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Sickle Cell Trait and SARS-CoV-2-Induced Rhabdomyolysis: A Case Report

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Patient: **Male, 38-year-old**
Final Diagnosis: **Sickle cell trait and SARS-CoV-2 induced rhabdomyolysis**
Symptoms: **Dyspnea requiring oxygen support • lower back pain • lower limbs hypostenia • pharyngodynia**
Medication: —
Clinical Procedure: —
Specialty: **Nephrology**

Objective: **Rare coexistence of disease or pathology**
Background: Rhabdomyolysis is a syndrome characterized by muscle necrosis and the subsequent release of intracellular muscle constituents into the bloodstream. Although the specific cause is frequently evident from the history or from the immediate events, such as a trauma, extraordinary physical exertion, or a recent infection, sometimes there are hidden risk factors that have to be identified. For instance, individuals with sickle cell trait (SCT) have been reported to be at increased risk for rare conditions, including rhabdomyolysis. Moreover, there have been a few case reports of SARS-CoV-2 infection-related rhabdomyolysis.
Case Report: We present a case of a patient affected by unknown SCT and admitted with SARS-CoV-2 pneumonia, who suffered non-traumatic non-exertional rhabdomyolysis leading to acute kidney injury (AKI), requiring acute hemodialysis (HD). The patient underwent 13 dialysis sessions, of which 12 were carried out using an HFR-Supra H dialyzer. He underwent kidney biopsy, where rhabdomyolysis injury was ascertained. No viral traces were found on kidney biopsy samples. The muscle biopsy showed the presence of an "open nucleolus" in the muscle cell, which was consistent with virus-infected cells. After 40 days in the hospital, his serum creatinine was 1.62 mg/dL and CPK and Myoglobin were 188 U/L and 168 ng/mL, respectively; therefore, the patient was discharged.
Conclusions: SARS-CoV-2 infection resulted in severe rhabdomyolysis with AKI requiring acute HD. Since SARS-CoV-2 infection can trigger sickle-related complications like rhabdomyolysis, the presence of SCT needs to be ascertained in African patients.

Keywords: **Acute Kidney Injury • COVID-19 • Rhabdomyolysis • Sickle Cell Trait**

Full-text PDF: <https://www.amjcaserep.com/abstract/index/idArt/934220>



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Background

Rhabdomyolysis is a syndrome characterized by muscle necrosis and the subsequent release into the bloodstream of intracellular muscle constituents such as CPK and myoglobin, which are the most sensitive markers of this condition.

The severity of the illness can vary from an asymptomatic elevation in serum muscle enzymes to a life-threatening disease associated with AKI, which is the most serious complication of rhabdomyolysis, regardless of its cause [1].

The causes of rhabdomyolysis are generally divided into 3 categories: traumatic rhabdomyolysis (\pm muscle compression), non-traumatic exertional rhabdomyolysis, and non-traumatic non-exertional rhabdomyolysis (including drugs, toxins, infections) [2].

Although SCT alone is unlikely to cause muscle damage leading to rhabdomyolysis, simultaneous risk factors, such as infections, could explain some forms of non-traumatic, non-exertional rhabdomyolysis related to this benign heterozygous carrier condition. Indeed, in a recent cross-sectional study reviewing hemoglobin phenotypes in African Americans with end-stage renal disease, SCT was found to be twice as common than in the wider population [2].

Case Report

We report here the case of a 38-year-old African man with no past medical history, who presented to the emergency room with dyspnea requiring oxygen support (the oxygen saturation was 95% with 2 L/min of oxygen therapy via nasal cannula), lower back pain, lower limbs hypostenia, and pharyngodynia. At presentation the arterial blood pressure was 135/80 mmHg, the heart rate was 65 bpm, the body weight was 90 kg, the body temperature was 36.5°C. The patients denied exposure to medication, illicit drug use, or alcohol abuse. No strenuous physical activity was reported. Physical examination showed peripheral edema in the absence of jugular vein distention. Both rapid anti-COVID antigenic and molecular swabs were positive. High-resolution computed tomography showed peripheral ground-glass opacities consistent with SARS-CoV-2 pneumonia.

