Coexistence of Light- and Heavy-Chain Deposition Disease and Immunotactoid Glomerulopathy in a Patient with Multiple Myeloma: A Case Report

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Abstract
Multiple myeloma is a malignant neoplasm leading to a variety of renal diseases. Although most patients have only one pattern of renal pathology, two or more patterns can exist in some patients. Here, we report a 61-year-old man with multiple myeloma developed proteinuria, hematuria, hypertension, and renal insufficiency. A combined presentation of light- and heavy-chain deposition disease and immunotactoid glomerulopathy was proved by kidney biopsy. Treatment of multiple myeloma resulted in a complete resolution of the renal manifestations. This case illustrates the complexity of paraprotein associated renal lesions and emphasizes that further studies examining the physiologic properties and pathologic effects of monoclonal immunoglobulin are needed.

Introduction
The kidney is one of the major organs targeted by paraproteins in multiple myeloma \cite{1}. The spectrum of associated kidney diseases includes cast nephropathy (CN), amyloidosis, monoclonal immunoglobulin (MIg) deposition disease (MIDD), and more rarely, proliferative...
glomerulonephritis with Mlg deposits (PGNMID), immunotactoid glomerulopathy (ITG),
light-chain proximal tubulopathy, etc. Occasionally, two or more conditions can coexist in the
setting of an underlying plasma cell dyscrasia, for example, CN, amyloidosis, and light-chain
deposition disease (LCDD) [2]. Here, we reported an unusual case of light- and heavy-chain
deposition disease (LHCDD), coexisting with ITG in a patient with multiple myeloma.

Case Report

A 61-year-old man was referred to our hospital for hypertension and bilateral leg swelling
in July 2018. The patient was found to have hypertension of 160/90 mm Hg 2 months prior
to admission and was prescribed amlodipine for blood pressure control. One month ago, he
presented to the outside facility and was found to have elevated serum creatinine of 1.7 mg/
dl (reference range 0.7–1.2 mg/dL). Urinalysis revealed proteinuria and occult blood. No
treatment was initiated except blood pressure control. However, at the follow-up, the patient
developed bilateral leg edema and was admitted to our hospital. There was no additional
medical problem or family history of kidney disease.

On physical examination, he was hypertensive at 168/90 mm Hg. There were mild pale
mucosa and pitting edema of the lower extremities, with no rash or organomegaly. Urinalysis
showed a specific gravity of 1.007 with 2+ protein. Urinary sediment examination revealed
increased red blood cells of 78/μL, 95% of which were dysmorphic. Twenty-four-hour urine
protein was 3.38 g/d, and the molecular weights were above 68 kd by urine electrophoresis. The
serum creatinine level at admission was 1.5 mg/dL but increased to 2.0 mg/dL during hospital-
ization, with an estimated glomerular filtration rate of 35 mL/min/1.73 m². Other laboratory
findings are listed as follows: hemoglobin, 8.6 g/dL; erythrocyte sedimentation rate, 53 mm/1 h;
serum total protein, 6.3 g/dL; serum albumin, 3.2 g/dL; serum lactate dehydrogenase, 181 U/L;
serum calcium 8.6 mg/dL; serum IgG, 1,830 mg/dL (normal range, 720–1,680 mg/dL); and
serum β2 microglobulin, >8 mg/L. A monoclonal IgG κ in serum and a monoclonal κ light chain
in the urine were identified on immunofixation. The serum free light-chain assay showed elevated
free κ of 136 mg/L and an increased κ:λ ratio of 10.07 (reference range 0.26–1.65). Serum comple-
ments were within the reference ranges. Additional blood tests including antinuclear antibodies,
antineutrophil cytoplasmic antibodies, anti-glomerular basement membrane antibody, cryo-
globulins, HIV, and hepatitis B and C serologies were negative. Bone marrow examinations
demonstrated 42% κ light-chain restricted plasma cells. Computed tomography scans revealed
an osteolytic lesion in the left ilium. Therefore, the initial impression was that of multiple myeloma
based on the findings of 42% monoclonal plasma cells in the bone marrow, monoclonal protein
identified in the serum and urine, anemia, renal insufficiency, and lytic bone lesion.

