Loperamide Toxicity Revealing Apical Hypertrophic Cardiomyopathy

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ABSTRACT: Loperamide, a μ-opioid receptor agonist, can cause cardiotoxicity by inhibiting the potassium ion channel and slowing cardiomyocyte repolarization. This, in turn, can lead to frequent early afterdepolarizations, the most common mechanism of drug-induced long QT syndrome and torsades de pointes. Apical hypertrophic cardiomyopathy (AHCM) is a nonobstructive hypertrophic cardiomyopathy rarely associated with malignant arrhythmias. We present a case of loperamide-induced malignant ventricular arrhythmia revealing underlying AHCM in a 25-year-old woman with a history of sudden cardiac arrest (SCA) and opioid use.

It is important to evaluate for structural heart disease in all patients presenting with SCA, regardless of presumed etiology such as drug-induced cardiotoxicity, to prevent missed opportunities for adequate treatment. Furthermore, the diagnosis of AHCM in SCA warrants further genetic evaluation for variances with a predilection for malignant arrhythmias.

BACKGROUND

Apical hypertrophic cardiomyopathy (AHCM) involves nonobstructive apical thickening of the left ventricle and is rarely associated with malignant arrhythmias. It is twice as prevalent in men than in women and accounts for up to 25% of all HCM cases.[1] As an autosomal dominant disorder, AHCM pathogenesis involves mutations in more than 10 genes encoding sarcomeric proteins, and these genes have been identified in 70% of nonfamilial cases and 30% of familial cases.[1,2] However, AHCM is known to have fewer identified genetic variances than HCM.

The opioid epidemic became a public health emergency in early 2017 when it led to more than 40,000 deaths, more than any year prior according to the Centers for Disease Control and Prevention. Patients with opioid use disorder have been observed ingesting high doses of loperamide, which is a weak μ-opioid receptor agonist typically used in symptomatic treatment of diarrheal illnesses. Loperamide is often used to achieve the same altered sensorium as recreational use of prescription opioids; however, such high doses increase the risk of cardiotoxicity from malignant ventricular arrhythmias. Although the exact mechanism of loperamide-induced cardiotoxicity is unknown, it is thought to involve the blockade of the potassium ion channel (IKr) through dose-dependent inhibition of the human ether-a-go-go-related gene (hERG), which encodes a subunit of IKr based on animal studies.[3] Blockade of IKr slows cardiomyocyte repolarization, leading to frequent early afterdepolarizations, the most common mechanism of drug-induced long QT syndrome and Torsades de Pointes. To the best of our knowledge, we describe the first case of loperamide-associated malignant ventricular arrhythmia revealing AHCM, with a possible clinically significant heterozygous copy number variant in the KCNA5 gene encoding a subunit of IKr.

CASE REPORT

A 25-year-old woman with a history of sudden cardiac arrest (SCA) and opioid use presented at Houston Methodist with palpitations. She had been discharged from an outside hospital 2 days prior after receiving treatment with medical therapy for ventricular tachycardia (VT) arrest in the setting of chronic loperamide abuse (ingested 400 mg daily for 3 years). She denied past syncopal episodes or family history of SCA.

On admission to our facility, her vital signs and physical examination were normal. Electrocardiography (ECG) revealed QT prolongation and giant inverted T waves in V4-V6 (Figure 1), raising suspicion for AHCM. Subsequent transthoracic echocardiogram showed left ventricular (LV) hypertrophy of the apical segments. Cardiac magnetic resonance imaging (CMR) confirmed the diagnosis of AHCM with the classic "ace of spades sign" at end-diastole and localized hypertrophy of the apical septum (Figure 2). The maximum LV wall thickness measured 19 mm in the anteroseptal segment. The total scar burden involved 6% of LV mass with focal late gadolinium enhancement seen in the apical, septal, and basal inferolateral LV wall segments.[4] LV systolic function was normal (LV ejection fraction = 62%, end-diastolic volume = 118 mL/m^2, end-systolic volume = 45 mL/m^2), with obliteration of the apical ventricular cavity at end-systole. Right ventricular (RV) systolic function was mildly decreased globally (RV ejection fraction = 48%). There

was no evidence of systolic anterior motion of the mitral valve leaflet or LV outflow tract obstruction.

