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KM55 in the Evaluation of IgA-Containing Glomerular Diseases

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Keywords
KM55 · IgA · Galactose-deficient IgA · IgA nephropathy · Membranoproliferative glomerulonephritis

Abstract
Introduction: Mucosal-derived galactose-deficient IgA is central to the pathogenesis of primary IgA nephropathy (IgAN). Recent reports suggest similar pathogenesis in Henoch-Schonlein purpura (HSP) and secondary IgAN. Its role in other IgA-containing glomerular diseases is still under investigation. It can be detected in glomeruli with the recently described antibody KM55. We aimed to evaluate the role of KM55 by immunostaining a wide spectrum of IgA-containing glomerular diseases. ***Methods:*** After standardization and colocalization in a case of IgAN, a spectrum of 60 cases including IgAN, HSP, chronic liver disease (CLD)-related IgAN, other secondary IgAN, IgA-dominant/codominant membranoproliferative glomerulonephritis (MPGN), and lupus nephritis were subjected to immunofluorescence with KM55. KM55 was used to resolve diagnostic dilemma in cases of IgA deposition with confounding histology. ***Results:*** The group of primary IgAN (17 cases), HSP (4 cases), and secondary IgAN (19 cases) including CLD showed 2–3+ granular staining with KM55, suggesting mucosal-derived IgA. In contrast, cases of IgA-dominant/codominant MPGN (8 cases) and lupus nephritis (12 cases) were negative for KM55, suggesting systemic derivation of IgA. In cases of IgA deposition with confounding histology such as membranoproliferative or diffuse endocapillary proliferative pattern, KM55 helped to resolve the diagnosis. ***Discussion/Conclusion:*** This cross-sectional study concludes that KM55 is useful in the evaluation of IgA-containing glomerular diseases from a pathogenetic perspective and is a practical tool in resolving differential diagnosis in cases with overlapping histopathological features.

Introduction

IgA is an integral part of the routine immunofluorescence (IF) panel in evaluation of glomerular diseases. Though its presence in the mesangium is diagnostic for primary IgA nephropathy (IgAN), it may also accompany other immune reactants in a variety of other glomerular diseases which may present as diagnostic dilemmas.

From a pathophysiological perspective, IgA that deposits in the glomeruli may be secreted by *mucosal* plasma cells or by *systemic* plasma cells. Mucosal plasma cells

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secrete IgA1 or IgA2 which bind to each other to form dimeric or large polymeric forms. These, along with the secretory component of the polymeric IgA receptor form the "secretory IgA," which plays a major role in human mucosal immunity [1]. Mucosal-derived IgA is poorly *O*-galactosylated, likely due to an evolutionary mechanism to counteract the activity of IgA1 proteases released by bacteria trying to circumvent the mucosal immune system. On the other hand, the IgA synthesized in the bone marrow is monomeric in nature, heavily *O*-galactosylated, and in much smaller amounts, with ill-defined function [2].

The mesangial deposits in primary IgAN are composed of galactose-deficient (GD) IgA1 in a polymeric form. This, with the well-recognized clinical observation of association of hematuria with mucosal infections of the upper respiratory or gastrointestinal tract, provides circumstantial evidence of a mucosal origin of IgA in primary IgAN. It is hypothesized that defective trafficking of these mucosal plasma cells into the bone marrow results in an increased systemic production of GD-IgA1 [1, 2]. The plethora of histomorphological variations of IgAN and the presence of codominant IgA deposits in various other glomerular diseases often pose problems in arriving at a diagnosis in glomerular diseases with IgA deposition. Recently KM55, an antibody directed against GD-IgA1 [3, 4], has been evaluated in glomerular diseases with IgA deposition with variable results [5–13]. We aimed to evaluate utility of KM55 in the differential diagnosis of IgA-containing glomerular diseases. We present case scenarios where it was used to resolve differential diagnoses.

Materials and Methods

The study protocol was approved by the Ethics Committee, All India Institute of Medical Sciences, New Delhi (Reference No: IECPG-484/29.11.2017, RT-13/20.12.2017). Cases with significant (2–3+ on a scale of 0–3+) glomerular IgA deposits were identified from the databases of the Department of Pathology, between 2016 and 2020, and those with sufficient tissue for further IF were included in the study.

Cases were divided into IgAN – primary (including Henoch-Schonlein purpura [HSP]) or secondary. The medical records of all cases of primary IgAN were scrutinized to ensure that there is no association with any described secondary causes of IgAN. Other IgA-containing diseases considered for analysis included lupus nephritis, IgA-dominant infection-related glomerulonephritis (IRGN) (IgA-IRGN) and immune complex (IC)-mediated membranoproliferative glomerulonephritis (MPGN) (IC-MPGN). Histological diagnosis and the pattern of glomerular injury along with IF and, when available, electron microscopy of these cases were reviewed. An external cohort of IgAN secondary to chronic liver disease (CLD) was included from the National Reference Laboratory, Lal Path Labs, New Delhi.

The histological diagnosis of *IgAN* as elaborated in the Oxford classification [14] was adhered to as follows: "IgA nephropathy is defined by the presence of IgA-dominant or -codominant immune deposits within glomeruli. Not all glomeruli need to show positivity. SLE nephritis should be excluded. The intensity of IgA staining should be more than trace. The distribution of IgA staining should include the presence in the mesangium, with or without capillary loop staining, excluding a pure membranous, diffuse, global granular glomerular basement membrane staining pattern or a linear glomerular basement membrane (GBM) staining pattern. IgG and IgM may be present but not in greater intensity than IgA, except that IgM may be prominent in sclerotic areas, and C3 may be present. The presence of C1q staining in more than trace intensity should bring up consideration of lupus nephritis." Glomerular patterns of injury including a mesangioproliferative pattern of injury with or without focal segmental glomerulosclerosis and/or endocapillary hypercellularity and/or crescents were noted. Capillary wall reduplication and necrotizing lesions if present were recorded. *IgA-dominant/codominant MPGN* was defined by significant IgA deposits (2–3+) accompanied by classical MPGN morphology including extensive GBM reduplication. *IgA-IRGN* was considered when a diffuse proliferative and exudative pattern of glomerular injury with additional bright C3 IF was noted with the presence of subepithelial humps on electron microscopy. *Lupus nephritis* was classified according to the ISN/RPS 2018 classification and included cases with mesangial and/or capillary wall granular deposits of IgA. It was recognized that many of these entities had overlapping histology, IF, and ultrastructural findings, and the best possible diagnosis was offered with clinicopathological correlation.

KM55 IF was standardized to be performed in our laboratory conditions for formalin-fixed paraffin-embedded tissue sections using a previously published paraffin IF protocol [15]. Briefly, 3-μm FFPE tissue sections were cut on to APTES-coated slides and were dewaxed and treated with proteinase K. Subsequently, the slides were treated with Anti-Human Gd-IgA1(KM55) Rat IgG MoAb (IBL; Code No. 10777) at a concentration of 50 μg/mL and incubated in a moist chamber for 2 h, followed by application of a biotinylated universal secondary antibody and last by streptavidin-conjugated phycoerythrin. The slides were then mounted using glycerol and were viewed using a fluorescence microscope. The intensity of IF was semiquantitatively graded from 0 (complete absence of staining) to 3+ (maximum-observed intensity of staining) by 2 pathologists (R.R. and G.S.).

A colocalization study using double-IF staining was done with KM55 and IgA on the same glass slide. Images were captured using appropriate filters for both fluorochromes and were merged using suitable software (Nikon NIS-Elements). For the negative control, glomerular diseases negative for IgA on IF were chosen.

Results

KM55 staining was standardized in the laboratory, and colocalization with IgA demonstrated on a case of IgAN (Fig. 1).

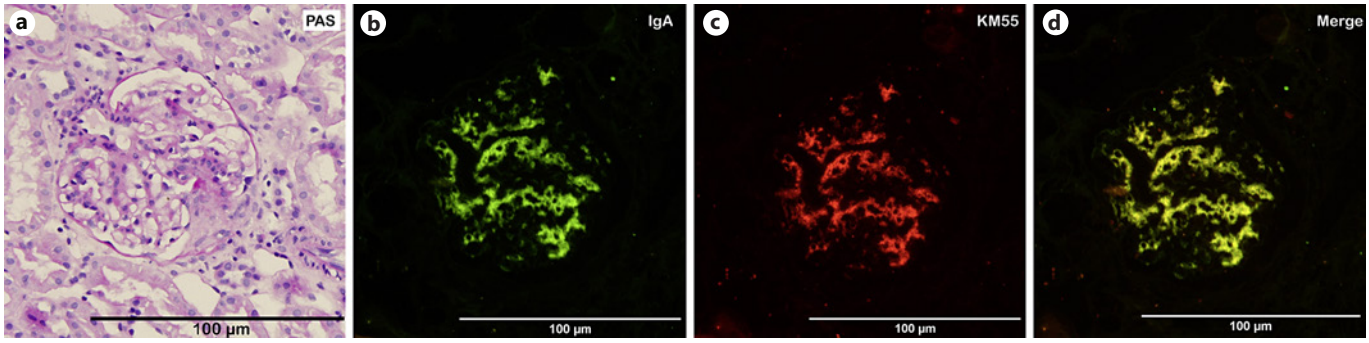

Fig. 1. A case of IgAN with mild mesangial hypercellularity and segmental sclerosis (**a**, periodic acid-Schiff, ×20); 3+ mesangial granular staining for IgA (**b**, IgA-FITC, ×20), and KM55 (**c**, KM55-phycoerythrin, ×20). Colocalization of IgA and KM55 demonstrated on double-IF staining (**d**, IgA-FITC and KM55-phycoerythrin, ×20). IgAN, IgA nephropathy; IF, immunofluorescence.

