

[CASE REPORT]

Development of Myeloperoxidase Anti-neutrophil Cytoplasmic Antibody-positive Necrotizing Crescentic Glomerulonephritis in an Elderly Patient with Immunological Kidney Disease

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Abstract:

A 78-year-old man presented with hypercalcemia and renal disease with high serum IgG4 and positive myeloperoxidase anti-neutrophil cytoplasmic antibody (MPO-ANCA), exhibiting sarcoidosis-like chest findings. A renal biopsy revealed tubulointerstitial nephritis, membranous nephropathy (MN), and sub-capsular lymphoid aggregates without fulfilling the diagnostic criteria of IgG4-related disease or sarcoidosis. Steroid therapy ameliorated the serological and renal abnormalities. After 5 years, following gradual increases in the neutrophil count and upper respiratory infection (URI), necrotizing crescentic glomerulonephritis (NCGN) developed with an increased serum MPO-ANCA level. These results suggest that in the presence of MPO-ANCA in immune senescence, the persistent neutrophil increase with URI may lead to the development of NCGN.

Key words: hypercalcemia, IgG4-RKD, immune senescence, lymphoid aggregates, membranous nephropathy, sarcoidosis

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Introduction

Clinical surveys on anti-neutrophil cytoplasmic antibody (ANCA)-associated vasculitis revealed geographic and racial differences in the prevalence with the predominance of myeloperoxidase (MPO)-ANCA over proteinase 3 (PR3)-ANCA in Japan, whereas the opposite findings have been reported in Europe and North America. ANCA-positive glomerulonephritis (GN) is commonly diagnosed in patients older than 50 years of age and thereafter becomes more prevalent with aging (1-3). In a large cohort study in the

United States on renal biopsy samples obtained from patients older than 80 years, ANCA-associated pauci-immune GN was the most frequent diagnosis, and the number of patients with MPO-ANCA was more than 3-fold higher than those with PR3-ANCA (4). Since MPO-ANCA is an autoantibody that is mostly detected in elderly populations, and aging-associated immune dysfunction increases susceptibility to various autoimmune diseases (5), the co-occurrence of MPO-ANCA with other immunological diseases is expected (6). We herein report the development of MPO-ANCA-positive pauci-immune necrotizing crescentic glomerulonephritis (NCGN) during the remission of tubu-

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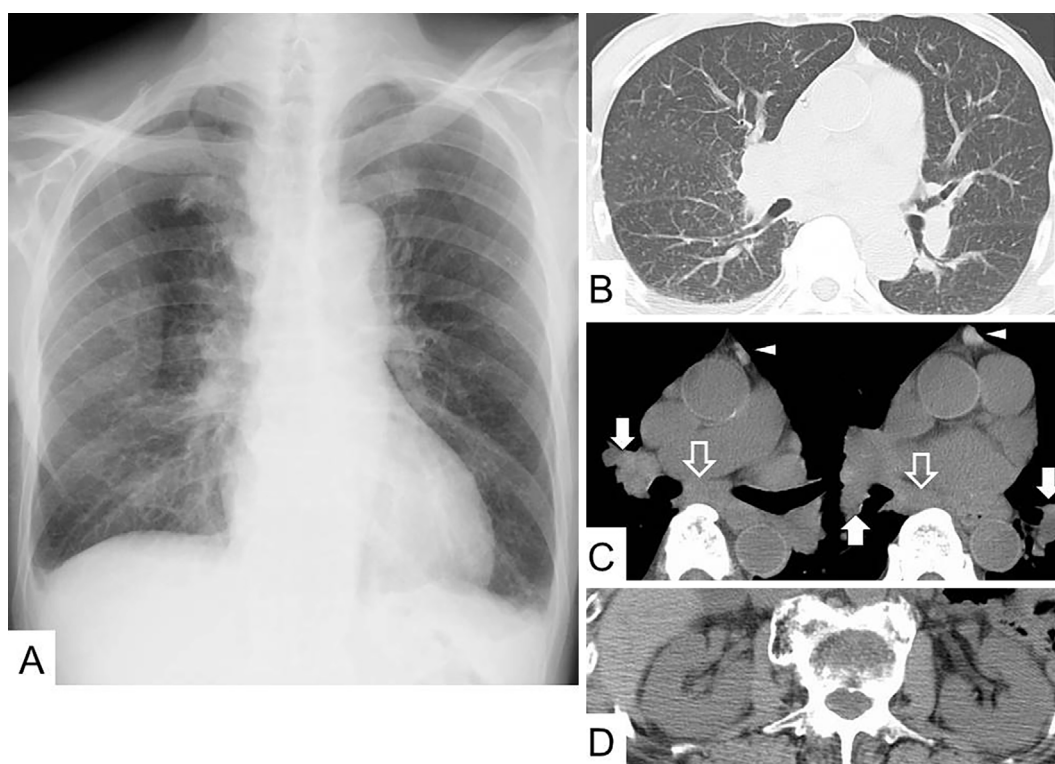


