Membranous Nephropathy With Monoclonal IgM Lambda Deposits in a Patient With IgM Monoclonal Gammopathy: A Case Report

Go Hirose¹, Takahiro Uchida¹, Aki Kojima¹, Kentaro Sugisaki¹, Muneharu Yamada¹, Yoshihiro Nagase², Takashi Takaki², Kiyotaka Nagahama³ and Takashi Oda¹*

¹Department of Nephrology and Blood Purification, Kidney Disease Center, Tokyo Medical University Hachioji Medical Center, Hachioji, Tokyo, Japan, ²Division of Electron Microscopy, Showa University School of Medicine, Tokyo, Japan, ³Department of Pathology, Kyorin University School of Medicine, Tokyo, Japan

We report a case of membranous nephropathy with monoclonal immunoglobulin (Ig)M lambda deposits in a patient with IgM monoclonal gammopathy, in whom histological changes were observed on repeat renal biopsy. A 72-year-old Japanese woman was referred to our hospital because of massive proteinuria. A prominent increase in monoclonal IgM lambda level was identified, and she was diagnosed as having IgM monoclonal gammopathy of undetermined significance. Renal biopsy showed glomerular subepithelial electron-dense deposits that were found to be granular deposits of IgM lambda but not kappa or IgG by immunofluorescence staining, resulting in a diagnosis of membranous nephropathy with monoclonal IgM deposits. The second biopsy, which was performed 2 years later because of exacerbation of her nephrotic syndrome, demonstrated less immunofluorescence staining of IgM, and dominant IgG2 deposition without light chain restriction. Interestingly, immunostaining for thrombospondin-type-1-domain-containing-7A was positive in both renal biopsy tissues, although the second biopsy showed clearly stronger immunoreactivity. The effect of steroid therapy was limited; however, rituximab treatment improved both the hematological and renal abnormalities. Solitary deposition of IgM in membranous nephropathy is a quite rare condition. To our knowledge, this is the first case of monoclonal gammopathy of renal significance presenting as membranous nephropathy with monoclonal IgM deposits, in which chronological immunohistochemical changes were observed and rituximab therapy was effective.

Keywords: membranous nephropathy, immunoglobulin M, monoclonal gammopathy of renal significance (MGRS), rituximab, thrombospondin-type-1-domain-containing-7A

INTRODUCTION

Membranous nephropathy (MN) is a type of glomerular disease that causes the deposition of immune complexes along the subepithelial region of the glomerular basement membrane, and often clinically results in nephrotic syndrome in adults. MN is broadly separated into the following two categories: idiopathic MN, in which patients do not have an underlying disease, and secondary MN, which is associated with...
a causative systemic disease, such as infection, autoimmune
disease, or malignancy. Podocyte phospholipase A2 receptor
(PLA2R) was the first reported target antigen for the immune
complexes observed in patients with idiopathic MN (1).
Subsequently, another target antigen, thrombospondin-type-
1-domain-containing-7A (THSD7A) (2), was identified, and
more recently, several other antigens have been proposed (3).
Importantly, these antigens have been suggested to be associated
with the etiology of patients with MN (3, 4), and the expression
to the existence of masked Ig deposits, we further performed IF
staining for light chains demonstrated the deposition of only
lambda chains but not kappa chains (Figures 1F,G). To rule out
the existence of masked Ig deposits, we further performed IF
staining for IgG, IgA, IgM, and light chains on FFPE sections
after protease digestion as previously described (13), which also
showed the granular deposition of IgM and lambda chains on the
capillary walls, but with no deposition of IgG or kappa chains
(Supplementary Figure 1).

A prominent increase in the level of IgM and a decrease
in the levels of other Igs prompted us to perform a detailed
examination. A computed tomography scan did not display any
bone lesions or lymphadenopathy. Serum protein electrophoresis
showed a peak for monoclonal IgM lambda, and urine protein
electrophoresis detected lambda-type Bence Jones protein.
Concentrations of serum light-chain kappa and lambda were
12.9 and 62.7 mg/mL, respectively, and the free light-chain
to was slightly low (0.21; reference range, 0.26–1.65). Bone
marrow aspiration showed hypoplastic bone marrow with <10% plasma cells, which met the diagnostic criteria for monoclonal
gammopathy of undetermined significance (data not shown).

