

NEPHROTIC SYNDROME AND NEOPLASIA: OUR EXPERIENCE AND REVIEW OF THE LITERATURE

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The glomerular lesion of paraneoplastic nephrotic syndrome usually presents as membranous nephropathy, minimal change disease or membranoproliferative glomerulonephritis. We present six cases of paraneoplastic nephrotic syndrome. Four cases were associated with epithelial malignancies (lung, gastric and colon cancer), and two cases with lymphoproliferative malignancies (Hodgkin's lymphoma and chronic lymphocytic leukemia). On the basis of light microscopy, immunofluorescence study and electron microscopy, membranous nephropathy, minimal change disease, and membranoproliferative glomerulopathy were established. We concluded, that the search for malignancy is warranted in patients over the age of 55 presenting with nephrotic syndrome, particularly in cases of membranous nephropathy.

Key words: nephrotic syndrome, malignancy, glomerulonephritis, cancer.

Introduction

Nephrotic syndrome is one of the best known presentations of kidney disease. This term describes the association of proteinuria greater than 3.5 g/1.73 m² body surface area/24 hours with hypoalbuminemia, oedema and hyperlipidemia. Glomerular diseases manifesting the nephrotic syndrome are caused by defects in the glomerular filtration barrier. The glomerular filtration barrier comprises cellular and extracellular structural elements including: the glomerular basement membrane (GBM), endothelial cells, visceral epithelial cells (podocytes), and interposed slit diaphragms. Disruption of the glomerular filtration barrier may be due to: immune-complex deposition, circulating permeability factors, T-lymphocyte abnormalities, genetic defects in podocyte proteins, viral infections, stretch injury, toxins, drugs, glomerular inflammation, and physicochemical alterations [1].

It is estimated that cancer occurs in 11% to 13% of patients with the nephrotic syndrome [2, 3]. However, the determination of the real incidence and prevalence of paraneoplastic nephrotic syndrome is very difficult, because most often, associations between nephrotic syndrome and neoplasia are

described as case reports and case series making the risk assessment difficult. Criteria for the diagnosis of paraneoplastic glomerulopathy are as follows: a clinical and histological remission after complete surgical removal of the tumour, or chemotherapy-induced complete remission of the disease, renal relapse associated with recurrence of the neoplasia, a pathophysiologic link established between the two diseases, including the detection of tumour antigens and anti-tumour antibodies within immune deposits [4]. A causal relationship is suggested if nephrotic range proteinuria develops either 6 months before or after the diagnosis of malignancy [5].

The pathogenesis of the paraneoplastic syndrome includes involvement of tumour associated antigens, re-expressed foetal antigens and/or viral antigens, host-antibody response of the shedding of tumour antigen, circulating tumour antigen-antibody complexes which may inhibit or suppress tumour-specific cell-mediated immunity [6]. Numerous attempts have been made to identify tumour antigens or their specific antibodies in kidneys of cancer patients, however antigens/antibodies have been demonstrated in only several cases of paraneoplastic glomerulopathy [7]. Tumour antigens implicated in the formation of

immune deposits have been the carcinoembryonic antigen, prostate-specific antigens, the renal tubular epithelial antigen (RTE), and other unidentified tumour products [8-12]. The presence of tumour antigens and their corresponding antibodies in patients with paraneoplastic glomerulopathies does not mean, however, that they are involved in the initial pathogenetic process leading to the formation of immune deposits. These components can become passively deposited because of increased glomerular permeability to proteins as a result of the initial insult [6]. Birkeland and Storm [13] suggested an association between nephrotic syndrome with malignancies and persistent virus infections, which cause glomerulonephritis first and then malignancies.

The concept of paraneoplastic glomerulopathy was introduced in 1922 by Galloway [14]. In 1939, Cornig [15] reported the first case of nephrotic syndrome and Hodgkin's disease. The first convincing clinicopathologic study was published in 1966 by Lee *et al.* [2]. Out of their 101 adult patients who presented with the nephrotic syndrome, 11% were found to have carcino-

