Lupus Nephritis with Thymoma Managed by Thoracoscopic Surgery and Prednisolone

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Abstract:
A 48-year-old woman was admitted to our hospital to undergo evaluation for fatigue, severe weight loss, and nephrotic range proteinuria. Light microscopy of a renal biopsy specimen revealed class III (A) lupus nephritis, while immunofluorescence and electron microscopy only showed sparse immune deposits with findings that were not typical of lupus nephritis. Computed tomography revealed a mass in the anterior mediastinum, which was resected. The examination of the surgical specimen revealed type A noninvasive thymoma. In combination with thymomectomy, postoperative steroid therapy achieved the prompt remission of lupus nephritis. In this patient, thymoma-related autoimmunity may have contributed to the exacerbation of lupus nephritis.

Key words: systemic lupus erythematosus, thymoma, nephrotic syndrome

Introduction
Thymoma has been reported to co-exist in some patients with autoimmune diseases such as myasthenia gravis, pure red cell aplasia, and systemic lupus erythematosus (SLE). It has been argued that the association of SLE and thymoma is not merely a coincidence (1); however, whether thymoma has a role in the development of SLE is unclear. In SLE patients with thymoma, the clinical course after the resection of the tumor is highly variable (2-4). In addition, two mouse models of SLE showed an opposite course after thymectomy (5, 6), suggesting the heterogeneity of SLE and a significant role of the thymus in the disease.

A potential association between nephrotic syndrome and thymoma has also been reported (7), with the order of the diagnosis of these two conditions being variable. In patients with nephrotic syndrome and thymoma, the most commonly reported renal histology is minimal change disease (8).

We report a patient with SLE and nephrotic syndrome in whom a noninvasive thymoma was detected, and in whom a good response to corticosteroid therapy was obtained after the resection of the tumor.

Case Report
In August 2013, a 48-year-old woman was referred to our hospital to undergo evaluation for marked weight loss (12 kg in 6 months), normochromic normocytic anemia (hemoglobin, 9.5 g/dL; mean corpuscular volume, 86.4 fL; and mean corpuscular hemoglobin concentration, 33.3%), and high-grade fever. Earlier in the same year, a routine health check-up had shown that her hemoglobin was 13.0 g/dL. Seven months before the detection of anemia, she developed fatigue and loss of appetite; she also noticed alopecia in April. In June, bilateral leg edema developed and she occasionally had fever (body temperature, 38°C). She consulted a doctor. Neither gastrointestinal fiberscopy nor a gynecological examination revealed a cause of her anemia. Before referral to our hospital, scleritis was identified by an ophthalmologist.

On admission, a physical examination revealed pedal
edema, but there was no malar rash, discoid rash, oral ulceration, or arthritis. The admission laboratory data are shown in Table. The antinuclear antibody titer was 1 in 5,120 and the anti-dsDNA antibody titer was 4,200 IU/mL (normal <12 IU/mL). She also had proteinuria in the nephrotic range (3.73 g/day) with no M-protein. SLE was diagnosed according to the Systemic Lupus International Collaborating Clinics (SLICC) criteria (9).

A renal biopsy was performed to evaluate the patient’s nephrotic syndrome. Light microscopic examination of a biopsy specimen containing 68 glomeruli revealed global sclerosis in only 1 glomerulus. Endocapillary glomerulonephritis, with karyorrhexis, fibrinoid necrosis, and rupture of the glomerular basement membrane, cellular crescents, and hyaline thrombus were observed (Fig. 1a). However, there was no definite spike formation in the capillary walls (Fig. 1b). Because <50% of all of the glomeruli were affected, class III (A) lupus nephritis was diagnosed according to the International Society of Nephrology/Renal Pathology Society (ISN/RPS) classification (10). An immunohistochemical examination revealed faint staining for IgG and C3 deposition in the mesangial and subendothelial regions (Fig. 1c). Electron microscopy showed very small mesangial and subendothelial deposits, but there was diffuse and advanced effacement of the foot processes of podocytes (>70%) (Fig. 1d).

