

[CASE REPORT]

Proliferative Glomerulonephritis with Monoclonal Immunoglobulin Deposits without Conspicuous Mesangial Proliferation, Complicated with Squamous Cell Lung Carcinoma

Takaaki Higashihara^{1,2}, Akira Okada², Yasuna Nakamura^{1,2}, Hanako Saigusa^{1,2}, Shiko Homma¹, Mimiko Matsumura¹, Taiko Kusano¹, Akira Shimizu³ and Hideki Takano¹

Abstract:

We performed a renal biopsy for nephrotic syndrome in a patient with squamous cell lung carcinoma, which can worsen the prognosis. Chemoradiation therapy was effective for the cancer and proteinuria; we thus inferred that the nephrotic syndrome had been closely associated with the carcinoma. A pathological analysis of the kidney showed monoclonality for λ chain, satisfying the diagnostic criteria of proliferative glomerulonephritis with monoclonal immunoglobulin deposits (PGNMID); however, conspicuous mesangial proliferation was not observed. This is the first case of PGNMID complicated with lung carcinoma; furthermore, our findings underscore the importance of examining renal lesions and assessing monoclonality in cancer patients.

Key words: paraneoplastic syndrome, proliferative glomerulonephritis with monoclonal immunoglobulin deposits, lung carcinoma

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Introduction

The field of onconeurology was recently developed in order to improve the quality of nephrology care in cancer patients, and it has been attracting the attention of nephrologists (1). One of the connections between the kidney and cancer is paraneoplastic syndrome, which is a group of clinical manifestations that have a causal relationship with malignant neoplasms and occur remotely from the tumors (2). Since the first description of nephrotic syndrome as a paraneoplastic manifestation of a tumor by Galloway in 1922 (3), tumor-associated glomerulopathies, mainly in the form of membranous nephropathy (MN), have been reported (4). Paraneoplastic glomerulopathies include MN, immunoglobulin (Ig) A nephropathy, membranoproliferative glomerulonephritis, and amyloidosis, which manifest mainly in the form of a nephrotic syndrome (5).

We herein report the first case of proliferative glomerulonephritis with monoclonal Ig deposits (PGNMID) complicated with squamous cell lung carcinoma (SCLC). In this case, the pathology of the patient's disease satisfied the diagnostic criteria of PGNMID, but the absence of conspicuous mesangial proliferation hindered an immediate diagnosis. We also discuss the diagnostic and management approach for nephrotic syndrome complicated with a solid tumor with monoclonal Ig deposits.

Case Report

A 66-year-old man with no history of urinary abnormalities was admitted to our hospital because of a mass shadow on chest X-ray. A systemic examination, including bronchoscopy, led to the diagnosis of primary SCLC stage IIIB. At the same time, the urine dipstick test result revealed a score of 3+ (protein concentration >300 mg/dL) with no micro-

¹Department of Nephrology, Tokyo Teishin Hospital, Japan, ²Division of Nephrology and Endocrinology, The University of Tokyo Graduate School of Medicine, Japan and ³Department of Analytic Human Pathology, Graduate School of Medicine, Nippon Medical School, Japan
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Correspondence to Dr. Akira Okada, aokada-ky@umin.ac.jp

Table. Laboratory Test Results.

Blood test		γ -glutamyl transferase	29 IU/L	Cryoglobulin	Negative
White blood cell count	5,400 / μ L	Fasting blood glucose	103 mg/dL	MPO-ANCA	Negative
Hemoglobin	8.9 g/dL	Hemoglobin A1c	5.1 %	PR3-ANCA	Negative
Platelet count	31.2 \times 10 ⁴ / μ L	APTT	41.6 s	Anti-GBM	Negative
Sodium	139.1 mEq/L	PT-INR	0.94	HIV	Negative
Potassium	4.9 mEq/L	C-reactive protein	4.5 mg/dL	HCV antibody	Negative
Chloride	105.4 mEq/L	SCC	6.6 ng/mL	HBs antigen	Negative
Calcium	8.5 mg/dL	CYFRA	3.5 ng/mL	TPHA	Negative
Phosphate	3.8 mg/dL	IgA	207 mg/dL	Urine test	
Creatinine	0.95 mg/dL	IgG	926 mg/dL	pH	7.5
Urea nitrogen	14.1 mg/dL	IgM	36 mg/dL	Occult blood	Negative
Uremic acid	5.5 mg/dL	IgE	9 IU/mL	Glucose	Negative
Total protein	5.4 g/dL	C3	157 mg/dL	White blood cells	Negative
Albumin	2.2 g/dL	C4	46 mg/dL	Urine protein	7.19 g/gCr
LDH	181 IU/L	CH50	55 U/mL	NAG	16.3 U/L
AST	12 IU/L	Serum immunoelectrophoresis	Negative	β 2-MG level	907 ng/mL
ALT	6 IU/L	Anti-nuclear antibody	Negative	Urine immunoelectrophoresis	Negative

