SAGE Open Medical Case Reports
Volume 12: 1–5

DOI: 10.1177/2050313X241233432
journals.sagepub.com/home/sco
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A case report of QTc prolongation: Drug induced or myocarditis in Severe Acute Respiratory Syndrome Coronavirus 2

Mahboobeh Gholipour[1], Pirooz Samidoost[2], Mani Moayerifar[2] and Golshan Ghasemzadeh[3]

Abstract

Remdesivir is a nucleotide prodrug of an adenosine analog. It binds to the viral Ribonucleic Acid (RNA)-dependent RNA polymerase and inhibits viral replication by terminating RNA transcription prematurely. Remdesivir has demonstrated in vitro and in vivo activity against Severe Acute Respiratory Syndrome Coronavirus 2; it also acts in vitro neutralization activity against the Omicron variant and its subvariants. We reported a 54-years-old woman admitted with Coronavirus disease 2019. Considering to require a high fraction of inspired oxygen therapy (⩾0.6) and based on lung high resolution computed tomography, Remdesivir therapy was ordered for 5 days. She experienced palpitations and dizziness 2 days after starting Remdesivir therapy. Her QTc interval was prolonged on the electrocardiogram without any significant electrolyte abnormalities or concomitant use of medications. Although the cardiac side effects of Remdesivir therapy have been well documented, in a few cases reported the association between Remdesivir therapy and QTc interval prolongation. Since, QTc interval prolongation has the potential risk of sudden cardiac death, the clinicians should be aware of mentioned association and check electrocardiogram daily, as well as other laboratory exams.

Keywords

Remdesivir, SARS-CoV-2, long QT syndrome, electrocardiography

Date received: 5 November 2023; accepted: 31 January 2024

Introduction

Coronavirus disease 2019 (COVID-19) also named Severe Acute Respiratory Syndrome Coronavirus 2 (SARS-CoV-2); it is an infectious disease which was found in China for the first time, but a few months later World Health Organization declared it as a novel worldwide pandemic.[1] By October 2021, a total of 259 million cases of infection and 5 million deaths due to COVID-19 involvement have been confirmed globally.[2]

The US Food and Drug Administration (FDA) approved the Remdesivir for the treatment of COVID-19 in hospitalized patients in October 2020.[3] It is a nucleotide prodrug of an adenosine analog. It binds to the viral RNA-dependent RNA polymerase and inhibits viral replication by terminating RNA transcription prematurely. Remdesivir therapy has common side effects such as hypersensitivity reactions, increased liver aminotransferases, and renal laboratory data.[1] However, common use of this drug may be challenged by reporting cardiovascular complications such as bradycardia, atrial fibrillation, and prolonged QTc interval.

The QTc interval refers to measuring the time it takes for the heart to recharge its electrical system before each beat. It is specifically used to assess the electrical activity of the heart's ventricles. In terms of clinical implications, a prolonged QTc interval is associated with an increased risk of ventricular arrhythmias, which are abnormal heart rhythms that can be life-threatening. Certain medications, genetic conditions, and electrolyte imbalances can contribute to a prolonged QTc interval. In this case report, we presented an

[1]Department of Cardiology, Healthy Heart Research Center, Heshmat Hospital, School of Medicine, Guilan University of Medical Sciences, Rasht, Iran
[2]Department of Razi Clinical Research Development Unit, Guilan University of Medical Sciences, Rasht, Iran
[3]Healthy Heart Research Center, Heshmat Hospital, School of Medicine, Guilan University of Medical Sciences, Rasht, Iran

Corresponding Author:
Mani Moayerifar, Department of Razi Clinical Research Development Unit, Guilan University of Medical Sciences, Rasht 41939-5558, Iran.
Email: manimoayeri1397@gmail.com

Table 1. Timeline of laboratory tests before and after Remdesivir injection.

