International Journal of the Cardiovascular Academy 2 (2016) 71–73

Contents lists available at ScienceDirect

International Journal of the Cardiovascular Academy

journal homepage: www.elsevier.com/locate/ijcac

Short communication

Coronary thrombus in 34-year-old female patient with 4G/4G polymorphism in the PAI-1 gene

Sinan Varol [a,*], Muhsin Kalyoncuoglu [b], Burak Ayça [a], İrfan Şahin [a], Gökmen Kum [a], Sevgi Özcan [a], Ertugrul Okuyan [a]

[a] Bagcilar Training & Research Hospital, Cardiology, Istanbul, Turkey
[b] Haseki Training & Research Hospital, Cardiology, Istanbul, Turkey

ARTICLE INFO

Article history:
Received 30 August 2015
Received in revised form 7 March 2016
Accepted 9 March 2016
Available online 7 April 2016

Keywords:
Coronary
Thrombus
PAI-1 gene
Polymorphism

ABSTRACT

Genetic factors and hypofibrinolytic state may contribute to the likelihood of developing in myocardial infarction (MI) in young women rather than traditional risk factors. High plasminogen-activator inhibitor-1 (*PAI-1*) level and *PAI-1* gene polymorphism have been shown to be associated with thrombotic events such as myocardial infarction, deep venous thrombosis, and stroke. We determined *4G/4G* polymorphism in a 34-year-old female patient with subacute anterior myocardial infarction and coronary thrombus in left anterior descending artery on coronary angiogram.

Introduction

The pathogenesis of myocardial infarction (MI) is complex and multifactorial, including multiple interacting environmental and genetic factors. Traditional risk factors such as hypertension, diabetes mellitus, and hypercholesterolemia are less pronounced in the younger patients in development of the myocardial infarction. Therefore, additional factors such as genetic factors and hypofibrinolytic state may contribute to the likelihood of developing in the myocardial infarction and may be required to determine in young participants.[1] Plasminogen-activator inhibitor-1 (*PAI-1*) is a member of serpin superfamily of protease inhibitors and a key regulatory protein of fibrinolysis cascade by inhibiting plasminogen activators which are tissue plasminogen activator (t-PA) and urokinase (u-PA).[2] High plasma *PAI-1* levels have been shown to be associated with atherosclerosis, restenosis, and in the pathogenesis of disorders associated with thrombotic events such as myocardial infarction and deep venous thrombosis.[2–4] It was reported that *PAI-1* gene polymorphism such as *4G/5G* and *4G/4G* genotypes has been associated with the higher gene expression and higher *PAI-1* levels in the circulation resulting in an increased risk for thrombotic events such as MI and stroke.[5–10]

Case report

A 34-year-old female patient had been admitted for chest pain of about 5 days, which accelerates with exertion and resolves with rest. She has no any history of smoking, alcohol, drug abuse, systemic disease, or family history of cardiovascular disease. Blood pressure was 115/70 mm Hg and heart rate was 88 BPM. Cardiac auscultation was normal heart sounds with no murmur. Other physical examination findings were normal. ECG revealed loss of R progression on V2–3, ST segment elevation on V2–5, and new developed deep inverted T waves on V1–V6 (Fig. 1). Two weeks before symptoms, ECG was normal with positive T waves. Echocardiography was normal with absence of any wall motion abnormalities. Blood tests were troponin 0.419 mcg/L, CK-MB <21 ng/mL. Coronary angiogram revealed long intracoronary thin thrombus adjusted to endothelium at LAD artery (Fig. 2). Because of lack of response to repeated dosages of intracoronary nitroglycerin, and typical thin trombus appearance, vasospastic angina was excluded. Patient has received tirofiban infusion for 24 hours. Repeat coronary angiogram has shown partial resolution of coronary thrombus (Fig. 3). During hospital care, chest pain diminished with enoxaparine 6000 IU twice daily, clopidogrel 75 mg, acetyl salicylic acid 300 mg, metoprolol 50 mg, and nitrate therapy. Statin therapy was not initiated because of absent conventional risk factors. ECG follow-up showed that resolution of ST segment elevation, but negative T waves were persisted. Warfarin was started and acetyl salicylic acid dose was adjusted as 100 mg per day. Patient has been discharged with prescribing same medical treatment. Genetic analysis showed that negative for protrombin gene mutation (*G20210A*), Factor V Leiden

* Corresponding author. Tel.: +00905556223410.
E-mail addresses: sinanvarol@gmail.com (S. Varol), mkalyoncuoglu80@gmail.com (M. Kalyoncuoglu), burakayca@yahoo.com.tr (B. Ayça), dr.irfansahin@gmail.com (İ. Şahin), dr_gkum@hotmail.com (G. Kum), sevgibozcan@gmail.com (S. Özcan), dreokuyan@hotmail.com (E. Okuyan).