LDH: lactate dehydrogenase, AST: aspartate aminotransferase, ALT: alanine aminotransferase, APTT: activated partial thromboplastin time, PT-INR: prothrombin time-international normalized ratio, SCC: squamous cell cancer antigen, CYFRA: cytokeratin-19 fragments, Ig: immunoglobulin, ANCA: anti-neutrophil cytoplasmic antibody, MPO: myeloperoxidase, PR3: proteinase-3, GBM: glomerular basement membrane, HIV: human immunodeficiency virus, HCV: hepatitis C virus, HBs: hepatitis B surface, TPHA: Treponema pallidum hemagglutination test, NAG: N-acetyl-D-glucosamine, β 2-MG: β 2-microglobulin

scopic hematuria, and bilateral leg edema was noted. One week later, monthly chemotherapy with cisplatin and docetaxel was initiated with radiation therapy. After the third chemotherapy cycle, the urine protein temporarily disappeared. Before the fourth cycle, the dipstick test result revealed a score of 3+ again, and the urine protein level was 7.19 g/gCr; he was therefore referred to our department. Detailed laboratory analyses showed normal serum creatinine levels (0.95 mg/dL) with an estimated glomerular filtration rate of 62 mL/min/1.73m² and hypoalbuminemia (2.2 g/dL) and confirmation of no hepatitis B or C virus or human immunodeficiency virus infections, autoimmune disorders, or abnormalities in immunoelectrophoresis tests of serum and urine (Table). The renal lesion affected the patient's quality of life and risked worsening his prognosis; therefore, after careful consideration, we performed a renal biopsy for the differential diagnosis of nephrotic syndrome and other potential diagnoses, such as drug-induced glomerulonephritis, in order to determine the appropriate chemotherapy regimen for the patient and help him achieve a better prognosis.

A light microscopic analysis of the specimen revealed 18-23 glomeruli, of which 1-2 were obsolescent, and the others exhibited irregular subepithelial deposits with no conspicuous mesangial proliferation or double contouring of the glomerular basement membrane. Immunofluorescence staining was positive for IgG1- λ along with glomerular capillaries and negative for IgA and IgM. Irregular peripheral deposition of C3 and a few C1q depositions were noted in the glomeruli. Electron microscopy revealed irregular and non-organized subepithelial electron-dense deposits (Fig. 1). These manifestations met the criteria for PGNMID because of the presence of non-organized monoclonal IgG1- λ deposits mimicking immune complex glomerulonephritis without

cryoglobulinemia. However, the pathological findings had two characteristics: predominant membranous features and PGNMID without conspicuous mesangial proliferation; the electron microscope analysis favored the former, whereas the light microscopic analysis supported the latter. We ultimately concluded that the diagnosis was PGNMID without conspicuous mesangial proliferation because the pathological findings met the criteria and PGNMID can phenotypically be MN (6, 7).

Several immunosuppressive therapies were considered for the treatment of the glomerulonephritis, but the patient's proteinuria improved (protein level 0.34 g/gCr) immediately after the next (fourth) cycle of chemotherapy (Fig. 2D), and his hypoalbuminemia improved as well (albumin level >3.5 g/dL). At the same time, the effect of chemotherapy on the tumor was confirmed, as the tumor size and squamous cell cancer antigen (SCC) level decreased (Fig. 2A, B). This therapeutic response suggested that the nephrotic syndrome had been due to paraneoplastic glomerulonephritis. Thereafter, the chemotherapy regimen was changed to carboplatin and paclitaxel in an effort to achieve complete remission.

As time passed, however, the tumor became increasingly resistant to chemotherapy; 10 months after the initiation of the chemoradiation therapy, the SCC level slightly increased again (Fig. 2D), and tumor invasion was observed, despite the absence of recurrence of nephrotic-range proteinuria (Fig. 2C, D). After seven cycles of the second regimen, the SCLC became uncontrollable, and the patient died of hemoptysis from the original disease 531 days after the first admission.

