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Primary AL Amyloidosis: An Experience with a Patient Accompanied by Immunoglobulin M Monoclonal Gammopathy

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Abstract

Amyloid light chain amyloidosis (AL amyloidosis) is a systemic disease induced by tissue deposition of amyloid fibrils originated from monoclonal immunoglobulin (Ig) light chains. Various types of paraproteins can lead to amyloid deposits, with the free lambda light chain IgG and IgA being the most common components, while the disease associated with IgM paraproteinemia is an extremely uncommon variant. We herein report such a case in a 66-year-old male patient presenting with nephrotic syndrome. The management concerns of IgM-related AL amyloidosis are also discussed. We believe that an awareness of the link between AL amyloidosis and IgM paraproteinemia remains a challenge for physicians because of its rarity; we therefore strongly recommend the accumulation of more cases similar to our own, allowing us to clarify the nature of the disease more precisely.

Keywords: *AL amyloidosis, IgM, monoclonal gammopathy, nephrotic syndrome, abdominal fat biopsy*

Introduction

Amyloid light chain (AL) amyloidosis is a systemic disease induced by tissue deposition of amyloid fibrils originating from monoclonal immunoglobulin (Ig) light chains produced in a wide spectrum of hematological conditions ranging from indolent monoclonal gammopathy to drastic malignancy [1,2]. Various types of paraproteins can lead to amyloid deposits, with the free lambda (λ) light chain IgG and IgA being the most common components, while AL amyloidosis associated with IgM paraproteinemia is an extremely uncommon variant, representing approximately 5% of patients with the disease [3-6].

In this report, we describe one such rare case in a male patient presenting with nephrotic syndrome. The management concerns as well as the characteristics of IgM-related AL amyloidosis are also discussed.

Case Report

A 66-year-old man was admitted to our hospital complaining of progressive swelling of his lower extremities. Three months before, the patient had recognized the leg manifestation when he was found to have a reduced serum albumin (sAlb) level of 2.6 g/dL and 4+ proteinuria by his general practitioner. Subsequently, the symptoms gradually worsened, and he was thus referred and admitted for a further workup. Other medical histories included hypertension and type 2 diabetes, for which he had received standard medical care for 6 years, controlling his blood pressure to the ranges of 110/60 to 120/70 mmHg and hemoglobin (Hb) A1c (HbA1c) levels at 6.5% to 7% with steady serum creatinine (sCr) levels of around 0.9 mg/dL. A urinalysis had not been performed on a regular basis.

At the time of admission (clinical day 0), the patient was alert with a temperature of 36.9 °C and a blood pressure of 110/57 mmHg, and he had gained approximately 9 kg in the previous 12 weeks, bringing his weight to 82.7 kg. There were no episodes of postural hypotension, and the findings of electro- and echocardiograms were unremarkable. The neurological examination confirmed a proportional decrease of sensation in the left and right plantar surfaces. Renal sonography revealed the right and left kidney long-axis dimensions to measure 10.4 mm and 11.7 mm, respectively, with increased renal cortex

echogenicity, which was greater than that of the liver, accompanied by a maintained corticomedullary definition.

The laboratory data on admission are summarized in **Table 1**. Serum free light chains were 31.0 mg/L in kappa (κ) and 62 mg/L in λ, with a κ/λ ratio of 0.5. Immunofixation electrophoresis demonstrated a monoclonal IgM bearing the λ-type light chain in serum and urine. An increased serum viscosity of 8.29 cP (reference range: 4.34-5.45) was also noted. The patient's urine contained 10.5 g of protein in a 24-h specimen with a creatinine clearance of 44.3 mL/min. Radiologic imaging studies demonstrated hepatomegaly and lymphadenopathy in the paraaortic and bilateral inguinal regions but not osteostructural abnormalities. Findings of an endoscopic examination were unremarkable, whereas an abdominal fat biopsy and histopathology of inguinal lymph nodes (**Figure 1A**) as well as a bone marrow aspiration revealed amorphous acellular Congo red-positive amyloid deposits with apple-green birefringence on polarization. Furthermore, the bone marrow examinations revealed approximately 3% plasma cells without any abnormal distributions of myeloid cells and/or plasmacytoid lymphocytes. No specific Ig restrictions or monoclonal disturbances were shown by a concurrent flow cytometric analysis on mononuclear cells in the peripheral or bone marrow blood.