Laboratory tests revealed high urea and creatinine levels (220 mg/dL and 11.18 mg/dL, respectively), electrolytes imbalances, with hyponatremia (126 mmol/L), hypocalcemia (6.0 mg/dL), hyperkalemia (8.7 mmol/L) and hypermagnesemia (4.0 mg/dL), along with elevated levels of liver enzymes (AST 2953 U/L, ALT 623 U/L), LDH (20 881 U/L) and CPK (>20 000 U/L). A diagnosis of rhabdomyolysis with AKI in a SARS-CoV-2-infected patient was done. The patient's daily laboratory values are shown in **Table 1**.

Table 1. Patient's daily laboratory values.

Days	Creatinine (0.5-1.2 mg/dL)	Urea (17-43 mg/dL)	Potassium (3.5-5.0 mEq/L)	Calcium (9.5-5.0 mg/dL)	Phosphate (3-4.5 mg/dL)	Myoglobin (17-105 ng/mL)	CPK (< 170 U/L)
1	11.18	220	8.7	6.0	9.5	19 756	>20 000
2	8.60	121	6.9	7.0	8.1	22 760	21 223
3	6.98	93	6.3	7.8	7.3	25 520	28 855
4	6.81	91	5.9	8.0	7.1	19 640	38 123
5	7.0	95	6.0	8.1	7.2	12 094	64 682
6	7.5	95	5.2	7.9	7.5	5562	39 253
7	8.1	90	5.2	8.12	7.3	4519	18 213
8	8.3	111	4.9	9.0	7.5	3978	11 254
9	8.6	123	5.6	9.6	7.6	2950	5254
10	8.64	136	6.2	8.7	7.3	1602	2299
13	9.32	156	5.2	7.7	9.3	1323	1821
17	10.4	192	3.6	7.6	12.8	776	1486
22	7.3	110	3.5	8.1	7.3	621	1334
25	1.37	41	4.3	9.3	3.5	550	982

The normal reference range of the laboratory test results is shown in parentheses. CPK – creatine-phosphokinase.

Table 2. Reduction rates per session (RRs,%) of laboratory parameters during HFR-Supra H dialysis.

Parameter	MW (kDa)	RRs (%)	Range (min-max)
Beta 2 microglobulin	12	64.3	55.1-66.7
Procalcitonin	13	41.6	47.0-19.4
Myoglobin	17	57.3	49.1-66.5
Kappa light chains	22.5	56.6	46.6-60.6
Interleukin-6	24	11.1	-39.9-40.7
Lambda light chains	45	32.7	28.7-34.5
Albumin	69	2	0-8

MW – molecular weight; kDa – kilodaltons. All dialysis sessions lasted 240 minutes. The values measured at end of dialysis were corrected for hemoconcentration according to Bergström and Wehle's formula [16].

Primary human immunodeficiency virus, cytomegalovirus, and Epstein-Barr virus infections were excluded, as well as autoimmune myopathy.

Renal ultrasound did not show any signs of chronic injury, but showed kidneys of increased size (right: 12.5 cm, left: 13 cm), with normal cortical thickness (20 mm) and slightly hyper-echoic bilaterally, supporting the diagnosis of acute kidney damage. The patient was anuric.

A central venous hemodialysis catheter (Mahurkar® Medtronic, Minneapolis, USA, 24 cm length, 12 french diameter) was placed in the right femoral vein and emergency extracorporeal treatment was immediately started through bicarbonate dialysis.

Moreover, high doses of furosemide (250 mg/day) were administered after the first dialysis session. As the need for oxygen support was associated with lung overhydration more than related to the severity of COVID-19 pneumonia, and according to infectious disease experts, steroids were not required.

After the first session of bicarbonate dialysis, urea and creatinine were 121 mg/dl and 8.6 mg/dL, respectively, potassium was 6.9 mEq/l, and myoglobin was 22 760 ng/mL. A new central venous catheter (Mahurkar® Medtronic, 20 cm length, 12 french diameter) was placed in the right jugular vein and the Supra-hemodiafiltration H with endogenous reinfusion technique (HFR-Supra H, Bellco/Medtronic, Mirandola, Italy) was used to increase the removal of myoglobin, to reduce the inflammatory status and to maintain the fluid balance

When the fluid balance was corrected, the oxygen support was withheld and intravenous fluids were administered combined with high-dose furosemide.

