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Prinzmetal angina in a patient with previous coronary artery disease. Topic review and case report

Angina de Prinzmetal em paciente com doença arterial coronariana prévia. Revisão do tema e relato de um caso

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ABSTRACT – Prinzmetal angina is described as episodes of chest pain that occur at rest, associated with electrocardiographic changes in the ST-segment, which may or may not evolve to ischemia, and are not caused by coronary artery disease, having more recently been related to a coronary vasospasm. This diagnosis becomes especially challenging in patients who have already undergone previous percutaneous coronary procedures. We report a case of a patient diagnosed with Prinzmetal angina with a recent percutaneous coronary intervention due to coronary artery disease.

Keywords: Coronary artery disease; Coronary vasospasm; Angina pectoris, variant

RESUMO – A angina de Prinzmetal foi descrita originalmente como uma precordialgia que se apresentava ao repouso, associada a alterações do segmento ST no eletrocardiograma, podendo ou não cursar com isquemia, não causada por doença arterial coronariana, tendo sido posteriormente relacionada ao vasoespasmo coronariano. Esse diagnóstico se torna especialmente desafiador em pacientes que já se submeteram a intervenções coronárias percutâneas prévias. Relatamos um caso de difícil diagnóstico de um paciente com angina de Prinzmetal com recente intervenção coronária percutânea decorrente de doença arterial coronariana.

Descritores: Doença da artéria coronariana; Vasoespasmo coronário; *Angina pectoris* variante

INTRODUCTION

Prinzmetal angina, or variant angina, was described by Dr. Myron Prinzmetal, in 1959, as a tightness chest pain that, unlike typical angina, occurs at rest, especially at night, usually waking up the patient, who has no coronary lesions that would justify the angina and the changes in the ST-segment on electrocardiography (ECG). Therefore, this special type of angina was later interpreted as resulting from coronary vasospasm, which is a phenomenon that can occur in patients with or without coronary atherosclerotic lesions. Coronary vasospasm may be focal or diffuse, sometimes with changing patterns in the same patient,[1] and is associated with several different clinical settings, such as stable angina, acute coronary syndrome, arrhythmia, syncope, or sudden cardiac death.[2,3]

The pathophysiology of coronary vasospasm to date has not been completely elucidated, but it is believed that some mechanisms involved are related to hyperreactivity of the arteries and hypercontractility of the coronary muscle.[4] Rho-kinases are involved in regulation of contractility and may play a crucial role in the pathogenesis of coronary artery spasm, by a vasoconstrictor stimulus related to calcium sensitization.[4] This happens due to increase in intracellular calcium, which promotes hypercontraction of the coronary artery, leading to coronary vasospasm. Since calcium channel blockers prevent calcium from entering cells, this explains their efficacy in suppressing coronary spasm. A dysfunction in the local production of nitric oxide, which is a potent vasodilator, has also been related to coronary vasospasm. A higher incidence of Prinzmetal angina was

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also observed in patients of Japanese ethnicity, smokers, or in situations related to use of some drugs or medications.[5] The long-term prognosis of patients with Prinzmetal angina is generally good, but there are reports of patients with major cardiac events, including myocardial infarction (MI) and sudden cardiac death.

The objective of the study was to report a case of difficult diagnosis of Prinzmetal angina, in a patient with a recent percutaneous coronary intervention (PCI) associated with coronary artery disease (CAD).

The Research Ethics Committee of the *Hospital de Urgências de Goiânia*, linked to the *Plataforma Brasil*, approved the present study (CAAE: 94882318.7.0000.0033).

CASE REPORT

A 64-year-old male patient, with history of hypertension, dyslipidemia, paroxysmal atrial fibrillation, fibromyalgia, gout, elective PCI procedures on February 11, 2016 and May 6, 2020 due to CAD, after which no significant lesions remained. He was on metoprolol, clopidogrel, apixaban, atorvastatin, pantoprazole and hydralazine.

