Case Report

Prolonged QT Interval in a Patient With Coronavirus Disease-2019: Beyond Hydroxychloroquine and Azithromycin

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Abstract

Recent reports have suggested an increased risk of QT prolongation and subsequent life-threatening ventricular arrhythmias, particularly torsade de pointes, in patients with coronavirus disease-2019 (COVID-19) treated with hydroxychloroquine and azithromycin. In this article, we report the case of a 75-year-old female with a baseline prolonged QT interval in whom the COVID-19 illness resulted in further remarkable QT prolongation (>700 ms), precipitating recurrent self-terminating episodes of torsade de pointes that necessitated temporary cardiac pacing. Despite the correction of hypoxemia and the absence of reversible factors, such as adverse medication effects, electrolyte derangements, and usage of hydroxychloroquine/azithromycin, the QT interval remained persistently prolonged compared with the baseline with subsequent degeneration into ventricular tachycardia and death. Thus, we highlight that COVID-19 illness itself can potentially lead to further prolongation of QT interval and unmask fatal ventricular arrhythmias in patients who have a prolonged QT and low repolarization reserve at baseline.

Keywords

COVID-19, cardiac arrhythmia, prolonged QTc, torsade de pointes

Introduction

Coronavirus disease-2019 (COVID-19), caused by severe acute respiratory syndrome coronavirus-2 infection, has resulted in significant morbidity and mortality globally.[1] Accumulating evidence has demonstrated an increased frequency of cardiovascular complications, including cardiac arrhythmias, with possible implications for prognosis and survival.[1] In a Chinese cohort of 138 hospitalized COVID-19 patients, 16.7% of the patients had cardiac arrhythmias, which were more common in the intensive care unit than in non–intensive care unit patients (44.4% vs 6.9%).[2] Although the data on arrhythmogenic events are anecdotal, the most commonly reported arrhythmias in COVID-19 patients include atrial fibrillation (AF), atrial flutter, monomorphic or polymorphic ventricular tachycardia, atrioventricular heart block, and pulseless electrical activity.[3] Several recent reports have suggested an increased risk of QT prolongation and subsequent risk of life-threatening ventricular arrhythmias, particularly torsade de pointes (TdP), in COVID-19 patients who received pharmacologic treatment with hydroxychloroquine/chloroquine and azithromycin.[1] We report the case of a 75-year-old patient with a baseline prolonged QT interval in whom the COVID-19 illness resulted in further remarkable prolongation of QT interval (>700 ms), leading to fatal ventricular arrhythmias and death, in the absence of pharmacological treatment with hydroxychloroquine/azithromycin.

Case Description

A 75-year-old female with a past medical history of paroxysmal AF, nonischemic cardiomyopathy with recovered ejection fraction, type 2 diabetes mellitus, hypertension, chronic kidney disease stage IV, and hypothyroidism presented with a worsening cough and shortness of breath for 3 days and was diagnosed with COVID-19. Initial vital signs were blood pressure 148/76 mm Hg, heart rate 120 beats per minute,