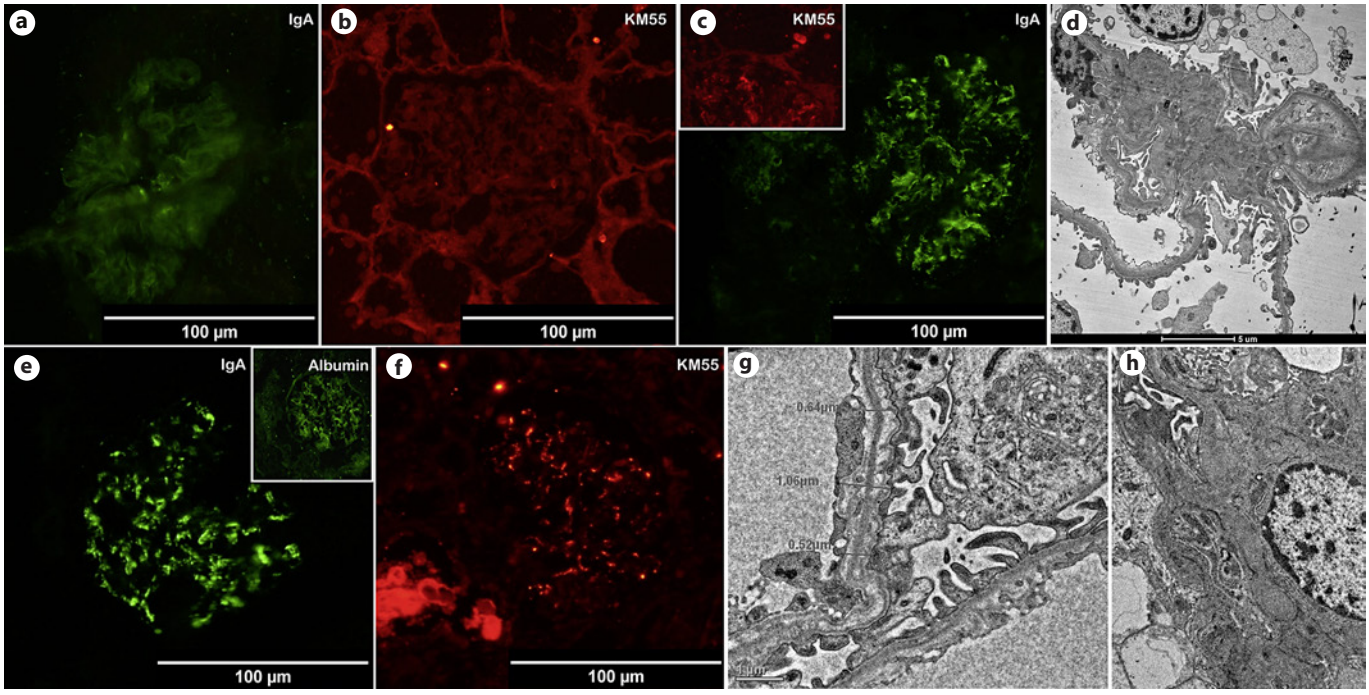

Fig. 2. A case of minimal-change disease with negative IF for IgA (**a**, IgA-FITC, ×20) and KM55 (**b**, KM55-Phycoerythrin, ×20). A case of focal segmental glomerulosclerosis with nonspecific staining pattern for IgA (**c**, IgA-FITC, ×20) and a similar pattern of staining on KM55 (**c**, **inset**, KM55-phycoerythrin, ×20). Electron microscopy performed on the case showed foot process effacement and microvillous transformation. No EDDs were identified (**d**, uranyl acetate-lead citrate, ×940). A case of suspected Alport syndrome with nonspecific staining pattern for IgA (**e**, IgA-FITC, ×20). The **inset** shows IF for albumin with similar staining pattern . Similar discontinuous pattern of staining of KM55 in the case. Also note the positive staining of the hyaline cast (**f**, KM55-Phycoerythrin, ×20). Electron microscopy performed showed GBM thickening with lamellation, rarefaction, and tenting of the external surface (**g**, uranyl acetate-lead citrate, ×2,250), and the mesangium appeared unremarkable without the presence of EDDs (**h**, uranyl acetate-lead citrate, ×2,250). IF, immunofluorescence; GBM, glomerular basement membrane; EDD, electron-dense deposit.

Table 1. Distribution of cases of IgA-containing glomerular disease

Primary diagnosis	Cases, *n*
Primary IgAN*	17
HSP	4
CLD-IgAN	15
Other secondary IgAN	4
IgA-dominant MPGN	8
Lupus nephritis	12
Total	60

IgAN, IgA nephropathy; CLD-IgAN, chronic liver disease-associated IgA nephropathy; HSP, Henoch-Schonlein purpura; MPGN, membranoproliferative glomerulonephritis.

KM55 IF on Non-IgA-Containing Glomerular Diseases

As negative controls, 3 cases of minimal-change disease (Fig. 2a, b), 1 case of focal segmental glomerulosclerosis, 1 case of membranous nephropathy, and 1 case of suspected Alport syndrome were stained. A nonspecific staining pattern was noted in 2 of these proteinuric patients (FSGS Fig. 2c) and suspected for Alport syndrome (Fig. 2e, f), while the rest were completely negative. The observed staining in the 2 cases correlated with nonspecific staining of IgA along with other immunoglobulins on IF. In both cases, lack of electron-dense deposits was confirmed on electron microscopy (Fig. 2d, g, h), with evidence of podocyte effacement and GBM changes of collagenopathy, respectively. This "nonspecific" pattern of KM55 staining was recognized as negative and different from the confluent mesangial granular pattern noted in true cases of IgAN. Nonspecific KM55 staining was also noted in hyaline casts similar to IgA (Fig. 2f). A spectrum of 60 cases of IgA-containing glomerular diseases was then subjected to KM55 IF (Table 1).

Primary IgAN (11 + 6 Cases)

In cases of classic primary IgAN, KM55 staining performed showed 2–3+ confluent mesangial granular staining (scale 0–3+). The cases had classically described histological features including mesangial hypercellularity (10/11), segmental sclerosis (9/11), segmental endocapillary hypercellularity (4/11), and crescents (6/11) with variable tubulointerstitial fibrosis. Confounding histology was noted in 6 cases, 4 of which showed membranoproliferative pattern of glomerular injury, and 2 showed an endocapillary proliferative pattern of glomerular injury, raising the differential diagnosis of IRGN. All 6 cases showed 2–3+ granular staining for KM55. Representative cases from this cohort are described below.

HSP (4 Cases)

Four cases with a clinical diagnosis of HSP were included and showed similar staining pattern of KM55 as primary IgAN (Fig. 3a).

Non-CLD, Secondary IgAN (4 Cases)

These included a case of Sjogren's syndrome, sarcoidosis, and rheumatic heart disease and a case with both rheumatic heart disease and sarcoidosis. All the cases showed significant mesangial granular staining for KM55 (Fig. 3b–d).

CLD-IgAN (15 Cases)

In secondary IgAN, CLD-associated IgAN (CLD-IgAN) formed the largest cohort of 15 cases including cases from both centers. The liver disease was of variable etiologies including hepatitis B, alcohol abuse, etc. In 14 cases (93.33%), 2+ and 3+ confluent mesangial granular staining for KM55 was noted (scale 0–3+) with evidence of capillary wall extension (Fig. 4). In 1 case, staining was 1–2+ variable and limited to the mesangium. Endocapillary proliferative or early membranoproliferative pattern of glomerular injury was frequently seen (13/15 cases, 86.66%). In addition, 2 cases had focal necrotizing lesions, and 3 showed the presence of cellular/fibrocellular crescents. Clinical details, histopathology, IF, and electron microscopy features are included in Table 2.

