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ADVANCED

CASE REPORT: EDITOR'S HIGHLIGHTS

White Clot Formation at Acetylcholine Testing

A Change of Heart in MINOCA?

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ABSTRACT

Coronary intraluminal white clot formation, apparently in response to acetylcholine testing, may explain a woman's long-term history of daily chest pain and multiple myocardial infarctions. Acetylcholine testing reproduced chest pain and revealed luminal filling defects in multiple vessels; imaging showed fresh white platelet clots. Antiplatelet prasugrel has substantially suppressed her symptoms. (**Level of Difficulty: Advanced.**) (J Am Coll Cardiol Case Rep 2021;3:801–5)

INTRODUCTION

In transient, resting chest pain with negative baseline coronary angiography—either coronary insufficiency with no obstructive coronary artery disease (INOCA) or myocardial infarction (MI) with no obstructive coronary artery disease (MINOCA) (1,2)—ischemic spells are thought to be caused by either transient epicardial or microvascular coronary obstruction that resolves quickly and spontaneously (as in spastic angina) or prolonged ischemia and irreversible myocardial damage with normal coronary arteriograms at follow-up angiography (MINOCA) (2,3).

We present an exceptional case of INOCA/MINOCA probably related to white clot formation caused by episodic platelet dysfunction, which acetylcholine (ACh) testing apparently revealed or reproduced and prasugrel seems to have cured.

LEARNING OBJECTIVES

- To evaluate a patient with chest pains and myocardial scars but no coronary stenosis (MINOCA).
- To perform acetylcholine testing safely in the presence of endoluminal clotting and to investigate effective long-term preventive antiplatelet treatment.
- To establish a general theory on a potential new disease entity.

HISTORY OF PRESENTATION

A 49-year-old White woman was referred to us for re-evaluation of recurrent, intractable, angina-like chest pain that typically lasted from a few minutes to several hours and occurred consistently at rest.

MEDICAL HISTORY

The patient's 7-year history included 10 emergency center admissions and elective evaluation at hospitals specializing in INOCA/MINOCA; she had undergone 4 heart catheterizations, at least 3 cardiac magnetic resonance (CMR) imaging studies with late

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ABBREVIATIONS AND ACRONYMS

ACh = acetylcholine

CAD = coronary artery disease

CMR = cardiac magnetic resonance imaging

ECG = electrocardiogram

INOCA = ischemia with no obstructive coronary artery disease

LAD = left anterior descending coronary artery

LGE = late gadolinium enhancement

MI = myocardial infarction

MINOCA = myocardial infarction with no obstructive coronary artery disease

gadolinium enhancement (LGE), and 10 echocardiographic assessments. No definitive diagnosis of acute MI was ever made, although CMR-LGE indicated recurrent, multiple non-Q-wave MIs with occasional mild troponin elevations. Transient dyspnea and occasional left-flank pain frequently accompanied the angina pain.

Over time, several diagnoses and treatment plans were proposed; pharmacotherapy included metoprolol, nondihydropyridine calcium-channel blockers, amiodarone, ranolazine, nitroglycerin, long-acting nitrates, and L-arginine. Sublingual nitroglycerin only partially improved chest pain. Endothelial function studies (1 ergonovine, 2 ACh) at specialized centers were inconclusive or negative; in 1 instance, ACh testing was accompanied by unexplained severe, sustained chest pain.

Initially, palpitations co-occurred with chest pain episodes. An electrophysiological study followed by radiofrequency ablation immediately (but transiently) reduced the frequency of ventricular tachycardia and premature contractions. Left ventricular ejection fraction during prolonged chest pain episodes undulated between 65% and 40%. Suspected microvascular spasm was ventilated, but to our knowledge, no fixed epicardial obstructive coronary artery disease (CAD) or definite spasm was ever documented. Rivaroxaban 2.5 mg twice a day was tried briefly. Finally, myocardial bridging was hypothesized as the cause, with surgical treatment considered to suppress the angina (the reason for referral to our center).

Previous genetic studies showed homozygosity for the *eNOS* (possibly predisposing to coronary spasm) and *MTHFR* mutations (relatable to hyperhomocysteinemia).

Treatment for anxiety and hypochondriac neurosis produced little improvement.

