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CASE REPORT

BEGINNER

CLINICAL CASE

# Myocardial Infarction and Persistent Angina With No Obstructive Coronary Artery Disease

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## ABSTRACT

Women with myocardial infarction with no obstructive coronary artery disease (MINOCA) are increasingly recognized. Women with MINOCA are at high risk for major adverse cardiovascular events. In this case, we focus on the importance of early identification and management of MINOCA to improve patients' angina and related quality of life. (**Level of Difficulty: Beginner.**) (J Am Coll Cardiol Case Rep 2020;2:9–14) © 2020 The Authors. Published by Elsevier on behalf of the American College of Cardiology Foundation. This is an open access article under the CC BY-NC-ND license (http://creativecommons.org/licenses/by-nc-nd/4.0/).

## HISTORY OF PRESENTATION

A 60-year-old woman with a history of myocardial infarction with no obstructive coronary artery disease (MINOCA) presented to the clinic for resting and exertional angina that persisted for hours and responded to nitroglycerin. During the clinic visit, she did not complain of any chest pain or shortness of breath. Her medication regimen included aspirin, isosorbide mononitrate, and sublingual nitroglycerin as needed for chest pain. Electrocardiograms taken 1 year before

## LEARNING OBJECTIVES

- To identify patients with persistent angina with MINOCA.
- To demonstrate the role of invasive and noninvasive coronary reactivity testing in patients with MINOCA.
- To demonstrate the importance of diagnostic and therapeutic management in patients with MINOCA to improve angina and related quality of life.

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Informed consent was obtained for this case.

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**ABBREVIATIONS AND ACRONYMS**

**CAD** = coronary artery disease

**CMD** = coronary microvascular dysfunction

**cMRI** = cardiac magnetic resonance imaging

**MINOCA** = myocardial infarction with no obstructive coronary artery

her presentation and during her clinic visit are shown in **Figures 1A and 1B**, respectively. Echocardiography showed normal left ventricular ejection fraction and wall motion. Carvedilol was added to her regimen for persistent angina. She was discharged from the clinic and scheduled for follow-up in 4 weeks.

## PAST MEDICAL HISTORY

The patient had a history of asthma, hypertension, and multiple presentations to the emergency department for chest pain that was diagnosed as noncardiac. She underwent coronary angiography 1 year before presentation due to non-ST-segment elevation myocardial infarction, which showed luminal irregularities of the right coronary artery.

## DIFFERENTIAL DIAGNOSIS

A differential diagnosis of epicardial coronary vasospasm, myocarditis, coronary microvascular dysfunction (CMD), or spontaneous coronary artery dissection for the prior MINOCA was considered.

## INVESTIGATIONS

The patient was enrolled in the WISE-CVD (Women's Ischemia Syndrome Evaluation-Coronary Vascular Dysfunction; NCT00832702) continuation study, a prospective cohort study designed to investigate the diagnostic and prognostic utility of invasive and noninvasive assessment of coronary vascular dysfunction in women by using intracoronary flow measures and cardiac magnetic resonance imaging (cMRI), respectively.

**Figure 2** and Video 1 illustrate the baseline cMRI showing the presence of an ischemic-pattern focal scar identified by late gadolinium enhancement on cMRI. cMRI at the 1-year follow-up showed interval myocardial changes of mid-anteroseptal and basal inferoseptal areas (**Figure 3**, Video 2). Because of the absence of active myocarditis on cMRI but presence of the mid-myocardial scar pattern, further evaluation with positron emission tomography-computed Tomography was performed, which showed no evidence of cardiac sarcoidosis. Therefore, the patient underwent clinical invasive coronary reactivity testing, as previously reported, (Videos 3, 4, and 5) to further understand the mechanisms of her prior MINOCA (1).

The coronary reactivity testing showed mild luminal irregularities of the distal right coronary artery, normal left ventricular end-diastolic filling pressure of 11 mm Hg, normal coronary flow reserve of >2.5 in response to intracoronary adenosine, abnormal coronary blood flow change (−26%) in response to intracoronary acetylcholine infusion, and diffuse coronary vasospasm >75% of the left anterior descending artery in response to 108 μg of intracoronary acetylcholine, which was reversed with a 200-μg intracoronary bolus injection of nitroglycerin. The final clinical diagnosis, management, and follow-up are shown in **Figure 4**.

