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Massive Rhabdomyolysis; A Rare Cause of Hepatocellular Dysfunction

Authors' Contribution:
Study Design A
Data Collection B
Statistical Analysis C
Data Interpretation D
Manuscript Preparation E
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Patient: Male, 54
Final Diagnosis: Rhabdomyolysis
Symptoms: Thigh pain • thigh swelling
Medication: —
Clinical Procedure: Hepatectomy
Specialty: Surgery

Objective: Rare co-existance of disease or pathology

Background: Rhabdomyolysis syndrome is a rare surgical complication. It is infrequently reported in prolonged operations under lateral decubitus position. This syndrome mainly impacts kidney function and electrolytes levels; liver is another organ that is uncommonly affected.

Case Report: A 54-year-old male underwent a partial hepatectomy in the supine position, the procedure lasted three hours. After five days of uneventful recovery from surgery, he was readmitted to the hospital with rhabdomyolysis syndrome involving his lower limbs. No predisposing factors other than surgery could be identified. Based on blood tests, the only affected organ was the liver. Upon aggressive hydration, the creatinine kinase, hepatic enzymes, bilirubin levels, and prothrombin time were normalized. The patient regained normal physical strength over the next few weeks.

Conclusions: Liver dysfunction secondary to rhabdomyolysis is rare but should be considered when other causes are excluded. Prothrombin time, bilirubin levels and albumin levels may help to identify concomitant liver damage. Rhabdomyolysis is rarely reported in liver resection surgeries.

MeSH Keywords: Hepatectomy • Liver Diseases • Rhabdomyolysis

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Background

Muscle necrosis with release of intracellular muscle constituents, including electrolytes, myoglobin, and other sarcoplasmic proteins (creatinine kinase (CK), lactate dehydrogenase, alanine aminotransferase, and aspartate aminotransferase) into the circulation, is referred to as rhabdomyolysis [1].

Multiple predisposing factors for muscle cell death have been reported, including direct trauma, prolonged surgery in a decubitus position, ischemia, drugs, toxins, metabolic disorders, and infections [2]. Some studies revealed higher frequency of trauma and immobilization as a leading cause among hospitalized patients [3].

The severity of this syndrome varies depending on the etiology and the extent of muscle necrosis. Some patients experience asymptomatic elevations in serum muscle enzymes, or complain of muscle pain, weakness, and dark urine [4], others may develop life-threatening disease associated with multiorgan injury and electrolyte disturbances [5].

Myalgia, when present, is typically prominent in affected muscle groups, which commonly involves thighs, shoulders, lower back, and calves [6]. This may be accompanied by muscle swelling and occasionally skin changes similar to discoloration and blister formation [7].

We present a rare case of delayed rhabdomyolysis, developed five days post hepatic segmental resection for hepatocellular carcinoma. The principal cause was not identified; however, multiple contributing factors were suggested.

Case Report

A 54-year-old male, non-smoker, who worked as a silicon (glass) laboratory technician (used chloroform in his work for 30 years), was not known to have diabetes mellitus, hypertension, neuromuscular disease, or any medical illness. His surgical history was positive for laparoscopic cholecystectomy performed a few years ago. The patient complained of vague upper abdominal pain that lasted several weeks. On workup, a computerized tomographic (CT) scan revealed two liver lesions: one homogeneous 8 cm mass in the right lobe (involving segments 7 and 8), and a second smaller (2 cm) mass in the left lateral segment. Fine needle aspiration from the right lobe lesion was performed, the appearance was suggestive of well-differentiated hepatocellular carcinoma (HCC), therefore a liver resection was planned. Open resection of liver segments VII, VIII, and II was conducted and the procedure took three hours, with the patient in a supine position. During the surgery, the patient was given two units of packed red blood cells for blood loss. The rest of the operation was uneventful. After surgery, the patient was observed in the intensive care unit for the first 24 hours, then discharged to a regular floor room. The post-operative course was normal with no fever, rash, chest complaints, or change in urine color or amount. The urine catheter was removed after 24 hours and the patient was discharged on post-operative day 6. Histopathology confirmed the diagnosis of well-differentiated hepatocellular carcinoma.