Table1. *Laboratory data on admission*

White blood cells	8000/μL	(3900-9800)
neutrophils	68.0%	(42.0-72.2)
eosinophils	0.7%	(0.0-5.8)
basophils	0.3%	(0.0-1.7)
monocytes	10.0%	(2.5-11.1)
lymphocytes	21.0%	(19.9-46.1)
Hemoglobin	14.1 g/dL	(13.5-17.6)
Platelet count	39.8×10^4/μL	(13.0-36.9)
Fibrinogen/fibrin degradation product	29.5 μg/dL	(0-5)
D-dimer	21.1 μg/dL	(0-1.5)
Blood urea nitrogen	24 mg/dL	(8-20)
sCr	1.09 mg/dL	(0.63-1.03)
Total protein	6.4 g/dL	(6.9-8.4)
Albumin	1.7 g/dL	(3.9-5.1)
Sodium	140 mmol/L	(136-148)
Potassium	4.3 mmol/L	(3.6-5.0)
Chloride	105 mmol/L	(96-108)
Calcium	9.1 mg/dL	(8.8-10.1)
Phosphorus	4.0 mg/dL	(2.4-4.6)
Asparate aminotransferase	59 U/L	(11-30)
Alanine aminotransferase	50 U/L	(4-30)
Fasting plasma glucose	114 mg/dL	(70-120)
Hemoglobin A1c	6.2%	(4.6-6.2)
C-reactive protein	0.26 mg/dL	(0-0.14)
IgG	220 mg/dL	(870-1700)
IgA	655 mg/dL	(110-410)
IgM	1755 mg/dL	(33-160)
C3	127 mg/dL	(86-160)
C4	21 mg/dL	(17-45)

The reference ranges for each parameter used at our institute are indicated in parentheses.

A renal biopsy performed on clinical day 21 revealed 3 cores of renal parenchyma with 27 glomeruli, 2 of which were globally sclerotic. The rest of the glomeruli exhibited Congo red-positive amyloid deposits. These amyloid deposits showed a negative result for anti-κ light chain staining but active anti-λ-immunoreactivity on immunohistochemistry, while a direct immunofluorescence study demonstrated positive staining for IgM but not for amyloid A. On electron microscopy, the presence of randomly arrayed microfibrils was confirmed at the dependent portion of the deposits (**Figure 1B to 1F**). Given these findings, he was diagnosed with nephrotic syndrome due to systemic primary IgMλ-related AL amyloidosis.

