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【 CASE REPORT 】

# IgA Nephropathy with Dominant IgA2 Deposition Accompanied by Mantle Cell Lymphoma

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**Abstract:**
Malignant lymphoma is rarely complicated by secondary IgA nephropathy. We encountered a 74-year-old man with rapidly progressive glomerulonephritis due to IgA nephropathy with predominant deposition of IgA 2, instead of IgA1, in the glomerulus that was eventually diagnosed as secondary IgA nephropathy due to mantle cell lymphoma. Renal impairment was improved by chemotherapy for the mantle cell lymphoma. IgA came from the colonic mucosa that was stimulated by the infiltrated lymphoma cells, instead of the tumor itself. We should consider mantle cell lymphoma as a cause of secondary IgA nephropathy, although its prevalence may not be very high.

**Key words:** rapidly progressive glomerulonephritis, IgA subclass, renal infiltration

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## Introduction

IgA nephropathy is a major glomerulonephritis associated with mucosal immunity. In primary IgA nephropathy, increased IgA1 immune complexes are deposited in the mesangial region and induce glomerular injury (1). Secondary IgA nephropathy is caused by various etiologies, including chronic hepatitis, live cirrhosis, inflammatory bowel disease, bacterial infection, and autoimmune disease (2). Malignant lymphoma rarely accompanies secondary IgA nephropathy.

The pathophysiology of secondary IgA nephropathy remains unclear. It is challenging to distinguish secondary nephropathy from primary nephropathy by a histopathological assessment alone. Nevertheless, such efforts to determine etiologies are essential for deciding on an appropriate therapeutic strategy. IgA is sub-classified into IgA1 and IgA2. In general, IgA1 deposits glomerulus in patients with primary IgA nephropathy. In the same manner, IgA1 deposition is dominant in the secondary IgA nephropathy (3, 4).

We encountered a patient with IgA nephropathy who was eventually diagnosed with secondary IgA nephropathy due to mantle cell lymphoma. Interestingly, the deposit was IgA 2-dominant.

## Case Report

A 74-year-old man with histories of diabetes mellitus for 25 years and old myocardial infarction 8 years earlier was admitted to our institute presenting with appetite loss and fatigue, accompanied by abnormal urine test results (urine protein +++, 3.3 g/g of creatinine, and occult blood +++) and progressive renal impairment (serum creatinine level from 1.10 mg/dL to 2.11 mg/dL).

### On admission

His blood pressure was 120/68 mmHg, and his body temperature was 37.0 °C. He had pitting edema on both lower legs without purpura. His white blood cell count was 14,960/μL, and his hemoglobin level was 9.7 g/dL (Table). The serum IgA level was markedly increased (1,583 mg/dL). We suspected rapidly progressive glomerulonephritis.

### Renal biopsy findings

A renal biopsy obtained 29 renal corpuscles, 8 of which had global sclerotic glomerulus, while the others had mild mesangial proliferation and extracapillary proliferative lesions (Fig. 1A). A total of 14% of glomeruli showed cres-

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**Table.** **Laboratory Data on Admission.**

| Laboratory test | Value |
|---|---|
| Urinalysis | |
| Urine specific gravity | 1.012 |
| Urine protein | (3+) |
| Urine occult blood | (3+) |
| Urine sedimentation | |
| Red Blood cells, /high power field | ≥100 |
| White Blood cells, /high power field | 1-4 |
| Granular casts, /low power field | 3-9 |
| Complete blood cell counts | |
| White Blood cells, /μL | 14,340 |
| Red blood cells, /μL | $340\times10^4$ |
| Hemoglobin, g/dL | 9.7 |
| Platelets, /μL | $21.9\times10^4$ |
| Serum chemistry | |
| Total protein, g/dL | 7.3 |
| Albumin, g/dL | 2.8 |
| Aspartate aminotransferase, IU/L | 26 |
| Alanine aminotransferase, IU/L | 16 |
| Lactate dehydrogenase, IU/L | 188 |
| Blood urea nitrogen, mg/dL | 23 |
| Creatinine, mg/dL | 2.11 |
| Total cholesterol, mg/dL | 145 |
| Low density lipoprotein cholesterol, mg/dL | 99 |
| High density lopoprotein cholesterol, mg/dL | 30 |
| Triglyceride, mg/dL | 76 |
| Sodium, mEq/L | 138 |
| Potassium, mEq/L | 5.6 |
| Chloride, mEq/L | 102 |
| Calcium, mg/dL | 8.9 |
| Serum immunological test | |
| Hemoglobin A1c, % | 6.3 |
| C-Reactive Protein, mg/dL | 0.21 |
| Immunoglobulin G, mg/dL | 1,324 |
| Immunoglobulin A, mg/dL | 1,583 |
| Immunoglobulin M, mg/dL | 104 |
| Complement 3, mg/dL | 78.9 |
| Complement 4, mg/dL | 27.8 |
| 50% hemolytic complement activity, U/mL | 44 |
| Antinuclear antibody | negative |
| Myeloperoxidase-ANCA | negative |
| Proteinase 3-ANCA | negative |
| Anti-glomerular basement membrane antibody | negative |
| Soluble interleukin-2 receptor, U/mL | 5,282 |