Test	Admission day	Second day	Third day	sixth day	At discharge	Reference interval
Complete blood count (CBC)						
White blood cell (WBC) (per microliter)	9750	17,600	18,500	14,300	12,200	
Neutrophil	14,080	15,725	11,440	8540	6825	
Lymphocyte	3520	1850	2860	3660	3400	
HB (g/dl)	9.1	8.8	9	9.9	10.5	
Creatinine(mg/dl)	1.1	0.95	1.1	1	1.2	0.7–1.3
Blood urea nitrogen (BUN) (mmol/L)	26.4	33.2	35	28	25.2	3.5–7.2
Na (mmol/L)	135	133	135	136	136	135–145
K (mmol/L)	4.1	3.5	3.8	4	4.2	3.5–5.1
Mg (mmol/L)	1.9	2	2.1	2.5	2.5	
Alanine transaminase (ALT) (Unit/L)	30	36	32	32	25	
Asparate aminotransferas (AST) (Unit/L)	24	30	29	26	25	
Lactate dehydrogenase (LDH) (Unit/L)	210	225	240	200	192	
Erythrocyte sedimentation rate (ESR)	85	90	95	80	50	
C-reactive protein (CRP) (mg/L)	125	145	150	85	55	0–9
D-dimer (μg/mL, nl<0.5)	5.2				0.5	0.27–0.5
Albumin (g/dL)	3			3.6		
Procalcitonin (ng/mL)	0.65				0.1	0–0.08
N-terminal pro b-type natriuretic peptide (NT-pro BNP) (pd/mL))	125		125		135	
Troponin I (ng/L, normal range <14 ng/L)	4				4	

Iranian woman with COVID-19, who became bradycardia and prolonged QT after receiving Remdesivir.

Ethical statement

This study approved by the local ethics committee of Guilan University of Medical Sciences (Code: IR.GUMS.REC.1402.371). The study was conducted in accordance with the ethical standards laid down in the 1964 Declaration of Helsinki and its later amendments. Written informed consent was obtained from patient.

Case presentation

A 54-year-old female presented to the Emergency Department with dyspnea, cough, and gastrointestinal symptoms. Her medical comorbidity included diabetes mellitus, dyslipidemia, hypertension, asthma, and hypothyroidism. Her medications were Losartan 25 mg, Atorvastatin 40 mg, Acetylsalicylic acid (ASA) 80 mg, Metformin 500 mg, Turbuhaler Budesonide/Formoterol 320 μg, and Levothyroxine 100 μg. Written informed consent was obtained from the patient for her anonymized information to be published.

In first evaluation, her O_2 saturation was 88% at rest, and she had a temperature of 37.4°C, a heart rate of 76 bpm, blood pressure of 140/80 mmHg, and respiratory rate of 31 breaths/min. A few crackles were heard in both lungs; heart sounds and abdominal exam were normal. In addition, laboratory data are mentioned in Table 1. In addition, liver, renal, thyroid function tests, and cardiac biomarkers were normal.

In the first day of hospitalization, a lung high-resolution computed tomography (HRCT) revealed bilateral patchy airspace opacities that were mostly peripheral with blunting of the costophrenic angles (Figure 1). In addition, echocardiographic findings showed an ejection fraction higher than 55%, mild tricuspid valve regurgitation, and right ventricular systolic pressure of 25 mmHg. The polymerase chain reaction test was positive for SARS-CoV-2 on a nasal swab.

She admitted to the intensive care unit (ICU) and received noninvasive ventilation alternating with a high flow nasal oxygen to maintain her saturation over 90%. Meropenem 500 mg IV every 12 h and Dexamethasone 6 mg IV per day were prescribed. Subcutaneous Enoxaparin injection was given once daily to prevent deep vein thrombosis. Considering to require a high fraction of inspired oxygen therapy (⩾0.6), Remdesivir therapy was ordered for 5 days. The patient experienced palpitation and dizziness 2 days after starting Remdesivir therapy, she did not have any hemodynamic instability except hypotension with blood pressure 90/60 mmHg. Serum electrolyte was normal (Table 1). The electrocardiogram monitoring displayed bradycardia and QTc prolongation (QT/QTc = 560/513 msec) (Figure 2).

