Case Report

Arterial Occlusion in Nephrotic Syndrome: Report of Four Cases in Siriraj Hospital

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Venous thrombosis is commonly found in nephrotic syndrome, but arterial occlusion is never report in Thailand. Four cases with cerebral and femoral arteries occlusion were demonstrated. The early diagnosis and appropriate intervention can improve outcomes, reduce mortality and morbidity significantly.

Keywords: *Nephrotic syndrome, Arterial occlusive diseases*

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Thromboembolic complications in nephrotic syndrome have long been recognized as squealae of hypercoagulable state and increased incidence to venous thrombosis. In this condition, arterial thrombosis has been infrequently reported. Even in Thailand, such condition would not frequently found. We collected four cases of nephrotic syndrome that had thromboembolic complication and were treated in Siriraj Hospital. Review literature including the prevalence, aetiology, and therapeutic considerations were also reported.

All of the patients' data were approved by Ethics Committee, Faculty of Medicine Siriraj hospital, Mahidol University.

Case Report

Case 1

A 28-year old man with nephrotic syndrome for 9 years. He was given prednisolone and cyclophosphamide. His symptom remitted and relapsed after drug withdrawal. One week prior to the admission, he developed right leg pain and cyanosis in right big toe. The physical examination revealed temperature of 37°C, pulse rate of 96 beats per minute and blood pressure of 160/100 mmHg. Other were unremarkable. His right leg was swollen with cold skin. Delay of capillary refill in right leg and the absence of right superficial, femoral, popliteal, posterior tibial and dorsalis pedes pulse were noted. The results of the urine and blood chemistry were shown in Table 1.

The Doppler ultrasound revealed no flow to right superficial femoral, popliteal, posterior tibial and dorsalis pedes arteries. Computerized tomographic angiography showed total occlusion at the proximal to mid part of the right superficial femoral artery with reconstitution at mid-part of the right superficial femoral artery and total occlusion at distal part of the right popliteal artery with reconstitutions at right anterior tibial, peroneal artery. Faint filling of contrast only accumulated at proximal part of anterior tibial, posterior tibial, peroneal artery without opacification of the rest of these three branches (Fig. 1, 2).

Unfractionated heparin intravenous intralesional infusion with recombinant human tissue-type plasminogen activator was given. The angiographic finding after the procedure showed the residual clot in femoral artery (Fig. 3, 4). The surgical angioplasty was done for femoral revascularization. After successful angioplasty, the physician gave him oral anticoagulant drug and perdnisolone 40 mg/day. The patient improved.

Case 2

A 28-year old man with idiopathic nephrotic syndrome for 4 years. He responded well with prednisolone alone and he was lost to follow-up. He

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sometimes bought diuretic to relieve his leg edema. Two weeks prior to the admission, he developed numbness in his left hand but it returned to normal after 2 days. Nine hours before admission, he had severe headache and horizontal diplopia. His left hand was painful and all fingers were cyanosed which progressed to upper arm. He had a history of heavy smoking and was also an alcohol consumer. On physical examination, his temperature was 37°C, pulse rate of 96 beats per minute, blood pressure of 160/100 mmHg. He was conscious, with normal standing and gait. Eyes examination showed limitation of lateral gaze. He could not move his left arm and leg voluntary. The deep tendon reflex was also absent in left side. Laboratory values are shown in Table 2.

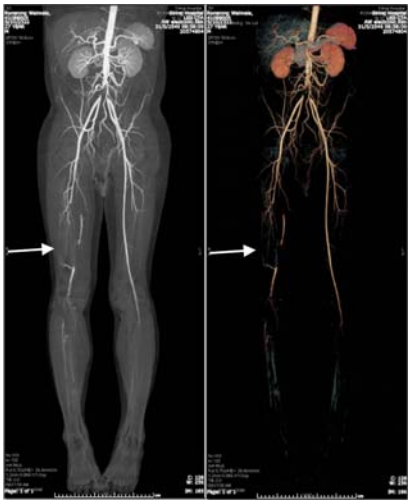
Computerized tomographic angiography showed no intracerebral hemorrhage, but suspected hypodensity area at right pon compatible with small pontine infarction was noted. The nature of this might be thrombosis.

