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CASE REPORT

Fulminant Red Yeast Rice-Associated Rhabdomyolysis with Acute Liver Injury and Hyperkalemia Treated with Extracorporeal Blood Purification Using CytoSorb

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Abstract: Rhabdomyolysis is a pathophysiological process characterized by the destruction of muscle cells and the release of intracellular contents into the systemic circulation, which can lead to acute kidney injury (AKI) and failure. Causes are classified mainly as traumatic and non-traumatic, with statin-induced rhabdomyolysis being widely recognized. Other causes are seldomly reported, one being red yeast rice (RYR) or its active ingredient, monacolin K. We present a life-threatening case of fulminant rhabdomyolysis with severe hyperkalemia, accompanied by ECG changes, tetraparesis, impending compartment syndrome, and liver injury requiring intensive care treatment. Prompt renal replacement therapy was commenced, initially for the treatment of hyperkalemia and subsequently for myoglobin adsorption using the CytoSorb membrane. High doses of corticosteroids were administered as the trigger factor was initially unknown. The condition gradually improved, and the patient regained full functionality. The diagnosis of toxic rhabdomyolysis was confirmed only after the patient was discharged from the intensive care unit. An over-the-counter supplement containing red yeast rice (RYR) was identified as the sole possible triggering factor, with symptoms occurring two days after beginning the self-treatment.

Keywords: rhabdomyolysis, red yeast rice, monacolin K, intensive care unit, CytoSorb, SLEDD, over-the-counter medications

Introduction

Rhabdomyolysis is a pathophysiological process characterized by the destruction of muscle cells and the release of their intracellular contents into the bloodstream. It represents the most severe form of muscle injury, with presentations ranging from mild symptoms to life-threatening conditions requiring intensive care treatment. Mild cases often manifest as myalgia, limb weakness, tenderness, and elevated levels of serum creatine kinase (CK), lactate dehydrogenase (LDH), and myoglobin, which typically return to normal once the underlying cause is resolved.[1] Severe cases, however, may progress to acute kidney injury (AKI) and/or hyperkalemia, leading to potentially fatal complications, most notably malignant cardiac arrhythmias. Immediate management includes ECG monitoring, fluid replenishment, and correction of electrolyte imbalances. Renal replacement therapy (RRT) remains the definitive treatment for severe cases of hyperkalemia.[2,3]

The causes of rhabdomyolysis are diverse. While trauma and crush injuries account for a significant number of cases, a broader spectrum of non-traumatic factors also exists, including toxic agents, alcohol abuse, arterial occlusion, hyperthermia, infections, electrolyte disturbances, genetic disorders, and numerous medications (eg, antibiotics, antimycotics, antipsychotics, propofol). Among these, statin-induced myopathy is the most well-recognized.[1,2,4] Statins are commonly prescribed for both primary and secondary cardiovascular prevention. The exact pathophysiology of statin-induced myotoxicity remains speculative. Current hypotheses suggest mechanisms involving alterations in membrane fluidity, depletion of ubiquinone

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(coenzyme Q10), disruption of calcium homeostasis, induction of apoptosis, and genetic predispositions. Additionally, factors such as drug-drug interactions (eg, with verapamil or amiodarone) and higher statin doses are known to significantly increase the risk of myotoxicity.[1,5]

Some patients are hesitant to take statins and instead opt for "natural-based" alternatives.[6] One such product is red yeast rice (RYR), a traditional Chinese medicine containing monacolin K, a compound structurally identical to lovastatin. Monacolin K exerts lipid-lowering effects by inhibiting 3-hydroxy-3-methylglutaryl coenzyme A (HMG-CoA) reductase, the rate-limiting enzyme in cholesterol synthesis, equivalent to synthetic statins. Consequently, RYR demonstrates comparable pharmacological properties to statins, making it an appealing option for patients seeking natural therapies and is listed in the 2019 ESC/EAS guidelines for the management of dyslipidemias.[7,8] However, despite its natural origin, RYR is not without risk. Adverse reactions associated with RYR supplementation mirror those of statin-induced myotoxicity, including muscle pain, weakness, and rhabdomyolysis. While RYR is commonly marketed as a safe and natural alternative to statins, patients may not disclose their use of over-the-counter supplements, making it challenging to identify triggers of adverse reactions.