ANCA: anti-neutrophilic cytoplasmic autoantibody

cent formation and hyalinization of the arteriole (Fig. 1B).

The fluorescent antibody method was used to determine the deposition of IgA and C3 in the mesangial lesion (Fig. 1C, F). IgG was weakly positive in the mesangial lesion and linear capillary wall (Fig. 1D). IgM and C1q were negative (Fig. 1E, G). Electronic microscopy revealed hemispherical deposits in the para-mesangial area (Fig. 1H).

We diagnosed him with IgA nephropathy given these findings. Infiltration of lymphocytes with lymphoid follicle-like lesion was observed in the renal interstitium (Fig. 2A, B).

### Diagnostic strategy

Given the elevated serum IgA level and the lymphocyte infiltration in the renal interstitium, we suspected lymphoproliferative disorders or viral infection as a cause of secondary IgA nephropathy. We therefore conducted a detailed histopathological assessment and surveillance for systemic disease.

### Detailed histopathological assessments

Immunohistological analyses of the infiltrated lymphocytes showed positivity for B-cell marker (CD20; Fig. 2C), negativity for germinal center marker (CD10), aberrantly expressed T-cell marker (CD5), and positivity for cyclin D1 (Fig. 2D). We therefore suspected renal invasion of mantle cell lymphoma (MCL). The fluorescent antibody method showed IgA2-dominant deposition compared with IgA1 in the glomerulus (Fig. 3). There was no difference between kappa and lambda deposition.

### Systemic assessments

Fluoro-2-deoxy-D-glucose-positron emission tomography (FDG-PET) showed multiple systemic points of accumulation at the lymph nodes, spleen, stomach, and intestine (Fig. 4). Upper and lower endoscopies showed multiple small nodular or polypoid tumors (Fig. 5). An endoscopic biopsy showed sub-mucosal nodular infiltration of small lymph cells (Fig. 6A). Given the positivity for CD20, CD5, and cyclin D1 and negativity for CD10 and CD3 (Fig. 6B-E), he was diagnosed with MCL. A bone marrow biopsy also showed invasion of MCL. He was eventually classified as Lugano stage IV.

Immunohistological analyses showed no malignant cells that were positive in IgA in any obtained tissues (Fig. 7A-C), except for the submucosal tissue of the colon adjacent to the lymphoma, which had infiltration of IgA2-positive plasma cells (Fig. 7D-F). IgA2 was negative in the bone marrow, renal intestine, and duodenum. We did not perform an endoscopic assessment of the small intestine.

### Clinical course

The clinical course is summarized in Fig. 8. We performed R-CHOP chemotherapy consisting of rituximab, cyclophosphamide, doxorubicin, vincristine, and prednisolone. The renal impairment improved as the serum creatinine level decreased to 0.79 mg/dL, but he ultimately died due to the progression of MCL at 9 months following the biopsy.

## Discussion

We encountered a patient with rapidly progressive glomerulonephritis due to IgA nephropathy with the predominant deposition of IgA2 in the glomerulus, which was eventually diagnosed as secondary IgA nephropathy due to MCL. Renal impairment was improved by chemotherapy for

