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【 CASE REPORT 】

POEMS Syndrome with Biclonal Gammopathy and Renal Involvement

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Abstract:

Polyneuropathy, Organomegaly, Endocrinopathy, M-protein and Skin changes (POEMS) syndrome manifests as elevated levels of vascular endothelial growth factor (VEGF) and monoclonal gammopathy. We treated a case of POEMS syndrome showing monoclonality in both IgA-λ and IgG-κ. Serial renal biopsies before treatment and after normalization of the VEGF levels suggested that glomerular microangiopathy had developed due to VEGF, while biclonal gammopathy was not eliminated. The renal pathology, proteinuria, and renal function all clearly improved. Although severe polyneuropathy limited activities of daily living and enforced a bedridden state, the patient dramatically regained his motor function, achieving crutch walking after induction of remission. This case is highly notable due to the presence of biclonality and repeated biopsies.

Key words: proteinuria, POEMS syndrome, polyneuropathy, VEGF, biclonal gammopathy

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Introduction

Polyneuropathy, Organomegaly, Endocrinopathy, M-protein and Skin changes (POEMS) syndrome is characterized by elevated levels of vascular endothelial growth factor (VEGF) and multiorgan involvement in the form of polyneuropathy, organomegaly, endocrinopathy, monoclonal gammopathy, and skin changes (1, 2). Among these, the identification of polyneuropathy is essential to reach the diagnosis and is a significant symptom in POEMS syndrome. Renal involvement in this disease has been well described, and membranoproliferative glomerulonephritis (MPGN)-like lesions, microangiopathic lesions, and mesangiolytic lesions are usual pathological manifestations (3) but are often overlooked, as renal involvement is not necessarily included among the diagnostic criteria or is not considered among the dominant characteristics of POEMS syndrome. Some studies have indicated pathogenic roles of interleukin (IL)-6 and VEGF in POEMS syndrome, particularly with regard to the intrarenal pathological changes and the fact that no characteristic or specific pattern of immunoglobulin deposition is usually seen in glomeruli (4-6).

Biclonal gammopathy is rarely shown in multiple myeloma (MM) and POEMS (7, 8). Light chains may be responsible for the development of specific features of POEMS syndrome, and most case series and examinations using genetic approaches have shown a critical contribution of λ-chains to the development of POEMS syndrome (9, 10). Rare cases involving κ-type POEMS syndrome present with MPGN-like changes (11), but the role of gammopathy in the pathogenesis of POEMS syndrome is not yet fully understood.

We encountered a case with renal involvement of POEMS syndrome with biclonal gammopathy comprising IgA-λ and IgG-κ and performed repeated renal biopsies before and after treatment.

Case Report

An 80-year-old man visited our hospital for the investigation of severe and prolonged polyneuropathy and leg edema.

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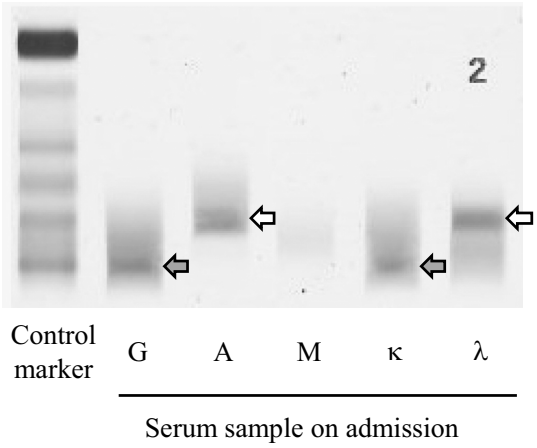


Figure 1. Result of immunofixation electrophoresis. Serum immunofixation electrophoresis reveals IgG-κ (gray arrows) and IgA-λ (white arrows) biclonal gammopathy.

His medical history was unremarkable, and he had worked daily as an engineer. He had experienced gradual weakness over a period of eight months, resulting in reduced activities of daily living. Leg edema and pleural effusion were subsequently observed. Two months prior to admission, the patient had visited another hospital for the investigation of edema and pleural effusion, but no definitive diagnosis had been reached. On admission to our department for further investigations, his physical status had substantially declined to performance status 3, and he was using a wheelchair but needed assistance with moving around and daily meals. On admission, his body temperature was 37.6℃, blood pressure was 135/76 mmHg, and heart rate was 90 beats/min. Some spots of hemangioma were seen on the skin of his chest.

