JACC: CASE REPORTS VOL. 4, NO. 5, 2022

CASE REPORT

INTERMEDIATE

CLINICAL CASE

Recurrent Myocardial Infarction in a Patient With MINOCA and a Negative Ergometrine Provocation Test

Hana Mizutani, MD, Shiro Nakamori, MD, Tairo Kurita, MD, Kaoru Dohi, MD

ABSTRACT

This case highlights the diagnostic challenge associated with coronary vasospasm, especially when accompanied by no provoked spasms on the ergometrine test in the acute setting of myocardial infarction with nonobstructive coronary arteries. Inexplicable myocardial infarction with nonobstructive coronary arteries after extensive evaluation should alert the clinician to the possibility of coronary vasospasm and the necessity of acetylcholine provocative testing in spite of a negative ergometrine provocation test. (**Level of Difficulty: Intermediate.**) (J Am Coll Cardiol Case Rep 2022;4:294–297)

HISTORY OF PRESENTATION

A 63-year-old woman presented to the emergency department with chest pain, palpitation, and exertional dyspnea. Chest pain was characterized as nonfocal chest pressure or discomfort with radiation to the left shoulder/arm and the lower jaw, and the duration lasted longer than 30 minutes. There was no current or past use of tobacco, cocaine, or other stimulants. Her blood pressure was 131/71 mm Hg; heart rate, 76 beats/min; respiratory rate, 13 breaths/min; and oxygen saturation, 98% on room air. Her cardiac examination revealed no murmurs, rubs, or gallops. There were no signs of fluid overload, abnormal breath sounds, or abdominal distension.

LEARNING OBJECTIVES

- To recognize the possibility of coronary vasospasm in cases of inexplicable MINOCA after extensive evaluation.
- To recognize that a negative ergometrine test cannot always exclude coronary vasospasm in patients with MINOCA.

PAST MEDICAL HISTORY

The patient had a history of paroxysmal atrial fibrillation.

DIFFERENTIAL DIAGNOSIS

Her initial differential diagnosis included acute coronary syndrome, arrhythmias, acute decompensated heart failure, acute myocarditis/pericarditis, Takotsubo cardiomyopathy, acute aortic dissection, and pulmonary embolism.

INVESTIGATIONS

Electrocardiography showed negative or flat T waves in leads II, III, aVF, and V_5 to V_6. Laboratory examinations revealed a troponin level of 1,055 pg/mL (normal range, ≤15.6 pg/mL), brain natriuretic

From the Department of Cardiology and Nephrology, Mie University Graduate School of Medicine, Tsu, Mie, Japan.
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.

Manuscript received September 24, 2021; revised manuscript received October 8, 2021, accepted October 12, 2021.

ISSN 2666-0849 https://doi.org/10.1016/j.jaccas.2021.10.011

peptide level of 22.2 pg/mL (normal range, ≤18.4 pg/mL) and D-dimer level of 0.30 μg/mL (normal range, ≤1.00 μg/mL).

MANAGEMENT

Echocardiography revealed mild hypokinesis in the inferior wall without right ventricular volume and pressure overload. There was no evidence of intracardiac thrombi or pericardial effusion. Coronary angiography confirmed normal coronary arteries, followed by a negative provocation test with intracoronary injections of ergometrine (**Figure 1A,** Videos 1 and 2). There was no coronary artery dissection or plaque disruption after careful review of the angiogram. On cardiovascular magnetic resonance (CMR), high signal intensity was observed in the inferior segment on T2-weighted images accompanied by endomyocardial enhancement on late gadolinium-enhanced (LGE) CMR (**Figure 1B**), excluding myocarditis, Takotsubo syndrome, and cardiomyopathies. The "pill-in-the-pocket" approach with verapamil to paroxysmal atrial fibrillation had been administered. Because of the possibility of coronary microvascular dysfunction and coronary embolism with partial lysis, the calcium channel blocker benidipine at 4 mg per day, a statin atorvastatin at 10 mg per day, and a novel oral anticoagulant, dabigatran, at 60 mg per day, were initiated and continued after her discharge. Three days after the prior discharge, the patient developed recurrent chest pain with a high cardiac troponin level of 6,385 pg/mL due to coronary vasospasm, which was diagnosed by acetylcholine provocative testing under above-mentioned medications, ultimately leading to transmural LGE considered to be no viable myocardium on follow-up LGE CMR (**Figure 2,** Videos 3 and 4).