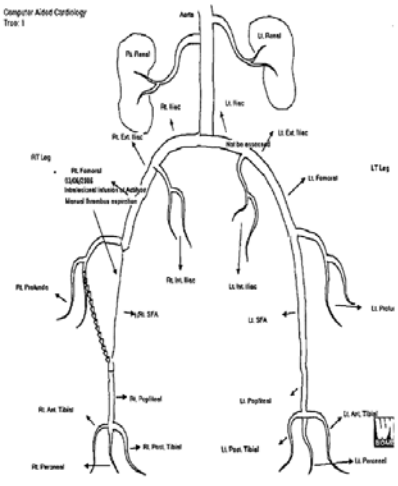
Table 1. The laboratory data of the patient, case 1

Blood chemistry	BUN 17 mg/dl, Cr 0.9 mg/dl, Chol 365 mg/dl, TG 208 mg/dl
LFT	TB 0.2 mg/dl, DB 0 mg/dl, SGOT 28 U/L, SGPT 3 U/L, ALP 93 U/L, GGT 55 U/L, Alb 1.1 g/dl, Glob 3.6 g/dl
Coagulation	Protein C > 125% , Protein S 99.0%, Antithrombin III 70.2%, PT 12 s, aPTT 27.3 s
Urinalysis	pH 6.0, sp.gr. 1.020, Albumin 4+, Sugar negative, WBC 0-1 /HP, RBC 0-1 /HP
24 hrs urine protein	5.96 g

Table 2. The laboratory data of the patient, case 2

Blood chemistry	BUN 12 mg/dl, Cr 0.7 mg/dl, Chol 897 mg/dl, TG 153 mg/dl
LFT	TB 0.2 mg/dl, DB 0 mg/dl, SGOT 28 U/L, SGPT 3 U/L, ALP 93 U/L, GGT 55 U/L, Alb 1.1 g/dl, Glob 3.6 g/dl
Coagulation	PT 11.3 s, aPTT 28 s, Protein C > 125% , Protein S 94%, Antithrombin III 46.4%, Lupus anticoagulant 1: 48.8 S, Lupus anticoagulant 2: 34.4 S
Urinalysis	pH 6.0, sp.gr. 1.020, Albumin 3+, Sugar negative, WBC 0-1 /HP, RBC 10-20 /HP
24 hrs urine protein	15.83 g/d





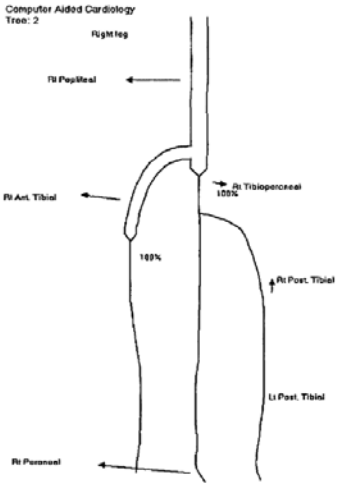


Fig. 1 Fig. 2 Fig. 3 Fig. 4

Fig. 1-4 The provisional diagnosis was acute right femoral arterial occlusion

Table 3. The laboratory data of the patient, case 3

Blood chemistry	BUN 13 mg/dl, Cr 0.6 mg/dl, Chol 588 mg/dl, TG 252 mg/dl
LFT	TB 0.1 mg/dl, DB 0 mg/dl, SGOT 39 U/L, SGPT 22 U/L, ALP 105 U/L, GGT 35 U/L, Alb 1.5 g/dl, Glob 2.8 g/dl
Coagulation	PT 13.5 s, aPTT 27.8 sProtein C > 125 , Protein S 83, Antithrombin III 40.1LA1: 48.8, mixing LA1: 43.1, LA2: 34.4
Urinalysis	pH 6.0, sp.gr. 1.020, Albumin 3+, Sugar negative, Acetone negative, occult blood negative, Leukocyte negative, WBC 0-1 /HP, RBC 0-1 /HP
24 hrs. urine protein	17.58 g/day

Transbrachial embolectomy and intra-arterial thrombolysis with streptokinase (75,000 units via the ulnar artery and 75,000 u via radial artery) was performed. The operative finding was axillary arterial clot and suspected thrombosis at left palmar arch. The physician gave him oral anticoagulant drug and prednisolone 40 mg/day. He improved after admission for 2 weeks.

Case 3

A 34-year-old man was admitted because of left hemiparesis lasting 3 hours. One week prior, he noticed in his edema legs. Three hours before admission, he had headache, left hemiparesis and was unable to speak. He had a history of five pack years of cigarette smoking and drank 3 bottles of beer 3-4 times a week for 14 years. The body temperature was 37°C, the pulse was 80 per minute and BP of 160/100 mmHg. He had generalized edema and left sided hemiparesis. The deep tendon reflexes were absent on the left side. The laboratory values were shown in Table 3.

