

CASE PRESENTATION

Thrombophilia as a cardiovascular risk factor for acute myocardial infarction at young age – case report

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Abstract: Introduction – Acute myocardial infarction (MI) can occur in young subjects, and typical precipitating factors may include hyperlipidaemias, hypercoagulable state, cocaine abuse and other factors. Thrombophilia is defined as an increased risk factor for thrombosis. The central pathogenic event of any thrombotic episode is the alteration of haemostasis due to genetic or environmental causes. **Case presentation** – We present the case of a 27 years old male patient, with obesity stage 3, smoker - one pack of cigarettes per day (for 10 years), who was admitted into our clinic 12 hours after the onset of a constrictive chest pain spreading to the interscapular-vertebral space and to the left upper limb and dyspnoea. The electrocardiogram showed features of anterior acute myocardial infarction. The blood work at admission revealed increased enzymes for myocardial necrosis. The echocardiographic examination showed significant changes in left ventricular movement, EF = 40 %, mild ischemic mitral regurgitation. Coronary angiography disclosed thrombotic occlusion of the proximal left anterior descending coronary artery. Due to massive thrombosis in the left anterior descending artery and to the young age for myocardial infarction, the patient was suspected and evaluated for a cause of the hypercoagulable state. Blood tests revealed hyperhomocysteinaemia, a heterozygote mutation of the A1298C in the human methylenetetrahydrofolate reductase gene and low levels of antithrombin III (78.5%). Management of this patient included dual antiplatelet and oral anticoagulation therapy. **Conclusion** – Thrombophilia induces a hypercoagulable state, which, along with other cardiovascular risk factors, can lead to arterial thrombosis at young ages.

Key words: thrombophilia, verapamil, anterior acute myocardial infarction, hypercoagulable state, young age.

Abstract: Introducere – Infarctul miocardic acut (MI) poate apărea la tineri, iar factorii precipitanți includ dislipidemia, hipercoagulabilitatea, abuzul de cocaină și alții. Trombofilia reprezintă un factor de risc crescut pentru tromboză. Evenimentul central patogen în orice episod trombotic este alterarea hemostazei din cauze genetice sau de mediu. **Prezentare de caz** – Prezentăm cazul unui pacient de 27 de ani, cu obezitate gradul 3, fumător - un pachet de țigări pe zi (de 10 ani), care a fost internat în clinica noastră la 12 ore de la debutul unui dureri retrosternale cu caracter constrictiv cu iradiere în spațiul interscapulo-vertebral și în membrul superior stâng, însoțită de dispnee. Electrocardiograma a relevat aspect de infarct miocardic acut anterior. Probele biologice au evidențiat creșterea enzimelor de citoliză miocardică. Ecocardiografic s-au decelat tulburări de cinetică parietală la nivelul ventriculului stâng, FE=40% și regurgitare mitrală ischemică ușoară. La angiocoronarografie s-a remarcat ocluzie trombotică la nivelul segmentului proximal al arterei descendente anterioare. Din cauza trombozei masive la nivelul arterei descendente anterioare și vârstei tinere de apariție a infarctului miocardic, pacientul a fost suspectat și evaluat pentru o cauză de hipercoagulabilitate. S-au efectuat teste care au evidențiat hiperhomocisteinemie, mutația heterozigotă la nivelul genei metilentetrahidrofolat reductazei A1298C și nivel scăzut al antitrombinei III (78.5%). Tratamentul acestui pacient a inclus dubla antiagregare plachetară și anticoagulare orală. **Concluzii** – trombofilia induce starea de hipercoagulabilitate care, alături de alți factori de risc cardiovasculari, poate declanșa tromboză arterială la vârste tinere.

Cuvinte cheie: trombofilie, verapamil, infarct miocardic acut anterior, hipercoagulabilitate, vârstă tânără.

BACKGROUND

Acute myocardial infarction (MI) mainly occurs in patients over 45 years old, but young adults can also suffer a MI. Causes of MI in young adults usually include: 1. atheromatous coronary artery disease (CAD); 2. non-atheromatous CAD; 3. hyper-coagulable states; 4.

substance abuse¹. Although the incidence of MI among young people is not common, its consequences are significant, due to high morbidity, psychological effects and financial costs.

Atheromatous CAD is linked to conventional risk factors in adults. In the study of Zimmermann et al,

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smoking was the most common risk factor (92%) in young adults². The cut-off age of 45 years old has been used in most of the studies to differentiate CHD or MI in young patients.