Continuous cardiac monitoring did not detect any episodes of nonsustained VT during hospitalization. The patient was discharged with metoprolol succinate 12.5 mg daily and a wearable cardioverter defibrillator. At a follow-up visit with a cardiologist, genetic testing revealed heterozygosity for a variant of uncertain clinical significance in the KCNA5 gene, which encodes a subunit of the voltage-gated potassium channel Kv1.5.

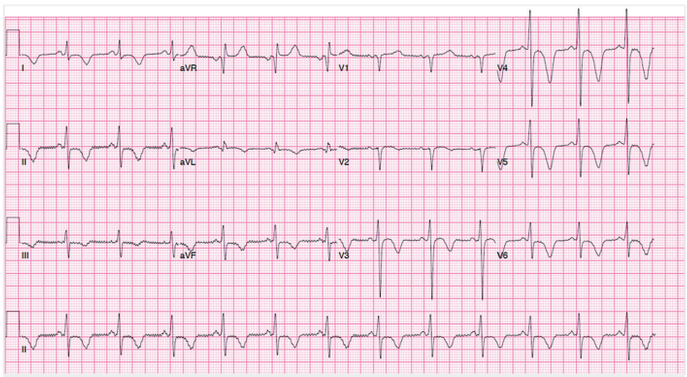

Figure 1.
A 12-lead electrocardiogram showing giant, inverted T waves (> 10 mm) in V4-V6 and QT interval prolongation (QTc = 506 ms).

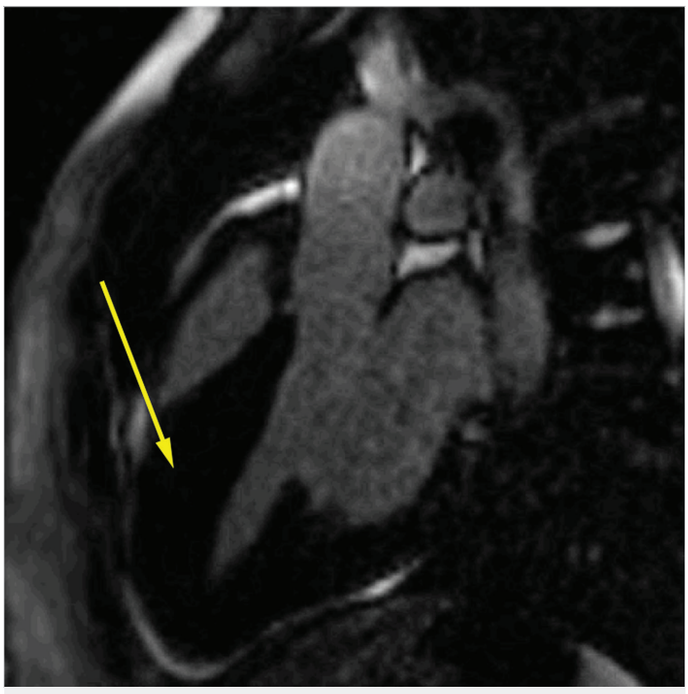

Figure 2.
Cardiac magnetic resonance imaging demonstrating localized apical hypertrophy and the "ace of spades" sign at end-diastole (arrow). Maximum left ventricular (LV) wall thickness is 19 mm in the anteroseptal segment. Focal late gadolinium enhancement is seen in the apical, septal, and basolateral walls with total scar burden involving 6% of LV mass.

Three months later, the patient presented with palpitations again. She reported abstinence from loperamide, and a urine drug screen was negative for opioid metabolites. A 12-lead ECG showed a corrected QT interval measuring 463 ms and the same inverted T-waves in the anterolateral leads (Figure 3). After continuous cardiac monitoring revealed no dysrhythmias over 48 hours, she was discharged home. The patient followed up with an electrophysiologist and underwent successful Boston Scientific Emblem MRI subcutaneous implantable cardioverter-defibrillator (S-ICD) placement 3 months later in the setting of a genetic variance with a possible predisposition for high arrhythmogenic burden. No ICD shocks have occurred since implantation.