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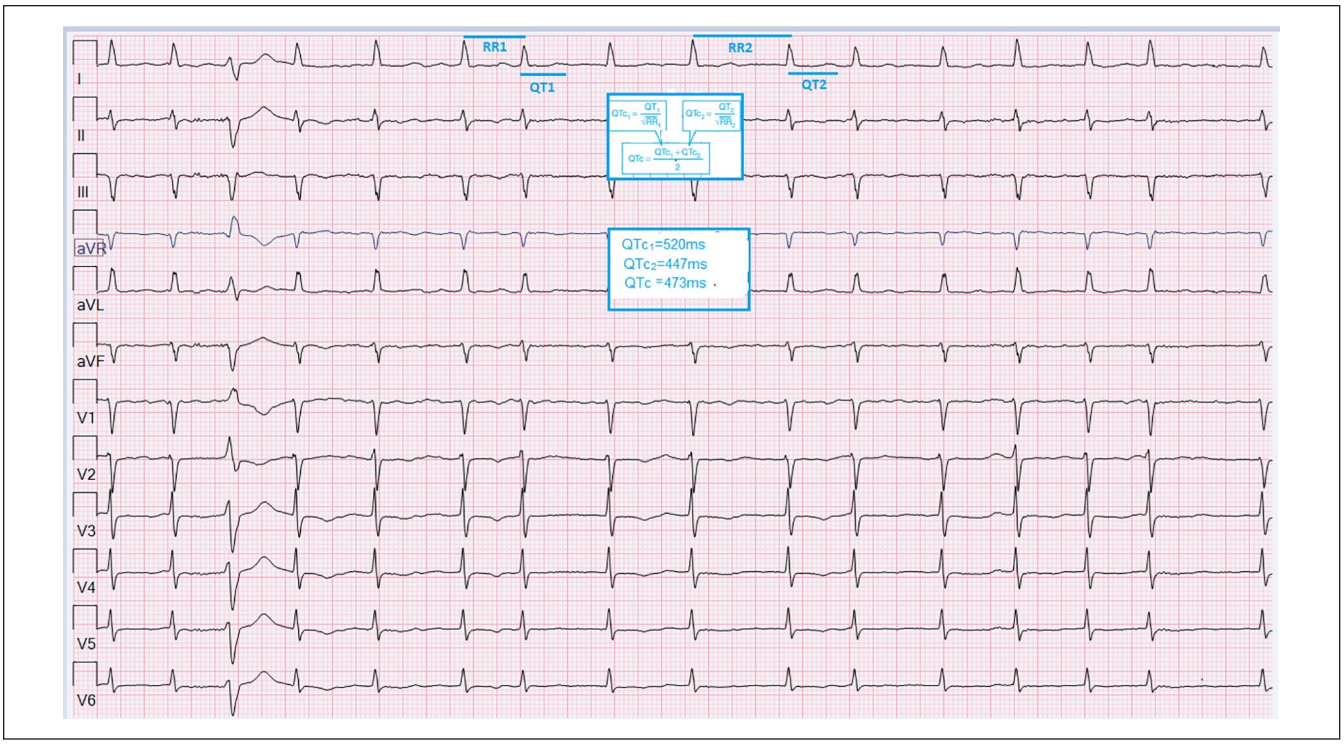

Figure 1. Electrocardiogram on admission demonstrates atrial fibrillation with premature ventricular complexes, a ventricular rate of 95 beats per minute, and corrected QT of 473 ms. Bazett formula is used to correct the QT interval (QTc) for heart rate. There is no consensus regarding the measurement of QT interval in patients with atrial fibrillation. Some suggest averaging the measured QT interval over 10 beats or averaging the QT intervals with the shortest and longest preceding RR intervals.[7] In the above electrocardiogram, it is difficult to discern the QT interval for 10 successive beats. Hence the QT interval is calculated by averaging the shortest and longest QT interval.

respiratory rate 32 breaths per minute, temperature 36.2 °C, and oxygen saturation 96% on 2 liters oxygen. Physical examination revealed respiratory distress, scattered bilateral lung crackles, and no peripheral edema. Initial electrocardiogram (ECG) demonstrated AF with premature ventricular complexes and a corrected QT (QTc) interval of 473 ms (Figure 1). The patient was found to have prolonged QTc at baseline ranging from 460 to 510 ms on reviewing several ECGs from previous admissions (Figure 2). Chest X-ray showed diffuse bilateral patchy opacities (Figure 3). Clinical laboratory findings at admission were white blood cell count 2400 cells/μL, creatinine 2.51 mg/dL (baseline creatinine = 2.5 mg/dL), bicarbonate 17 mmol/L, potassium 4.9 mmol/L, magnesium 2.9 mmol/L, corrected calcium 9.2 mg/dL, thyroid-stimulating hormone 0.923 μ/mL, ferritin 2242 ng/mL, erythrocyte sedimentation rate 74 mm/h, D-dimer 1.24 μg/mL, lactate dehydrogenase(LD) 599 U/L, C-reactive protein (CRP) 91.5 mg/L, troponin T 0.06 ng/mL, N-terminal pro-B-type natriuretic peptide 8216 pg/mL, and interleukin-6 (IL-6) 14 pg/mL (Table 1). The patient's home medications, including insulin, metoprolol, levothyroxine, and losartan, were continued along with supportive care. She did not receive hydroxychloroquine and azithromycin due to prolonged QTc. On hospital day 2, the patient developed worsening hypoxia, requiring intubation and mechanical ventilation. Computed tomography scan of the thorax demonstrated worsening diffuse bilateral ground-glass opacities (Figure 4). Repeat ECG showed sinus bradycardia with first-degree heart block, deep T-wave inversions in the inferolateral leads, and markedly prolonged QTc of 718 ms (Figure 5). Arterial blood gas obtained immediately after intubation showed hypoxemia and acidosis. A repeat metabolic panel showed normal serum electrolytes (Table 1). Intravenous magnesium was administered, home metoprolol was discontinued due to bradycardia, and close cardiac monitoring was instituted. The patient continued to have persistently prolonged QTc, ranging from 600 ms to 720 ms along with intermittent bradycardia and deep T-wave inversions on telemetry monitoring, despite the correction of hypoxemia, acidosis, and aggressive electrolyte replacements. Head computed tomography head showed no acute intracranial pathology. Transthoracic echocardiogram showed an estimated left ventricular ejection fraction of 50% with no regional wall motion abnormalities. On hospital day 5, the patient developed recurrent self-terminating episodes of TdP without hemodynamic collapse (Figure 6). After loading with 2 g of intravenous magnesium, isoproterenol infusion was started. A temporary transvenous pacemaker was inserted with a