DISCUSSION

Myocardial infarction with nonobstructive coronary arteries (MINOCA) is found in up to 6% of patients with acute myocardial infarction who are referred for coronary angiography (1). MINOCA is initially considered to be a working diagnosis at the time of coronary angiography and is a distinct clinical diagnosis with many different pathophysiological causes for which extensive evaluation should be performed for all patients.

Coronary vasospasm is a common cause of MINOCA. In a study by Montone et al. (2), coronary vasospasm was diagnosed in 46% of patients with MINOCA undergoing provocation testing. We now use the ergometrine or acetylcholine spasm provocation test to establish the diagnosis. Ergometrine is markedly different from acetylcholine as a spasm provocation test. Ergometrine acts on smooth muscle mainly via activation of serotonergic receptors to produce vasoconstriction, whereas acetylcholine acts on the endothelium and smooth muscle via muscarinic receptors. Sueda et al (3) found no difference in the prevalence of provoked spasm between the agents in patients with ischemic heart disease, but

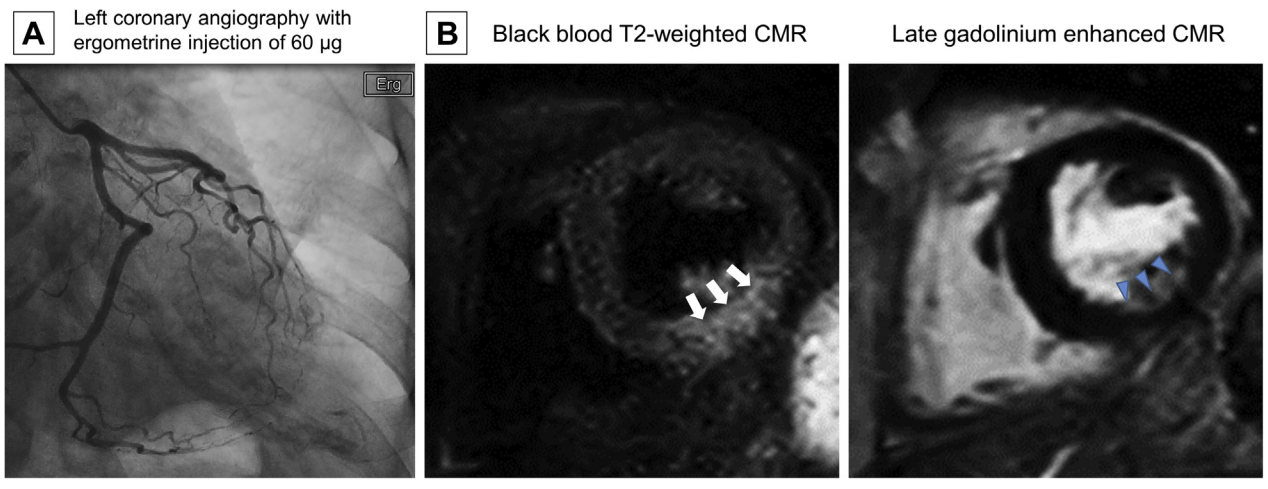
ABBREVIATIONS AND ACRONYMS

CMR = cardiac magnetic resonance

LGE = late gadolinium-enhanced

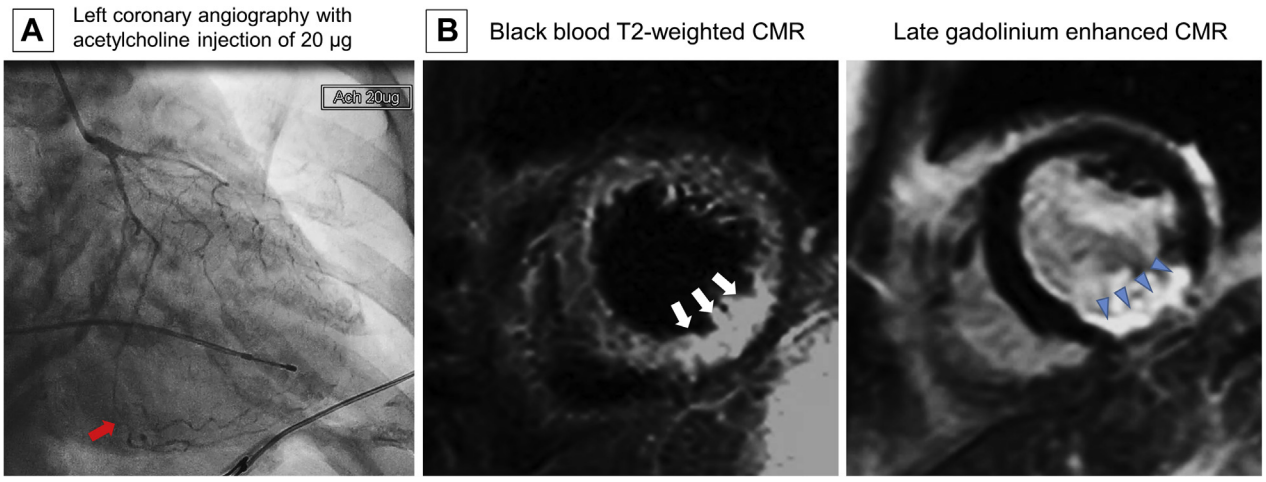
MINOCA = myocardial infarction with nonobstructive coronary arteries

FIGURE 1 Coronary Angiography and CMR at the Time of Initial Admission



(A) No coronary vasospasm after intracoronary injections of ergometrine. **(B)** There was high signal intensity **(arrows)** on T2-weighted images and subendocardial enhancement **(arrowheads)** on LGE-CMR in the mid-apical inferior segments. CMR = cardiovascular magnetic resonance; LGE = late gadolinium-enhanced.

FIGURE 2 Coronary Angiography and CMR at the Time of Second Admission