Figure 1. Radiographic findings in the first admission. A: Chest X ray showing diffuse fine nodular shadows with dull costo-phrenic angles. B: Computed tomography (CT) showing the diffuse distribution of fine nodules. C: CT images showing bilateral hilar lymph node swelling (closed arrows), mediastinal lymph node swelling (open arrows) and an anterior mediastinal nodule (arrow heads), with small volume of bilateral pleural effusion. D: A CT image showing mild to moderate swelling of both kidneys, within the normal size range.

linterstitial nephritis (TIN) with hypercalcemia suggesting sarcoidosis and plasma cell infiltration diagnosed as possible IgG4-related kidney disease (IgG4-RKD), associated with membranous nephropathy (MN). The results of this retrospective investigation suggest that a persistent increase of neutrophils associated with MPO-ANCA in immune senescence and incidental upper respiratory infection may have predisposed our patient to develop MPO-ANCA-associated NCGN, probably by exposing MPO antigen to anti-MPO antibodies as well as to memory T cells for the antibody production.

Case Report

A 78-year-old man with a 3-year history of right hemiparesis visited Department of Internal Medicine, Obama Municipal Hospital in October 2013 with anorexia symptoms experienced for the past 2 weeks. He had a past history of cerebral infarction in the left basal ganglia which had developed in November 2010. He had no allergic history, nor dry eye or dry mouth suggesting Sjögren syndrome. Ophthalmologic examinations did not show any specific changes on ocular surface or ocular fundus. He had been taking daily medications of clopidogrel sulfate 75 mg, rabeprazole sodium 10 mg, allopurinol 200 mg and zopiclone 7.5 mg for the past 3 years, without any adverse events.

His blood pressures were 163/91. Chest X-ray and computed tomography (CT) showed diffuse reticular-granular shadows in the lungs, bilateral hilar-mediastinal lymphadenopathy (BHL) and small volume of bilateral pleural effusion with a small nodule in the anterior mediastinum (Fig. 1A-C). On abdomen CT, both kidneys showed mild to moderate swelling within the normal size range (Fig. 1D), with a fine stone in the right kidney (figure, not shown). The CT images showed degenerative changes of thoracic and lumbar spine with no findings of osteolysis or ossification (figure, not shown). 18-Fluorodeoxyglucose-positron emission tomography (FDG-PET)/CT images revealed mild positivity in the mediastinal and bilateral lymph nodes, but not in the anterior mediastinal nodule, suggesting a thymic cyst or benign thymoma (figure, not shown). Tuberculosis (TB) was excluded based on a negative sputum culture and T-SPOT.TB® (interferon- γ releasing assay). Electrocardiography showed a complete right bundle branch block. The blood examinations 9 months before the onset of the present illness showed WBC 3,850/ μ L and Hb 11.4 g/dL, with normal levels of aspartate aminotransferase (AST) of 26 IU/L, alkaline phosphatase (ALP) of 287 IU/L, calcium 9.2 mg/dL, and creatinine (Cr) of 0.81 mg/dL. As shown in the column for the first biopsy in the Table, urinalysis revealed proteinuria of 1.66 g/day, occult blood 2+, and a high level of *N*-acetyl- β -D-glucosaminidase (NAG). A serological ex-

Table. Laboratory Data from 1st (November 2013) and 2nd (October 2018) Renal Biopsies.

