Case Report

Post Myocardial Ischemia-Associated Torsades De Pointes in a Patient Carrying a KCNQ1 G643S Variant

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Abstract

Polymorphic ventricular tachycardia, which occurs during the subacute phase of myocardial infarction (MI) or ischemia and is not related to ongoing ischemia, has recently been reported. It has characteristics of typical pause-dependent torsades de pointes (TdP) following excessive QT prolongation (post MI/ischemia-associated TdP). We describe a male patient with post MI/ischemia-associated TdP. The patient experienced recurrent TdP with excessive QT prolongation 2 days after transient myocardial ischemia. Genetic screening of the major LQTS-causing genes identified a KCNQ1 G643S variant. This gene variant could be a genetic predisposition to the development of TdP during the subacute phase of MI/ischemia.

Key words: myocardial infarction, myocardial ischemia, torsades de pointes, long QT syndrome, KCNQ1


Introduction

Polymorphic ventricular tachycardia (VT) or ventricular fibrillation remains the major cause of sudden death in association with acute myocardial infarction (MI) or ischemia. There are at least two distinct etiologies of polymorphic VT during the acute phase of MI/ischemia. Polymorphic VT during the hyperacute phase of MI/ischemia, which is clearly related to ongoing ischemia and is not associated with QT prolongation, accounts for the majority of those related to acute MI/ischemia. On the other hand, another rare form of acute MI/ischemia-related polymorphic VT, which occurs during the subacute phase (a few days after ongoing ischemia) and is not related to ongoing ischemia, has recently been reported (1, 2). The latter has characteristics of typical pause-dependent torsades de pointes (TdP) following excessive QT prolongation, thus it is thought to be a variant of the acquired long QT syndrome (post MI/ischemia-associated TdP) (1). As in other forms of acquired long QT syndrome, there may be a genetic predisposition to the development of post MI/ischemia-associated TdP (3).

Here, we present a male patient with post MI/ischemia-associated TdP, who had never had any prior evidence of congenital long QT syndrome (LQTS). The patient experienced recurrent polymorphic VT, TdP, with excessive QT prolongation 2 days after transient myocardial ischemia. Genetic screening of major LQTS-causing genes identified a KCNQ1 G643S variant.

Case Report

A 73-year-old man, who had been suffering from atrial fibrillation for several weeks, was admitted to the hospital to undergo defibrillation. His 12-lead ECG presented with rapid atrial fibrillation (heart rate: 140 bpm) with QTc interval of 390 ms (Fig. 1A). His chest X-ray showed cardiomegaly, congestion in lung field, and bilateral pleural effusion (Fig. 1B), although he had been asymptomatic. A blood test revealed that brain natriuretic peptide (396.7 pg/mL) was elevated, but there were no other abnormalities including electrolytes. Echocardiography revealed that the left ventricular wall motion was not impaired (ejection fraction: 56%), whereas moderate functional mitral regurgitation was observed. Because the patient had been taking warfarin for over 4 weeks, the patient underwent direct current countershock (DCC: 150 J), without performing transesophageal echocardiography, two times after intravenous infusion of
Figure 1. (A) 12-lead ECG, and (B) chest X-ray on admission. (C) Time-dependent ECG changes before the occurrence of torsades de pointes (TdP). 12-lead ECGs recorded before direct current countershock (DCC), at 20, 28, and 44 hours after DCC.

Polysicainide (50 mg); then his heart-beat recovered to sinus rhythm. Because of congestive heart failure, possibly induced by the prolonged rapid atrial fibrillation, carperitide (0.05 μg/kg/min) was administered and diltiazem (3 mg/h) was also administered in order to decrease his heart rate. The congestive heart failure gradually improved; however, his heart-beat returned to atrial fibrillation again at 20 hours after DCC. At that time his 12-lead ECG presented with ST-segment elevation in leads V2, 3 with T-wave inversion (Fig. 1C). ST-segment elevation was followed by excessive QT prolongation (QTc: 665 ms, at 44 hours after DCC) with T-wave inversion in leads V1-4 (Fig. 1C), although the patient had been asymptomatic.