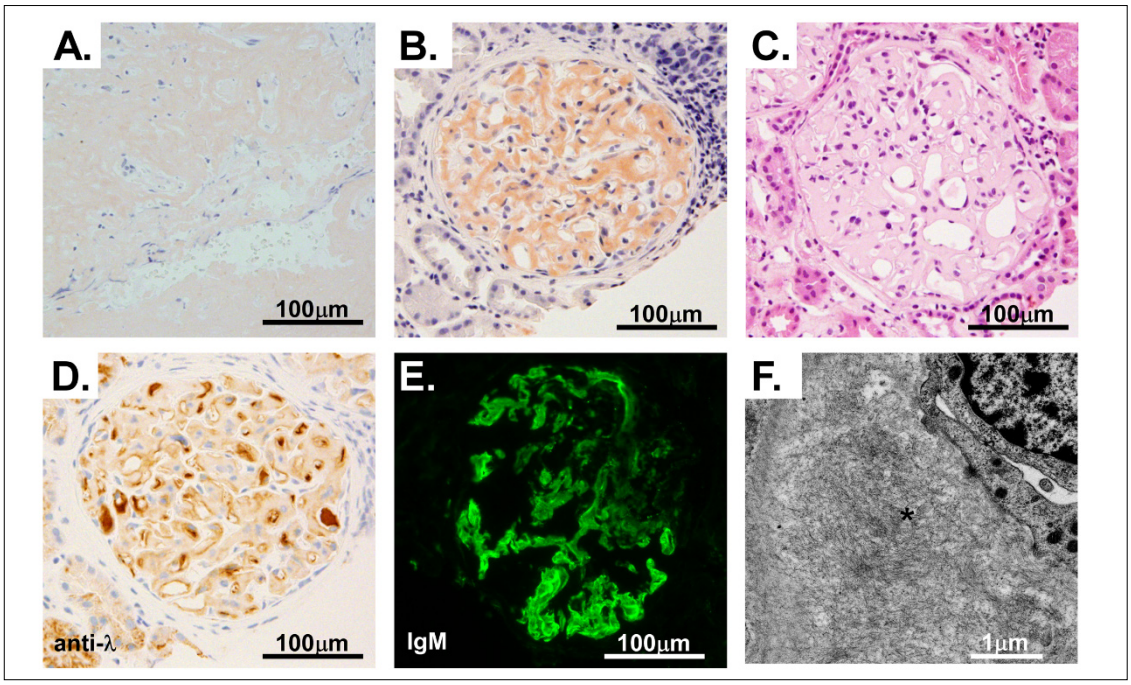

Figure1. *Photomicrographs of the biopsy specimens. Amorphous acellular deposits stained salmon pink with Congo red are shown in the inguinal lymph nodes **(A).** Similar characteristic Congo red-positive deposits are shown in the corresponding regions of the glomeruli **(B)** that are associated with homogenous eosinophilic material-rich expanded mesangium and thickened peripheral capillary walls **(C**, hematoxylin and eosin stain). Active anti-λ-immunoreactivity **(D)** and positive staining for IgM **(E)** are also shown on immunohistochemistry and direct immunofluorescence studies, respectively. On electron microscopy, randomly disposed, rigid, non-branching, and variably long microfibrils with a diameter of about 8-10 nm can be seen in the mesangial **(*)** and paramesangial areas **(F)**. The scale bar is indicated in each panel.*

Approximately seven weeks after the renal biopsy, hemodialysis was started because of the patient's progressive renal failure. He also received melphalan (5 mg/m^2) and dexamethasone (20 mg) on clinical day 88, 89, 90, and 91; however, his severe renal failure did not recover. He also began to manifest a low blood pressure, ranging from 70/40 to 90/60 mmHg, at all times. Finally, the patient developed multiple organ failure and died 10 months after the diagnosis of the disease was made. At the postmortem autopsy, no solid malignant lesions were noticed on macroscopic investigation. The deposition of amyloid fibrils was shown in the kidneys, lungs, liver, spleen, adrenals, bone marrow, thyroid gland, lymph nodes, and blood vessels, while the cardiac amyloid deposition was marginal in the myocardium but notable in the pericardium and vasculature. No distinct amyloid deposition was noted in the brain or digestive tract. Neither abnormal proliferation nor infiltration of lymphoplasmacytic cells was shown by standard pathologic investigations.

Discussion

The clinical scenario of the current patient, characterized by a set of conditions including nephrotic syndrome and AL amyloidosis, may not be surprising

[3]. However, we believe an awareness of the link between AL amyloidosis and IgM paraproteinemia remains a challenge for physicians because of its rarity. Systemic studies on this topic are obviously lacking, so we strongly recommend the accumulation of more cases similar to our own, thereby allowing us to clarify the nature of IgM-related AL amyloidosis more precisely.

