RENAL FAILURE

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CASE REPORT

Renal involvement in Waldenström's macroglobulinemia: case report and review of literature

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Abstract

Waldenström's macroglobulinemia (WM) is a rare lymphoid neoplasia, accounting for 2% of all hematological malignancies. Renal complications occur rather rarely compared to multiple myeloma. The most common renal manifestations are mild proteinuria and microhematuria. We describe a case of MW presenting with acute renal failure and NS. A 67-year-old man was referred to our hospital for sudden onset nephrotic syndrome. Electrophoresis revealed a monoclonal component in the gamma region, which was classified as an IgM k. During hospitalization, acute kidney injury developed, with creatinine up to 5 mg/dL, despite adequate hydration and alkalinization. A kidney biopsy was performed, showing minimal change disease (MCD) with interstitial and capsular lymphoid infiltrates of B-Lymphocytes CD20+. B-lymphocytes infiltration suggested the possibility of renal localization of lymphoproliferative disorder. So, bone marrow histology was performed, revealing lymphoplasmacytic lymphoma (WM). The patient was treated with bortezomib, desamethasone, and rituximab, with partial recovery of renal function (creatinine 1.5 mg/dL) and complete remission of proteinuria after 8-month follow-up. The remission of NS in our patient with rituximab seems to emphasize the pathogenetic role of B cells in MCD, although a coincident effect of immunosuppression on both the underlying renal disease and the hematologic disease cannot be excluded.

Keywords

Minimal change disease, nephrotic syndrome, renal failure, rituximab, Waldenström macroglobulinemia

History

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Introduction

Waldenström's macroglobulinemia (WM), first described by J. Waldenström in 1944, is a rare lymphoid neoplasia, accounting for 2% of all hematological malignancies. The WHO defines WM as a lymphoplasmacytic lymphoma associated with a monoclonal immunoglobulin M (IgM) protein. Most WM patients have symptoms and signs related to tumoral infiltration (cytopenia and hepatosplenomegaly), monoclonal protein accumulation in the circulation (cryoglobulinemia and serum hyperviscosity syndrome), monoclonal protein accumulation in tissues (amyloidosis), or autoantibody production (neuropathy and hemolytic anemia).[1] Hepatomegaly occurs in 20%, splenomegaly in 15%, and lymphadenopathy in 15% of the patients. The most common presenting symptom is fatigue related to a normochromic normocytic anemia. The presence of ≥10% clonal lymphoplasmacytic cells in bone marrow confirms the diagnosis.[2]

Renal complications occur rather rarely in WM compared to multiple myeloma. The most common renal manifestations are mild proteinuria and microhematuria. Nephrotic syndrome (NS) is rare. Bence-Jones proteinuria is present only in 10–15% of cases.[3] Only less than 3% of patients develop end-stage renal failure.[4]

We describe a case of MW presenting with acute renal failure (ARF) and NS.

Case report

In January 2012, a 67-year-old man was referred to our hospital for sudden onset of edema, weight gain (10 kg during a month), and renal failure. Physical examination showed generalized edema, without hepatosplenomegaly or lymphadenopathy. Blood pressure was normal. Laboratory tests yielded the following values: hemoglobin 14.4 g/dL, white blood cell count 9390/mm^3 with 71% polymorphonuclear leukocytes and 18% lymphocytes, platelet count 428,000/mm^3, urea 112 mg/dL, creatinine 1.8 mg/dL, creatinine clearance 38 mL/min, calcium 8.5 mg/dL, uric acid 5.5 mg/dL, LDH 191 U/L (n.v. <480), total protein 5.1 g/dL with albumin 1.4 g/dL, alpha1-globulin 6%, alpha2-globulin 18%, beta-globulin 9.6%, and gamma-globulin 39.5%. Blood glucose, hepatic tests, lipids, coagulation, HBV, and HCV markers were normal. Cryoglobulins were absent. Serum complement was normal. Urine sediment contained many granular casts and 10–15 dysmorphic erythrocytes. Proteinuria was 9.4 g/24 h. Electrophoresis revealed a monoclonal component in the gamma region, which was classified as an IgM k. Immunoglobulins and light chains were as follow: IgG

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265 mg/dL (normal 681–1648), IgA 155 mg/dL (normal 87–474), IgM 2460 mg/dL (normal 48–312), kappa light chains 1296 mg/dL (normal 629–1350), lambda light chains 138 mg/dL (normal 313–723), kappa–lambda ratio 9.3. Bence-Jones proteinuria was negative.