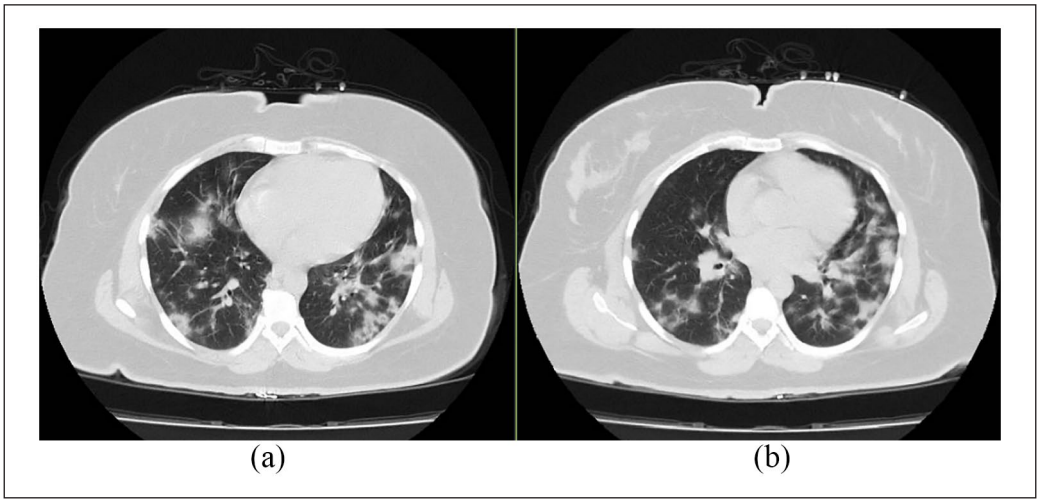

Figure 1. Lung high-resolution computed tomography compatible with Severe Acute Respiratory Syndrome Coronavirus 2 pneumonia (a and b).

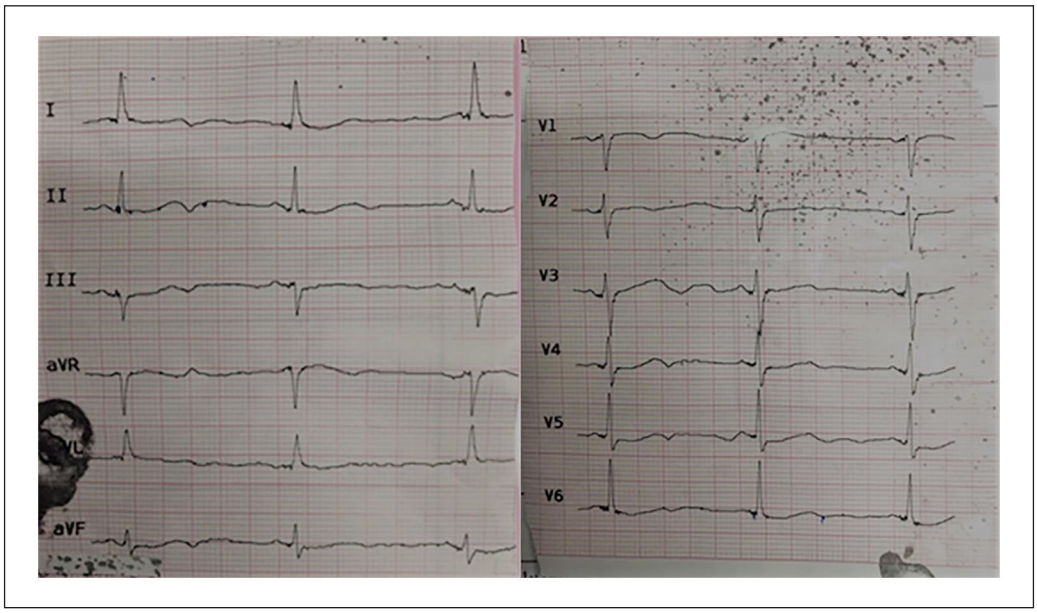

Figure 2. Electrocardiography after 3 doses of Remdesivir: sinus bradycardia with long QTc.

Remdesivir was discontinued and the ECG was monitored. Daily monitoring showed no worsening of the QTc prolongation. Her QTc interval decreased to 466 msec in the third day of admission (Figure 3).

The patient received three doses of Remdesivir, and her laboratory tests are as follows (Table 1).

