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Case Report

Coronary Vasospasm and Heart Rhythm Disorders: A Case Report

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Abstract:

Vasospastic angina (VSA), also known as variant angina, is a condition characterized by recurrent episodes of chest pain, frequently during the night or in the early hours in the morning, due to spasm and contraction of the muscular tonaca of the coronary arteries, differentiating therefore from classic angina. The real physiopatological mechanisms of VSA are still a field of considerable research, although it is now clear that inflammation plays an important role in the genesis of the spasm. Pharmacological therapy, based today primarily on the use of nitrates and calcium channel blockers, is also an area of study to guarantee a bassetter prognosis for these patients.

Key words: vasospasm; vasospastic angina; coronary angiography; electrocardiogram, atrioventricular block; inflammation

Introduction

We present the case of a 56-year-old patient, affected by arterial hypertension and with no cardiac history, who called the Emergency number because of an episode of resting angina at home. When emergency vehicles arrive the patient was initially asymptomatic and electrocardiogram was normal. For recurrence of chest pain, a second ECG tracing was performed and it highlighted a second degree atrio-ventricular block, Mobitz 2, ST-segment elevation in the infero-lateral and sub-ST segment in leads V1-V2 **(Figure. 1).** The patient was then taken to the Hemodynamics of our Hospital for urgent coronary angiography. The exam did not find significant coronary atherosclerosis affecting the epicardial coronary arteries (only a 30-40% stenosis of the right coronary artery in the middle section was described). At the transthoracic echocardiogram performed in the Coronary Unit, significant valvular defects were excluded, the left ventricular ejection fraction (LVEF) was preserved with only a mild hypokinesia of the inferior-posterior wall. In the suspicion of vasospastic angina on the documented atherosclerotic plaque of the right coronary artery, Diltiazem i.v. was introduced into therapy and then orally. In the following 48 hours the patient experienced two different episodes of angina with an ECG tracing compatible with inferior-STEMI and third degree atrioventricular block **(Figure. 2).** The symptoms rapidly reduced after intravenous nitroglycerin administration, with prompt restoration of sinus rhythm **(Figure. 3).** Enzyme curve was not significant (hs-TnT 10 ng/L, Ck-Mb 3.4 mcg/L). During the hospitalization the therapy with calcium channel blocker was up-titrated and nitrate was also introduced, without further anginal episodes or major brady-arrhythmias. Considering the mild coronarosclerosis and the high lipoprotein-A levels (Lp(a) 85 mg/dl), we decided to maintain the therapy with acetylsalicylic acid and the Rosuvastatin/Ezetimibe combination. After 5 days the patient was transferred, asymptomatic and with good haemodinamic status, to a cardiac rehabilitation facility. At the follow-up visit in the Day Hospital Ambulatory, 3 months later, the echocardiogram was normal, and the drug therapy was well tolerated. No new arrhythmic events were detected at the control Holter ECG.