Peer review under responsibility of The Society of Cardiovascular Academy.

http://dx.doi.org/10.1016/j.ijcac.2016.03.002

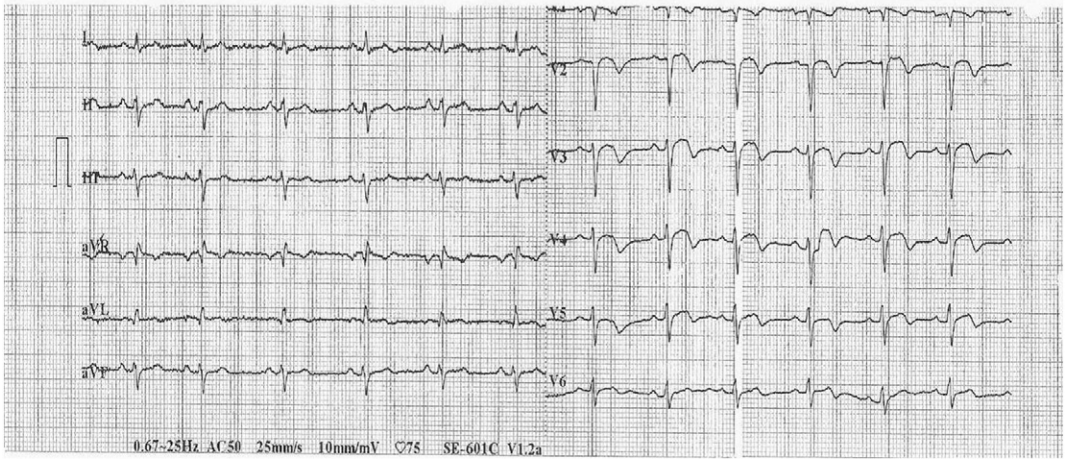

Fig. 1. ECG on admission.

(*G1691A*), Factor XIII *V34L*, *MTHFR* (*C677T*), Protein C and Protein S mutation, antithrombin III, antiphospholipid antibody.

Lupus anticoagulant had a weak positive result of 1.35, thought as clinically irrelevant (cut-off value: negative: <1.2; weak positive: 1.2–1.5, positive: >1.5, markedly positive: >2.0). Heterozygot *MTHFR* (*A1298C*) mutation has been revealed as positive, but homosistein levels were normal, and there was weak evidence of developing thrombus with this mutation in current literature. Protrombine Activator Inhibitor 1 (*PAI-1*) serpine 4G/4G mutation has been revealed by genetic analysis. This mutation has been known to be a high risk for thrombotic events. So we thought it was responsible for this event. During follow-up, the patient has complained of intermittent chest pain with short duration as couple of minutes and resolves spontaneously. After 2 months, ECG findings were similar with negative T waves on V1–V6, and there was short duration of angina attacks. At 4 months, ECG revealed that negative T wave was only at V2–V3 leads, and at 5 months, ECG was normal with positive T waves and clinically asymptomatic.

