

## Monoclonal Immunoglobulin Deposition Disease and Related Diseases

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Abnormal proliferation of plasma cells and some monoclonal B cells frequently cause the secretion of monoclonal immunoglobulins or immunoglobulin fragments into the serum, causing monoclonal gammopathy, which leads to various diseases including renal diseases. Therefore, monoclonal gammopathy is frequently associated with kidney diseases, including glomerular and tubulointerstitial diseases. Glomerular disease, with the deposition of monoclonal immunoglobulins or their components, includes monoclonal immunoglobulin deposition disease (MIDD), AL or AH amyloidosis, type I cryoglobulinemia, proliferative glomerulonephritis with monoclonal IgG deposits (PGNMID), immunotactoid glomerulopathy, and fibrillary glomerulonephritis. In addition, tubulointerstitial diseases with the deposition of monoclonal immunoglobulins or their components are constituted by light chain (myeloma) cast nephropathy, light chain associated Fanconi's syndrome (light chain proximal [crystal] tubulopathy), and crystal-storing histiocytosis. In the present review article, we demonstrate the clinicopathological characteristics of MIDD, which is one of the representative diseases of plasma cell dyscrasias, and discuss various renal diseases with the deposition of monoclonal immunoglobulins or their components in glomeruli and the tubulointerstitium. We recommend that these renal diseases are arranged as one disease category, "renal diseases with deposition of monoclonal immunoglobulins or their components", in order to simplify the understanding of complicated diseases in plasma cell dysplasia.

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**Key words:** monoclonal immunoglobulin deposition disease (MIDD), light chain deposition disease (LCDD), glomerular deposition disease, monoclonal gammopathy of renal significance (MGRS), monoclonal gammopathy of undetermined significance (MGUS)

### Introduction

Monoclonal immunoglobulin deposition disease (MIDD) is found in approximately 0.5% of the renal biopsy cases in Japan<sup>1</sup>, and in 28.8% of the renal biopsies from patients with monoclonal gammopathy, which is second to cryoglobulinemic glomerulonephritis (GN) (30.3%)<sup>2</sup>.

MIDD is defined by the pathologic accumulation of abnormally truncated monoclonal immunoglobulin molecules in vascular basement membranes, glomerular basement membranes (GBMs), and tubular basement membranes (TBMs) without a fibrillary, crystalline, or microtubular appearance on electron microscopy<sup>3,4</sup>. These de-

posits are characterized by negative Congo red staining, a single light chain isotype and/or single heavy chain subclass in immunofluorescence, and a powdery deposition on electron microscopy. MIDD includes light chain deposition disease (LCDD), heavy chain deposition disease (HCDD), and light and heavy chain deposition disease (LHCDD). Among the three diseases, LCDD is the most prevalent and constitutes approximately 80% of MIDD, whereas LHCDD and HCDD are considered to be extremely rare.

MIDD was initially reported in 1957 by Kobernick et al. as a non-amyloid kidney disease resembling diabetic

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glomerulosclerosis in non-diabetic myeloma patients<sup>5</sup>. In 1976, Randall et al. described systemic LCDD with nodular sclerosing glomerulopathy (GP)<sup>6</sup>. Therefore, MIDD is occasionally referred to as Randall-type MIDD. Preud'homme et al. subsequently reported LHCDD characterized by the deposition of both monoclonal immunoglobulin light and heavy chains in several organs<sup>7</sup>, followed by the report by Tubbs et al. that HCDD is characterized by glomerular and tubular depositions of monoclonal heavy chains without associated light chains<sup>8</sup>. According to these similar clinical and pathological findings, Buxbaum et al. proposed the term MIDD, as defined by monotypic light or heavy chain deposits in tissue<sup>9</sup>.

### Diagnosis of MIDD: Clinical and Pathological Findings and Useful Tools for Its Diagnosis

#### Clinical Characteristics

Underlying disorders in MIDD include multiple myeloma (11–65%), lymphoproliferative disorders (2–3%), and macroglobulinemia (2%) or monoclonal gammopathy of undetermined significance (MGUS) (32–86.8%)<sup>10–12</sup>.