He was readmitted one day later to our hospital with generalized weakness and malaise associated with muscle cramps in the lower limbs (thighs) and black urine. He denied any trauma. There was no change in the color of the stool, skin itching, jaundice, mental status changes or feeling of hotness. His vital signs were stable all the time. On physical examination, his abdomen was soft with healthy looking wounds, both thighs were swollen but soft and tender, with a few skin blisters appearing two days later. The distal lower limb pulses were normal. Electrocardiogram showed normal sinus rhythm. Table 1 summarizes the post-operative trend of the main blood tests, including CK, liver enzymes, bilirubin, potassium, creatinine, and prothrombin time. The rest of the biochemical laboratory test results showed no evidence of acidosis, alteration in blood glucose levels, other electrolytes disturbances, hematuria, or urinary tract infection. Abdominal CT and ultrasound revealed no evidence of ascites, fluid collection, intra- or extra-hepatic vasculature abnormalities (with normal portal flow on Doppler). The patient was treated with aggressive hydration at a rate of 400 cc/hour for 24 hours; then 200 cc/hour for the next 48 hours, then continued maintenance fluid therapy for five more days in-hospital. Physical therapy was started three days after readmission to assist patient recovery, and encourage walking and mobility.

Discussion

The hallmark of rhabdomyolysis syndrome is an increase in intracellular free ionized calcium due to depletion of adenosine triphosphate (ATP) and rupture of sarcolemma [7]. The increased mitochondrial and cytoplasmic calcium triggers a complex cascade of protease-mediated reactions, which intensifies skeletal muscle cell contractility, induces mitochondrial dysfunction, and increases the production of reactive oxygen species, ultimately resulting in skeletal muscle cell death [2]. As a consequence, leakage of cellular contents, including; electrolytes, myoglobin, and sarcoplasmic proteins, e.g., CK, lactate dehydrogenase, alanine aminotransferase (ALT), and aspartate aminotransferase (AST), takes place [8].

ALT is a cytosolic enzyme which has the highest concentration in the liver and it is considered a more specific marker of hepatic injury [9], while AST, which is found mainly in the

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Table 1. Postoperative trend of biochemical blood tests.

Post-operative Day (no.)	CK U/L	KFT[a]		LFT[b]				WBC	INR
		K	Cr[c]	Total protein	TB (total bilirubin)	ALP[d]	ALT[f]		
				Albumin	DB (direct bilirubin)	AST[e]	GGT[g]		
90	138	4.5	51	82	20	307	43	15.4k	1.3
				42	8.2	33	49		
16	1394	3.8	35	61	66	876	186	13k	–
				32	40	304	344		
15	2253	4.5	33	56	68	815	269	14.5k	1.6
				27	29	381	351		
13	5989	3.2	36	50	68	711	538	12.5k	1.6
				25	41	486	330		
12	8930	4.2	44	51	75	796	838	15.5	1.5
				26	50	586	368		
9	74630	5	42	47	48	428	1972	23k	1.7
				24	29	653	226		
8	73801	4.3	40	47	51	406	1808	15.7k	1.5
				22	38	596	202		
7 readmission	112564	4.8	53	57	57	338	2737	20k	1.5
				28	41	648	181		
4	–	3.7	44	48	41	181	197	11	1.3
				24	26	367	70		
1	–	4.3	55	58	26	157	631	17	1.3
				27	14	490	24		

[a] – Kidney function test; [b] – liver function test; [c] – creatinine; [d] – alkaline phosphatase; [e] – aspartate aminotransferase; [f] – alanine amino transferase; [g] – gamma-glutamyl transferase. Normal values: total protein: 64–83 gm/L, albumin: 35–52 gm/L, TB: 5–21 µmole/L, DB: ≤5 µmole/L, ALK: 80–260 U/L, ALT: 0–50 U/L, AST: 0–40 U/L, GGT: 8–61 U/L, Na: 135–153 mmol/L, K: 3.3–5.1 mmol/L, urea: 2.14–7.14 mmol/L, Cr: 62–106 µmole/L, WBC: 3.5–11.