DIFFERENTIAL DIAGNOSIS

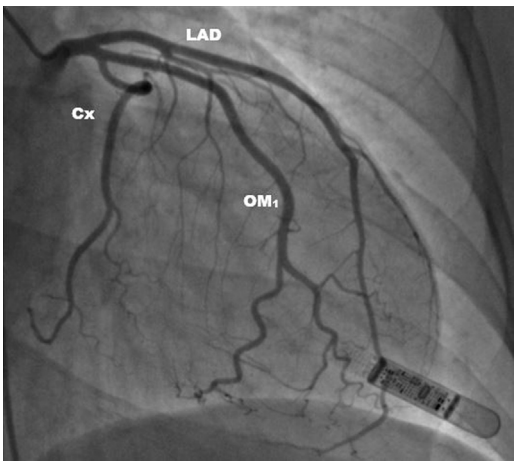
The differential diagnosis included myocardial bridging (with possible coronary spastic tendency), coronary dissection, and noncardiac pain. Redo coronary angiography and ACh testing were indicated, especially to rule out spasm at a myocardial bridge.

INVESTIGATIONS

At our center, the patient's physical examination findings were within normal limits (blood pressure, 125/70 mm Hg; cardiac rhythm, 70 beats/min, regular; body mass index, 23 kg/m^2; fasting blood sugar, 100 mg/dl). Electrocardiography (ECG) indicated no Q-wave myocardial scarring or resting ischemia. Her lipid panel showed mild, untreated hypercholesterolemia (total cholesterol, 212 mg/dl; low-density lipoprotein cholesterol, 116 mg/dl). Repeated submaximal treadmill testing was normal, with normal blood pressure rise and no angina or arrhythmia.

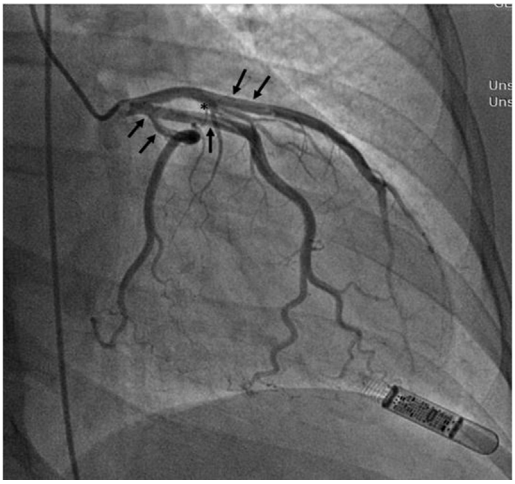
New angiography confirmed the absence of fixed CAD or significant myocardial bridging, even after nitroglycerin administration (**Figure 1**). Intracoronary ACh infusion was halted after 3 min (at 48 μg) because of the onset of severe chest pain requiring high doses of fentanyl and midazolam. Intracoronary nitroglycerin was administered repeatedly, without success. Repeated angiography showed no spasm but multiple intraluminal linear filling defects at the proximal left anterior descending coronary artery (LAD), at the first septal branch and its distal bifurcation, and at the circumflex and obtuse marginal branches (**Figure 2,** Video 1). Under heparinization that was started after the appearance of angiographic changes, a 0.014-inch coronary guidewire was introduced; intravascular ultrasonography at the LAD and circumflex revealed unattached intraluminal clots but no CAD or ulcerative plaques at sites of luminal filling defects (**Figure 3,** Video 2). Right coronary artery angiography findings were normal in previous studies and thus this was not repeated.

FIGURE 1 Baseline Angiogram



Right anterior oblique, left coronary angiogram shows the circumflex (Cx), left anterior descending (LAD), and first obtuse marginal (OM1) coronary arteries with no obstructive lesions. A subcutaneous Reveal loop monitor (Medtronic, Dublin, Ireland) is shown over the apex.

FIGURE 2 Angiogram After Acetylcholine Infusion



Acetylcholine 48 μg was administered over 2 min, until the onset of severe chest pain. A still image from a right anterior oblique, left coronary angiogram shows multiple luminal filling defects **(arrows)** at the proximal left anterior descending, first septal, circumflex, and obtuse marginal sites. A subcutaneous Reveal loop monitor (Medtronic) is shown over the apex. No electrocardiogram changes were seen. See Video 1.