MGUS is considered to be a premalignant condition characterized by the presence of monoclonal gammopathy (<3.0 g/dL) without clinical features or organ damage. However, several renal diseases, such as AL amyloidosis, MIDD, and proliferative glomerulonephritis (GN) with monoclonal IgG deposits (PGNMID), can develop in MGUS<sup>13</sup>, and adequate treatment is considered to be necessary for these diseases. Therefore, a new term “monoclonal gammopathy of renal significance (MGRS)”, rather than MGUS, was recently proposed for MGUS with concurrent renal disease<sup>14</sup>. Some recent reviews address the diagnostic algorithms and clinicopathological findings of MGRS lesions<sup>15,16</sup>. However, the spectrum of MGRS is wide and the proposed algorithms still have difficulties in the diagnosis and classification of these diseases<sup>17</sup>.

The kidney is the major target organ in MIDD, and renal symptoms, primarily proteinuria or nephrotic syndrome, often dominate the clinical presentation. It has been generally considered that monoclonal light chains are directly toxic to renal tissues, including glomerular endothelial cells and tubular epithelial cells. The light chain in LCDD exhibits somatic mutations in the L12a gene<sup>18</sup>. These mutations may change the structure of the light chains, leading to abnormal deposition and nephrotoxicity. The abnormal light chains in LCDD may induce several pathological processes underlying nodular glomerulosclerosis<sup>19,20</sup>. In some cases, light chains act on

the tubules and cause acute kidney injury (AKI) or adult (or acquired) Fanconi's syndrome. Inflammatory light chain-related tubular interstitial nephritis also occurs in LCDD<sup>21</sup>. Rare cases of LCDD without glomerular findings have also been reported<sup>22</sup>.

Renal and patient survival rates were significantly worse in LCDD patients with coexistent light chain (myeloma) cast nephropathy<sup>23</sup>. Combined LCDD and myeloma cast nephropathy exhibits clinical features and outcomes that more closely resemble those in myeloma cast nephropathy. Lin et al. has suggested that the consideration of coexistent LCDD and myeloma cast nephropathy is important for the patient's prognosis and proposed the term “pure MIDD,” which excludes LCDD with myeloma cast nephropathy<sup>23</sup>.

Approximately 35% of patients with LCDD have extrarenal lesions. Extrarenal deposits occur in the hepatic sinusoids, choroid plexus, or myocardium and cause liver dysfunction, neuropathy or heart failure, respectively. Interestingly, in some cases, the M-spike cannot be detected on serum and/or urine protein electrophoresis or immunofixation electrophoresis.

#### Pathological Findings

A definitive diagnosis of renal diseases associated with plasma cell dyscrasias requires a renal biopsy. Light and electron microscopy and immunofluorescence studies are performed for the diagnosis of MIDD.

##### Light microscopic examinations

In MIDD, LCDD, LHCDD, and HCDD are morphologically similar. In patients with early MIDD, findings in the glomeruli can appear, at times, to be essentially unremarkable. MIDD produces nodular glomerulosclerosis with a disease progression that mimics nodular diabetic glomerulosclerosis in 75–80% of cases (Fig. 1). In addition, increased lobulation and duplication of the GBM, which shows endocapillary proliferation and membranoproliferative glomerulonephritis (MPGN) lesions, are prominent in the glomeruli. The formation of crescents is also occasionally observed. Rare cases of LCDD showing linear light chain deposits along the TBMs without glomerular lesions have also been reported<sup>24</sup>. The deposits of MIDD are negative upon Congo red staining.

##### Immunofluorescence studies

Monoclonal immunoglobulins are detected by immunostaining for a single heavy chain subclass and a single light chain isotype. The diagnostic immunohistological finding of LCDD is the exclusive deposition of a light chain isotype (kappa ( $\kappa$ ) or lambda ( $\lambda$ ) chain) without  $\gamma$  (IgG),  $\alpha$  (IgA),  $\mu$  (IgM) deposits in the GBMs and

TBMs (Fig. 1). Unlike amyloid deposits, which are more frequently  $\lambda$  chains, deposits of LCDD are most commonly  $\kappa$  chains.

