CASE REPORT

Coronary artery disease associated with factor V Leiden mutation: a case report

Faktör V Leiden mutasyonu ile ilişkili koroner arter hastalığı: Olgu sunumu

Roberto Muniz Ferreira, M.D.,[1,2] Paolo Blanco Villela, M.D.,[1,2]
José Ary Boechat Salles, M.D.,[1] João Mansur Filho, M.D.[1]

[1]Department of Cardiology, Samaritano Hospital, Rio de Janeiro, RJ, Brasil,
[2]Federal University of Rio de Janeiro, Edson Saad Heart Institute, Rio de Janeiro, RJ, Brasil

Summary– The prevalence of coronary artery disease in young adults (<45 years of age) has been increasing steadily in recent decades. Although traditional cardiovascular risk factors can be identified in most cases, newly recognized associations are becoming progressively more relevant. The relationship between the factor V Leiden mutation and atherosclerosis has been a matter of debate due to conflicting data presented in previous studies. Presently described is the case of a previously asymptomatic 37-year-old woman with a significant family history of coronary artery disease who developed rapidly progressive angina within 1 month. After a positive non-invasive evaluation, coronary angiography demonstrated a significant obstruction in the proximal left anterior descending artery. Optical coherence tomography revealed a highly vulnerable lipid-rich atherosclerotic plaque. Coronary angioplasty followed by the implantation of 1 drug-eluting stent was successfully performed. A subsequent thrombophilia screening identified a heterozygous factor V R506Q mutation (factor V Leiden). Since there was no history of thromboembolic events, the patient was discharged using only aspirin, clopidogrel, atorvastatin, and atenolol. Further studies are needed to define the most appropriate management of young patients who manifest clinically significant atherosclerotic disease in association with hereditary thrombophilia.

Özet– Genç erişkinlerde (45 yaş altı) koroner arter hastalığının prevalansı son onyıllarda sürekli artmıştır. Olguların çoğunda geleneksel risk faktörleri tanımlanabilmesine rağmen yeni fark edilmiş ilişkiler giderek daha fazla belirgin hale gelmiştir. Faktör V Leiden mutasyonu ile ateroskleroz arasındaki ilişki daha önceki çalışmalarda sunulan çelişkili veriler nedeniyle tartışma konusu olmuştur. Bu yazıda önemli ailevi bir koroner arter öyküsü olan ve bir ay içinde hızla ilerleyen anjina gelişen 37 yaşındaki asemptomatik bir kadın olgu sunuldu. Girişimsel olmayan değerlendirmelerin pozitif sonlanması üzerine yapılan koroner anjiyografi sol ön inen arterin proksimalinde önemli bir obstrüksiyonun varlığını gösterdi. Optik koherens tomografide parçalanabilir lipitten zengin, hassas bir aterosklerotik plak varlığı tespit edildi. Koroner anjiyoplasti ardından bir ilaç salınımlı stent başarıyla takıldı. Daha sonraki trombofili tarama testinde heterozigot faktör V R506Q mutasyonu (faktör V Leiden) olduğunu belirlendi. Tromboembolik olay öyküsü olmadığından hasta aspirin, klopidogrel, atorvastatin ve atenolol kullanmak üzere taburcu edildi. Kalıtsal trombofiliyle ilişkili klinik açıdan önemli aterosklerotik hastalık gösteren genç hastaların en uygun tedavisini tanımlamak için ileri çalışmalara gerek vardır.

