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【 CASE REPORT 】

Acute Brachial Arterial Embolic Occlusion Following Anticoagulant Discontinuation in a Renal Biopsy of a Nephrotic Syndrome Patient

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Abstract:
A 73-year-old woman with atrial fibrillation treated with rivaroxaban was hospitalized for nephrotic syndrome. After discontinuation of rivaroxaban to lower the risk of hemorrhagic events, a renal biopsy was performed. Rivaroxaban was scheduled to resume a week after the biopsy to prevent renal hemorrhaging. However, she developed acute brachial arterial embolic occlusion and mural thrombosis in the abdominal aorta before resuming rivaroxaban. If immune-mediated renal diseases are suspected in anticoagulated patients at a risk of thrombotic events, physicians should consider initiating glucocorticoid therapy without a renal biopsy in order to avoid hemorrhagic and thrombotic events.

Key words: renal biopsy, nephrotic syndrome, atrial fibrillation, anticoagulant discontinuation, thromboembolism

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Introduction

Renal biopsies are essential procedures for determining the diagnosis, prognosis, and treatment of patients with kidney disease. Most complications of renal biopsies are associated with bleeding (1). Major hemorrhagic complications include massive bleeding requiring angiographic intervention, massive transfusion, and nephrectomy, while minor complications include self-limited anemia, gross hematuria, and perinephric hematoma (1, 2). Therefore, periprocedural anticoagulant discontinuation is required when patients who have taken anticoagulants undergo a biopsy. While coagulopathy is rare as a complication of a renal biopsy (3, 4), these patients are at risk of thromboembolism due to anticoagulant discontinuation during renal biopsies.

We herein report a case of nephrotic syndrome in which periprocedural anticoagulant discontinuation contributed to acute brachial arterial embolic occlusion following a renal biopsy.

Case Report

A 73-year-old woman was hospitalized for nephrotic syndrome. Her medical history included atrial fibrillation (AF) with a CHADS2 score of 1 treated with rivaroxaban. A urine protein level of 3+ was first observed approximately seven months before admission and persisted for some time (four months before admission, 3+; two days before admission, 3+). In addition, the patient complained of lower limb edema about four months before admission and subsequently complained of shortness of breath about two months prior to admission. Chest X-ray taken two days before admission revealed bilateral pleural effusion, and the patient was referred to our hospital with suspected nephrotic syndrome.

Her vital signs included a blood pressure of 143/92 mmHg, a heart rate of 91 beats/min, a body temperature of 36.6℃, a respiratory rate of 18 breaths/min, a blood oxygen saturation level of 96% without oxygen administration, and Glasgow Coma Scale score of E4 V5M6. A physical exami-

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Table. Laboratory Findings on Admission.

Blood cell count		CA19-9	4.6 U/mL	MPO-ANCA	1.8 IU/mL
WBC	8,230 /μL	Protein C activity	≥151 %	PR3-ANCA	2.1 IU/mL
RBC	4.87×10^6 /μL	Protein S activity	52 %	Transferrin	128 mg/dL
Hb	16.3 g/dL	Protein profiling		Bence-Jones protein	Negative
Hct	46.5 %	Alb	34.7 %	Urinalysis	
Plt	34.7×10^4 /μL	α1-globulin	4.7 %	pH	6.5
Blood chemistry		α2-globulin	26.3 %	Protein	(3+)
CRP	0.47 mg/dL	β-globulin	13.5 %		11.9 g/gCre
TP	4.4 g/dL	γ-globulin	20.8 %	Occult blood	(2+)
Alb	1.1 g/dL	Coagulation		RBC	50-99 /HPF
AST	35 U/L	PT-INR	0.98	WBC	Negative
ALT	20 U/L	APTT	28.1 s	Granular casts	Few/LPF
LDH	351 U/L	Fibrinogen	621.1 mg/dL	Fatty casts	Few/LPF
T-Bil	0.4 mg/dL	Immunochemistry		Dysmorphic RBC	Positive
BUN	11.2 mg/dL	IgG	834 mg/dL	Cre	30.2 mg/dL
Cre	0.84 mg/dL	IgA	294 mg/dL	NAG	11.5 U/L
Na	137 mEq/L	IgM	142 mg/dL	β_2MG	629 μg/L
K	3.7 mEq/L	C3	101.9 mg/dL	Bence-Jones protein	Negative
Cl	101 mEq/L	C4	32.1 mg/dL	Transferrin	37.0 mg/dL
Ca	8.0 mg/dL	CH50	57.9 U/mL	IgG	33.8 mg/dL
Total cholesterol	331 mg/dL	ANA	×40 titer		
Triglycerides	260 mg/dL	Anti-ds DNA antibody	20.0 IU/mL		
LDL cholesterol	197 mg/dL	Anti-CL IgG antibody	Negative		
HDL cholesterol	82 mg/dL	Anti-CL-β2GP1 complex antibody	Negative		
HbA1c (NGSP)	5.6 %	Lupus anticoagulant	Negative		
CEA	7.6 ng/mL				