The aim of our case report is to highlight a patient with life-threatening fulminant rhabdomyolysis complicated by severe hyperkalemia with ECG changes, tetraparesis, impending compartment syndrome, and liver injury. The patient required intensive care treatment, including prompt renal replacement therapy (RRT) with CytoSorb hemadsorption to correct electrolyte imbalances and myoglobin clearance. Methylprednisolone boluses were administered due to suspected autoimmune-mediated necrotizing myositis. The patient's condition gradually improved following multiple RRT sessions with CytoSorb for myoglobin adsorption, along with fluid resuscitation and corticosteroid therapy. It was only after the patient was discharged from the intensive care unit (ICU) that it was discovered she had recently begun taking an over-the-counter lipid-lowering supplement, Biostatine, which contained RYR extracts. Notably, her life-threatening symptoms developed in a fulminant manner after just two days of taking Biostatine, despite the product containing a dose of RYR deemed safe.[7] Upon further analysis, this supplement was identified as the sole potential trigger, as it is known to cause rhabdomyolysis and hepatitis-like acute liver injury with marked elevation of transaminases.[9]

Case Presentation

A 68-year-old female patient with a reported penicillin allergy and psoriasis, on long-term disease-modifying treatment with apremilast, was waiting at the checkout in an air-conditioned store. She had no prior history of chest pain, dyspnea, muscle weakness, or syncope. Suddenly, she experienced generalized muscle weakness, followed by a brief episode of visual blackout and loss of consciousness, resulting in a collapse. Cardiopulmonary resuscitation was not required, as her breathing remained stable, and she regained consciousness spontaneously within one minute. She walked unassisted to the ambulance and was transported to our hospital. Upon the arrival of emergency services, she was fully alert with stable vital signs, and reported no chest pain, dyspnea, headache, or residual muscle weakness.

When first assessed at the hospital around 10 a.m., the patient was fully alert and mobile, with no neurological deficits. Her vital signs were stable: blood pressure (BP) 120/68 mmHg, pulse 68/min, SpO_2 98%, and body temperature 36.0°C (96.8°F). Electrocardiogram (ECG) and chest X-ray findings were unremarkable. Laboratory tests revealed slight hypokalemia, mildly elevated transaminases, D-dimer, and lactate levels (Table 1). Polymerase chain reaction (PCR) tests for respiratory infections, including SARS-CoV-2, were negative. (At that time, testing for respiratory infections was standard practice for all patients scheduled for admission or prolonged observation). Despite no reported changes in diet or medication regimen over the past several months, the clinical examination revealed clear signs of volume depletion, including collapsed jugular veins, dry mucous membranes, absence of axillary sweat, and prolonged skin turgor.

She was admitted for observation, parenteral rehydration with potassium supplementation (1500 mL of Ionolyte [Fresenius Kabi Deutschland GmbH] with 40 mmol of potassium chloride parenteral slow infusion), and continuous ECG monitoring. Follow-up laboratory tests conducted at 4 p.m. showed an increase in serum lactate. Bedside echocardiography at that time revealed a hypercontractile left ventricle and a completely collapsed inferior vena cava (IVC). Parenteral rehydration was continued (additional 1500 mL of Ionolyte solution) without further potassium supplementation, and additional laboratory tests were scheduled for 6 p.m.

Table 1 Timeline of Main Laboratory Findings

Time / Test[$]	Day 0				Day 1		Day 2	Day 3		Day 4	Day 7[&]
	10:20	**16:03**	**18:11**	**01:14[+]**	**05:00**	**17:00**	**5:00**	**5:00**	**19:30**	**5:00**	**5:00**
AST [µkat/L; <0.52]	1.26			**37.70**	**54.68**		**132.60**	**111.57**		**64.03**	**9.30**
ALT [µkat/L; 0.56]	1.81			**7.44**	**10.38**		**28.33**	**30.78**		**28.82**	**22.00**
Creatinine [µmol/L; 44–80]	63			68	31	29	41	36	31	37	48
Urea [mmol/L; 1.7–8.3]	8.5			6.5	2.9	1.9	3.9	5.5	2.7	5.0	7.4
Potassium [mmol/L; 3.80–5.50]	3.23	4.29		**6.91**	3.94	4.27	4.27	3.62	3.20	3.59	3.62
Sodium [mmol/L; 135–145]	138.3	134.3		128.2	133.1	139.0	137.3	139.1	139.1	141.7	139.9
Chloride [mmol/L; 95–105]	101.9	99.8		97.1	103.5	107.0	107.5	107.6	106.7	108.0	101.4
C-reactive protein [mg/L; <5]	2.7			17.6	37.9	117.2	115.0	36.4		12.2	6.3
Lactate [mmol/L; 0.5–2.2]	**3.4**	**6.3**	**7.5**	**5.5**	2.0	1.3	1.0	1.0		1.3	1.5
LDH [µkat/L; 4.13]				**25.49**	**35.83**	**96.43**		**131.22**		**123.36**	
Creatine kinase [µkat/L; <2.41]			**403.1**	**>2,000**	**>3,000**		**>6,000**		**1,618.2**		103.63
Myoglobin (serum) [µg/L; <58]			**>30,000**	**>30,000**	**>30,000**	**>30,000**		**24,898**	**8,029**	**6,279**	**857**
Myoglobin (urine) [µg/L; 0]				**16,505**							
D-dimer [µg/L FEU; <500]	522		1284	1191							
Hemoglobin [g/L; 120–150]	134			146	132		129	118		111	127
Leukocyte count [10^9/L; 4–10]	3.9			21.5	16.3		13.8	9.4		10.6	9.1
Thrombocyte count [10^9/L; 150–450]	184			209	137		163	137		134	158
INR [0.90–1.27]	1.03			1.03	1.17	1.49	1.02	0.95		1.07	