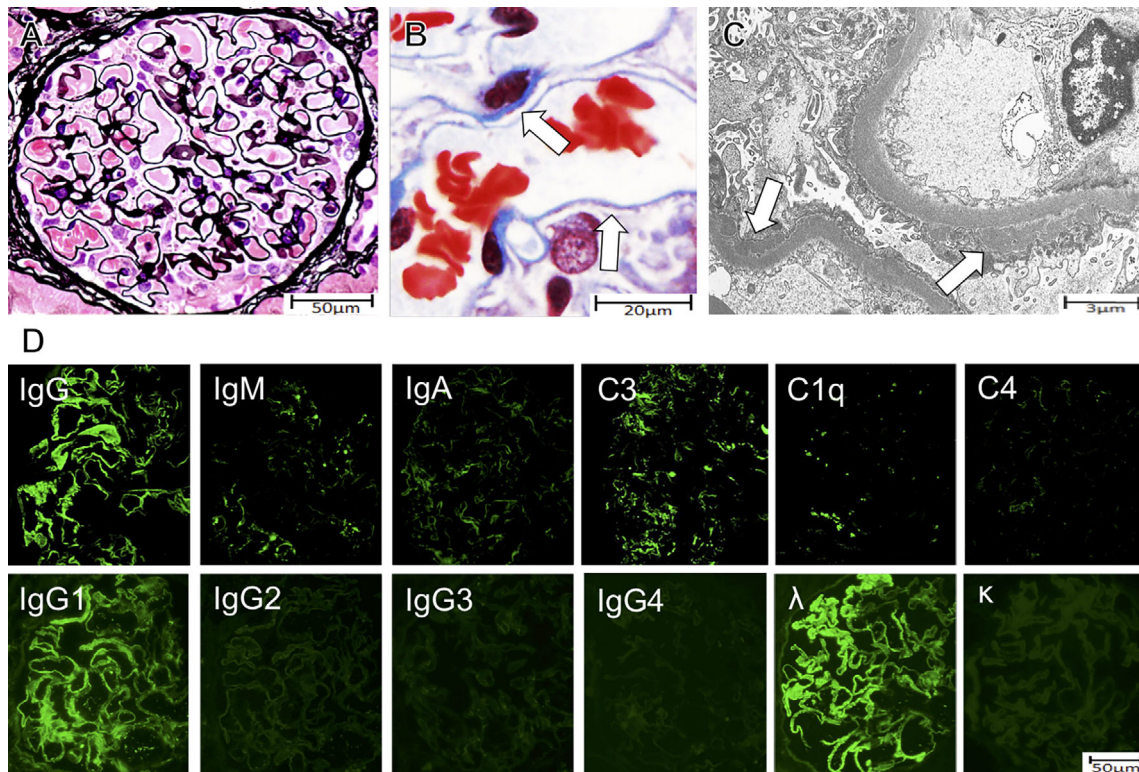


Figure 1. Pathological features of the renal biopsy specimen. (A, B) Light microscopy reveals irregular subepithelial deposits (arrows) with no mesangial proliferation or double contouring of the glomerular basement membrane (A: periodic acid-silver methenamine stain; original magnification, $\times 600$, scale bar = $50\ \mu\text{m}$; B: Masson trichrome stain; original magnification, $\times 1,500$, scale bar = $20\ \mu\text{m}$). (C) Electron microscopy reveals irregular subepithelial electron-dense deposits (arrows) (original magnification, $\times 8,000$, scale bar = $3\ \mu\text{m}$). (D) Immunofluorescence staining is positive for immunoglobulin (Ig) G1- λ along with glomerular capillaries, with irregular C3 and few C1q deposits, and negative for IgM or IgA (original magnification, $\times 600$, scale bar = $50\ \mu\text{m}$).

Discussion

Paraneoplastic syndromes are clinical manifestations caused by tumors that indirectly affect various organs, including the kidneys (4). Paraneoplastic glomerulopathies have been reported in 10.9-14.1% of patients with nephrotic syndrome or glomerulonephritis complicated by cancer (8, 9). The most common cancer type involved is lung cancer, particularly squamous cell carcinoma, which affects 41.7% of nephrotic patients with malignancy (10). However, it is sometimes difficult to determine the complexity of the association of renal lesions with cancer (11).

