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Membranous-like glomerulopathy with masked IgG kappa deposits

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The diagnostic classification of glomerulonephritis is determined by the interplay of changes seen using light, immunofluorescence, and electron microscopy of the renal biopsy. Routine direct immunofluorescence on fresh tissue is currently considered the gold standard for the detection and characterization of immune deposits. We recently found a peculiar form of glomerular immune complex deposition in which masked deposits required an antigen-retrieval step to be visualized. Over a 2-year period, 14 cases were characterized by numerous, large subepithelial deposits visualized by electron microscopy and C3-predominant staining by routine immunofluorescence on fresh tissue with weak to negative immunoglobulin staining. Repeat immunofluorescence after digestion of the formalin-fixed paraffin-embedded tissue with pronase elicited strong IgG-κ staining restricted within the deposits. The patients were often young with a mean age of 26 years and commonly had clinical evidence of vague autoimmune phenomenon. The clinicopathologic findings in this unusual form of glomerulopathy do not fit neatly into any currently existing diagnostic category. We have termed this unique form of glomerulopathy membranous-like glomerulopathy with masked IgG-κ deposits.

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Glomerular nephropathies with immune-complex deposition are placed in diagnostic categories on the basis of the morphologic findings on renal biopsy using light microscopy (LM), immunofluorescence (IF), and electron microscopy (EM). These disease categories are useful in that they are reproducible and group patients according to unique pathogenic mechanisms, and they provide both treatment and prognostic information to the treating clinician. Although many of these diseases such as membranous glomerulopathy were first described >40 years ago,[1] others such as C3 glomerulopathy[2] and proliferative glomerulonephritis with monoclonal IgG deposits (PGNMIDs)[3] have been recognized for <10 years.

We have recently observed a peculiar form of glomerular immune-complex deposition with unique clinical and pathologic characteristics. The pattern of deposition is most akin to membranous glomerulopathy by LM and EM in that most cases show no evidence of endocapillary proliferation, and the deposits are largely subepithelial by EM. Routine IF studies show isolated C3 staining in these deposits. However, the deposits appear to be 'masked' in that the true nature of the deposits is not evident until an antigen-retrieval step (pronase digestion) is added to reveal the presence of IgG-κ restriction. Most of the patients are relatively young women who frequently have vague autoimmune phenomenon. The clinical and demographic findings in these patients do not correspond with those typically found in patients with monoclonal membranous glomerulopathy or the more recently described diagnosis of PGNMID. To our knowledge, this is the first description of this unique form of glomerulopathy, which we have termed membranous-like glomerulopathy with masked IgG-κ deposits (MGMIDs).

RESULTS

Clinical features

The first observation of MGMID came about in an effort to further evaluate for the presence of immunoglobulins in case 2 after it was found to be C3-only by routine IF. We subsequently found that this phenomenon was not unique to this patient, and we began collecting these cases with masked subepithelial deposits in an effort to determine whether there were any commonalities between them. This series includes all cases of MGMID for which a biopsy was received in our laboratory since the initial recognition 2 years ago. We identified 14 cases of MGMID during this 2-year period of

study out of 10,956 native kidney biopsies (0.13%). The demographic and clinical details at the time of presentation are detailed in Table 1. The patients were predominantly female (12/14), and multiple ethnicities were represented in this cohort including 8 Caucasians, 2 African Americans, 3 Hispanics, and 1 Pacific Islander. All patients were found to be negative for hepatitis C, hepatitis B, and HIV. In addition, 7/7 patients tested for rheumatoid factor were negative and 11 patients had a serum and urine protein electrophoresis study with no evidence of a paraprotein. None of the patients reported recent infections at the time of clinical presentation. Serum C3 and C4 were normal in all patients at the time of presentation and throughout follow-up. Anti-streptolysin O was negative in all patients. The primary indication for biopsy in 13/14 patients was proteinuria, with 5 of 14 displaying the nephrotic syndrome. Patient 14 was the exception, in whom the primary indication for biopsy was acute renal failure. Eleven of the patients were not on any medication at the time of the biopsy, and there were no drugs in common among the remaining three patients.