Radiographic imaging of the bones and a total body computed tomography did not show, respectively, lytic lesions and organomegaly or lymphadenopathy. PET-CT scan was negative for any abnormal metabolic activity. Bone marrow aspiration was normal.

During hospitalization, acute kidney injury developed, with creatinine up to 5 mg/dL, despite adequate hydration and alkalinization. Renal US showed normal-sized kidneys with no signs of obstruction, and Doppler examination ruled out renal vein thrombosis.

A kidney biopsy was performed to determine the cause of proteinuria and decreased renal function.

Renal biopsy showed minimal change disease (MCD) with small foci of parenchymal scleroatrophy (Figure 1), interstitial and capsular lymphoid infiltrates of B-Lymphocytes CD20+ (Figure 2). Immunofluorescence showed widespread granular deposition of IgM in mesangium. Stains for IgG, IgA, and kappa and lambda chains were negative. Congo red staining was negative. Electron microscopy did not reveal clear electron-dense deposits in the glomerular basement membrane but showed diffuse loss of podocyte foot processes (Figure 3).

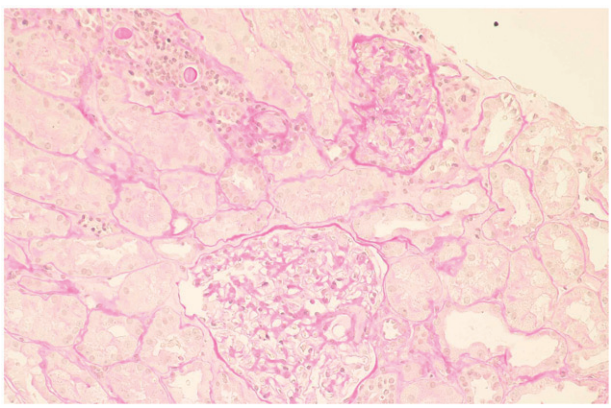

Figure 1. Light microscopy: PAS staining, normal glomeruli (200×).

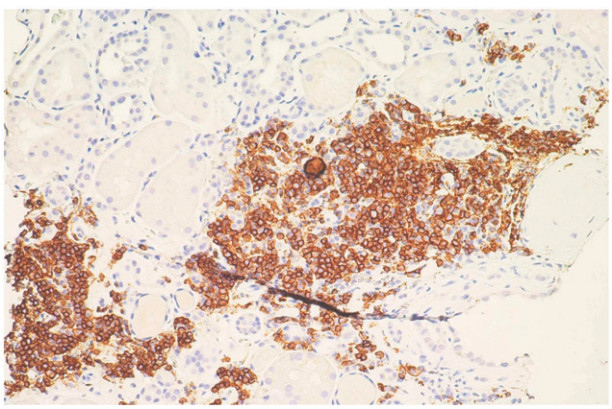

Figure 2. Immunohistochemistry for CD20: interstitial lymphoid infiltrates of B lymphocytes (200×).

B-lymphocytes infiltration suggested the possibility of renal localization of lymphoproliferative disorder. So, bone marrow histology was performed, showing micronodular infiltration of lymphoid cells with phenotype CD20+ CD5- (90%), CD 138+(10%), consistent with a diagnosis of lymphoplasmacytic lymphoma (WM).

The patient was treated with bortezomib, dexamethasone, and rituximab, with partial recovery of renal function (creatinine 1.5 mg/dL) and complete remission of proteinuria after 8-month follow-up (Figure 4).

