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A Rare Case of Focal Segmental Glomerulosclerosis in a Patient with Grade a Benign Thymoma: A Case Report and Review of the Literature

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Abstract

Thymoma is a rare mediastinal tumour that is often (40%) accompanied by different paraneoplastic syndromes and glomerulonephritis is one of the recognized entities. Minimal change disease is the most common paraneoplastic glomerulonephritis associated with thymoma, followed by membranous nephropathy, focal segmental glomerulosclerosis, rapidly proliferative glomerulonephritis and lupus nephritis. Literature review illustrates that most of the thymoma associated nephropathy cases were reported in association with more malignant thymic tumors like WHO grade B and C tumours. Herein we report a rare case of focal segmental glomerulosclerosis in a patient with grade A benign thymoma, a combination which has never been reported previously. She had poor response to corticosteroids and died due to neutropenic sepsis following azathioprine therapy.

Keywords: Thymoma-associated nephropathy; Focal segmental glomerulosclerosis; Paraneoplastic glomerulonephritides; Grade A thymoma

Introduction

Paraneoplastic glomerulonephritides are glomerular lesions that are not directly related to tumor burden, invasion, or metastasis, but rather are induced by products from tumor cells [1]. The concept of paraneoplastic glomerulopathy was introduced by Galloway [2] and Cornig [3] reported the first case of nephrotic syndrome and Hodgkin's disease. Solid tumor-associated membranous nephropathy and Hodgkin lymphoma-associated minimal change disease (MCD) have become recognized as 'classic' paraneoplastic glomerulonephritides. Other glomerulonephritides, however, including focal segmental glomerulosclerosis (FSGS), membranoproliferative glomerulonephritis, IgA nephropathy, and rapidly progressive glomerulonephritis (RPGN), are also associated with malignancy [4]. Apart from malignant tumors, nephrotic syndrome has been described in association with benign tumors such as meningioma [5] Thymoma is a rare mediastinal tumour that is often (40%) accompanied by different paraneoplastic syndromes, such as Myesthenia Gravis, Pure red cell aplasia, Pemphigus vulgaris and SLE [4]. Among the different aspects of autoimmunity that have been observed, renal involvement has already been reported in patients with thymic tumours [6,7]. Minimal change disease is the most common paraneoplastic glomerulonephritis associated with thymoma, followed by membranous nephropathy, FSGS, RPGN, and lupus nephritis [4].

There are four reported cases of FSGS in the background of thymoma by Scadding et al. Jayasena et al. [8], Karras et al. [7] and Yamauchi et al. [9]. Thymic histologies were malignant (not specified), not available, Grade AB mixed and grade B2 respectively, which are considered as having malignant courses. In this report we illustrate a case of a 52 year old Sri Lankan female presented with nephrotic syndrome who was found to have renal histology of FSGS and a Grade A benign thymoma, a combination which has never been reported previously.

Case Report

A 52yo Sri Lankan female with no significant past medical history presented to our hospital with generalized swelling of body for two months prior to admission. She has noticed progressively worsening B/L ankle swelling and facial puffiness without significant dyspnea, wheezing or cough. She has also noted froth in urine but there was no red or cola colour urine. The patient denied any significant medication in the past, or family history of renal disease or connective tissue diseases. The patient denied taking alcohol, smoking or illicit substance use. On physical examination she was an obese patient with BMI of 30.1 and appeared not in distress. She was afebrile, not pale, anicteric but there was facial puffiness and gross bilateral symmetrical pitting ankle edema extending up to thigh. There were no oral ulcers, no observable rashes, petechiae, purpura or lymphadenopathy. Abdominal examination revealed abdominal wall edema but there was no hepatospleenomegaly, ballotable masses or ascites. Cardiovascular, respiratory and neurological examination was unremarkable apart from blood pressure of 150/100 mmHg in both arms.

UFR persistently showed 4+ protein, 1-2 pus cells and no red cells or casts. 24 hour urinary protein excretion was 4.5 g which confirmed nephrotic range proteinuria. Serum creatinine was normal (93 µmol/l) and so were the electrolytes. (Na+ 140, K+ 3.9). Blood counts and blood picture didn't reveal significant abnormality (Hb 11.3, MCV 86, WBC 8460, N% 48, L%40, E% 1.1, Plt 255) but ESR was 90 mm/1 hr and CRP was 1.1 mg/l. Liver enzymes and INR were normal but serum albumin was very low 18 g/l (ALT 16, AST 23, Gamma GT 26 µ/l, Total bilirubin 4.79 µmol/l, Direct 0.61 µmol/l, Total protein 43.75 g/l, Albumin 18 g/l, Globulin 25 g/l, INR 0.95). Serum total cholesterol level was elevated 352 mg/dl. Since the clinical picture and above investigations are suggestive of nephrotic syndrome with bland urinary

sediments, we did further investigations to find etiology and to look for complications.

Chest roentgenogram PA and left lateral views showed a large anterior mediastinal mass towards left side which was delineated in ultrasound chest as 6 cm 5.5 cm hypoechoic, homogenous mass seen anterior to the heart. Contrast CT of chest and abdomen was performed which confirmed the mass and differential diagnoses were lymphoma or thymoma. There was no significant cardiac or great vessel compression, intrathoracic or abdominal lymphadenopathy, renal parenchymal/vessel/tract abnormalities (Kidney sizes R/9.5 cm L/9.4 cm), ascites, liver lesions or other intra-abdominal masses. 2D echocardiogram, lower limb venous duplex, thyroid functions, HIV screening were normal and ANA was negative.

