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【 CASE REPORT 】

A Severe Case of Rhabdomyolysis Requiring Renal Replacement Therapy Following COVID-19 mRNA Vaccination

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Abstract:
A 60-year-old man who developed rhabdomyolysis and severe acute kidney injury (AKI) after the fourth COVID-19 mRNA vaccination, necessitating renal replacement therapy (RRT). The patient presented to the hospital two days post-vaccination with muscle pain in both lower extremities and anuria. Diagnostic tests revealed elevated creatinine kinase (CK) levels of 160,000 IU/L and serum creatinine levels of 6.59 mg/dL, confirming AKI due to rhabdomyolysis. Intravenous therapy was ineffective, leading to the utilization of online hemodiafiltration. Following treatment, CK levels normalized, and the renal function fully recovered.

Key words: Rhabdomyolysis, mRNA vaccine, COVID-19, Acute Kidney Injury, Online Hemodiafiltration, Statin

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Introduction

Rhabdomyolysis is characterized by acute breakdown of skeletal muscle cells, leading to the release of substantial intracellular muscle components, including creatine kinase (CK), myoglobin, electrolyte substances, and lactate dehydrogenase, into the bloodstream. The clinical presentation of rhabdomyolysis varies, ranging from mild cases with asymptomatic elevated CK levels to severe cases involving electrolyte imbalances and acute kidney injury (AKI). Various factors, such as acute trauma, statin medications, muscle ischemia, genetic disorders, metabolic diseases, and infections, can precipitate rhabdomyolysis (1). Notably, recent reports have linked rhabdomyolysis to COVID-19 infection and vaccination (2). Although the majority of these reports describe mild cases that respond well to intravenous therapy, we present a distinctive case of a Japanese patient who experienced severe AKI due to rhabdomyolysis after receiving COVID-19 vaccination, necessitating renal replacement therapy (RRT).

Case Report

A 60-year-old man presented to the hospital with muscle pain and anuria 2 days after receiving his fourth COVID-19 vaccination. The patient had a history of schizophrenia and dyslipidemia and a history of psychotropic drug and statin use. No kidney disease or autoimmune disease was noted in his family history. Initial blood tests revealed elevated levels of CK (160,000 IU/L) and serum creatinine (sCr); 6.59 mg/dL, leading to a diagnosis of AKI attributed to rhabdomyolysis. Intravenous therapy was initiated by the attending physician; however, there was no improvement in anuria or the renal function. Consequently, the patient was transferred to our hospital for further management following intravenous fluid therapy. On arrival, the patient exhibited bilateral lower leg grasping pain with no other notable physical findings. Subsequent blood tests indicated severe renal dysfunction, including a blood urea nitrogen level of 95.4 mg/dL, sCr level of 8.86 mg/dL, and an estimated glomerular filtration rate of 5 mL/min (Fig. 1). In addition, evidence of rhabdomyolysis was observed, with CK levels of 77,923 IU/

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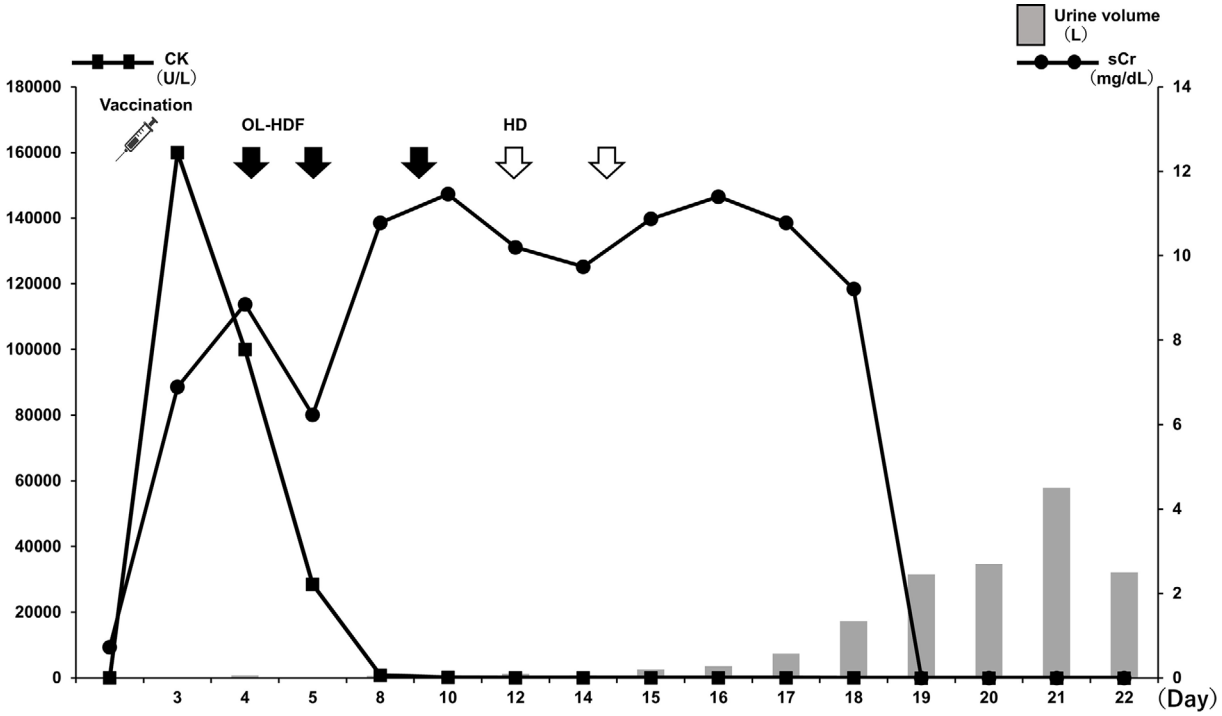