As shown in **Table 2**, a significant reduction of myoglobin, procalcitonin, and beta 2 microglobulin blood levels per session was obtained after 9 daily dialysis sessions with HFR-Supra

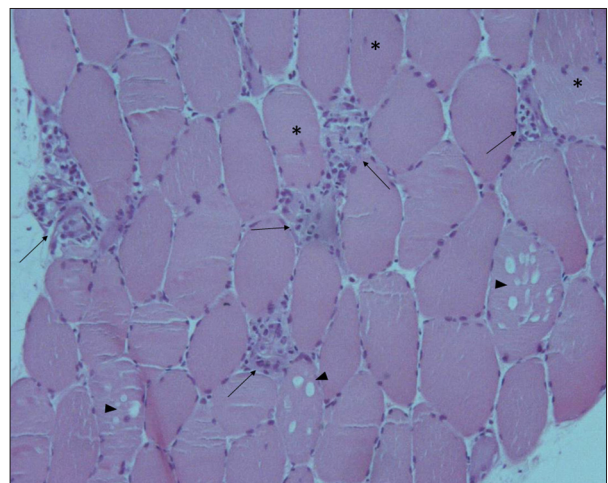


Figure 1. Hematoxylin and eosin staining on muscle biopsy showing multiple fiber cells with severe necrotic, degenerative changes and inflammatory cells infiltrate (arrows), some with large sarcoplasmic vacuoles (arrowheads) and isolated inner nuclei (black stars).

H. After 9 HFR-Supra H dialysis sessions, urea and creatinine were 136 mg/dl and 8.64 mg/dL, respectively, potassium was 6.2 mEq/l, and myoglobin was 1602 ng/mL. Dialysis was progressively reduced according to a gradual restoration of urine output, for a total of 13 dialysis sessions.

Both muscle and kidney biopsies were carried out. The former was conducted 11 days after admission, when daily diuresis was about 2 liters/day and serum creatinine was 8.64 mg/dL (eGFR 7 ml/min), while the latter was carried out 8 days later, when daily diuresis was over 3 liters/day and serum creatinine was 7.3 mg/dl (eGFR 9 ml/min).

Quadriceps muscle biopsy showed overwhelming necrosis (**Figure 1**) along with CD68 macrophages infiltration, likely associated with rhabdomyolysis (**Figure 2**). The ultrastructural appearance of muscle cell nuclei showed that some of them

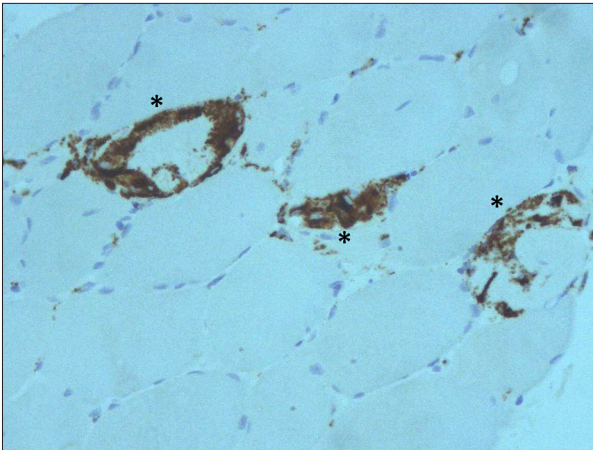


Figure 2. Immunohistochemistry on muscle biopsy for CD68 shows endomyisial infiltrate especially characterized by CD68 macrophages (black stars).

