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ORIGINAL ARTICLE

The Clinicopathologic Significance of Endothelial Tubuloreticular Inclusions in Glomerular Diseases

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ABSTRACT

Background: The presence of tubuloreticular inclusions (TRIs) in endothelial cells (ECs) always evokes suspicion of an association with underlying viral infections or autoimmune diseases. However, other underlying diseases can be associated with TRI expression. Since identification of the underlying disease is of primary consideration for management of glomerulonephritis (GN), it is important to clarify the clinical significance of TRI expression.

Methods: The authors studied 104 renal biopsy cases having TRI. They investigated their clinicopathological profiles and focused on potential connections with underlying diseases.

Results: Among 104 renal biopsy cases, 62 cases (59.6%) were associated with lupus nephritis (LN) and 20 cases (19.2%) were associated with a viral infection (hepatitis B virus (13), hepatits C virus (4), and human immunodeficiency virus (3)). Other underlying disease groups included membranous GN (MGN) (7), IgA nephropathy (7), Henoch-Schoenlein purpura (HSP) nephritis (2), and others (6). The incidence of TRIs in both LN and viral infections was significantly higher than for other diseases ($p < 0.0001$). Among 7 MGN cases, 2 cases were diabetes, 1 case was associated with lung cancer, another case with antineutrophilic cytoplasmic antibody (ANCA), and the others showed no evidence of systemic disease. On immunofluorescence (IF) study, 2 MGN cases, 2 IgA nephropathy cases, and 1 HSP nephritis case showed C1q deposition, with no evidence of SLE.

Conclusions: TRIs were identified in MGN and other glomerular diseases, including IgA nephropathy and HSP nephritis. However, a diagnosis of LN should be considered because TRIs associated with a full-house IF pattern are usually found in LN.

Keywords: Endothelial cells, lupus nephritis, membranous glomerulonephritis

Tubuloreticular inclusions (TRIs) are unique subcellular structures characterized by small clusters of anastomosing tubule-like structures that arise from the membranes of the rough endoplasmic reticulum in a variety of cell types [1,2]. The induction of TRIs in nonlymphoid or peripheral blood mononuclear cells might relate to the biological activities of alpha- or beta-interferons (IFN) and, consequently, may correlate clinically with alpha-IFN treatment [3,4].

TRIs are most commonly found in endothelial cells (ECs) and lymphocytes of patients with autoimmune or collagen vascular disorders. In acquired immunodeficiency syndrome (AIDS) patients, TRIs have been described in various tissues throughout the body, including the lung, kidney, liver, muscle, and skin [5].

In a variety of glomerular diseases, the presence of TRIs in ECs always evokes suspicion of their association with underlying viral infections or autoimmune diseases such as systemic lupus erythematosus (SLE). However, some other underlying diseases might be associated with TRI expression [6]. Identification of

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the underlying diseases is the primary consideration for the management of glomerular diseases.

To clarify the clinical significance of TRI expression in glomerulonephritis (GN), 104 renal biopsy cases with an ultrastructural appearance of TRIs in glomerular ECs were recruited. We investigated their clinical and pathological profiles and focused on potential connections with an underlying disease.

MATERIALS AND METHODS

Among 2472 native renal biopsy cases received and processed at the Department of Pathology, Chungnam National University Hospital, from July 2002 to June 2011, 104 cases (4.2%) showing an ultrastructural appearance of TRIs in glomerular ECs were reviewed retrospectively. We analyzed their clinicopathological profiles and focused on potential connections with an underlying disease.

Examination of Renal Biopsies

Histologic slides from each biopsy, stained with hematoxylin and eosin, periodic acid–Schiff (PAS), silver methenamine, and Masson's trichrome stains, were reviewed by a renal pathologist (Suh) who was blind to the clinical data.

For immunofluorescence (IF) study, 3-μm cryostat sections were stained with fluorescein isothiocyanate (FITC)-conjugated polyclonal rabbit IgA, IgG, IgM, C3, C1q, and fibrinogen (Dako, Glostrup, Denmark). An average of 10.8 glomeruli/case were examined for the IF study. The intensity of the IF reaction was graded on a scale of 0, trace (±), 1+, 2+, and 3+. The pattern of IF reaction was classified as granular or linear. The location of IF reaction was classified as glomerular capillary walls, mesangial areas, or both. The location (mesangial, subendothelial, subepithelial, or intramembranous) and relative amount of electron-dense deposits within glomeruli on a scale of 0, 1+, 2+, and 3+ were also recorded.

