Unusual T-wave changes and extreme QTc prolongation in a 71-year-old man with asymptomatic COVID infection

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Introduction

The QT interval represents the time between onset of ventricular depolarization (QRS complex) and conclusion of repolarization (terminal T wave), as detected by surface electrocardiogram (ECG). A prolonged corrected QT interval (QTc) is associated with increased risk of torsades de pointes, which can lead to ventricular fibrillation and sudden cardiac arrest. Several processes can result in prolonged QT interval, including congenital long QT syndrome, drug-mediated effects, metabolic abnormalities, and structural or electrical heart disease.[1]

Several cases of patients with COVID-19 developing T-wave inversion and QT prolongation have been reported. However, most of these patients had severe COVID-19 infection. Below we report a unique case of severe QT prolongation and T-wave inversions in an asymptomatic patient with COVID-19.

Case report

A 71-year-old man with a history of coronary artery disease with prior coronary artery bypass grafting, stroke, and peripheral artery disease presented to the hospital with 1 day of lightheadedness and intermittent diplopia. Vital signs were notable for temperature of 37.5°C, blood pressure of 108/74 mm Hg, and oxygen saturation of 98% breathing ambient air. Physical exam was notable for normal cardiopulmonary findings and euvolemia. Admission polymerase chain reaction testing for SARS-CoV-2 was positive. Laboratory testing revealed hypoglycemia with serum glucose concentration of 50 mg/dL (ref 70–105 mg/dL). Initial ECG showed normal sinus rhythm with a stable right bundle branch block, pathologic Q waves in the inferior leads, new T-wave inversions in leads I, II, and V_4–V_6, and a QTc of 563 ms by the Bazett formula (Figure 1B). His baseline QTc on prior ECG was 464 ms (Figure 1A). Troponin T was <0.010 ng/mL (ref 0.00–0.03 ng/mL), and N-terminal pro B-type natriuretic peptide (NT-proBNP) was 3037 pg/mL (ref 0–125 pg/mL). Computed tomography angiography of the head and neck obtained, owing to concern for stroke, showed no evidence of acute intracranial processes but did reveal patchy ground-glass opacities within the bilateral lung apices, concerning for an infectious or inflammatory process.

The patient was admitted to the hospital with hypoglycemia related to suspected sulfonylurea overdose, as he was taking glimeperide 8 mg daily. His hypoglycemia resolved within the first 2 days of admission. However, subsequent ECGs showed persistent deep T-wave inversions and progressive QTc prolongation, with a peak QTc of 720 ms on hospital day 7 (Figure 1C). Supplemental magnesium was administered. His electrolytes remained within normal ranges throughout his hospital stay. The patient consistently denied chest pain, shortness of breath, palpitations, or any symptoms attributable to COVID-19. He denied any known family history of long QT syndrome, sudden unexplained death, or sudden cardiac arrest. Repeat serum troponin T assays remained undetectable. Erythrocyte sedimentation rate and C-reactive protein were mildly elevated and peaked at 81 mm/h (ref 0–20 mm/h) and 11.5 ng/mL (ref <10 ng/mL), respectively. Serum ferritin and lactate dehydrogenase were also elevated and peaked at 743 mg/mL (ref 30–400 mg/mL) and 281 U/L (ref 0–249 U/L), respectively. QTc gradually improved between hospital days 8 and 15, though his marked T-wave inversions remained.

Transthoracic echocardiogram showed a normal left ventricular ejection fraction and no regional wall motional abnormalities; however, global longitudinal strain was reduced at -14.7%. Cardiac magnetic resonance imaging was

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KEY TEACHING POINTS

- QT prolongation may complicate COVID-19.
- Clinicians should consider the risk of severe QT prolongation in patients with baseline elevated corrected QT interval and cardiac comorbidities who contract COVID-19.
- Given the predisposition to arrhythmia in patients with COVID-19 and other systemic inflammatory states, care should be taken to avoid additional QT-prolonging medications where possible.

