Off-pump coronary artery bypass graft surgery after stent implantation in a patient with combined thrombophilic risk factors

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The case of coronary artery bypass graft surgery in a 51-year-old woman with a heterozygous form of factor V Leiden, prothrombin mutation G20210A and tumour necrosis factor- α -308 G-A associated with high lipoprotein(a) and homocysteinemia levels, as well as elevated factors VIIIc and IX, is presented. She suffered from recurrent episodes of venous thromboembolism and left anterior descending artery subtotal occlusion eight months after percutaneous transluminal coronary angioplasty and stent implantation.

Key Words: Coagulation factors, Coronary artery disease; Factor V Leiden; Prothrombin mutation G20210A; Tumour necrosis factor- α -308 G-A polymorphism

CASE PRESENTATION

A 51-year-old obese woman with a history of smoking presented with unstable angina three months after acute myocardial infarction (AMI). Her past medical history included noninsulin-dependent diabetes mellitus, recurrent deep vein thrombosis and long-standing hypertension treated with a beta-blocker, a calcium antagonist and a diuretic. She was on chronic anticoagulation therapy during 1999 and 2000. She had a strong family history of coronary artery disease – her father and mother died at the ages of 38 and 46 years, respectively.

On physical examination, she was overweight (body mass index of 28 kg/m²). Laboratory findings demonstrated a supranormal lipid profile: total cholesterol 5.4 mmol/L (normal level for individuals older than 50 years of age 3.1 mmol/L to 5.2 mmol/L), high-density lipoprotein 1.15 mmol/L (normal range for women 0.8 mmol/L to 2.1 mmol/L), low-density lipoprotein 3.33 mmol/L (normal range less than 3.3 mmol/L), very low density lipoprotein 0.84 mmol/L (normal range less than 1 mmol/L). Protein C, protein S and antithrombin levels were within normal range.

DNA was extracted by conventional techniques. The G-to-A transition at nucleotide 1691 in the factor V gene and the G-to-A transition at nucleotide position 20210 of the prothrombin gene locus (factor II 20210A) were analyzed according to previously reported techniques (1,2). Intrinsic coagulation factors (factors VIIIc and IX) were measured by one-stage clotting assay using commercial reagents (Sigma Diagnostics Inc, USA). Levels of von Willebrand factor were measured using an immunoturbidometric assay (STA-Liatest-vWF kit,

Un pontage aortocoronarien à cœur battant après l'implantation d'une endoprothèse chez une patiente présentant des facteurs de risque thrombophiliques combinés

Les auteurs présentent le cas d'une femme de 51 ans atteinte d'une forme hétérozygote de facteur V Leiden, de mutation G20210A de la prothrombine et d'un facteur de nécrose tumorale α -308 G-A associé à des taux élevés de lipoprotéines et d'homocystéinémie, ainsi que des facteurs VIIIc et IX élevés. Elle a souffert d'épisodes récurrents de thromboembolisme veineux et d'occlusion subtotale de l'artère antérieure gauche descendante huit mois après une coronarographie transluminale percutanée et l'implantation d'une endoprothèse.

Diagnostica Stago, France). All measurements were performed in duplicate. Mean $\pm$ SD factor VIIIc and IX levels of normal individuals at the Ankara University School of Medicine (Ankara, Turkey) are 1139.8 $\pm$ 338.6 U/L and 1096.9 $\pm$ 311.1 U/L, respectively. The present patient had a high factor VIIIc level (3520 U/L; normal range 700 U/L to 1500 U/L) and a high factor IX level (2389 U/L; normal range 500 U/L to 1500 U/L), with a normal von Willebrand factor level (78%; normal range 50% to 160%). Her lipoprotein(a) level was elevated (5.6 mmol/L; normal range 0 mmol/L to 1.1 mmol/L) and her fasting homocysteine level was elevated (16.5 μ mol/L; normal 5 μ mol/L to 15 μ mol/L). DNA analysis revealed heterozygosity for factor V 1691 A, prothrombin 20210 A and tumour necrosis factor- α -308 (TNF- α -308) A.

