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Recurrent chest pain: 'what is essential is invisible to the eye?'

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Introduction

About 90% of patients with clinical presentation of acute myocardial infarction (AMI) undergoing coronary angiography have obstructive coronary artery disease (CAD) (i.e. ≥50% stenosis). These patients have well-established therapeutic management.[1,2] However, 10% of patients with AMI have no-significant epicardial CAD on coronary angiography, that includes both patients with normal coronary arteries and patients with mild coronary atheromatosis (stenosis < 50%). The aetiology of the myocardial necrosis is not immediately apparent, and there are few data about therapeutic strategies.[3,4] Importantly, identifying the pathophysiological mechanism of myocardial infarction with no obstructive coronary arteries (MINOCA) is key for prognostic assessment and therapeutic approach.[5–7]

Case presentation

A 65-year-old Caucasian man, with history of hypertension and type II diabetes mellitus, presented to our emergency department with stuttering chest pain of 6 h duration, radiating to the left arm and relieved by sublingual administration of short-acting nitrates.

The presenting electrocardiogram (ECG) showed an atrial fibrillation with normal ventricular response and negative-ischaemic T waves in leads V1–V4. On admission, the Hs-troponin I concentration was 0.149 ng/mL, peaking at 0.521 ng/mL on the first day then down trending. D-Dimer and C-reactive protein were normal. The echocardiogram showed preserved ejection fraction ≈ 55% with normal regional motion, normal right sections, and trivial mitral regurgitation.

The patient's medical history included chronic kidney disease (Stage III) and previous liver transplantation (HCV related), whereby he was receiving immunosuppressive therapy (everolimus). Ten years before the patient had undergone mitral valvuloplasty for severe mitral regurgitation. Furthermore, he was symptomatic for several episodes of paroxysmal atrial fibrillation with rapid ventricular rate and a bicameral pacemaker has been implanted because of sick sinus syndrome. On admission, the therapy included Metoprolol 50 mg/b.i.d. and oral anticoagulant. Upon these data, differential diagnoses of chest pain were considered including type 1 AMI, myocardial injury due to tachyarrhythmias, myocarditis in immunodeficiency patients, takotsubo syndrome, or non-cardiac chest pain. As type 1 AMI was the most probable medical therapy for non-ST-segment elevation acute coronary syndrome (ACS) was initiated. The GRACE 2.0 and CRUSADE risk scores were 124 points (intermediate-risk) and 46 points (high-risk), respectively.

Coronary angiography was performed 24 h after admission, and an intermediate stenosis of the proximal tract of left anterior descending (LAD) artery was observed. The optical frequency-domain imaging (St. Jude Medical) was used to further evaluate the underlying mechanism of the ACS. This high-resolution intracoronary imaging showed, in the proximal tract of the LAD, a smooth, mainly fibrotic coronary plaque, without signs of rupture and/or erosion, and a diffuse intimal thickening of the entire LAD. Calculated minimal lumen area was 3.1 mm^2, whereas area stenosis was 57%, indicating a non-significant stenosis (*Figure 1*).[8]

The first clinical decision was to optimize anti-anginal drug therapy by doubling the dose of Metoprolol (100 mg/b.i.d.). However, few days later new angina attacks occurred, caused by slight efforts. Therefore, coronary angiography was repeated and fractional flow reserve (FFR) was performed to better characterize LAD stenosis. The invasive FFR measurement, after intracoronary injection of adenosine, was 0.90, confirming a non-significant stenosis (*Figure 2*).

According to our systematic algorithm of investigation of patients with AMI with no obstructive coronary

