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

Akira Takahashi1,2, Takamasa Miyauchi1, Narihito Tatsumoto1, Mercury Y. Lin1, Jean Hou1, Toshiki Doi2, Takao Masaki2 and Michifumi Yamashita 1

1Department of Pathology and Laboratory Medicine, Cedars-Sinai Medical Center, Los Angeles, CA, USA and 2Department of Nephrology, Hiroshima University Hospital, Hiroshima, Japan

Correspondence to: Michifumi Yamashita; E-mail: Michifumi.Yamashita@csmc.edu

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

Received: 20.10.2020, Editorial decision: 22.12.2020
© The Author(s) 2021. Published by Oxford University Press on behalf of ERA-EDTA. This is an Open Access article distributed under the terms of the Creative Commons Attribution Non-Commercial License (http://creativecommons.org/licenses/by-nc/4.0/), which permits non-commercial re-use, distribution, and reproduction in any medium, provided the original work is properly cited. For commercial re-use, please contact journals.permissions@oup.com
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 autoreactive 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 thymoma-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 native kidney 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 practices, 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 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 parathyroid 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 albumin (g/dL) | Proteinuria (g/day) | Thymic pathology (treatment) | Associated diseases | Length between thymoma/MG and nephropathy (months) | Immunosuppression at nephropathy onset | Renal pathology |
|-------------|-------------|-----|------|--------------------------|----------------------|---------------------|-----------------------------|-------------------|-----------------------------------------------|--------------------------------------|----------------|
| 1           | 54/M        | W   | 1.0  | 1.9                       | >3.5                 | T-AB (S)            | Hypo-TH                    |                   | 61                                            | HCQ                                  | MCD            |
| 2           | 60/M        | W   | 1.4  | >3.5                      | T-AB (S + R + CH)    |                     |                             |                   | 13                                            |                       | MCD            |
| 3           | 66/F        | W   | 2.4  | ND                        | T-AB (S)             | Hypo-TH + L         | 61                          | C + Hypo-TH       | 29                                            |                       | TIN            |
| 4           | 73/M        | W   | 1.1  | 2.3                       | T-B3 (S)             | Hypo-TH + L         | 170                         | Others            |                                         |                       | MCD            |
| 5           | 73/M        | W   | ND   | ND                        | T-NA (CH)            | MG + Hypo-TH        | 39                          |                   | Granulomatous TIN                              |                       | MCD            |
| 6           | 67/F        | W   | 4.0  | ND                        | T-NA (S)             | MG + Hypo-TH        | 39                          |                   | Granulomatous TIN                              |                       | MCD            |
| 7           | 54/F        | B   | 4.5  | 1.9                       | T-NA (S)             | L                    | 36                          | CS + HCQ          | MCD + IC                                   |                       | TIN + IC       |
| 8           | 19/F        | W   | 0.5  | 2.7                       | T-NA (S)             | MG                   | 60                          |                   | TIN + IC                                   |                       | TIN + IC       |
| 9           | 38/F        | B   | 3.0  | 3.2                       | T-NA (S)             | MG                   | 72                          |                   | TIN + IC                                   |                       | TIN + IC       |
| 10          | 65/M        | W   | 3.0  | 1.4                       | T-NA (CH + R)        | MG                   | 12                          |                   | MCD + IC                                   |                       | TIN + IC       |
| 11          | 22/M        | B   | 8.9  | ND                        | T-NA (S + R)         | NA                   | 180                         |                   | MCD                                        |                       | TIN + IC       |
| 12          | 55/M        | W   | 1.3  | 2.0                       | T-NA (S + R + CH)    | MG                   | 180                         |                   | ATN                                       |                       | TIN + IC       |
| 13          | 79/M        | W   | 2.5  | 2.7                       | ND                   | MG                   | NA                          |                   | ATN + Myoglobin casts |                       | TIN + IC       |
| 14          | 58/F        | A   | 1.5  | 2.8                       | 9.5                 | MG                   | 48                          |                   | DGS                                        |                       | TIN + IC       |
| 15          | 79/F        | A   | 4.6  | 1.9                       | >3.5                 | MG                   | 72                          |                   | DGS                                        |                       | TIN + IC       |
| 16          | 35/F        | W   | 2.9  | <1.0                      | >3.5                 | MG                   | 60                          | CS + AZA          | MCD + IC                                   |                       | TIN + IC       |
| 17          | 67/M        | W   | ND   | ND                        | >3.5                 | MG                   | NA                          |                   | DGS                                        |                       | TIN + IC       |
| 18          | 38/F        | A   | 3.2  | 1.8                       | 11                   | MG                   | 46                          | AZA               | MCD + IC                                   |                       | TIN + IC       |
| 19          | 36/F        | W   | 0.5  | ND                        | 1.7, g/gCr           | MG + Hypo-TH         | 48                          |                   | IgAN                                      |                       | TIN + IC       |
| 20          | 65/F        | W   | 8.9  | 4.6                       | 2+                   | MG                   | 17                          |                   | ATN + Myoglobin casts |                       | TIN + IC       |
| 21          | 78/F        | W   | 1.8  | 2.9                       | 3.2, g/gCr           | MG                   | 18                          |                   | MIDD                                      |                       | TIN + IC       |
| 22          | 68/M        | W   | 3.0  | 3.2                       | g/gCr                | MG                   | NA                          | CS + MMF          | MN                                        |                       | TIN + IC       |

