# TWO CASES WITH MEMBRANOUS NEPHROPATHY AND MALIGNANCY

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*SUMMARY : The association of malignancy with nephrotic syndrome has been known for years. Membranous nephropathy is the most frequently found condition in carcinomas. We present two cases of membranous glomerulonephritis associated with malignancy.*

***Key Words :** Nephrotic Syndrome, Membranous Glomerulonephritis, Malignancy.*

## INTRODUCTION

The possibility of a relationship between the presence of nephrotic syndrome and malignancy was first described in 1922 by Galloway in a patient with Hodgkin's Disease who developed massive proteinuria. This association was confirmed in 1966 when in a retrospective study Lee et al. found 11 patients with cancer in a group of 101 patients with nephrotic syndrome. In the last twenty years at least 194 cases of malignancy-associated glomerular disease have been described (12). The most frequently found combinations are membranous nephropathy in carcinomas, minimal change nephropathy in Hodgkin's disease and membranoproliferative glomerulopathy in chronic lymphatic leukemia (2, 8, 12).

The development of glomerulopathy in a patient with a malignancy can be considered as a paraneoplastic phenomenon. The incidence is between 3-13 %, with a mean of 7 % for the whole spectrum of glomerulopathies associated with solid tumors, but reaches 22 % in patients over 60 years of age with membranous nephropathy (5, 10, 12). Membranous glomerulonephritis (MG) is the most common glomerular lesion seen in association with carcinomas (2, 4, 5, 10, 12).

The pathogenesis is far from clear, but mechanisms proposed to explain the renal pathologic findings include autologous non-tumor antigens, tumor antigens, fetal antigen expresion; immune complex deposition; viral antigens and disordered T cell function (2, 3, 7, 8, 10, 12, 13).

**CASE 1 :** A 57 year old man was admitted to the hospital with fatigue, weight loss, swelling in extremities for one month. On physical examination; the conjunctivas were pale and bilateral ankle edema was present. The laboratory findings were as follows; Hgb : 7.4 g/dl, Htc : 22.9 %, Erythrocyte sedimentation rate (ESR) : 133 mm/hr, Ferritin : 572 ng/ml (21-453 ng/ml), Blood urea nitrogen (BUN) : 25 mg/dl (7-25 mg/dl), Creatinine : 1.8 mg/dl (0.5-1.5 mg/dl), Total serum protein : 4.2 g/dl (6-8.5 g/dl), Albumin : 1.8 g/dl (3.5-5.5 g/dl), Cholesterol : 221 mg/dl (120-200 mg/dl), Triglyceride : 111 mg/dl (50-170 mg/dl). Urinalysis demonstrated (+++) protein, 2-3 erythrocytes and granular casts. Daily urinary protein excretion was 2.6 gr and the creatinine

clearance (CrCl) was 91 ml/minute. A renal biopsy was performed. Light microscopy of the biopsy showed membranous glomerulonephritis (Fig. 1). In immunofluorescent microscopy, Ig G, A, M were negative. Because of the weight loss (18 kg in two months), severe anemia and high ESR, malignancy was suspected. Investigations revealed adenocarcinoma of sigmoid colon. An operation was performed and the tumor was totally excised. Two months after the operation, the patient was admitted again for massive edema and dyspnea. Examination revealed right pleural effusion and ascites. Daily urinary protein excretion was 18 gr.

