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CASE REPORT

Lupus-like membranous nephropathy during the postpartum period expressing glomerular antigens exostosin 1/exostosin 2 and phospholipase A2 receptor: a case report

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Abstract

Recently, several target antigens of membranous nephropathy (MN), such as phospholipase A2 receptor (PLA2R) and exostosin 1/exostosin 2 (EXT1/2), have been discovered. A 30-year-old woman was referred to our hospital with nephrotic range proteinuria and microscopic hematuria. She was first noted to have proteinuria before pregnancy, and her proteinuria worsened in the postpartum period. A renal biopsy showed MN. Immunofluorescence microscopy showed IgG, IgA, IgM, C3, C4, and C1q depositions in the mesangial area and glomerular capillary walls (GCWs). Regarding the IgG subclass, IgG1 and IgG3 were detected on glomeruli. Electron microscopy showed subepithelial electron-dense deposits (EDDs). EDDs were also detected in paramesangial and subendothelial areas. The diagnosis of membranous lupus nephritis (MLN) was suspected, but she did not fulfill the criteria for systemic lupus erythematosus. Neither anti-nuclear antibody nor hypocomplementemia were detected. We further evaluated glomerular EXT1/2 expressions, which were evident on GCWs. In addition, PLA2R was also detected on GCWs, although serum antibody for PLA2R was negative. She responded to immunosuppressive therapy with decreased proteinuria. In the present case, glomerular PLA2R expression implied the possibility of primary MN. However, pathological findings with a full-house staining pattern and glomerular EXT1/2 expressions were very similar to those of lupus-associated MN. Glomerular PLA2R expression appeared not to reflect immunocomplexes of PLA2R and autoantibody when considering the results for glomerular IgG subclass and the absence of serum anti-PLA2R antibody. Collectively, it is plausible that this was a case of a relatively young postpartum female who developed latent MLN rather than primary MN.

Keywords Membranous nephropathy (MN) · Membranous lupus nephropathy (MLN) · Primary membranous nephropathy · Exostosin 1/exostosin 2 (EXT1/2) · Phospholipase A2 receptor (PLA2R)

Introduction

Membranous nephropathy (MN) is a well-known glomerular disease that can induce nephrotic syndrome in adults [1]. To date, MN has been classified as either primary or secondary, based on the identifiable causes [1, 2]. Around 80% of patients with MN were reported to be categorized as primary MN without any underlying cause, and the remaining cases were associated with medications or other diseases such as systemic lupus erythematosus (SLE), hepatitis virus infection, or malignancies [2]. However, MN is currently recognized to be an antibody-mediated autoimmune glomerular disease characterized by subepithelial immune deposits [3].

Recent technical advances in mass spectrometry and laser microdissection have successively discovered target antigens of MN [3]. Phospholipase A2 receptor (PLA2R), a membrane glycoprotein localized to podocytes, was identified by Salant's group as the target antigen in patients with primary MN [4]. In addition to PLA2R, thrombospondin type 1 domain-containing 7A (THSD7A), neural epidermal growth factor-like 1 protein (NELL-1), and others have already been uncovered as target antigens for circulating and deposited antibodies in patients with primary MN [5, 6]. Moreover,

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exostosin 1 and exostosin 2 (EXT1/2) on the glomerular basement membrane (GBM) have been highlighted as novel putative antigens in secondary MN with autoimmune diseases such as lupus nephritis (LN) [7]. Of note, recent articles [7–9] mentioned that glomerular EXT1/2 expressions could be an essential clue for diagnosing membranous lupus nephropathy (MLN), which is SLE-related MN and classified as type V of LN [10, 11]. In agreement with a recent analysis, expression rates of glomerular EXT1/2 antigens were significant in MLN [7–9, 12, 13].