ma. In 1977, Eagen and Lewis [16] collected 171 cases of nephrotic syndrome associated with cancers including carcinoma, Hodgkin's disease, non-Hodgkin's lymphoma, leukaemia, and plasma cell dyscrasia. The glomerular lesion of paraneoplastic nephrotic syndrome usually presents as membranous nephropathy (MN) in patients with solid tumours, particularly adenocarcinomas of the lung and gastrointestinal tract [2-5, 15-18]. Minimal change disease (MCD) is strongly associated with Hodgkin's lymphoma (HL), whereas the most common lesions observed in patients with chronic lymphocytic leukaemia (CLL) are membranoproliferative glomerulopathy (MPGN) and membranous nephropathy [2, 4, 5, 15-21]. Extracapillary crescentic glomerulopathy, IgA nephropathy and focal segmental glomerulosclerosis can also be associated with neoplasia [5, 22-25]. Glomerulopathies presented with nephrotic syndrome associated with neoplasm reported in the literature are shown in Table I [26-48] and Table II [49-61]. Nephrotic syndrome is rarely observed in patients with benign tumours (Table III) [62-66].

Table I. Glomerulopathies with nephrotic syndrome associated with the neoplasm reported in the literature

TYPE OF MALIGNANCY	THE MOST FREQUENT TYPE OF MALIGNANCY-RELATED GLOMERULOPATHY WITH THE NEPHROTIC SYNDROME	REFERENCES
Lung carcinoma	MN	[26, 27, 28, 29, 30, 31, 32]
Gastric adenocarcinoma	MN	[33, 34, 35, 36]
Colon adenocarcinoma	MN	[37, 38, 39]
Prostatic adenocarcinoma	MN	[40, 41]
Breast carcinoma	MN	[42, 43, 44, 45]
Renal cell carcinoma	MN	[46, 47, 48]

MN – membranous nephropathy

Table II. The rare cases of paraneoplastic nephrotic syndrome reported in the literature

TYPE OF NEOPLASM	TYPE OF GLOMERULOPATHY	REFERENCES
Neuroblastoma	MN	[49]
Mixed cell germinal ovary tumour	MPGN	[50]
Neuroendocrine small cell carcinoma of the endometrium	MN	[51]
GIST	MN	[52]
Hepatocellular carcinoma	MN	[53]
Oesophageal carcinoma	MN	[54]
Malignant thymoma	MCD	[55, 56]
Choriocarcinoma	MN	[57]
Nasopharyngeal carcinoma	MN	[58]
Bronchial carcinoid tumour	MN, MPGN	[59, 60]
Mesothelioma of the testis	MCD	[61]

MN – membranous nephropathy, MCD – minimal change disease, MPGN – membranoproliferative glomerulonephritis

Table III. The association of nephrotic syndrome with benign solid tumours

TYPE OF NEOPLASM	TYPE OF GLOMERULOPATHY PRESENTED WITH NEPHROTIC SYNDROME	REFERENCES
Juxtaglomerular cell tumour	MN	{62}
Adrenal ganglioneuroma	MN	{63}
Neurilemmoma	MCD	{64}
Bilateral adrenal myelolipomas	FSGS	{65}
Adenolymphoma of parotid gland	MN	{66}

MN – membranous nephropathy, MCD – minimal change disease, FSGS – focal segmental glomerulosclerosis

Table IV. Clinical data and the type of glomerulopathy in patients with paraneoplastic nephrotic syndrome

AGE (YEARS)	MALE/FEMALE	CLINICAL PRESENTATION	TYPE OF MALIGNANCY	TYPE OF GLOMERULOPATHY
60	Male	nephrotic syndrome 1 month prior to the renal biopsy (anasarca, proteinuria 8 g/24 h, hyperlipidemia, hypoalbuminemia) renal insufficiency (serum creatinine: 2.5 mg/dl)	small cell lung carcinoma	MN
65	Male	nephrotic syndrome 3 months prior to the diagnosis of gastric carcinoma (anasarca, proteinuria 11 g/24 h, hyperlipidemia, hypoalbuminemia)	gastric adenocarcinoma	MN
57	Male	nephrotic syndrome 4 months prior to the diagnosis of colon carcinoma (anasarca, proteinuria 6 g/24 h, hyperlipidemia, hypoalbuminemia)	colon adenocarcinoma	MN
55	Female	nephrotic syndrome 1 month after the diagnosis of colon carcinoma (anasarca, proteinuria 10 g/24 h, hyperlipidemia, hypoalbuminemia)	colon adenocarcinoma	MN
58	Female	nephrotic syndrome 3 months prior to the diagnosis of cHL (anasarca, proteinuria 9 g/24 h, hyperlipidemia, hypoalbuminemia)	classical Hodgkin's lymphoma cHL, subtype mixed cellularity (MC)	MCD
61	Female	nephrotic syndrome 6 months after the diagnosis of CLL (anasarca, proteinuria 13 g/24 h, hyperlipidemia, hypoalbuminemia)	chronic lymphocytic leukaemia (CLL)	MPGN type I