Discussion

Renal involvement in patients with WM is rare as compared with those of multiple myeloma, because hypercalcemia is uncommon and Bence-Jones proteinuria is usually small in amounts. In autopsy series of WM, only 3.8% to 7.4% of the patients developed renal failure. While proteinuria and

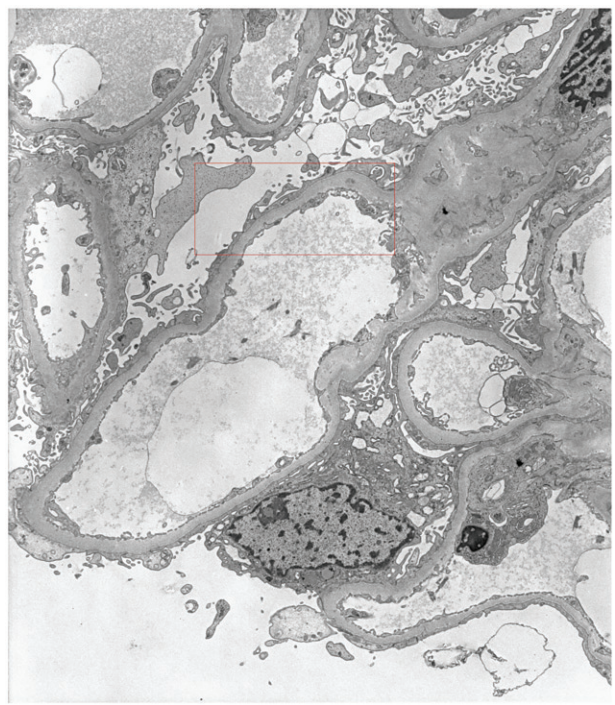

Figure 3. Electron microscopy: widespread foot process fusion in the absence of electron-dense deposits, UrPb (5000×).

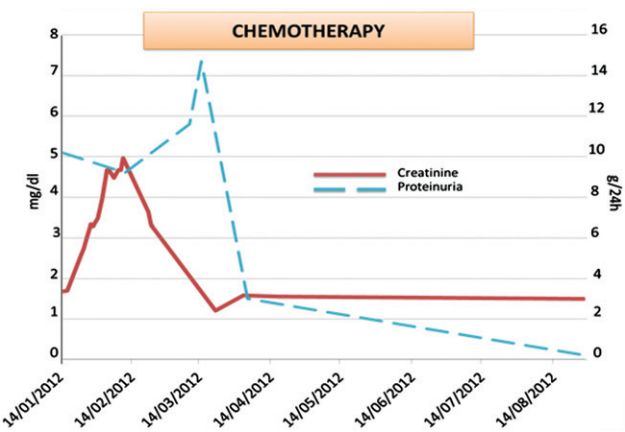

Figure 4. Trends of creatinine and proteinuria.

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Table 1. Cases of biopsy-proven renal involvement during WM reported in literature since 1975.