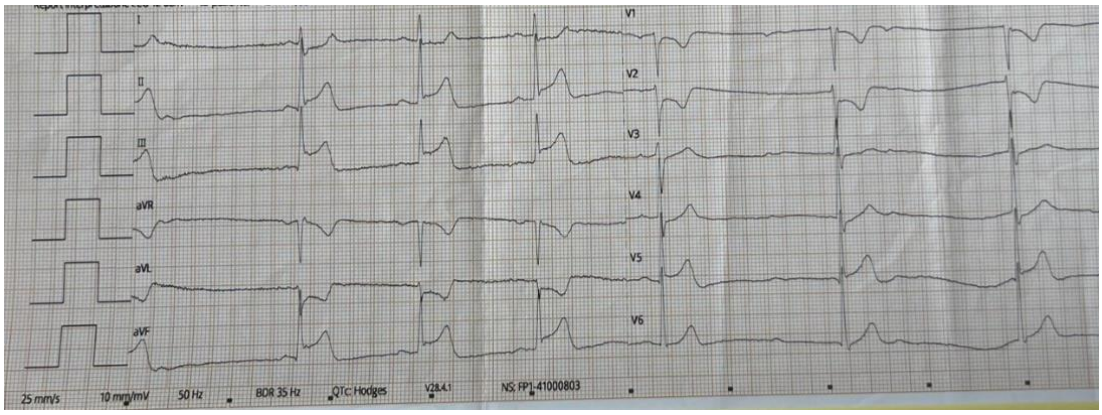

Figure. 1: ECG performed by the Emergency Service at first contact with the patient experiencing chest pain