HCDD is defined as staining for a single class of immunoglobulin on the GBM and/or TBM, negative light chain staining, and the presence of typical powdery electron dense deposits<sup>25</sup>. Aucouturier et al. previously reported that monoclonal antibodies of the  $\gamma$ -heavy chain constant region CH1, CH2, or CH3 reacted abnormally to the renal deposits in patients with HCDD<sup>26</sup>. Danevad et al. also have reported that the free heavy chains present in the serum and urine of patients with HCDD lacked the CH1 domain by an amino acid sequence analysis<sup>27</sup>. Although a deletion of the CH1 domain is commonly observed in HCDD, this is thought to cause premature secretion of the molecule into the blood rather than direct precipitation. Among the heavy chain types,  $\gamma$  (IgG)-HCDD is the most prevalent, but  $\alpha$  (IgA)-HCDD and  $\mu$  (IgM)-HCDD have also been reported. Deposition of C3 or C1q is occasionally observed in the deposited IgG that bind complement components. CH2 domains containing a typical binding site for complement have the potential to activate complement, causing tissue damage following deposition<sup>25</sup>. Among the IgG subclasses, complement activation via the classical or alternative pathway is found to be due to IgG1 and IgG3, therefore,  $\gamma$ 1- or  $\gamma$ 3-HCDD often show hypocomplementemia and the level of complement in the serum reflects the disease activity in these cases<sup>28</sup>.

LHCDD is defined as the finding of both monoclonal heavy chain and light chain deposition in the tissues. Similarly,  $\gamma$  (IgG)- $\kappa$ -LHCDD is the most prevalent type. Cohen et al. reported the first case of  $\gamma$ 1- $\kappa$ -LHCDD associated with a deletion of CH1<sup>29</sup>. In several cases, however, LHCDD showed monoclonal light chain deposits with a normal heavy chain.

#### Electron microscopic examination

Electron microscopy features of MIDD include granular or powdery continuous electron-dense deposits found in the area between the lamina densa and subendothelial space, which extend to the mesangial matrix (Fig. 1). The deposits, which tend to form a band along the inner aspect of the GBM, are also observed along the outer aspect of the TBMs, in the arterioles' intima and BMs, or interstitial capillary BMs. Immunoelectron microscopy of  $\kappa$  or  $\lambda$  chains is a useful tool when the depositions cannot be precisely detected by immunofluorescence or electron microscopy<sup>30</sup>.

### Useful Support Tools for the Diagnosis of MIDD: Serum Free Light Chain Measurements for Monoclonal Gammopathy

Heavy and light chains are produced within the same plasma cells. Because plasma cells typically produce more light chains than heavy chains, free light chains, which are not attached to the heavy chains, enter the bloodstream. The serum levels of free light chains are representative of their production rates and renal clearance. Therefore, the serum free light chain concentrations increase with adaptive immune activity, whereas the  $\kappa/\lambda$  ratio remains unchanged. In contrast, an abnormal  $\kappa/\lambda$  ratio indicates monoclonal excess of one free light chain type in patients with monoclonal gammopathy<sup>31</sup>. A normal  $\kappa$  to  $\lambda$  ratio ranges from 0.26 to 1.65. Patients with ratios  $<0.26$  are defined as having monoclonal  $\lambda$  light chains and those with ratios  $>1.65$  have monoclonal  $\kappa$  free light chains<sup>32</sup>. However, it should be noted that  $\kappa$  to  $\lambda$  ratio ranges slightly increase in patients with renal impairment (0.37 to 3.1) due to a change in the dynamics of serum FLC clearance<sup>33</sup>. In addition to the clinical and laboratory parameters, including serum and urine protein electrophoresis, the measurement of serum free light chains is useful for the detection of monoclonal gammopathy. Indeed, Gerth J et al. have suggested that the  $\kappa/\lambda$  ratio showed a good sensitivity for predicting MIDD<sup>34</sup>. Because free light chains have a short serum half-life, they can act as a marker of the myeloma response to chemotherapy<sup>35</sup>.