Case No.	References	Age/sex	Serum creatinine (mg/dl)	Proteinuria (g/24 h)	Mono-clonal protein	Bence-Jones proteinuria	Cryoglobulins	Renal disease	Renal biopsy		
									IF	Electron microscopy: deposits	Interstitial infiltrates
1	Martelo[10]	53/M	1.4	11	IgM k	Present	Absent	ICGN	IgG, IgM, C3	Intramembranous	NA
2	Lindstrom[6]	67/M	normal	8.8	IgM k	NA	Absent	MCD	IgM	Subendothelial, localized	Atypical lymphocites and histiocytes
3	Meyrier[11]	75/M	2.8	0.8	IgM k	NA	Absent	CGN	IgG, C3	NA	Lymphoid cells, rare plasma and histiocytic cells
4	Nakamoto[12]	54/M	2.3	2	IgM k	NA	Absent	LCDD	k	Subendothelial, mesangial	NA
5	Hory[5]	64/F	1.14	15	IgM k	Absent	Present	MCD	NA	No deposits	NA
6	Ogami[13]	74/M	3	1	IgM k	Absent	Absent	AMYL+CGN	Negative	No deposits	Lymphoid cells
7	Tsuji[14]	83/M	1	20	IgM k	NA	Present	MPGN	IgM	Scattered electron-dense deposits	Absent
8	Gonzalez[15]	62/M	mild ↑	0.25	NA	NA	Present	MN + CGGN	NA	NA	Lymphoplasmocytic cells
9	Veltman[16]	53/M	1.57	0.83	IgM k	Present	Absent	MPGN	k	No deposits	Lymphocites, histiocytes, plasma cells
10	Soetekouw[17]	66/F	0.91	8.43	IgM λ	Absent	Absent	AMYL + IgM	IgM	Subendothelial	NA
11	Dussol[18]	59/M	2.25	3	IgM λ	Absent	Absent	FG + AMYL	Negative	Criss-crossing fibrils	Lymphocytes
12	Harada[19]	69/M	0.97	7	IgM λ	NA	Present	ICMDD	IgM, λ	NA	NA
13	Wong[8]	59/M	1.3	4.4	IgM λ	Absent	Absent	ATN	Unremarkable	NA	Lymphoplasmocytic cells
14	Yonemura[20]	53/M	3	5	NA	NA	Present	CGGN	IgM, IgG, C3	Subendothelial	NA
15	Da'as[21]	46/F	NA	>3.5	NA	NA	Present	MPGN	NA	NA	NA
16	Haraguchi[4]	72/M	0.9	5.5	IgM λ	Absent	Absent	ICGN	IgG, IgA, IgM, C4, k, λ	Subendothelial	Mononuclear cells
17	Isaac[3]	73/F	7.5	3.1	IgM λ	Present	NA	CN	IgG, IgA, IgM, C4, k, λ	No deposits	Lymphocytes, rare giant cells and eosinophils
18	Garcia[22]	56/M	4.4	5.5	IgM k	NA	Absent	CGN	IgM, k	NA	Lymphoid cells, some with plasmacytoid features
19	Terrier[7]	55/F	1.58	12.2	IgM k	Present	NA	MCD + ICMDD	NA	NA	Lymphoplasmocytic cells
20	Audard[23]	74/F	5.3	8	IgM λ	Present	Absent	ICMDD	IgM, λ, C3	NA	Absent
21	Audard[23]	67/F	1.97	4.5	IgM k	Present	Absent	ICMDD	IgM, k, λ	Intracapillary	Lymphocytes
22	Audard[23]	62/M	5.11	1.3	IgM k	Present	Present	ICMDD	IgM, k, λ, C3	NA	Lymphocytes
23	Audard[23]	63/M	2.03	2	IgM k	Present	Absent	MPGN	IgM, k, λ	NA	Lymphocytes
24	Colovic[24]	58/M	2.26	54	IgM k	NA	Absent	MPGN	IgM, k	NA	NA
25	Kawano[25]	53/M	1.6	3.7	IgM k	Present	Present	CGGN	NA	Subepithelial, subendothelial, intramembranous, mesangial	Polymorphonuclear cells and lymphocytes
26	Kim[26]	61/F	1.4	>3.5	IgM k	Absent	Present	CGGN	IgM	Subendothelial, mesangial	NA
27	Martina[27]	39/M	1.2	4.7	IgM k	Absent	Present	CGGN	NA	NA	Lymphocytes
28	Lee[28]	44/M	1.1	7.8	IgM λ	Absent	Absent	MN	IgM, k	Subepithelial	Absent
29	Gnemmi[1]	66/F	13.6	0.15	k FLC	NA	NA	CN + LCDD	k	Dense granular deposits along tubular basement membranes	Lymphocytes and plasma cells
30	Gnemmi[1]	82/M	4.2	3	k FLC	NA	NA	CN + LCDD + AMYL	k	No deposits	Lymphocytes (scattered)
31	Perez[29]	76/F	9.03	3	IgM k	Present	NA	CN	K	NA	NA
32	Present case	67/M	5	9.4	IgM k	Present	Absent	MCD	IgM	No deposits	Lymphocytes

Note: ICGN = immune complex-mediated glomerulonephritis; CGN = crescentic glomerulonephritis; LCDD = light-chain deposition disease; AMYL = amyloidosis; MN = membranous nephropathy; CGGN = cryoglobulinemic glomerulonephritis; FG = fibrillary glomerulopathy; ATN = acute tubular necrosis; ICMDD = intracapillary monoclonal deposits disease; CN = cast nephropathy; FLC = free light chain; NA = not available.

