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KM55 Monoclonal Antibody and IgA Variant of Proliferative Glomerulonephritis With Monoclonal Ig Deposits

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Received 9 January 2020; revised 8 March 2020; accepted 16 March 2020; published online 30 March 2020

Kidney Int Rep (2020) **5,** 946–950; https://doi.org/10.1016/j.ekir.2020.03.018

INTRODUCTION

Proliferative glomerulonephritis with monoclonal IgG deposits (PGNMID) is characterized by monotypic IgG deposition, most commonly IgG3-κ. Monoclonal Ig, albeit less commonly, may also consist of IgM, or rarely IgA, with κ- or λ-light chain restriction. Recently, a multicenter study including 14 patients and a few case reports described the possibility of a monoclonal IgA variant of PGNMID.[1–9,S1] IgA nephropathy (IgAN) is frequently seen worldwide, and galactose-deficient IgA1 (Gd-IgA1) has been identified as the key pathogenic factor in IgAN. Owing to the increased affinity of polymeric IgA λ binding to mesangial cells,[S2] a certain ratio of light chain–restricted primary IgAN (especially λ-restricted) was observed, which makes it difficult to differentiate between light chain–restricted primary IgAN and IgA variant of PGNMID using routine immunofluorescence (IF). To the best of our knowledge, this is the first report of 2 cases of IgA variant of PGNMID (IgA-λ) that exhibited membranoproliferative glomerulonephritis with negative Gd-IgA1-specific monoclonal antibody (KM55) staining. However, KM55 monoclonal antibody was positive in other λ-restricted primary IgAN, suggesting that the staining of KM55 monoclonal antibody could be a powerful tool to differentiate between monoclonal IgA variant of PGNMID and light chain–restricted primary IgAN.

CASE PRESENTATION 1

A 49-year-old female patient visited our clinic on April 9, 2019, because of edema of bilateral lower extremities for 1 week. She underwent treatment with angiotensin-converting-enzyme inhibitor and some Chinese medicine. During the course of the disease, she had no complaints of skin rashes, arthralgia, blurred vision, chest tightness, or gastrointestinal symptoms. She reported a history of hypertension for 1 year, no history of diabetes mellitus or recent infection, and no other family history of renal disease. Physical examination revealed normal body temperature (36.9 °C), blood pressure (120/75 mm Hg), heart rate (85 beats per minute), and body mass index (22.94 kg/m^2). Her bilateral lower extremities appeared to show pitting edema.

Investigations were indicative of nephritic range of proteinuria (24-hour proteinuria: 2.56 g) and microhematuria (3+). Renal function was normal (serum creatinine level: 55 μmol/l), serum albumin was 33.8 g/l and serum complement 3 (C3) level was low (0.63 g/l). Liver function, hepatitis, HIV, and syphilis tests were negative. Immunology tests (double-stranded DNA, antinuclear antibody, anti-neutrophil cytoplasmic antibody, antistreptolysin O, and rheumatoid factor) were normal. Inflammatory markers, such as C-reactive protein and procalcitonin, were negative. Serum and urinary protein immunoelectrophoresis showed IgA-λ monoclonal paraprotein. Abdominal ultrasound detected normal size and morphology of the kidneys bilaterally.

A kidney biopsy was performed. On light microscopy, the specimen contained 2 cores with 28 glomeruli, 4 of which showed global sclerosis and 5 showed segmental sclerosis. The remaining glomeruli showed a severe increase in mesangial matrix and cellularity. There was diffuse endocapillary hypercellularity with extensive duplication of the glomerular

