VIA MEDICA

CASE REPORT

Cardiology Journal
2009, Vol. 16, No. 5, pp. 458–461

ISSN 1897–5593

Acute myocardial infarction in a patient with hemophilia A and factor V Leiden mutation

Meral Günaldi[1], Ayşen Helvaci[1], Naciye Demirel Yildirim[1], Muharrem Kiskaç[1], Reyhan Diz Küçükkaya[2]

[1]2nd Clinic for Internal Diseases, Okmeydani Education and Research Hospital, Istanbul, Turkey
[2]Istanbul University, Istanbul Medicine Faculty, Istanbul, Turkey

Abstract

Factor VIII:C, epsilon amino-caproic acid or tranexamic acid are prophylactic agents used in preventing hemorrhage pre-operatively in patients with hemophilia A. Although hemophilia A seems to be a factor that avoids the development of acute myocardial infarction (AMI) as it tends to be associated with increased bleeding, it should be kept in mind that prothrombotic agents used pre-operatively for prophylaxis may increase the risk for AMI in the presence of the factor V Leiden mutation. In this report, we discuss the development of AMI following the use of recombinant factor VIII and tranexamic acid for prophylaxis in a patient with known hemophilia before a tooth extraction in conjunction with the relevant literature. (Cardiol J 2009; 16, 5: 458–461)

Key words: hemophilia A, myocardial infarction, factor V Leiden mutation

Introduction

Some prophylactic agents are used pre-operatively in order to avoid bleeding in patients with hemophilia A. Such prophylactic agents include factor VIII:C (FVIII), epsilon amino-caproic acid or tranexamic acid [1]. The present paper reports the case of a 49 year-old male patient, previously diagnosed with severe hemophilia A, who developed hyperacute inferoposterolateral and right ventricular myocardial infarction as assessed by electrocardiography (ECG), based on the complaints of chest pain, agitation and perspiration by the patient following the use of recombinant factor VIII and tranexamic acid for prophylaxis before a tooth extraction. Based on this experience, thrombotic complications, which may rarely develop during the factor replacement therapies in patients with hemophilia A, were studied and reviewed in conjunction with the literature.

Case report

The 49 year-old male was diagnosed with severe hemophilia A when his FVIII level was found to be less than 1% on examination as a result of a history of intra-articular hemorrhage when he was one year old. The patient consistently described oral mucous and intra-articular hemorrhage from time to time. He received prophylactic tranexamic acid cap 20 mg/kg/day for ten days before the tooth extraction, followed by recombinant FVIII 40 U/kg immediately prior to extraction.

Initially manifesting stress resulting from agitation and perspiration before the tooth extraction, followed by chest pain, the patient presented to the emergency service after three hours of pain. During the physical examination, the findings for cardiovascular system except ECG, respiratory system and gastrointestinal system were normal. The ECG findings of ST elevation at DII-DIII-aVF, ST depres-

Address for correspondence: Meral Günaldi, Atakent Mah. Ikitelli Cad. Ihlamurevleri, B2 Blok, K2, NO: 10, Halkali/Küçükçekmece, Istanbul, Turkey, tel: 212 221 77 77, e-mail: meralgunaldi@hotmail.com