Children born to parents with premature CHD have a tendency to higher incidence for lipid abnormalities, insulin resistance and obesity, a fact that can be linked to genetic inheritance³.

According to US data, about 80% of young subjects with MI are overweight or obese and at least one of the cardiovascular risk factors is the most important trigger in 96% of cases⁴. Novel risk factors such as increased lipoprotein (a) and hyperhomocysteinaemia have recently been shown to have the same effects as conventional risk factors in younger people^{5,6}.

Many epidemiological studies and reports have established hyperhomocysteinaemia as an independent risk factor for cardiovascular disease, cerebrovascular disease, dementia-type disorders and osteoporosis-associated fractures. Although combined folic acid and B-vitamin therapy has been shown to lower the levels of homocysteine, the controversial results of clinical trials have discarded the monitoring of these patients for risk follow-up⁷.

Unexplored areas such as psycho-social stress, anger, anxiety and the burn-out syndrome can accelerate coronary artery calcification and occurrence of MI in young adults⁸.

Among non-atheromatous causes of CAD, congenital coronary artery anomalies can manifest as MI in young adults. These cases are rare and come as a surprise in the cath-lab. Myocardial bridging, especially during systole, can also lead to MI⁹. Dissection in coronary arteries can suddenly happen in young adults, the left anterior descending artery being the culprit artery in most of the cases. Treatment by stenting or surgery represents the successful approach in all of the mentioned situations¹⁰.

Another cause of MI in young patients may be represented by septic emboli from vegetations occurring in aortic valve endocarditis, paradoxical emboli or emboli originating from coronary artery aneurysms¹¹.

Hypercoagulable states, which occur in the antiphospholipid syndrome (APL), the nephrotic syndrome, factor V Leiden mutations or the use of contraceptive pills, are a developing cause of MI in young patients.

APL syndrome implies recurrent arterial and venous thrombosis; it can be associated with other autoimmune diseases. The patients have premature atherosclerosis and increased platelet adhesivity. The level of antiphospholipid antibodies is closely linked to di-

sease activity and a careful evaluation is required for diagnosis^{12,13}.

Another cause of MI in young patients is related to the use of recreational drugs, the most frequently incriminated substance being cocaine, in about 48% of cases. A conventional risk factor added to substance abuse is smoking, leading to an exponential increase of MI risk occurrence¹⁴.

We present the case of a 27 years old male, physically fit without prior cardiovascular history, with acute myocardial infarction and thrombophilia.

CASE PRESENTATION

A 27 years old male patient was admitted to our clinic 12 hours after onset of a constrictive chest pain spreading to the interscapular-vertebral space and left upper limb and dyspnoea.

Family history was positive for hypertension on the maternal side; the mother also suffered 6 spontaneous abortions in her lifetime; the father was not aware of any heart disease. No brothers or sisters. Conventional cardiovascular risk factors included dyslipidaemia (total cholesterol = 215 mg%, triglycerides = 225 mg%), obesity (body weight = 145 kg, H = 180 cm, BMI = 44.75 kg/m²) and cigarette smoking (one pack/day for the last 10 years). The cardiovascular clinical examination revealed: blood pressure = 130/80 mmHg, heart

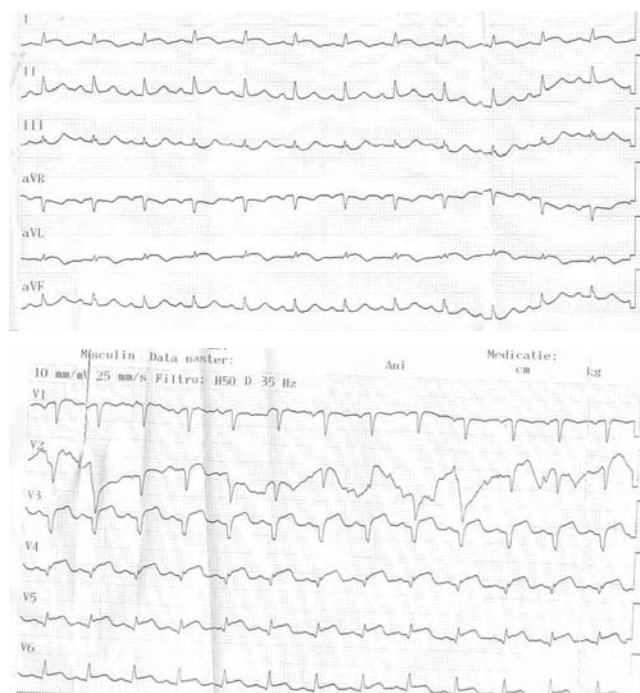


Figure 1. ECG on admission: sinus rhythm, Q wave in V₁-V₄, ST segment elevation of 3-4 mm in V₂-V₆ and 1-2 mm in DI, aVL.

