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Received: 29.1.2018; Editorial decision: 6.6.2018

*Nephrol Dial Transplant* (2019) 34: 711–717  
doi: 10.1093/ndt/gfy256  
Advance Access publication 16 August 2018

## Monoclonal immunoglobulin G deposits on tubular basement membrane in renal allograft: is this significant for chronic allograft injury?

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### ABSTRACT

**Background.** Tubular basement membrane immune deposits (TBMID) has rarely been observed in renal allografts. It is usually found in BK virus nephropathy and immune complex glomerulonephritis; however, its significance is not well understood. We conducted a retrospective clinicopathological study on monoclonal immunoglobulin G (IgG) TBMID.

**Methods.** We studied 7177 renal allograft biopsy specimens obtained from Tokyo Women's Medical University from 2007 to 2015 and performed light microscopic, electron microscopic and immunofluorescence studies.

**Results.** Tubular basement membrane (TBM) deposits of IgG were found in 73 biopsies from 61 patients and the IgG subclass

was obtained in 31 biopsies. There were no cases of monoclonal IgA or IgM TBMID. In total, 13 biopsies from 10 patients showed monoclonal IgG TBMID. Of these, seven showed monoclonal IgG1κ TBMID and one each showed monoclonal IgG2κ, IgG2λ and IgG3κ TBMID. Conversely, eight patients showed polyclonal IgG TBMID. In electron microscopy, large granular electron-dense deposits (EDDs) in the TBM were detected in all patients with monoclonal IgG1κ TBMID. EDDs were absent in TBM in patients with monoclonal IgG2κ, IgG2λ or IgG3κ TBMID. Progression of interstitial fibrosis and tubular atrophy (IFTA) was significantly higher in patients with monoclonal IgG1κ TBMID than in those with polyclonal IgG TBMID ( $P < 0.05$ ). There were no significant differences in the

other clinical parameters between monoclonal IgG1 $\kappa$  and polyclonal IgG TBMID.

**Conclusions.** This is the first study of patients with monoclonal IgG TBMID in renal allografts. We found that monoclonal IgG1 $\kappa$  TBMID was associated with EDD formation in TBM and IFTA progression.

**Keywords:** electron-dense deposits, renal pathology, transplantation, tubular cells, tubular basement membrane immune deposits

## INTRODUCTION

In renal biopsy diagnosis, glomerular immunoglobulin (Ig) deposits on immunofluorescence (IF) are very important in diagnosing glomerular abnormalities. We rarely observe immune deposits in the tubular basement membrane (TBM). TBM immune deposits (TBMID) are observed in cases of lupus nephritis, membranoproliferative glomerulonephritis, membranous nephropathy, drug-induced tubulointerstitial nephritis, Sjögren's syndrome, IgG4-associated nephritis and other autoimmune diseases in native kidney [1, 2]. In renal allograft, TBMID are associated with immune complex glomerulonephritis, Alport syndrome, chronic or acute rejection and BK virus nephropathy [2–4]. The proximal tubular epithelium is responsible for protein, vitamin and trace element reabsorption and active sodium transport [5], and tubular lesions may damage these functions. However, their significance and mechanism regarding how immune deposits are formed in the TBM are not well understood.

Nasr *et al.* [6] reported monoclonal glomerular IgG deposition as proliferative glomerulonephritis with monoclonal immunoglobulin deposition (PGNMID). Some studies have reported that the clinical features and pathogenesis of PGNMID are different from those of glomerulonephritis with polyclonal IgG deposition [7]. We also found several cases of monoclonal TBMID, but there are no reports on monoclonal IgG TBMID to our knowledge.

In this study, we analyzed the biopsy specimens with monoclonal IgG TBMID in renal allografts. We performed a retrospective clinicopathological study to determine pathological features and association with clinical prognosis of monoclonal IgG TBMID.