For electron microscopic study, samples were fixed in 2.5% glutaraldehyde and 0.1 M sodium phosphate butter at pH 7.2 and postfixed in 1% osmium tetroxide. Semithin sections (1 μm) were stained with toluidine blue. An average of 2.3 glomeruli/case were examined by electron microscopy. These were embedded in Epon and sectioned using an ultramicrotome. After uranyl acetate and lead citrate staining, electron microscopic examination was performed under a transmission electron microscope (H-7650, Hitachi, Japan) equipped with a soft imaging system (Morada, Japan). We examined an average of 1.3 grids from each specimen, with special attention to the presence of unequivocal TRIs in glomerular ECs. The location (mesangial, subendothelial, subepithelial, or intramembranous) and relative amount of electron-dense deposits within glomeruli on a scale of 0, 1+, +2, and 3+ were also recorded.

Clinicopathologic Correlations

To search for the underlying disease, we carefully reviewed patient records with respect to their clinical and laboratory information related to autoimmune diseases, viral infection episodes, neoplasias, and diabetes mellitus. Laboratory findings, including HBsAg, anti-HCV, anti-HIV, anti-streptolysin O (ASO), antinuclear antibodies (ANA), anti-double-stranded DNA (anti-ds DNA), anti-neutrophilic cytoplasmic antibodies (ANCA), and complements were screened at the time the renal biopsy was performed. Association of TRIs with any infections, such as streptococci, syphilis, mycoplasma, and rubella, was also analyzed. All study procedures were approved by the Institutional Review Board of Chungnam National University Hospital.

Statistical Analysis

The relative incidences of diseases with TRIs were compared using the chi-square test. For statistical analyses, $p < 0.05$ was considered statistically significant. Statistical analysis was performed using SPSS version 15.0 (SPSS Inc., Chicago, IL, USA) software.

RESULTS

Histologic Findings

Among 104 renal biopsy cases (Table 1), 62 cases (59.6%) were associated with lupus nephritis (LN) and 20 cases (19.2%) were associated with viral infections (hepatitis B virus (HBV) (13 cases), hepatitis C virus (HCV) (4 cases), and human immunodeficiency virus

TABLE 1. Underlying diseases showing tubuloreticular inclusions in endothelial cells.

Underlying diseases	Cases with TRIs No. (%)	Total case No. (%)
Lupus nephritis	62 (59.6)	120 (4.9)
Virus infection	20 (19.2)	39 (1.6)
Hepatitis B	13	28
Hepatitis C	4	8
HIV	3	3
Others	22 (21.2)	2313 (93.6)
Membranous GN	7	325
IgA Nephropathy	7	1069
Henoch-Schoenlein purpura	2	72
Diabetes mellitus	1	97
Reumatoid arthritis	1	
Multiple myeloma	1	2
Preeclampsia	1	2
Focal segmental glomerulosclerosis	1	
Fibrillary GN & amyloidosis	1	26
Other diseases	0	720
Total	104 (100.0)	2472 (100.0)