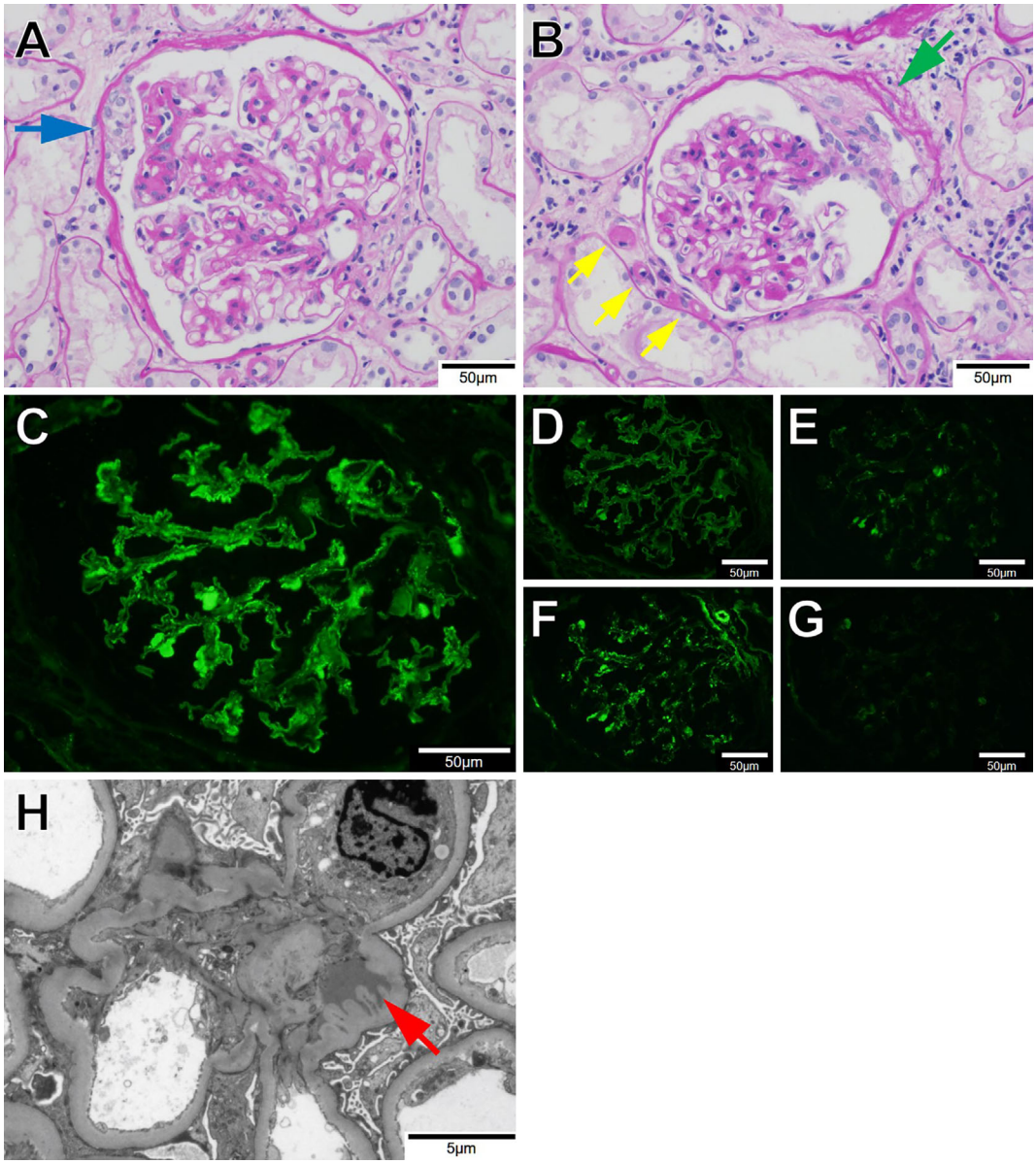


**Figure 1.** **Histopathological findings in the glomerulus A: Mild mesangial proliferation in the glomerulus with capsular adhesion and extracapillary proliferative lesion (blue arrow) (Periodic acid-Schiff stain, original magnification ×200). B: Crescentic formation (green arrow) with hyaline arteriolosclerosis (yellow arrow) (Periodic acid-Schiff stain, original magnification ×200). C: Deposition of IgA in the mesangial lesion (direct immunofluorescence, original magnification ×200). D: Weak deposition of IgG in the mesangial lesion and linear capillary wall (direct immunofluorescence, original magnification ×200). E: IgM negativity (direct immunofluorescence, original magnification ×200). F: Deposition of C3 in the mesangial lesion (direct immunofluorescence, original magnification ×200). G: C1q negativity (direct immunofluorescence, original magnification ×200). H: Hemispherical electron-dense deposits in the paramesangial lesion (red arrow) with diffuse thickness in the glomerular basement membrane (electron microscopy, original magnification ×3,000).**

the MCL.

### MCL

MCL is a B-cell non-Hodgkin lymphoma that develops from normal B cells and consists of the mantle layer in the germinal center of a lymph node. The prevalence of MCL is 3-10% among cases of adult-onset non-Hodgkin lymphoma. CD5 and cyclin D1 are positive in MCL, and chromosomal translocation specific to this lymphoma is t (11;14)(q13;q32). MCL often invades outside of the lymph nodes, including into the bone marrow, spleen, and gastrointestinal tract (5).