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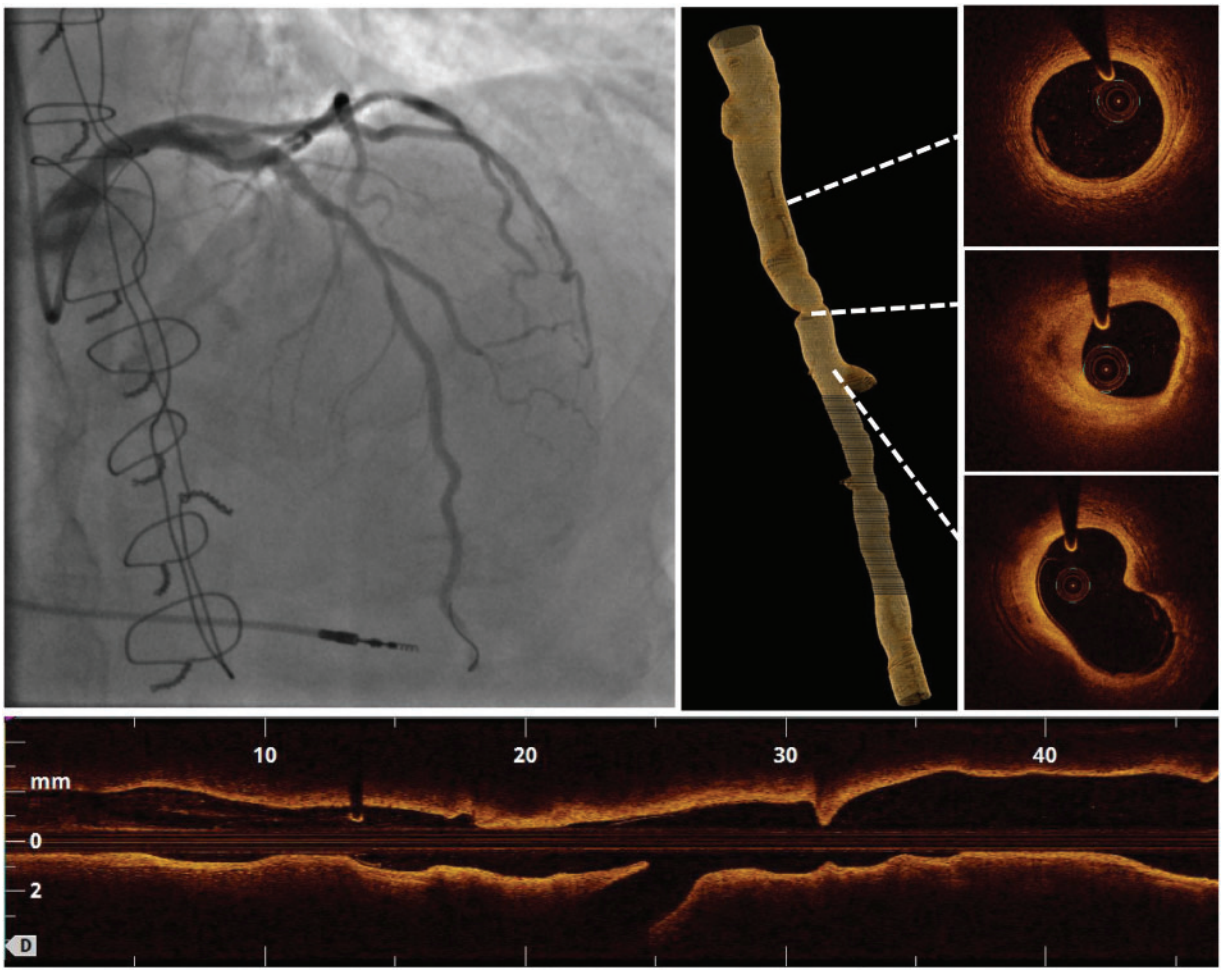

Figure 1 Optical coherence tomography imaging of the left anterior descending artery showing a stenosis with a non-critical minimal luminal area of 3.1 mm^2.

atherosclerosis (MINOCA),[9] we administered intracoronary acetylcholine at increasing dosages. Low dose (50 μg in 10 ml of saline) elicited occlusive diffuse spasm, which involved the medium and distal tracts of the LAD. The patient had chest pain, described as identical to that occurring during spontaneous event. ECG was not informative because of pacemaker rhythm. Intracoronary nitrates were rapidly administered resulting in the relief of both coronary spasm and chest pain (*Figure 3A, B*). Beta-blockers were suspended and diltiazem was added to the patient's drug regimen and titrated up to 360 mg/daily, with no symptoms recurrence or hospital admission up to 12 months later.

Discussion

A sizeable proportion of patients presenting with ACS are found to have absent or only angiographically mild coronary lesions. Dynamic changes in epicardial coronary artery tone, alone or in combination with abnormalities of coronary microcirculation, are an important cause of MINOCA.[3,5,6] It is worth noting that spasm can also occur at the site of atherosclerotic plaques and in concomitance with coronary stenoses at other sites. The susceptibility to spasm can be unmasked by selective intracoronary administration of ergonovine or acetylcholine; the latter is an endothelium-dependent vasodilator and a direct constrictor of vascular smooth muscle cells,[10] because its dual action on muscarinic receptors. Therefore, the impaired vasodilatory response to intra-arterial administration of acetylcholine results from several coexisting abnormalities in endothelial function. Indeed, in arteries lacking endothelium, or where endothelium is dysfunctional, the prevailing effect is vasoconstriction.[11]