In our case, there were no signs or symptoms, such as electrolyte imbalance or neurologic or endocrine manifestations, other than nephrotic syndrome, which was complicated by SCLC. This strong association was supported by the patient's clinical course. The anti-cancer therapy induced resolution of the nephrotic range of proteinuria, although a moderate to mild level of proteinuria persisted as the SCLC became resistant to chemotherapy (Fig. 2). In addition, the timing of the onset of the nephrotic syndrome supported the attribution of the PGNMID to the SCLC because a previous

paper mentioned that the development of nephrotic syndrome within 12 months of the diagnosis of cancer supported tumor-related glomerulonephropathy (11). Furthermore, immunohistochemistry of the patient's specimen revealed negative PLA2R staining (Fig. 3), which strengthened the possibility of a paraneoplastic glomerulonephropathy (12), considering that the clinical data negated the possibility of other secondary glomerulonephropathies caused by lupus nephritis, hepatitis B or C virus, or syphilis-involved nephropathy. Furthermore, repeated results of urine and serum immunoelectrophoresis and the free light chain ratio showed no abnormalities (Fig. 4), which negated the presence of monoclonal gammopathy of renal significance induced by hematologic diseases. In summary, the nephrotic syndrome in our patient was not just coexistent but a complicated disease strongly associated with lung cancer.

Our case was classified as PGNMID on the grounds that it had non-organized monoclonal IgG1- λ deposits mimicking immune complex glomerulonephritis without cryoglobulinemia. PGNMID is a recently described entity mimicking immune complex glomerulonephritis with granular, non-organized, electron-dense deposits, typically with a subendothelial or mesangial distribution with monoclonality (6).