### Renal dysfunction induced by malignant lymphoma

Several mechanisms have been proposed to explain the renal impairment induced by malignant lymphoma. Most

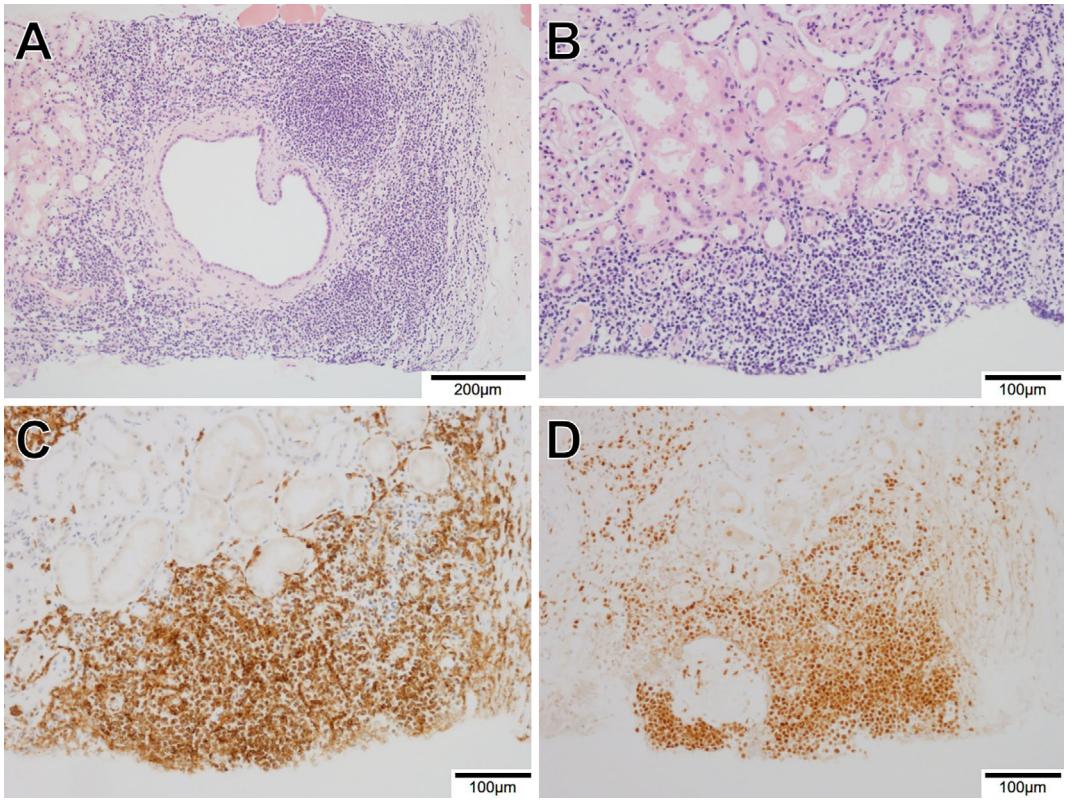


**Figure 2.** **Histopathological findings in the renal interstitium. A: Infiltration of lymph cells with lymph follicle-like structure in the renal interstitium [Hematoxylin and Eosin (H&E) staining, original magnification ×50]. B: Infiltration of lymph cells in the renal interstitium (H&E staining, original magnification ×100). C: CD20 positivity (immunoenzyme, original magnification ×100). D: Cyclin D1 positivity (immunoenzyme, original magnification ×100).**