Notes: The most significant data are highlighted in bold. Elevated AST and ALT indicate liver injury. A marked increase in potassium (accompanied by ECG changes) required immediate ICU admission. Elevated serum lactate values indicate anaerobic metabolism. Increased levels of LDH, creatine kinase, and myoglobin (in both serum and urine) indicate cell breakdown, consistent with rhabdomyolysis. Additional Information (not included in the table): Throughout the entire hospital admission, total, direct, and indirect bilirubin levels remained within the normal range. levels were only mildly elevated, with the highest recorded value of 1.86 µkat/L on the fourth day of ICU treatment (normal value <0.63 µkat/L). [+]Intensive care unit admission. [&]Intensive care unit discharge. [$]Test name [unit, normal value].

Abbreviations: GGT, Gamma-glutamyl transferase; ALT, alanine transaminase; AST, aspartate aminotransferase; FEU, fibrinogen equivalent units; INR, international normalized ratio; LDH, lactate dehydrogenase.

During that time, her condition began to deteriorate with progressive muscle weakness and paresthesias primarily affecting the lower extremities. A neurologist examined her just before 6 p.m., noting diminished myotatic reflexes in both lower limbs with preserved sensation. The cranial nerves and upper limbs remained unaffected. A cranial computed tomography (CT) scan was performed and revealed no abnormalities. She was diagnosed with acute paraparesis and referred for an urgent evaluation by a trauma surgeon, who ordered an emergency magnetic resonance imaging (MRI) of the thoracic and lumbosacral spine. Clinical examination at that point showed flaccid paraparesis of both lower limbs. The MRI showed no acute pathology, and the findings were confirmed by both a radiologist and a neurosurgeon. Additionally, an abdominal ultrasound (US) was ordered, revealing no significant pathology aside from mild urinary retention. A urinary catheter was placed, collecting 1000 mL of dark urine. Urinalysis findings are presented in Table 2. Follow-up laboratory tests showed a continued rise in lactate, along with significantly elevated levels of creatinine kinase (CK) and serum myoglobin, which exceeded the upper measurement limit of 30,000 µg/L. The patient's condition continued to deteriorate, with diffuse pain in both lower limbs and diminishing muscle strength in the upper extremities. She was re-examined by the neurologist, who noted complete flaccid tetraparesis with pain in all major muscle groups.

Table 2 Urinalysis Report at the Emergency Department

Test	Result	Reference value
Relative density	1.024	1.005–1.040
pH	7.0	4.5–8.0
Protein^{+}	4	
Glucose^{+}	1	
Ketone bodies^{+}	0	
Urobilinogen^{+}	0	
Bilirubin^{+}	0	
Nitrites^{+}	Negative$^{\&}$	
Sulfosalicylic Acid^{+}	4	
Erythrocytes*	5–10	≤ 3
Leukocytes*	0–5	≤ 5
Bacteria*	1	0
Creatinine [µmol/L]	2577	2470–19200
Urea [mmol/L]	118	141–494
Potassium [mmol/L]	127	20–80
Sodium [mmol/L]	65	54–190
Chloride [mmol/L]	92	46–168

Notes: $^{+}$Semiquantitative tests (reference value for all is 0, with the maximum value of 4 indicating "very high"). $^{\&}$Reference value is "negative" (can be either "negative" or "positive"). *Values are determined (counted) under the microscope and represent the average number of cells per field of view at 400x magnification. Comment: Low numbers of erythrocytes, leukocytes, and bacteria indicated a suboptimal sample, as urine microbiology was negative. The same applies to blood cultures.

The presentation of ascending paresis suggested the diagnosis of Guillain–Barré syndrome, and a lumbar puncture was recommended for confirmation. The intensivist was consulted regarding ICU admission due to the patient's rapid deterioration. After reviewing all available tests and laboratory findings, the intensivist, neurologist, and internist agreed that the diagnosis of fulminant idiopathic rhabdomyolysis was more likely than Guillain–Barré syndrome. During the consultation, the patient's ECG showed rapidly rising T waves, prompting urgent ICU admission for hyperkalemia correction and continued management of fulminant idiopathic rhabdomyolysis. The decision was made to forgo the lumbar puncture. An infectious disease specialist was consulted regarding a possible infectious cause of rhabdomyolysis. However, given the lack of relevant medical history, clinical findings, and elevated inflammatory markers, an infectious etiology was deemed unlikely.