According to the diagnostic algorithm proposed by De Vriese As et al. [14], absence of serum antibody for PLA2R and negative for glomerular PLA2R antigen in biopsy-proven MN indicates secondary rather than primary MN. In the previous reports, serum antibody for PLA2R and glomerular PLA2R antigen were not detected in patients with secondary MN including LN [15–17]. On the other hand, Sethi et al. [7] reported that PLA2R antigen on glomeruli was all negative in MLN patients with glomerular EXT1/2 expressions. These reports led to the conclusion that the glomerular immunostaining pattern for PLA2R or EXT1/2 could be an effective indicator to differentiate two pathomorphologically similar diseases, which are primary MN and MLN. However, a recent analysis and case report showed inconsistent results, in which patients with primary MN showed glomerular EXT1/2 expressions, and MLN patients showed PLA2R deposition on glomeruli [12, 18, 19]. Therefore, immunostaining for glomerular PLA2R and EXT1/2 antigens might not be a definitive diagnostic tool.

The case of a relatively young female with non-lupus full-house MN during the postpartum period with glomerular EXT1/2 and PLA2R expressions is reported. In the present case, it was critical to differentiate lupus-associated MN and PLA2R-related MN. Based on the detailed assessment, the validity of the diagnosis of lupus-like MN is discussed. Moreover, the possibility that this case may be a latently developed MLN, an atypical type of MLN preceding the development of SLE, is also considered.

Case report

A 30-year-old woman was admitted to our hospital because of nephrotic range proteinuria (NRP) and microscopic hematuria. She seemed to have felt a slight discomfort in her wrist joints since her early 20s, but she had not visited a medical institution for a specific examination. Episodes such as gross hematuria after upper respiratory tract infection and purpura on the limbs had not occurred. Around 4 years previously, she became pregnant for the first time and gave birth without any problems. Twenty-five months previously, she was first noted to have proteinuria at a health checkup in which the urine protein/creatinine (Cr) ratio was 0.46 g/gCr. Nineteen months previously, she was referred to our hospital because of proteinuria and microscopic hematuria when she became pregnant for the second time. At that time, her proteinuria was 1.1 g/gCr, and her urinary sediment showed 10–19 red blood cells (RBCs) per high-power field (HPF). The serum Cr level was 0.6 mg/dL. Then, 13 months previously, she delivered her second child without any complications. During that second pregnancy, the urine protein (UP) level remained around 1.0–1.5 g/gCr without aggravation. However, her UP worsened to 4.8 g/gCr after giving birth. Eventually, she was hospitalized for further examination.

On admission, her temperature was 36.8 °C, her pulse was 85 beats per minute, and her blood pressure was 102/63 mmHg. Findings on physical examination were unremarkable. She had neither a skin rash nor arthralgia. Chest radiography showed no pleural effusion. Whole-body computed tomography and abdominal ultrasonography showed no mass or specific space-occupying lesions. Laboratory tests showed: white blood cell count, 6,500/mm^3; erythrocyte count, 436×10^4/μL; hemoglobin, 13.3 g/dL; hematocrit, 39.0%; platelet count, 31.9×10^4/mm^3; erythrocyte sedimentation rate, 7 mm/h; total protein, 6.3 g/dL; albumin, 3.7 g/dL; blood urea nitrogen, 12.9 mg/dL; Cr, 0.7 mg/dL; estimated glomerular filtration rate, 80.0 mL/min/1.73 m^2; total cholesterol, 261 mg/dL; C-reactive protein, 0.03 mg/dL; matrix metalloproteinase-3 (MMP-3), 162 ng/mL; IgG, 891 mg/dL; IgA, 210 mg/dL; and IgM, 103 mg/dL. Serum hepatitis B surface antigen and anti-hepatitis C virus antibody were negative, and serum complement levels were within normal limits. No anti-nuclear antibody, anti-double-stranded DNA, anti-Ro, anti-La, or anti-Sm antibodies were detected. Similarly, anti-cardiolipin β2GPI antibody, lupus anticoagulant, anti-neutrophil cytoplasmic antibodies, and anti-citrullinated peptide antibody were absent. A 24-h urine collection showed 2.6 g of protein. The urinary sediment contained 10–19 RBCs per HPF.