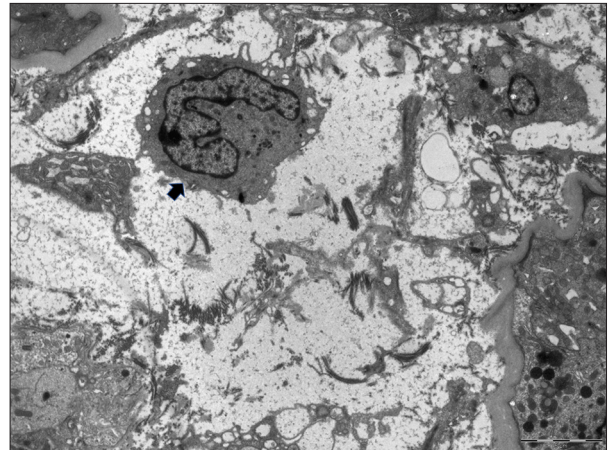


Figure 5. Electron microscopy. The extracellular space of kidney biopsy sample is enlarged due to interstitial edema and inflammatory infiltrate; the short arrow indicates a monocyte with horseshoe-shaped nucleus.

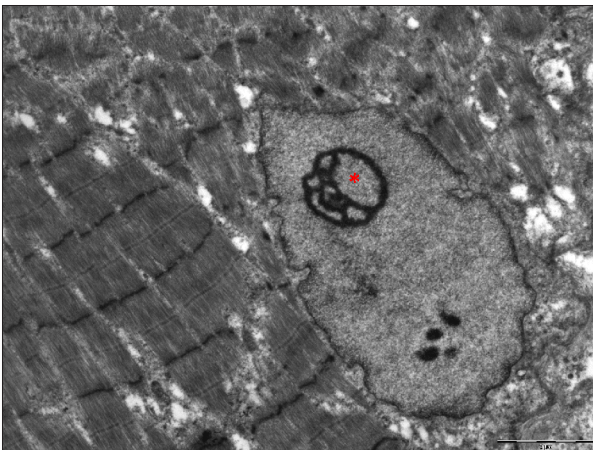


Figure 3. Electron microscopy of muscle biopsy samples shows an altered nucleus with dispersed heterochromatin and a ring-shaped "open" nucleolus (red star).

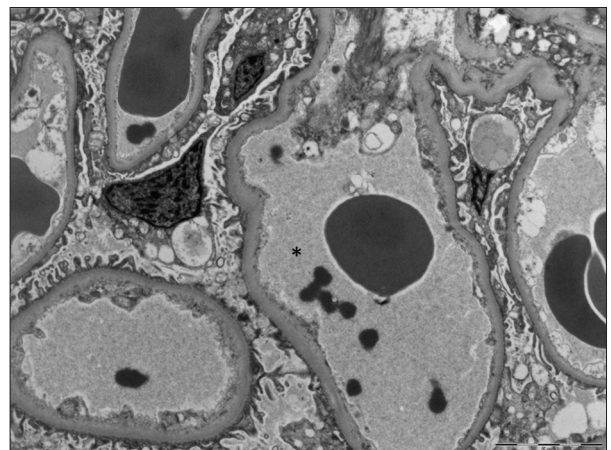


Figure 6. Electron microscopy. Red blood cells and hemoglobin/myoglobin casts (asterisk) are seen inside an otherwise normal glomerular capillary lumen.

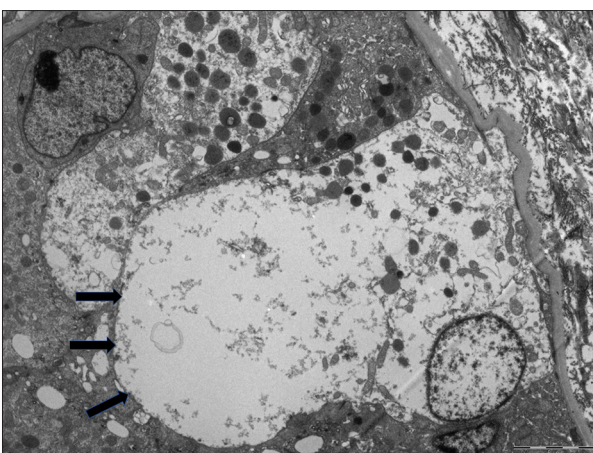


Figure 4. Electron microscopy of kidney biopsy samples. The arrows show a necrotic tubular epithelial cell.