Intriguingly, in our patient, administration of low-dose acetylcholine triggered focal coronary spasm not at the level of the proximal atherosclerotic plaque, but rather downstream. This suggests that endothelial dysfunction is not responsible *per se* for coronary spasm, as its anatomical hallmark (diffuse intimal thickening) was present along the entire course of the LAD and was probably even more severe at the site of the proximal atherosclerotic plaque.[11-13]

Our case suggests that a careful elucidation of the specific pathophysiological mechanism operating in each

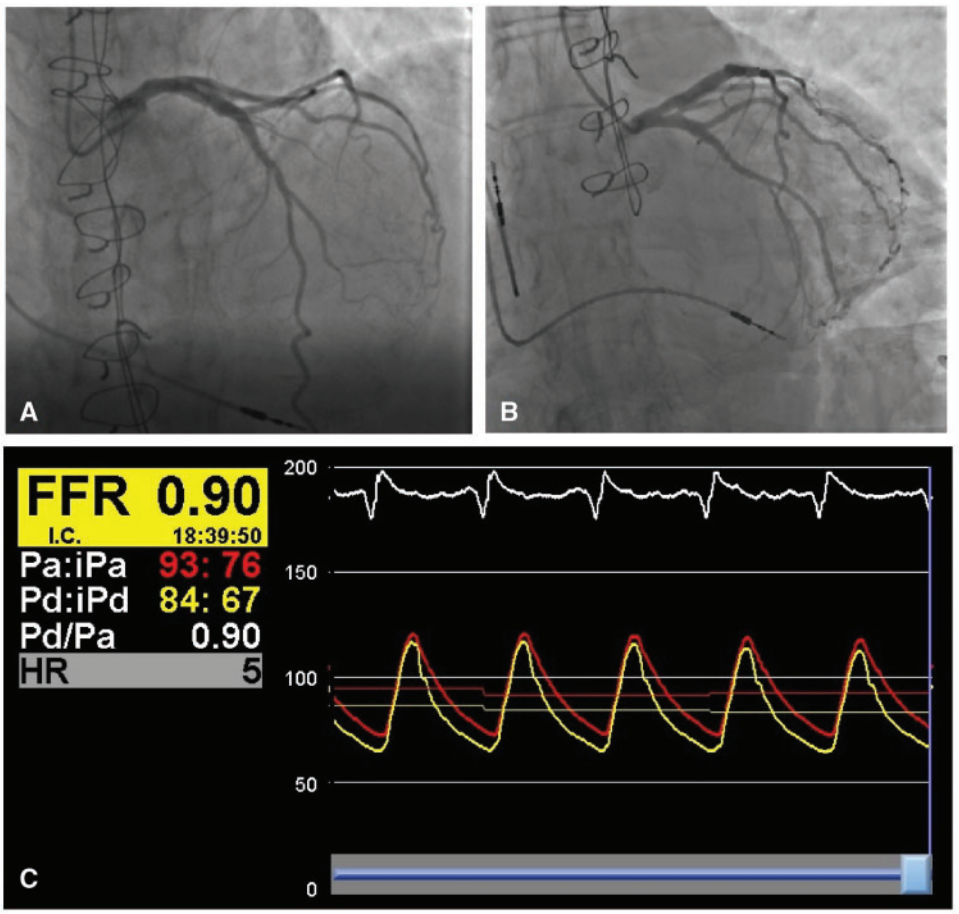

Figure 2 Measurement of fractional flow reserve across the left anterior descending artery stenosis showing a non-critical value of 0.9.

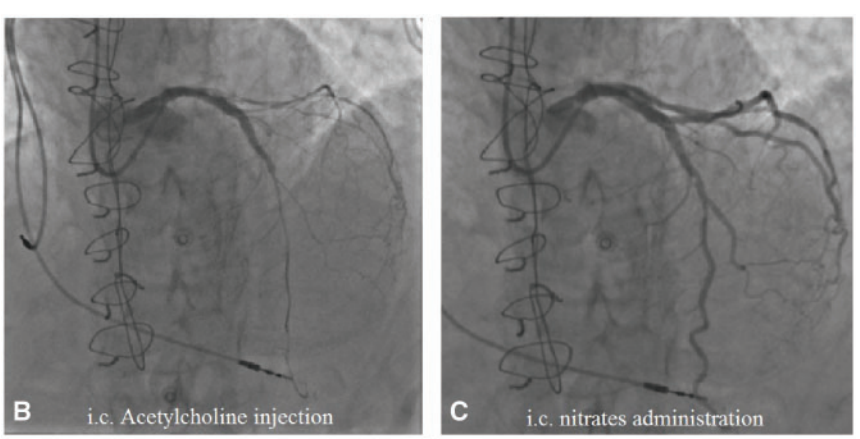

Figure 3 Acetyl choline testing shows spasm of the middle and distal left anterior descending artery associated to the habitual anginal pain.

individual patient presenting with ACS, is crucial for risk stratification and optimization of pharmacological therapy. Coronary epicardial or microvascular vasoconstriction/spasm is a plausible mechanism of the syndrome in a subset of these patients[3,5,6] and should be systematically investigated in MINOCA patients.[14]

Consent statement

The patient consent to report the case has been obtained.

