Medical Castration is a Rare but Possible Trigger of Torsade de Pointes and Ventricular Fibrillation

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Summary

Prostate cancer is the most common non-cutaneous malignancy in men and has been steadily rising in an aging society. Medical castration therapy is effective for metastatic prostate cancer, but the proarrhythmic properties have not been reported. We present a 71-year-old Japanese man with metastasis prostate cancer that, during medical castration therapy, had torsades de pointes (TdP) with a QT prolongation and ventricular fibrillation (VF). His QT interval diminished after discontinuing the medical castration, and he developed no further VF recurrences for 15 months. Medical castration is a rare but possible trigger of TdP with QT prolongation and VF.

Key words: Long QT syndrome, QT prolongation

Torsades de pointes (TdP) is a life-threatening arrhythmia associated with prolongation of the QT interval. Numerous drugs, including widely used antibiotics, antidepressants, cardiovascular drugs, and many others, can cause prolongation of the QT interval, alone or in combination, potentially leading to TdP.1) Recent studies have suggested that sex hormones, including testosterone, influence cardiac repolarization and control of the QT intervals.2-4) Therefore, the use of drugs affecting the testosterone status may cause QT prolongation and TdP. Medical castration therapy is effective for metastatic prostate cancer,5) but the proarrhythmic properties have not been reported. We describe for the first time a case of a medically castrated man in whom testosterone was strongly suppressed with the development of prominent QT prolongation, TdP, and ventricular fibrillation (VF).

Case Report

A 71-year-old man with metastatic prostate cancer was admitted to our hospital with repeated palpitations and dizziness attacks. The patient also presented with dyspnea on exertion for 3 months and leg edema for 10 days. He had undergone medical castration therapy (gonadotropin releasing hormone agonists [Leuprolin injection, 11.25 mg per 12 weeks] and anti-androgens [Bicalutamide oral administration, 80 mg per day]) for 6 months. He had no risk of cardiovascular disease or family history of cardiac disease, including sudden death or QT prolongation.

Eleven months before the medical castration, his 12 lead ECG showed sinus rhythm, complete right bundle branch block, and a normal QT interval range (QT/QTc = 438/431 ms; Figure 1A). The chest X-ray was normal (cardiothoracic ratio [CTR] = 47%) without any congestion. At that time, echocardiography demonstrated a normal left ventricular (LV) wall motion (ejection fraction [EF] = 57%) with a dilated LV chamber size (end-diastolic internal dimension = 57 mm). The peak early filling (E-wave) and late diastolic filling (A-wave) velocities of the mitral inflow were 52.4 cm/second and 83.4 cm/second, respectively. The ratio of the E-wave to A-wave for the diastolic mitral inflow (E/A ratio) was 0.6 (normal range [elderly people], < 1.0) and the deceleration time (DcT) of the mitral E-wave 268 ms (normal range, > 140), suggesting an impaired relaxation pattern of the LV.6)

On admission, his consciousness level was clear, and his plasma electrolyte levels, including potassium level (4.5 mEq/L), albumin-collected serum calcium level (9.6 mg/dL; normal range, 8.8-10.1 mg/dL), and magnesium level (2.1 mg/dL; normal range, 1.7-2.7 mg/dL), were within normal range. The plasma brain natriuretic peptide (BNP) level increased up to 673 pg/mL (normal range: < 18.4 pg/mL). The biochemical markers, including troponin T, creatinine kinase (CK), CK-MB, aspartate aminotransferase, and alanine aminotransferase, were not elevated. The plasma testosterone level was suppressed to a level of 0.26 ng/mL (normal range: 1.92-8.84 ng/mL). The 12-lead
Figure 1. A: Twelve lead ECGs before the medical castration, on admission, and 40 days after cessation of the medical castration. B: Tracings of the bedside continuous single lead ECG monitoring after admission. (Upper tracing) Torsade de pointes (TdP) spontaneously occurred with typical initiating “short-long-short” sequences. (Lower tracing) Ventricular fibrillation occurred during transvenous ventricular pacing. The arrowheads and arrows indicate premature beats and ventricular paced beats, respectively.

ECG exhibited normal sinus rhythm, complete right bundle branch block, a leftward axis, negative T waves in leads V2-V6, and QT prolongation (QT/QTc = 494/516 ms) (Figure 1A). A chest X-ray demonstrated moderate cardiomegaly (CTR = 66%) and congestion (Figure 2A). Echocardiography disclosed LV dilatation with an end-diastolic internal dimension of 66 mm and diffusely hypokinetic LV wall motion with an EF of 21% (Figure 2B). The peak E-wave velocity increased to 84.7 cm/second, but the peak A-wave velocity decreased to 17.7 cm/second. The E/A ratio increased to 4.8 and DcT shortened to 167.8 cm/second, suggesting a restrictive pattern of the LV.6)

 Shortly after admission, intermittent runs of TdP initiating “short-long-short” sequences (Figure 1B, upper panel) and VF developed. He was treated with overdrive transvenous ventricular pacing (90 pacing/minute), and the medical castration therapy was stopped. However, he still had frequent ventricular premature beats, which caused frequent runs of TdP, and premature beats triggering VF recurred (Figure 1B, lower panel). Finally, an intravenous landiolol infusion suppressed the premature beats and VF. Coronary angiography showed no significant stenoses of the coronary arteries. No abnormal findings were found in
Figure 2. A: Chest X-rays on admission and 40 days after cessation of the medical castration. B: Two-dimensional echocardiography on admission and 1 year after cessation of the medical castration. Ao indicates aorta; LA (V), left atrium (ventricle); and RV, right ventricle.

late gadolinium enhanced MRI, 18F-FDG PET imaging, or 99mTc-pyrophosphate scintigraphy. The patient refused an endomyocardial biopsy.