On day 2 after admission, a percutaneous renal biopsy (RB) was performed to obtain a definitive diagnosis. A total of 21 glomeruli were available. Neither global sclerosis nor crescent formation were observed. Light microscopic (LM) examination of the glomeruli showed partial, very mild thickening of the GBM with segmental mesangial hypercellularity (Fig. 1a). In addition, LM showed spike formation of the GBM (Fig. 1b, c). The tubulointerstitium showed focal cellular infiltration and tubular dilatation. No features of arteritis were noted. Immunofluorescence (IF) microscopy showed segmental or global deposits of IgG, IgA, IgM, C3, C4, and C1q along the glomerular capillary walls (GCWs) (Fig. 2a–f). These positive findings were also seen segmentally in the mesangial or paramesangial areas. In terms of glomerular IgG subclasses identified by IF staining (Fig. 2g–j), IgG1 was intensely positive on GCWs and the mesangial area (Fig. 2g), and IgG3 was mildly to moderately

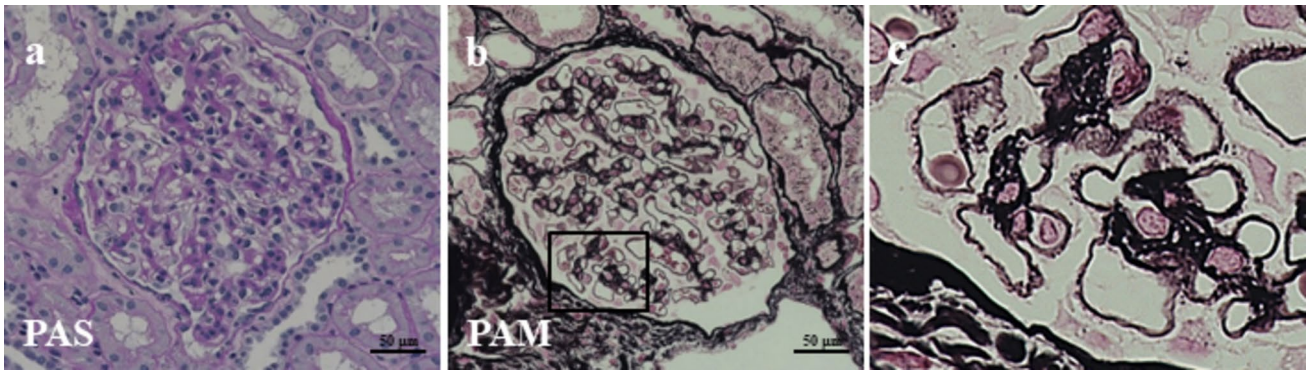

Fig. 1 Light microscopy findings. The glomerulus shows very mild thickening of the capillary basement membrane with segmental, mild mesangial hypercellularity (**a**) (periodic acid-Schiff stain; original magnification ×400). Stippling and spike formation of the glomerular basement membrane are detected segmentally (**b**) (periodic acid-silver methenamine stain; original magnification ×400). An enlarged view of the square part of the glomerulus in (**b**) shows apparent spike formation on the GBM (**c**)