Conflict of interest: F.C. has received honoraria for speaking from BMS, Menarini, Novartis, Sanofi, Servier, as well as grants from Biotronic and Boeringer Ingelheim. The authors didn't receive

any financial support in terms of honorarium by Servier for the supplement articles.

References

1. DeWood MA, Spores J, Notske R, Mouser LT, Burroughs R, Golden MS, Lang HT. Prevalence of total coronary occlusion during the early hours of transmural myocardial infarction. *N Engl J Med* 1980;**303**: 897–902.
2. Roffi M, Patrono C, Collet JP, Mueller C, Valgimigli M, Andreotti F, Bax JJ, Borger MA, Brotons C, Chew DP, Gencer B, Hasenfuss G, Kjeldsen K, Lancellotti P, Landmesser U, Mehilli J, Mukherjee D, Storey RF, Windecker S; ESC Scientific Document Group. 2015 ESC Guidelines for the management of acute coronary syndromes in patients presenting without persistent ST-segment elevation: Task Force for the Management of Acute Coronary Syndromes in Patients Presenting without Persistent ST-Segment Elevation of the European Society of Cardiology (ESC). *Eur Heart J* 2016;**37**:267–315.
3. 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.
4. Lindahl B, Baron T, Erlinge D, Hadziosmanovic N, Nordenskjöld A, Gard A, Jernberg T. Medical therapy for secondary prevention and long-term outcome in patients with myocardial infarction with non-obstructive coronary artery disease. *Circulation* 2017;**135**: 1481–1489.
5. Agewall S, Beltrame JF, Reynolds HR, Niessner A, Rosano G, Caforio AL, De Caterina R, Zimarino M, Roffi M, Kjeldsen K, Atar D, Kaski JC, Sechtem U, Tornvall P; WG on Cardiovascular Pharmacotherapy. ESC working group position paper on myocardial infarction with non-obstructive coronary arteries. *Eur Heart J* 2017;**38**:143–153.
6. Lanza GA, Careri G, Stazi A, Villano A, De Vita A, Aurigemma C, Crea F. Clinical spectrum and outcome of patients with non-ST-segment elevation acute coronary syndrome and no obstructive coronary atherosclerosis. *Circ J* 2016;**80**:1600–1606.
7. Planer D, Mehran R, Ohman EM, White HD, Newman JD, Xu K, Stone GW. Prognosis of patients with non-ST-segment-elevation myocardial infarction and nonobstructive coronary artery disease: propensity-matched analysis from the Acute Catheterization and Urgent Intervention Triage Strategy trial. *Circ Cardiovasc Interv* 2014;**7**: 285–293.
8. Gonzalo N, Escaned J, Alfonso F, Nolte C, Rodriguez V, Jimenez-Quevedo P, Bañuelos C, Fernández-Ortiz A, Garcia E, Hernandez-Antolin R, Macaya C. Morphometric assessment of coronary stenosis relevance with optical coherence tomography: a comparison with fractional flow reserve and intravascular ultrasound. *J Am Coll Cardiol* 2012;**59**:1080–1089.
9. Niccoli G, Scalone G, Crea F. Acute myocardial infarction with no obstructive coronary atherosclerosis: mechanisms and management. *Eur Heart J* 2015;**36**:475–481.
10. Crea F, Camici PG, Bairey Merz CN. Coronary microvascular dysfunction: an update. *Eur Heart J* 2014;**35**:1101–1111.
11. Kinlay S. Coronary artery spasm as a cause of angina. *Circulation* 2014;**129**:1717–1719.
12. Lanza GA, Careri G, Crea F. Mechanisms of coronary artery spasm. *Circulation* 2011;**124**:1774–1782.
13. Shimokawa H. 2014 Williams Harvey Lecture: importance of coronary vasomotion abnormalities-from bench to bedside. *Eur Heart J* 2014; **35**:3180–3193.
14. Montone RA, Niccoli G, Fracassi F, Russo M, Gurgoglione F, Cammà G, Lanza GA, Crea 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.