## MATERIALS AND METHODS

This study included 7177 renal biopsy specimens obtained from 2007 to 2015 at Tokyo Women's Medical University. In our laboratory, all renal biopsies were examined with standard light microscopy (LM) and IF. For LM, all biopsies were routinely stained with hematoxylin and eosin, periodic acid–Schiff, Masson trichrome and periodic acid methenamine silver as well as immunostaining for Simian virus 40 (SV-40) (mouse monoclonal IgG2a, Merck, Darmstadt, Germany). Immunostaining with CD68, CD138 and IgG4 using antihuman antibodies was performed to evaluate plasma cell infiltration and IgG4-positive plasma cells (CD68: mouse monoclonal IgG1, Dako, Carpinteria, CA, USA; CD138: mouse monoclonal IgG1 $\kappa$ , Dako; IgG4: mouse monoclonal IgG1, Binding Site, San Diego,

CA, USA). For IF, 2- $\mu$ m cryostat sections were dried and stained with fluorescein isothiocyanate (FITC)-conjugated polyclonal antibodies against IgG, IgA, IgM, C3c, C1q, fibrinogen, C4d,  $\kappa$  light chain and  $\lambda$  light chain (Dako). IgG subclass measurement was performed on 2- $\mu$ m cryostat sections stained with FITC-conjugated monoclonal antibodies against IgG1, IgG2, IgG3 and IgG4 (Binding Site). Evaluation of the tubular segment was performed by staining monoclonal antibodies against CD10 and EMA (CD10: Leica Biosystems, Wetzlar, Germany; EMA: Dako). BK virus nephropathy was histologically diagnosed based on the Banff Working Group classification [8]. Rejection was histologically diagnosed according to the Banff classification of 2017 [9]. We defined monoclonal IgG TBMID as monoclonal staining for a single light chain isotype and a single heavy chain subclass in the TBM. Furthermore, we defined polyclonal IgG TBMID as both light chain positive and/or more than one  $\gamma$  heavy chain subclass positive in the TBM. Exclusion criteria were glomerular IgG codeposition and BK virus nephropathy. All biopsies that included the monoclonal and polyclonal groups were examined using transmission electron microscopy (EM) and the clinicopathological findings of both the monoclonal and polyclonal groups were compared and investigated. All biopsies were reviewed by three independent pathologists. Patient information was reviewed using medical records. All data were presented as absolute number and median value. Continuous variables were compared using the Mann–Whitney test and categorical variables were compared using Fisher's exact test. All statistical analysis was performed using JMP software (SAS Institute, Cary, NC, USA). All P-values were two-sided and  $P < 0.05$  was considered statistically significant. This research was conducted based on the Declaration of Istanbul [10]. This research was approved by the ethics committee of Tokyo Women's Medical University (no. 4334).

## RESULTS

In total, 7177 renal allograft biopsy specimens were obtained between 2007 and 2015. IgG deposition in the TBM was found in 73 biopsies from 61 patients and the IgG subclass was found in 31 biopsies. Monoclonal IgG TBMID were found in 13 biopsies from 10 patients. There were no cases of monoclonal IgA or IgM TBMID. No cases were found with glomerular IgG codeposition. SV-40 was negative and viral replication with intranuclear inclusion bodies has not been found in any biopsies previously performed. Polyclonal IgG TBMID were found in 18 biopsies from 17 patients. We excluded five biopsies due to BK virus nephropathy and six biopsies of glomerular IgG codeposition (five biopsies of membranous nephropathy and one biopsy of membranoproliferative glomerulonephritis). We defined six patients as a group of polyclonal IgG TBMID.

### Patient characteristics

Table 1 presents the clinical characteristics of the patients with monoclonal IgG TBMID. The patients included four males and six females. The median patient age at transplantation was 46.0 years (range 11–61). The median donor age at transplantation was 60.5 years (range 42–72 years). Overall, six patients were ABO compatible and four patients were incompatible.