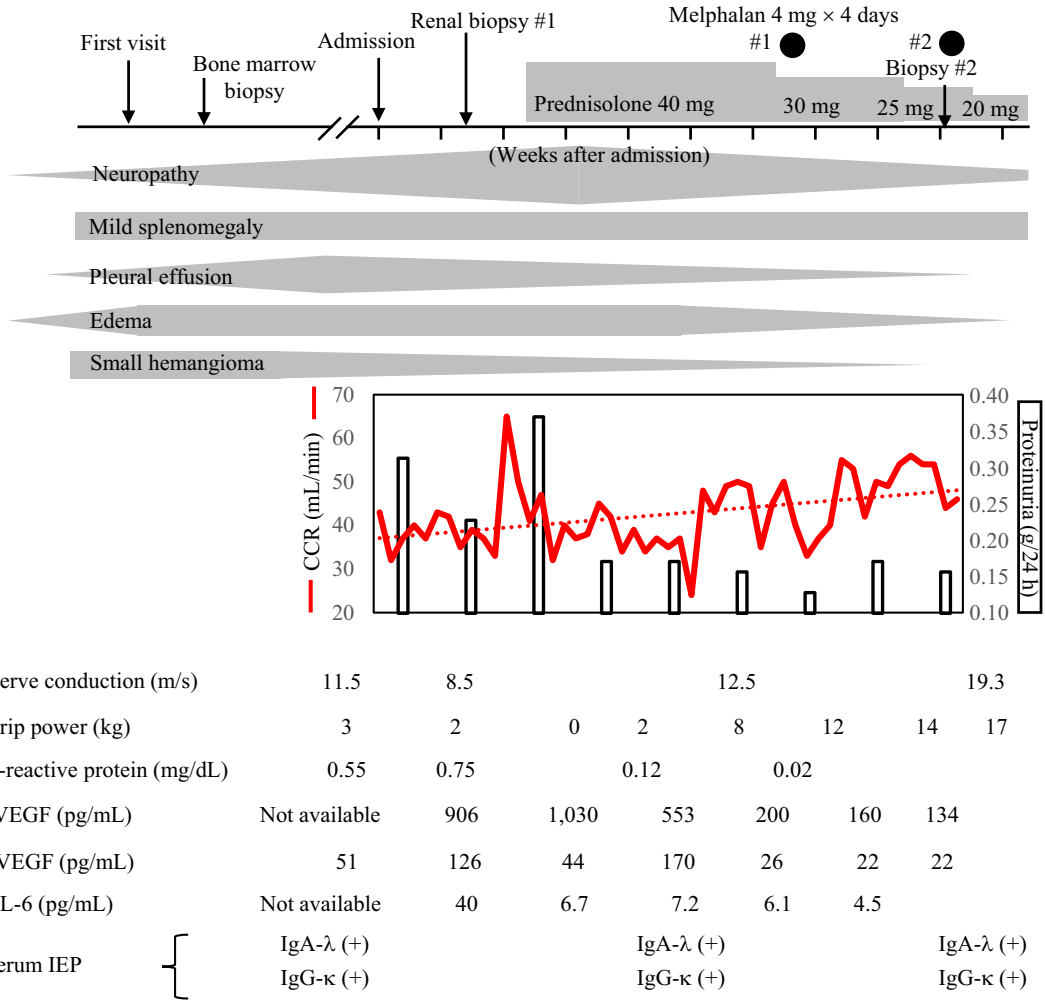
Laboratory studies showed moderate proteinuria (0.5 g/gCre) with no evidence of Bence-Jones proteins or hematuria. A hematological examination showed the following: hemoglobin, 9.2 g/dL; and platelet count, 10.2×10^4/μL. Mild renal impairment was apparent, as follows: serum creatinine, 1.07 mg/dL; estimated glomerular filtration ratio, 51.2 mL/min/1.73 m^2. C-reactive protein was slightly elevated (0.75 mg/dL), suggesting systemic inflammation. Serum IgA levels were increased (480 mg/dL), while IgG and IgM levels were within the reference limits (1,354 and 92 mg/dL, respectively). Complements C3 and C4 were within normal ranges, and anti-nuclear antibody, anti-neutrophil cytoplasmic antibody, and anti-glomerular basement membrane antibody findings were all negative. Immunofixation electrophoresis (IEP) revealed the bands as IgG-κ and IgA-λ, with these findings on admission matching those obtained at the previous hospital 1 month before this admission (Fig. 1). Both serum free light chain-κ and light chain-λ values were increased (250 mg/L and 140 mg/L, respectively), and the κ/λ ratio was slightly higher (1.78) than the normal limit (1.65). Maximum levels of serum IL-6, serum VEGF, and plasma VEGF were significantly elevated, at 40.0 pg/mL (normal upper limit, 7.0 pg/mL), 1,030 pg/mL (normal range not indicated), and 170 pg/mL (normal upper limit, 40 pg/mL), respectively. Screening of hormonal disorders detected elevation of prolactin at 26.1 ng/mL (normal, 4.3-13.7 ng/mL).

