Thymoma-associated nephrotic syndrome: report of seven cases

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Abstract

Background: Thymoma is often associated with a series of paraneoplastic syndromes. Among them, thymoma-related nephrotic syndrome is much rare.

Methods: This retrospective study collected data from patients with thymoma and renal involvement in Xiangya Hospital, Central South University in a period of 5 years to investigate the clinical characteristics of thymoma-associated nephrotic syndrome.

Results: Seven patients were studied (age: 51.1 ± 21.4 years old; male/female ratio: 5/2). Among them, thymic pathology revealed 2 cases of type A and 1 case of type B3, myasthenia gravis (MG) was found in 1 out of 7 cases. Renal pathology showed 2 cases of FSGS and 1 case of IgA nephropathy. 2 out of 7 cases who received combined therapy of steroid and immunosuppressive drugs achieved complete remission. Despite 3 out of 7 cases received surgical excision of thymoma, 2 of them experienced treatment failure in nephrotic syndrome.

Conclusions: nephrotic syndrome can be associated with thymoma. The FSGS is the most frequent thymoma-associated glomerular lesion in this study. IgA nephropathy may be another pathological type in thymoma-associated NS. Despite after surgical excision, long treatment periods with high dosage of steroid combined with immunosuppressants were needed to achieve complete remission.

Background

The thymus is an important central immune organ with important immune regulatory functions and is a site for T lymphocyte differentiation and maturation. Thymoma/thymic hyperplasia are often associated with multiple paraneoplastic syndromes, such as myasthenia gravis (MG), pure red-cell aplasia, systemic lupus erythematosus and pemphigus vulgaris^[1]. Among them, the incidence of thymoma-associated glomerular diseases is very low, about 2%^[2], which may easily be ignored. Among the glomerular diseases, about 77% of them may presented as nephrotic syndrome (NS). Thymoma-associated NS may appear before, after or at the same time as the primary tumor, or after thymectomy for a period of time^[3–5].

Nowadays, it is believed that the occurrence of NS may be related to the presence of microthymoma or immune regulation disorder after thymectomy^[6], insufficient expression of thymic autoimmune regulator (AIRE) and MHC class II may be another reason for the occurrence of paraneoplastic syndromes^[7]. The pathological changes of the kidney are most common in minimal change disease (MCD), followed by membranous nephropathy (MN), anti-neutrophil cytoplasm antibody (ANCA)-related crescentic glomerulonephritis, focal segmental glomerular sclerosis (FSGS), and thrombotic microangiopathy^[3; 8]. Antitumor therapy is the cornerstone of the treatment of thymoma-associated glomerular disease^[3; 9]. However, in clinical practice, treatment for thymoma/thymic hyperplasia combined with NS is difficult due to many patients are often complicated with infection, severe hypoalbuminemia, thrombosis, and acute kidney injury, and are difficult to tolerate surgery, radiation and chemotherapy. Moreover, the correlation between the clinical features and pathological type of thymoma and NS should be further eliminated.

The aim of this retrospective study was to identify such cases, diagnosed with thymoma/thymic hyperplasia and NS, and to investigate the clinical characteristics of thymoma-related NS in a Chinese population. Renal and thymic pathology were reviewed to understand the link between thymic T-cell production dysregulation and the induction of nephropathy.

Methods

1. Clinical data: including gender, age at diagnosed with NS, renal biopsy and thymoma, histological type, clinical stage, therapeutic schedule, and whether thymoma is accompanied by other paraneoplastic syndrome.
2. Laboratory examination: including renal pathological type, proteinuria in 24h, serum albumin (Alb), serumcreatinine (Scr), hemoglobin (Hb), anti-nuclear antibody (ANA), anti-dsDNA antibody, anti-soluble nuclear antigen (ENA) antibody, blood and urine immunofixation electrophoresis (IFE), serum m-type phospholipase A2 receptor (PLA2R) antibody.
3. Pathological examination of kidney: the deposition of IgG, IgA, IgM, C3, C1q, fibrin-related antigen and PLA2R were detected by immunofluorescence after conventional processing of biopsy specimens. Pathological changes of renal tissues were observed by light microscope (HE, PASM and Masson staining) and electron microscope.
4. Treatment and outcome: the follow-up time started from the time of renal biopsy, and the patient's treatment regimen, proteinuria, blood serum Alb, Scr and other indicators were recorded.
5. Definitions: (1) Classification of thymoma pathology was used the WHO thymic tumors' classification criteria (2004)^[10]. With this criterion, thymoma was classified into Type A, AB, B (B1,B2,B3) and C. (2) Clinical stage was used the Masaoka clinical stage of thymoma^[11], which was classified into stage I, IIa, IIb, III, IVa and IVb. (3) Diagnostic criteria of NS: serum Alb<30g/L and proteinuria >3.5g/24h. Efficacy evaluation criteria of treatment: complete remission (CR) was defined as proteinuria <0.3g/24h. Proteinuria in 24h decreased $\geq 50\%$ from baseline and <3.5g/24h were defined as partial remission (PR). Proteinuria in 24h decreased <50% from baseline, or >3.5g/24h was defined as treatment failure.