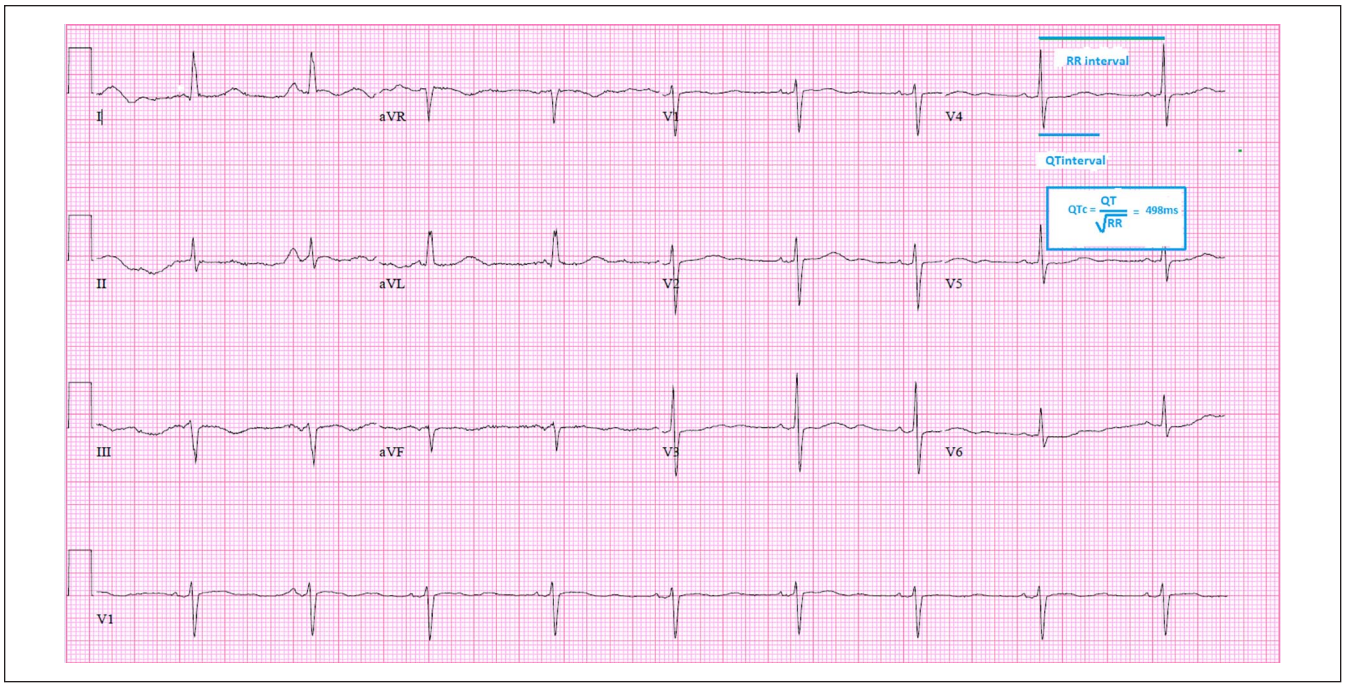

Figure 2. Electrocardiogram obtained during the previous hospitalization 6 months ago while on sinus rhythm demonstrates sinus bradycardia with a heart rate of 55 beats per minute and corrected QT (QTc) of 498 ms as per Bazett formula.