Nerve conduction testing was performed, but most leads yielded results below sensitivity, as his peripheral neuropathy had extremely progressed. Only one lead showed a result, confirming prolonged distal motor latencies, slowed nerve conduction velocities, and decreased compound muscle action potential amplitudes, compatible with diffuse peripheral sensorimotor polyneuropathy with demyelinating features and mixed with subsequent axonal changes. A bone marrow biopsy revealed mild infiltration of plasma cells with a normal immune phenotype and a frequency of 5-10% among total cells, so MM was excluded at that time. Skin and gastric biopsies were performed, and no evidence of amyloidosis was seen.

After admission, polyneuropathy worsened to the point of requiring complete bedrest, and nerve conduction gradually slowed. Furthermore, the patient continuously exhibited mild proteinuria, and a reduced renal function was indicated (Fig. 2). He was examined by a renal biopsy on day 10 of admission. Of the 23 glomeruli harvested, 5 showed global sclerosis. Diffuse global mesangiolysis, diffuse segmental double contour of glomerular capillary loops, and moderate glomerular enlargement (200 μm) were shown. Although hypercellularity was not shown in mesangial or endocapillary lesions, endothelial cell hypertrophy was obvious and resulted in a reduced diameter of the capillary lumen (Fig. 3A-C). Thrombotic microangiopathy (TMA)-like lesion formation was suggested due to the abnormal hyperpermeability of the glomerular endothelium, the cause of which was unclear. However, no thrombotic lesions were found in the specimen. Immunofluorescence studies revealed sparse staining for IgG, IgA, κ, and λ (Fig. 3D). No amyloid was identified. The renal pathology of the first biopsy was summarized as glomerular microangiopathy without obvious immunoglobulin deposition.

Given the above findings, the patient was diagnosed as a definitive case of POEMS syndrome based on a diagnostic criteria distributed by the Japan Intractable Disease Information Center (available on https://www.nanbyou.or.jp/entry/241) with renal involvement and biclonal gammopathy, so corticosteroids (oral prednisolone 40 mg, approximately 0.8 mg/kg/day) were administrated as the initial therapy. Following administration of prednisolone, the leg edema and performance status gradually improved week by week. The mild fever and proteinuria diminished, the level of C-reactive protein was normalized, and the serial measurement of IL-6 and VEGF also indicated the effectiveness of corticosteroid treatment (Fig. 2). To reduce the corticosteroid dose and eliminate possibly biclonal immunoglobulin-producing plasma cells, we decided to add the cytotoxic reagent melphalan at 4 mg/day for 4 days at monthly intervals.

Three weeks after the first administration of melphalan, we performed a second renal biopsy to obtain definitive evi-



Nerve conduction (m/s)	11.5	8.5			12.5			19.3
Grip power (kg)	3	2	0	2	8	12	14	17
C-reactive protein (mg/dL)	0.55	0.75		0.12		0.02		
sVEGF (pg/mL)	Not available	906	1,030	553	200	160	134	
pVEGF (pg/mL)	51	126	44	170	26	22	22	
sIL-6 (pg/mL)	Not available	40	6.7	7.2	6.1	4.5		
Serum IEP	IgA-λ (+) IgG-κ (+)			IgA-λ (+) IgG-κ (+)				IgA-λ (+) IgG-κ (+)

