Renal and thymic pathology in thymoma-associated nephropathy: report of 21 cases and review of the literature

Alexandre Karras1, Vincent de Montpreville2, Fadi Fakhouri1, Jean-Pierre Grünfeld1 and Philippe Lesavre1 for the Groupe d’Études des Néphropathies Associées aux Thymomes

1Service de Néphrologie, Hôpital Necker, Paris and 2Service d’Anatomie Pathologique, Hôpital Marie Lannelongue, Le Plessis Robinson, France

Abstract

Background. Acquired thymic disease (malignant thymoma or thymic hyperplasia) is associated with various autoimmune diseases, such as myasthenia gravis (MG), pure red-cell aplasia (PRCA), pemphigus vulgaris or systemic lupus erythematosus (SLE). Renal disease has rarely been observed in association with thymoma.

Methods. This retrospective, multicentric study collected data on patients with thymic disease and biopsy-proven renal involvement.

Results. Twenty-one patients were studied (age: 49±14 years; male/female ratio: 8/13). Thymic pathology revealed mostly high-grade malignant thymoma (B2 and AB type); two cases were associated with non-malignant thymic hyperplasia. MG was found in nine out of 21 cases, SLE in three, PRCA in three and pemphigus in two. In 47% of these cases, nephropathy occurred after curative treatment of thymoma (108±83 months; range: 8–180 months), mainly based on surgical thymectomy associated with radiotherapy. Clinical and laboratory findings included nephrotic syndrome (75%), renal failure (50%), frequent presence of antinuclear antibodies and hypogammaglobulinaemia. Renal pathology showed minimal change disease in 14 patients and focal segmental glomerulosclerosis (FSGS) in one. Membranous nephropathy was observed in four cases, ANCA-associated glomerulonephritis in two and thrombotic microangiopathy in one. Most patients with minimal change disease or FSGS (11/13) were steroid-sensitive.

Despite good response to steroids, 38% of patients died from thymoma and 17% developed end-stage renal failure.

Conclusions. Glomerulopathy can be associated with thymoma or thymic hyperplasia. The present series shows that minimal change disease is the most frequent thymoma-associated glomerular lesion and that it may occur several years after thymectomy.

Keywords: glomerulonephritis; minimal change disease; myasthenia gravis; thymoma

Introduction

Thymic hyperplasia and thymic epithelial tumours (thymoma) have been associated with a broad spectrum of autoimmune disorders, such as myasthenia gravis (MG), pure red-cell aplasia (PRCA), systemic lupus erythematosus (SLE) and pemphigus vulgaris [1]. Thymoma-related autoimmune diseases are probably due to the induction of autoreactive T-cell clones in abnormal thymic tissue or to the suppression of regulatory T-cells that control the immune response. Among the different aspects of autoimmunity that have been observed, renal involvement has already been reported in patients with thymic tumours [2–16] and in an animal model of thymoma-related MG [17], but this specific association is rare and has not been studied specifically.

The aim of this clinical study was to identify such cases, combining thymoma or thymic hyperplasia and biopsy-proven nephropathy, and to describe the clinical features of this association. Thymic pathology was reviewed according to newly recognized histological criteria and correlated with kidney disease, trying to understand the link between thymic T-cell production dysregulation and the induction of nephropathy.
Subjects and methods

Methods

This retrospective study was conducted during the year 2000. A letter was addressed to 282 nephrologists across France, working in nephrology departments of university hospitals, asking them if they had treated patients presenting both thymic and renal disease. An answer was obtained for 223 of these letters (79%) and was positive in 21 cases. Several of these cases had been reported before [1,6,12] or had not been explored extensively and were excluded from this study. Finally, clinical observations of 21 patients (including five cases in our hospital), coming from 15 different French centres, were collected for further analysis. All patients were first admitted in a nephrology department between the years 1978 and 2000.

