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Original Article

ORIGINAL ARTICLE

The histopathological spectrum of kidney biopsies in patients with thymoma and myasthenia gravis: a report of 24 biopsies from a single institution

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ABSTRACT

Background. Nephropathy in patients with thymic diseases such as thymoma and myasthenia gravis (MG) is rare and has been described mostly as isolated case reports. Here we evaluate a series of kidney biopsies from patients with thymoma and/or MG from a single institution in order to better define the spectrum and relative frequencies of thymic disease–associated nephropathies.

Methods. We conducted a retrospective case series study of 32 462 native kidney biopsies from January 2005 through December 2019 at Cedars-Sinai Medical Center, Los Angeles, CA, USA.

Results. Twenty-four biopsy specimens (0.07%) from patients with a history of thymoma and/or MG were identified. Two patients had repeat biopsies. The most common pathologic diagnosis that could be immunologically attributed to thymic disease was minimal change disease (MCD; 45%), followed by tubulointerstitial nephritis (TIN; 14%), immune complex (IC)-mediated glomerulonephritis (9%), membranous nephropathy (5%) and immunoglobulin A (IgA) nephropathy (5%). Interestingly, 50% of the MCD and 67% of TIN cases concomitantly showed mild IgG-dominant IC deposition in mesangial areas and/or in tubular basement membranes. In the two patients with repeat biopsies, mild mesangial IC deposition developed in the MCD patient but disappeared in the TIN patient with the second biopsy. Pathologic diagnoses unlikely related to the underlying thymic disease were diabetic glomerulosclerosis (9%), acute tubular necrosis (9%) and monoclonal Ig deposition disease (5%).

Conclusions. Thymic disease is associated with a wide spectrum of kidney diseases affecting the glomerular and tubulointerstitial compartments, often with low-grade IC deposition. These findings suggest a role of immunologic dysregulation in the pathogenesis of thymic disease–associated nephropathy.

Keywords: immune complex deposition, minimal change disease, onconephrology, paraneoplastic syndrome, thymus, tubulointerstitial nephritis

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INTRODUCTION

Thymoma is a rare tumor that is frequently associated with a wide spectrum of autoimmune paraneoplastic syndromes [1], including pure red cell aplasia, systemic lupus erythematosus (SLE) and functional thyroid disorders. Among them, myasthenia gravis (MG) is the most common disease, observed in 39–44% of thymoma patients with MG [1, 2]. In addition, ∼16–27% of patients with thymoma are also diagnosed with other autoimmune diseases.

The mechanism by which thymomas cause autoimmune diseases is unclear. However, one theory proposes a role of autoantigen presentation by medullary thymic epithelial cells and dendritic cells, which is essential for the negative selection of autoreactive T cells in the thymus [3]. Thymomas are typically composed of cortical epithelial cells and a spectrum of immature T cells that usually reside in the thymic cortex. However, these cells lack an essential medullary epithelial cell function, which is the negative selection of the developing T cells. It is thought the immature T cells generated by the thymoma are then exported out of the thymus and into peripheral circulation, which could trigger autoimmune diseases in thymoma patients.

The development of proteinuria and nephrotic syndrome has been associated with several hematologic and solid organ malignancies [4]. Among the paraneoplastic kidney diseases, membranous nephropathy (MN) and minimal change disease (MCD) are the most common [5]. An association with malignancy has been also described with immunoglobulin A nephropathy (IgAN) [6], IgA vasculitis [6] and amyloid A (secondary) amyloidosis [7].

Paraneoplastic nephropathy associated with thymoma is uncommon and has been the subject of isolated case reports [8], the first of which was by Posner *et al.* [9]. It is estimated to occur in ∼2% of thymoma patients, with nephrotic syndrome accounting for only 2 (0.2%) of the 960 thymoma cases [10]. To date, the largest case series of thymoma-associated renal diseases is a multicenter retrospective study of 21 cases from multiple hospitals in France [11]. Here we report the largest series of kidney biopsy specimens from patients with thymoma and/or MG in a single institution in order to define the spectrum and relative frequency of thymic disease–associated nephropathy. The findings and the possible pathogenic mechanisms are also discussed in the context of a brief review of the previously published literature.

MATERIALS AND METHODS

We retrospectively reviewed 32 462 renal biopsy specimens evaluated at Cedars-Sinai Medical Center, Los Angeles, CA, USA, from 1 January 2005 to 31 December 2019. The biopsy specimens were received from multiple medical centers mainly in the southwestern USA and represent the range of nephrology practice settings, from small community groups to tertiary referral centers. Twenty-four biopsy specimens (0.07%) were identified from patients with a history of thymoma and/or MG. All clinical information was obtained via patient data and medical records provided at the time kidney biopsy was requested. All renal biopsies were processed according to standard techniques for light microscopy, immunofluorescence and electron microscopy (EM) and were interpreted by one of five renal pathologists. Segmental MN is defined by the presence of only segmental subepithelial deposits, involving <75% and >25% of the glomerular capillary basement membranes (GBMs) [12]; MN is defined by the subepithelial deposits involving >75% of GBMs. This study (protocol Pro00054530) was approved by the Institutional Review Board of Cedars-Sinai Medical Center.

RESULTS

In total, 32 462 native kidney biopsies were reviewed between 1 January 2005 and 31 December 2019. Twenty-four biopsy specimens (0.07%) were from patients with thymoma and/or MG. Two patients had repeat biopsies.

The main clinical characteristics of the 22 patients (24 biopsies) with thymoma and/or MG are summarized in Table 1. The mean patient age was 56 (± 17) years at the time of the first biopsy and 55% were female. Patients were most commonly White [16 patients (72%)], whereas African Americans and Asians were less common [3 patients each (14%)]. No patients had a known family history of thymic disease. One patient (Patient 15) had a family history of unspecified kidney disease. Ten (45%) patients had hypertension. The mean serum creatinine of patients was 3.0 (± 2.3) mg/dL at the first renal biopsy. Acute kidney injury (AKI) was noted in 15 (68%) patients, of which 1 (Patient 11) required hemodialysis (HD). The mean serum albumin of all patients was 2.3 (± 0.8) g/dL, the mean serum albumin of the patients with MCD was 1.7 (± 0.3) g/dL and the mean serum albumin of the remaining patients with other diseases was 3.1 (± 0.7) g/dL. Nephrotic range proteinuria was noted in 13 (59%) patients, 12 of which presented with full nephrotic syndrome. Hematuria was noted in 9 (41%) patients.

Twelve of 22 (55%) patients had thymomas. According to the current World Health Organization (WHO) classification (Table 2), thymoma is generally classified as spindle cell thymoma (Type A), thymoma composed of both epithelial cells and lymphocytic cells (Type B) and mixed thymoma (Type AB). Type B thymoma is further classified in Types B1–B3 based on the ratio of epithelial cells and lymphocytic cells [13]. Histological findings of thymoma were available in four patients: three (Patients 1, 2 and 3) showed Type AB of the WHO classification and one (Patient 4) showed Type B3. In most cases (10 of 12), the thymoma was surgically removed, with radiotherapy in one patient (Patient 11) and chemoradiotherapy in two patients (Patients 2 and 12). The remaining two patients without surgical resection received chemotherapy (Patient 5) or chemoradiotherapy (Patient 10).