ANA: antinuclear antibody, ds DNA: double stranded deoxyribonucleic acid, CL: cardiolipin

nation revealed pitting edema of both the upper and lower extremities and coarse crackles on chest auscultation. An electrocardiogram showed an irregular rhythm consistent with AF. Blood tests revealed hypoproteinemia (4.4 g/dL), hypoalbuminemia (1.1 g/dL), and dyslipidemia. Urine tests revealed nephrotic-range proteinuria (11.9 g/gCre), a low selectivity index, granular and fatty casts, and dysmorphic red blood cells (Table). Computed tomography (CT) revealed bilateral pleural effusion with no evidence of atrophic kidneys, enlarged lymph nodes, intraperitoneal masses, surface nodularity of the liver, or splenomegaly.

After discontinuation of rivaroxaban (on hospital day 4) and intravenous administration of carbazochrome sodium sulfonate hydrate (several hours before the biopsy) to prevent hemorrhagic adverse events, a percutaneous renal biopsy was performed under ultrasound guidance on hospital day 5. The patient was placed in a dorsal position, and needle punctures were performed four times at the left kidney using a Bard® Monopty® Disposable Core Biopsy Instrument (18 gauge ×160 mm). After the biopsy, the patient remained in bed until the following day.

Minimal change disease with nephrosclerosis was suspected based on the renal pathological findings, highly selective proteinuria, medical history of hypertension, and long history of smoking; therefore, oral prednisolone (35 mg/day) was initiated on hospital day 7. The patient was at a high risk for hemorrhagic adverse events following the biopsy due to the presence of several hemorrhagic risk factors (use of anticoagulants, being a woman, and multiple punctures during the biopsy). At the same time, she was also at risk for thromboembolism due to the presence of several thrombotic risk factors (anticoagulant discontinuation, nephrotic syndrome, and initiation of oral prednisolone). It was initially estimated that the risk of bleeding was higher than that of thromboembolism, since there have been no reports of thromboembolism due to anticoagulant discontinuation following a renal biopsy. Furthermore, echocardiography performed before the biopsy revealed no evidence of left atrial expansion or thrombus in the left atrium. Therefore, rivaroxaban was scheduled to be resumed a week after the biopsy (on hospital day 12).

However, the patient suddenly complained of numbness and pain in her right forearm on hospital day 8. A physical examination revealed coldness of her right forearm and a faint pulse in her right brachial and radial arteries. Additional blood testing revealed a high level of D-dimer (14.8 μg/mL). Acute brachial arterial embolic occlusion was suspected, although we had never experienced thromboembolisms following a renal biopsy. Contrast-enhanced CT revealed filling defects in these arteries and a mural thrombus in the abdominal aorta (Fig. 1).

Emergent endovascular thrombectomy at the right brachial and radial arteries was performed on hospital day 9, resulting in successful recanalization and improvement of the

