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【 CASE REPORT 】

Waldenström's Macroglobulinemia/Lymphoplasmacytic Lymphoma Developing Renal AA Amyloidosis: A Case Report and Literature Review

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Abstract:
AA amyloidosis is a rare renal complication of Waldenström's macroglobulinemia/lymphoplasmacytic lymphoma (WM/LPL). A 66-year-old man with WM/LPL presented with nephrotic syndrome. A renal biopsy showed AA amyloidosis. Chemotherapy resulted in the remission of hematologic and nephrotic syndromes. Two years into follow-up, he became infected with coronavirus disease 2019 and had massive proteinuria, despite no relapse of WM/LPL. A second renal biopsy confirmed a diagnosis of AA amyloidosis. However, increased prednisolone did not improve proteinuria. The patient ultimately died of cryptococcal meningitis. This case highlights the diverse spectrum of renal involvement in monoclonal IgM-secreting diseases and difficulty in managing fatal complications.

Key words: monoclonal IgM-secreting disease, nephrotic syndrome, COVID-19, prednisolone

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Introduction

Amyloidosis is a group of diseases caused by the deposition of amyloid, an insoluble polymerized protein, in the extracellular regions of tissues and organs (1). A total of 42 amyloid fibril proteins have been identified, each affecting the function of various organs, including the kidney, liver, gastrointestinal tract, peripheral nerves, heart, blood vessels, lungs, skin, and soft tissues (2). AA amyloidosis occurs as a complication of chronic inflammatory conditions or infections, such as rheumatoid arthritis and familial Mediterranean fever, leading to persistently high levels of serum amyloid A (SAA) protein, an acute phase reactant produced by the liver (3). Although rare, cases of AA amyloidosis associated with hematological diseases have been reported (4).

Waldenström's macroglobulinemia/lymphoplasmacytic lymphoma (WM/LPL) is a B-cell lymphoproliferative disease characterized by bone marrow infiltration and immunoglobulin M (IgM) monoclonal gammopathy that causes renal involvement. In addition to tubulointerstitial lesions, such as lymphoma cell infiltration, and glomerular lesions, such as AL amyloidosis and cryoglobulinemic glomerulonephritis, are common (5). However, renal involvement associated with AA amyloidosis is rare in patients with WM/LPL, and only a few cases have been previously reported (6).

We herein report a unique case of AA amyloidosis in a patient with WM/LPL who developed both AA amyloidosis and cryptococcal meningitis and present a literature review of the disease.

Case Report

A 66-year-old man with a history of colon and gastric polyps was admitted to a general hospital with anemia, bilateral inguinal lymphadenopathy, and bilateral lower-

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Table 1. Laboratory Findings on Admission.

Urinalysis			**Blood urea nitrogen**				
Dipstick			Creatinine	26	mg/dL (8-20)	Anti-nuclear antibody	40× (0-80)
Protein	2+		eGFR	0.87	mg/dL (0.46-0.79)	Homogeneous	Negative
Blood	2+		AST	68	mL/min/1.73 m^2	Speckled	Negative
Protein	2.43	g/gCr	ALT	10	U/L (13-30)	Ferritin	1,085.5 ng/mL (50-200)
Red blood cell	5-9	cells/high-power field	ALP	11	U/L (7-23)	sIL-2R	660 U/mL (205-587)
			Uric acid	44	U/L (38-113)	Cryoglobulin	Negative
NAG	6.3	IU/gCr (0-5.6)	Total protein	2.8	mg/dL (2.6-5.5)	Haptoglobin	131.1 mg/dL (19-170)
			Albumin	3.2	g/dL (6.6-8.1)	FLC (κ)	25.7 mg/L (3.3-19.4)
Blood counts			Total cholesterol	1.7	g/dL (3.7-5.4)	FLC (λ)	108.5 mg/L (5.7-26.3)
White blood cell	0.7×10^3	cells/μL	Triglyceride	112	mg/dL (0-219)	FLC (κ/λ)	0.24 (0.26-1.65)
Red blood cell	2.27×10^6	cells/μL	C-reactive protein	95	mg/dL (0-149)	β2-Microglobulin	4.6 mg/L (0.9-2.0)
Hemoglobin	7.5	g/dL	IgG	0.05	mg/dL (0-0.14)	β-D-glucan	<6 pg/mL
Hematocrit	21.6	%	IgA	215	mg/dL (861-1,747)		
Platelet	83×10^3	platelets/μL	IgM	23	mg/dL (93-393)		
			C3	433	mg/dL (50-269)		
Coagulation			C4	58.8	mg/dL (73-138)		
PT-INR	1.08		CH50	26.5	mg/dL (11-31)		
APTT	40.7	s					
D-dimer	4.6	μg/mL		45.0	U/mL (31.6-57.6)		