Polysicainide VT began to occur repetitively 44 hours after DCC. The initiation sequence and QRS morphology of polysicainide VT had the characteristics of torsades de pointes. It initiated after a long-short sequence accompanied with a post-pause prominent U wave (Fig. 2). There was no electrolyte disturbance (K: 3.6 mEq/L, Ca: 9.2 mg/dL, Mg: 1.7 mg/dL) associated with TdP. Time-dependent ECG changes suggested that myocardial ischemia had been present, although the patient had been asymptomatic. Therefore, emergent coronary angiography was performed. Fifty percent stenosis was present in the proximal portion (segment 6) of the left anterior descending (LAD) artery, and 50-75% stenosis in the middle portion (segment 7) of the LAD artery. Although the stenosis of coronary artery was not significant, intra-aortic balloon pumping (IABP) was inserted, and a lidocaine infusion (1 mg/min) was started. The repetitive TdP ceased to occur after the insertion of IABP and lidocaine infusion. Echocardiography showed a moderate reduction in the antero-septal wall motion. Creatine kinase (CK) was slightly elevated after this episode (maximum CK: 401 IU/L).

The prolongation of the QT interval with inversion of T-wave in leads V1-4 had been normalized (QTc: 420 ms) 4 days after DCC (Fig. 3A). Thereafter, the IABP was removed, and lidocaine infusion was stopped. Carperitide and diltiazem infusion were also stopped after improvement of the congestive heart failure. His heart-beat spontaneously returned to sinus rhythm, and a drug provocation test was administered. Epinephrine, administered by Shimizu protocol (4), did not prolong the QTc interval (Fig. 3B). Polysicainide (50 mg) did not exhibit ST-segment elevation or QT prolongation or T-wave inversion in precordial ECG leads (Fig. 3C).

Genetic screening of six major LQTS-causing genes, including KCNQ1, KCNH2, SCN5A, KCNJ2, KCNE1, and KCNE2, was conducted after obtaining the appropriate approval from the institution review board and written informed consent from the patient. Although no mutations were identified, two nonsynonymous single nucleotide polymorphisms, a KCNQ1 G643S variant (heterozygous), which has been reported to be a modifier gene variant to predis-
Figure 2. TdP recorded in 12-lead ECG (A) and ECG monitors (B). TdP initiated after long-short sequence accompanied with post-pause prominent U wave (red arrows).

Figure 3. (A) Normalization of ECG after the occurrence of TdP. 12-lead ECGs recorded on 3, 4, and 7 days after DCC. QT prolongation and T-wave inversion were normalized 4 days after DCC. (B) Epinephrine provocation test. QTc interval of baseline and peak during epinephrine infusion was 426 ms and 447 ms, respectively. (C) Pilsicainide provocation test.

pose some set of patients to excessive QT prolongation (5) genes (Fig. 4), and a KCNE1 S38G variant (homozygous), which has been reported not to be related to prolongation of the QT interval in healthy subjects (6), were identified in these
eventually normalized. These time-dependent ECG changes T-wave inversion in leads V1-4, and these ECG changes ECGs presented with transient ST-segment elevation in the pause-dependent TdP.

diltiazem might also induce susceptibility to the initiation of lemia (K: 3.6 mEq/L) and a reduction of the heart rate by transient myocardial ischemia in the present case is consistent with post MI/ischemia-associated TdP. A slight hypokalemia (K: 3.6 mEq/L) and a reduction of the heart rate by diltiazem might also induce susceptibility to the initiation of pause-dependent TdP.

Discussion

Although the patient had been asymptomatic, his 12-lead ECGs presented with transient ST-segment elevation in the precordial leads, followed by transient QT prolongation with T-wave inversion in leads V1-4, and these ECG changes eventually normalized. These time-dependent ECG changes that occurred after DCC strongly suggest that he had had transient myocardial ischemia in the LAD artery. There have been several reports describing the induction of coronary artery spasm by DCC (7, 8). Therefore, it seems quite reasonable to assume that he had had a transient myocardial ischemia due to an LAD artery spasm induced by DCC. Otherwise, it might also be possible to speculate that acute coronary artery thromboembolism had occurred after DCC, followed by spontaneous reperfusion.