(A) Severe diffuse stenosis induced by acetylcholine injection of 20 μg was observed in the left coronary artery except for the left main trunk. Also, there was near total occlusion due to coronary vasospasm **(red arrow)** in the distal left circumflex artery. **(B)** Extensive high signal intensity **(white arrows)** on T2-weighted images and **(C)** transmural LGE **(arrowheads)** on LGE-CMR were observed in the midapical inferior wall. Abbreviations as in Figure 1.

noted significantly higher spasms with acetylcholine than with ergometrine in patients without coronary artery disease; thus, a negative ergometrine test cannot always exclude coronary vasospasm in patients with MINOCA. To our knowledge, this is the first report to describe severe reversible diffuse or focal vasoconstriction induced by acetylcholine despite a negative ergometrine provocation test in the acute setting of MINOCA. Interestingly, this case showed recurrent myocardial infarction due to coronary vasospasm at the same focal site. The pathogenesis of coronary vasospasm is likely multifactorial and heterogeneous. In a study by Klein et al (4), coronary vasospasm was associated with the severity of inflammation in the heart. Myocardial inflammation following acute inferior myocardial infarction induces more pronounced coronary endothelial dysfunction and may cause coronary vascular smooth muscle hyper-reactivity, facilitating the development of vasospasm of coronary arteries supplying the inferior wall. A 2019 American Heart Association scientific statement recently provided a clinically useful framework and algorithms for the diagnosis and management of MINOCA (5). However, no position can be made regarding the selection of agents for spasm provocation testing. This case highlights the diagnostic challenge associated with coronary vasospasm, especially when accompanied by no provoked spasms on the ergometrine test in the acute setting of MINOCA.

