A case of denosumab-associated membranous nephropathy in a patient with rheumatoid arthritis

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Abstract

We herein report a case of anti-RANKL monoclonal antibody-associated membranous nephropathy (MN). A 67-year-old woman with a history of rheumatoid arthritis treated with prednisolone and methotrexate for more than 30 years and osteoporosis treated with eldecalcitol and teriparatide for 4 years had achieved a stable disease condition. Her kidney function was normal and her urinalysis was negative for hematuria and proteinuria. An anti-RANKL monoclonal antibody (denosumab) was administered for the treatment of osteoporosis. Four months later, proteinuria appeared (2.3 g/g creatinine) and remained positive for about 6 months, therefore, she was admitted to our hospital. An immunofluorescence study revealed fine granular deposits of immunoglobulin G (IgG) and C3 along the capillary walls. Staining for IgG subclasses showed positive staining for IgG1 (3+), IgG2 (1+), IgG3 (1+), and IgG4 (1+); phospholipase A2 receptor was negative. Electron microscopy showed partial subepithelial and intramembranous deposits and focal thickening of the glomerular basement membrane. No evidence of malignancy or infectious disease was seen. After cessation of denosumab, the proteinuria gradually improved. Based on the renal biopsy results and clinical course (development of marked proteinuria in the presence of denosumab with subsequent amelioration in the absence of the drug), we diagnosed the patient with secondary MN due to denosumab. This is the first reported case of denosumab-associated MN.

Keywords Membranous nephropathy · Anti-RANKL monoclonal antibody · Rheumatoid arthritis

Introduction

Membranous nephropathy (MN) is the second common etiology of primary nephrotic syndrome in Japan [1]. About 80% of patients with MN are diagnosed with idiopathic MN, whereas about 20–25% are diagnosed with secondary MN due to autoimmune diseases, infections, malignancy, and drugs [2, 3]. Drug-induced MN (DIMN) accounts for 6.6% [4] to 14.0% [5] of all cases of MN. Secondary MN induced by drugs such as antirheumatic drugs, nonsteroidal anti-inflammatory drugs, and antihypertensive drugs has been reported [3].

Denosumab is a fully human monoclonal antibody that selectively binds with the receptor activator of nuclear factor kappa-B ligand (RANKL), a cytokine essential for the formation, function, and survival of osteoclasts [6]. By binding to RANKL on the surface of osteoclasts and their precursors, denosumab inhibits osteoclast-mediated bone resorption [7]. Denosumab is used to treat osteoporosis. Critical adverse effects of denosumab include hypocalcemia [8] and osteonecrosis of the jaw [9]. However, no case reports have described glomerulonephritis associated with denosumab.

We herein report a case of MN that developed during anti-RANKL monoclonal antibody treatment for osteoporosis.

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Case report

The patient was a 67-year-old Japanese woman with a history of rheumatoid arthritis treated with prednisolone and methotrexate for more than 30 years and osteoporosis treated with eldecalcitol and teriparatide for 4 years. Her disease

condition was stable throughout her treatment history. Her kidney function was normal, and her urinalysis was negative for hematuria and proteinuria. The patient was also being treated with bisphosphonate drugs (risedronate sodium hydrate and minodronic acid hydrate) because of low bone density (young adult mean 55%). However, she could not continue to use these drugs because of the development of fever. Therefore, she was administered denosumab, an anti-RANKL monoclonal antibody, for the treatment of osteoporosis. Three months later, proteinuria appeared (2.3 g/gCr) and remained positive for about 6 months. At this point, she was admitted to our hospital.

On admission, the patient was 155 cm tall and weighed 48 kg. Her blood pressure was 147/88 mmHg. Table 1 shows the examination findings upon admission. The spot urinary protein concentration was 2.8 g/gCr. She showed a decreased serum albumin concentration of 3.6 g/dL and a normal serum creatinine concentration of 0.8 mg/dL. Her serum

antinuclear antibody level was $\times 80$, but anti-ds-DNA and anti-ss-DNA antibodies were negative and complement levels were not decreased. Anti-hepatitis B surface antigen and anti-hepatitis C virus antibodies were negative. Computed tomography at the previous hospital revealed no evidence of a tumor.

