Membranous nephropathy caused by rheumatoid arthritis

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Abstract

Membranous nephropathy (MN) caused by disease-modifying antirheumatic drugs is relatively common in patients with rheumatoid arthritis (RA). However, MN rarely occurs due to RA itself. We describe a 61-year-old woman with RA who showed nephrotic syndrome. She was admitted because of systemic edema and severe arthritis. She had a long history of RA successfully treated with methotrexate (MTX), but discontinued all treatments 4 years before hospitalization. She had never been treated with bucillamine or gold. Laboratory test results were positive for anti-cyclic citrullinated peptide antibody and negative for anti-nuclear antibody. Renal pathologic findings were compatible with MN. Immunofluorescence microscopy showed IgG, IgA, κ , λ , and C3 along the glomerular capillary wall, whereas deposition of IgM or C1q was not detected. In terms of the IgG subclasses, only IgG2 findings were positive. Results for glomerular antigen and serum antibody for M-type phospholipase A2 receptor and thrombospondin type 1 domain-containing 7A were negative. HLA type did not include the HLA-DQA1 gene that is a concern in primary MN (PMN). She responded to intensive immunosuppressive therapy consisting of prednisolone, tacrolimus, and MTX with a parallel reduction of proteinuria. Based on assessments for differentiating PMN from secondary MN (SMN), the diagnosis of the present case was incompatible with PMN. Taken together, we consider that SMN in the present case was due to RA itself rather than drug-induced MN.

Keywords Membranous nephropathy (MN) · Rheumatoid arthritis (RA) · Disease-modifying antirheumatic drugs (DMARDs) · Anti-cyclic citrullinated peptide antibody (anti-CCP Ab)

Introduction

Rheumatoid arthritis (RA) is a chronic inflammatory disease that affects various organ systems and is associated with autoantibodies such as rheumatoid factor (RF) and anti-cyclic citrullinated peptide antibody (anti-CCP Ab) [1]. In patients with RA, renal involvement is relatively common; the main causes for renal involvement are secondary amyloidosis and nephrotoxic effects related to RA drugs such as D-penicillamine, bucillamine, cyclosporine, gold salt, nonsteroidal anti-inflammatory drugs, and anti-tumor necrosis factor- α drugs [2–5]. In addition, a previous study

of renal biopsy (RB) findings in patients with RA indicated that the predominant histopathologic finding is mesangial proliferative glomerulonephritis (GN), followed by amyloidosis, membranous nephropathy (MN), focal proliferative GN, minimal-change nephropathy, and acute interstitial nephritis [6]. Collectively, drug-induced MN is relatively common and clinically relevant in patients with RA as is AA amyloidosis. However, MN directly induced by RA, as in the case of membranous lupus nephritis in systemic lupus erythematosus, is infrequent.

Herein, we describe a patient with RA who was not receiving any nephrotoxic drugs, but who developed MN. In the present case, it is significant to distinguish primary MN (PMN) from secondary MN (SMN). We will discuss the validity of our diagnosis of MN related to RA itself based on our detailed assessment.

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Case report

A 61-year-old woman was admitted to our hospital because of nephrotic syndrome (NS) and severe polyarthritis. She had been suffering from RA with inflammatory pain and swelling in the metacarpophalangeal and interphalangeal joints of both hands and painful flexion–extension movement of both the wrists and ankles since age 29. After diagnosis of RA, her arthritis was treated with low-dose prednisone (PSL) and nonsteroidal anti-inflammatory drugs. In her mid-40s, treatment with methotrexate (MTX) (8 mg/week) combined with PSL (5 mg/day) was started because of active polyarthritis. Thereafter, her arthritis was successfully treated with MTX alone over the next 10 years. Unfortunately, all treatments were self-interrupted at the age of 57. After that, her physical condition deteriorated, and 4 years later, she was transferred to our hospital because of systemic edema and severe RA.

