

Torsades de Pointes Fueled by COVID-19, Aggravated by Remdesivir

Dr. Sabin Tripathee, MD^{1*}, Dr. Charishma Bhimineni, DO², Dr. Ruchi Devbhandari, MD³, Dr. Katherine Quiza, MD⁴, Dr. Kinga Grzybowski, MD⁵, Dr. Altynai Sakieva, MD⁶

Internal medicine, Jefferson Einstein Montgomery Hospital, USA.

Summary

The COVID-19 pandemic has unveiled numerous cardiovascular complications, among which Torsades de Pointes (TdP) stands out as a life-threatening arrhythmia. Remdesivir, a commonly used antiviral for COVID-19, has been implicated in significant cardiovascular adverse effects, including QTc prolongation.

We present an elderly female with COVID-19 pneumonia who developed TdP after remdesivir therapy. Despite treatment with magnesium sulfate and discontinuation of remdesivir, she experienced recurrent TdP, culminating in cardiac arrest.

Arrhythmias are significant complications of COVID-19, particularly in ICU patients. Hypoxia, myocardial inflammation, and viral effects on ion channel regulation may independently predispose patients to QTc prolongation. Remdesivir has been identified as a torsadogenic agent, warranting QT interval monitoring during therapy. This underscores the need for vigilant cardiac monitoring and further investigation into the cardiovascular risks associated with COVID-19 and its treatments. This case emphasizes the critical intersection of COVID-19 infection and its therapeutic interventions in the pathogenesis of TdP.

BACKGROUND

The COVID-19 pandemic has presented an unprecedented global health crisis, affecting nearly every organ system and revealing a wide spectrum of complications beyond its primary respiratory manifestations. Among these, cardiovascular complications have garnered significant attention, attributed to mechanisms such as virus-induced inflammation, hypoxia, electrolyte disturbances, and the adverse effects of therapeutic agents. These multifactorial processes contribute to the heightened cardiovascular morbidity observed in patients with COVID-19.

One particularly life-threatening arrhythmia linked to COVID-19 is Torsades de Pointes (TdP), characterized by QT interval prolongation and a propensity for rapid deterioration into ventricular fibrillation or sudden cardiac death. The risk of TdP in COVID-19 patients may be further heightened by the use of certain antiviral therapies. Remdesivir, a widely utilized RNA-dependent RNA polymerase inhibitor, has demonstrated efficacy in managing COVID-19 but carries the potential for notable cardiovascular side effects, including bradycardia, QTc

prolongation, atrioventricular (AV) nodal block, and tachyarrhythmias.

In this case report, we highlight a compelling instance of TdP in a patient with COVID-19, where the arrhythmia was likely exacerbated by remdesivir administration. This case illustrates the intricate interplay between the infection, its treatment, and resultant cardiovascular complications, emphasizing the need for vigilant monitoring and a cautious approach in managing high-risk individuals.

***Corresponding Author:** Dr. Sabin Tripathee, MD, Internal Medicine, Jefferson Einstein Montgomery Hospital 559 West Germantown Pike, East Norriton, PA, 19403

CASE PRESENTATION

An elderly female with a history of chronic obstructive pulmonary disease (COPD), chronic kidney disease stage 3B (CKD 3B), persistent atrial fibrillation, heart failure with preserved ejection fraction (HFpEF), type 2 diabetes mellitus, hypertension, and obstructive sleep apnea presented to the emergency department with fever, worsening shortness of breath and a productive cough with purulent sputum. On arrival, she was profoundly hypoxic, with oxygenation improving after initiation of BiPAP therapy and albuterol-ipratropium nebulizer treatments.

The patient was admitted for the management of COVID-19 pneumonia and started on remdesivir and dexamethasone. On the second day of hospitalization, a rapid response was initiated for an episode of torsades de pointes (TdP) (Figure 1). The patient was asymptomatic and hemodynamically stable during the event, which resolved after a single dose of intravenous magnesium sulfate (2 g). Telemetry preceding the episode revealed a QTc interval of 569 ms. A repeat EKG following the event showed rate-controlled atrial fibrillation with a persistently prolonged QTc of 524 ms.

