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Patient with hemophilia and coronary artery disease in the preoperative period of liver transplantation

Paciente hemofílico com doença arterial coronariana em pré-operatório de transplante de fígado

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ABSTRACT – Hemophilia A and B, although rare, are the most common clotting disorders in humans. With the advent of prophylaxis and improved clotting factor replacement therapy, patients with hemophilia have reached a life expectancy similar to that of the general population, leading to an increase in cardiovascular risk factors and consequently, coronary artery disease. The need for antiplatelet and anticoagulant therapy in these patients further increases the bleeding tendency. Evidence and recommendations for these patients in procedures such as percutaneous coronary intervention are scarce in the literature.

Keywords: Hemophilia; Coronary artery disease; Liver transplantation; Preoperative period

RESUMO – As hemofilias A e B, apesar de raras, são os distúrbios de coagulação que mais ocorrem em homens. Com o advento das profilaxias e a melhoria da terapia de reposição do fator de coagulação, pacientes com hemofilia têm atingido expectativa de vida semelhante à da população geral, levando ao aumento dos fatores de risco cardiovasculares e à consequente doença aterosclerótica coronariana. A necessidade de terapia antiplaquetária e anticoagulante nesses pacientes aumenta ainda mais a tendência a sangramentos. Evidências e recomendações para esses pacientes em procedimentos como intervenção coronária percutânea são escassos na literatura.

Descritores: Hemofilia; Doença da artéria coronariana; Transplante de fígado; Período pré-operatório

INTRODUCTION

Hemophilia A and B, although rare, are the most common clotting disorders in humans. The severity of hemophilia A depends on the plasma concentration of factor VIII, and is classified as mild (factor level >5% of normal), moderate (1% to 5% of normal), and severe (<1% of normal). Treatment of bleeding episodes consists of both an on-demand regimen (when bleeding episodes occur) and prophylactic regimens in patients with moderate and severe hemophilia.[1]

With the advent of prophylaxis and improved clotting factor replacement therapy, patients with hemophilia have reached a life expectancy similar to that of the general population, which leads to an increase in age-related comorbidities, such as cardiovascular risk factors and consequent coronary artery disease (CAD).[1] In addition, the presence of arthropathy further increases the incidence of obesity and hypertension, due to limited mobility.

Although some observational studies suggest that patients with hemophilia have lower mortality from cardiovascular disease, which can be attributed to a hypocoagulability state and reduced thrombus formation, they have the same degree of atherosclerosis and endothelial dysfunction as the general population.[2,3]

The need for antiplatelet therapy in these patients further increases the tendency to bleeding. Evidence and recommendations for these patients in procedures such as percutaneous coronary intervention (PCI) are scarce in the literature, hence the importance of this case report.

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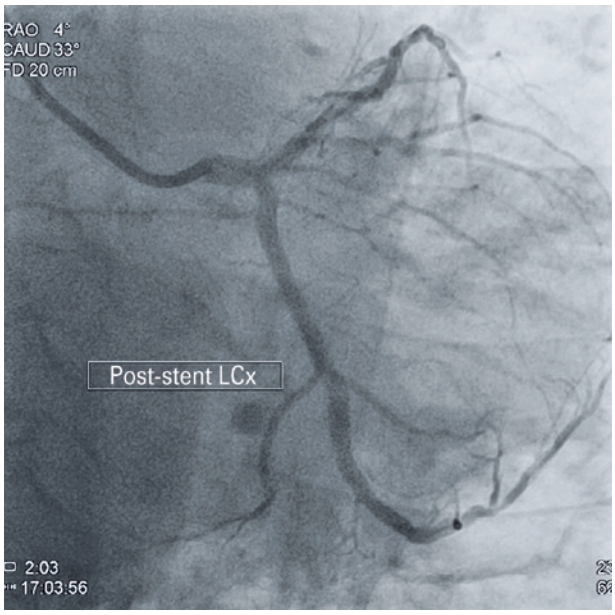
The objective of this study was to report the case of a patient with hemophilia undergoing liver transplantation, who developed angina with indication for PCI. The Research Ethics Committee of *Hospital Brigadeiro* UGA V-SP approved this study, with opinion 5.075.595 and CAAE 5223891.5.0000.0091.0091.

