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Arterial Thrombosis Associated with Nephrotic Syndrome

— A Case Report and review (Adult cases in the English literature) —

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The thromboembolic complications of nephrotic syndrome are reasonably common, including spontaneous peripheral venous and/or arterial, pulmonary arterial, and renal venous occlusions. However, in comparison to the relatively high incidence of the venous thromboembolic complications with hypercoagulable status, arterial thromboses have been reported much less and it was only 20 cases in the English literature so far. Furthermore, the most cases were pediatric patients rather than adults. Therefore, this report describes an adult nephrotic cases complicated by superior mesenteric artery thrombosis leading to death via catastrophic hospital course. Also, we reviewed the literature in English regarding cases of arterial thromboses in adult nephrotic patients with special interest to locations of thrombosis, underlyig histopathologic types of glomerulopathy, and use of steroids or diuretics before its development.

Key Words: *Arterial thromboses, Nephrotic syndrome, Adult, Mesenteric artery.*

INTRODUCTION

Thromboembolic phenomena due to hypercoagulability has been well known as one of the most serious complications in patients with nephrotic syndrome for over a century following the first mention by Addis in 1948, though exact pathogenesis as yet remains unclear. Venous thromboembolic complications, especially renal vein thromboses of a notable high incidence ranging from 8.5% to 44% on recent retrospective and prospective studies in nephrotic syndrome with hypercoagulable state (Kanfer et al., 1970, Kendall et al., 1971, Kauffman et al., 1978, Llach et al., 1980) have been well reported. Among various underlying renal histologies in the nephrotic patients with renal vein thrombosis, membranous nephropathy has been reported to have the highest incidence (7% to 62%) (Llach, 1983). However, the arterial thromboses reported in the literature in nephrotic syndrome were scattered, reported mainly in pediatric patients (Egli et al., 1974) and revealed that coronary, aortic, renal and femoral arteries were involved more than any other peripheral arteries including mesenteric arteries (Berlyne et al., 1969, Curry et al., 1977, Sullivan et al., 1983). We report a relatively rare case of superior mesenteric artery thrombosis at the proximal portion from the abdominal aorta in a 61-year-old man with a history of nephrotic syndrome due to to primary membranous glomerulopathy who was treated with steroids and diuretics for two months prior to the development of this serious complication leading to extensive resection of the small bowel and unfortunately to death. A review of cases of arterial thrombosis in adults associated with nephrotic syndrome published in English follows in this paper.

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CASE REPORT

A 61-year-old man had been diagnosed with nephrotic syndrome in June, 1991, and primary membranous nephropathy had been established by percutaneous renal biopsy. Thereafter, he had been treated with furosemide 40 to 80 mg/day, and pred-

nisolone 125mg, every other day. Two months later, in middle of August, 1991, he was hospitalized for sudden onset of severe colicky upper, but later diffuse abdominal pain accompanied by nausea, vomiting and diarrhea. On gross appearance, he was acutely ill with anasarca and pitting edema 2-3 (+) on both upper and lower extremities. Blood pressure was 110/70 mmHg, pulse 120/min, respiratory rate 30/min and temperature 38°C. Cardiac examination showed tachycardia (120/min) without murmur. Echocardiogram performed urgently didn't show any vegetation on the valves, mural thrombi or septal defects. Abdomen was distended, diffusely tender and hypoactive. About 30 ml of nonclotted blood was obtained on abdominal paracentesis, and analysis of it revealed many red blood cells, white blood cells with 350/cu mm and no bacteria. Peripheral arterial pulses including femoral and popliteal arteries were palpable. Other laboratory data showed a white blood cell count of 24,000/cu mm and hematocrit of 32%. The serum sodium level was 132 mEq/L, potassium 4.7 mEq/L, blood urea nitrogen (BUN) 23 mg/dL, serum creatinine 1.0 mg/dL, total serum protein 3.3 gm/dL with albumin 1.6 gm/dL and urine protein over 500 mg%. EKG, PT/PTT, chest and simple abdominal x-ray films were unremarkable.

Under the impression of panperitonitis, an exploratory laparotomy was performed on the same day of admission, and after opening the peritoneum, this showed an immotile purplish black whole small bowel (Fig. 1) with about 1000 ml of serosanguinous fluid in the peritoneal cavity. Pulsation of the superior mesenteric artery was not detected. There was a hard mass at the root of it from the abdominal aorta (Fig. 2). A large amount of thrombus was extracted with a Forgaty catheter, and good distal arterial flow was reestablished. Pathologic examination confirmed an organizing fibrin thrombus (Fig. 3). Following operation, albumin with furosemide, broad spectrum antibiotics and systemic heparinization were administered. 24 hrs later, the second-look operation revealed necrosis of the extensive small bowel which was resected in end to end fashion with the viable remaining healthy segment. This was complicated with oliguric acute renal failure and pulmonary edema leading to death on the fourth day of admission.

