Carcinoma of the oesophagus associated with membranoproliferative glomerulonephritis

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Summary
Nephrotic syndrome has been observed in association with different types of neoplasia. This appears to be the first report of the occurrence of the nephrotic syndrome due to membranoproliferative glomerulonephritis in association with carcinoma of the oesophagus. Although proteinuria was present before excision of the tumour, the nephrotic phase occurred subsequently. Eventually it disappeared leaving the patient with a clear urine and biochemical and histological improvement of the renal lesion (including immunofluorescent and electron microscopy studies). Possible mechanisms responsible for the nephrotic syndrome in this case are discussed.

Introduction
Nephropathy associated with extra-renal neoplasms has been well documented (Lee, Yamauchi and Hopper, 1966; Loughridge and Lewis, 1971; Higgins, Randall and Still, 1974; Eagen and Lewis, 1977). More recently, glomerular lesions associated with renal malignancy have been described (Ozawa et al., 1975; Cosby et al., 1974; Eagen and Lewis, 1977). A variety of morphological glomerular lesions have been associated with tumours. Membranous nephropathy, membranoproliferative glomerulonephritis, and lipoid nephrosis have been identified as the major renal histological pattern in these reports.

The authors report for the first time, the association of carcinoma of the oesophagus and nephrotic syndrome as a result of membranoproliferative glomerulonephritis, which presented following excision of the tumour, and resolved spontaneously. The patient remains well with no evidence of recurrence or metastases, maintaining normal renal function without proteinuria 24 months post-operatively.

Case report
A 59-year-old female was referred from another hospital with a 5-week history of bilateral lower limb oedema. An oesophagectomy had been performed 7 weeks previously for well differentiated squamous carcinoma of the middle third of the oesophagus. Urinalysis revealed 0.14 g protein with RBCs and granular casts at the time of operation.

Physical examination was unremarkable except for bilateral lower limb oedema. Pertinent laboratory investigations included a haemoglobin 12.6 g/dl, Haematocrit 45%, white cell count 7.1 x 10^9/l with a normal differential, serum urea 7 mmol/l, serum creatinine 80 µmol, serum proteins 51 g/l, serum albumin 21 g/l, serum cholesterol 10.36 mmol/l. A 24-hr urine collection demonstrated a total protein excretion of 10-64 g and a creatinine clearance of 1.84 ml/s. Microscopic examination revealed 30 RBCs/HPF with granular and cellular casts. The serum sodium was 136 mmol/l, potassium 4 mmol/l, chloride 94 mmol/l and bicarbonate 26 mmol/l. Serological studies including serum complement and anti-nuclear factor were negative.

A percutaneous renal biopsy was performed and the tissue was examined by light microscopy, immunofluorescent staining and electron microscopy. The first biopsy (Figs 1, 2 and 3) revealed a lesion characteristic of membranoproliferative glomerulonephritis with marked mesangial cell proliferation, mesangial and subendothelial deposits and mesangial interposition to form splits or duplications of the basement membrane. Immunofluorescence showed the presence of granular and...
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Fig. 1. A representative glomerulus from the first biopsy showing a marked increase in mesangial cells and matrix. There is an obvious decrease in capillary loop patency with the presence of subendothelial deposits (†) and mesangial interposition which is seen to better advantage in Fig. 2. (One-μm Epon section stained with Toluidine blue, original mag. × 200).

Fig. 2. Electron micrograph of a glomerular capillary loop showing electron dense deposits (†) on the inner aspect of the basement membrane and in the mesangium. The mesangial cell cytoplasm (M) and mesangial matrix (mm) is seen to extend peripherally for part of the circumference of the capillary to form a characteristic duplication of the basement membrane. (Original mag. × 2500). CL, capillary lumen; MN, mesangial cell nucleus.
aggregated deposits of IgM and complement (C3) on the basement membrane and mesangial deposits of complement. All glomeruli were equally involved.

The patient was treated with high protein, low salt diet and frusemide 40 mg/day for 3 weeks. Three months later she was readmitted for re-evaluation of her renal status. She was on no medication. Physical examination was unremarkable. Laboratory values disclosed the following: serum creatinine 53 µmol/l; urine microscopic examination revealed 5 RBCs/HPF with no casts; 24-hr urinary protein excretion was 1.1 g. Repeat renal biopsy (Fig. 4) revealed marked regression of mesangial cellularity with disappearance ultra-structurally of all evidence of mesangial interposition in the capillary walls. Isolated granular deposits of IgM and complement were present on the basement membrane in 4 of 5 glomeruli. No deposits were seen in the remaining glomerulus.

She remains well 2 years later with no evidence of metastases, and normal renal function without proteinuria.

Discussion
Proteinuria, often of sufficient magnitude to cause the nephrotic syndrome, is a recognized systemic manifestation of neoplastic diseases. Lee et al. (1966) were the first to emphasize the high incidence (11%) of carcinoma in the adult nephrotic population. The frequency of renal disease observed with malignancy suggests that this association is more than mere coincidence.

Nephropathy associated with extra-renal neoplasia has been well documented (Lee et al., 1966; Loughridge and Lewis, 1971; Higgins et al., 1974; Row et al., 1975; Eagen and Lewis, 1977), although reports of glomerular lesion with renal neoplasms are becoming more frequent (Cosby et al., 1974; Ozawa et al., 1975; Eagen and Lewis, 1977).

Various histological glomerular lesions have been described. Membranous nephropathy is the predominant lesion occurring in 70% of cases documented (Eagen et al., 1977). Membrano-proliferative and lipid nephrosis occur with less frequency. Renal vein thrombosis, amyloid and glomerular invasion of tumour must be considered in the aetiology of the paraneoplastic proteinuria. The neoplasms may be solid (Cantrell, 1969; Costanza et al., 1973; Couser et al., 1974; Eagen and Lewis, 1977), occasionally myeloproliferative disorders (Lowry, Munzenrider and Lynch, 1971; Row et al 1975; Eagen and Lewis, 1977), and rarely benign (Cosby et al., 1974).
The aetiology of the glomerular lesion is thought to be immune complex in origin as a result of antibody production to (1) tumour-associated antigens, (2) re-expressed fetal antigens, (3) viral antigens or (4) autologous non-tumour antigens. Evidence supporting this is the presence of circulating immune complexes in various forms of neoplasia (Rossen et al., 1976). Tumour-associated antigens have been found in glomerular deposits of tumour-related nephropathy (Lewis, Loughridge and Phillips, 1971; Couser et al., 1974). Costanza et al. (1973) found a tumour-expressed fetal antigen, and carcinoma embryonic antigen in glomerular immune deposits of a patient with colonic adenocarcinoma. Epstein-Barr virus antibody (Oldstone, 1974) and oncornavirus antigen (Sutherland and Mardiney, 1973) have been found in glomerular deposits. The presence of a high incidence of non-organ-specific antibody suggests the final possibility of auto-immunity against self antigens. The improvement in the subsequent renal biopsy on light microscopy with a marked decrease in immune complexes by immunofluorescence would support the view that immune complexes were the aetiological agents of the lesion in this patient. However, the underlying antigen remains unclear.

Although successful removal of a tumour may result in complete remission of proteinuria (Cantrell, 1969), the survival after clinical recognition of the neoplasia is generally 3 months (Eagen and Lewis, 1977).

The importance of the association between neoplasia and glomerulonephritis is stressed especially in the adult nephrotic patient with an underlying membranous nephropathy in whom early diagnosis and treatment of a neoplasia may result in a better prognosis.

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