After discontinuation of Remdesivir during hospitalization, on the fourth and fifth days, the QT interval ameliorated (Figure 4). Her respiratory symptoms improved after 10 days admission. The patient was discharged after improvement of gastrointestinal and respiratory symptoms. In follow-up, after 4 weeks she was visited in the outpatient clinic and the QTc interval became almost normal in the electrocardiogram record.

Discussion

Remdesivir is a nucleotide prodrug of an adenosine analog approved for the treatment of mild-to-moderate COVID-19 in high-risk, non-hospitalized and hospitalized patients aged ⩾12 years, and weighing ⩾40 kg. (1) It is a broad-spectrum antiviral medication that has been using intravenously in hospitalized patients with SARS COVID infection.[2] The FDA emergency use authorization recommends a loading dose of 200 mg (5 mg/kg) intravenous infusion once on the first day and 100 mg for the following days (for 5–10 days).[3] Given the ACCT 1 trial in patients with low oxygen saturation and the need to supplement oxygen therapy, Remdesivir

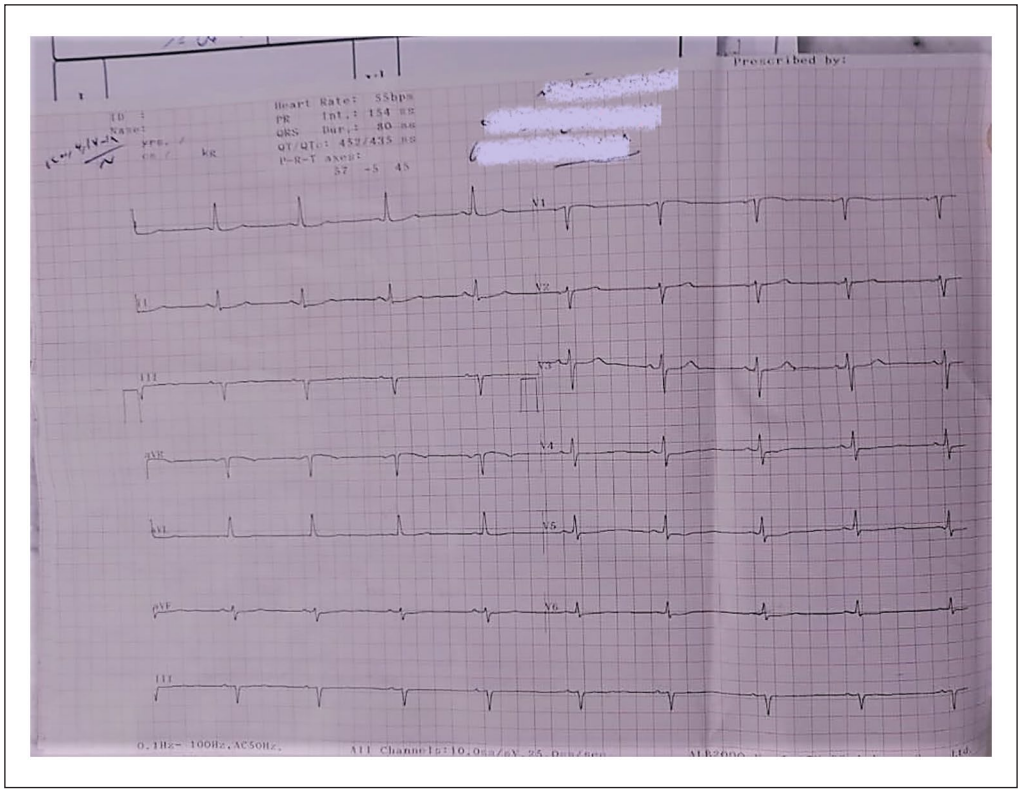

Figure 3. Electrocardiography after Remdesivir discontinuation: QTc improved up to near normal.

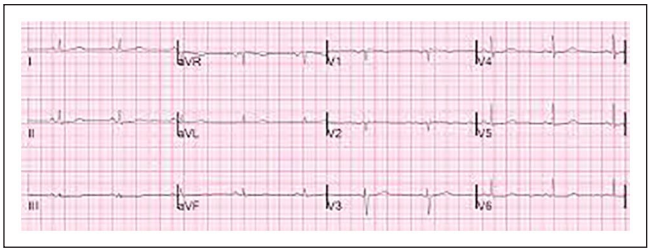

Figure 4. Electrocardiography after 4 weeks in outpatient clinic: QTc was normal.

administration has shortened the hospitalization period.[4] Based on low O_2 saturation and HRCT involvement, Remdesivir started; it seems the recovery time was shorter, but some side effects begun after two doses.