Computerized tomography showed hyperdensity of left internal carotid artery, left anterior cerebral artery, middle cerebral artery with demonstrable large wedge shape hypodensity area at the left fronto-temperoparietal area compatible with left anterior cerebral artery and middle cerebral artery occlusion. Left cerebral hemisphere was swelling and there was minimal midline shift to right, compatible with left internal carotid artery occlusion (Fig. 5).

Case 4

A 61-year-old man was admitted to the hospital because of a non-healing ulcer on the both legs for two months. Four months before admission, the patient was diagnosed with left femeropopliteal artery occlusion and underwent femeropopliteal bypass with warfarin 1.5 mg/day two months before, leg ulcers developed and did not respond to the treatment. He had history of intermittent leg edema and nocturia for 1 year. He did not smoke but was a social drinker. The family history was unremarkable for any acute or chronic medical problems.

General examination showed no abnormalities. The temperature was 37□C, the pulse was 86 beats per minute, and the respiratory rate was 18 breaths per minute. Blood pressure was 160/100 mmHg. On neurological examination, the patient's mental status, stance, and gait were normal. From the extremities exam, there were pitting edema both legs, cold skin and delayed capillary refill in both legs and decreased in superficial femoral, popliteal, posterior tibial and dorsalis pedes pulses. Laboratory values are shown in Table 4.

He was diagnosted of nephrotic syndrome and a renal biopsy revealed evidence of IgA nephropathy. The patient was treated with anticoagulant drug and debridement.

From the patients' data, the conclusion was shown in Table 5-7.

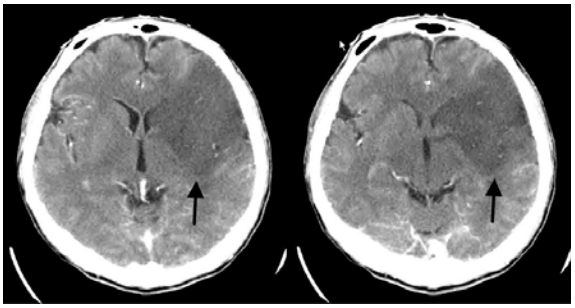


Fig. 5 Echocardiogram showed good left ventricular function, no significant valvular lesion, no intracardiac shunt and no intracadiac clot. After investigation, the diagnosis was nephrotic syndrome and a renal biopsy revealed evidence of IgM nephropathy. The physician gave him oral anticoagulant drug and prednisolone 60 mg/day. After that the patient was improved

Table 4. The laboratory data of the patient, case 4

Blood chemistry	BUN 22 mg/dl, Cr 1.4 mg/dl, Chol 236 mg/dl, TG 93 mg/dl, HDL 63 mg/dl
LFT	TB 0.4 mg/dl, DB 0.1 mg/dl, SGOT 28 U/L, SGPT 40 U/L, ALP 80 U/L, GGT 39 U/L, Alb 2.0 g/dl, Glob 3.9 g/dl
Urinalysis	pH 5.0, sp.gr. 1.015, Albumin 2+, Sugar negative, Acetone negative, occult blood negative, Leukocyte negative, WBC 2-3 /HP, RBC 0-1 /HP
24 hrs urine protein	14.36 g/day

Table 5. Baseline of the patients' characteristics and complications

Case	Age (years)	Sex	BP (mmHg)	Renal biopsy	Complication
1	28	M	160/100	IgMN	Femoral artery thrombosis
2	28	M	160/100	Not done	Axillary artery thrombosis Pontine infarction
3	34	M	160/90	IgMN	Internal carotid artery thrombosis
4	61	M	160/90	IgAN	Femoral artery thrombosis

Table 6. Laboratory data of the patients

Case	Hb/Hct ($^{12\text{-}18\ g/dl}/_{37\text{-}52\%}$)	Platelet/serum$_{a/b}$ ($^{150\text{-}440\ x10\ 3/ul}/_{3.5\text{-}5.5\ g/dl}$)	Serum$_{cho/TG}$ ($^{100\text{-}200\ mg/dl}/_{50\text{-}200\ mg/dl}$)	Serum$_{LDL/HDL}$ ($^{70\text{-}160\ mg/dl}/_{35\text{-}100\ mg/dl}$)	24 hr urine protein (g/day)
1	14.4/42.6	340/3.6	721/344	604.2/48	5.96
2	14.3/42.3	309/3.6	393/72	314.6/64	15.83
3	17.2/49.7	253/2.8	588/252	468.6/69	17.58
4	14.3/43.2	241/3.9	104/89	No data	14.36