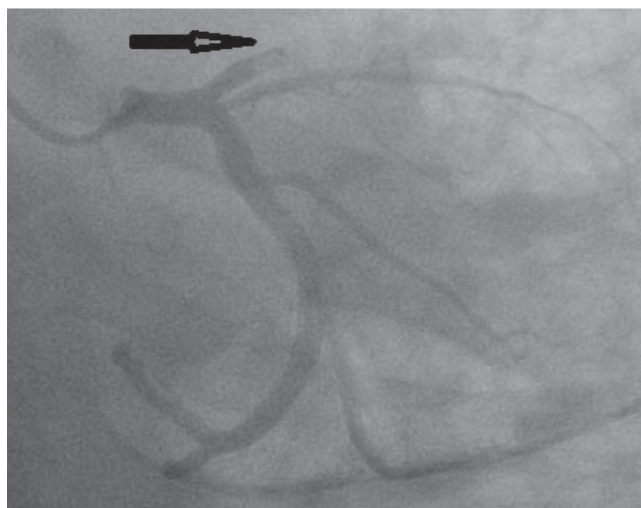


Figure 2. Coronary angiogram: thrombotic occlusion of the proximal left anterior descending (LAD) coronary artery.

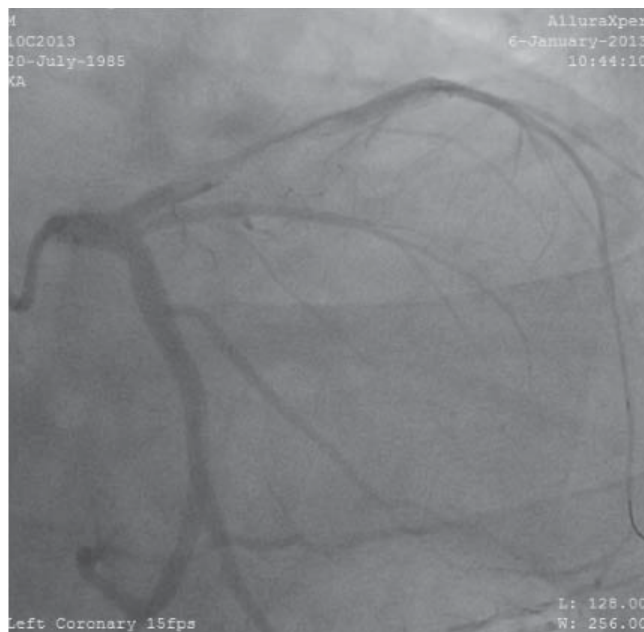


Figure 3. The aspect of the artery after multiple passes of thrombus aspiration and 250 mcg intracoronary nitroglycerine.

rate 120 b/min, rhythmic heart sounds, late inspiratory rales over posterior bases in both lungs, symmetrical peripheral pulse present bilaterally.

On the ECG sinus rhythm, Q wave in V_1 - V_4 , ST segment elevation of 3-4 mm in V_2 - V_6 and 1-2 mm in DI, AVL were present (**Figure 1**). The echocardiographic examination revealed a normal-sized left ventricle with significant changes in kinetics, no movement in the apical half of the interventricular septum and in the apical third of the inferior and anterior wall, hypokinetic basal interventricular septum, EF = 40%, mild ischemic mitral regurgitation, dilated left atrium, mild pulmonary hypertension, and no pericardial effusion.

