ESC European Society of Cardiology

European Heart Journal - Case Reports (2023) **7**, 1–6
https://doi.org/10.1093/ehjcr/ytad019

GRAND ROUND
Coronary intervention

Repetitive catamenial myocardial infarction due to coronary artery spasm: a case report

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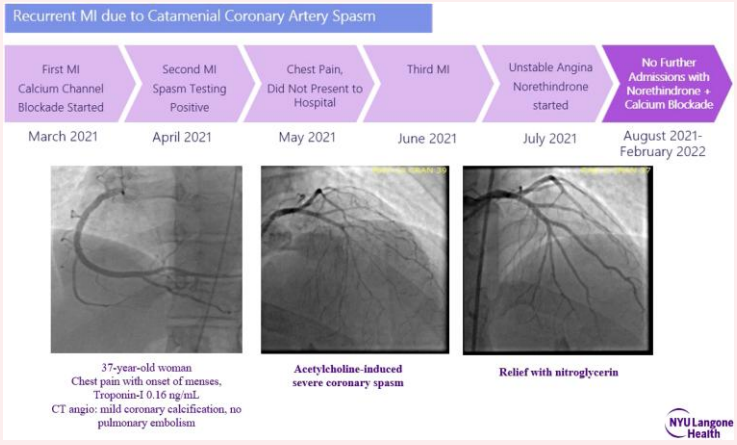
Received 18 February 2022; first decision 25 March 2022; accepted 9 January 2023; online publish-ahead-of-print 11 January 2023

Background Coronary artery spasm is an established mechanism of myocardial infarction with non-obstructive coronary arteries (MINOCA). Various mechanisms have been proposed, ranging from vascular smooth muscle hyperreactivity to endothelial dysfunction, to autonomic nervous system dysregulation.

Case summary We report a case of a 37-year-old woman who presented with recurrent non-ST elevation myocardial infarction (NSTEMI), coinciding with her menstrual periods. Intracoronary acetylcholine provocation testing resulted in coronary spasm in the left anterior descending artery (LAD) that was relieved with nitroglycerine. Initiating calcium channel blockade and suppressing cyclical variation in sex hormones resulted in improvement of her symptoms and cessation of monthly NSTEMI events due to coronary spasm.

Discussion Initiating calcium channel blockade and suppressing cyclical variation in sex hormones resulted in improvement of her symptoms and cessation of monthly NSTEMI events due to coronary spasm. Catamenial coronary artery spasm is a rare, but clinically important, presentation of myocardial infarction with non-obstructive coronary arteries (MINOCA).

Graphical Abstract



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Handling Editor: Francesco Moroni
Peer-reviewers: Lina Ya'qoub; Konstantinos Stathogiannis; Fabienne Vervaat
Compliance Editor: Oliver Ian Brown
Supplementary Material Editor: Ameenathul Mazaya Fawzy

Keywords Vasospasm • Women's Health • NSTEMI • Catamenial vasospasm • Acetylcholine provocation testing • Case report • Menstruation

ESC Curriculum 3.2 Acute coronary syndrome • 3.1 Coronary artery disease

Learning points

- To recognize reproductive hormone cycling as a trigger for coronary artery spasm
- To learn the diagnostic modalities and treatment options available for myocardial infarction with non-obstructive coronary arteries

Specialties involved other than cardiology

Gynaecology, Nursing.

Introduction

Coronary artery spasm is a mechanism of Type 2 myocardial infarction.[1] Spasm can occur in the epicardial arteries or coronary microvasculature, in patients with or without coronary artery atherosclerosis, and can be focal or diffuse.[2] A definitive diagnosis of coronary spasm may be established with coronary reactivity testing using intracoronary acetylcholine or ergonovine,[3] but this testing is not performed at all centres.

In this case, we describe a rare presentation of coronary artery vasospasm secondary to cyclical variation in hormones associated with menstruation.

Timeline

Timeline—all symptomatic episodes related to onset of menses

March 2021	Initial hospitalization, first NSTEMI • CTA demonstrated coronary artery calcification, ruled out pulmonary embolism • Cardiac MRI performed with normal findings • Echocardiogram performed, with no wall motion abnormalities • Cardiac catheterization performed, mild luminal irregularities
April 2021	Second hospitalization, second NSTEMI • Provocation testing with definitive diagnosis of vasospasm
May 2021	Recurrence of symptoms, patient did not present to hospital
June 2021	Third hospitalization, third NSTEMI
July 2021	Recurrence of chest pain, normal troponin
August 2021	Recurrence of mild chest pain, did not present for medical attention
September 2021	Chest pain and headache, negative troponin
October—December 2021	No symptoms

Case presentation

A 37-year-old woman presented with severe burning, pressure-like retrosternal and epigastric discomfort. Symptoms coincided with the onset of menses. The previous month, she experienced significant emotional distress due to the death of her sister. She had also received the second dose of a mRNA COVID-19 vaccine series 2 months prior to presentation.