Results

1. Basic data (Details are shown in table 2): among the 7 patients (5 males and 2 females), male: female =2.5:1, the average age of NS was 51.1 ± 21.4 years. Among them, 4 patients found NS and thymoma simultaneously, and the remaining 3 patients were: Case 3 presented NS before thymoma was found. NS was reported in the second month after thymectomy in case 4. Case 7 presented with thymoma and MG at the same time. The median follow up was 80 months.

2. Nephrotic syndrome: Of all the 7 patients, proteinuria ranged from 3.78 to 16.94g/24h and serum Alb ranged from 13.7 to 28.7g/L, meeting the diagnostic criteria of NS. Other complications including infection (5/7), anemia (3/7), hypertension (5/7), thromboembolic event (1/7), serological examination revealed that IgG level in three patients decreased, which may be associated with NS. 2 patients were positive with low ANA titer, 2 patients were positive with high ANA titer but negative with dsDNA antibodies, which did not meet the diagnostic criteria of systemic lupus erythematosus. Serum anti-PLA2R antibody was negative in all patients, and no monoclonal immunoglobulin was found in hematuria immunofixation electrophoresis (Details are shown in table 2).
3. Pathology of kidney: 3 patients received renal biopsy. Among them, case 2 was FSGS (apex type), case 3 was FSGS, and case 6 was IgA nephropathy (IgAN) (M1E0S0T0, Lee's classification grade II). 3 patients had tubular injury (Figure 1).
4. Thymus pathology: 3 patients underwent surgical excision, and the pathological types were as follows: Case 2 was type A (WHO classification), Masaoka clinical stage I; Case 3 was type A, Masaoka clinical stage IIb; Case 4 was type B3, Masaoka clinical stage I, and both the 3 cases did not accept postoperative chemoradiotherapy.
5. Clinical outcome: Among 7 patients, cases 1 and 6 were complete remission; Cases 3 and 5 showed partial remission; Cases 2, 4 and 7 were not alleviated. Case 1 received prednisone 30mg per day, tacrolimus 2mg per day and followed by a progressive tapering of the dose for one year, and finally achieved complete remission; Case 2 was admitted into our department because of NS, and his renal pathology revealed FSGS. In the period of curing NS, we found thymoma. Because the patient's serum albumin is very low, it's impossible to perform thymectomy, and after a series of hemodialysis, the patient's edema became a bit better, after prednisone 25 mg per day for one month, then prednisone 20mg per day and tacrolimus 1.5mg per day for 4 months, his serum albumin increased from 15.9g/L to 22.3g/L, then the patient received surgical excision. Until we finished this paper, the patient's symptoms did not relieve much; case 3 received prednisolone 10mg per day and tacrolimus 1mg per day for one year, then the treatment protocol was changed into prednisolone 10mg tertian day and azathioprine 100mg per day till now and the symptoms were partially relieved. Case 4 were treated with methylprednisolone 8mg per day after thymectomy for half a year, and the symptoms were not relieved. For case 5, the symptoms were partially relieved after 50mg prednisone for 8 months. In case 6, the result of renal biopsy was IgA nephropathy, and the symptoms were completely relieved after prednisone 30mg per day and followed by a progressive tapering of the dose for 9 months. In case 7, due to the severe symptoms of myasthenia gravis, the patient's symptoms improved after plasmapheresis, and the patient was given azathioprine 25mg twice per day for immunosuppressive therapy for 2 months, but the symptoms did not relieve (Details are shown in table 2).

Discussion

Thymoma often happened insidiously and is often missed because of lack of direct tumor's invasive symptoms. In our study, approximately 57.1% (4/7) patients were found to have thymoma during the diagnosis and treatment of NS. Karras analyzed 21 patients with thymoma-associated nephropathy, of which 47.6% (10/21) presented with nephropathy several months or years after diagnosis and treatment of thymic disease (mean interval: 108 ± 83 months; Range 8-180 months), only 23.8% (5/21) patients diagnosed both renal disease and thymoma simultaneously^[3]. Davison's study found that about 40% of patients with NS are often preceded the diagnosis of malignancy^[12]. Due to small number of cases enrolled, only 1 patient with NS prior to thymoma was found in this study. As NS is often characterized by hypoproteinemia and edema of bilateral lower limbs, it is more likely to be discovered. Therefore, it is particularly necessary to perform chest CT scan when screening and diagnosing the etiology of NS.