**Table 1. Patient characteristics of the patients with monoclonal IgG deposits in the TBM**

Patient	Age (years)/Sex	Primary disease	Donor [age (years)/sex]	ABO compatibility	DSA	Follow-up period (years)	Final follow-up Cr (mg/dL) and urinary findings
1	61/F	Unknown	60/M	Compatible	NE	7	Cr 1.26 U-pro, U-ob : unknown
2	57/F	CGN	61/M	Compatible	NE	6	Cr 1.19 U-pro -, U-ob -
3	57/F	IgAN	58/M	Incompatible	NE	10	Cr 1.19 U-pro -, U-ob -
4	11/M	Posterior urethral valve	44/F	Minor mismatch	+	18	ESRD
5	37/F	HSPN	51/M	Compatible	NE	12	Cr 0.88 U-pro 1+, U-ob -
6	44/F	DMN	64/F	Incompatible	NE	3	Cr 0.88 U-pro -, U-ob -
7	48/F	Unknown	72/F	Compatible	-	5	Cr 1.95 U-pro 1+, U-ob -
8	27/M	HSPN	61/M	Compatible	+	2	Cr 1.86 U-pro -, U-ob -
9	39/M	Unknown	42/F	Incompatible	NE	2	Cr 1.28 U-pro 1+, U-ob 1+
10	54/M	IgAN	70/M	Compatible	NE	10	Cr 3.20 U-pro 1+, U-ob 2+

IgAN, immunoglobulin A nephropathy; CGN, chronic glomerulonephritis; DMN, diabetic nephropathy; HSPN, Henoch-Schönlein purpura nephritis; M, male; F, female; DSA, donor-specific antibody; NE, not examined; Cr, creatinine; U-pro, urinary protein; U-ob, urine occult blood; +, positive; -, negative.

**Table 2. Pathological findings of the patients with monoclonal IgG deposits in the TBM**

Patient	Duration from transplantation (days)	Biopsy	Subclass and light chain in the TBM	Monoclonal IgG in the TBM	Light chain in the TBM	C3c in the TBM	C4 in the TBM	C4d in the TBM	Complications	IFTA (%)
1	1967	Diagnostic	IgG1κ	+	+	+	-	+	None	40
2	782	Surveillance	IgG1κ (granular)	2+	2+	+	-	+ ~ 2+	None	50
3	1130	Surveillance	IgG1κ (granular)	2+	+	+	-	+	IgAN	25
4	6058	Diagnostic	IgG1κ	+	+	+	-	-	CAAMR	60
5	1753	Diagnostic	IgG1κ	2+	2+	+	-	+	None	25
6	13	Surveillance	IgG2λ	+	+	-	-	-	None	15
7	216	Surveillance	IgG1κ	+	+	+	-	+ ~ 2+	ATMR	50
8	556	Diagnostic	IgG3κ	2+	2+	+	+	-	None	30
9	80	Diagnostic	IgG2κ	+	+	-	-	-	ATMR	5
10	969	Surveillance	IgG1κ	2+	2+	+	-	+	ATMR IgAN	60