Other autoimmune diseases are often observed in patients with thymoma and/or MG. In thymoma patients, it is called parathymic syndrome [14]. In our cohort of thymoma patients, MG was present in 4 of 12 (33%) patients. Besides MG and nephropathy, 7 of 22 (32%) patients manifested at least one other autoimmune disease. Two patients (Patients 3 and 7; 9%) had a diagnosis of SLE and six (27%) patients were diagnosed with hypothyroidism (hypo-TH). One patient (Patient 4; 5%) had autoimmune gastritis with vitamin B12 deficiency, psoriasis, migratory polyarthritis and pericarditis in addition to hypo-TH. Chronic *Candida albicans* infection, previously reported in patients with thymoma-associated immunodeficiency [15], was noted in one patient (Patient 2; 5%). Among thymoma patients, the types of renal pathology with extrarenal autoimmunity were similar to those without autoimmunity (Supplementary data, Table S1).

The time between diagnosis of thymoma and onset of nephropathy has been reported to be considerably variable [11]. In our study, only 1 (Patient 3; 8%) of the 12 thymoma patients had renal and mediastinal abnormalities diagnosed simultaneously. In nine (75%) patients, nephropathy occurred several months or

Table 1. Clinical and pathological characteristics

Patient no.	Age (years)/ sex	Race	Serum creatinine (mg/dL)	Serum album (g/dL)	Proteinuria (g/day)	Thymic pathology (treatment)	Associated diseases	Length between thymoma/ MG and nephropathy (months)	Immuno-suppression at nephropathy onset	Renal pathology
1	54/M	W	1.0	1.9	>3.5	T-AB (S)	Hypo-TH	61		MCD
2	60/M	W	1.4	1.8	>3.5	T-AB (S + R + CH)		13		MCD
	64/M	W	3.0	2.2	17.6	T-AB (S + R + CH)	C + Hypo-TH	61	CsA	MCD + IC
3	66/F	W	2.4	ND	–	T-AB (S)	Hypo-TH + L	0	HCQ	TIN + IC
	69/F	W	3.3	4.7	ND	T-AB (S)	Hypo-TH + L	29		TIN
4	73/M	W	1.1	2.3	9.7, g/gCr	T-B3 (S)	Hypo-TH + Others	170		MCD
5	73/M	W	ND	ND	16	T-NA (CH)		NA		MCD
6	67/F	W	4.0	ND	ND	T-NA (S)	MG + Hypo-TH	39		Granulomatous TIN
7	54/F	B	4.5	1.9	>3.5	T-NA (S)	L	36	CS + HCQ	MCD + IC
8	19/F	W	0.5	2.7	–	T-NA (S)	MG	60		TIN + IC
9	38/F	B	3.0	3.2	8	T-NA (S)	MG	72		IC-GN
10	65/M	W	3.0	1.4	14	T-NA (CH + R)	MG	12		MCD + IC
11	22/M	B	8.9 (HD)	ND	>3.5	T-NA (S + R)		NA		MCD
12	55/M	W	1.3	ND	2+	T-NA (S + R + CH)		180		IC-GN
13	79/M	W	2.5	2.7	ND		MG	NA		ATN
14	58/F	A	1.5	2.8	9.5		MG	48		DGS
15	79/F	A	4.6	1.9	>3.5		MG	72	MMF	MCD
16	35/F	W	2.9	<1.0	>3.5		MG	60	CS + AZA + CsA	MCD + IC
17	67/M	W	ND	ND	>3.5		MG	NA		DGS
18	38/F	A	3.2	1.8	11		MG	46	AZA	MCD + IC
19	36/F	W	0.5	ND	1.7, g/gCr		MG + Hypo-TH	48		IgAN
20	65/F	W	8.9	4.6	2+		MG	17		ATN + Myoglobin casts
21	78/F	W	1.8	2.9	3.2, g/gCr		MG	18		MIDD
22	68/M	W	3.0	ND	3.2, g/gCr		MG	NA	CS + MMF	MN

Sex: M, male; F, female. Race: W, white; B, black; A, Asian. ND, not described. Thymic pathology (treatment): T, thymoma; S, surgical excision; R, radiotherapy; CH, chemotherapy; NA, not available. Associated diseases: C, chronic *C. albicans* infection; L, lupus; Others include autoimmune gastritis with vitamin B12 deficiency, psoriasis, migratory polyarthritis and pericarditis. Length between thymoma/MG and nephropathy: NA, not applicable. Immunosuppression at nephropathy onset: HCQ, hydrochloroquine.

Table 2. WHO classification of thymoma

Type	Definition
A	Spindle cell thymoma; a thymic epithelial neoplasm composed of bland spindle/oval tumor cells with few or no admixed immature lymphocytes
AB	Mixed thymoma; a thymic epithelial neoplasm composed of type A component and type B-like component with a significant population of immature T cells
B1	Organoid thymoma; a neoplasm of thymic epithelial cells that closely resembles the normal thymus in terms of architecture and cytology
B2	Cortical thymoma; a lymphocyte-rich tumor composed of polygonal neoplastic epithelial cells set in a background of numerous immature T cells
B3	Epithelial thymoma; an epithelial-predominant thymic epithelial tumor composed of mildly or moderately atypical polygonal tumor cells showing a sheet-like, solid growth pattern

even years after thymoma had been diagnosed and treated [mean interval 71 ± 62 months (range 12–180)]. In the remaining two patients (Patients 5 and 11; 17%) with thymoma, the length of time between thymoma and nephropathy was unknown. The length between diagnosis of MG and kidney biopsy was also variable [mean interval 44 ± 20 months (range 17–72)]. Between these two groups there was no significant difference in the length between thymic disease (thymoma/MG) and kidney biopsy by Mann–Whitney test ($P = 0.6617$).

Recurrence of thymoma was reported in only one of our 12 patients (Patient 11; 8%) at the time of renal biopsy. In two thymoma patients with repeated renal biopsies (Patients 2 and 3), the recurrence of thymoma was not observed at the second biopsy. Six of 22 (27%) patients had been receiving immunosuppressants at the onset of nephropathy. The immunosuppressants included corticosteroids (CSs), mycophenolate mofetil (MMF), azathioprine (AZA) and cyclosporin A (CsA).

