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A Case of Waldenström Macroglobulinemia with Acute Kidney Injury as the First Manifestation and Literature Review

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Abstract: Waldenström macroglobulinemia is a rare lymphoid tumor accounting for 2% of all hematological malignancies. Renal complications are less common compared to multiple myeloma, with the most frequent renal manifestations being microproteinuria and microhematuria. This paper presents a case of Waldenström macroglobulinemia with acute kidney injury as the initial manifestation. A 75-year-old male was admitted to the Affiliated Hospital of Hebei University after elevated blood creatinine levels were detected for one day. Upon admission, his blood creatinine was 255 μmol/L, urine protein was 1+, urine erythrocytes were negative, electrophoresis showed IgM positivity in the κ-region, and a bone marrow biopsy indicated a tendency towards lymphoplasmacytic lymphoma. The patient was discharged after receiving a treatment regimen of prednisone acetate, thalidomide, and cyclophosphamide, and continued oral medication outside the hospital. The patient returned two weeks later due to diarrhea and was found to have a blood creatinine level of 985 μmol/L, along with severe acidosis and hyperkalemia. The patient refused renal replacement therapy and was not followed up, resulting in a poor prognosis. Additionally, a review of the literature is provided to contextualize this case within the broader scope of existing research.

Keywords: Waldenström macroglobulinemia; Acute kidney injury; Prognosis; Literature review

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1. Introduction

Waldenström macroglobulinemia is a chronic B-cell lymphoproliferative disorder characterized by the overgrowth of lymphoplasmacytic cells in the bone marrow and increased IgM immunoglobulin secretion in the serum, accounting for 2% of all hematological malignancies [1,2]. Amyloidosis, monoclonal IgM deposition disease, cryoglobulinemia, and direct infiltration by lymphoplasmacytic lymphoma are the most common renal pathological manifestations [3]. Acute kidney injury associated with Waldenström macroglobulinemia is rare compared to multiple myeloma [4].

This article describes a rare case of acute kidney injury associated with Waldenström macroglobulinemia, which unfortunately had a poor prognosis. By presenting this case, the article aims to raise awareness of renal

disease associated with Waldenström macroglobulinemia.

2. Case report

A 75-year-old Chinese male patient was admitted to the hospital with malaise and elevated blood creatinine. The patient had experienced syncope 30 and 10 years ago, respectively, but was not treated. Three months before admission, the patient experienced fatigue with no apparent cause, and elevated blood creatinine was detected at a local hospital one day earlier. The patient's vital signs were as follows: temperature 36.6°C, heart rate 78 beats/min, respiration 19 breaths/min, and blood pressure 122/66 mm Hg. The patient's general condition and laboratory findings are shown in **Table 1**.

Table 1. Clinical and laboratory data

Clinical data	
Age/gender	75 years/male
Complaint	Fatigue, elevated blood creatinine
Main clinical features	Renal failure
Laboratory data	
Leukocytes (10^9/L)	4.36
Hemoglobin (g/L)	67
Platelets (10^9/L)	69
Peripheral blood smear	Erythrocytes arranged in a cord-like pattern
CRP (mg/L)	34.00
LDH (U/L)	56
Total protein (g/L)	95
Albumin (g/L)	29
Urea nitrogen (mmol/L)	14.38
Creatinine (μmol/L)	256
Na (mmol/L)	138
K (mmol/L)	4.3
Cl (mmol/L)	107
IgA (g/L)	0.14
IgG (g/L)	5.08
IgM (g/L)	59.60
β2-MG (mg/L)	14.5
Monoclonal protein (g/L)	40.1
Proteinuria	1+

Further examination of electrophoresis showed positive IgM in the κ-region. A bone marrow examination was performed, revealing the following findings:

(1) Bone marrow image: Active bone marrow hyperplasia, suppressed granulocyte and erythroid hyperplasia, and significant lymphocyte line hyperplasia in 69% of the cases. Juvenile lymphocytes and

plasma cells were seen in 6% of the cases, along with lymphoid plasma cells. Six megakaryocytes were observed in the entire film, platelets were slightly rare, with normal morphology.

(2) Blood picture: Reduced white blood cell count, red blood cells arranged in cords, and slightly reduced platelets.