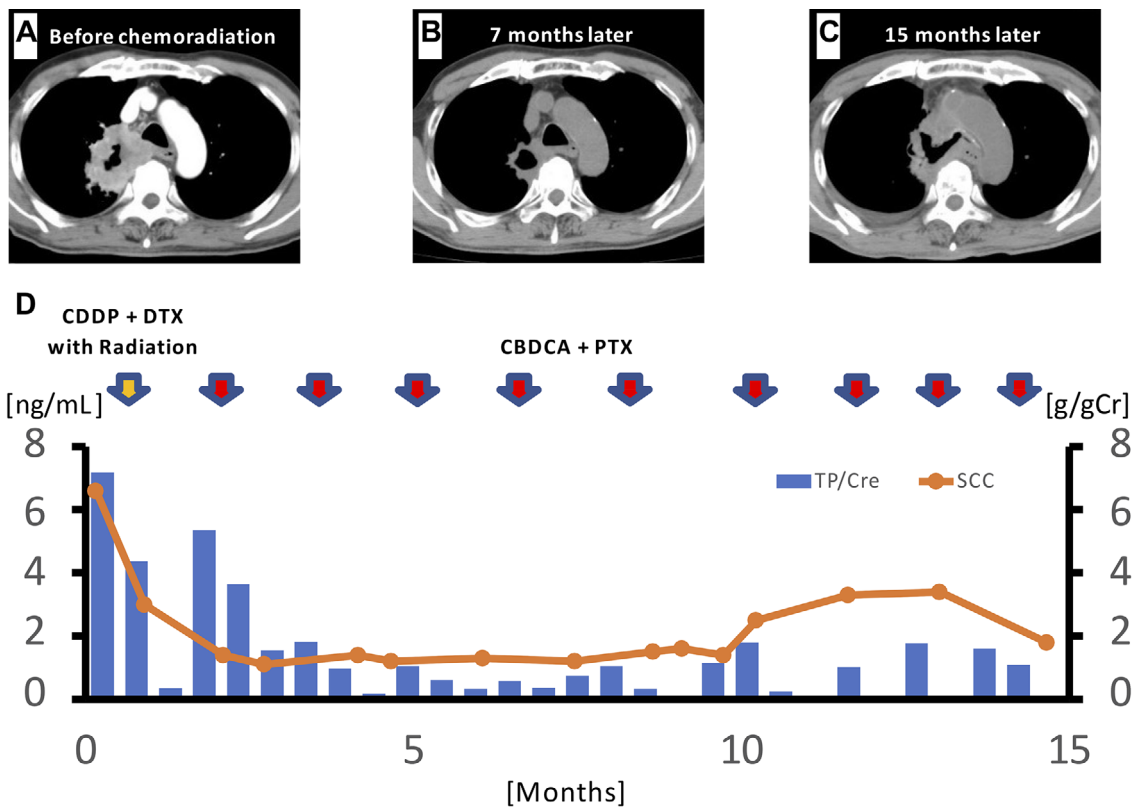


Figure 2. Patient's clinical course and computed tomography findings. (A-C) Images of contrast-enhanced or plain computed tomography (A) prior to chemoradiation therapy at 7 (B) and 15 months (C) following chemoradiation therapy. (D) The clinical course shows the levels of urinary total protein/creatinine (g/gCr) and the value of the tumor marker squamous cell cancer antigen (ng/mL) since the first consultation to our department. The patient received two chemotherapy regimens: first, cisplatin and docetaxel; and second, carboplatin and paclitaxel. The first regimen was combined with radiation therapy. Proteinuria immediately decreased, as a clear reduction in the size of the lung cancer is seen (compared to the volume reduction in the tumor size of A to that of B in parallel with urinary total protein/creatinine and squamous cell cancer antigen reduction shown in D). Gradually, the tumor became increasingly resistant to chemoradiation, which was eventually unable to hinder its growth (C). CBDCA: carboplatin, CDDP: cisplatin, Cre: creatinine, DTX: docetaxel, PTX: paclitaxel, SCC: squamous cell cancer antigen, TP: total protein

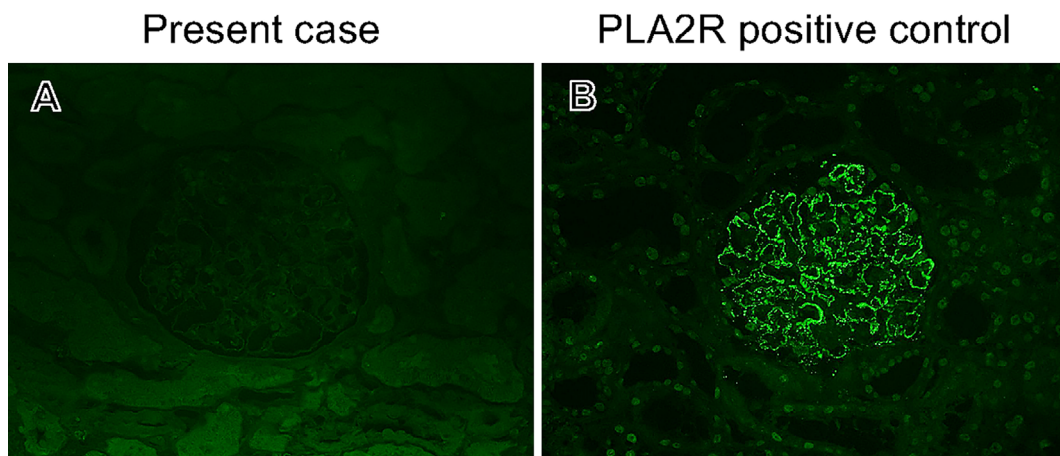


Figure 3. Immunofluorescence staining with the anti-PLA2R antibody. Immunofluorescence staining is negative for PLA2R in this patient (A), in contrast to that in a positive control (B).