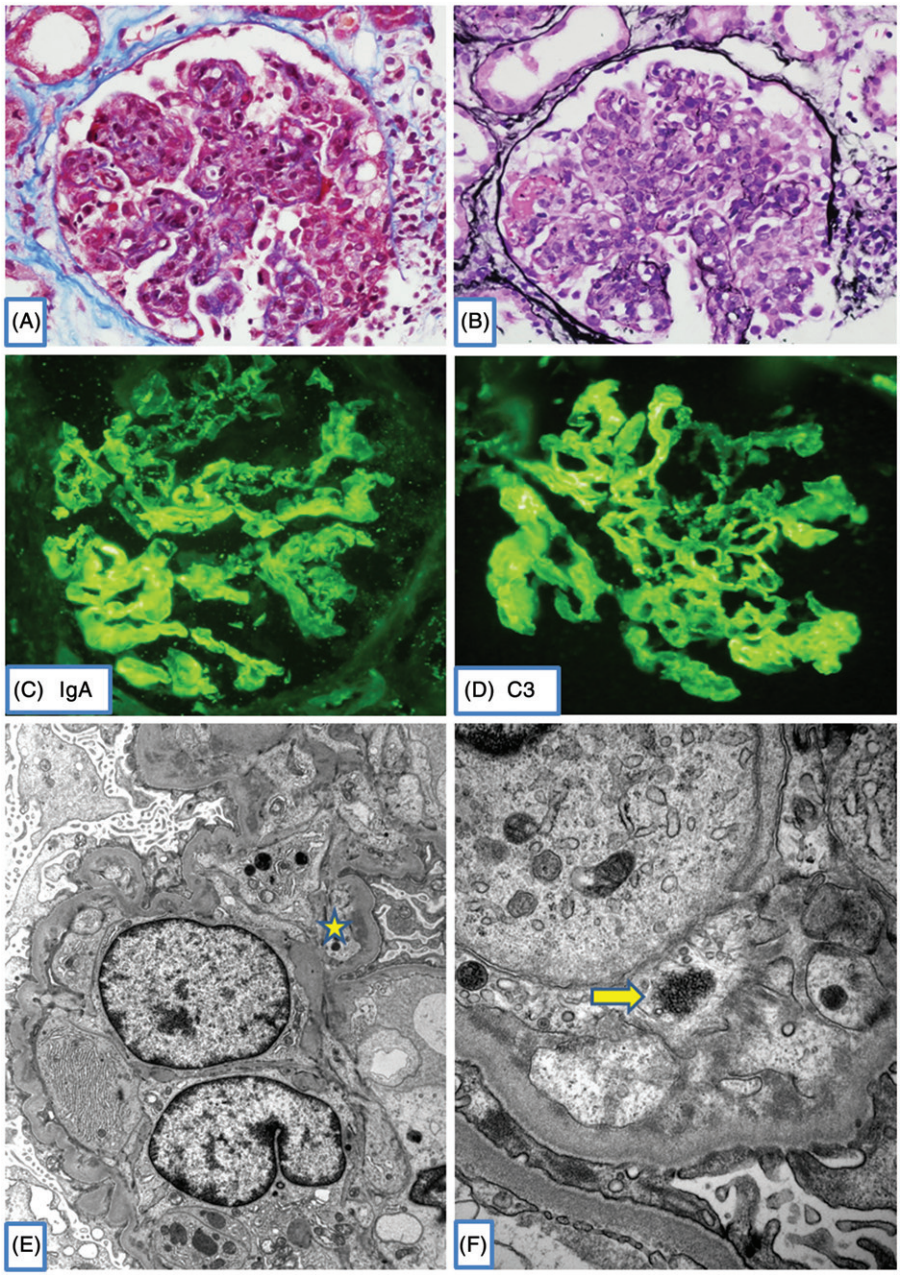

FIGURE 1. Diffuse endocapillary proliferative glomerulonephritis in a AIDS patient (case No. 70). Diffuse endocapillary proliferation with epithelial crescent formation, H&E, ×400 (A), PA-silver, ×400 (B). Granular deposits of IgA and C3 in mesangial spaces and along capillary walls. Immunofluorescence study for IgA, x400 (C), C3, ×400 (D). Endocapillary proliferation with electron-dense deposits in mesangial spaces (star) and tubuloreticular inclusions in endothelial cells (arrow), uranyl acetate and lead citrate, ×8,000 (E), 30,000(F).

(HIV) (3 cases), Figure 1). Other underlying disease groups and their number of associated cases included membranous GN (MGN) (7), IgA nephropathy (7), Henoch-Schoenlein purpura (HSP) nephritis (2), and others (6).

Clinical and Laboratory Findings

Clinical and laboratory findings of 7 MN cases showing TRIs are summarized in Table 2. Among 7 MGN cases, 2 cases (cases 41 and 94) were diabetes, 1 case (case 17) was associated with lung cancer, another case (case 91) with antineutrophilic cytoplasmic antibody (ANCA, Figure 2), 1 case (case 93) with gastric *Helicobacter pylori* (*H. pylori*) infection, and the others showed no evidence of systemic disease (Table 2). One HSP nephritis case (case 21) was associated with stomach cancer. In this case, mycoplasma antibody was weakly positive and rapid plasma reagin (RPR) was also positive. Among 7 IgA nephropathy cases, 1 case (case 104) was associated with mantle cell lymphoma (Table 4, Figure 3). Two cases (cases 68 and 90) showed an increased ASO titer, but there was no other clinical evidence of streptococcal infection.

TABLE 2. Membranous nephropathy showing tubuloreticular inclusions.

Case No.	Age/sex	Underlying disease	ANA/ Anti-ds DNA	HBsAg/Anti-HCV/ Anti-HIV	ASO (IU/mL)	C3/C4 (mg/dL)	Follow-up (months)
8	25/F	NED	−/−	−/−/−	<20	62/16	92
17	46/F	Lung cancer	−/−	−/−/−	94	122/48	12
41	48/F	DM	−/−	−/−/−	7	157/49	87
90	66/F	NED	−/−	−/−/not done	269	114/28	38
91	75/M	ANCA (MPO, PR3+)	−/−	−/−/−	86	97/32	32
93	62/F	*H. pylori* infection	−/−	−/−/−	48	103/37	32
94	50/F	DM	−/−	−/−/−	19	131/28	30

Normal range for ASO (0–200 IU/mL), C3 (86–160 mg/dL), C4 (17–45 mg/dL). NED, no evidence of disease.