(3) Comments: (a) Significant bone marrow lymphocyte hyperplasia; (b) Presence of lymphoid plasma cells. Further examination combining clinical context is recommended (**Figure 1**).

(4) Bone marrow pathology showed: (a) Microscopic findings: HE and PAS staining revealed active bone marrow hyperplasia (80%), diffuse proliferation of small lymphocytes (70%–80% of nucleated cells), increased plasma cells (5%–10%), and few tertiary hematopoietic cells. Reticulofibrillar staining (MF-1 grade) was observed. Congo red (-); (b) Immunohistochemistry: CD38 plasma cells +, CD138 plasma cells +, Kappa+, Lambda-, CD20 small lymphocytes +, PAX5 small lymphocytes; (c) Diagnostic findings: Predisposition to lymphoplasmacytic lymphoma. Further examination of immunofixation electrophoresis and MYD88 gene mutation is recommended (**Figure 2**).

(5) Bone marrow flow cytometry: Monoclonal B lymphocytes and monoclonal plasma cells were observed in the specimen with the following phenotypes: (a) Monoclonal B lymphocytes accounted for 40.38% of the nucleated cells, with small FSCs and SSCs that did not express CD5, and a small number that expressed CD10, and (b) monoclonal plasma cells accounted for 0.09% of the nucleated cells, with restricted light chain expression. Hence, the patient is possibly diagnosed with lymphoplasmacytic lymphoma (LPL), also known as Waldenström macroglobulinemia. Further examination combining pathology, immunofixation electrophoresis, and MYD88 gene mutation results is recommended.

(6) Bone marrow sequencing: MYD88 L265P missense point mutation, CXCR4 shifting mutation, ARID1A shifting mutation.

