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Posted Date: 22 August 2023

doi: 10.20944/preprints202308.1489.v1

Keywords: COVID-19; Rhabdomyolisys; Viruses; SARS-COV-2

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Rhabdomyolysis in BA.5 and BA.4 SARS-COV2 Variants: A Single Center Experience

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Abstract: Rhabdomyolysis is a serious clinical condition, which if left untreated can lead to kidney failure and in extreme cases, to death. It has also been reported in association with SARS COV2 infection and can be its initial presentation. COVID-19 is a disease caused by severe acute respiratory syndrome coronavirus 2(SARS-CoV-2), which has many variants that change the characteristics of the disease affecting, among other things, the method of transmission or treatment. Some investigators have implicated excessive immune response in the causes of muscle damage during SARS-CoV-2 infection. Others point to direct damage caused by the virus or involving immune factors. In this study we described cases of COVID-19 infection from 1 June 2022 to 15 July 2022 with elevated muscle enzymes in the blood and hospitalized to the first division of Cotugno hospital in Campania. Of 39 patients with SARS-CoV-2 infection, 15 patients presented also rhabdomyolysis. The most common symptoms were: asthenia, fever, arthomyalgia, lipothymia and syncope. No patient had myocardial infarction and 2 patients had atrial fibrillation. All patients were affected by omicron SARS-CoV-2 variants. Of these patients: 4 patients died (2 due to rhabdomyolysis and 2 due to sepsis) and only one patient presented acute kidney injury.

Keywords: COVID-19; rhabdomyolysis; viruses; SARS-COV-2

Introduction

Rhabdomyolysis is a serious clinical condition, which if left untreated can lead to kidney failure and, in extreme cases, to death.

Its severity is due to its pathophysiology, it is characterized by the destruction of the musculoskeletal system due to the alteration of three fundamental phases for its normal functioning, namely: the electrolytic exchange, the metabolism of ATP (adenosine triphosphate), and the alteration of the plasma myocyte membrane. The destruction of the musculoskeletal system determines the release of proteins, such as the creatine kinase (CK) and myoglobin (MB) into the bloodstream, which induce fluid sequestration and subsequent reduction in intravascular volume [1]. This process results in the renin-angiotensin-aldosterone system activation, leading to a decrease in renal blood flow through renal vasoconstriction [2–4]. A reduction in the renal blood flow is also

 doi:10.20944/preprints202308.1489.v1

compounded by the activation of vasopressin and the sympathetic nervous system, and the generation of several mediators e.g., thromboxane A2, endothelin-1, and nitric oxide deficiency [5].

The MB released from damaged muscles is also a major renal injury factor deposited in renal tubules [6] that is able to cause, through free radical production and lipid peroxidation, renal vasoconstriction and oxidative damage, which can contribute to the development of acute kidney injury (AKI) [2,6,7]. Metabolic acidosis and increased uric acid concentrations potentiate the nephrotoxic properties of MB favoring its precipitation and interaction with the Tamm-Horsfall protein to form casts in tubules [2,3,8]. Rhabdomyolysis also causes an increase in uric acid, which under acidic conditions is mainly deposited at the level of distal tubules in the form of crystals, impeding urine flow [2].

Rhabdomyolysis has been associated with viral infections and especially influenza [9]. It has also been reported in association with severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) infections causing the coronavirus disease 2019 (COVID-19). In fact, one retrospective cohort study of 140 patients admitted to hospital with COVID-19 showed a 16.9% incidence of rhabdomyolysis; patients who developed rhabdomyolysis were significantly more likely to die than those who did not (47.1% v. 26.4%) [10]. Although COVID-19 can be characterized by a variety of symptoms, the most common were fever, cough, fatigue, sputum production, shortness of breath, as well as myalgia and arthralgia. A recent report of renal histopathological features in post-mortem COVID-19 patients found pigmented casts in three cases; the authors stated that drug-relevant or hyperventilation-relevant rhabdomyolysis contributed, although they did not rule out a possible direct viral injury on muscle [11]. SARS-CoV-2 has indeed been isolated in multiple tissues as kidneys, liver, brain and heart, suggesting that the virus could also directly infect striated muscle tissues. Some investigators have implicated an excessive immune response in causing the muscle damage during SARS-CoV-2 infection [12]. Based on this evidence, rhabdomyolysis could be the initial presentation of COVID-19. Therefore, we conducted a retrospective observational chart review to identify cases with rhabdomyolysis related to SARS-CoV-2 infection.