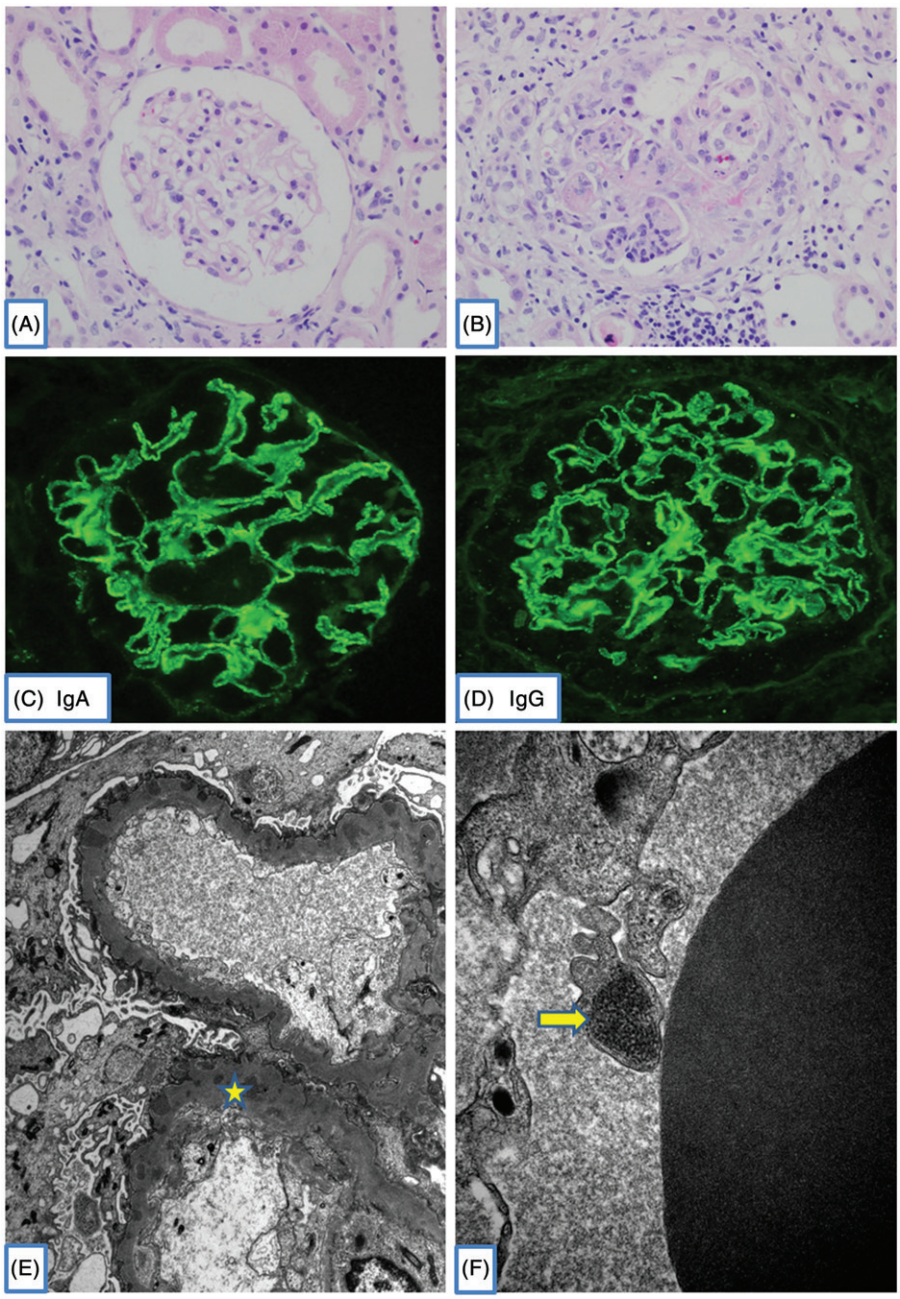

FIGURE 2. Membranous glomerulonephritis with anti-neutrophilic cytoplasmic antibody (case No. 91). Diffuse thickening of capillary walls (A) with epithelial crescent and fibrinoid necrosis (B). Granular deposits of IgA and IgG along capillary walls. Immunofluorescence study for IgA, ×400 (C), IgG, ×400 (D). Epimembranous electron-dense deposits along capillary walls (star) and tubuloreticular inclusions in endothelial cells (arrow), uranyl acetate and lead citrate, ×8,000 (E), 40,000(F).

