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Acute Arterial Thrombosis with Antithrombin III Deficiency in Nephrotic Syndrome: Report of a Case

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Abstract Nephrotic syndrome frequently causes venous thromboembolic complications. Arterial thrombosis has rarely been reported and is mainly observed in children. Only six cases of lower extremity arterial thrombosis in adults have been reported in the literature. The outcome in these cases was unsatisfactory because of the high rates of limb loss and recurrence of thrombosis. We report successful treatment of a 39-year-old man who suffered from right lower extremity arterial thrombosis associated with decreased levels of serum antithrombin III. He was admitted to our hospital with severe pain in his right foot. No pulse was palpable in his right dorsalis pedis or posterior tibial arteries. His right foot was cold and mottled, with a reduced sensation and motor activity. The laboratory data revealed a serum total protein concentration of 3.9 g/dl and an albumin concentration of 1.5 g/dl. The coagulation profile showed a fibrinogen level of 879 mg/dl and antithrombin III value of 9.5%. Right lower extremity arteriography showed a complete occlusion of the right deep femoral artery and popliteal artery, and a filling defect in the common femoral artery. An emergency thrombectomy was performed under general anesthesia. The patient was treated successfully, and surgical treatment was followed by anticoagulant therapy with 1 000 units of antithrombin III. A renal biopsy revealed histologic evidence of minimal change of glomerulonephritis. He was discharged 3 months later, and no recurrence of thrombosis has yet been observed.

Key Words Nephrotic syndrome · Lower extremity arterial thrombosis · Antithrombin III deficiency

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Introduction

Hypercoagulability is a recognized complication of nephrotic syndrome, which commonly affects the venous system. Arterial thrombosis has been only infrequently reported and is observed mainly in children. Reports of lower extremity arterial thrombosis with nephrotic syndrome have been limited. A review of the literature revealed only six cases of lower extremity arterial thrombosis in the adult population. Its management is unsatisfactory and contentious because of high rates of both limb loss and a recurrence of thrombosis. This report describes a 39-year-old man with nephrotic syndrome complicated by lower extremity arterial thrombosis associated with decreased levels of serum antithrombin III.

Case Report

A previously healthy 39-year-old man was admitted to our hospital with severe pain in his right foot. His vital signs were as follows: a blood pressure of 112/84 mmHg, a pulse of 82 beats/min in sinus rhythm, a temperature of 36.8°C, weight 85 kg, and height 170 cm. No arterial pulses were palpable in his right lower leg. The right foot was cold and mottled with a reduced sensation and reduced motor activity. Laboratory data revealed a white blood cell count of 13 500/mm^3, a hematocrit of 51.7%, platelet count of 182 000/mm^3, a sodium concentration of 134 mEq/l, a potassium concentration of 3.8 mEq/l, a chloride concentration of 102 mEq/l, a blood urea nitrogen concentration of 23.1 mg/dl, a creatinine concentration of 1.3 mg/dl, a serum total protein concentration of 3.9 g/dl, an albumin concentration of 1.5 g/dl, a total cholesterol concentration of 420 mg/dl, and a triglyceride concentration of 508 mg/dl. The coagulation profile showed a fibrinogen concentration of 879 mg/dl, antithrombin III value of 9.5%, and pro-