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, hydroxychloroquine.

Table 2. WHO classification of thymoma

| Type     | Definition |
|----------|------------|
| A        | Spindle cell thymoma; a thymic epithelial neoplasm composed of bland spindle/oval tumor cells with or 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 |

Of seven patients (7%) 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 interstitial nephritis (AIN) and focal glomerulosclerosis (FSGS) were observed in one patient each.

Of the 12 patients with thymoma, 4 (33%) showed thymic disease–associated nephropathy. The presence of granulomatous TIN in Patient 11; Hypo-TH in Patient 3; IgAN in Patient 2; and AIN in Patient 12 reflect the heterogeneity of the pathologic findings in patients with thymoma/MG.

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 interstitial nephritis (AIN) and focal glomerulosclerosis (FSGS) were observed in one patient each.

Of the 12 patients with thymoma, 4 (33%) showed thymic disease–associated nephropathy. The presence of granulomatous TIN in Patient 11; Hypo-TH in Patient 3; IgAN in Patient 2; and AIN in Patient 12 reflect the heterogeneity of the pathologic findings in patients with thymoma/MG.
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 | Immunosuppression at renal diagnosis | Response to Cs |
|---------------------|-----------------|------------------|---------------------|--------------------------------------------------|----------------|-------------|-------------------------------------|----------------|
| Hirokawa et al. [1] | 68/M            | T-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/T            | T-A              |                     | 12                                               | MN             | +           | –                    | CR             |
| McDonald et al. [5] | 70/M            | T-AB*            |                     | 14                                               | MCD            | +           | +                    | CR (+ CsA)      |
| Ogawa et al. [6]    | 49/F            | T-AB*            | L                   | 15                                               | LN             | +           | +                    | CR             |
| Zinger et al. [7]   | 69/T            | T-AB*            |                     | 10                                               | MCD            | –           | –                    | F              |
| Takahashi et al. [8]| 58/T            | T-AB*            | MG                  | 24                                               | MCD            | –           | –                    | CS + AZA        |
| Karras et al. [9]   | 62/T            | T-AB*            | C                   | –241                                             | 2 FSGS         | +           | –                    | 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/T            | T-B1*            | L                   | 0                                                | LN             | ND          | +                    | F              |
| Sirpal [14]         | 30/M            | T-B1*            |                     | 0                                                | MPGN           | ND          | +                    | CR             |
| Ishida et al. [15]  | 66/F            | T-B1*            |                     | 18                                               | 1 FSGS         | +           | –                    | F              |
| Schilling et al. [16]| 82/F            | T-B1*            | C                   | 18                                               | MCD            | +           | ND                   | Not used        |
| Valli et al. [17]   | 50/M            | T-B1*            | MG                  | 174                                              | MN             | ND          | ND                   | CS + AZA        |
| Posner et al. [18]  | 48/M            | T-B2*            | MG                  | 106                                              | CRGN           | +           | –                    | F              |
| Varsano et al. [19] | 56/F            | T-B2*            |                     | 39                                               | MN             | ND          | –                    | Not used        |
| Ogawa et al. [20]   | 45/T            | T-B2*            |                     | 12                                               | MCD            | ND          | ND                   | F              |
| Karras et al. [9]   | 33/T            | T-B2              | MG + PRCA           | –25                                              | CRGN           | +           | –                    | CS + AZA CR    |
| Hodgson et al. [6]  | 37/T            | T-B2              | MG                  | 24                                               | MCD            | +           | –                    | AZA CR (+ CsA) |
| 46/T                | 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/T                | 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 (+ CsA)     |
| Yamashita et al. [23]| 72/T           | T-B2              | Subclinical MG      | 0                                                | 1 FSGS         | ND          | ND                   | F              |