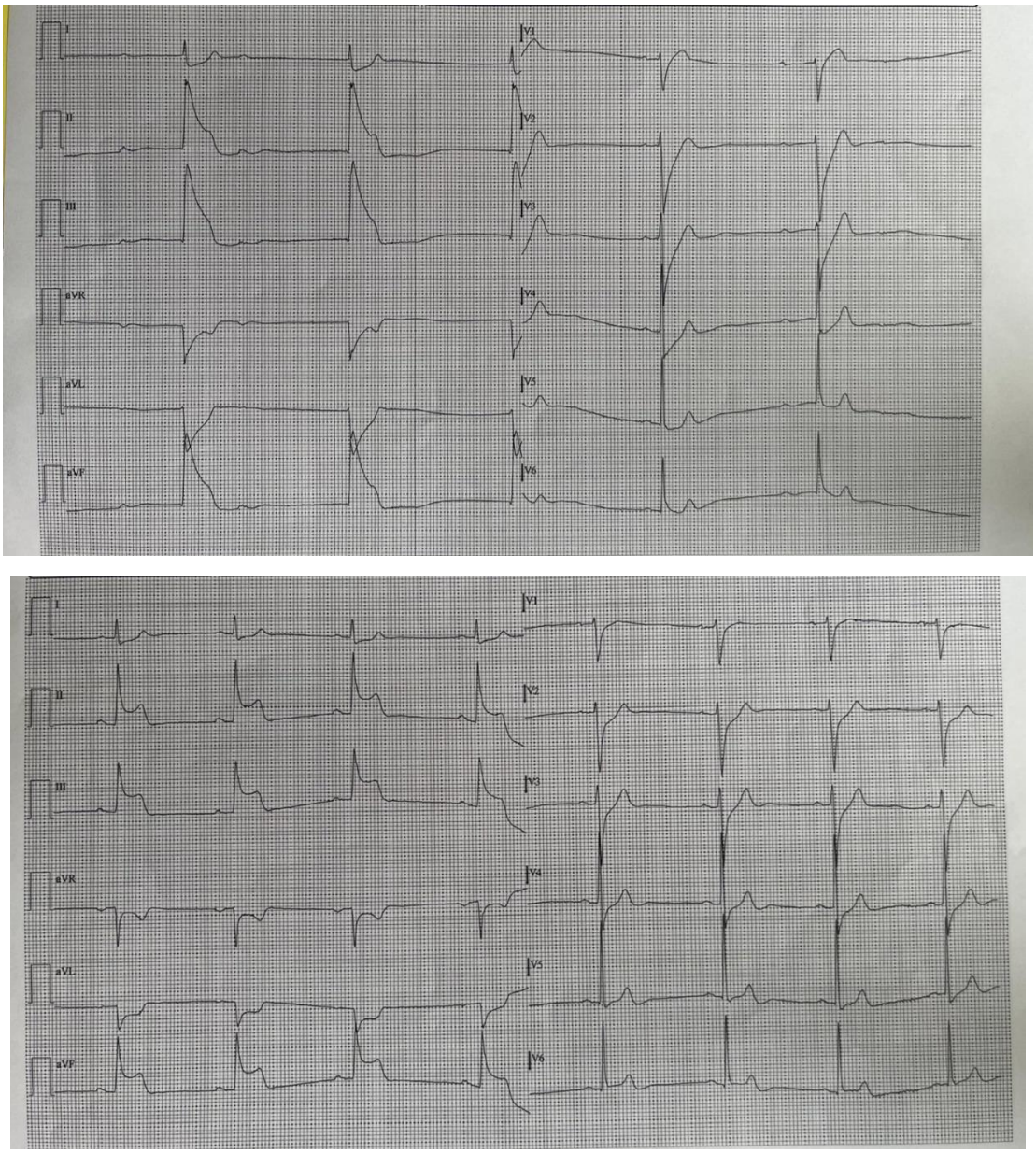

Figure. 2: ECG changes during angina attacks

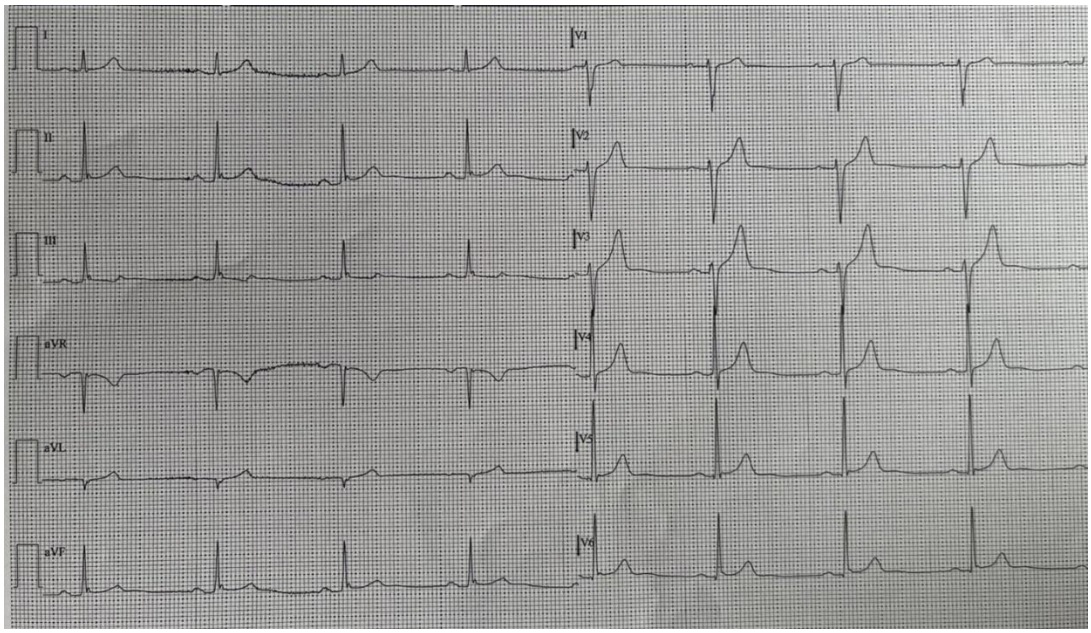

Figure. 3: Normalization of the trace and restoration of sinus rhythm after administration of nitrate i.v. during coronary spasm

Discussion

Printzmetal et. al introduced the concept of vasospastic angina (VSA), also known as variant angina, for the first time in 1959. It is a condition characterized by episodes of thoracic pain with onset independent of effort, often during the night or in the early hours in the morning, due to spasm and transient contraction of the muscular tunica of the coronary arteries with consequent myocardial ischemia [1,2]. The angina is not necessarily associated with concomitant alterations on the ECG trace. Coronary vasospasm is considered one of the aetiological causes of myocardial infarction without significant coronary obstruction (MINOCA), although today still underdiagnosed because provocative tests are not used as a routine tecnique [3]. The symptoms are certainly heterogeneous: chest pain, tachy- or brady-arrhythmias, syncope and dyspnea can occur [4]. Traditionally, vasospastic angina can be classified in relation to ECGgraphic disturbances of ventricular repolarization (i.e. ST-elevation or depression) or based on the anatomical location of the spasm: epicardial or microvascular, although the two can coexist [5]. ST elevation is usually the main and more frequent alteration, with the underlevelling in the specular leads, negative T waves are also frequent [6] **(Table. 1).**