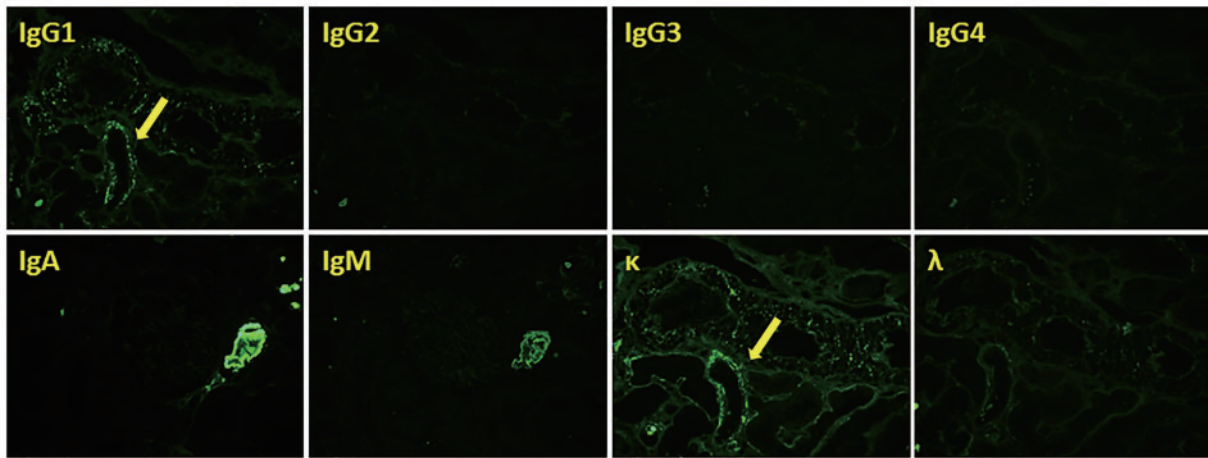
IgAN, immunoglobulin A nephropathy; CAAMR, chronic active antibody-mediated rejection; ATMR, acute T-cell-mediated rejection.

Donor-specific antibody (DSA) was detected in two patients. The median follow-up period from transplantation was 7.5 years (range 2–18). One patient progressed to renal graft failure. The median serum creatinine at the last follow-up was 2.5 mg/dL (range 0.88–6.12). No patient had hematologic disease.

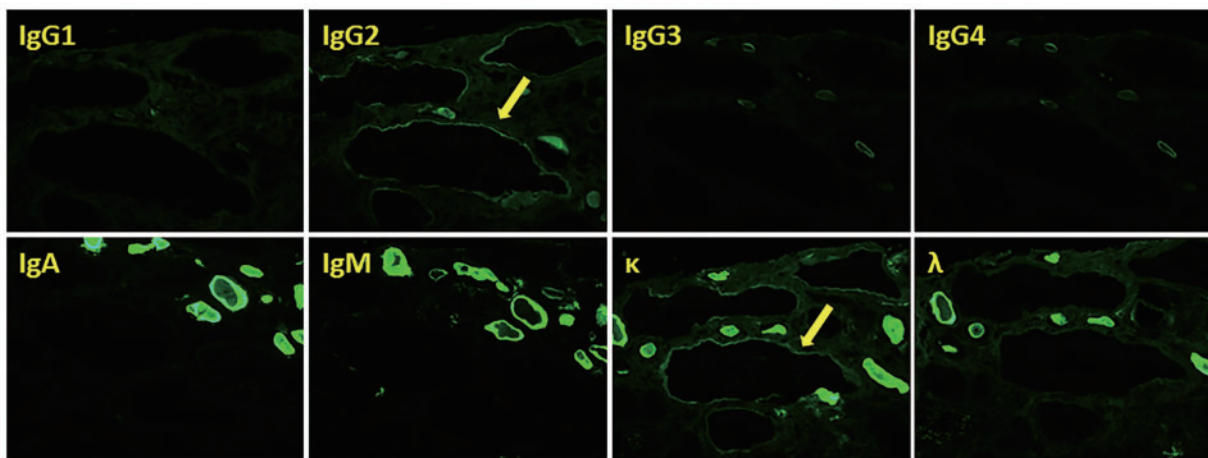
### Pathological findings

Pathological characteristics of monoclonal IgG TBMID are displayed in Table 2. The median duration of emerging deposits from transplantation was 875.5 days (range 13–6058). Five patients had diagnostic biopsies and five patients had surveillance biopsies. On IF, Ig and complement deposition were identified exclusively in the TBM except in two biopsies diagnosed

as IgA nephropathy with glomerular IgA and C3c deposition (Patients 3 and 10). IgG1–4 subclasses showed monotypic deposits, including seven IgG1κ, one IgG2κ, one IgG2λ and one IgG3κ. Two biopsies showed granular deposition with positivity randomly distributed in the cytoplasm (Figure 1), and eight biopsies showed linear deposition surrounding the tubular and corresponding perimeters (Figure 2). C3c staining occurred in eight biopsies, C4 in one biopsy and C4d in six biopsies. No biopsies showed positivity of IgA, IgM and C1q in the TBM. On EM, all biopsies of IgG1κ TBMID showed abundant and large granular electron-dense deposits (EDDs) in the TBM (Figure 3). Conversely, in IgG2 and IgG3 TBMID, EDDs were not present in the TBM. On IF and EM, immune deposits or