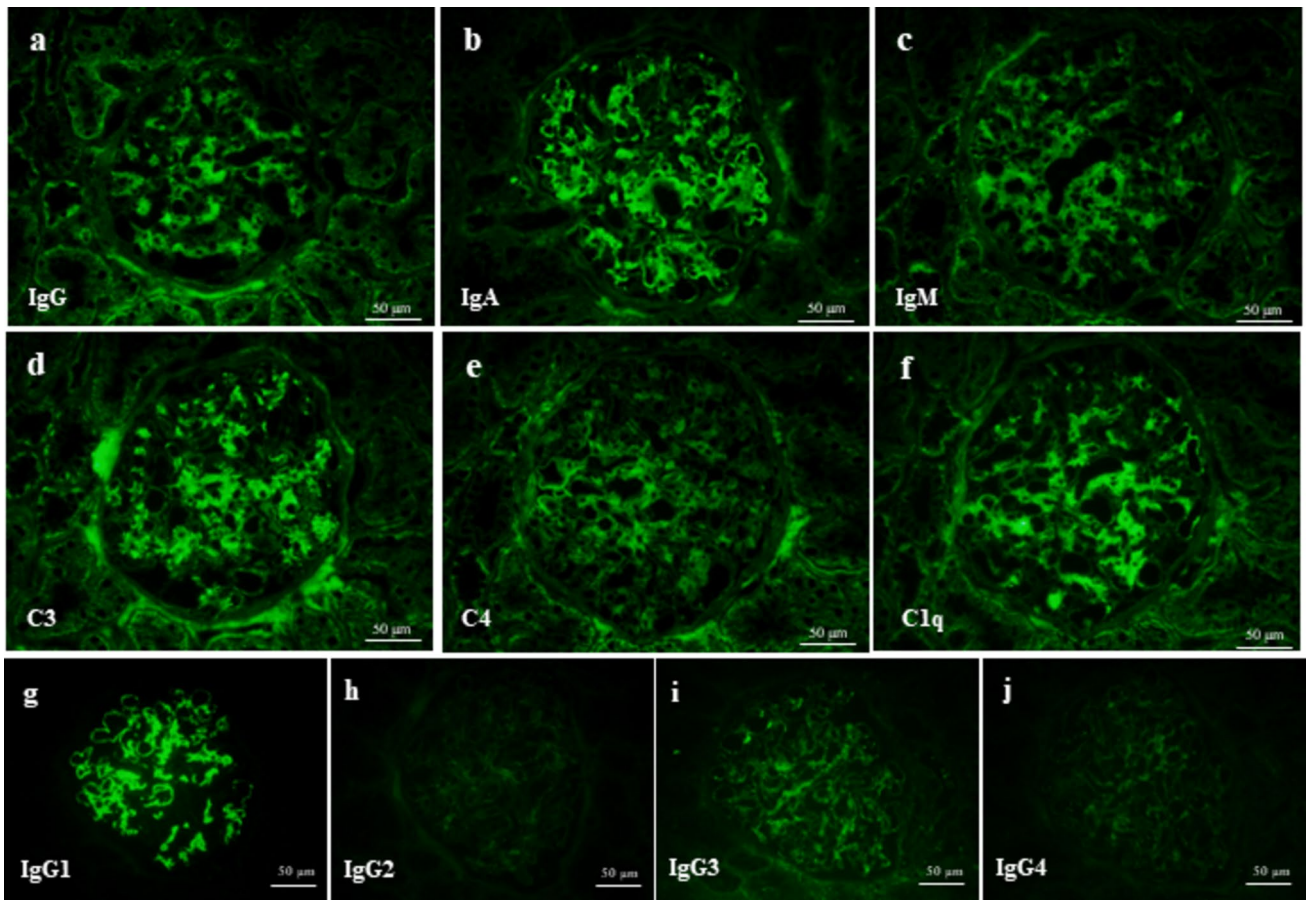

Fig. 2 Immunofluorescence microscopy findings. Immunofluorescence shows moderate staining for IgG (**a**), intense staining for IgA (**b**), mild to moderate staining for IgM (**c**), intense staining for C3 (**d**), mild staining for C4 (**e**), intense staining for C1q (**f**), intense staining for IgG1 (**g**), negative staining for IgG2 (**h**), mild to moderate staining for IgG3 (**i**), and faint staining for IgG4 (**j**) on the capillary wall and paramesangial area (original magnification ×400)

positive on glomeruli (Fig. 2i). Meanwhile, IgG2 was negative (Fig. 2h), and positivity for IgG4 was faint (Fig. 2j). An electron micrograph (EM) showed segmental subepithelial electron-dense deposits (EDDs) (Fig. 3a), and these subepithelial EDDs differed in size. The Ehrenreich and Churg classification [20] was stage 2 (Fig. 3b). Furthermore, EDDs