All 22 patients underwent at least one renal biopsy in order to assess renal pathology. In two patients (Patients 2 and 3) the second biopsy was performed several years after the first renal biopsy (48 and 29 months, respectively). The most frequent pathologic diagnosis was MCD (Figure 1A and B), found in 10 (45%) patients. Tubulointerstitial nephritis (TIN; Figure 1C) was observed in three (14%) patients, immune complex–mediated glomerulonephritis (IC-GN; Figure 1D and E) in two patients (9%) without obvious SLE and diabetic glomerulosclerosis (DGS) in two (9%) patients. MN (Figure 1F), IgAN (Figure 1G–I), acute

Table 3. Previously reported cases of glomerular disease associated with thymoma/MG

References	Age (years)/ sex	Thymic pathology	Associated diseases	Length between thymoma/MG and nephropathy, months	Renal pathology	Autoimmunity		Immuno-suppression at renal diagnosis	Response to CSs
						ANA	Anti-DNA		
Hirokawa *et al.* [1]	68/M	T-A[a]		0	MCD	ND	ND		F
Iijima *et al.* [2]	48/F	T-A	L	0	LN	+	+		CR
Ngoh *et al.* [3]	65/F	T-A		3	MCD	+	−		PR/CR (improved)
Lin *et al.* [4]	64/F	T-A		12	MN	+	−		CR
McDonald *et al.* [5]	70/M	T-AB[a]		14	MCD	+	+		CR (+ CsA)
Ogawa *et al.* [6]	49/F	T-AB[a]	L	15	LN	+	+		CR
Zinger *et al.* [7]	69/F	T-AB[a]		10	MCD	−	−		F
Takahashi *et al.* [8]	58/F	T-AB[a]	MG	24	MCD	−	−	CS + AZA	CR (+ AZA)
Karras *et al.* [9]	49/F	T-AB	C	−241	2°FSGS	+	−		CR
	62/F	T-AB	L	262	TMA	+	+	CS + HCQ	CR
	63/F	T-AB		−73	MCD	+	−		Not used
	55/F	T-AB	C	0	MN	+	−		CR
Hor *et al.* [10]	69/M	T-AB	MG	15	MCD	ND	ND	CS	PR/CR (improved)
Holmes and Sen [11]	7/F	T-B1	MG	−96	CRGN	−	−		CR (+ CP)
Long *et al.* [12]	58/M	T-B1		50	MCD	−	ND		PR
Claudy *et al.* [13]	68/F	T-B1[a]	L	0	LN	ND	+		F
Sirpal [14]	30/M	T-B1[a]		0	MPGN	ND	+		CR
Ishida *et al.* [15]	66/F	T-B1[a]		18	1°FSGS	+	−		F
	82/F	T-B1[a]	C	18	MCD	+	ND		F
Schillinger *et al.* [16]	60/F	T-B1[a]	PRCA	0	MN	−	ND		PR (+ CP for thymoma and CsA for PRCA)
Valli *et al.* [17]	50/M	T-B1[a]	MG	174	MN	ND	ND	CS + AZA	F
	80/M	T-B1[a]	MG	106	CRGN	+	−	CS	F
Posner *et al.* [18]	48/M	T-B2[a]		39	MN	−	ND		Not used
Varsano *et al.* [19]	56/M	T-B2[a]		42	MCD	ND	ND		F
Ogawa *et al.* [20]	45/F	T-B2[a]		12	MCD	−	ND		PR/CR (+ CP; improved)
Karras *et al.* [9]	33/F	T-B2	MG + PRCA	−25	CRGN	+	−	CS+AZA	CR
	37/F	T-B2	MG	24	MCD	+	−	AZA	CR (+ CsA)
	46/F	T-B2	L + PRCA + T	0	MCD	+	+		CR
	49/M	T-B2		16	MCD	−	−		PR
	41/M	T-B2		112	MCD	ND	ND		PR
	76/M	T-B2	MG + L + PM	−14	MCD	+	+	CS + HCQ	CR
	45/F	T-B2	MG	8	MCD	+	−		CR
Parambil *et al.* [21]	50/M	T-B2		5	CRGN	+	−	CS	PR (+ CP and AZA)
Yoshida *et al.* [22]	50/M	T-B2	MG	115	MCD	ND	ND		CR
Yamauchi *et al.* [23]	72/F	T-B2	Subclinical MG	0	1°FSGS	ND	ND		F
Faur *et al.* [24]	34/M	T-B2[a]		31	MCD	−	ND		CR
Kute *et al.* [25]	28/M	T-B2[a]	MG	7	MCD	−	−	CS + AZA	PR/CR (improved)
Gharwan *et al.* [26]	63/F	T-B2		29	MCD	ND	ND		CR (+ CP for thymoma and CsA)
Scadding *et al.* [27]	48/M	T-B3[a]	MG	144	1°FSGS	−	ND	CS + AZA	F
	64/F	T-B3[a]	MG	72	MCD	−	ND	CS + AZA	CR
	61/F	T-B3[a]	MG	36	MCD	−	ND	AZA	PR (+ AZA)
Almsaddi *et al.* [28]	43/F	T-B3[a]	MG + Hashimoto's thyroiditis	15	1°FSGS	+	ND	CS + AZA	Not used
Schillinger *et al.* [16]	65/M	T-B3[a]		0	MCD	−	ND		F
Lasseur *et al.* [29]	43/M	T-B3[a]	MG	0	MCD	−	−		F
Karras *et al.* [9]	70/M	T-B3	PRCA	61	MN	−	−		CR
	57/F	T-B3		0	MN	ND	ND		Not used
Teoh and El-Modir [30]	37/M	T-B3[a]	MG	187	MCD	ND	ND		PR (+ CP for thymoma)
Myoga *et al.* [31]	68/M	T-B3		84	MCD	+	ND		CR
Yoo *et al.* [32]	32/F	T-B3		0	1°FSGS	ND	−		PR (+ CP for thymoma)
Miyazaki *et al.* [33]	32/F	T-NA	MG	−156	IgAN	+	ND		Not used

(continued)

Table 3. (continued)

References	Age (years)/ sex	Thymic pathology	Associated diseases	Length between thymoma/MG and nephropathy, months	Renal pathology	Autoimmunity		Immuno-suppression at renal diagnosis	Response to CSs
						ANA	Anti-DNA		
Chan *et al.* [34]	57/F	T-NA	MG	168	MCD	+	−		F
	37/F	T-NA	MG	36	MCD	−	ND		CR
Jayasena *et al.* [35]	52/F	T-NA	MG	34	1°FSGS	−	+	CS + AZA	CR (+ CP)
Miyamoto *et al.* [36]	48/F	T-NA	MG	121	MCD	ND	ND	CS + AZA	PR (+ AZA and CsA)
Tomida *et al.* [37]	26/F	T-NA	MG	9	MN	−	+		CR
Lee *et al.* [38]	44/F	T-NA	MG	94	MCD	−	ND	AZA	CR
Karras *et al.* [9]	65/M	T-NA		174	MCD	+	−		F
	44/M	T-NA	MG	95	MCD	−	−		Not used
	55/M	T-NA	P	0	MN	+	−		CR
	45/F	T-NA	MG	180	MCD	+	−	CS + AZA	CR
	65/M	T-NA	MG	0	CRGN	+	−	CS	PR
Chung *et al.* [39]	50/F	T-NA	MG	179	1°FSGS	ND	ND	AZA	CR (+ tacrolimus)
Fukuda *et al.* [40]	65/M	T-NA		51	MCD	+	−		CR
Okamoto *et al.* [41]	42/M	T-NA		3	MCD	ND	ND		PR (+ CsA)
Bolz *et al.* [42]	42/M	T-NA	MG + CIDP	24	MN	ND	ND	CS+AZA	PR (+ IVIg)
Miyamoto *et al.* [43]	89/F	T-NA	MG	0	CRGN	−	ND		F
Calabrese *et al.* [44]	18/M	H	MG + L	32	LN	+	+		CR (+ AZA)
Miyazaki *et al.* [33]	29/M	H	MG	−12	IgAN	−	ND		Not used
Valli *et al.* [17]	30/F	H	MG	0	MN	+	−		Not used
Matsuda *et al.* [45]	46/F	H	MG	−28	MN	+	−		CR
Karras *et al.* [9]	24/F	H	MG + P	−135	MCD	−	−		PR
	43/F	H	MG	145	MCD	−	−		CR
Calvino *et al.* [46]	56/M	H	MG	−24	MN	−	ND		CR (+ chlorambucil)
Chen *et al.* [47]	24/F		MG	−24	MN	−	ND		PR/CR (improved)
Miyazaki *et al.* [33]	58/M		MG	−360	IgAN	−	ND		Not used
Innes *et al.* [48]	25/M		MG	60	IgAN	−	−	CS	Not used
Haslam *et al.* [49]	36/M		MG + Hypo-TH with thyroid autoantibody	0	LN	−	ND		PR
Konishi *et al.* [50]	46/F		MG	55	MN	ND	ND	CS + AZA	PR (+ CP)
Drube *et al.* [51]	53/F		MG	192	CRGN	−	−		PR (+ CsA)
Raillard-Gohin *et al.* [52]	62/F		MG	72	Necrotizing angiitis	−	−	AZA	F
Prasad *et al.* [53]	40/F		MG	0	MN	−	ND		F
Shioyama *et al.* [54]	40/M		MG	12	MN	ND	ND		PR (+ tacrolimus)
Omar *et al.* [55]	13/F		MG + Hypo-TH + L	36	LN	+	+		CR (+ CP)
Miskovic *et al.* [56]	48/F		MG + L	336	LN	+	+		PR/CR (+ MMF; improved)
Tsai and Tsai [57]	82/M		MG	0	MCD	−	ND		CR
Hanna *et al.* [58]	55/F		MG	0	MN	+	+		F
Nagarajan *et al.* [59]	38/F		MG + L	−3	LN	+	+		PR/CR (+ CP; improved)

