Variant Angina Associated with Coronary Artery Endothelial Dysfunction and Myocardial Bridge: A Case Report and Review of the Literature

Federico Nardi¹, Edoardo Verna², Gioel Gabrio Secco³, Andrea Rognoni⁴, Angelo Sante Bongo⁴, Gabriele Iraghi¹, Stefano Bertuol¹ and Alessandro Lupi¹

Abstract

The association of variant angina (VA) and myocardial bridges is a rare finding. We describe a case of VA with recurrent coronary spasm triggered by different stimuli at the site of a myocardial bridge. The interplay of endothelial dysfunction, coronary vasoconstriction and myocardial bridging was detected by intracoronary acetylcholine test and IVUS. We speculate that mechanical stimulation at the bridge site caused endothelial dysfunction and enhanced local susceptibility to vasoconstrictor stimuli. Variant angina should always be suspected in cases of ST-elevation acute coronary syndrome without any significant angiographic coronary stenosis.

Key words: variant angina, coronary spasm, myocardial bridge, myocardial ischemia, acute coronary syndrome

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Introduction

Variant angina (VA), first described by Prinzmetal et al in 1959, is caused by transient and recurrent coronary spasm leading to repetitive episodes of transmural myocardial ischemia (1-6). Endothelial dysfunction has been considered as an important predisposing condition for VA (7) and many different stimuli, such as hyperventilation, ergonovine, dobutamine or acetylcholine administration, cold pressor test, exercise and mental stress can trigger coronary spasm (8-10).

Myocardial bridging, which is when a segment of a major epicardial coronary artery runs intramurally through the myocardium, has been episodically associated with VA (11-13); a few published reports have indicated a causal relationship between these conditions (14-16).

We present an additional case of VA with evidence of coronary spasm related to an isolated myocardial bridging of the left anterior descending coronary artery (LAD). In this case we explored the relationship between bridging, plaque burden and endothelial dysfunction by provocative tests for coronary spasm and intravascular ultrasound (IVUS).

Case Report

A 43-year-old man without previous cardiovascular events or coronary risk factors was admitted to the Emergency Department (ED) of a primary care hospital for the sudden onset of chest pain. The physical examination revealed a normal heart rate (85 beats/minute) with slightly high blood pressure (150/95 mmHg); serial 12-lead electrocardiograms showed the evidence of anterior-lateral ST elevation (Fig. 1, panel A). The patient was treated with oxygen, aspirin 300 mg, clopidogrel loading dose 600 mg, intravenous infusion of nitroglycerin, betablocker and rTPA according to GUSTO protocol, with rapid resolution of ECG changes (Fig. 1, panel B). Baseline CK-MB and cardiac troponin I (cTnI) levels

¹Department of Cardiology, Ospedale Castelli, Italy, ²Department of Cardiology, Ospedale di Circolo and University Hospital, Italy, ³Division of Cardiology, University of Eastern Piedmont, “Maggiore della Carità” Hospital, Italy and ⁴Division of Cardiology II, “Maggiore della Carità” Hospital, Italy

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Correspondence to Dr. Alessandro Lupi, lupialessandro1@tin.it
were within normal ranges at admission but were significantly increased after a few hours. The patient was then referred to a tertiary care hospital in order to perform cardiac catheterization that demonstrated mild disease of the mid-LAD and mild apical hypokinesia with a normal contractility of the remaining segments.

Five days later the patient was discharged on aspirin 100 mg od, clopidogrel 75 mg od, carvedilol 6.25 mg bid, ramipril 2.5 mg od, rosuvastatin 10 mg od, PUFA-Omega3 1 g od and pantoprazole 20 mg od and with a diagnosis of “aborted STEMI with angiographically non-significant coronary artery disease”.

One week later the patient was readmitted to the ED for recurrent chest pain and ECG evidence of anterior-lateral ST elevation, rapidly relieved by i.v. nitrate infusion. As variant angina was suspected, beta-blocker was substituted by diltiazem 120 mg tid. The patient was then evaluated by treadmill exercise test which, at high workload, resulted in typical angina, peaking of the T wave in the anterior leads and ST depression in the inferior leads.

