Internal Medicine
The Japanese Society of Internal Medicine
doi: 10.2169/internalmedicine.7542-21
Intern Med 61: 361-364, 2022
http://internmed.jp

【 CASE REPORT 】

Endovascular Treatment for Lower-extremity Arterial Thrombosis in a Patient with Congenital Afibrinogenemia and a History of Bleeding Complications

Daisuke Hiramatsu[1], Yoshito Ogihara[1], Takeshi Matsumoto[2], Kei Sato[1], Akihiro Takasaki[1], Tairo Kurita[1], Ryuji Okamoto[1], Hideo Wada[3] and Kaoru Dohi[1]

Abstract:
Congenital afibrinogenemia is a rare autosomal recessive blood disorder that accompanies thrombotic complications and is associated with bleeding tendency. The management of these opposing complications remains a challenge. Endovascular treatment (EVT) for peripheral arterial thrombosis has not been described in previous studies. A 57-year-old man with congenital afibrinogenemia developed back pain and left lower leg pain. The cause of the pain was confirmed to be renal infarction and lower extremity arterial thrombosis by Doppler ultrasound and contrast-enhanced computed tomography. He was treated with EVT for the lower extremity arterial thrombosis, leading to an excellent short-term improvement without bleeding.

Key words: congenital afibrinogenemia, peripheral arterial thrombosis, endovascular treatment, bleeding

(Intern Med 61: 361-364, 2022)
(DOI: 10.2169/internalmedicine.7542-21)

Introduction

Congenital afibrinogenemia is a rare autosomal recessive disease caused by mutations in any of the three genes (FGA, FGB, and FGG) that encode respective polypeptide chains of fibrinogen (Aα, Bβ, and γ), resulting in a disorder of stability or secretion of fibrinogen (1, 2). The main symptoms are bleeding complications, such as intramuscular bleeding or submucosal bleeding. In addition, thrombotic complications have been reported, including venous thrombosis and relatively uncommon arterial thrombosis, such as myocardial infarction, renal infarction, and peripheral arterial thromboembolism (2-4). The management of these opposing complications remains a major problem.

We herein report a patient with congenital afibrinogenemia and a history of repetitive bleeding complications who developed renal infarction and lower extremity arterial thrombosis. We performed endovascular treatment (EVT) for the lower extremity arterial thrombosis, leading to an excellent short-term outcome.

Case Report

The patient was a 57-year-old man with a history of hypertension and congenital afibrinogenemia. He had previously been diagnosed with afibrinogenemia by a genetic analysis, which demonstrated a homozygous point mutation in exon 5 of the FGA gene c.991A>G (p.Thr331Ala) and a homozygous deletion mutation in intron 3 to intron 4 of the FGA gene (g.7039_8279del), resulting in deletion of exon 4. He had had bleeding tendency episodes including epistaxis, bleeding from cut wounds, and subcutaneous hematoma since his childhood. Regular fibrinogen replacement therapy (FRT) was started with intravenous administration of fibrinogen concentrate (FC) 2 g on day 1 of a 10- to 14-day cycle at 37 years old.

Three months before his admission to our department, he presented with sudden right epigastric pain, right lower back pain, vomiting, and a fever. A laboratory evaluation showed

[1]Department of Cardiology and Nephrology, Mie University Graduate School of Medicine, Japan, [2]Department of Transfusion Medicine and Cell Therapy, Mie University Hospital, Japan and [3]Department of General and Laboratory Medicine, Mie Prefectural General Medical Center, Japan; Associated Department with Mie Graduate School of Medicine, Japan
Received: March 15, 2021; Accepted: June 22, 2021; Advance Publication by J-STAGE: July 30, 2021
Correspondence to Dr. Yoshito Ogihara, yoshito@clin.medic.mie-u.ac.jp