Computed tomography was performed to investigate systemic complications and an anterior mediastinal mass (29x15x26 mm), that showed marked enhancement by contrast medium (Fig. 2a). As the patient had no symptoms related to myasthenia gravis, such as muscle weakness or dysphagia, and the above-mentioned renal biopsy indicated lupus nephritis with the need for long-term immunosuppression, we decided to prioritize the surgical resection of the mediastinal tumor, the diagnosis of which was undetermined. The mass was resected by video-assisted thoracoscopy. Macroscopic inspection of the resected mass revealed a yellowish-white tumor (29x15x26 mm) with a fibrous capsule that featured the proliferation of spindle-like cells in bundles mixed with lymphoid cells (Fig. 2b). The final diagnosis was noninvasive thymoma [type A (according to the WHO classification) and Masaoka stage 1].

One week after the resection of the thymoma, the patient’s high-grade fever persisted; however, her proteinuria was reduced (3.81 g/g creatinine to 1.20 g/g creatinine). Thus, treatment was initiated with intravenous methylprednisolone pulse therapy (1,000 mg/day for 3 days), followed by oral prednisolone (30 mg/day). Her fever subsided rapidly and her urinary protein excretion also improved to 0.42 g/day after 1 week, while her leukopenia and hypocomplementemia resolved after 2 weeks (Fig. 3), after which she was discharged.

After the patient’s discharge, the prednisolone dose was tapered; tacrolimus (2 mg, daily) was added when the prednisolone dosage was reduced to 20 mg daily. Although the recrudescence of arthralgia and the increase in the ds-DNA level was seen when tacrolimus was switched to mycophenolate mofetil (1,000 mg daily; at the time, the prednisolone dosage was 12.5 mg), immediate control was achieved after restarting tacrolimus at the same dosage. At present, the patient remains well under daily treatment with prednisolone (5 mg), mycophenolate mofetil (1,500 mg), and tacrolimus (2 mg).

**Discussion**

In contrast with the comparatively clearer benefit of thymectomy in patients with myasthenia gravis (11), the outcomes of the resection of thymoma in SLE patients are variable and the role of resection is unclear. Because the order of onset varies in patients with thymoma and SLE (2, 3), the interpretation of the relationship between the two conditions is difficult. It has been argued that thymectomy should not be attempted in SLE patients unless a thymoma is present (2). This contention is substantially supported by at least five reports in the English literature (11-15), which have even reported new-onset SLE after

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### Table. The Patient’s Laboratory Data on Admission.

|                     | measured value | normal limits and unit |
|---------------------|----------------|------------------------|
| **Hematology**      |                |                        |
| WBC                 | 2,700          | 3,200-7,900 /μL        |
| RBC                 | 2.8            | 3.70-5.07 million/μL   |
| Hb                  | 8.3            | 11.3-15.0 g/dL         |
| MCV                 | 87.6           | 83-99 fl              |
| Platelet            | 228            | 155-350 thousand /μL   |
| Reticulocyte        | 31             | 27-89 thousand /μL     |
| **Blood chemistry** |                |                        |
| TP                  | 7.1            | 6.9-8.4 g/dL           |
| Alb                 | 2.3            | 3.9-5.2 g/dL           |
| AST                 | 41             | 13-33 IU/L            |
| ALT                 | 20             | 6/27 IU/L             |
| LD                  | 337            | 119-229 IU/L           |
| Measured value | Normal limits and unit |
|----------------|------------------------|
| GGT            | 30 9-109 IU/L          |
| Amy            | 233 42-127 IU/L        |
| UN             | 11 8-21 mg/dL          |
| sCr            | 0.66 0.46-0.78 mg/dL   |
| Na             | 139 139-146 mmol/L     |
| K              | 4.0 3.7-4.8 mmol/L     |
| Cl             | 107 101-109 mmol/L     |
| Ca             | 7.5 8.7-10.1 mg/dL     |
| IP             | 1.9 2.8-4.6 mg/dL      |
| Fe             | 49 80-120 ug/dL        |
| UIBC           | 160 195-273 ug/dL      |
| Ferritin       | 502 5-80 ug/L          |
| T-bil          | 0.3 0.3-1.1 mg/dL      |
| IgG            | 2.902 870-1,700 mg/dL  |
| IgA            | 451.4 110-410 mg/dL    |
| IgM            | 190.1 35-220 mg/dL     |
| CH50           | 21 30-50 U/mL          |
| C5             | 41 86-160 mg/dL        |
| C4             | 12 17-45 mg/dL         |
| CRP            | 0.3 0.0-0.3 mg/dL      |
| ANA            | 5,120.0 <40 fold       |
| Anti-double stranded DNA antibody | 4,200.0 <12 IU/mL |
| Lupus anticoagulant | 1.03 <1.3 |
| Antibodies to beta2-glycoprotein I | <1.2 <3.5 U/mL |
| sIL2R          | 1.820 145-519 U/mL     |
| Interleukin-6  | 12.2 <4.0 mg/L         |
| Vascular endothelial growth factor | 26.7 <38.3 pg/mL |
| Anti-acetylcholine receptor antibody (binding type) | 2.4 <0.2 nmol/L |
| PT-INR         | 1.0 0.80-1.20          |
| APTT           | 28.8 <15 s             |
| Erythrocyte sedimentation rate | >110 <15 mm/h |
| D-dimer        | 26.9 <1 ug/mL          |
| Free-triodothyronine | 2.5 2.29-4.17 pg/mL |
| Free-thyroxine | 0.8 0.72-1.52 ng/dL    |
| Thyroid stimulating hormone | 2.0 0.54-4.26 uIU/mL |
| Hepatitis B surface antigen | 0.2 <1.0 Cut off index |
| Anti-hepatitis C antibody | 0.4 <1.0 Cut off index |
| Syphilis RPR test | 0.7 <1.0 U |
| Specific gravity | 1.018                  |
| pH             | 6.0                    |
| Protein        | 622 3-60 mg/dL         |
| uCr            | 201 45-224 mg/dL       |
| Erythrocyte    | 1-4 <1 /High power field |
| Leukocyte      | 11-30 <1 /High power field |
| Epithelial cell | 5-10 <1 /High power field |
| Casts          | Only hyaline casts negative |
The renal biopsy findings. (a) Periodic acid-Schiff staining (×400). Endocapillary proliferation was observed with karyorrhexis, fibrinoid necrosis, glomerular basement membrane rupture, cellular crescents, and hyaline thrombus. (b) Periodic acid-methenamine-silver staining (×400). There was no definite spike formation in the capillary walls or mesangial proliferation. (c) Immunohistochemistry revealed faint staining for IgG and C3 deposition in the mesangial and subendothelial regions. (d) Electron microscopy showed very small mesangial and subendothelial deposits, with diffuse and advanced effacement of the foot processes.