On admission, her temperature was 36.7 °C, her pulse was 77 beats per minute, and her blood pressure was 171/95 mmHg. Her body weight was 64.1 kg and had increased by 14 kg in a short period. Physical examination revealed severe limb edema and tenosynovitis of both wrists and the left ankle. Chest radiography revealed massive pleural effusion. Whole-body computed tomography showed no mass or specific space-occupying lesions. Laboratory tests showed white blood cell count, 8900/mm³; erythrocyte count, 454 × 10⁴/μL; hemoglobin, 12.7 g/dL; hematocrit, 39.1%; platelet count, 41.1 × 10⁴/mm³; erythrocyte sedimentation rate (ESR), 76 mm/h; total protein, 5.0 g/dL; albumin (Alb), 1.4 g/dL; blood urea nitrogen, 21.1 mg/dL; creatinine (Cr), 0.7 mg/dL; estimated glomerular filtration rate (eGFR), 65.1 mL/min/1.73 m²; total cholesterol, 395 mg/dL; C-reactive protein, 0.25 mg/dL; IgG, 514 mg/dL; IgA, 228 mg/dL; and IgM, 125 mg/dL. Serum hepatitis B surface antigen and anti-hepatitis C virus antibody findings were negative, and serum complement levels and circulating immune-complex findings were within normal limits. No anti-nuclear antibody, anti-double-stranded DNA, anti-Ro, anti-La, or anti-Sm antibodies were detected. Likewise, anti-neutrophil cytoplasmic antibodies were absent. Levels of tumor markers drawn for CEA, CA-19-9, SCC, and soluble interleukin-2 receptor were all within the normal range. Anti-CCP Ab findings were positive (32.2 U/mL; normal range < 4.5 U/mL), and increased levels of RF (82 IU/mL; normal range, 0–40) and matrix metalloproteinase-3 (MMP-3) (213.8 ng/mL; normal range 17.3–59.3) were detected. A 24-h urine collection showed 6.7 g of protein. The urinary sediment contained more than 100 red blood cells per high-power field. The Cr clearance was 65.4 mL/min.

On day 15 after admission, a percutaneous RB was performed to obtain a definitive diagnosis. A total of 11

glomeruli were available. Neither global sclerosis nor crescent formation was observed. Light microscopic examination of the glomeruli showed very mild thickening of the capillary basement membrane with segmental mesangial hypercellularity (Fig. 1a). The tubulointerstitium showed a mild degree of cellular infiltration and tubular dilatation. No features of arteritis were noted. Congo red stain findings were negative. Immunofluorescence microscopy revealed significant deposits of IgG, IgA, and C3 along the glomerular capillary wall (Fig. 1b–d); κ and λ were also deposited on the glomerular capillary wall (Fig. 1e, f). Furthermore, those positive findings were also segmentally seen in the mesangial or paramesangial areas. On the other hand, no deposits of IgM or C1q were seen. Glomerular antigen of M-type phospholipase A2 receptor (PLA2R) and thrombospondin type 1 domain-containing 7A (THSD7A) findings, assessed as previously described [7, 8], were both negative (Fig. 1g, h). In terms of IgG subclasses, only IgG2 findings were positive (Fig. 1i–l). An electron micrograph revealed marked subepithelial electron-dense deposits (EDD) (Fig. 2a). Different-sized EDD partially consisting of gross components were evident in the subepithelial area (Fig. 2b). Ehrenreich and Churg classification [9] was stage 2.

Based on these histologic findings, we suspected that the patient had MN associated with RA. To clearly distinguish our diagnosis from PMN, we examined the presence of serum anti-PLA2R antibody (Ab) and anti-THSD7A Ab by cell-based indirect immunofluorescence assay [7, 8, 10]. HLA type was also assessed to evaluate findings regarding the presence of the HLA-DQA1 gene, which is associated with PMN [11]. Anti-PLA2R Ab and anti-THSD7A Ab findings were both negative. Her HLA types were as follows: A-Locus 24, 31; B-Locus 39, 54; C-Locus w1, w7; DR-Locus 4, -; and DQ-Locus 4, -, which did not include the HLA-DQA1 gene. Therefore, we considered that diagnosis of the patient was more likely to be RA-associated SMN rather than PMN.

The patient was treated with corticosteroids (PSL, 40 mg/day) on day 21 after admission. Tacrolimus (Tac) (2 mg/day) was combined with PSL therapy on day 23 after admission, and then its dose was increased to 3 mg/day. Subsequently, PSL was gradually tapered, and administration of MTX was started at the dose of 4 mg/week from day 139 and increased to 8 mg/week to prevent the activation of RA. Intensive immunosuppressive therapy of PSL, Tac, and MTX resulted in a favorable outcome. MMP-3 levels and ESR decreased to 31.9 mg/L and 1.61, respectively, which correlated with a decrease in urinary protein (UP) from 16.4 to 1.2 g/gCr and an increase in the serum Alb level from 1.4 to 3.9 g/dL (Fig. 3). Currently, UP levels remain below 0.3 g/gCr, and polyarthritis is controlled. No adverse effects of the immunosuppressive therapy have been detected.