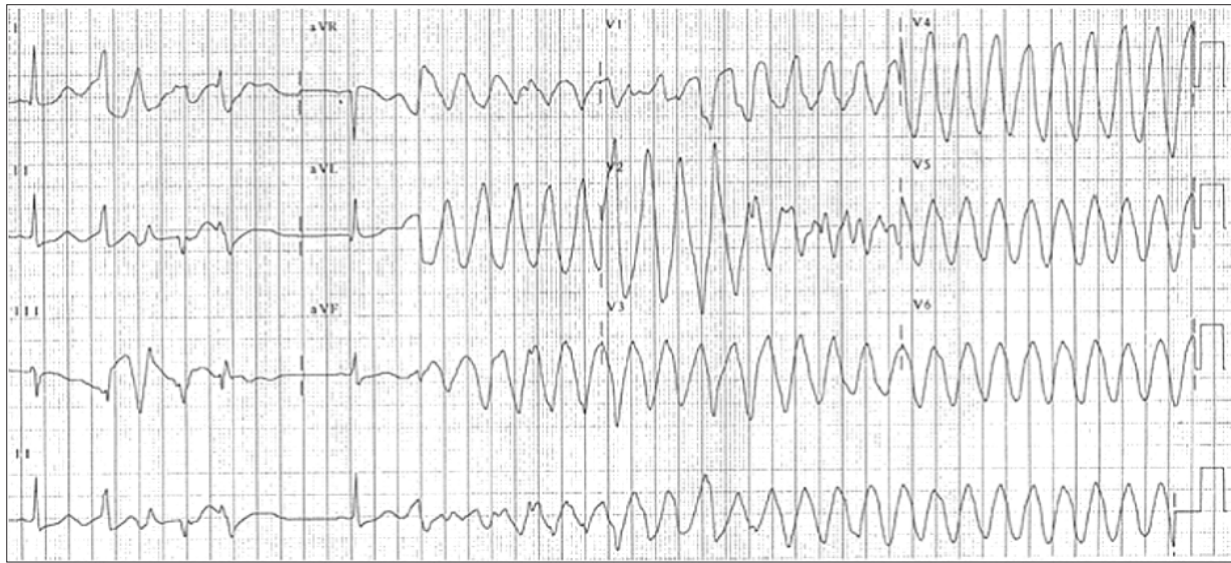


Figure 1. Telemetry strip showing Torsades de pointes.

Given her stable electrolytes and no new medications other than remdesivir, it was suspected as a potential trigger for TdP and subsequently discontinued. Dexamethasone was continued for COVID-19 management. Despite discontinuing remdesivir and optimizing electrolytes, the patient continued to have recurrent, self-resolving episodes of TdP. Her magnesium levels were maintained at ≥ 3 mg/dL per cardiology recommendations.

On the 10th day of hospitalization, a code blue was called for cardiac arrest secondary to recurrent TdP. The patient was successfully resuscitated after six rounds of CPR, receiving epinephrine, amiodarone, and magnesium sulfate (2 g) as per ACLS protocol. She was transferred to the intensive care unit (ICU) and placed on mechanical ventilation.

Cardiac electrophysiology was consulted and identified prolonged QTc as the likely driver of TdP, though the exact etiology of the QTc prolongation remained unclear. Their recommendations included initiating an isoproterenol infusion at 5 mcg/min, a lidocaine drip, and maintaining

potassium >4 mEq/L and magnesium >2 mg/dL. They also suggested implantation of a dual-chamber ICD for secondary prevention of sudden cardiac death.

However, the patient's condition deteriorated even before the procedure could be planned. Following an extensive goals-of-care discussion with her family, palliative extubation was performed. The patient passed away peacefully in the presence of her loved ones.

INVESTIGATIONS

Laboratory evaluation showed elevated blood urea nitrogen (BUN) and creatinine levels at 40 mg/dL and 1.72 mg/dL, respectively, consistent with her baseline CKD. A mild leukocytosis was noted with a WBC count of $12.6 \times 10^3/\mu\text{L}$ and a neutrophil predominance of 83.6%. Electrolytes were within normal limits, with sodium at 144 mEq/L, potassium 4.1 mEq/L, calcium 9 mg/dL, and magnesium 1.8 mg/dL.