Materials and Methods

From June 1, 2022 to July 15, 2022, 39 patients with SARS-CoV2 infection were hospitalized to the UOC Emerging Infectious Disease with High Contagiousness of the Cotugno hospital in Naples (Italy). Of these patients, 15 developed rhabdomyolysis. The rhabdomyolysis was diagnosticated with elevated levels in the blood of creatine phosphokinase (CPK), MB, Troponins, CPK-MB mass. Patients were evaluated for AST, ALT, renal function, fibrinogen, D-dimer (DD), interleukin 6 (IL6), antispike antibodies, and C-reactive protein (PCR). The control of renal function and muscle enzymes was practiced every two days from onset until normalization of the same. Chung Score was used to evaluate the value of chest CT severity score (CT-SS) in differentiating clinical forms of coronavirus disease 2019 (COVID-19). Antigen research for SARS-CoV-2 was carried out on the nasal swab (Methodical: Chemiluminescence Enzyme ImmunoAssay), also the search for viral RNA was carried out with the Real time PCR. The antispike antibodies were dosed by the chemoluminescence method. All patients were affected by omicron SARS-CoV-2 variants, because it was the variant circulating in Campania in those months.

Results

The characteristics of the 15 patients with rhabdomyolysis and SARS-CoV-2 infection hospitalized to the UOC Emerging Infectious Disease with High Contagiousness of the Cotugno hospital in Naples (Italy) during study period are described in Tables 1–3. Of the 15 patients, 12 (80%) were males and 3 (20%) females; their pathologies are shown in Table 2. The positivity of the nasopharyngeal swab for COVID-19 preceded the onset of symptoms by a maximum of a couple of days. The symptoms, illustrated in Table 1, were essentially asthenia (10 patients), fever (7 patients), arthomyalgia (7 patients), lipothymia and syncope (5 patients), followed by dyspnoea (2 patients), cough (2 patients), soporous state (3 patients). All patients enrolled in this study presented with

 doi:10.20944/preprints202308.1489.v1

alteration of muscle enzymes (Table 1). The muscle enzyme were very elevated and normalized after hydration with physiological solution 0.9% NaCl, except in one case.

No patient had myocardial infarction and 2 patients had atrial fibrillation. Ten patients had alteration of transaminases. All 15 patients had elevated PCR, fibrinogen and DD. Eleven patients received three doses of COVID-19 vaccine, 1 patient four doses, 2 patients one dose and only one patient was not vaccinated. 6 patients had Covid-19 pneumoniae. Five patients received remdesivir for 5 days, only one received molnupinavir, and 9 patients did not receive antiviral treatment. The evolution was fatal for 4 patients: 2 patients deceased for severe rhabdomyolysis caused from COVID-19 and 2 patients deceased from sepsis. The other 11 patients had benign evolution with the normalization of muscle enzymes and inflammation indices. All patients received hydration. Only 2 patients did not negativize the nasopharyngeal swab for COVID-19: these 2 patients died. Among these 15 patients, only one presented AKI. The hospitalization duration ranged 3-21 days with a median of 14 days and mean ± standard deviation of 13.46 ± 4.1. The mean age was 68.3 and the range was 34-85. The two younger patients were: one 34 years old female patient affected by Huntington's Korea; and one 49 years old male patient affected by Multiple sclerosis.

Patients were in treatment with antihypertensive drugs, hypoglycemic agents, statins, and cortisone.

One patient presented severe rhabdomyolysis leading to acute renal failure and pulmonary edema due to respiratory distress after 10 days of positive nasopharyngeal swab for COVID-19. This 59-years-old patient with arterial hypertension and lichen myxedematous started molnupinavir immediately after the positivity of the nasopharyngeal swab with subsequent negativization of the molecular nasopharyngeal swab for SARS-CoV-2. During therapy with molnupinavir he presented asthenia and leg pain, for which he was hospitalized.

Table 1. The demographic, laboratory and clinical characteristics of the 15 patients with rhabdomyolysis in SARS-COV2 infection.