Variable	1st Biopsy	2nd Biopsy	Variable	1st Biopsy	2nd Biopsy
<Urinalysis>			HDL-cholesterol	33 mg/dL	37 mg/dL
pH	7.0	5.5	Total protein	7.5 g/dL	6.1 g/dL
Specific gravity	1.010	1.005	Albumin	3.4 g/dL	3.2 g/dL
Protein	92 mg/dL	104 mg/dL	Sodium	141 mEq/L	136 mEq/L
	1.66 g/day	1.61 g/day	Potassium	3.2 mEq/L	3.2 mEq/L
Occult blood	2+	3+	Chloride	101 mEq/L	102 mEq/L
Sediment RBC	20-29 /HPF	>100 /HPF	Calcium	12.0 mg/dL	6.3 mg/dL
Sediment WBC	1-4 /HPF	10-19 /HPF	Adjusted calcium	12.6 mg/dL	7.1 mg/dL
Sediment Cast (H/G)	5-10 / 1-4	20-29 /-	Phosphorus	2.8 mg/dL	3.0 mg/dL
NAG ^a (<5.0)	11.8 U/L	n.d. ^b	Creatinine	1.35 mg/dL	3.17 mg/dL
<CBC>			Urea nitrogen	17.0 mg/dL	51.3 mg/dL
WBC	4,710 / μ L	6,850 / μ L	Uric acid	6.5 mg/dL	5.5 mg/dL
RBC	281 \times 10 ⁴ / μ L	374 \times 10 ⁴ / μ L	Sugar	95 mg/dL	104 mg/dL
Hemoglobin	9.1 g/dL	11.8 g/dL	<Infection and Immunology>		
Hematocrit	26.7 %	34.5 %	Procalcitonin	<0.5 ng/mL	<0.5 ng/mL
Platelet	18.3 \times 10 ⁴ / μ L	32.8 \times 10 ⁴ / μ L	CRP (<0.5)	0.20 mg/dL	4.67 mg/dL
Neutrophil (1,640-5,950)	2,070 / μ L	5,360 / μ L	IgG	2,131 mg/dL	1,550 mg/dL
Lymphocyte (1,120-3,330)	1,800 / μ L	800 / μ L	IgA	217 mg/dL	203 mg/dL
Monocyte (180-610)	330 / μ L	600 / μ L	IgM	68 mg/dL	59 mg/dL
Eosinophil (20-480)	480 / μ L	70 / μ L	IgE (<170)	4,243 IU/mL	117 IU/mL
Basophil (10-100)	30 / μ L	20 / μ L	IgG4 (4.8-105)	253 mg/dL	74.5 mg/dL
<Biochemistry>			sIL2R ^c (145-519)	1,758 U/mL	676 U/mL
Total bilirubin (0.2-1.2)	0.8 mg/dL	0.9 mg/dL	CH ₅₀	n.d.	>60.0
AST (8-38)	47 IU/L	17 IU/L	C3 (86-160)	76 mg/dL	108 mg/dL
ALT (4-44)	12 IU/L	7 IU/L	C4 (17-45)	22 mg/dL	38 mg/dL
ALP (104-338)	1,180 IU/L	218 IU/L	ANA ^d	n.d.	40+, Homo ^e
LD (106-211)	310 IU/L	208 IU/L	Anti-dsDNA IgG	<10 IU/mL	n.d.
CK (56-244)	177 IU/L	159 IU/L	MPO-ANCA (<3.5)	16.3 U/mL	>300 U/mL
Total cholesterol	162 mg/dL	165 mg/dL	PR3-ANCA (<1.0)	<1.0 U/mL	<1.0 U/mL
Triglycerides	65 mg/dL	67 mg/dL	Anti-GBM (<2.0)	<2.0 U/mL	n.d.

Data obtained approximately one month before biopsy are shown to exclude the effects of the immunosuppressive treatment. Reference ranges are shown in the parentheses of variables, except for the sediment cast of H: hyaline and G: granular casts/whole field. NAG^a: N-acetyl- β -D-glucosaminidase, n.d.^b: not done, sIL2R^c: soluble IL2 receptor, ANA^d: anti-nuclear antibody, Homo^e: Homogenous

amination showed a high adjusted value for calcium of 12.6 mg/dL and elevated Cr level of 1.41 mg/dL, with high IgG, IgG4, IgE, soluble interleukin 2 receptor (sIL2R), AST, ALP, and MPO-ANCA levels and a low C3 level. Negative serum findings were obtained for angiotensin-converting enzyme (ACE), monoclonal γ -globulin, procalcitonin, CRP, PR3-ANCA, the anti-dsDNA antibody, and anti-glomerular basement membrane (GBM) antibody. Regarding hypercalcemia, elevations were observed in the urinary Ca level (304 mg/day, reference range; 100-300 mg/day) and urinary Ca/Cr ratio (0.258, reference range; 0.05-0.15). His serum intact parathyroid hormone (PTH) level was low at 7.3 pg/mL (reference range; 10-65 pg/mL) and the PTH-related peptide was negative. His serum 1 α , 25-dihydroxy vitamin D3 level had decreased to 8.6 pg/mL (reference range; 20.0-60.0 pg/mL).