A renal biopsy was performed to histologically analyze the
cause of the massive proteinuria. Sections of 11 glomeruli
were analyzed by light microscopy (LM), which showed that
2 of the glomeruli were globally sclerotic. There were no
proliferative changes, and the glomerular capillary walls were
not thickened (Figure 1A). There were minimal tubulointerstitial
changes. Routine IF staining on frozen tissue sections showed
granular 2+ deposition of IgM (Figure 1B) on the capillary
walls, without deposition of IgG (Figure 1C), IgA, complement
C1q, or C3 (data not shown). Immunoperoxidase staining for
IgM on formalin-fixed, paraffin-embedded tissue (FFPE) sections
were performed using an automatic staining machine by a
clinical laboratory testing company (SRL, Inc., Tokyo, Japan).
The stained slides further confirmed the deposition of IgM on
the glomerular capillary walls (Figure 1D). Subepithelial
electron-dense deposits were found on electron microscopy, but
spike formation of the glomerular basement membrane was
obscure (Figure 1E). Although stage I MN was suggested, IF
staining for light chains demonstrated the deposition of only
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(Supplementary Figure 1).

According to these findings, a diagnosis of MN with
monoclonal IgM lambda deposits was made, and the patient
was at first conservatively treated with an angiotensin II type
1 receptor blocker (ARB), because her clinical symptoms were
mild with minor abnormalities in laboratory data, such as
serum albumin and creatinine levels, and she did not wish to
undergo aggressive treatment. However, although the level
of IgM remained unchanged, her level of proteinuria increased,
and she developed full nephrotic syndrome (urinary protein
excretion, 11.0 g/day and TP/Alb, 5.2/1.1 g/dL) about 2 years
after the first biopsy. Her renal function also worsened, and her
serum creatinine level was increased to 1.47 mg/dL [estimated

**CASE PRESENTATION**

A 72-year-old Japanese woman, who was married and was
unemployed, was found to have proteinuria at her local clinic,
and was referred to our hospital for further examination. Her
presenting symptoms were peripheral edema in both lower
legs and a recent 2 kg increase in body weight. Her vital
signs were normal. Her medical history included well-controlled
dyslipidemia and osteoporosis. She had no family history of
renal disease.

Her urinalysis showed a protein level of 4.6 g/day but no
hematuria (1–4 red blood cells/high-power field). The results
of her blood analyses were as follows: white blood cell count,
4.9 × 10^3/µL; hemoglobin level, 13.8 g/dL; platelet count, 32.9
× 10^4/µL, serum creatinine, 0.48 mg/dL; blood urea nitrogen,
13.5 mg/dL; total protein/albumin (TP/Alb), 7.6/3.1 g/dL; and
IgG, IgA, and IgM, 474, 79, and 1,940 mg/dL, respectively.
Antinuclear antibody titer was 1:80, which was slightly positive,
but hypocomplementemia was absent. C-reactive protein and
cryoglobulin were negative, and soluble IL-2 receptor level was
338 U/mL (reference range, < 486 U/mL). Viral antibodies for
hepatitis B and C were negative.

A prominent increase in the level of IgM and a decrease
in the levels of other Igs prompted us to perform a detailed
examination. A computed tomography scan did not display any
bone lesions or lymphadenopathy. Serum protein electrophoresis
showed a peak for monoclonal IgM lambda, and urine protein
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of IgM remained unchanged, her level of proteinuria increased,
and she developed full nephrotic syndrome (urinary protein
excretion, 11.0 g/day and TP/Alb, 5.2/1.1 g/dL) about 2 years
after the first biopsy. Her renal function also worsened, and her
serum creatinine level was increased to 1.47 mg/dL [estimated
glomerular filtration rate (eGFR), 27.3 mL/min/1.73 m². At that point, her serum proteins were re-evaluated for the presence of M-protein by immunofixation, which again showed only the monoclonal IgM lambda protein, thereby ruling out the presence of another paraprotein. A second renal biopsy was therefore performed to re-evaluate her renal histology about 2 years after the first biopsy. LM observation of sections showed that 2 of the 28 glomeruli analyzed were obsolescent, and interstitial fibrosis and tubular atrophy were moderate. Thickening of the glomerular capillary walls accompanied by spike formation and a bubbly appearance was also observed, suggesting disease progression of MN (Figure 2A). IF staining of frozen tissue sections demonstrated weakened IgM staining (Figure 2B) and augmented IgG staining (Figure 2C), in which IgG2 was dominant with weaker deposition of IgG4 (Figure 2D). Light chain restriction was not observed by IF staining this time, and both lambda and kappa light-chain deposits were observed at almost equal levels (Figures 2E,F). Thus, in the second renal biopsy, routine IF staining on a frozen tissue section showed weak IgM staining in glomeruli; however, immunoperoxidase staining for IgM on a FFPE section after antigen retrieval showed strong IgM deposition on the glomerular capillary walls (Figure 2G).