Figure 1. **Time-course of creatine kinase (CK), serum creatinine levels and urine volume in relation to dialysis modalities. After three rounds of online hemodiafiltration (OL-HDF), CK levels returned to the normal range. Hemodialysis therapy was discontinued, as the patient's urine output recovered after two rounds of the therapy.**

Table 1. **Laboratory Findings at Admission. A Diagnosis of Acute Kidney Injury Due to Rhabdomyolysis was Made Based on Elevated Creatinine Kinase, Myoglobin, and Creatinine Levels.**

Blood test		**Spot urine test**	
Albumin (g/dL)	2.9	Specific gravity	1.18
Urea nitrogen (mg/dL)	95.4	Potential hydrogen	5.5
Creatinine (mg/dL)	8.86	Blood	3+
Urine acid (mg/dL)	15.4	Protein	3+
Creatine kinase (U/L)	77923	Glucose	2+
Myoglobin (ng/mL)	29830	Ketones	-
Sodium (mEq/L)	135	White blood cell	-
Potassium (mEq/L)	4.9	**Spot urinalysis**	
Chloride (mEq/L)	99	Urea nitrogen (mg/dL)	122
Corrected calcium (mEq/L)	8.0	Creatinine (mg/dL)	89.2
Phosphorus (mEq/L)	6.4	Myoglobin (ng/dL)	3570
C-reactive protein (mg/dL)	4.5	Sodium (mEq/L)	78
IgG (mg/dL)	631	Potassium (mEq/L)	38
IgA (mg/dL)	92	Chloride (mEq/L)	67
IgM (mg/dL)	27	Protein (g/gCre)	3.60
Complement C3 (mg/dL)	101	β2-Microgrobulin (ng/mL)	1427
Complement C4 (mg/dL)	23	N-acetyl-β-D-glucosaminidase (U/L)	119.1
Anti-nuclear antibody titer (x)	<40	Fractional excretion of sodium (%)	5.7
PR3-ANCA (IU/mL)	0.2	Fractional excretion of urea nitrogen (%)	11.7
MPO-ANCA (IU/mL)	0.6	**Urine sediment**	
Anti-GBM antibody (U/mL)	<0.2	Red blood cell (/HPF)	50-99
White blood cell (/μL)	9,500	White blood cell (/HPF)	10-19
Hemoglobin (g/dL)	12.2		
Platelet ($\times 10^3$/μL)	189		

L and myoglobin levels of 29,830 ng/mL (Table 1).

To identify the underlying cause of AKI, blood tests were conducted, which were negative for antinuclear antibodies, myeloperoxidase antineutrophil cytoplasmic antibody, proteinase-3-antineutrophil cytoplasmic antibody, and anti-glomerular basement membrane (GBM) antibodies, ruling out rapidly progressive glomerulonephritis, vasculitis, and anti-GBM nephritis. Urinary biochemistry revealed a urinary protein-to-creatinine ratio of 3.597 g/g creatinine, fractional sodium excretion level of 5.7%, and urinary myoglobin level

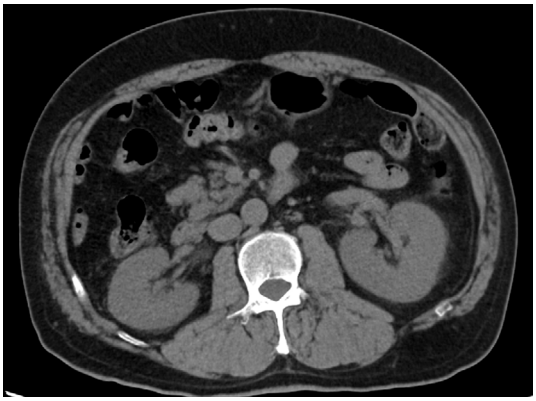

Figure 2. Normal abdominal CT findings. Abdominal CT showed no bilateral hydronephrosis or abnormal renal morphology.

of 3,570 ng/mL. A urinary sediment analysis revealed a urinary erythrocyte count of 50-99/high-power field (HPF) and gross hematuria. Postrenal AKI was ruled out because no bilateral hydronephrosis or abnormal renal morphology was observed on abdominal ultrasound or computed tomography (CT) (Fig. 2). Based on these comprehensive assessments, the patient was diagnosed with AKI secondary to rhabdomyolysis.