IgA-Dominant/Codominant MPGN (8 Cases)

On review of cases of IC-MPGN, 8 cases showed significant IgA deposits of 2–3+ intensity in a capillary wall granular and mesangial location. These were accompanied by variable IgG deposits in 6 cases (traces to 3+), IgM in 8 cases (traces to 3+), C3 in 7 cases (1+ to 3+), and C1q in 6 cases (trace to 3+). All cases had polytypic deposits, and there was no evidence of light-chain restriction. On histology, well-developed membranoproliferative features were noted, including lobular accentuation, mesangial hypercellularity, variable endocapillary hypercellularity, and widespread reduplication of the GBM identified on silver methenamine. Cellular/fibrocellular crescents were identified in 2 cases. One case (case 5) showed large subendothelial deposits forming "hyaline thrombi," and cryoglobulinemic glomerulonephritis (GN) was suspected. However, the deposits were unorganized on electron microscopy, and serum cryoglobulin was negative (Fig. 5). All the cases of IgA-dominant/co-

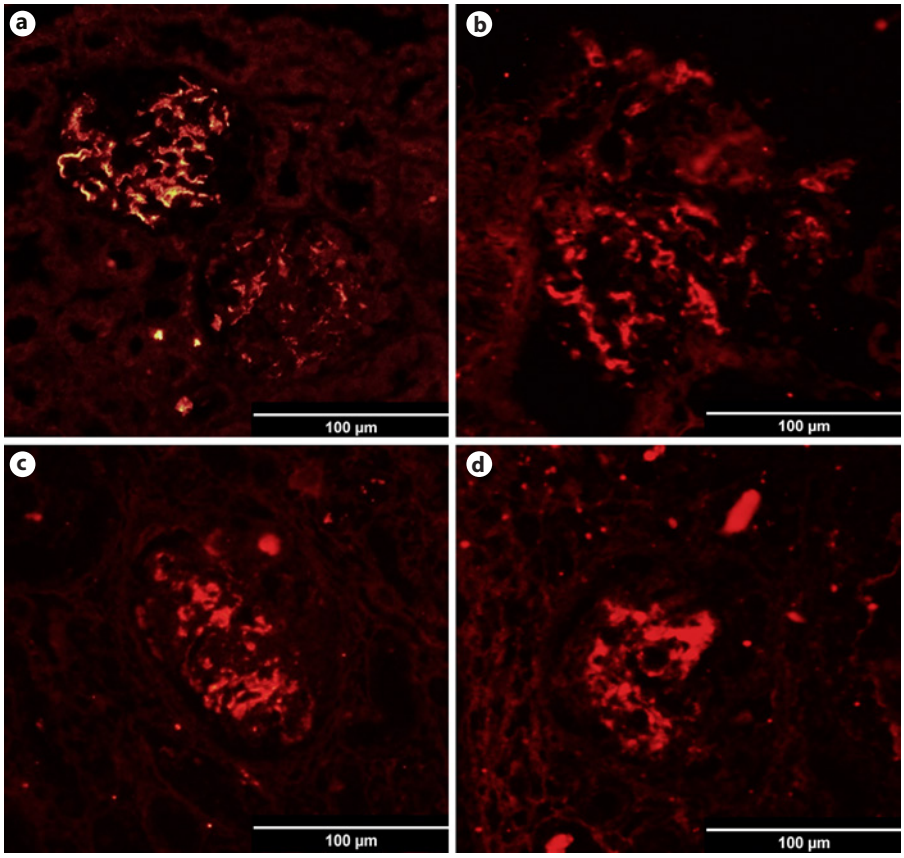

Fig. 3. KM55 IF in a case of HSP (**a**), Sjogren's syndrome (**b**), rheumatic heart disease (**c**), and sarcoidosis (**d**) (KM55-phycoerythrin, ×10). HSP, Henoch-Schonlein purpura; IF, immunofluorescence.

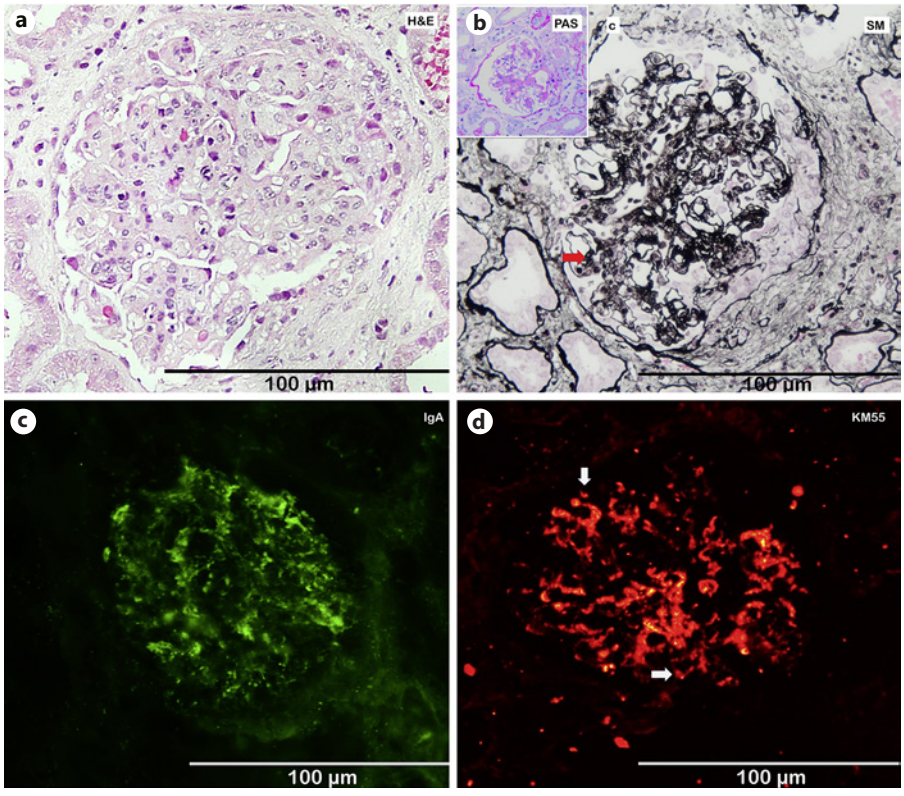

Fig. 4. A case of CLD-IgAN with evidence of endocapillary hypercellularity including neutrophils and a cellular crescent (**a**, hematoxylin-eosin, ×40). On silver methenamine, segmental GBM reduplication is noted (red arrow) (**b**, Jones methenamine silver, ×40), while other glomeruli appear to show only mesangial hypercellularity (**b**, **inset**, PAS, ×20). IF for IgA shows 2+ mesangial granular staining (**c**, IgA-FITC, ×20), and KM55 shows 3+ mesangial granular staining with capillary-wall extension (white arrows) (**d**, KM55-phycoerythrin, ×20). CLD-IgAN, chronic liver disease-associated IgA nephropathy; GBM, glomerular basement membrane; IF, immunofluorescence.

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Table 2. Demographic, clinical, histological, and IF findings in cases of CLD-IgAN

S No.	Age/ sex	Etiology of CLD	Presenting complaints	Serum creatinine, mg/dL	Urine protein strip test/ 24-h protein	Urine RBCs/hpf	Pattern of glomerular injury	Tubulo-interstitial chronicity, %	IgA	IgG	IgM	C3	C1q	Kappa	Lambda	EM	KM55
1	48/M	Unknown	Pedal edema, gross hematuria, and decreased urinary output	1.6	2+/7.3 g	Full field	M + E + N + C	<5	3+ mes and cw	Traces	Traces	1+ mes and cw	Traces	2+ mes and cw	3+ mes and cw	–	2 + mes and cw
2	34/M	HepB	Pedal edema	1.7	2+/5.1 g	20	M + SS + seg GBM reduplication	15	3+ mes and cw	3+ mes and cw	2+ mes and cw	2+ mes and cw	1+ mes and cw	2+ mes and cw	2+ mes and cw	–	3+ mes and cw
3	18/F	EHPVO	Proteinuria detected on evaluation	0.4	2+/1.38	Nil	M + seg GBM reduplication	<5	3+ mes and cw	0	3+ mes and cw	3+ mes and cw	3+ mes and cw	3+ mes and cw	3+ mes and cw	–	3+ mes and cw
4	56/F	NAFLD	Hypertensive for 2 years and pedal edema	2.18	2+/–	12	M + E + C + seg GBM reduplication	30	2–3+ mes and cw	0	3+ mes and cw	3+ mes and cw	0	Traces	3+ mes and cw	–	3+ mes and cw
5*	54/M	HepC	Hypertensive and pedal edema	1.3	2+/–	10	M + E + SS	10–15	3+ mes	0	0	1+ mes	–	3+ mes	3+ mes	Mes, parames, few subendo EDDs	2–3+ mes and cw
6*	28/M	HepB	Pedal edema and anasarca	1.2	3+/–	10–12	M + E + SS + C	15–20	2+ mes and cw	0	0	1+ mes and cw	0	1–2+ mes and cw	2+ mes and cw	Mes, parames EDDs	3+ mes and cw
7*	37/M	Alcohol	Microscopic hematuria	2.65	–/2 g	25–30	M + SS	25–30	3+ mes	0	0	1+ mes	0	1–2+ mes	3+ mes	–	Variable, 1–2+ mes
8*	49/M	HepB	Oliguria	2.6	–/2.58 g	3–5	M + E + N + SS	30–35	3+ mes	0	0	1+ mes	0	1–2+ mes	2+ mes	Mes, parames EDDs	3+ mes and cw
9*	26/M	Unknown	Hepatic encephalopathy	1.9	2+/–	1–2	M + E + SS	25–30	3+ mes	1+ mes	0	0	0	1–2+ mes	3+ mes	–	*2+ mes and cw*
10*	22/F	HepC	Anasarca	1.4	–	–	M + E + seg GBM reduplication + SS + C	20–25	3+ mes and cw	0	0	2+ mes and cw	0	2+ mes and cw	3+ mes and cw	–	2+ mes and cw
11*	35/F	Unknown	Pedal edema and microscopic hematuria	0.7	1+/1.4 g	Full field	M + E + SS + C	10–12	3+ mes	0	0	1+ mes	0	2+ mes	3+ mes	–	3+ mes and cw
12*	31/M	HepB	Hypertension and pedal edema	-	–	–	M + E + SS	10–15	3+ mes	0	0	1+ mes	0	2+ mes	3+ mes	–	3+ mes and cw
13*	30/M	Unknown	Pedal edema, gross hematuria, and renal dysfunction	-	–	–	M + E + SS	25–30	3+ mes	0	0	2+ mes	0	2+ mes	3+ mes	–	3+ mes and cw
14	42/M	Alcoholic	Gross hematuria	3.1	1+/1.69 g	Full field	M + E + seg GBM reduplication + C	20	3+ mes and cw	0	0	3+ mes and cw	0	2+ mes and cw	3+ mes and cw	–	3+ mes and cw
15	42/M	Unknown	Incidentally detected renal dysfunction	1.5	2+/0.7 g	25	M + E+ seg GBM reduplication + SS	30	3+ mes and cw	0	1+ mes and cw	2+ mes and cw	0	0	3+ mes and cw	Mes, subendo and occasional subepithelial EDDs	3+ mes and cw

