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WJH covers topics concerning experimental, clinical, oncological and transplant hematology, transfusion science, hemostasis and thrombosis, evidence-based medicine, epidemiology and nursing. Priority publication will be given to articles concerning diagnosis and treatment of hematological diseases. The following aspects are covered: Clinical diagnosis, laboratory diagnosis, differential diagnosis, imaging tests, pathological diagnosis, molecular biological diagnosis, immunological diagnosis, genetic diagnosis, functional diagnostics, and physical diagnosis; and comprehensive therapy, drug therapy, surgical therapy, interventional treatment, minimally invasive therapy, and robot-assisted therapy.

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Management of unstable angina in a patient with Haemophilia A

Andreina Carbone, Tiziana Formisano, Francesco Natale, Maurizio Cappelli Bigazzi, Donato Tartaglione, Enrica Golia, Felice Gragnano, Mario Crisci, Renato Maria Bianchi, Raffaele Calabrò, Maria Giovanna Russo, Paolo Calabrò

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Author contributions: Carbone A, Formisano T, Natale F, Tartaglione D, Golia E and Gragnano F designed the report; Cappelli Bigazzi M and Crisci M performed clinical evaluation and interventional procedure; Gragnano F and Bianchi RM collected the patient's data; Carbone A, Calabrò R, Russo MG and Calabrò P analyzed data and wrote the paper.

Institutional review board statement: This case report was exempt from the Institutional Review Board standards at Second University of Naples.

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Abstract

Hemophilia A is an X-linked recessive disorder characterized by a deficiency of coagulation factor VIII (FVIII) and therefore by a greater risk of bleeding during percutaneous interventional procedures and during the dual antiplatelet therapy (DAPT) in patients with ischemic heart disease. Information regarding safe percutaneous procedures in hemophiliacs is limited. Since the introduction of FV VIII concentrates, the life expectancy of hemophiliac patients has improved and consequently, the rate of ischemic heart disease in this population is increased. Frequently the replacement therapy can trigger the onset of an acute coronary syndrome. We report a case of a patient with mild Hemophilia A, who presents with unstable angina, treated successfully with coronary angioplasty and drug eluting stent implantation without replacement of FV VIII, treated with long term DAPT without major bleeding after six months of follow up.

Key words: Hemophilia A; Unstable angina; Dual antiplatelet therapy; Drug eluting stent; Coagulation factors replacement therapy

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Core tip: Hemophilia is a rare condition, but in some

cases, could create difficulties in the management of other disease, such as acute coronary syndrome and unstable angina. Data in literature regarding this condition are lacking. This case report would be an example of the management of patients with mild deficit of Factor VIII activity according to the recent consensus.

Carbone A, Formisano T, Natale F, Cappelli Bigazzi M, Tartaglione D, Golia E, Gragnano F, Crisci M, Bianchi RM, Calabrò R, Russo MG, Calabrò P. Management of unstable angina in a patient with Haemophilia A. *World J Hematol* 2017; 6(2): 28-31 Available from: URL: <http://www.wjgnet.com/2218-6204/full/v6/i2/28.htm> DOI: <http://dx.doi.org/10.5315/wjh.v6.i2.28>

INTRODUCTION

Hemophilia A is an X-linked recessive disorder with frequency of approximately 1 in 8500 live births, characterized by a deficiency of coagulation factor VIII (FVIII) and therefore by a greater risk of bleeding. Hemophilia A is defined "mild" when the activity of FVIII is greater than 5% (> 0.015 IU/mL) and presents episodes of bleeding after hematological stress (surgery, childbirth, trauma). It is a moderate disorder for levels of FVIII activity between 1% and 5% (0.01-0.05 IU/mL)^[1]. The severe form, in which the activity of FVIII is $< 1\%$ (< 0.01 IU/mL), represents 50% of cases and is characterized by spontaneous bleeding in the joints and muscles and high risk of intracranial hemorrhage^[1]. Since the introduction of FVIII concentrates in 1960 and the preventive treatment in 1970 the life expectancy of this patients, in developed countries, has improved. Consequently, the rate of ischemic heart disease in this population is increased. Kulkarni *et al*^[2] assessed the prevalence of ischemic heart disease in 3422 American patients with hemophilia, analyzing discharge records from the hospital between 1993 and 1998. The prevalence of coronary heart disease was 0.05% in patients under 30 years of age and 15.2% in those aged 60 or more^[2], similar to the general population^[3]. Girolami *et al*^[4,5] have shown that most of thrombotic cardiovascular events in hemophiliac patients occur during the infusion of recombinant FVIII or DDAVP.

