Multivessel coronary thrombosis and acute myocardial infarction associated to two genetic mutations for thrombophilia

Trombosis coronaria de múltiples vasos e infarto agudo de miocardio asociado a dos mutaciones genéticas para trombofilia

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Abstract

Several studies suggest that gene mutations from thrombophilia may constitute a significant risk factor for coronary artery disease, especially in young patients with normal coronaries and non-significant lesions. It is presented a case of a 42-year-old male patient who arrived at the emergency room due to an acute myocardial infarction. The electrocardiogram showed an ST elevation with upward convexity of 4 mm from V1 to V4 and of 1 mm at V5 and V6. Cardiac enzymes were positive (troponin I 8.4 ng/dl, normal range < 1 ng/dl). It was found septum and apical hypokinesia, with an ejection fraction of 44%. The culprit lesion of the infarction was treated with primary angioplasty, successfully dilating the left anterior descending coronary artery. However, spontaneous thrombi appeared at the middle third of the circumflex artery, an area without occlusive lesions previously. A full laboratory assessment for prothrombotic state diseases revealed positivity for gene mutations at A1298C from the methylene tetrahydropholate reductase (MTHFR) and plasminogen activator inhibitor-1 (PAI-1). Gene mutations at A1298C from the MTHFR and PAI-1 should be considered in young patients with acute coronary syndrome, mainly when thrombi are found in non-culprit arteries with no or non-significant coronary lesions.

Keywords: Myocardial infarction. Genetic testing. Coronary vessels.

Resumen

Las mutaciones genéticas de la trombofilia pueden constituir un factor de riesgo significativo para la enfermedad de la arteria coronaria, especialmente en pacientes jóvenes con arterias coronarias normales y lesiones no significativas. Se presenta el caso de un paciente masculino de 42 años con infarto agudo de miocardio. El electrocardiograma demostró una elevación del ST con convexidad ascendente de 4 mm de V1 a V4 y de 1 mm en V5 y V6. Las enzimas cardíacas fueron positivas (troponina I 8.4 ng/dl, rango normal < 1 ng/dl). Se observó hipocinesia septal y apical con fracción de eyección de 44%. La lesión causante del infarto fue tratada con angioplastia primaria, dilatando con éxito la arteria coronaria descendente anterior. Sin embargo, aparecieron trombos espontáneos en el tercio medio de la arteria circunfleja, que previamente no presentaba lesiones ateroscleróticas oclusivas. Al evaluar enfermedades protrombóticas se reveló positividad para

mutaciones del gen A1298C de la metileno tetrahidrofolato reductasa (MTHFR) y del inhibidor del activador del plasminógeno (PAI-1) del genotipo heterocigoto 675G. Las mutaciones en A1298C del gen MTHFR y del PAI-1 deben considerarse en jóvenes con síndrome coronario agudo, principalmente cuando se encuentran trombos en arterias no culpables sin lesiones coronarias significativas.

Palabras clave: *Infarto de miocardio. Test genético. Vasos coronarios.*

Introduction

Atherosclerotic coronary disease is the main mechanism to develop an acute myocardial infarction. Other mechanisms are non-atherosclerotic coronary disease and hypercoagulability states, like gene mutations associated with hereditary thrombophilia. Several studies suggest that gene mutations from thrombophilia may constitute a significant risk factor for coronary disease, especially in young patients with normal coronaries and non significant lesions[1-6]. The previous studies show that this combination, of common risk factors and thrombophilia, is associated with a high risk of death and recurrence of acute myocardial infarction within 2 years after the first episode[1,2].

Therefore, it is presented a clinical case consistent with several common risk factors for coronary heart disease with multiple thrombi in different coronary arteries, even in a non-culprit coronary vessel during acute myocardial infarction. Despite the presence of conventional coronary risk factors, it was not enough to explain spontaneous thrombi appearing during primary percutaneous coronary intervention in a vessel not related to the infarction and without any angiographic lesion to blame at this site. Therefore, laboratory assessment to search for primary and secondary risks factors for thrombosis was justified with the finding of two gene mutations for thrombophilia.