The first renal biopsy in November 2013 showed TIN and MN with the scattered interstitial infiltration of lymphocytes, plasma cells, and a few eosinophils as well as the focal tubular deposition of calcium (Fig. 2A, B, E-G). There were

no findings of noncaseating epithelioid granuloma formation, which is characteristic of sarcoidosis, or interstitial storiform fibrosis specific to IgG4-RKD. Immunofluorescent (IF) staining showed granular IgG and C3 deposition along glomerular capillaries. Immunoenzyme staining also revealed fine granular IgG, but not IgG4, deposition along glomerular capillaries (Fig. 2G). IgG- and IgG4-positive plasma cells were observed in the interstitium, with approximately 30% positivity for IgG4 among IgG-positive cells and with more than 10 IgG4-positive cells/high power field (HPF) (Fig. 2C, D). Staining for the M-type phospholipase A2 receptor (PLA2R) was negative (Fig. 2H). In addition, focal lymphocyte aggregates adjacent to a small vein were located in the sub-capsular regions (Fig. 2I, J). A lymphoid follicular structure with interstitial cells surrounding a high endothelial venule (HEV)-like vessel contained clusters of IgG-positive cells, but rarely IgG4-positive cells (Fig. 2J-L).

Since hypercalcemia and renal dysfunction worsened despite the infusion of saline and furosemide, the administration of prednisolone (PSL) was initiated at 20 mg/day in

