Case Report

Eighty-four-year-old female with deep femoral artery thrombosis under edoxaban treatment

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Abstract: The deep femoral artery (DFA) is important for collateral circulation. There have been no previous reports of idiopathic and isolated DFA thrombosis. We report the case of an 84-year-old female with idiopathic and asymptomatic right DFA thrombosis under edoxaban treatment for atrial fibrillation (AF). Since the patient was at high risk of bleeding, we switched treatment to heparin, followed by oral warfarin instead of an antiplatelet agent. However, the DFA thrombosis was unexpectedly exacerbated. The dosage of edoxaban, which had been reduced to 15 mg/day soon after hospitalization, was switched back to 30 mg/day, which reduced the DFA thrombosis. Although reasons for the difference in response of the DFA thrombosis between heparin/warfarin and the direct oral anticoagulant (DOAC) edoxaban are unclear, a DOAC may be superior to other anticoagulant therapies for DFA thrombosis in patients with high bleeding risk in whom combination of anticoagulant and antiplatelet therapy is contraindicated.

Key words: deep femoral artery thrombosis ／ direct oral anticoagulant

Background

The DFA is known to play an essential role as a collateral vessel during occlusion of the superficial femoral artery and the popliteal artery[1)].

Previous case reports showed that isolated DFA thrombosis had occurred in the course of deep femoral artery aneurysms[2)] or protein C deficiency[3)], indicating that DFA thrombosis can occur against particular backgrounds. Supporting this notion is the fact that there have been a few reports of DFA thrombosis. A case of asymptomatic DFA thrombosis, which has no established treatment, has also been reported[3)]. In this case report, we present a case of asymptomatic right DFA thrombosis occurring after decreasing the edoxaban dose. Interestingly, the response of the DFA thrombosis differed between heparin/warfarin and edoxaban treatment; it was more favorable with the latter.

Case presentation

An 84-year-old female (Height: 135.9 cm, Body Weight 35.5 kg, Body Mass Index: 19.22 kg/m^2) with chronic heart failure, atrial fibrillation (AF), and chronic kidney disease (CKD) was admitted to our department with dyspnea on exertion. She noticed exertional dyspnea and edema of the lower extremities one month before admission and these symptoms had progressively worsened.

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The patient's medications included carvedilol 10 mg/day, sacubitril/valsartan 400 mg/day, and dapagliflozin propanediol hydrate 10 mg/day for chronic heart failure, edoxaban 30 mg/day for AF, and molidustat sodium 25 mg/day for CKD. On admission, she complained of exertional dyspnea and had pitting edema in the lower extremities without psychroesthesia, intermittent claudication, or rest pain. She had no history of drinking or smoking and no allergy to foods or drugs.

As shown in Table 1, laboratory data revealed elevated creatinine (cre 1.45 mg/dL) and brain natriuretic hormone (BNP 900.7 pg/dL). D-dimer was slightly elevated (3.0 μg/mL), but tumor markers including ferritin (32.4 ng/mL), carcinoembryonic antigen (CEA 3.3 ng/mL), carbohydrate antigen 19-9 (CA19-9 7.1 U/mL) were within normal ranges. With regard to screening for thrombogenesis parameters, such as protein C/S or antiphospholipid antibody, all were normal (Table 2).

Ankle-brachial index (ABI) and cardio ankle vascular index (CAVI) were either in the normal range or comparable for her age (ABI Right/Left = 1.13/1.07, CAVI Right/Left = 9.1/8.6, respectively), indicating that her atherosclerosis was not advanced. Transthoracic echocardiography

Table 1. Laboratory data Ⅰ (day of admission)

Alb (g/dL)	3.6	WBC (/μL)	5.6×10^3
AST (U/L)	18	RBC (/μL)	420×10^4
ALT (U/L)	19	Hb (g/dL)	12.5
LDH (mg/dL)	227	PLT (10^3/μL)	250×10
HbA1c (%)	5.5	APTT (sec)	33.9
BUN (mg/dL)	29	PT-INR	1.43
Cre (mg/dL)	1.45	D-dimer (μg/mL)	3.0
Na (mEq/L)	143	AT-Ⅲ (%)	83
K (mEq/L)	4.3	Ferritin (ng/mL)	32.4
CRP (mg/dL)	0.3	CEA (ng/mL)	3.3
BNP (pg/dL)	900.7	CA19-9 (U/mL)	7.1