### Useful Support Tools for the Diagnosis of MIDD: Laser Microdissection/Mass Spectrometry (LMD/MS)

The proteomic analysis of laser microdissected glomeruli has become increasingly investigated for its use in identifying kidney diseases with organized deposits. LMD/MS has been used for the diagnosis of LCDD and HCDD<sup>36,37</sup>. LMD/MS is useful in determining the type of glomerular deposition disease, particularly in cases with diagnostic difficulties solely according to immunofluorescence and electron microscopy.

### Renal Diseases with the Deposition of Monoclonal Immunoglobulins or Their Components

The term MIDD has been used by some investigators in the past as a general term for all diseases caused by monoclonal immunoglobulin localization in tissues, including AL or AH amyloidosis, light chain (myeloma) cast nephropathy, LCDD, HCDD, and LHCDD. Importantly, MIDD is currently referred to as the collective no-



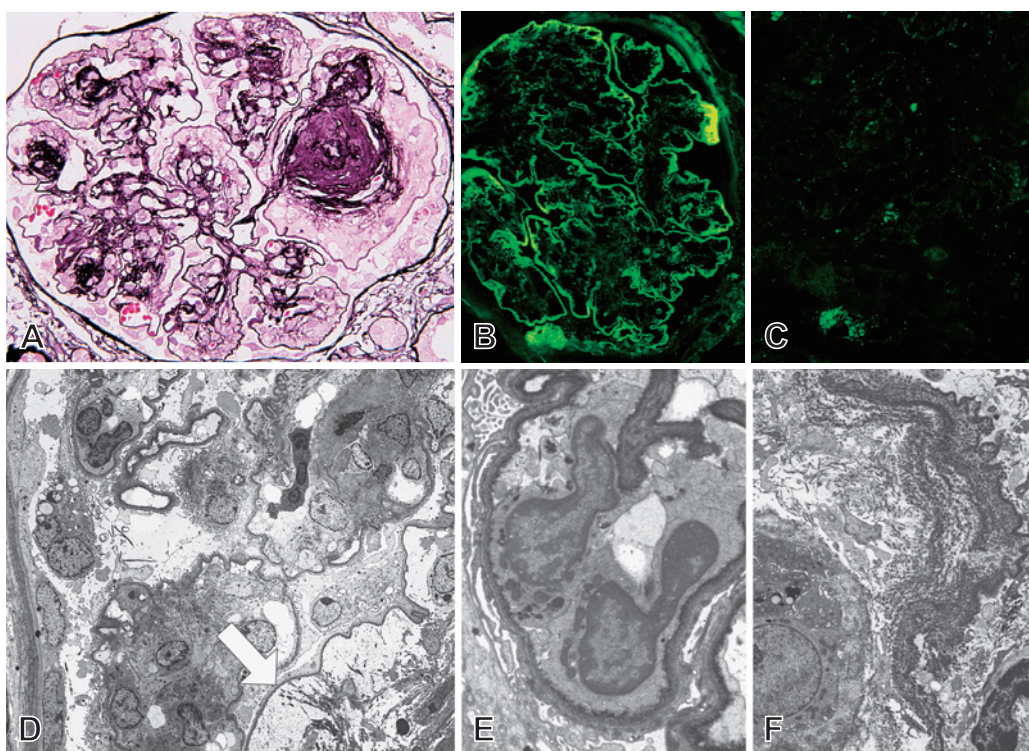


Fig. 1 Light chain deposition disease (LCDD)

Nodular glomerular sclerosis of LCDD (A) cannot be distinguished from nodular diabetic glomerulosclerosis by light microscopy (PAM stain, 600x). Immunofluorescence demonstrates positive staining for the  $\kappa$  light chain (B, 600x), but negative staining for the  $\lambda$  light chain (C, 600x) in the glomerular basement membrane (GBM). In the development of LCDD, a mesangiolytic lesion (arrow in D, 1,200x) is noted, which is likely associated with endothelial cell injury. Granular and powdery electron-dense deposits (E, 8,000x) are predominantly noted in the lamina rara interna and inner portion of the lamina densa of the GBM. Powdery deposits are also noted in the outer aspect of the basement membrane of the proximal tubules (F, 10,000x).