Laboratory findings on admission revealed increased enzymes of myocardial necrosis (CPK = 2288 U/l, CPK-MB = 227 U/l). The diagnosis was acute anterior ST-elevation myocardial infarction (STEMI). The patient underwent an emergency coronary angiography that pointed out a thrombotic occlusion of the proximal left anterior descending (LAD) coronary artery (**Figure 2**), without the visualization of the distal territory. Export catheter was used and thrombus aspiration was performed. Multiple passes of thrombus aspiration were performed. Afterwards, intracoronary eptifibatide in a dose of 2 mcg/kg and 250 mcg of nitro-glycerine were given. A 90% atherosclerotic stenosis was detected

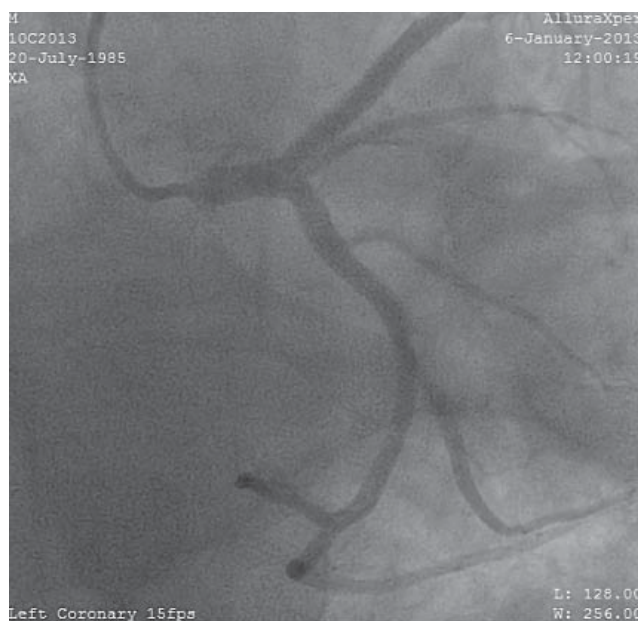


Figure 4. Caudal left-anterior-oblique view - final result after stenting.

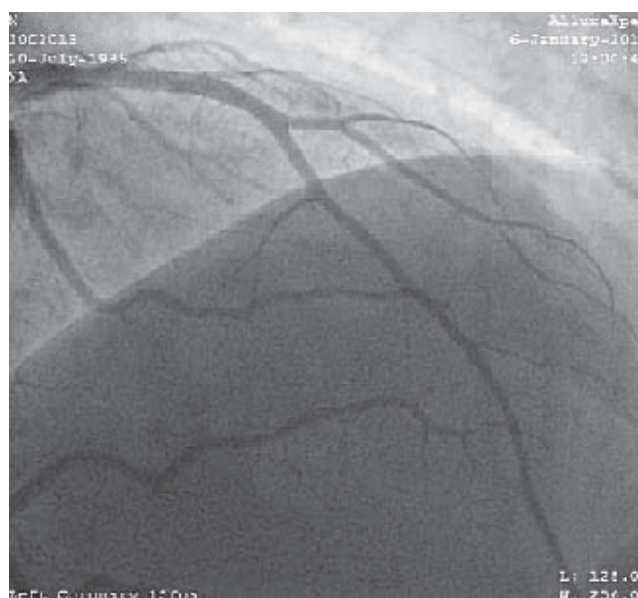


Figure 5. Cranial right-anterior-oblique view - final result after stenting.

with a remaining thrombus inside the LAD (**Figure 3**). The next step was stenting of the culprit artery – proximal LAD with the seizing of the remaining thrombus between the stent and the vessel wall. Approximately one minute after stenting, 500 mcg verapamil were given intracoronary through the guide catheter. The final result was good, without any remaining stenosis, no dissection proximally or distally, TIMI III and myocardial blush stage 3 (**Figure 4** and **Figure 5**).

Massive thrombosis in the LAD occurring at a young age required further investigation of causes responsible for hypercoagulable states (C and S proteins, Factor II – G20210A, Factor V Leiden, polymorphism of the human methylenetetrahydrofolate reductase gene, antithrombin III, homocysteine, lupus anticoagulant). The screening for thrombophilia, performed on the fourth day after stenting, revealed an increased homocysteine level = 19,12 $\mu\text{m/l}$ (NV <10 $\mu\text{m/l}$), a heterozygote mutation in the methylenetetrahydrofolate reductase gene - A1298C, low levels of antithrombin III (78.5%, with NV of 79,4-112) and normal values for protein C and S. The lupus anticoagulant was absent. Factor II, Factor V and methylenetetrahydrofolate reductase gene – C677T

mutations were absent. The screening for thrombophilia was made 48h after the last dose of heparin.