Discussion

An increased capacity to form blood clots or decreased fibrinolytic capacity due to high plasma *PAI-1* levels has been shown to play an important role in the pathogenesis of disorders associated with thrombotic events such as MI and ischaemic stroke.[1,8,11,12] It was also found that increased levels of *PAI-1* were associated with coronary endothelial dysfunction, plaque progression, and vulnerability leading to unstable angina pectoris and acute myocardial infarction.[2,13–15] It has been also reported that several genetic variations in coagulation and fibrinolytic proteins were associated with the development of the risk of MI.[7] The *PAI-1* gene known as *SERPIN 1* gene in humans is located on chromosome 7q22.[4] Two genetic variations, which were guanosine insertion/deletion, −675 *4G/5G*, and −844 G/A promoter polymorphisms in the *PAI-1* gene, have been associated with increased *PAI-1* levels and linked to various vascular diseases such as MI and deep vein thrombosis.[5,7,13,16,17] Homozygosity for the deletion genotype (*4G/4G*) has been associated with higher gene expression than those associated with the insertion genotype (5G/5G) resulting in higher *PAI-1* levels in the circulation and an increased risk for venous thrombosis, pulmonary thromboembolism, and MI through impairment of fibrinolytic function by elevated *PAI-1* activity.[5,7,8,16,18] Plasma levels of *PAI-1* have a wide and peak in the morning, whereas concentrations of t-PA exhibit less prominent circadian variation, and a relative hypofibrinolytic state may occur in the morning with increased platelet reactivity. That condition may contribute to the increased risk of MI seen during this period. In a study, it has been also reported that morning increase in *PAI-1*

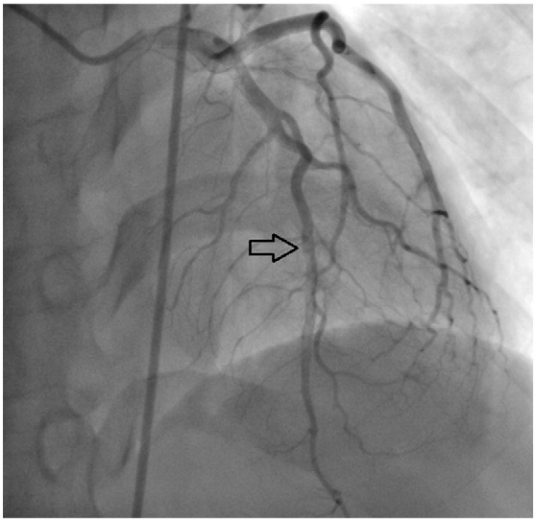

Fig. 2. Coronary thrombus on left anterior descending artery.

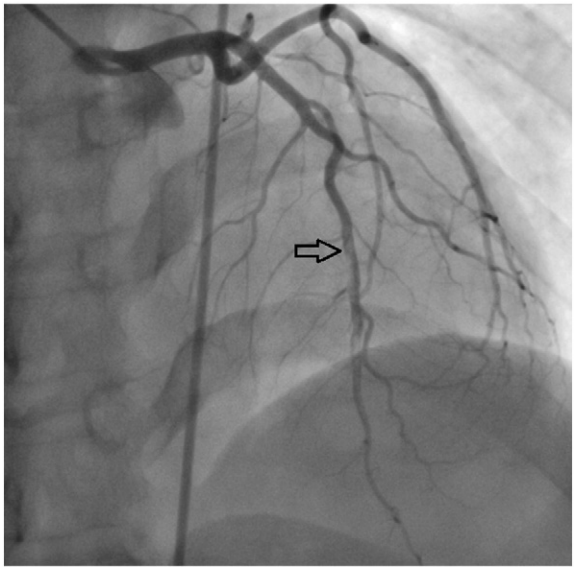

Fig. 3. After tirofiban infusion, thrombus with partial resolution persisted on the left anterior descending artery.

activity may be determined in *4G/4G* genotype subjects.[13] Boekholdt et al. showed that homozygosity for the *PAI-1 4G* allele was significantly associated with increased risk of myocardial infarction.[7] In a large Japanese study, the *PAI 4G/5G* polymorphisms appeared to be a risk factor for myocardial infarction in women.[19] In a recent study, Ismail et al. found that *PAI-1* genotype was higher in Egyptian patients with myocardial infarction. There was about twofold increased risk of MI associated with *4G4G + 4G5G* compared with *5G5G*. However, in that study, the *PAI-1* polymorphism (*4G*) was not found associated with MI, whereas modest risk could not be excluded.[13] While the mentioned data suggested positive association between the development of MI and *PAI-1* gene polymorphism, Atherosclerosis, Thrombosis, and Vascular Biology Italian Study Group (2003), did not find any association between *PAI-1* gene polymorphisms and the development of acute MI at a young age (under the age of 45 years).[20] Ding et al. also found that *PAI-1* gene polymorphisms were associated with high plasma *PAI-1* levels, whereas they were not associated with MI or stroke.[21]