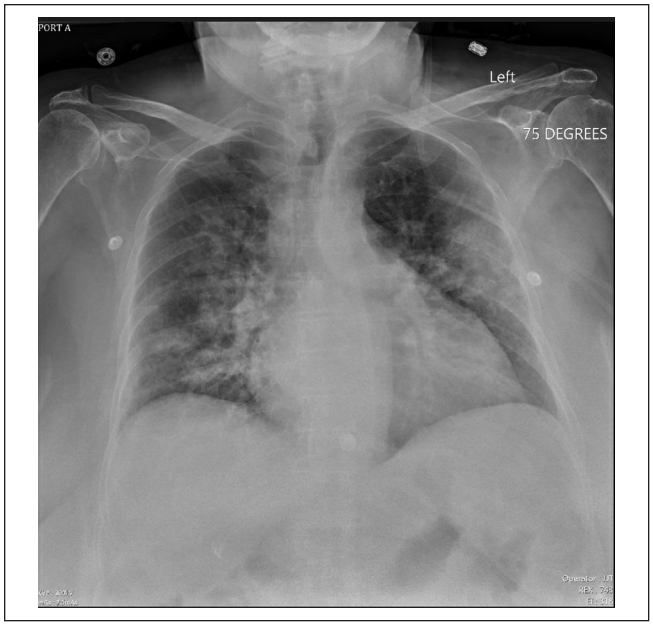

Figure 3. Chest X-ray on admission shows patchy bilateral opacities.

pacing rate of 100/min to induce tachycardia and improve QTc duration. On hospital day 10, the pacemaker was removed, as the patient's intrinsic heart rate was maintained around 80 to 90 beats per minutes. With initially improved respiratory function, the patient was extubated on hospital day 14. However, the repeat COVID-19 test remained positive, and the patient experienced worsening respiratory distress. The patient and family decided on a do not resuscitate/do not intubate order. Unfortunately, on hospital day 20, the patient had several runs of ventricular tachycardia/ventricular fibrillation with underlying prolonged QTc of >600 ms, culminating in cardiac arrest and death (Figures 7 and 8).

Discussion

Long QT syndrome (LQTS) is characterized by prolongation of QTc intervals on surface ECG >440 ms. QTc intervals of 440 to 460 ms in men and 440 to 470 ms in women are considered borderline; the risk of arrhythmias increases with values ≥500 ms.[4] LQTS is associated with risk of TdP, a life-threatening polymorphic ventricular tachycardia that is usually self-limited but may degenerate into ventricular fibrillation and cause sudden cardiac death. Acquired LQTS is a disorder of cardiac repolarization characterized by pathologic excessive prolongation of the QT interval that occurs on exposure to the external trigger and reverts to normal following the trigger's removal.[4] Acquired LQTS is mostly secondary to adverse effects of medications and electrolyte abnormalities, such as hypokalemia, hypomagnesemia, and hypocalcemia.[4,5] Phase 3 of the ventricular myocyte action potential is characterized by efflux of potassium ions predominantly through 2 subtypes of delayed rectifier potassium current, IKr (rapid), and IKs (slow), leading to myocardial repolarization.[4,5] IKr current proteins are

Table 1. Serial laboratory values along with the reference range.