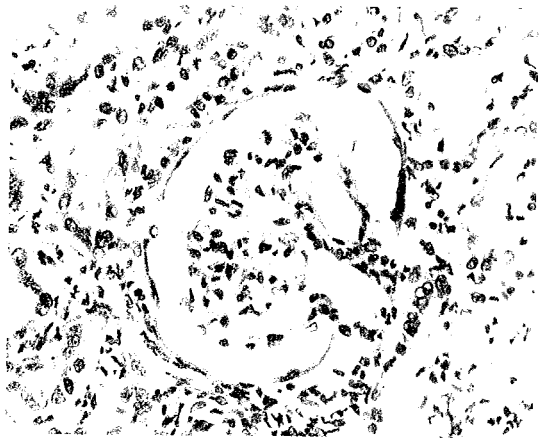

Fig - 1

**CASE 2 :** A 69 year old woman was admitted to the hospital because of peritoneal carcinomatosis. She had been operated for ovarian adenocarcinoma 6 weeks ago. On physical examination; palpable masses in abdomen and inguinal region were found. There was no edema. The laboratory findings were as follows: Albumin : 2 g/dl, Total serum protein : 5.5 g/dl, BUN : 24 mg/dl, Cr : 0.8 mg/ dl, Cholesterol:219mg/dl.Daily urinary protein excretion was 4.6 g and CrCl was 80 ml/min. CA-125 was 910 U/ml (0-35 U/ml).Because of proteinuria, a renal biopsy was performed which showed membranous glomerulonephritis (Fig. 2). After five cycles of carboplatin and cyclophosphamide,serum albumin was 4.7 g/dl and daily urinary protein excretion was 625 mg.

## DISCUSSION

Membranous nephropathy is one of the best defined glomerular diseases and the most common

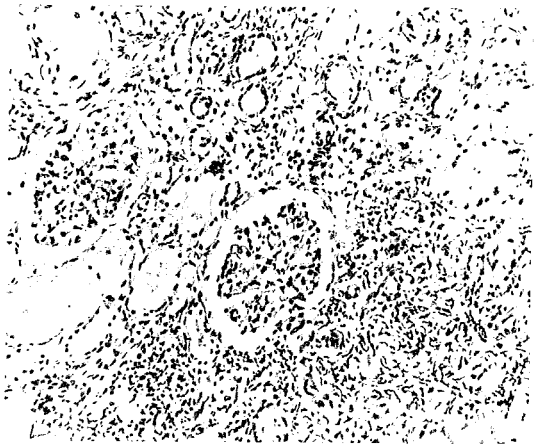

Fig - 2

glomerulonephritis causing nephrotic syndrome in adults (11). Most cases are associated with drug abuse, neoplasia, SLE, diabetes mellitus or infections (particularly hepatitis B virus) (10).

Neoplastic disorders associated with membranous glomerulonephritis are quite diverse: however carcinomas are found more commonly than lymphoma, leukemia and sarcomas. Carcinomas of the lung,colon, rectum, breast, stomach,kidney and melanoma are among the most frequently encountered neoplasms associated with secondary membranous glomerulonephritis. Occasional case reports have appeared linking membranous glomerulonephritis with cancers of adenocarcinoma of the ovary, bladder, prostate, larynx and pharynx, uterine cervix, bile duct, thyroid, skin and with neuroblastomas (1, 2, 4, 6, 9, 10). Additionally, isolated case reports noted the presence of the membranous nephropathy in patients with lymphoma and leukemia. However the incidence of membranous glomerulonephritis is much less common in hematologic malignancies than in carcinoma (4, 8).

The underlying pathogenic mechanisms responsible for the association of MG with neoplasia remain obscure; however, tumor specific antigens (related to bronchial carcinoma, melanoma and colon carcinoma) have been identified within the subepithelial glomerular deposits of immunoglobulin. Circulating immune complexes are found commonly among patients with malignant disease and the possibility that MG in association with neoplasia is due to the passive trapping of cir-

culating immune complexes composed of tumor specific antigens and autologous antibody is an attractive hypothesis.However it is also possible that circulating cationic tumor-specific antigens form an in situ immune complex.Additinally, autoantibody formation against intrinsic structural glomerular antigens could account for the development of MG under some circumstances (Particularly lymphoma and leukemia) (2, 3, 7, 8, 10, 12, 13).

The incidence of malignancy associated membranous nephropathy increases with age (4, 5, 10, 12). Both of our cases were elderly and at risk for malignancy.

It is generally agreed that, three of every four patients with underlying neoplasia have the neoplastic process recognized before or at the same time with renal biopsy. In some patients the neoplastic process is not recognized at the time of renal biopsy. It may appear many months or occasionally several years after the discovery of nephrotic syndrome (1, 2, 4, 6, 9, 10).

With successful tumor removal or successful chemotherapy and radiotherapy, clinical manifestations including nephrotic syndrome may disappear. Recurrence of clinical manifestations often appear with relapse or appearance of metastatic disease ( 2, 4, 6, 9, 10 ). On the other hand, a few case reports have mentioned the absence of any improvement in clinical renal disease after partial or complete remission of the tumor and /or metastases ( 12 ) as in our case 1.

We conclude that the possibility of a malignancy should be considered especially in elderly patients with MG, because MG is the most common glomerular lesion seen in association with carcinoma.

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