At the time of ICU admission, the patient was alert, with normal pupillary responses, lower limb paresis, and minimal active movement of the distal muscle groups in the upper extremities. Passive movement of the extremities was possible but painful. Peripheral edema was absent; however, signs of early muscle stiffness suggested the potential development of compartment syndrome in the lower extremities. ECG monitoring revealed worsening T wave elevation, although no cardiac dysrhythmias were observed. Empirical treatment was initiated with calcium gluconate (3000 mg over 5 minutes) and glucose-insulin therapy (500 mL of 10% glucose with 10 units of fast-acting human insulin over 20 minutes). Despite preserved diuresis, acute RRT was commenced, consisting of a six-hour session of conventional hemodialysis primarily aimed at correcting hyperkalemia. Given the serum myoglobin and CK levels exceeding the upper reference limit, a CytoSorb membrane was incorporated to reduce serum myoglobin and protect renal function.[10–12] Additionally, hemadsorption with CytoSorb provided the added benefit of cytokine removal. At that time, the exact etiology of rhabdomyolysis remained unknown, and an immune-mediated cause was still under active consideration. Laboratory

samples collected at ICU admission confirmed marked hyperkalemia, elevated CK, myoglobin levels exceeding the upper reference limit, myoglobinuria, and liver injury with significantly elevated transaminases (Table 1).

By morning, serum potassium levels had normalized, while myoglobin and CK values remained extremely elevated, and transaminase levels continued to rise. A toxicology consultation ruled out apremilast as a potential cause, as no reports or data on apremilast-induced rhabdomyolysis were found in the literature. Given that an immune-mediated etiology remained a likely differential diagnosis, rheumatology was consulted. They recommended a muscle biopsy and a three-day course of 500 mg intravenous methylprednisolone boluses, followed by a daily dose of 40 mg until the muscle biopsy report became available. Muscle ultrasound (Figure 1) of both gastrocnemius muscles revealed a disrupted fibrillar structure and thickened fascia. During the first 24 hours of ICU treatment, the patient received 11 liters of parenteral fluids (Ionolyte) and produced 4 liters of spontaneous diuresis. Despite this, bedside cardiac echocardiography continued to demonstrate a collapsed IVC. The patient's extremities, particularly the lower limbs, became increasingly swollen. A trauma surgeon assessed her for compartment syndrome but concluded that surgical intervention was not necessary. By the end of the first day, her muscle strength had not improved. Additional RRT was performed throughout the day. With stable potassium levels, the treatment focus shifted to myoglobin adsorption, leading to an eight-hour session of sustained low-efficiency daily diafiltration (SLEDD) with a CytoSorb hemadsorption membrane.

By the end of the second day, marked clinical improvement was observed: the patient could move all four extremities, and her muscle pain began to subside. Due to persistently high myoglobin and CK levels, along with rising transaminases, a third SLEDD RRT session was conducted, this time using a TheraNova membrane. On the third day of ICU treatment, she regained the ability to move all four extremities but was still unable to eat independently or stand upright. Myoglobin levels dropped under the upper measurable limit for the first time but remained elevated, while liver enzymes began to stabilize. Methylprednisolone pulse therapy was concluded, and a maintenance dose of 40 mg daily parenteral methylprednisolone was initiated. Spontaneous diuresis normalized to approximately 1.6 liters per day, appropriate for her body weight of 70 kg.

The following day, a muscle biopsy and electromyography (EMG) of the lower extremities were performed. EMG revealed acute axonal injury of the fibular nerve, most likely at the fibular head due to sub-compartment syndrome pressure, as well as myopathic motor unit potentials. Additionally, positive sharp waves and fibrillation potentials with numerous myotonic discharges were detected in the right anterior tibial muscle. The muscle biopsy report, completed