Although various designations have been used in previous studies, coronary artery disease in young adults is generally defined as a diagnosis established before 45 years of age. This subgroup of patients composes up to 6% of all acute coronary syndromes, whereas the prevalence of occult disease can be as high as 11%, according to coronary computed tomography (CT) studies.[1,2] Furthermore, autopsy reports of individuals younger than 34 years of age have found a 50% prevalence of incipient coronary atherosclerotic disease.[1]

Abbreviations:

ADCA	*Anterior descending coronary artery*
CT	*Computed tomography*
ECG	*Electrocardiogram*
OCT	*Optical coherence tomography*
RCA	*Right coronary artery*

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Correspondence: Dr. Roberto Muniz Ferreira. Rua Rodolpho Paulo Rocco 255, Ilha Do Fundão 21941 Rio De Janeiro - Brazil.
Tel: +552134441000 e-mail: betomf@terra.com.br

Hereditary thrombophilias are associated with an increased risk of thromboembolic events, both venous and arterial. These complications are associated with significant morbidity and mortality, and the risk is greater in individuals with homozygous mutations or those with a combination of defects.[3] Most heterozygous mutations are discovered incidentally through laboratory screening and are associated with a lower thrombotic risk. One of the most common mutations results in a defect in the factor V gene that makes it resistant to protein C inactivation. This is known as factor V Leiden, which was first described in 1994 by Bertina et al.[4]

A higher prevalence of thrombophilia, such as factor V Leiden, in patients with coronary artery disease has been previously reported, although it is still a matter of debate.[5] An interaction between atherosclerosis and a thrombotic predisposition has become an emergent topic of research, but the exact mechanisms of this association remain elusive. Described here is the case of a 37-year-old woman with unstable angina and severe proximal obstruction of the anterior descending coronary artery (ADCA) in association with a heterozygous factor V Leiden mutation.

CASE REPORT

A previously asymptomatic and physically active 37-year-old woman developed retrosternal chest pain radiating to the neck and left arm associated with physical activity. The pain had begun 1 month earlier and was progressive. She had a history of dyslipidemia managed without medication, well-controlled hypothyroidism (levothyroxine 88 mcg once a day) and a family history of premature coronary artery disease. Her father underwent coronary artery bypass grafting at 44 years of age. No other comorbidities were reported and there was no history of tobacco use.

Due to her worsening symptoms, the patient was evaluated in an emergency department, where she arrived hemodynamically stable and the results of the physical exam were normal. On admission, an electrocardiogram (ECG) demonstrated a normal sinus rhythm, with T-wave inversion from V3 to V6 without dynamic ST-segment deviations. The initial blood work showed normal levels of high-sensitivity troponin T and D-dimer, which remained stable after 6 hours. Transthoracic echocardiography did not reveal any changes in biventricular function, valvular disease, or pericardial effusion.

The patient was transferred to the coronary intensive care unit with a diagnosis of unstable angina, where dual antiplatelet therapy with aspirin (100 mg once a day) and clopidogrel (loading dose of 300 mg) was initiated in association with enoxaparin (1 mg/kg twice a day), atorvastatin (80 mg once a day) and atenolol (25 mg once a day). On the following day, CT coronary angiography was performed and demon-

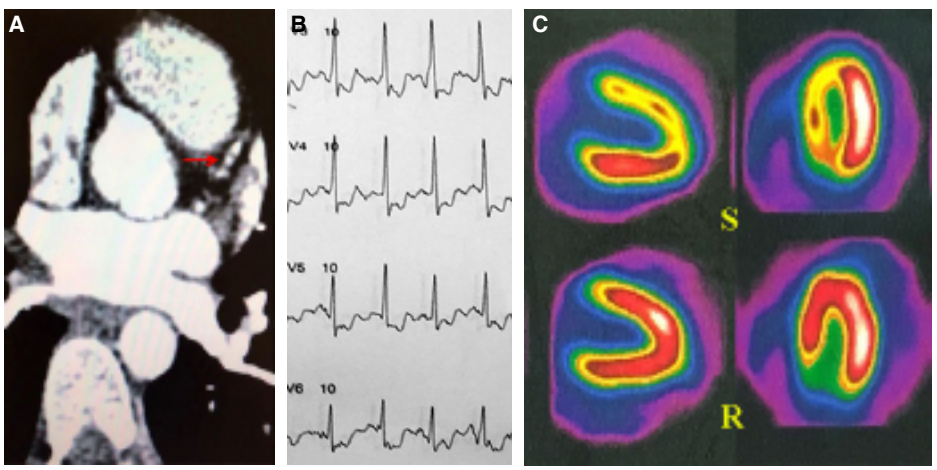

Figure 1. Non-invasive coronary risk stratification. **(A)** Coronary computed tomography demonstrating a 60% obstruction (arrow) in the proximal anterior descending coronary artery (ADCA); **(B)** Electrocardiogram results indicating a ST-segment depression of 3 mm in leads V3 to V6 after 6 metabolic equivalents of exercise intensity. **(C)** Myocardial perfusion scintigraphy during stress (S) and at rest (R) demonstrating a large area of ischemia in the territory of the ACDA.

