

NEPHROTIC SYNDROME IN THE ELDERLY

Krešimir Galešić¹, Danica Ljubanović¹, Mirjana Sabljari-Matovinović², Inge Prkačin², Ivica Horvatić¹ and Ivana Račić¹

¹Dubrava University Hospital; ²Merkur University Hospital, Zagreb, Croatia

SUMMARY – The incidence of certain types of glomerular diseases is different in the elderly as compared with younger patients. Many different histologic appearances can be identified, however, membranous nephropathy is the most common type. Underlying malignancy has been thought to be responsible for 5 to 10 percent of cases of membranous nephropathy in adults, with the highest risk in patients over age 60. A solid tumor such as carcinoma of the lung or colon is most frequently involved. It is presumed that tumor antigens are being deposited in the glomeruli, which is followed by antibody deposition and complement activation, leading to epithelial cell and basement membrane injury and proteinuria due to the associated increase in glomerular permeability. In the present study, 33 patients aged over 60 with nephrotic syndrome were analyzed. Fourteen (42%) patients had membranous nephropathy, three of them with underlying malignancy.

Key words: *Kidney diseases – diagnosis; Kidney diseases – pathology; Nephrotic syndrome – pathology; Biopsy; Age factors; Aged*

Introduction

Nephrotic syndrome is a common mode of presentation of glomerular disease in the elderly, and deserves to be investigated in a manner different from that taken in younger patients^{1,2}. Many different histologic appearances can be identified, however, the most common type is membranous nephropathy similar to that reported in younger adult patients with nephrotic syndrome¹. The nephrotic syndrome occurring in patients over the age of 60 is usually thought to be a symptom of another disease such as neoplasm³. Several clinical and immunologic observations support the hypothesis of a relationship between the nephrotic syndrome and neoplasm. The nephrotic syndrome often constitutes the prodromal stage of malignant disease². Removal or irradiation of the tumor is usually associated with dramatic diminution of proteinuria, whereas recurrence of the neoplasm is followed by increased proteinuria⁴.

Tumor specific antigens and antibodies have been identified in the glomeruli of patients with the nephrotic syndrome and carcinoma^{5,6}. Antibodies eluted from the kidney in patients with carcinoma and nephrotic syndrome were found to react specifically with tumor extract⁵.

We present data on 33 patients aged over 60 with nephrotic syndrome. We think these patients should be regarded as a special group with particular etiologic and therapeutic aspects. The purpose of this report is to enhance awareness of the association between nephrotic syndrome in the elderly and neoplasia.

Patients and Methods

Thirty-three patients aged over 60, 20 male and 13 female, were studied at the onset of the disease. Data files of these patients were analyzed to identify indications for renal biopsy and to examine the clinical characteristics of patients presenting with nephrotic syndrome or renal functional impairment. Patients were considered to have nephrotic syndrome if urinary protein excretion exceeded 3.5 g/24 h. Renal function impairment was confirmed by the increase in serum creatinine recorded at the time of renal biopsy. Percutaneous needle biopsy was performed in all

Correspondence to: *Assist. Prof. Krešimir Galešić, M.D., Ph.D.*, Dubrava University Hospital, Av. Gojka Šuška 6, HR-10000 Zagreb, Croatia
E-mail: kresog@zagreb.kbd.hr

Received May 29, 2003, accepted in revised form December 8, 2003

patients. Kidney tissue was examined by light microscopy, immunofluorescence and electron microscopy. For the purpose of this study, we defined complete remission as the absence of proteinuria and the presence of normal urinary sediment, plasma creatinine within the normal range (53-106 $\mu\text{mol/L}$), and blood pressure <140/90 mm Hg.

Improvement was defined as persistent proteinuria without nephrotic syndrome, renal failure or high blood pressure. Persistence of the nephrotic syndrome was regarded as unchanged state. Four patients (one patient with lupus nephritis and three nonazotemic patients with focal segmental glomerulosclerosis) were treated with corticosteroids, and 11 patients (six patients with membranous nephropathy and five patients with rapidly progressive glomerulonephritis) with corticosteroids plus cyclophosphamide. Azotemic patients ($n=18$) were treated only symptomatically.

Results

Membranous nephropathy was the most common histologic type, which was observed in 14 patients (Table 1). Rapidly progressive (crescentic) glomerulonephritis was present in five patients. Other types of glomerular disease were focal segmental glomerulosclerosis, diabetic nephropathy and mesangioproliferative glomerulonephritis, amyloidosis and systemic lupus erythematosus (Table 1). Complete remission was achieved in 12 patients, whereas five patients died: three from malignant disease associated with glomerulonephritis, one from primary amyloidosis, and one from infection (sepsis). The three patients with malignancy had membranous nephropathy. So, membranous nephropathy was associated with pleural mesothelioma, lung carcinoma and breast carcinoma in one patient each. All these patients presented clinically with resistant

nephrotic syndrome and massive proteinuria (>30 g/day). All three patients died several months of the diagnosis of malignancy.