Due to presence of thrombophilia, dual antiplatelet therapy was associated with oral anticoagulant treatment. Evolution under therapy was very good, with a significant decrease of myocardial necrosis enzymes after three days.

The patient was discharged after eight days with dual antiplatelet and oral anticoagulant therapy, a beta-blocker, diuretic and a statin. The treatment was well tolerated and no ischemic recurrence was detected.

DISCUSSIONS

Atherosclerotic disease is a generalized disorder of the vascular system characterized by long-term atheromatous plaque formation developing in athero-thrombotic obstructive lesions that leads to tissue damage¹⁵.

Angina and acute myocardial infarction (MI) are the clinical manifestations of the chronic development of coronary artery atheroma. The underlying processes that lead to atheroma formation and coronary thrombosis are complex, involving imbalance of various systems that regulate vasoactivity, adhesion molecules, in-

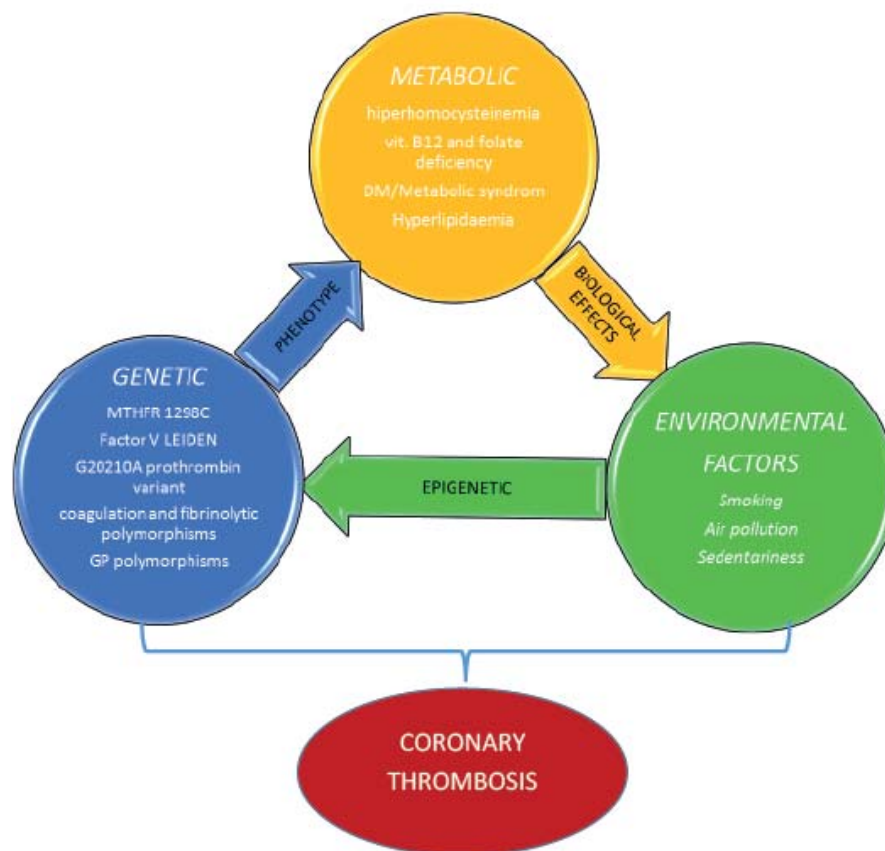


Figure 6. Interplay of genetic, metabolic and environmental factors in inherited hypercoagulable states.

flammation, lipid metabolism, coagulation and fibrinolysis¹⁵.

The pathogenesis of arterial thrombotic disease involves multiple genetic and environmental factors related to atherosclerosis and thrombosis. The generally accepted conventional risk factors include smoking, hypertension, hyperlipidaemia, obesity, diabetes and a positive family history^{15,16}.

Acute coronary syndrome is rarely encountered in young adults and may have unusual causes. Atherosclerotic plaque is not always present and non-atherosclerotic causes of coronary artery disease such as thrombophilia should be considered especially in young patients with myocardial infarction.

Thrombophilia can be defined as a hereditary or acquired increased risk of thrombosis. The hereditary causes of thrombophilia are deficiencies of protein C, protein S and antithrombin III, factor V Leiden, hyperhomocysteinaemia, prothrombin G20210A polymorphism and elevated levels of factor VIII, von Willebrand factor (vWF) and fibrinogen levels. The acquired causes are antiphospholipid antibodies, cancer and hyperhomocysteinaemia due to mild nutritional folic acid, vitamin B12 or B6 deficiencies or associated hyperlipidaemia. Acquired thrombophilia can also occur in persistent inflammatory conditions and myelo-proliferative disorders¹⁷.

