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Clinical Case Report

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A case report of acute inferior myocardial infarction in a patient with severe hemophilia A after recombinant factor VIII infusion

Silva Zupančić-Šalek, MD, PhD[a,b,c,*], Marijo Vodanović, MD[a], Dražen Pulanić, MD, PhD[a,b,c], Boško Skorić, MD, PhD[b,d], Irina Matytsina, MD[e], Jolanta Klovaite, MD, PhD[e]

Abstract

Rationale: The extent of protective effects of hemophilia against thrombotic events such as myocardial infarction (MI) and other acute coronary syndromes remains to be determined, as major risk factors for cardiovascular disease exist despite factor VIII (FVIII) deficiency. We present a case report of a 41-year-old male with severe hemophilia A and several cardiovascular risk factors.

Patient concerns: This morbidly obese patient developed chest pressure, followed by chest pain and difficulty in breathing shortly after receiving on-demand treatment with intravenous recombinant FVIII (rFVIII) (turoctocog alfa) dosed per body weight.

Diagnoses: An electrocardiogram revealed a diagnosis of inferior ST-segment elevation MI.

Interventions: The patient underwent an urgent coronary angiography using a radial artery approach. During the next 12 months, he received dual antiplatelet treatment, acetylsalicylic acid 100 mg, and clopidogrel 75 mg daily. His treatment for severe hemophilia A was changed to plasma-derived FVIII replacement therapy.

Outcomes: During this 12-month period, he experienced several small bleeds in his elbows.

Conclusions: The temporal relationship between rFVIII infusion and onset of the MI suggests a possible association; however, apart from obesity, the patient also had other major risk factors for arterial thrombosis, such as hypertension and smoking. Furthermore, atherosclerotic disease and underlying atherosclerotic changes could not be excluded with certainty. This case highlights the importance of studies assessing the impact of excess body weight on rFVIII dosing.

Abbreviations: FVIII = factor VIII, HDL = high-density lipoprotein, MI = myocardial infarction, RCA = right coronary artery, rFVIII = recombinant FVIII.

Keywords: hemophilia A, myocardial infarction, obesity, rFVIII

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[a] Unit for Haemostasis, Thrombosis and Benign Diseases of Haematopoietic System, Division of Hematology, Department of Internal Medicine, University Hospital Centre Zagreb, [b] Medical School University of Zagreb, Zagreb, [c] Faculty of Medicine Osijek, J.J. Strossmayer University of Osijek, Osijek, [d] Department of Cardiovascular Diseases, University Hospital Centre Zagreb, Zagreb, Croatia, [e] Novo Nordisk A/S, Søborg, Denmark.

[*] Correspondence: Silva Zupančić-Šalek, Unit for Haemostasis, Thrombosis and Benign Diseases of Haematopoietic System, Division of Hematology, Department of Internal Medicine, University Hospital Centre Zagreb, Kišpatićeva 12, 10 000 Zagreb, Croatia (e-mail: silva.zupancic-salek@zg.htnet.hr).

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1. Introduction

Myocardial infarction (MI), or other acute coronary syndromes in patients with hemophilia A, are not exceptional events.[1] Even severe clotting factor VIII (FVIII) deficiency does not offer protection against atherothrombotic complications,[2] although MI may occur infrequently in these patients.[3,4] Conditions predisposing to arterial occlusion, such as obesity, hypertension, smoking, hypercholesterolemia, and diabetes mellitus, play a dominant role in the pathogenesis of MI, with obesity being endemic in the hemophilia community.[1,5] However, in several reported cases, MI in patients with hemophilia occurred during or immediately after the administration of antibleeding therapy, without clear correlation to the state of the coronary arteries.[6] Here, we discuss the case report of a patient with severe hemophilia A and cardiovascular risk factors, who had an event of acute MI that developed soon after administration of recombinant FVIII (rFVIII).

2. Case study

A 41-year-old white male with severe hemophilia A (diagnosed 6 months after birth; baseline FVIII levels <1%) had been treated with intravenous rFVIII (turoctocog alfa; NovoEight, Novo Nordisk A/S, Bagsværd, Denmark) for just over 7 months (informed consent was provided). Treatment was given as intermittent, on-demand therapy performed in the home setting to allow for early treatment of bleeding episodes that occurred

approximately once every 2 months. The patient's medical history included morbid obesity (weight: 130 kg; body mass index: 41.03 kg/m^2), arterial hypertension, and smoking (20 cigarettes per day). He did not have a prior history of diabetes mellitus or cardiovascular disease. As the patient had been adopted, a family history of hemophilia A or cardiovascular disease was not available.

On the evening before hospital admission, the patient experienced pain in the left ankle and, suspecting bleeding in the joint, he injected himself with 30 IU/kg body weight turoctocog alfa. Ten minutes after the injection, the patient developed chest pressure, followed by chest pain and difficulty in breathing. He attempted to alleviate the pain with tramadol. However, the pain continued to get worse and, after midnight, he was admitted to the emergency department. His blood pressure was 150/120 mm Hg and his heart rate was 100 bpm. Acetylsalicylic acid and nitroglycerine were immediately administered. He had severe arthropathy of both knees, right hip, both elbows, and right ankle. Otherwise, his physical examination was unremarkable except for tenderness and slight restriction of movement in the left ankle.

