

CASE PRESENTATION

Prinzmetal's angina with multivessel spasm successfully treated by using two different types of calcium channel blockers

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Abstract: Prinzmetal's angina is characterized by recurrent episodes of chest pain which occur during rest or sleep, associated with transient elevation of the ST segment on the electrocardiogram. The underlying mechanism is focal or diffuse coronary artery spasm that can affect one or multiple coronary artery sites simultaneously or consecutively. We report the case of a 53-year-old woman with persistent angina which presented with multivessel spasm recorded during coronary angiography without provocation test. The symptomatology of the patient was effectively relieved by combining two calcium channel blockers with a selective inhibitor of phosphodiesterase-3 and a long-lasting nitrate.

Keywords: Prinzmetal angina, coronary artery spasm, treatment.

Rezumat: Angina Prinzmetal se caracterizează prin episoade recurente de durere toracică care apar în repaus sau în somn, asociate cu supradenivelarea tranzitorie a segmentului ST pe electrocardiogramă. Mecanismul care stă la baza apariției anginei este spasmul arterei coronare focal sau difuz care poate afecta una sau mai multe zone ale arterei coronare simultan sau consecutiv. Prezentăm cazul unei femei de 53 de ani cu angină persistentă prezentată cu spasm multivascular înregistrat în timpul angiografiei coronariene fără teste de provocare. Simptomatologia pacientei a fost controlată prin combinarea a două blocante ale canalelor de calciu cu un inhibitor selectiv al fosfodiesterazei-3 și un nitrat cu efect de lungă durată.

Cuvinte cheie: Angina Prinzmetal, spasm coronarian, tratament.

INTRODUCTION

Typical angina is characterized by recurrent attacks of chest pain, caused by exertion, and relieved by rest or by administration of nitroglycerin. In 1959, Myron Prinzmetal and his colleagues first described an atypical form of angina, which they named 'variant angina'¹. Chest pain in variant angina is not caused by physical exercise, it almost always occurs at rest or during sleep, and it is usually associated with transient ST segment elevation on the electrocardiogram. Even though it is uncommon, Prinzmetal's angina has important implications for patient's quality of life, morbidity and cardiac mortality, being associated with potentially lethal complications, such as ventricular tachycardia, ventricular fibrillation, advanced atrioventricular block and asystole^{2,3}.

CASE PRESENTATION

A 53-year-old woman presented to the emergency department for repeated episodes of constrictive chest pain with irradiation at the submandibular level, 2-3 minutes in duration, occurring during sleep, in case of emotional stress or small physical exertion. She had suffered from the anginal attacks for 4 years, but in the previous month, episodes increased in frequency and appeared during mild exertion, as well. Coronary angiography was performed three years prior, when a severe spasm of the right coronary artery was triggered by contrast injection (Figure 1, A-D). At that point, the patient was treated with Verapamil 240 mg/day, Isosorbide dinitrate 20 mg bid, Atorvastatin 40 mg/day, Aspirin 100 mg/day, Trimetazidine 35 mg bid. Other clinical history included recent menopause and

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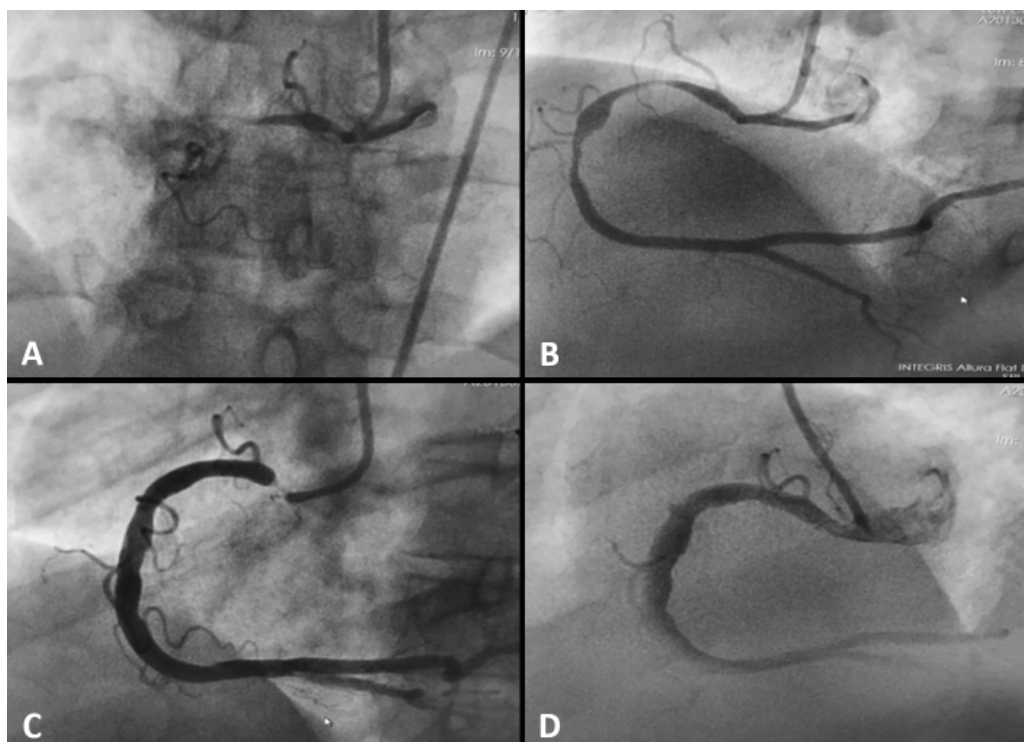