Definitions

When tissue specimens were still available, thymic pathology was retrospectively re-evaluated by a single pathologist according to the World Health Organization (WHO) thymic tumours’ classification [18]. In this newly established classification (Table 1), unavailable when most of these patients were operated on, thymic epithelial tumours are stratified into types A, AB, B1, B2 and B3 thymomas and a group of thymic carcinomas called type C thymomas. This classification is based upon well-defined histological criteria and has been shown to be an important prognostic marker for the survival of patients with malignant thymoma.

Clinical staging according to Masaoka criteria [19] was carried out in parallel for all patients with malignant thymoma. This staging system, based on invasion of surrounding organs and/or presence of distant metastatic lesions (stages I–IV), has also been reported as determinant for the post-operative survival of patients with malignant thymoma.

Partial remission of nephrotic syndrome was defined as loss of oedema and proteinuria falling to 0.3–3 g/day with normalization of serum albumin level. Complete remission of nephrotic syndrome was achieved when proteinuria dropped to <0.3 g/day with normalization of serum albumin and creatinine levels. Steroid resistance was defined as persistent nephrotic syndrome despite a minimum 3 month course of high-dose steroid therapy.

Results

The main clinical characteristics of the 21 patients are summarized in Tables 2 and 3. The mean age was 49±14 years and the male:female ratio was 1:1.3. None of them had a family history of nephropathy or thymoma.

Our study was not designed to determine the frequency of the thymoma–nephropathy association. However, among 260 patients with malignant thymoma operated on in Marie Lannelongue Hospital between 1988 and 2001, renal involvement was noted in only five cases (2%). The rarity of this association is also reflected in the low percentage of French nephrologists (10%) who have observed a thymoma-associated renal disease.

Thymic disease

Thymic pathology was available in 19 patients, based on tissue samples that had been obtained by percutaneous biopsy or surgical thymectomy. Initial diagnosis was malignant thymoma in 17 cases (thymic epithelial tumour in 16 and thymic carcinoma in one) and benign thymic hyperplasia in two. Two additional patients were considered to have a thymic tumour despite the absence of histological proof. This hypothesis was supported by typical radiological findings and simultaneous paraneoplastic syndromes, such as MG and pemphigus vulgaris.

Pathological re-evaluation of 14 malignant thymomas according to the WHO classification showed that the most frequently observed type was B2 (n = 7), followed by AB (n = 4), B3 (n = 2) and C (n = 1). With respect to Masaoka clinical staging, most thymic tumours were stage III or IV (in seven and five cases, respectively), showing invasion of adjacent organs or distant metastasis.

In most cases (18/19), thymic tumour was surgically removed; adjuvant radiotherapy was administered to 13 patients and cytotoxic chemotherapy to four. Exclusive radiotherapy was chosen for one patient with massive and particularly invasive thymoma.

Parathymic diseases

Parathymic syndromes were observed frequently among these 21 patients and 15 (71%) had at least one paraneoplastic disease, besides nephropathy. MG was present in nine cases (43%), with constant positivity of anti-acetylcholine receptor antibodies. SLE (according to modified ACR criteria) had been diagnosed previously in three cases (14%). Pemphigus vulgaris

<table>
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<tr>
<th>Type</th>
<th>Definition</th>
<th>Myasthenia</th>
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<tbody>
<tr>
<td>A</td>
<td>Epithelial cells with spindle/oval shape with few or no normal lymphocytes</td>
<td>–</td>
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<tr>
<td>AB</td>
<td>Foci with features of type A thymoma and lymphocyte-rich areas</td>
<td>–</td>
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<tr>
<td>B1</td>
<td>Normal cortical thymus aspect with areas resembling thymic medulla</td>
<td>+</td>
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<tr>
<td>B2</td>
<td>Foci of polygonal epithelial cells within a large population of immature lymphocytes</td>
<td>+</td>
</tr>
<tr>
<td>B3</td>
<td>Predominant epithelial population with minor lymphocytic component</td>
<td>+</td>
</tr>
<tr>
<td>C</td>
<td>Thymic carcinoma without any significant lymphocytic component</td>
<td>–</td>
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</table>
was present in two cases, PRCA in three, polymyositis in one and autoimmune thrombocytopenia in one. Chronic *Candida albicans* infection, which has been observed frequently in patients with thymoma-associated immunodeficiency, was noted in two cases.