DISCUSSION

This case illustrates the successful diagnosis of a possible arrhythmogenic variant of AHCM after a malignant ventricular arrhythmia occurring in the setting of high-dose loperamide. Although the patient's classic ECG findings ultimately initiated the workup that resulted in the AHCM diagnosis, the diagnosis was delayed because she was not evaluated for structural heart disease after she was stabilized at the outside hospital. The European Society of Cardiology recommends resting ECG as the initial screening modality for AHCM due to its high sensitivity and giant inverted T waves (> 10 mm) in the anterolateral leads. AHCM diagnostic criteria comprises an apical wall thickness > 15 mm and a ratio > 1.5 of apical to basal maximum LV short-axis thickness on echocardiography or CMR.[4]

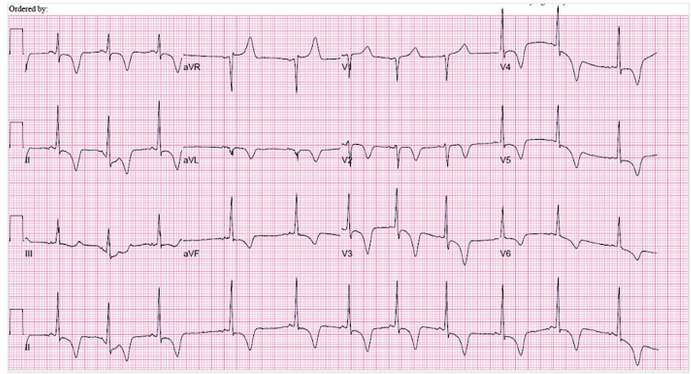

Figure 3.
A 12-lead electrocardiogram showed a corrected QT interval measuring 463 ms and the same inverted T-waves in the anterolateral leads.

Although most cases of loperamide-induced arrhythmias involve ingestion of 60 to 400 mg daily and feature either QRS or QT interval prolongation, loperamide cardiotoxicity is an unusual cause of SCA.[5] However, loperamide overdose was thought to have precipitated the SCA in this patient, with a variant of AHCM possibly with a higher predisposition for malignant ventricular arrhythmias.

While AHCM is rarely associated with fatal arrhythmias due to its dependence on genetic pathogenesis, it is crucial to investigate specific cardiac genes that may impact the action potential to understand the etiology of SCA in our patient. An autosomal dominant disorder, AHCM is most commonly associated with mutations in genes ACTC1, TPM1, MYBPC3, and MYH7, in which a variety of sarcomeric proteins are encoded with altered function, thus resulting in an increased risk of SCA.[1] Recent studies suggest that mutations in genes encoding ion channels may increase the arrhythmogenicity of certain previously recognized "benign" variants. This patient has genetic heterozygosity of the KCNA5 gene that encodes a subunit of the voltage-gated potassium channel Kv1.5. This channel is predominantly located in the intercalated disks of myocytes in the atria but may be found in ventricles. Mutations in this channel are known to be arrhythmogenic in rat models.[6] One study suggested that two N-terminal mutations of KCNA5, P91L, and E33V may functionally impact the heart through extracellular manipulation of protein binding, increasing the propensity of developing malignant arrhythmias.[6]

While published investigations of KCNA genes are limited, studies have linked mutations of other genes encoding IKr subunits, such as the KCNE gene family. KCNE genes are responsible for encoding β subunits of potassium ion channels. An animal model highlighted rare genetic variants, p.M1T in KCNE3 and p.E141A in KCNE4, that are potentially associated with arrhythmogenicity by altering charge potentials of these potassium channels.[7] Additionally, two other variants, p.D85N in KCNE1 and p.T8A in KCNE2, are linked with drug-induced ventricular fibrillation. While these studies do not provide direct evidence of genetic mutations altering cardiac electrophysiology in humans, they demonstrate the need for further research elucidating mutations that contribute to malignant arrhythmias in AHCM.

CONCLUSION

It is important to evaluate for structural heart disease in all patients presenting with SCA—regardless of presumed etiology, such as drug-induced cardiotoxicity—to prevent missed opportunities for adequate treatment. Furthermore, the diagnosis of AHCM in SCA warrants further genetic evaluation for variances with a predilection for malignant arrhythmias.

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