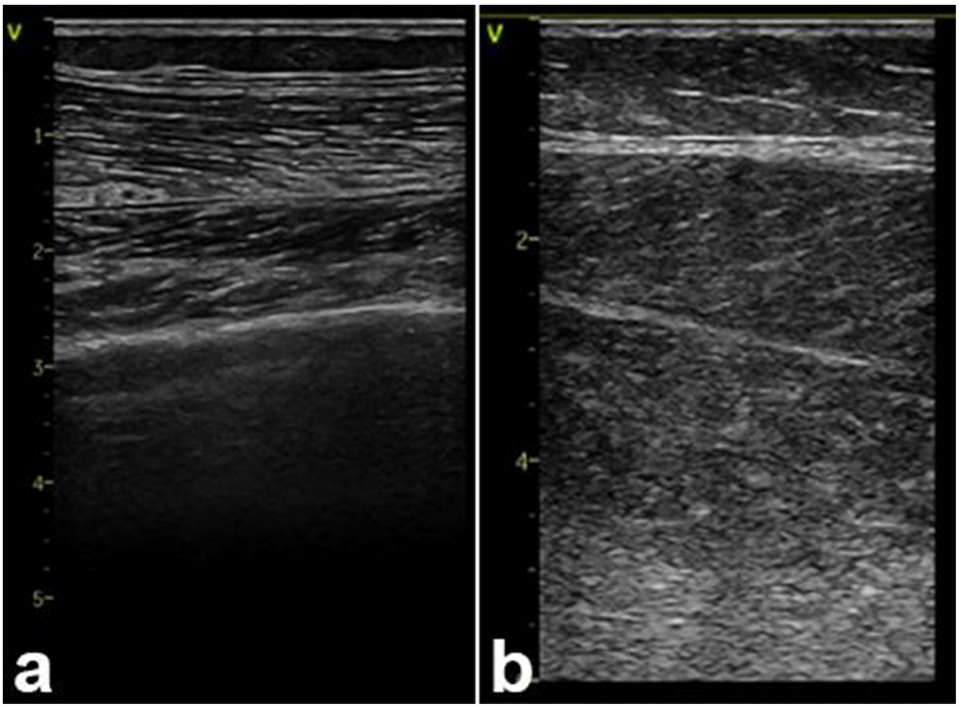

Figure 1 (**a**) Normal skeletal muscle ultrasound. (**b**) Skeletal muscle ultrasound of our patient with rhabdomyolysis with disrupted muscle structure.

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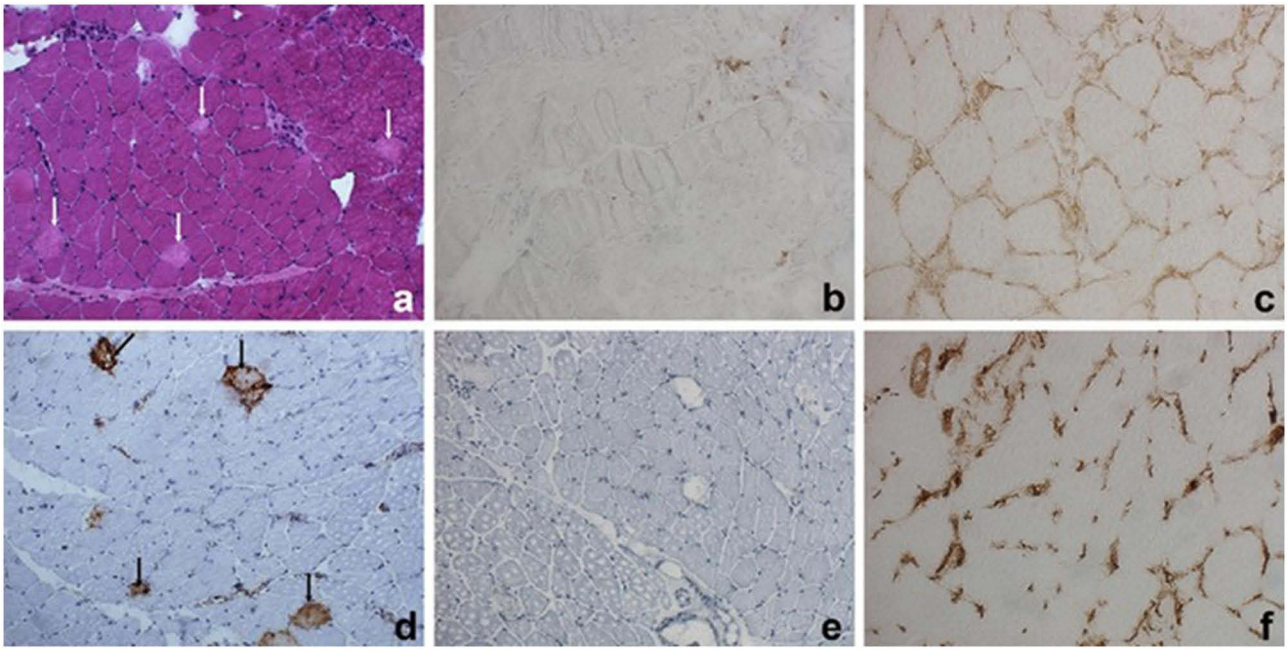

Figure 2 Muscle biopsy of our patient. (**a**) Hematoxylin-eosin stain: Among the abnormalities, individual necrotic fibers (arrows) stand out; otherwise, the morphology is normal. (**b**) Anti-CD3: A small cluster of T lymphocytes (the antibody marks both helper T lymphocytes and cytotoxic T lymphocytes). (**c**) HLA-1: The sarcolemma is not immunoreactive (normal). (**d**) C5b9: Accumulation of the activated terminal complement component in necrotic fibers (arrows). (**e**) CD8: Cytotoxic T lymphocytes are not present (the T lymphocytes shown in (b) are helper T cells). (**f**) HLA-DR: The sarcolemma is not immunoreactive (normal).

a few days after the patient had already been transferred out of the ICU, revealed numerous necrotic fibers with sparse inflammatory cells and no expression of human leukocyte antigen-1 (HLA-1) or human leukocyte antigen-DR isotype (HLA-DR) on the sarcolemma (Figure 2). These findings were consistent with toxic myopathy. McArdle disease, phosphofructokinase deficiency, and myoadenylate deaminase deficiency were ruled out. Her condition continued to improve rapidly, and additional RRT sessions were not required. Liver function also improved.