CASE REPORT

A 52-year-old former smoker patient, with hypertension, diabetes, dyslipidemia, moderate hemophilia A. Due to chronic hepatitis C, which progressed to hepatocellular carcinoma, a liver transplantation was indicated. The patient was already on the transplant waiting list when he started to experience chest pain on exertion and, later, even at rest. Due to the high risk of bleeding, a pharmacological stress test with myocardial perfusion scintigraphy was conducted, with a negative result for ischemia. Due to the cardiovascular risk factors and persistent symptoms even after therapeutic optimization, a cardiac catheterization was requested, which was performed through radial approach and showed: a 30% obstruction in the distal third of the left main coronary artery (LMCA), a 40% obstruction in the proximal third of the left anterior descending artery (LAD), an 80% obstruction in the middle third of the left circumflex artery (LCx), and a 70% obstruction in the middle third of the right coronary artery (RCA). A PCI with bare-metal stent implantation in the LCx (Cronus 3.0mm x 29mm) and RCA (Rebel 3.0mm x 3mm) (Figures 1 to 4) was conducted. The patient received factor VIII immediately before the procedure. He was pre-treated with 9,000IU of unfractionated heparin intravenously, and a 300-mg dose of acetylsalicylic acid (ASA), and a 600-mg loading dose of clopidogrel. The arterial sheath was removed after partial reversal of heparin with protamine. The patient reported improved symptoms after the procedure.

The patient received dual antiplatelet therapy (DAPT) for one month concomitantly with a twice-daily infusion of higher doses of factor VIII and, from the second month onwards, when he was using only aspirin, we



LCx: left circumflex artery.
Figure 2. Angiographic control after stent implantation in the left circumflex artery.

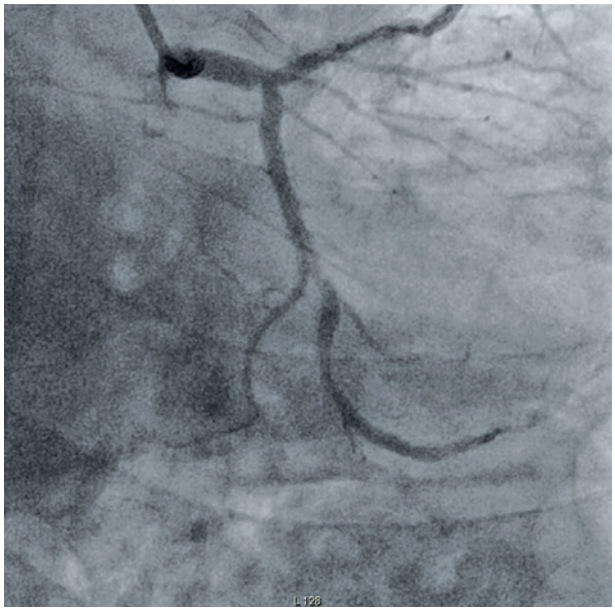


Figure 1. Severe left circumflex artery lesion.

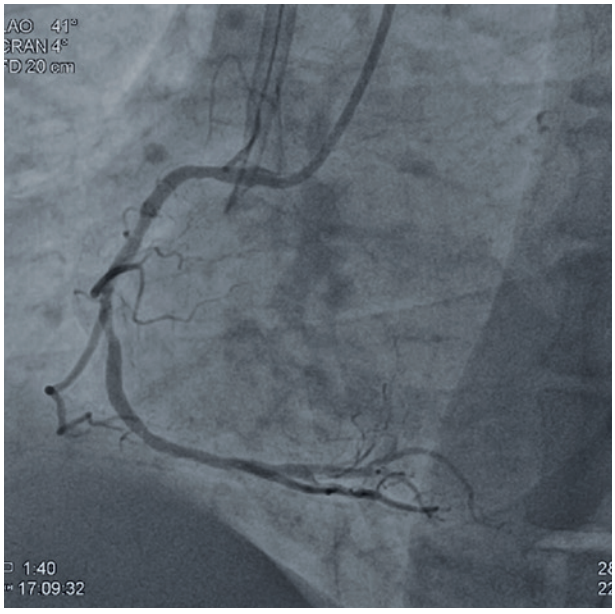


Figure 3. Severe right coronary artery lesion.

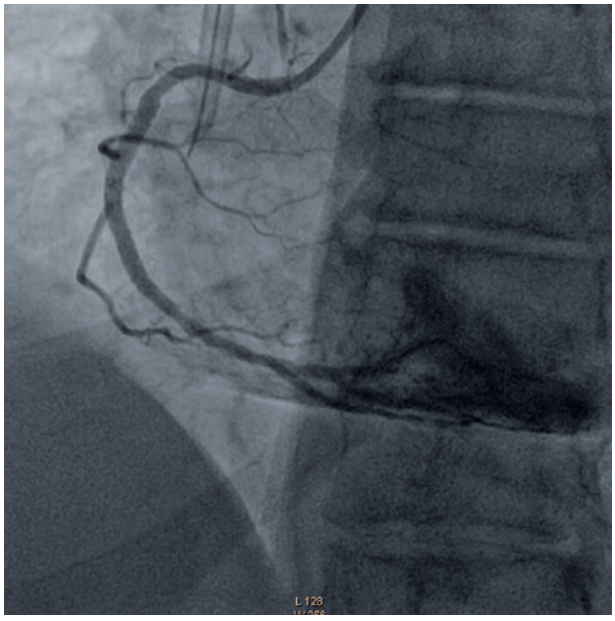


Figure 4. Angiographic control after stent implantation in the right coronary artery.

opted for a factor VIII infusion three times a week, once a day. The patient underwent implantation of a long-term catheter (port-a-cath) to ensure venous access, remaining hospitalized for 15 days, and a family member with nursing expertise was responsible for handling the catheter at his home. The patient did not experience bleeding during this entire period. Five months later, he underwent successful liver transplantation. ASA was suspended 7 days before surgery and restarted as soon as the patient resumed oral feeding.

