Nephrotic Syndrome Preceding Multiple Myeloma: Case Report

Nefrotik Sendroma Öncelik Eden Multipl Miyeloma

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ABSTRACT Membranoproliferative glomerulonephritis (MPGN) is the most common cause of nephrotic syndrome in young adults. This is a unique clinical entity developing secondary to autoimmune disorders or infections, and renal failure may be the presenting feature of the disease. Here we reported a case with nephrotic syndrome (NS) diagnosed 2 years before with multiple myeloma (MM). At the beginning, hypertension, edema, anemia, moderate renal failure, hypoalbuminemia, severe proteinuria and dyslipidemia were found. She was treated with prednisolone plus conservative measures including anti-hypertensives, angiotensin converting enzyme inhibitor (ACEI), dipyridamol and low salt diet. Two years later, MM was detected and treated with anti-neoplastic agents. Remission was achieved both for the MM and for the renal disease. At the end of 4 years after the diagnosis of MM, relapse occurred without renalfailure. It is known that NS accompanies to MM, but NS preceding MM is very rare. For this reason, the possibility of the development of a malignant disease should be considered in cases with idiopathic glomerulonephritis.

Key Words: Multiple myeloma; proteinuria; renal insufficiency

ÖZET Membranoproliferatif glomeruloneprit (MPGN), genç erişkinlerde nefrotik sendromun (NS) en sık nedenidir. Otoimmün hastalıklar enfeksiyon hastalıklarına sekonder gelişebilir ve böbrek yetersizliğine neden olabilir. Burada multipl myeloma (MM) tanısından 2 yıl önce NS'li bir olgu sunulmuştur. Başlangıçta hipertansiyon, böbrek yetersizliği hipoalbuminemi, şiddetli proteinüri ve dislipidemi saptandı. Prednison ve angiotensin dönüştürücü enzim inhibitörü, dipiridamol, ve düşük tuzlu diyetle iyileşme sağlandı. İki yıl sonra MM tanısı konuldu ve anti-neoplastik ilaçlarla tedavi edildi. Böbrek hastalığı ve MM için remisyon elde edildi Dört yıl sonra MM relaps gösterdi bu sırada böbrek fonksiyon bozukluğu ve proteinüri gelişmedi. NS'nin MM'ye eşlik ettiği bilinmektedir ancak MM'ye öncülük etmesi oldukça nadirdir. Bu nedenle idiyopatik glomerulonefritlerde malign hastalık dikkate alınmalıdır.

Anahtar Kelimeler: Multipl miyelom; proteinüri; böbrek yetmezliği

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It is very well known that there is an association between glomerular lesions and malignant disorders. The relationship between cancer and NS has been firstly reported by Lee et al in 1966.[1] NS cases associated with MM have been uncommonly reported. Membranoproliferative glomerulonephritis (MPGN) is the most common cause of nephrotic syndrome in young adults. This is a unique clinical entity developing secondary to autoimmune disorders or infections and renal failure may be the presenting feature of the disease. Here we reported a case with nephrotic

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syndrome (NS) diagnosed 2 years before the diagnosis of multiple myeloma (MM).

CASE REPORT

A 32-year-old woman admitted to the hospital with a 7- month history of hypertension and one-month history of pretibial edema, fatigue and anorexia. Rilmenidin 1 mg daily had been prescribed for hypertension. Physical examination showed high blood pressure (BP): 150/100 mmHg and pretibial (++) edema. Complete blood count showed mild anemia; hemoglobin was 11.6 g/dL Blood urine nitrogen was 21 mg/dL, creatinine 2 mg/dL, total protein/albumin was 4.5/3 g/dL. Serum lipid profile: cholesterol, LDL, HDL and triglyceride were 309, 217, 67 and 124 mg/dL, respectively. Ca/P was 9/4 mg/dL, erythrocyte sedimentation rate was 7 mm/h, 24 hour urine protein was 7 g. Serum complement level was found to be normal, viral serology was negative. Abdominal ultrasound showed grade II renal parenchymal disease and ascites. Chest X-ray was normal. On systemic evaluation, there was no evidence of infection and/or malignant disease. Laboratory findings at the beginning and in the follow up period are shown in Table 1. Renal biopsy showed basement membrane thickening and mesangial nodules, and these nodules showed PAS positivity (Figure 1, 2). Kappa and lambda light chains were explored by by immunohistochemistry and there was no staining in the renal tissue. In addition, IgG, IgM, IgA, C3, C1q, C4, fibrinogen, kappa and lambda light chains were found to be negative with direct immunoflouresceint method in renal biopsy.