Cr: creatinine, NAG: N-acetyl-glucosaminidase, PT-INR: prothrombin time-international normalized ratio, APTT: active partial thromboplastin time, eGFR: estimated glomerular filtration rate, AST: aspartate aminotransferase, ALT: alanine aminotransferase, ALP: alkaline phosphatase, IgG: immunoglobulin G, IgA: immunoglobulin A, IgM: immunoglobulin M, C3: complement C3, C4: complement C4, CH50: 50% hemolytic complement activity, sIL-2R: soluble interleukin-2 receptor, FLC: free light chain

extremity edema. Laboratory investigations showed that the IgM and soluble interleukin-2 receptor (sIL-2R) levels were markedly elevated to 2,803 mg/dL and 12,224 U/mL, respectively. C-reactive protein (CRP) level was also elevated to 7.44 mg/dL. The serum creatinine and urine protein/creatinine ratio were 1.55 mg/dL and 1.9 g/gCr. Anti-nuclear antibody, anti-double-stranded DNA antibody, and anti-neutrophil cytoplasmic antibodies were all negative. Computed tomography revealed enlarged abdominal para-aortic lymph nodes (LNs). An LN biopsy revealed CD20+ B-cell lymphoma with suspected low-grade lymphoma. After receiving one cycle of rituximab-bendamustine (R-Benda) and rituximab-cyclophosphamide-doxorubicin-vincristine-prednisolone (R-CHOP) chemotherapy, the patient continued to receive prednisolone because of persistent massive proteinuria. Three months later, the patient was transferred to our hospital on Day 107 because of small intestinal bleeding and chemotherapy-induced pancytopenia.

On admission, physical findings were as follows: height, 168.9 cm, body weight, 48.2 kg, blood pressure, 110/63 mmHg. There were no abnormalities in the conjunctiva, heart, lungs, or abdomen and no swollen lymph nodes on the surface of the body. A urinalysis revealed microscopic hematuria, with a urine protein/creatinine ratio of 2.43 g/gCr. Laboratory tests revealed a serum creatinine of 0.87 mg/dL, serum albumin of 1.7 g/dL, serum ferritin level of 1,085.5 ng/mL, and alkaline phosphatase level of 44 U/L. IgM, sIL-2R, and C-reactive protein levels were 433, 660 U/mL and 0.05 mg/dL, respectively, all of which were remarkably improved over the initial data of the previous hospital. Other laboratory findings are shown in Table 1. Serum immunoelectrophoresis revealed an IgM-λ type M-protein. A flow cytometric analysis of the lymph node samples showed approximately 14% CD45+, CD19+, CD20+, CD22+, CD79b+, and Igλ+ cell populations. A bone marrow aspiration sample showed 3% abnormal cells that appeared to be LPL. Based on these findings, the patient was diagnosed with WM/LPL.

First, a renal biopsy was performed. Among the 22 glomeruli, 8 exhibited global sclerosis. The remaining glomeruli exhibited a moderate segmental increase in mesangial matrix. Most revealed deposition of acellular, weakly periodic acid-Schiff (PAS)-positive material in the segmental mesangium and blood vessels, both positive for direct first scarlet (DFS) staining and serum amyloid A staining. Immunostaining for IgG, IgA, IgM, κ, and λ light chains was negative (Fig. 1A). Electron microscopy revealed a random array of fibrils without immune complex deposits (Fig. 1B). Based on these findings, the patient was diagnosed with AA amyloidosis.