Received: 26.10.2008 Accepted: 11.01.2009

sion at V1 and V2 and ST elevation at V4 on the right derivations resulted in admission to the coronary intensive care unit. He was diagnosed with hyperacute inferoposterolateral and right ventricular myocardial infarction. The biochemical results were as follows — urea: 26 mg/dL, creatinine: 1.0 mg/dL, cholesterol: 187 mg/dL, triglycerides: 155 mg/dL, LDL cholesterol: 130 mg/dL, ALT: 38 U-L, AST: 154 U-L, LDH: 392 U-L, and CK-MB: 170 U-L. A complete blood count showed white blood cell: 13×10^9/L, hematocrit: 40.3%, hemoglobine: 14.2 g/dL and platelet 363×10^9/L. The patient did not undergo any invasive intervention as percutaneous transluminal coronary angioplasty (PTCA) is not available in our center and it would have taken time to transfer him to another hospital. The coagulation results were as follows — PT: 13 sn (normal value: 12–15), APTT: 82 sn (normal value: 20–40). No thrombolytic agent (such as streptokinase, t-PA) was given to the patient as it increases mortality in patients with hemostatic defects such as hemophilia A. Therefore, he started to receive enoxaparin 100 IU/kg SC twice a day, acetyl salicylic acid (ASA) 100 mg/day, metoprolol 50 mg/day, and atorvastatin 20 mg/day PO. The levels of anticardiolipin antibodies IgM (–), IgG (–), ANA (–), antidsDNA (–), and protein C, protein S, antithrombin III and homocysteine, which were monitored in the patient with no risk factors other than smoking for arterial thrombosis, were found to be normal. Genotyping from the genomic DNA of the patient revealed that he had no prothrombin gene 20210 G > A mutation, and investigation of factor V Leiden 1691 G > A mutation by polymerase chain reaction (PCR) revealed that he had heterozygous (+) active protein C resistance (factor V Leiden mutation). His family story was that his father had died from colon carcinoma, his mother had no disease other than being a carrier for hemophilia A and his brother had hemophilia A. His uncle (mother's brother) had hemophilia A and died of lung cancer. Living members of his family have no thrombosis and no factor V Leiden mutation.

His FVIII level was controlled, and he underwent coronary angiography using recombinant FVIII 50 U/kg. During the coronary angiography, a stent was implanted at right coronary artery (RCA). The patient had 40% stenosis at the S1 bifurcation of the left anterior descending artery (LAD) and 90% at the medial of the RCA proximal, and was discharged from hospital with ASA 100 mg/day and clopidogrel 75 mg/day PO. During the follow-up by the cardiology and hematology polyclinics, ASA was discontinued because of the spontaneous hemorrhage of the oral mucosa, and maintenance of clopidogrel treatment for nine months was recommended. No complication was observed in the patient, who was followed-up for approximately six months (Figs. 1, 2).

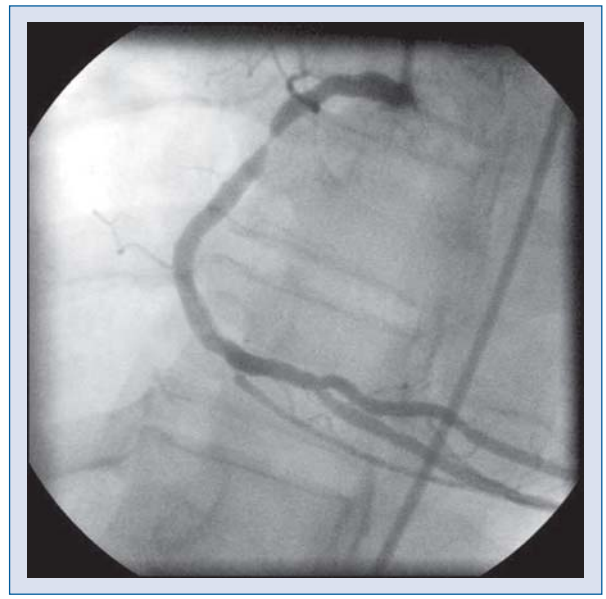

Figure 1. Coronary angiography of the right coronary artery in the patient; upon first visualization, the vessel is proximally occluded.

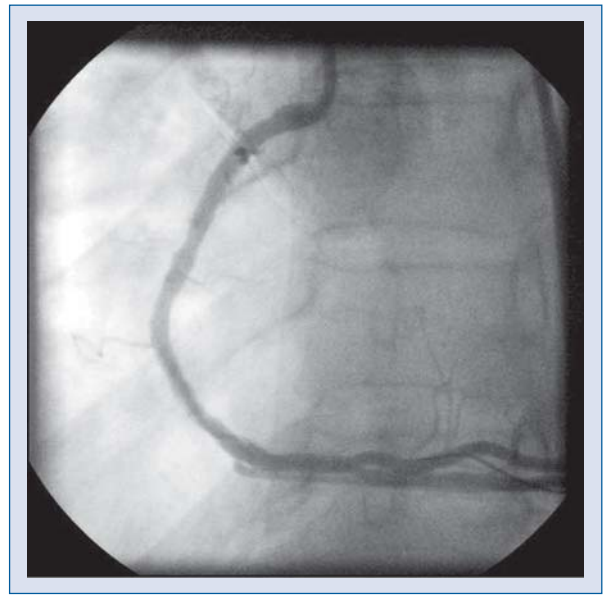

Figure 2. Coronary angiography of the right coronary artery in the patient; after stent placement, the right coronary artery is fully patent again with good peripheral blood flow.