There were nine patients (64%) with some evidence of autoimmune disease either at the time of presentation or in their past medical history. Although six of the patients had a positive anti-neutrophil antibody, only one of the six met ARA criteria for a diagnosis of systemic lupus erythematosus. Patients 3 and 7 had a remote history of systemic lupus erythematosus but did not show systemic manifestations of systemic lupus erythematosus outside the kidney at the time of renal biopsy. Patient 14 had a history of inflammatory arthritis, but was not being treated at the time of the biopsy. Patient 2 had negative serologies but a past medical history significant for idiopathic thrombocytopenic purpura.

Light microscopy

The morphologic features of each biopsy are detailed in Table 2. The major finding was the presence of membranous glomerulopathy features. Silver positive glomerular basement membrane (GBM) 'spikes' or silver negative GBM 'pin holes' were present in a segmental distribution ($<50\%$ of loops) in five cases (Figure 1). The remaining nine cases showed global

Table 1 | Clinical characteristics at time of presentation for renal disease

Patient	Age	Gender	Cr (mg/dl)	Prot (g)	ANA (titer)	dsDNA	ANCA	Hematuria	PMH
1	22	F	0.7	1.4	−	−	NP	+	Proteinuria discovered during pregnancy
2	17	F	0.6	3.2	−	−	NP	+	ITP, hemolytic anemia
3	27	F	0.8	1.3	+ (NT)	+	−	−	SLE
4	24	F	1.9	8	−	−	−	+	None
5	17	F	0.6	2.1	+ (NT)	−	NP	+	Fever of unknown origin
6	34	M	0.7	3.5	+ (1:80)	−	−	+	Diabetes mellitus, type 2, and hypertension
7	32	F	0.8	0.5	−	−	−	+	Remote history of SLE
8	49	F	0.9	2.9	+ (1:160)	−	NP	+	Remote autoimmune hemolytic anemia
9	21	F	0.5	5.4	−	−	−	+	Proteinuria discovered during pregnancy
10	26	M	1.5	5	−	−	NP	+	None
11	20	F	0.6	1.9	−	−	−	+	None
12	19	F	0.7	2	+ (1:80)	BL +	NP	+	None
13	15	F	0.8	4.7	+ (1:80)	−	−	+	None
14	37	F	1.9	4.5	−	−	−	+	Inflammatory arthritis

Abbreviations: ANA, anti-neutrophil antibody; ANCA, anti-neutrophil cytoplasmic antibody; BL, borderline; Cr, serum creatinine; dsDNA, double-stranded DNA; F, female; ITP, idiopathic thrombocytopenic purpura; M, male; NP, not performed; NT, no titer; PMH, past medical history; Prot, 24-h proteinuria; SLE, systemic lupus erythematosus.

Table 2 | Morphologic features on initial biopsy

Patient	LM pattern	Fresh IgG	Fresh κ	Fresh λ	Pron IgG	Pron κ	Pron λ	Fresh C3	Deposit location	Hump-like deposits	Hinge-region deposits
1	Normal	0	0	0	3	3	0	3	m, sp	Yes	Yes
2	Normal	0	0	0	3	3	0	2	m, sp	No	Yes
3	Normal	1	0	0	3	3	0	3	m, sp	Yes	Yes
4	Focal crescentic	0	0	0	3	3	0	3	m, sp	Yes	Yes
5	Normal	0	0	0	2	2	0	2	m, sp	No	Yes
6	Normal	0	0	0	3	2	0	1	m, sp	No	No
7	Normal	0	0	0	2	2	0	1	m, sp	No	Yes
8	Normal	0	0	0	3	3	0	3	m, sp	Yes	No
9	Normal	0	0	0	3	3	0	0	sp	No	No
10	Normal	1	0	0	3	3	0	1	sp	No	No
11	Normal	0	0	0	3	3	0	2	m, sp	Yes	No
12	Normal	0	0	0	3	3	0	1	m, sp	Yes	Yes
13	Focal crescentic	Tr	Tr	0	2	2	0	2	m, sp	No	No
14	Focal crescentic	Tr	0	0	3	3	0	2	m, sp	Yes	Yes

Abbreviations: LM, glomeruli on light microscopy; m, mesangial; Pron, pronase; sp, subepithelial; Tr, trace.