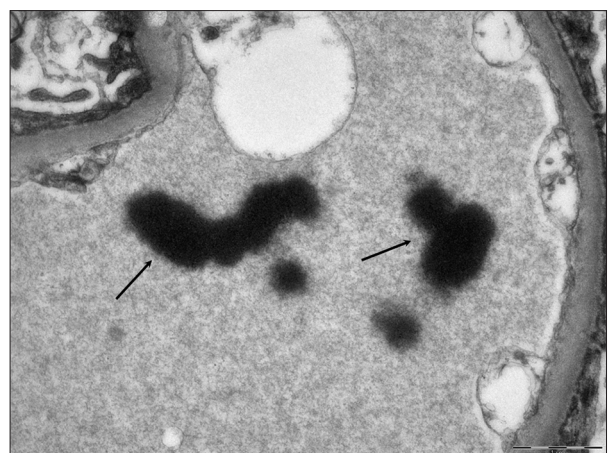


Figure 7. Electron microscopy. High-resolution detail of hemoglobin/myoglobin casts (thin arrows).

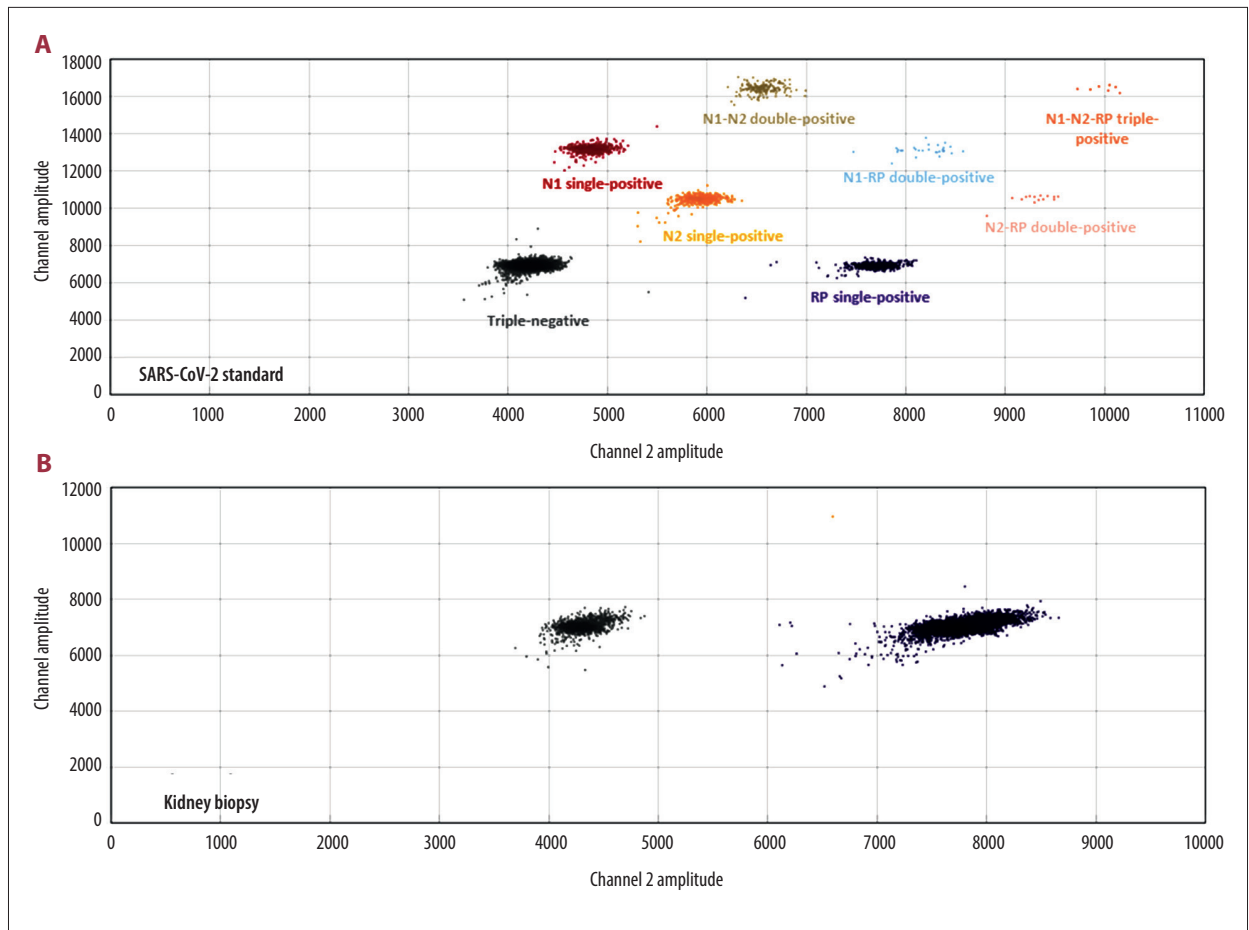


Figure 8. Analysis of SARS-CoV-2 target regions with droplet digital PCR assay. A) Reference positive sample; B) No copies of the SARS-CoV-2 genome were detectable in the kidney biopsy.

were characterized by normal outline but by anomalous distribution of chromatin, which was very finely distributed, with some giant perichromatin granules (Figure 3). In particular, the nucleoli of these altered nuclei showed a very peculiar meandering appearance or sometimes they are ring-shaped, indicating an “open” aspect where the nucleolonema is thin thread-like and spread-out as previously described in different types of malignant tumors (Figure 3).

Kidney biopsy showed no glomeruli by light microscopy along with mild-to-moderate acute tubular injury characterized by a focal diffuse globular reddish cast in the distal tubular lumina. Immunofluorescence studies were not performed due to insufficient renal samples. Electron microscopy, conducted on kidney biopsy samples, revealed acute tubular injury (Figure 4), and interstitial edema with minimal mononuclear cell infiltrates (Figure 5); electron-dense granules with fluffy outline, consistent with hemoglobin/myoglobin casts, were seen in some glomerular capillaries (Figures 6, 7). No electron-dense deposits were found along the glomerular capillary wall, nor were dysmorphic red blood cells casts. The mesangium was

unremarkable. The foot process effacements were mild. No viroplasmic changes were found in glomerular structures or tubules.