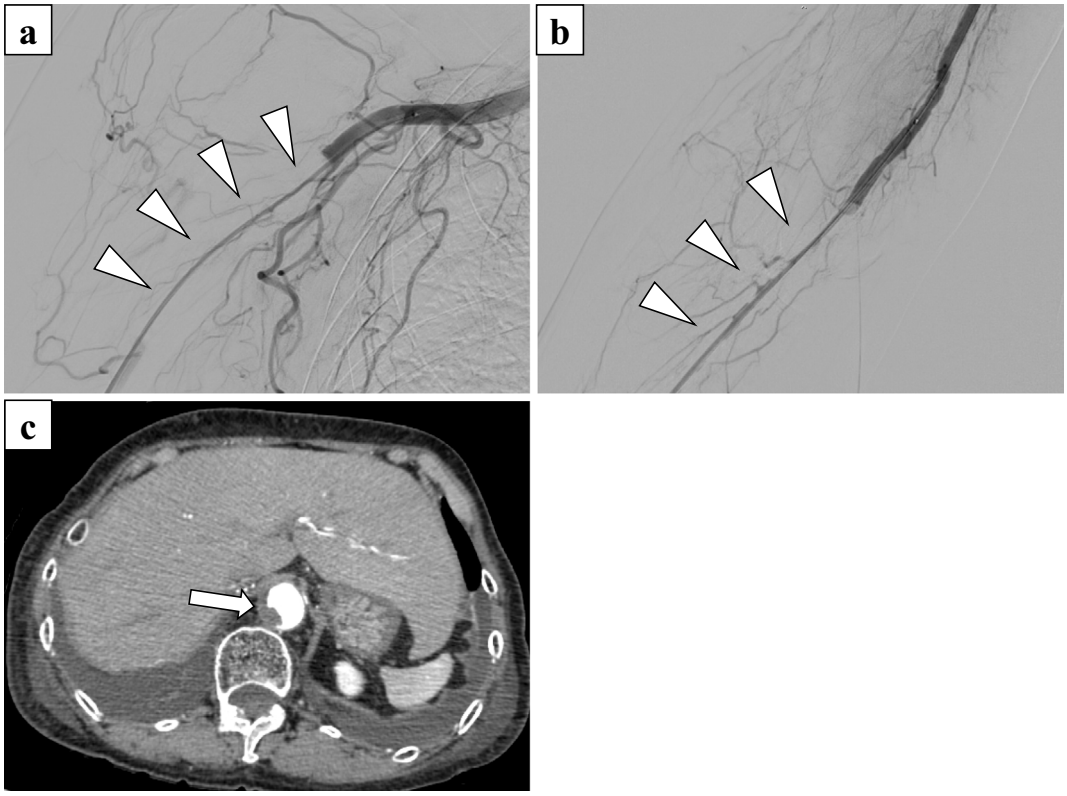

Figure 1. Angiography and contrast-enhanced CT performed on hospital day 9. a, b: Angiography revealed filling defects in the right brachial and radial arteries (white arrowheads). c: Contrast-enhanced CT revealed mural thrombus in the abdominal aorta (white arrow). CT: computed tomography

numbness and pain in the right forearm. A dose of 5,000 U of heparin was administered intravenously, and rivaroxaban was resumed. Follow-up CT recorded on hospital day 11 revealed no evidence of arterial embolic occlusion in the right arm, although the mural thrombus in the abdominal aorta remained. No hemorrhagic adverse events or further thromboembolisms were detected after resumption of rivaroxaban. Additional laboratory testing to evaluate thrombogenic factors reported low activity of protein S and a slightly elevated serum level of anti-double stranded deoxyribonucleic acid antibody (anti-dsDNA antibody) but no elevation in serum levels of antiphospholipid antibodies. However, we deemed the probability of inherited protein S deficiency or systemic lupus erythematosus (SLE) to be low, since the low activity of protein S could be explained by massive protein loss in urine related to nephrotic syndrome, and there were no symptoms or renal pathological findings specific to SLE.

Proteinuria improved with glucocorticoid therapy, and complete remission from nephrotic syndrome was observed on hospital day 32. The patient was discharged on hospital day 36. A schematic illustration of the clinical course is shown in Fig. 2.

Discussion

The present report describes a patient with nephrotic syndrome in which anticoagulant discontinuation contributed to acute brachial arterial embolic occlusion following a renal biopsy. This case suggests the possibility that anticoagulant discontinuation following a renal biopsy can result in thromboembolism in patients with thrombotic risk factors who have taken anticoagulants. Coagulopathy is a rare complication of renal biopsies (3, 4), and to our knowledge, this is the first report to describe thromboembolism associated with anticoagulant discontinuation following a renal biopsy.