One rare form of acute MI/ischemia-related polymorphic VT, which occurs during the subacute phase (a few days after acute MI/ischemia) and is not related to ongoing ischemia, has been reported (post MI/ischemia-associated TdP) (1, 2). It has characteristics of typical pause-dependent torsades de pointes following excessive QT prolongation, and is thought to be clearly different from that which occurs during the hyperacute phase of MI/ischemia and is related to ongoing ischemia (1). It is also different from polymorphic VT after MI originating from local Purkinje network, which is not associated with QT prolongation (9). The occurrence of typical TdP with excessive QT prolongation 2 days after transient myocardial ischemia in the present case is consistent with post MI/ischemia-associated TdP. A slight hypokalemia (K: 3.6 mEq/L) and a reduction of the heart rate by diltiazem might also induce susceptibility to the initiation of pause-dependent TdP.

Hu et al reported that loss-of-function SCN5A mutation, G400A, is associated with the development of an arrhythmic storm during the hyperacute phase of ischemia (10). On the other hand, as in other forms of acquired long QT syndrome, Hu et al also hypothesized that there might be a genetic predisposition to develop post MI/ischemia-associated TdP (3). They screened major LQTS-causing genes and detected a KCNH2 K897T variant in 6 (75%) of 8 patients who developed TdP after MI (3). Although the functional effects of the K897T variant remain controversial (11-13), they presumed that the variant might contribute to the development of TdP. A genetic analysis of the present patient identified a KCNQ1 variant, G643S. The allele frequency of the G643S variant has been reported to be approximately 10%, detected primarily in Asians and Blacks in comparison to Whites or Hispanics, and is thought to be a common polymorphism (14, 15). However, Kubota et al reported that carriers of the G643S variant are at higher risk for life-threatening arrhythmias in the presence of appropriate precipitating factors, such as bradycardia and hypokalemia (5). A functional analysis revealed that the G643S variant reduced approximately 30% of the function of KCNQ1/KCNE1 channels, whereas the reduction is less than other long QT syndrome type 1-associated KCNQ1 mutations (5). Therefore, carriers of the G643S variant are thought to have a mild phenotype in the absence of precipitating factor(s) for QT prolongation. Indeed, the patient had never had any prior evidence of LQTS before experiencing myocardial ischemia, and had a normal response of the QT interval to Epinephrine provocation.

A rat experimental model of MI showed that downregulation of potassium channel gene expression (ERG, KCNE1, KCNQ1) and potassium currents (IKr, IKs) occurs in surviving myocytes from infarct zone 2 days after MI (16). This suggests that major repolarizing currents, IKr and IKs, may be reduced in the actual setting of the subacute phase of MI/ischemia in humans, which may contribute to the prolongation of repolarization and the development of TdP. Therefore, it is conceivable that genetic variants, such as KCNQ1 G643S, which cause a mild reduction of repolarizing currents and mild phenotype in the absence of precipitating factor(s) for QT prolongation, but are unmasked by the additional reduction of repolarizing currents during acute MI/ischemia, may be a genetic background for the development of post MI/ischemia-associated TdP. Since the KCNQ1 G643S variant is relatively common in Asians and Blacks (15), this variant may be a major underlying genetic factor for post MI/ischemia-associated TdP in these races. However, not all KCNQ1 G643S variant carriers always experience TdP in the setting of subacute phase of MI/ischemia, and therefore additional factor(s) may also contribute to the development of TdP.

In conclusion, the KCNQ1 G643S variant was detected in a patient with post MI/ischemia-associated TdP. This gene variant could be a genetic predisposition to the development of TdP during the subacute phase of MI/ischemia. Since this
gene variant is primarily detected in Asians and Blacks (15), there may be an ethnic difference in the genetic background of the disease. Therefore, our data may facilitate clarification of whether or not carriers of the G643S variant indeed have an increased risk for developing post MI/ischemia-associated TdP.

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References