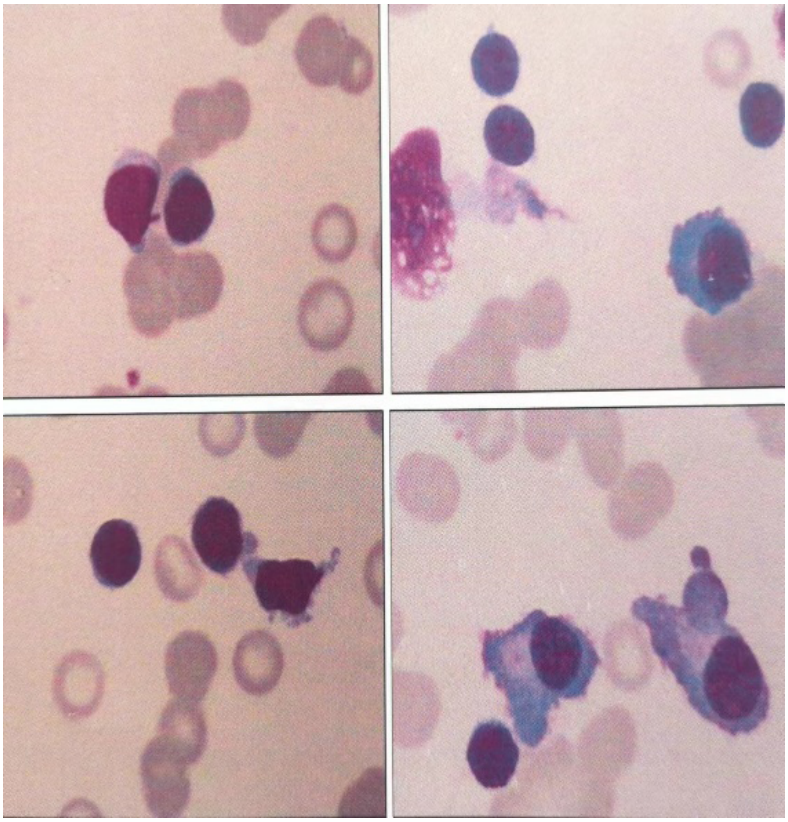

Figure 1. Peripheral blood smear

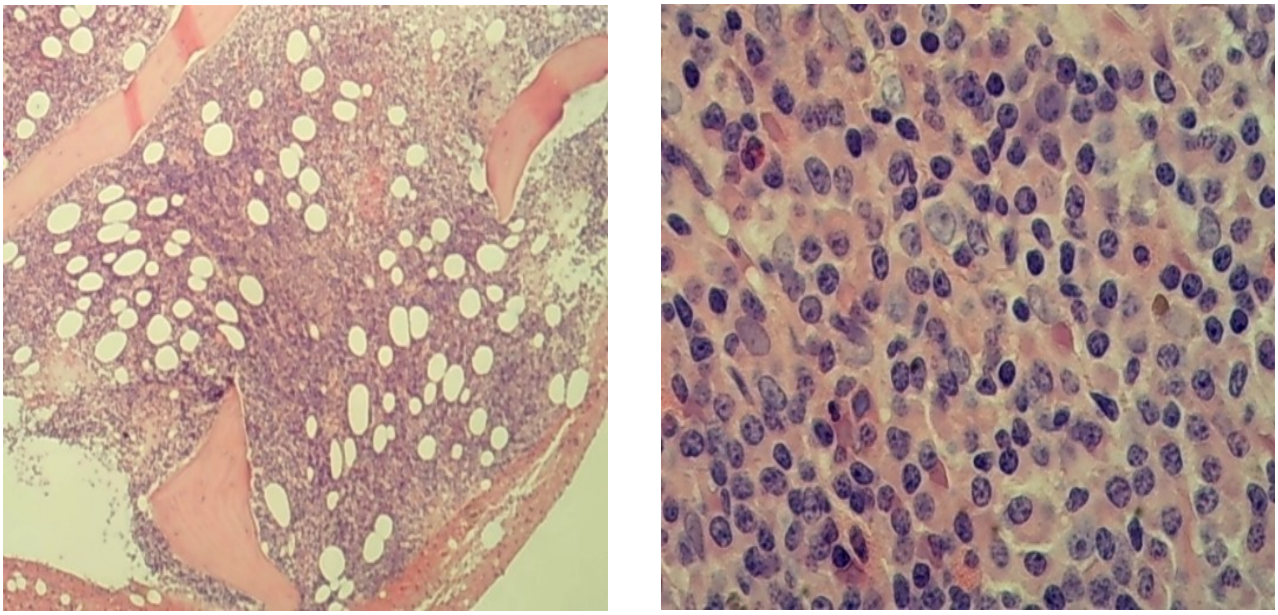

Figure 2. Bone marrow pathology

Unfortunately, the patient did not undergo a renal biopsy, so the renal pathological manifestations were not known. The patient eventually received a regimen of prednisone acetate (30 mg/day), thalidomide (50 mg/night, gradually increasing to 100 mg/night), and cyclophosphamide (50 mg/day). The patient was readmitted to the hospital 2 weeks later with diarrhea, and the laboratory results are shown in **Table 2**. The patient refused renal replacement therapy and rehospitalization, resulting in a poor prognosis.

Table 2. Laboratory data of patients after 2 weeks

Laboratory data	
Leukocytes (10^9/L)	4.08
Hemoglobin (g/L)	81
Platelets (10^9/L)	42
Urea nitrogen (mmol/L)	64.20
Creatinine (μmol/L)	985
Na (mmol/L)	128
K (mmol/L)	6.3
P (mmol/L)	2.38

3. Literature review

The manifestation of renal involvement in Waldenström macroglobulinemia is rare. A large cohort study by Vos *et al*. found that the cumulative incidence of Waldenström macroglobulinemia-associated nephropathy at 5, 10, and 15 years was 2.9%, 3.8%, and 5.1%, respectively [3].

A case of acute kidney injury associated with Waldenström macroglobulinemia was first reported by Argani and Kipkie as early as 1964. At that time, severe dehydration was thought to be the probable cause of renal insufficiency; however, a renal biopsy revealed that the deposition of proteolytic material in the glomerular capillaries led to acute kidney injury [5]. Yonemura *et al*. reported a case of acute kidney injury associated

with Waldenström macroglobulinemia and cryoglobulinemia type 1. They hypothesized that intraglomerular proliferation and deposition of monoclonal immunoglobulin M in glomerular capillaries could lead to glomerular capillary occlusion, reducing glomerular filtration rate and causing acute kidney injury. However, the exact pathogenesis was unknown as no renal biopsy was performed [4]. Salviani *et al*. reviewed extensive literature and found that acute kidney injury is a rare manifestation of Waldenström macroglobulinemia and is usually associated with the deposition of various proteins in the glomerulus, including IgG, IgM, cryoglobulins, fibronectin, light chains, complement, and even amyloid. They speculated that severe mesangial lymphocytic infiltration is the primary cause of acute kidney injury [1].