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microhematuria are not infrequent, incidence of NS is reported to be less than 7%. AL amyloidosis is commonly considered as the main cause of NS.[4] Moreover, there are sporadic reports of associated membranous nephropathy, MCD, crescentic glomerulonephritis, immune complex-mediated glomerulonephritis, cast nephropathy, and Fanconi's syndrome. MCD is more frequently associated with Hodgkin's lymphoma; to date, only three cases have been reported in literature in patients with MW.[5–7] However, direct infiltration of the kidney by atypical lymphoid cells remains the most common finding, occurring in 50–60% of the patients, together with large intracapillary aggregates of IgM (pseudothrombi).[8] Different patterns of renal damage can be present in the same patient. The largest series of renal symptoms and histologic lesions was described by Morel-Maronger et al. in 1970. Of 16 patients, only 5 underwent renal biopsy, while in the others renal histology was provided by autopsy. Three patients had NS, five patients presented with renal failure, and in two cases it was superimposed on NS. The most common histologic findings were intraglomerular thrombi, present in five cases; three patients had AL amyloidosis, one had only endomembranous deposits, and in seven cases no detectable lesions were found.[9]

We reviewed the literature about kidney involvement during WM from 1970 up till now (Table 1).

We found 32 cases of WM with histologically proven renal involvement, including our report. NS was present in 20 patients (62.5%). Twenty patients presented renal failure defined as serum creatinine >1.5 mg/dL; in eight cases it was superimposed on NS. A number of histological lesions were described; moreover, in five patients the coexistence of different glomerular diseases was observed. Direct infiltration of the kidney by atypical lymphoid cells was present in 17 cases. Most common histologic findings included intracapillary thrombi (five cases) and membranoproliferative glomerulonephritis (five cases) and cryoglobulinemic glomerulonephritis (five cases) followed by AL amyloidosis (four cases), cast nephropathy (four cases), and cryoglobulinemic glomerulonephritis (four cases); three patients presented light-chain deposition disease and three had MCD.

Our patient presented with NS due to MCD and ARF. ARF is an uncommon presentation of WM, usually associated with glomerular deposition of various proteins including IgM, IgG, cryoglobulins, fibrin, light chains, complement, or even amyloid proteins.[22] Most common causes of acute renal failure in monoclonal gammopathies, such as hypercalcemia, uric acid nephropathy, dehydration, cast nephropathy, drug-induced ARF, and sepsis, were excluded. We postulate that the severe interstitial lymphocytic infiltrate was the preeminent cause of acute renal failure. MCD is the most common cause of nephrotic syndrome in children, accounting for 90% of cases under the age of 10; in adults of all ages, it is responsible for 15% of NS cases.[30] The pathophysiology of MCD remains poorly understood. It is well known that the release of cytokines by T cells plays a key role. More recently, however, accumulating data has pointed toward a strong contribution of B-cell immunity. In particular, an unidentified circulating permeability factor may be directly released from B cells or be secondary to aberrant cross-talk between T and B cells.[31] Gilbert et al.[32] recently reported long-term remission using rituximab, an anti-CD20 monoclonal antibody, in a child with steroid-dependent MCD, despite failure of multiple other therapies. The child remained in remission, while the CD19 (B-cell) counts were undetectable, but relapsed after 9 months when CD19+ cells returned. The remission of NS in our patient with rituximab seems to emphasize the pathogenetic role of B cells in MCD, although a coincident effect of immunosuppression on both the underlying renal disease and the hematologic disease cannot be excluded. Further studies are needed to better understand the exact role of B cells in the pathogenesis of renal diseases, especially when they occur during hematologic disorders.

Declaration of interest

The authors report no conflicts of interest. The authors alone are responsible for the content and writing of the paper.

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