Renal disease

In half of these cases (10/21), nephropathy occurred several months or even years after thymic disease had been diagnosed and treated (mean interval: 108 ± 83 months; range 8–180 months). Metastasis of thymoma was detected in three patients (patients 4, 9 and 12) when the nephrotic syndrome was diagnosed. Interestingly, in seven of these patients there was no overt recurrence of thymic tumour at nephropathy onset.

In six patients, thymoma was discovered long after nephropathy diagnosis had been made (mean delay: 97 ± 83 months; range: 14–241 months). However, three of these patients had active renal disease at thymectomy.

In the five remaining cases, renal and mediastinal abnormalities were diagnosed simultaneously.

**Renal disease: pathological findings**

All 21 patients underwent at least one kidney biopsy in order to assess renal pathology. The most frequently described type of glomerular involvement was minimal change disease (MCD), found in 14/21 cases (67%). Membranous nephropathy (MN) was observed in four cases (19%), anti-neutrophil cytoplasm antibody (ANCA)-related crescentic glomerulonephritis in two, focal segmental glomerulosclerosis (FSGS) in one and thrombotic microangiopathy in one patient with SLE.

One patient had presented with a pauci-immune crescentic glomerulonephritis 2 years before re-admission for the nephrotic syndrome, revealing MCD and associated malignant thymoma. Most patients (eight out of nine) with MG presented with minimal-change nephrotic syndrome. Among patients with SLE diagnosis (*n* = 3), two were diagnosed as having nephrotic syndrome related to MCD, with no detectable immune deposit.

Despite the limited number of patients, we can underline some correlation between thymic pathology and renal biopsy results. All patients with B2 type malignant thymoma (*n* = 7) had minimal-change nephrotic syndrome. On the other hand, both patients with B3 type thymoma had paraneoplastic MN. In the two cases of thymic hyperplasia associated with MG, the renal disease was a minimal-change nephrotic syndrome.

**Renal disease: clinical findings**

Nephrotic syndrome was present in 16 patients (77%). The mean level of proteinuria was 12.8 g/24 h and the mean serum albumin was 21 ± 9 g/l. Microscopic haematuria was noted in six cases (never in patients...
Most patients (13/15) presenting with MCD or FSGS were treated initially with steroids. Dosage and duration of steroid therapy varied considerably, but the most frequent regimen employed was prednisolone 1 mg/kg/day until remission, followed by a progressive tapering of the dose. This treatment was effective in 11/13 cases (84%), with complete remission in seven and partial remission in four. One patient died before response to corticosteroids could be considered. Only one patient had steroid-resistant nephrotic syndrome, although serial renal biopsies confirmed minimal change nephropathy with no glomerulosclerosis. Two patients who initially achieved complete remission presented subsequent relapses following tapering of corticosteroids. One patient with frequent relapses and two with partial response to steroids were treated successfully with other immunosuppressive drugs, such as cyclosporin (n = 2) or cyclophosphamide (n = 1). One patient with partial response and secondary relapse was given chlorambucil, with no major effect on proteinuria level. We were unable to identify any clinical or pathological factors associated with steroid dependence or steroid resistance among patients with minimal change nephropathy.

The effect of thymectomy upon renal symptoms is difficult to ascertain. Among patients with paraneoplastic membranous nephritis, treatment of thymoma...
Thymoma-associated nephropathy

(surgical excision in two, radiotherapy in two and chemotherapy in one) led to nephrotic syndrome remission in all cases, although concomitant corticosteroid treatment was given to only one of them. In two MCD patients with nephrotic syndrome at thymectomy, renal improvement can either be attributed to thymoma treatment or to simultaneous use of corticosteroids.

**Prognosis**

Eight patients (38%) died during follow-up, essentially among patients with grade IV thymoma. The most common cause of death ($n=6$) was extension or recurrence of malignancy. One patient died from uncontrolled MG and one from severe sepsis under corticosteroid treatment. In two MCD patients with nephrotic syndrome at thymectomy, renal improvement can either be attributed to thymoma treatment or to simultaneous use of corticosteroids.