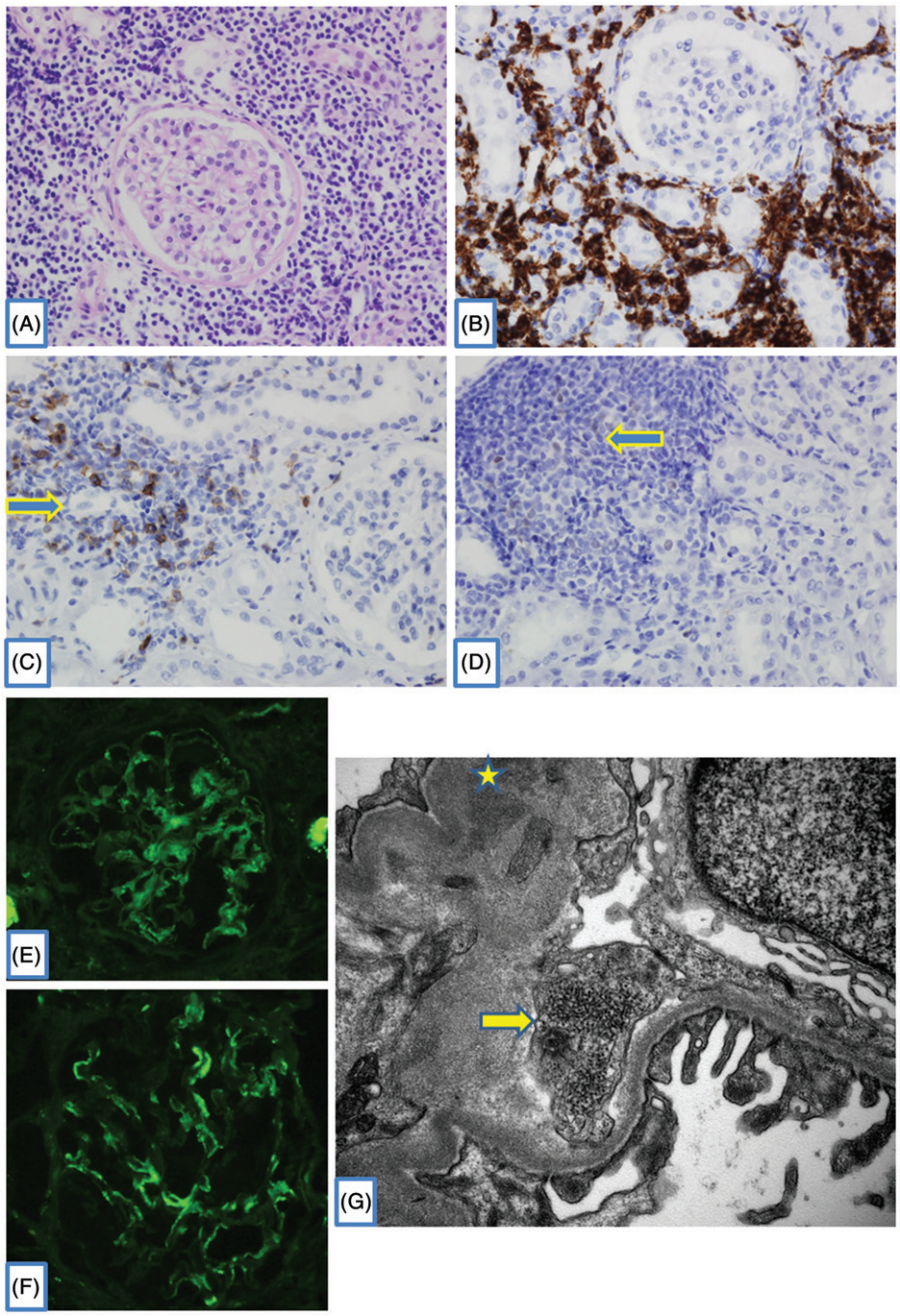

FIGURE 3. Focal proliferative glomerulonephritis with mantle cell lymphoma (case No. 104). Nodular periglomerular infiltrate of atypical lymphoid cells, H&E, ×400 (A), Immunohistochemical stain for anti-CD20, ×400 (B), Anti-CD5 (C), Anti-cyclin D1 (D). Granular deposits of IgA and C3 in mesangial spaces and along capillary walls. Immunofluorescence study for IgA, ×400 (E), C3, ×400 (F). Electron-dense deposits in mesangial spaces (star) and tubuloreticular inclusions in endothelial cells (arrow), uranyl acetate and lead citrate, ×30,000(G).