Prednisolone (30 mg/day) was administered after transfer to our hospital. Once the serum IgM level was elevated to 1,056 mg/dL, the patient received 4 cycles of rituximab. These treatments were effective; IgM was in the 400s mg/dL, and proteinuria decreased to 0.19 g/gCr. The prednisolone dose was then reduced to 3 mg/day, and the patient was discharged on Day 131.

Two years into follow-up, serum IgM levels were elevated again; therefore, four additional cycles of rituximab were administered, and serum IgM levels decreased without re-

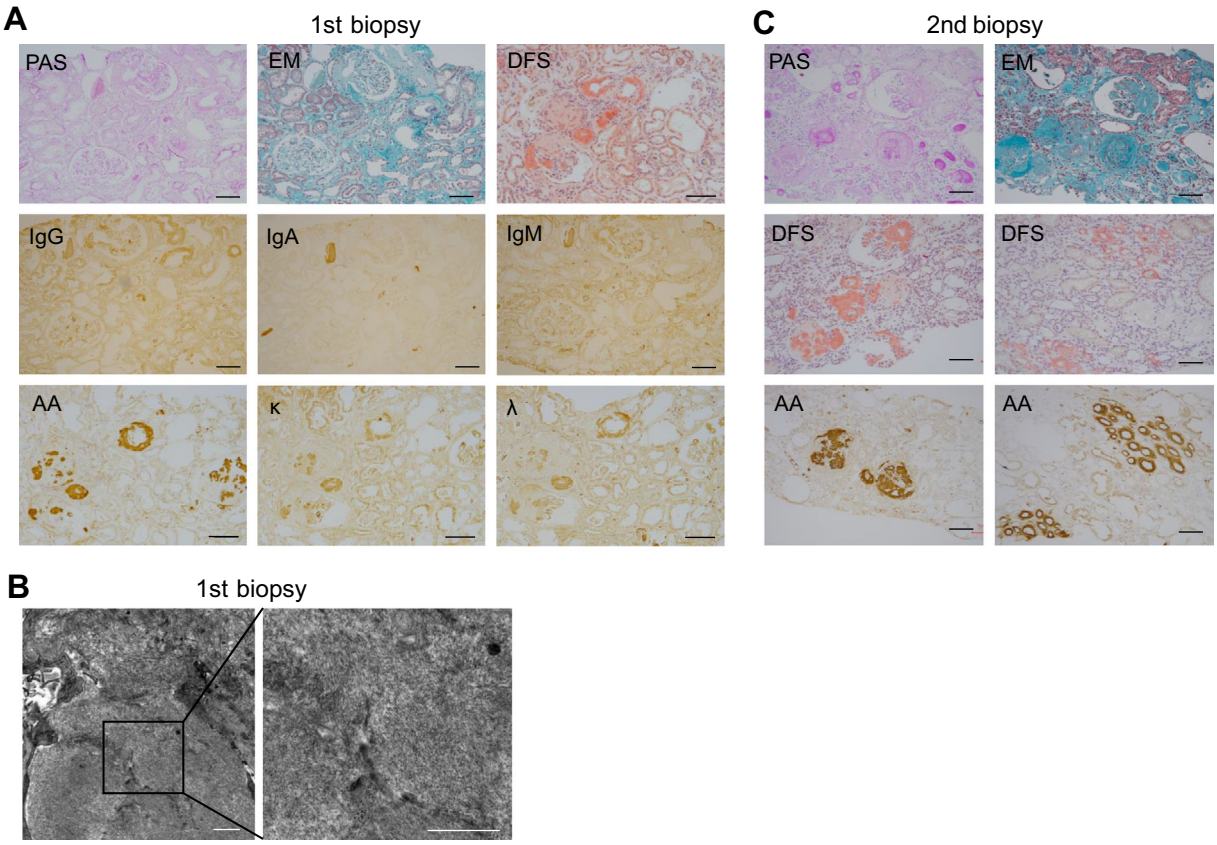

Figure 1. **The renal biopsy findings. A: Photomicrographs of periodic acid-Schiff (PAS), elastica-masson (EM), direct fast scarlet (DFS) staining, immunohistochemistry for immunoglobulins (IgG, IgA, and IgM), serum amyloid A (AA) protein, and light chains (κ and λ) from the first biopsy. Scale bar=100 μm. B: Electron microscopy of the first renal biopsy specimen. The scale bar=1 μm. C: PAS, EM, DFS staining, and immunohistochemistry of serum amyloid A in the second renal biopsy. Scale bar=100 μm.**

lapse of WM/LPL. Subsequently, the patient became infected with coronavirus disease 2019 (COVID-19), and his urinary protein and serum C-reactive protein levels increased to 7 g/gCr and 5.92 mg/dL, respectively. A second renal biopsy was performed on Day 929. A total of 32 glomeruli were examined, of which 22 showed global sclerosis. PAS-positive amorphous deposits were evident in the glomeruli. Immunoglobulin and light chain deposition were negative, whereas amyloid A deposition and DFS staining were strongly positive in the glomerular, vascular, and tubular areas. These findings were consistent with renal AA amyloidosis, and the deposition area was enlarged compared with that of the first biopsy (Fig. 1C). The prednisolone dose was initially increased to daily 30 mg, but proteinuria persisted at approximately 3 g/gCr.

