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COVID-19 PNEUMONIA ASSOCIATED WITH RHABDOMYOLISIS IN A PATIENT WITH PREVIOUS CHRONIC THERAPY WITH STATIN: COINCIDENCE OR RELATED CONDITIONS?

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Abstract

Severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) is a novel coronavirus which causes coronavirus disease 2019 (COVID-19). It was first identified amid an outbreak of respiratory illness cases in Wuhan, China. The manifestation of COVID-19 ranges from asymptomatic or mild symptoms to severe illness or death. The most serious complication of COVID-19 is a type of pneumonia that has been named COVID-19 pneumonia presents as an atypical pneumonia, with diffuse bilateral lung involvement. Severe cases present with acute lung injury, and acute respiratory distress syndrome. Rhabdomyolisis can be an initial manifestation of COVID-19, but it is also a life-threatening disorder. Rhabdomyolysis is the breakdown of skeletal muscle by releasing its cellular content into the systemic circulation.

A 73-year-old man was admitted to our hospital with bilateral pneumonia, muscle pain, and worsening symptoms. His oxygen saturation got low, so we started treatment with oxygen inhalation by a high-flow mask. On the 14th hospital day, the muscle enzymes started to increase. After adequate treatment the patient was discharged on hospital day 28.

Patients with COVID-19 pneumonia can develop rhabdomyolysis because of SARS CoV-2 infection. There is a risk of developing rhabdomyolysis after using drugs for treatment of COVID-19. Our patient was on previous chronic therapy with statins, but with normal liver and muscle enzymes. During his hospitalization and deterioration of his clinical condition the enzymes increased and rhabdomyolysis developed. Our findings indicate that rapid clinical recognition and positive hydration treatment of COVID-19–associated rhabdomyolysis can reduce the risk of serious complications.

***Keywords*:**SARS-CoV-2, COVID-19, COVID-19 pneumonia, rhabdomyolysis, chronic statin therapy

Introduction

Multiple complications of COVID-19 including acute respiratory distress syndrome (ARDS), acute respiratory failure (ARF), myocarditis, heart failure, arrhythmias, acute coronary syndrome (ACS), disseminated intravascular coagulation (DIC), venous thromboembolism, secondary infection, acute kidney injury, pancreatic injury, and neurological complications such as seizures, meningitis, encephalitis, encephalopathy, ataxia, and neuralgia have been reported in the literature this far [1].

Apart from typical symptoms leading to typical diagnosis of COVID-19 on admission, SARS-CoV-2 related with rhabdomyolysis should also be kept in mind. COVID-19 mostly affects the respiratory system, ranging from mild flu-like symptoms to severe pneumonia, but extra-respiratory multisystemic involvement has also been reported [2].

Rhabdomyolysis is the breakdown of skeletal muscle by releasing its cellular content into the systemic circulation. Rhabdomyolysis is a life-threatening disorder that manifests with myalgia, fatigue, and pigmenturia; it can also manifest as acute renal failure. The inducing factors of rhabdomyolysis include autoimmune myopathies, septicemia, electrolyte abnormalities, substance abuse, alcohol use, or infection. Viral infection, especially influenza virus infection, can lead to rhabdomyolysis. Here, we describe a case of a male patient who was presented with COVID-19 pneumonia and rhabdomyolysis as a potential complication associated with COVID-19 or induced by statins [6].

In our case, the patient came to our hospital approximately 10 days after the onset of symptoms [3]. An alternative explanation for rhabdomyolysis in our case as in others is the prolonged periods of bedrest and immobility in convalescent elderly patients along with dehydration.

Our patient denied any trauma, seizures, or substance abuse [7]. He was taking atorvastatin.

Highlights:

We present a case of a patient with COVID-19 pneumonia with reported comorbidity (st. post PCI/stenting aa. femoralis) on chronic statin therapy.

High creatine kinase level could be related to rhabdomyolysis, which requires an aggressive treatment to prevent further complications such as acute kidney injury.

Rhabdomyolysis can be an initial presentation of COVID-19 and it is also associated with antiviral drugs or statins.

Guidelines advocate continuation of statin therapy in COVID-19 patients with a history of atherosclerotic cardiovascular disease or diabetes.

In some cases, during treatment of COVID-19 patients discontinuation of chronic statin therapy is warranted.

