Acute Myocardial Infarction in a Young Woman With Heterozygous Polymorphism for Methylenetetrahydrofolate Reductase and Prothrombin Gene Mutation

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ABSTRACT

Many publications demonstrate a relationship between acute myocardial infarction and genetic mutations. In our case, a 26-year-old young woman was admitted to the hospital with complaints of severe chest pain. She had no risk factors for coronary heart disease but two of her sisters and one of her brothers had suffered sudden cardiac death. DNA samples obtained from peripheral blood were studied by polymerase chain reaction (PCR) and showed mutations in methylenetetrahydrofolate reductase (MTHFR) gene region C677T and heterozygous mutation in prothrombin gene region G20210A.

Key words: *Acute coronary syndrome, prothrombin, methylenetetrahydrofolate reductase,*

Heterozigot Metilentetrahidrofolat Redüktaz ve Protrombin Gen Mutasyonu Olan Genç Bir Kadında Akut Myokardiyal İnfarktüs

ÖZET

Bir çok yayında akut myokardiyal infarktüs ile gen mutasyonları arasında ilişki bildirilmiştir. Bizim olgumuzda 26 yaşında şiddetli göğüs ağrısı nedeniyle başvuran hastaneye yatırılan bir hast sunulmuştur. Hastanın koroner hastalık yönünden hiçbir risk faktörü içermiyordu ve kardeşlerinde ani ölüm hikayesi vardı. Periferik kandan DNA örnekleri alındı ve PCR çalışması ile MTHFR (C677T) ve protrombin (G20210A) gen mutasyonu gösterildi.

Anahtar kelimeler: *Akut koroner sendrom, protrombin, methylenetetrahydrofolate redüktaz*

INTRODUCTION

Coronary artery disease (CAD) is characterized by the deposition of atherosclerotic plaque on the coronary artery wall. This chronic disease frequently progresses as an asymptomatic process but due to instability of the atherosclerotic plaques, it may come up with acute myocardial infarction (AMI) (1). In addition to classical risk factors for coronary artery disease, endothelial dysfunction and genetic disturbances leading to thrombosis are gaining more interest lately. Hereditary defects of the homocysteine metabolism and coagulation cascade give rise to thrombophilia and increase the risk of arterial and venous thrombosis (2). In this paper, we describe a young female patient in whom we considered heterozygous methylenetetrahydrofolate reductase (MTHFR) C677T polymorphism and heterozygous prothrombin G20210A mutation as a probable cause of AMI and recurrent cardiac event.

CASE

A 26-year-old female patient was admitted to the emergency room with intensive chest pain of new onset. Her medical history revealed two of her sisters and one of her brother had suffered sudden cardiac death at 18, 20, and 22 years of age respectively. There were no other

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major coronary risk factors. There were no ST-T changes on admission ECG. Her blood pressure (120/80 mmHg), pulse rate (75 beats /min), and other clinical parameters were stable. She was taken to the cardiology invasive care unit and underwent emergent coronary angiography due to ongoing chest pain. There was high thrombus burden causing 85% obstruction in the proximal portion of the left anterior descending (LAD) coronary artery (Figure 1). Other coronary arteries were normal, having no significant stenosis. Percutaneous coronary angioplasty (PTCA) was not performed; instead, antiaggregant and anticoagulant therapy was initiated. Two days later control coronary angiography showed resolution of the thrombus. Cardiac enzymes (CK-MB, troponin I) increased up to three times normal levels after the AMI returned to normal on the third day. DNA samples isolated from the peripheral blood were analyzed by polymerase chain reaction (PCR) and the patient was found to be heterozygous for the prothrombin G20210A mutation and heterozygous for MTHFR C677T polymorphism. Factor V Leiden mutation was absent. In addition, homocysteine, Protein-C, Protein-S, antithrombin III, fibrinogen, Lipoprotein a, Anti Mitochondrial Antibody, ANA, Anti dsDNA, Anti Cardiolipin IgG and IgM were all evaluated. Except for high homocysteine and fibrinogen levels, all other tests were within normal limits. The patient consulted with a hematology clinic and along with antiaggregant and anticoagulant therapy with warfarin, she was prescribed vitamin B12 and folic acid. She was scheduled for international normalized ratio (INR) follow-up. The patient was admitted to the emergency room again after eighteen months with chest pain. She was diagnosed with acute coronary syndrome and taken to the coronary angiography unit. At the time of transfer, she had ventricular fibrillation and defibrillated with 360 joules and then sinus rhythm ensued. Coronary angiography revealed 85% stenosis in the proximal portion of the LAD (Figure 2). PTCA was performed and TIMI 3 flow was achieved. After the procedure, she was given tirofiban infusion for twelve hours. Admission INR was 2,5. The dosage of warfarin was increased and a predischarge INR of 3,0 was attained.