REVIEW

21 cases of arterial thrombosis including this case report in nephrotic adult patients (Table 1) have been reported in the English literature. Male patients were predominant with a sex ratio of almost 10:1 male:female (19 men, 2 women). The mean age was 39±16

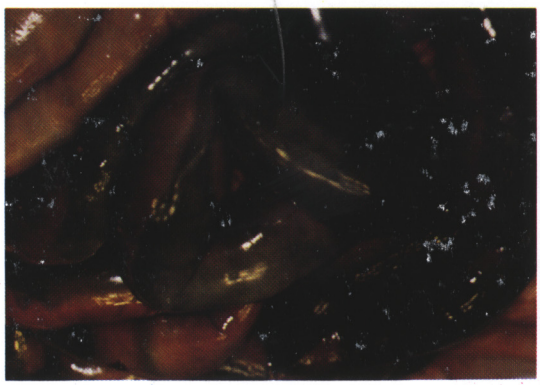

Fig. 1. Exploratory laparotomy on the first day of admission showing an immotile purplish black small bowel due to acute occlusion of the proximal superior mesenteric artery.

Fig. 2. Discoloured appearance of the proximal part of the superior mesenteric artery (black arrows) due to occlusion in exploratory lapartotomy on the first day of admission.

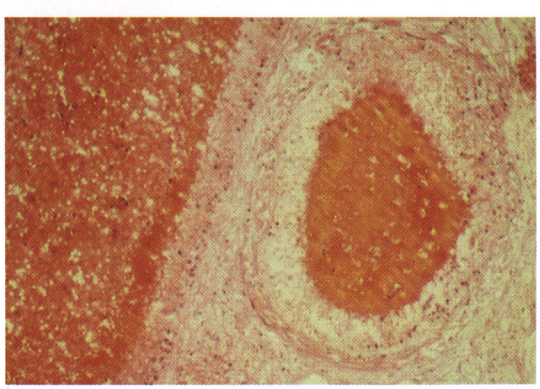

Fig. 3. Section demonstrating an organizing thrombus in the superior mesenteric artery without inflammatory changes. (Hematoxylin-eosin; magnification ×200)

Table 1. Arterial thromboses in adults with nephrotic syndrome in the English literature.

Case	Age/Sex	Renal dis*	Site	Serum albumin (gm/dL)	Tx** (S/D)	Outcome	Reference
1	47M	MNS	Renal		D		Laforet
2	59M	BNS	Renal		D		Laforet
3	73M	MCD	Aortic	0.5	S/D		Gubbay et al
4	39M	Unknown	Renal	3.0	S/D		Berlyne et al
5	34M	FSG	Aortic, iliac femoral		D		Patel et al
6	19M	MGN	Coronary, carotid innominate, aortic renal, subclavian, popliteal	1.4	S/D		Goodwin et al
7	24M	MPGN	Femoral	1.5	S		Mukherjee et al
8	28F	MPGN	Renal		S		Mukherjee et al
9	37M	MGN	Ophthalmic				Kanfer et al
10	55M	MGN	Coronary, cerebral renal, mesenteric	1.2	S/D	died	Kendall et al
11	44M	MCD	Mesenteric	1.2	S	died	Kendall et al
12	26M	FSG	Subclavian, vertebral	1.5	S/D		Menon et al
13	25F	Unknown	Iliac	0.8	S/D		Menon et al
14	70M	Amyloid	Aortic		None		Kauffmann et al
15	29M	MCD	Subclavian, brachial	1.3	S/D	recovered	Sullivan et al
16	40M	MPGN	Femoral	1.5	S/D	recovered	Nitatori et al
17	25M	MPGN	Femoral	0.92	S/D	recovered	Nitatori et al
18	23M	MCD	Cerebral, femoral	0.7	None	died	Parag et al
19	36M	MPGN	Cerebral	2.4	None	recovered	Marsh et al
20	34M	MGN	Cerebral	2.7	None	recovered	Marsh et al
21	60M	MGN	Mesenteric	1.6	S/D	died	present study

*MNS: malignant nephrosclerosis, BNS: benign nephrosclerosis, MCD: minimal change disease, FSG: focal segmental glomerulosclerosis, MGN: membranous glomerulonephritis, MPGN: membranous proliferative glomerulonephritis.
**Tx: treatment, (S/D): (Steroids/Diuretics).

(±SD) years (range, 19 to 73 years). The locations of the most commonly involved arterial thromboses in sequence were renal (5 pts.), aortic (4), femoral (4), cerebral (3), and mesenteric arteries (3) followed by coronary (2), iliac (2), subclavian (2) and six other peripheral arteries (1). The underlying renal disease was membranous glomerulonephritis in five patients, membranoproliferative glomerulonephritis in five, minimal change disease in four, focal segmental glomerulosclerosis in two, amyloidosis in one, malignant nephrosclerosis in one, benign nephrosclerosis in one and unknown type in two. Based on the fact that the prevalent histopathologic types of adult nephrotic syndrome were reportedly membranous glomerulonephritis (25%), minimal change disease (28%), focal glomerular sclerosis (15%), membranoproliferative glomerulonephritis (12%), and other (20%) (Cameron et al., 1988), this review showed a similar prevalence of underlying histopathologic types between the nephrotic patients with arterial thromboses and general population with adult nephrotic syndrome.