Case report

A 73-old-man presented to the emergency department with a five-day history of dry coughing and fever of 38^{o}C and suffering from severe myalgia predominantly in his legs. The patient also reported generalized weakness and malaise. He had not taken any medications, except paracetamol to control the fever. He did not report nausea, vomiting, urinary or neurological symptoms, but he reported diarrhea (3 times daily). He had no known allergies. His past medical history included type II diabetes mellitus, essential hypertension and st. post PCI/STENT aa. femoralis, on a daily therapy with antihypertensive and statin (atorvastatin 20 mg).

Physical examination on admission. Blood pressure was 130/80 mmHg, respiratory rate 18/minutes, heart rate 95/minutes, temperature 38^{o}C, and oxygen saturation 90 on room air. He was oriented and had a clear mind. He had a regular heart rhythm. During auscultation of the chest there were crepitations bibasal of inferior lobes in the lung. D-dimers were slightly increased (888 ngr/mL). Electrocardiogram (ECG) was normal. Chest radiograph on admission demonstrated a right midzone consolidation (Figure 1a). Initial laboratory findings showed increased levels of C-reactive protein (CRP) and IL6, his ferritin and lactic dehydrogenase levels were high as well and slightly elevated alanine aminotransferase (ALT) and aspartate aminotransferase (AST) (Table 1). Subsequently, COVID-19 was confirmed from nasopharyngeal swab by reverse transcriptase polymerase chain reaction (RT-PCR) assay for severe acute respiratory syndrome Coronavirus 2 (SARS-CoV-2).

Treatment: The patient was admitted to the COVID-19 department. We started an initial treatment with fluids; intravenous sodium bicarbonate was used for alkalization of urine, and oxygen inhalation by a nasal mask (5 l/min, SpO2 92%-94%). Meropenem, azithromycin, enoxaparin, fluconazole, pantoprazole and a high dose of methylprednisolone ware immediately given.

The patient condition deteriorated on day 5 of hospitalization; suddenly his oxygen saturation was 83%, he was significantly tachypneic with respiratory rate of 25/minute, so he required oxygen with a high-flow mask (10 l/min, SpO2 94%-96%). The chest x-ray showed further progression of the pulmonary consolidation in both lungs (Figure 1b).

The patient had a clinical picture of cytokine storm, so we included compassionate drug therapy and started with remdesivir in the next 5 days and convalescent plasma in one return. Due to the persistence of the febrile condition, microbiological analysis of sputum was performed, where no pathogenic bacteria were found, but *Candida albicans* was isolated. Over the next 3 days, his condition continued to deteriorate with hypoxia; the, patient felt pain and weakness in his lower limbs. Routine blood analysis showed CRP, IL6, muscle enzymes (CK), liver enzymes and D-dimers to be increased (Table 1). His urinalysis revealed white blood cells and protein without any red blood cells, which was suspicious for

myoglobinuria (Table 1). Partial thromboplastin time (APTT) got shorten so we started with therapy doses of enoxaparin. His ferritin and lactic dexydrogenase levels were high as well (Table 1).

A lung CT scan showed bilateral diffuse infiltrates with areas of consolidation and extensive ground-glass opacities as well as fibroses in the middle parts (Figure 2).