Abnormal thymic tissue can lead to regulatory disorders produced by T cells: AIRE deficiency, decreased MHC II expression, decreased Tregs, autoantibodies against I interferons, abnormally high CD8 + CD45RA + T cells and cytokines for age were the possible underlying mechanism^[13; 14]. On the other hand, the occurrence of thymoma itself can alter the thymic architecture, which may disrupt regional immune microenvironment, and lead to immature autoactive T cell activation which can escape negative selection in the thymus and further evade peripheral tolerance mechanism^[15]. This autoimmune response and immune compounds can thereby increase the permeability of glomeruli, leading to the occurrence of NS^[3].

Previous studies have shown that minimal-change nephropathy is the most common nephropathy caused by thymoma, followed by membranous nephropathy, and also includes focal segmental glomerular sclerosis^[3]. Posner first reported a case of thymic carcinoma with membranous glomerulonephritis in 1980^[16]. Jhaveri's study found that membranous nephropathy is a common type of renal pathology associated with solid tumors^[2]. In our study, 2 of the 3 patients with biopsy were FSGS and 1 was IgA nephropathy. The possible reason may be: among the 21 patients analyzed by Karras, 14 patients' thymus underwent pathological reassessment, according to WHO grading standards, the thymus pathology were as follows: B2 (n = 7), AB (n = 4), B3 (n = 2) and C (n = 1). According to the Masaoka stage, 12 cases were stage III or IV (7 cases for stage III; 5 cases for stage IV). While in our study, two cases were type A, Masaoka clinical stage I and IIb respectively. One case was type B3 and Masaoka clinical stage I. The thymus pathology type was different from that of Karras's study, which may be the reason for the inconsistency of the two types of renal pathology. We speculated that different types of thymopathologic type may lead to different types of renal pathology. The other reason may be, for 4,910 patients who received renal biopsies in China, the most common forms of primary glomerulonephritis were membranous nephropathy (MN, 37.2%) and IgA nephropathy (IgAN, 29.9%)^[17]. With the same study area of Karras' study, Simon's study showed that the most common primary glomerular diseases was also IgAN (2.4/1000, 3.6/1000 in males and 1.3/1000 in females) in 898 patients in a region of France^[18]. While, in Karras' study, there is no case of IgA, which may be associated with bias or renal pathology related to thymic pathology type. This study demonstrated for the first time that IgA nephropathy may be a new pathological type in thymoma-associated NS.

There is no standard treatment protocol about the dosage and duration of steroid and/or immunosuppressants of thymoma-associated NS. Adequate duration of steroids combined with immunosuppressants are more effective than steroids only in treating NS, whether or not the thymus is removed. In Karras's study, 11 out of 13 patients presented with MCD or FSGS were initially treated with steroids, the effective rate was 84% (54% CR, 30%PR)^[3], but in our study, even by combining steroid, immunosuppressants and thymectomy, the effective rate is only 57% (4/7). Immunosuppressive drugs, such as cyclosporine,

cyclophosphamide, chlorambucil, and azathioprine, are the common choice^[3; 19]. In our study, we chose tacrolimus, a more powerful and new immunosuppressive agents, to suppress the immune function, and the patients (2/2) achieved partial remission.

A short combination therapy, insufficient dosage of steroid and/or immunosuppressants and persistent existence of the primary etiology may be the fail reason of case 2, 4 and 7. On the other hand, Shin Hye Yoo reported a patient with metastatic thymoma accompanied by NS (surgical staging: Masaoka stage IVa, World Health Organization type B3), which is the same WHO classification stage of case 4, with 6 cycles of chemotherapy and removal of left diaphragm, left pleura and anterior thymectomy, the patient achieved complete remission, and no signs of recurrence of thymoma and NS were observed after that^[20]. For those who underwent surgical excision in our study, only case 3 achieved CR, but for those who did not undergo surgical excision, the treatment in 3 out of 4 patients were effective. With limited data, we were unable to identify the absolute correlation between thymectomy and the remission of NS, but we can ascertain that combination therapy (combing steroids, immunosuppressants and thymectomy) may be effective way to reduce proteinuria.