Discussion

Hemophilia A is an X-linked congenital bleeding disorder caused by FVIII deficiency. No deterioration is observed in platelet functions in this disease. It manifests with bleeding into the soft tissue in 1/10,000 men. There is a close correlation between FVIII activity and the clinical significance of hemorrhage. The spontaneous bleeding in patients with a FVIII activity < 1% is associated with serious symptoms, while the frequency of bleeding episode is lower in patients with a FVIII activity of 1 to 5%. If it is more than 5%, the disease takes a mild course, and the bleeding is secondary to traumas [1]. Coronary artery disease and related mortality have been reported very rarely in hemophiliacs compared to the normal population [2]. Some American and European studies compared the mortality rates for ischemic heart disease between patients with hemophilia and the general population, and found that the mortality rate was lower in hemophiliacs than the general population [3]. Circulatory disease including acute myocardial infarction (AMI) has been reported as the second most common cause of death in patients with hemophilia in the screening studies conducted between 1995 and 1998 in the USA [4]. It has been reported that thrombotic complications develop in patients with hemophilia, usually following the factor replacement therapies [5]. Also in the case we present, AMI is observed after factor replacement.

Prothrombin complex concentrate which may be used for the treatment of bleeding in patients with hemophilia has a thrombogenic potential. Thrombosis usually occurs in the presence of conditions requiring long-term immobilization such as a surgical operation or underlying cardiovascular disease as well as the presence of related risk factors when high doses of prothrombin complex concentrates are used [6]. Following the infusion of recombinant FVIII, an occlusion was detected at LAD in the coronary angiography of a patient who had a severe chest pain with a subsequent variation observed in the anterior derivation during the ECG [1]. It has been reported that treatment by prothrombin complex concentrate and desmopressin triggered AMI in a patient with hemophilia A [7]. Furthermore, various thromboembolic events such as pulmonary embolism, deep vein thrombosis and amaurosis fugax were reported with factor concentrate replacement therapy [8].

Recently, two prothrombotic molecular defects were defined in the general population: factor V Leiden mutation and G20210A prothrombin gene mutation [9]. It has been reported that these molecular defects, when accompanied with severe hemophilia A, delay onset of the bleeding symptoms, which substantially alter the clinical effects of the disease, and may result in reduction in the bleeding episodes [9]. Furthermore, thrombotic events were previously defined in patients with hemophilia A, and the factor V Leiden mutation was demonstrated in these patients [10]. Although both mutations may increase the risk of venous thrombosis, Rosendaal et al. [3] proposed that prothrombin gene mutation is a risk factor for coronary artery disease. In a study by Mansourati et al. [11], it was shown that the prevalance of factor V Leiden mutation was higher in patients with MI compared to the control group.

In hemophiliacs who had AMI, percutaneous transluminal coronary angioplasty (PTCA) is safer than other methods of myocardial revascularization, with a mortality rate of 0.9%. Following PTCA, dissection, occlusion, spasm, emboli and rupture were reported in 13% of patients [12]. Experience with coronary stents is limited in patients with hemophilia [1]. After PTCA, antiplatelet agents may be required, so the risk of hemorrhage is high in patients with severe hemophilia [13]. Some studies showed that ASA was associated with increased hemorrhagic diathesis in hemophiliacs [14]. Although ASA plus clopidogrel may increase the risk of bleeding, it has been shown that these agents were effective in preventing subacute stent thrombosis and did not increase the risk of bleeding so that they are recommended in patients with hemophilia who underwent stent implantation [15]. Recently, the combination of aspirin and clopidogrel provided more reliable and effective results than the combination of aspirin and ticlopidin [1].

As an alternative method, coronary artery bypass was performed in hemophiliacs for myocardial revascularization. However, post-operative bleeding is a significant cause of mortality in patients with hemophilia in coronary bypass operations [16]. Therefore, it is likely that PTCA is superior to coronary artery bypass grafting [1].