## MANAGEMENT

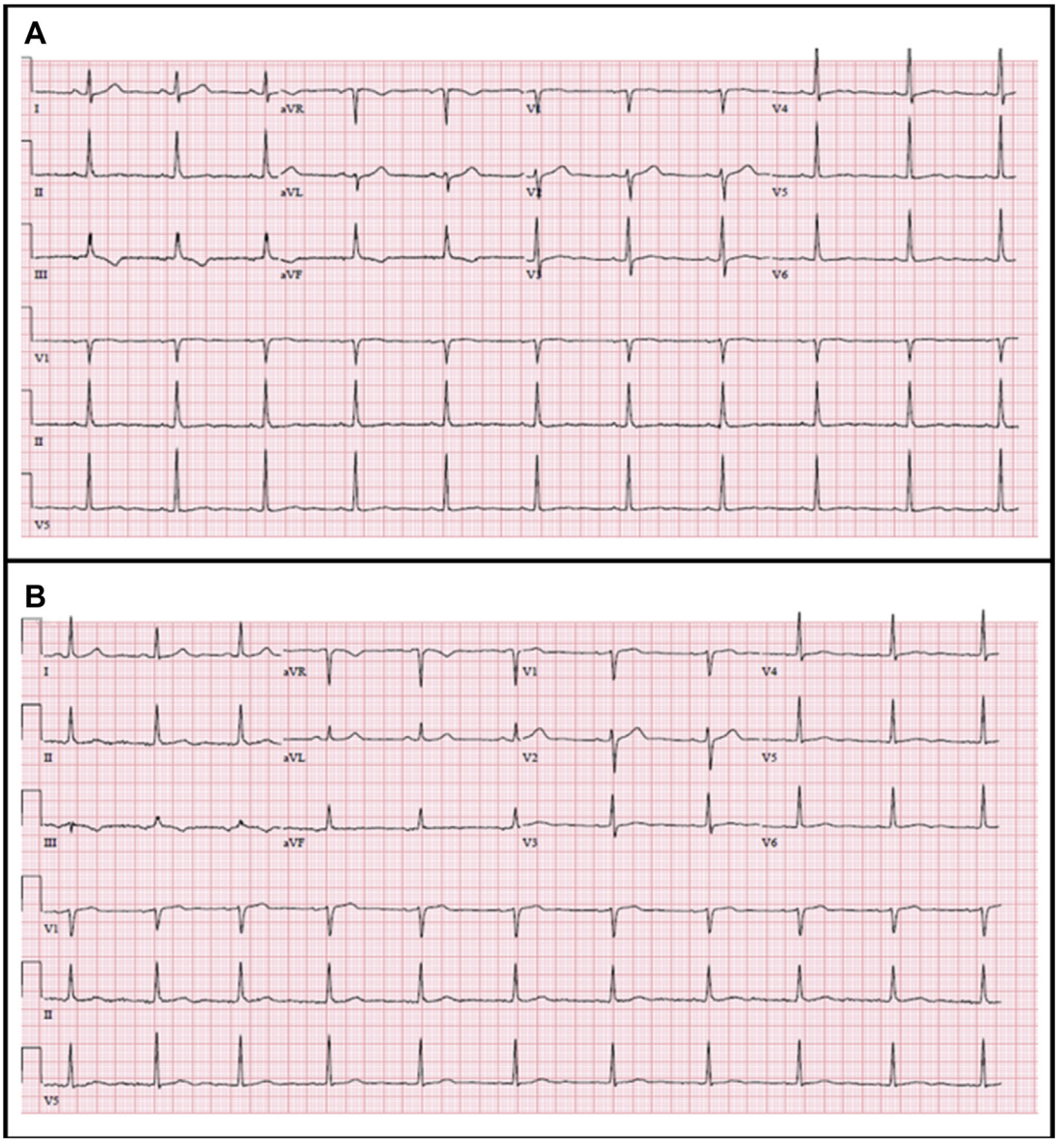
Given the lack of prospective randomized controlled trials and limited evidence-based literature, in the current case, the patient was started on diltiazem to target coronary vasospasm (2). A statin and angiotensin-converting enzyme inhibitor were initiated because they have been shown to decrease major adverse cardiovascular events (3). Aspirin was continued for secondary prevention of myocardial infarction, and carvedilol was discontinued.