unfortunately nondiagnostic owing to motion artifact. An extended toxicology screen was sent to identify possible surreptitious use of QT-prolonging agents and was negative. Genetic testing was also sent to assess for the presence of 51 genes associated with congenital causes of long QT, and was uninformative. Empiric treatment for viral myocarditis due to COVID-19 was discussed but was not pursued, given limited biochemical and radiological evidence of myocarditis and overall clinical stability. The patient was eventually discharged on hospital day 15 with a QTc of 568 ms. He was provided with a wearable external cardioverter-defibrillator and plan for close follow-up in cardiology clinic. Monthly follow-up ECGs showed gradual improvement in QT prolongation, with ECG 4 months after discharge showing a QTc of 488 ms (Figure 1D).

Discussion

Several infectious and inflammatory conditions have been noted to cause QT prolongation. In a study of patients with acute infection, inflammatory makers such as CRP, IL-6, and IL-1 correlated with QT prolongation, and QT intervals improved with normalization of these markers.[2] High levels of circulating cytokines, specifically IL-6, TNF-α, and IL-1, have been shown to affect cardiac Ca^{2+} and K^{+} currents in animals and in vitro studies.[2] Additionally, IL-6 has been shown to block I_{kr} and reduce expression of the human ether-a-go-go-related gene (hERG) potassium channel, akin to the mechanism of drug-induced QT prolongation.[3] Additionally, IL-1 and CRP levels have been linked to reduced mRNA expression of cardiac K^{+} ion channels in patients with acute infection.[3]

COVID-19 also appears to be associated with prolonged QT and increased risk of arrhythmia, an unsurprising finding given the cytokine storm associated with severe disease. A study of 1258 patients diagnosed with COVID-19 noted prolonged QT (QTc >500 ms or >550 ms for QRS >120 ms) in 5% of patients.[4] Another study of over 3000 hospitalized patients with COVID-19 found QT interval prolongation in 18% and unexplained T-wave inversions in 6%, of which about one-quarter had elevated serum troponin concentrations.[5] Both T-wave inversions and QT prolongation appear to be associated with more severe disease and with cardiac