He was admitted due to chest pain with tightness sensation, irradiating to the back; the myocardial necrosis markers were measured and a serial ECG was performed, with no changes suggestive of MI. The admission ECG showed sinus rhythm and left ventricular overload.

The patient was classified as unstable angina of moderate risk, with a Thrombolysis in Myocardial Infarction (TIMI) score of 4, and an elective coronary angiography (CA) was requested for evaluation.

However, during admission at the intensive care unit (ICU), on October 28, 2020, the patient experienced a very intense typical angina episode, associated with sweating and skin paleness, and a new ECG was performed at the time of pain, which showed sinus tachycardia and the presence of ST-segment depression in the anteroseptal wall (Figure 1), which normalized on following ECGs.

The patient was referred to the cath lab to perform an emergency CA, which showed a moderate 60% lesion in the middle third of the left anterior descending artery (LAD) (Figure 2A), a 60% lesion in the distal third of the right coronary artery (RCA) (Figure 2B), a 70% lesion at the origin of the posterior descending artery (PDA), and a 70% lesion at the origin of the right posterior ventricular artery (PVA) (Figure 2C).

At that moment, it was decided not to perform PCI, because, despite the evidence of CAD, the exam did not show a critical injury or unstable plaque that would justify an immediate intervention. All arteries had TIMI 3 flow, and the patient anginal condition resolved with the use of morphine and nitroglycerin. In addition, the very rapid progression of these lesions (over a 7-month period) raised the presumptive diagnosis of coronary vasospasm.

To proceed with the investigation of the case, a myocardial scintigraphy was performed, on October 29, 2020, to evaluate perfusion, and the presence of a small ischemic area in the inferior wall of the left ventricle (5% ischemic burden) was noticed, affecting the topography of the territory irrigated by the RCA (Figure 3).

The treadmill test showed the persistence of the up to 2.0mm horizontal ST-segment depression in DII, DIII, V4,