	Vasospastic angina	Classic angina
Clinical manifestations	- Chest pain not related to physical exertion - Frequent during the night or in the early morning - Tachy- and brady-arrhytmias	- Chest pain due to physical exertion or emotional stress, usually it reduces with rest.
ECG changes	- ST-elevation o depression - T-waves inversion	- ST-segment depression ore elevation (STEMI)
Physiopatology	- Coronary spasm (local or diffuse)	- Coronary atherosclerosis
Drug treatments	- ASA and statins have no effect on the prgnosis - B-blockers are not recommended - Nitrates and calcium channel blockers can reduce symptoms	- ASA, RAAS-i, B-blckers and statins improve prognosis - Nitrates and calcium channel blockers coud reduce symptoms

Epidemiology:

Calculating the exact prevalence of VSA is not so simple because provocative tests are not frequently used in clinical practice. A recent meta-analysis which involved 6500 patients without obstructive CAD calculated a prevalence of epicardial vasospasm of 40% and 24% for microvascular spasm [3]. In patients with angina attacks and with no coronary artery disease a further trial reported that vasospasm was present in 62% of cases (45% epicardial, 55% microvascular respectively) [7]. According to data from Hung et. al VSA is more frequent among the Asian population, primarily Japanese, and in a smaller percentage among the Caucasian ethnic group [8].

Pathophysiological mechanisms:

The precise mechanism responsible for coronary vasospasm is still not completely clear. Among the factors that can favor the development of this condition there are certainly inflammation, oxidative stress, endothelial dysfunction, genetic and lifestyle factors. Numerous evidences show that inflammation of the perivascular and myocardial tissue may be involved in the genesis of spasm [9]. To confirm this

hypothesis, it is estimated that coronary vasospasm is responsible for angina symptoms in approximately 70% of patients with viral myocarditis [10]. Klonaris et al. described a case of myocarditis in a patient with VSA in 1978. In patients with VSA the inflammation of the adventitia of the coronary arteries was also confirmed by the increased uptake of fluorodeoxyglucose (18 F-FDG) at PET [11]. In 1991 Kounis and Zavras discovered that the inflammatory response secondary to an anaphylactic reaction can be responsible for coronary artery spasm with increased risk of sudden cardiac death. The hyper-reactivity of the smooth muscle cells of the vessels (VSCM) certainly plays a central role. This condition is favored by the production of vasoconstrictor molecules such as endothelin-1 and oxygen free radicals (ROS), and also by the deficiency of vasodilatory factors such as nitric oxide (NO) or prostaglandins with consequent endothelial dysfunction and alteration of vasomotor tone: this condition prevents the adaptation of coronary flow in relation to oxygen demand with consequent vasoconstriction [9].

If the association between the inflammatory substrate and atherosclerotic coronary artery disease is now well established, it is now increasingly evident that the levels of pro-inflammatory mediators (CRP, IL-1, IL-6...) are also increased in patients with VSA. Tanaka et. al propose Tocilizumab, an anti-IL-6, as a potential therapeutic agent in these patients. The greater M1-differentiation of macrophages, responsable of endothelial dysfunction, was also confirmed in these subjects [12]. Other inflammatory metabolites involved in the pathophysiology of VSA are IFN-alpha, PD-L1, macrophage inflammatory protein (MIP)-1alpha and MIP-1beta. A recent Japanese trial, performed on 5720 patients with VSA (average age 67 years), and without atherosclerotic disease, showed that the RNF213 gene, especially in its missense variant, is frequently associated with vasospastic angina. This gene codes for NO synthase and its mutation determines a reduced activity of the enzyme with consequent lower production of NO [13]. Another trial examined the function of RNF213 by showing how its activity increases in response to blood vessel shear stress [14].