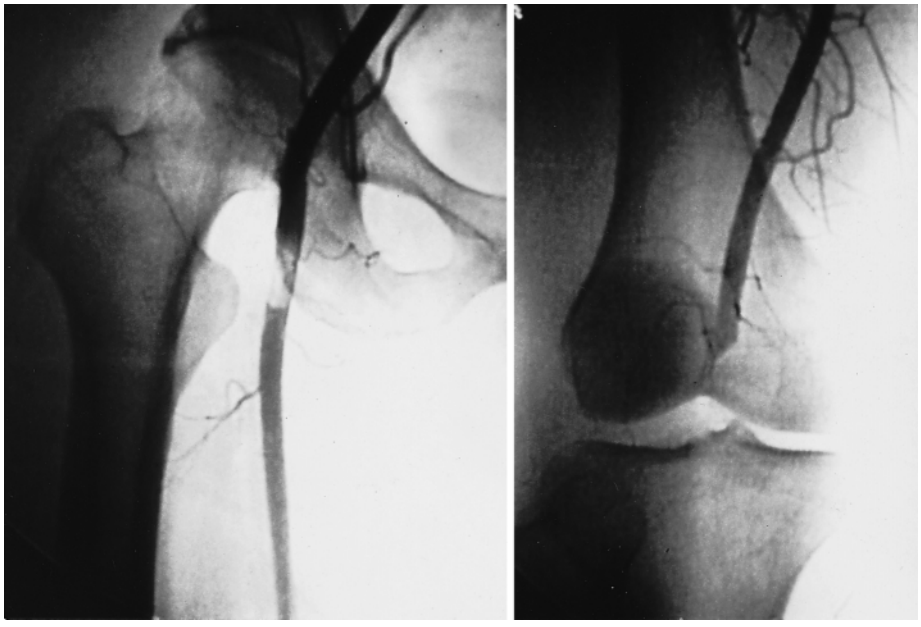

Fig. 1. Arteriogram of the right lower extremity showing a complete occlusion of the deep femoral artery (*left*) and popliteal artery (*right*)

thrombin time of 10.5 s. Under the diagnosis of acute right lower extremity arterial occlusion, right lower extremity arteriography was performed after the administration of urokinase and heparin. A complete occlusion of the right deep femoral artery and popliteal artery was observed with a filling defect in the common femoral artery (Fig. 1). Four hours after admission, a thrombectomy was performed through the right common femoral artery under general anesthesia. We advanced a Fogarty catheter beyond the popliteal artery and trifurcation, and also advanced it to the deep femoral artery. A large amount of the thrombus was extracted. A good distal arterial flow was reestablished and 1000 units of antithrombin III were given intravenously. An arterial infusion catheter was inserted into the superficial femoral artery. The infusion of 10000 units of heparin, 240000 units of urokinase, and 10 μg of prostaglandin E_1 per day was started intraoperatively and continued for 1 week. As anticoagulant therapy, warfarin (5 mg/day) and aspirin (81 mg/day) were administered. An urinary analysis showed 16 g/day protein loss. Prednisolone therapy was also started with the diagnosis of nephrotic syndrome. Although enhanced computed tomography showed an inferior vena cava thrombus, perfusion scintigraphy showed no evidence of pulmonary embolism. Two weeks later, because no remission in the urinary protein and serum albumin levels was observed, steroid pulse therapy (methylprednisolone 1 g/day for 3 days) was prescribed. Thereafter, the patient's urinary protein level decreased to less than 0.1 g/day and the serum albumin level was 3.5 g/dl. A renal biopsy revealed histologic evidence of minimal change of glomerulonephritis. He was discharged 3 months later without any recurrence of thrombosis. Table 1 shows the laboratory data on admission and at discharge.

Table 1. Laboratory data on admission and at the time of discharge

	Admission	Discharge
TP (g/dl)	3.9	5.3
Alb (g/dl)	1.5	3.6
T-Cho (mg/dl)	420	251
TG (mg/dl)	508	309
U-P (g/day)	16	0.1
PT (s)	10.5	13.0
Fib (mg/dl)	879	368
FDP (μg/ml)	16.5	7.0
AT III (%)	9.5	111.4

TP, total protein; Alb, albumin; T-Cho, total cholesterol; TG, triglyceride; U-P, urinary protein loss; PT, prothrombin time; Fib, fibrinogen; FDP, fibrin degradation product; AT III, antithrombin III