References are in a supplementary file.

Thymic pathology: T, thymoma; a, thymic pathology was not originally indicated by the WHO classification and the WHO classification of thymoma was determined based on the description in the reports; H, thymic hyperplasia.

Associated diseases: PRCA, pure red-cell aplasia; T, autoimmune thrombocytopenia; PM, polymyositis; P, pemphigus; CIDP, chronic inflammatory demyelinating polyneuropathy. Length between thymoma/MG and nephropathy: negative numbers indicate that nephropathy occurred before thymic disease. Renal pathology: 1°, primary 2°, secondary; TMA, thrombotic microangiopathy. Response to CSs: F, failure; CR, complete remission; PR, partial remission; CP, cyclophosphamide; IVIg, intravenous Ig.

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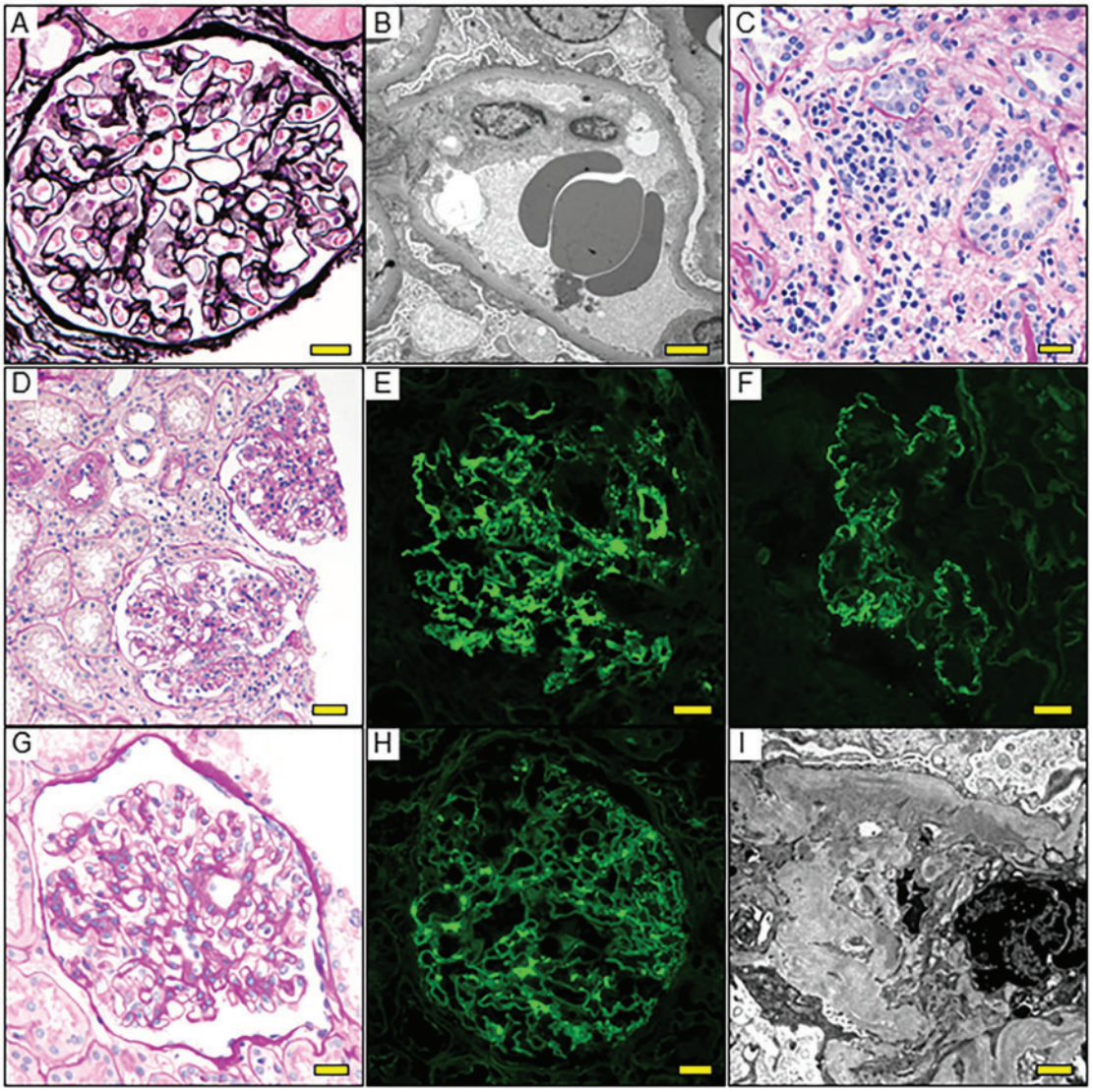

FIGURE 1: (**A** and **B**) MCD (Patient 11). (**A**) Periodic acid–methenamine (PAM) silver stain shows an unremarkable glomerulus without hypercellularity (bar: 20 μm). (**B**) EM shows global podocyte foot process effacement with microvillous transformation (original magnification 7200×; bar: 2 μm). (**C**) Active TIN (Patient 3). Periodic acid–Schiff (PAS) stain shows lymphocytic inflammation in the interstitium and tubular walls (bar: 20 μm). (**D** and **E**) IC-GN (Patient 9). (**D**) PAS stain shows mild mesangial expansion with mild mesangial hypercellularity (bar: 40 μm). (**E**) Direct immunofluorescence for IgG reveals fine granular IgG staining in the mesangial area (bar: 20 μm). (**F**) MN (Patient 22). Direct immunofluorescence for IgG shows fine granular reactivity along glomerular capillary loops (bar: 20 μm). (G–I) IgAN (Patient 19). (**G**) PAS stain shows mild mesangial expansion without hypercellularity (bar: 20 μm). (**H**) Direct immunofluorescence for IgA exhibits fine granular staining in the mesangial area (bar: 20 μm). (**I**) EM shows electron-dense deposits in the mesangial area (original magnification 10 000×; bar: 1 μm). All electron micrographs stained with uranyl acetate and lead citrate.

tubular necrosis (ATN), ATN with focal myoglobin casts or monoclonal Ig deposition disease (MIDD) was observed in one (5%) patient each.