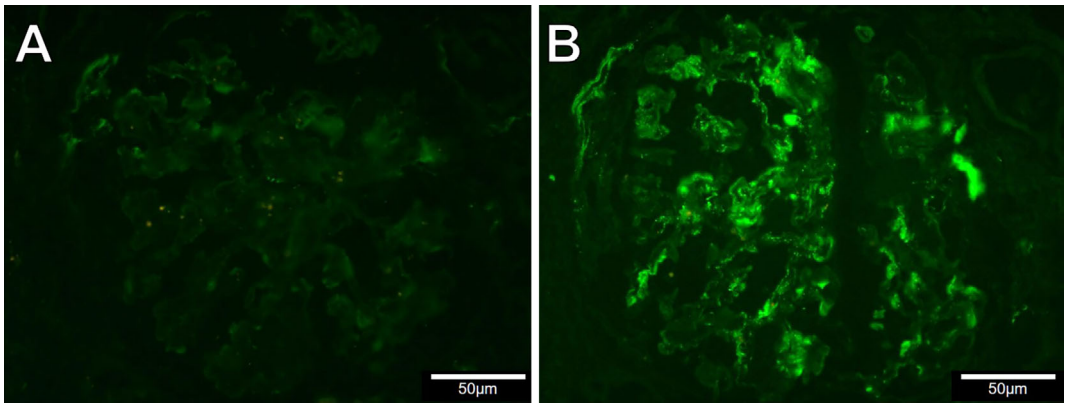


**Figure 3.** **IgA subclass, immunofluorescence findings in the glomerulus. A: IgA1 (direct immunofluorescence, original magnification ×200). B: IgA2 (direct immunofluorescence, original magnification ×200). IgA2 deposition is observed predominantly.**

cases involve the direct invasion of lymphoma cells into the kidney (6). Obstruction of a urinary duct due to the tumor, hypercalcemia, glomerular and tubular disorders due to paraproteinemia, and tumor lysis syndrome due to chemotherapy are other causes of renal impairment (7). Given that the renal impairment in the present patient was improved by chemotherapy, lymphoma cells may have directly invaded the kidney in our patient.

### *Glomerular lesions accompanied by malignant lymphoma*

Among malignant lymphoma, Hodgkin lymphoma is a predominant cause of nephrotic syndrome. Most instances are minimal change disease due to T-cell-related immune abnormality (8, 9). Non-Hodgkin lymphoma is associated with membranoproliferative glomerulonephritis, membranous nephropathy, focal segmental glomerulosclerosis, and cres-