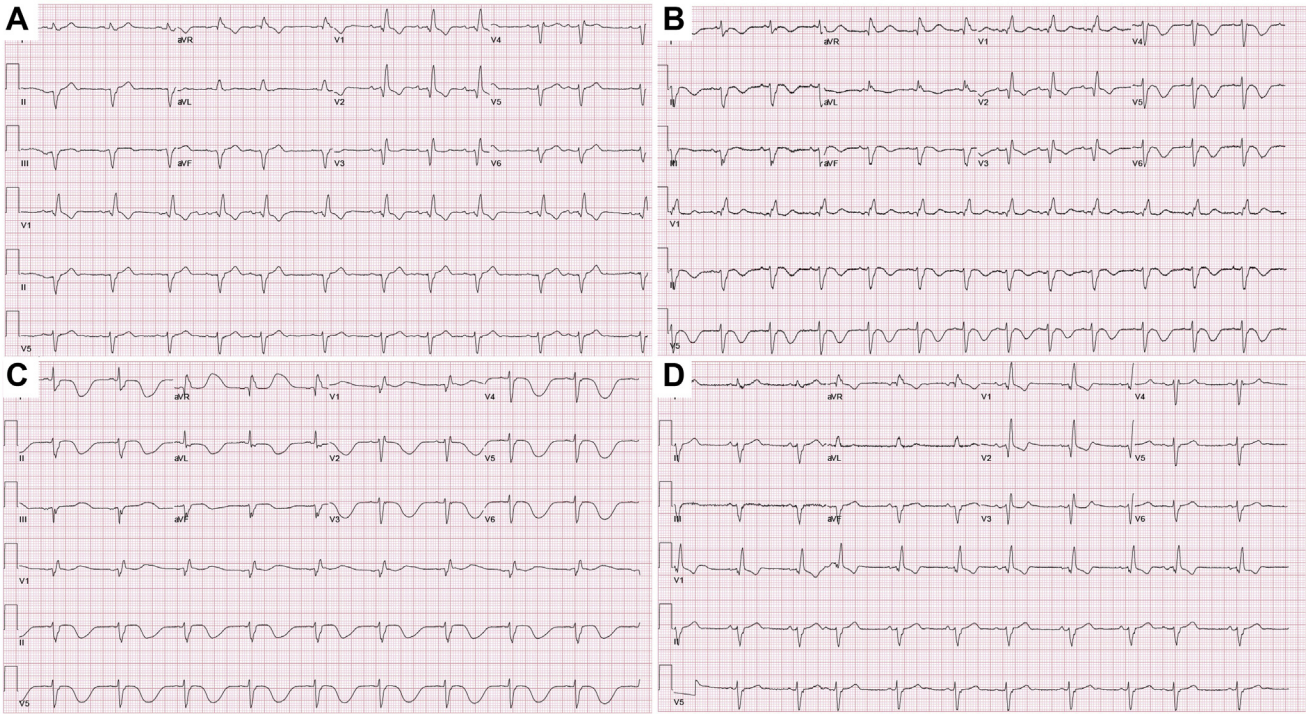

Figure 1 **A:** Baseline electrocardiogram (ECG) 1 month prior to hospital admission (corrected QT interval [QTc] = 464 ms). **B:** ECG on hospital day 1 (QTc = 563 ms). **C:** ECG on hospital day 7 (QTc= 720 ms). **D:** ECG 4 months after hospital discharge (QTc = 488 ms).

injury in patients with COVID-19.[6] Two case reports describe mechanically ventilated patients with SARS-CoV-2 infection who were found to have deep T-wave inversion and persistent severely prolonged QTc (560–730 ms), without evidence of ischemia or myocarditis.[7,8] In 1 case, the patient developed torsades de pointes and other malignant ventricular arrhythmias.[8]

Historically, concern for QT prolongation in patients with COVID-19 has been related to the use of therapeutic agents known to prolong QT interval, such as hydroxychloroquine and azithromycin.[9] Myocardial inflammation can be a trigger for ECG changes and arrhythmias in patients with COVID-19; however, in many cases there is no evidence of myocardial injury.[10] Other suggested mechanisms for these electrophysiologic findings include microvascular injury due to the endothelial effects of the virus,[6] or myocardial inflammation and ion channel changes in the setting of systemic viral infection.[10,11]

It is also notable that our patient was hypoglycemic on presentation, related to glimepiride use. Severe hypoglycemia has been associated with serious arrhythmias and sudden cardiac arrest,[12] and glyburide has been linked to QT prolongation.[13] However, this effect has not been observed with other agents such as glimepiride.[13] Additionally in our case, the patient's QT prolongation worsened over the course of his hospital stay, peaking on hospital day 7, well after normalization of his blood sugar and metabolic clearance of glimepiride.

Although patients in prior case reports of severely prolonged QT intervals with SARS-CoV-2 infection have all been critically ill, there is increasing evidence that even those with mild disease may experience cardiac complications of SARS-CoV-2. Cardiac magnetic resonance imaging in patients who had recovered from COVID-19 showed cardiac involvement in 78%, unrelated to severity of COVID disease.[14] Additionally, epidemiologic studies suggest an increase in out-of-hospital cardiac arrest during the COVID-19 pandemic.[15]

To our knowledge, this is the first reported case of dramatic QT prolongation and T-wave inversions in an asymptomatic patient with SARS-CoV-2 without evidence of myocardial injury. While QT prolongation in COVID-19 has generally been attributed to elevated cytokine levels and myocardial ischemia, the presence of severe QT prolongation in this asymptomatic patient suggests that the SARS-CoV-2 virus itself may have intrinsic effects on cardiac repolarization.

Conclusion

This case suggests that significant electrophysiologic cardiac complications of SARS-CoV-2 infection can rarely occur even in asymptomatic individuals, who represent a significant portion of those with COVID-19, and may explain some of the increase in out-of-hospital cardiac arrest during the pandemic. High-risk individuals, including those with baseline prolonged QT interval and cardiac comorbidities, who contract SARS-CoV-2 may still be at risk of developing ECG abnormalities and arrhythmias, even in the absence of overt COVID-19 symptoms.

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