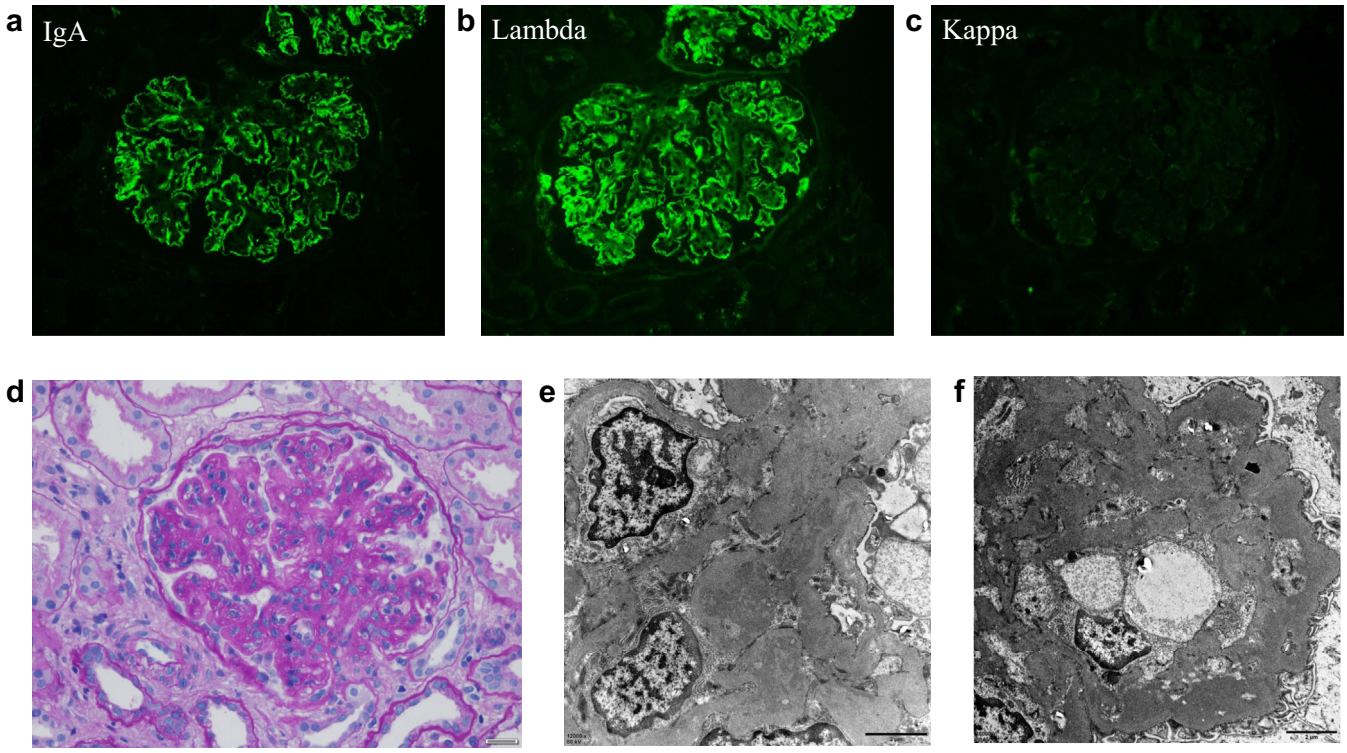

Figure 1. Renal biopsy of case 1. (a–c) Glomerular capillary loop and mesangial staining for IgA (3+) and λ-light chain (3+) was seen on immunofluorescence. No significant staining was noted for κ-light chain (original magnification ×400). (d) Marked mesangial and endocapillary hypercellularity with a lobular appearance and double contours of the glomerular basement membrane were shown on periodic acid–Schiff stain (original magnification ×400). (e,f) On electron microscopy, massive mesangial and subendothelial deposits were found. Foot processes showed segmental effacement (e, original magnification ×12,000; f, original magnification ×10,000).