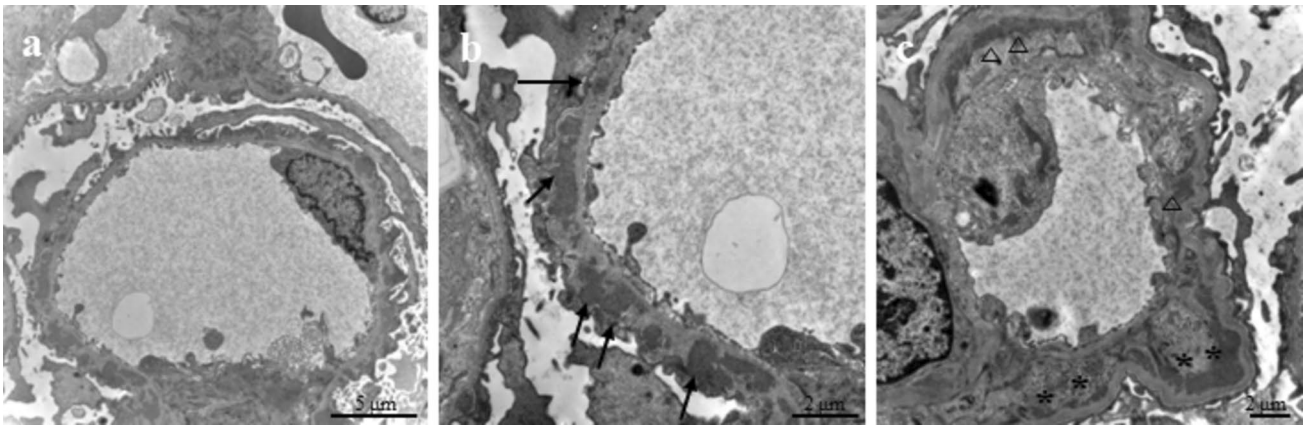

Fig. 3 Electron microscopy findings. An electron micrograph shows subepithelial electron-dense deposits (EDDs) (**a**) (original magnification ×6000). Marked EDDs in the subepithelial area (arrow) are different in size and categorized as stage 2 in the Ehrenreich and Churg classification (**b**) (original magnification ×12,000). EDDs are detected in paramesangial (asterisks) and subendothelial (triangle) areas (**c**) (original magnification × 10,000)

were also detected in paramesangial and subendothelial areas (Fig. 3c). Finger print and other organized deposits such as tubuloreticular inclusions were not detected. Taken together, the RB findings were summarized as follows: (1) LM showed MN with mild mesangial proliferative change; (2) IF analysis showed a full-house staining pattern on glomeruli; and (3) EDDs were seen in not only epithelial areas, but also subendothelial and paramesangial areas. These pathological findings led to a likely presumptive diagnosis of secondary MN, especially MLN, rather than primary MN. However, the patient did not fulfill the criteria for SLE proposed by the American College of Rheumatology [21] and the Systemic Lupus International Collaborating Clinics group in 2012 [22]. Therefore, a definitive diagnosis was not possible, and she opted for conservative treatment without drugs because she was breast-feeding.

Further examinations were performed to identify the glomerular antigens of MN and clarify the pathogenesis of this disease, since persistent NRP was observed. Glomerular antigens EXT1/2 and PLA2R were assessed by IF staining, as previously described [9, 15, 23]. IF analysis showed segmental granular depositions of EXT1/2 on GCWs (Fig. 4a, b), and global granular PLA2R depositions on GCWs (Fig. 4c). Next, the presence of serum anti-PLA2R antibody (Ab) was investigated by enzyme-linked immunosorbent assay kits [14, 15], which showed the absence of anti-PLA2R Ab. Based on the additional evaluation, it was considered that the patient had lupus-like MN rather than primary MN, although glomerular PLA2R antigen was detected. The possibility of a case with MN that presents like MLN before fulfilling the diagnostic criteria for SLE was strongly suspected. Consequently, around 12 months after RB, the patient agreed to receive steroid therapy in outpatient care and she was started on treatment with corticosteroids (prednisolone [PSL], 25 mg/day, 05 mg/kg). Subsequently, the PSL was gradually tapered to 15 mg/day during 6 months, and current UP level was decreased around 1.0 g/gCr without aggravation of renal function (Fig. 5).

