifocal atrophy of type 2 fibers, degenerating, and necrotic fibers undergoing phagocytosis by infiltrating macrophages, in which the main lesion was necrosis. In lesion areas, an abundance of B lymphocytes infiltrated with perivascular distributions, and a few T lymphocytes infiltrated with perimysial distributions. The biopsy results demonstrate changes of toxic myopathy and pathological features that were only secondary phenomenon following necrosis. We can also conclude that the level of CK and LDH need a long time to recover. However, the pathogenesis of toxic myopathy following monensin exposure is still unclear and futher studies are needed. Monensin toxicity in humans mainly results in severe skeletal and cardiac muscle lesions. It is lethal in severe cases, while mild muscle lesions may remain in survivors for years.

Disclosure of conflict of interest

None.

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