Figure 2. Clinical features and course of the case. POEMS syndrome is definitively diagnosed based on the progressive polyneuropathy, biclonal gammopathy (in IgG-κ and IgA-λ; Fig. 1), and elevated serum levels of VEGF. Complications, such as edema, pleural effusion, and organomegaly, support this diagnosis. The creatinine clearance and quantitative proteinuria were calculated using 24-h collected urine. Results of nerve conduction tests and grip power tests reflect the severity and recovery of polyneuropathy. Serum and plasma levels of VEGF declined promptly after treatment. Serum immunofixation contentiously detected biclonal gammopathy. IEP: immunofixation electrophoresis, VEGF: vascular endothelial growth factor

dence of remission of POEMS beyond measurement of proteinuria and serum levels of VEGF. Renal pathology indicated the attenuation of endothelial cell hypertrophy (Fig. 4A-C) and sparse deposition of immunoglobulins (Fig. 4D). Despite clinical and pathological improvement of POEMS syndrome, serum biclonality of IgG-κ and IgA-λ remained evident (Fig. 4E). Treatment was tapered to 25 mg of corticosteroid and melphalan without any exacerbations of neuropathy or nephropathy, and the patient finally achieved drastic improvement of his motor function and was able to walk with crutch. He was discharged on hospital day 71.

Discussion

The renal involvement seen with POEMS syndrome has been clarified to mostly present as glomerular microangiopathy and amyloidosis. Membranoproliferative properties and endothelial damage are the findings most commonly detected from a renal biopsy specimen on light microscopy (12). In our case, no amyloid was detected, but findings were pathologically compatible with microangiopathy. Renal injury is generally mild in POEMS syndrome, and only about 9% of patients usually have urinary protein ≥0.5 g/day and serum creatinine >1.5 mg/dL (13). Regarding these renal features of POEMS syndrome, our patient was considered to show a typical clinicopathological presentation, aside from the presence of biclonal gammopathy.

In POEMS syndrome, >80% of patients have monoclonal gammopathy with IgG-λ or IgA-λ (5, 8). Conversely, very few reported cases have shown biclonal gammopathy as a combination of IgG and IgA (14, 15) or IgG-κ/IgG-λ (16). One possible reason for this is that the biclonal gammopathy was incidental, as a unifying feature of POEMS cases is the

