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CASE REPORT

BEGINNER

CLINICAL CASE SERIES

Acquired Long QT and Ventricular Arrhythmias in the Setting of Acute Inflammation

A Case Series

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ABSTRACT

We report a case series of 4 patients with transient marked QTc prolongation and ventricular arrhythmias in the setting of inflammation with very high ferritin levels. Three patients were positive for coronavirus disease-2019. In the setting of an acute rise in inflammatory markers, electrocardiography screening for QTc prolongation is warranted.

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Accumulating data implicate inflammation as a potential cause of acquired long QT syndrome (LQTS) (1,2). This case series highlights the importance of acute inflammation for QT prolongation in cases of acquired LQTS.

PATIENT #1

A 49-year-old man with thalassemia major complicated by iron overload due to chronic exchange transfusions and end-stage renal disease (ESRD) on hemodialysis presented with hypotension and fever. Echocardiography showed a preserved left ventricular (LV) systolic function, moderate LV hypertrophy, and a large circumferential pericardial effusion (2.7 cm) with tamponade physiology attributed to missed dialysis sessions. The patient underwent successful pericardiocentesis. Results of an infectious work-up, including for coronavirus disease-2019 (COVID-19), were negative, and he defervesced without antibiotic therapy. The hospital course was complicated by atrial fibrillation for which he was initiated on amiodarone. The patient's baseline QTc was 450 ms. Amiodarone was stopped after 24 h due to sinus bradycardia and acute QTc prolongation up to 687 ms (**Figure 1**), which led to several self-limiting episodes of torsades de pointes (TdP). Besides amiodarone, no other QT-prolonging medications were administered. Potassium and magnesium levels at the time of and leading up to QT prolongation and TdP were 4.6 to 6.1 mmol/l and 2.2 mg/dl, respectively.

LEARNING OBJECTIVES

- To appreciate the link between acute inflammation, transient QT prolongation, and ventricular arrhythmias.
- To highlight the importance of QT ECG surveillance in the setting of COVID-19 infection.

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The authors attest they are in compliance with human studies committees and animal welfare regulations of the authors' institutions and Food and Drug Administration guidelines, including patient consent where appropriate. For more information, visit the Author Center.

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ABBREVIATIONS AND ACRONYMS

ECG = electrocardiogram

ESRD = end-stage renal disease

LQT = long QT interval

LQTS = long QT syndrome

LV = left ventricular

TdP = torsades de pointes

TnI = troponin I

As a result of the patient's hemoglobinopathy and iron overload, his ferritin levels were chronically elevated ~10 to 15 times above normal levels. However, during this hospitalization, ferritin levels peaked at 45,927 ng/ml (>110 times the upper limit of normal), after which ferritin levels rapidly declined to baseline (Table 1). Troponin I (TnI) level peaked at 0.34 ng/ml, coinciding with the maximum QTc prolongation and ferritin elevation. Genetic testing was negative for pathogenic LQTS variants.