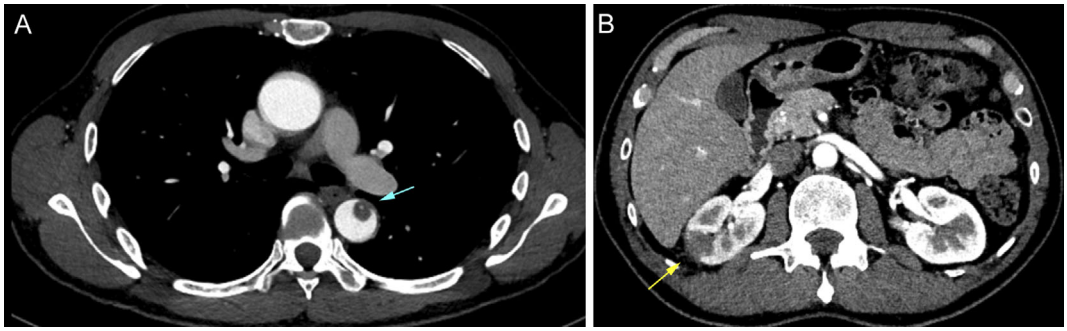

Figure 1. Contrast-enhanced CT. CT revealed the thrombus in the discending aorta (blue arrow) (A) and a perfusion defect of the upper right kidney (yellow arrow) (B).

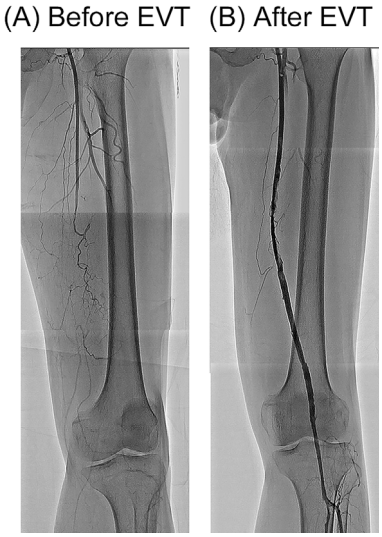

Figure 2. Angiography before EVT (A) and after EVT (B). Angiography before EVT revealed occlusion of the left superficial artery. After EVT, good antegrade flow was obtained in the left superficial artery, popliteal artery, anterior tibial artery, and peroneal artery.

increased serum creatinine and C-reactive protein (CRP) levels and microscopic hematopyuria. He was diagnosed with a urinary tract infection and administered antibiotics. His symptoms improved after eight days; however, he developed left thigh pain at rest with swelling and left lower leg pain during walking. The symptoms were presumed to be caused by intramuscular hematoma, and FC was administered. The lower leg pain persisted for a month, although the thigh pain and swelling improved. The ankle brachial index (ABI) was 1.10 on the right and 0.51 on the left, leading to suspicion of left lower extremity arterial thrombosis. He was referred to our department for further testing and treatment.

Laboratory testing demonstrated normal levels of liver- and muscle-related enzymes and CRP and normal urinalysis findings but an elevated serum creatinine level at 1.37 mg/dL. A coagulation test showed a low fibrinogen level at 57 mg/dL, unmeasurable prothrombin time (PT) due to low fibrinogen levels, and a normal activated partial thromboplastin time (APTT) at 30 seconds. Soluble fibrin and D-dimer levels were lower than the detection limit.

Thrombotic occlusion of the femoropopliteal artery and tibial arteries except for the anterior tibial artery (ATA) was found by Doppler ultrasound. Contrast-enhanced computed tomography (CT) revealed a large thrombus in the descending aorta and a perfusion defect of his upper right kidney (Fig. 1). Transthoracic echocardiography with agitated saline revealed no cardiac or pulmonary shunts. These results suggested that the lower extremity arterial thrombosis and renal infarction ascribed to the thrombus in the aorta caused the left lower leg pain and previous back pain, respectively. We held a discussion about the treatment for the lower extremity arterial thrombosis and the residual aortic thrombosis with a risk of recurrent thromboembolism, resulting in the decision to first perform initiation of safer pharmacological antithrombotic therapy rather than invasive procedures, including EVT and surgical thrombectomy.

He received antithrombotic therapy with apixaban 5 mg and cilostazol 100 mg twice daily for 2 weeks to achieve regression of arterial thromboembolism. He was maintained on regular FRT for bleeding tendency, which consisted of FC 2 g twice every week during the antithrombotic therapy. His lower leg pain was not improved, although no new events of thromboembolism developed. Thus, he was admitted to our hospital for EVT for lower extremity arterial thrombosis.