| Faur et al. [24]    | 34/M            | T-B2*            |                     | 31                                               | MCD            | –           | ND                   | CR             |
| Kute et al. [25]    | 28/M            | T-B2*            | MG                  | 7                                                | MCD            | –           | –                    | CS + AZA PR/CR (improved) |
| Gharwan et al. [26] | 63/T            | T-B2              |                     | 29                                               | MCD            | ND          | ND                   | PR (+ CP for thymoma and CsA) |
| 48/M                | T-B3*            | MG                |                     | 144                                              | 1 FSGS         | –           | ND                   | CS + AZA F     |
| 64/T                | T-B3*            | MG                |                     | 72                                               | MCD            | –           | ND                   | CS + AZA CR    |
| 61/T                | T-B3*            | MG                |                     | 36                                               | MCD            | ND          | AZA                  | PR (+ AZA)     |
| 43/T                | T-B3*            | MG + Hashimoto's thyroiditis | 15 | 1 FSGS | + | ND | CS + AZA | Not used |
| Scadding et al. [27]| 65/M            | T-B3*            | MG                  | 0                                                | MCD            | –           | ND                   | F              |
| 43/M                | T-B3*            | MG                |                     | 0                                                | MCD            | –           | –                    | F              |
| Karras et al. [9]   | 70/M            | T-B3              | PRCA                | 61                                               | MN             | –           | –                    | CR             |
| 57/T                | T-B3              |                     |                     | 0                                                | MN             | ND          | ND                   | Not used        |
| 37/T                | T-B3              |                     |                     | 187                                              | MCD            | ND          | ND                   | CR (+ CP for thymoma) |
| Myogu et al. [31]   | 68/M            | T-B3              |                     | 84                                               | MCD            | +           | ND                   | CR             |
| 32/T                | T-B3              |                     |                     | 0                                                | 1 FSGS         | ND          | –                    | PR (+ CP for thymoma) |
| Miyazaki et al. [33]| 32/T            | 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 at renal diagnosis | Immunosuppression at renal diagnosis | Response to CSs |
|------------------|-----------------|------------------|---------------------|-----------------------------------------------|----------------|---------------------------------|-------------------------------------|----------------|
| 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                                            | 1FSGS          | –                              | CS + AZA                                          | CR (+ CP) |
| Miyamoto et al. [36] | 48/F      | T-NA             | MG                  | 121                                           | MCD            | ND                             | ND + AZA                                      | CR (+ 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             |
| Karss et al. [9]  | 65/M            | T-NA             | MG                  | 174                                           | MCD            | +                              |                                     | F              |
| Jayasena et al. [35] | 44/M         | T-NA             | MG                  | 95                                            | MCD            | –                              | ND + AZA                                      | CR             |
| Miyamoto et al. [36] | 55/M       | T-NA             | P                   | 0                                             | MN             | +                              | ND + AZA                                      | CR             |
| Lee et al. [38]  | 48/F            | T-NA             | MG                  | 180                                           | MCD            | +                              | CS + AZA                                      | CR             |
| Chung et al. [39] | 50/F            | T-NA             | MG                  | 179                                           | 1FSGS          | ND                             | ND + AZA                                      | CR (+ Tacrolimus) |
| Fukuda et al. [40] | 65/M         | T-NA             | MG                  | 51                                            | MCD            | –                              |                                     | CR             |
| Okamoto et al. [41] | 42/M         | T-NA             | MG                  | 3                                             | MCD            | ND                             | ND + AZA                                      | CR (+ CsA) |