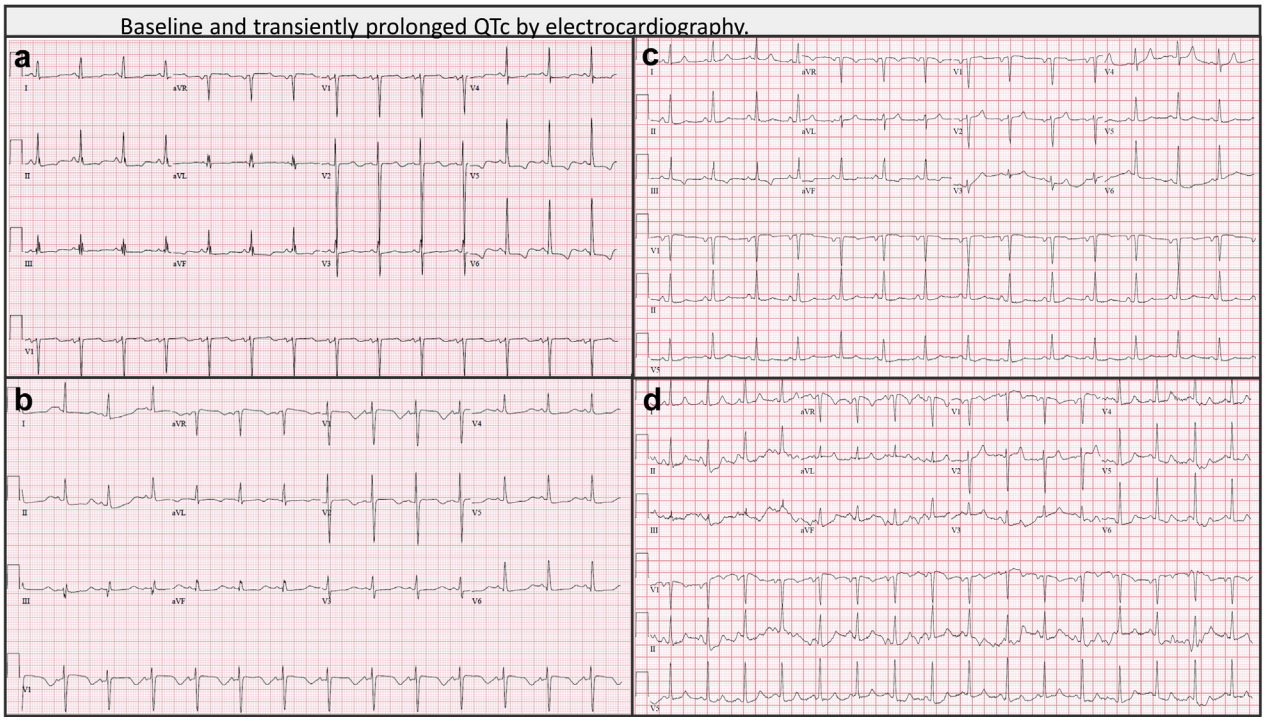
PATIENT #2

A 59-year-old woman with dementia presented to an outside hospital with respiratory distress and hypotension in the setting of COVID-19 infection. Given hypoxia, she underwent endotracheal intubation. An electrocardiogram (ECG) showed diffuse ST-segment depressions and a QTc interval of 393 ms. Thirty minutes after intubation, the patient developed ventricular fibrillation. After successful defibrillation, she was started on norepinephrine and vasopressin and was transferred to our facility. Intravenous vancomycin 1 g, cefepime 1 g, and azithromycin 500 mg were administered. An echocardiogram showed a LV ejection fraction of 70% to 75% and a moderate pericardial effusion. Her TnI level peaked at 3.24 ng/ml. Ferritin was found to be markedly elevated at 63,425 ng/ml (>150 times the upper limit of normal) (Table 1), and in this setting the patient's QTc interval prolonged to 586 ms. Within the next 4 days, her QTc normalized. Given refractory shock, the family withdrew care, and the patient died on hospital day 5.

PATIENT #3

A 50-year-old woman with a history of ESRD presented to the emergency department with tachycardia, cough, and shortness of breath and was found to be positive for COVID-19. She was empirically started on aztreonam 500 mg and doxycycline 100 mg twice daily. An echocardiogram showed an LV ejection fraction of 40% to 45%, severe mitral regurgitation, and a small circumferential pericardial effusion. Her TnI level was elevated at 0.22 ng/ml (Table 1). One

FIGURE 1 Electrocardiograms at Baseline and During Acute QTc Prolongation for Patient #1 and #4



Baseline **(a, c)** and transiently prolonged QTc **(b, d)** electrocardiogram for Patient #1 **(a, b)** and #4 **(c, d)**. QTc: **a**, 453 ms; **b**, 687 ms; **c**, 428 ms; **d**, 483 ms.

week into her hospitalization, the patient's ferritin levels rose from 2,881 ng/ml to 68,634 ng/ml accompanied by worsening respiratory failure requiring endotracheal intubation. During this time period, her QTc increased from a baseline of 446 to 490 ms. She later developed atrial fibrillation and was started on amiodarone. As ferritin levels decreased, her QTc shortened to baseline levels despite amiodarone. Her 10-week hospital course was complicated by bacteremia, fungemia, and septic shock, to which she ultimately succumbed.

PATIENT #4

A 64-year-old woman with ESRD, diabetes mellitus, and hypertension presented with fever (39.2°C), shortness of breath, and COVID-19 infection. Given bilateral pulmonary infiltrates, she was treated with ceftriaxone 1 g and azithromycin 500 mg daily. Her inflammatory markers were markedly elevated, including ferritin levels of 21,535 ng/ml (Table 1). Her TnI level was elevated at 0.12 ng/ml. An ECG showed a QTc of 483 ms, increased from a baseline of 440 ms (Figure 1C) in the absence of hypokalemia/hypomagnesemia or QT-prolonging medications other than azithromycin. An echocardiogram was not performed. She improved on supportive therapy and was discharged on hospital day 10.

