Asymptomatic COVID-19 Infection-Induced Rhabdomyolysis in the Backdrop of Statin-Cyclosporine Drug Interaction

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CASE REPORT

TITLE:

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PATIENT CONSENT STATEMENT

The attending physician Dr. Kotresha Neelakantappa has obtained written, informed consent from the patient. The signed consent form can be made available if requested.

KEY CLINICAL MESSAGE

Rhabdomyolysis can occur during asymptomatic COVID-19 infection, especially when risk factors like statin-cyclosporine drug interaction are present. It may be worth monitoring creatine kinase levels in COVID-19-positive patients with risk factors for rhabdomyolysis, even if they are otherwise asymptomatic. Early identification of rhabdomyolysis may help prevent complications like AKI.

INTRODUCTION

Rhabdomyolysis refers to the breakdown of skeletal muscle cells with the release of their intracellular constituents into circulation, such as myoglobin, enzymes (creatine kinase, transaminases, lactate dehydrogenase) and electrolytes (potassium, phosphate) [1-3]. Its causes may be physical such as trauma/ crush injury, prolonged immobilization, intense muscle activity (seizure, exertion, neuroleptic malignant syndrome), burns, and electrocution. It can have non-physical causes such as drugs, toxins, venoms, infections, genetic myopathies, dyselectrolytemia, ischemia and more. These non-physical causes induce muscle damage by direct sarcolemmic injury, ATP-depleting and other metabolic mechanisms [2, 3]. Drugs like statins and colchicine cause direct myotoxicity whereas cocaine and amphetamines cause vasoconstrictive ischemia [4, 5]. Concurrent usage of statins with other drugs like steroids, cyclosporine, gemfibrozil and CYP450 inhibitors in general, increases the risk of statin-induced rhabdomyolysis. Of the many complications of rhabdomyolysis, pigment (myoglobin)-induced acute kidney injury (AKI) is common, seen in up to 30% of cases, especially so when CK levels are more than 5000 IU/L [2].

COVID-19 is a known infectious cause of rhabdomyolysis, however, literature suggests that usually only severe COVID-19 leading to hypoxia causes rhabdomyolysis due to energy supply-demand mismatch [1]. Often, other risk factors are concurrently present with severe COVID-19, that may contribute to this, such as old age, diabetes, hypertension, hypothyroidism, injury, inborn errors of metabolism, and use of myotoxic drugs like statins, fluoroquinolones, macrolide antibiotics, HIV protease inhibitors, antipsychotics, and chemotherapy agents [1, 6]. Notably, the SARS CoV-2 virus spike protein is known to cause host cell mitochondrial dysfunction, leading to altered bioenergetics and cellular breakdown in muscles [1]. Asymptomatic COVID-19-associated rhabdomyolysis and AKI is a less reported occurrence [7]. This article will discuss this rare scenario, focusing on underlying risk factors.

CASE PRESENTATION

A middle-aged male in his early 50s, presented to the ED after a fall. He had a past medical history that was significant for nephrotic syndrome secondary to focal segmental glomerulosclerosis (FSGS), on cyclosporine therapy with partial response, chronic kidney disease (CKD) stage-3a, hypoalbuminemia, hypothyroidism, hyperlipidemia, epilepsy, disorganized schizophrenia, and bipolar disorder. He reported that he had chronic bilateral lower extremity swelling due to his kidney disease, which had been worsening for the last 2 weeks, leading to difficulty with ambulation. He said that he was going to the hospital and fell while going past the door. The ambulance was called and he was brought to the ED. He was conscious and moving at that time. There was no major injury, head-strike, tongue-biting or urinary incontinence. His last reported seizure was 2-3 years ago, and he endorsed taking all medications as prescribed. He denied any dark urine or decreased urine output. He denied fever, chills, night sweats, cough, sore throat, chest pain or myalgia. There was no history of smoking, alcohol consumption and intravenous drug use. The patient had a family history of cardiovascular disease.

The patient's home medications included atorvastatin for hyperlipidemia, cyclosporine for steroid & cyclophosphamide-resistant nephrotic syndrome secondary to FSGS, antiepileptics (Divalproex, levetiracetam, lacosamide, and lamotrigine), levothyroxine for hypothyroidism, psychiatric medications for schizophrenia (aripiprazole, risperidone, and benztropine), and enalapril for proteinuria. He was last seen in the renal clinic more than a month ago, when his latest urine protein/creatinine ratio was 2758, which had fallen significantly from 4237 about 9 months ago. Of note, his cyclosporine dose was increased by 25% a month before admission, due to sub-therapeutic levels in the blood, after which it had attained therapeutic levels for a while.

On arrival at the emergency department, the patient was afebrile and hemodynamically stable, with a

physical exam notable for 3+ pitting edema of bilateral lower extremities up to the hip with mild tenderness, chronic scrotal edema, flat abdomen and chest clear to auscultation. Other systemic examinations were within normal limits.