In total, 7 of 22 (32%) patients also exhibited low-grade IgG-dominant immune-complex deposition. Five of these were observed in cases of MCD [5/10 (50%)]. Four of the MCD patients (Patients 2, 7, 16 and 18) exhibited mesangial deposition (Figure 2A–C) and one patient (Patient 10) showed mesangial deposition with segmental subepithelial deposition (Figure 2D). These cases were not diagnosed as IC-GN or MN because these patients showed heavy proteinuria and the extent of IC deposition was very mild and not enough to cause nephrotic syndrome.

True IC-GN was observed in only two patients, one of which demonstrated IgG-dominant IC deposits in the mesangium (Patient 9); the other showed similar deposits in the mesangium and segmentally in the subepithelial deposits (Patient 12). There was no evidence of SLE clinically in either patient. Patient 22 had MN with typical subepithelial electron-dense deposits. Immunohistochemical staining for phospholipase A2 receptor (PLA2R) and thrombospondin type 1 domain-containing 7A (THSD7A) was negative in both patients (Patients 12 and 22) with MN.

Among the three TIN patients, one patient developed granulomatous TIN (Patient 6; Figure 2E) without evidence of infection or sarcoidosis and two patients (Patients 3 and 8) showed TIN with mild and fine granular IgG staining in mesangial areas and tubular basement membranes (Figure 2F–H) and mesangium only, respectively.

In the two cases (Patients 2 and 3) with repeat biopsies, the primary diagnoses (MCD and TIN) remained unchanged

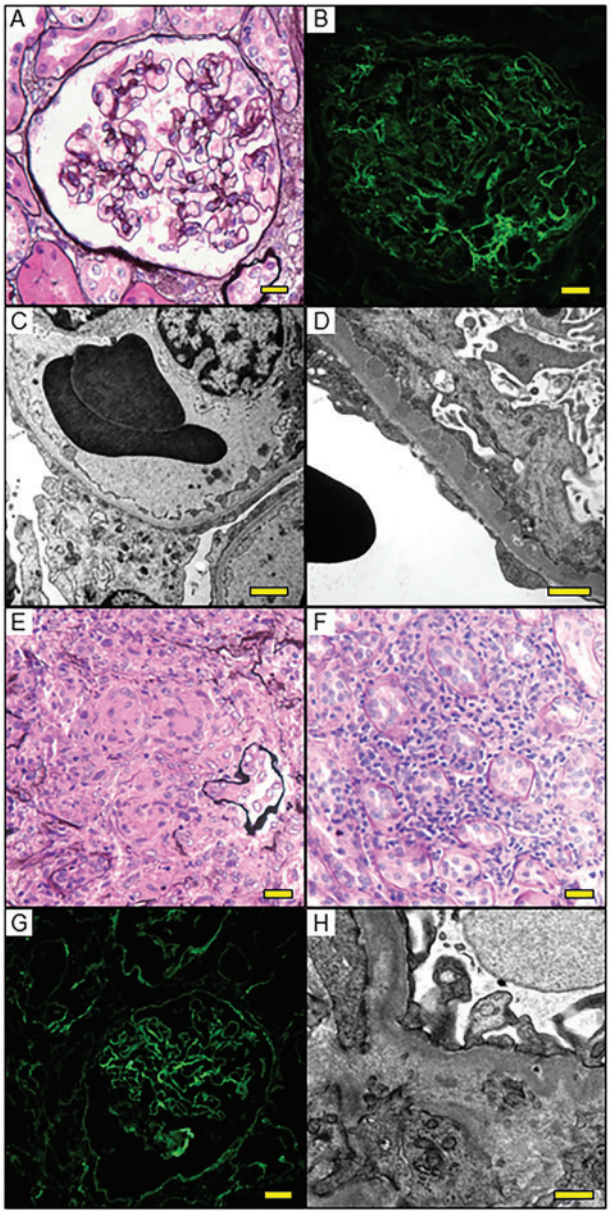

FIGURE 2: (**A–C**) MCD with IC deposition (Patient 16). (**A**) PAM stain shows an unremarkable glomerulus without hypercellularity (bar: 20 μm). (**B**) Immunofluorescence study shows fine granular mesangial IgG staining in a mild degree (bar: 20 μm). (**C**) EM shows global podocyte foot process effacement (original magnification 14 000×; bar: 1 μm). (**D**) MCD with IC deposition in the mesangial area and segmentally in the subepithelial area (Patient 10). EM reveals electron-dense deposits in subepithelial space (original magnification 19 000×; bar: 1 μm). (**E**) Granulomatous TIN (Patient 6). PAM stain shows interstitial areas with inflammatory cells and multinucleated giant cells (bar: 20 μm). (**F–H**) TIN with IC deposition in the mesangium and tubular basement membranes (Patient 8). (**F**) PAS stain shows active lymphocytic inflammation in interstitial area and tubular walls (bar: 20 μm). (**G**) Direct immunofluorescence for IgG shows fine granular staining in the mesangial area and focally in tubular basement membranes (bar: 20 μm). (**H**) EM shows small electron-dense deposits in the mesangial area (original magnification 15 000×; bar: 500 μm). All electron micrographs stained with uranyl acetate and lead citrate.