Among 7 MGN cases, 7 IgA nephropathy cases, and 2 HSP nephritis cases, 1 MGN case (case 8), 1 HSP nephritis case (case 21), and 1 IgA nephropathy case (case 92) exhibited a decrease in the serum C3 level with no evidence of SLE (Tables 2, 4). On IF study, 2 MGN cases (cases 8 and 17), 2 IgA nephropathy cases (cases 47 and 92), and 1 HSP nephritis case (case 60) showed C1q deposition in glomeruli, with no clinical evidence of SLE. On ultrastructural examination, 4 MGN cases showed mesangial and/or subendothelial electron-dense deposits, in addition to epimembranous deposits. One HSP nephritis case and 4 IgA nephropathy cases showed epimembranous deposits, in addition to mesangial and/or subendothelial deposits (Tables 3, 5).

Clinical Follow-up

The follow-up period of 7 MGN cases, 7 IgA nephropathy cases, and 2 HSP nephritis cases ranged from 8 months to 92 months after renal

TABLE 3. Immunofluorescence and ultrastructural findings of membranous nephropathy showing tubuloreticular inclusions.

	Immunofluorescence study						EM study (electron-dense deposits)		
Case No.	IgA	IgG	IgM	C1q	C3	Fibrinogen	Epimembranous	Mesangial	Subendothelial
8	–	++, C	±, C	±, C	±, C	±, C	+++	–	–
17	±, C	+, C	±, C	±, C	±, C	±, C	+++	+	–
41	–	+, C	–	–	–	–	+++	–	–
90	±, C	+++, C	±,C	–	++,C	+,C	+++	+	+
91	++,C	++, C	+, C	–	+, C	±, C	+++	+	+
93	±, C	+++,C	+, C	–	+, C	±, C	+++	+	+
94	±, M	±, C	±, M	–	–	±, M	+++	–	–

M, mesangial; C, along capillary walls.

TABLE 4. IgA nephropathy and Henoch-Schoenlein purpura nephritis* showing tubuloreticular inclusions.

Case No.	Age/Sex	Underlying disease	ANA/ Anti-ds DNA	HBsAg/Anti-HCV/ Anti-HIV	ASO (IU/mL)	C3/C4 (mg/dL)	Follow-up (months)
*21[a]	77/F	Stomach cancer, HSP	–/–	–/–/–	52	53/26	10
47	9/F	NED	–/–	–/–/–	77	150/33	12
*60	34/F	HSP	–/–	–/–/not done	32	89/30	32
64	59/M	NED	–/–	–/–/–	57	77/21	10
68	22/F	NED	–/–	–/–/–	287	115/25	63
92[b]	34/F	NED	–/–	–/–/–	32	56/11	32
97	42/F	NED	–/–	–/–/–	65	78/29	26
99	37/F	NED	–/–	–/–/–	83	82/28	8
104	45/F	Mantle cell lymphoma	–/–	–/–/–	31	88/23	31

[a]Mycoplasma weakly positive and RPR reactive.
[b]Rubella antigen 27.0 IU/mL (10 years ago).

TABLE 5. Immunofluorescence and ultrastructural findings of IgA nephropathy and Henoch-Schoenlein purpura nephritis* showing tubuloreticular inclusions.

	Immunofluorescence study						EM study (electron-dense deposits)		
Case No.	IgA	IgG	IgM	C1q	C3	Fibrinogen	Epimembranous	Mesangial	Subendothelial
*21	+, M	–	–	–	±, M	–	–	+	+
47	±, C	+, C	±, C	±, C	±, C	±, C	–	+	–
60*	++, M+C	+, M+C	±, M+C	±, M+C	++, M+C	±, M+C	+	+++	++
64	–	+, C	–	–	–	–	–	+++	+
68	++,M	±, M	+, M	–	++,M	±, M	+	++	+
92	++, M+C	±, M+C	+, M+C	±, M+C	+++, M+C	±, M+C	+	+++	+
97	±, M	–	±, M	–	±, M	±, M	+	–	–
99	++, M+C	±, M+C	+, M+C	–	++, M+C	+, M+C	++	–	+
104	+++, M+C	±, M+C	+, M+C	–	++, M+C	±, M	–	+++	+

M, mesangial; C, along capillary walls.

biopsy, with a mean follow-up time of 34.2 months (SD 25.7 months). During the follow-up period, there was no serologic and/or clinical evidence of SLE or any viral infection, even though an anti-HIV test was not performed in 2 cases (cases 60 and 90).