M, mesangial hypercellularity; e, endocapillary hypercellularity; N, necrotizing lesion; C, crescents; mes, mesangial; parames, paramesangial; subendo, subendothelial; cw, capillary wall; tr, trace; SS, segmental sclerosis; seg, segmental; GBM, glomerular basement membrane; hpf, high-power field; EDD, electron-dense deposit; NAFLD, nonalcoholic fatty liver disease; EHPVO, extrahepatic portal-vein obstruction; Hep C, hepatitis C; Hep B, hepatitis B; –, not available; CLD-IgAN, chronic liver disease-associated IgA nephropathy; RBC, red blood cells; IF, immunofluorescence. *Cases from LalpathLab.

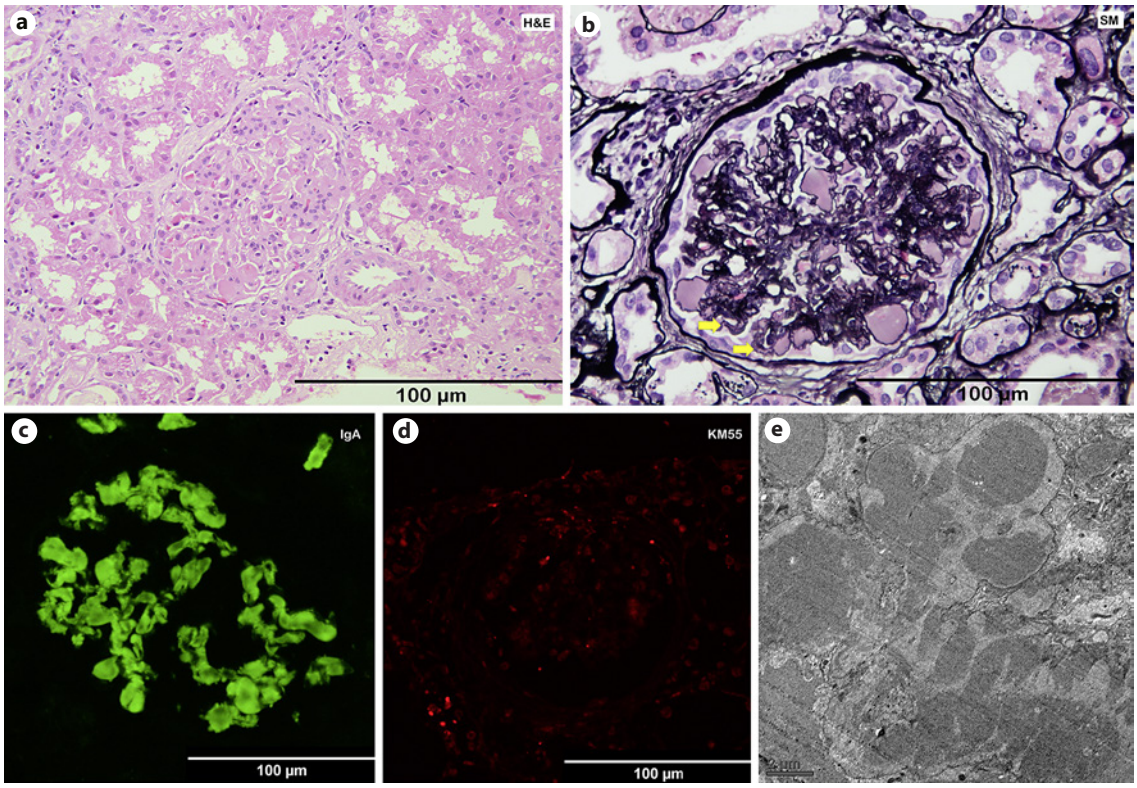

Fig. 5. A case of MPGN with mesangial/endocapillary hypercellularity, irregular capillary-wall thickening, and hyaline thrombi (**a**, hematoxylin-eosin, ×20). Silver-negative large subendothelial deposits with evidence of extensive GBM reduplication noted (**b**, Jones methenamine silver, ×40). IF for IgA shows 3+ staining in the deposits (**c**, IgA-FITC, ×40), while KM55 is negative (**d**, KM55-phycoerythrin, ×20). Immune-type unorganized EDDs are identified in a subendothelial, subepithelial, transmembranous, and mesangial location on electron microscopy (**e**, uranyl acetate-lead citrate, ×2,050). MPGN, membranoproliferative glomerulonephritis; IF, immunofluorescence; EDD, electron-dense deposit.

dominant MPGN were negative for KM55. Clinical details, IF, and electron microscopy features are included in Table 3.

Lupus Nephritis (12 Cases)

Twelve cases of lupus nephritis with sufficient tissue were included. These included class II (2 cases), class IV (7 cases), and class V (3 cases). All cases showed IgA as part of a full-house IF in either mesangial- or capillary-wall location; however, they were negative for KM55.

Diagnostic Dilemmas

Membranoproliferative Pattern of Glomerular Injury

Case 1. A 25-year-old hypertensive male presented with renal dysfunction (serum creatinine – 1.7 mg/dL), nephrotic-range proteinuria (24-h urine protein – 6.5 g and serum albumin – 3.8 g/dL), and bland urinary sediment. Autoimmune workup was negative. Renal biopsy revealed moderate mesangial matrix expansion, mesangial hypercellularity, and irregular capillary-wall thickening with accumulation of subendothelial fuchsinophilic material on staining with Masson trichrome. Silver methenamine stain showed basement membrane reduplication. On IF, capillary-wall and mesangial granular deposits of IgA (3+), IgG (3+), IgM (3+), C3 (2+), C1q (3+), kappa (3+), and lambda (3+) were seen. No tubulovascular deposits were seen. Tissue submitted for EM did not have any glomeruli. KM55 staining showed 3+ confluent mesangial granular deposits (Fig. 6), after which the histological diagnosis was revised from IC-MPGN to IgAN with a membranoproliferative pattern of glomerular injury.

Case 2. A hypothyroid and hypertensive male, aged 72 years, presented with bilateral pedal edema and facial puffiness. Microscopic hematuria was documented with 24-h urine protein of 5.7 g and serum albumin of 2.8 mg/dL. Serum creatinine was 3.1 mg/dL, and anti-neutrophil-

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Table 3. Demographic, clinical, autoimmune, and other basic laboratory parameters, along with histological and IF findings in cases of IgA-dominant/codominant MPGN – KM55-negative