At the beginning, the patient was accepted as idiopathic MPGN because we did not have electron microscopic evaluation. After the diagnosis of MM, electron micrographic evaluation showed punctate subendothelial electron dense material and mesangial light chain deposits (Figure 3). Any clinical and laboratory finding related to malignant disease or diabetes mellitus (DM) were not found. Treatment consisting of methylprednisone, ACE inhibitor (fosinopril), calcium antagonist (amlodipin), beta

TABLE 1: Biochemical parameters during follow-up period.

	Baseline Nov 24, 05	3rd month Feb 02, 06	6th month May 03, 06	12th month Oct 06, 06	18th month May 01, 07	24th month Nov 27, 07	60th month Oct 27, 10	75th month Jan 16, 2012
Glucose (mg/dL)	92	74	74	72		91		
Blood urea nitrogen (mg/dL)	21	54	23	16	15	24	17	13
Creatinine (mg/dL)	2.0	2.0	1.9	1.0	0.8	1.1	1.0	0.79
Total protein (gr/dL)	4.5	5.6	6.5	6.5	6.5	6.7	7.2	5.9
Albumin (gr/dL)	3.0	3.7	4.1	4.2	4.2	4.6	4.7	3.9
Calcium (mg/dL)	9.0	8.9	9.0	9.2	9.5	11.3	9.4	
Phosphorus (mg/dL)	4.4	5.2	4.1	3.2	3.8	3.0	3.2	
Uric acid (mg/dL)	5.6	8.5	8.4	5.5	3.1	6.4	2.0	
AST(IU/L)	26	19	17	14		13	19	10
ALT(IU/L)	23	31	41	12		9	14	15
Total cholesterol (mg/dL)	309	163		188			166	239
LDL (mg/dL)	217	65		91			91	137
HDL (mg/dL)	67	55		9			50	75.6
Triglyceride (mg/dL)	124	215		146			97	131
ESR (mm/h)	7		15	7	2	2		11
Hemoglobin (g/dL)	11,6	11.5	9.1	10.7	13.5	12.3	14.1	12.6
Hematocrit (%)	33	34.4	26.8	32.2	39	37.4	42.3	38
Platelet	394000	433000	296000	289000	235000	195000	267000	172000
White blood cell	5600	7000	7900	5900	6800	7500	4600	3910
Daily proteinuria (g/day)	7	1.4	1	0.324	0.079	0.098		+-

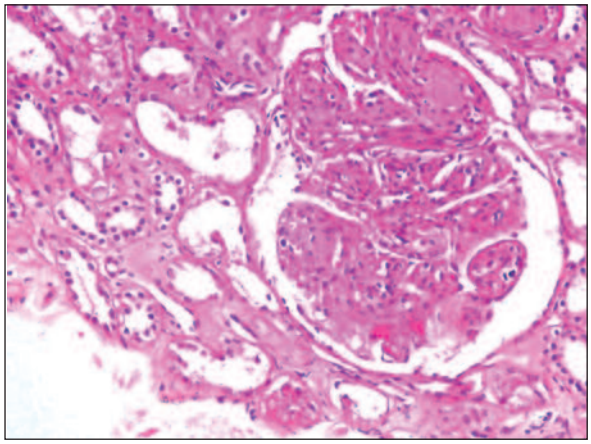

FIGURE 1: Renal biopsy showed thickened basement membrane and mesangial nodules (HE x40).
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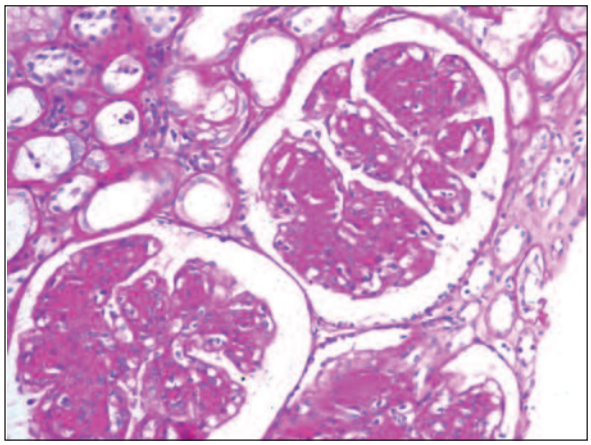