Table 7. Laboratory of the patients

Case	Anticardiothropin IgG (< 6.5 GPI/ml)	Protein C (72-146%)	Protein S (64-129%)	Antithrombin III (70-125%)	PT/aPTT (S)
1	No data	125	99	70.2	12/27.3
2	0.82	125	94	46.4	11.3/28
3	0.01	125	83	40.1	13.5/28.7
4	6.61	No data	No data	No data	no data

Discussion

Four cases of nephrotic syndrome with thromboembolic phenomenon in various organs were reported. According to these patients several similar aspects such as these complications developed within the active nephrotic period. All patients had high BP. The level of protein C and protein S was normal (different from previous reports). Only low antithrombin III levels were similar to previous reports. Regarding to the former conditions these blood tests, including ANA, Anti-dsDNA, Anticardiolipin IgG and ANCA, they showed unremarkable result.

Thromboembolic complications in nephrotic syndrome

Nephrotic syndrome itself can alter the turnover and concentration of plasma protein which eventually affect normal hemostasis. Subsequently, prior reports of thromboembolic complications in multiple organs of nephrotic syndrome patients were

announced. The causes of thromboembolic complications in patients with nephrotic syndrome were believed to be of hypercoagulable state. In addition, declining of coagulation factors was also found in nephrotic syndrome patients.

During 1964-1967, 8 cases[4-6] of nephrotic syndrome that developed pulmonary artery thrombosis were collected. None of them had prior congenital or acquired cardiovascular disease. Three cases[7,8] of femoral artery thrombosis occurred after femoral venipuncture; from this data a resume could be made that indicated such procedure could actuate thrombosis in patients with nephrotic syndrome who had pre-existing risk factors. On the other hand, the data in adult patients was still obscured although higher incidence of thrombosis was found on adult patients. Frequent sites of thrombosis were summarized in Table 8.

Coagulation abnormalities in nephrotic syndrome

A number of reports have been published about a lower level of factor XII in nephrotic syndrome, supposing from impaired production, increased destruction of factor XII, or from extravascular distribution. Notwithstanding, this is no research about the synthetic rate and extra vascular distribution of factor XII, for factor IX, the lower level of factor IX was a consequence of urinary loss. Moreover, factor IX deficiency would occur when the level of proteinuria was more than 15 grams per day. However, these patients often had a factor IX level more than 10% and no spontaneous bleeding was observed.

Multiple researches[10,21] have shown higher level of factor VIII in nephrotic syndrome patients. This is believed to be the increased production by the endothelial cells and from the reduction of intravascular distribution. Higher level of factor VIII could shorten the partial thromboplastin time (PTT) which might obscure the lessening of other coagulation level factors tested by the PTT.

Most of nephrotic syndrome patients had higher factor V procoagulant level. Kanfer et al reported patients with factor V level more than 100%. There was no correlation between factor V level and hypoalbuminemia or hyperlipidemia. The higher level of factor V is believed to be caused by the increased production accompanied with the deterioration in intravascular distribution[10,21,22].

Antithrombin III

Antithrombin III is the main inhibitor against thrombin, moreover it inhibits factor IXa, Xa, XIa and plasmin. Kauffman et al[23] reported acquired antithrombin III deficiency in patients with nephrotic syndrome. This deficiency is often accompanied by a serum albumin level less than 2 g/dl. In addition, the severity of antithrombin III deficiency is relevant to the occurrence of thromboembolic complication in such patients.

Alterations in coagulation inhibitors

The incidence of thromboembolic complications will be increased when the level of AT-III is less than 75% of normal range. Alpha-1 antitrypsin has no clinical significance. Alpha-2 macroglobulins inhibit only thrombin. Kauffman et al[23] measured the level of AT in patients with proteinuria and they found the correlation between AT-III concentration and the urine

Table 8. Frequent sites of thrombosis

Mesenteric artery	Egli et al, 1974, Kandall et al, 1971, Miller et al, 1969
Axillary artery	Andrassy et al, 1980
Femoral artery	Cameron et al, 1971, Egli et al, 1974, Goldbloom et al, 1967, Harrison et al, 1972, Kanfer et al, 1970, Miller et al, 1969, Mukherjee et al, 1970, Parrish et al, 1976
Ophthalmic artery	Kanfer et al, 1970
Carotid artery	Egli et al, 1974
Cerebral artery	Andrassy et al, 1980, Calcagno et al, 1961, Egli et al, 1974, Harrison et al, 1972, Kandall et al, 1971, Mukherjee et al, 1970,
Renal artery	Canavase et al, 1982, Mukherjee et al, 1970, Temes et al, 1979
Pulmonary aretry	Egli et al, 1974, Girardet et al, 1969, Gootman et al, 1964., Habib et al, 1968, Kanfer et al, 1970, Levin et al, 1967, Lieberman et al, 1968, Rosenkranz et al, 1967, Symchych et al, 1965, Van et al, 1968
Coronary artery	Alexander et al, 1974, Andrassy et al, 1980, Berlyne et al, 1969, Curry et al, 1977, Parrish et al, 1976