**FIGURE 1:** Representative images for granular type of monoclonal TBMID. This case (Patient 2) showed that granular IgG1 and light chain  $\kappa$  depositions in TBM (yellow arrow). IgG2, IgG3, IgG4, IgA, IgM and light chain  $\lambda$  were negative in TBM.



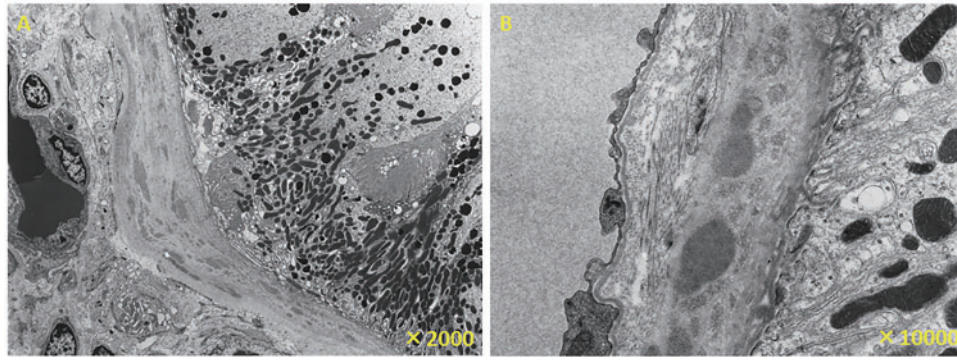
**FIGURE 2:** Representative images for linear type of monoclonal TBMID. This case (Patient 9) showed that linear IgG2 and light chain  $\kappa$  depositions in TBM (yellow arrow). IgG1, IgG3, IgG4, IgA, IgM and light chain  $\lambda$  were negative in TBM.

EDDs were located in the TBM of proximal tubules in all cases (Figure 4). One patient was diagnosed with chronic active antibody-mediated rejection (AMR) (g1, ptc1, cg3 and C4d2 according to the Banff classification, severe peritubular capillary (PTC) basement membrane multilayering and serologic evidence of DSA) (Patient 4). One patient showed moderate microvascular inflammation and chronic tissue injury (g1, ptc1, cg0 and C4d0 according to the Banff classification and severe PTC basement membrane multilayering). However, this patient did not meet the diagnostic criteria for chronic active AMR, because DSA was not detected and C4d was negative in the PTC (Patient 7). Three patients were diagnosed with acute T-cell-mediated rejection (TMR) (i2, t3, v1, cv0, ti2, i-IFTA0; i2, t2, v0, cv0, ti2, i-IFTA0; and i2, t3, v0, cv0, ti2, i-IFTA0 according to the Banff classification for Patients 7, 9 and 10, respectively). Plasma cell infiltration and CD68, CD138 and IgG4 immunostaining were not identified in any patients. Vacuolization in the tubular epithelium was found in one biopsy (Patient 9). Median progression of interstitial fibrosis and tubular atrophy (IFTA) of monoclonal IgG TBMID was 36% (range 5–60). The median