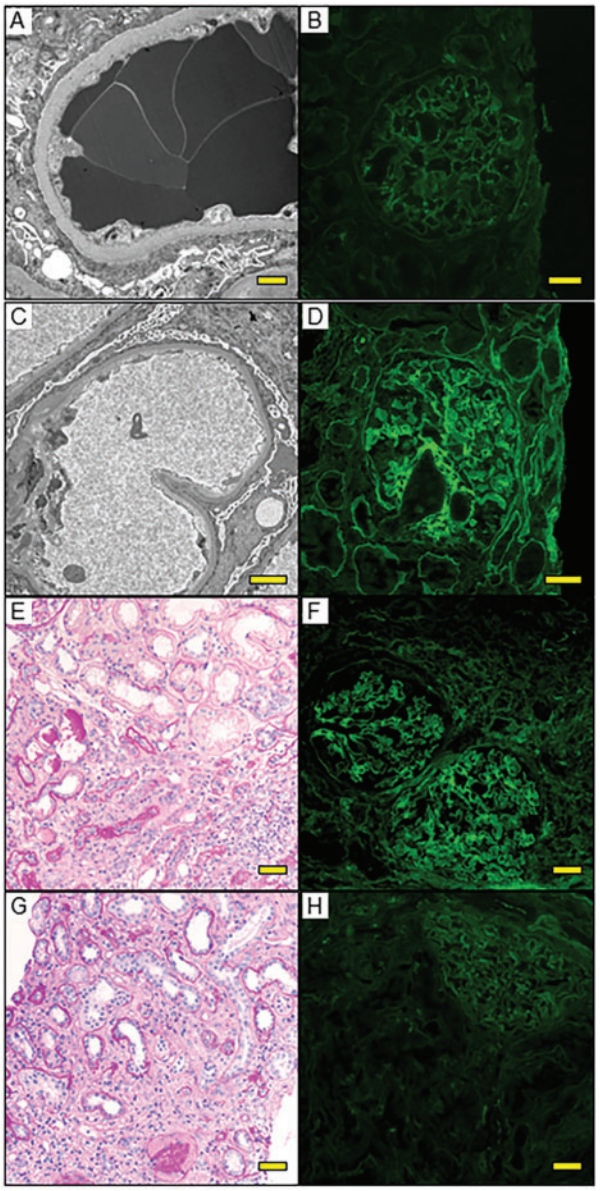

FIGURE 3: (**A and B**) MCD without IC deposition (Patient 2; first biopsy). (**A**) EM shows global podocyte foot process effacement (original magnification 14 000×; bar: 1 μm). (**B**) Direct immunofluorescence for IgG shows negative staining in the glomerulus (bar: 30 μm). (**C** and **D**) MCD with IC deposition (Patient 2; second biopsy). (**C**) EM shows global podocyte foot process effacement with microvillous transformation (original magnification 3000×; bar: 2 μm). (**D**) Immunofluorescence study shows mild fine granular IgG staining in the mesangial area (bar: 30 μm). (**E** and **F**) TIN with IC deposition (Patient 3; first biopsy). (**E**) PAS stain shows lymphocytic interstitial inflammation with mild tubulitis (bar: 40 μm). (**F**) Direct immunofluorescence for IgG shows minimal fine granular staining in the mesangial area (bar: 30 μm). (**G** and **H**) TIN without IC deposition (Patient 3; second biopsy). (**G**) PAS stain shows the similar findings to (E) (bar: 40 μm). (**H**) Immunofluorescence study shows negative staining of IgG in the entire tissue (bar: 40 μm).

between the first and the second biopsies. However, Patient 2 with MCD (Figure 3A and B) subsequently developed low-grade IgG deposition in mesangial areas (Figure 3C and D) without significant associated glomerular proliferative features (i.e. endocapillary and mesangial hypercellularity or crescents). Conversely, Patient 3, who had TIN with IgG deposits in mesangial areas in the first biopsy (Figure 3E and F), showed a loss of these deposits in the second biopsy (Figure 3G and H).

In our cohort, 17 (77%) cases were glomerular disease and 5 (23%) cases were tubulointerstitial disease. Among the glomerular diseases in our study, 12 cases manifested clinically as nephrotic syndrome including MCD and DGS, and 5 cases

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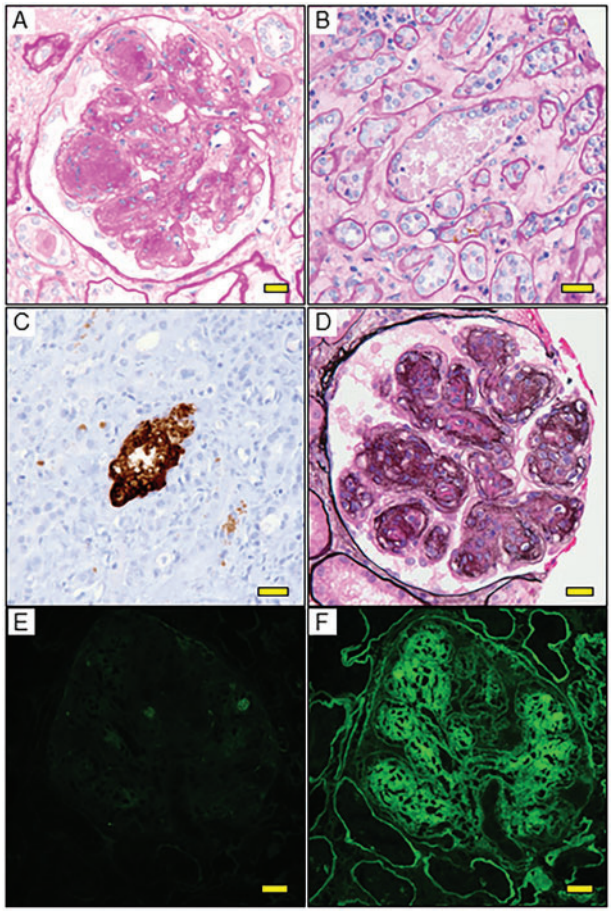

FIGURE 4: (**A**) DGS (Patient 17). PAS stain shows mesangial expansion and segmental Kimmelstiel–Wilson nodules (bar: 20 μm). (**B** and **C**) ATN with focal myoglobin casts (Patient 20). (**B**) PAS stain shows epithelial flatting and necrosis with intraluminal PAS-negative amorphous material (bar: 20 μm). (**C**) Immunohistochemistry of myoglobin shows strong staining in the amorphous tubular cast (bar: 20 μm). (**D–F**) MIDD (Patient 21). (**D**) PAM stain shows a membranoproliferative pattern of glomerular injury (bar: 20 μm). (**E**) Direct immunofluorescence for kappa light chain shows negative reaction in a glomerulus (bar: 20 μm). (**F**) Immunofluorescence study shows positive lambda light chain staining in a glomerulus and tubular basement membranes (bar: 20 μm).

exhibited a nephritic presentation, including IC-GN, IgAN, MIDD and MN. Thymoma was observed in 58% (7/12) of nephrotic patients and 40% (2/5) of nephritic patients. MG was observed in 50% (6/12) of nephrotic patients and 80% (4/5) of nephritic patients.

In the MCD patients, 70% (7/10) had thymoma and 40% (4/10) had MG. On the other hand, in patients with non-MCD glomerular disease, only 29% (2/7) had thymoma but 86% (6/7) had MG. In patients with tubulointerstitial disease, 60% (3/5) had thymoma and 80% (4/5) had MG. All three patients who demonstrated primarily interstitial pathology had thymoma and of (66%) patients had MG.

Eighty percent (8/10) of the MCD patients, 86% (6/7) of the non-MCD patients and 100% (5/5) of the tubulointerstitial disease patients had autoimmune diseases including MG. All patients with MCD had nephrotic syndrome; only 29% (2/7) of the non-MCD glomerular disease patients had nephrotic syndrome. Hematuria was noted in four (40%) patients with MCD, four (57%) patients with non-MCD glomerular disease and one (20%) patient with tubulointerstitial disease. Seven (70%) patients with MCD had AKI; four (57%) patients with non-MCD glomerular disease and four (80%) with tubulointerstitial disease also presented with AKI.

Renal diseases less likely related to thymoma and/or MG immunologically were also observed. DGS was seen in two patients (Patients 14 and 17; Figure 4A). ATN was observed in two elderly patients (Patients 13 and 20). Patient 20 showed an additional finding of focal myoglobin tubular casts (Figure 4B and C) without overt clinical evidence of rhabdomyolysis. Lastly, MIDD was seen in one patient (Patient 21; Figure 4D–F), showing a membranoproliferative pattern of glomerular injury and IgG3-λ restriction.