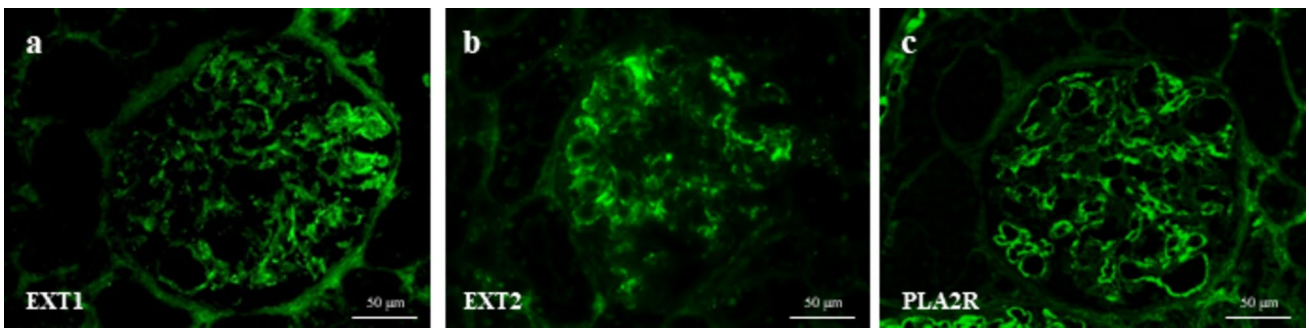

Fig. 4 Glomerular EXT1, EXT2, and PLA2R expressions identified by immunofluorescence staining. Immunofluorescence analysis shows segmental granular deposits of EXT1 (**a**), segmental granular deposits of EXT2 (**b**), and global granular deposits of PLA2R (**c**) on glomerular capillary walls (original magnification ×400)