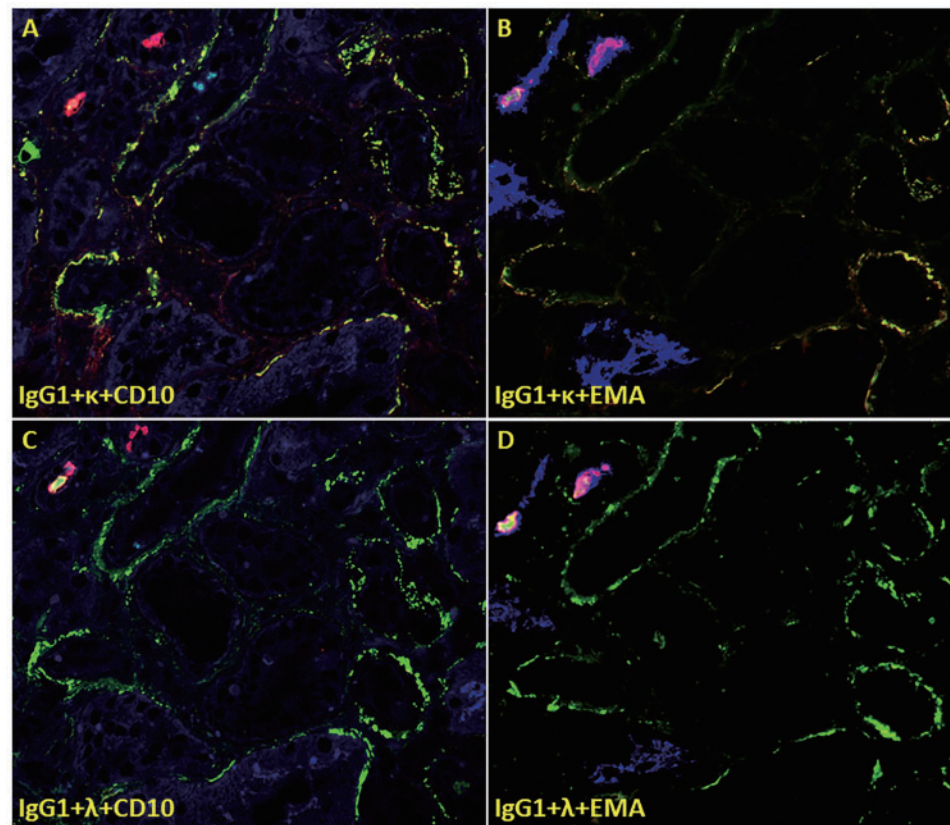
IFTA in IgG1 $\kappa$  TBMID was 50% (range 25–60). Nine of 10 cases exhibited tubulointerstitial scarring without inflammatory cell infiltrations (i-IFTA0 according to the Banff classification). One case (Patient 7) exhibited moderate mononuclear cell infiltration around atrophic tubules (i-IFTA2 according to the Banff classification).

#### Clinicopathological comparison between monoclonal and polyclonal IgG TBMID

Table 3 shows the statistical analysis comparing monoclonal IgG TBMID, monoclonal IgG1 $\kappa$  TBMID and polyclonal IgG TBMID. There were no significant differences between the study groups in patient age and sex, donor age, ABO compatibility, duration of emerging deposits from transplantation, diagnostic biopsy, codeposition with C3c, presence of AMR and TMR, presence of DSA, follow-up period and serum creatinine at the last follow-up. Monoclonal IgG deposition, particularly IgG1 $\kappa$  deposition, had a significantly higher degree of IFTA than polyclonal IgG deposition ( $P = 0.010$  and  $P = 0.00060$ , respectively).



**FIGURE 3:** EM revealed granular EDDs in the TBM without an organized structure [(A)  $\times 2000$ ; (B)  $\times 10\,000$ ].



**FIGURE 4:** IF findings of tubular segment markers and heavy and light chain staining in Patient 2. (A) IgG1 (green) and  $\kappa$  (red) are merged in the tubules that showed CD10 (blue) positivity. (B) IgG1 (green) and  $\kappa$  (red) are merged in the tubules that showed EMA (blue) negativity. (C) Both IgG1 (green) and CD10 (blue) are positive in tubules that showed  $\lambda$  (red) negativity. (D) IgG1 (green) is positive in tubules that showed no staining for  $\lambda$  (red) or EMA (blue).