MN – membranous nephropathy, MCD – minimal change disease, MPGN – membranoproliferative glomerulonephritis

Case presentation

We present 6 cases of nephrotic syndrome and neoplasia. Clinical data and the types of glomerular injury are shown in Table IV. Age of the patients was 55-65 years, mean age = 59.3, male/female ratio was 3/3. Three patients clinically manifested the nephrotic syndrome prior to the diagnosis of the tumour. Epithelial malignancies (1 case of small cell lung carcinoma, 1 case of gastric adenocarcinoma and 2 cases of colon adenocarcinomas) were associated with membranous nephropathy. In 2 cases of lymphoproliferative malignancies (chronic lymphocytic leukaemia and Hodgkin's lymphoma), renal biopsy revealed membranoproliferative glomeru-

lonephritis and minimal change disease, respectively. In light microscopy, immunofluorescence study and electron microscopy, the renal lesions did not differ from idiopathic forms of glomerulopathies. In membranous nephropathies, uniform thickening of the glomerular capillary walls was seen (Fig. 1) due to diffuse subepithelial and intramembranous immune deposits (Fig. 2). An increase in mesangial matrix was present in three cases of paraneoplastic membranous nephropathy. Immunofluorescence study in paraneoplastic MN revealed strong granular staining of IgG and C3 along glomerular capillary loops. In the patient with paraneoplastic minimal change disease, diffuse effacement of the podocyte foot process-

es and microvillous transformation were seen in electron microscopy (Fig. 3). In this case of paraneoplastic MCD, light microscopy did not reveal any abnormalities, and immunofluorescence was completely negative. The renal biopsy in the patient with paraneoplastic membranoproliferative glomerulonephritis showed accentuated lobular configuration in glomeruli and variable thickening of capillary walls. An increase in mesangial matrix and mesangial cells was seen in light microscopy (Fig. 4). Electron microscopy revealed subepithelial, as well as mesangial deposits. Granular staining of IgG, C3 and IgM in the mesangium and along the periphery of capillary loops was present in the immunofluorescence study. The patient with paraneoplastic MN due to small cell lung cancer died within 4 months after the renal biopsy. A transient amelioration of the nephrotic syndrome after excision of the tumour was seen in the patient with gastric adenocarcinoma and paraneoplastic MN. Resolution of the nephrotic syndrome after surgical removal of the tumour was noted in 2 patients with MN and colon adenocarcinoma. In the patient with paraneoplastic MCD and Hodgkin's lymphoma and in the patient with chronic lymphocytic leukaemia and paraneoplastic MPGN, the resolution of the nephrotic syndrome after chemotherapy was observed.

Discussion

In our study light microscopy, immunofluorescence study and electron microscopy revealed membranous nephropathy in all cases of epithelial malignancies. It is well known that MN is the most common nephropathy associated with neoplasm. This occurs in approximately 70% of patients reported to have a malignancy-associated nephrotic syndrome [5]. The most frequent type of malignancy related to membranous glomerulopathy is carcinoma of the colon, lung, stomach, pancreas, kidney, prostate, and melanoma of the skin [2-6, 16-18]. Out of the patients with carcinoma and membranous glomerulopathy, 40% to 45% clinically manifest the nephrotic syndrome prior to the diagnosis of the tumour [5]. In our study, in 3 patients with malignancies and paraneoplastic MN, nephrotic syndrome preceded the diagnosis of the lung, gastric and colon cancer. In one patient with colon adenocarcinoma, nephrotic syndrome due to paraneoplastic membranous nephropathy was observed after the diagnosis of the tumour. In our study, the clinical remission after surgical removal of the tumour indicates the relationship between malignancy and glomerulopathy. The age of patients with paraneoplastic nephrotic syndrome due to membranous nephropathy was from 55 to 65, and the mean age was almost 60. It must be stressed that the incidence of malignancy