Kidney biopsy was performed to determine the cause of kidney injury. Tissue submitted
for light microscopy contained 22 glomeruli, none of which was globally sclerosed. Glomeruli
displayed a mild to moderate increase in mesangial matrix. Markedly expanded mesangial
regions and double contour formation were noted in some area (shown in Fig. 1a). Glomerular
basement membranes were irregularly thickened. Tubular epithelial cells showed granular
degeneration, vacuolization, and focal atrophy. Mild interstitial fibrosis and mononuclear
cells infiltration were present.

Immunofluorescence microscopy showed diffuse linear staining along glomerular and
tubular basement membranes for IgG2 (++) (shown in Fig. 1b) and κ light chains (++) (shown
in Fig. 1c) but negative for IgA, IgM, C3, and λ light chains (shown in Fig. 1d). Immunohisto-
chemistry confirmed that glomeruli and tubules stained intensely for κ light chains but were
negative for λ light chains. Neither CD38 nor CD138 was positively stained in the interstitium.
Congo red stains for amyloid deposits gave negative results.
Electron microscopy demonstrated punctate granular electron-dense material deposited in the mesangium and along the glomerular and tubular basement membranes (shown in Fig. 2a). Interestingly, hollow microtubules with a diameter of 35 nm were observed in mesangial regions and the capillary wall at high magnification (shown in Fig. 2b). An immunoelectron microscope confirmed a positive staining for κ light chains in glomeruli and tubules (shown in Fig. 2c, d) but no staining for λ light chains. Thus, the kidney biopsy diagnoses were (1) LHCDD and (2) ITG.

The patient was admitted to the department of hematology and received systemic anti-myeloma therapy. After 4 cycles of chemotherapy with bortezomib, cyclophosphamide, and dexamethasone, a complete hematologic remission was obtained. Then the patient received autologous hematopoietic stem cell transplantation in February 2019. His serum creatinine came down from a peak of 2.5 mg/dL to 0.8 mg/dL, and urine protein excretion decreased to 0.06 g/24 h at the final follow-up in September 2020.

**Discussion**

Renal involvement is common in multiple myeloma and frequently the first manifestation of disease [3]. Mlg secreted by myeloma cells may result in a wide spectrum of kidney lesions. Although most patients have only one pattern of renal pathology, two or more patterns occurring in the same patient has been described. CN and LCDD appear to be the most common
combination [4]. In this case presentation, we illustrate a case of multiple myeloma with features of both LHCDD and ITG, which has not been described before.

Renal presentations and hematologic characteristics are varied among MIg-associated renal diseases, which could aid in the management of patients when kidney biopsy is delayed or contraindicated. For example, CN is typically manifested by acute kidney injury. Serum-free light-chain (κ or λ) levels would be more than 500 mg/L in most patients. Nephrotic syndrome without hematuria and hypertension usually indicates the underlying renal involvement to be amyloidosis, of which the pathogenic light chain is more often λ than κ. Most patients with MIDD present with proteinuria, nephrotic syndrome, and renal insufficiency. The deposits are most commonly composed of κ light chains for LCDD and γ heavy chains for heavy-chain deposition disease (HCDD). ITG and PGNMID are always characterized by significant proteinuria, variable degrees of hematuria, hypertension, and renal insufficiency. The MIg most often contains heavy chain γ. Serum complement component C3 levels can be very low in patients with MIg-associated C3 glomerulopathy. In our case, the patient had multiple myeloma and displayed manifestations of renal damage. However, his clinical presentation was atypical for amyloidosis in that he had overt microscopic hematuria and hypertension. The clinical course also departed from CN in that his renal function did not deteriorate progressively, and the serum-free light chains were less than 500 mg/L. In contrast, the typical manifestations of nephritic features in our patient implied that the renal involvement was likely to be MIDD, PGNMID, or ITG. However, accurate diagnosis requires kidney biopsy.