## DISCUSSION

In recent years, glomerulonephritis characterized by monoclonal IgG deposition was reported as PGNMID [6]. Previous studies reported that PGNMID could recur frequently and progress to graft failure [7, 11]. PGNMID was considered a new entity to be distinguished from glomerulonephritis with immune complex deposition.

Our study demonstrated monoclonal IgG TB MID in renal allografts. Previous reports have shown that TB MID in renal allografts are associated with glomerulonephritis, BK virus

nephropathy and rejection [2–4]. In this study, monoclonal IgG deposition was exclusively found in the TBM, not glomerulus. Present or past BK virus nephropathy was not found. Four patients experienced rejection during the clinical course. These results indicate that the prognosis of monoclonal IgG TB MID is different from that in TB MID, as in past reports.

In our patients, monoclonal IgG1 $\kappa$  TB MID was found in seven biopsies and IgG2 $\kappa$ , IgG2 $\lambda$  and IgG3 $\kappa$  TB MID were each found in one biopsy. C3c was positive in monoclonal IgG1 $\kappa$  and IgG3 $\kappa$  TB MID but negative in monoclonal IgG2 $\kappa$  and IgG2 $\lambda$  TB MID. On EM, EDDs in the TBM were found in only

**Table 3. Statistical analysis of the patients with monoclonal IgG deposits in the TBM**

	①Monoclonal IgG deposition/ (n = 10)	②IgG1κ deposition (n = 7)	③Polyclonal IgG deposition (n = 6)	P-value (comparison ① and ③/ (comparison ② and ③)
Age (years)	46 (11–61)	54 (11–61)	47 (21–63)	0.77/0.81
Sex (male)	6	5	4	1/1
Donor age (years)	60.5 (42–72)	60 (44–72)	53.3 (34–65)	0.17/0.23
ABO incompatible	4	2	4	0.61/0.59
Duration from transplantation (days)	875.5 (13–6058)	1130 (216–6058)	971.5 (645–3608)	0.49/0.84
Diagnostic biopsy Subclass	5 IgG1κ, 7; IgG2κ, 1; IgG3κ, 1; IgG2λ, 1	3 IgG1κ, 7	3	1/1
C3 codeposition	8	7	6	0.50/1
AMR	2	2	2	0.52/1
TMR	3	2	0	0.25/0.46
DSA	2	1	2	0.60/0.56
Follow-up period (years)	7.5 (2–18)	10 (5–18)	6 (1–17)	0.77/0.28
IFTA (%)	36 (5–60)	50.0 (25–60)	10 (5–20)	0.010/0.00060
Final follow-up creatinine (mg/dL)	2.5 (0.88–6.12)	1.26 (0.88–6.12)	1.52 (0.93–1.97)	1/0.81

Data are presented as median (range). Categorical variables were compared by Fisher's exact test and continuous variables were compared by Mann-Whitney test.

monoclonal IgG1κ TBMID. Conversely, EDDs were absent in the TBM in monoclonal IgG2κ, IgG2λ and IgG3κ TBMID.

There are two main theories regarding the pathogenesis of immune complex formation in glomeruli: circulating immune complex trapping and *in situ* immune complex formation. However, it is likely that the pathogenesis of the TBM immune complex formation is different from that of glomeruli [12, 13]. It is presumed that immune complex in TBM is formed *in situ* in DNA or DNA binding proteins, such as already deposited protein or endogenous tubular epithelial protein [12].