Discussion

The exact incidence of glomerular disease in the elderly is difficult to determine because special renal diagnosis is frequently not made in this population, as the treating physicians decide the risk of biopsy being too high. The first report of renal biopsy findings in the elderly was that by Moorthy and Zimmerman, who published a retrospective analysis of the single center experience with 115 patients aged >60 presenting with renal disease⁷. Since then, there have been a number of further reports⁸⁻¹¹. These reports indicate that glomerular disease in the elderly is not infrequent. The most common reason for kidney biopsy in elderly patients is nephrotic syndrome, followed by renal function impairment. It seems that elderly patients are unlikely to undergo renal biopsy after presenting with asymptomatic proteinuria and/or hematuria. Nephrotic syndrome is not so rare in adults aged over 60. It is usually considered to be an accompanying sign of malignancy^{2,12-14}. The distribution of histologic types in our study was comparable with other reports of the nephrotic syndrome in the elderly. The most common histologic type of glomerulonephritis in the elderly in this study as well as in other reports was membranous nephropathy, usually manifesting as the nephrotic syndrome. In the elderly, membranous nephropathy has been associated with malignancy¹⁵⁻¹⁷. The reported incidence of malignant tumors and membranous nephropathy comorbidity varies, ranging from 1.4% to 10%. Carcinomas of the lung, colon or gastrointestinal tract are the most common malignancies associated with membranous nephropathy^{10,14,15}.

Table 1. Histologic findings in elderly patients with glomerulonephritis

	No. of cases	Complete remission	Improvement	Death
Membranous nephropathy	14	7	4	3
Crescentic glomerulonephritis	5	1	3	1
Focal segmental glomerulosclerosis	6	2	4	–
Diabetic nephropathy	1	–	1	–
Mesangioproliferative glomerulonephritis	5	2	3	–
Systemic lupus erythematosus	1	–	1	–
Amyloidosis	1	–	–	1
Total	33	12	16	5

The pathogenesis of membranous nephropathy associated with malignant tumors is not well understood. Several mechanisms have been suggested, i.e. humoral response to tumor antigens and immune complex glomerulopathy; presence of oncogenic virus inducing the development of cancer and glomerulonephritis; and defect in immune surveillance allowing for the survival of neoplastic cells and formation of antibodies to some nontumor related antigens, particularly to viral antigens¹⁸⁻²⁰.

In our study, the incidence of malignant tumors associated with membranous nephropathy was 21%. In one patient, nephrotic syndrome was associated with pleural mesothelioma, which we have previously described as a rare association of nephrotic syndrome and glomerular disease with mesothelioma²¹. One patient had lung carcinoma and breast carcinoma each. Other types of malignancy associated with glomerulonephritis in the elderly are lymphoma and leukemia^{22,23}. Rare reports note improvement or remission of the nephrotic syndrome upon removal of the carcinoma or treatment of leukemia or lymphoma⁴. Malignancy associated with membranous nephropathy may occur either before, simultaneously with membranous nephropathy, or 10 to 18 months of its initial manifestation. Although some tumors may be easily detected after the diagnosis of membranous nephropathy, some authors suggest that up to 70% of patients bear an initially occult malignancy⁴. In two of our patients, the diagnosis of membranous nephropathy and malignant disease (i.e. lung carcinoma and breast carcinoma) was made simultaneously. In yet another patient with mesothelioma, the diagnosis of malignant disease was made 10 months of the diagnosis of membranous nephropathy. These data as well as data from the literature suggest an exhaustive search for malignancy in all adult patients presenting with membranous nephropathy, especially the elderly ones (complete clinical history, basic hematologic and clinical tests for malignancy of the lung, breast, gastrointestinal and genitourinary tracts). If abnormalities are detected, a more aggressive search for an occult tumor should be undertaken. Additionally, these patients need to be followed up closely over the next 12 to 18 months to identify possible manifestation of malignancy on time^{22,23}.