There are some studies in the literature that reported that *PAI-1* antigen levels are positively correlated with cholesterol, LDL-cholesterol, VLDL, and triglyceride levels and negatively with HDL cholesterol.[4,18,22] In addition, it was suggested that the 4G/4G genotype has been reported to be associated with high cholesterol levels.[22] It was also claimed that the increase in *PAI-1* levels resulting from the activation of the renin–angiotensin system and hypertension in subjects with the *4G/4G* genotype.[4] It was also found that smoking by patients carrying the 4G allele may have an important impact on the frequency of MI.[13] Consequently, data about the relation of *PAI-1* with myocardial infarction are still inconclusive and contradictory.

The etiology of cardiovascular disease is multifactorial and strongly involves genetic and environmental factors. The interaction of genetic and traditional risk factors such as smoking, hypertension, hypercholesterolaemia may have a role in the development of MI. So that, identifying them for primary prevention early in life, especially in the presence of genetic predisposition, is important. Despite aforementioned data, the clinical use of fibrinolytic markers to determine coronary risk offers only marginal value and no data available suggest analysis of fibrinolytic function in addition to traditional risk scores. We propose that the determination of well-described polymorphisms in the *PAI-1* promoter and other components of the fibrinolytic system as a novel risk factor in addition to traditional risk factors is important.

Conclusion

Certain genetic disorders have tendency to myocardial infarction. Genetic testing should be considered for patients with young age, atypical presentation, and who have specific angiographic findings.

Conflict of interest

No conflict of interest.

