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Nephrotic syndrome and thymoma recurrence: a case report

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Abstract

Paraneoplastic syndromes, such as myasthenia gravis, pure red-cell aplasia and systemic lupus erythematosus are well-documented in thymoma. Association with glomerulopathies is rare and may occur several years after thymectomy. We report a case of a 60-year-old male presenting with nephrotic syndrome after thymectomy due to thymoma. The kidney biopsy showed minimal change disease. The patient went into complete remission after treatment with corticosteroids. The pathogenesis of glomerular lesions associated with thymic disease remains controversial.

Keywords: Glomerular disease; Minimal change disease; Nephrotic syndrome; Thymoma.

Introduction

Glomerular diseases are a rare complication of both solid and hematologic malignancies often described as paraneoplastic syndrome. Cancer-associated glomerulopathies are not directly related to tumor burden, invasion or metastasis, but are most likely due to abnormal secretion of hormones, growth factors, cytokines and tumor antigens by the tumor cells [1]. Treatment and prognosis of these conditions are different from primary glomerulopathies since they usually improve with remission of the underlying malignancy. Therefore, early recognition of these disorders is very important.

While membranous nephropathy is the most common glomerular pathology described in patients with solid tumors, minimal change disease (MCD) has been reported in association

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with hematologic malignancies, like Hodgkin lymphoma [1]. Cancer-associated glomerulopathies encompass a plethora of etiologies.

Thymoma is a rare mediastinal tumor that develop from thymic epithelial cells and it is an uncommon neoplasm with an annual incidence of 0.13 per 100.000 individuals in the United States of America. This disease is frequently associated with autoimmune and immunologic disorders such as myasthenia gravis, systemic lupus erythematosus, pure red-cell aplasia, hypogammaglobulinemia or pemphigus vulgaris2 and rarely (~2%) glomerulopathies [1].

We report a case of thymoma recurrence, nine years after successful thymectomy, presenting nephrotic syndrome. Paraneoplastic syndromes are sometimes the only clue for the diagnostic of thymoma or its recurrence, highlining the importance of high clinical suspicion.

Case report

A 60-year-old male was admitted to the emergency department with generalized pitting edema, dyspnea and orthopnea. Nine years earlier he was diagnosed with an invasive type B3 thymoma associated with myasthenia gravis. Extended thymectomy (with right pneumonectomy and partial pericardiectomy) and adjuvant chemo-radiotherapy with 3 cycles of CAP (cyclophosphamide, adriamycin and platinum) was performed. No evidence of thymoma recurrence was documented during follow-up. Myasthenia gravis symptoms control was achieved with low dose pyridostigmine (60mg/day).

Past medical history included controlled hypertension and dyslipidemia. No history of renal disease was reported in his family. On physical examination he was hypertensive (blood pressure 155/95 mmHg) and afebrile. He presented generalized pitting edema and bilateral basal inspiratory crackles; the remainder physical examination was unremarkable.

First laboratory-test results revealed elevated serum creatinine (1.4 mg/dL) and urea (115 mg/dL), without electrolyte or acid-base disturbances. He also had dysproteinemia with hypoalbuminemia (1.8 g/dL) and dyslipidemia (total cholesterol 344 mg/dL and triglycerides 187 mg/dL). Urinalysis revealed specific gravity of 1.035, proteins 1000 mg/dL, erythrocytes 5-10 cells per high-powered field (HPF) and leukocytes were less than 2-3/HPF.

The urine protein/creatinine ratio was 5g/g. No cytopenias or elevated inflammatory markers were found. Uric acid was 6.4 mg/dL. Thyroid function and B-type Natriuretic Peptide (NT-

proBNP) were normal. Other laboratory parameters were unremarkable.

Viral serologies, autoimmune study (antinuclear antibody, anti-double stranded DNA antibody, antineutrophil cytoplasmic antibodies and rheumatoid factor), serum complement fractions and immunoglobulins were negative. Serum protein electrophoresis and serum immunofixation test were normal. Anti-phospholipase A2 receptor antibodies were also negative.

Renal ultrasonography showed normal-sized kidneys with preserved cortical thickness and corticomedullar differentiation. Considering the past medical history, a chest computed tomography (CT) scan was performed and did not reveal any suspicious lesions.

The patient was admitted to the Nephrology Department where he started diuretics, high dose of statins, antihypertensive drugs and anticoagulation. Due to the diagnosis of nephrotic syndrome, a percutaneous kidney biopsy was performed. We obtained 18 non-sclerotic glomeruli with normal features on light microscopy (Figure 1).