Alb: albumin, AST: aspartate aminotransferase, ALT: alanine aminotransferase, LDH: lactate dehydrogenase, HbA1c: hemoglobin A1c, BUN: blood urea nitrogen, Cre: creatinine, CRP: C-reactive protein, BNP: brain natriuretic hormone, WBC: white blood cell count, RBC: red blood cell count, Hb: hemoglobin, PLT: platelet count, APTT: Activated partial thromboplastin time, PT-INR: prothrombin time – International normalized ratio, AT-Ⅲ : antithrombinⅢ, CEA: carcinoembryonic antigen, CA19-9: carbohydrate antigen 19-9

Table 2. Laboratory data Ⅱ (day of admission)

Plasminogen (%)	78	C3 (mg/dL)	85
FDP (μg/mL)	＜3	C4 (mg/dL)	17
Pr C (%)	92	RF (IU/mL)	＜3
Pr S (%)	115	ANA	＜40
LA	0.9	RIA (IU/mL)	1.4
TM (FU/mL)	29.9	aCL (U/mL)	6.9
IgG (mg/dL)	1280	ANCA (U/mL)	＜1.0
IgM (mg/dL)	79	MPO-ANCA (U/mL)	＜1.0

FDP: fibrin/fibrinogen degradation products, Pr C: protein C, Pr S: protein S, LA: lupus anticoagulant, TM: thrombomodulin, RF: rheumatoid factor, ANA: antinuclear antibody, RIA: anti-double stranded DNA IgG antibody, aCL: anti-cardiolipin antibody, ANCA: anti-neutrophil cytoplasmic antibody, MPO-ANCA: myeloperoxidase anti-neutrophil cytoplasmic antibody

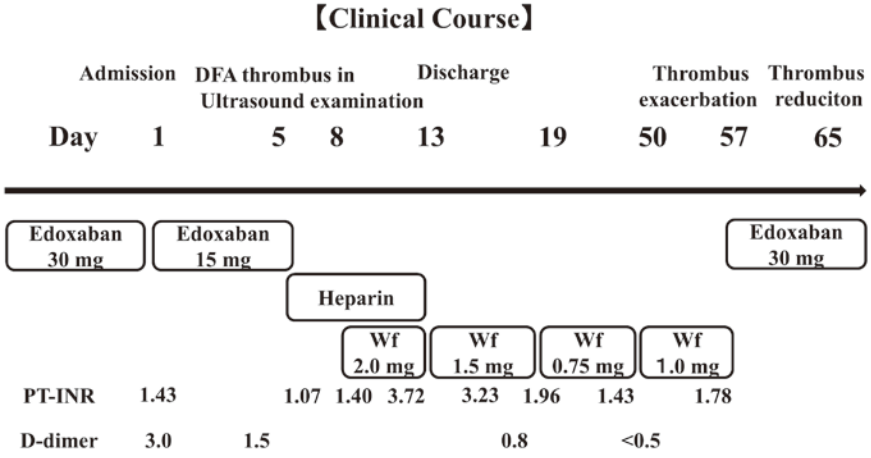

Figure 1. Clinical course in this case

The patient had been receiving a DOAC (edoxaban 30 mg/day) for atrial fibrillation (AF). After admission, edoxaban was reduced from 30 mg/day to 15 mg/day because she was elderly and had impaired renal function.

On the 5th day after admission, right DFA thrombosis was detected in the lower extremity by echography. After treatment with heparin and oral warfarin, right DFA thrombosis was exacerbated on the 57th day after admission. After switching to oral administration of edoxaban 30 mg/day on the same day, the DFA thrombus decreased.