Most complications of renal biopsies are associated with bleeding (1). Therefore, periprocedural anticoagulant discontinuation is required when patients are biopsied. Several recommendations for the periprocedural management of anticoagulants have been published; however, in clinical practice, anticoagulants are empirically resumed after renal biopsies, depending on the evaluated hemorrhagic and thrombotic risks. According to the previous version of the renal biopsy guideline published by Japanese Society of Nephrology in 2004, anticoagulants should be discontinued for one or two weeks after renal biopsies because of delayed hemorrhagic complications (5, 6). However, in the new version of the guideline, published in 2020, anticoagulants should be resumed one or two days after renal biopsies or when medical tests reveal no evidence of aggravated renal bleeding (7). This recommendation was based on three reasons. First, a questionnaire survey revealed that approximately 60% of specialized medical centers in Japan performed periprocedural management where anticoagulants were resumed one

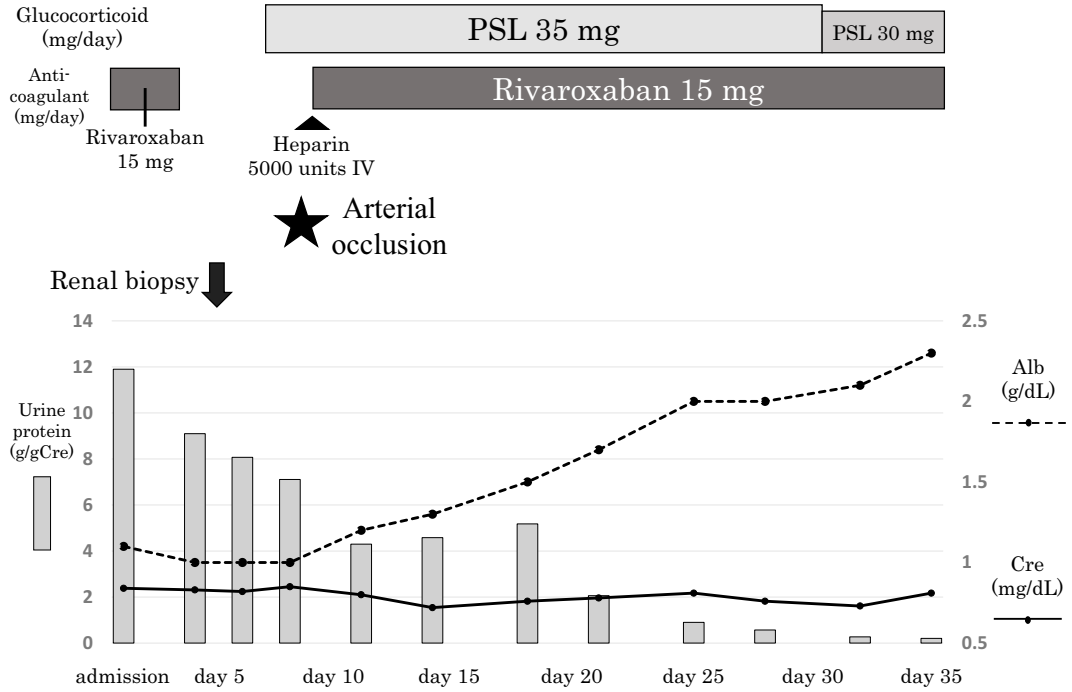

Figure 2. The clinical course. PSL: prednisolone, IV: intravenous, Alb: serum albumin level, Cre: serum creatinine level

or two days after renal biopsies or once biopsied patients were under hemorrhagic control (7). Second, the Japanese guidelines for gastrointestinal endoscopy for patients taking antithrombotic drugs recommend that patients undergoing anticoagulant therapy be treated as a high-risk group for thromboembolisms (8). Third, according to the guidelines of the American College of Chest Physicians, recommended perioperative management includes continuing therapeutic-dose heparin until 4 to 6 hours before surgery and resuming it 48 to 72 hours after surgery in patients at high risk of thromboembolism (9). Despite these recommendations, the length of periprocedural anticoagulant discontinuation varies among medical institutions, as no high-quality clinical trials exist regarding the periprocedural management of anticoagulants.

In the present case, the timing of the resumption of rivaroxaban presented a dilemma because the patient was at high risk of both hemorrhagic and thrombotic events. Hemorrhagic risk factors following renal biopsies include the renal function, underlying renal diseases, patients' medical background, and procedure-related factors. Risk factors associated with the renal function are chronic kidney disease, acute kidney injury, and rapidly progressive glomerulonephritis (10-13). Risk factors associated with underlying renal diseases are thin basement membrane syndrome, vasculitis, acute interstitial nephritis, and amyloidosis, which confer a high risk (13, 14). Risk factors associated with the medical background of the patients are hypertension (≥160/100 mmHg), female sex, anemia, low platelet count, and the use of antithrombotic drugs (15). The main risk factor associated with the procedure itself is a high number of punctures (≥4) (16); the size of the biopsy needle does not contribute to major hemorrhagic complications (17). Hemorrhagic risk factors in the present case were a female sex, use of anticoagulants, and frequent punctures, suggesting that this case had a relatively high risk of bleeding. In contrast, the thrombotic risk factors in this case were anticoagulant discontinuation, nephrotic syndrome, and the use of oral glucocorticoids, suggesting a high risk for thromboembolism.