## DISCUSSION

MINOCA (<50% luminal stenosis) is challenging to assess, diagnose, and manage because of the lack of evidence-based guidelines (2,4). The prevalence of MINOCA ranges from 1% to 14% of all patients having acute infarction, and patients with MINOCA are more likely to be women and younger compared with patients with obstructive coronary artery disease (CAD) (5). After 1 year of follow-up, MINOCA patients experience an angina burden at least as high as those with obstructive CAD (6). MINOCA may be attributed to several specific pathologies, including atherosclerotic etiologies, such as plaque disruption, and nonatherosclerotic etiologies, such as epicardial coronary vasospasm, CMD, coronary embolism/thrombosis, and spontaneous coronary artery dissection (2). Invasive and noninvasive methods assessing the functional status of the coronary vessels have been described. Noninvasive testing includes positron emission tomography, transthoracic echo Doppler, and cMRI to assess the presence CMD in patients with no obstructive CAD (4).

In the current case, our patient underwent invasive coronary reactivity testing so we could better understand the contributing mechanisms behind her persistent symptoms. Coronary reactivity testing assesses the functional reactivity of the epicardial and microvascular coronary arteries, including endothelial and nonendothelial pathways. Prior longer-term follow-up of the original WISE cohort showed that women with abnormal coronary vascular function are

**FIGURE 1** **Electrocardiography**

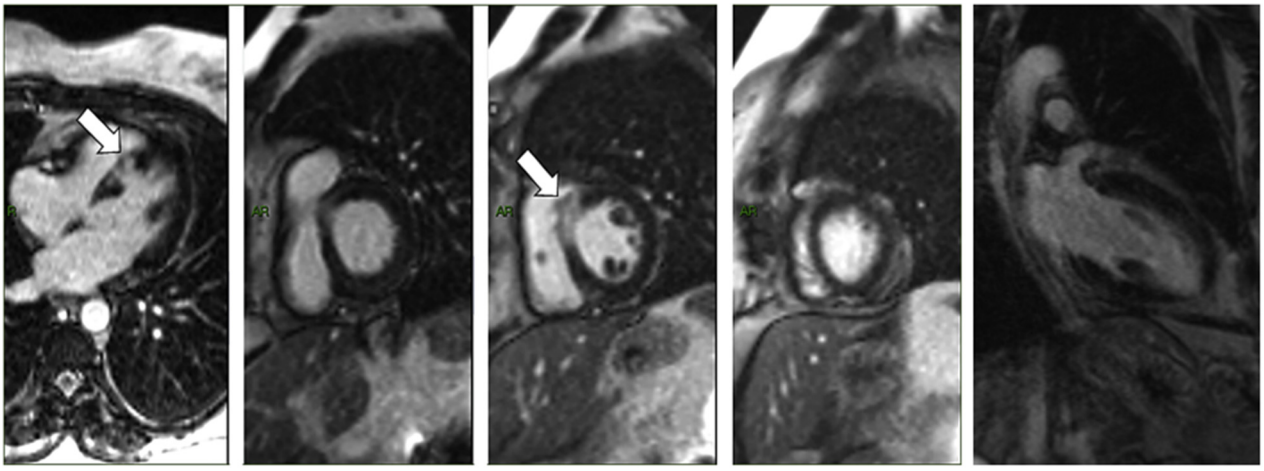



**(A)** One year before clinic presentation: normal sinus rhythm with prominent T-wave inversion in leads III and aVF. **(B)** At clinic presentation: normal sinus rhythm and T-wave inversion in lead III and flattening of the T-wave in lead aVF, which could be suggestive of right coronary artery disease.

at increased risk of developing future cardiovascular events compared with those with normal coronary vascular function (7).