Computed tomography and the microscopic appearance of the thymoma. (a) Computed tomography revealed an anterior mediastinal mass (29×15×26 mm) with marked enhancement by contrast medium. (b) Hematoxylin and Eosin staining of resected thymoma (×40).

On the other hand, the effect of chemotherapy in patients with relapsed thymoma was investigated based on the measurement of the T cell subsets in a patient with minimal change disease (MCD) (16). The study found that Th17 cells decreased and that proteinuria resolved after chemotherapy. In addition, the improvement of the renal function was reported in a patient with focal segmental glomerulosclerosis (FSGS) after surgical resection and adjuvant radiotherapy for invasive thymoma (17).

Several lines of evidence from animal studies have indicated that only neonatal fully functioning thymus resection negatively affected the immunological tolerance (18) and that the removal of the normal functioning thymus can generate de novo autoimmune disease even in normal young mice (19). These two reports suggest that the loss of the thymectomy.
normal function of the thymus, which can also be induced by thymoma, is important in the escape from tolerance. Thus thymomectomy - that is, the removal of abnormal thymoma - does not necessarily have the same role as resection of the thymus in a normal patient or a patient with myasthenia gravis and may potentially have beneficial effects, as was seen in our case.

Thymoma arises from the thymus, which plays a very important role in the development of both helper T cells and regulatory T cells which are major sources of both autoimmunity and tolerance. Our patient was diagnosed with SLE and showed nephrotic range proteinuria, hypoalbuminemia, edema, a paucity of deposits, and diffuse and severe foot process effacement, fulfilling all of the criteria for the diagnosis of lupus podocytopathy that were advocated by Hu et al., other than MCD and an FSGS-like non-proliferating picture (20). Furthermore, the presence of a lupus podocytopathy-like pathogenesis in this case was not incongruent considering the relatively bland urine sediment and the absence of a membranous renal pathology and multiorgan-targeted antibody production (including anti-acetylcholine receptor antibody) in the present patient. The partial improvement of nephrotic proteinuria after thymomectomy and the resolution of the patient’s symptoms after the initiation of methylprednisolone pulse therapy support this hypothesis. Further studies on the changing roles of the thymus that occur in association with the development of thymoma will contribute to understanding the full extent of this patient’s pathology.

The authors state that they have no Conflict of Interest (COI).

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