Figure 1. Coronary angiography from 2015. Severe right coronary artery spasm with complete occlusion (A); persistence of diffuse spasm predominant in the proximal and middle segments (B); severe focal spasm at the origin of right coronary artery (C); the vessel after almost complete remission of the spasm (D).

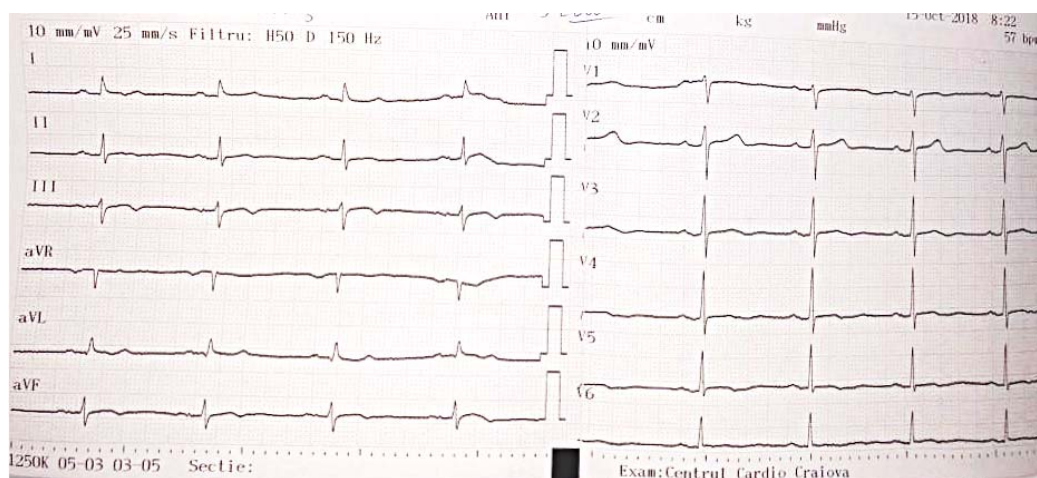


Figure 2. Resting electrocardiogram at presentation, without chest pain.

significant family history (brother died suddenly at age 45).

Clinical exam revealed an overweight patient (BMI 26.2 kg/m²), blood pressure was 140/80 mmHg, heart rate was 55 bpm, rhythmic heart sounds with no murmurs and no pulmonary rales.

The resting electrocardiogram (ECG) at presentation showed sinus rhythm, heart rate of 55 bpm, QRS

axis 0°, negative T waves in infero-lateral leads (Figure 2).

On transthoracic echocardiography, left ventricular structure and systolic function were normal, with an ejection fraction of 65% calculated with the Simpson's biplane method, and normal segmental contraction. Transmitral diastolic flow derived from Doppler echocardiography as well as the E/e' ratio showed normal

diastolic function of the left ventricle and normal filling pressures. No abnormal findings were reported during echocardiography.

Standard blood tests were within normal range, including the myocardial necrosis specific markers which were normal at admission and without any change during hospitalization.

Due to the unstable symptoms, the patient was hospitalized for further assessment and treatment. During hospitalization, the patient presented several episodes of severe chest pain, 2 to 3 minutes in duration, associated with ST segment elevation of up to 4 mm in leads D_{II}, D_{III}, aVF, V₅-V₆, and ST segment downward depression in V₁-V₂ (Figure 3).

24-hour ECG monitoring revealed episodes of transient ST segment elevation with a duration of up to 2 minutes without conduction or rhythm disturbances.