Fig. 2. Representative kidney biopsy findings by electron microscopy. a Powdery electron-dense material depositing in the mesangium and along the tubular basement membranes (arrows) (×6,000). b Microtubules in mesangial regions (arrows) (×6,000). c, d Immunoelectron microscopy showing positive staining for κ light chains in the mesangium (c) and along the glomerular and tubular basement membranes (c, d, arrows) (×11,500 (c), ×20,500 (d)).
Histologically, our patient typically showed a renal injury pattern of MIDD, which was characterized by the deposition of MIg along the glomerular and tubular basement membranes. MIDD is classified into three types: LCDD when deposits are composed of light chains only, HCDD when deposits are composed of heavy chains only, and LHCDD when deposits are composed of both monoclonal light and heavy chains. In this case, both the deposition of γ2 and κ light chains along glomerular and tubular basement membranes were detected by immunofluorescence microscopy, indicating the possibility of LHCDD. MIDD is a common renal involvement associated with multiple myeloma, but LHCDD is rare. A recent study of 64 patients with MIDD showed that 97% of the patients had an underlying monoclonal gammopathy, and 59% of the patients had multiple myeloma. However, only 6 patients were diagnosed to be LHCDD in this study. The monoclonal protein components were γ and κ detected by immunofluorescence in 4 of the 6 patients with LHCDD, which is in consistent with our case [5]. It has been reported that codeposits of C3 and C1q and resulting hypocomplementemia through activation of the classical complement pathway are common in LHCDD and HCDD, particularly the γ1 and γ3 subtypes [5, 6]. However, serum complement levels were normal, and the staining of complement components was negative in the present case. We assume that this might attribute to the deposition of γ2, which has a weak effect on complement system activation.

In addition, glomerular deposits with a microtubular substructure on electron microscopy were revealed in this patient, indicating a coexisting diagnosis of ITG. ITG is a rare glomerular disease but always associated with MIg and lymphoproliferative disorder. The misfolding and deposition of MIg heavy chains might be responsible for the microtubules in ultrastructure. In a previous study of 16 patients with ITG, an M spike was detected in 63% of the patients, and a hematologic malignancy was present in 38% of cases, which included chronic lymphocytic leukemia, lymphoplasmacytic lymphoma, and rarely multiple myeloma [7]. In another case series of 14 patients with ITG, IgG deposits were monotypic in all but 1 patient. Nevertheless, none of the patients was diagnosed with multiple myeloma [8]. As described above, ITG is an unusual entity induced by multiple myeloma and rarer when concurring with LHCDD, which should be particularly considered in clinical settings.

There are several different features between MIDD and ITG. MIDD involves both glomeruli and tubules, as well as extrarenal organs, while deposition in ITG is generally limited to glomeruli. The deposits are organized in ITG but nonorganized in MIDD. Laser microdissection and mass spectrometry analysis also shows different proteomic profiles in MIDD and ITG [9, 10]. The fact that only one kind of abnormal MIg was isolated from our patient suggests that a biclonal process was not present and implies that the same MIg was responsible for both patterns of renal damage in this case. It is currently unknown whether there is a common underlying pathogenesis responsible for the concurrence of MIDD and ITG. Generally, physicochemical properties of the offending MIg as well as the renal microenvironment are thought to determine which pattern of renal injury occurs in multiple myeloma [11]. Further research is warranted to illustrate the complex pathophysiological effects of MIg within the kidney.

**Conclusion**

We describe an interesting case of concurrent LHCDD and ITG induced by multiple myeloma. Although LHCDD or ITG has been described respectively in previous literatures, the presentation of both in a patient with multiple myeloma is unusual. Rare renal lesions such as LHCDD and ITG should be considered in a setting of multiple myeloma. Renal manifestations and immunoserology could provide some clues in differential diagnosis. Importantly, kidney biopsy in patients with multiple myeloma is necessary and remains the gold standard for definitive diagnosis of the underlying kidney lesions.
Statement of Ethics

Written informed consent for publication of his clinical details and clinical images was obtained from the patient. This case study was conducted ethically in accordance with the World Medical Association Declaration of Helsinki. This study protocol was reviewed, and the need for approval was waived by the Ethics Committee of Peking University People’s Hospital.

Conflict of Interest Statement

The authors have stated that they have no conflicts of interest.

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Author Contributions

L.Y., D.B., and Y.Y. participated in the clinical care of the patient. L.Y. and Y.Y. analyzed the patient data and wrote the manuscript. D.B., J.L., L.X., and S.C. performed renal biopsy and the histological examinations. Z.L. critically reviewed the manuscript and supervised the whole process. All the authors read and approved the final manuscript.

Data Availability Statement

All data analyzed during the current study are included in this article. Further inquiries can be directed to the corresponding author.

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