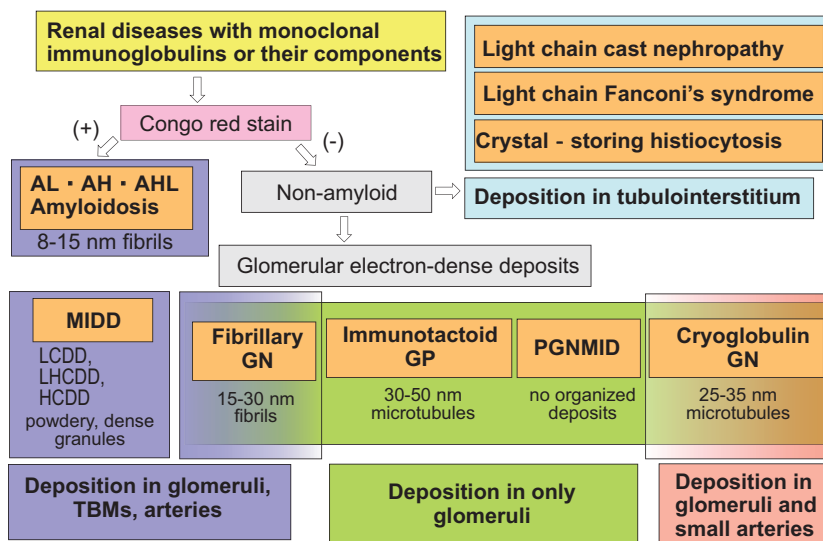
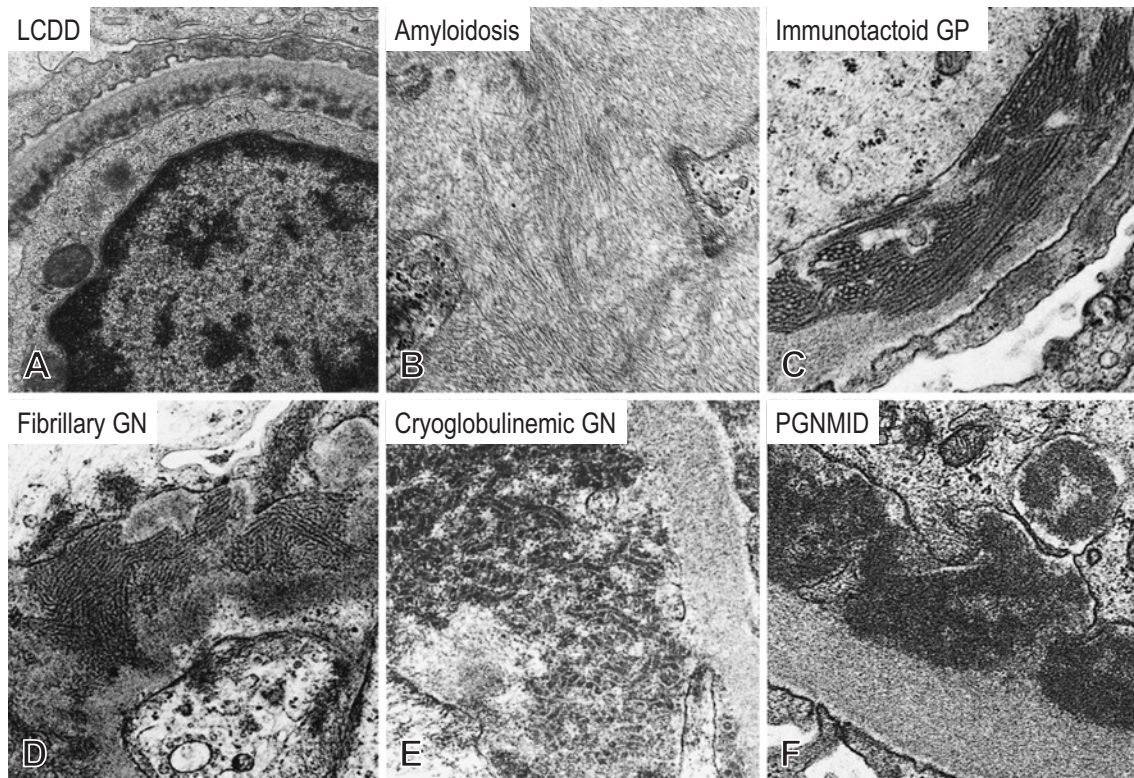