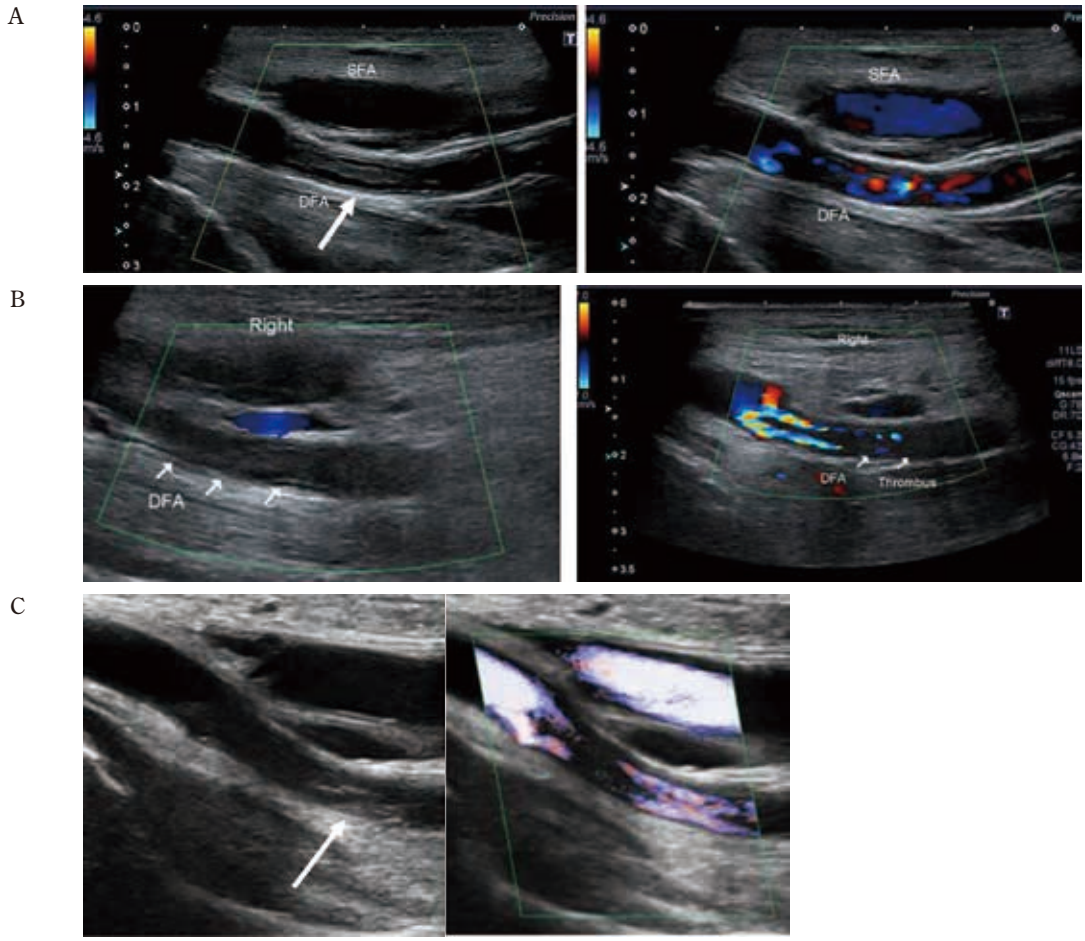

Figure 2. Echographic findings for right deep femoral artery (DFA)

A: Right DFA thrombosis was detected during treatment with edoxaban 15 mg on the 5th day after admission

B: Right DFA thrombosis was exacerbated after intravenous administration of heparin and treatment with warfarin on the 57th day after admission. (Left Figure)

We observed disruption of blood flow signals due to the distal thrombus (Right Figure)

C: Right DFA thrombosis decreased after treatment with edoxaban 30 mg on the 65th day after admission. Blood flow signals were constant. (Size of thrombosis, Entire length: 30 mm, Proximal diameter: 2.2 mm, Distal diameter 2.0 mm)

showed no evidence of thrombosis or patent foramen ovale.

We made a diagnosis of acute exacerbation of chronic heart failure and continued treatment of carvedilol 10 mg/day, sacubitril/valsartan 400 mg/day, and dapagliflozin propanediol hydrate 10 mg/day, with bed rest. Although she had been taking edoxaban 30 mg/day for AF on the day of admission, the dosage was reduced to 15 mg/day based on her age and impaired renal function, as shown in Figure 1.

On the 5th day of hospitalization, venous ultrasonography revealed a linear thrombus in the right deep femoral artery (DFA) without venous thromboembolism, as shown in Figure 2A. As thrombosis had occurred while under edoxaban treatment, we switched to heparin, followed by oral warfarin treatment. Since symptoms and biomarkers of heart failure including BNP improved, she was discharged on day 13 of hospitalization. PT-INR was 3.23 when she was discharged, but PT-INR had been low after discharge. Follow-up ultrasonography of the DFA was performed at 57 days after admission (Figure 2B), unexpectedly showing exacerbation of the DFA thrombosis. The patient had no symptoms of limb ischemia and rejected hospitalization, so we switched not to heparin but to edoxaban 30 mg/day. With a switch to edoxaban 30 mg/day, the DFA thrombosis had decreased on the 65th day after admission, as shown in Figure 2C. The patient had no subsequent exacerbation of DFA thrombosis.