The patient had prior diagnoses of migraine, attention deficit hyperactivity disorder for which she was taking lisdexamfetamine, as well as MTHFR (methylenetetrahydrofolate reductase) and heterozygous Factor V Leiden mutations identified by genetic screening. Her family history was significant for multiple malignancies, including colon cancer in paternal grandfather, ovarian cancer in a paternal aunt, thyroid cancer in a maternal aunt and paternal grandmother, multiple myeloma in maternal grandmother, polycythaemia vera in a maternal aunt, and thrombophilia in father and mother. She had no other cardiovascular risk factors.

Physical examination was unremarkable. Laboratory testing was significant for an initial Troponin-I level of 0.16 ng/mL (ULN <0.04 ng/mL) which then down-trended. The electrocardiogram revealed T-wave flattening and inversion in the inferior leads and T-wave inversion in V3 (*Figure 1*), that later normalised.

The patient underwent CT angiography of the thorax, which ruled out pulmonary embolism and demonstrated a small, calcified plaque in the left anterior descending artery (*Figure 2*). The study was not gated to evaluate coronary artery patency. The patient developed pruritus following the study that was attributed to an allergic reaction to IV contrast. Transthoracic echocardiography revealed normal cardiac structure and function, with a left ventricular ejection fraction of 65%. There were no regional wall motion abnormalities. Invasive coronary angiography, performed after steroid pre-medication for contrast allergy, was notable for minimal luminal irregularities in the left anterior descending (LAD) artery and right coronary arteries, and an angiographically normal left circumflex artery (*Figure 3*). Intracoronary optical coherence tomography was not performed due to a mild contrast allergy following CT angiography. She was assigned a provisional diagnosis of myocardial infarction with non-obstructive coronary arteries (MINOCA). Cardiac magnetic resonance imaging was performed as per clinical practice guidelines and demonstrated normal myocardium without late gadolinium enhancement or oedema.[4] She was discharged with prescriptions for aspirin 81 mg, statin therapy, beta blockade, and amlodipine 10 mg. Lisdexamfetamine was discontinued. The dose of amlodipine was reduced at an outpatient visit to 5 mg due to lower extremity oedema.

One month following her initial hospital presentation, again at the onset of menses, the patient developed recurrent chest pain and NSTEMI with recurrence of T-wave inversion in a similar pattern to the month prior and peak troponin 0.11 ng/mL (upper limit of normal 0.04 ng/mL)br, declining to normal (See Timeline Table).

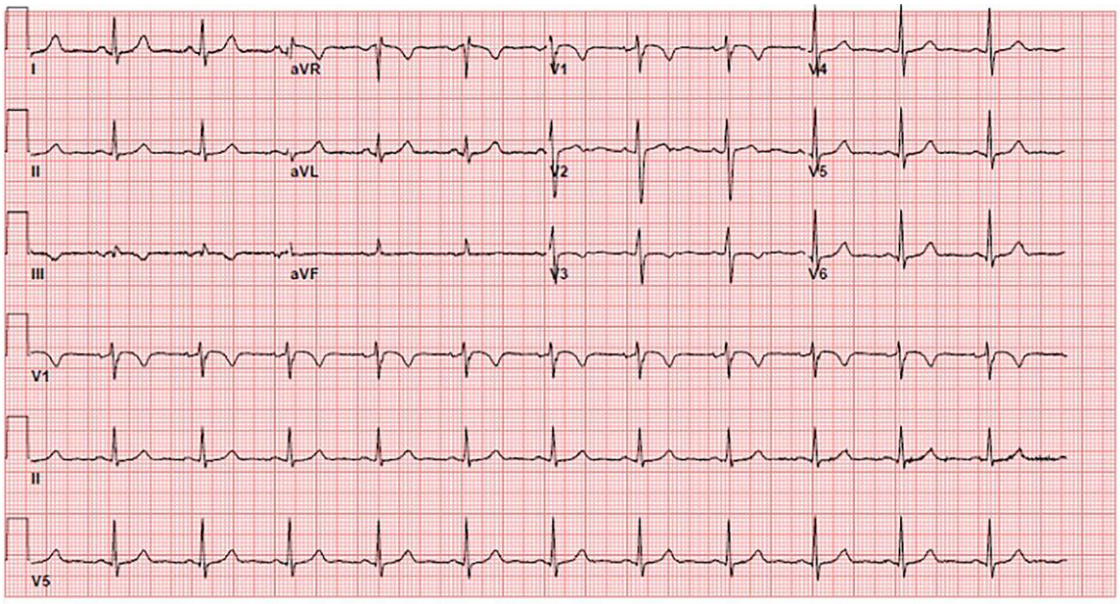

Figure 1 Electrocardiogram showed sinus rhythm with non-specific T-wave changes.