INVESTIGATIONS

Initial labs (Table 1) were suggestive of mild normocytic anemia with hemoglobin of 12.7 g/dL (baseline 12-13), AKI on CKD (Creatinine = 3.52 mg/dL, baseline of 1.6-1.8), elevated serum CK (> 22,000 IU/L), and BNP > 3000 pg/mL. Liver function tests showed markedly elevated transaminases and hypoalbuminemia. In addition, he had an elevated ESR. Thyroid function testing revealed an elevated TSH with normal T3 and T4. Urinalysis showed cloudy-orange appearing urine with dipstick "large" positive for blood, but only 2 RBCs per high power field (HPF), a disparity highly suggestive of myoglobinuria versus hemoglobinuria. The former was more likely given elevated CK and transaminases, raising suspicion for rhabdomyolysis. Overall his labs were significant for rhabdomyolysis and AKI on CKD. However, serum electrolytes and arterial blood gas analysis were normal.

The patient also underwent further workup of etiology for rhabdomyolysis. Urine drug screen was negative. EEG was normal and seizures were ruled out based on history. On routine respiratory pathogen panel testing for infectious etiology, he was found to be COVID-19 PCR positive on a nasopharyngeal swab. However serial chest X-rays (Fig 1) were negative for pneumonia. Given the absence of fever, cough or chest x-ray findings, and normal oxygen requirements, this was an asymptomatic COVID-19 infection. Given the pedal edema, a lower extremity duplex scan was performed and was negative for deep vein thrombosis. In addition, transthoracic echocardiography showed normal cardiac function, and ECG showed a normal sinus rhythm. Further cardiac evaluation was deferred since the elevated BNP was presumed to be due to impaired excretion in the setting of renal dysfunction. Liver ultrasound showed normal echogenicity. Renal ultrasound showed increased echogenicity of the right kidney, with normal echogenicity of the left kidney. Therapeutic drug testing of blood showed elevated levels of levetiracetam (93 mcg/mL; range: 10- 40), sub-therapeutic levels of valproate (29.1 mcg/mL, range 50-100), and sub-therapeutic levels of cyclosporine (35.7 ng/mL; range 100-400).

TREATMENT

The patient was treated with IV fluids and IV 25% albumin. Renal function gradually improved, with serum creatinine, CK and transaminases trending down (Fig 2). Hypoalbuminemia also improved with albumin supplementation. Urine output was normal throughout this admission. Given that the patient was polyuric and in the recovery phase of AKI, IV fluids were discontinued. Albumin supplementation alone was continued, and renal function, CK and transaminases further trended towards the baseline. ESR also declined. Also, given elevated TSH, his dose of levothyroxine was increased.

OUTCOME AND FOLLOW-UP

Over the course of treatment, the patient developed increasing edema due to over-hydration. However, he was treated with diuretics at the expense of some increase in creatinine, with edema eventually subsiding to his baseline. He never had any respiratory symptoms or oxygen requirements throughout this admission. He received physical therapy to assist with ambulation. Eventually, he was discharged to a rehabilitation facility. He has been well since then until his last follow-up four months later.

DISCUSSION

Patients with rhabdomyolysis usually present with myalgia, weakness, dark urine (myoglobinuria), and prodromal systemic symptoms like fever and malaise [2]. Rhabdomyolysis itself as the presenting feature of an otherwise asymptomatic COVID-19 infection, is rare [7]. Diagnosis of rhabdomyolysis is made by consistent clinical features and serum CK potassium and phosphate, all released from lysed myocytes. Hypocalcemia can occur secondary to intravascular calcium-phosphate binding. However, this patient did not have any electrolyte abnormalities. Increased creatinine above the baseline, indicates pigment-induced AKI, which this patient had [2, 3]. A diagnosis of myoglobinuria is suggested by dipstick positive for blood (by detecting

myoglobin), but no RBCs on microscopy, and simultaneously elevated CK and transaminases in blood (to differentiate from haemoglobinuria) [8].

Rhabdomyolysis is managed by aggressive intravenous fluid resuscitation to prevent or treat AKI, with careful titration to the urine output. It may be prudent to consider the volume status of the patient as well. In this particular case, it can be stated retrospectively that over-hydration should have been prevented, given the patient was already volume-overloaded at the time of presentation. Intravenous albumin supplementation alone may have been sufficient to increase intravascular volume. Whenever CK levels are more than 30,000 IU/L, forced alkaline diuresis with sodium bicarbonate is a good option, whereby the urine is alkalinized to prevent precipitation of myoglobin in the distal convoluted tubules. Treatment of the cause and treating electrolyte abnormalities are also important [2, 9, 10].

The patient in this case had a few risk factors for the development of rhabdomyolysis such as medications (atorvastatin, levetiracetam and antipsychotics), statin-cyclosporine interaction resulting in elevated statin levels, and hypothyroidism. He also had hypoalbuminemia secondary to FSGS, which is a poor prognostic factor, increasing the risk of AKI in rhabdomyolysis [3]. The patient had no documented evidence of rhabdomyolysis in the past. Furthermore, the potential triggers he had for rhabdomyolysis were injury due to the fall, possible seizure, and the incidentally discovered COVID-19 infection. However, the likely etiology is the COVID-19 infection, and in the trailing discussion, we have tried to rule out all other possible triggers.