References

1. Siegerink B, Meltzer ME, de Groot PG, Algra A, Lisman T, Rosendaal FR. Clot lysis time and the risk of myocardial infarction and ischaemic stroke in youn women: results from the RATIO case-control study. *Br J Haematol* 2011;**156**:252–258.
2. Figueras J, Monasterio J, Domingo E, Meneses B, Nieto E, Cortadellas J, Garcia-Dorado D. Prothrombotic profile in patients with vasospastic or non vasospastic angina and nonsignificant coronary stenosis. *Thromb J* 2011;**9**:10.
3. De Young MB, Tom C, Dichek DA. Plasminogen activator inhibitor type 1 increases neointima formation in balloon-injured rat carotid arteries. *Circulation* 2001;**104**: 1972–1976.
4. Katrancioğlu, Nurkay, et al. PAI-1 4G/4G gene polymorphism is associated with higher serum lipid level in Turkish population. *Cumhuriyet Med J [S.l.]* 2011 Sep.;**33**(3): 307–311http://dx.doi.org/10.7197/cmj.v33i3.1008000938 (ISSN 1305-0028 . Available at: <http://dergi.cumhuriyet.edu.tr/cumucmj/article/view/1008000938>. Date accessed: 30 Dec. 2015).
5. Assawamakin A, Sriratanaviriyakul N, Lalerd Y, et al. Meta-analysis of the plasminogen activator inhibitor-1 (PAI-1) gene with insertion/deletion 4G/5G polymorphism and its susceptibility to ischemic stroke in Thai population. *Asian Biomed* 04/2012;**6**(2):203–217 (Available at: < https://www.researchgate.net/publication/224221857_Meta-analysis_of_the_plasminogen_activator_inhibitor-1_PAI-1_gene_with_insertiondeletion_4G5G_polymorphism_and_its_susceptibility_to_ischemic_stroke_in_Thai_population>. Date accessed: 30 Dec. 2015. doi:).
6. Bang CO, Park HK, Ahn MY, Shin HK, Hwang KY, Hong SY. 4G/5G polymorphism of the plasminogen activator inhibitor-1 gene and insertion/deletion polymorphism of the tissue type plasminogen activator gene in atherothrombotic stroke. *Cerebrovasc Dis* 2001;**11**:294–299.
7. Boekholdt SM(SMB), Bijsterveld NR, Moons AHM, et al. Genetic variation in coagulation and fibrinolytic proteins and their relation with acute myocardial infarction. *Circulation* 2001;**104**:3063–3068.
8. Balta G, Altay C, Gurgey A. PAI-1 gene 4G/5G genotype: a risk factor for thrombosis in vessels of internal organs. *Am J Hematol* 2002;**71**:89–93.
9. Eriksson P, Kallin B, van't Hooft FM, Bavenholm P, Hamsten A. Allele-specific increase in basal transcription of the plasminogenactivator inhibitor 1 gene is associated with myocardial infarction. *Proc Natl Acad Sci U S A* 1995;**14**:1851–1855.
10. Spronk HMH, van der Voort D, ten Cate H. Blood coagulation and the risk of atherothrombosis: a complex relationship. *Thromb J* 2004;**2**:12.
11. Kohler HP, Grant PJ. Mechanisms of disease; plasminogen-activator inhibitor type 1 and coronary artery disease. *New Engl J Med* 2000;**342**:1792–1801.
12. Guimaraes Ana HC, Bruijne Emile LE, Lisman T, et al. Hypofibrinolysis is a risk factor for arterial thrombosis at young age. *Br J Haematol* 2009;**145**:115–120.
13. Ismail S, Abdel azeem AA, Abdel Hamid MA, Nowier SR, Morad H. The role of 4G/5G genetic polymorphism of plasminogen activator inhibitor-1 gene in myocardial infarction among Egyptans. *Life Sci J* 2011;**8**(1):32–39 (Avaible at: https://www.google.com.tr/url?sa=t&rct=j&q=&esrc=s&source=web&cd=1&ved=0ahUKEwjum_e3gITKAhVI_SwKHWvrCv8QFggaMAA&url=http%3A%2F%2Fwww.lifesciencesite.com%2FIsj%2Flife0801%2F06_4152life0801_32_39.pdf&usg=AFQjCNFUJ3U-xrc7LSfz9zT0Xldw_BDyNw&bvm=bv.110151844,d.bGg&cad=rja).
14. De Young MB, Tom C, Dichek DA. Plasminogen activator inhibitor type 1 increases neointima formation in balloon-injured rat carotid arteries. *Circulation* 2001;**104**: 1972–1976.
15. Figueras J, Monasterio Y, Lidon RM, et al. Thrombin formation and fibrinolytic activity in patients with acute myocardial infarction or unstable angina. In-hospital course and relationship with recurrent angina at rest. *J Am Coll Cardiol* 2000;**36**:2036–2043.
16. Oszajca K, Wronski K, Janiszewska G, Bienkiewicz M, Bartkowiak J, Szemraj J. The study of t-PA, u-PA, and PAI-1 genes polymorphisms in patients with abdomimal aortic aneurysm. *Mol Biol Rep* 2014;**41**:2859–2864.
17. Buchholz T, Lohse P, Rogenhofer N, et al. Polymorphisms in the ACE and PAI-1 genes are associated with recurrent spontaneous miscarriages. *Hum Reprod* 2003;**18**(11): 2473–2477.
18. Yamada Y, Izawa H, Ichihara S, et al. Prediction of the risk of myocardial infarction from polymorphisms in candidate genes. *N Engl J Med.* 2002;**347**:1916–1923.
19. Atherosclerosis, Thrombosis, and Vascular Biology Italian Study Group (2003). No evidence of association between prothrombotic gene polymorphisms and the development of acute myocardial infarction at a young age. *Circulation* 2003;**107**: 1117–1122.
20. Ding J, Nicklas BJ, Fallin MD, et al. Plasminogen activator inhibitor type 1 gene polymorphisms and haplotypes are associated with plasma plasminogen activator inhibitor type 1 levels but not with myocardial infarction or stroke. *Am Heart J* 2006;**152**(6):1109–1115.
21. Tsantes AE, Nikolopoulos GK, Bagos PG, Bonovas S, Kopterides P, Vaiopoulos G. The effect of the plasminogen activator inhibitor-1 4G/5G gene polymorphism on the thrombotic risk. *Thromb Res* 2008;**122**:736–742.
22. Boncoraglio GB, Bodini A, Brambilla C, Carriero MR, Ciusani E, Parati EA. An effect of the PAI-1 4G/5G polymorphism on cholesterol levels may explain conflicting associations with myocardial infarction and stroke. *Cerebrovasc Dis* 2006;**22**(2-3):191–195.