Heavy proteinuria following urinary diversion

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Summary

Two patients are described, both of whom developed heavy glomerular proteinuria in excess of 10 g/24 hr after urinary diversion operations.

KEY WORDS: nephrotic syndrome; urinary diversion; glomerulosclerosis, polycythaemia.

Introduction

The development of heavy glomerular proteinuria may occur in a variety of situations. It is most common in children, where the only pathological change in the glomeruli is observed on electron microscopy, i.e. effacement of the epithelial cell foot processes in minimal change disease. In adults it is usually seen in association with the deposition of immunoreactive material within the glomeruli (the immune complex-mediated glomerulonephropathies), giving rise to the histologically distinct entities of membranous, proliferative and other nephritides. Such lesions usually arise in the absence of known predisposing or precipitating conditions, although identical pathological changes can develop in association with certain microbial infections, following exposure to drugs and toxins, and occasionally may be a non-metastatic manifestation of malignancy (Brenner and Stein, 1982). Glomerulopathy is also observed in the collagen and multisystem diseases such as systemic lupus erythematosus and the Henoch-Schönlein syndrome, and specific pathology may be detected in diabetes mellitus and amyloidosis. Certain familial disorders, e.g. Alport's syndrome, similarly may have unique histological changes in the glomeruli.

Occasional reports have noted the association of the nephrotic syndrome with such conditions as thyroid disease (Weetman *et al.*, 1981) and sarcoidosis (Taylor, Fisher and Hoffbrand, 1982), where the nephropathy is probably immune complex mediated (Mallick, Short and Manos, 1983). The nephrotic syndrome has also been observed in patients with apparently primary haemodynamic abnormalities such as renal artery stenosis (Berlyne, Tavill and

Baker, 1964) and constrictive pericarditis (Pastor and Cahm, 1960). Heavy proteinuria may also appear in subjects with vesico-ureteric reflux (VUR) (Dayan and Smith, 1976). I report here two patients who developed proteinuria of nephrotic proportions after urinary diversion procedures.

Case reports

Case 1

A 24-year-old male taxi driver had been born with a meningocele which was repaired in the neonatal period. The neurological result was perfectly satisfactory save for the development of a neuropathic bladder. This resulted in chronic retention with overflow incontinence, and throughout childhood he suffered from recurrent urinary tract infections which were treated with a variety of antibiotics. In 1972 (at the age of 15 years), intravenous urography revealed bilateral hydronephroses with megaureters, but no bladder neck obstruction. Both ureters were then diverted to form permanent ureterostomies in the right iliac fossa. He was followed up in the medical clinic at 4-6 monthly intervals with impaired, but stable, renal function with a serum creatinine of 150-210 $\mu\text{mol/l}$. Haemoglobin and haematocrit rose steadily from 1977 and raised blood pressure warranted treatment from 1978.

Albuminuria was not detected in uninfected urine pre-operatively, and in 1973 two consecutive 24-hr urine collections revealed less than 300 mg of protein on both occasions. This rose to 1-2 g by 1975 but subsequently disappeared again. In 1979, 7 years post-operation, proteinuria was recorded at 15 g/24 hr, but plasma albumin never fell below 35 g/l. Detailed assessment in 1982 revealed no family history of renal disease, or history of exposure to known glomerulotoxins and no evidence of neoplasia or systemic disease. There were no clinical abnormalities except for previous operation scars and a smooth liver edge palpable 4 cm below the costal margin. Investigations: haemoglobin 17.8 g/dl; haematocrit

56; white cell count $7 \times 10^9/l$; platelets $269 \times 10^9/l$; ESR 1 mm/hr; red cell volume 35 ml/kg (normal 26–33); plasma volume 36 ml/kg (normal 40–50); bone marrow normal; plasma creatinine 206 $\mu\text{mol/l}$; plasma albumin 35 g/l. Proteinuria 7–9 g/24 hr; urine mid-stream specimen no growth; creatinine clearance 40 ml/min; urine electrophoresis marked generalized proteinuria; intravenous urogram (IVU) showed normal sized kidneys but with irregular margins and loss of cortical thickness of the upper poles. The following were normal or negative: plasma calcium, phosphate, alkaline phosphatase, alanine amino transferase, bilirubin, serum IgG, IgA and IgM; serum electrophoresis; ASO titre, LE cells, rheumatoid latex test, antinuclear factor, anti-ds-DNA antibodies, complement profile hepatitis B, antigen (HBsAg) and WR. Fasting lipoprotein profile showed Fredrickson type IV.

Percutaneous right lower pole renal biopsy specimen showed two normal and 12, either partly or totally, sclerosed glomeruli. There was also advanced tubular damage and some interstitial fibrosis and round cell infiltration. Immunofluorescent examinations demonstrated only minor amounts of IgM and C3 in one of the two non-sclerosed glomeruli. Repeated urine cultures have shown intermittent asymptomatic infection on subsequent follow up of this patient, with persisting proteinuria of 4–10 g/24 hr.

Case 2

In 1973, a 40-year-old housewife was investigated for progressive urinary incontinence which had developed following a hysterectomy 3 years earlier. Urine cultures were sterile, WR negative and a fasting blood sugar was normal, as was an IVU and serum creatinine level. Albuminuria was noted pre-operatively on three separate occasions at ++ but was never quantitated and plasma albumin remained at 38 g/l.