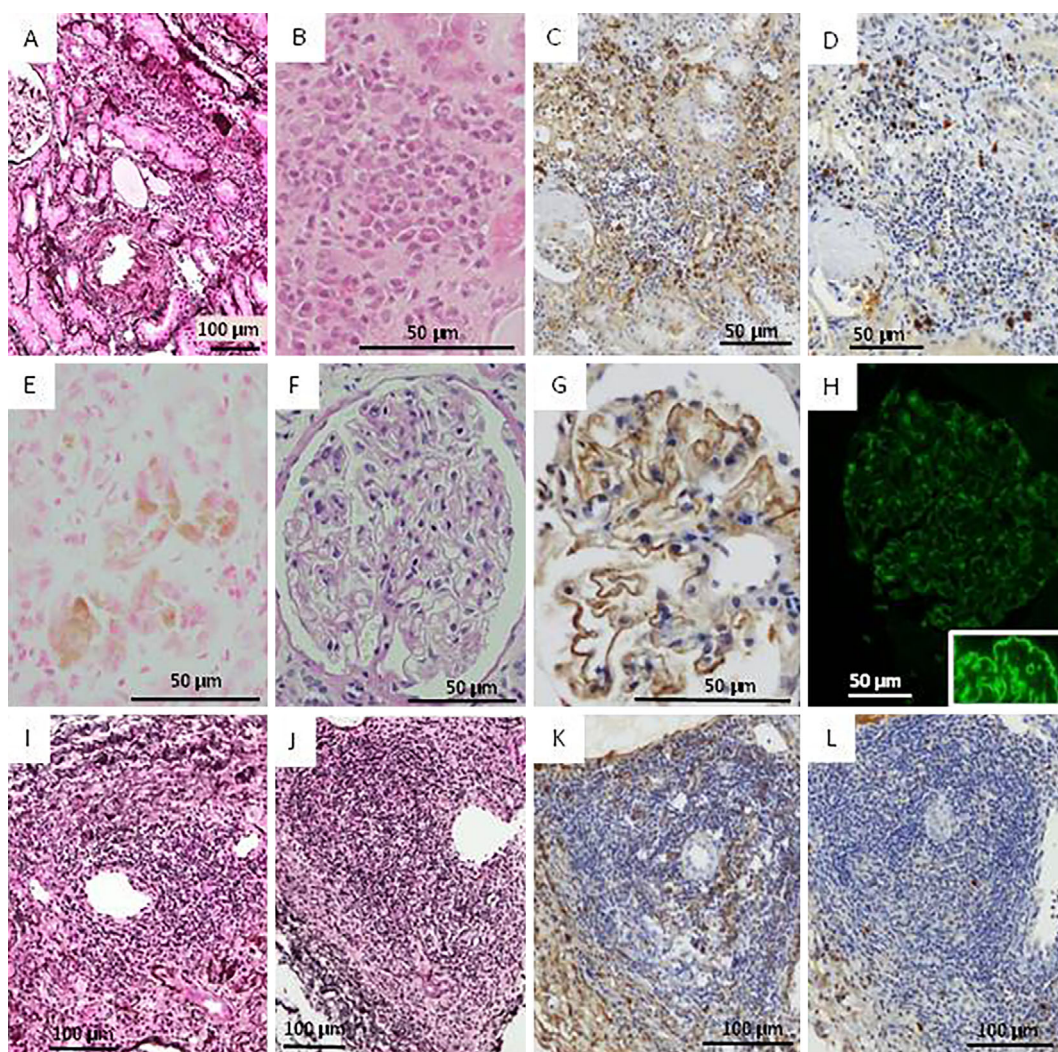


Figure 2. The first renal biopsy in November 2013 showed 30 glomeruli (GL) with minimal changes and 6 with global sclerosis. In the tubulointerstitial region, areas of interstitial mononuclear cell infiltration were focally observed with tubular atrophy [A; periodic acid-Schiff (PAS)-methanamine (PASM) staining]. B: The interstitial infiltration of lymphocytes and plasma cells with a small number of eosinophils (Hematoxylin and Eosin staining). C: The focal interstitial infiltration of IgG-positive plasma cells by immunoenzyme staining. D: Interstitial IgG4-positive cells by immunoenzyme staining. Parts C and D are serial sections. The IgG4+/IgG+ cell ratio was approximately 30%. E: Proximal tubules were focally positive with a brown color by Kossa staining for calcium. F: An enlarged glomerulus with membranous thickening (PAS staining). G: Fine granular IgG distribution along glomerular capillaries by immunoenzyme staining. H: Negative glomerular staining against the M-type phospholipase A2 receptor by an immunofluorescent method. A positive control is shown in the insert. I: Sub-capsular lymphoid aggregates surrounding a small vein (PASM staining). J: Sub-capsular lymphoid follicular tissue adjacent to a small vein (PASM staining). K: Clusters of IgG-positive cells in lymphoid tissue with a high endothelial venule (HEV)-like vessel in the center (immunoenzyme staining). L: A few IgG4-positive cells in lymphoid tissue with a HEV-like vessel in the center (immunoenzyme staining). Parts J-L are serial sections. The scale is shown with a scale bar at the bottom in each part.

November 2013 and thereafter was gradually tapered to a maintenance dose of 2.5 mg from January 2016 (Fig. 3). Hypercalcemia and the high Cr level completely recovered after 2 weeks of PSL therapy, and this was followed by negative urinary occult blood and normal blood pressure. In response to PSL, the mild increase of the serum AST level of 47 IU/L was normalized in 2 weeks and the high serum

ALP level of 1,180 IU/L gradually decreased to within the reference range after 6 months. However, approximately 15 months was required to achieve negative urinary protein in March 2015 despite the early amelioration from 3+ to 1+ after 4 weeks of PSL therapy. The patient did not subsequently exhibit any clinical signs or renal symptoms in outpatient consultations every 1-2 months until 2017.

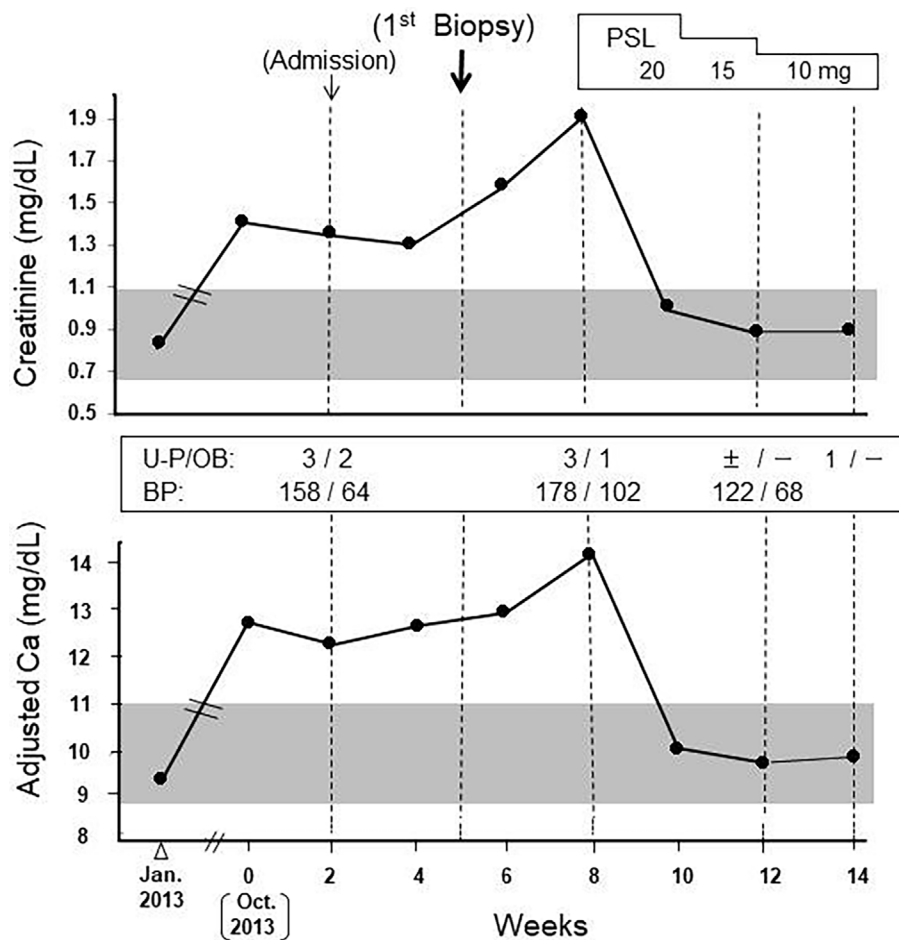


Figure 3. Sequential changes in serum creatinine (upper part) and adjusted serum calcium (Ca) (lower part) in the first renal biopsy. Changes in urinary protein and occult blood (U-P/OB) and blood pressure (BP) are shown in the middle part. Oral prednisolone (PSL) administration from 20 to 10 mg/day is depicted at the top. Shaded areas indicate the reference ranges of each measurement.

