ARTERIAL THROMBOSIS IN NEPHROTIC SYNDROME

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SYNOPSIS

This paper describes two nephrotic patients with arterial thrombosis and reviews the literature on the subject.

INTRODUCTION

A hypercoagulable state occurs in nephrotic syndrome (NS) and may manifest as arterial or venous thrombosis in nephrotic patients (Kendall et al, 1971). Thrombosis in a number of major vessels has been reported. We include two patients with arterial occlusions in previously unreported sites and review the literature on arterial thrombosis in nephrotic syndrome.

Case 1

A 26 year old Indian male motor mechanic was investigated for ankle swelling and proteinuria. He had pedal oedema and the blood pressure was 130/80 mmHg. Haemoglobin was 17.0 gm/100 ml, haematocrit 51%. ASO titre was 100 Todd units, L.E. cells were negative three times. Serum albumin was 1.5 gm/100 ml and globulin 2.6 gm/100 ml. 24 hour urinary protein was 6.0 gm. Cholesterol was 430 mg/100 ml, serum creatinine 1.0 mg/100 ml, urea 10.0 mg/100 ml. Intravenous urogram was normal. Renal biopsy showed focal hyalinosis in 2 out of 13 glomeruli. He was given diuretics. Prednisolone was added later. At this time he noticed numbness and weakness of the left hand and forearms. These symptoms were aggravated by activity and relieved by resting the arm. There was no history of trauma. Three weeks later he began having cramping central abdominal pain which started towards the end of his meals and was associated with vomiting and loose stools. He returned to our care at this stage. The left hand was cool, the fingers had a cyanotic tinge and a few splinter haemorrhages. Pain and tactile sensations were blunted and the pulse was only palpable in the subclavian artery. The abdomen was soft but

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TABLE I—Arterial Thrombosis in Nephrotic Syndrome

Authors	No. of patients	Age (yrs) Sex	Site(s) of arterial lesion(s)	Renal pathology	Duration of NS	Remarks
1. Berlyne et al (1964)	1	7½/F	renal	proliferative GN	5 y	Cholesterol 390 mg%. Albumin 2.8 Gm%. Diuretics, anti-hypertensives and steroids 4 years.
2. Gootman et al (1964)	2	4/M	pulmonary	membranous GN	2½y	Cholesterol 864 mg%. Albumin 1.1 Gm%. Thiazides and steroids.
		5/M	pulmonary	minimal change GN	16 mths	Cholesterol 450 mg%. Albumin 2.7 Gm%. Thiazides and steroids.
3. Symchych et al (1965)	5	3/M	pulmonary	glomerular BM thickening	9 mths	Mercurial diuretics only. No steroid.
		4/F	coronary arteries	"proliferative changes"	1½ y	No steroid.
		6/M	pulmonary	"diffuse BM thickening"	6 mths	Steroids and nitrogen mustard.
		20 mths M	pulmonary	"minimal BM thickening"	4 mths	Steroids, cyclophosphamide and chlorothiazide.
		6½/M	pulmonary mesenteric	"focal thickening of BM with focal hyalinisation"	5½ y	Steroids and nitrogen mustard given intermittently for 4½ yrs.
4. Levin et al (1967)	1	3¼ M	pulmonary	minimal change GN	5½ mths	Cholesterol 440 mg%. Ablumin 0.9 Gm%. Steroids for 5 mths.
5. Goldbloom et al (1967)	3	1½/M	femoral	—	—	Steroids } lesions followed
		1¼/F	femoral	"chronic GN"	—	Steroids } femoral venepuncture
		16 mths	femoral	—	2 weeks	Steroids for 10 days } in all three.
6. Virabhak (1967)	1	3/F	aorta	—	7 y	Cholesterol 315-520 mg%. Albumin 3.47-0.8 Gm%. Steroids for 7 yrs. Thrombosis followed a fall, landing on buttocks.
7. Berlyn et al (1969)	5	30/M	coronary artery disease	focal proliferative GN	3 y	Cholesterol 530 mg%. Steroids given.
		37/M		membranous GN	7 mths	Cholesterol 600 mg%. Steroids 2 yrs.
		30/M		—	10 mths	Cholesterol 650 mg%.
		41/F		profiferative GN	3 y	Cholesterol 460 mg%.
		37/M		membranous GN	6 y	Cholesterol 340 mg%.

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TABLE I—Arterial Thrombosis in Nephrotic Syndrome—(Cont.)

Authors	No. of patients	Age (yrs) Sex	Site(s) of arterial lesion(s)	Renal pathology	Duration of NS	Remarks
8. Porro et al (1969)	2	35/M	coronary artery	—	1 y	Cholesterol 350-400 mg%. Azathioprine for 1 year.
		37/M	disease	membranous GN	13 mths	Cholesterol 460 mg%. Azathioprine for 13 mths.
9. Mukherjee et al (1970)	2	35/M	coronary	minimal change GN	25 y	Cholesterol 950-1900 mg%. Albumin 2 Gm%.
		24/M	femoral			Steroids for 10 mths.
10. Cameron et al (1971)	1	2½/F	femoral	proliferative GN	4 mths	Cholesterol 350 mg%. Albumin 0.075 Gm%. Steroids for 14 weeks.
11. Kendall et al (1971)	2	55/M	mesenteric coronary & cerebral	minimal change GN	7 mths	Steroids for 7 mths. Thrombosis followed femoral venepuncture.
		44/M	mesenteric	membranous GN	1 y	Cholesterol 195 mg%. Albumin 1.2 Gm%. Given diuretics, azathioprine and steroids for 6 weeks.
12. Harrison et al (1972)	1	3/M	femoral	minimal change	—	Cholesterol 957 mg%. Albumin 1.2 Gm%. Steroids given for 1 week.
13. Alexander et al (1974)	10	range 30—69	4 coronary	mesangial proliferative GN	1 week	Steroids and frusemide for few days. Pressure on leg while sleeping.
			4 coronary & cerebro vascular	—	—	Hyperlipidaemia higher in those with coronary artery disease than in those without. Details of therapy for NS not specified.
			1 coronary & femoral			
			1 cerebrovascular			