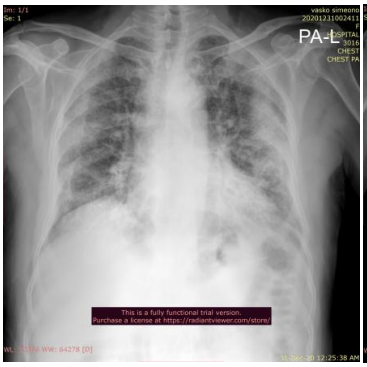

Figure 1a

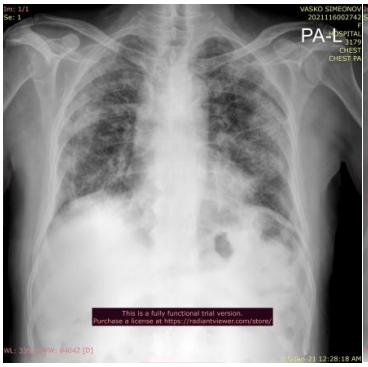

Figure 1b

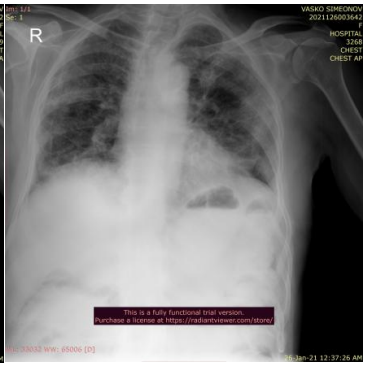

Figure 1c

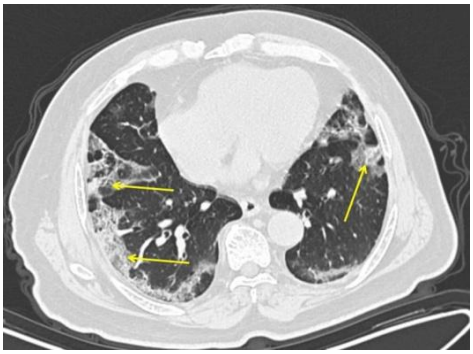

Figure 2. CT scan showed bilateral diffuse infiltrates with areas of consolidation and extensive ground-glass opacities

In the beginning the patient was not with hyperglycemia, so we did not proceed with administration of an intravenous bolus dose of insulin.

The plasma glucose concentration after the 5th day started to increase and basal insulin every 8 hours was administered. We started therapy for rhabdomyolysis with aggressive intravenous fluids and diuretic was initiated being concerned about the evolving volume overload to prevent acute kidney injury (AKI). During the hospitalization period the patient was with normal degradation products, normal renal function and diuresis.

Patients affected with rhabdomyolysis should receive aggressive fluid administration to prevent AKI. This must be done with caution, especially in the elderly population where the coexistence of heart failure is more common.

Treating rhabdomyolysis in elderly patients infected with COVID-19 is even more challenging. Liberal strategies of fluid administration have shown to worsen oxygenation in studies of patients with ARDS independent of the cause.

Additionally, in our patient bicarbonate levels dropped. We used 130 meq/L of sodium bicarbonate (3 ampules) mixed with 1 liter of 5% dextrose in water and infused it at 200 ml/hour via a separate intravenous line. The rate is adjusted to achieve a urine PH of > 6.5.

This has been postulated to decrease the breakdown of myoglobin into nephrotoxic metabolites and decrease crystallization of uric acid. This must be done with caution to avoid hypokalemia, hypocalcemia, volume overload and PH shifts.

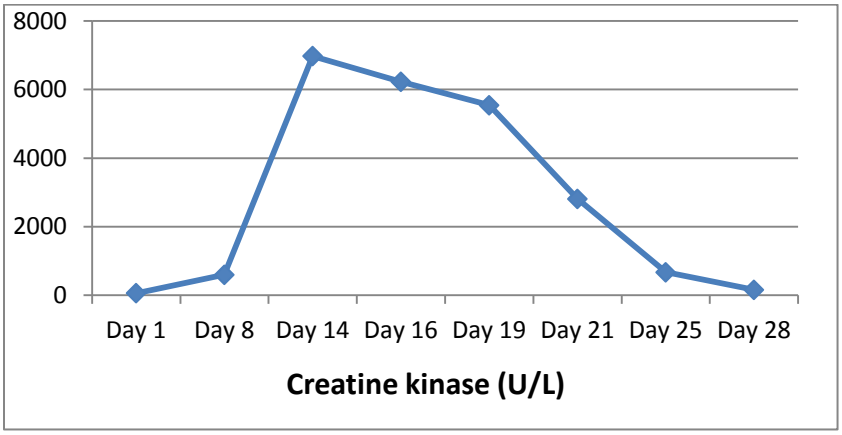

Figure 3. Changes of creatine kinase levels in U/L during hospital stay by days and after discontinued statin administration

On the 14th hospital day, patient's muscle enzymes were markedly elevated and liver enzymes were high as well (Figure 3). Serial ECGs demonstrated no evidence of ST elevations indicating for myopericarditis. Troponin was normal, besides significantly elevated CK levels.

We performed a thoracic cardiac echosonography (TTE) to rule out differential diagnostic myocarditis. Echosonography showed normal dimension, and normal systolic left and right ventricular function (LV 55/40 mm, RV 26 mm) with no signs of myocarditis. Despite intense rehydration, CK levels remained elevated.