DISCUSSION

The literature suggests the possibility of PCI in patients with hemophilia, employing the same antithrombotic strategies and bleeding prevention methods as non-hemophilia individuals, including patients with acute myocardial infarction (MI), provided they receive adequate clotting factor replacement beforehand.[1,3]

Although the coagulation cascade is impaired in patients with hemophilia, the number and function of platelets are normal and, therefore, DAPT is recommended to prevent stent thrombosis. Since DAPT increases the risk of bleeding, it should be performed in the shortest possible time. Therefore, the use of bare metal stents was a consensus.[3,4] However, the new generation of drug-eluting stents, polymer-free or with biocompatible polymeric coatings, which allow a reduction in the duration of DAPT, rendered obsolete the option of using bare metal devices,[3] despite the lack of sufficient experience in patients with hemophilia.

The clotting factor should always be administered intravenously immediately before the procedure. Most recommendations advise maintaining clotting factor levels >80% of normal during the first 48 hours after the procedure (suggesting the use of a dose of 40IU of factor VIII per kg of body weight every 12 hours) and ≥30% in the remainder of the month during DAPT[3,4] (suggesting the use of a dose of 15IU of factor VIII per kilogram of body weight every 12 hours during this period). In patients with a clotting factor level ≥25%, this pre-PCI prophylaxis is not necessary.[4,5]

Clopidogrel leads to a lower risk of bleeding compared to prasugrel and ticagrelor.[4] Preference should be given to unfractionated heparin due to its shorter half-life, the possibility of laboratory evaluation using activated partial thromboplastin time (aPTT) and the possibility of reversal using protamine sulfate.[3,4] A daily dose of 80mg to 100mg of ASA continued indefinitely is generally well tolerated in patients with mild and moderate hemophilia, with no need for clotting factor prophylaxis. In severe hemophilia patients, the maintenance of ASA associated with clotting factor prophylaxis may be tried and should be discontinued in case of bleeding.[5]

The radial access is recommended because it minimizes bleeding, allows early detection of bleeding and facilitates compression.[3,4] As to patients with ST-segment elevation MI, thrombolysis is not recommended.[1,5,6] Glycoprotein IIb-IIIa inhibitors are also not recommended and are rarely used, due to very little experience, even in situations of high thrombus burden.[4-6] Patients with non-ST-segment elevation MI follow the same recommendations as for elective PCI.[5]

In summary, percutaneous coronary interventions and the consequent need for DAPT are relatively safe in hemophilia patients, when clotting factor replacement is administered at the correct dose and time. Table 1 summarizes the main recommendations for the management of these

Table 1. Summary of management recommendations in patients with hemophilia undergoing percutaneous coronary procedures

	Management
Clotting factor	Immediate infusion before the procedure Coagulation factor levels >80% before PCI and in the first 48 hours Levels >30% in the next 28 days while on DAPT, with a reduction to 5%-10% after this period maintaining aspirin, if necessary
Arterial access	Radial
Antithrombotic therapy	Unfractionated heparin
Antiplatelet therapy	DAPT for 1 month associated with higher doses of clotting factor Clopidogrel is preferable to prasugrel and ticagrelor Loading doses of ASA and clopidogrel may be used Maintenance of ASA indefinitely, usually with on-demand use of clotting factor

Source: adapted from Ferraris et al.,[1] Theodoropoulos et al.,[3] Jabbar et al.,[4] Schutgens et al.[5] and Staritz et al.[6]
PCI: percutaneous coronary intervention; DAPT: dual antiplatelet aggregation therapy; ASA: acetylsalicylic acid.

patients. As this type of patient was not included in the studies designed to inform the guidelines, the individual assessment should be prioritized even more. In the case of this particular patient, the use of DAPT for the shortest possible time was also due to the urgent need for liver transplantation.

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None.

CONFLICTS OF INTEREST

The authors declare there are no conflicts of interest.

CONTRIBUTION OF AUTHORS

Conception and design of the study: PNCK and VNC; data collection: PNCK; data interpretation: PNCK; text writing: PNCK and VNC; approval of the final version to be published: PNCK and VNC.

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