DNA screening, including of KCNQ1, KCNH2, SCN5A, ANK2, KCNE1, KCNE2, KCNJ2, CACNA1C, CAV3, SCN4B, AKAP9, SNTA1, and KCNJ5, demonstrated that the patient had no mutations related to long QT syndrome. He was diagnosed with latent long QT syndrome with congestive heart failure due to medical castration. He received an implantable cardioverter-defibrillator with atrial overdrive pacing (80 pacing/minute), and received an oral administration of β-blockers (bisoprolol, 2.5 mg per day). He was also treated with diuretic agents and an angiotension-converting enzyme inhibitor. Forty days later (at the time of discharge), his QT interval dramatically shortened (QT/QTc = 407/472 ms; Figures 1A, 3A) and the CTR improved (Figure 2A). The BNP level decreased to 41 pg/mL (Figure 3B). However, the hypokinetic LV wall motion did not change (EF = 31%).

Fifteen months after cessation of the medical castration, the testosterone level gradually elevated, but the level was under the normal range (Figure 3A). Although his QT interval was normal, the QTc interval was slightly prolonged, and it did not completely recover (Figure 3A). The LV wall motion improved to the level of that before
Discussion

It is well-known that men have a shorter and faster cardiac repolarization and less risk of arrhythmias associated with long QT syndrome, such as TdP or VF, than women. The gender difference in the sex hormones is considered to be the main reason for this sex difference of lethal arrhythmias. It is now becoming clear that sex hormones, including testosterone, play an important role in cardiac repolarization and the control of the QT intervals. The non-genomic action of testosterone regulates the cardiac ion channels that contribute to the cardiac repolarization process and control of the QT intervals. Medical castration, an androgen-deprivation therapy, is the mainstay treatment of patients with advanced prostate cancer, and strongly suppresses testosterone. Therefore, medical castration could affect the QT intervals. Only two studies have reported the relationship between castration and QT intervals: one study reported that there were longer QTc intervals in castrated men than in non-castrated men. Another study revealed that medical and surgical castration results in prolonged QT intervals in castrated men. However, to the best of our knowledge, there have been no reports of medical castration causing TdP or VF. In the present case, marked QT prolongation, TdP, and VF occurred during medical castration, and disappeared shortly after cessation of the medical castration, indicating that the medical castration caused the TdP and VF.

It might be difficult to precisely explain why this patient presented with marked QT prolongation during the medical castration, leading to TdP and VF. However, several factors might have played an important role in the development of that in this patient. First, as described above, with the decreased testosterone level, as well as other ac-
tions as yet undetermined precisely, the medical castration using gonadotropin releasing hormone agonists with/without anti-androgens caused the prolongation of the QT interval. In fact, a previous study\textsuperscript{15} reported that a marked prolongation of the QTc interval occurs in 1% of patients who receive leuprolerin. Second, the medical castration-induced cardiac dysfunction and overt heart failure exaggerated the prolongation of the QT intervals. Before the medical castration, the patient had a slightly dilated LV with a normal wall motion. An impaired relaxation pattern of the LV, which might be normal in elderly people, was also present.\textsuperscript{6,14} We did not perform any tissue velocity\textsuperscript{13} or strain imaging\textsuperscript{14,16} in this patient. However, all of those measurements indicated that the patient might have subclinical diastolic dysfunction before the castration therapy. On admission with the castration therapy for 11 months, the patient developed overt heart failure with systolic dysfunction. Testosterone plays a role in the cardiomyocyte Ca\textsuperscript{2+} handling and cardiac contractility.\textsuperscript{71} In recent studies, it was also shown that bicalutamide, medical castration, and suppressing or blocking testosterone are significant and great risk factors for hypocontractility and heart failure.\textsuperscript{2,14-20} In this patient, under the presence of subclinical diastolic dysfunction, the medical castration therapy might have worsened the cardiac function and caused the overt heart failure with systolic dysfunction. With cessation of the castration therapy, the prolonged QT interval and depressed ventricular function improved in parallel with an increase in the serum testosterone level, which supported the idea. A recent study demonstrated that sensitivity to the marked prolongation of the QT interval, and, finally, resulted in TdP and VF. Third, there still was the possibility of a genetic factor that was vulnerable to QT prolongation during the medical castration. The DNA screening did not reveal any common mutations related to long QT syndrome. However, although this idea was only speculative, this patient might have had other genetic factors that were vulnerable to QT prolongation during the medical castration and that were as of yet undetermined.

In the present case, the heart failure rapidly compensated with the administration of drugs for heart failure. However, it took 11 months for the LV function to improve to the same level of that before the medical castration, and the QTc and testosterone did not completely recover to the level of that before the medical castration at the 15-month follow-up. We think that, even after the cessation of the medical castration, it continued to act long term on the myocardium and/or might have caused some irreversible damage to the ventricular myocardium.

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**Disclosures**

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**References**