Discussion

Thrombotic complications in the venous system in nephrotic syndrome have been widely reported. Arterial occlusion is rare and has been reported to occur in the aortic, renal, coronary, mesenteric, axillary, brachial, carotid, middle celebral, ophthalmic, and femoral arteries. These complications have been recognized as sequelae of a hypercoagulable state due to the following factors: (1) altered levels of coagulation factors, (2) platelet dysfunction, and (3) increased viscosity of the

Table 2. Reported cases of lower extremity arterial thrombosis in adult cases of nephrotic syndrome

Case; First author[Ref.]	Age (years)/sex	Prior treatment	Serum albumin (g/dl)	Renal histology	Outcome
1. Mukherjee[4]	24/M	S	0.65	PGN	RAKA
2. Patel[5]	34/M	D	—	FPGN	BBKA
3. Nitatori[6]	40/M	S/D	1.5	PGN	RAKA
4. Nitatori[6]	25/M	S/D	0.92	PGN	Recovered
5. Parag[7]	23/M	None	0.7	MCGN	Died
6. Khatri[8]	29/M	S	1.5	MCGN	Recovered
7. Present case	39/M	None	1.5	MCGN	Recovered

PGN, proliferative glomerulonephritis; FPGN, focal proliferative GN; MCGN, minimal change GN; RAKA, right above-knee amputation; BBKA, bilateral below-knee amputation; S, steroids; D, diuretics

blood. The mechanism of hypercoagulability, however, has not yet been clearly elucidated. A reduction in low molecular weight coagulation factors (XI, XII) results from an increased loss in the urine, so that levels of high molecular weight factors (V, VII, VIII, IX, X, XIII) become elevated as a result of increased protein synthesis. Notably, an elevation in the fibrinogen level is a significant abnormality in nephrotic syndrome and has been shown to considerably alter the plasma viscosity. Antithrombin III, an important anticoagulant factor, has a molecular weight similar to that of albumin and is lost in much the same manner. There is also a significant positive correlation between the serum levels of antithrombin III and albumin. Low levels of antithrombin III have been shown to occur in as many as 80% of patients with nephrosis.[1] Various other conditions associated with nephrotic syndrome, including plasma lipid abnormalities, hypovolemia with hypoalbuminemia, hypertension, circulating immune complexes, and susceptibility to infection, are also considered to be factors contributing to the hypercoagulable state in nephrotic syndrome. Recently, a deficiency in free protein S has also been implicated as a contributing factor in thrombotic diathesis.[2] The use of diuretics increases the viscosity of the blood. Steroids alter the coagulation state by increasing factor VIII and other serum proteins, and by decreasing the fibrinolytic activity. Cameron et al.[3] recommended that steroid therapy should be replaced by cyclophosphamide therapy.

Table 2[4–8] summarizes the reported cases of lower extremity arterial thrombosis in adult patients with nephrotic syndrome. The findings clearly reflect the poor outcome. Three cases culminated in an amputation of the leg and two of these three also sustained recurrent thrombosis. Patel et al.[5] reported a case of recurrent thrombosis 9 h after thrombectomy. Tarry et al.[9] reported recurrent thrombosis of the brachial artery on postoperative day 1. Kioka et al.[10] reported a patient who experienced three episodes of arterial thrombosis. Anticoagulation therapy is essential to prevent thrombosis, to improve the outcome, and to prevent progressive glomerular mesangial fibrosis. Though Nitatori et al.[6] recommend long-term heparin therapy, heparin may be ineffective for the treatment of antithrombin III deficiency in nephrotic syndrome, because the mechanism of heparin is the enhancement of the antithrombin III activity. However, the extent of antithrombin III deficiency in nephrosis is usually such that substantial heparin resistance is not encountered.

Therefore, if extremely low levels of antithrombin III are documented, operative treatment should be accompanied by the administration of antithrombin III so that adequate anticoagulation can be achieved with heparin. It is also necessary to closely monitor the occurrence and recurrence of thrombosis when steroids are administered because steroids tend to worsen the preexisting tendency of the blood to coagulate.

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