The first line therapy of Acute Coronary Syndromes is the percutaneous transluminal coronary angioplasty (PTCA) and stent implantation. In hemophiliacs, invasive treatment is more dangerous because they have increased risk of bleeding during the procedure and with the use of anticoagulants and antiplatelet agents. The management of unstable angina in this population is suggested by a Consent Document of the World Federation of Hemophilia^[6]. Experts recommend levels of FVIII activity of 80%, during the PTCA, and in 48 h, achieved through the infusion of recombinant FVIII.

We show a case of a patient with mild Hemophilia A who presents with unstable angina, not triggered

by the infusion of clotting factor concentrate, treated successfully with coronary angioplasty and drug eluting stent (DES) implantation without replacement of FVIII.

CASE REPORT

A 55 years old age man with mild deficit of FVIII activity (FVIII activity of 50%), HCV-related liver disease, tobacco use, hypertension, dyslipidemia, family history of cardiovascular disease, prostate cancer in treatment with anti - androgen hormone therapy, came to our attention for worsening of constrictive chest pain at rest persisting for a month, for which he performed ECG exercise test positive. The patient did not report neither history of coronary heart disease nor intra-articular or intramuscular hemorrhage. He was admitted to the Department of Cardiology for practicing coronary angiography and eventually angioplasty and coronary stenting. During hospitalization, despite optimal anti-ischemic drug therapy (bisoprolol 2.5 mg, nitroglycerin patch of 10 mg, atorvastatin 80 mg, telmisartan 80 mg; Cardioaspirin 100 mg, the patient experienced recurrent episodes of constrictive chest pain with no changes of electrocardiogram and negative cardiac marker of necrosis. The level of FVIII activity, before the procedure, was 50% defining a very mild deficit. Catheterization was performed through the right radial artery with 6 F sheath. The coronary angiogram revealed the presence of 70% calcified stenosis of the left anterior descending artery at its middle part, involving the bifurcation of the first diagonal branch, with a calcific stenosis at its middle portion (Figure 1). During the procedure Bivalirudin was administered as a bolus and Clopidogrel loading dose of 600 mg was given before the procedure. PTCA and stenting with 2 Zotarolimus eluting stents DES 2.75 mm \times 18 mm and 3.0 mm \times 26 mm was performed using Minicrush technique (Figure 2A). Lastly, we performed a post-dilation with kissing balloon technique with non-compliant balloons, 5 mm \times 15 mm (on the LAD) and 3.0 mm \times 15 mm (on the diagonal branch). The final angiographic result was excellent with TIMI flow 3 (Figure 2B). The hemostasis at the puncture site was performed using Radistop, which was removed after eight hours without evidence of bleeding or hematoma. After the procedure, the patient was monitored in the Cardiology ward and the clinical conditions were good and hemodynamically stable during the hospitalization. In particular, there were no bleeding or further episodes of chest pain. The patient was discharged after 72 h of observation on DAPT (Aspirin 100 mg/d; Clopidogrel 75 mg/d) for one year, in addition to anti ischemic therapy previously reported. At six months follow up, the patient did not report any major bleedings and was asymptomatic.

DISCUSSION

PTCA in hemophiliacs has a greater risk of bleeding than in general population for many reasons. Arterial puncture

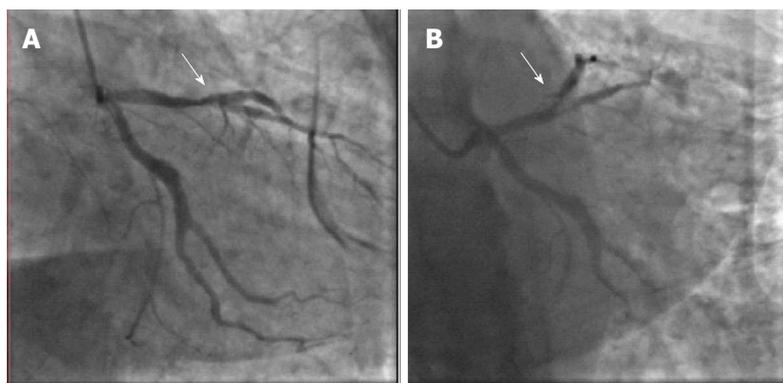


Figure 1 Left coronary angiogram. Preintervention angiogram of the left anterior descending artery revealed the presence of 70% calcified stenosis of its middle part (A), involving the bifurcation of the first diagonal branch, with a calcific stenosis at its middle portion (B). Arrow indicates the site of the lesions.