protein excretion. Not only is antithrombin of small molecular-size, but it also has a high renal clearance rate. In cases with proteinuria less than 10g/24 hours, the level of AT-III will be below 85%. Even in the cases with proteinuria less than10g/24 hours, the level of AT-III will also diminish. When the kidney function was impaired, the level of AT-III would be rapidly decreased from urinary loss. But at that time, the synthesis of AT-III by the liver would not be accelerated[16]. The level of AT-III would be raised after the treatment with corticosteroid. The function of protein C is to inactivate procoagulant factors (factor V and factor VIII). Protein C has a high inhibitory effect on those procoagulant factors. Protein C is an important anti-thrombotic regulatory molecule. Generally the level of protein C below 50% can eventually induce thrombosis. Protein S is an anti-thrombotic regulatory molecule which requires protein C in its function. Impaired anticoagulant activity of protein S can also lead to thrombosis.

Alterations in platelet function and components of platelet reaction in thrombogenesis

Bang et al reported several factors that affected platelet function which were degree of proteinuria, plasma fibrinogen concentration, and serum albumin concentration. Accelerated rate of ADP and collagen-induced platelet aggregation in nephrotic syndrome has also been shown in the study from Bang et al[25]. They concluded that in nephrotic syndrome caused losing antagonists to platelet aggregation by urinary loss. Remuzzi et al[27] investigated the serum albumin level in patients with nephrotic syndrome and showed an increasing rate of platelet aggregation corresponding to the lower albumin level when arachidonic acid was added. Besides arachidonic acid, ADP also had the same effect.

Alterations in the fibrinolytic system

There were several reports supporting the impairment of the fibrinolytic system associating with thrombosis. The plasma level of plasminogen and antiplasmin activity (alpha-1 antitrypsin) in nephrotic syndrome has been basically decreased. This finding is related to the lower level of serum albumin and the extent of proteinuria in these patients. The fifth inhibitor in fibrinolytic system has subsequently been discovered which named alpha-2 antiplasmin. Du et al[28] has shown the increased level of alpha-2 antiplasmin in nephrotic syndrome, and they concluded the higher level of alpha-2 antiplasmin might aggravate the risk of developing thrombosis. Treatment in nephrotic syndrome with thromboembolic complication includes diuretics, corticosteroid, anticoagulant and antiplatelets.

Conclusion

Thromboembolic complications in nephrotic syndrome are commonly found in various sites. However, there was arterial occlusion in these patients which, although rare, early detection and proper management, could reduce morbidity and mortality. Surgical intervention must also be considered in order to improve outcomes.

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รายงานผู้ป่วยกลุ่มอาการเนโฟรติคที่มีหลอดเลือดแดงอุดตัน และทบทวนวรรณกรรมที่เกี่ยวข้อง

ธนกร ลักษณ์สมยา, ทวี ชาญชัยรุจิรา, บุณยฤทธิ์ ชื่นสุชน, ไพศาล ปาริชาติกานนท์, ลีนา องอาจยุทธ

พบหลอดเลือดดำอุดตัน ในผู้ป่วยกลุ่มอาการเนโฟรติคได้บ่อย แต่หลอดเลือดแดงอุดตันในผู้ป่วยกลุ่มนี้ยังไม่เคยมีรายงานในประเทศไทย ผู้นิพนธ์ได้รายงานผู้ป่วย 4 รายที่มีหลอดเลือดแดงอุดตันที่สมอง และที่ขา ซึ่งทั้ง 4 ราย เกิดภาวะแทรกซ้อนในขณะที่อาการเนโฟรติคกำเริบรุนแรง หลังการรักษาโดยวิธีผ่าตัด และให้ยากันเลือดแข็ง ผู้ป่วยทั้ง 4 รายมีอาการดีขึ้น แพทย์ควรคิดถึงภาวะนี้ในผู้ป่วยที่เป็นเนโฟรติค การวินิจฉัยที่ถูกต้องจะช่วยป้องกันมิให้ผู้ป่วยเกิดความพิการตามมาได้