Vos *et al*. found from a pathological study of nephropathy associated with Waldenström macroglobulinemia that amyloidosis, monoclonal IgM deposition disease/cryoglobulinemia, and lymphoplasmacytic lymphocytic infiltration were the most common renal pathological manifestations, accounting for 25%, 23%, and 18% of the cases, respectively. Other pathological manifestations included light-chain deposition disease (9%), light-chain tubulointerstitial nephropathy (9%), thrombotic microangiopathy (7%), microscopic lesion nephropathy (5%), light-chain tubulopathy (2%), and membranous nephropathy (2%) [3]. A study by Uppal *et al*. concluded that nephropathy associated with Waldenström macroglobulinemia results from direct infiltration of malignant cells, immune-mediated cellular reactions, or abnormal production of paraproteins, which aligns with previous studies [6].

In this paper, the patient was diagnosed with Waldenström macroglobulinemia by bone marrow biopsy; however, the cause of his acute kidney injury remains unknown due to the absence of a renal biopsy, highlighting a limitation in this case.

The International Prognostic Scoring System for Waldenström Macroglobulinemia has been widely used for risk stratification before initial treatment, but its role in treatment decisions is limited. Given the increasing prevalence of Waldenström macroglobulinemia with age and the emergence of new prognostic markers, the RIPSSWM was introduced in 2019 [7]. In a Mayo Clinic study of 889 patients aged over 65 years, LDH > upper limit of normal and serum albumin < 3.5 g/dL were found to be independent prognostic factors. Patients were categorized as low, intermediate, or high risk based on the presence of 0, 1, or ≥ 2 risk factors, respectively [8]. In this simplified model, overall survival was 14.6 years in the low-risk group, 11 years in the intermediate-risk group, and 7.2 years in the high-risk group [8]. However, there is a paucity of data on the prognosis and outcome of renal injury associated with Waldenström macroglobulinemia. This literature search revealed that Vos *et al*. studied 1,391 patients with Waldenström macroglobulinemia, 44 of whom had renal biopsy-proven Waldenström macroglobulinemia-associated nephropathy. The median overall survival for these 44 patients was 11.5 years, compared to 16 years for the remaining patients. Those patients who had stable or improved renal function after treatment appeared to have a higher survival rate [3]. The study recommended monitoring renal function in patients with Waldenström macroglobulinemia and performing renal biopsies in cases of unexplained acute kidney injury or nephrotic syndrome [6].

Higgins *et al*. at the Mayo Clinic evaluated post-treatment outcomes in patients, finding that three patients with non-amyloid-associated glomerulopathy achieved complete remission, while two patients with amyloid-associated glomerulopathy and one with tubulointerstitial nephropathy achieved partial remission. Patients with non-amyloid-associated glomerulopathy appeared to have longer survival. Patients with amyloid-associated nephropathy had the highest chance of progression to end-stage renal disease [9].

The panel concluded that treatment for Waldenström macroglobulinemia should begin when hemoglobin is < 10 g/L and/or platelet count is less than 100×10^9/L, attributable to hypertrophic adenopathy or organomegaly, or in cases of severe disease-related complaints, including recurrent fevers, night sweats, weight loss, malaise, or systemic manifestations such as high blood viscosity syndrome, symptomatic neuropathy, nephropathy, amyloidosis, symptomatic cryoglobulinemia, or evidence of disease transformation [7]. Renal injury

associated with Waldenström macroglobulinemia should be promptly treated with hematological therapy. Current treatments include oral alkylating agents, corticosteroids, purine nucleoside analogs, and rituximab. Additionally, novel therapies such as the rapamycin inhibitor everolimus and Bruton's kinase inhibitor ibrutinib have shown promising clinical results [10].

4. Conclusion

Waldenström macroglobulinemia belongs to the category of hematological diseases, and its associated renal injury, characterized by rarity, insidious onset, and lack of specific clinical manifestations, poses a diagnostic and therapeutic challenge. In elderly men with unexplained gradual renal function deterioration, it is crucial to identify the primary disease and consider rare conditions to achieve early detection and treatment, thereby improving patient survival rates.

Disclosure statement

The authors declare no conflict of interest.

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