An electrocardiogram showed signs of previous anteroapical AMI (Q waves in leads V1 through V3) and current ST segment elevations in the anterolateral leads (V1, V6, D1 and aVL). On admission to the hospital, her creatine phosphokinase (myocardial) and troponin I levels were 6.2 U/L and 2.5 μ g/L, respectively. A transthoracic echocardiogram showed an akinetic anterior wall and a hypokinetic interventricular septum, as well as first-degree mitral and aortic regurgitation. Cardiac catheterization revealed an ejection fraction of 32%, with significant disease affecting the left anterior descending (LAD) artery, intraluminal filling defect with haziness in the LAD, and mild stenosis in the first diagonal, obtuse marginal and distal circumflex arteries. The right coronary artery had diffuse disease, but no significant stenotic lesions. Percutaneous transluminal coronary angioplasty was

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performed on a mid-LAD lesion; however, a coronary dissection developed during the procedure. Two stents were implanted to prevent further dissection. Tirofiban was given as a bolus at a dose of 0.4 µg/kg/min, and the patient was maintained on 0.1 µg/kg/min after the completion of the procedure. The patient was discharged at the end of the first week with acetylsalicylic acid, clopidogrel, atorvastatin and an angiotensin-converting enzyme inhibitor.

After eight months of follow-up, the patient presented to the emergency room with a new onset of mild retrosternal chest pain; an electrocardiogram showed anterior ST segment elevation AMI but no enzymatic changes. Repeat coronary angiography showed that the LAD artery had a proximal thrombus associated with a subtotal occlusion involving the area adjacent to the first diagonal branch, with Thrombolysis In Myocardial Infarction (TIMI-1) grade 1 flow, delayed antegrade flow and anteroapical akinesia; however, the patient refused any attempts for further percutaneous transluminal coronary angioplasty or stent implantation. The patient was referred for a viability assessment study with the thallium-201 rest-reinjection technique. Exercise and rest-reinjection thallium-201 single photon emission computed tomography verified a large amount of viable tissue within the apical half of the septal wall corresponding to the territory of the LAD artery. The patient underwent coronary artery bypass graft surgery, and the left internal thoracic artery was anastomosed to the LAD artery using the off-pump technique. Her recovery was uneventful, and she was discharged on the fifth postoperative day with 300 mg acetylsalicylic acid, 75 mg clopidogrel, 40 mg atorvastatin and 150 mg irbesartan daily. Her one-year postoperative course was satisfactory, without any cardiovascular complaints or bleeding episodes.

DISCUSSION

There are many well-known secondary risk factors responsible for venous thromboembolism. The most commonly reported congenital risk factors are a factor V Leiden mutation, a factor II 20210A mutation, and deficiencies in proteins C and S, as well as antithrombin III. A history of unexplained recurrent deep vein thrombosis in the present patient directed us to investigate her thrombophilic profile.

It has been reported that carriers of the factor V Leiden mutation have a 40% increased risk of AMI (OR 1.4, 95% CI 0.8 to 2.2) (2). In a population-based, case-controlled study among women 18 to 44 years of age, Rosendaal et al (3) reported that the risk of MI associated with carriership of the prothrombin 20210A allele was 4.1 (95% CI 1.1 to 15.2). Furthermore, the risk of AMI increased considerably when a coagulation

defect was present simultaneously with a cardiovascular risk factor, such as diabetes, obesity or smoking. Elevated lipoprotein(a) was shown to be an independent risk factor for premature coronary artery disease in both sexes. Patients with hyperhomocysteinemia have a two- to threefold increase in risk of developing cardiovascular disease or venous thrombosis (4).

Although the TNF2 allele (A) is more rare than TNF1, it is much a stronger transcriptional activator (5). Our case was a rare combination of a heterozygous form of factor V Leiden, the prothrombin mutation G20210A and the TNF-α -308 (G to A) polymorphism associated with hyperhomocysteinemia and high lipoprotein(a) levels. Other than the common thrombophilic factors, our patient also had TNF-α -308 G to A in heterozygous form.

Furthermore, the patient showed high levels of factors VIIIc and IX. She presented with an unfavourable complication (stent restenosis) after eight months of follow-up and required coronary artery bypass graft surgery using an arterial graft. Although rare, inherited gene defects should be suspected in young patients who have a strong positive family history for coronary artery disease. These patients should be considered to be at high risk for coronary events, and every effort should be made, such as with arterial revascularization, drug-eluting stent implantation or dual antiplatelet therapy, to decrease the risk of thrombosis. Careful follow-up of this group of patients and family screening is recommended. Our patient's combination of factors stand out as an area in need of further investigation. Combined thrombophilic risk factors can be important not only in the development of venous thrombosis, but also for coronary events. Further research on whether dual antiplatelet therapy should be continued beyond one year in patients with multiple thrombophilic risk factors is warranted.

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