DISCUSSION

This study provides the kidney biopsy findings from our institution, of patients with thymic diseases: namely thymoma and MG. To our knowledge, this is the largest clinicopathologic series to date on this topic from a single institution. In our native kidney biopsy cohort, the patients with thymic diseases were extremely rare and found in 24 of 32 462 biopsies (0.07%). MCD was most common [45% (10/22)], followed by TIN [14% (3/22)],

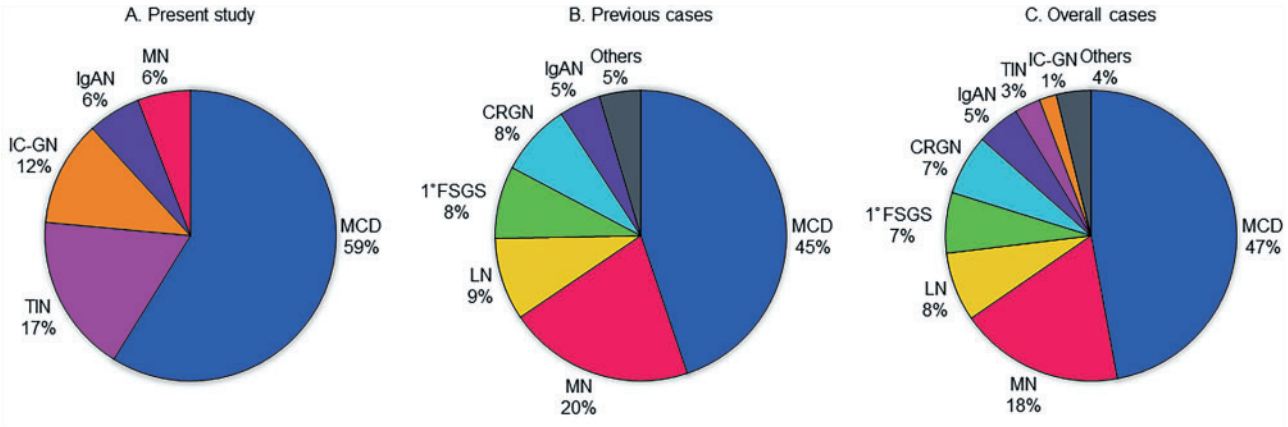

FIGURE 5: Summary of renal pathology in patients with thymoma and/or MG. (**A**) 17 patients in this study: MCD [59% (10/17)], TIN [17% (3/17)], IC-GN [12% (2/17)], IgAN [6% (1/17)] and MN [6% (1/17)]. (**B**) 87 patients in previously reported cases: MCD [45% (39/87)], MN [20% (18/87)], LN [9% (8/87)], 1°FSGS [8% (7/87)], CRGN [8% (7/87)], IgAN [5% (4/87)] and Others [5% (4/87), which includes secondary FSGS, TMA, necrotizing angiitis and membranoproliferative GN]. (**C**) Overall 104 patients: MCD [47% (49/104)], MN [18% (19/104)], LN [8% (8/104)], 1°FSGS [7% (7/104)], CRGN [7% (7/104)], IgAN [5% (5/104)], TIN [3% (3/104)], IC-GN [1% (2/104)] and Others [4% (4/104)].

Table 4. Kidney diseases in patients with or without thymoma

Renal pathology	Present study, *n* (%)	Previous cases, *n* (%)	Overall cases, *n* (%)
Renal pathology in patients with thymoma			
MCD	7 (58)	36 (55)	43 (55)
MN	0	10 (15)	10 (13)
1°FSGS	0	7 (11)	7 (9)
CRGN	0	6 (9)	6 (8)
LN	0	3 (4)	3 (4)
TIN	3 (25)	0	3 (4)
IC-GN	2 (17)	0	2 (2)
IgAN	0	1 (2)	1 (1)
Others	0	3 (4)	3 (4)
Total	12	66	78
Renal pathology in patients with only MG (no thymoma)			
MN	1 (20)	8 (38)	9 (35)
MCD	3 (60)	3 (14)	6 (23)
LN	0	5 (24)	5 (19)
IgAN	1 (20)	3 (14)	4 (15)
CRGN	0	1 (5)	1 (4)
Others	0	1 (5)	1 (4)
Total	5	21	26

IC-GN [9% (2/22)], DGS [9% (2/22)], ATN [9% (2/22)], MN [5% (1/22)], IgAN [5% (1/22)] and MIDD [5% (1/22)]. Excluding cases of DGS, ATN and MIDD, this identifies 17 cases (77%) that could be immunologically related to underlying thymic disease.

This study revealed several new findings. Our study evaluated 24 biopsies from 22 patients (2 with repeat biopsies). Similar to the previous reports [11], MCD was the most common disease [45% (10/22)] in the patients with thymic diseases. Interestingly, half of the MCD patients (5/10) also demonstrated mild IgG-dominant IC deposition: 4 patients in mesangial areas only and 1 patient with both mesangial and subepithelial deposits. We also identified three patients with TIN without suspicion for drug- or medication-induced TIN. Two of the three TIN patients also exhibited mild IgG-dominant IC deposition: one patient in mesangial areas only and the other in both mesangial areas and tubular basement membranes. In the two patients with repeated biopsies, mild mesangial IC deposition developed in MCD (Patient 2) but disappeared in the TIN patient (Patient 3) with the second biopsy. These findings suggest the involvement of immunological dysregulation in the pathogenesis of thymic disease–associated nephropathy.

In 2005, Karras *et al.* [11] reported 21 cases and summarized an additional 40 cases from other case reports. We performed an extensive literature search and updated the summary of nephropathies in patients with thymoma and/or MG (Table 3). There are a total of 104 cases (including our 17 cases, which we thought most likely attributable to underlying thymic disease).

The most common renal pathology finding in the overall cases reported (Figure 5 and Table 4) is MCD [47% (49/104)], followed by MN [18% (19/104)], lupus nephritis [LN; 8% (8/104)], primary focal segmental glomerulosclerosis [1°FSGS; 7% (7/104)], crescentic GN [CRGN; 7% (7/104)], IgAN [5% (5/104)], TIN [3% (3/104)], IC-GN [1% (2/104)] and others [4% (4/104)]. The major differences between this study and the previously reported cases are (i) this study first reported TIN (17%) and IC-GN (12%) and (ii) MN was relatively less (6%) than the previous reports (20%). Regarding kidney diseases with or without thymoma (Table 4), MCD is the most common type of kidney disease in the patients with thymoma while MN is most common in those without thymoma (MG only). Generally, among paraneoplastic glomerulopathies associated with solid tumors other than thymoma, MN is most common and MCD is less frequently reported [8]. This suggests that thymic disease–associated nephropathy is unique, in that MCD is the common and that 50% of the MCD cases in our cohort also demonstrated concomitant IgG-dominant IC deposition.