During the ICU stay, inflammatory markers increased without any accompanying clinical signs of infection. A repeat PCR test for respiratory infections confirmed SARS-CoV-2 positivity, suggesting an incidental in-hospital infection, as the initial test upon hospital admission had been negative. Despite extremely elevated serum myoglobin levels, renal function remained stable, with polyuria observed during the first two days of treatment. After the third day in the ICU, the treatment focus shifted primarily to intensive physical therapy. No specific liver support measures were implemented.

She was transferred to the rheumatology department on the seventh day. At the time of transfer, all laboratory values were trending toward normalization, and her physical condition was steadily improving, although signs of fibular nerve injury persisted. She remained in the rheumatology department for an additional 24 days, during which she underwent daily physiotherapy and regained nearly complete motor function. Upon receiving the muscle biopsy report (performed during her ICU stay), methylprednisolone was discontinued (total corticosteroid therapy duration was 14 days), leading to the development of adrenal insufficiency that required hydrocortisone supplementation. After leaving the ICU, she experienced an episode of chest pain. Her ECG was normal, but elevated troponin levels were detected. Cardiac MRI and coronary angiography ruled out myocarditis and coronary artery disease. The elevated troponin was attributed to rhabdomyolysis[13,14] and the levels normalized without any recurrence of symptoms.

After studying the biopsy report, considerable speculation arose regarding the possible trigger of the toxic myopathy. A thorough investigation into the patient's history and medications, including discussions with her and her family, revealed that she had started taking two supplements only two days before her collapse: Dr. Böhm Immun Complex (Apomedica, Austria) and Biostatine (Pharmalife Research, Italy). Since both were available over-the-counter, she did not consider them significant enough to mention in her initial medical history. A closer examination revealed that Biostatine contained red yeast rice extract with monacolin K. The recommended daily dose of two tablets provides

2.9 mg of monacolin K. RYR is known to cause both rhabdomyolysis and severe liver injury.[9] The patient had no prior history of statin or other lipid-lowering medication use. Although SARS-CoV-2 is a recognized potential cause of rhabdomyolysis,[15,16] it was excluded as a trigger in this case because the PCR test confirming the infection was positive only after the patient had already recovered from the acute phase. No other potential triggers were identified during the investigation (complement components C3, C4, and anti-dsDNA were also within reference ranges).

Our patient was discharged home after 31 days of hospital care. Upon discharge, her laboratory values had normalized, and she was able to walk with the assistance of a walker and orthosis due to persistent fibular nerve injury. Her chronic psoriasis therapy with apremilast was resumed, and B1 and B6 vitamins were prescribed to support recovery from axonal injury. Lipid-lowering therapy was deemed unnecessary as her cholesterol, LDL, and HDL levels were within the normal range. A follow-up one year later confirmed full recovery, including resolution of the axonal injury and restoration of normal motor function. The only remaining issue was adrenal insufficiency, for which hydrocortisone supplementation was still required.

Discussion

Rhabdomyolysis is a serious condition characterized by the breakdown of damaged skeletal muscle, leading to the release of intracellular contents, including myoglobin, into the bloodstream. It is broadly classified into traumatic and non-traumatic types, with non-traumatic causes being more prevalent. Alcohol abuse and medicinal drug use are the most frequent non-traumatic causes.[17] The exact pathophysiology of rhabdomyolysis remains incompletely understood, but several mechanisms have been proposed based on clinical and experimental studies. The first differential diagnosis considered was immune-mediated necrotizing myopathy,[18] a condition is characterized by persistent muscle weakness and elevated CK levels even after discontinuing statins, indicating an ongoing immune-mediated process. In our case, the histopathological report suggested toxic myopathy due to the absence of HLA-1 and HLA-DR expression on the sarcolemma. However, the presence of sparse inflammation is consistent with immune-mediated necrotizing myopathy. Myositis-specific antibodies and anti-HMGCR antibodies, which could differentiate between toxic and immune-mediated necrotizing myopathy, were not tested. Ultimately, the clinical course ruled out an immune-mediated etiology. The second possible diagnosis was rhabdomyolysis related to SARS-CoV-2 infection. This was ruled out due to the negative PCR test at the time of the admission, as discussed previously. Although cocaine is a known trigger of rhabdomyolysis, based on the patient's history, clinical data, and available socioeconomic information, illicit drug use was deemed unlikely, and additional toxicology testing was not performed.[19] Among drug-related causes, statins are widely recognized. These lipid-lowering medications exert their primary effect by inhibiting HMG-CoA reductase, the rate-limiting enzyme in the cholesterol biosynthetic pathway in the liver.[20] Their side effects are thought to result from inhibition of the mevalonate pathway,[21,22] which reduces CoQ10 levels and impairs mitochondrial energy production.[5] Additionally, statins may disrupt calcium homeostasis in muscle cells by inhibiting calcium channels or altering calcium signaling pathways.[23] Demographic risk factors for statin-induced rhabdomyolysis include age and gender. Females may have a higher risk, although evidence is limited. Individuals aged 65 years and older have a fourfold increased risk of hospitalization for rhabdomyolysis compared to younger users.[24] Evidence suggests that elderly women are particularly susceptible, possibly due to differences in muscle mass, hormonal influences, and pharmacokinetics between genders. However, products containing red yeast rice extracts are not explicitly mentioned in this context.[25]