Ultrasound guided biopsy of the mediastinal mass and left kidney were performed which gave the diagnosis as grade A benign thymoma with spindle cells and renal histology as non-collapsing focal segmental glomerulosclerosis.

She was started on high dose oral prednisolone 60 mg daily and referred to cardiothoracic surgeon for thymectomy. In addition she was put on enoxaparin prophylaxis for DVT as serum albumin was less than 20 g/l. Surgery was scheduled to be done in 3 months' time and she didn't respond to initial steroid treatment despite 4 weeks of treatment. Her renal functions started deteriorating after contrast CT chest and serum creatinine went up to 270 μmol/l. This was attributed to contrast nephropathy and later settled. Because of continuous proteinuria and resistant edema she was started on azathioprine 75 mg/d to which she had a good response as proteinuria came down to 1+. In the 4th week of azathioprine treatment she developed severe neutropenia followed by neutropenic sepsis and multiorgan failure. Despite ICU care with high end antibiotics and supportive treatment she succumbed to her illness before going for definitive surgery.

Discussion

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 [7].

World Health Organization Classification of Thymic Epithelial Tumours		
Type	Pathologic classification	Prognosis
A	Medullary thymoma Spindle cell thymoma	Benign clinical course
AB	Mixed thymoma	
B1	Lymphocyte rich thymoma Lymphocytic thymoma Predominantly cortical thymoma Organoid thymoma	Moderately malignant clinical course
B2	Cortical thymoma	
B3	Epithelial thymoma Atypical thymoma Squamoid thymoma Well differentiated thymic carcinoma	
C	Thymic carcinoma	Highly malignant clinical course

Table 1: World health organization classification of thymic epithelial tumours.

Nephrotic syndrome in a patient with thymic diseases has been reported as thymoma-associated nephropathy [9]. Both Thymic hyperplasia and thymoma has been implicated in this entity [7]. The prevalence of paraneoplastic glomerular diseases in patients with thymoma is about 2%, higher than that for Hodgkin lymphoma [4]. Association of glomerulonephritis and thymic tumour was first described by Posner et al. [6]. Most of these patients have minimal change nephropathy, which usually occurs after treatment of the thymoma. This association implies that severe T-cell dysregulation occurs in patients with thymoma-a feature that may be implicated in the pathogenesis of thymoma-associated paraneoplastic glomerulonephritis [4]. Karras et al. [7] reported the largest series of paraneoplastic glomerulonephritis associated with thymoma. In this study 21 cases of diagnosed thymoma patients with different thymic histologies were assessed with regard to different types of biopsy proven glomerulonephritides. 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). In six patients, thymoma was discovered long after nephropathy diagnosis had been made (mean delay: 97 ± 83 months; range: 14-241 months). In the five remaining cases, renal and mediastinal abnormalities were diagnosed simultaneously [7].

In this study thymoma histology was reported according to WHO classification of thymic epithelial tumors given below and histologic type was available only in 16 patients.

Thymoma histology	No. of patients	Renal histology
Thymic hyperplasia	2	MCD
Grade A	-	-
Grade AB	4	MCD, FSGS, MN, TMA
Grade B	9	MCD-6, MN-2, ECPGN-1
Grade C	1	MCD
Malignant, but not classified	3	MCD
Biopsy no histology	2	MN-1, ECPGN-1
MCD: Minimal Change Disease; MN: Membranous Nephropathy; FSGS: Focal Segmental Glomerulosclerosis; TMA: Thrombotic Microangiopathy; ECPGN: Extracapillary Proliferative Glomerulonephritis		

Table 2: Results obtained.

Karras et al. [7] also reviewed another 21 cases from French and English literature where thymic pathology was given as either malignant thymoma or hyperplasia as WHO classification was not available during that period (Tables 1 and 2).

Thymic pathology	No. of patients	Renal pathology
Malignant	16	MCD-10, MN-3, FSGS-1, ECPGN-1, LGN-1
Hyperplasia	4	MN-2, LGN-2
Not available	1	FSGS
MCD: Minimal change disease, MN: Membranous nephropathy; FSGS: Focal segmental Glomerulosclerosis; TMA: Thrombotic Microangiopathy; ECPGN: Extracapillary Proliferative Glomerulonephritis; LGN: Lupus Glomerulonephritis		

Table 3: Results obtained

There was another reported case of FSGS in 2010 by Yamauchia et al. [8] in a patient with invasive grade B Thymoma which has resolved after thymectomy. In conclusion, most of the patients had renal histology of minimal change disease regardless of the histological type of thymoma. Combinations of treatment including corticosteroids, azathioprine, HCQ, surgical excision, chemotherapy and radiotherapy were offered to these patients and treatment outcome was extremely variable [7]. Several patients could achieve complete or partial remission of renal disease, but there were no particular patterns in relation to thymic histology. Out of the 43 patients described in above studies only 10 patients had thymic hyperplasia and AB thymoma which are considered to have a benign course, and they had MCD, MN, FSGS, TMA or lupus nephritis as renal histology. A patient with a Grade A benign thymoma has never been reported to have glomerulonephritis (Table 3).

The patient we presented had a Grade A benign thymoma which was diagnosed simultaneously with nephrotic syndrome and she had poor response to oral corticosteroid treatment. She had a fair response to azathioprine but died unfortunately due to its complication before definitive surgery.

Conclusion

We reported a rare case of focal segmental glomerulosclerosis in a patient with grade A benign thymoma, a combination which has never been reported previously. Literature review illustrates that thymoma associated nephropathy is a diverse group of disease which can occur before, with or several years after the diagnosis of thymoma.

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