FC was administered to maintain a serum fibrinogen level of more than 1.5 g/L before the procedure. On the second hospital day, angiography confirmed thrombotic occlusion of the left superficial femoral artery (SFA), popliteal artery (POPA), ATA, posterior tibial artery (PTA), and peroneal artery (PA) (Fig. 2A). Unfractionated heparin (UFH) was administered to maintain an activated clotting time of 250-300 seconds during the procedure. Thrombus aspiration followed by balloon angioplasty for the SFA, POPA, ATA, PA, and dorsal pedis artery was performed, and blood reperfusion was successfully obtained, although small thrombi diffusely remained. On the third hospital day, angiography showed re-occlusion of the left SFA due to ATA dissection. Balloon angioplasty was re-performed for the occluded left SFA, POPA, ATA, and PA, and good antegrade flow was obtained. Urokinase was administered after the first and second

sessions of EVT; however, it was discontinued because of excessively reduced serum fibrinogen and extended APTT levels in both sessions. On the fourth hospital day, treated lesions were patent on angiography (Fig. 2B). A therapeutic dose of UFH was administered for two days after the second procedure.

Cilostazol 100 mg twice daily was restarted to prevent reocclusion, while regular FRT was not readministered due to the possibility of arterial thrombosis. He had an uneventful postoperative course without recurrence and was discharged on the seventh day.

One week after his discharge, he developed pain in his left lower limb due to intramuscular bleeding. In addition, he had subcutaneous hematoma and oral bleeding. Therefore, regular FRT (FC 2 g once every two weeks) was restarted, resulting in the improvement of pain and bleeding. Two months after EVT, the ABI remained in the normal range, and ultrasonography of the leg artery showed the patency of the treated lesions. However, reocclusion of the lesions developed with lower leg pain after four months.

Discussion

In the present case, a patient with congenital afibrinogenemia and a history of bleeding complications developed arterial thrombotic complications. EVT with adjusted-dose FRT and UFH was performed for lower extremity arterial thrombosis refractory to antithrombotic therapy, leading to an excellent short-term outcome without bleeding complications. To our knowledge, this is the first case report to describe EVT for peripheral arterial thrombosis in a patient with congenital afibrinogenemia

Patients with congenital afibrinogenemia are predisposed to bleeding complications. However, venous and arterial thrombotic complications have also been reported despite deficiency of fibrinogen. The mechanism underlying the thrombotic complications remains unclear, but an increase in activated thrombin may have partially contributed to thrombotic events in patients with afibrinogenemia (3). In general, fibrin down-regulates the generation of thrombin by reducing prothrombin activation (5). The loss of anti-thrombin activity may lead to an increase in circulating thrombin, resulting in the activation of platelets in thrombus formation. (6, 7)

The diagnosis and treatment of patients who have two opposing comorbidities remain to be established. The clinical manifestations of afibrinogenemia are mainly due to bleeding, which may lead to a misdiagnosis and delayed diagnosis of thrombotic complications. In addition, treatment needs to be tailored to each individual's clinical status. FRT is used for bleeding complications of afibrinogenemia (8); however, it may lead to thrombotic compliations. Thus, FC is preferred in fibrinogen supplementation, as it does not contain coagulation factors, unlike cryoprecipitate and fresh-frozen plasma (3). As the present case had a history of severe bleeding, long-term prophylaxis with FRT was administered once every 1 or 2 weeks in order to maintain the plasma fibrinogen level at >0.5 g/L. In addition, for invasive procedures, such as surgery with major hemorrhaging, FRT should be administered at 50-100 mg/kg adjusted to maintain a plasma fibrinogen level of more than 1.0-1.5 g/L. (3, 9) For the treatment of thrombosis, a variety of pharmacological treatments, such as anticoagulants, antiplatelets, fibrinolytics, and vasodilators, have been reported to be effective in previous case reports and case series (4, 10-15). Concomitant FRT may be also administered to reduce the risk of hemorrhaging (4, 10-15). When no improvement in thrombosis is achieved by such pharmacotherpies, then surgery and EVT may be considered (3). Le Quellec et al. and Falsoleiman et al. reported the performance of coronary artery bypass grafting or a percutaneous coronary intervention with adjusted-dose FRT and UFH in patients with myocardial infarction, resulting in favorable outcomes (14, 16). In the present case, EVT was performed because of resistance to pharmacotherapy. The development of ATA dissection associated with EVT nessesitated a second-line sessoin for patency of the true lumen. After the EVT, cilostazol was selected to prevent thrombosis due to the activation of platelets and dilating peripferal artery (17). Continuous anticoagulant therapy was not pereformed in consideration of the high risk of bleeding events. However, the post-EVT treatment did not allow the maintenance of long-term patency after EVT. As indicated by the previous report of succesful treatment for recurrent thrombosis asociated with afribrinogenemia (18), combination therapy with continous antiplatelet and anticoagulant drugs and frequent FRT might have been more helpful. The further accumulation of cases and data is needed for the establishment of safe EVT procedures and pharmacotherapy after the procedures in order to maintain long-term patency following EVT.