Discussion

We experienced the case of an elderly Japanese female with DFA thrombosis during anticoagulant therapy. Anatomically, the DFA plays a pivotal role as a collateral vessel in occlusion of the superficial femoral artery[1]. Since the DFA is surrounded by the adductor muscle and is resistant to atherosclerotic and aneurysmal change, solitary DFA thrombosis rarely occurs[2]. Previous case reports concerned secondary DFA thrombosis due to DFA aneurysm[2], protein C deficiency[3] and catheter procedure complications[4].

Therefore, cases of solitary DFA thrombosis have not been reported before. The patient had no history of trauma or surgery, and blood tests showed no obvious predisposition to thrombosis. Potential causes of DFA thrombosis include arteriosclerosis, trousseau syndrome or AF.

First, atherosclerotic lesions are unlikely in this case because ABI and CAVI for this patient were within normal ranges and there were no atherosclerotic lesions, including calcification and stenosis, on ultrasonography.

Second, Trousseau syndrome is also unlikely because tumor markers were within normal ranges, and non-contrast CT imaging showed no evidence of tumors[5].

Third, in the absence of transesophageal echocardiography, thromboembolism due to AF cannot be clearly excluded.

Therefore, for this patient, we considered the etiology of DFA thrombosis to be idiopathic. In general, antiplatelet drugs are used to treat aortic thrombosis[6]. However, the HAS-BLED score for this patient was 2 points, suggestive of medium risk of bleeding, so we did not add antiplatelet therapy to the anticoagulant therapy[7]. For patients who require anticoagulant therapy and have a high risk of bleeding there is often difficulty in selecting treatment for asymptomatic peripheral arterial thrombus, as in this case. Warfarin is a vitamin K antagonist and direct oral anticoagulants (DOACs) are antagonists of thrombin or factor Xa. In patients with CKD, DOACs are as likely as warfarin to prevent all strokes and systemic embolic events without increasing risk of major bleeding events, so we switched to a DOAC from warfarin[8].

There was no exacerbation of the thrombus after treatment with edoxaban 30 mg/day. DOACs are known for their ability to provide consistent therapeutic effects with reduced inter-individual variability and minimal food and

concomitant drug interactions, which were limitations of warfarin. These characteristics of DOACs may contribute to thrombus regression.

In antithrombotic therapy, rivaroxaban monotherapy was non-inferior to combination therapy in terms of efficacy and superior in terms of safety in patients with AF and stable coronary artery disease[9]. Considering these results, DOACs may inhibit the progression of DFA thrombosis in the absence of an antiplatelet drug when bleeding risk is high.

There are some limitations in this report. First, although the fecal occult blood test for this patient was positive, we could not perform endoscopy because the patient declined. Second, we did not conduct contrast-enhanced CT or lower extremity CT angiography because of impaired renal function on admission. Therefore, Arteriosclerosis obliterans (ASO) and malignancy could not be conclusively ruled out. Third, we could not rule out left atrial thrombus due to lack of transesophageal echocardiography.

In conclusion, we experienced a rare case of idiopathic and asymptomatic DFA thrombosis. A DOAC may be appropriate medical therapy for DFA thrombosis, without an antiplatelet drug when bleeding risk is high.

Conflict of interest

The authors declare that they have no conflict of interest (C.O.I)

Informed consent

Written informed consent was obtained from the patient for publication of this case report and any accompanying images.

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エドキサバン治療中に発症した深大腿深動脈血栓症の１例

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要旨：深大腿動脈（DFA）は側副血行にとって重要である。われわれは，心房細動（AF）に対するエドキサバン治療下に，特発性かつ無症候性の右DFA血栓症を呈した84歳女性の症例を報告する。本症例では出血のリスクが高く，抗血小板薬の代わりにヘパリン，次いでワルファリンの経口投与に治療を切り替えた。しかし，DFA血栓症は予想外に増悪し，入院後すぐに15 mgに減量したエドキサバンの投与量を30 mgに戻したところ，DFA血栓症は軽減した。ヘパリン／ワルファリンと直接経口抗凝固薬（DOAC）エドキサバンとのDFA血栓症に対する反応の違いの理由は不明であるが，抗凝固薬と抗血小板薬の併用療法が禁忌である出血リスクの高い患者のDFA血栓症に対しては，DOACが他の抗凝固薬よりも優れている可能性がある。

索引用語：　深大腿動脈血栓症　／　直接経口抗凝固薬

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