	Median	**Mean ± DS**
Age (range: 34-85)	75	68.3 ± 16.51
CPK (vn<15)	378	848 ± 1423
CK-MB mass (vn<3.6)	4	4 ± 2.19
Myoglobin (vn<106)	6167,4	2074 ± 9950
Troponin (vn<116)	38.4	1100 ± 3513.37
AST (vn <34)	42	123.26 ± 225.71
ALT (vn<49)	45	45 ±321.03
PCR (vn<1)	4.5	8.5 ± 9.7
IL6 (vn<5)	21.17	40.06 ± 45.81
DD (vn<250)	340	2971.26 ± 9067.68
Fibrinogen (vn<417)	424	410.33 ± 142.84
creatinine	1.2	1.23 ± 0.42
days of hospitalization (range:3-21)	14	13.46 ± 4.1
Sex: - M: 12 (80%) - F: 3 (20%)		
ECG: - myocardial infarction: 0 patient - FA: 2 patients (13.33%) - Normal: 13 patients (86.66%)		
Antiviral therapy: - Remdesivir: 5 patients (33.33%) - Molnupinavir: 1 patient (6.66%) - Nirmatrelvir/ritonavir: 0 patient		

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Covid 19 Vaccination: - 0 dose: 1 patient (6.66%) - 2 dose: 2 patients (13.33%) - 3 doses: 11 patients (73.33%) - 4 doses: 1 patient (6.66%)
Symptoms of onset: - Syncope, lipothymia: 5 patients (33.33%) - Arthromyalgia: 7 patients (46.6%) - Asthenia: 10 patients (66.66%) - Fever: 7 patients (46.6%) - Dyspnea: 2 patients (13.33%) - Cough: 2 patients (13.33%) - Soporous state: 3 patients (20%)
Evolution: - Benign: 11 patients (73.33%) - Exitus: 4 patients (26.66%)
TNF negative upon discharge: 13 patients (86.66%)

Table 2. Pathologies of the 15 covid 19 positive patients who presented with rhabdomyolysis; chronic obstructive bronchopathy (FA); atrial fibrillation (FA); diabetes mellitus type 2 (DM type 2).

Patient 1: Hypertension
Patient 2: BPCO
Patient 3: Hypertension, heart failure, diabetes
Patient 4: Multiple sclerosis, Hypertension
Patient 5: HIV, Hypertensione
Patient 6: psoriasis, FA
Patient 7: Hudginton's Korea
Patient 8: Alzheimer's disease, hypertension, dyslipidemia, pulmonary enphysema
Patient 9: Parkinson's disease, depression
Patient 10: prostate adenocarcinoma, psoriasis, pulmonary enphysema
Patient 11: primary adrenocortical insufficiency, esophagitis, hyperprolactin, gastroduodenitis
Patient 12: FA, ictus cerebri
Patient 13: Hypertension, dyslipidemia, senile dementia, BPCO
Patient 14: DM type 2, post liver transplant biliary stenosis
Patient 15: licheun myxedematos, hypertension

Table 3. HR chest CT scan of 15 patients with rhabdomyolysis in SARSCOV-2 infection.

Patient 1: Covid-19 pneumonia (chung score 3/20)
Patient 2: Covid-19 pneumonia (chung score 2/20)
Patient 3: no pneumonia
Patient 4: bacterial pneumonia
Patient 5: no pneumonia
Patient 6: no pneumonia
Patient 7: bacterial pneumonia
Patient 8: bacterial pneumonia
Patient 9: covid-19 pneumonia (chung score 13/20)
Patient 10: Covid-19pneumonia (chung score 3/20)
Patient 11: no pneumonia
Patient 12: no pneumonia
Patient 13: no pneumonia

 doi:10.20944/preprints202308.1489.v1

Patient 14: chung score 4/20 + bacterial pneumonia
Patient 15: chung score 3/20

Discussion and conclusion

Rhabdomyolysis is a recognized complication of bacterial and viral infections [11]. It has a variety of clinical features ranging from the asymptomatic form to a life-threatening one. It can be associated with electrolyte imbalance, impairment of renal function up to the development of AKI, and rarely disseminated intravascular coagulation (DIC) [13]. The hypothesized mechanisms for viral-induced rhabdomyolysis are the direct viral invasion of muscle tissue, the toxin-induced damage, the innate inflammatory response, or the combination of the above mechanisms [11]. Rhabdomyolysis was already associated with COVID-19 infection in previous reports [13–26]. Although data on the association between SARS-CoV-2 infection and rhabdomyolysis are limited, no direct correlation was observed between the severity of COVID-19 illness and the incidence of rhabdomyolysis. Early studies during the pandemic suggested an association between rhabdomyolysis after COVID-19 illness and an increased risk of hospital admission, morbidity, and mortality [23]. However, this could be due to the onset of rhabdomyolysis more frequent in patients critically ill and with longer hospitalization [28,29]. Rhabdomyolysis is a rare complication of COVID-19 occurring in approximately 0.2–2.2% of hospitalized patients. Typical symptoms are muscle pain and weakness, swelling, tea-colored urine, and increased levels of CK [30]. However, it can also determine life-threatening consequences. In a report by Hannah et al., slightly more than half of patients with rhabdomyolysis developed AKI. In addition, multiple organ failure or death are possible complications [31]. A study also found an increased risk of renal replacement therapy and death in patients with rhabdomyolysis and COVID-19 [10]. However, we observed AKI just in one patient, and arthromyalgia and asthenia in the majority of patients.