Fig. 2 Renal diseases with deposition of monoclonal immunoglobulins or their components

We recommend that renal diseases associated with plasma cell dyscrasia or paraproteinemia are arranged as the disease category, “renal diseases with the deposition of monoclonal immunoglobulins or their components”. The diagnosis of renal diseases with the deposition of monoclonal immunoglobulins or their components is facilitated by following the pathology in this algorithm, which begins with whether the deposits are Congo red positive amyloidosis or negative, followed by immunofluorescence (IF) for monoclonal immunoglobulins (single light and/or heavy chains). Diseases with deposition of monoclonal immunoglobulins or their components are divided into two groups, such as glomerular diseases and tubulointerstitial diseases. Glomerular diseases in this category include MIDD, fibrillary GN, immunotactoid GP, PGNMID, and cryoglobulinemic GN. Tubulointerstitial diseases in this category included light chain cast nephropathy (also referred to as myeloma cast nephropathy), light chain associated Fanconi’s syndrome (also referred to as light chain crystal tubulopathy or light chain proximal tubulopathy), and crystal-storing histiocytosis.



**Fig. 3** Glomerular diseases with the deposition of monoclonal immunoglobulins or their components  
 The deposits of light chain deposition disease (LCDD) are characterized by small granular and powdery electron-dense deposits on the inner side of the glomerular basement membrane (A, 25,000 $\times$ ) and outer side of the tubular basement membrane. Amyloid deposits are composed by relatively straight, non-branching, randomly arranged amyloid fibrils (B, 40,000 $\times$ ), mostly 10 nm (8-12 nm) in diameter. The deposits in immunotactoid glomerulopathy are composed of closely packed, hollow microtubules in longitudinal and cross-sectional arrays (C, 30,000 $\times$ ) around 30 nm (20-90 nm) in diameter. The deposits in fibrillary glomerulonephritis (GN) consist of randomly arranged, non-branching fine fibrils (D, 40,000 $\times$ ) with a width of approximately 20 nm (10-30 nm). The deposits in cryoglobulinemic GN are characterized by curved, cylinder-like structures with thick-walled microtubular or annular, frequently curved structures (E, 50,000 $\times$ ) that measure 10-25 nm in width. The deposits in proliferative GN with monoclonal IgG deposits (PGNMID) are non-organized electron-dense deposits (E, 50,000 $\times$ ), which are similar to those in immune complex type glomerular diseases.

menclature for three diseases, LCDD, LHCDD, or HCDD. Although various diseases are accompanied by monoclonal immunoglobulins or their components, the term MIDD must be used specifically for LCDD, HCDD, and LHCDD.

Renal diseases with the deposition of monoclonal immunoglobulins or their components include not only MIDD, but also AL or AH amyloidosis, type I cryoglobulinemia, PGNMID, light chain (myeloma) cast nephropathy, light chain associated Fanconi's syndrome (light chain proximal [crystal] tubulopathy), and crystal-storing histiocytosis (**Fig. 2**). In addition, diseases occasionally including monotypic immunoglobulins include immunotactoid GP and fibrillary GN. The distribution of deposits of these diseases is varied in the glomeruli, arteries, and/or tubulointerstitium<sup>38</sup>.

Joh recently proposed the term "glomerular deposition

disease" for glomerular diseases which are accompanied by deposition with organized structures (fibrillary or microtubules)<sup>39</sup>, as shown in **Figure 3**. However, this category includes deposition in the extracellular matrix or banded collagen fibers, as fibronectin GP or collagenofibrotic GP, respectively, due to the presence of organized deposition in the glomeruli. In addition, renal diseases with the deposition of monoclonal immunoglobulins or their components in the tubulointerstitium (**Fig. 4**), such as light chain (myeloma) cast nephropathy, light chain associated Fanconi's syndrome (light chain proximal [crystal] tubulopathy), and crystal-storing histiocytosis, are not included in the category of glomerular deposition disease. Therefore, we recommend that these glomerular and tubulointerstitial diseases are arranged as the disease category, "renal diseases with the deposition of monoclonal immunoglobulins or their components", as shown in