basement membrane, along with a large number of subendothelial and mesangial deposits. No crescentic lesion or fibrinoid necrosis was seen. Patchy interstitial fibrosis and minimal inflammation were noted in the interstitium. Mild tubular atrophy was observed. Congo red staining for amyloid was negative. On IF, glomerular capillary loop and mesangial staining for IgA (3+), IgM (trace), C3 (2+), and λ-light chain (3+) was seen. No significant staining was noted for IgG, C1q, or κ-light chain. On electron microscopy (EM), massive mesangial and subendothelial deposits were found. No organized structure deposits were identified (Figure 1). Therefore, a diagnosis of IgA-variant PGNMID was suspected. Furthermore, double staining with anti-IgA polyclonal antibody and KM55 monoclonal antibody was performed on this biopsy specimen. Gd-IgA1, detected by KM55 monoclonal antibody (Immuno-Biological Laboratories, Fujioka, Japan), was negative in the glomeruli, but clearly localized to a pattern similar to that of IgA in the cytoplasm of proximal tubular epithelial cells (Figure 2). Finally, the patient was diagnosed as IgA-variant of PGNMID. She refused to undergo bone marrow aspiration and other additional detection tests. Treatment with angiotensin-converting-enzyme inhibitor and the Chinese medicine was continued; however, there was no improvement during the 8-month follow-up period.

CASE PRESENTATION 2

A 39-year-old man with no significant past medical history was admitted in our hospital owing to acute onset of edema. Physical examination showed no other positive signs, expect for edema of bilateral lower extremities. Laboratory evaluation showed that his serum creatinine level was 67.2 μmol/l, 24-hour urine protein was 4.9 g, and serum albumin level was 34.8 g/l. Microhematuria (1+) was indicated by urinalysis. Extensive laboratory findings, including serum complement levels, double-stranded DNA, antinuclear antibody, anti-neutrophil cytoplasmic antibody, rheumatoid factor, hepatitis B and C, HIV, syphilis, serum and urine immunofixation, and serum free light chain ratio, were within the normal ranges. Computed tomography did not show hepatosplenomegaly or lymphadenopathy, whereas bone marrow aspiration and biopsy showed myelodysplasia with 2% plasma cells, which did not exhibit any abnormal clonal population in flow cytometry.