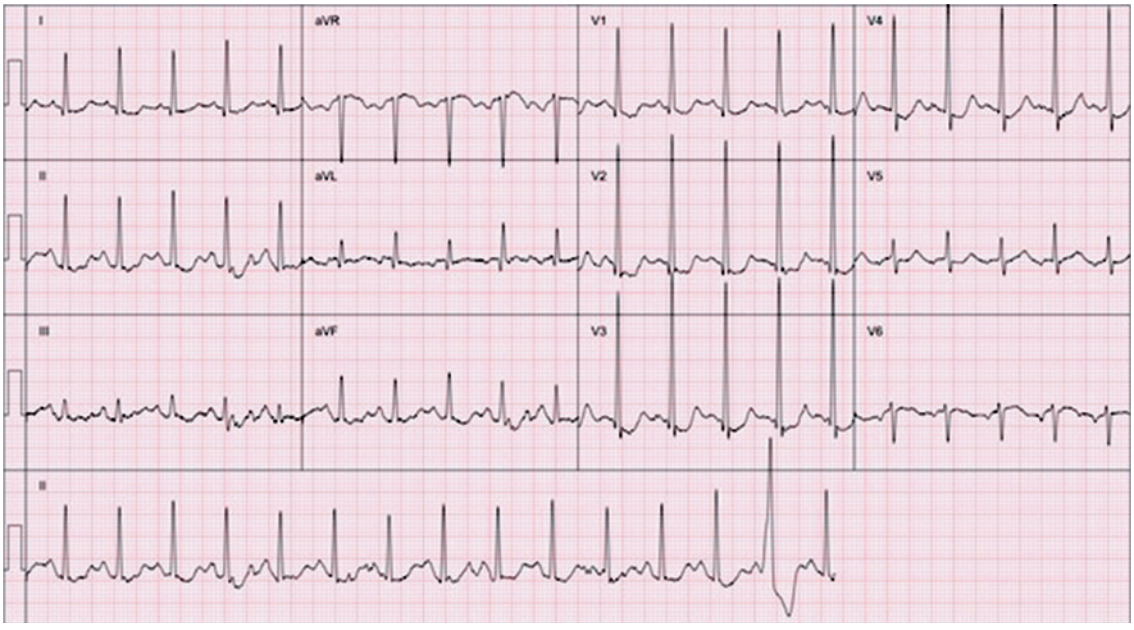
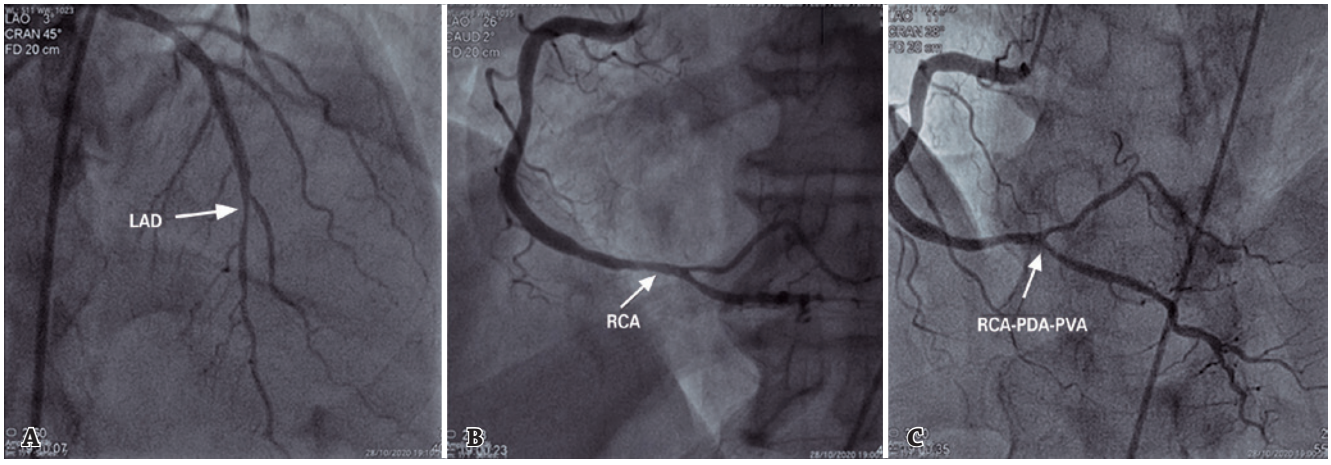


Figure 1. Electrocardiogram of October 28, 2020 showing sinus tachycardia (heart rate of 122bpm) associated with ST-segment depression in the anteroseptal wall.

V5, V6, CM5, suggestive of myocardial ischemia. After a discussion by the Heart Team, we decided to perform the PCI in the PDA and PVA (RCA territory), and to evaluate the LAD with the fractional flow reserve technique (FFR), due to the patient's angina condition that was refractory to optimized medical treatment. However, when injecting the contrast into the described coronary arteries, we observed the disappearance of these lesions (Figures 4A and 4B), therefore concluding that it was a coronary vasospasm, with no need for stent implantation. The patient was discharged asymptomatic and prescribed isosorbide mononitrate, hydralazine, amlodipine, metoprolol, clopidogrel, apixaban, and atorvastatin.



LAD: left anterior descending artery; RCA: right coronary artery; PDA: posterior descending artery; PVA: posterior ventricular artery.
Figure 2. Catheterization of October 28, 2020. (A) 60% lesion in the middle third of the left anterior descending artery. (B) 60% lesion in the distal third of the right coronary artery. (C) 70% lesions at the origin of the posterior descending artery and the right posterior ventricular artery.