Numerous data have confirmed that the signaling promoting the hyper-reactivity of vascular smooth muscle cells is responsible for an amplification of the inflammatory response, determining a process that worsens coronary spasm. Finally, T lymphocytes are involved in this process and are hyper-activated [9].

Drug therapy

VSA therapy is based on the use of nitrates, currently first-line drugs, to reduce the frequency of angina attacks although they ca not favorably modify the long-term prognosis [9]. Bugiardini et. al report that the use of nitrates can, however, be associated with a reduction in coronary flow reserve with a consequent increase in the discrepancy between myocardial oxygen demand and supply [15]. The other major pharmacological class commonly used in patients with VSA is represented by calcium channel blockers, capable of reucing myocardial contractility and O2 consumption by decreasing calcium intake into the myocardiocyte during depolarization, and increasing blood flow. The positive effects of this class of drugs in alleviating the symptoms of vasospasm have been known since 1980 [16], subsequent studies have shown how they are also able to control arrhythmic events [9]. Beta-blockers, particularly non-selective ones, have been found to be contraindicated in the treatment of VSA since by potentially also acting on alpha-adrenergic receptors they could reduce the dilation capacity of the artery with consequent possible intensification of vasospasm. Antiplatelet agents are commonly used in patients with VSA and concomitant atherosclerosis (approximately 60% of cases) [17]. Statins still have a controversial role: in the study by Ishii et al. their use was associated with a lower incidence of cardiovascular events and an improvement in prognosis although in two subsequent trials, conducted by S.R. Kim, high-dose statins improved the lipid profile without impacting outcomes in terms of symptom reduction [18].

Cases in literature

Costa et. al [19] describe the case of a 70-year-old patient, hypertensive and with no cardiological history, who entered the emergency department for recurrent chest pain and syncope. Episodes of angina were frequent, especially during the night. In the previous days the woman perform a 24-hour Holter ECG monitoring which she was wearing at the moment of Emergency department admission. Although the echocardiogram and ECG were normal, the Holter ECG showed ST-segment elevation during the night and also in the occasion of syncope, followed by second degree atrioventricular block type 1 and 2. Non significant coronary atherosclerosis was documented at the angiography. Authors decided to introduce pharmacological therapy with Isosorbide dinitrate 40 mg, Amlodipine 5 mg and atorvastatin 40 mg with clinical benefit and without further similar episodes.

Ferreira et. al [20] instead present the case of a young pre-menopausal woman, dyslipidemic and smoker, who underwent a cardiological evaluation for repeated episodes of chest pain, independent of physical exertion, and syncope. Among the documentation viewed by the patient, an ECG-Holter highlighted moments of third degree AV block with pauses of up to 4.5 seconds associated to ST-segment elevation. During the evaluation the patient experienced angina and on the ECG tracing she presented ischemic changes in the ventricular repolarization in the inferior leads. After sublingual nitrate administration ECG returned gradually normal. Also in this situation coronary arteries have no significant stenosis; therapy with nitrates, nifedipine and statin was introduced. At the follow-up control the patient still complained of recurrent symptoms, and at the control ECG-Holter significant pauses persisted. The nitrate was replaced with Verapamil and definitive PM implantation was performed. In the our case, device implantation was postponed considering the complete resolution of the symptoms after the medical therapy optimization and because no further brady-arrhythmias were documented.

Conclusions:

Significant progress has been made to understand the exact pathophysiological mechanism underlying VSA- The fundamental role played by inflammation is now clear but it is surely a field that will need to be explored in ever greater depth in the years to come. In the future it will also be necessary to resolve the current uncertainties regarding the optimal therapeutic management of these patients, in particular to guarantee them a better long-term prognosis and not just a lower recurrence of symptoms. Another notable question regards the predisposing factors of coronary vasospasm developement. Current research is concerned with providing answers to our countless questions as soon as possible.

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