FIGURE 2: On renal biopsy, PAS positive mesangial nodules accompanied thickened basement membrane (PAS x40). Positivity of mesangial nodules (PAS x40).
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blocker (atenolol), atorvastatin, dipyridamole were started and a low salt diet was proposed. Three months later, proteinuria decreased to 1.4 g/day. Six months later her complaints disappeared. At this time, anti-osteoporosis treatment including calcium and vitamin D was added to her treatment. One year later, proteinuria was 324 mg/day, BUN/creatinine were within normal limits but the patient complained of leg pain. Twenty-four months later, proteinuria was 79 mg/day. Two years later, hypercalcemia developed (11.3 mg/dL) and vitamin D and calcitriol were stopped. She admitted one year later and severe hypercalcemia was detected. For hypercalcemia, bone marrow aspiration and biopsy were done. Bone marrow biopsy showed 60% plasma cell infiltration with kapa (κ) clonality (Figure 4). Patient was treated with VAD (vincrisitine, doxorubicine, dexamethasone) plus zoledronic acid. After 3 cycles, bone marrow plasme cell infiltration was less than 5%. High dose chemotherapy and autologous transplantation was planned but the patient rejected this therapy, VAD regimen was completed to 6 cycles. In September 2009, disease recurrence was detected and bortezomib was prescribed. After four cycles remission was achieved, but stem cell transplantation was rejected again by the patient. Bortezomib containing regimen was completed to 8 cycles. However in

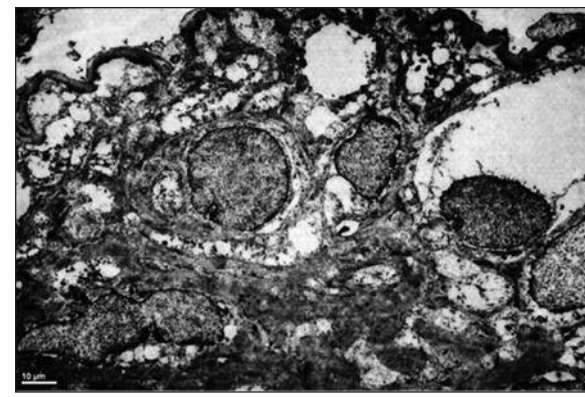

FIGURE 3: Electron micrographic evaluation showed punctate subendothelial electron dense material and mesangial light chain deposits (this findings was obtained during re-evaluation).

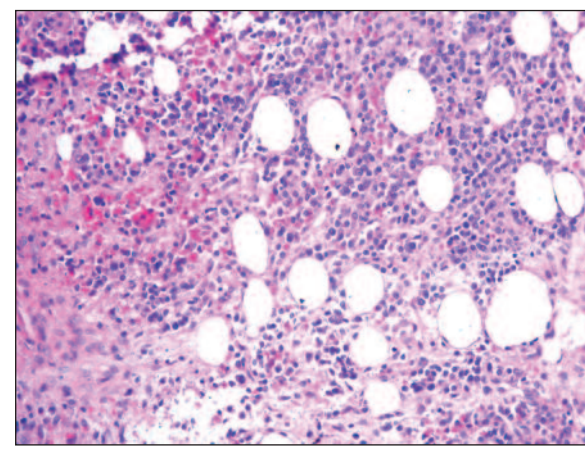

FIGURE 4: On bone marrow biopsy increased plasma cells (%89) with kappa clonality was found (HE, x 20).
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July 2011 disease recurred. At this time, a lenalidomide containing regimen was given. After 3 cycles, partial response was detected. but stem cell transplantation was rejected again by the patient. She is receiving a lenalidomide containing regimen with good clinical status.