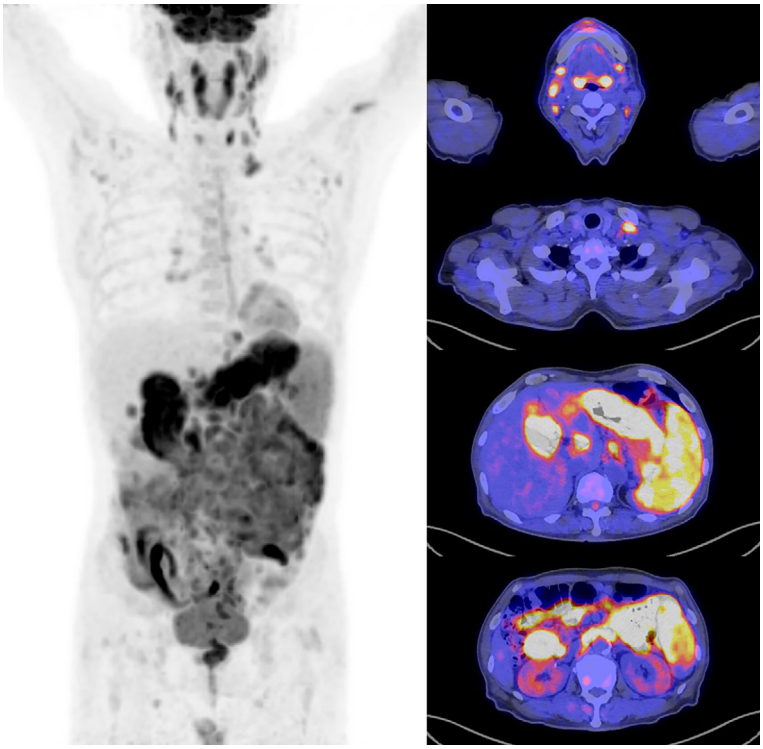

**Figure 4.** **Fluorodeoxyglucose-position emission tomography.**

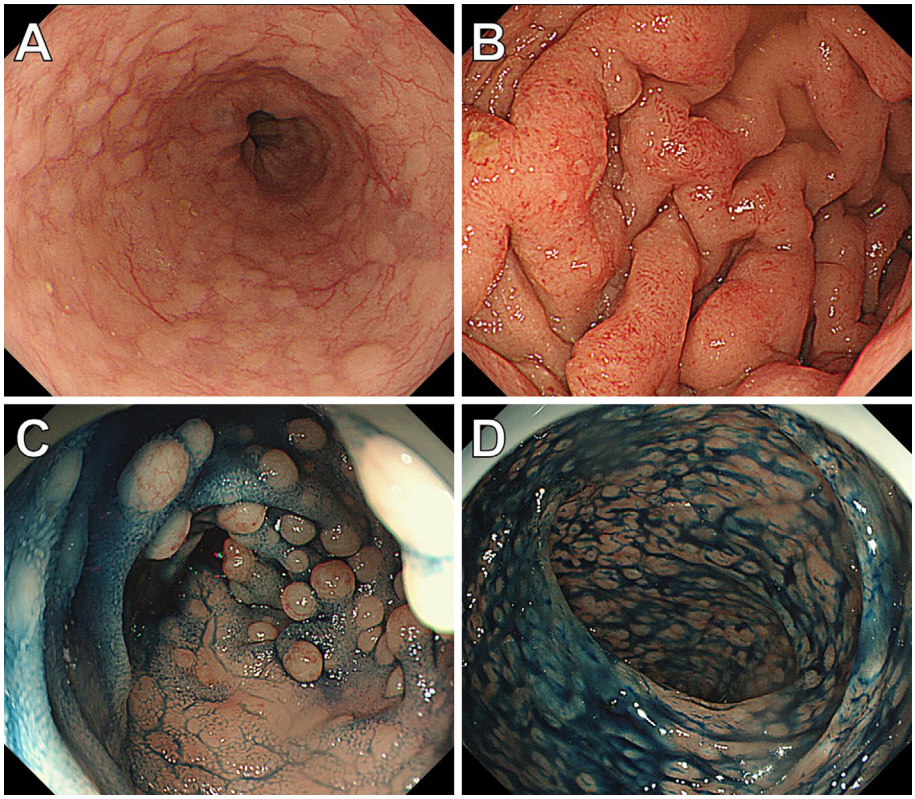


**Figure 5.** **Endoscopic findings. A: Esophagus: multiple white elevated lesions. B: Stomach: large cerebroid folds, multiple erosions and ulcers. C: Cecum: multiple nodular or polypoid tumors (indigo carmine contrast method). D: Rectum: multiple white elevated lesions (indigo carmine contrast method).**

centic glomerulonephritis (10). MCL is sometimes accompanied by antineutrophil cytoplasmic antibody-positive crescentic glomerulonephritis (11, 12).