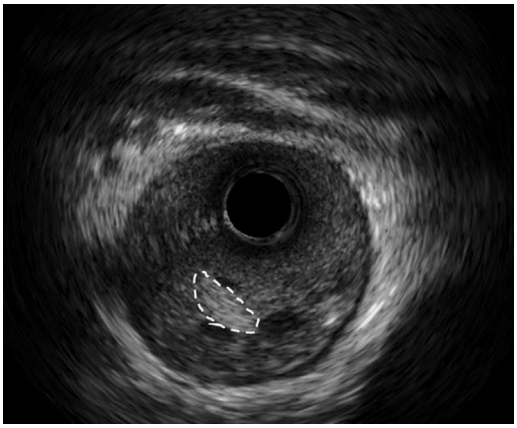
Selective thrombolysis infusion at the left main trunk (reteplase 6 mg over 10 min) and thrombectomy by Pronto Extraction Catheter (Vascular Solutions, Inc.) yielded an abundance of separate, jelly-like white clots from the 3 main arteries, substantially remediating the intraluminal clotting (**Figure 4,** Video 3).

Subsequent CMR-LGE imaging revealed multiple old scars and 1 fresh one in an anteroseptal location (**Figure 5**). At cytology smear preparation, the extracted clots appeared as loose aggregates of fibrin and platelets. After the procedure, troponin T peaked to 5.17 ng/l; serum homocysteine, folate, and vitamin B_{12} levels were normal.

ANTICOAGULANT MANAGEMENT

An oral prasugrel 60-mg loading dose was given after the appearance of suspicious images of intraluminal clotting. Angina pain resolved after 90 min. No ST-segment changes were seen, either with 3-lead ECG monitoring during the procedure or with a 12-lead ECG afterward. Follow-up hematologic testing ruled out a prothrombotic state and indicated that prasugrel was functioning adequately (residual 10% platelet aggregation). Daily prasugrel 10 mg with aspirin 81 mg and atorvastatin 20 mg were begun as chronic treatment.

FIGURE 3 Intravascular Ultrasonogram

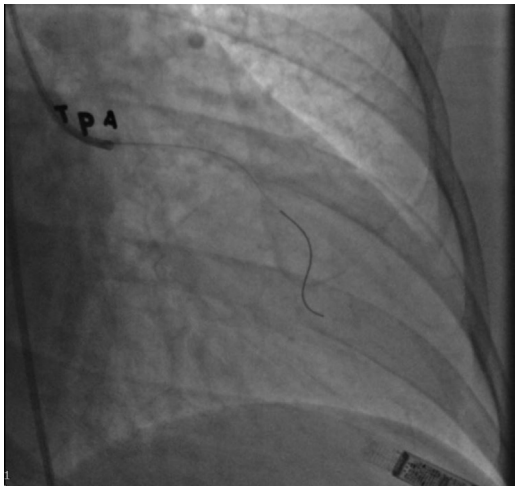


A still image from intravascular ultrasound imaging (right anterior oblique projection) shows nonocclusive filling defects compatible with free clots (**dashed line**: 11 × 5-mm area). See Video 2.

DISCUSSION

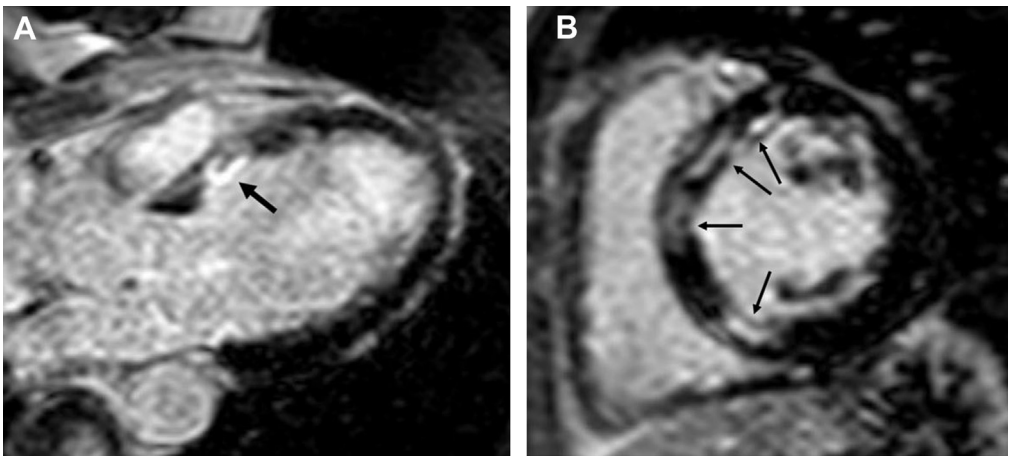
Diagnosing angina, coronary ischemia, or MI in patients with normal or nonstenotic coronary arteries at baseline angiography is difficult because of diverse possible etiologies, both coronary (spasm, dissection)

FIGURE 4 Final Coronary Angiogram



A coronary angiogram after thromboaspiration and thrombolysis shows the substantial resolution of intraluminal clots, except for those remaining in a branch of the first septal artery (occluded). See Video 3.