In a case series of 38 patients with rhabdomyolysis and COVID-19, 17 (44.7%) patients died and 2 of the remaining survivors required hemodialysis on discharge [32]. Thus, suggesting that rhabdomyolysis following SARS-CoV-2 infection could occur more frequently in patients with an increased risk of death. In our cases, two patients died for rhabdomyolysis. It is still unclear why rhabdomyolysis does not occur in all patients affected by COVID-19, and risk factors for rhabdomyolysis have not been identified yet. Generally, rhabdomyolysis after SARS-CoV-2 infection seems more common among older adults [33]. Accordingly, we found a mean age of 68.3 (±16.51). Moreover, the two younger patients were affected by debilitating diseases such as the Huntington's Korea and multiple sclerosis. Ramos-Casals et al. pointed out that there are differences in the characteristics of clinical symptoms depending on age, gender or ethnicity [34]. This was supported by the observation of Hannah et al., who noted that most patients with rhabdomyolysis and COVID-19 were male (77%). They also pointed out that comorbidities, such as arterial hypertension, obesity, and diabetes mellitus, increase the risk of rhabdomyolysis in the course of COVID-19. Potential triggers of rhabdomyolysis in SARS-CoV-2-infected patients also included drugs, especially statins and antibiotics [31]. Accordingly, our cases mainly referred to male patients (80%) treated with antihypertensive and hypoglycemic medicines, and statins.

We also observed COVID-19 vaccination as three doses in 11 patients, four doses in 1 patients, and one dose in 2 patients. Therefore, the role played by COVID-19 vaccination cannot be excluded. Previous evidence have hypothesized that vaccine-induced rhabdomyolysis may be caused by the viral invasion of myocytes or the exaggerated immunological reactions, analogous to cytokine storm. This could support the significantly higher risk with mRNA vaccination which have a more potent immune response than traditional vaccines [35]. Studies have reported the onset of rhabdomyolysis after mRNA COVID-19 vaccination, with patients generally developing muscle pain and fatigue after two weeks from vaccination [35–37]. Moreover, another study investigated the association between COVID-19 vaccination and rhabdomyolysis using pharmacovigilance data from the Vaccine Adverse Event Reporting System (VAERS). This study found rhabdomyolysis more frequently reported with

COVID-19 vaccination than all other type of vaccinations, but with rates similar to the general population. Moreover, rhabdomyolysis was not found different among COVID-19 vaccines (such as Pfizer, Moderna, or Johnson & Johnson) [38]. Other vaccine-induced rhabdomyolysis were reported in the literature, in particular with the H1N1 and influenza vaccination [39–41].

In conclusion, we observed 15 cases of rhabdomyolysis in patients with COVID-19. Rhabdomyolysis also was the main cause for the hospitalization in these patients. Therefore, clinicians should pay attention to the development of muscle skeletal symptoms in patients with COVID-19, especially those with predisposing factors such as comorbidities and medicines. Indeed, it is important to detect and commence the treatment of rhabdomyolysis promptly, mainly with early aggressive fluid resuscitation, to have a major clinical benefit in COVID-19 patients.

Study limitations

The limits of this study are: 1) small number of patients for which it is not possible to carry out an accurate statistical analysis; 2) the lack of sequencing of the Covid-19 viral variants for the enrolled patients. Indeed, since variant typing was not practiced for such patients, it was not possible to trace the real cause of rhabdomyolysis. However, considering national data related to the period from June 2022 to July 2022 showing that the SARS-CoV2 variants circulated in Campania were: BA.4 and BA.5 [42], our patients almost certainly had BA.5 or BA.4 variants and BA.4 and BA.5 subvariants.

Conflicts of Interest: The authors declare no conflict of interest

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