y = years
mth = months

M = male
F = female

G N = glomerulonephritis
B M = basement membrane

during the episodes of pain it was guarded and tender and the bowel sounds were also hyperactive. Haemoglobin was 13.4 gm/100 ml, haematocrit 39%, platelet count 399,000/mm,^{3} fibrinogen 480 mg/100 ml and euglobin lysis time was prolonged at 440 mins. The arteriogram showed occlusion beyond the left subclavian artery and irregular filling defects in the subclavian and the left vertebral artery. A plain X-ray of the abdomen showed multiple fluid levels but abdominal aortogram could not be done. He was treated with anticoagulants, gastric suction and intravenous infusion with relief of his abdominal symptoms. Thrombectomy of the axillary artery was unsuccessful and an extensive saphenous vein bypass graft was inserted. No local cause for the thrombosis was found.

Case 2

A 25 year old Malay woman had NS for a year and was treated with prednisolone and diuretics. Three days prior to admission she developed a painful cold right leg. She was given anticoagulants but by the time she was referred to the University Hospital the right leg was gangrenous. There was also bilateral leg oedema, and blood pressure was 120/80 mmHg. Her haemoglobin was 12.1 gm/100 ml, haematocrit 38%, platelet count 121,000/mm,^{3} thrombotest 100%, bleeding time 3 mins 30 secs and clotting time more than 10 mins; albumin 0.8 gm/100 ml, globulin 4.7 gm/100 ml, cholesterol 245 mg/100 ml, 24 hour urinary protein 7.2 gm and urea 44 mg/100 ml. An arteriogram showed occlusion of the right common iliac artery. When consent for operation was finally granted a hind quarter amputation was necessary. She remained toxic, her general condition deteriorated and she died on the eighth hospital day.

COMMENTS

Addis in 1948 noted the increased tendency to venous thrombosis in patients with NS. Later reports drew attention to arterial lesions though these appear less common. The table lists the various sites of arterial occlusions that have been described in patients with NS. There were 45 lesions in 36 patients: 19 had coronary artery involvement, 7 with pulmonary artery lesions, 8 involving the femorals, 6 with cerebrovascular disease, 3 with mesenteric and 1 each with renal and aortic lesions. Our two patients had spontaneous arterial occlusions; the first in the left upper limb (subclavian, axillary and brachial), vertebral and probably the superior mesenteric artery; the second patient had occlusion of the right common iliac artery.

The factors said to contribute to increased thrombosis in NS are abnormal plasma protein concentration, hypovolaemia, hyperlipidaemia, abnormal platelet activity and steroid therapy. Thompson et al (1974) considered the increased coagulability to be due to an increased production of proteins by the liver, while there is continued loss of low molecular weight protein in the urine resulting in increased plasma fibrinogen, factors V and VIII. There is also decreased fibrinolytic activity (Cotton, 1967). As a result of severe hypoalbuminaemia there is hypovolaemia and increased haematocrit resulting in a sluggish circulation which aggravates the hypercoagulability state.

Bang et al (1973) found that plasma from patients with NS caused increased aggregation of platelets from normal persons whereas plasma from normal persons did not. Accelerated atherogenesis related to hyperlipidaemia may further increase the thrombotic tendency and Berlyne et al (1969) considers this the major factor in the increased incidence of coronary artery disease in these patients. Steroid therapy has been shown to increase blood coagulability (Cosgriff et al, 1950) and this effect is further worsened by the presence of hypercholesterolaemia (Aldersberg et al, 1955). Furthermore, patients with NS on steroid therapy have also been found to have accelerated thromboplastin generation time (Mukkerje et al, 1970). There is no evidence that different mechanisms are involved in venous and arterial thrombosis.

In the cases previously described (see table) many patients had hypercholesterolaemia and hypoalbuminaemia. 19 patients were given steroids but the use of diuretics is only mentioned in 7 patients. Details of coagulation studies were not given. However 5 patients also had local causes such as venepuncture (four) and direct pressure (one patient).

In view of the absence of a local cause for the arterial thrombosis in our two patients, the lesions must have resulted from a hypercoagulable state. The first patient had increased fibrinogen, prolonged euglobin lysis time and hypercholesterolaemia. Coagulation studies could not be done in the second patient. Steroid therapy could have contributed to the thrombosis in the second patient but is unlikely to have played a significant role in the first patient as the symp-

toms started at the same time as therapy was started.

We conclude that arterial thrombosis is a significant complication of nephrotic syndrome and it may occur at any site. The underlying pathogenetic factors do not differ from that of venous thrombosis. There is a preponderance of coronary artery thrombosis in those patients with hypercholesterolaemia and femoral artery thrombosis following local trauma. Every effort should be directed at reducing hemoconcentration, repleting the intravascular volume and avoiding trauma. In patients at risk for coronary thrombosis, dietary and possibly drug control of hypercholesterolaemia may be necessary. Finally an increased awareness of incipient thrombosis is essential to avert the disappointing or fatal results as in our two patients.

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