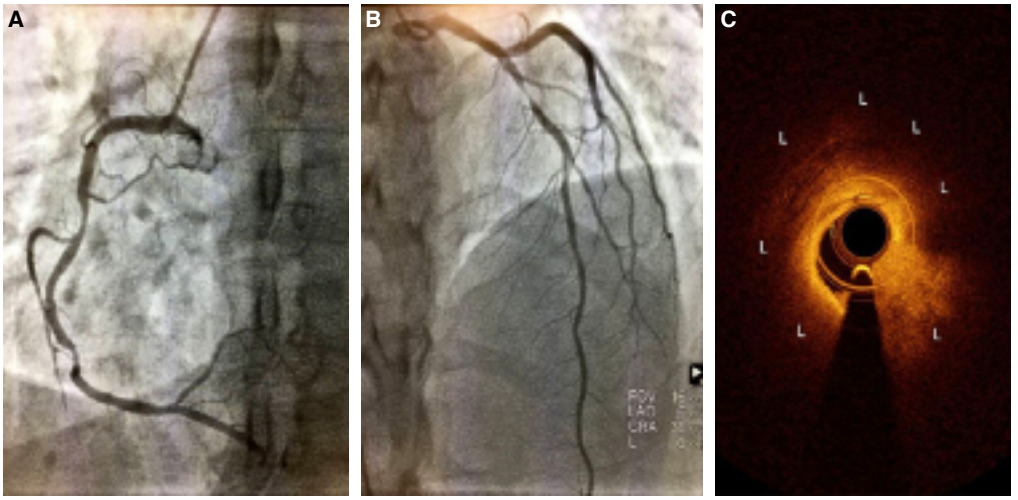

Figure 2. Coronary angiography findings. **(A)** Sequential intermediate lesions in the right coronary artery (fractional flow reserve of 0.84). **(B)** Significant 99% obstruction of the proximal anterior descending coronary artery (ADCA). **(C)** Optical coherence tomography demonstrating a plaque with a lipid-rich core (L) in the ADCA.

strated a 60% obstruction in the proximal ACDA (Fig. 1a). Three days later, during a myocardial scintigraphy with a treadmill exercise protocol, the patient developed typical chest pain after 6 metabolic equivalents of task, in association with a 3-mm ST-segment depression from V3 to V6 on the ECG (Fig. 1b). A 30% ischemic burden was identified compromising the apical, apical septal, apical anterior, mid-anterior, and mid-anteroseptal regions (Fig. 1c).

On the next day, coronary angiography was performed through the right radial artery and revealed a 99% obstruction in the proximal ACDA (Fig. 2a) and sequential intermediate lesions in the right coronary artery (RCA) (Fig. 2b). Optical coherence tomography (OCT) identified a plaque with a lipid-rich core in the ACDA, suggesting a high degree of lesion vulnerability (Fig. 2c). Angioplasty and stenting were subsequently performed in the ACDA with 1 everolimus-eluting stent (Synergy; Boston Scientific Corp., Marlborough, MA, USA) implantation. The RCA was not treated since the periprocedural fractional flow reserve of both lesions was 0.84.

Considering the lack of significant identifiable cardiovascular risk factors other than the positive family history, a thrombophilia screening was performed after the intervention. Antiphospholipid antibodies, proteins C and S, prothrombin G20210A and methylenetetrahydrofolate reductase mutations, and homocysteine levels were either absent or normal. However, a heterozygous R506Q mutation on the factor V gene was identified, consistent with factor V Leiden. The patient was discharged 2 days later using aspirin, clopidogrel, atorvastatin, and atenolol; oral anticoagulation was not prescribed.