Malignant lymphoma rarely complicates IgA nephropathy,

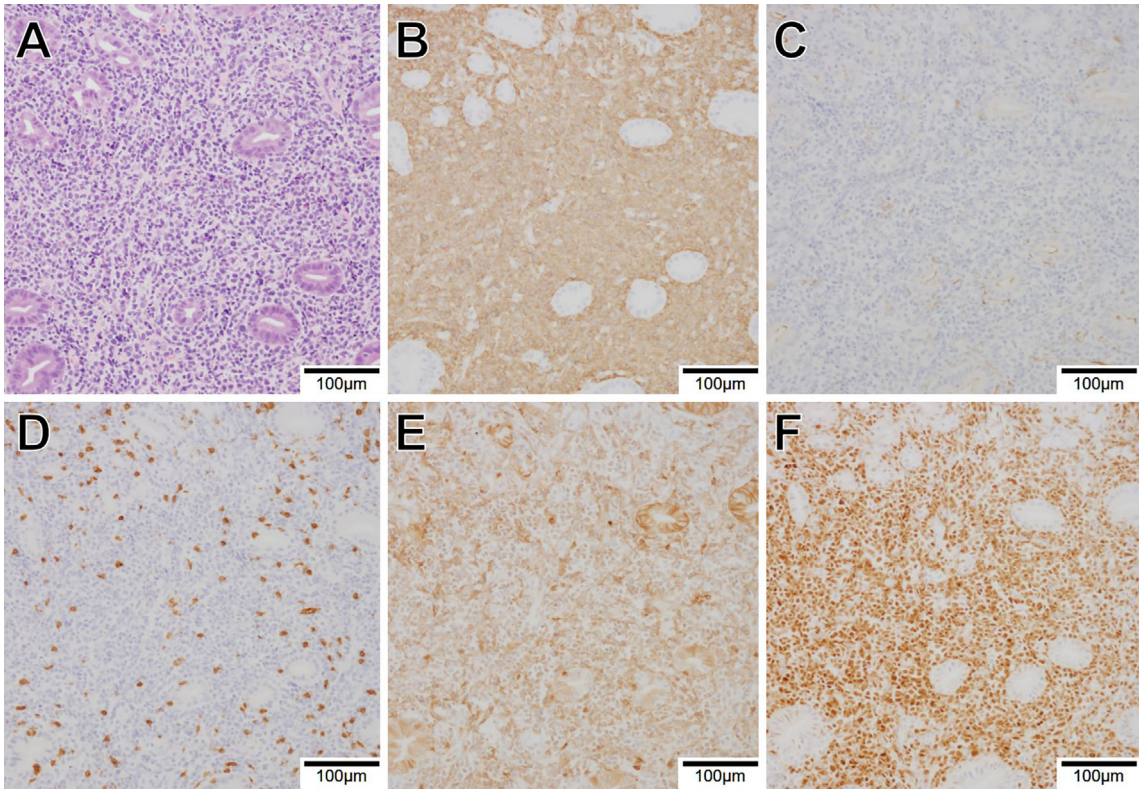


**Figure 6.** **Duodenum mucosa. A: Diffuse and nodular infiltration of small lymph cells between lamina propria and submucosal tissue (Hematoxylin and Eosin staining, original magnification ×100). B: CD20 positivity (immunoenzyme, original magnification ×100). C: CD10 negativity (immunoenzyme, original magnification ×100). D: CD3 negativity (immunoenzyme, original magnification ×100). E: CD5 positivity (immunoenzyme, original magnification ×100). F: Cyclin D1 positivity (immunoenzyme, original magnification ×100).**

except for Hodgkin lymphoma (13, 14), angioimmunoblastic T-cell lymphoma (15), mucosa-associated lymphoid tissue lymphoma (16), and low-grade B-cell lymphoma (17). To our knowledge, this is the first report of IgA nephropathy secondary to MCL.

### Secondary IgA nephropathy

In general, galactose-deficient IgA1 is deposited in the glomerulus (1). IgA1 is also deposited in cases of secondary IgA nephropathy (3, 4). However, IgA2 deposition was observed in our patient. We did not perform an immunofluorescent analysis of galactose-deficient IgA1 using the KM55 antibody. However, the result would probably have been negative, given the negative staining of IgA1. We therefore assumed this case to be secondary IgA nephropathy, given the dominancy of IgA2.

IgA, which consists of IgA1 and IgA2 subtypes, is secreted predominantly at the mucosa and plays a major role in mucosal immunological protection. IgA2 is particularly important for achieving mucosal protection against bacteria, given its resistance to bacterial protease. The ratio of the IgA subtype varies among tissues (i.e., 89:11 in serum and 35:65 in the colon for IgA1:IgA2) (18).

The origin of IgA deposited in the glomerulus in our patient is of great interest. When IgA is secreted from the tumor, IgA deposition should be monoclonal with proliferative glomerulonephritis (19). In our patient, however, there was no M-protein in blood or urine, and the deposited IgA2 was polyclonal. Given the lack of IgA expression in the lymphoma cells, the origin of IgA2 was not a tumor.

IgA2-positive plasma cells were observed in the lamina propria of the colon surrounding the infiltrated lymphoma. IgA2 might have been inappropriately secreted by the digestive mucosa via stimulation of lymphoma. IgA2 was negative in the bone marrow tissue. While we cannot exclude the small intestine as another origin of IgA2, given the positive findings on FDG-PET, we do not have any histopathological data to support this.

We did not measure the serum concentrations of the IgA sub-class. Of note, the markedly elevated serum IgA level decreased immediately after the chemotherapy administration. Excessive IgA2 might have been deposited in the glomeruli. IgA2 does not have an O-linked glycan on its hinge part, and the detailed mechanism of why IgA2 was deposited in the glomeruli remains unclear. IgA2, which can cause nephritis, might be secreted in certain cases, such as cases of lymphoma.