In our hemophilia A case, the research carried out due to development of arterial thrombotic complication following the use of tranexamic acid and factor VIII concentrate, showed that only smoking was present among the known risk factors for arterial thrombosis. However the patient was heterozygous for the factor V gene 1691 G > A mutation. Although the role of factor V Leiden mutation is controversial in arterial thrombosis, it may increase the development of thrombosis in those patients.

Finally, in severe hemophiliacs, thromboembolic complications may rarely occur during factor replacement therapy. In our case, smoking and the presence of factor V Leiden mutation, may have contributed to the development of acute myocardial infarction.

Acknowledgements

The authors do not report any conflict of interest regarding this work.

References

1. Alsolaiman MM, Chang K, Arjomand H, Oza R, Costacurta G. Acute left anterior descending artery occlusion in a hemophiliac A patient during recombinant factor VIII infusion: Treatment with coronary angioplasty. Catheter Cardiovasc Interv, 2000; 50: 468–472.
2. Rosendaal FR, Briet E, Stibbe J et al. Hemophilia protects against ischaemic heart disease: a study of risk factors. Br J Haematol, 1990; 75: 525–530.
3. Rosendaal FR, Varecamp I, Smitt C et al. Mortality and causes of death in Dutch haemophiliacs, 1973–1986. Br J Hematol, 1989; 71: 71–76.
4. Kularni R, Soucie M, Hoots Keith et al. Prevalance and risk factors for heart disease among males with hemophilia. Am J Hematol, 2005; 79: 36–42.
5. Kerkhoffs J-L, Atsma DE, Pranobe V et al. Acute myocardial infarction during substitution with recombinant factor VIII concentrate in a patient with mild haemophilia A. Thromb Haemost, 2004; 92: 425.
6. Iannaccaro P, Santoro R, Sottilotta G, Papaleo G, Muleo G. Thrombosis in hemophiliacs with prothrombotic molecular defect. Clin Appl Thromb Hemost, 2005; 11: 359–360.
7. Bond L, Bevan D. Myocardial infarction in a patient with hemophilia treated with DDAVP. N Engl J Med, 1988; 318: 121.
8. Chavin SI, Siegel DM, Rocco TA Jr, Olson JP. Acute myocardial infarction during treatment with an activated prothrombin complex concentrate in a patient with factor VIII deficiency and factor VIII inhibitor. Am J Med, 1988; 85: 245–249.
9. Pruthi RK, Heit JA, Gren MM et al. Venous thromboembolism after hip fracture surgery in patient with haemophilia B and factor 5 Arg506 Gln (factor 5 Leiden). Haemophilia 2000; 6: 631.
10. Burzotta F, Paciaroni K, Andreotti F et al. G20210A prothrombin gene polymorphism and extent of coronary disease. Thromb Haemost, 2000; 84: 142–143.
11. Mansourati J, Da Costa A, Munier S et al. Prevalence of factor V Leiden in patients with myocardial infarction and normal coronary angiography. Thromb Haemost, 2000; 83: 822–825.
12. Roldán V, González-Conejero R, Marín F, Pineda J, Vicente V, Corral J. Five prothrombotic polymorphisms and the prevalence of premature myocardial infarction. Haematologica, 2005; 90: 421–423.
13. Forman MB, Kopelman HA, Gleaton JH, Janco RL, Perry JM. Percutaneous transluminal coronary angioplasty in hemophilia. Am Heart J, 1986; 111: 169–172.
14. Praga C, Cortellaro M. Effect of aspirin platelet aggregation and bleeding time in hemophilia and von Willebrand disease. Actamed Scand Suppl, 1971; 525: 219–221.
15. Virtanen R, Kauppila M. Percutaneous coronary intervention with stenting in a patient with hemophilila A and acute myocardial infarction following a single dose of desmopressin. Thromb Haemost, 2004; 92: 1154–1156.
16. Lee DH, Walker IR, Teitel J et al. Effect of the factor 5 Leiden on the clinical expression of severe haemophilia A. Thromb Haemost, 2000; 83: 387.