An electrocardiogram (EKG) revealed atrial fibrillation with aberrancy, a prolonged QTc of 521 ms, and anterior

and inferior infarct patterns. Comparison with a prior EKG from a cardiology visit one month earlier showed rate-controlled atrial fibrillation with a narrow QRS complex, normal QTc, and similar infarct patterns. A review of her medication history revealed no QT-prolonging agents or over-the-counter supplements that could explain the newly prolonged QTc interval.

A transthoracic echocardiogram (TTE) revealed a left ventricular ejection fraction (LVEF) of 50% (low-normal systolic function), moderate right ventricular dilatation with normal systolic function, mild mitral annular calcification, and aortic valve sclerosis without other significant valvular abnormalities or pericardial effusion.

Left heart catheterization (LHC) was performed to rule out obstructive coronary artery disease. The LHC showed patent epicardial coronary arteries, ruling out ischemia as a cause for her polymorphic ventricular tachycardia.

A repeat TTE post cardiac arrest showed no changes from the prior findings.

DIFFERENTIAL DIAGNOSIS

Given her extensive cardiac history, the initial concern was whether obstructive coronary artery disease could be a trigger for Torsades de Pointes (TdP). However, left heart catheterization revealed patent coronary arteries, effectively ruling this out. A transthoracic echocardiogram (TTE) demonstrated normal ventricular function without any evidence of myocardial scar tissue or structural heart disease, further reducing the likelihood of these as contributing factors. A review of her home medications found no agents known to prolong the QT interval, and her potassium, magnesium, and calcium levels were normal, which excluded electrolyte imbalances. The EKG displayed new QTc prolongation that was not present in prior records, ruling out congenital QT prolongation syndromes. Importantly, the QTc prolongation was evident upon admission before the initiation of remdesivir, suggesting that COVID-19 was the primary trigger, potentially exacerbated by the medication. Despite discontinuing remdesivir, persistent QTc prolongation and recurrent TdP strongly implicated COVID-19 as the underlying cause of her condition.

TREATMENT

1. Dexamethasone and remdesivir for COVID-19 pneumonia
2. Magnesium sulfate during episodes of Torsades de Pointes
3. Epinephrine and amiodarone as per ACLS protocol during cardiac arrest

4. Isoproterenol infusion and lidocaine infusion post cardiac arrest for inotropy and as an anti-arrhythmic therapy for recurrent TdP respectively.

OUTCOMES AND FOLLOW-UP

Patient expired after palliative extubation.

DISCUSSION

Arrhythmias pose a significant threat in COVID-19 patients, with reported incidences of 17% in non-ICU hospitalized patients and up to 44% in ICU patients [1]. SARS-CoV-2 has been shown to have a profound impact on the cardiovascular system, with the potential for direct myocardial injury and arrhythmogenesis. In critically ill patients, especially those requiring mechanical ventilation, arrhythmias are more common, often due to the compounded effects of hypoxia, mechanical support, and drug side effects. Studies have shown that more than 20% of hospitalized COVID-19 patients experience QTc prolongation, which is strongly associated with diabetes, heart failure, and the use of QT-prolonging medications. However, the direct impact of COVID-19 itself on QTc prolongation remains an area of ongoing investigation.

The arrhythmias may range from tachyarrhythmias, such as atrial fibrillation and ventricular tachycardia, to bradyarrhythmias, including sinus bradycardia and heart block, with an increased incidence observed in hospitalized patients. Elevated troponin levels, indicative of myocardial injury, correlate with a heightened risk of arrhythmias and poor clinical outcomes, including increased mortality. The pathophysiology of these arrhythmias is multifactorial, with contributing factors such as pre-existing cardiovascular conditions, hypoxia, electrolyte disturbances, and viral-induced myocardial damage.

The involvement of ACE-2 receptors in cardiac cells has been suggested as a potential mechanism. The virus binds to ACE-2 receptors in the heart, leading to disruption of the renin-angiotensin-aldosterone system (RAAS), reducing the conversion of angiotensin II to angiotensin 1-7, a process that typically helps mitigate inflammation. As a result, the pro-inflammatory state induced by this downregulation can contribute significantly to the development of arrhythmias in COVID-19 patients [1]. Yet more studies are needed to elucidate this relationship.