S No.	Age/ sex	Presenting complaints	Serum creatinine, mg/dL	Positive serology (low serum C3, HBsAg, anti HCV Ab, ANA, dsDNA, and RF)	Urine protein strip test/24-h urine protein	Urine RBCs/hpf	IgA	IgG	IgM	C3	C1q	Kappa	Lambda	EM	IS received	Follow-up (duration postbiopsy)
1	6/F	Anasarca	0.1	Nil	2+/1.3 g	8–10	3+ mes and cw	2+ mes and cw	3+ mes and cw	2+ mes and cw	1–2+ mes and cw	2+ mes and cw	2+ mes and cw	Subendothelial, subepithelial, and mes EDDs (focally organized)	Lost to follow-up	
2	52/M	Hypertensive × 1 yr. Presented with anasarca and progressive renal dysfunction	2.73	ANA+	3+/8 g	1–2	3+ mes and cw	0	Traces	2+ mes and cw	–	2+ mes and cw	3+ mes and cw	Subendothelial, transmembranous, and mes EDDs	Lost to follow-up	
3	22/M	Hypertensive with anasarca	1.4	Nil	2+/6 g	4–6	3+ mes and cw	1+ mes and cw	3+ mes and cw	1+ mes and cw	Traces	2+ mes and cw	1+ mes and cw	–	Steroid 1 mg/ kg/day	S Cr 1.2 mg/dL, 24-h urine protein – 7.3 g (6 months)
4	14/F	Anasarca, with no response to steroids. Malar rash and knee arthritis present	0.4	Low C3 (40 mg/ dL)	3+/–	150–200	2–3+ mes and cw	2–3+ mes and cw	2+ mes and cw	2–3+ mes and cw	2–3+ mes and cw	2+ mes and cw	3+ mes and cw	Subendothelial, transmembranous, and mes/parames EDDs	Pulse	S Cr 0.43 mg/dL, urine routine – 2+ protein, no RBCs; S albumin – 2.87 mg/dL (25 months)
5	43/M	Pedal edema for 2 yr	0.9	RF+	2+/–	25–30	3+ mes and cw*	3+ mes and cw*	3+ mes and cw*	0	2+ mes and cw*	3+ mes and cw*	3+ mes and cw*	Subendothelial and mesangial and occasional subepithelial EDDs	Lost to follow-up	
6	28/M	Pedal edema and hematuria	1.96	Nil	–/9.56 g	2–3	2+ mes and cw	3+ mes and cw	2+ mes and cw	3+ mes and cw	3+ mes and cw	3+ mes and cw	3+ mes and cw	–	Lost to follow-up	
7	37/F	Anasarca and proteinuria	2.4	Nil	–/5 g	10–15	3+ mes and cw	–	1–2+ mes and cw	3+ mes and cw	–	0-Traces	1–2+ mes and cw	Subendothelial and mesangial EDDs	Lost to follow-up	
8	58/M	Hematuria and rising serum creatinine	4.7	Nil	–/14 g	Full field	2+ mes and cw	Traces	2+ mes and cw	Trace to 1+ mes and cw	Trace to 1+ mes and cw	1+ mes and cw	1+ mes and cw	–	Steroid 1 mg/ kg/day + MMF 1.5 g/day	S Cr 12.9 mg/dL (9 months)

ANA, antinuclear antibody; RBC, red blood cells; UP, urine protein; EDDs, electron-dense deposits; dsDNA, double-stranded DNA; mes, mesangial; cw, capillary wall; parames, paramesangial; RF, rheumatoid factor; –, not available; IS, immunosuppression; IF, immunofluorescence. * And positive in intraluminal hyaline thrombi.

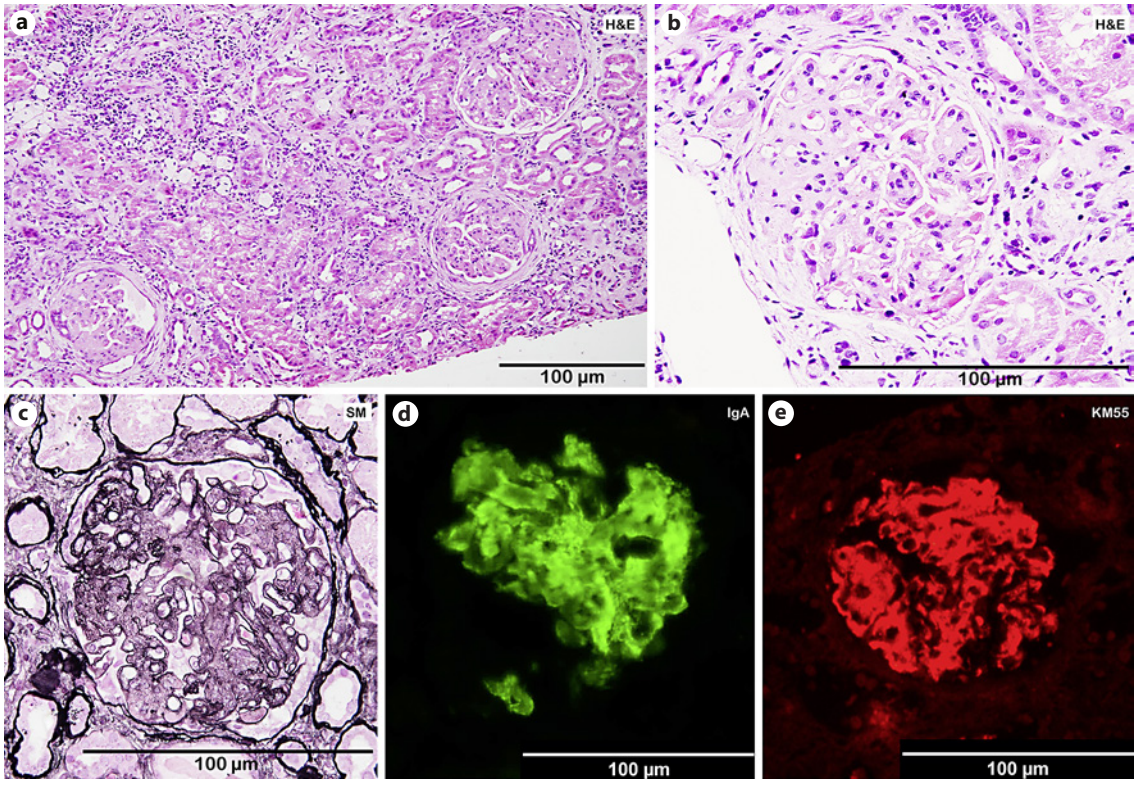

Fig. 6. A case of IgAN with a membranoproliferative pattern of glomerular injury, with moderate mesangial matrix expansion, mesangial hypercellularity (**a**, hematoxylin-eosin, ×10; **b**, hematoxylin-eosin, ×20), and irregular capillary-wall thickening (**c**, Jones methenamine silver, ×20). IF for IgA shows 3+ capillary-wall and mesangial granular deposits (**d**, IgA-FITC, ×20), and KM55 shows 3+ capillary-wall and mesangial granular staining (**e**, KM55-phycoerythrin, ×20). IgAN, IgA nephropathy; IF, immunofluorescence.

ic cytoplasmic antibody and double-stranded DNA were negative. The serum C3 level was within normal limits. Light microscopy revealed mesangial matrix expansion and irregular capillary-wall thickening with extensive GBM reduplication on silver methenamine. IF showed large capillary-wall and mesangial granular deposits of IgA (3+), IgG (3+), IgM (3+), C3 (3+), and C1q (trace-1+). There was no evidence of light-chain restriction (Fig. 7). EM showed large unorganized immune-type subendothelial deposits. KM55 staining showed 3+ confluent mesangial granular deposits after which the histological diagnosis was revised from IC-MPGN to IgAN with a membranoproliferative pattern of glomerular injury.

Endocapillary Proliferative and Crescentic Pattern of Glomerular Injury Raising the Differential Diagnosis of IgA-IRGN

Case 3. A diabetic and hypertensive male, aged 55 years who has history of recurrent cerebrovascular accidents and past history of pulmonary tuberculosis, developed rapidly progressive renal failure with generalized body swelling and a palpable skin rash. On investigation, the following parameters were observed: serum creatinine – 5 mg/dL, serum C3/C4 – normal, autoimmune markers and viral markers – negative, urine spot protein/creatinine ratio – 6.71, and ultrasound showed normal sized kidneys with raised echogenicity. There was no history of febrile illness, although during his course, urine culture grew *Klebsiella pneumoniae* and later *Enterococcus faecium*. The chest CT scan and sputum GeneXPert assay suggested reactivation of tuberculosis. Renal biopsy revealed moderate mesangial expansion, hypercellularity, and Kimmelstiel-Wilson nodules in the glomeruli examined, along with variable endocapillary hypercellularity and neutrophil exudation. Cellular crescents were also seen in 2 glomeruli. In addition, there were features of diffuse acute tubular injury, marked interstitial edema, and thickening of tubular basement membranes. Interstitial fibrosis/tubular atrophy involved