Myocarditis should be considered as a cause of MINOCA when 2 out of 3 criteria are present on cMRI: myocardial edema, hyperemia, or fibrosis (8). Our patient had normal T2 mapping values on cMRI, indicating absence of myocardial edema and suggesting no active myocarditis. The absence of coronary artery tear on angiography is an argument against spontaneous CAD and confirms the diagnosis of MINOCA with diffuse coronary vasospasm indicated by abnormal endothelium-dependent coronary epicardial function. The diagnostic challenge in these

**FIGURE 2 Baseline Cardiac Magnetic Resonance Imaging**



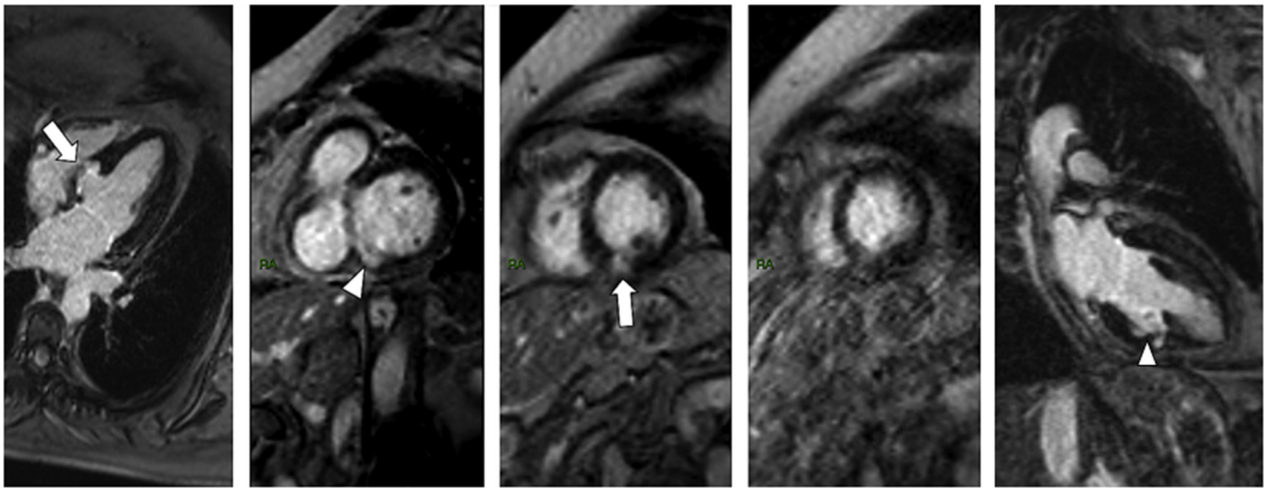
Subendocardial to transmural late gadolinium enhancement consistent with focal scar involving the mid-anteroseptal area **(white arrows)**.

cases seems to be augmenting the potential therapeutic shortfalls for patients with MINOCA. Approximately one-third of all women with suspected ischemia and no obstructive CAD have late gadolinium enhancement, suggestive of myocardial scar (9). The absence of an evidence-based treatment may be another key factor contributing to the undertreatment of patients with MINOCA when compared with patients with obstructive CAD before and after angiography (10).

## FOLLOW-UP

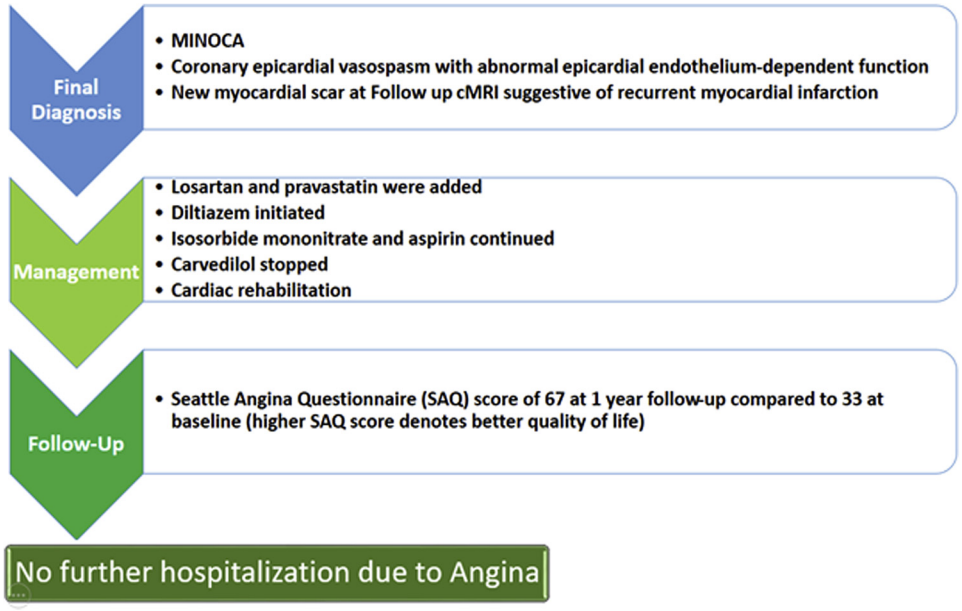
The patient's symptoms improved significantly after treatment and required no further hospitalizations at the subsequent 1-year follow-up.