The investigation of viral traces on RNA extracted from kidney tissue biopsy was performed using droplet digital PCR (ddPCR) technology and SARS-CoV-2 ddPCR assay (Bio-Rad Laboratories Srl, Cat. 12013743). This highly sensitive assay is able to evaluate viral load by multiplex quantification of SARS-CoV-2 N1 and N2 targets, and human RNase P target as an endogenous internal amplification control (Figure 8A). Of note, while the RNase P target was detected at high concentrations (2123 copies/ μ l), no positivity was observed for N1 and N2 targets (Figure 8B). Altogether, these results excluded the role of SARS-CoV-2 as a direct cause of AKI.

Considering the low hemoglobin level (7.0 g/dL) and mean cell volume (64 fL), we investigated for pathologic hemoglobin phenotypes. HbS and HbF were 21%, and 3.3%, respectively, consistent with an SCT diagnosis. Then, the patient received a single-unit red blood cell transfusion.

Table 3. Previous reports of SARS-CoV-2 infection associated with rhabdomyolysis.

Author	Pts (n)	Age (years)	Sex	History	Vital signs at admission	Laboratory peak values	Dialysis	Outcome
Valente-Acosta et al. 2020 [7]	1	71	M	Smoking	BP 120/68 mmHg HR 90 bpm RR 22/min BT 36.5°C OS 84%	CPK 8,720 U/L Myoglobin 2079 ng/mL Creatinine 1.68 mg/dL	NO	Alive
Guan et al. 2020 [8]	2	NA	NA	NA	NA	NA	NA	Alive
Suwanwongse et al. 2020 [9]	1	88	M	Hypertension, CKD, HF	RR 22/min OS 94%	CPK 13 581 U/L Creatinine 1.34 mg/dL	NO	Alive
Jin et al. 2020 [10]	1	60	M	NA	BP 135/91 mmHg HR 89 bpm RR 18/min BT 38.5°C OS 93%	CPK 17 434 U/L Creatinine 0.82 mg/dL	NO	Alive
Chedid et al. 2020 [11]	1	51	M	Hypertension, DM, CKD	RR 20-30/min BT 39.4° OS 95%	CPK 464 500 U/L Myoglobin 15 175 ng/mL Creatinine 19.09 mg/dL	YES	Alive, chronic dialysis therapy

CKD – chronic kidney disease; HF – heart failure; DM – diabetes mellitus; BP – blood pressure; HR – heart rate; bpm – beats/minute; RR – respiratory rate; BT – body temperature, OS – oxygen saturation; CPK – creatine-phosphokinase; NA – not assessed.