The fall episode as described by the patient did not sound seizure-related, and he did not recount any recent episode of seizure. Creatine kinase levels in rhabdomyolysis secondary to seizure activity peak within 24-72 hours and the rate of decline is also relatively constant, decreasing by about 39 per cent of the previous day's value, in a regular downward trend [5]. In this patient the CK was already or had peaked before admission. Two days after the fall, CK was 11671 and rose to 13539 the day after, then dropped by 27.4 per cent in a day to 9699, suggesting an irregular pattern. Furthermore, the rhabdomyolysis was unlikely to have been caused by the fall itself, as the patient neither sustained significant muscle injury nor was he immobilized for long. Most cases of rhabdomyolysis, severe enough to cause AKI, are seen in patients who fall unconscious and are unable to move for many hours and develop enough trauma to the muscles just from body weight. This patient sustained minimal trauma from the fall, without being immobile on the floor for any length of time. Also, high levels of CK were seen on the same day as the fall and thereafter only trended downwards. Muscle injury induces a rise-peak-fall type of CK pattern, hence making it unlikely to be the trigger here [2]. The patient had also complained of increasing bilateral lower extremity swelling with pain over a few days before admission, suggesting that rhabdomyolysis likely predates his admission. In addition, his raised ESR with subsequent falling trend, points more towards infection versus inflammatory state. Thus, COVID-19 was the most likely trigger for rhabdomyolysis.

Of the risk factors predisposing the patient to rhabdomyolysis, atorvastatin with concomitant use of cyclosporine appears the most important. Statins are well-known to cause a spectrum of myopathies, ranging from myalgia to rhabdomyolysis [11]. The risk of rhabdomyolysis with statin is usually within one month after its onset or when the dose is intensified. Our patient was taking the same dose of statin for many years. However, considering that he is also on cyclosporine, which has pharmacokinetic interactions with statins and increases statin levels, the risk is increased more than with statin alone. Also, his cyclosporine dose was increased a month before his admission, given the sub-therapeutic levels. Atorvastatin has been reported to cause rhabdomyolysis when used along with cyclosporine, and its pharmacokinetic and pharmacological properties make such a drug interaction likely [12]. Levetiracetam may also cause rhabdomyolysis as one of its rare side effects, but it's usually observed within three days of initiation of the drug [13, 14]. This patient has been taking levetiracetam for years. However, levetiracetam levels were found to be elevated in this patient, almost double the therapeutic maximum, which could be due to impaired excretion in the setting of AKI. Rhabdomyolysis is a rare complication of hypothyroidism but is only seen if the patient is not adherent to treatment, which is not the case here [15]. Lastly, the patient was on antipsychotics, which are known to cause rhabdomyolysis even in the absence of neuroleptic malignant syndrome [16, 17]. Both aripiprazole and risperidone have been implicated in this regard [18, 19]. However, the patient had been

taking them for a few years, hence they are unlikely to be the cause of rhabdomyolysis.

CONCLUSION

Overall, this is likely a case of rhabdomyolysis triggered by an otherwise asymptomatic COVID-19 infection. Yet, it is important to note that COVID-19-induced rhabdomyolysis has occurred in the backdrop of several risk factors, most significantly statin-cyclosporine drug interaction. This pharmacokinetic interaction leads to elevated plasma levels of statin, thus risking skeletal muscle damage. COVID-19 may have just been the trigger that pushed statin-induced myopathy towards full-blown rhabdomyolysis.

Rhabdomyolysis and AKI may be the only presenting features of COVID-19 infection. Also, it may be worth monitoring CK levels in those patients who test positive for COVID-19, especially if they have pre-existing risk factors or symptoms of rhabdomyolysis. Early initiation of intravenous fluid therapy is the key to management, both to prevent and treat myoglobin-induced AKI.

FIGURE LEGENDS

Fig 1: Chest radiograph showing no evidence of pneumonia. Also seen are discoid atelectasis in the left lung base and blunting of the costophrenic angles, possibly due to minimal effusion. Remaining lung fields show no active infiltrates or consolidations.

Fig 2: Line graph showing the daily trends in serum creatine kinase (CK) and serum creatinine levels. While CK shows an overall downward trend, creatinine values initially fall with ongoing intravenous hydration, but rise on day 13 as a response to additional diuretics to reduce edema, to eventually fall again.

Table 1: Initial Laboratory Investigations. **(H)** – High; **(L)** – Low

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`Fig 1. Chest x-ray.docx` available at https://authorea.com/users/820557/articles/1219028-asymptomatic-covid-19-infection-induced-rhabdomyolysis-in-the-backdrop-of-statin-cyclosporine-drug-interaction

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`Fig 2. Graph- CK and Creatinine trend.docx` available at https://authorea.com/users/820557/articles/1219028-asymptomatic-covid-19-infection-induced-rhabdomyolysis-in-the-backdrop-of-statin-cyclosporine-drug-interaction