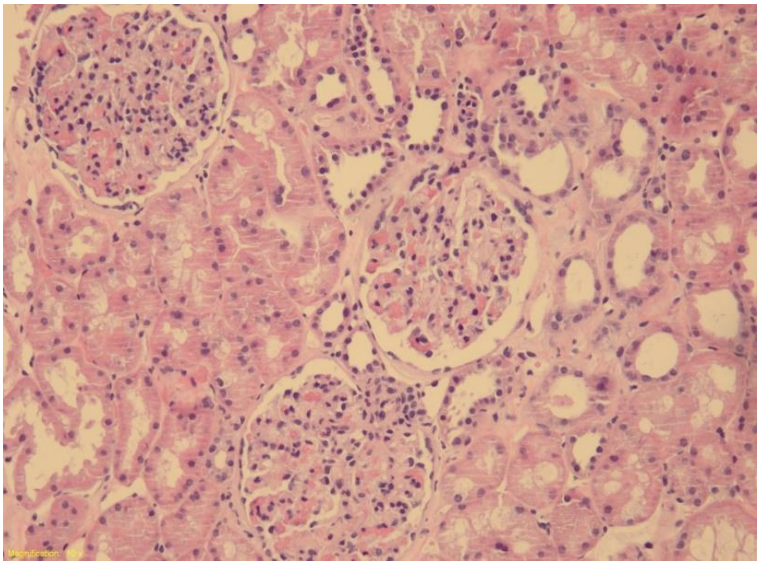

Figure 1. Glomeruli with normal features on light microscopy, mild endocapillary cellularity. [hematoxylin-eosin staining, x10].

There was mild fibrosis and tubular atrophy (10%) and moderate interstitial mononuclear inflammatory cells infiltration. Immunofluorescence was negative for immunoglobulins, complement fragments, albumin and fibrin. Electron microscopy showed diffuse foot process effacement (>80%) and condensation of podocytes nuclear

chromatin (Figure 2). A diagnosis of MCD was made.

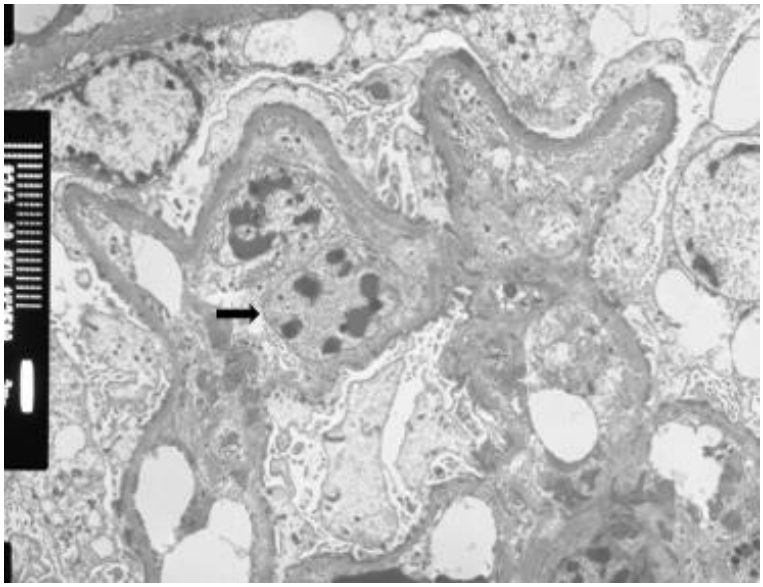

Figure 2. Diffuse foot process effacement and podocyte hypertrophy on electron microscopy. Atypical cells in the capillary lumen (arrow) [x2500].

In order to exclude malignancy, an 18F-Fluorodeoxyglucose positron emission tomography (FDG-PET) was performed which revealed diffuse FDG uptake in the anterior mediastinum (SUV max of 5.3) located next to the ascending aorta (Figure 3). There was no other metabolic evidence of malignancy in the exam.

An increase of pyridostigmine dose (120mg/day) was necessary due to worsening of myasthenia gravis symptoms with mild dysphonia and dysphagia. Based on these findings, the diagnosis of paraneoplastic MCD associated with thymoma recurrence was discussed with the oncology department and oral prednisolone (1mg/kg/day) was started with progressive clinical improvement.

Two months after starting treatment with corticosteroids, the patient went into complete remission of the nephrotic syndrome with normal serum albumin (4.1 g/dL), protein-creatinine ratio from a single urine sample of 0.1 g/g and stable estimated glomerular filtration rate (CKD-EPI GFR 50 mL/min/1.73 m2).

Currently, the patient maintains nephrology, oncology and neurology follow-up and prednisolone and pyridostigmine have been progressively tapered without evidence of disease recurrence.