Renal biopsy was performed 6 months after administration of denosumab. Light microscopy showed 12 normal glomeruli and 1 globally sclerotic glomerulus (Fig. 1a). Immunofluorescence staining showed deposition of immunoglobulin G (IgG) and C3 in the glomerular basement membrane. Staining for IgA and IgM was negative (Fig. 1b). IgG subclass analysis revealed predominant deposition of IgG1 and weak deposition of IgG2, IgG3, and IgG4. Staining for the phospholipase A2 receptor (PLA2R) was negative (Fig. 2). Electron microscopy revealed granular electron-dense deposits in the subepithelial and intramembranous regions of the glomerular basement membrane (Fig. 3). The

Table 1 Laboratory data at admission

Peripheral blood		Serological test	
White blood cell	6570/ μ L	Immunoglobulin G	1022 mg/dL
Red blood cell count	428×10^4 / μ L	Immunoglobulin A	242 mg/dL
Hemoglobin	12.6 g/dL	Immunoglobulin M	76 mg/dL
Hematocrit	38.8%	Complement activity	69 U/mL
Platelets	32.9×10^4 / μ L	C3 component	105 mg/dL
Blood chemistry		C4 component	20 mg/dL
Total protein	6.5 g/dL	Antinuclear antibody	80
Albumin	3.6 g/dL	Anti-ds-DNA	0.8 IU/mL
Aspartate aminotransferase	38 IU/L	Anti-ss-DNA	1.5 AU/mL
Alanine aminotransferase	42 IU/L	Rheumatoid factor	60 U/mL
Lactate dehydrogenase	283 IU/L	Anti-CCP antibody	1.1 U/mL
Total cholesterol	235 mg/dL	Anti-RNP antibody	0.3 U/mL
LDL cholesterol	141 mg/dL	Anti-Scl-70 antibody	7.0 U/mL
Triglycerides	104 mg/dL	Anti-Sm antibody	0.3 U/mL
Uric acid	4.5 mg/dL	Anti-SS-A/Ro antibody	0.2 U/mL
Urea nitrogen	7.8 mg/dL	Anti-SS-B/La antibody	0.2 U/mL
Creatinine	0.77 mg/dL	Anti-centromere antibody	1.3 U/mL
eGFR	57 mL/min/1.73 m ²	MPO-ANCA	0.1 U/mL
Sodium	145 mEq/L	PR3-ANCA	0.1 U/mL
Potassium	4.2 mEq/L	Hepatitis B virus, surface antigen	(–)
Chloride	106 mEq/L	Hepatitis C virus antibody	(–)
C-reactive protein	0.28 mg/dL	Urinalysis	
SAA	54.1 μ g/mL	Gravity	1.005
		pH	6.5
		Protein	2+
			2.8 g/gCr
		Occult blood	(–)
		Glucose	(–)
		Ketone	(–)
		NAG	4.5 U/L
		β 2MG	294 μ g/L

Fig. 1 Light microscopy and immunofluorescence findings. **a** Light microscopy findings. Renal biopsy samples revealed 12 normal glomeruli and 1 globally sclerotic glomerulus. There were no remarkable changes (original magnification $\times 200$). **b** Immunofluorescence findings. Granular deposition of IgG was noted as a peripheral pattern. IgA and IgM were not seen. Granular deposition of C3 was also noted as a peripheral pattern

histological features were compatible with the diagnosis of secondary MN.

At 4–6 months after beginning the administration of denosumab, the urinary protein concentration was about 2 g/gCr, but it gradually decreased. In contrast, the serum albumin concentration was elevated (Fig. 4). We diagnosed MN associated with denosumab and did not administer denosumab thereafter. In patients with severe symptoms of nephrotic syndrome and/or lack of improvement after withdrawal, immunosuppressive therapy may be warranted [10]. In the present case, the patient had no symptoms and the urinary protein concentration was not severe. Therefore, she underwent follow-up with no treatment for MN. About 2.5 years after beginning the administration of denosumab, her urinary protein concentration was almost normal (0.1 g/gCr).