Statistical Comparisons of the Relative Incidence of TRIs among Different Groups

Among 2473 native renal biopsy cases reviewed, 159 cases (6.4%) were either LN or GN associated with viral infection and 2313 cases (93.6%) were other diseases. Among 159 LN or GN associated with viral infection, TRIs were identified in 82 cases (51.6%). For other disease cases (2313 cases), 22 cases (1.0%) showed TRIs. For other diseases, 22 cases (4.2%) showed TRIs. The incidence of TRIs in both LN and viral infection was significantly higher than for other diseases ($p < 0.0001$) (Table 6).

DISCUSSION

In vivo, TRIs occur most frequently in endothelial cells and lymphocytes in patients with autoimmune diseases, viral infections, and almost all HIV

TABLE 6. Comparisons of the incidence of diseases showing tubuloreticular inclusions in endothelial cells.

Underlying diseases	Cases with TRIs (%)	Cases with no TRIs (%)	Total cases (%)	*p* Value (chi-square)
Lupus nephritis and Viral infection	82 (78.8)	77 (3.3)	159 (6.4)	<0.0001
Other diseases	22 (21.2)	2291 (96.7)	2313 (93.6)	
Total	104 (4.2)	2368 (95.8)	2472 (100.0)	

infections. The inducers of TRIs in vivo are not firmly established. However, clinical and experimental studies indicate that the occurrence of these structures in these diseases is directly related to the endogenous elevation of α- and β-interferon (INF) but not of γ-INF [1].

Under normal physiological conditions, IFN genes are generally silent in cells [7]. Production of IFNs requires stimulation by viruses, microbial products, or specific chemicals via triggering of the signaling systems linked to Toll-like receptors (TLRs) [7,8].

In our series, 62 cases (59.6%) out of 104 renal biopsy cases with TRIs were associated with LN and 20 cases (19.2%) were associated with a viral infection. Other underlying disease groups included MGN (7 cases), IgA nephropathy (7 cases), HSP nephritis (2 cases), and others (6 cases). In this study, the incidence of TRIs in both LN and GN associated with viral infection was significantly higher than for other diseases ($p < 0.0001$) (Table 6).

A "full-house" IF pattern is defined as simultaneous detection of IgA, IgG, IgM, C1q, and C3 deposits in renal biopsy specimens [9]. Association of endothelial TRIs with the full-house pattern is highly suggestive of lupus nephritis [10]. Expression of endothelial TRIs is a more significant early sign of SLE than full-house IF glomerulopathy, especially in pediatric cases [10]. Pathologically, patients in the autoimmune group tended to have more heterogeneous membranous deposits with frequent mesangial and subendothelial deposits. While all patients of the autoimmune group presented complement C1q in glomeruli, more than two-thirds of the patients in others groups were negative for C1q. In this study, 1 MGN case, 1 HSP nephritis case, and 2 IgA nephropathy cases showed the full-house IF pattern. Four MGN cases showed mesangial and/or subendothelial electron-dense deposits, in addition to epimembranous deposits. However, there was no clinical or laboratory evidence of SLE. One HSP nephritis case (case 21) associated with stomach cancer showed a weakly positive reaction for mycoplasma antibody and a positive reaction for RPR. Several cases of GN have been reported to be associated with *Mycoplasma pneumoniae* infection [11–13]. Ishida et al. [14] reported that the elevation of serum interferon-γ and IL-6 may have played a central role in a patient with hemophagocytic lymphohistiocytosis secondary to *Mycoplasma pneumoniae* infection. TRIs in the HSP nephritis case (case 21) might be associated with *Mycoplasma pneumonia* infection.

Among 7 MGN cases and 7 IgA nephropathy cases, 1 MGN case and 2 IgA nephropathy cases exhibited a decrease in the serum C3 level with no evidence of SLE. Two MGN cases and 2 IgA nephropathy cases showed C1q deposition in glomeruli, with no clinical evidence of SLE.

TRIs are considered to be a specific ultrastructural marker for AIDS in various organs [15]. According to Haas et al. [16], lupus-like GN, defined by the presence of a full house of glomerular immunoglobulin and complement deposits on IF in the absence of serologic evidence of SLE, was found in 14 of 77 (18%) native renal biopsies from HIV-positive patients. This group was second to collapsing FSGS (HIV-associated nephropathy) (present in 37 biopsies, 6 with concurrent immune complex GN) among the most common glomerular lesions in HIV-positive patients undergoing a renal biopsy during this 5-year period. In our series, among 3 HIV-positive renal biopsy cases with endothelial TRIs, a 50-year-old male AIDS patient showed lupus-like diffuse proliferative GN.