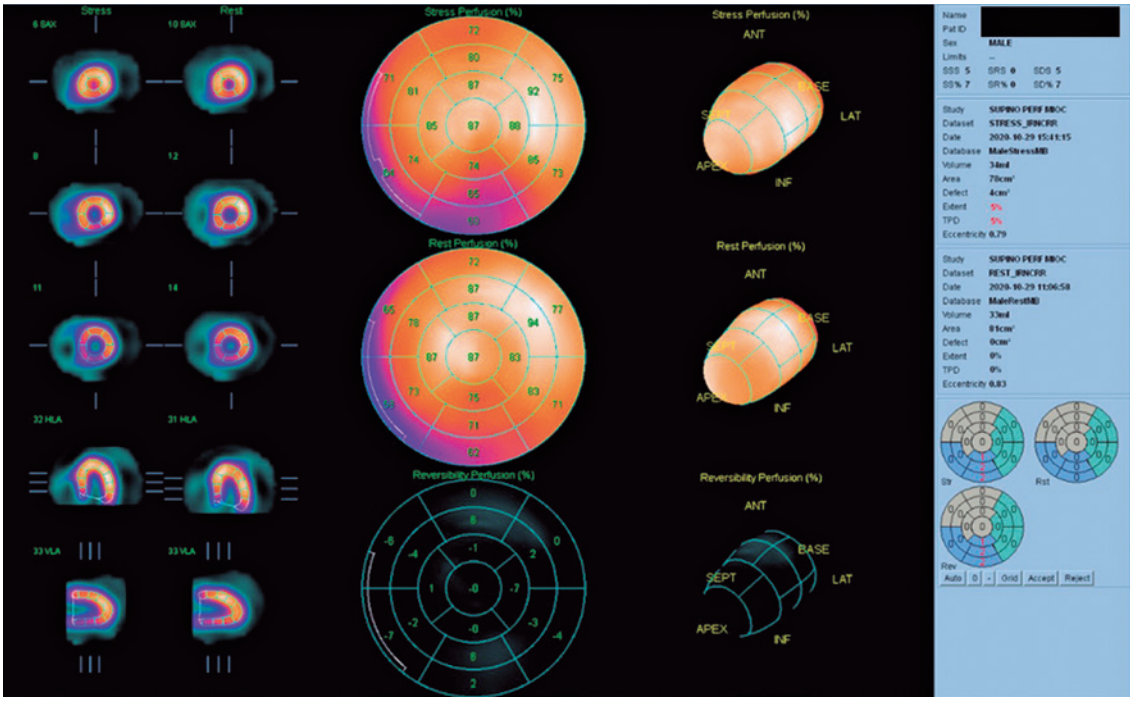
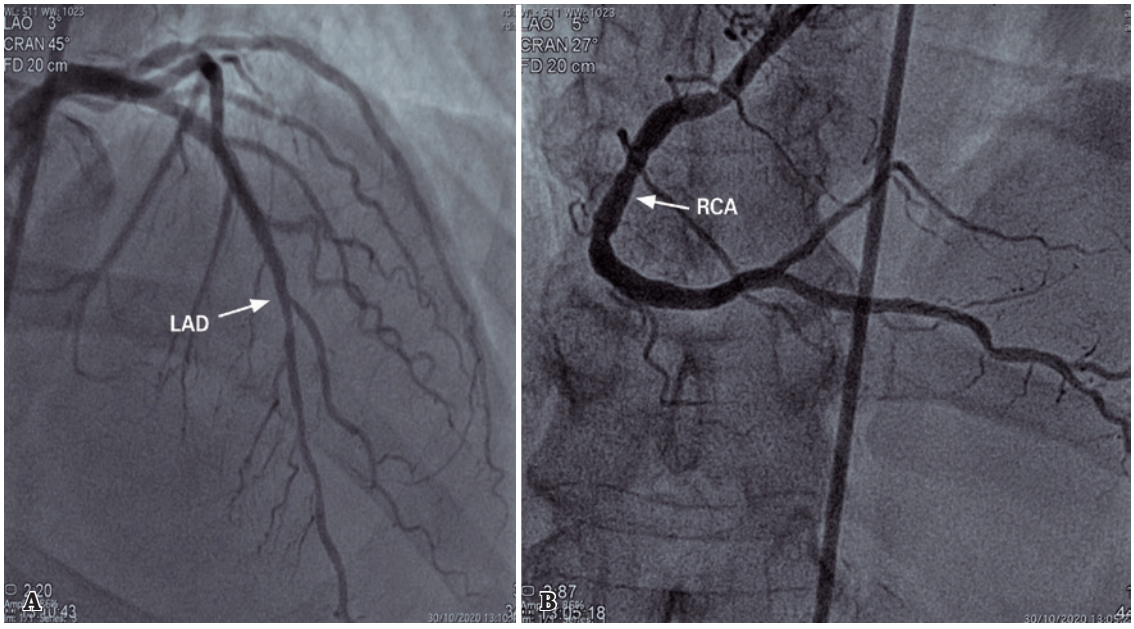