In general, anticoagulation therapy for AF is based on the CHADS2 score, and either a direct oral anticoagulant or warfarin is chosen. A high CHADS2 score is associated with a high annual incidence rate of stroke, and anticoagulant discontinuation results in the development of stroke in patients with AF with a high CHADS2 score (18, 19). In the present case, the patient had AF with a CHADS2 score of 1 and had been receiving rivaroxaban for a considerable time; therefore, periprocedural discontinuation of rivaroxaban may have increased her thrombotic risk. Furthermore, nephrotic syndrome and the use of oral glucocorticoids may contribute to the development of thromboembolism. According to previous reports, approximately 25% of cases of nephrotic syndrome are complicated by thromboembolism (20), with annual incidence rates of venous and arterial embolism of 1.02% and 1.48%, respectively (21). The use of glucocorticoids, especially their initiation, is associated with an increased thrombotic risk (22). In the present case, additional blood tests to evaluate other thrombogenic factors revealed low serum levels of protein S and a slightly elevated serum level of anti-dsDNA antibody. However, the probability of inherited protein S deficiency, SLE, or antiphospholipid antibody syndrome was deemed low. Given the previous reports and clinical findings above, acute arterial embolic occlusion

may have developed due to the simultaneous presence of anticoagulant discontinuation, nephrotic syndrome, and initiation of glucocorticoid therapy.

Therefore, it is better to initiate glucocorticoid therapy without performing a renal biopsy when immune-mediated renal diseases are suspected in anticoagulated patients, since renal biopsies in these patients are associated with a high risk of hemorrhagic and thrombotic events. The present patient was provisionally diagnosed with minimal change disease because of the highly selective proteinuria; hence, it would have been desirable to evaluate the reactivity of glucocorticoid therapy in this patient without performing a renal biopsy in order to avoid the occurrence of hemorrhagic and thrombotic events.

Two clinical issues in the present case report remain to be addressed. First, thromboembolism may occur in the natural course of nephrotic syndrome, regardless of anticoagulant therapy discontinuation; indeed, approximately 25% of nephrotic syndrome cases develop thromboembolism (20). However, anticoagulant discontinuation was very likely an exacerbating factor for thromboembolism in this case, as supported by previous reports of anticoagulant discontinuation-associated thromboembolism in patients with AF (18, 23). In those reports, AF patients who discontinued anticoagulants had a higher incidence and poorer prognosis of thrombotic events than those who did not discontinue anticoagulants. Furthermore, most thrombotic events occurred within one or two weeks after anticoagulant discontinuation. Indeed, acute brachial arterial embolic occlusion occurred four days after anticoagulant discontinuation in this case, suggesting that anticoagulant discontinuation may have contributed to the pathophysiology, in addition to nephrotic syndrome. Second, whether or not the early resumption of rivaroxaban was clinically appropriate in this case, as recommended in the new version of the renal biopsy guideline published by Japanese Society of Nephrology in 2020, is unclear (7). There have been no high-quality clinical studies concerning the safety of the early resumption of anticoagulants following renal biopsies; whether or not anticoagulants should be resumed in the early postprocedural period in patients undergoing renal biopsies thus remains controversial.

In conclusion, we present a case of nephrotic syndrome in which periprocedural anticoagulant discontinuation contributed to acute brachial arterial embolic occlusion following a renal biopsy. This case suggests that anticoagulant discontinuation-associated thromboembolism can develop a after renal biopsy, although coagulopathy is generally rare as such a complication. If immune-mediated renal diseases are suspected in patients with a relatively high risk of thrombotic events who have taken anticoagulants, physicians should consider initiating glucocorticoid therapy without a renal biopsy to avoid hemorrhagic and thrombotic events.

Informed consent was obtained from all participants included in the study.

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

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