| Bolz et al. [42] | 48/M            | T-NA             | MG + CIDP           | 24                                            | MN             | ND                             | CS + AZA                                      | CR (+ IVIg) |
| Miyazaki et al. [33] | 29/M      | H                | MG                  | –12                                           | IgAN           | –                              | ND + AZA                                      | CR (+ Aza) |
| Calabrese et al. [44] | 30/F     | H                | MG + L             | 32                                            | LN             | +                              |                                     | F              |
| Miyazaki et al. [33] | 46/F      | H                | MG                  | –28                                           | MN             | +                              |                                     | CR             |
| Matsuda et al. [45] | 24/F          | H                | MG + P             | –135                                          | MCD            | –                              |                                     | PR             |
| Karras et al. [9] | 43/F            | H                | MG                  | 145                                           | MCD            | –                              |                                     | CR             |
| Calvino et al. [46] | 56/M         | H                | MG                  | –24                                           | MN             | –                              | ND + AZA                                      | CR (+ Chlorambucil) |
| Chen et al. [47]  | 24/F            | H                | MG                  | –24                                           | MN             | –                              | ND + AZA                                      | PR/CR (improved) |
| Miyazaki et al. [33] | 58/M        | H                | MG                  | –360                                          | IgAN           | –                              | ND + AZA                                      | Not used       |
| Innes et al. [48] | 25/M            | H                | MG                  | 60                                            | IgAN           | –                              | – + AZA                                       | Not used       |
| Haslam et al. [49] | 36/M            | H                | MG + Hypo-TH with thyroid autoantibody | 0                                            | LN             | –                              | ND + AZA                                      | PR             |
| Konishi et al. [50] | 46/F          | H                | MG                  | 55                                            | MN             | –                              | ND + AZA                                      | PR (+ CF) |
| Drube et al. [51] | 53/F            | H                | MG                  | 192                                           | CRGN           | –                              | ND + AZA                                      | PR (+ CsA) |
| Raillard-Gohn et al. [52] | 62/F    | H                | MG                  | 72                                            | Necrotizing angiitis | –                              | – + AZA                                      | F              |
| Prasad et al. [53] | 40/F            | H                | MG                  | 0                                             | MN             | –                              | ND + AZA                                      | F              |
| Shioyama et al. [54] | 40/F         | H                | MG                  | 12                                            | MN             | ND                             | ND + AZA                                      | CR (+ Tacrolimus) |
| Omar et al. [55]  | 13/F            | H                | MG + Hypo-TH + L    | 36                                            | LN             | +                              |                                     | CR             |
| Miskovic et al. [56] | 48/F        | H                | MG + L             | 336                                           | LN             | +                              |                                     | PR/CR (+ MMF; improved) |
| Tsai and Tsai [57] | 82/M            | H                | MG                  | 0                                             | MCD            | –                              | ND + AZA                                      | CR             |
| Hanna et al. [58] | 55/F            | H                | MG                  | 0                                             | MN             | +                              |                                     | F              |
| Nagarajan et al. [59] | 38/F       | H                | 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; CF, cyclophosphamide; IVIg, intravenous Ig.
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.
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
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-κ 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 4](https://academic.oup.com/ckj/advance-article/doi/10.1093/ckj/sfaa276/6078581)