Discussion

We here reported a case of denosumab-associated MN in a patient with rheumatoid arthritis. The Japan renal biopsy registry showed that glomerular disorders are the most common cases of drug-induced kidney diseases, in particular, MN accounts for 60% of glomerular disorders [11]. Several culprit drugs of MN have been reported, including gold salts, penicillamine, bucillamine, mercury, captopril, and nonsteroidal anti-inflammatory drugs [10]. The pathogenesis

Fig. 2 IgG subclass findings. Immunofluorescence IgG subclass analysis showed a predominance of IgG1 deposition followed by IgG2, IgG3, and IgG4 in a peripheral granular pattern. Anti-PLA2R deposits were negative

Fig. 3 Electron microscopic findings. Focal thickening of the glomerular basement membrane was seen. In some glomerular capillary walls, **a** subepithelial (arrows) and **b** intramembranous small dense deposits (arrows) were seen

Fig. 4 Clinical course. After administration of denosumab, urinary protein was positive. After cessation of denosumab, urinary protein gradually decreased and the serum albumin concentration gradually recovered. About 2.5 years after administration of denosumab, urinary protein was almost normal (0.1 g/gCr). *sAlb* serum albumin, *UP/UCr* urine protein/urine creatinine ratio, *eGFR* estimated glomerular filtration rate

of drug-induced MN involves an immune response to a therapeutic agent or its byproduct; specifically, cationic drug-derived antigens that traverse the glomerular basement membrane are planted at the subepithelial aspect of the glomerular basement membrane, and become bound in situ to circulating antibodies directed against these antigens [10]. Pathologic findings do not distinguish between primary MN and drug-induced MN, highlighting the importance of obtaining a detailed clinical history regarding drug use [10].

Denosumab is an anti-RANKL monoclonal neutralizing antibody used to treat osteoporosis and cancer-induced bone diseases. RANKL and its receptor RANK are important regulators of T cells [12]; however, RANKL and RANK mechanism of kidney disease are not fully understood. Liu et al. reported that RANKL and RANK were increased in the two human podocyte diseases: minimal change nephrotic syndrome and MN, and RANK was localized in podocytes in a podocyte injury rat model [13]. Based on these previous reports, we speculate that denosumab can bind to RANKL/RANK on podocytes, which alters the RANK structure and induces the formation of antibodies against RANK. This results in the formation of subepithelial immune complexes and the subsequent development of MN. Another possibility is that administration of denosumab directly affects T-cell functions, thereby resulting in the formation of renal subepithelial RANK–RANKL immune complexes.

Recently, the PLA2R has been identified as a target antigen in primary MN. The serum anti-PLA2R antibody titer is positive in 70% of patients with primary MN [14]. Conversely, the prevalence of anti-PLA2R antibody in Japanese patients with primary MN is 50% [15]. Considering histological findings, the prevalence of anti-PLA2R antibody increased to 70% [16]. Furthermore, the main IgG subclass of IgG deposition in idiopathic MN is IgG4. In contrast,

IgG1 and IgG2 are dominant in secondary MN due to systemic lupus erythematosus [17]. In cases of MN associated with bucillamine, which is used for rheumatoid arthritis therapy, IgG1 or IgG2 is equivalent or dominant to IgG4 [18]. Moreover, the IgG subclasses in patients with malignancy-associated MN are similar to those in patients with bucillamine-associated MN [19].

In the present case, immunostaining of glomerular anti-PLA2R antibody was negative, and IgG1 immunostaining was dominantly positive. Although the renal histology findings did not confirm primary or secondary MN, other causes of secondary MN, such as infection, malignancy, autoimmune disease other than rheumatoid arthritis, and potential drugs were ruled out. We are aware that this patient had a history of rheumatoid arthritis, which is also a main cause of secondary MN, for more than 30 years; however, at the time of this writing, her renal function was still very stable and she was negative for proteinuria. Furthermore, the patient had been transiently treated with a gold salt drug more than 30 years previously and had never been treated with bucillamine.

The most important point in this patient's clinical course is that marked proteinuria appeared after a single administration of denosumab, and it was ameliorated after discontinuation of the drug. With respect to the very slow improvement of this patient's proteinuria, we speculate that because denosumab is a very long-acting drug that should be administered once every 6 months, improvement of the patient's proteinuria took a long time.

The culprit drugs of drug-induced MN are mainly oral drugs administered every day. However, we must pay attention to the fact that long-acting drugs such as denosumab (administered every 6 months) can also cause drug-induced MN.

The patient's renal biopsy results and clinical course (appearance of marked proteinuria in the presence of denosumab with gradual amelioration after discontinuation of the drug) led to the diagnosis of secondary MN associated with denosumab. Denosumab is now used as an antiresorptive drug for the treatment of osteoporosis in multiple countries, thus, routine urinalysis should be considered whenever denosumab is administered.

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Compliance with ethical standards

Conflict of interest All the authors have declared that they have no competing interest.

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 all individual participants included in the study.

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