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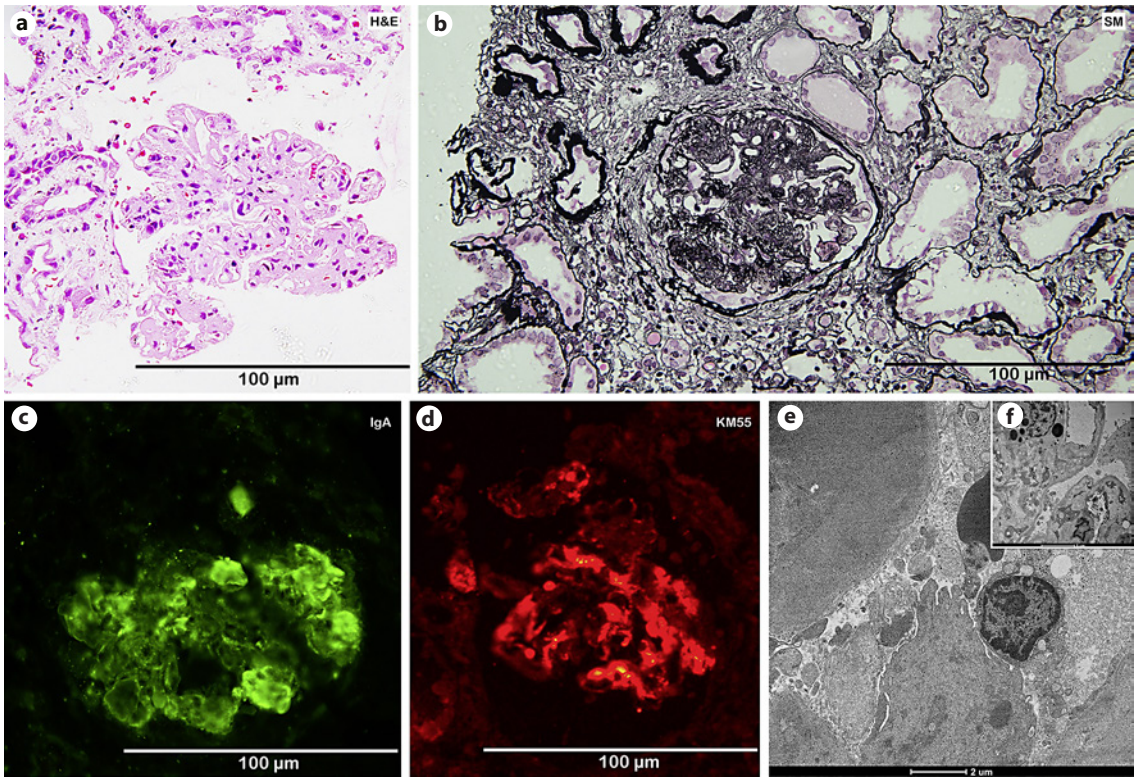

Fig. 7. A case of IgAN with a membranoproliferative pattern of glomerular injury, with mesangial-matrix expansion (**a**, hematoxylin-eosin, ×20), irregular capillary-wall thickening, and GBM reduplication (**b**, Jones methenamine silver, ×20). IF for IgA shows large capillary-wall and mesangial granular deposits (**c**, IgA-FITC, ×20), and KM55 shows 3+ confluent mesangial granular deposits (**d**, KM55-Phycoerythrin, ×20). Large unorganized immune-type subendothelial deposits were seen on electron microscopy (**e**, uranyl acetate-lead citrate, ×940; **f**, uranyl acetate-lead citrate, ×2,250). IgAN, IgA nephropathy; GBM, glomerular basement membrane; IF, Q7 immunofluorescence.

30–40% of the biopsied cortex. IF microscopy performed on formalin-fixed paraffin-embedded sections showed linear glomerular and tubular basement membrane accentuation of IgG with variable granular mesangial deposits of IgA (2–3+), IgG (2+), kappa (1–2+), and lambda (1–2+) and negative staining for C3. A provisional diagnosis of an IgA-dominant IC-mediated proliferative GN with crescents was made with a differential diagnosis of IgAN favored over IgA-IRGN. No tissue was sent for electron microscopy. Further immunostaining with KM55 revealed mesangial granular staining of 2–3+ intensity, which paved the way for the diagnosis of IgAN, overlying diabetic nephropathy. KM55 immunostaining of the patient's skin biopsy also showed deposits of GD-IgA1 on the walls of dermal capillaries (Fig. 8). The patient remained dialysis-dependent, did not receive any immunosuppression for his kidney disease, and died on the 2nd admission due to severe hospital-acquired pneumonia.

Case 4. A 55-year-old male, hypertensive since 15 years, was detected recently to have carcinoma of the hypopharynx and had undergone partial laryngectomy and radiotherapy. He had a history of lower respiratory tract infection 2 months prior (culture negative), which was followed by an episode of acute kidney injury, with serum creatinine level of 4.3 mg/dL and nephrotic-range proteinuria (3+ on dipstick) and microscopic hematuria. Autoimmune workup consisting of antinuclear antibody, double-stranded DNA, anti-neutrophilic cytoplasmic antibody, and anti-GBM was negative. Light microscopy of the biopsy showed moderate mesangial expansion and hypercellularity, endocapillary hypercellularity, and neutrophilic exudates in all glomeruli. Fibrocellular crescents were seen in 3 glomeruli, and an equal number showed cellular crescents. Interstitial fibrosis and tubular atrophy involved 10–15% of the biopsied cortex. IF showed mesangial and focal capillary-wall granular positivity for IgA

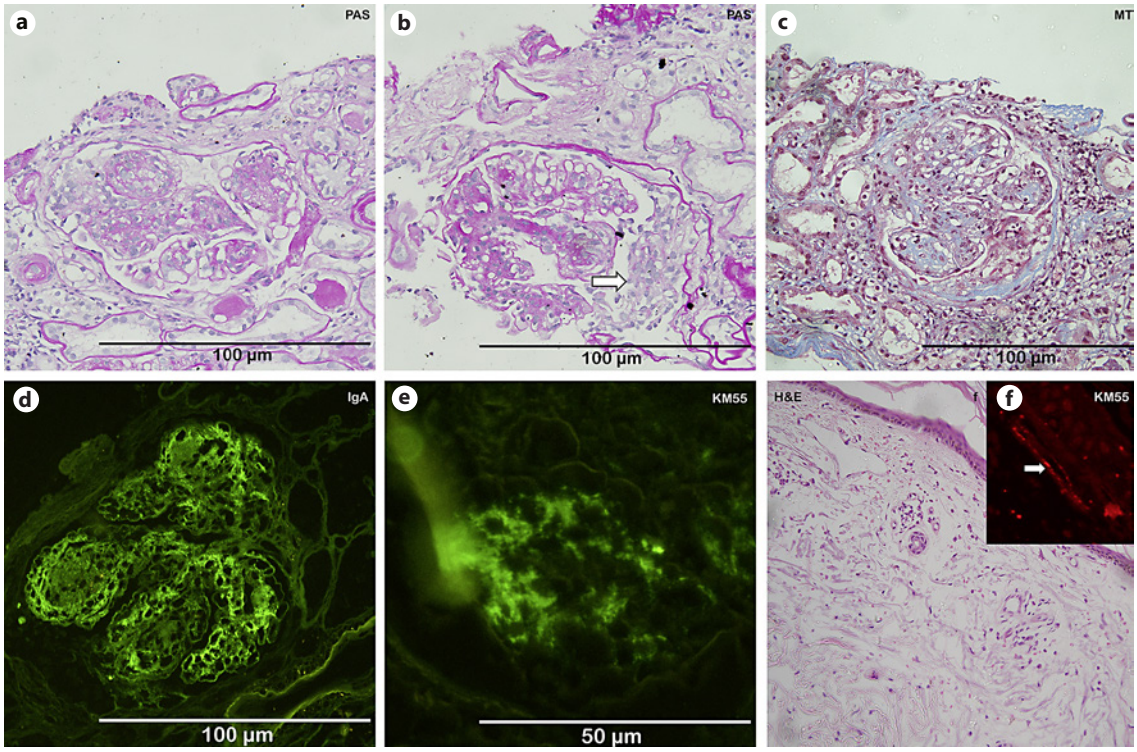

Fig. 8. A case of IgAN in a diabetic and hypertensive male, showing moderate mesangial expansion and hypercellularity (**a**, periodic acid-Schiff, ×20; **b**, periodic acid-Schiff, ×20) and the presence of crescents (**b**, periodic acid-Schiff, ×20, white arrow) and Kimmelstiel-Wilson nodules (**c**, Masson's trichrome, ×20). IF for IgA shows 2–3+ mesangial granular deposits of IgA (**d**, IgA-FITC, ×20) and 2–3+ mesangial granular deposits on IF for KM55(**e**, KM55-phycoerythrin, ×40). KM55 immunostaining of the patients' skin biopsy highlights deposits of GDIgA on the walls of dermal capillaries (**f**, KM55-phycoerythrin, ×20, white arrow). IgAN, IgA nephropathy; IF, immunofluorescence.

(3+), C3(2+), and lambda light chain (1–2+) and negativity for IgG, IgM, C1q, and kappa light chain. Differential diagnoses of IgA-IRGN and IgAN were considered. Electron microscopy revealed large immune-type unorganized electron-dense deposits in the mesangium and paramesangium and occasionally in a subendothelial location. Furthermore, immunostaining of the biopsy using KM55 showed 2–3+ mesangial and focal capillary-wall granular staining. A diagnosis of IgAN was made based on these findings. He was lost to the follow-up and died due to severe stridor within a year (Fig. 9).

Discussion

KM55 is a recently described marker for GD-IgA both in tissue and the serum, and previous experience with it is reviewed in Table 4. The collective experience of 107 cases of IgAN demonstrates that it is a consistent marker for the same and is completely negative in lupus nephritis as noted in 24 cases. The experience in other IgA-containing glomerular diseases remains variable. As we performed KM55 staining on our cohort of IgA-containing glomerular diseases, a distinct pattern emerged, of KM55-positive and KM55-negative cases.