Although IF staining of IgG was augmented in the renal tissue of the second renal biopsy, serum anti-PLA2R antibody level measured by enzyme-linked immunosorbent assay, and IF staining for PLA2R on FFPE sections were both negative (Supplementary Figure 2). Immunoperoxidase staining for neural epidermal growth factor-like 1 protein (NELL-1) on FFPE sections was also negative (Supplementary Figure 2), whereas that for THSD7A on FFPE sections showed a diffuse positive staining pattern on the glomerular capillary walls (Figure 2H). Immunoperoxidase staining for THSD7A on FFPE sections of the first renal biopsy was therefore performed and the staining result was compared with that of the second renal biopsy. Compared to the second renal biopsy, which showed diffuse and global strong staining, the staining result of the first renal biopsy showed focal and segmental granular immunoreactivity on the glomerular capillary walls (Supplementary Figure 3). THSD7A was negative in cells of the bone marrow by immunoperoxidase staining of FFPE sections (Supplementary Figure 3). Immunoperoxidase staining for amyloid P, a recently identified marker of membranous-like glomerulopathy with masked IgG deposits (1-4), was negative in the FFPE sections of both renal biopsy tissues (Supplementary Figure 2). Because of her severe nephrotic syndrome, the patient started steroid therapy; however, the effects were limited both for her renal and hematological abnormalities; i.e., her heavy proteinuria persisted and her serum IgM level remained high. On the contrary, 2 injections of rituximab (375 mg/m² per injection) substantially improved both abnormalities; her renal function (eGFR), urinary protein level, and serum IgM level were maintained at more than 60 mL/min/1.73 m², <1 g/day, and <1,000 mg/dL, respectively, after 2 rituximab injections. Her clinical course is shown in Figure 3.
**DISCUSSION**

MN is the most common cause of nephrotic syndrome in adults, and IgG4 deposition without light chain restriction is usually observed in the glomerular immune deposits of patients with idiopathic MN. However, in the present patient, the first renal biopsy showed isolated glomerular IgM lambda deposits, resulting in a diagnosis of MN with monoclonal IgM deposits. Larsen et al. (14) recently reported that serum amyloid P was a sensitive and specific marker of membranous-like glomerulopathy with masked IgG kappa deposits; however, immunostaining for amyloid P was negative in renal biopsy tissues of the present patient. In addition, IF staining using FFPE sections also showed deposition of IgM and lambda chains on the capillary walls, but with no deposition of IgG or kappa chains, which further supported our diagnosis. Kitazawa et al. (15) reviewed 18 reported cases and their own case of so-called MIDD associated with membranous features, that is, MN with monoclonal Ig deposits. The glomerular immune deposits of most of these patients consisted of IgG, and only 2 patients showed IgA-type monoclonal deposition. To the best of our knowledge, our present patient is the first patient to date showing MGRS presenting as MN with IgM-type monoclonal deposition. Among them, there has been a case of a patient with IgM lambda-type MN accompanied with Waldenström macroglobulinemia (WM), who was treated effectively with rituximab and fludarabine. Consistent with these previous reports, steroid therapy was ineffective, but rituximab treatment improved both the hematological and renal abnormalities of our present patient.

Interestingly, the IF staining pattern was clearly different in the second renal biopsy of our patient compared with the first. In the second biopsy, glomerular IgM staining appeared weaker, whereas IgG staining was augmented, in which IgG2 was dominant with weaker deposition of IgG4. In addition, both lambda and kappa light-chain deposition were almost equally observed. The serum anti-PLA2R antibody level, as well as immunostaining for PLA2R and NELL-1, a recently identified antigen observed in a distinct type of MN (18) were negative, whereas that for THSD7A showed diffuse and global granular-positive staining on the glomerular capillary walls. It was reported that anti-THSD7A antibodies were predominantly of the IgG4 subclass (2), which might explain the appearance of the IgG4 subclass in the second renal biopsy of the present patient. On the other hand, focal and segmental granular-positive immunostaining for THSD7A was already observed in the first renal biopsy tissue. In this regard, we considered the possibility that specific immune responses occurring during the progression of MN in this patient induced the exposure of THSD7A epitopes, resulting in the production of THSD7A autoantibodies.
Consistent with this scenario, Tominaga et al. (19) recently reported two cases of patients with MN-lesions, in which both myeloperoxidase and PLA2R were detected in the glomerular subepithelial deposits, suggesting that a specific inflammatory environment led to the abnormal exposure of PLA2R epitopes. Another possibility is that IgM lambda antibodies, which were observed to be deposited in the first renal biopsy tissue, were already bound to THSD7A, and IgG antibodies to THSD7A developed thereafter by Ig class switching. Although THSD7A was reported to be expressed in the malignant tumor tissue of a patient with THSD7A-associated MN (5), immunoperoxidase staining for THSD7A was negative in the bone marrow tissue of the present patient (Supplementary Figure 3).

