CORRESPONDENCE

Treating a Patient of Dysfibrinogenemia with Acute Thromboembolism by Rivaroxaban and Cilostazol

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Abstract Congenital dysfibrinogenemia is a rare autosomal recessive bleeding disorder, which is characterized by the absence of functional fibrinogen. Patients may have bleeding and paradoxical arterial and venous thrombotic problems from early childhood. The optimal antithrombotic therapy in these patients hasn't been determined yet. In this report we present a dysfibrinogenemic patient, who has suffered recurrent arterial thrombosis under aspirin treatment. Intravenous fibrinogen concentrates (fc) along with reduced doses of rivaroxaban (10 mg daily), cilostazol (50 mg bid) and aspirin (100 mg daily) were given as antithrombotic treatment. The pain and the cyanosis clinically recovered within 6 weeks. This is, to our knowledge, the first time in which a new oral anticoagulant, rivaroxaban and cilostazol combination was used in a dysfibrinogenemic patient with thrombotic episodes. We determined the type, the dosage and the duration of antithrombotic treatment according to the clinical progress of the symptoms. Rivaroxaban, cilostazol and fibrinogen concentrate replacement; combination may represent a useful alternative for the antithrombotic treatment in dysfibrinogenemic patients.

Keywords Dysfibrinogenemia · Bleeding · Cilostazol · Rivaroxaban · Thrombosis

Introduction

Congenital dysfibrinogenemia is a rare autosomal recessive bleeding disorder, which is characterized by the absence of functional fibrinogen. Patients may have bleeding episodes and paradoxical arterial and venous thrombotic problems from early childhood. The optimal antithrombotic therapy in these patients is unknown. In this report we present a dysfibrinogenemic patient, who has suffered recurrent arterial thrombosis under aspirin treatment.

Case Report

56-year-old male was admitted to vascular surgery clinic with painful cyanosis and skin ulceration of the 2nd right toe (Fig. 1a, b). There were no other local or systemic signs. Anterior tibial artery and dorsalis pedis artery pulses could not be palpated. The patient was followed at the hematology clinic in Cerrahpaşa Hospital of Istanbul University since 11 years old where he was diagnosed to have dysfibrinogenemia. Mutation analysis was performed and he was found to be a new type of dysfibrinogenemia, hence the mutation was named “fibrinogen-istanbul” [1].

The patient's laboratory examinations at admission demonstrated low fibrinogen levels and infinitely prolonged prothrombin (PT) and activated partial thromboplastin time (apTT). An arterial doppler of the right lower limb revealed monophasic blood flow in the anterior tibial artery. In his medical history, the patient told that he had myocardial infarction when he was 28 years old and a

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Fig. 1 **a, b** Dorsal and plantar view of the foot before treatment. **c, d** Dorsal and plantar view of the foot after treatment

similar problem at the same foot in the 3rd toe 6 months ago, which disappeared spontaneously without any treatment. The patient was suspected to have acute toe ischemia due to embolism and consulted to the hematologist and cardiologist for further investigation and treatment.

The patient underwent echocardiography followed by coronary and peripheral arterial computerized tomographic (ct) angiography. Echocardiography was in normal limits. The ct angiography revealed mild right coronary artery stenosis and occluded right anterior tibial artery.

After 1 week of symptomatic treatment with combination of pain killers, and iv fibrinogen concentrates (fc) treatment to maintain fibrinogen levels above 0.8 g/L, reduced doses of rivaroxaban (10 mg daily) and aspirin (100 mg daily) were given as antithrombotic treatment. The cyanosis diminished with the initiation of the treatment but not disappeared totally (Fig. 1c, d). At the end of the first week, cilostazol (50 mg bid) treatment was added to the regimen. The pain and the cyanosis clinically recovered within 6 weeks. The patient received iv fc once weekly during this treatment to avoid thrombosis and hemorrhage. By the end of 6th week of the treatment, similar symptoms were observed in the 3rd toe, which then resolved spontaneously in 1 week. Therefore the treatment was

prolonged for another 6 weeks. At the end of the 3rd month, the patient was free of embolic and hemorrhagic symptoms. Control doppler ultrasound revealed monophasic blood flow in the occluded artery. Anticoagulant treatment was stopped, whereas 300 mg of aspirin treatment is still ongoing. No thromboembolic recurrences were observed during the follow up.

Discussion

In dysfibrinogenemia, hemorrhagic episodes are more common than thrombotic events. A prothrombotic trigger has been addressed to an increased thrombin generation seen in afibrinogenemic patients [2]. The treatment of thrombotic complications in these patients is a challenge and many dys/afibrinogenemic patients with thrombotic complications die due to bleeding or uncontrolled thrombotic disease. Management of thromboembolic complications is still not established and it is chosen on patient's clinical profile balancing bleeding risk and thrombosis progression [3].

Fibrinogen administration in dysfibrinogenemic patients is associated with the risk of arterial and venous thrombosis [4, 5]. In some afibrinogenemic patients, fibrinogen concentrate infusion and high level of free thrombin available in the plasma of these patients were suggested to be associated with thrombosis. The management of thrombotic episodes is very challenging due the high bleeding risk, and various treatments were tried.

This is, to our knowledge, the first time in which a new oral anticoagulant, rivaroxaban (factor Xa inhibitor) and cilostazol (phosphodiesterase 3 inhibitor used in peripheral arterial diseases) combination was used in a dysfibrinogenemic patient with thrombotic episodes. Our therapeutic approach was effective; we tried to stay on the safe side by lowering the doses of rivaroxaban and cilostazol to half of the dose used for thromboembolic events and peripheral arterial diseases. Further studies to improve the knowledge of pathogenesis and the anti-thrombotic management are needed not only to determine the treatment methods but also to establish the prophylactic therapies. We determined the type, the dosage and the duration of antithrombotic treatment according to the clinical progress of the symptoms.

It is not convenient to suggest a treatment just by relying on clinical judgment, however every case will enlighten the practice with rare diseases and their rare complications. Rivaroxaban, cilostazol and fibrinogen concentrate replacement; combination may represent a useful alternative for the antithrombotic treatment in dysfibrinogenemic patients.

Compliance with Ethical Standards

Conflict of interest As authors of this manuscript, we do not have potential conflict of interest.

Human and Animal Rights Statement All procedures performed in studies involving human participants were in accordance with the ethical standards of the institutional and/or national research committee and with the 1964 Helsinki declaration and its later amendments or comparable ethical standards. For this type of study, formal consent is not required.

Informed Consent Informed consent was obtained from the patient.

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