To manage the condition, the patient received high-dose infusion of bicarbonate Ringer's solution therapy and underwent postdilution online hemodiafiltration (OL-HDF) using an asymmetric triacetate fine-flux dialyzer (NIPRO FIX-250 Seco®; [Nipro Pharma Corporation]). Following three sessions of OL-HDF, CK levels were normalized. Subsequently, OL-HDF was switched to hemodialysis (HD) using a conventional polymethylmethacrylate (PMMA) high-flux dialyzer (Toray NF-2.0H®; [TORAY INDUSTRIES, INC.]). With the patient's urine output returning after two rounds of HD, HD therapy was discontinued. Over time, the urine output increased, and we determined that no additional HD was needed after approximately three weeks (Fig. 1).

Discussion

With the widespread implementation of vaccination programs, rhabdomyolysis has emerged as an adverse reaction associated with COVID-19 vaccination (3). However, only a few cases have led to severe AKI necessitating RRT. We encountered a case of rhabdomyolysis following COVID-19 vaccination that resulted in severe AKI requiring RRT. We also identified six published case reports of severe AKI requiring RRT due to rhabdomyolysis following COVID-19 vaccination (Table 2). Among these cases, three were fatal. Ajmera (4) reported an 85-year-old patient who developed severe rhabdomyolysis with AKI after receiving the Moderna COVID-19 vaccine and required RRT. Despite intensive care, mechanical ventilation, and RRT, the patient's renal function did not recover, and he died. Kamura et al. (5) described a 57-year-old patient who experienced multi-organ failure due to rhabdomyolysis and thrombotic microangiopathy, ultimately leading to death 14 days after receiving the first vaccine dose. In addition, Huang et al. (6) reported a 44-year-old man who developed fulminant myositis and renal failure after receiving the ChAdOx1-nCoV-19 vaccine. In addition to these fatal cases, Ruijters et al. (7) reported an 80-year-old man who did not regain his renal function and remained dependent on HD. Conversely, in two cases, urine production gradually resumed, leading to discontinuation of HD (8).

Rhabdomyolysis has been reported as an adverse event associated with various vaccines, including influenza, tetanus, diphtheria, and pertussis. Several mechanisms have been proposed to explain vaccine-associated rhabdomyolysis. Some studies have suggested that an autoimmune reaction may trigger vaccine-related rhabdomyolysis. For instance, Vojdani et al. (9) reported homology between the SARS-CoV-2 spike protein and F-actin, which could induce an autoimmune response in muscle tissues. Steroid therapy has been used in some reported cases to address the autoimmune aspect of post-vaccination rhabdomyolysis (10, 11). Li et al. posited that the drugs themselves do not directly cause specific drug reactions but may do so when combined with danger signals generated by stress-injured cells (12). COVID-19 mRNA vaccination-induced rhabdomyolysis may involve immunological mechanisms distinct from those of other etiologies. While exertional or drug-induced rhabdomyolysis is primarily attributed to direct muscle injury or metabolic disturbances, mRNA vaccines have been associated with immune activation, including elevated levels of cytokines, such as IL-6. The transient increase in IL-6 levels observed following vaccination could contribute to systemic inflammation and muscle breakdown. Previous studies have suggested that immune-mediated pathways, including cytokine storms, may exacerbate muscle cell membrane instability, leading to rhabdomyolysis. Although the potential role of IL-6 in the pathogenesis of rhabdomyolysis induced by COVID-19 mRNA vaccination has been noted, we regret that time-course data for IL-6 were unavailable in this case. The absence of these data limits our ability to directly correlate cytokine dynamics with the progression of muscle injury.

Reports of AKI associated with rhabdomyolysis following COVID-19 mRNA vaccination indicate two distinct clinical trajectories: one group demonstrating full recovery and another with persistent renal impairment or fatal outcomes. Several factors may contribute to these differences, including the baseline renal function, severity of muscle damage, as reflected by peak creatine kinase values, earlier initiation of renal replacement therapy, and multiorgan failure. However, robust comparative data remains limited, and further large-scale analyses are required to identify consistent predictive markers. In addition, differences in outcomes between recipients of Pfizer-BioNTech and those of other vaccines have been observed in previous case reports. It has been suggested that additives, such as trometamol, which are not

Table 2. Published Cases with Severe Acute Kidney Injury Requiring Renal Replacement Therapy Due to Post-vaccination Rhabdomyolysis.