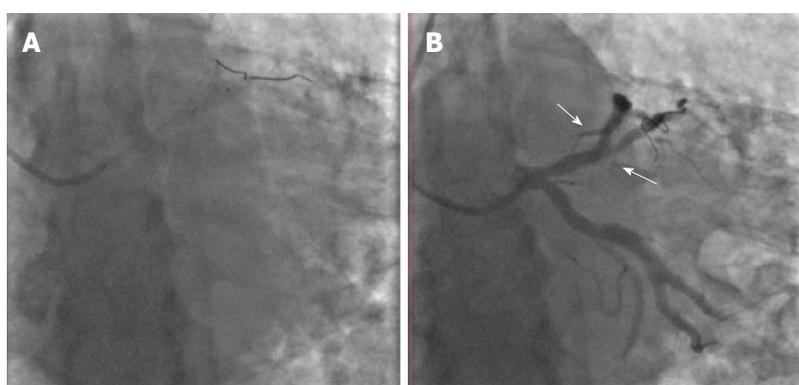


Figure 2 Stents implantation and final result. Angiogram (A) shows PTCA and stenting with 2 Zotarolimus eluting stents DES 2.75 mm × 18 mm and 3.0 mm × 26 mm performed using Minicrush technique; B: Post-intervention angiogram of the LAD. Arrows indicate site of stents placement. PTCA: Percutaneous transluminal coronary angioplasty; DES: Drug eluting stent; LAD: Left anterior descending.

is related to high risk of local complications, reduced by recombinant FVIII administration, by radial artery puncture and using effective hemostasis system for the puncture site. The management of unstable angina in hemophiliacs is suggested by a Consent Document of the World Federation of Hemophilia^[6]. Experts recommend levels of FVIII activity of 80%, during the PTCA, and in the following 48 h, achieved through the infusion of recombinant FVIII, but this increases the risk of acute thrombosis in patients with unstable plaques. Many cases of myocardial infarction have been described during administration of coagulation factor concentrates, prothrombin complex and desmopressin^[5,7]. Moreover, Girolami *et al*^[4,5] have shown that most of thrombotic cardiovascular events in hemophiliac patients occur during the infusion of recombinant FVIII or desmopressin.

In the reported case, we decided to not pretreat the patient with replacement therapy, taking in account the clinical history free of major bleeding and the level of FVIII activity. To improve procedural safety, we undertook angiography using a radial approach, minimizing the risk of local complications. As anticoagulant during the interventional procedure we used Bivalirudin, a direct thrombin inhibitor, associated with lower rate of

bleeding and with positive results in hemophiliac patient. Antiplatelet agents are needed to prevent in-stent thrombosis. The current guidelines suggest 1 year of dual antiplatelet therapy (DAPT) for DES and one month for bare metal stent^[8]. Considering that Haemophilia is not associated with any platelet defect, antiplatelet agents should be given according to guidelines: indeed, acute stent thrombosis in patients with coagulation defects not receiving DAPT after stenting have been described in literature^[9]. In the past BMS were preferred to DES for the shorter duration of DAPT^[10]. New generation of DES do not need long-term DAPT, making treatment duration similar to that required for BMS. Moreover, drug-coated stent demonstrates superior safety and efficacy with one month of DAPT in patients at high bleeding risk^[10].

In summary, we described the case of a patient with mild Haemophilia A presenting with unstable angina, treated with PTCA and stenting of the LAD at a bifurcation site with DES. The procedure was carried out safely, using the new generation DES. After six months of follow up the patient was in therapy with DAPT and had not experienced any complications and had no FVIII replacement.

COMMENTS

Case characteristics

A 55-year-old age man with mild deficit of factor VIII (FVIII) activity came to the authors' attention for worsening of constrictive chest pain at rest persisting for a month.

Clinical diagnosis

Unstable angina in patient with mild hemophilia.

Differential diagnosis

Acute myocardial infarction, atypical chest pain.

Laboratory diagnosis

Deficit of FVIII activity.

Imaging diagnosis

The coronary angiogram revealed the presence of 70% calcified stenosis of the left anterior descending artery.

Pathological diagnosis

Unstable angina due to significant stenosis of one epicardial coronary artery.

Treatment

Angioplasty and stenting of the coronary stenosis, dual antiplatelet treatment for one year.

Related reports

Hemophilia A is an X-linked recessive disorder characterized by a deficiency of coagulation FVIII and therefore by a greater risk of bleeding. Angioplasty and stenting is more dangerous in this population and also the use of anticoagulants and antiplatelet agents.

Term explanation

Angioplasty, also known as balloon angioplasty and percutaneous transluminal angioplasty, is a minimally invasive, endovascular procedure to widen narrowed or obstructed arteries.

Experiences and lessons

Guidelines about the management of acute coronary syndrome in hemophiliacs don't exist, and their treatment should be tailored. Mild hemophilia should be not pretreat with recombinant factor therapy, considering the low bleeding risk.

Peer-review

This case report is very interesting and clinically relevant.

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