After 22 days, blood tests revealed a progressive normalization of myoglobin and CPK levels (621 ng/mL and 1334 U/L, respectively, compared to 19 756 ng/mL and 20 000 U/L at the time of the admission).

After 40 days in the hospital, as the serum creatinine reached a value of 1.62 mg/dL, urine output was regular, and CPK and myoglobin were 188 U/L and 168 ng/mL, respectively, the patient was discharged and so his renal function has remained normal, with negative urine sediment.

Discussion

We describe a case of non-exertional rhabdomyolysis complicated by AKI due to 2 concomitant factors, a SARS-CoV-2 infection and an SCT. The presence of an “open nucleolus” in the muscle cell seems to reflect a metabolically active cell, as in both virus-infected cells and neoplastic cells [3]. A recent application of a machine-learning model of RNA subcellular localization to SARS-CoV-2 demonstrated viral RNAs showing residency signal for host mitochondria and nucleoli [4].

Rhabdomyolysis has been associated with viral infections: influenza A and B, coxsackievirus, Epstein-Barr virus, primary human immunodeficiency virus, and SARS [5,6]. To date,

SARS-CoV-2 infection has been considered to be pathogenetic in 6 adult patients affected by rhabdomyolysis (Table 3). Valente-Acosta et al reported the case of a 71-year-old man with AKI KDIGO stage I and respiratory failure who required invasive mechanical ventilation and recovered with supportive therapy and tocilizumab [7]. Guan et al, among 1099 patients affected by SARS-CoV-2 infection in China, reported 2 patients with rhabdomyolysis but they did not show any signs of respiratory failure [8]. Suwanwongse et al described a case of rhabdomyolysis as the presenting problem in an 88-year-old patient with SARS-CoV-2 infection, without respiratory failure but with AKI KDIGO stage I [9]. Jin and Tong described a 60-year-old patient with SARS-CoV-2 pneumonia without the need of mechanical ventilation after 9 days in the hospital, who recovered after treatment with antibiotics, interferon inhalation, hydration, alkalization, plasma transfusion, gamma globulin, and symptomatic supportive therapy, and did not show signs of AKI [10]. Finally, Chedid et al described a 51-year-old man with CKD stage 2 who developed SARS-CoV-2 infection and rhabdomyolysis at presentation. The patient did not show any need for mechanical ventilation or for intensive oxygen support. Nonetheless, he developed AKI stage 3 requiring dialysis and, when the AKI did not subside, long-term dialysis was started [11]. However, none of these patients had other risk factors for rhabdomyolysis aside from SARS-CoV-2 infection.

SCT is a genetic risk factor for rhabdomyolysis, especially after strenuous physical activity, but also during viral illness [12]. SCT is present in 7-9% of the African American population [13]. There have been numerous cases documenting severe non-traumatic rhabdomyolysis, particularly among young African Americans participating in strenuous physical activity [2,12]. Nonetheless, conditions of increased oxygen demand may trigger sickle-related complications, even in heterozygotes [14]. Tafty et al described the case of a 33-year-old soldier with SCT admitted for rhabdomyolysis complicated by SARS-CoV-2 infection without pneumonia. Unfortunately, no kidney or muscle biopsies were carried out. He also required hemodialysis for acute kidney injury but recovered his renal function [15].

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Conclusions

In our patient, since the muscle biopsy was consistent for SARS-CoV-2 dissemination, even if no viral particles were found, the real cause of rhabdomyolysis must have been the combination of SARS-CoV-2 infection and the hypoxemia caused by SARS-CoV-2 pneumonia that resulted in red blood cell deformation or sickling. SARS-CoV-2 infection may result in severe rhabdomyolysis with acute kidney injury requiring acute dialysis prescription. Since SARS-CoV-2 infection can trigger sickle-related complications like rhabdomyolysis, the presence of SCT needs to be ascertained in African patients.

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