In this context, coronary angiography reevaluation was considered appropriate and revealed a 70% stenosis in the first diagonal branch of left anterior descending artery (Figure 4, A). Although the area supplied by the affected artery did not seem significant, it was decided to electively implant a stent in a programmed procedure. Within 72 hours, a second coronary angiography was performed with the intent of percutaneous coronary intervention (PCI), but it revealed normal flow in the first diagonal and severe spasm in the middle segment of left anterior descending artery, which was rapidly relieved after intracoronary nitroglycerin administration (Figure 4, B-D). The second coronary angiography allowed us to conclude that coronary vasospasm with multiple localizations (right

coronary artery, left anterior descendent artery, and diagonal branch) was the underlying mechanism for the clinical symptoms.

The persistence of angina episodes forced us to try uncommon therapeutic solutions: the association of two calcium channel blockers and Cilostazol. The patient was treated with 360 mg of Diltiazem, 5 mg of Amlodipine, 40 mg of Isosorbide dinitrate, 200 mg of Cilostazol, 70 mg of Trimetazidine, 75 mg of Clopidogrel, 40 mg of Atorvastatin and 1000 mg of Magnesium orotate. The angina episodes were not repeated during hospitalization. At the most recent follow-up visit, almost one year after the hospitalization, the patient reported no recurrence of chest pain.

DISCUSSION

The case presented here raises some important issues which are worth discussing: (i) the occurrence of multivessel spasm in vasospastic angina recorded during coronary angiography without provocation; (ii) why a previously well-controlled patient became unstable; (iii) the medical options in patients with symptoms not controlled by single calcium channel blocker administration.

Vasospastic angina is a form of angina in which coronary artery spasm is causing ischemia. Use of the term Prinzmetal's angina (variant angina), should be restricted to cases in which there is transient ST segment elevation during anginal episodes.

According to the *Coronary Vasomotion Disorders International Study Group (COVADIS)* the diagnosis of vasospastic angina requires the fulfillment of three types

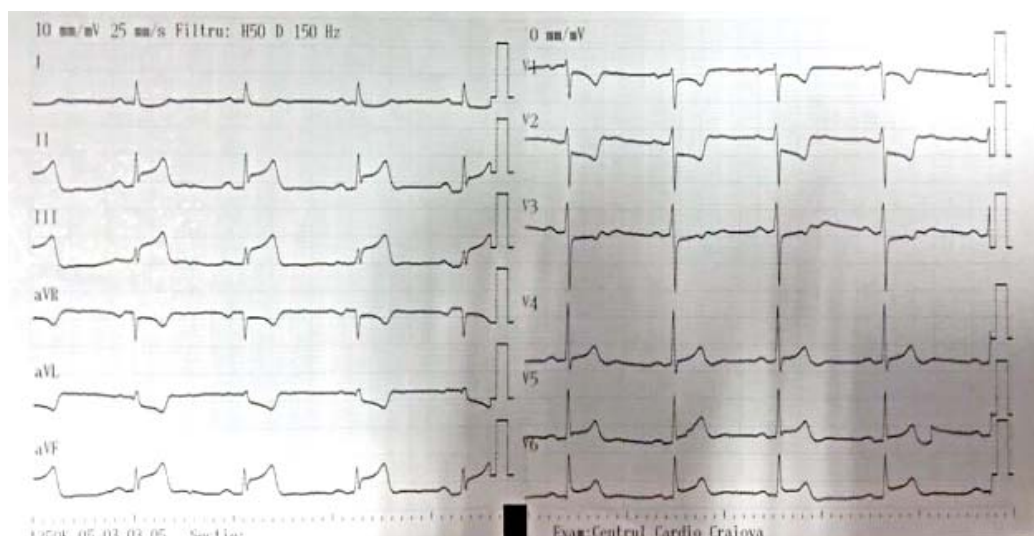


Figure 3. Electrocardiogram recorded during chest pain episode.