Variables	Reference range	On admission	Day 2	Day 5	Day 20
White blood cell count	4-10 × 10^3/μL	2.4 × 10^3	2.3 × 10^3	7.4 × 10^3	11.0 × 10^3
Absolute lymphocyte	1.2-4.0 × 10^3/μL	0.3 × 10^3	0.29 × 10^3	0.98 × 10^3	0.89 × 10^3
Absolute neutrophil	1.8-7.0 × 10^3/μL	1.46 × 10^3	1.89 × 10^3	4.6 × 10^3	1.25 × 10^3
Hemoglobin	11.5-15.5 g/dL	12.1	12.5	9.4	8.0
Platelets	150-400 × 10^3/μL	246 × 10^3	301 × 10^3	226 × 10^3	268 × 10^3
Sodium	136-145 mmol/L	142	140	137	139
Potassium	3.4-5.1 mmol/L	4.9	4.1	4.8	4.4
Chloride	98-107 mmol/L	110	109	108	102
Bicarbonate	22-29 mmol/L	17	15	16	24
Blood urea nitrogen	8-23 mg/dL	55	53	76	23
Creatinine	0.50-0.90 mg/dL	2.51	2.24	1.95	0.86
Glucose	70-140 mg/dL	125	262	249	176
Magnesium	1.6-2.4 mg/dL	2.9	2.6	3.4	2.0
Phosphorus	2.5-4.5 mg/dL	2.4	4.3	2.9	3.4
Calcium	8.8-10.2 mg/dL	8.6	8.6	8.5	8.4
Albumin	3.5-5.2 g/dL	3.2	3.2	2.3	N/A
Alanine transaminase	<33 U/L	16	14	19	N/A
Aspartate transaminase	<32 U/L	43	49	36	N/A
Alkaline phosphatase	35-104 U/L	86	89	105	N/A
Total bilirubin	<1.2 mg/dL	0.3	0.3	0.5	N/A
Ferritin	30-400 ng/ml	2242	N/A	1276	404
C-reactive protein	<8.0 mg/L	91.5	N/A	271.7	66
Lactate dehydrogenase	122-225 U/L	599	N/A	N/A	N/A
D-dimer	<0.50 μg/mL	1.24	N/A	8.81	1.70
Erythrocyte sedimentation rate	<20 mm/h	74	N/A	112	47
Procalcitonin	<0.10 ng/mL	0.28	N/A	N/A	N/A
Interleukin-6	<5 pg/mL	14	N/A	N/A	N/A
Pro-B-type natriuretic peptide	<125 pg/mL	8216	N/A	N/A	N/A
Troponin T	<0.01 ng/mL	0.06	0.05	0.03	0.03
Thyroid-stimulating hormone	0.270-4.2 μ/mL	0.923	N/A	N/A	N/A
pH	7.38-7.44	7.4	7.25	7.33	N/A
pO_2, arterial	95-100 mm Hg	101	97	142	N/A
FiO_2	N/A	0.28	0.60	0.40	N/A
pCO_2, arterial	35-40 mm Hg	27	38	34	N/A
Blood culture	Positive or negative	Negative	N/A	N/A	N/A
Sputum culture	Positive or negative	Negative	N/A	N/A	N/A

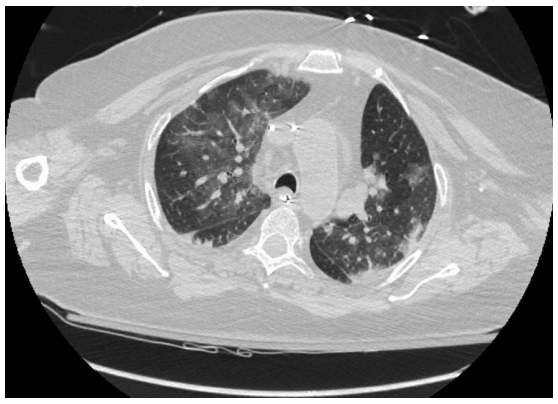

Figure 4. Computed tomography of the thorax shows diffuse bilateral ground-glass opacities.

encoded by the human ether-a-go-go-related gene (hERG). The blockade IKr or interaction with hERG by specific drugs characterize acquired LQTS and TdP, causing a delay in phase 3 rapid repolarization of the action potential and subsequent QT prolongation.[4,5] Pharmacologic treatments for COVID-19, such as hydroxychloroquine/chloroquine and lopinavir/ritonavir, have been shown to prolong QT directly through inhibition of the hERG-potassium channel and indirectly by increasing circulating levels of other concomitant QT-prolonging drugs by cytochrome 450 enzyme inhibition.[6]

Cardiac arrhythmias are likely multifactorial in COVID-19 patients and may be attributable to acute myocardial injury or secondary to hypoxia, metabolic derangements, neurohormonal/catecholaminergic stress, antiviral drugs, and severe systemic inflammation in the acute viremia context.[1,6] Acute