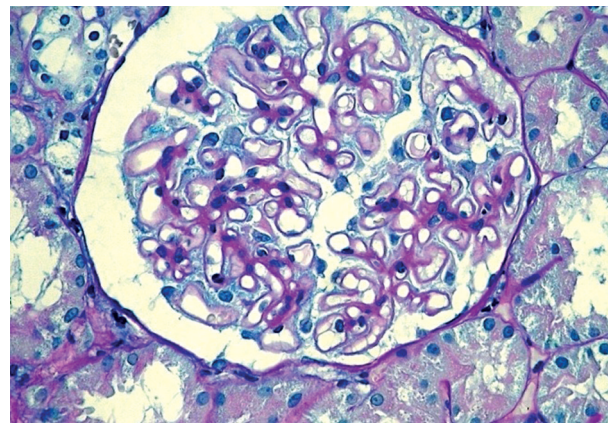


Fig. 1. The uniform thickening of the glomerular capillary walls in paraneoplastic MN in a patient with colon carcinoma. PAS + Alcian blue staining, magnification 400×

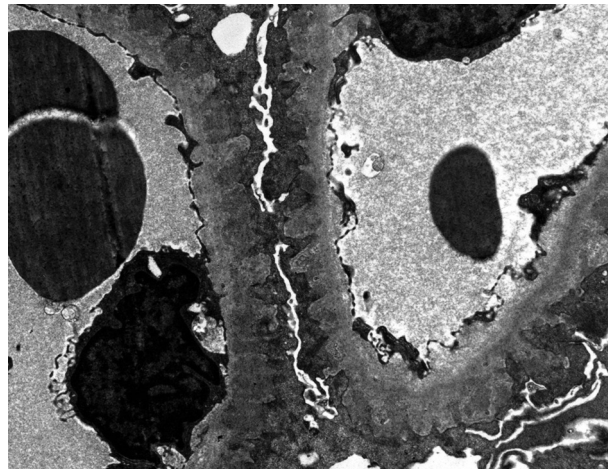


Fig. 2. Electron photomicrograph of paraneoplastic MN in a patient with gastric adenocarcinoma. Diffuse subepithelial and intramembranous immune deposits. Thickening of the glomerular basement membrane and diffuse fusion of podocyte foot processes. Magnification 10 000×

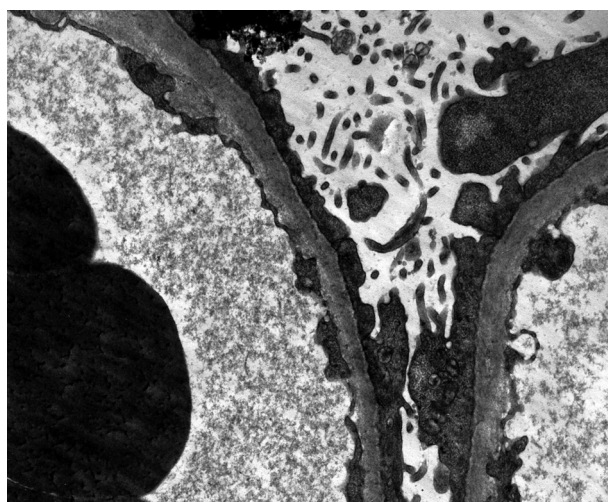


Fig. 3. Electron photomicrograph of paraneoplastic MCD in a patient with Hodgkin's lymphoma. Diffuse effacement of the podocyte foot processes and microvillous transformation. Magnification 10 000×

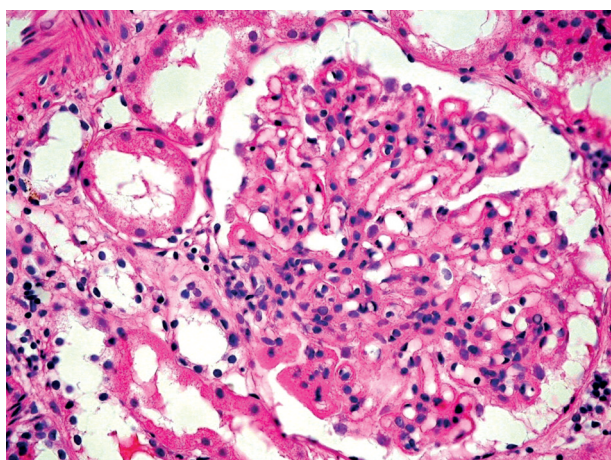


Fig. 4. Paraneoplastic MPGN in a patient with CLL. Focal thickening of glomerular peripheral capillary walls, mesangial hypercellularity and segmental increase in mesangial matrix. HE staining, magnification 400×