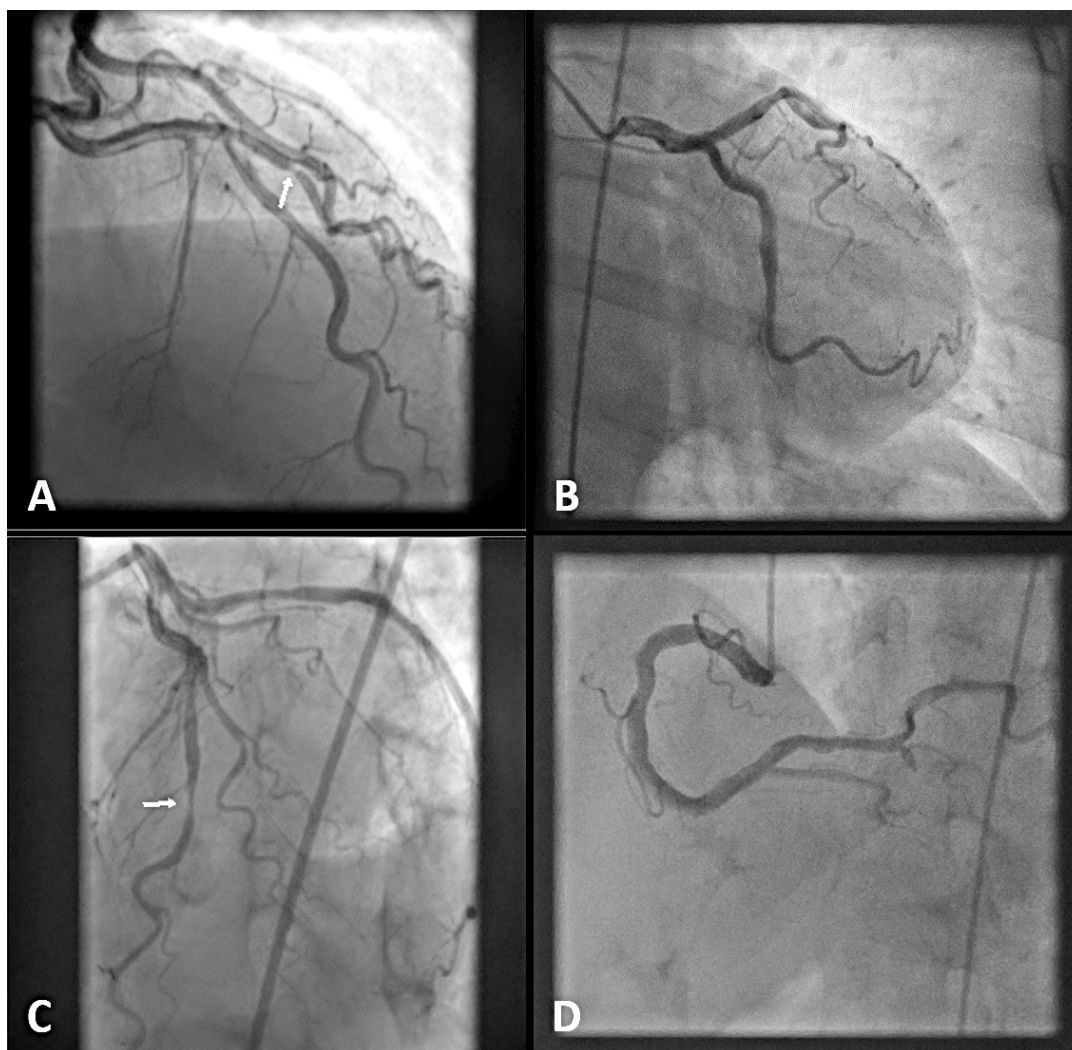


Figure 4. Coronary angiography from 2018. 70% stenosis of first diagonal branch of left anterior descending artery (A); left circumflex artery without significant lesions (B); diffuse spasm of left anterior descending artery with severe obstruction in middle segment and diffuse spasm of first diagonal branch but without focal obstruction (C); right coronary artery with diffuse atheroma plaques but no stenosis or spasm (D).

of criteria: classical clinical manifestations, transient ECG changes during chest pain episodes, angiographic demonstration of coronary artery spasm⁴ (Table I).

Coronary artery spasm is the central mechanism of ischemia in Prinzmetal's (variant) angina^{5,6}. A temporary increase in vascular tonus in a subepicardial coronary artery with or without atherosclerotic changes may temporarily cause critical hypoperfusion in a myocardial area, resulting in symptoms specific to variant angina and transient electrocardiographic abnormalities. The mechanism of coronary spasm is complex and involves multiple pathogenic pathways such as: endothelial dysfunction, smooth muscle cell hyperreactivity, inflammation, decreased nitric oxide availabi-

lity, oxidative stress, magnesium deficiency, autonomic nervous system imbalance, genetic polymorphisms^{7,8}.