Three years into follow-up, he developed persistent nausea, headache, and repeated focal consciousness impairment. Cerebrospinal fluid (CSF) samples showed typical findings of *Cryptococcus* infection (Fig. 2A, B). Both the blood and CSF cultures were positive for *Cryptococcus neoformans*. Antifungal medications were ineffective, and the patient died at 69 years old on Day 1,155. The clinical course of the patient is shown in Fig. 3.

Discussion

We encountered a case of renal AA amyloidosis complicated with WM/LPL. Chemotherapy caused remission of the hematologic disease and a decrease in proteinuria; however, during follow-up, massive proteinuria recurred after COVID-19 infection. The patient ultimately developed fatal cryptococcal infection despite receiving anti-fungal therapy.

Because the patient tested positive for M-protein, AH/AL amyloidosis was suspected. However, immunoglobulin and light chain deposits were negative, while serum amyloid A deposits were strongly positive, leading to a diagnosis of AA amyloidosis. Other possible causes of AA amyloidosis, such as autoimmune diseases and chronic infections, were clinically and serologically negative. Based on these findings, WM/LPL was considered to be the cause in this case.

AA amyloidosis is an extremely rare form of renal involvement in WM/LPL. A retrospective study of 57 renal biopsies from patients with WM/LPL and other IgM-secreting B-cell lymphoproliferative diseases reported monoclonal Ig-related amyloidosis in 19 patients. However, no case of AA amyloidosis has been reported (7). In another study of 54