**Discussion**

Thymoma is a rare mediastinal tumour that is often (40%) accompanied by different paraneoplastic syndromes, such as MG, PRCA or SLE. Association of glomerulonephritis and thymic tumour was first described in 1980 by Posner et al. [2]. The incidence of this association is probably quite low, as occurrence of nephropathy is rarely reported in most retrospective surgical series (<1%). Twenty-one cases have been reported to date in the French and English literature (Table 4), suggesting that nephropathy can be part of the large spectrum of thymoma-associated features [2–16].

The present study represents the largest series of thymoma-associated renal disease to date. In previously published cases of thymoma-related nephropathy, thymic pathology has rarely been reported or studied according to the newly recognized WHO thymic tumours’ classification. Our study shows that...
parathyroid nephropathy is associated mostly with histological subtypes AB, B2 and B3, which have also been observed preferentially with other thymoma-associated autoimmune disorders, such as MG.

Four of our patients presented with biopsy-proven MN. The association of MN with neoplasia, including a large variety of carcinomas and haematopoietic malignancies, has been documented in many studies. Although this glomerular disease is not the most frequently described nephropathy in patients with malignant thymoma, either in the literature or in the present series (MN represents 24 and 19% of cases, respectively), some interesting points can be noted. Among our patients, MN was always associated with active thymic disease (either newly diagnosed malignant thymoma or recurrence of metastatic lesions).

Malignancy was treated in three cases and resulted in rapid improvement of nephrotic syndrome. This feature was also noted in two previous reports [12,16], suggesting a paraneoplastic effect of thymoma on MN.

Our retrospective series and previously reported data strongly support the hypothesis of a particular link between thymic disease and MCD. The predominance of this type of glomerular disease (Figure 1) suggests that renal disease is not a coincidental event in patients with thymoma. We collected data on our 14 MCD patients and 10 previously published similar cases in order to study this specific association (Table 5). Age at initial presentation was 51 ± 16 years and the male:female ratio was 1:1.4. Thymic pathology was consistent with malignant thymoma in 22 cases (92%) and benign hyperplasia in two. In most cases (16/24), glomerular disease appeared after thymoma had been treated successfully (61 ± 60 months). MG was present in 11 cases (46%). Interestingly, six of these patients had been receiving immunosuppressive drugs (steroids and/or azathioprine) for MG (or for prevention of crescentic glomerulonephritis relapse in our first case) when proteinuria was first detected.

Treatment of MCD with high-dose corticosteroids was administered to 21 patients. Complete remission was noted in eight cases (38%) and partial improvement in five (24%). Seven patients failed to respond to a full course of steroids and one patient rapidly died of severe sepsis. Other immunosuppressive drugs were given to 10 patients, because of either frequent relapses or steroid resistance. Three patients were treated successfully with cyclosporin and three out of six patients showed a significant response to oral cyclophosphamide.

The link between thymic disease and most paraneoplastic syndromes remains elusive, but a dysregulation of immunity seems to be related to thymic cell proliferation. The thymus is a primary lymphoid organ, where T lymphocytes become mature and get through positive and negative selection. Autoimmune diseases result from an imbalance between autoreactive lymphocytes and immunoregulatory mechanisms. As thymus appears to be essential for the suppression of the immune response against autoantigens, it is not surprising to find that thymomas are associated with immunological disorders. Generation and education of lymphocytic populations in thymus are disturbed in patients with thymoma or thymic hyperplasia, before, and even after, thymectomy [20, 21]. In MG, thymectomy has demonstrated a beneficial effect on the course of neurological symptoms. However, some parathyroid syndromes, such as PRCA, SLE or pemphigus, can appear several months or even years after thymectomy, without recurrence of the thymic tumour [22]. In some experimental models of autoimmunity, such as murine lupus in (NZB × NZW) F1 mouse, removal of the thymus can accelerate the disease. Thus, the immune dysregulation observed in parathyroid syndromes could be due either to the thymic cell proliferation or to the suppression of an immunoregulatory lymphocytic subpopulation after thymectomy.