TABLE 1 Relevant Bloodwork Results at the Time of Dramatic QT Prolongation and TdP

	Patient #1	Patient #2	Patient #3	Patient #4	Units	Reference Range
Cardiac						
TnI peak	0.34	3.24	0.22	0.12	ng/ml	<0.04
Metabolic panel						
Sodium	136	151	131	133	mmol/l	135-148
Potassium	5.1	4.5	4.1	4.8	mmol/l	3.5-5.1
Chloride	96	116	97	89	mmol/l	96-109
Carbon dioxide	21	13	23	21	mmol/l	21-31
Urea nitrogen	19	67	69	82	mmol/l	7-16
Creatinine	7.7	1.9	5.3	8.8	mg/dl	0.6-1.3
Calcium	7.5	7.2	8.7	8.1	mg/dl	8.4-10.5
Albumin	3	2.9	2.2	3.9	g/dl	3.5-5.3
Magnesium	2.2	2.5	1.9	2.2	mg/dl	1.6-2.4
pH	7.3^{V}	7.3^{A}	7.3^{A}	7.5^{V}		7.35-7.45
pCO_2	NA	59	46	NA	mm Hg	35-45
pO_2	NA	26.6	84	NA	mm Hg	75-100
Inflammation						
Ferritin peak	45,927	63,425	68,634	21,535	ng/ml	30-400
CRP*	NA	9.1	4.3	12.3	mg/dl	200-400
Interleukin-6*	NA	211.5	6,229.30	53.5	pg/ml	<10
ESR*	NA	NA	<1	NA	mm/h	1-29
WBC*	31.9	15.9	4.4	9.1	K/cu mm	4.5-11.0
Neutrophils*	82	81.7	77	84.8	%	31-76
Lymphocytes*	5	13.6	16	7.8	%	24-44
Body temperature*	36	41.3	37.5	38.2	Celsius	36-37.8

*Remainder of inflammatory markers and body temperature were measured at the time of peak ferritin levels. Superscript A and V designate arterial and venous blood gas samplings, respectively.

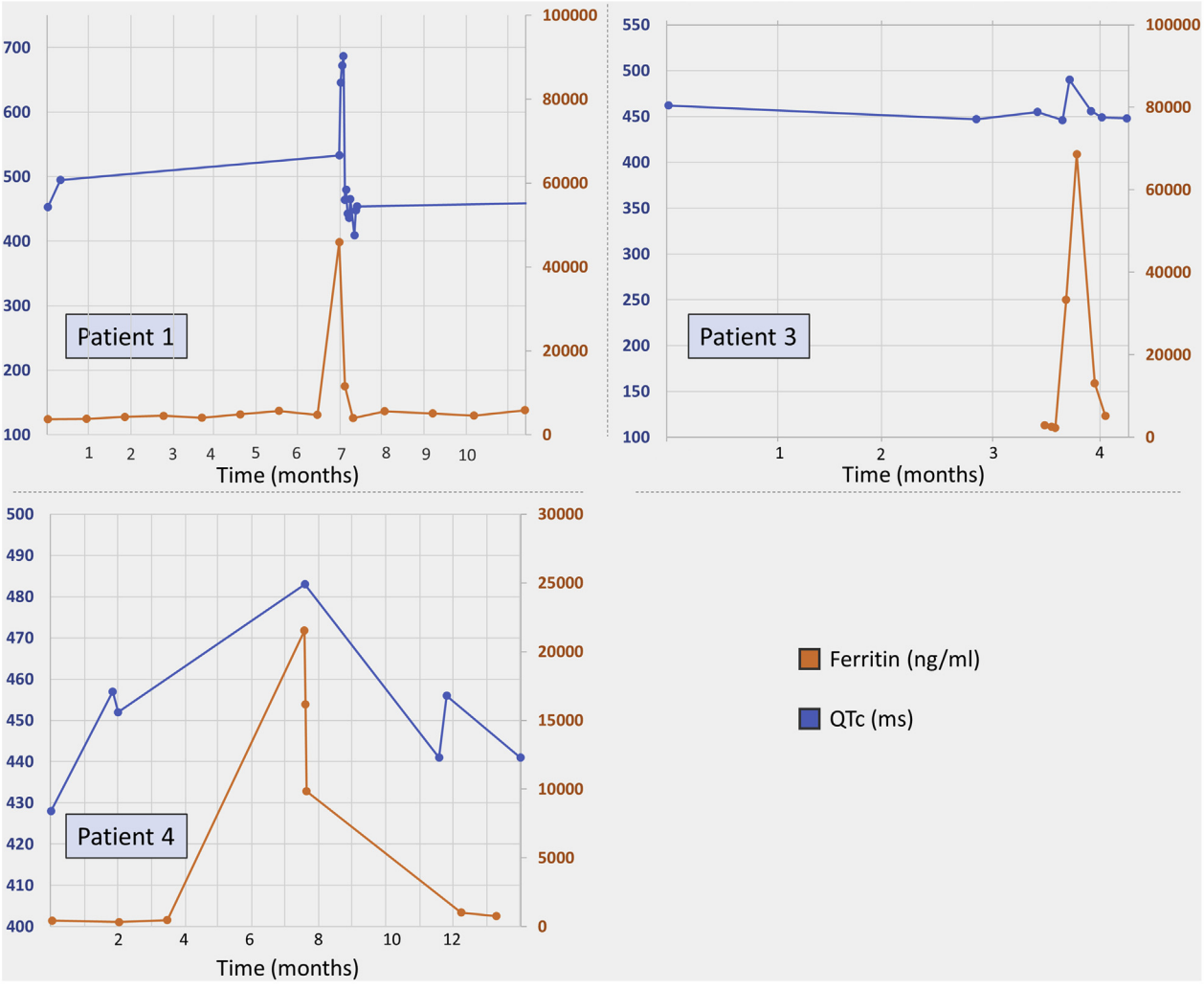
CRP = C-reactive protein; ESR = erythrocyte sedimentation rate; NA = not available; pCO_2 = partial pressure of carbon dioxide; pO_2 = partial pressure of oxygen; TdP = torsades de pointes; TIBC = total iron-binding capacity; TnI = troponin I; WBC = white blood cell.