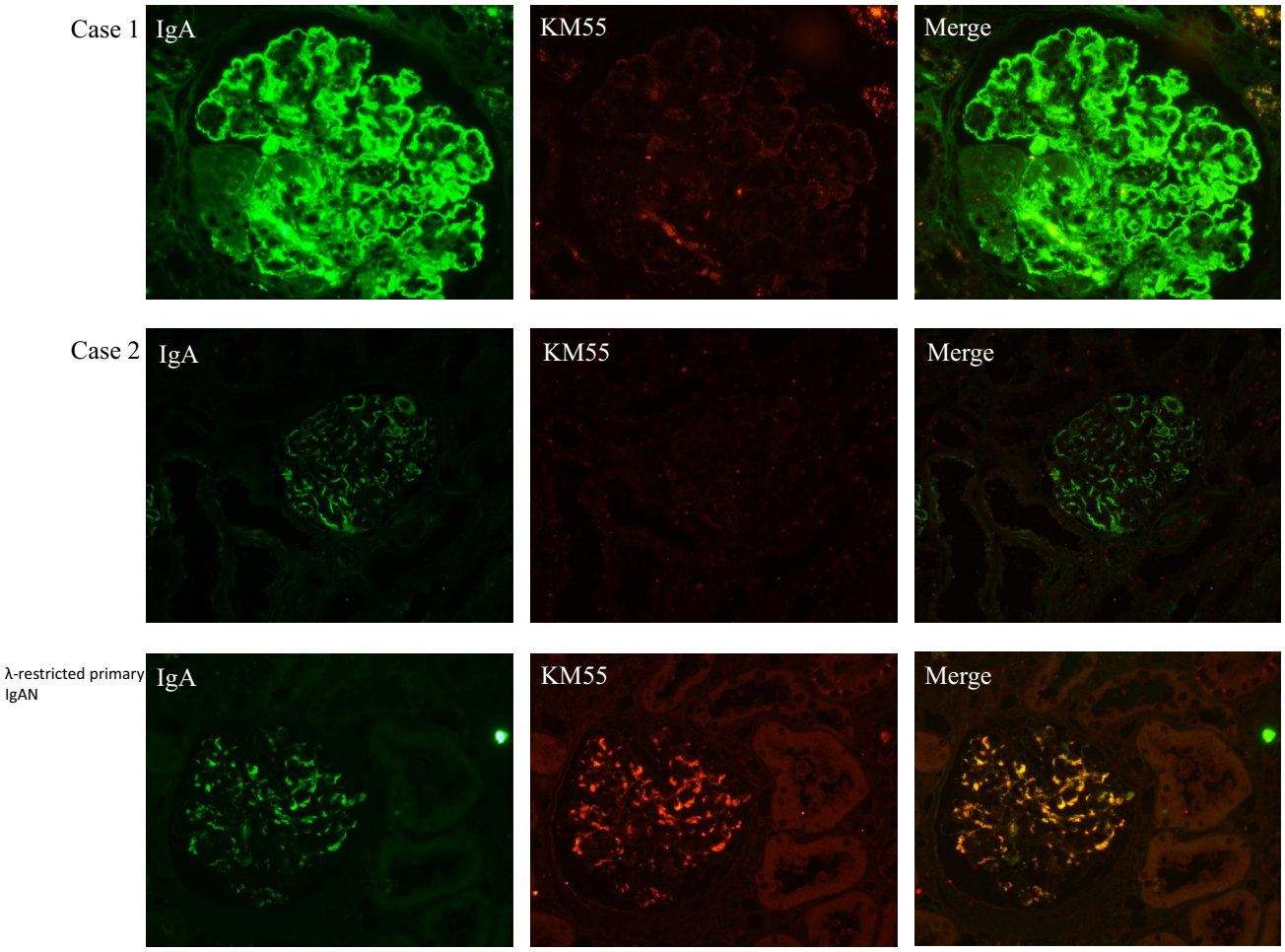

Figure 2. KM55 monoclonal antibody staining in IgA variant of proliferative glomerulonephritis with monoclonal IgG deposits (PGNMID) and λ-restricted primary IgA nephropathy (IgAN). Double staining with anti-IgA polyclonal antibody and KM55 monoclonal antibody was performed on biopsy specimens from 2 patients with IgA variant of PGNMID and 1 patient with λ-restricted primary IgAN. KM55 monoclonal antibody staining was negative in the glomeruli in cases of IgA variant of PGNMID, whereas it was positive in patients with λ-restricted primary IgAN (case 1, original magnification ×400; case 2, original magnification ×200; λ-restricted primary IgAN, original magnification ×200).

Kidney biopsy was performed. The biopsy sampled the kidney cortex with a total of 29 glomeruli. One glomerulus showed global sclerosis, and one showed segmental sclerosis. Segmental double-contour appearance of the glomerular basement membrane with mild mesangial proliferation was seen in a minority of the glomeruli. There was mild tubular atrophy and interstitial fibrosis, accompanied by a minimal interstitial inflammatory infiltrate composed of mainly lymphocytes. Endocapillary hypercellularity was occasionally seen. Chunky mesangial and capillary loop staining for IgA (3+), IgM (1+∼2+), C3 (+), C1q (+), and λ light chain (3+) was shown on IF. Subendothelial and mesangial deposits were seen on EM (Figure 3). Further study showed negative glomerular KM55 staining for this patient (Figure 2). Subsequently, the patient was diagnosed as proliferative glomerulonephritis with monotypic IgA-λ deposits. He was treated with 4 courses of rituximab, which significantly improved the clinical parameters.