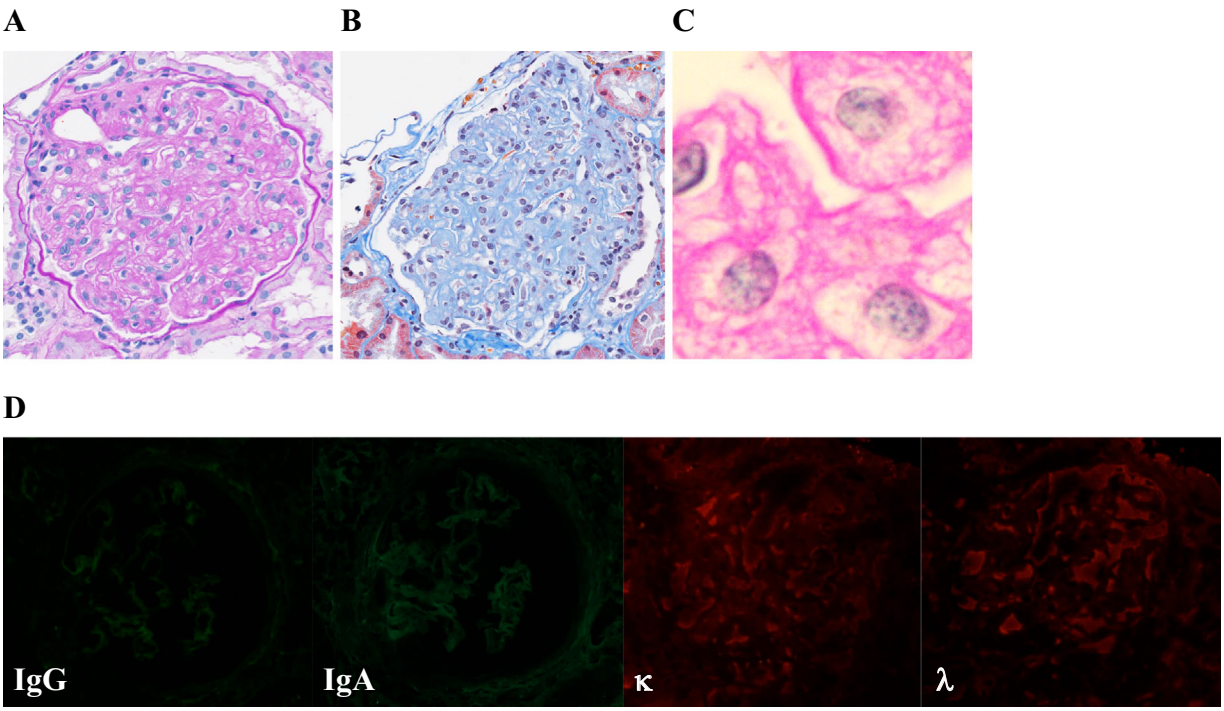


Figure 3. Renal pathological findings before treatment. Light microscopy of hypertrophic glomeruli shows narrowing of glomerular capillary loops by periodic acid-Schiff staining (A, C) and Masson's trichrome staining (B). High-power view using an oil immersion lens (C). Immunofluorescence studies revealed sparse staining for IgG, IgA, κ, and λ (D).

presence of monoclonal serum against a polyclonal background, and more than one monoclonal immunoglobulin may be present (6, 8). Nevertheless, those previous cases of biclonal POEMS syndrome did not show any renal involvement, so the presentation of our case might therefore be very informative.

Light chains may be responsible for the development of specific features of POEMS syndrome, which is generally associated with λ light chain restriction (9, 10), although its role in the pathogenesis of POEMS syndrome remains poorly understood (17). Currently, no evidence suggests which deposition of light chains is responsible for renal involvement, as the research materials obtained have been bone marrow. Our case showed the faint deposition of both κ and λ light chains in glomeruli of the biopsy specimen before treatment and suggest no dominance of direct renal significance between IgG-κ and IgA-λ. Recovery of endothelial cell hypertrophy and the improved diameter of capillary lumens at the second biopsy in this case suggested that these improvements were concurrent with reductions in levels of IL-6 and VEGF following mild corticosteroid treatment and low-dose melphalan. We are therefore convinced that IL-6 and VEGF were indispensable for the development of renal pathological changes in this case, even though biclonal gammopathy and plasma cells were not completely eliminated in this POEMS patient (Fig. 4).

Polyneuropathy in POEMS syndrome is a major and essential symptom, often leading to a bedridden state in severe cases. The most appropriate way of measuring a patient's renal function needs some consideration due to fluctuations in physical condition. As the eGFR correlates with the muscle mass, this value may result in overestimation, as muscle metabolism can dynamically alter with immobilization and rehabilitation during hospitalization. Although most reports in the literature only examined the serum creatinine concentration (4, 5), the creatinine clearance and proteinuria should be calculated based on the 24-h collected urine. According to reliable examinations of the renal function and proteinuria, treating this patient with moderate-dose corticosteroid followed by the alkylator melphalan seemed clinically sufficient.

Regarding disease entities, this case was partially compatible with TAFRO syndrome, which is characterized by thrombocytopenia (T), anasarca (A), fever (F), reticulin fibrosis (R), organomegaly (O), and elevated IL-6 levels (18). No consensus concerning the relationship between TAFRO syndrome and POEMS syndrome has yet been developed. Renal biopsy results have rarely been shown for TAFRO cases, as severe thrombocytopenia occasionally occurs, making it difficult to perform kidney biopsies in patients with TAFRO syndrome (19). Nevertheless, recent case reports and case series have suggested that MPGN-like changes and TMA-like lesions may be characteristic findings in TAFRO syndrome with renal involvement (18-20). Some reports have indicated that the clinical manifestations of TAFRO and POEMS syndromes may overlap (21). Based on our judgment, polyneuropathy was the critical and predominant disorder and a determinant of the prognosis in this case, so