**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). (D) PAS stain shows epithelial flating 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).

**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)], 1FCGS [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)], 1FCGS [7% (7/104)], CRGN [7% (7/104)], IgAN [5% (5/104)], TIN [3% (3/104)], IC-GN [1% (1/104)] and Others [4% (4/104)].
Thymic disease–associated nephropathy

There are a total of 104 cases (including our 17 cases, which we added 40 cases from other case reports. We performed an extensive literature search and updated the summary of ne-

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 study, Karras [11] reported 21 cases and summarized 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 pathogene-

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.

Parathyphic 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 restric-

### Table 4. Kidney diseases in patients with or without thymoma

| Renal pathology | Present study, n (%) | Previous cases, n (%) | Overall cases, n (%) |
|-----------------|----------------------|------------------------|----------------------|
| 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                   |

- **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.
- **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.

Parathyphic 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 restric-

Thymic disease–associated nephropathy | 9

Downloaded from https://academic.oup.com/ckj/advance-article/doi/10.1093/ckj/sfaa276/6078581 by guest on 26 February 2021
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 L1 Ab [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 mesasies, 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 nephritic 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 IgD 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.

**FUNDING**

M.Y. was supported by American Heart Association Scientist Development Grant 17SDG33660947, UCLA CT SI grant KLZTR001882, and Cedars-Sinai CT SI Clinical Scholar grant.

**CONFLICT OF INTEREST STATEMENT**

None declared.