Clinical case

A 42-year-old male patient arrived at the emergency room due to an acute myocardial infarction. He came to the emergency room due to chest pain, oppressive, retrosternal, radiating to the left arm, at rest, and mild-to-moderate intensity. He denied having dyspnea, cold sweats, nausea, vomits, or other symptoms. He also denied arterial hypertension, diabetes, dyslipidemia, or thyroid disease. He did not have family history of coronary artery disease. He is a former smoker, not alcohol consumer, neither of illicit drugs. At physical examination, he was obese (BMI = 35 kg/m^2), the pulmonary examination was normal, no signs of breathing difficulty, normal vital signs, blood pressure 140/87 mmHg, heart beat 95/min,

respiratory frequency of 20/min, body temperature of 36.5°C, and oxygen saturation of 96% in room air.

A 12-lead conventional electrocardiogram (ECG) showed an ST elevation with upward convexity of 4 mm from V1 to V4 and of 1 mm at V5 and V6 (Fig. 1A). Further conventional ECG showed T negative waves from V1 to V6 and D1 to aVL (Fig. 1B). Chest X-ray showed no cardiomegaly or signs of pulmonary edema. On laboratory tests, assessment showed that cardiac enzymes were positive (troponin I = 8.4 ng/dl, normal range < 1 ng/dl). He had a high cholesterol test of 327 mg/dl (normal range < 200 mg/dl), high density lipoprotein cholesterol 25 mg/dl (normal range > 40 mg/dl), low-density lipoproteins cholesterol 244 mg/dl (normal range < 100 mg/dl), and very low-density lipoprotein cholesterol 58 mg/dl (normal range < 40 mg/dl). He had normal levels of fasting glucose, hemoglobin A1C, uric acid, creatinine, and homocysteine. At trans-thoracic echocardiography, the diameters of the left ventricle at diastole and systole were 56 mm and 45 mm, respectively. The ejection fraction by Simpson method was 44% with septal hypokinesia (medium-apical) and apical hypokinesia. No thrombus was found in the left ventricle. The patient was started on treatment with dual anti-platelet therapy with aspirin and clopidogrel, anticoagulation with low molecular weight heparin, atorvastatin, angiotensin convertor enzyme inhibitor, betablocker, and aldosterone inhibitor.

A coronary angiography was performed, showing a total occlusion of the left anterior descending coronary artery in the middle segment which represents the culprit lesion of the infarct. There were other occlusions such as at a proximal level in the second marginal branch of the circumflex artery and a severe lesion in the distal segment of the right coronary artery (Fig. 2). The culprit lesion of the infarction was treated with primary angioplasty, successfully dilating the artery with a balloon, with a resultant thrombolysis in myocardial infarction (TIMI) 2 flow in the middle and distal segments of the vessel. Just before the stent placement, there were spontaneous thrombi appearing at the middle segment of the circumflex artery, at an area that did not present previously occlusive atherosclerotic lesions
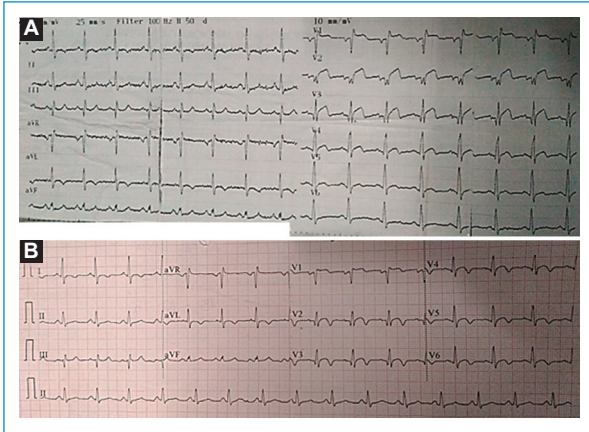
Figure 1. A: electrocardiogram (ECG) at the emergency room with ST segment elevation with an upward convexity of 4 mm from V1 to V4, 1 mm at V5-V6. **B:** ECG following angioplasty shows near normal ST segment, with symmetric T negative waves from V1-V6, D1-aVL.