The clinical manifestations of thrombophilia are venous thromboembolism at a young age, thrombosis at different sites (cerebral sinuses, portal), recurrent foetal loss, pre-eclampsia, premature atherosclerosis, and myocardial infarction at a young age without any conventional risk factors and family history of venous thromboembolism¹⁷.

The main event in the pathogenesis of any thrombotic event is the perturbation of haemostasis¹⁷. This perturbation may be genetically determined (**Figure 6**). But, since the onset of thrombosis in the majority of cases is at a later stage, it is unlikely that genetic causes may be the sole determinant. This points towards a gene-environment interaction in thrombosis. There are certain distinctions between arterial and venous thrombosis. The thrombus is platelet rich in arterial thrombosis and fibrin rich in venous thrombosis. Additionally in arterial thrombosis, there is presence of atheroma which represents vascular wall damage¹⁵.

In the particular case of our patient, multiple conventional cardiovascular risk factors were present such as: sex, dyslipidaemia, obesity and smoking. Still, these factors cannot explain the occurrence of MI at such a young age and the massive thrombosis in the LAD.

After multiple passes of thrombus aspiration in the proximal and medium segments of LAD and retrieval of a large quantity of thrombus, a long 90% stenosis was noticeable along with a massive remaining thrombus in the proximal segment of LAD (**Figure 3**).

The remaining thrombus in the coronary artery could not be retrieved even after intracoronary eptifibatide administration. Afterwards, stenting of the lesion in the culprit artery was performed (prolonged inflation of 45 seconds), with seizing of the remaining thrombus between the stent wall and the vessel wall. One minute after stenting, although in the absence of any no-reflow phenomenon, 500 cmg verapamil were given intracoronary through the guide catheter. Verapamil is a calcium channel blocker that improves relaxation in the vascular wall and increases myocardial perfusion through the blockage of calcium in the calcium channel in the coronary arteries¹⁸.

Intracoronary verapamil administration can prevent negative ventricular remodelling and can improve left ventricular function due to microvascular dysfunction recovery. The mechanism of action of verapamil is decrease of microcirculation spasm and by improvement of myocardial blood flow in patients with AMI.

The suspicion of thrombophilia has arisen due to massive thrombosis in LAD and to a history of 6 spontaneous abortions on the maternal side. The evaluation of the patient included, on the fourth day after onset of symptoms, detection of thrombophilia markers that revealed hyperhomocysteinaemia, heterozygote mutation of the human methylenetetrahydrofolate reductase gene and low levels of antithrombin III.

Evaluation of thrombophilia markers in the mother was declined.

Because the patient had thrombophilia and massive thrombus in the LAD, at discharge, we opted for indefinite anticoagulant therapy associated in the first 6 months with dual antiplatelet therapy (clopidogrel + acetyl salicylic acid), and after six months, with just one antiplatelet drug (acetyl salicylic acid).

At discharge, we did not prescribe any homocysteine lowering drugs (folic acid, vitamins B6 and B12) because the clinical trials in this area were negative for reducing the risk for cardiovascular events after AMI. On the contrary, they can exert a harmful action, one of the reasons why they are not generally recommended²⁰.

CONCLUSIONS

Inherited thrombophilia is a genetic disorder predisposing to thrombosis which may manifest occasionally, usually in the presence of trigger factors. Thrombophi-

lia induces a hypercoagulable state, which, together with other cardiovascular risk factors, may explain the arterial thrombosis in this young patient. It is very important to early diagnose these genetic disorders, because they influence long-term treatment and outcomes. Due to poor long-term prognosis, it is vital to diagnose this condition before a thrombotic event. This is difficult to achieve, because the evaluation expenses are high and they must be covered by the patient. In the case of our patient, the fact that the mother had six miscarriages before, should have led to the suspicion of thrombophilia as cause for the spontaneous abortions. Early diagnosis could have changed the outcomes in this patient. In practice, this condition is responsible for a small percentage of acute myocardial infarctions, in patients who are mostly young, and the prognosis is poor. Usually, in the absence of a proper diagnosis, these patients do not receive adequate treatment.

Conflict of interest: none declared.

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