Fig. 4 shows the clinical and laboratory courses from September 2016 (0 month) to September 2018 (24 months) leading to the development of MPO-ANCA-associated NCGN. At 0 month, MPO-ANCA was negative, similar to that in May and December 2014, with a normal serum Cr level (0.83 mg/dL) and normal urinalysis. At 6 months, peak increases in WBC count to 7,160 and neutrophil count to 4,790 with an elevated monocyte count of 880/ μ L were observed with a normal serum Cr level (0.79 mg/dL) and normal urinalysis. At 10 months, WBC and neutrophil counts decreased to trough levels of 4,740 and 2,170, respectively, with the monocyte count remaining at nearly the upper limit of the reference range. At 14 months, an ocular examination for the blurred vision showed moderate cataracts of both eyes but no evidence of uveitis. At 15 months, serum $1\alpha, 25$ -dihydroxy vitamin D3 level was increased to 67.0 pg/mL with a lower adjusted Ca of 8.7 mg/dL. At 16 months, CT images showed persisting chest findings of BHL and small nodular lung opacity although pleural effusion and kidney swelling were not observed after the steroid therapy (figure, not shown). Bronchoscopy performed 3 weeks later revealed a CD4/CD8 ratio of 1.44, with macrophages 86%, neutrophils 9% and lymphocytes 5% in bronchoalveolar lavage

fluid (BALF) from right B⁵, while transbronchial lung biopsy from right B², B³ and B⁸ showed non-specific inflammation without epithelioid granuloma or IgG4-positive plasma cells. At 17 months, the only abnormal serological result of a high MPO-ANCA titer of 160 U/mL with a normal serum Cr level of 0.85 mg/dL and normal urinalysis was observed in the middle of increases in the WBC and neutrophil counts. At 20 months, peak increases were observed in the WBC count to 7,880 and the neutrophil count to 6,090 with a CRP level of 0.65 mg/dL, which were accompanied by slight abnormalities in urinary protein (\pm) and occult blood 1+. One month later, the patient unexpectedly developed an upper respiratory infection with a cough, rhinorrhea, and a sore throat, and, thus, clarithromycin was administered for 7 days. Throughout the course, the changes observed in the neutrophil count were parallel with those in the WBC count and greater than those in WBC.

At 24 months (September 2018), the patient developed general malaise and leg edema with a serum Cr level of 1.99 mg/dL, urinary proteinuria 2+, and occult blood 3+. A serological examination showed a high CRP level of 4.67 mg/dL without an increase in the serum level of procalcitonin and, thus, the dose of PSL administered was increased