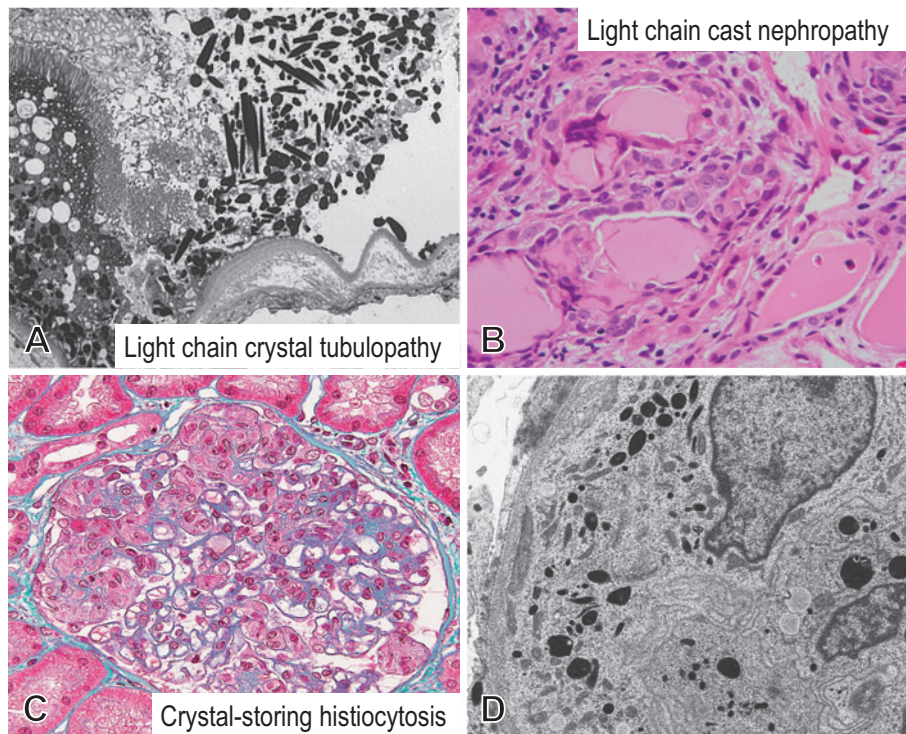


Fig. 4 Tubulointerstitial diseases with the deposition of monoclonal immunoglobulins or their components In light chain crystal tubulopathy (A, 10,000 $\times$ ), numerous crystals are evident in degenerated tubular epithelial cells. This case exhibited Fanconi's syndrome (also referred to as light chain associated Fanconi's syndrome). In light chain myeloma cast nephropathy (B, HE stain, 600 $\times$ ), large, acellular, hyaline casts show a cleavage plane or "fracture", and the cast is surrounded by large multinucleated giant cells. In cases with paraproteinemia, the glomeruli show endocapillary hypercellularity with infiltration of mononuclear cells (C, Masson's trichrome stain, 600 $\times$ ), which are CD68+ macrophages<sup>40</sup>. In electron microscopy (D, 10,000 $\times$ ), phagolysosomes and crystals are noted in infiltrating macrophages, indicating crystal-storing histiocytosis in the glomeruli. The macrophages with abnormal intra-lysosomal accumulation of immunoglobulins as crystals also infiltrated the interstitium.

**Figure 2**, because all or a part of these diseases share characteristic features that include the deposition of monoclonal immunoglobulins or their components in the kidney, organized electron dense deposits, and/or presence of paraproteinemia.

### Conclusion

MIDD includes a paraprotein-related renal disease defined as the deposition of non-amyloid monoclonal immunoglobulins in the kidney. More recently, however, renal diseases in plasma cell dyscrasias or paraproteinemia have varied morphology, and various renal diseases with monoclonal immunoglobulins or their components have been known. We therefore recommend that these glomerular and tubulointerstitial diseases be arranged as the category of, "renal diseases with the deposition of monoclonal immunoglobulins or their components". When we make a diagnosis of renal disease associated with plasma cell dyscrasias and/or paraproteinemia, this novel category may help us to clarify the renal diseases

that should be considered as differential diagnoses.

**Conflict of Interest:** None declared.

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