DISCUSSION

Homocysteine is a sulfured amino acid and a metabolite of methionine metabolism. There are two major roles for homocysteine metabolism: remethylation to methionine by using vitamin B12 as cofactor, or conversion to cysteine by using vitamin B6 as cofactor (3). Frequent causes of hyperhomocysteinemia are C677T gene polymorphism coding methylenetetrahydrofolate reductase (MTHFR) enzyme and low plasma folate levels (4). Experimental evidence suggests homocysteine induces cell hyperplasia and fibrosis leading to atherogenesis and thrombosis. Homocysteine also facilitates oxidative stress, impairs vasomotor regulation of the endothelium, and alters the balance of the coagulation system (5). McCully was the first to describe the detrimental effects of hyperhomocysteinemia on the cardiovascular system in 1969 (6). Fatal endpoints were observed in 25% of patients with hyperhomocysteinemia before the age of 30 (7). In another study, hyperhomocysteinemia was defined as a cardiovascular risk factor just as smoking and hyperlipidemia (8).

Prothrombin is the precursor of thrombin, which is a serine protease and plays a key role in the coagulation system by activating platelets and forming fibrin (9). In 1996, Poort et al. defined the association between increased risk of venous thrombosis and increased levels of prothrombin due to prothrombin gene mutation (10). In a study involving young women, there was an increased risk of myocardial infarction in patients carrying the prothrombin G20210A mutation (11). The clinical significance of the prothrombin G20210A mutation, while introduced as a risk factor for venous and arterial thrombosis in some studies, is still debated. In this case, the prothrombin G20210A mutation was detected and thrombus was resolved with medical therapy so the patient was prescribed warfarin. The issue of triple antiaggregant and anticoagulant therapy after MI is still a matter of controversy. Thrombosis despite triple antiaggregant therapy in this case suggests multiple genetic disorders. Particularly in young patients, using of drugs such as cocaine heroin and amphetamine, can cause vasospasm which evokes AMI. But in our case there was not any history of drug use.

There have been reports about arterial and venous thrombosis associated with MTHFR C677T and prothrombin G20210A gene mutations in the literature. This is the first case we know of having two different genetic abnormalities occurring together. In our case, coexistence of MTHFR C677T and prothrombin G20210A mutations probably triggered endothelial dysfunction and coagulation system abnormalities, leading to atherosclerosis and myocardial infarction. There is an increasing num-

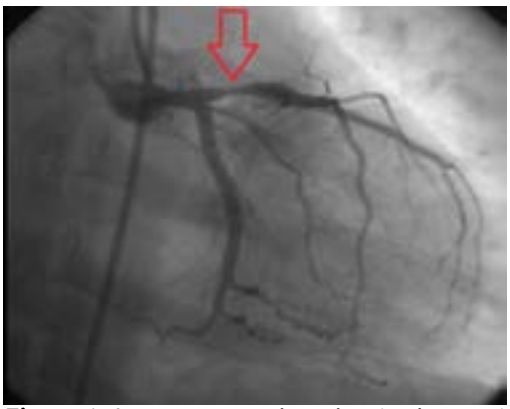

***Figure 1**. Intracoronary thrombus in the proximal portion of the left anterior descending artery*

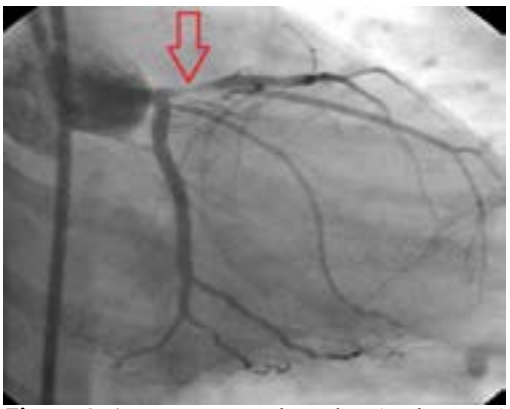

***Figure 2**. Intracoronary thrombus in the proximal portion of the left anterior descending artery*

ber of projects trying to identify certain genetic abnormalities that are responsible for atherosclerosis but to date there is still no genetic marker accepted worldwide. This is in part due to multiple genetic factors, triggering each other or completely independent, that play a role in this complex process.

There is still not a standardized genetic panel to investigate young patients presenting with AMI. Despite the use of aggressive antithrombotic therapy, cardiac events were not well controlled in this case due to multiple genetic abnormalities. For this reason, determination of genetic abnormality may play an important role to identify high-risk patients and the need for close monitoring.

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