### Conclusion

We should consider MCL as a potential cause of secon-

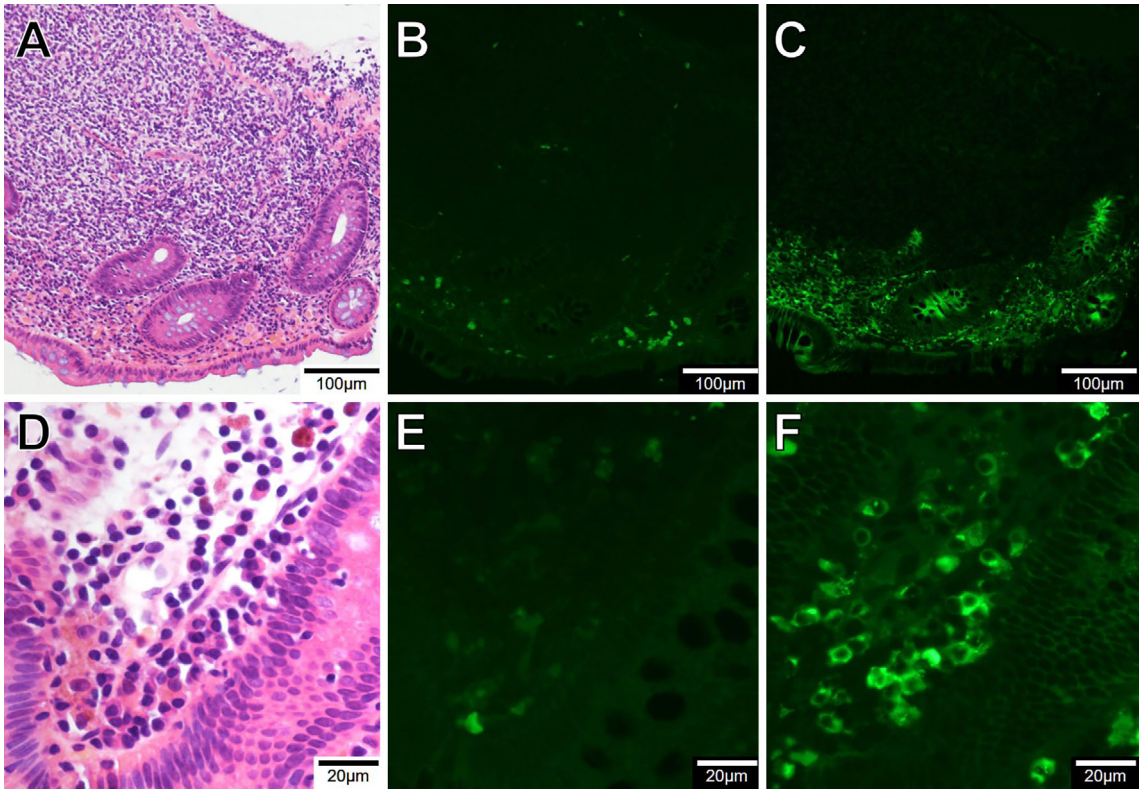


**Figure 7.** **Colonic mucosa. A: Diffuse and nodular infiltration of small lymph cells between the lamina propria and submucosal tissue [Hematoxylin and Eosin (H&E) staining, original magnification ×100]. B: Negative staining of IgA1 in the lymphoma cells (direct immunofluorescence, original magnification ×100). C: IgA2 is negative in the lymphoma cells but positive in the surrounding mucosal epithelial cells (direct immunofluorescence, original magnification ×100). D: Infiltration of plasma cells in the lamina propria (H&E staining, original magnification ×400). E: IgA1-negative plasma cells infiltrating in the lamina propria (direct immunofluorescence, original magnification ×400). F: IgA2-positive plasma cells infiltrating in the lamina propria (direct immunofluorescence, original magnification ×400).**

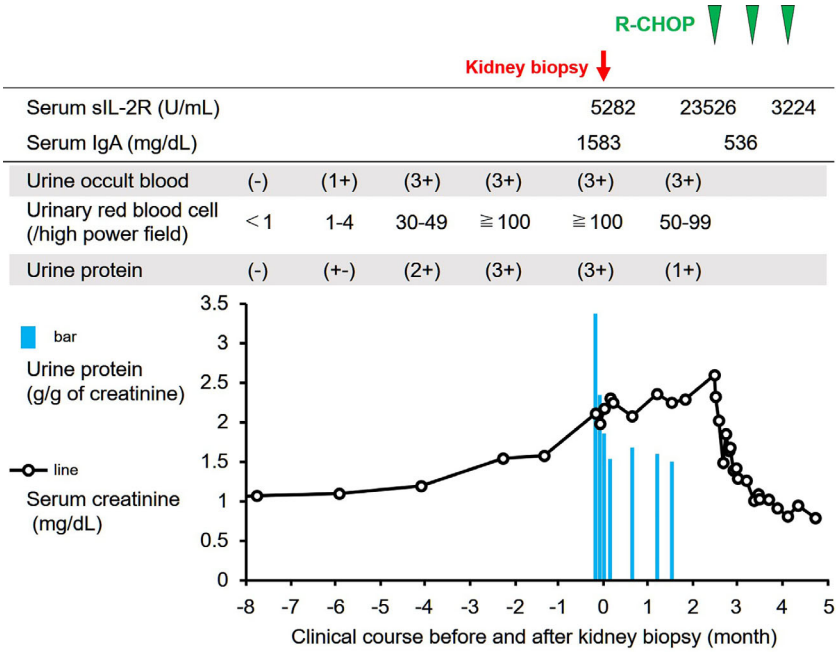


**Figure 8.** **Clinical course. sIL-2R: soluble interleukin-2 receptor, R-CHOP: rituximab plus cyclophosphamide, doxorubicin, vincristine, and prednisolone**

dary IgA nephropathy, although its prevalence might not be very high.

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

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