FIGURE 5 Cardiac Magnetic Resonance Imaging With Late Gadolinium Enhancement



(A) Cardiac magnetic resonance imaging with late gadolinium enhancement (long-axis, 2-chamber view) shows an area of recent scarring in the upper septum **(arrow)**. **(B)** The cross-sectional, midventricular section view shows multiple scars at the interventricular septum. **Arrows** indicate separate scarring events.

and noncoronary (gastrointestinal, neuropathic, psychological, musculoskeletal). Our patient had a multiyear history of disabling angina and probable ischemic events (per troponin elevation), resulting in multiple scars that we and others initially assumed were related to vasospastic disease. Low-dose ACh testing immediately reproduced chest pain and showed de novo left coronary luminal platelet/fibrin clots in different branches of the left coronary artery. Intravascular (white) sudden-onset clotting has not been previously mentioned in the literature; rather, coronary luminal clots are usually mixed components attached to ulcerated endothelial lesions at sites of plaque disruption. Optical coherence tomography imaging in patients with spastic angina and no CAD frequently shows attached thrombi at sites of inducible spasm (4). Hyperhomocysteinemia has been mentioned as a potential cause of clotting (5-7), but our patient's homocysteine level was normal at the current evaluation.

Conceptually, one could define INOCA/MINOCA according to its transient nature (spontaneous ischemic spells, not reproducible by exertion) and recurrent resting ischemia or chest pain, with or without residual myocardial scarring. In this context, ACh testing might identify increased spasticity or precipitate intravascular white clotting. Although no total occlusion of any visible coronary branches occurred, the patient's severe chest pain could have been caused by unseen microemboli. Thus, 3 different factors could have been at work: 1) intravascular (arterial) platelet aggregation; 2) microemboli (which could explain microvascular dysfunction); or 3) macrothrombi in epicardial arteries, even if nonocclusive.

Platelet aggregation overexpression could be caused by rare congenital mutations that predispose the patient to arterial thrombosis (8,9), but a precipitating factor must be transiently present to explain our case presentation. The probability of spontaneous or ACh-related platelet hyperaggregability has not been discussed in the literature (10). In vitro assessment of platelet function (8) while administering ACh could be a novel, potentially useful procedure, but it has not been prospectively tested.

Our observations are exceptional and could represent a breakthrough, but they require prospective testing in a larger INOCA/MINOCA population to better characterize the nature and prevalence of similar events (11). We recognize that, in clinical practice, INOCA/MINOCA is often not well explained or effectively treated, whereas ACh testing usually proceeds without complications.

FOLLOW-UP

The patient's dramatic resolution of chest pains has persisted for 3 years. She has resumed advanced gymnastic exercises and is happy and hopeful. Her only residual symptom is infrequent, minor resting chest pain, for which she takes sublingual nitroglycerin. She has never returned to an emergency center.

At the 1-year follow-up, her left ventricular ejection fraction was 58%. A plan to hold prasugrel for 8 days (to study in vitro platelet response to ACh, on and off prasugrel) was aborted after 3 days, when chest pain recurred. She is hesitant to abandon the medication.

CONCLUSIONS

Before the patient arrived at our center, extensive workup had not identified a plausible cause for her recurrent angina and myocardial scarring. Surprisingly, anticoagulation with prasugrel has substantially abolished new episodes of INOCA/MINOCA.

Still, questions remain: 1) Is hers indeed an exceptional case? 2) How should we conduct effective testing in similar cases? Is ACh the only possibility for testing apparent transient platelet dysfunction? 3) Should initial treatment with prasugrel (or another platelet antiaggregant) be initiated without further proof of the nature of this anomaly? 4) Should we establish a new in vitro ACh test for patients with similar chest pain, troponin elevation, and myocardial scarring?

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KEY WORDS angina pectoris, coronary artery disease, coronary vasospasm, myocardial infarction, platelet aggregation, platelet aggregation inhibitors

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