Ten patients with a diagnosis of λ-light chain–restricted primary IgAN were enrolled. The diagnostic criteria were as follows: (i) Renal biopsy showed that IgA was the dominant or codominant Ig with lambda light chain restriction in glomeruli, usually accompanied by complement C3, but without C1q deposition on IF. Mesangial hypercellularity and matrix increase with or without crescents was the main pattern on light microscopy, and electron-dense deposits were observed in the mesangial region and/or paramesangial region on EM. (ii) The patients with secondary IgAN, such as IgA vasculitis, chronic liver disease, chronic infections, autoimmune disorders, and neoplasms were excluded. The findings of serum and urine immunofixation, serum free light chain ratio, and urinary Bence-Jones protein in these patients were normal, and there was no evidence of monoclonal Ig disease during a long-term follow-up period. (iii) Younger patients with typical symptoms, such as gross/microscopic hematuria and nephritic-range

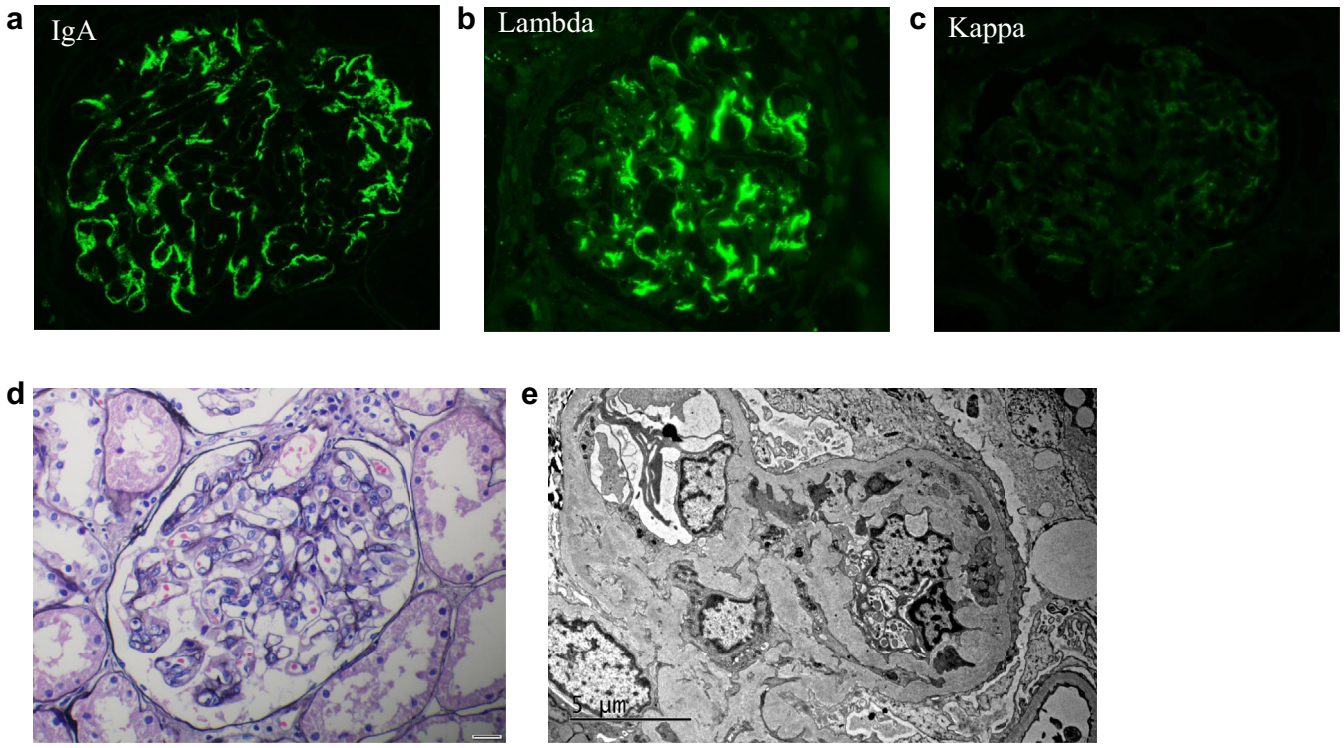

Figure 3. Renal biopsy of case 2. (a–c) Deposits stained with IgA and λ, in a chunky irregular mesangial and capillary loop pattern on immunofluorescence. κ-light chain staining was negative (original magnification ×400). (d) Segmental double-contour appearance of the glomerular basement membrane with mild mesangial proliferation was seen on Jones silver stain (original magnification ×400). (e) Subendothelial and mesangial deposits were seen on electron microscopy. Foot processes showed segmental effacement (original magnification ×5800).

proteinuria, were included. Double staining of IgA and KM55 was performed in these renal biopsy specimens; KM55 staining was localized predominantly in the mesangial region as IgA deposition (Figure 2).