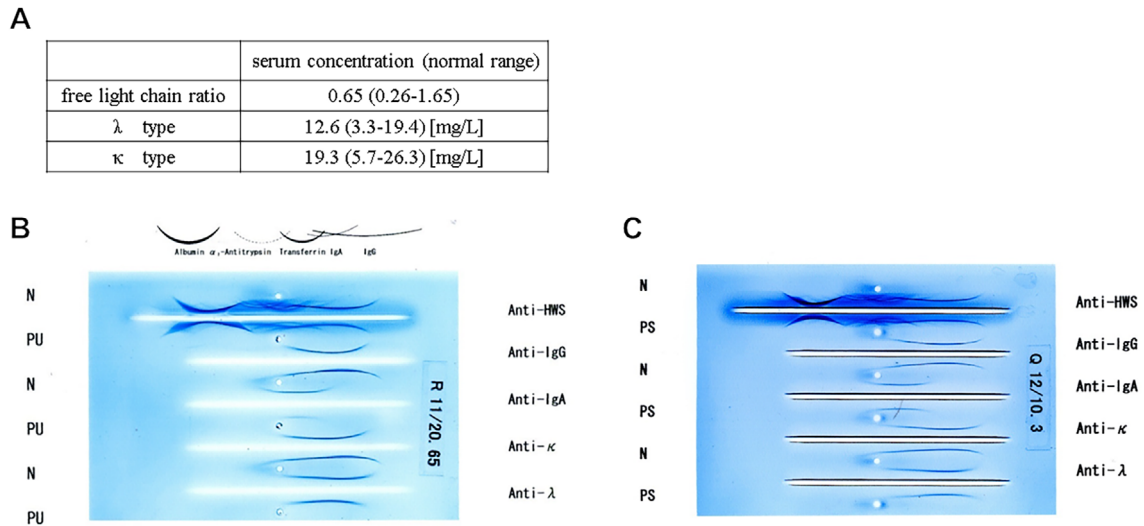


Figure 4. Serum free light chain ratio and immunoelectrophoresis test findings. The serum concentration of κ and λ light chains and the free light chain ratio are within the normal range. (A) There are no abnormalities in the urine or serum immunoelectrophoresis tests (B-C). HWS: human whole serum, Ig: immunoglobulin, N: normal serum, PU: patient's urine, PS: patient's sample

PGNMID is distinguished from other paraprotein-related diseases, such as amyloidosis, cryoglobulinemia, C3 glomerulopathy, and monoclonal Ig deposition disease (MIDD) characterized by nodular sclerosing glomerulopathy (13). These diseases are divided into two categories by electron microscopy, depending on whether deposits are organized or non-organized. The latter includes MIDD, C3 glomerulopathy, and PGNMID. In our case with non-organized electron-dense deposits, MIDD and C3 glomerulopathy were excluded because of the absence of diffuse linear immunofluorescence staining along the tubular and vascular basement membranes and absence of predominant immunofluorescence staining of C3, respectively (Fig. 1C, D) (13). The current diagnostic criteria (6) led us to the diagnosis of PGNMID; however, the pathological features of PGNMID detected by light microscopy are, in general, membranoproliferative glomerulonephritis or endocapillary proliferative glomerulonephritis, as the name indicates. Although Nasr et al. (7) showed that 5.4% of cases of PGNMID have predominantly membranous features, as in our case, the pathology of the cases was characterized by focal endocapillary hypercellularity and segmental membranoproliferative features. The absence of mesangial proliferation in this case prevented us from making a prompt diagnosis of PGNMID, but the current diagnostic criteria guided us to diagnose the patient's renal lesion as PGNMID without conspicuous mesangial proliferation.

Although our case of PGNMID had predominantly membranous features, some researchers classified monoclonal Ig deposits with membranous features into a new category. Komatsuda et al. (14) reported very few cases of patients with monoclonal Ig deposition disease associated with membranous features, i.e. non-organized and non-Randall-type MIDD. This is a new and extremely rare entity, and the bi-

opsy incidence was reported to be 0.055% (14). Best Rocha et al. (15), by contrast, reported that approximately 1% of cases of biopsy-proven MN had monoclonal IgG deposits. These two newly defined groups had in common monoclonality and membranous features with subepithelial dense deposits, and the pathology of our case resembled that of these cases. However, the pathophysiology and points of distinction remain to be fully clarified.

Our case may suggest one possibility. Some of the patients who are initially diagnosed with MN may present with monoclonal IgG deposits detected by the use of staining for κ and λ light chains and electron microscopic analyses, as observed in the present case. This is supported by the report by Best Rocha et al. (15), as discussed above. Therefore, the prevalence of immunohistochemistry for κ and λ staining will help physicians accurately diagnose PGNMID in patients without conspicuous mesangial proliferation rather than make a rushed diagnosis of membranous nephropathy. Furthermore, our findings in this case will spark a more profound discussion regarding this disease.

In conclusion, we encountered a patient with nephrotic syndrome caused by PGNMID complicated with SCLC. Our patient was challenging to diagnose, as this was a very rare case of nephrotic syndrome with monoclonal Ig deposits complicated by malignancy; however, there may be more cases of nephrotic syndrome presenting with monoclonal Ig deposits with membranous features. Therefore, our case sheds renewed light on the importance of kidney pathology for determining the true pathophysiology of MN by performing detailed histological analyses to distinguish κ and λ light chains and using electron microscopy, particularly in patients with monoclonal IgG deposits.

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

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