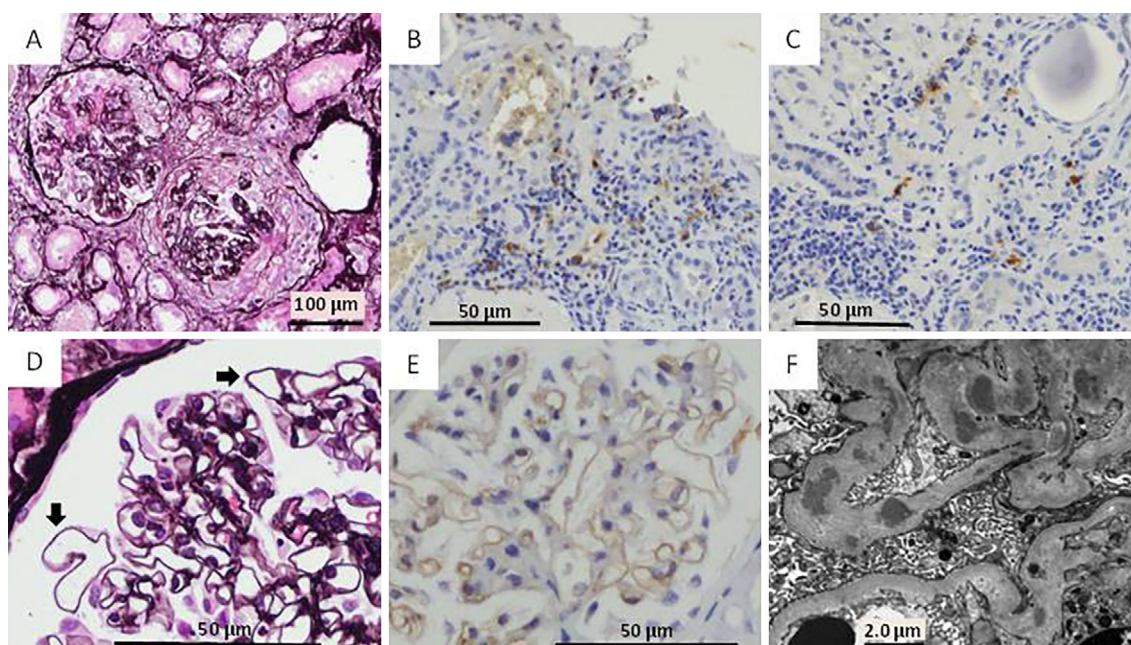


Figure 5. In the second biopsy in November 2018, 21 glomeruli (GL) were obtained, 8 of which showed global or severe sclerosis. In the remaining 13 GL, 8 (62%) showed fibrocellular crescent formation with 2 exhibiting fibrinoid necrosis (A, PASM staining). Partial tubular atrophy with interstitial fibrosis and the focal infiltration of lymphocytes and plasma cells were observed in the tubulointerstitial region. There were no findings of peritubular capillaritis. B: Focal interstitial infiltration of IgG-positive plasma cells by immunoenzyme staining. C: Interstitial IgG4-positive plasma cells by immunoenzyme staining. Parts B and C are serial sections. The ratio of IgG4-positive cells/IgG-positive cells was approximately 20%. D: Epimembranous spike formation in some glomerular capillaries (arrows, PASM staining). E: Fine granular IgG distribution along the glomerular capillaries by immunoenzyme staining. F: Intramembranous dense deposits in the glomerular capillaries by electron microscopy. The scale is shown with a scale bar at the bottom in each part.

responsiveness of the high serum ALP level with a mild increase of the AST level thus suggesting a diagnosis of hepatic sarcoidosis (8, 10). Since serum sIL2R in sarcoidosis is derived from the cell surface of activated helper T1 (Th1) cells, a high level of sIL2R may be related to the proliferation of macrophages, which contributes to the formation of granuloma (9). In addition, the proliferation of macrophages is presumed not only based on a high macrophage ratio in BALF, but also hypercalcemia, which is derived from high 1α , 25-dihydroxy vitamin D3 levels by 1α -hydroxylase secreted from activated macrophages (11). In the present case, the decreased serum 1α , 25-dihydroxy vitamin D3 level in the first admission may have been attributed to inhibited synthesis by a diseased kidney with tubular dysfunction. Its level subsequently increased in the convalescent phase without renal symptoms. With regard to the differential diagnosis of immunological TIN, Sjögren syndrome and tubulointerstitial nephritis and uveitis (TINU) syndrome should be considered. However, the lack of sicca syndrome and uveitis by ophthalmologic examinations in this case did not support the diagnosis of these syndromes. In addition, anti-SSA and anti-SSB antibodies specific for Sjögren syndrome later measured on a preserved serum sample obtained at the second biopsy were negative. Instead, the renal finding of TIN

and the serological results of high IgG4, IgE, and sIL2R levels in addition to pulmonary findings and kidney swelling supported the diagnosis of IgG4-RKD (12, 13). However, a renal biopsy did not fulfil the requirements for the definite criteria, namely, the IgG4/IgG plasma cell ratio more than 40% and interstitial storiform fibrosis, with the ultimate diagnosis of possible IgG4-RKD (12).

Therefore, the characteristic disease profile at the first admission was summarized as the co-expression of partial diagnostic markers of different disease categories, including sarcoidosis, IgG4-RKD, and MPO-ANCA-related NCGN without histological confirmation. Previous studies on the age of onset of these diseases in Japan reported that sarcoidosis has two peaks at 20-29 years and older than 50 years (7), the mean age of IgG4-RKD was 63.7 years (12), and the mean age of ANCA-related GN was 69.7 years (3). In a recent Japanese study on the prevalence of elevated serum IgG4 levels in 93 patients with sarcoidosis-like chest findings, which included 49 definite cases and 44 suspected cases, the suspected group showed a higher prevalence of elevated IgG4 levels (13.6%) with an older mean age (56.3 years) than the definite group (4.1% and 47.0 years, respectively), thus suggesting the high frequency of the co-occurrence in the older age (14). Therefore, the various im-

munological abnormalities of lymphoid proliferation, polyclonal IgG increases with high IgG4 levels, and the autoantibody production of MPO-ANCA with later positivity for antinuclear antibodies seem to reflect immune senescence in the elderly, perceived as T-cell dysfunction in the acquired immune response, low-grade sustained inflammation, and autoantibody production (5). These immune abnormalities may not manifest as a pathological disease without a triggering factor.