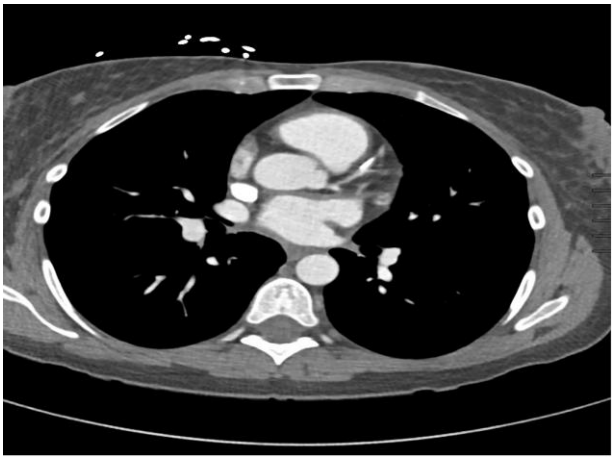

Figure 2 CT coronary angiography revealed a small, calcified lesion in the left anterior descending artery (arrow). The remainder of the CT shows normal cardiac anatomy.

Heterophile antibodies drawn at a haematology visit earlier that week were negative.

Given the strong suspicion of coronary artery spasm as the cause of recurrent catamenial MI, the patient was referred for cardiac catheterization with coronary reactivity testing. Angiography again revealed no significant narrowing. Intracoronary provocation testing with escalating doses of acetylcholine resulted in coronary spasm in the LAD after the 100 mcg dose that was relieved with nitroglycerine (*Figure 4*). There was also common femoral artery spasm that resolved after nitroglycerine (*Figure 5*). Coronary angiography post-nitroglycerin revealed a myocardial bridge with systolic compression in the distal LAD, not noted on the earlier angiogram. Coronary physiology studies to evaluate microvascular function were also performed in the LAD, with a normal non-hyperaemic pressure ratio (resting full cycle ratio, or RFR) of 0.96 in the distal vessel (normal > 0.89), normal coronary flow reserve (CFR) of 3.8 (normal > 2.0–2.5), and normal index of microcirculatory resistance of 17 (normal < 25). Since the mechanism of MINOCA was attributed to coronary spasm, additional intravascular imaging was not performed.

After definitive diagnosis of coronary artery spasm, we started verapamil. She was unable to tolerate long-acting nitrates due to severe headaches. Despite escalating doses of verapamil, her symptoms continued to recur with subsequent menstrual periods. Due to the catamenial nature of her symptoms, an etonorgestrel device was implanted. However, she continued to have recurrent NSTEMI at the beginning of each menstrual cycle. She did not present to an emergency room the month after the spasm diagnosis, due to a religious holiday. When chest pain recurred, the 5th month in a row with menses, she was hospitalized and found to have NSTEMI (peak troponin 0.06). Gynaecology was consulted, etonorgostrel device was removed, and oral progesterone therapy, norethindrone 10 mg/day, was initiated to suppress hormonal cycling. She was also started on magnesium to mitigate coronary spasm based on small clinical trials that showed it reduced vasospasm and induced coronary artery dilation.[5]

The following month, she had recurrence of anginal symptoms, but without electrocardiogram changes and troponin was within normal limits.

After starting norethindrone with calcium channel blockade, there were three more episodes of chest pain menses, with no further elevation in troponin. The next two menstrual periods occurred with no chest pain. After a full year of norethindrone medical therapy, the patient tried weaning off the medication. However, she had recurrence of symptoms, so she restarted the medication.