Her symptoms persisted and in July of 1974 she had an isolated ileal conduit fashioned and both ureters were diverted to it. One year later she presented with a nephrotic syndrome; progressive oedema up to her thighs, plasma albumin of 19 g/l (6 months earlier it had been 40 g/l) and proteinuria of 23 g/24 hr. No underlying cause was demonstrated, and renal biopsy revealed mild mesangial proliferation and immune complex deposition, with some IgM and C₃ on immunofluorescence, but an unremarkable interstitium. Heavy proteinuria persisted for 18 months with plasma albumin levels of 20–25 g/l and serum creatinine values of 90–120 $\mu\text{mol/l}$. The proteinuria decreased spontaneously to 4–5 g/24 hr, with a concomitant rise in plasma albumin to 38 g/l. She had suffered from recurrent urinary tract infec-

tions with *Proteus* and *Klebsiella* spp. since the ureteric diversion.

Detailed investigations in 1980 revealed no family history of renal disease or history of recent exposure to known glomerulotoxins and there was no clinical or historical evidence of neoplasia or connective tissue disease. Investigations: haemoglobin 16.8 g/dl; haematocrit 50; white cell count and platelets normal; proteinuria 6–8 g/24 hr, urine mid-stream specimen no growth; creatinine clearance 60 ml/min; urine electrophoresis, generalized proteinuria; IVU showed normal kidneys and normal sized diverted ureters. ESR 11 mm/hr; plasma creatinine 110 $\mu\text{mol/l}$; plasma albumin 38 g/l. The following were normal or negative: plasma calcium, phosphate, alkaline phosphatase, bilirubin, serum IgG, IgA and IgM, ASO titre, LE cells, rheumatoid latex test, ANF, anti-ds-DNA antibodies, HBsAg, WR, fasting lipoprotein profile.

A further renal biopsy was performed 18 months later because proteinuria persisted at a level of 4 g/24 hr. It showed seven glomeruli with total or segmental sclerosis in 4 and mesangial expansion in the others with predominantly IgM and C₃ deposited as scattered granules.

Discussion

Both these patients, drawn from a pool of 250 nephrotic, or previously nephrotic, subjects who currently attend the clinic, developed heavy proteinuria following urinary diversion, and both had predominantly sclerosing lesions affecting most of the glomeruli in the biopsy material. The younger subject had little if any evidence of glomerular disease pre-operatively and certainly normal protein excretion rates at least 1 year after operation. The older female patient had proteinuria pre-operatively but this was unlikely to have been very heavy.

The development of glomerulosclerosis and proteinuria in subjects with VUR has recently been reviewed (Cotran, 1982) and the possible pathogenetic mechanisms discussed. Patient 1 did have evidence of bilateral VUR but this was relieved many years before the development of heavy proteinuria. In the second patient, no evidence of VUR was demonstrated in so far as a recent IVU showed no evidence of hydronephrosis, renal scarring or megau-reter. It was not completely excluded however, since a conduitogram has not been performed.

Recently, Brenner, Meyer and Hostetter (1982) have proposed their hyperfiltration hypothesis which suggests that modern man's dietary habits lead to a sustained protein load on the kidney resulting in more permanent, rather than intermittent, changes in intra-renal haemodynamics with outer cortical nephrons being subjected to a greater work load. In

normal kidneys this may have no deleterious effect, but with already diseased organs this could result in further damage, leading possibly to both increased proteinuria and a reduction in functioning nephron mass. In the first patient, a modification of this mechanism could be involved since there was undoubtedly some nephron damage before the development of heavy proteinuria. It is unlikely to account for the proteinuria in the second case since renal function was previously normal.

It is pertinent to consider the origin of the protein in the urine in both these patients, since it is recognized that subjects with nephro-urological abnormalities may develop tubular proteinuria. In both the patients reported here values in excess of 10g/24 hr were noted, which is far greater than the 1-2 g usually associated with tubular damage. More specifically, the electrophoretic patterns of the urine were consistent with glomerular rather than tubular lesions.

It is, of course, possible that heavy glomerular proteinuria developed in these patients quite coincidentally. However, the major feature common to both subjects, apart from the urinary diversion operations, is the presence of urinary tract infection, albeit asymptomatic for much of the time. For the present, the relevance of such infection to the pathogenesis of the glomerular lesions in terms of immune complex mediation must remain speculative.

The other abnormality shared by both patients is their high haematocrit values. Secondary polycythaemia has been reported in a number of renal diseases, including glomerulonephritis, and in Case 1 red cell mass was raised and plasma volume decreased. These values were not determined in Case 2 and no erythropoietin studies were performed on either patient. At the time of investigation neither patient was taking diuretics but both smoked in excess of 30

cigarettes per day. The cause of the erythrocytosis in both subjects remains uncertain.

Although this report concerns only two patients it could prove interesting to determine the incidence of development of heavy proteinuria in patients undergoing urinary diversion procedures. The relationship between such an abnormality and reflux, infection or some other mechanism could then be further explored.

Acknowledgments

I wish to thank Dr N. P. Mallick and Professor A. W. Asscher for assistance and encouragement in the preparation of this report, and Miss T. Wright for secretarial assistance above and beyond the call of duty.

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(Accepted 24 October 1983)