DISCUSSION

Kidney disease is a common complication of monoclonal gammopathies, which manifests as a wide range of renal lesions. These patterns are mostly determined by the physicochemical characteristics of the pathogenic monoclonal Ig. PGNMID was first described by Nasr *et al.*[S3,S4] as a new entity characterized by proliferative glomerulonephritis caused by glomerular deposits of monoclonal IgG (most commonly IgG3 kappa). Recently, rare cases of renal disorders similar to PGNMID (with monotypic IgA, but not IgG deposits) have been reported, which are known as IgA-PGNMID.[2–9,S1] One-third of the patients with IgA-PGNMID were initially misdiagnosed as IgAN.[1] Light microscopy in these patients showed membranoproliferative, mesangial proliferative, or endocapillary proliferative glomerulonephritis, with or without membranous features. In most cases, EM exhibited nonorganized deposits, typically in a subendothelial and mesangial distribution. A small number of cases showed deposits organized in a paracrystalline lattice-like or microtubular substructure. No case showed deposits involving tubular basement membranes, interstitium, or arteries. In contrast to the immune complex–mediated glomerulonephritis, the glomerular deposits on IF appeared monoclonal staining for a single light chain isotype (the proportion of κ and λ is similar), and a single IgA heavy chain subtype (5 cases were available, 4 patients were IgA1 and 1 patient was IgA2). Clinical presentations included proteinuria, renal insufficiency, and microhematuria. Besides routine explorations, monoclonal IgA was identified in more than half of these cases by more sensitive techniques, such as flow cytometry, molecular

Table 1. Distinct teaching points

IgA-variant PGNMID and a small ratio of primary IgAN could both manifest as light chain restriction. The proportion of κ and λ is similar in PGNMID, whereas the λ-restricted type is commonly seen in the IgAN.
IgA-variant PGNMID mainly shows a membranoproliferative pattern on light microscopy, and IgAN exhibits mesangial proliferation more frequently.
The entity of IgA deposition in primary IgAN and IgA-variant PGNMID is quite different. The staining of KM55 monoclonal antibody might be significant in distinguishing the 2 diseases.

IgAN, IgA nephropathy; PGNMID, proliferative glomerulonephritis with monoclonal IgG deposits.

studies of bone marrow, immunoblot, and polymerase chain reaction analysis of serum/urine.

IgAN is a common disease worldwide, especially in Asian countries. There is a certain ratio of light chain–restricted primary IgAN (especially λ-restricted) owing to the possibility of preferential binding capability of IgA-λ to the mesangial cells,[S2] but it is not related to monoclonal IgA production caused by hematological neoplasms. Previous reports described that light chain–restricted IgA deposition was observed in 0% to 42.2% of patients with IgAN.[S5–S10] A study on 65 patients with primary IgAN revealed that 6 cases (9.2%) had monoclonal IgA deposits (5 IgA-λ type, 1 IgA-κ *type*); however, there was no significant difference in the clinicopathological findings and renal outcomes between patients with monoclonal and polyclonal IgA deposits.[S11] The percentage of λ light chain–restricted primary IgAN was 7.8% ($n = 63$) in our laboratory in the past 2 years, which is similar to that in Japan.[S11] Monoclonal IgA in serum and urine was not found during long-term follow-up in these patients. Therefore, the pathological significance of monoclonal IgA deposits in glomeruli is undetermined, and it is difficult to distinguish monoclonal IgA variant of PGNMID from light chain–restricted primary IgAN by routine IF findings.