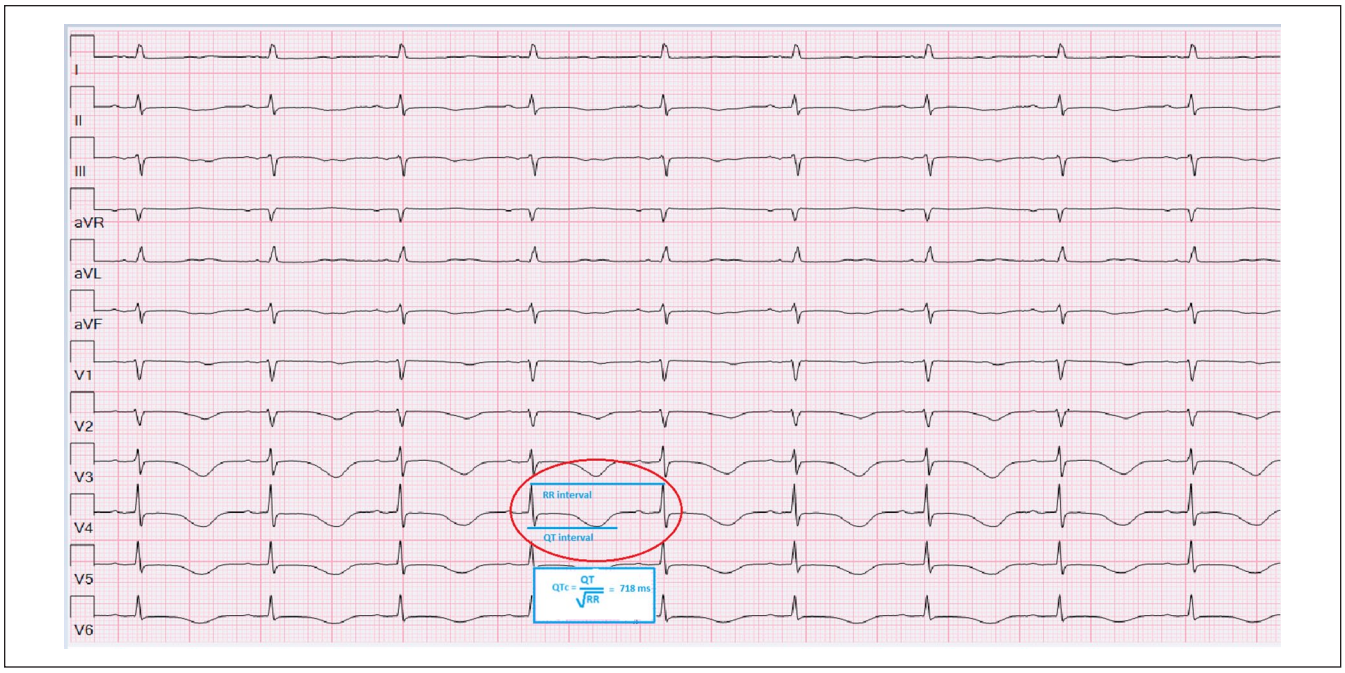

Figure 5. Electrocardiogram on hospital day 2 demonstrates sinus bradycardia with a ventricular rate of 54 beats per minute, inferolateral deep T-wave inversions, and corrected QT of 718 ms per Bazett formula. Notably, the heart rate decreased significantly compared with day 1, and rhythm reverted to sinus likely related to intubation, mechanical ventilation, and usage of sedative agents such as propofol.

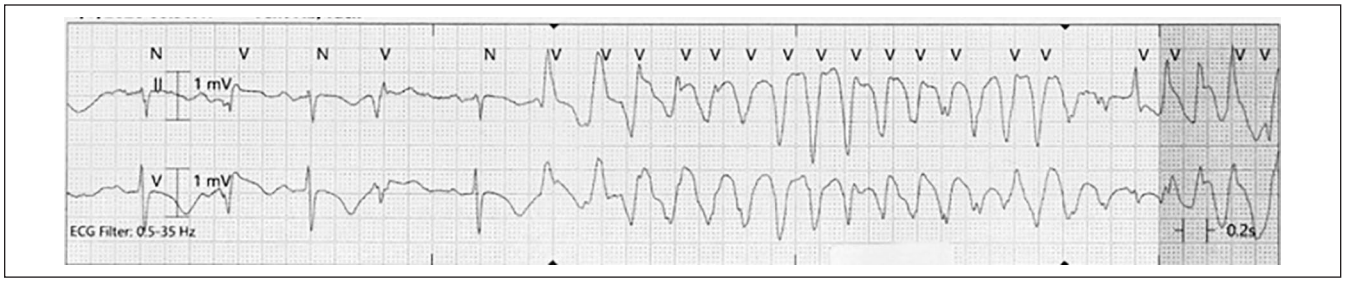

Figure 6. The telemetry strip on day 5 demonstrates a self-terminating episode of polymorphic ventricular tachycardia. Note the varying amplitude, axis, and duration of QRS complexes suggestive of torsade de pointes (TdP). At the beginning of the strip, there are 2 runs of bigeminy (narrow complex QRS followed by a premature ventricular complex [PVC] at the end of the T-wave). The PVC rising in the third beat initiates TdP.