Study	Sex/Age	Vaccine type	Vaccine doses	CK peak	sCr peak	Medication	Outcome
Current Case	M/60	Pfizer	4	160,000	8.86	Blonanserin, Paliperidone, and Pravastatin	Recovery
Ruijters et al. 2022	M/80	Pfizer	2	280,600	N/A	Rosuvastatin	Recovery
Imhof et al. 2022	M/65	Pfizer	2	90,373	13.7	Rosuvastatin	Recovery
Banamah et al. 2022	F/58	Pfizer	3	42,670	8.57	Flupenthixol, Trifluoperazine, and Benztropine mesylate	Recovery
Kamura et al. 2022	M/57	Moderna	1	74,804	N/A	No medication	Death
Huang et al. 2022	M/44	AstraZeneca	2	151,058	4.6	No medication	Death
Ajmera et al. 2022	F/85	Moderna	2	14,000	6.0	Rosuvastatin	Death

included in the monovalent vaccine, may be involved in the development of rhabdomyolysis caused by the Omicron strain of the bivalent vaccine. However, owing to the rarity of such adverse events, these observations warrant cautious interpretation and further investigation.

The nephrotoxicity of myoglobin, which is released in large quantities during rhabdomyolysis, leads to AKI (13). Under acidic urine conditions, myoglobin is converted into nephrotoxic hematin, impairing the renal tubules. The substantial production of uric acid from muscle disintegration can crystallize and obstruct renal tubules (14). Myoglobin can directly damage the kidneys by constricting renal vessels and inducing oxidative stress-related mitochondrial dysfunction (15). Consequently, standard rhabdomyolysis treatments involve the use of saline solutions, urine alkalinization, and RRT. However, the efficacy of RRT as a treatment for AKI due to rhabdomyolysis has not been definitively established (16, 17). The molecular weight of myoglobin is 17,800 Da, and its half-life in cases of rhabdomyolysis is 12-24 h (18). In our case, we employed post-dilution OL-HDF with a fine-flux membrane to efficiently remove myoglobin. After confirming the CK reduction, we switched to HD using a PMMA membrane. Rhabdomyolysis intensifies the production of inflammatory cytokines such as tumor necrosis factor-alpha, interleukin (IL)-1β, IL-6, and monocyte chemoattractant protein-1 (19). PMMA membranes can adsorb various proteins and effectively remove high-molecular-weight proteins, including IL-6 (20, 21). RRT with a PMMA dialyzer may thus prove beneficial in AKI cases related to rhabdomyolysis because it facilitates myoglobin removal and IL-6 absorption. The initial use of OL-HDF was selected for its enhanced capacity to clear large molecules, such as myoglobin, owing to its combined convection and diffusion mechanisms. However, after the initial phase of treatment, the transition to conventional HD was made based on the patient's clinical stability. Although OL-HDF offers superior middle-molecule clearance, no definitive evidence currently supports its superiority over conventional hemodialysis in improving long-term outcomes, specifically for rhabdomyolysis-induced AKI. Further studies are required to establish the optimal dialysis modality in this context.

Statins and antipsychotics are well-known medications that are associated with the side effects of rhabdomyolysis. In recent years, some case reports have linked rhabdomyolysis in statin users with COVID-19 infection or vaccination. Of the seven cases of post-vaccination rhabdomyolysis resulting in severe AKI requiring RRT, including our report, five involved patients taking statins or psychotropic drugs (Table 2). Imhof et al. conducted a prospective study of 100 renal transplant recipients, measuring CK levels before vaccination and 7 and 28 days after vaccination (22). Among the five participants with CK levels exceeding 200 IU/L on day 7, three were on statins. Although this study was based on a relatively small sample size and did not provide definitive conclusions, it underscores the importance of measuring CK levels in patients with myalgia after vaccination to predict rhabdomyolysis. The causal relationship between statins, antipsychotic medications, vaccination, rhabdomyolysis, and severe AKI remains unclear. Nonetheless, our findings, along with data from published literature, suggest that patients taking statins and antipsychotics face a higher risk of developing severe AKI due to rhabdomyolysis, indicating that the risk hypothesis of the cumulative stress of vaccination and these medications may contribute to the severity of AKI.

In conclusion, based on this case and the existing literature, we emphasize that rhabdomyolysis following mRNA COVID-19 vaccination, although uncommon, is an important adverse event to consider, particularly in patients taking statins or antipsychotics. Healthcare providers should be vigilant and consider rhabdomyolysis as a potential diagnosis in patients taking statins or antipsychotics who report myalgia or gross hematuria after vaccination.

The authors state that they have no Conflict of Interest (COI).

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