mitochondria, is present in several organs, including liver, heart, kidneys, pancreas, and other organs. Few studies have demonstrated a biochemical evidence of liver injury as a component of systemic manifestations of massive rhabdomyolysis. The exact mechanism of hepatocellular damage in this syndrome is not well understood. Some studies have suggested a multifactorial hypothesis that involves a combination of hyperpyrexia, hypotension, and proteases-released from injured muscles – induced liver injury [10]. Prothrombin time, and bilirubin levels and albumin levels have been used to differentiate whether AST and ALT elevation is attributed to muscle injury solely, or to a concomitant liver damage. In one study by Akmal and Massry [10], liver dysfunction was observed in 25% (34) of patients with non-traumatic rhabdomyolysis, all of them had hyperbilirubinemia and abnormal prothrombin time lasted from 1–13 days. Weibrecht et al. [11] found that AST concentrations had a linear correlation with CK, while ALT/CK trends were not parallel.

Serum CK levels start to rise two to 12 hours after the onset of muscle trauma and peak within 24 to 72 hours. A decline is usually seen within three to five days of cessation of muscle injury. Failure of CK to decline may indicate an ongoing muscle injury or development of the compartment syndrome [5,12].

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Apart from muscles and liver, organs that can potentially be affected in severe forms of rhabdomyolysis are the kidneys, where volume depletion, tubular obstruction due to heme pigment casts, and tubular injury from free iron, all manifest as acute kidney injury [13]. Massive rhabdomyolysis may be associated with cardiac arrhythmias, compartment syndrome, and the development of disseminated intravascular coagulation (DIC) secondary to the release of thromboplastin and other prothrombotic substances from the damaged muscle [14].

The incidence of rhabdomyolysis in partial liver resection surgeries seems to be very rare, which excludes its direct correlation with this type of surgery. Park and Jee [15], in their review, described rhabdomyolysis in a single case during laparoscopic hepatic segmentectomy, in which their patient complained of multiple other comorbidities that increase the risk of rhabdomyolysis. Another similar case was reported by Lee et al. [16], for a donor who underwent right liver lobe resection. We think that in all these cases, along with other possible mechanisms aforementioned, the patients may have had a vulnerable liver from the segmentectomy they underwent.

Our case is interesting from several aspects. First, our patient underwent an average-duration surgery in a supine position, while most surgical rhabdomyolysis is related to lengthy operations in a lateral decubitus or other positions. Second, our patient was devoid of symptoms in the first few days after surgery, then started to complain of weakness and red urine on post-operative day 6. Third, although kidneys are the most commonly affected extra-muscular organs, our patient's kidney function was completely preserved throughout the course of illness. Fourth, despite the extremely high CK levels that reflect the extent of muscle necrosis, our patient suffered no other life-threatening systemic manifestations (e.g., cardiac arrhythmias, compartment syndrome, or hyperkalemia).

We think that liver injury in this patient, shown mainly by hyperbilirubinemia, prolonged prothrombin time, and elevated transaminases, was more likely secondary to rhabdomyolysis because, first, there was no evidence of hepatic surgical complications (i.e.; vascular thrombosis, bile leak, or hematomas) to explain the deterioration in liver function. Second, most liver enzymes normalized before starting to rise again along with CK elevation. Third; liver impairment was reversed with the treatment of rhabdomyolysis. It should be emphasized that segmental liver resection itself, and the fact that the patient had HCC to begin with, made the patient more susceptible to liver injury.

Conclusions

Liver dysfunction secondary to rhabdomyolysis is rare but should be considered when other causes are excluded. Prothrombin time, bilirubin levels, and albumin levels may be used to differentiate whether AST and ALT elevations are attributed to muscle injury solely, or to concomitant liver damage. Rhabdomyolysis is rarely reported in liver resection surgeries.

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