We assumed that glomerular IgM deposition was not decreased in the second biopsy, but may have been difficult to detect owing to the deposition of polyclonal IgG, thereby interfering the immuno-reactivity of anti-IgM antibody. IgG subclass staining showed dominant IgG2 deposition in the second renal biopsy tissue. Although several new antigens in MN have recently been proposed (3), no corresponding antibodies predominantly of the IgG2 subclass have been identified to date. Thus, polyclonal IgG antibodies that react with monoclonal IgM, which are deposited on the glomerular capillary walls, may be produced via autoimmune mechanisms in this patient. Indeed, immunoperoxidase staining on FFPE sections of the second renal biopsy after antigen retrieval showed strong IgM deposition on the glomerular capillary walls (Figure 2G). Strong IgM deposition along the capillary walls was also shown by IF staining on a fresh frozen tissue section of the second renal biopsy after pretreatment with acidic buffer for antigen retrieval (Supplementary Figure 4).

Regarding treatment regimens for MGRS patients, targeting the causative B-cell clone is considered to be a reasonable therapeutic strategy (8). Indeed, in our patient, improvement of her nephrotic syndrome as well as an adequate hematological response was achieved not by ARB or steroid therapy but by rituximab treatment. It should be noted, however, that favorable therapeutic effects of rituximab have been widely reported in the treatment of nephrotic syndrome.

In conclusion, we reported a case of a patient with MGRS presenting as MN with monoclonal IgM lambda deposits accompanied by IgM lambda monoclonal gammapathy, in which improvement of renal and hematological abnormalities was achieved by rituximab treatment. It should be noted, however, that favorable therapeutic effects of rituximab have been widely reported in the treatment of nephrotic syndrome.

DATA AVAILABILITY STATEMENT

The original contributions presented in the study are included in the article/Supplementary Material, further inquiries can be directed to the corresponding author/s.

ETHICS STATEMENT

Ethical review and approval was not required for the study on human participants in accordance with the local legislation and institutional requirements. The patients/participants provided their written informed consent to participate in this study. Written informed consent was obtained from the individual(s) for the publication of any potentially identifiable images or data included in this article.

PATIENT’S PERSPECTIVE

The patient has remained in a stable and improved condition, as the peripheral edema in her lower legs, as well as other presenting symptoms, resolved after rituximab treatment.

AUTHOR CONTRIBUTIONS

GH and TU: writing the manuscript draft. TO: critical manuscript revision. GH, AK, and MY: clinical care of the patient. TU, KS, YN, TT, KN, and TO: histological evaluation. All authors contributed to the article and approved the submitted version.

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SUPPLEMENTARY MATERIAL

The Supplementary Material for this article can be found online at: https://www.frontiersin.org/articles/10.3389/fmed.2021.608741/full#supplementary-material

**Supplementary Figure 1** | Immunofluorescence staining of formalin-fixed, paraffin-embedded tissue (FFPE) sections showed granular deposition of immunoglobulin (IgM (A) and lambda chain (B) on the glomerular capillary walls, whereas there was no deposition of IgG (C), IgA (D), or kappa chain (E).

**Supplementary Figure 2** | Immunofluorescence staining for the phospholipase A2 receptor (A) and immunoperoxidase staining for neural epidermal growth factor-like 1 protein (B) on FFPE sections of the second renal biopsy tissue.
Immunoperoxidase staining for amyloid P on FFPE sections of the first renal biopsy tissue (C) and the second renal biopsy tissue (D).

**Supplementary Figure 3** | Immunoperoxidase staining for thrombospondin-type-1-domain-containing-7A (THSD7A) on FFPE sections of renal biopsy tissues and bone marrow tissue. The staining was weak, focal, segmental, and granular on the capillary walls of the first renal biopsy tissue (A), whereas the staining was strong, diffuse, global, and granular on the capillary walls of the second renal biopsy tissue (B). Bone marrow cells, including neoplastic plasma cells, were negative for THSD7A by immunoperoxidase staining (C).

**Supplementary Figure 4** | Immunofluorescence staining for IgM on fresh frozen tissue sections of the second renal biopsy. Acetone-fixed cryostat sections of fresh-frozen renal biopsy tissues, with or without incubation with acidic buffer consisting of 0.1 M potassium chloride and 0.1 M hydrochloric acid for 30 min at room temperature, were immunohistochemically stained for IgM. Note that preincubation with the acidic buffer demonstrated extensive IgM deposition along the capillary walls (A: without acidic buffer, B: with acidic buffer).

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**Conflict of Interest:** The authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.