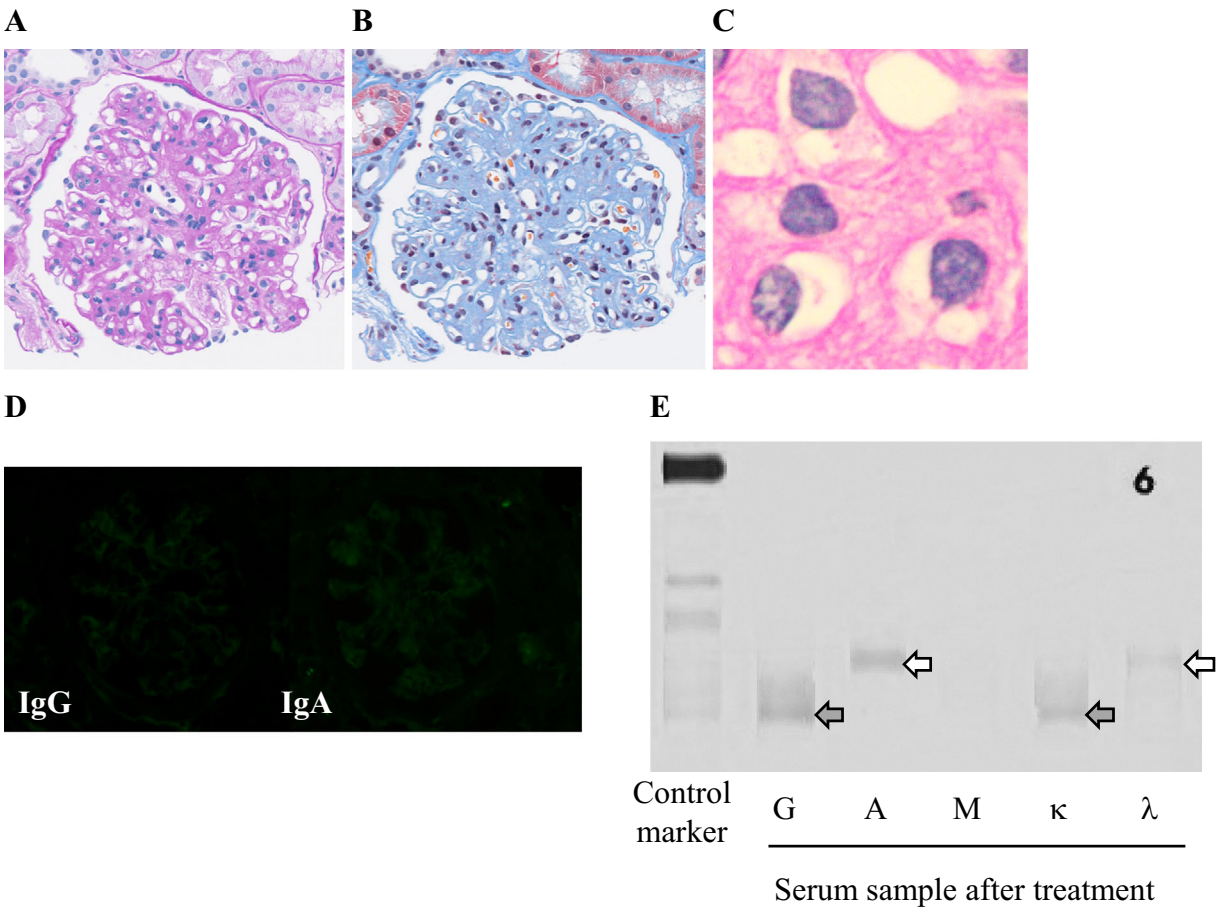


Figure 4. Renal pathology and immunofixation electrophoresis after treatment. The resolution of narrowed glomerular capillary loops following treatment is shown by periodic acid-Schiff staining (A, C) and Masson's trichrome staining (B). C: High-power view using an oil immersion lens. D: Immunofluorescence staining for IgG, IgA. E) Serum immunofixation electrophoresis shows that biclonal gammopathy of IgG-κ (gray arrows) and IgA-λ (white arrows) remain after induction therapy.

POEMS syndrome was differentially diagnosed.

To our knowledge, this is the first report to show the renal pathology of POEMS syndrome with biclonal gammopathy. With suppression of IL-6 and VEGF by corticosteroids and melphalan, the renal clinicopathological involvement was dramatically attenuated along with polyneuropathy, despite biclonal gammopathy remaining. Even when serum biclonal proteins are recognized in patients, concomitant or "incidental" MGUS is likely to be diagnosed (8). In such situations, a renal biopsy can provide clues for an accurate diagnosis and can lead to the definitive diagnosis and treatment of POEMS.

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

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