The administration of atorvastatin was stopped. In the following days, the patient showed fast recovery of symptoms, reported less pain and fatigue in his lower limbs and normalization of CK levels was seen (Figure 3).

On the 20th day, the respiratory function was normalized (SpO2 95-96%) on nasal mask at 4l/min. The chest x-ray showed regression of pulmonary consolidation (Figure 1c).

Finally, on the 25th day of the hospital stay (and 11 days after discontinuation of statin administration) there was a decrease of the enzyme values (Table 1), and normal respiratory function; he was also successfully weaned off the supplemental oxygen (SpO2 95-96%) on room air.

The patient was successfully discharged on day 28 with normal values of creatine kinase (CK), but slightly elevated liver enzymes and feeling significantly better with the resolution of his myalgia and dyspnea. The patient came for a control examination after two weeks with completely normal enzyme values and a neat auscultatory finding.

Table 1: Laboratory parameters by day during hospital stay

ND - not done; RBC - red blood cells; WBC - white blood cells

Variable	Reference range	On admission	8th day	14th day	16th day	19th day	21st day	25th day	28th day
Hemoglobin (g/l)	(115-180)	125	113	123	116	139	120	125	115
White cell count (x10/L)	(4.0-11.0)	7,7	8,4	10,2	13,4	12,5	10,1	6,9	6,3
Lymphocytes %	(0,21-0,25)	0,09	0,05	0,11	0,06	0,08	0,11	0,13	0,18
Platelet count (x10/L)	(150-400)	230	301	210	224	286	225	200	150
Creatinine (mmol/L)	(62-133)	92	92	84	96	91	70	79	88
Urea (mmol/L)	(1,7-8,3)	5	9,3	9,7	11,8	11,9	10,8	8,3	8,5
Electrolytes									
*Sodium (mmol/L)	(135-145)	145	144	142	143	137	137	143	140
*Potassium (mmol/L)	(3.5-5.5)	3,3	3,3	3,1	3,1	3	3	5	4
Lactic dehydrogenase (U/L)	(120-246)	500	398	580	677	981	759	458	344
ALT (U/L)	(10-52)	61	83	174	233	300	202	160	187
AST (U/L)	(10-47)	79	41	328	297	271	99	53	51
Creatine kinase (U/L)	(30-170)	65	599	6976	6226	5541	2811	672	160
Glucosis (mmol/L)	(4.1-6.3)	7,4	6,9	5,7	7,2	8,5	9,1	6,5	5,2
C-reactive protein (mg/dL)	(0-10)	240	58	13	5	3	1	4	2
D-dimer (ngr/mL)	(0-500)	887.8	3073	2956	1008	942	885	650.9	444.9
Ferritin (ng/mL)	(20-274)	1480	ND	800	ND	ND	320	ND	150
IL-6 (pg/mL)	(<7.0)	38,6	ND	20,6	ND	ND	6,86	ND	ND
NLR		9,5	18,2	7,5	14,8	11	7,6	7	4
Troponin I (pg/mL)	(<34,2)	ND	15,4	20,6	18,5	ND	15,5	ND	ND
Urinalysis	pH 6.5-7.5	ND	ND	Clear, pH 6.5 white blood cells, protein >500, 0-2 RBC, 0-5 WBC		ND	Clear, pH 6.0 white blood cells, protein 100, 0-2 RBC, 0-2 WBC		ND
	RBC 0-1								
	WBC 0-2								

Discussion

Patients with COVID-19 infection have an increased risk of cardiovascular complications and thrombotic events. Statins are known for their pleiotropic anti-inflammatory, antithrombotic and immunomodulatory effects. They may have potential role as adjunctive therapy to mitigate endothelial dysfunction and dysregulated inflammation in patients with COVID-19 infection. Statins have anti-inflammatory effects including augmentation of ACE2 expression.

Angiotensin-converting-enzyme 2 (ACE2) is the receptor that allows SARS-CoV-2 to gain entry into the host cells. Alveolar epithelial type II cells account for 83% of ACE2-expression cells in the lung [4]. The ACE2 receptor is also expressed in extrapulmonary tissues such as the heart, vasculature, brain, gastrointestinal tract, and kidneys. Infection with SARS-CoV-2 causes down-regulation of ACE2. This increases vulnerability to damaging effects of AT II, which is thought to be responsible for the lung injury seen in many COVID-19 patients. Statins are known for their pleiotropic anti-inflammatory effect, including augmentation of ACE2 expression and inhibition of the toll-like receptor (TLR) [5].