Figure 3. Myocardial scintigraphy conducted on October 29, 2020, showing mild and small transient hypoperfusion involving the inferior wall of left ventricle (5%), and inferior left ventricular hypokinesia in the stress stage.



LAD: left anterior descending artery; RCA: right coronary artery.
Figure 4. Cardiac catheterization of October 30, 2020. (A) Absence of significant lesions in the left anterior descending artery. (B) Absence of significant lesions in the right coronary artery.

DISCUSSION

In patients with previous PCI due to CAD who present with angina-type chest pain, the main presumptive diagnoses are in-stent restenosis, rupture of vulnerable atherosclerotic plaques, or development of atheromatous plaques to major obstructive lesions. It is unlikely that the hypothesis of coronary vasospasm angina will be considered, because the most likely cause would be established CAD.

The ISCHEMIA[6] study stated that, in a population of patients with stable CAD and moderate to severe ischemia in a non-invasive stress test, routine invasive therapy does not reduce major adverse cardiac events when compared to optimized medical therapy. It is important to note that the ISCHEMIA results do not apply to patients with current/recent acute coronary syndrome, highly symptomatic patients, left main coronary artery stenosis, or left ventricular ejection fraction below 35%, which justified the choice of the Heart Team for performing PCI in the territory of the RCA.

Several factors have been pointed out as being related to the occurrence of macro and microvascular vasospasm of the coronary circulation, such as muscle hypercontractility, endothelial dysfunction, electrolyte imbalance with magnesium deficiency and oxidative stress. Nonetheless, there is no evidence of a single factor as the central mechanism of action.[7] It is noteworthy, however, that coronary inflammation can be a relevant factor, especially in individuals undergoing PCI, because, in a study with animal models, the implantation of an everolimus-eluting stent induced greater inflammation in the adventitia layer, and inhibited Rho-kinase activity near the implantation sites.[8]

The so-called vulnerable plaques are those prone to rupture, with a thin fibrous layer, and a large lipid core populated by numerous inflammatory cells, which are therefore at high risk of causing thrombotic complications.[9] Even coronary arteries that look perfectly normal by angiographic criteria often have a substantial burden of atherosclerosis. Plaques with substantial positive remodeling, or "compensatory increase", can have thin fibrous layers and large amounts of lipids without invading the lumen. These "hidden" lesions not only escape angiographic detection, but also do not produce symptoms until triggering thrombosis.[10]

Rapidly progressing CAD can be associated with several factors, such as chronic kidney disease,[11] HIV infection, familial hypercholesterolemia, and hyperhomocysteinemia.[12,13] The grouping of these risk factors associated with those that are more frequent, including hypertension, diabetes, obesity, sedentary habits, and smoking, is very important for the risk of coronary events increases not in a simple additive way, but in geometric progression.[14]

What draws attention in the specific case reported is the patient had undergone a PCI seven months earlier, which is considered a short time for the development of a significant atheromatous plaque, since no lesion remained, not even moderate lesions with roughly 50% obstruction that could have possibly developed over the 7-month period. Another curious fact is, in the new catheterization during hospital stay, there were no in-stent restenotic lesions that could justify the clinical picture, and the lesions found were approximately 70%. This fact greatly reduced the probability of rupture of small lesions, considering that, in such cases, the most common progression is to total occlusion

of the artery or subocclusive lesions.[14] It is important to note that, persistent vasospasms in angiography can easily be mistaken for obstruction by atheromatous plaques - in particular in patients with previously documented CAD.