Paraproteinemia represents a group of related disturbances characterized by a clone of plasma cells or B lymphocytes with the capability to produce a homogeneous Ig and/or its components [7]. Several illnesses, including plasma cell dyscrasia, leukemia, and/or lymphoma, have been shown to be associated with this abnormality [8,9], while Waldenström's macroglobulinemia may be a distinct pathology, particularly in some patients with IgM monoclonal protein [10,11]. By contrast, numerous monoclonal gammopathies identified on serum and/or urine electrophoresis can be classified as monoclonal gammopathy of undetermined significance, although some subsets may eventually progress to symptomatic disease states [8,9]. According to a study using the dysproteinemia database of the Mayo Clinic, AL amyloidosis was found in only approximately 2% of patients with an IgM paraprotein, although such patients accounted for 17% of overall patients with serum monoclonal heavy chains [4]. While such a combination was described only anecdotally in the late 1960s [13,14], the cumulative number of publications concerning this clinical entity has been slowly growing, and at present, about 600 cases have been identified in the international literature [15]. The incidence of IgM-related AL amyloidosis remains unclear, as the current data are largely limited to retrospective studies, and the number of patients with this disease state might be underdiagnosed [4-6,16-20]. Given that the age-adjusted incidence of overall AL amyloidosis has been determined to be 9 per million person-years [21], we may be able to roughly estimate the incidence of IgM-related AL amyloidosis at approximately 0.45 per million person-years [4-6,15,21]. Many patients are advanced in age, but patients 39 to 89 years old have been affected, with a slight predominance of the male sex [15].

Patients with IgM-related AL amyloidosis share numerous clinical features with patients with non-IgM type AL amyloidosis; however, previous studies have identified several clinical manifestations that may help distinguish these entities, proposing that IgM-related AL amyloidosis be regarded as a distinct clinical entity [4-6, 16-20]. As is often the case with primary AL amyloidosis, the kidney is one of the most frequently involved organs, and patients with the disease may be more likely to have peripheral neuropathy as well as amyloid deposits in the lungs and lymph nodes than those with non-IgM type AL amyloidosis [4,16-18,20,21]. Lower serum levels of the involved free light chain may also be seen in such subjects [17,18,20]. In addition, it has been shown that cardiac involvement is less common in patients with IgM-related AL amyloidosis than in those with non-IgM-type AL amyloidosis [6]. Similar trends have been confirmed in the serum levels of cardiac biomarkers, including troponin (Trop) and/or N-terminal pro-brain natriuretic peptide (NT-proBNP), although the diagnostic sensitivity as well as the specificity of these variables has yet to be determined [18-20,22]. The pathogenic basis for these characteristics remains to be delineated; however, we believe that the involved light chains produced by IgM clones should posses specific amyloidogenic nature, at least in part, presumably resulting from a peculiar trend of tissue affinity [18,20].

Finally, the diagnostic process in the present case was quite straightforward, and our patient's clinical characteristics, including the pathologic findings, were not substantially different from those of previously reported examples [4-6, 15-20]. Our experience rather highlights the limited applicability of therapeutic regimens involving oral melphalan combined with dexamethasone, which may be beneficial in some subsets of patients who are accompanied by IgM-related AL amyloidosis [18]. Other agents that may be useful in therapeutic regimens for this disease include chlorambucil, bortezomib, cyclophosphamide, vincristine, doxorubicin, purine analogs, rituximab, and prednisolone [6,15,18]. Some of these agents are preferred for administration to subjects with plasma cell predominance in the bone marrow, depending on the context, while other patients may benefit more from regimens directed at lymphoproliferative disorders [6,15,17]. While the therapeutic strategy for AL amyloidosis has greatly expanded in recent years [23], consensus criteria for selecting the most

appropriate chemotherapy for patients with this disease have not yet been determined, resulting in poor hematological responses with low complete remission rates [6,15,19]. Further detailed studies regarding the hematopathologies leading to IgM paraproteinemia, which would allow us to design more favorable treatment protocols, are therefore needed. In addition, determining therapeutic guidelines for IgM-related AL amyloidosis with normal or non-diagnostic bone marrow findings, which is seen in approximately 30% of patients with this disease [4-6,17], including the present patient, should be another prerequisite subject.

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