After a detailed review of our patient's medical history and reported use of routine medications, Biostatine, a product containing red yeast rice (RYR), was identified as the most likely cause of rhabdomyolysis. RYR is a supplement known for its cholesterol-lowering properties, primarily due to its bioactive compound monacolin K, which structurally matches lovastatin. Monacolin K's bioavailability increases when taken with a meal, which is linked to its metabolism via the cytochrome P450 3A4 (CYP3A4) enzyme system.[26] Drugs or foods metabolized through CYP450 can inhibit enzyme activity, leading to elevated serum concentrations of lovastatin, and similar interactions are likely relevant for monacolin K. However, differences in the pharmacokinetics of monacolin K and pure lovastatin have been reported. Chen et al demonstrated that monacolin K exhibits more effective inhibition of CYP450 and P-glycoprotein (P-gp) compared to lovastatin. Additionally, variations in the inhibition of CYP450 and P-gp have been observed among different RYR products, even those with identical lovastatin content.[27] Given this metabolic pathway, the concomitant use of drugs interacting with statins, such as CYP450 inhibitors, could pose a clear risk factor for rhabdomyolysis. However, no such medications or food products were identified in our patient's medical history.[28] The

only regularly used medication was apremilast, a phosphodiesterase 4 (PDE4) inhibitor. While it shares a metabolic pathway via the cytochrome P450 enzyme system, apremilast neither inhibits nor induces CYP enzymes, reducing the likelihood of a direct interaction.[29]

The primary analysis of RYR adverse effects comes from a 2023 report by Banach and Norata,[9] which documents rare cases of RYR-associated rhabdomyolysis and hepatitis. In our review of reported cases, we identified a 28-year-old female,[30] a 65-year-old male with concomitant hepatitis,[31] and a 50-year-old female patient.[32] None of these cases required ICU admission, and none reported the dose of RYR consumed. One 65-year-old male patient experienced both hepatitis and rhabdomyolysis, but his clinical course was significantly less severe. Wang et al reported a case of a 76-year-old man who developed rhabdomyolysis-induced acute kidney injury (AKI) following the administration of a RYR supplement.[33] While there are notable similarities, key differences distinguish their case from ours, particularly in the duration of supplement use, dosage of the active ingredient, and clinical presentation. In Wang's case, the patient had been taking the supplement for three months at a dosage of 24 mg per day, with a gradual onset of symptoms over several weeks, eventually leading to mild extremity weakness. In contrast, our patient had taken the supplement for only two days at a dosage of 2.9 mg per day. Despite the significantly lower dose and shorter duration, the clinical presentation was fulminant, manifesting as tetraparesis within less than 24 hours from the onset of symptoms and necessitating intensive care unit (ICU) treatment. Our patient presented with fulminant rhabdomyolysis and subsequently developed liver injury, possibly transient hepatitis, with transaminase levels 200 times the upper normal limit. Despite this, her serum bilirubin and international normalized ratio (INR) remained normal, and gamma-glutamyl transferase (GGT) was only mildly elevated (Table 1).[34] While corticosteroid therapy did not significantly impact the rhabdomyolysis, it may have prevented progression to fulminant liver failure.

Rhabdomyolysis can lead to AKI through various mechanisms such as myoglobin toxicity,[35,36] tubular obstruction,[37] renal vasoconstriction,[38] and electrolyte imbalances.[39] Myoglobin, filtered by the kidneys, can precipitate with the Tamm-Horsfall protein in acidotic urine, forming casts that obstruct the tubular lumen and cause acute tubular necrosis (ATN).[35,36] Additionally, myoglobin exerts direct nephrotoxic effects through the oxidation of hydroxyl radicals.[2,36,39] Given the central role of myoglobin in AKI pathophysiology, early renal replacement therapy is critical in severe rhabdomyolysis to facilitate myoglobin extraction. Advanced hemodialysis membranes, including high-cutoff, medium-cutoff, and synthetic hemadsorption membranes like CytoSorb, are effective for this purpose. CytoSorb, originally developed for cytokine adsorption in hyperinflammatory conditions,[40] non-selectively captures molecules smaller than 60 kDa[41] and has demonstrated efficacy in removing myoglobin from the blood of patients with severe rhabdomyolysis.[11,12,42,43] Studies have shown significant myoglobin reduction during the initial hours of CytoSorb use,[43] with evidence suggesting faster kidney recovery and lower myoglobin levels compared to RRT alone, as demonstrated by Gräfe et al in a prospective single-center study.[41] However, CytoSorb's efficacy may be limited by membrane saturation, reducing adsorption capacity as early as three hours after initiation. This limitation highlights the importance of timely adsorber replacement in severe cases.[44] In our patient's case, the sustained high myoglobin levels following initial SLEDD sessions with CytoSorb could be attributed to this constraint, especially as elevated CK levels indicated ongoing rhabdomyolysis.