Myocarditis and pericarditis are other important cardiac manifestations of SARS-CoV-2, which can contribute to arrhythmias through mechanisms such as myocardial scarring, membrane lysis, ischemia, and altered calcium homeostasis. Inflammation due to excessive cytokine

release, particularly interleukin-6 (IL-6) and tumor necrosis factor- α (TNF- α), also plays a crucial role in the development of arrhythmias by disrupting cardiac ion channels [1] [2] [3] [4]. Recent studies indicate that SARS-CoV-2 may influence K⁺ channel expression, potentially disrupting the action potential and calcium handling in heart cells. This disruption could lead to impaired cardiac contractility and a heightened risk of arrhythmias [4].

The use of medications to treat COVID-19, such as remdesivir, hydroxychloroquine, azithromycin, and lopinavir-ritonavir, can prolong the QT interval and heighten the risk of life-threatening arrhythmias. For patients with pre-existing conditions like long QT syndrome, Brugada syndrome, and chronic heart failure, the risk of arrhythmias is amplified, and additional caution is necessary when managing these individuals during infection [5].

Patients with COVID-19-related arrhythmias require vigilant monitoring, particularly with respect to the QT interval and troponin levels, as these are key predictors of mortality. Electrocardiographic changes, such as poor R wave progression and premature atrial contractions (PACs), may serve as early indicators of cardiac dysfunction, which, in combination with elevated troponin levels, are associated with poor outcomes [6]. Monitoring and correcting electrolyte imbalances, discontinuing non-essential QT-prolonging medications, and ensuring continuous ECG surveillance are essential components of managing these patients.

The role of remdesivir in the treatment of COVID-19 further complicates the management of arrhythmias. Although it has demonstrated some benefit in reducing recovery time and preventing progression to mechanical ventilation, remdesivir has been associated with QT prolongation and rare arrhythmias, including torsades de pointes. The drug's structural similarity to adenosine, which can have both antiarrhythmic and proarrhythmic effects, adds to the concerns regarding its cardiovascular safety. Studies in human cardiomyocytes have shown that remdesivir can cause significant cardiotoxicity, especially at higher concentrations, raising concerns about its safety in patients with underlying heart disease or severe COVID-19. These findings underscore the importance of regular ECG monitoring and close management of drug toxicity, especially in patients with pre-existing cardiac conditions [7] [8].

This case underscores the complex interplay between COVID-19 infection, its treatment with remdesivir, and the risk of life-threatening cardiovascular complications such as torsades de pointes. While COVID-19 itself appears

to be a significant contributor to QTc prolongation, the addition of QT-prolonging medications like remdesivir can exacerbate this risk. This highlights the importance of close cardiac monitoring in vulnerable patients receiving remdesivir or other QT-prolonging therapies. Our study on torsades de pointes (TdP) aims to contribute insights for future research, addressing the complexities of cardiovascular issues in COVID-19.

LEARNING POINTS

1. Interplay of COVID-19 and TdP: COVID-19 predisposes patients to life-threatening arrhythmias like Torsades de Pointes (TdP) through mechanisms such as hypoxia, inflammation, electrolyte imbalances, and ion channel dysregulation.
2. Remdesivir's Role: Remdesivir, widely used for COVID-19, has been associated with significant cardiovascular side effects, including QTc prolongation, and may exacerbate TdP risk, especially in vulnerable patients.
3. Case Highlights: An elderly female with COVID-19 pneumonia developed recurrent TdP after remdesivir initiation. QTc prolongation persisted despite discontinuation, suggesting COVID-19 as a major driver, worsened by the drug.
4. Vigilant Monitoring: The case underscores the importance of continuous cardiac monitoring, QT interval surveillance, and careful medication review to mitigate risks in ICU patients.
5. Future Implications: The case emphasizes the need for further research into cardiovascular risks associated with COVID-19 and its therapies, highlighting the critical balance between treatment efficacy and safety.

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