(Fig 3A). An abciximab infusion was started as continuous infusion for 24 h. He also received nitroglycerin infusion for 36 h due to a mild elevation of blood pressure. After 48 h, a new coronary angiography showed a reocclusion at the middle segment of the left anterior descending coronary artery, with a decrease in the thrombus burden in the circumflex artery. Dilation with a balloon and placement of a zotarolimus-eluting stent resulted in a TIMI 3 flow through the artery (Fig. 3B). Patient evolved without complications during the rest of the hospital stay. A new echocardiography showed a left ventricle ejection fraction of 47% (Simpson method).

Due to the spontaneous thrombi found at the coronary artery that did not relate to the myocardial infarction territory, without any atherosclerotic plaques to blame in a young patient, it was mandatory to perform a laboratory assessment for prothrombotic states diseases. The results were negative for antiphospholipid antibodies (lupus anticoagulant = 0.83, NV < 1.2; anticardiolipin IgG = 1.4, NV < 10 GPL-U/ml; anticardiolipin IgM = 0.4, NV < 7 MPL-U/ml; anti-beta 2 glycoprotein I IgG = 1.4, NV < 5 U/ml; and anti-beta 2 glycoprotein IgM = 0.4, NV < 5 U/ml). Other genetic mutations associated with thrombophilia resulted negative, such as mutations for factor V (Leiden, Cambridge, Liverpool, and Hong Kong), for prothrombin mutation (M 20210A), negative for MTHFR 677T mutation (methylene tetrahydropholate reductase), but positive for mutations at A1298C from the MTHFR gene heterozygote genotype and plasminogen activator inhibitor-1 (PAI-1).

Therefore, this patient was considered at high risk for trombophilia and thrombosis with two genetic mutations. An anticoagulant treatment was installed with Vitamin K antagonists for a goal of international normalized ratio (INR) 2 to 3 as a secondary prevention. Furthermore, long-term dual antiplatelet therapy was started due to stent implantation, with a low risk of bleeding for triple therapy (Precise-DAPT score 8; HAS-BLED score 1). The patient was discharged in well condition and comes to consultation regularly at the cardiology department, without myocardial ischemic symptoms or other thrombotic complications, no bleeding as well (Figs. 1-3).

Discussion

This was a young patient with several common risk factors for coronary artery disease but also with primary risk factors such as thrombophilia with two genetic mutations, in this case, gen mutations at A1298C from the MTHFR and PAI-1. The previous studies have shown that this combination of common risk factors for atherosclerosis and thrombophilia is associated with a high risk of death and recurrence of acute myocardial infarction within 2 years after the first episode[1,2]. Furthermore, in the absence of classic risk factors or without significant occlusions, hereditary thrombophilia predispose to the development of the first myocardial infarction[3-5].