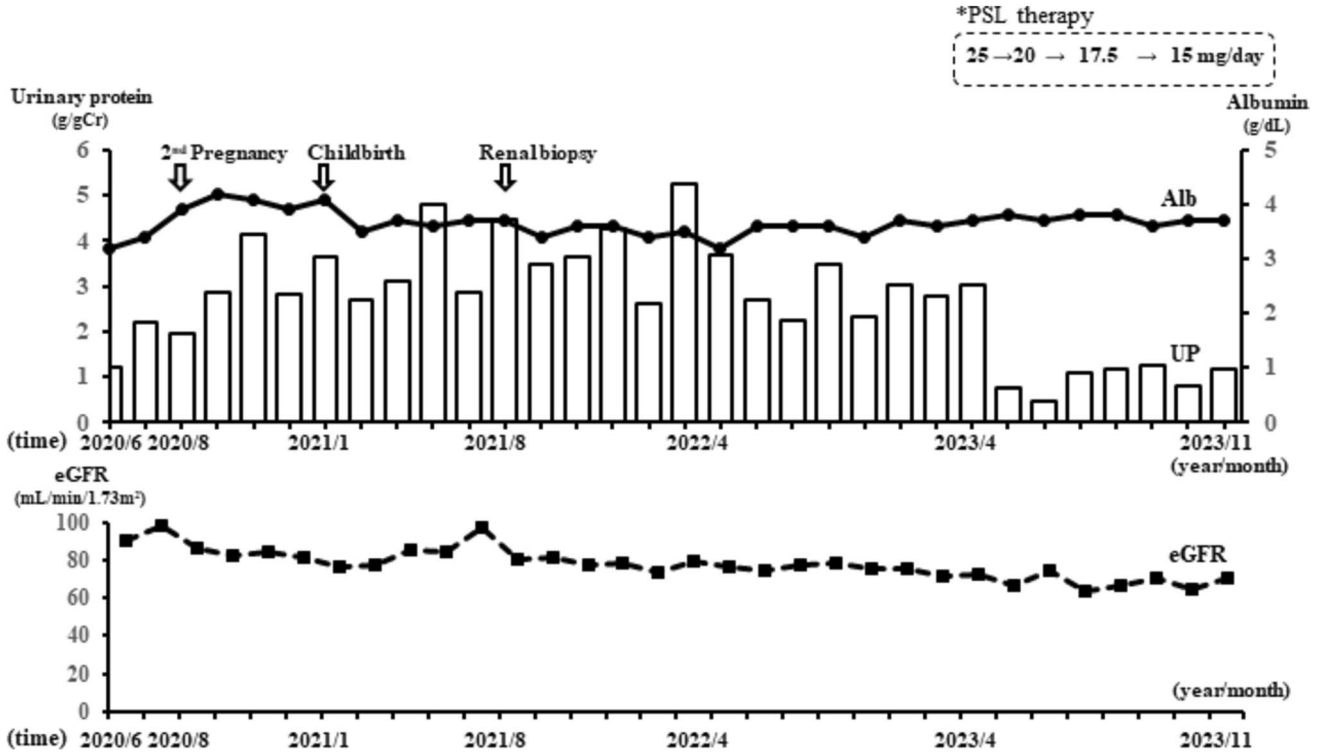

Fig. 5 Clinical course and treatment of the patient. Alb, Albumin; Cr, creatinine; eGFR, estimated glomerular filtration rate; PSL, prednisolone; UP, urinary protein. *Treatment with oral prednisolone (25 mg/day) was started, and then steroid therapy was gradually tapered to 15 mg/day during 6 months

Discussion

In the clinical setting, the presence of SLE and the glomerular full-house staining pattern are crucial to differentiate between MLN and primary MN. An indeterminate SLE-diagnosis with a glomerular full-house staining pattern leads to confusion in distinguishing between MLN and primary MN. However, there have been several reports [24–32] regarding MN cases that presented with lupus-like MN without fulfilling the criteria for SLE. Moreover, a recent analysis reported that normal complement and autoantibody levels are not uncommon in MLN [9]. Miyake et al. [10] also mentioned that around 40% of MLN patients did not show low serum complement and elevated anti-DNA antibody titers. Thus, several clinicopathological findings in the present case, including the patient's female sex, relatively young age, discomfort in wrist joints with elevated MMP-3 levels, full-house staining pattern on GCWs, focal mesangial proliferative changes with apparent mesangial EDDs, and presence of endothelial EDDs, raised the suspicion of a diagnosis of lupus-associated MN despite normal complement levels and absence of autoantibodies. Furthermore, it was reported that some patients with primary MN achieved complete remission without any treatment [33], which suggest that this case may not be a primary MN. No other common causes of secondary MN were detected. Taken together, the diagnosis of the present case was likely to be lupus-like MN.

To date, there have been few reports of lupus-like MN similar to the present case. Sam et al. noted that some patients with lupus-like MN who were initially labeled as "latent lupus" and "non-SLE at the time of RB" were subsequently diagnosed as having SLE years later [28]. Their literature review showed that approximately 25% of the 95 patients with such lupus-like MN developed SLE after a mean follow-up period of 5 years [28]. In other reports, cases of latently developed MLN such as the present one have been described as: MN cases preceding the emergence of SLE [34]; late-onset SLE and lupus-like MN in apparent idiopathic MN [30]; delayed appearance of SLE in MN [26, 35]; originally non-lupus full-house MN [25]; and MLN cases initially seen as primary MN [24]. Moreover, a recent case–control study described a case similar to that of the present patient in which a patient showing lupus-like MN with a full-house staining pattern during the postpartum period was eventually diagnosed as having SLE 8 years after onset of MN [36]. Another case report also presented lupus-like MN during pregnancy who eventually developed MLN 11 years after onset [27]. Although the pathogenesis of such a type of MLN remained unelucidated, renal-limited in situ immune complex formation that consisted of endogenous

glomerular antigen and its autoantibody may be involved in the developmental mechanism. Collectively, those previous reports could support the validity of the suggestion of latently developed MLN in the present case.

To the best of our knowledge, evidence that recognizes pregnancy itself as an inducing factor for the development of MN has not been reported. With regard to the MN associated with gestational trophoblastic disease (GTD), as described previously [37], an extensive gynecological examination showed no GTD during pregnancy or the postnatal period in the present case. Therefore, the possibility of de novo MN caused by pregnancy itself or pregnancy-related MN is considered to be low. Meanwhile, it is necessary to keep in mind the influence of pregnancy-induced immune tolerance on the development of lupus-like MN in the present case. The appearance of autoantibodies and hypocomplementemia may be masked by pregnancy. Moreover, a recent study from Mexico [36] reported that 4 (6.5%) of 62 patients who received RB in pregnancy or shortly after delivery termination showed full-house lupus-like MN without fulfilling the criteria of SLE, as in the present case. They mentioned that such full-house lupus-like MN may be triggered by pregnancy [36]. However, convincing evidence elucidating the pathogenesis of pregnancy-induced lupus-like MN has not been established. Indeed, in the present case, the appearance of autoantibodies or hypocomplementemia was not found despite the reversal of immune tolerance after giving birth. The causal relationship between pregnancy and the development of lupus-like MN remained obscure.