Furthermore, superimposed paroxysmal atrial fibrillation, in addition to a negative ergometrine provocation test, may lead to the erroneous suspicion of embolic myocardial infarction. CMR is recommended as a key investigation in the diagnostic workup of patients with MINOCA and can help confirm the diagnosis in 74% of patients by facilitating the identification of cardiomyopathies, such as myocarditis, pericarditis, acute myocardial infarction, and Takotsubo, in patients presenting with MINOCA (6); however, CMR cannot differentiate myocardial infarction secondary to coronary vasospasm from embolic infarction with spontaneous recanalization or no evidence of intracardiac thrombus. Currently, spasm provocation testing is restricted to specialized centers in the United States and Europe. Procedure-related arrhythmias developed in 5% of patients and no major adverse events, including death or recurrent infarction, were reported (2). We recommend the supplementary use of pharmacological spasm provocation tests if patients with suspected coronary spasm have no provoked spasms by a single ergometrine or acetylcholine test.

FOLLOW-UP

The patient received dual therapy (calcium channel blockers: benidipine at 4 mg per day, amlodipine at 2.5 mg per day, plus statin) as the cornerstone treatment. However, in this patient, neither calcium

channel blocker treatment nor statin treatment, which is known to improve endothelial function, improved the patient's symptoms. Additional administration of nicorandil led to a significant improvement in the patient's symptoms and quality of life. Finally, cine CMR revealed a reduced left ventricular ejection fraction (from 63% to 57%) with severe hypokinesis of the midapical inferior wall, and 1-month follow-up electrocardiogram showed small pathologic Q waves in the inferior leads.

CONCLUSIONS

Inexplicable MINOCA after extensive evaluation should alert the clinician to the possibility of coronary vasospasm and the necessity of uptitration of calcium-channel blockers or acetylcholine provocative testing despite a negative ergometrine provocation test.

FUNDING SUPPORT AND AUTHOR DISCLOSURES

The authors have reported that they have no relationships relevant to the contents of this paper to disclose.

ADDRESS FOR CORRESPONDENCE: Dr Shiro Nakamori, Department of Cardiology and Nephrology, Mie University Graduate School of Medicine, 2-174 Edobashi, Tsu, Mie 5148507, Japan. E-mail: n-shiro@med.mie-u.ac.jp.

REFERENCES

1. Pasupathy S, Air T, Dreyer RP, Tavella R, Beltrame JF. Systematic review of patients presenting with suspected myocardial infarction and nonobstructive coronary arteries. *Circulation*. 2015;131:861–870.

2. Montone RA, Niccoli G, Fracassi F. Patients with acute myocardial infarction and non-obstructive coronary arteries: safety and prognostic relevance of invasive coronary provocative tests. *Eur Heart J*. 2018;39:91–98.

3. Sueda S, Kohno H, Fukuda H, et al. Induction of coronary artery spasm by two pharmacological agents: comparison between intracoronary injection of acetylcholine and ergonovine. *Coron Artery Dis*. 2003;14:451–457.

4. Klein RM, Schwartzkopff B, Strauer BE. Evidence of endothelial dysfunction of epicardial coronary arteries in patients with immunohistochemically proven myocarditis. *Am Heart J*. 1998;136:389–397.

5. Tamis-Holland JE, Jneid H, Reynolds HR, et al, American Heart Association Interventional Cardiovascular Care Committee of the Council on Clinical Cardiology, Council on Cardiovascular and Stroke Nursing, Council on Epidemiology and Prevention; and Council on Quality of Care and Outcomes Research. Contemporary diagnosis and management of patients with myocardial infarction in the absence of obstructive coronary artery disease: a scientific statement from the American Heart Association. *Circulation*. 2019;139:e891–e908.

6. Dastidar AG, Baritussio A, De Garate E, et al. Prognostic role of CMR and conventional risk factors in myocardial infarction with nonobstructed coronary arteries. *J Am Coll Cardiol Img*. 2019;12:1973–1982.

KEY WORDS acetylcholine, atrial fibrillation, coronary vasospasm, ergonovine, myocardial infarction with nonobstructive coronary arteries

APPENDIX For supplemental videos, please see the online version of this paper.