Discussion

Initial diagnosis of MINOCA requires ischaemic signs/symptoms, rise and fall of cardiac troponins with one value greater than or equal to

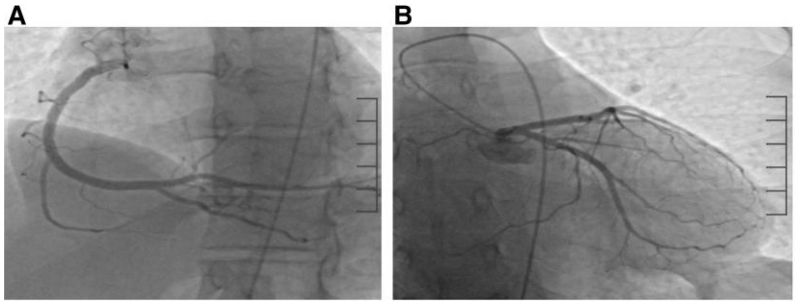

Figure 3 Coronary angiography demonstrated minimal luminal irregularities in both right coronary system (*A*) and left coronary system (*B*).

the 99th percentile upper limit of normal, and non-obstructive CAD identified on imaging.[4] Once alternate aetiologies are excluded, diagnostic work-up includes cardiac MRI imaging, with consideration for functional testing for coronary spasm and intravascular imaging via intravenous ultrasound or optical coherence tomography, to further ascertain the aetiology of MINOCA.[6]

Various mechanisms for coronary artery vasospasm have been proposed, including vascular smooth muscle hyperreactivity, endothelial dysfunction, magnesium deficiency, autonomic nervous system dysregulation, and low-grade inflammation.[2,7] First-line treatment, calcium channel blockade, is aimed at reducing intracellular calcium, to limit contraction and spasm of coronary smooth muscle.

Cyclical variations in sex hormones may play a role in endothelial dysfunction in patients with catamenial vasospasm. The endothelium plays an important role in regulation of coronary artery tone via release of vasodilatory substances such as prostaglandins, nitric oxide and endothelium derived hyperpolarizing factor. Oestrogen, in particular, increases nitric oxide synthase activity, thus relaxing coronary artery smooth muscle.[8,9] In a clinical study of ten women with variant angina, ischaemic episodes were most frequent in the menstrual phase, when oestradiol levels were lowest, and least frequent in the follicular phase, when oestradiol levels were highest.[10] Catamenial chest pain was also recently described in a case series in patients with spontaneous coronary artery dissection, a condition strongly associated with hormonal changes.[11]

In this case, we demonstrate that interruption of sex hormone cycling can terminate catamenial coronary spasm, which in this case caused chest pain in seven successive months, including at least three NSTEMI events. Catamenial symptoms are related to a rapid relative decline in sex steroids immediately prior to menses,[11] although hormone levels remain far higher than in menopause. The etonogestrel implant was ineffective, likely because it suppresses ovulation, but does not suppress the hypothalamic–pituitary–ovarian axis. GnRH agonists, such as depot leuprolide acetate, result in complete ovarian suppression, but the resultant severe decrease in hormone levels could have provoked even more severe coronary spasm. Combined hormonal contraceptives (oestrogen and progestin) were considered, but we avoided this approach due to prothrombotic risks of oestrogen, given the patient's known genetic predisposition for coagulopathy.

In the present case, the initial trigger for recurrent episodes of catamenial myocardial chest pain remains unknown. It is likely that the patient's recent social stressors contributed to the onset of catamenial chest pain. A retrospective, propensity-score-matched study of 30 000 participants identified a higher prevalence of anxiety and depression among patients with coronary artery spasm compared with those with coronary artery disease or those without either coronary