Various cardiac symptoms observed in patients with COVID-19. Acute myocarditis, myocardial infarction, pulmonary embolism, bradycardia, and tachycardia (sinus bradycardia, torsade point, atrial fibrillation, ventricular tachycardia) have been reported. Most of arrhythmias are declared in the setting of myocardial involvement. Life-threatening arrhythmia in acute myocarditis is associated with hemodynamic instability and cardiac enzyme rising.[2] When sinus bradycardia and long QT interval were observed in the patient, echocardiogram findings and cardiac enzymes were normal and her hemodynamic condition was stable. According to these findings, acute myocarditis was rule out.

Long QTc can be a side effect of COVID-19 treatments (Azithromycin, Hydroxychloroquine, Lopinavir ritonavir, Remdesivir); it can also be seen in direct myocardial infection. All causes of long QTc syndrome and bradycardia were considered in the patient examination. All laboratory data were checked and most of them were normal.

Other study reported age, the history of cardiovascular diseases, obesity, hypertension, diabetes, electrolyte imbalances like hypokalemia, and renal impairments significantly increase the prevalence of QTc prolongation.[5] The studied patient was a 54-year-old woman with normal Body mass index (BMI), and other risk factors for long QT were controlled. Serum potassium (K) was normal, indicating nonsignificant role of potassium. Other studies discovered the significant correlation between COVID-19 and biomarkers such as NT-Pro BNP and Troponin. One of the salient theories is that angiotensin-converting enzyme-2 receptors are vital for the entrance of SARS-CoV-2 to the host cells. These receptors exist in the heart muscle and lungs, they might be the cause of cardiorespiratory manifestations of COVID-19.[6,7]

In our case report, the QT prolongation seems more to be due to drug toxicity. After discontinuation of Remdesivir, the QT prolongation was better (560 msec to 466 msec); after the patient's discharge, the QT and QTc were normal in the clinic.

Limitations

The patient was admitted to ICU with low O_2 saturation and could not undergo cardiac Magnetic resonance imaging (MRI). Acute myocarditis could be confirmed by cardiac MRI, but it was not performed. We recommend another research to evaluate myocardial involvement by cardiac MRI and compare which of them—myocardial involvement or drug toxicity-induced long QTc.

Conclusion

The patient had long QT interval after two doses of Remdesivir. Other adverse effects of Remdesivir including, atrial fibrillation and malignant arrhythmia, but myocarditis was not seen. In this case, only hypotension and sinus bradycardia were detected. COVID-19 disease still is an independent risk factor for long QT interval. Clinicians should be cautious about the risk of worsening the QT prolongation with Remdesivir therapy. In addition to check other laboratory tests after beginning Remdesivir, a baseline ECG and cardiac monitoring is recommended to prevent malignant arrhythmia.

Acknowledgements

We greatly appreciate the officials and staff of Razi and Dr. Heshmat Educational and Remedial Center.

Author contributions

M.G. contributed to Conceptualization, Methodology, Project administration, Supervision, Writing—Review & Editing. P.S. contributed to Data curation, Investigation, Resources, Software, Visualization, Writing—Review & Editing. M.M. contributed to Data curation, Investigation, Resources, Validation, Writing—Original Draft. G.G. contributed to Formal analysis, Methodology, Writing—Original Draft.

Declaration of conflicting interests

The authors declared no potential conflicts of interest with respect to the research, authorship, and/or publication of this article.

Funding

The authors received no financial support for the research, authorship, and/or publication of this article.

Ethical approval

Ethical approval to report this case was obtained from Research Ethics Committees of Guilan University of Medical Sciences (APPROVAL NUMBER: IR. GUMS. REC. 1402. 371).

Informed consent

Written informed consent was obtained from the patient for their anonymized information to be published in this article.

ORCID iD

Mani Moayerifar https://orcid.org/0000-0001-6468-6687

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