Primary IgAN, HSP, and secondary IgAN including those related to liver disease all contain KM55-positive GD-IgA and therefore appear to have a common underlying pathogenesis. This is consistent with reports from Sugiyama et al. [12] and Suzuki et al. [6] which demonstrate the GD nature of IgA in HSP similar to primary IgAN. Also reports from Cassol et al. [7] and Wang et al. [8] depicted similar staining in cases of secondary IgAN. In this group, liver disease-associated IgAN is the most common and is discussed further. It can be hypothesized that these diseases all share a common pathogenesis of systemic overproduction of the "*mucosal*-type" IgA, which may be exacerbated by the secondary causes with

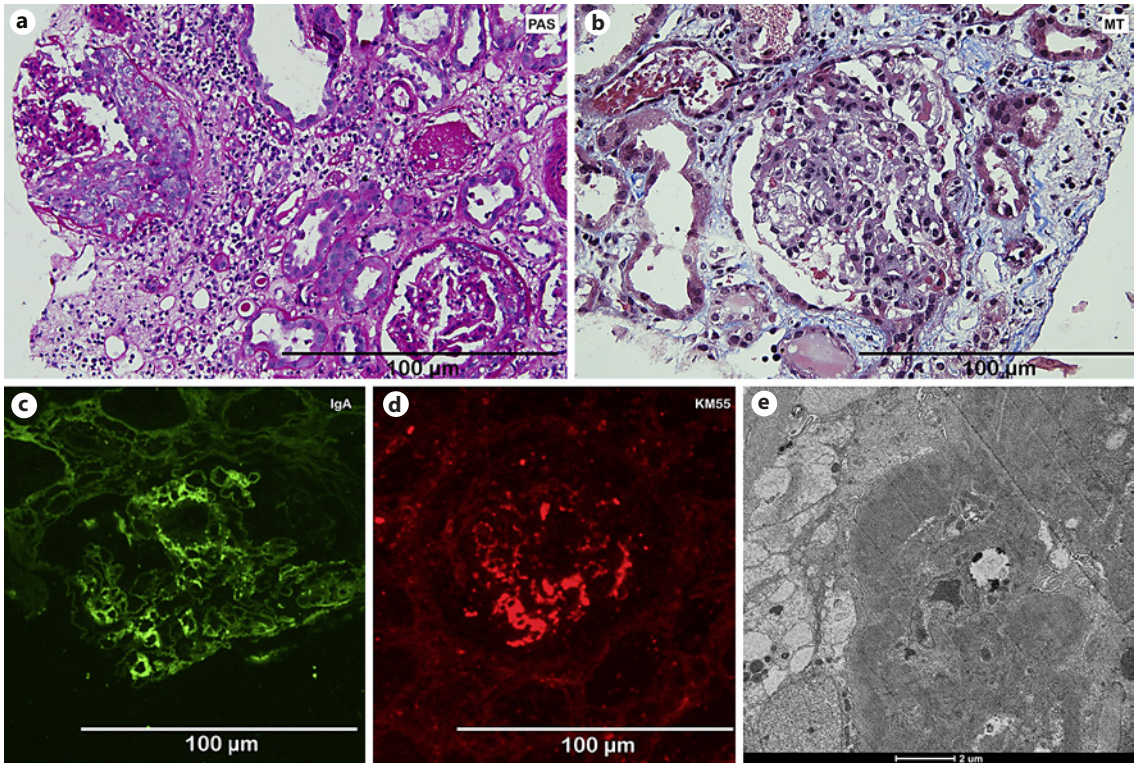

Fig. 9. A case of IgAN showing fibrocellular crescents (**a**, periodic acid-Schiff, ×20), moderate mesangial expansion, and hypercellularity along with endocapillary hypercellularity (**b**, Masson's trichrome, ×20). IF showed 2–3+ mesangial and focal capillary wall granular positivity for IgA (**c**, IgA-FITC, ×20). KM55 immunostaining shows 2–3+ mesangial and focal capillary-wall granular staining (**d**, KM55-Phycoerythrin, ×20). Electron microscopy shows large immune-type unorganized EDDs in the mesangium (**e**, uranyl acetate-lead citrate, ×2,250). IgAN, IgA nephropathy; IF, immunofluorescence; EDD, electron-dense deposit.

which it is associated. Sjogren's syndrome, for example, results in increased mucosal inflammation. In other cases, there may be no direct effect of the perceived secondary cause, and the case may just be a coincidental co-occurrence.

CLD-IgAN constitutes the largest group within the so-called secondary IgAN. From early autopsy studies, it was recognized that IgA glomerular deposits were common in this cohort and often subclinical. The 1st report of a similar underlying pathogenesis as primary IgAN was from a French group in 2011 where it was demonstrated that increase in levels of GD-IgA1-containing ICs could be identified in the circulation in patients with alcoholic cirrhosis [18]. This was further confirmed by Wang et al. [8], when they tested for GD-IgA1 in the serum and tissue of a wide range of secondary IgAN including 20 cases of cirrhosis (5 of which also had tissue staining). Our study confirms the GD nature of IgA deposits in cases of CLD-IgAN.

In the setting of CLD, the following features would exacerbate deposition of GD-IgA1 in the kidney:

1. Defective intestinal barriers with an increased chance of bacterial infection and enhanced mucosal production of mucosal-type IgA with portosystemic shunting, enabling easy entry into the systemic circulation.
2. Reduced clearance of GD-IgA1 due to its reduced binding to the asialoglycoprotein receptor which is dependent on the terminal galactose. In addition, the hepatocellular damage would result in loss of hepatocytes and aberrant distribution of the asialoglycoprotein receptor which would further dampen clearance of GD-IgA1.

Further genome-wide association studies would be interesting in this cohort to determine if they have a genetic background similar to primary IgAN. Although pathogenetically related, subtle histological differences have been recognized in the literature between different forms of IgAN. We recognize that HSP-related nephritis tends

Table 4. Results of previous studies on tissue and serum testing for KM55 in the literature

References	Plasma testing	Case details	Results of plasma testing	Tissue testing	Case details	Results of tissue testing
Junichi et al. [3]	ELISA for plasma GD-IgA1 and HAA lectin-based assay	Primary IgAN – 152, other glomerular diseases – 20, and no kidney disease – 71	Significant increase in GD-IgA1 serum levels in primary IgAN compared to other glomerular diseases ($p < 0.001$) and nonrenal diseases ($p < 0.001$)	IF for KM55 with IgA colocalization	IgAN and MCD	Diffuse and global staining in IgAN, while negative in MCD
Wada et al. [5]	ELISA for plasma GD-IgA1	Primary IgAN – 111, HSP – 18, lupus GN – 29, ANCA GN –28, and MCD –13	Significant increase in GD-IgA1 serum levels in primary IgAN and HSP compared to lupus GN, ANCA GN, and MCD ($p < 0.001$)	IHC for KM55	Primary IgAN – 50, HSP – 18, lupus GN – 3, and MCD – 3	Significant staining for KM55 in cases of IgAN and HSP, while very faint staining in lupus GN and MCD
Cassol et al. [7]		–	–	IF for KM55 with IgA colocalization	Primary IgAN – 44, secondary IgAN –27, SAGN-13, incidental IgA – 8, and lupus nephritis – 8	Colocalization of KM55 with IgA in all cases of primary and secondary IgAN. Cases of lupus nephritis were negative. Cases of SAGN and incidental IgA showed mostly weaker staining
Bagchi et al. [16]	ELISA for plasma GD-IgA1	Primary IgAN-136, non-IgA glomerular diseases – 60, and healthy volunteers – 50	Significant increase in GD-IgA1 serum levels in primary IgAN compared to non-IgA glomerular diseases and healthy volunteers ($p < 0.0001$)	–	–	–
Wang et al. [8]	ELISA for plasma GD-IgA1 and IgA/IgG ICs	Secondary IgAN ($n = 100$) – 20 cirrhosis, 19 rheumatoid arthritis, 9 ankylosing spondylitis, 10 Sjogren's syndrome, 25 psoriasis, 1 ulcerative colitis, 3 neoplasia, 3 with infections, 6 chronic obstructive bronchiolitis, and 4 pulmonary fibrosis Primary IgAN ($n = 32$) Other renal diseases ($n = 41$) Healthy controls ($n = 39$)	No significant difference between primary and secondary IgAN in plasma GD-IgA1 levels ($p = 0.7$) and IgA1-IgG ICs ($p = 0.88$)	IF for KM55 with IgA colocalization	Secondary IgAN – 5 cirrhosis, 1 rheumatoid arthritis, 1 ankylosing spondylitis, 1 Sjogren's syndrome, 1 psoriasis, 1 ulcerative colitis, and 1 neoplasia Primary IgAN – 2 lupus nephritis	Colocalization of KM55 with IgA in all cases of primary and secondary IgAN. Case of lupus nephritis was negative
Suzuki et al. [17]	–	–	–	IF for KM55 with IgA colocalization	Secondary IgAN – 4 cases	Colocalization with KM55 in 3 cases with underlying rheumatoid arthritis, SLE, and Crohn's disease) and negative staining in 1 case with underlying HCV infection
Zhao et al. [10]				IF for KM55 with IgA colocalization	Primary IgAN – 40, IgAN with HbAg deposits – 14, IgA vasculitis – 16, lupus nephritis – 13, incidental IgA deposits – 13, and negative controls – 6	Colocalization of KM55 with IgA with a mean intensity of 3+ in IgAN, 2+ in IgA vasculitis, 3+ in IgA with HBsAg deposits, 1+ in lupus nephritis, 1+ in incidental IgA deposits, and 0 in negative controls
Zhang et al. [11]	ELISA for plasma GD-IgA1	75 patients of IgAN and 80 healthy controls	Patients with IgAN had significantly higher GD-IgA1 levels compared with those in healthy controls	IHC for KM55	15 patients of IgAN	Positive KM55 staining in IgAN