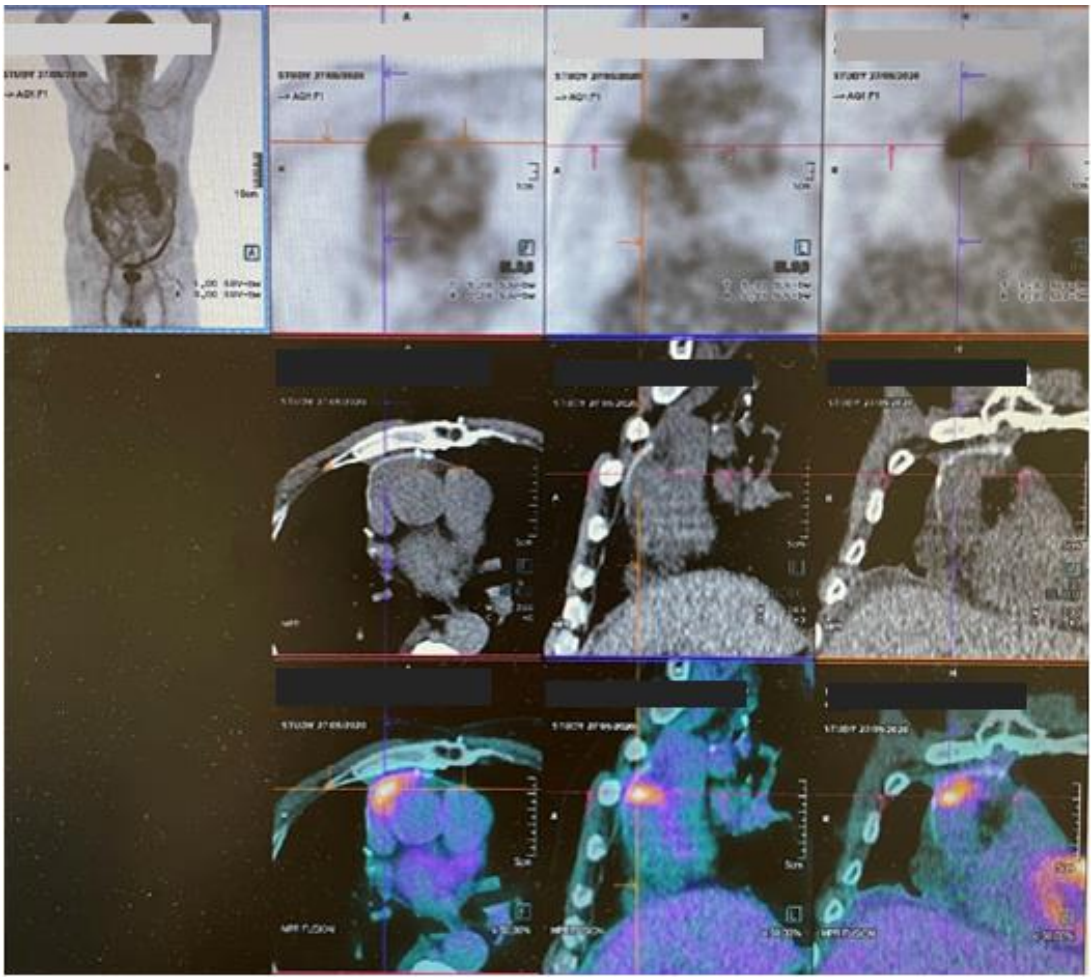

Figure 3. FDG-PET images show uptake in the anterior mediastinum (SUV max of 5.3) located next to the ascending aorta.

Discussion and Conclusion

We report a case with particular features. A 60-year-old patient with history of B3 subtype thymoma, with no signs of glomerular disease who underwent successful thymectomy and chemoradiotherapy. After nine years of follow-up with no evidence of recurrence, the first manifestation of tumor recurrence was nephrotic syndrome. In this case the nephrotic syndrome did not follow the course of thymoma. How could this be explained?

The thymus is a primary lymphoid organ, in which T lymphocytes become mature and get through positive and negative selection. Since it is essential for the suppression of the immune response against autoantigens, it is not surprising to find that thymomas are associated with immunological disorders [2].

Lymphocytic populations seem to be disturbed in patients with thymoma, before and even after thymectomy. Likewise, some parathymic syndromes can develop several months or even

years after thymectomy, with or without recurrence of the thymic tumor [3]. In some experimental models' removal of the thymus can accelerate the disease. Thus, the immune dysregulation observed in parathymic syndromes can be due either to the thymic cell proliferation or to the suppression of an immunoregulatory lymphocytic subpopulation after thymectomy [2].

Glomerulopathies related to thymic tumors are rare and were first described in 1980 by Posner et al. [4] As demonstrate by Karras et al, MCD is the most common thymoma related glomerular disease. Histological subtypes AB, B2 and B3 are mostly associated with parathymic nephropathy [2].

The pathogenesis of glomerular lesions in minimal change nephrotic syndrome remains controversial. A variety of immunological abnormalities have been described affecting both humoral and cell-mediated immunity. Modification of the type 1 T-helper cell (Th1) and type 2 T-helper cell (Th2) balance and abnormal T cell response have been noted in primary MCD.

The relationship between Th2 response and MCD has been further demonstrated in thymomas. Animal models of thymoma show a similar phenomenon in which MCD persists despite thymectomy. In these mice, there is increased Th2-mediated cytokines, and suppression of the Th2 axis improves the degree of proteinuria [5].

In our case, when the diagnosis of thymoma was made, there was no evidence suggesting renal involvement. This may be due to prompt initiation of treatment (thymectomy and adjuvant chemoradiotherapy) or the presence of normal thymic tissue which may have prevented significant immune dysregulation. Nine years later, the recurrence of thymoma in the presence of a thymectomy could explain the immune dysregulation associated with the thymic cell proliferation and the development of MCD.

This case report highlights the importance of early recognition of cancer related glomerulopathies and how that could influence follow up, treatment and prognosis of the patient.

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