Steroids and diuretics were used in 12 and 13 of 20 patients with arterial thromboses in adult nephrotic patients, respectively. This high prevalence (60 and 65%) with steroids and diuretics treatment among adult nephrotic patients with arterial thromboses would suggest that steroids or diuretics had a possible role as one of the contributable factors, but not as one of the definite causative factors because of the common usage of these medications in the treatment of the nephrotic syndrome.

The mean serum albumin level available in 15 of 21 adult nephrotic patients with arterial thromboses was 1.5±0.7 (±SD) gm/dL (range, 0.5 to 3.0 gm/dL). Twelve out of fifteen patients (80%) had severe hypoalbuminemia less than 2.0 gm/dL.

The outcome data for arterial thromboses with adult

nephrotic syndrome were available in 9 of 21 patients and four of these nine patients died. Notably, three of these four expired patients had mesenteric arterial thrombosis, and this observation would be consistent with a poor prognosis for mesenteric artery occlusion in general (Pierce et al, 1970).

DISCUSSION

The risk of thromboembolic complications in nephrotic syndrome is among the highest encountered in any disease (Llach, 1984). Though a clinical correlation or causal relationship between the hypercoagulability and the subsequent development of thrombosis has not been clearly proven or established, the presence of the hypercoagulable state in the nephrotic syndrome is likely an important factor in the high incidence of thromboembolic complications (Kanfer et al., 1970, Kendall et al., 1971). The hypercoagulable state present in nephrotic syndrome is characterized by low zymogen factors, a marked increase in level of cofactors (Factors V and VIII), an increase in plasma fibrinogen levels, a decrease in the levels of antithrombin III and antiplasmin activity, thrombocytosis, increased platelet aggregation, and an increase in levels of beta-thromboglobulin (Llach, 1985). At present, the validity of equating high levels of circulating procoagulants with hypercoagulability is in doubt. A more convincing relationship between low antithrombin III levels and thrombosis has been demonstrated in reports which showed serum antithrombin III levels below 70% of normal in eight of the nine patients with thrombosis (Kauffman et al., 1978) and a significant negative correlation between serum antithrombin III levels and the urine protein excretion as well as a significant positive correlation between serum levels of antithrombin III and albumin (Lau et al., 1980).

Besides the above described reasons in favor of hypercoagulable state in nephrotic syndrome, the commonly used steroids or diuretics, such as thiazides or furosemide, for the treatment of nephrotic syndrome may contribute to the thrombotic diathesis of the nephrotic syndrome. Corticosteroid-induced increases of factor VIII and other serum proteins (Ozsolyu et al., 1962), or decreased fibrinolytic activity with incomplete breakdown of the thrombus (Lieberman et al., 1968) may account for the hypercoagulable state. Diuretics would favor the development of thrombotic complications with their volume-depleting effects leading to hemoconcentration. Various other conditions associated with nephrotic syndrome, including plasma lipid abnormalities (Kendall et al., 1971), hypovolemia with hypoalbuminemia, hypertension, circulating immune complexes (Ooi et al., 1978) and susceptibility to infections, have been considered as contributable factors for hypercoagulable state in nephrotic syndrome. In our patient with membranous glomerulonephritis and nephrotic syndrome, disorders of blood coagulation factors were not assessed, but severe hypoalbuminemia (1.6 gm/dL) and usage of steroids and furosemide was noted. Also, in the review of arterial thromboses, a severe degree of hypoalbuminemia and treatment with steroids and/or furosemide in mode than half of the cases were shown.

Since the first report of arterial thrombosis by Fishberg, 1954, it has been observed mainly in nephrotic children with the prevalent site of the femoral artery attributed mainly to femoral venifunctures (Goldbloom et al., 1967., Lau SO et al, 1980). This review of 21 cases of arterial thromboses showed renal, aortic and mesenteric arteries besides the femoral artery as commonly involved arterial vessels and didn't revel any relationship between femoral artery thrombosis and trauma by femoral punctures. Though the number of cases with descriptions of the outcomes in this review are very few, the mortality rate of arterial thromboses seemed to be high, especially with mesenteric thrombosis as in our catastrophic case report. In conclusion, though the incidence of arterial thrombosis in adult nephrotic syndrome, and the exact underlying mechanisms of the hypercoagulable state of the nephrotic syndrome remain unclear, adult nephrotic patients, especially, with severe hypoalbuminemia and on diuretics or steroid treatment should be considered for the possible serious complication of arterial thrombosis other than venous thrombosis, such as renal vein thrombosis, as thromboembolic complications of nephrotic syndrome and treated more aggressively for better results.

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