The diagnosis of Prinzmetal angina is not always easy using provocative pharmacological stimulus (acetylcholine, ergonovine or methylergonovine) or non-pharmacological stimulus (hyperventilation or cold pressure) tests, associated with a modality of vasomotor response assessment, which may include symptoms of angina, ischemic ECG changes, or angiographic images. The gold standard approach uses invasive coronary angiography to directly obtain images of the coronary spasm, with pharmacological challenge. A positive pharmacological provocative test for coronary artery spasm should induce all of the following in response: reproduction of the usual chest pain; ischemic ECG changes, and 90% or more vasoconstriction at angiography. The test result is considered ambiguous if the provocative stimulus does not induce all three components.[7]

According to the Coronary Vasomotor Disorders International Study Group (COVADIS), testing with stimulus is recommended (class 1) in patients with a suspected history of Prinzmetal angina with no documented episode, especially if there is angina at rest responsive to nitrate, and/or diurnal variation with no symptoms at the beginning of exercise, and/or angina at rest without obstructive CAD; if there is no response to empirical therapy; if there is an acute coronary syndrome in the absence of a culprit lesion; in case of unexplained resuscitated cardiac arrest; if unexplained syncope with previous chest pain has been recorded; and if there is recurrent angina at rest after successful PCI.[8] The European Society of Cardiology (ESC) recommends that intracoronary provocative tests should be considered to identify coronary spasm in patients with lesions in coronary arteriography and clinical picture of coronary spasm (class IIA, Level of Evidence C).[9]

COVADIS contraindicates provocative tests in patients with no symptoms suggestive of vasospastic angina (class III), and in patients at high risk of a life-threatening complication of induced coronary spasm, such as patients with acute coronary syndrome; severe fixed multivessel CAD, including left main coronary artery stenosis; severe cardiac dysfunction; and untreated congestive heart failure (Class IIb if symptoms are suggestive of vasospasm).[8]

Once the diagnosis of Prinzmetal angina has been defined, drug treatment is indicated. Nitrates and calcium channel blockers are the main forms of treatment for these patients. During the episode of coronary vasospasm, sublingual or intravenous nitroglycerin can be used, but resolution of the clinical picture is not always achieved, and in rare cases, percutaneous treatment is necessary. Long-acting nitrates and calcium channel blockers are useful to prevent recurrence and should be prescribed at the maximum tolerated doses.[15] Similar rates of efficacy have been observed among the various types of calcium channel blockers. Prazosin, a selective alpha-adrenoreceptor blocker, is also effective in some patients, and is considered a second-line drug in the treatment of Prinzmetal angina.[16]

A possible factor that contributes to coronary spasm is magnesium deficiency, since it has a blocking effect on calcium channels and can prevent contraction of vascular smooth muscle. Therefore, magnesium infusion is used to reduce spasms in these patients.[16]

There is an association between the use of acetylsalicylic acid and coronary vasospasm, a fact especially significant in patients with previous PCI. The administration of high doses of aspirin (>325mg per day) blocks the production of prostacyclin, a potent endogenous vasodilator. Therefore, it may worsen the coronary artery vasospasm,[17] although aspirin when administered at low doses blocks thromboxane A2, which is also involved in coronary artery spasm.[18]

In summary, Prinzmetal angina or variant angina, although well described in literature, remains with gaps regarding its pathophysiology. The multifactorial causes involved in the coronary vasospasm process and the transient nature of the event render both the diagnosis and treatment of this condition a challenge. The difficulty in making diagnosis is even greater in patients with concomitant CAD, for coronary vasospasm is rarely suspected in them.

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None.

DECLARATION OF CONFLICTS OF INTEREST

The authors declare having no conflicts of interest.

CONTRIBUTION OF AUTHORS

Conception and design of the study: FPB and GG; data collection: LVA and DFRR; data interpretation: PAFB, ACCN, FPB and GG; text writing: LVA, DFRR and GG; approval of the final version to be published: LVA, DFRR, PAFB, FPB, ACCN and GG.

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