To conclude, we believe that statins might mitigate the effects of COVID-19 infection in selected patients based on our understanding of its associated coagulopathy, endothelial dysfunction, and dysregulated inflammation. However, in the absence of reliable evidence, the role of statins remains uncertain, and this undoubtedly contributes to the hesitancy to administer a yet unproven treatment. Statins may cause myotoxicity in some patients. Features of statin-induced myotoxicity differ from those from myalgia to myopathies and rarely rhabdomyolysis. Rhabdomyolysis is a life-threatening disorder that manifests with myalgia, fatigue and also as acute renal failure [6].

The inducing factors of rhabdomyolysis include autoimmune myopathies, septicemia, electrolyte abnormalities, substance abuse or infection [7].

Myalgia, increased creatine phosphokinase, rhabdomyolysis, and acute kidney injury occur in patients with COVID-19 as well [8]. In addition, some risk factors such as advanced age and liver and kidney impairments are common between statin-induced myopathies and infection with SARS-CoV-2 [9].

Recently, severe acute respiratory syndrome coronavirus (SARS-CoV-2) has also been associated with rhabdomyolysis [10,11]. Rhabdomyolysis has been infrequently reported in patients with COVID-19. Viruses could directly invade the myocytes, which has been seen in SARS-CoV infection [12-14]. The pathogenesis is still unclear, but it is known that immunological mechanisms play a major role. A heightened immunologic reaction resulting in "cytokine storm" can further lead to disseminated tissue damage including rhabdomyolysis [15].

Our knowledge of the novel disease, COVID-19, is still evolving, and the pathogenesis is unclear. Possible mechanisms may include direct muscle invasion by SARS-CoV-2 *versus* oversized immunologic response to the virus causing collateral muscle damage.

Less than 10% of patients with rhabdomyolysis present with the classical triad of weakness, myalgia, and tea-colored urine; hence clinical suspicion and close monitoring are cornerstones for diagnosing rhabdomyolysis [16-18]. Often ALT and AST are also elevated, though AST has a much higher concentration in the muscles. CPK elevations five to ten times of normal are diagnostic of rhabdomyolysis [17,18].

General muscle pain and fatigue are common symptoms of COVID-19, but clinicians should consider the diagnosis of rhabdomyolysis when patients have focal muscle pain and fatigue [19]. CK and myoglobin levels are important indexes for rhabdomyolysis [7]; however, they are not tested routinely, so rhabdomyolysis is easily misdiagnosed. The key to avoid acute renal failure from rhabdomyolysis is early detection and treatment with aggressive hydration [20].

Management is usually multipronged. Furthermore, clinical improvement of the patient and normalization of laboratory parameters are also important markers.

We treated our patient with aggressive intravenous fluids to maintain the recommended urine output, while concurrently correcting electrolyte disorders. For treatment of the hypoxia, the patient was on supplemental oxygen therapy which was slowly weaned over days. We also treated the patient with remdesivir for COVID-19 according to our institutional protocols.

Conclusion

Rhabdomyolysis, especially in association with AKI, carries a high mortality. In the settings of a pandemic and due to infrequent presentation, we suggest that clinicians consider rhabdomyolysis in COVID-19 patients in order to be able to diagnose and treat such life-threatening condition early. Statin treatment can cause liver injury, myotoxicity, rhabdomyolysis and kidney injury.

Furthermore, statin therapy and COVID-19 both increase liver enzymes that are hard to differentiate from each other. These conditions may occur more frequently in patients with severe COVID-19 infection [19].

In our patient, we hypothesized that rhabdomyolysis was secondary to SARS-CoV-2-induced myositis in the absence of other etiologies, in combination with chronic statin therapy.

Patients with common comorbidities, including hypertension, cardiovascular diseases, atherosclerosis, and diabetes, are at a greater risk for SARS-CoV-2 infection and its related ARDS and mortality. Most of these patients are taking statins routinely for their diabetes and cardiovascular problems. There is no evidence for discontinuing statins in these patients during the COVID-19 episode, but in our case simvastatin administration was stopped.

After that, the patient finally showed fast recovery of symptoms and normalization of CK levels and liver function.

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