DISCUSSION

Atherosclerotic cardiovascular disease in young adults has become an emerging health issue worldwide. In approximately 80% of patients with coronary artery disease in this subgroup, atherosclerosis is the underlying cause.[1] Symptoms are usually scarce, and most patients suffer an acute coronary syndrome as the first clinical manifestation of the disease. Also, because this age group largely consists of an economically active population, the financial burden affecting the healthcare system is increased.

The involvement of the proximal ACDA has been reported to be higher in young women than in young men and old women with AMI.[6] Even though single-vessel coronary disease is most frequently identified (58%), the prognosis may be adversely affected when certain clinical characteristics are present. A prospective study with 843 patients under 40 years of age with known coronary artery disease found a 30% mortality over 15 years of follow-up. Diabetes, previous MI, tobacco use, and left ventricular dysfunction were associated with a poorer prognosis, whereas any form of revascularization was predictive of an im-

proved outcome.[7]

In almost 90% of cases, at least 1 traditional cardiovascular risk factor, such as hypertension, diabetes, dyslipidemia, tobacco use, or a positive family history of premature disease, can be identified.[1] Although there is a predominance of male patients, the prevalence of these risk factors appears to be well balanced between genders.[7] New disease interactions are gradually being recognized in this age group, albeit with variable levels of impact on the atherosclerotic pathogenesis. Among these, the most significant associations involve hereditary thrombophilia (e.g., factor V Leiden), infections (e.g., HIV), familial hypercholesterolemia (e.g., mutations affecting the ApoB, ApoE, and PCSK9 genes), autoimmune diseases (e.g., systemic lupus erythematosus), endocrine diseases (e.g., hypothyroidism), and drug abuse (e.g., cocaine).[1]

The degree of influence of factor V Leiden in the development of atherosclerotic vascular disease is controversial. Previous studies have demonstrated varied results, but research of large patient population groups suggest that a relationship does in fact exist.[8,9] Both heterozygous and homozygous genotypes have been associated with the presence of obstructive coronary artery disease, with a greater prevalence of multivessel involvement seen in homozygous individuals.[8] The mechanisms behind this association are not fully understood, although an interaction between elevated levels of low-density lipoproteins and factor V Leiden appears to be a possibility.[10]

Such a hypothesis is compatible with previous reports in which the factor V mutation was diagnosed in association with peripheral and cerebral arterial disease, suggesting a systemic effect on the arterial vasculature.[11,12] Some researchers have also proposed systematic screening for hereditary thrombophilia in young patients without apparent cardiovascular risk factors who manifest clinically significant atherosclerotic disease.[12] Although the basis of this recommendation would be to prescribe chronic oral anticoagulation to those with a positive screening, there is still no evidence that such a strategy would either delay the progress of the disease or prevent clinically relevant adverse outcomes.

In the present case, there were no traditional cardiovascular risk factors other than the patient's family history. As such, the diagnosis of the factor V Leiden mutation emerged as a relevant potential risk factor for the significant atherosclerotic coronary disease that was found. The obstruction of the proximal ACDA is consistent with previous reports describing similar manifestations in young women, particularly because the lesions in the RCA were deemed insignificant. The lipid-rich core that was seen using OCT suggested a plaque with a higher risk of acute complications, such as erosion or rupture. Perhaps this pathophysiological pattern explains why acute coronary syndromes are the form of disease presentation more frequently seen in this age group. However, the impact of factor V Leiden mutations in this clinical aspect warrants further investigation.

In conclusion, the prevalence of coronary artery disease in patients younger than 45 years of age has risen steadily in the last decades. As such, it is imperative to understand if previously underrecognized cardiovascular risk factors could in fact have a more relevant role in this context. The association between hereditary thrombophilia and atherosclerosis as seen in this case further emphasizes the need for greater advances in this area. Until then, the management of patients in this scenario will remain speculative, especially when oral anticoagulation is considered.

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