In the course of the treatment of NS, most patients were admitted into our department because of lower extremity edema, anemia and infection. In the routine examination after admission, we found thymoma occasionally. Due to the existence of infection, severe hypoalbuminemia, perinephric effusion, or with the use of steroid and /or immunosuppressants, it will increase the possibility of infection, severely postpone the operation of thymoma. It also explained why the cases of thymectomy were less in this study.

Conclusion

In conclusion, in this study, we demonstrated that FSGS is the most frequent thymoma-associated glomerular lesion. IgA nephropathy may be a new pathological type in thymoma-associated NS. Combination therapy may be an effective way to achieve complete remission for both thymoma and NS. The effect of thymectomy upon renal symptoms is difficult to ascertain. Standardized, unified and effective treatment protocol should be exerted to relieve misery of these patients.

Declarations

Ethics approval and consent to participate

This study was approved by the medical ethics committee of Xiangya Hospital, Central South University. All participants or their authorized bailors were consent to the study.

Consent for publication

All participants or their authorized bailors were consent to the study's publication.

Availability of data and material

None.

Competing interests

The authors declared they do not have anything to disclose regarding conflict of interest with respect to this manuscript.

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Authors' contributions

WH and ZP involved in the study design. WH and YX were responsible for data collection and analysis. WH wrote the manuscript. ZP and HX modified and revised the manuscript. All authors have read and approved the final version of the manuscript.

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None.

Abbreviations

MG myasthenia gravis

NS nephrotic syndrome

AIRE autoimmune regulator

MCD minimal change disease

MN membranous nephropathy

ANCA anti-neutrophil cytoplasm antibody

FSGS focal segmental glomerular sclerosis

Alb albumin

Scr serum creatinine

Hb hemoglobin

ANA anti-nuclear antibody

ENA extractable nuclear antigen

IFE immunofixation electrophoresis

PLA2R phospholipase A2 receptor

CR complete remission

PR partial remission

IgAN IgA nephropathy

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Tables

Table 1 Clinical data regarding thymoma

Patient No.	Gender	Follow up(months)	Age at thymoma	Thymic pathology	Masaoka clinical stage	Thymoma treatment	Associated diseases
1	M	82	64	T-NA	NA	NA	
2	M	6	59	T-A	I	surgical excision	
3	M	225	51	T-A	IIb	surgical excision	
4	M	61	63	T-B3	I	surgical excision	
5	F	81	41	NA	NA	NA	
6	F	80	10	NA	NA	NA	
7	M	3	71	NA	NA	NA	MG

Gender: M, male; F, female.

NA: not available.

Thymic pathology: T, malignant thymoma; 0, no histology; A, AB, B1, B2, B3, C, pathological classification of thymomas according to WHO;

Table 2 Clinical data regarding nephropathy

Patient No.	age at renal biopsy	Renal pathology	Age at nephropathy	Urine protein [g/24h]	Serum Alb (g/L)	Scr (umol/L)	hemodialysis	steroid	Immunosuppression	Outcome
1	NA	NA	64	5.38	13.7	263.4	NA	prednisone 30mg per day and followed by a progressive tapering of the dose for one year	tacrolimus 2mg per day	CR
2	59	FSGS(apex type)	59	16.94	15.9	296.5	Yes	methylprednisolone sodium succinate 20mg per day for 10 days→prednisone 25mg per day	tacrolimus 1.5mg per day. prednisone 20mg per day	F(+S)
3	51	FSGS	46	3.78	22.5	97	NA	prednisone 10mg per day	tacrolimus 1mg per day/ azathioprine 100mg per day	PR (+S)
4	NA	NA	63	4.12	22.3	535	NA	methylprednisolon 8mg per day		F(+S)
5	NA	NA	41	3.80	15.1	369	NA	prednisone 50mg per day		PR
6	10	IgA nephropathy	10	3.95	25.4	53	NA	prednisone 30mg per day and followed by a progressive tapering of the dose to 15mg per tertian day		CR
7	NA	NA	75	4.78	28.7	99	plasmapheresis	not used	azathioprin 50mg per day	F

Steroid effect: F, failure; R, relapse at tapering; CR, complete remission; PR, partial remission; in association with surgery (+S), chemotherapy (+C) or radiotherapy (+R) for thymoma.

Figures

Figure 1

Figure 1 Pathological changes of renal tissue in patients with thymoma-related nephrotic syndrome: Case 2 (FSGS): (a) Masson staining (*400), (b) PASM staining (*400), (c) Electron microscope; Case 3 (FSGS): (d) Masson staining (*400), (e) PASM staining (*400); Case 6 (IgA nephropathy): (f) Masson staining (*400), (g) PASM staining (*400), (h) Electron microscope