In conclusion, a careful examination should be performed in consideration of the possibility of not only bleeding complications but also thrombotic complications in patients with afibrinogenemia. EVT is a promising treatment option for thrombotic occlusion refractory to pharmacotherapy.

The authors state that they have no Conflict of Interest (COI).

References

1. de Moerloose P, Schved JF, Nugent D. Rare coagulation disorders: fibrinogen, factor VII and factor XIII. Haemophilia **22** (Suppl 5): 61-65, 2016.
2. de Moerloose P, Casini A, Neerman-Arbez M. Congenital fibrinogen disorders: an update. Semin Thromb Hemost **39**: 585-595, 2013.
3. Korte W, Poon MC, Iorio A, Makris M. Thrombosis in inherited fibrinogen disorders. Transfus Med Hemother **44**: 70-76, 2017.
4. Sartori MT, Milan M, de Bon E, Fadin M, Pesavento R, Zanon E. Thrombosis of abdominal aorta in congenital afibrinogenemia: case report and review of literature. Haemophilia **21**: 88-94, 2015.
5. Mosesson MW. Update on antithrombin I (fibrin). Thromb Haemost **98**: 105-108, 2007.
6. de Bosch NB, Mosesson MW, Ruiz-Saez A, Echenagucia M,

Rodriguez-Lemoin A. Inhibition of thrombin generation in plasma by fibrin formation (Antithrombin I). Thromb Haemost **88**: 253-258, 2002.

7. Dupuy E, Soria C, Molho P, et al. Embolized ischemic lesions of toes in an afibrinogenemic patient: possible relevance to *in vivo* circulating thrombin. Thromb Res **102**: 211-219, 2001.

8. Bornikova L, Peyvandi F, Allen G, Bernstein J, Manco-Johnson MJ. Fibrinogen replacement therapy for congenital fibrinogen deficiency. J Thromb Haemost **9**: 1687-1704, 2011.

9. Levy JH, Welsby I, Goodnough LT. Fibrinogen as a therapeutic target for bleeding: a review of critical levels and replacement therapy. Transfusion (Paris) **54**: 1389-1405, 2014.

10. Castaman G, Lunardi M, Rigo L, Mastroeni V, Bonoldi E, Rodeghiero F. Severe spontaneous arterial thrombotic manifestations in patients with inherited hypo- and afibrinogenemia. Haemophilia **15**: 533-537, 2009.

11. Ozker E, Atalay F, Gulmez O, Saritas B. Treating a patient of dysfibrinogenemia with acute thromboembolism by rivaroxaban and cilostazol. Indian J Hematol Blood Transfus **33**: 431-433, 2017.

12. Ozdemir MA, Isik B, Patiroglu T, et al. A case of congenital afibrinogenemia complicated with thromboembolic events that required repeated amputations. Blood Coagul Fibrinolysis **26**: 354-356, 2015.

13. Margaglione M, Vecchione G, Cappucci F, et al. Venous thrombosis in afibrinogenemia: a successful use of rivaroxaban. Haemophilia **21**: e431-e433, 2015.

14. Le Quellec S, Desjonqueres A, Rugeri L, et al. Combined life-threatening thromboses and hemorrhages in a patient with afibrinogenemia and antithrombin deficiency. Thromb J **16**: 6, 2018.

15. Kumar N, Padma Kumar R, Ramesh B, Garg N. Afibrinogenaemia: a rare cause of young myocardial infarct. Singapore Med J **49**: e104-e106, 2008.

16. Falsoleiman H, Daloee MH, Dehghani M, Rohani A, Bayani B. Percutaneous coronary intervention in a case of afibrinogenemia. Asian Cardiovasc Thorac Ann **21**: 358-359, 2013.

17. Schrör K. The pharmacology of cilostazol. Diabetes Obes Metab **4** (Suppl 2): S14-S19, 2002.

18. Nagler M, Kremer Hovinga JA, Alberio L, et al. Thromboembolism in patients with congenital afibrinogenaemia. Long-term observational data and systematic review. Thromb Haemost **116**: 722-732, 2016.