Coronary artery spasm usually involves a major artery or large branches, it can be focal or diffuse, it can affect one site or multiple sites of one artery, or more than one vessel at a time, and in some patients it has migratory character^{9,10}. Multivessel spasm has variable prevalence, being reported in 9-52% of patients^{11,12} and it is one of the predictors of major adverse cardiac events, as part of the clinical risk score developed by the Japanese Coronary Spasm Association¹³. In patients with variant angina, catheter stimulation of a coronary artery during angiography may precipitate spasm with angina and ST-segment elevation. Catheter-

Table 1. Vasospastic angina diagnostic criteria⁴

<p>1. Nitrate-responsive angina during spontaneous episode, with at least one of the following:</p> <ul style="list-style-type: none">a. Rest angina, especially between night and early morningb. Marked diurnal variation in exercise tolerance, reduced in the morningc. Hyperventilation can precipitate an episoded. Calcium channel blockers (but not β-blockers) suppress episodes <p>2. Transient ischemic ECG changes during spontaneous episode, including any of the following (in at least two contiguous leads):</p> <ul style="list-style-type: none">a. ST segment elevation ≥ 0.1 mVb. ST segment depression ≥ 0.1 mVc. New negative U waves <p>3. Coronary artery spasm defined as transient total or subtotal coronary artery occlusion ($>90\%$ constriction) with angina and ischemic ECG changes either spontaneously or in response to a provocative stimulus (typically acetylcholine, ergot, or hyperventilation)</p>
<p>Definitive vasospastic angina is diagnosed if nitrate-responsive angina is evident during spontaneous episodes and either the transient ischemic ECG changes during the spontaneous episodes or coronary artery spasm criteria are fulfilled.</p> <p>Suspected vasospastic angina is diagnosed if nitrate-responsive angina is evident during spontaneous episodes, but transient ischemic ECG changes are equivocal or unavailable and coronary artery spasm criteria are equivocal.</p>

ter-induced spasm is usually located in the proximal segment of the right coronary artery.

Prinzmetal's angina can have a cyclical evolution, with long periods of calm followed by reappearance of anginal attacks. The exact cause of this is not known yet, but it could be related to the variability in the degree of local vascular hypersensitivity, or in the intensity of an unknown provoking stimulus¹⁴. The patient we presented had recently begun menopause. Lower levels of estradiol aggravate endothelial dysfunction and are associated with an increased frequency of angina attacks. Also, the premenopausal period determines variations in estrogen hormone levels which, according to the results of Kawano et al.¹⁵, induce changes in endothelial function and the cyclical appearance of myocardial ischemia in women with vasospastic angina depending on the period of menstrual cycle associated with the level the lowest estrogen hormone. In a study on 15 women estrogen supplementation suppressed the hyperventilation-induced attacks in women with variant angina, an effect which could be explained by an improvement of endothelial function¹⁶.

Nitrates and calcium channel blockers are the mainstay of treatment in vasospastic angina⁷. Long-acting calcium channel blockers are highly effective in reducing angina frequency and also improve long-term prognosis¹⁷. A combined use of two calcium channel blockers in patients with refractory symptoms has been proposed by some authors, but evidence about its effectiveness is scarce¹⁰. In a 1980 report by Kishida¹⁸ the use of Nifedipine and Diltiazem in 15 patients completely suppressed angina in 11 patients and decreased the episodes by at least half in 4 patients. This approach has some pharmacological basis, as there are significant differences in the mechanism of action between the three main types in the class¹⁹. In our

patient we preferred to associate Amlodipine to Diltiazem due to the low heart rate, as Verapamil is known to be more bradycardia inducing.

Short-acting nitrates are very effective in treating anginal attacks. For reducing the frequency of chest pain episodes in patients with vasospastic angina current guidelines recommend the use of long-acting nitrate agents in combination with calcium channel blockers in patients who remain symptomatic⁷.

Other agents have been tried with variable success, including endothelin antagonists²⁰, Nicorandil, Fasudil (Rho-kinase inhibitor)⁷, Cilostazol²¹ or Magnesium²². The use of non-selective beta-blockers should be avoided as they cause a blockade of vasodilatory effects on β -adrenergic receptors, covering the effects of sympathetic stimulation in a pure α -adrenergic vasoconstrictor response²³. Also, high doses of Aspirin, which may decrease prostaglandin production and worsen coronary artery spasm, should be avoided²⁴.

CONCLUSION

Coronary artery spasm in Prinzmetal's angina may be extremely variable in terms of localization and appearance over time. In subjects with persistent episodes of chest pain despite conventional treatment, a combination between two calcium channel blockers, a long-lasting nitrate and a selective inhibitor of phosphodiesterase-3 could be helpful to relieve symptoms.

Conflict of interest: none declared.

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