Studies have shown that polymorphism of mutations at A1298C from MTHFR gene predisposes to coronary artery disease in some patients[6]. The prothrombotic mechanism described is the lower activity of 5,10-methylene tetrahydrofolate reductase enzyme, which catalyzes methylation from homocysteine to methionine, producing high levels of homocysteine. There is a strong relationship between high levels of homocysteine and cardiovascular disease[7-9]. The mechanisms include lower production of nitric oxide from endothelium, proliferation of smooth muscle fibers, endothelium dysfunction, and effects on platelets and coagulation[8]. The patient in the present case had normal levels of homocysteine. A decreased function of MTHFR enzyme activity can lead to the high levels of homocysteine. This does not necessarily happen, especially in countries like USA, where food is enriched with folate. In that part of the world, the mutation in the absence of the high levels of homocysteine does not constitute a risk factor for heart disease. Even with the high levels, the treatment to reduce it, do not improve the risk of recurrent events[7]. The Thrombosis Interest Group of Canada do
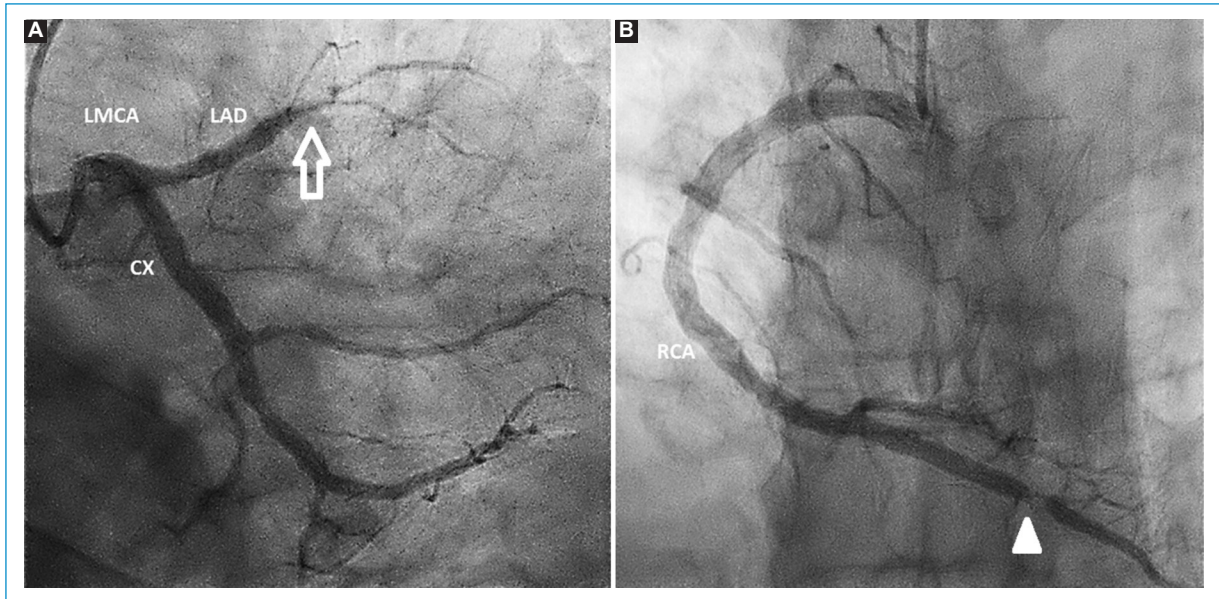
Figure 2. Coronary angiography. **A:** complete occlusion of the left anterior descending coronary artery in its middle third (arrow). **B:** severe occlusion at the last third of right coronary artery (arrow head).
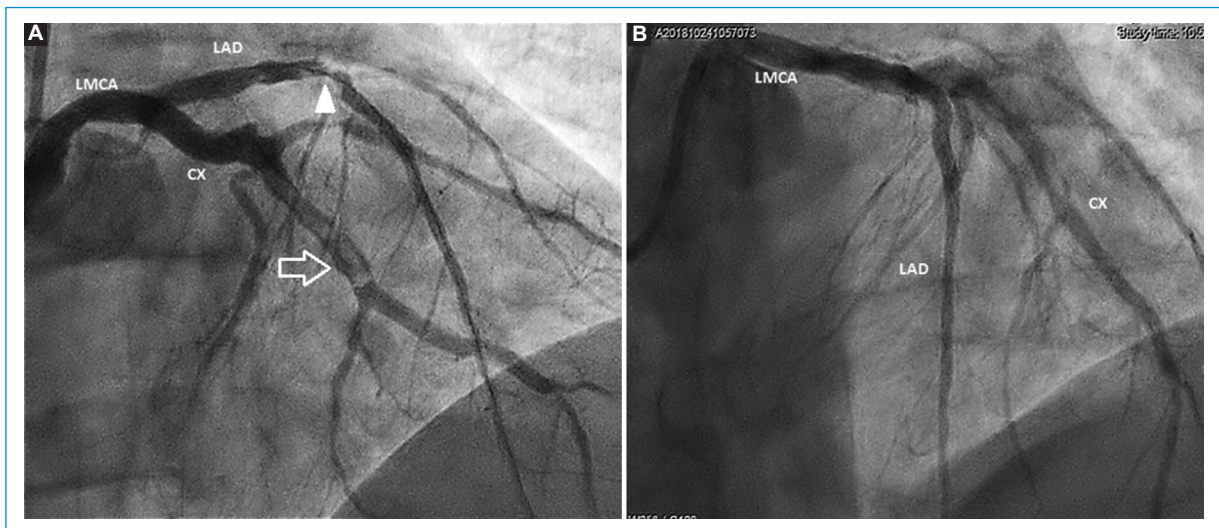