Human IgG is categorized into four subclasses according to its heavy chains, which elicit different immunological and inflammatory responses [14]. IgG1 is the most prevalent (60.3–71.5%), followed by IgG2 (19.4–31%), IgG3 (5–8.4%) and IgG4 (0.7–4.2%), which were accounted for in small amounts in serum [15]. IgG1 and IgG3 demonstrate activation of the complement system, whereas IgG2 and IgG4 have poor activation of the complement system [16]. The significance of IgG subclasses in TBMID is unclear. One previous report showed that IgG1 and IgG3 play important roles in complement activation associated with IgG4-related tubulointerstitial nephritis [17], whereas another report showed that IgG subclass distribution does not account for the differences in the histologic finding of lupus nephritis [12]. In the present study, EDDs in the TBM were found in the only patient with monoclonal IgG1κ TBMID, where IFTA was significantly progressed, suggesting that IgG1 had an affinity to the protein in the TBM. Next, the formed EDDs induced complement activation, resulting in tubulointerstitial damage. However, previous studies focused only on polyclonal IgG TBMID, and association of the monoclonal IgG subclass and TBM were not examined in either the clinical or experimental settings [12, 17–19]. Therefore further studies are needed to confirm how immune complex is formed in the TBM and to determine association between the IgG subclass and the TBM.

The histological data suggest that all patients with monoclonal IgG1κ TBMID progressed to moderate to severe IFTA (25–

60%) and those in the other subclasses (IgG2κ, IgG2λ, IgG3κ) progressed to mild to moderate IFTA (5–30%). The patients with polyclonal TBMID progressed to mild IFTA (5–20%) and those with monoclonal IgG, particularly IgG1κ TBMID, demonstrated a significantly higher degree of IFTA in follow-up biopsy compared with patients with polyclonal IgG TBMID ( $P < 0.05$ ). There were no significant differences between monoclonal IgG, monoclonal IgG1κ and polyclonal IgG TBMID in recipient and donor age, duration of emerging deposits from transplantation, follow-up period, acute and chronic rejection or serum creatinine at the last follow-up, factors that are considered to increase the risk of IFTA [20, 21]. Under normal conditions, protein is taken up from the urine by endocytosis into the tubular epithelial cells [22]. EDD formation causes tubular alterations such as thickening and splitting of the TBM. In disease conditions there may be alterations of the protein in any of the tubular compartments and these alterations enhance complement activation, endocytic activity and upregulation of genes, leading to the production of mediators that induce inflammation, tubular degeneration and fibrosis [23]. The deposition of immune material in TBM is part of a spectrum of ultrastructural changes that may cause functional changes in the tubular epithelium [24]. Such changes are expected to be associated with progressive tubular atrophy.

We acknowledge that there are several limitations in this study. First, cases of monoclonal IgG TBMID are very rare. We have found only 10 patients in our institution in 8 years. Second, because this is a retrospective study, some laboratory data were not obtainable. Although SV-40 staining was negative in all biopsies, plasma or urine DNA loads and decoy cells in urine cytology were not investigated. Similarly, autoantibodies known to cause IgG deposition in TBM, such as in Sjögren's syndrome, were not examined. Therefore the possible association of monoclonal IgG TBMID, past BK virus infection and autoimmune diseases was not completely excluded. Third, in this research, monoclonality was prescribed only by IF. In PGNMID, paraprotein was not detected by immune

electrophoresis or immunofixation and deviation of serum free light chain was not found [6]. However, sensitive evaluation techniques, such as serum immunoblot and molecular studies of bone marrow, revealed a subtle plasma cell proliferation in most patients with IgA proliferative glomerulonephritis with monoclonal Ig deposits [25]. We did not perform immunofixation, immune electrophoresis or  $\kappa:\lambda$  ratio measurement in the present study. Therefore further investigation is required to define pathogenesis, clinical significance and association with hematological or autoimmune disorders.

In conclusion, this is the first research on cases of monoclonal IgG TBMID in renal allografts. Our research indicates that monoclonal IgG1 $\kappa$  TBMID is associated with EDD formation in the TBM and progression of IFTA.

## ACKNOWLEDGEMENTS

We thank Hideki Nakayama and Mayuko Ohno for their technical support. We thank Hideo Nakazawa for statistical analysis. The authors would like to thank Enago (<http://www.enago.jp>) for the English language review.

## CONFLICT OF INTEREST STATEMENT

None declared.

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Received: 8.12.2017; Editorial decision: 4.7.2018