The recognition of statins as a potential cause of muscle pain and possible rhabdomyolysis[45] often guides clinical management, but it is equally important to consider other contributing factors. In this case, had the use of over-the-counter (OTC) supplements, specifically Biostatine containing red yeast rice, been disclosed, it could have led to a quicker recognition of the underlying cause and more targeted therapeutic interventions. Unfortunately, patients frequently fail to disclose OTC supplement use, as was the case with our patient. A multicenter European study conducted across 18 countries revealed that many patients are unaware of the potential effects of OTC supplements on laboratory results, with a significant number failing to disclose their use to healthcare providers.[46] A major factor contributing to this nondisclosure is the lack of specific inquiry by healthcare providers about OTC supplement use. Research indicates that patients are more likely to disclose supplement use when directly asked by their healthcare providers.[47] Furthermore, many patients perceive OTC supplements as benign or unrelated to their primary healthcare concerns, contributing to their reluctance to mention them.[48] This case highlights the critical need for healthcare providers to make direct inquiries regarding all medications and supplements a patient may be using. The literature

strongly emphasizes the need for improved communication and education between patients and providers regarding OTC supplement use and its potential impact on patient health.

To the best of our knowledge, this is the first report of fulminant rhabdomyolysis and liver injury occurring after the ingestion of only a few tablets containing red yeast rice extracts. Notably, the dosage of monacolin K in this case was low, below the 10 mg daily threshold previously associated with significant safety concerns.[49] While most reported cases of rhabdomyolysis linked to RYR have been mild and resolved spontaneously upon discontinuation, our patient's condition was more severe. A three-day bolus corticosteroid therapy with subsequent maintenance daily dose was initially administered under the assumption that the rhabdomyolysis was autoimmune in origin. However, subsequent biopsy findings suggested toxic rhabdomyolysis, indicating that corticosteroids likely had limited efficacy in improving the condition. The rise in liver transaminases, observed during treatment, was not immediately prioritized due to the clinical focus on impending compartment syndrome and tetraparesis. The diagnosis of acute liver injury or possible acute hepatitis became evident only after further analysis. The role of corticosteroids in treating liver injury caused by RYR extracts remains unclear, as no specific treatment guidelines exist. Additionally, a liver biopsy was not performed, and any discussion regarding the precise nature of liver involvement is speculative. According to a review by Weibrecht et al,[50] elevated transaminase levels in the context of rhabdomyolysis do not necessarily correlate with liver injury, although the enzyme levels in our case were significantly higher than those typically reported.

Limitations

There are a few limitations to this case report. First, as a single case report, it inherently holds a low level of general evidence and cannot be directly extrapolated to larger populations. Second, while the causal link between the RYR supplement and rhabdomyolysis is meticulously argued, it remains implied rather than definitively proven, as direct objective evidence cannot be established. Third, the patient had never taken any other over-the-counter or statin-based lipid-lowering medications prior to this episode, making it impossible to confirm whether chemically synthesized statins would have caused a similar reaction. Finally, despite extensive investigation, the potential role of other confounding factors, including genetic predisposition or unidentified environmental influences, cannot be entirely ruled out.

Conclusion

Our report highlights a case of fulminant rhabdomyolysis and liver injury following the use of a low-dose, over-the-counter drug containing red yeast rice extracts for just a few days. The patient's acute tetraparesis was attributed to severe muscle injury, supported by myoglobinuria, hyperCKemia, muscle ultrasound, electromyography, and muscle biopsy findings. Subclinical liver injury was evidenced by markedly elevated liver transaminases. Due to the extremely high myoglobin levels, SLEDD with CytoSorb hemadsorption was employed, which played a crucial role in preventing acute and potentially long-term renal failure. High doses of methylprednisolone were initially administered under the suspicion of immune-mediated myopathy but were discontinued when the biopsy confirmed toxic myopathy and liver enzymes normalized. Only one hemodialysis session was performed due to acute hyperkalemia from rapid muscle breakdown. This case underscores the importance of caution in prescribing and using over-the-counter medications, as their potential side effects can be life-threatening. Given that red yeast rice and its active ingredient, monacolin K, share similar pharmacological effects and risks as lovastatin, healthcare professionals must remain vigilant and proactively inquire about both prescription and over-the-counter medications that patients may be using.

Data Sharing Statement

No additional data to publish.

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Author Contributions

All authors made a significant contribution to the work reported, whether that is in the conception, study design, execution, acquisition of data, analysis and interpretation, or in all these areas; took part in drafting, revising or critically reviewing the article; gave final approval of the version to be published; have agreed on the journal to which the article has been submitted; and agree to be accountable for all aspects of the work.

Institutional Review Board Statement

Ethical review and approval were waived as for case report nature of the article.

Informed Consent Statement

We have received verbal and written consent to publish this case report from the patient.

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