An electrocardiogram showed ST-segment elevation in leads II, III, and aVF, and a diagnosis of inferior ST-segment elevation MI was established. The patient received 600 mg of clopidogrel and underwent an urgent coronary angiography using a radial artery approach. This procedure revealed an acute thrombotic occlusion of a dominant right coronary artery (RCA) at the turn of the middle to distal segment. No significant atherosclerotic changes in other coronary arteries were detected and we proceeded with percutaneous coronary intervention of the RCA. A partial recanalization of the thrombotic occlusion was achieved using a coronary wire passage. However, due to the residual haziness at the site of the lesion, we decided to complete the procedure with a single bare metal stent (3.0/18 mm) implantation. During the procedure, the patient received 9000 IU of unfractionated heparin, intracoronary.

Laboratory analysis showed an increase of troponin-T from 0.023 μg/L initially to >10 μg/L on the same day (normal upper limit 0.014 μg/L). Blood lipid test results were as follows: total cholesterol 4.5 mmol/L (normally <5.0 mmol/L); triglycerides 2.83 mmol/L (normally <1.7 mmol/L); high-density lipoprotein (HDL) 0.82 mmol/L (normally >1.0 mmol/L); and low-density lipoprotein 2.34mmol/L (normally <3.0 mmol/L). FVIII level of activity on admission was 0.90 k/IU/L. An investigation for congenital prothrombotic conditions yielded no positive results (no Factor V Leiden mutation and no mutations in prothrombin or *JAK2* genes). Chest X-ray showed an enlarged heart and possible minor pleural effusion. Cardiac ultrasound indicated a dilated left ventricle with an ejection fraction of 45% and mild hypocontractility of the lateral wall, as well as inferior wall akinesia with a small aneurism.

The rest of patient's clinical course was unremarkable and he was discharged from the hospital 6 days later. During the next 12 months, he received dual antiplatelet treatment, acetylsalicylic acid 100 mg, and clopidogrel 75 mg daily. During this period, he experienced several small bleeds in his elbows. The patient's treatment for severe hemophilia A was changed to plasma-derived FVIII replacement therapy (1500–2000 IU delivered intravenously, twice weekly).

3. Discussion

When MI is reported in patients with hemophilia A, it sometimes occurs during or immediately after the infusion of concentrates containing activated factors, such as plasma-derived activated prothrombin complex concentrate or recombinant activated FVII concentrates.[1] MI has also been reported in association with an infusion of FVIII concentrates[7,8] and with desmopressin[9] in patients with hemophilia, and described less frequently in severe versus nonsevere hemophilia.[3,4] Nevertheless, the risk of same-day thrombotic events following FVIII infusion appears to be lower than other clotting factor products (odds ratio: 0.70; 95% confidence interval: 0.09–5.51) in patients with or without FVIII deficiency.[6] The most likely explanation for this association is an acute elevation of clotting factors and/or the appearance of activated clotting factors in the circulation contributing to an ongoing process that concludes with the formation of a pathologic thrombus. In the majority of these cases, the presence of extensive atherosclerotic lesions, and multiple associated thrombosis risk factors, makes the relative contribution of each risk factor difficult to ascertain.

In this case, the temporal relationship between the infusion of coagulation factor and the onset of the MI suggests a certain degree of causality. Nevertheless, several patient-related factors may have contributed to the MI. The coronary artery was occluded by fresh thrombus without apparent atherosclerotic changes shortly after the administration of rFVIII. However, elevated total cholesterol and low HDL suggest a risk of atherosclerotic disease. The patient had several major risk factors for arterial thrombosis, such as morbid obesity, hypertension, and smoking.

Obese patients are at a high risk of cardiovascular diseases, which can in part be explained by disturbances in the hemostatic and fibrinolytic systems. Adipocytes, growing in size and number, are stimulated to secrete tissue factor, plasminogen activator inhibitor, and other substances that may promote clot initiation and formation.[10] Also, obesity is associated with increased levels of fibrinogen, Factor VII, von Willebrand factor in plasma, disturbances in the protein C system, increased blood viscosity, and erythrocyte hyperaggregability[10,11] All of these obesity-related changes can occur in patients with hemophilia.[5]

Furthermore, to avoid overtreating obese individuals, rFVIII dosing should be adapted individually, taking into account not only body weight but also other anthropomorphic measures, such as ideal body weight, as plasma volume is not proportional to body weight.[12] In our case report, at admission (1 hour after the injection of rFVIII), the FVIII level of activity was 90%. In a person with normal weight, assuming that every IU/kg of FVIII injected raises the level by approximately 2%, the FVIII level expected after administration of 30 IU/kg is 60%. Most likely, in this case, the patient could have benefited from a lower dose of rFVIII, possibly reducing the risk of hypercoagulation superimposed over obesity-associated cardiovascular risk.

In conclusion, the temporal relationship between the onset of acute MI and the use of replacement therapy with rFVIII suggests an association in this individual. At the same time, it is possible that these two events were coincidental, taking into consideration the underlying high cardiovascular risk. This case illustrates the importance of further studies assessing the impact of excess body weight on rFVIII dosing and adequate changes in the guidelines for the management of hemophilia in different subgroups.

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