**REFERENCES**

1. Bernard C, Frih H, Pasquet F et al. Thymoma associated with autoimmune diseases: 85 cases and literature review. Autoimmun Rev 2016; 15: 82–92
2. Souadjian JV, Enriquez P, Silverstein MN et al. The spectrum of diseases associated with thymoma. Coincidence or syndrome? Arch Intern Med 1974; 134: 374–379
3. Fujii Y. Thymus, thymoma and myasthenia gravis. Surg Today 2013; 43: 461–466
4. Jhaveri KD, Shah HH, Calderon K et al. Glomerular diseases seen with cancer and chemotherapy: a narrative review. Kidney Int 2013; 84: 34–44
5. Pani A, Forta C, Cosmai L et al. Glomerular diseases and cancer: evaluation of underlying malignancy. J Nephrol 2016; 29: 143–152
6. Mustonen J, Pasternack A, Helin H. IgA mesangial nephropathy in neoplastic diseases. Contrib Nephrol 1984; 40: 283–291
7. Vanatta PR, Silva FG, Taylor WE et al. Renal cell carcinoma and systemic amyloidosis: demonstration of AA protein and review of the literature. Hum Pathol 1983; 14: 195–201
8. Lien YH, Lai LW. Pathogenesis, diagnosis and management of paraneoplastic glomerulonephritis. Nat Rev Nephrol 2011; 7: 85–95
9. Posner MR, Prout MN, Berk S. Thymoma and the nephrotic syndrome: a report of a case. Cancer 1980; 45: 387–391
10. Rosenow EC 3rd, Hurley BT. Disorders of the thymus. A review. Arch Intern Med 1984; 144: 763–770
11. Karras A, de Montpreville V, Fakhouri F et al. Renal and thymic pathology in thymoma-associated nephropathy: report of 21 cases and review of the literature. Nephrol Dial Transplant 2005; 20: 1075–1082
12. Kudose S, Santoriello D, Debiec H et al. Renal and thymic pathology in thymoma-associated nephropathy: report of 21 cases and review of the literature. Nephrol Dial Transplant 2005; 20: 1075–1082
13. Travis WD, Brambilla E, Burke A et al. WHO Classification of Tumours of the Lung, Pleura, Thymus and Heart. Lyon, France: International Agency for Research on Cancer, 2015
14. Padda SK, Yao X, Antonicelli A et al. Paraneoplastic syndromes and thymic malignancies: an examination of the international thymic malignancy interest group retrospective database. J Thorac Oncol 2018; 13: 436–446
15. Kelesidis T, Yang O. Good’s syndrome remains a mystery after 55 years: a systematic review of the scientific evidence. Clin Immunol 2010; 135: 347–363
16. Lalle M, Minellli M, Tarantini P et al. Cellular and humoral immune alterations in thymectomized patients for thymoma. Ann Hematol 2009; 88: 847–853
17. Takahama Y. Journey through the thymus: stromal guides for T-cell development and selection. Nat Rev Immunol 2006; 6: 127–135
18. Takaba H, Takayanagi H. The mechanisms of T-cell selection in the thymus. Trends Immunol 2017; 38: 805–816
19. Crotty S. T follicular helper cell biology: a decade of discovery and diseases. Immunity 2019; 50: 1132–1148
20. Mevorach D, Perrot S, Buchanan NM et al. Appearance of systemic lupus erythematosus after thymectomy: four case reports and review of the literature. Lupus 1995; 4: 33–37
21. Lassere C, Combe C, Deminiere C et al. Thymoma associated with myasthenia gravis and minimal lesion nephrotic syndrome. Am J Kidney Dis 1999; 33: e4
22. Jamin A, Berthelot L, Couderc A et al. Autoantibodies against podocytic UCHL1 are associated with idiopathic nephrotic syndrome relapses and induce proteinuria in mice. J Autoimmun 2018; 89: 149–161
23. Vivarelli M, Massella L, Ruggiero B et al. Minimal change disease. Clin J Am Soc Nephrol 2017; 12: 332–345
24. Candelier JJ, Lorenzo HK. Idiopathic nephrotic syndrome and serum permeability factors: a molecular jigsaw puzzle. Cell Tissue Res 2020; 379: 231–243
25. Shalhoub RJ. Pathogenesis of lipid nephrosis: a disorder of T-cell function. Lancet 1974; 304: 556–560
26. Gharwan H, Tomita Y, Lee MJ et al. Alterations of immune cell subsets in relapsed, thymoma-associated minimal change disease: a case report. Oncol Lett 2015; 10: 1155–1158
27. Sellier-Leclerc AL, Duval A, Riveron S et al. A humanized mouse model of idiopathic nephrotic syndrome suggests a pathogenic role for immature cells. J Am Soc Nephrol 2007; 18: 2732–2739
28. Delville M, Sigdel TK, Wei C et al. A circulating antibody panel for pretransplant prediction of FSGS recurrence after kidney transplantation. Sci Transl Med 2014; 6: 256ra136
29. Yang T, Nast CC, Vo A et al. Rapid remission of steroid and mycophenolate mofetil (MMF)-resistant minimal change nephrotic syndrome after rituximab therapy. Nephrol Dial Transplant 2007; 23: 377–380
30. Perez-Gomez MV, Sanchez-Nino MD, Ortiz A. Megalin/lipoprotein receptor-related protein 2 autoimmunity and kidney disease. Clin Kidney J 2020; 13: 281–286
31. Boonen A, Rennenberg R, van der Linden S. Thymoma-associated systemic lupus erythematosus, exacerbating after thymectomy. A case report and review of the literature. Rheumatology (Oxford) 2000; 39: 1044–1046
32. Thivolet J, Monier JC, Ruel JP et al. Antinuclear autoantibodies in Swiss mice thymectomized at birth. Nature 1967; 214: 1134–1136
33. Hang L, Theofoopoulos AN, Balderas RS et al. The effect of thymectomy on lupus-prone mice. J Immunol 1984; 132: 1809–1813
34. Vincent A, Willcox N. The role of T-cells in the initiation of autoantibody responses in thymoma patients. Pathol Res Pract 1999; 195: 535–540