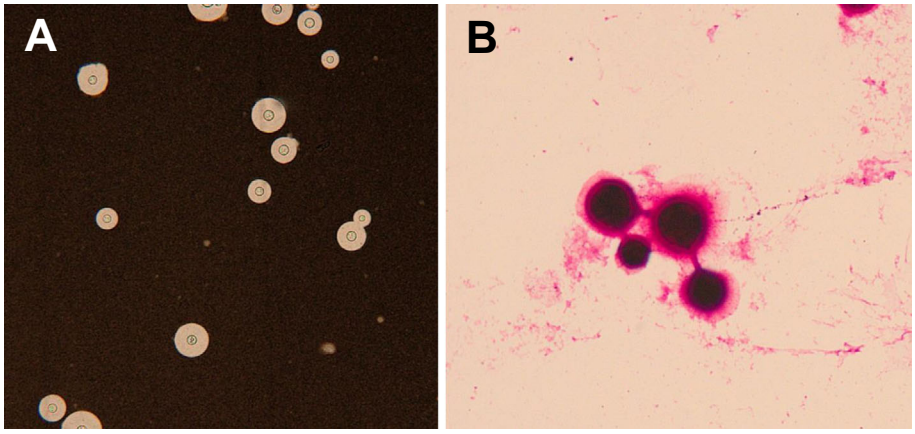

Figure 2. **The cerebrospinal fluid sample findings. India ink staining of cerebrospinal fluid (CSF) samples showing yeast cells with a surrounding halo (A). Gram staining of CSF samples (B).**

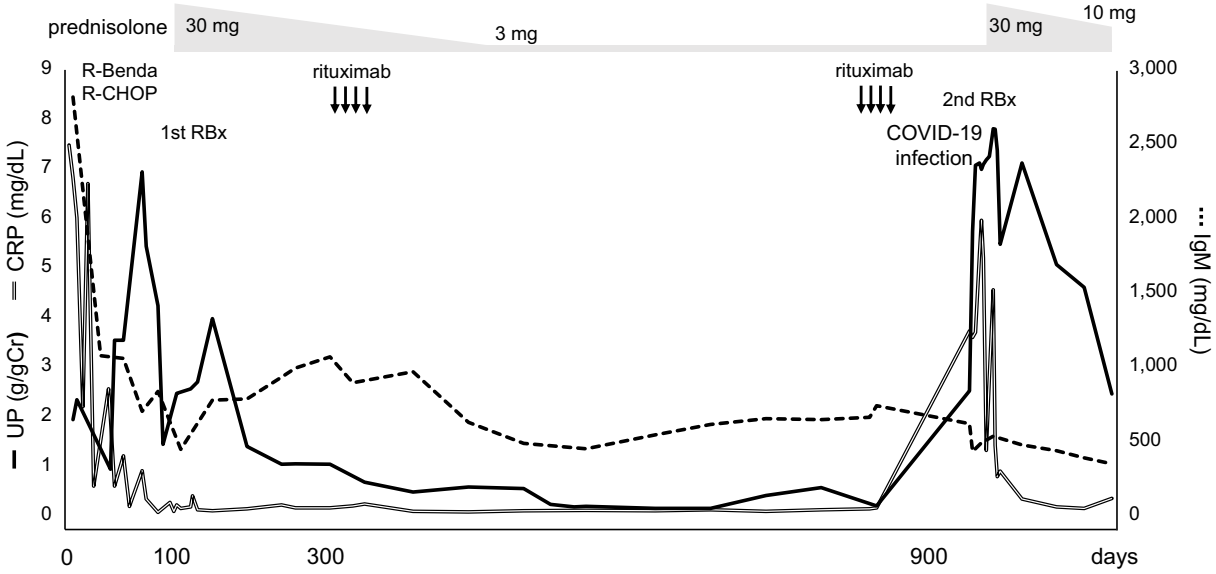

Figure 3. **The clinical course of this case. UP: urinary protein, CRP: C-reactive protein, R-Benda: rituximab-bendamustine, R-CHOP: rituximab-cyclophosphamide-doxorubicin-vincristine-prednisolone, RBx: renal biopsy**

amyloidosis cases with WM/LPL, only two cases exhibited AA amyloidosis (6).

To our knowledge, eight cases of AA amyloidosis with WM/LPL have been identified in the literature (6, 8-13). Details of these 7 previous cases and our own are presented (Table 2). The average age was 69 years old, and most patients were treated with chemotherapy; however, some patients were administered only immunosuppressive therapy, such as steroids. The prognosis appeared to be poor, with four patients dying.