Fig. 1 Light microscopy and immunofluorescence microscopy findings. The glomerulus shows very mild thickening of the capillary basement membrane with segmental mild mesangial hypercellularity (a) [Periodic acid-Schiff (PAS) stain; original magnification $\times 400$]. Immunofluorescence shows intense granular staining for IgG (b), mild staining for IgA (c), intense staining for C3 (d), intense stain-

ing for κ (e), intense staining for λ (f), negative staining for PLA2R (g), negative staining for THSD7A (h), negative staining for IgG1 (i), moderate staining for IgG2 (j), negative staining for IgG3 (k), and negative staining for IgG4 (l) on the capillary wall and paramesangial area (original magnification $\times 400$)

Fig. 2 Electron microscopy findings. An electron micrograph shows marked subepithelial electron-dense deposits (EDD) (a). Different-sized EDD partially consisting of gross components are evident in the subepithelial area (b) (original magnification $\times 1000$)

Fig. 3 Clinical course and treatment of the patient. *Alb* albumin, *ESR* erythrocyte sedimentation rate, *MMP-3* matrix metalloproteinase-3, *MTX* methotrexate, *PSL* prednisone, *RB* renal biopsy, *Tac* tacrolimus, *UP* urinary protein

Discussion

PMN is currently recognized to be an antibody-mediated autoimmune glomerular disease characterized by subepithelial immune deposits. PLA2R, a membrane glycoprotein localized to podocytes, was identified by Salant's group as the target antigen in patients with PMN [12]. THSD7A, another podocyte membrane antigen, was also recently identified as a target antigen [13]. In addition to PLA2R and THSD7A, α -enolase, neutral endopeptidase (NEP), aldose reductase, and superoxide dismutase have also been identified as target antigens for circulating and deposited antibodies in allo-immune neonatal and adult idiopathic MN, respectively [14, 15]. However, there is no doubt that PLA2R and THSD7A are highlighted as the major autoantigens in the pathogenesis of PMN. According to previous reports, glomerular IgG subclass deposition in PMN is usually IgG4 dominant [16], and most patients with PMN have IgG4 antibodies to podocyte-expressed PLA2R or THSD7A, which are considered to be present in the circulation as well as deposited in glomeruli [10]. Therefore, not only glomerular IgG subclass deposition but also serum antibodies and glomerular antigen of PLA2R or THSD7A are significant indicators that differentiate PMN from SMN. The present case was diagnosed as SMN according to the diagnostic algorithm [10] based on the presence of such antibodies or antigens and selectivity of glomerular IgG subclass. With regard to the possibility of other autoantigen-associated PMN such as α -enolase or NEP-related nephropathy, it was difficult to make this diagnosis in the present case because

the findings of glomerular IgG subclasses in the present case were incompatible with previous reports [15, 17].

Generally, SMN is induced by various clinical conditions including systemic lupus erythematosus, infections (hepatitis, syphilis), cancers, and drug exposure to agents such as disease-modifying antirheumatic drugs (DMARDs) including D-penicillamine, bucillamine, and gold salt [4–6]. In the present case, there was no history of the use of the above-mentioned DMARDs. Additionally, other secondary causes of MN were not confirmed based on laboratory data or imaging findings. Consequently, the diagnosis of SMN due to RA itself was conceivable. Moreover, the fact that the onset of NS and improvement of proteinuria in the present case were almost parallel with the activity of RA supports our diagnosis.

Thus far, several clinical reviews [3–5] and case reports [2, 18] have shown the possibility of MN caused by RA itself, but its incidence and pathogenetic mechanisms are unknown. Regarding pathogenetic mechanisms, Honkanen et al. [18] found that 2 of 3 patients with MN directly induced by RA had positive findings for HLA DR4 antigen, as in the present case. They speculated that such specific HLA antigens might cause MN due to RA [18]. Furthermore, they mentioned the possibility of involvement of RF-like complexes in the development of this type of MN [18]. However, definitive explanations for the development of this kind of MN have not been reported.

Immunologically, anti-CCP antibodies are autoantibodies that are directed against cyclic citrullinated peptides [19–21]. In the present case, serum anti-CCP Ab was

strongly positive at the time of RB; therefore, we suspected the involvement of anti-CCP Ab in the development of MN directly due to RA. To date, there have not been any reports proving the deposition of such anti-citrullinated protein/peptide antibody (ACPA) in tissue although some basic researches indicated the expression of citrullinated protein in mouse or human synovium [22–24]. However, we found an intriguing report showing that vimentin, a representative protein to be citrullinated, was clearly expressed on epithelial side of human fetal glomeruli [25]. Additionally, the proportion of IgG2 among the serum IgG subclasses of ACPA is not rare (32%) [21]. Taken together, it was postulated that glomerular IgG2 detected in this case may be originated from serum anti-CCP Ab. We hypothesized that patient's anti-CCP Ab may cause to form MN-like in situ immune complexes with citrullinated vimentin on capillary loop. Further study which demonstrates the presence of ACPA on the glomerulus will be definitely needed to make our hypothesis convincing.

In conclusion, we herein reported a relatively rare case of non-drug-induced MN in a patient with RA. Based on our detailed assessment, the present case was incompatible with PMN, but was more plausibly to be SMN directly due to RA itself. Accumulation of similar cases and further analysis are necessary to elucidate pathogenetic mechanisms of this type of nephropathy.

Compliance with ethical standards

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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