DISCUSSION

We report a series of 4 patients with transient QT prolongation in the presence of very high inflammatory markers. In addition, evidence of acute or chronic kidney injury and myopericarditis with pericardial effusion was invariably present. Two patients developed ventricular arrhythmias.

Ferritin is primarily an intracellular iron storage protein, but it also has an important role as a stress response protein known to increase significantly in the presence of an infection. Of note, although patient #2, #3, and #4 presented with COVID-19 infection (3), the etiology of the rise in inflammatory markers in patient #1 remained elusive. Importantly, in this case series, electrolyte abnormalities, which are commonly associated with acquired LQTS, were not present (Table 1). QT-prolonging medications including azithromycin in patient #2 and #4 and amiodarone in patient #1 could have contributed to the QTc prolongation; however, the transient rise of QTc observed in patient #1 is inconsistent with the long half-life of amiodarone, and amiodarone administration was also not correlated with QT prolongation in patient #3. We believe that the acute inflammation in patient #1 led to a transient reduction of the repolarization reserve, thus exacerbating amiodarone's QT-prolonging effect during the brief period of acute inflammation (Figure 2). This is consistent with the "multiple hit hypothesis" (4,5) in acquired LQTS in which multiple QT-prolonging conditions must occur simultaneously to lead to significant QT prolongation and TdP. Although we cannot exclude that the hypoxia seen in patient #2 led to myocardial ischemia and contributed to QT prolongation, the mild degree of TnI elevation and the absence of significant ST-T-wave changes in the remaining 2 patients make myocardial ischemia as a main contributor to QT prolongation unlikely. Similarly, although QTc prolongation in myocarditis has been associated with an increased risk of adverse outcomes, QTc prolongation is seen in a minority of myocarditis patients and is more likely a reflection of

FIGURE 2 Temporal Association Between the Acute Rise in Ferritin and QT Interval Prolongation



Available QTc interval and blood ferritin measurements are plotted over time for patient #1, #2, and #4. Insufficient blood ferritin measurements did not allow graphical display of QTc and ferritin over time for patient #2.

the underlying inflammatory process than a sequitur of the resulting myocardial injury (6). Interestingly, a genetic LQTS panel was negative in patient #1, who exhibited the longest QTc interval.

Accumulating data indicate inflammatory activation as a potential cause of acquired LQTS. The putative cytokine-mediated mechanisms are complex and include both direct actions on cardiomyocyte ion channel function and indirect effects resulting from sympathetic activation (2,7). A recent study showed that the inflammatory marker interleukin-6 (IL-6) was sufficient to cause QT prolongation via suppressing the delayed rectifier K current, I_{Kr}. Block of IL-6 receptor or Janus kinase reversed the inhibitory effects of IL-6 on I_{Kr} (8). Clinical studies are needed to determine whether anti-inflammatory medications, including corticosteroids and tocilizumab, could be of therapeutic benefit in cases of acquired LQT in the setting of cytokine storm.

We conclude that acute inflammation is a clinically important QT-prolonging condition. In the setting of an acute rise of inflammatory markers, ECG screening

for QTc prolongation is warranted, and QT-prolonging drugs should be avoided.

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