SAA is specifically synthesized in hepatocytes as an acute-phase reactant under inflammatory conditions with elevated levels of cytokines such as interleukin-6. In WM/LPL, MYD88 mutations are frequent and may activate the NF-κB pathway and produce proinflammatory cytokines (14, 15). Therefore, patients with WM/LPLs may exhibit inflammatory features leading to AA amyloidosis. Acute-phase reactants are often elevated in amyloidosis cases owing to monoclonal gammopathies, including WM (12). In the present case, elevated CRP levels were observed by a previous physician.

Suppression of inflammatory cytokines may be an important factor in improving the prognosis of AA amyloidosis (3). In the present case, chemotherapy for WM/LPL resulted in hematological remission and proteinuria reduction. This finding suggests a causal relationship between upstream hematological disease activity and secondary amyloidosis. However, proteinuria increased two years after the COVID-19 infection in our patient, and a second renal biopsy led to the same diagnosis of AA amyloidosis as the first biopsy. In addition, it showed an enlarged amyloid fibril-positive area, suggesting that the AA amyloidosis had progressed. Interestingly, COVID-19 has been reported to worsen mortality in patients with AA amyloidosis (16). In addition, a case of

Table 2. Summary of AA Amyloidosis Cases in WM Patients

Age/Sex	Baseline laboratory tests	Treatment	Clinical outcome	Ref
74/M	sCr 265 μmol/L UP 1 g/day IgM 1,483 mg/dL	PSL	Death	(8)
79/M	sCr N.A. IgM 2,500 mg/dL	Chlorambucil	Death	(9)
44/M	sCr N.A. SAA 99.9 mg/mL IgM 880 mg/dL	Chemotherapy (R-CHOP), PSL	Recovering	(10)
65/F	sCr<1 mg/dL UP 0.05-0.1 /24h IgM 2,180 mg/dL	Chemotherapy melphalan-based ASCT	Recovering	(11)
74/M	sCr N.A. SAA 10 mg/L CRP 13.5 mg/dL	IL1-RA	N.A.	(12)
84/F	sCr N.A. Nephrotic syndrome IgM 710 mg/dL CRP>2 mg/dL	Rituximab	Death	(13)
66/M	sCr 0.87 mg/dL UP 2.43 g/gCr IgM 2,803 mg/dL CRP 7.44 mg/dL	Chemotherapy (R-Benda/R-CHOP) rituximab, PSL	Death	Current case

WM: Waldenström's Macroglobulinemia, M: male, F: female, sCr: serum creatinine, UP: urinary protein, SAA: Serum Amyloid A, CRP: C-Reactive Protein, PSL: prednisolone, R-CHOP: rituximab-cyclophosphamide-doxorubicin-vincristine-prednisolone, ASCT: Auto Peripheral Blood Stem Cell Transplantation, R-Benda: rituximab-bendamustine, IL1-RA: interleukin 1 receptor antagonist, NA: not available

rapidly progressive renal failure and AA amyloidosis following COVID-19 has been reported (17). One explanation for the outcome in this case is that the viral infection caused systemic inflammation and may have triggered the relapse of nephrotic syndrome, even in the absence of relapse of WM/LPL.

The present patient eventually died of cryptococcal meningitis, which was in the course of subacute and chronic meningitis. *Cryptococcus* is prevalent in cases of acquired immunodeficiency due to human immunodeficiency virus (HIV) infection but is also seen in non-HIV-infected patients, including those with cancer, idiopathic CD4 lymphopenia, sarcoidosis, or solid-organ transplant and those using corticosteroids, calcineurin-directed therapy, mammalian target of rapamycin inhibitors, or monoclonal antibodies (18). In an analysis of cancer patients infected with *Cryptococcus*, hematological malignancies accounted for 80% of the cases, and the central nervous system was more frequent than other malignancies (19). Therefore, cryptococcal meningitis should be considered in patients with neurological symptoms.

In conclusion, this case has helped us understand the diverse spectrum of renal involvement in IgM-secreting diseases, such as WM/LPL. Managing complications, including renal damage and fatal infections, may be difficult in patients with amyloidosis and hematological disorders.

The authors state that they have no Conflict of Interest (COI).

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