cardiac injury characterized by elevated cardiac biomarkers is a frequently reported cardiac complication and likely a potential trigger for heightened arrhythmic risk in COVID-19 patients. Accordingly, a new-onset malignant arrhythmia in COVID-19 patients associated with elevated cardiac markers should raise the possibility of underlying myocarditis.[1,6] However, another potentially essential trigger for arrhythmias is a high-grade systemic inflammatory state characteristic of COVID-19.[6] Increasing evidence strongly suggests systemic inflammation as a significant risk factor for QT prolongation and TdP via inflammatory cardiac channelopathies.[4,6] Cytokines such as IL-6, tumor necrosis factor-α, and interleukin-1 can directly modulate the expression and function of several cardiomyocyte ion channels and prolong the ventricular action potential duration.[4,6] IL-6 has been shown to prolong QT directly by inhibiting the hERG-potassium channel and indirectly by inhibiting CYP3A4, increasing the bioavailability of QT-prolonging agents.[6] Systemic inflammation can also induce cardiac sympathetic system hyperactivation through direct stimulation of the autonomic nervous system and hence increase the heart's electrical instability.[6] QTc prolongation has commonly been seen in patients with elevated CRP due to other inflammatory conditions.[4,6]

Severe COVID-19 illness is associated with a hyperinflammatory state similar to cytokine storm syndrome, characterized by an uncontrolled dysfunctional host immune