References

- EAGEN JW, LEWIS EJ. Glomerulonephritis of neoplasia. *Kidney Int* 1971;11:297-300.
- GHOSH L, MUEHRCKE RC. The nephrotic syndrome: a prodrome to lymphoma. *Ann Intern Med* 1970;72:379-82.
- BURSTEIN DM, KORBET SM, SCHWARTZ MM. Membranous glomerulonephritis and malignancy. *Am J Kidney Dis* 1993;22:5-10.
- PLAGER J, STUTZMAN L. Acute nephrotic syndrome as a manifestation of Hodgkin's disease: report of four cases and review of the literature. *Am J Med* 1971;50:56-66.
- LEWIS MG, LONGRIDGE LW, PHILIPS TM. Immunological studies in nephrotic syndrome associated with extrarenal malignant disease. *Lancet* 1971;2:134-5.
- CONSTANZA ME, PINN V, SCHWARTZ RS, NATHANSON L. Carcinoembryonic antigen-antibody complexes in a patient with colonic carcinoma and nephrotic syndrome. *N Engl J Med* 1973;289:520-2.
- MOORTHY AV, ZIMMERMAN SW. Renal disease in the elderly: clinicopathologic analysis of renal disease in 115 elderly patients. *Clin Nephrol* 1980;14:223-9.
- KINGSWOOD JC, BANKS RA, TRIBE CR, OWEN-JONES J, MACKENZIE JC. Renal biopsy in the elderly: clinicopathologic correlations in 143 patients. *Clin Nephrol* 1984;22:183-7.
- MBAKOP A, CHATELANAT F. Ponctions biopsies renales chez le sujet age: a propos de 119 cas. *Ann Pathol* 1985;2:101-5.
- DAVISON AM, JOHNSON PJ. Idiopathic glomerulonephritis in the elderly. *Clin Nephrol* 1993;105:38-48.
- KOMATSUDA A, NAKAMOTO Y, IMAI H, *et al.* Kidney diseases among the elderly – clinicopathologic analysis of the 247 elderly patients. *Intern Med* 1993;32:377-81.
- GAGLIANO RG, COSTANZI JJ, BEATHARD GA, SARLES HE, BALL JD. The nephrotic syndrome associated with neoplasia. An unusual paraneoplastic syndrome. *Am J Med* 1976;60:1026-31.
- BARTON CH, VAZIRI ND, SPEAR GS. Nephrotic syndrome associated with adenocarcinoma of breast. *Am J Med* 1980;68:308-12.
- CHARLES E, COTRAN A, COTRAN R. Neoplasia and glomerular injury. *Kidney Int* 1985;30:465-73.
- COUSER WG, WAGENFELD JB, SPARGO BH. Glomerular deposition of tumor antigen in membranous nephropathy associated with colonic carcinoma. *Am J Med* 1974;57:962-70.
- KEUR I, KREDIET RT, ARISZ I. Glomerulopathy as a paraneoplastic phenomenon. *Neth J Med* 1989;34:270-84.
- BRUGGEMEYER CD, RAMIREZ G. Membranous nephropathy. A concern for malignancy. *Am J Kidney Dis* 1987;9:23-6.
- PASCLA RR, SLOVIN ST. Tumor-associated antibody and carcinoembryonic antigen in the glomeruli of patients with gastric carcinoma. *Hum Pathol* 1989;11:679-82.
- WEKSLER ME, CERREY T, DAY N, SUSIN M, SHERMAN R, BACKER C. Nephrotic syndrome in malignant melanoma. Demonstration of melanoma antigen-antibody in the kidney. *Kidney Int* 1974;6:112A.
- BEAUFILS H, JOUANNEAU C, CHOMETTE G. Kidney and cancer. Results of immunofluorescence microscopy. *Nephron* 1985;40:303-8.
- GALESIC K, BOZIC B, SCUKANEC-SPOLJAR M, BOZIKOV V. Pleural mesothelioma and membranous nephropathy. *Nephron* 2000;84:71-4.

22. SENEY TD Jr, PEDERGREEN WR, STEIN H, KASHGARIN M. A review of nephrotic syndrome associated with chronic lymphocytic leukemia. *Arch Intern Med* 1986;148:137-41.
23. HYMAN LR, BURKHOLDER PM, JOO PA, SEGAR WE. Malignant lymphoma and nephrotic syndrome. A clinicopathologic analysis with light microscopy, immunofluorescence and electron microscopy of renal lesion. *J Pediatr* 1973;82:207-17.

Sažetak

NEFROTSKI SINDROM U STARIJIH OSOBA

K. Galešić, D. Ljubanović, M. Sabljar-Matovinović, I. Prkačin, I. Horvatić i I. Račić

Incidencija pojedinih tipova glomerulonefritisa u starijih osoba razlikuje se u usporedbi s mlađim bolesnicima. U starijih osoba mogu se dijagnosticirati različiti oblici glomerulonefritisa, no najčešća je membranska nefropatija. Ovaj oblik glomerulonefritisa je u 5% do 10% bolesnika povezan s malignim tumorom. Najčešći oblici malignih tumora udruženih s membranskom nefropatijom su karcinomi pluća i kolona. Pretpostavlja se da se tumorski antigen odlaže u glomerulima, što izaziva taloženje protutijela i aktiviranje komplementa. To pak izaziva oštećenje epitelnih stanica i bazalne membrane glomerula te proteinuriju. U radu je analizirano 33 bolesnika s nefrotskim sindromom. Svi su bolesnici bili stariji od 60 godina. Membranska nefropatija je dijagnosticirana u 14 (42%) bolesnika, a kod troje bolesnika je ovaj oblik glomerulonefritisa bio udružen s malignom bolešću.

Ključne riječi: Bubrežne bolesti – dijagnostika; Bubrežne bolesti – patologija; Nefrotski sindrom – patologija; Biopsija; Starosni čimbenici; Starije osobe