nancy-associated MN among patients over the age of 60 is 19.4% [67], whereas cancer rates can reach as high as 24.7% in patients over the age of 64 [68]. The literature data indicate that the renal lesions seen in paraneoplastic membranous nephropathy are similar to those of idiopathic MN, although several authors have noted the presence of numerous polymorphonuclear leukocytes in capillary loops, occasionally associated with intravascular hyaline thrombi in the absence of renal vein thrombosis [69]. Lefaucher *et al.* [70] showed that the number of inflammatory cells infiltrating glomeruli is significantly higher in patients with cancer-associated MN, and the best cutoff value for distinguishing malignancy-related cases from idiopathic is 8 cells per glomerulus in patients with cancer-associated MN. Ohtani *et al.* [71] pointed out that in malignancy-associated MN, the staining for IgG1 and IgG2 is of the greatest intensity. In our study, light and electron microscopy did not reveal any differences in comparison to idiopathic forms of membranous nephropathy. Immunofluorescence evaluation showed strong granular staining of IgG and C3 along glomerular capillary walls. We did not study subclasses of IgG, because in the routine practice such evaluation is used very rarely.

In patients with nephrotic syndrome and lymphomas, light microscopy, immunofluorescence and electron microscopy evaluation of the renal tissue revealed minimal change disease and membranoproliferative glomerulonephritis. Hodgkin's lymphoma was associated with MCD, and chronic lymphocytic leukaemia with MPGN. The association between Hodgkin's disease and glomerulopathy is probably the best known of the hemopathy-induced paraneoplastic glomerulopathies, although in two large series collecting 1,700 Hodgkin's disease patients, only

0.4% of them had MCD [72, 73]. Moulin *et al.* [74] have identified approximately 100 reports of Hodgkin's-disease-associated glomerulopathy, mainly amyloidosis (37%) and MCD (42%). The development of MCD may precede or be simultaneous with the diagnosis of Hodgkin's disease. The morphological subtype is predominantly mixed cellularity (MC) form of classical Hodgkin's lymphoma [75], however in a more recent review, nodular sclerosis (NS) was reported as a predominant morphological subtype associated with paraneoplastic nephrotic syndrome and cHL [19]. Effective treatment of the hemopathy is associated with the disappearance of MCD [18]. In our study, in the patient with Hodgkin's lymphoma (subtype mixed cellularity) nephrotic syndrome preceded the diagnosis of the lymphoma, and the resolution of the nephrotic syndrome after chemotherapy was observed. In this case of paraneoplastic glomerulopathy, the renal lesions did not differ in comparison to the idiopathic form of MCD.

Paraneoplastic nephrotic syndrome due to MCD may also be associated with solid tumours, especially with thymoma, renal cell carcinoma, colorectal carcinoma, and lung carcinoma. Taniguchi *et al.* [76] described a patient with rectal adenocarcinoma associated with MCD and elevation of vascular endothelial growth factor (VEGF). What is more, after tumour resection, proteinuria disappeared and VEGF decreased to the normal level. The link between thymoma and MCD is very interesting. In an animal model of paraneoplastic glomerulopathy, the Buffalo/Mna rat (spontaneous thymoma, myasthenia and glomerulopathy due to genetic abnormality) had proteinuria and nephrotic syndrome leading to MCD and FSGS [77].

Nephrotic glomerulopathies rarely occur in association with acute leukaemia, but they have been described in chronic lymphocytic leukaemia. Membranoproliferative glomerulopathy and membranous nephropathy are the most common lesions observed in CLL [78, 79]. In a review by Seney *et al.* [80], nephrotic syndrome occurred in less than 1-2% of CLL. In the presented case, in the patient with chronic lymphocytic leukaemia, nephrotic syndrome appeared 6 months after the diagnosis of CLL. Complete remission of nephrotic syndrome after chemotherapy was noted. In this case, light microscopy, immunofluorescence and electron microscopy evaluation of the renal biopsy revealed membranoproliferative glomerulonephritis, similar to the idiopathic type of MPGN,

In conclusion, the glomerular lesion of paraneoplastic nephrotic syndrome usually presents as membranous nephropathy, minimal change disease or membranoproliferative glomerulonephritis. The clinical remission after surgical removal of the tumour, or chemotherapy-induced complete remission of the

disease indicates the relationship between malignancy and glomerulopathy. The search for malignancy is warranted in patients over the age of 55 presenting with nephrotic syndrome, particularly in the cases of membranous nephropathy.

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