According to recent reports, EXT proteins in the Golgi apparatus of podocytes and truncated EXT proteins, which might be secreted from podocytes to the GBM side, are postulated to affect the development of MN [7, 9]. In an analysis using proteomics and immunohistochemistry (IHC), significant expressions of EXT1/2 were detected on the GBM of PLA2R-negative MLN, whereas EXT1/2 expressions were absent in all presented cases of PLA2R-associated MN [7]. With regard to the prevalence rate of glomerular EXT1/2-positive in patients with MLN, 35.0–44.4% were reported to be positive by IHC [7, 8, 13]. Ten (90.9%) of eleven Japanese patients with MLN showed bright granular GBM staining for EXT1/2 on IF [9]. Notably, glomerular EXT1/2 expressions have the potential to be a predictor of MLN. In the validation cohort that consisted of 18 cases of MLN [7], two cases were initially diagnosed as primary MN weakly and partially positive for EXT1/2, but negative for PLA2R on glomeruli in the first RB; subsequently, around 6–10 years later, these two cases developed full-blown clinical lupus, and glomerular EXT1/2 staining by IF turned strongly positive at the second or third RB. These previous reports could support our diagnosis of latent type MLN. However, unexpectedly, the present case showed the presence of glomerular PLA2R antigen. These inconsistent findings of IF staining resulted in confusion, but Iwakura et al. reported two cases of MN with dual-positive EXT1/2 and PLA2R on glomeruli by IHC [12, 19]. In the recent cohort study of patients with LN, glomerular PLA2R antigen was detected in 5 (71.4%) of 7 patients with MLN [18]. Although the mechanism of dual positivity of EXT1/2 and PLA2R on GBM was not clarified and simultaneous expressions of several glomerular antigens may be coincident or reactive changes to GBM damage, it is critical to determine which antigen is the component of ICs that consisted of target antigen and autoantibody on the GBM.

It is well known that IgG1, IgG2, and IgG3 tend to be highly expressed in patients with LN, whereas IgG1 and IgG4 tend to be highly expressed in primary MN [2, 6, 14]. Beck et al. demonstrated that the IgG subclass reacted to the PLA2R antigen on GBM was mainly IgG4 in primary MN [4]. Furthermore, of note, the present case showed absence of serum anti-PLA2R Ab, even though EM showed a relatively early phase of MN (a pattern of stage II) exhibiting NRP, which is incompatible with the finding of PLA2R-related MN. Although its serum Ab is not necessarily detected in patients with primary MN [14, 15], the prevalence of serum Ab in primary MN was considered to be high in the early phase of primary MN with massive proteinuria [38]. On the other hand, the IgG subclass in EXT1/2-associated MN was reported to be IgG1-dominant [3, 7]. In addition, a recent clinical report presented a case with MLN in which expressions of EXT2 and IgG3 were merged on the GBM on IF [13]. Therefore, glomerular IgG1 and IgG3 deposition in the present case might reflect the antibodies for EXT1/2 antigens rather than PLA2R.

In conclusion, a rare case of lupus-like MN during the postpartum period expressing glomerular antigens of EXT1/2 and PLA2R was described. Although it is impossible to completely exclude the possibility of PLA2R-related MN or other types of MN related to unevaluated antigens including THSD7A, NELL-1, and others, we presume that the present case was one of latently developed MLN based on the detailed assessment. Thus, the present patient requires careful follow-up, especially to monitor for further progression of SLE.

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Declarations

Conflict of interest All the authors have declared no competing interests.

Human and animal rights This article does not contain any studies with human participants or animals performed by any of the authors.

Informed consent Informed consent was obtained from the patient described in the present case.

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