The patient was referred again to the Catheterization Laboratory for a new coronary angiography and functional coronary testing. Immediately before the procedure the patient experienced recurrent chest pain, anxiety, tachycardia, hypertension and diffuse anterolateral ST segment depression. The subsequent coronary angiography showed multifocal epicardial coronary spasm involving the mid-LAD, the diagonal and septal branches and the left circumflex (Fig. 1, panel C). Repeated contrast injection following intracoronary (i.c.) nitrates showed the resolution of coronary spasms (Fig. 1, panel D) but unmasked a long intramyocardial tract of the LAD (Fig. 2, panel A and B). Probably this finding was not highlighted by the previous coronary angiogram because the patient was on beta-blockers. An IVUS examination was then performed, showing diffuse coronary atherosclerosis without significant coronary stenosis in the mid-LAD and the LCFx and confirming the presence of a muscular bridge on mid-LAD with significant systolic luminal narrowing (Fig. 2, panel C and D). Acetylcholine 10 mcg was then administered in the left main through the guiding catheter, causing the recurrence of coronary spasm only at the site of the LAD bridge in the absence of any apparent dilation of the angiographically normal coronary segments (Fig. 2, panel E).

The patient was then discharged on aspirin 100 mg od, nebivolol 5 mg od, ramipril 2.5 mg od, rosuvastatin 20 mg od, transdermal nitroglycerin patch and pantoprazole 20 mg od as medical treatment; the final diagnosis of variant angina was made. At the 6-month follow-up visit he was asymptomatic and reported no cardiac events; the ECG treadmill test, performed on medical therapy, was normal; no change was made in pharmacological therapy.

Figure 1. Panel A shows 12-lead ECG of the patient at admission with anterior-lateral ST-segment elevation. Panel B shows 12-lead ECG of the patient after intravenous nitroglycerin and rTPA bolus with resolution of the ST-segment abnormalities present at admission. Panel C shows spontaneous multifocal spasm of the left anterior descending, the diagonal and the septal branches and the left circumflex coronary arteries. Panel D shows resolution of spasms with intracoronary nitroglycerin administration.
We encountered an uncommon case of VA, characterized by the coexistence of multifocal coronary spasm and a LAD myocardial bridge. In this patient IVUS demonstrated the presence of diffuse angiographically silent coronary atherosclerosis and the acetylcholine test unmasked diffuse endothelial dysfunction with diffusely blunted coronary vasodilation and severe vasoconstriction at the site of the bridge.

In 1959 Prinzmetal et al described a variant form of angina pectoris (1, 2), characterized by typical anginal pain at rest and striking ECG changes with ST-segment elevation. In VA chest pain frequently recurs at regular intervals, early in the morning, and it may be associated with severe tachy- or bradyarrhythmias with a small but not negligible risk of sudden death or evolution to acute myocardial infarction (1-6). The pathophysiological mechanism of variant angina, suggested in the original description of Prinzmetal, was confirmed by Maseri et al (17) by observing that chest pain episodes in VA were not preceded by increases in heart rate, blood pressure or the 1st derivative of the left ventricular pressure curve (dP/dt), thus excluding an increase in myocardial oxygen consumption as the mechanism of the angina symptoms. Thus a transient dynamic cause of reduction of coronary blood flow, namely coronary spasm, should be operating in VA patients (4).

Coronary spasm which can occur in one of the epicardial branches of the coronary arteries, is usually focal and tends to recur in the same location, generally at the site of an atherosclerotic lesion (5). However coronary spasm can be multifocal or diffuse and can affect coronary arteries that appear normal on coronary angiography (6-18). In such cases IVUS and necroscopy almost always reveal angiographically silent atherosclerosis at the site of the spasm (19-21).

Coronary spasm causes transmural myocardial ischemia, but sometimes it can trigger coronary thrombosis, with a potential evolution to myocardial infarction or sudden cardiac death (5). Actually patients with VA often experience elevation of fibrinopeptide A or plasminogen activator antigen levels, generally early in the morning (22, 23).

The mechanisms operating in VA are not fully understood. Neurological, humoral and local factors have been proposed, but no conclusive data have been reported to date. A central nervous mechanism is unlikely to cause coronary
spasms, as it can occur in transplanted denervated hearts (24). A diffuse coronary hypersensitivity to vasoconstrictive stimuli has been described by some authors (25) but it has been excluded by others (26). Spasm recurrence at the same coronary segment suggests that local factors could be important (27). Reduced endothelial vasodilatory function has been described in VA and it could represent a predisposing condition, even if the presence of abnormal nitric oxide activity at the site of coronary spasm is controversial (28, 29). Increased smooth muscle contractility also seems to play an important role in coronary spasm, possibly caused by leukotrienes, serotonin and vasoconstrictive mitogens, as well as by high concentrations of vasoconstrictive substances in areas adjacent to active atherosclerotic plaques (30). The most likely scenario behind focal coronary spasm is the presence of blunted endothelial function that cannot balance with flow-mediated vasodilation the nonspecific vasoconstrictor stimuli such as catecholamine, serotonin, histamine, thromboxane A2 and endothelin at the vascular smooth muscle level (31). Actually many nonspecific stimuli, such as i.c. infusion of ergonovine or acetylcholine, cold pressor test, exercise, dobutamine stress and mental stress have been used for coronary spasm provocative tests (32).