Approximately 75% of MGN cases are thought to represent primary disease, whereas the remaining 25% of cases represent secondary forms of MGN that are most commonly related to SLE, infection (i.e., hepatitis B or C virus), malignancy, or drugs [6]. The ultrastructural finding of TRIs in MGN always evokes suspicion of an association with underlying diseases such as viral infections and autoimmune diseases. However, it is not clear whether some other underlying diseases are associated with TRI expression in MGN [6].

Recently, Yang et al. [6] analyzed 36 cases of idiopathic MGN with the ultrastructural appearance of TRIs in glomerular ECs. Among 36 cases, one-third showed no identifiable underlying etiology. Other underlying disease groups included autoimmune disease (25.0%), hepatitis (14.7%), potential *H. pylori* infection (16.7%), diabetes (5.6%), and lymphoma (5.6%). In our 104 renal biopsy cases, 7 cases (6.7%) were MGN. Among these, 2 cases were diabetes, 1 case was associated with lung cancer, another case with antineutrophilic cytoplasmic antibody (ANCA), one case with *H. pylori* infection and the others showed no evidence of systemic disease. Among 7 IgA nephropathy cases, 1 case was associated with mantle cell lymphoma.

The authors of several studies in Japan and Taiwan have proposed a pathogenic association of *H. pylori* infection with MGN [6,17,18]. They detected the *H. pylori* antigen in the glomeruli of patients with

MGN. They also addressed the pathogenetic role of *H. pylori* infection in MGN because remission of proteinuria was followed by eradication of *H. pylori* infection in some patients. Yang et al. [6] commented that finding glomerular TRIs in the *H. pylori* infection group implies a potential connection of INF-associated tissue response with *H. pylori* infection. In our study, 1 MGN case (case 93) was associated with gastric *H. pylori* infection. However, we did not perform an immunohistochemical stain for the *H. pylori* antigen.

Only rare cases of concurrent MGN and ANCA-associated necrotizing and crescentic GN (NCGN) have been reported. Gaber et al. [19] reported a case of MGN superimposed on ANCA-positive Wegener granulomatosis in 1993. The pathogenesis of MGN and ANCA-associated NCGN are distinct and both conditions are diagnosed simultaneously in the majority of cases. MGN with ANCA-associated NCGN represents a chance occurrence of two unrelated disease processes [20]. MGN with ANCA-associated NCGN is a rare dual glomerulopathy seen in patients with heavy proteinuria, acute renal failure, and active urine sediment. In 2 cases out of 14 MGN with ANCA-associated NCGN, TRIs were identified in endothelial cells [20]. In this study, a 75-year old male patient (case 91) who had MGN with positive ANCA exhibited TRIs. A 53-year old male patient (case 86) with C-ANCA associated NCGN exhibited TRIs.

Collapsing FSGS may occur after treatment with IFN-α, -β, or -γ and is typically accompanied by the ultrastructural finding of endothelial TRIs [21]. In this study, one FSGS case exhibited endothelial TRIs.

Glomerular diseases are associated with both chronic lymphocytic leukemia and non-Hodgkin lymphoma, particularly with B-cell lymphocytic type NHL [22–24]. Membranoproliferative GN is the most commonly reported histological diagnosis. Minimal change disease, FSGS, MGN, mesangial proliferative GN, IgA nephropathy, and monoclonal immunoglobulin deposit diseases have also been reported. Glomerular involvement has preceded, coexisted with, and even followed a diagnosis of lymphoma by several years [24–26]. Among 7 IgA nephropathy cases in this study, a 45-year old male patient (case 104) had mantle cell lymphoma. Renal parenchyma was also involved with mantle cell lymphoma (Figure 3). Even though the pathogenesis of non-Hodgkin lymphoma-associated paraneoplastic GN is poorly understood, a current concept focuses on immune complexes containing tumor antigens that are deposited in the glomeruli [25,26]. Autoimmune mechanisms and T-lymphocyte dysfunction have also been postulated to play a role in pathogenesis [25,26].

Future studies should be conducted to better understand the clinicopathological context of TRI expression in glomerular diseases. These studies should include well-designed serial long-term follow-up data.

DECLARATION OF INTEREST

The authors report no conflicts of interest. The authors alone are responsible for the content and writing of the paper.

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