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Table 4 (continued)

References	Plasma testing	Case details	Results of plasma testing	Tissue testing	Case details	Results of tissue testing
Sugiyama et al. [12]	ELISA for plasma GD-IgA1	IgAN – 56, IgA vasculitis – 24, lupus nephritis – 6, minimal change disease – 6, ANCA-associated vasculitis – 6	Patients with IgAN and IgA vasculitis had significantly higher levels of GD-IgA1 when compared to other cohorts	IHC for IgA and KM55	IgAN – 56, IgA vasculitis – 24	Similar intensity of IgA and KM55 staining in cases of IgAN and IgA vasculitis
Zhang et al. [13]				IF for KM55 with IgA colocalization	IgA variant of PGNMID – 2, primary IgAN – 1	
Ishiko et al. [9]				IF for KM55 with IgA colocalization in pediatric cases	IgAN – 17, IgA vasculitis – 6, lupus nephritis – 9, MPGN – 5, membranous nephropathy – 2, idiopathic nephrotic syndrome – 11, oligomeganephronia– 3, Alport syndrome – 2, dense-deposit disease – 1, C3 GN – 1, post-streptococcal acute GN – 1, hemolytic uremic syndrome – 1	All cases of IgAN, IgA vasculitis with nephritis, lupus nephritis, and membranous nephropathy stained positive with KM55. Three out of 4 cases of MPGN stained positive with KM55 All the other cases showed negative staining
Suzuki et al. [6]				IF for KM55 with IgA colocalization	IgAN – 48, IgA vasculitis with nephropathy – 14, idiopathic membranous nephropathy – 5, secondary membranous nephropathy, HCV-related nephritis – 3, hepatic glomerulosclerosis – 1, ANCA-related nephropathy – 2, granulomatous with polyangiitis – 1, MPGN – 1, MCD – 3, non-IgA PGN – 2, nonspecific renal tubular atrophy – 1, acute post-streptococcal GN – 1, nephrosclerosis – 1, and minor glomerular abnormalities – 2	All cases of IgAN and IgA vasculitis stained positive for KM55, while all the other cases stained negative

GD-IgA1, galactose-deficient IgA; IgAN, IgA nephropathy; MCD, minimal-change disease; IF, immunofluorescence; IHC, immunohistochemistry; HSP, Henoch-Schonlein purpura; GN, glomerulonephritis; ANCA, anti-neutrophilic cytoplasmic antibody; SAGN, *Staphylococcus*-associated glomerulonephritis; PGNMID, proliferative glomerulonephritis with monoclonal immune deposits; MPGN, membranoproliferative glomerulonephritis.

to have more proliferative features (endo- and extra-capillary) and necrotizing lesions compared to IgAN. This is accompanied by increased capillary-wall subendothelial deposits [19]. Similarly, subtle differences in histology were noted in CLD-IgAN, prompting the term "hepatic glomerulosclerosis." This included a more common segmental capillary-wall subendothelial deposition, resulting in an MPGN pattern and additional deposits of C1q noted in half to 2/3rd of cases [20].

A very clearly KM55-negative group of IgA-containing glomerular disease in our study is that of lupus nephritis, in contrast to studies by Ishiko et al. [9] and Zhao et al. [10]. We feel that the interpretation of KM55 IF as positive in these cases may be attributed to interpretation differences in terms of nonspecific staining and lower thresholds.

The presence of dominant or codominant IgA and a membranoproliferative pattern of glomerular injury in a non-lupus patient is one which elicits diagnostic confusion. In our series, this morphology was identified in cases of

1. CLD-IgAN (15 cases) – KM55-positive
2. Primary IgAN (4 cases) – KM55-positive
3. IgA-dominant/codominant MPGN (8 cases) – KM55-negative

Thus, a cohort of KM55-negative IgA-dominant/codominant MPGN remains (Table 3), where the source of the ICs appears systemic but unknown. Those with a full-house IF profile may represent seronegative lupus and would need close clinical and serological follow-up. The possibility of a chronic underlying infection is also worth investigating, although as discussed later, the nature of IgA in these cases is still controversial. In the limited follow-up available for this cohort, immunosuppression was attempted with disease variably remaining stable or progressing.

This study also confirms that there is a subset of IgAN which presents with an MPGN pattern of injury. In a series by Andeen et al. [21], 15 similar cases of IgA-dominant GN with an MPGN pattern of injury, without liver disease were identified. They had nephrotic-range proteinuria, hematuria, renal insufficiency, negative serological studies, and no history of infection. Three (27%) progressed to end-stage renal disease. One had recurrent IgA-dominant GN in the renal allograft <1 year post-transplant. Four of 5 patients with repeat biopsies had persistent IgA-dominant MPGN. The authors concluded that these represented either a unique clinicopathological entity or an aggressive form of IgAN. We believe that KM55 staining would help resolve this differential as it did in our cohort. With the current understanding of MPGN and the importance of determining underlying etiology, KM55 may serve as a useful marker to carve out IgAN from the larger cohort of IC-MPGN.

Our series lacked a wider spectrum of secondary IgAN including inflammatory bowel disease and celiac disease-associated IgAN. However, the biggest pitfall of this study is the lack of IgA-IRGN or *Staphylococcus*-associated GN (SAGN). This patient cohort of usually elderly diabetics or IV drug abusers is relatively uncommon in our practice, and we did not have a single case of documented Staphylococcal infection in our records. In 2 cases of proliferative and crescentic GN, where it was suspected, a strong KM55 staining and a lack of clinical correlation to favor IgA-IRGN or SAGN confirmed the cases to be of proliferative IgAN. Cassol et al. [7] had found significantly weaker (negative to traces) staining in 8 of 13 cases of SAGN in their series, although a few cases had strong 2–3+ staining intensity. The authors speculated on whether these represented cases of IgAN with an infectious trigger. They concluded that a negative KM55 in the setting of a proliferative IgA-containing GN should definitely raise suspicion for an infection and trigger investigations to uncover an infective focus.

The significance of trace amounts of KM55 staining is debatable, but in our study, it was commonly noted even in non-IgA-containing glomerular diseases such as FSGS. This appearance likely represents nonspecific staining in proteinuric patients such as is also noted with IgA. This is not surprising as GD-IgA is normally present in the circulation, though in a smaller proportion [8, 16], and therefore, such interrupted staining may be disregarded. Similar to IgA, nonspecific cast staining with KM55 was also noted. To be considered positive, a "confluent granular staining pattern" in a mesangial or capillary-wall location should be considered.

Conclusion

KM55 is a useful stain to detect GD-IgA and suggests *mucosal*-origin IgA as opposed to *systemic-origin* IgA as the driver of the glomerular pathology. Its presence in both primary and perceived secondary IgAN points toward a common pathogenesis. It can be helpful in resolving differential diagnoses in overlapping patterns of glomerular injury; however, it must be interpreted with caution.

Statement of Ethics

The study was approved by the Institute Ethics Committee for Post Graduate Research (Basic science), All India Institute of Medical Sciences, New Delhi; Reference number: IECPG-484/29.11.2017, RT-13/20.12.2017. The Ethical Committee approved the study without the need for written informed patient consent as no additional biopsy was required, and only tissue left in the paraffin blocks after completion of diagnostic workup was used for the same.

Conflict of Interest Statement

The authors have no conflicts of interests to declare.

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Author Contributions

Geetika Singh contributed to the conception and design of the work. Rahul Raj, Geetika Singh, and Alok Sharma contributed to data collection. Geetika Singh and Rahul Raj contributed to data analysis and interpretation. Geetika Singh and Rahul Raj drafted the article. Sanjay Kumar Agarwal and Geetika Singh contributed to critical revision of the article. Rahul Raj, Alok Sharma, Adarsh Barwad, Soumita Bagchi, Sanjay Kumar Agarwal, Arvind Bagga, Amit Kumar Dinda, and Geetika Singh contributed to the final approval of the version to be published.

Data Availability Statement

All data generated or analyzed during this study are included in this manuscript, and the tables attached. Further inquiries can be directed to the corresponding author.

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