**FIGURE 3 1-Year Follow-Up Cardiac Magnetic Resonance Imaging**



New near-transmural scar extending from the subendocardium in the basal inferoseptum and a small segment of the basal anteroseptum and mid-myocardial scar in the mid-inferoseptum. Compared with the prior scan, delayed enhancement was more prominent in the basal anteroseptum **(white arrow)** and not seen in the basal inferoseptum **(arrowheads)** to the extent it is present in the current study.

**FIGURE 4** Overview of the Final Clinical Diagnosis, Management, and Follow-Up




The flowchart demonstrates the importance of diagnosing myocardial infarction with no obstructive coronary artery (MINOCA) with comprehensive assessment, followed by initiation of diagnosis-specific therapy. This approach resulted in significant improvement in the quality of life in our patient.

## CONCLUSIONS

There are increasing reports of patients with MINOCA with recurrent angina symptoms. Invasive and noninvasive methods are being used to further address the mechanistic pathways of MINOCA. Despite the fact that patients with MINOCA are at an increased risk of adverse cardiovascular outcomes, no definitive diagnostic or treatment guidelines exist to approach these patients and alleviate their symptoms in an effective way. To improve patients' quality of life and cardiovascular outcomes, future clinical trials are recommended to focus on identifying and appropriately managing MINOCA.

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## REFERENCES

**1.** Pepine CJ, Anderson RD, Sharaf BL, et al. Coronary microvascular reactivity to adenosine predicts adverse outcome in women evaluated for suspected ischemia results from the National Heart, Lung and Blood Institute WISE (Women's Ischemia Syndrome Evaluation) study. J Am Coll Cardiol 2010;55:2825–32.

**2.** Tamis-Holland JE, Jneid H, Reynolds HR, et al. 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:e891–908.

**3.** Lindahl B, Baron T, Erlinge D, et al. Medical therapy for secondary prevention and long-term outcome in patients with myocardial infarction with nonobstructive coronary artery disease. Circulation 2017;135:1481–9.

**4.** Bairey Merz CN, Pepine CJ, Walsh MN, Fleg JL. Ischemia and no obstructive coronary artery disease (INOCA): Developing evidence-based therapies and research agenda for the next decade. Circulation 2017;135:1075–92.

**5.** 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;131:861–70.

**6.** Grodzinsky A, Arnold SV, Gosch K, et al. Angina frequency after acute myocardial infarction in patients without obstructive coronary artery

disease. European Heart J Qual Care Clin Outcomes 2015;1:92–9.

**7.** AlBadri A, Bairey Merz CN, Johnson BD, et al. Impact of abnormal coronary reactivity on long-term clinical outcomes in women. J Am Coll Cardiol 2019;73:684–93.

**8.** Friedrich MG, Sechtem U, Schulz-Menger J, et al. Cardiovascular magnetic resonance in myocarditis: A JACC white paper. J Am Coll Cardiol 2009;53:1475–87.

**9.** Wei J, Bakir M, Darounian N, et al. Myocardial scar is prevalent and associated with subclinical myocardial dysfunction in women with suspected ischemia but no obstructive coronary artery disease: From the Women's ischemia syndrome evaluation-coronary vascular dysfunction study. Circulation 2018;137:874–6.

**10.** De Ferrari GM, Fox KA, White JA, et al. Outcomes among non-ST-segment elevation acute coronary syndromes patients with no angiographically obstructive coronary artery disease: observations from 37,101 patients. Eur Heart J Acute Cardiovasc Care 2014;3:37–45.

**KEY WORDS** coronary reactivity, endothelial function, MINOCA, persistent angina

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