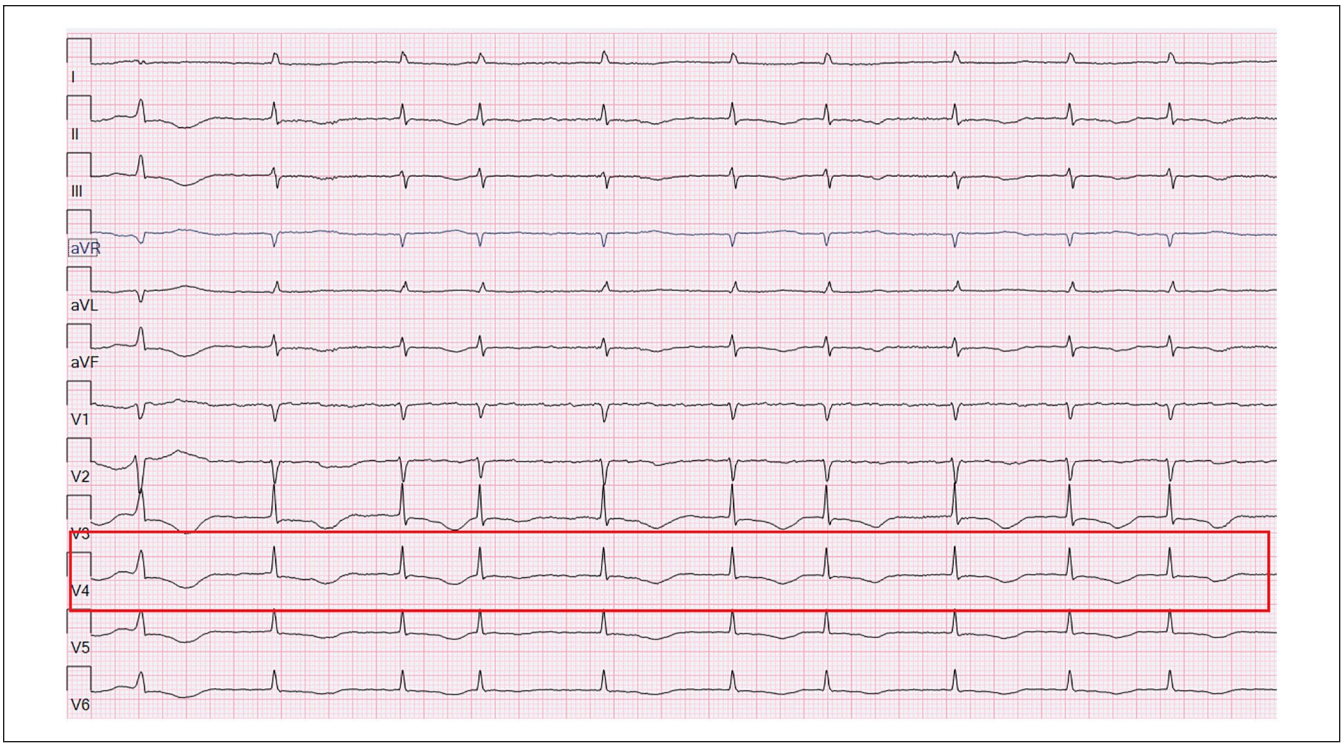

Figure 7. Electrocardiogram on day 20 demonstrates atrial fibrillation with prolonged QTc of 622 ms. The QT intervals are corrected for preceding RR intervals using Bazett formula and averaged over 9 successive beats in lead V4.[7]

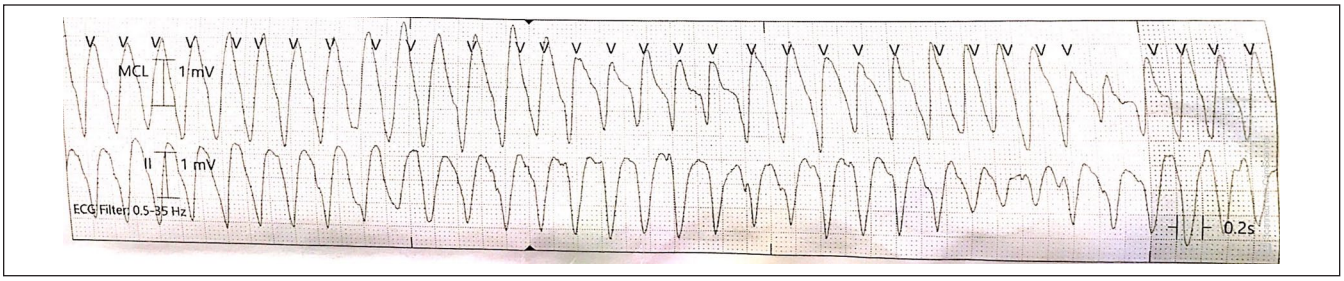

Figure 8. The telemetry strip on day 20 demonstrates ventricular tachycardia associated with hemodynamic collapse.

response, resulting in elevated pro-inflammatory markers (serum ferritin, CRP, D-dimer, and LD) and cytokines such as IL-6 that manifest clinically as rapid progression to acute respiratory distress syndrome, shock, and multiorgan failure.[1] Studies have shown higher prevalence of cardiovascular complications, including cardiac arrhythmias, when these biomarkers are elevated.[1] The baseline prolonged QT interval in our elderly female patient with multiple medical comorbidities may be secondary to undiagnosed inherited ion-channel disorders, or the previous cardiomyopathy. In the setting of prolonged baseline QT and low repolarization reserve, the COVID-19 illness–associated severe systemic inflammation (as evidenced by high serum concentration of ferritin, LD, CRP, erythrocyte sedimentation rate, D-dimer, and IL-6) likely led to further severe prolongation the QT interval. In our patient, QTc remained persistently prolonged despite the correction of hypoxemia and metabolic derangements. There was no evidence of myocardial infarction, myocarditis, or heart failure, based on modest troponin elevation and no regional/global wall motion abnormalities in echocardiography. Our patient was not treated with hydroxychloroquine/azithromycin or other common medications associated with QTc prolongation. Thus, severe systemic inflammation in the context of acute viremia due to persistent SARS-CoV-2 infection is the most plausible explanation for markedly prolonged QTc and subsequent TdP and malignant ventricular arrhythmias in our patient. Further studies are required in the future to elucidate the predominant mechanisms and treatment strategies for COVID-19 related cardiac arrhythmias.

Conclusion

We report an elderly female COVID-19 patient who developed worsening pathologic and excessive prolongation of QTc from baseline degenerating to TdP and malignant ventricular arrhythmias. Although COVID-19–related cardiac arrhythmias are multifactorial in etiology, we suggest that a robust systemic inflammatory response associated with severe COVID-19 is likely the predominant mechanism for severe QT interval prolongation and subsequent TdP in our patient.

Declaration of Conflicting Interests

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

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Ethics Approval

Our institution does not require ethical approval for reporting individual cases or case series.

Informed Consent

Informed consent for patient anonymized information to be published in this article was not obtained from the patient's family because our institution does not require informed consent for individual case reports.

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