Previous studies reported that MN developed in association with IgG4-RKD or sarcoidosis (15, 16). Recent findings on glomerular PLA2R immunostaining may contribute to the discrimination of secondary MN associated with IgG4-RKD or sarcoidosis from idiopathic MN. Idiopathic MN was previously described as PLA2R-positive in approximately 70% of MN cases (17), while MN associated with active sarcoidosis was reported to be positive in 56% (5/9 cases) (16). In contrast, PLA2R staining was negative in all 13 cases of MN with IgG4-RKD (15, 18). Therefore, the negative PLA2R staining observed in the present case was not decisive for a diagnosis of secondary MN. Since MN was initially associated with suspected sarcoidosis and/or possible IgG4-RKD and was later observed with NCGN, it may have developed based on aging-associated immune dysfunction. It is important to note that sub-capsular focal lymphoid aggregates in the first biopsy were observed independently of interstitial cellular infiltration containing many IgG 4-positive cells. Lymphoid follicular tissue encircling a HEV-like vessel contained IgG-positive cells, but rarely showed positivity for IgG4. Therefore, these lymphoid aggregates may be regarded as a senescence-associated immune abnormality because the presence of different stages of tertiary lymphoid tissues, such as dense clusters of lymphocytes and lymphoid follicles, were recently characterized in aged, but not young, kidneys with chronic inflammation (19).

It seems likely that the circulating monocytic increase is attributed to a virus infection which has subsequently caused gradual decrease of neutrophil from 6 months toward 10 months as shown in Fig. 4. Then, infection-associated proinflammatory cytokines may have stimulated the innate immune system to induce primed neutrophils in the persistent increase of neutrophil counts nearly 3 times from the trough to the peak. It is well-known that the primed neutrophils express MPO on the cell surface leading to interact with circulating anti-MPO antibodies which may also bind to Fc γ receptors on the neighboring neutrophil surface (1). On the other hand, with regard to the neutrophil life cycle, a persistent increase in the neutrophil counts may probably be associated with an increased number of apoptotic cells, because neutrophils are short-lived cells with a circulatory half-life of several days and their death occurs by apoptosis. An ultrastructural study has shown that unprimed neutrophils in apoptosis express MPO-containing granules on the cell surface making accessible to anti-MPO antibodies (20). Third, it has been shown that soluble MPO released by activated

neutrophils binds to unstimulated non-apoptotic neutrophils thereby making them reactive to anti-MPO antibodies (21). It seems likely that certain amounts of serum anti-MPO antibodies were circulating around 17 months (Fig. 4) when a high MPO-ANCA titer was detected, and they might have reacted with MPO diversely expressed on the cell surface of neutrophils, producing ANCA-activated neutrophils. Further, circulating neutrophils with MPO antigens could have caused them to function as antigen presenting cells similar to macrophages and dendritic cells, and thus might have caused higher levels of MPO-ANCA leading to NCGN (22).

At 17 months, a high MPO-ANCA titer of 160 U/mL was detected as the neutrophil count increased. However, additional inflammatory stimuli appeared to be required to induce NCGN. At 21 months, the upper respiratory infection treated by clarithromycin might have exerted its effect as the predisposing factor needed to induce a very high MPO-ANCA titer with the development of NCGN at 24 months. Since the serum level of procalcitonin, which is a marker of infection by bacteria, fungi, and parasites, was within the normal range despite the high CRP level at the highest MPO-ANCA titer, the direct participation of these pathogens may be excluded (23). The role of bacterial lipopolysaccharides, concurrent viral infection, or related pro-inflammatory cytokines, such as tumor necrosis factor- α , has been suggested for neutrophil priming with further progression to glomerular capillary attachment and respiratory burst (1).

Regarding the care of ANCA-associated vasculitis including rapidly progressive glomerulonephritis, the usefulness of the routine monitoring of serum ANCA every 2-3 months in remission has been reported (24). We regret that we did not regularly assess MPO-ANCA because the MPO-ANCA titer was relatively low at the first admission and the first renal biopsy did not show NCGN, but instead identified TIN suspicious of sarcoidosis and IgG4-RKD. The present report suggests that precise assessments on serial differential leukocyte counts as well as an incidental upper respiratory infection and repetitive tests on MPO-ANCA may be essential in regular consultations for ANCA-positive patients.

The authors state that they have no Conflict of Interest (COI).

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