The pathogenesis of glomerular lesions in minimal-change nephrotic syndrome remains controversial. The beneficial effect of immunosuppressive therapy suggests a link between the immune system and the mechanisms of selective proteinuria associated with this disorder. A wide variety of immunological abnormalities have been described in MCD, affecting both humoral and cell-mediated immunity. Modification of the Th1/Th2 balance in circulating lymphocyte populations and abnormal T-cell response have been noted in patients with idiopathic nephrotic syndrome. In MCD and primary FSGS, a circulating vascular permeability factor is suspected to be responsible for the glomerular injury. Although the exact nature of this factor remains unknown, experimental observations suggest that it is produced by a T-cell population [23]. The association of MCD with Hodgkin’s lymphoma [24] lends support to the idea that cell-mediated immunity plays an important role in this specific nephropathy. One can postulate that thymoma-associated T-cell lymphoproliferation can explain the secretion of a lymphokine that increases the glomerular basement membrane permeability.

Interestingly, a well-known spontaneous experimental model, the Buffalo/Mna rat, combines thymoma, myasthenia and glomerulopathy. In this animal strain, thymoma-associated neurological disease, sharing
### Table 5. Association of MCD and thymoma

<table>
<thead>
<tr>
<th>Patients</th>
<th>Age</th>
<th>Sex</th>
<th>Thymic pathology</th>
<th>Associated diseases</th>
<th>Thymoma treatment</th>
<th>Delays thyrectomy – MCD (months)</th>
<th>Immunosuppression at MCD diagnosis</th>
<th>Serum creatinine mg/dl (μmol/l)</th>
<th>Albuminaemia (g/l)</th>
<th>Autoimmunity</th>
<th>Response to corticosteroids</th>
<th>Other treatments</th>
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<tr>
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<td>T</td>
<td>S</td>
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<td>−</td>
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<td>M</td>
<td>T</td>
<td>S</td>
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<td>2.48 (220)</td>
<td>17</td>
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<td>−</td>
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<td>F</td>
<td>CP (F)</td>
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<tr>
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<td>F</td>
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<td>T</td>
<td>S + R + CH</td>
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<td>19</td>
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<td>−</td>
<td>−</td>
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<td>MG</td>
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<td>4.29 (380)</td>
<td>15</td>
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<td>0.93 (83)</td>
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</table>

Sex: F, female; M, male.
Thymic pathology: T, malignant thymoma; H, benign thymic hyperplasia.
Associated diseases: L, lupus; P, pemphigus; T, autoimmune thrombopenia; PM, polymyositis; PRCA, pure red-cell asphasia; MG, myasthenia gravis.
Treatment for thymoma: S, surgical excision; R, radiotherapy; CH, chemotherapy.
Delay between thyrectomy and MCD. Negative numbers indicate that nephropathy occurred before thyrectomy.
Immunosuppression and other treatments: CS, corticosteroids; AZA, azathioprine; CP, cyclophosphamide; HCQ, hydroxychloroquine; CB, chlorambucil; CsA, cyclosporin A.
Response to corticosteroids and to other treatments: CR, complete remission; PR, partial remission; F, failure; NA, not available.
some homology with human MG, is characterized by muscle weakness and presence of anti-ryanodine receptor antibodies. Nephrotic syndrome appears at 1 month of age and renal pathology initially shows MCD-like glomerular disease followed by late development of FSGS. Recently, Le Berre et al. [17] suggested that nephropathy in this model is related to a circulating vascular permeability factor that explains the recurrence of proteinuria after renal transplantation. Although early studies have suggested that thymectomy does not modify the incidence of nephropathy in this animal model, the link between thymoma, myasthenia and nephropathy has yet to be clarified.

In conclusion, glomerular disease and, particularly, MCD may be one of the consequences of the immune dysregulation associated with acquired thymic disease. The study of this rare association, combining nephrotic syndrome and thymoma, either in patients or in the Buffalo/Mna animal model, could help us understand the pathophysiology of idiopathic nephrotic syndrome and the role of immunity in its development.


Conflict of interest statement. None declared.

References

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