DISCUSSION

It is very well known that there is an association between glomerular lesions and malignant disorders. The relationship between cancer and NS has been first reported by Lee et al. in 1966.[1] Membraneous nephritis is the most common accompanying lesion in solid tumors. Other renal lesions associated with neoplastic diseases are minimal change disease, tubulointerstitial disorders and membranoproliferative-focal necrotising-cryoglobulinemic glomerulonephritis.[2,3]

NS cases associated with MM have been uncommonly reported. In a large study covering 1027 cases with MM, NS was reported in only 13 cases; seven of them had amyloid light-chain amyloidosis, two had DM, two had light chain disease, one had glomerulosclerosis and in one case etiology could not be determined.[4] In another retrospective study covering 204 cases, renal involvement was detected in 27% of the cases and NS was found in one forth of these cases. Renal biopsy showed myeloma cast nephropathy in 60% of the cases, tubulointerstitial nephritis in 14%, amyloidosis in 11%, nodular glomerulosclerosis and plasma cell infiltration in 3.6% of the cases.[5]

Renal biopsy performed in 5443 cases with monoclonal immunoglobulin disease showed membranous glomerulonephritis in only three cases.[6] Additionally, membranous glomerulonephritis have been reported in two cases with MM .[7]

In a study covering 81 cases with MPGN, the relationship between MPGN and monoclonal gammopathy have been explored and renal biopsies have been re-evaluated. Among these cases serum and/or urine immune electrophoresis have been found to be positive for monoclonal gammopathy in 40% of the cases. In this study, MPGN has been found to be most frequently related to monoclonal gammopathy of undetermined significance, and other etiologic factors were MM, low grade B cell lymphoma and chronic lymphocytic leukemia.[8]

After the diagnosis of MM, we re-evaluated renal biopsy with immunohistochemistry, immunfluorescence microscopy (IF) and electron microscopy (EM). There was no evidence of deposition of Ig, complement or light chains. Demonstration of monoclonal light chains using immunofluorescence and/or immunohistochemistry is not always possible. There are three possibilities for this: commercially available antibodies may not be able to detect the light chain deposits in tissues which is composed of physicochemical abnormal light chains. The second reason may be related to paraffinized sections. Third point can be due to heavy chain deposition, not light chain. In heavy chain deposition disease, stains for kappa and lambda are negative, staining for one of the immunoglobulins in the peripheral capillary wall and mesangial area. We could not find staining for IgG, IgA or IgM. The heavy chain can also be IgD or IgE. We could not apply IgD and IgE with IF. We found punctate subendothelial electron dense material and mesangial light chain deposits with EM, and negative immune-complex deposition suggested heavy chain deposition disease. Punctate subendothelial electron dense deposits in the glomerulus is a more specific finding for monoclonal immunoglobulin deposition disease (MIDD). Diabetic nephropathy and monoclonal immunoglobulin deposition disease could not be easily differentiated from MPGN only by light microscopy. Morphologically, we detected nodular glomerulopathy which is the most characteristic finding in a patient with MIDD (Figure 3). Mesangial nodules have some variations according to the stage of the disease. Glomerular basement membrane and tubular basement membrane are thickened because of deposition of heavy or light chains. In our case, nephrotic syndrome preceded the development of MM. Therefore, our case was different from most of the other cases. In our case, renal biopsy was evaluated as MPGN at the beginning. Due to the technical problems at that time, electron microscopic and immunofluorescent evaluation could not be made. Patient responded very well to

steroids and conservative treatment as MPGN, renal failure and proteinuria regressed in a short time. However, 3 years later severe hypercalcemia developed. At this time, bone marrow biopsy was done and MM was diagnosed. The patient was treated with zoledronic acid plus anti-myeloma treatment. Her condition was very well at the end of first therapy. High dose chemotherapy and stem cell transplantation was advised but she rejected this modality. After 2 years, MM relapsed and lenalidomide plus dexamethasone treatment was started. At this relapse, renal dysfunction and proteinuria did not recur.

In conclusion, we reported a case with renal failure, and NS preceding the diagnosis of MM. At the beginning , the patient was treated as NS. Three years later MM was detected without overt renal failure. It is generally known that glomerulonephritis develops during the follow up period of MM, but glomerulonephritis preceding MM is rare. Renal biopsy cannot be diagnostic, and in this situation, immunofluoresence and electron microscopic examinations and re-evaluation of all renal biopsy findings should be performed. In an adult, malignant disease should be considered in cases with idiopathic glomerulonephritis.

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