The mechanical stimulation of myocardial bridging, a common congenital coronary abnormality, has been causally associated with variant angina in a few published cases (11-13). The pathophysiological mechanism proposed to explain the association of coronary bridges and spasm is chronic mechanical stress determining focal endothelial dysfunction, with enhanced local vascular reactivity to systemic vasoconstrictor stimuli (14).

In the present case, VA mimicked aborted myocardial infarction. Generally rapid relief by nitroglycerin administration and the absence of myocardial enzyme leakage, leukocytosis, neutrophilia or increased sedimentation rate are useful clues for the correct diagnosis of variant angina, even if prolonged and severe episodes of coronary spasm are associated with the rise of more sensible myocardial damage markers like troponins. Unfortunately in the present case the co-administration of nitrates and thrombolitics rendered it difficult to ascertain if the rapid resolution of the attack was due to spasm or thrombolysis. Moreover in our case the CK-MB curve was negative but cTnI rose in the range of the “Universal definition of MI” (3 times or more the upper reference limits), further complicating the differential diagnosis. Takotsubo cardiomyopathy, another possible clinical condition to take into account in the differential diagnosis. Thus, multifocal coronary spasm could be induced by various nonspecific vasoconstrictor stimuli but recurs most frequently at the site of the most damaged endothelium, the LAD bridge tract. In the present case the atherosclerotic burden was not greater at the site of the coronary bridge, the preferred site of spasm recurrence. However, the degree of atherosclerosis is only mildly correlated with endothelial dysfunction (34), which generally anticipates advanced atherosclerotic changes (35). Actually low dose Ach infusion, which unmasks endothelial dysfunction, reproduced coronary spasm only at the site of the LAD bridge.

Finding the appropriate therapeutic options with the coexistence of VA and myocardial bridging can be troublesome. The principal objective in treating VA is to prevent coronary spasm. Sublingual nitroglycerin makes an angina episode pass in a few minutes and transdermal or long-acting oral nitrates and high dose calcium channel blockers are the mainstream of VA treatment, while beta-blockers could enhance spasm by blocking beta-2 receptors of coronary smooth muscle cells and are therefore contraindicated in this clinical setting. On the other hand, ischemia associated with myocardial bridges is due to an imbalance of myocardial oxygen consumption (physical effort, tachycardia) and myocardial oxygen supply brought on by the shortening of the diastole and systolic compression of the intramyocardial coronary segment. Thus, beta-blockers are the therapy of choice for patients with myocardial bridges suspected to cause effort-induced ischemia (36).

In the present case the features of treadmill exercise test could have been the result of systolic coronary compression, effort-induced coronary spasm or both, further complicating the clinical decision-making.

The presence of the LAD bridge, as well as the importance of the sympathetic stimuli in provoking coronary spasms (early morning recurrence of spontaneous episodes, mental stress and anxiety, exercise) prompted us to seek for
an alternative strategy. We hypothesized that a new generation beta-blocker with NO donor activity like nebivolol (37) could reduce myocardial squeezing of the LAD bridge without exacerbating coronary spasm, thanks to the increased NO concentrations in the vessel walls. Actually the patient did well in the follow-up with nebivolol 5 mg od and a maximal exercise test did not induce symptoms or signs of myocardial ischemia.

In conclusion, the present case underscored the need for careful evaluation in patients with ST-elevation acute coronary syndrome, in the absence of angiographically significant coronary stenosis, to rule out VA, as the medical treatments recommended for this clinical condition differ profoundly from standard treatment of atherothrombotic acute coronary syndromes and takotsubo cardiomyopathy. In selected cases a thorough evaluation with IVUS and endothelial function tests can reveal complex scenarios and provide important findings to facilitate challenging therapeutic decisions.

The authors state that they have no Conflict of Interest (COI).

References


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