This study may provide some insights in clinical situations. Analyzing overall cases including our cases and previous reports, there were 78 thymoma patients with any kidney diseases, among whom 64 patients manifested nephrotic syndrome or heavy proteinuria (>3.5 g/day). A total of 55% (43/78) of kidney pathologies of the thymoma patients were MCD, while 64% (41/64) of the patients with heavy proteinuria showed the diagnosis of MCD. Therefore, if we see thymoma patients with heavy proteinuria, kidney pathology would more likely be MCD. In addition, our study showed that 50% of MCD patients exhibited mild IC deposition. Hence, if we encounter MCD with IgG deposition in the kidney biopsy, this finding might suggest that the patient has already developed or will develop thymoma. This warrants a survey of thymoma and other malignancies by the clinician.

In the previous study [11], 28% (6/21) of cases exhibited nephropathy before thymoma was identified. In 24% (5/21) of patients, nephropathy and thymoma were identified simultaneously, and in almost half of the cases [48% (10/21)], nephropathy was demonstrated after thymectomy. In the last group, the time to onset of nephropathy following thymectomy was quite variable, ranging from 8 to 180 months. In our study, 10 of 12 thymoma patients underwent thymectomy; 9 had documentation of the duration between thymectomy and nephropathy. In eight patients, nephropathy occurred 13–180 months after thymectomy, consistent with previous reports. In one patient with TIN and mild IC deposition (Patient 3), thymoma was discovered when nephropathy developed and at the time of the first renal biopsy. Although this patient received thymectomy 2 months after the first biopsy, the patient still developed acute on chronic kidney disease. Therefore the second renal biopsy was performed 29 months after the thymectomy, revealing persistent TIN.

Parathymic nephropathy was associated mostly with thymoma histologic subtypes AB, B2 and B3 [11], which has also been observed preferentially with other thymoma-associated autoimmune disorders. MCD was usually associated with lymphocyte-predominant thymoma, while MN typically was associated with epithelial-predominant thymoma and malignant thymoma. Unfortunately the pathology of the thymomas was very limited for our patients, documented in only 4 of 12 patients. Two patients were diagnosed with thymoma AB and MCD, one patient with thymoma AB and TIN and one patient with thymoma B3 and MCD. Analyzing the distribution of the thymoma subtypes in all thymoma patients, thymoma patients with MCD and thymoma patients with IC-GN (Supplementary data, Table S2), the distribution is comparable between the former two groups and the latter group has a very limited number of cases.

Patients with thymoma have been well documented to have impaired cellular and humoral immunity [16]. The thymus is the primary lymphoid organ where T lymphocytes undergo maturation [17]. Immature T cells undergo rigorous selection (i.e. positive and negative selections) that depends on interactions with thymic cells that shape the mature repertoire of T cells to ensure self–major histocompatibility complex restriction as well as self-tolerance [18]. In addition, the thymus is

important for B cell activation and differentiation into plasma cells and antibody production. B cell activation requires interaction between antigen and helper T (Th) cells, which are developed in the thymus [19]. Therefore thymoma, as well as thymectomy, may contribute to the dysregulation of both T cell and B cell–mediated immunity [20].

The cause of MCD in patients with thymic diseases is unclear, but accumulating evidence suggests that T cell [21] and B cell dysfunction result in the production of glomerular permeability factors such as anti-ubiquitin carboxyl-terminal hydrolase L1Ab [22], cardiotrophin-like cytokine factor 1, soluble urokinase-type plasminogen activator receptor and interleukin-13 [23, 24]. Atopic individuals with Th2-prone immunity are at higher risk for the development of MCD. The remission of MCD can be induced by measles, an infection known to modify cellular immunity [25]. A case report described that a patient with thymoma-associated MCD showed a shift from Th2 cells to an increase in the Th1:Th2 ratio with an associated reduction in proteinuria after administration of systemic antitumor therapy [26]. Relatively undifferentiated T cells have been implicated in the pathogenesis of MCD. In an animal experiment, non-obese diabetic/severe combined immunodeficiency mice with engraftment of CD34-positive T cells but not CD34-negative T cells from MCD patients developed proteinuria and foot process effacement [27]. In addition, Lien and Lai [8] reported, using the Buffalo/Mna rat model of spontaneous thymoma and nephrotic syndrome, that polarization of the immune response toward a Th2 profile is associated with the development of glomerular disease. Regarding the role of B cells in MCD, few autoantibodies were reported as circulating glomerular permeability factors [22, 28]. More importantly, a number of publications have shown the favorable effect of rituximab, a chimeric monoclonal antibody that depletes the CD20-positive B cell population, on MCD, suggesting that a glomerular permeability factor could be produced by B or T cells through pathways regulated or stimulated by B cells [29]. In our cohort, 11 of 22 (50%) patients showed IC-associated kidney diseases (IC-GN, MN and IgAN) or mild IC deposition in other kidney diseases (MCD and TIN). These findings suggest that dysregulation of B cells, as well as T cells, are involved in the disease process.

Related to TIN and MN, anti-low-density lipoprotein receptor-related protein 2 nephropathy often exhibits TIN, with IC deposits in both segmental GBMs (segmental MN) and in tubular basement membranes [30]. Our cases (Patients 3 and 8) lack the subepithelial deposits (MN pattern). Patient 3 showed TIN with mild IgG deposits in the mesangium only and Patient 8 exhibited TIN with mild IgG deposits in mesangial areas and tubular basement membranes. Nonetheless, these entities might have a shared pathomechanism behind the similar morphological changes.

The effect of thymectomy on the immune system is variable in both humans and mice. Boonen *et al.* [31] reported clinical outcomes in eight SLE patients with thymectomy: thymectomy had no clear effect on SLE in five cases, an exacerbation was reported in two cases and SLE was attenuated in one case. In two mouse models of SLE [32, 33], the disease activity showed opposite courses after thymectomy, suggesting the complexity in the immunological background of SLE and/or in the effects of thymectomy. This could likely be true in MCD and other IC-associated kidney diseases.

Our study and other reports have demonstrated the onset of or worsening of kidney disease long after thymectomy. This may be attributed to the persistence of impaired cellular and humoral immunity. It is possible that autoreactive T lymphocytes, once exported from thymoma, could remain in the periphery for a long duration, thus accounting for the late onset of autoimmune paraneoplastic disorders after thymectomy [34].

Our study has several limitations. The retrospective, observational study design limits any findings to hypothesis generation rather than validation, and patient and renal outcomes were not examined. Clinical information and laboratory data were provided by the referring nephrologists at the time of biopsy and could not be independently verified. Complete pathologic information about thymoma and clinical features of the MG was not available. The nephropathy patients who later developed thymoma and/or MG could not be detected.

In conclusion, thymic diseases such as thymoma and MG are associated with a spectrum of kidney diseases likely related to immunologic dysregulation. The most common diagnosis found on kidney biopsy was MCD (45%), which differs from paraneoplastic nephropathy associated with other solid tumors. In addition to glomerular diseases, TIN was also identified in 14% of patients without a suspicious medication history for a drug-induced TIN. Lastly, about half of the biopsies including MCD and TIN exhibited IC deposition in various degrees, suggesting dysregulation of cellular and humoral immunity. Thymoma and/or MG is very rare in the general population as well as in kidney disease patients. However, a high degree of clinical suspicion is needed for the early diagnosis and an appropriate treatment for these thymic disease–associated kidney diseases.

SUPPLEMENTARY DATA

Supplementary data are available at ckj online.

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CONFLICT OF INTEREST STATEMENT

None declared.

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