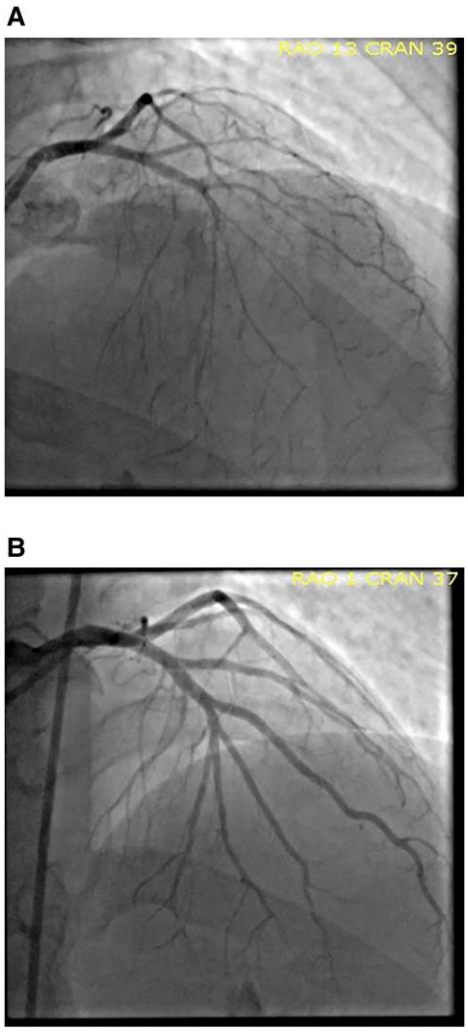

Figure 4 Repeat coronary angiography in which vasospasm was provoked by acetylcholine (*A*) and subsequently relieved by nitroglycerin (*B*). Vasospasm can be observed diffusely throughout the left anterior descending artery and the diagonal branches, as well as throughout the left circumflex artery and the obtuse marginal branches. Angiography after nitroglycerin also revealed a myocardial bridge with systolic compression in the distal LAD.

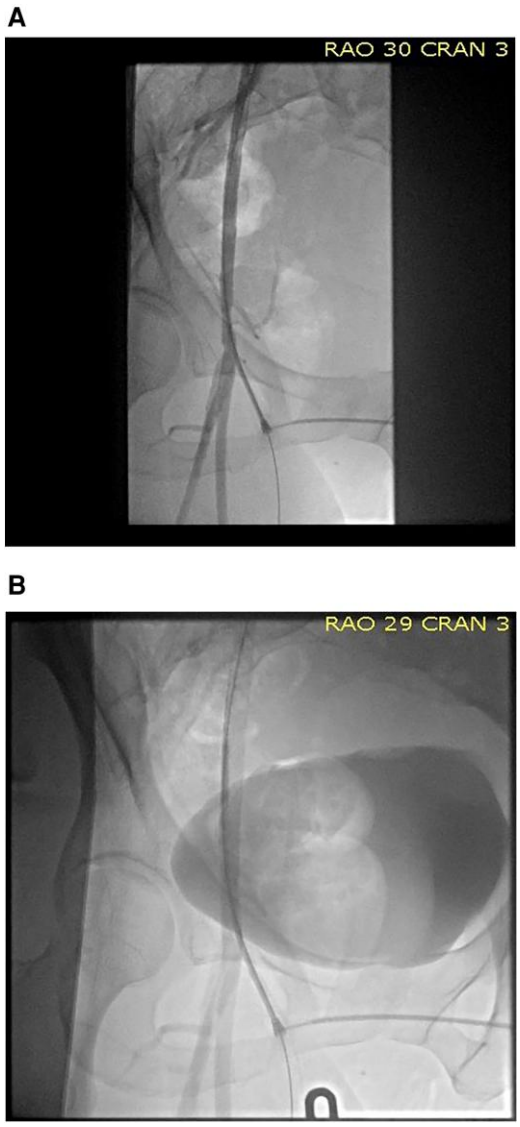

Figure 5 Femoral artery vasospasm mimicking atherosclerotic disease (*A*) subsequently relieved by nitroglycerin (*B*).

artery disease or spasm.[12] During periods of simulated mental stress, such as public speaking or mental arithmetic exercises, coronary artery vasoconstriction was observed in patients with and without coronary artery disease.[13]

Conclusion

Treatment of coronary artery spasm requires a multifaceted approach, including reduction of intracellular calcium, maintenance of endothelial integrity and reduction of triggers or stimuli, in this case, sex hormone cycling.

In this case, suppression of sex hormone variation in addition to calcium channel blockade put an end to repeated monthly NSTEMI events due to coronary spasm. Further investigation is needed to better understand risk factors, optimal management, and outcomes of patients with MINOCA due to coronary spasm.

Lead author biography

Nina Talmor, MD, is an Internal Medicine resident physician at New York University Langone Health Center in New York, NY, USA. She will begin Cardiology Fellowship at NYU in 2022 and plans to pursue a career in interventional cardiology. Her research interests include sex differences in cardiovascular disease, complications occurring during or after angiography, and adult congenital heart disease management.

Supplementary material

Supplementary material is available at *European Heart Journal – Case Reports*.

Slide sets: A fully edited slide set detailing this case and suitable for local presentation is available online as Supplementary data.

Consent: The patient has provided consent for her case to be reported in accordance with COPE guidelines.

Conflict of interest: H.R.R. has received in-kind donation of OCT catheters from Abbott Vascular and CMR software from Siemens for an American Heart Association-funded study of OCT and CMR in MINOCA and in-kind donation from Philips for a study in takotsubo syndrome. N.S. is supported, in part, by the National Heart, Lung, And Blood Institute of the National Institutes of Health under Award Number K23HL150315. N.S. serves on an advisory board as a consultant to Abbott Vascular.

Funding: None declared.

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