Figure 3. A: primary angioplasty of the left anterior descending artery shows a severe lesion at the junction of the proximal and middle third (arrow head). During the procedure, spontaneous cloths were found in the middle third of circumflex artery (arrow). **B:** 48 h after the angioplasty, after IIb/IIIa glycoprotein inhibitors, decreased thrombus burden in the circumflex artery.

not recommend testing serum levels of homocysteine in samples of patients with heart disease and venous thromboembolism. They do not recommend testing for MTHFR mutation as part of the routine examination for thrombophilia[9]. However, such scenario does not apply to our country population due to ethnic and dietary differences. A regional study in Latin-American population showed high prevalence of MTHFR gene mutation and its association with hyper-homocysteine and heart disease development[10]. In patients with reduced MTHFR enzyme activity and consequently hyper-homocysteinemia, daily low-dose folic acid supplementation can reduce and often normalize their homocysteine levels. However, this measure has not been shown to improve

clinical outcomes[11]. Clinical trials and meta-analyzes have shown that lowering homocysteine levels with Vitamin B6, B9 (folic acid), and B12 supplementation did not reduce cardiovascular complications even in patients with elevated baseline levels[12]. At present, based on available data, treatment of hyper-homocysteinemia is not recommended in patients with cardiovascular disease.

Regarding plasminogen activator inhibitor-1 (PAI-1), this is an important inhibitor of the fibrinolytic system and it is produced at the vascular endothelium and is also present in platelets[13]. Suppression of fibrinolysis happens with the high levels of PAI-1 and with high levels of factor VII, fibrinogen, and von Willebrand factor, a myocardial infarction can be the result of this combination[14]. Besides, the high levels of plasminogen activator (t-PA) and dimers-D increase the risk of myocardial infarction[15]. The high levels of PAI-1 were associated with vascular inflammation, atherosclerosis, and metabolic syndrome[16]. High activity of PAI-1 has been detected in atherosclerosis of patients with obesity and Type 2 diabetes mellitus. The high levels of PAI-1 were described related to the development of first myocardial infarction[17] and with progression of coronary syndromes and coronary artery disease in patients with the previous myocardial infarction.

Although the present patient described also had several common risk factors for coronary heart disease, it was not enough to explain spontaneous thrombi appearing during the procedure in a vessel not related to the infarction and without any angiographic lesion previously. Therefore, laboratory assessment to search for primary and secondary risks factors for thrombosis was justified, with positive findings in more than one gene mutation. As for therapeutics, dual anti-platelet therapy alone cannot prevent new thrombotic events due to two mechanisms involved, thus triple therapy should be considered with long-term anticoagulation to prevent new episodes.

Conclusion

Gen mutations at A1298C from the MTHFR and PAI-1 should be considered in young patients with acute coronary syndrome, mainly when thrombi are found in non-culprit arteries with no or non-significant coronary lesions.

Funding

Conflicts of interest

The authors declare no conflicts of interest

Ethical disclosures

Protección de personas y animales. Los autores declaran que para esta investigación no se han realizado experimentos en seres humanos ni en animales.

Confidencialidad de los datos. Los autores declaran que han seguido los protocolos de su centro de trabajo sobre la publicación de datos de pacientes.

Derecho a la privacidad y consentimiento informado. Los autores han obtenido el consentimiento informado de los pacientes y/o sujetos referidos en el artículo. Este documento obra en poder del autor de correspondencia.

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