Gd-IgA1 has been proposed as an important effector molecule in primary IgAN. Patients with IgAN had significantly higher average Gd-IgA1 levels than those with other renal diseases and nonrenal diseases.[S12] Furthermore, using the KM55 antibody, Suzuki *et al.*[S13] found that Gd-IgA1 was consistently deposited in the mesangial and capillary regions overlapped with IgA deposits in IgAN and IgA vasculitis, whereas KM55 monoclonal antibody staining was negative in other glomerular diseases with and without mesangial IgA deposits. Here, we present 2 patients with membranoproliferative pattern on light microscopy, accompanied with monoclonal IgA-λ on IF. EM revealed electron-dense deposits, mimicking ordinary immune complex glomerulonephritis. Based on these findings, we suspected a diagnosis of IgA variant of PGNMID. It is noteworthy that KM55 was localized predominantly in the cytoplasm of the proximal tubular epithelial cells overlapped with IgA, which indicated that a certain level of Gd-IgA1 existed in the serum of the patient. However, KM55 staining was negative in the glomeruli, which varied from that in patients with confirmed diagnosis of λ-restricted primary IgAN. This result suggested that the IgA1 glycosylation in IgA variant of PGNMID was either normal or altered in a fashion that was different from IgAN.

The present study has several limitations. First, we did not measure the plasma Gd-IgA1 levels in these patients because their blood samples were not collected. Second, we did not use more sensitive techniques, such as serum immunoblot analysis and polymerase chain reaction analysis of Ig heavy chain rearrangement in bone marrow smears.[1] Third, the follow-up period for the 2 patients was not long enough.

CONCLUSION

We reported 2 rare cases of IgA variant of PGNMID with negative KM55 staining in glomeruli, unlike that seen in λ-restricted primary IgAN, suggesting that the staining of KM55 monoclonal antibody might be a useful tool in distinguishing the 2 diseases (Table 1).

DISCLOSURE

All the authors declared no competing interests.

ACKNOWLEDGMENTS

We thank the 2 patients for their consent to the publication of this work.

SUPPLEMENTARY MATERIAL

Supplementary File (PDF)

Supplementary References.

REFERENCES

1. Vignon M, Cohen C, Faguer S, et al. The clinicopathologic characteristics of kidney diseases related to monotypic IgA deposits. *Kidney Int*. 2017;91:720–728.
2. Soares SM, Lager DJ, Leung N, et al. A proliferative glomerulonephritis secondary to a monoclonal IgA. *Am J Kidney Dis*. 2006;47:342–349.
3. Sethi S. Membranous glomerulonephritis with monoclonal immune deposits and crescents. *Nephrol Dial Transplant*. 2005;20:1768–1769.
4. Kaneko S, Usui J, Narimatsu Y, et al. Renal involvement of monoclonal immunoglobulin deposition disease associated with an unusual monoclonal immunoglobulin A glycan profile. *Clin Exp Nephrol*. 2010;14:389–395.
5. Herrmann SM, Govani MV, Fidler ME, et al. Recurrence of monoclonal IgA lambda glomerulonephritis in kidney allograft associated with multiple myeloma. *Clin Nephrol*. 2015;84:241–246.
6. Horino T, Ichii O, Terada Y. IgA-proliferative glomerulonephritis with monoclonal immunoglobulin deposits. *Am J Med*. 2019;132:e542–e545.
7. Kitazawa A, Koda R, Yoshino A, et al. An IgA1-lambda-type monoclonal immunoglobulin deposition disease associated with membranous features in a patient with IgG4-related kidney disease: a case report. *BMC Nephrol*. 2018;19:330.
8. Singh G, Bhardwaj S, Singh L, et al. Proliferative glomerulonephritis with monotypic IgA-kappa deposits in a 10-year-old. *Kidney Int*. 2017;92:765–766.
9. Okabayashi Y, Tsuboi N, Nakaosa N, et al. A case of hepatic glomerulosclerosis with monoclonal IgA1-kappa deposits. *Case Rep Nephrol*. 2018;2018:4748357.