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Focal segmental glomerulosclerosis associated with papillary thyroid carcinoma in a patient with polycystic kidney disease

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Abstract

Focal segmental glomerulosclerosis (FSGS) is the most common histological pattern of nephrotic syndrome which has been mainly reported in adults with hematological malignancies. However, the association of FSGS with carcinoma especially solid tumor of the thyroid has not been reported. Here, we present a case of nephrotic syndrome developed due to renal failure in a 21-year old woman with autosomal dominant polycystic kidney disease (ADPKD). Pathological examination of renal biopsy revealed the characteristic changes of FSGS. On further evaluation, the patient had right thyroid lobe swelling clinically which result in total thyroidectomy. The pathological study was inconsistent with papillary thyroid carcinoma (PTC). Regardless of the therapeutic interventions, her renal function worsened gradually and she ultimately required hemodialysis. This case presented an unreported co-incidence of PTC and nephrotic syndrome due to FSGS. The underlying mechanism for the development of malignancies after nephrotic syndrome is still unknown. Hence, underlying malignancy should be considered in young adult patients presenting with nephrotic syndrome.

Keywords: Focal segmental glomerulosclerosis, Papillary thyroid carcinoma, Renal dysfunction, Polycystic kidney disease

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Introduction

Focal segmental glomerulosclerosis (FSGS) is the most common glomerular disease of an idiopathic nephrotic syndrome characterized by progressive deterioration of the renal function (1-3). The coincidental occurrence of cancer and nephrotic syndrome due to membranous glomerulonephritis (MCN) was frequently observed; however, on rare occasions, FSGS was presented in patients with solid tumors (4-6).

Although a causal relationship has not been recognized between malignancy and glomerular injuries, many studies have provided immunological evidence in the pathogenesis of malignancy associated with nephropathy. The nephrotic syndrome caused by FSGS has not yet been documented in a patient with papillary thyroid carcinoma (PTC) in the literature. Herein, we describe a rare case of ADPKD and PTC with the concurrence of nephrotic syndrome caused by FSGS. The clinical course of this case, management of PTC along with FSGS are discussed.

Case Presentation

We present a 21-year-old female patient referring to general clinic due to detection of proteinuria on her routine controls. Through 24-hour urine investigation, nephrotic syndrome was diagnosed following laboratory results indicating protein exertion of 4322 mg/d, serum creatinine (sCr) of 2.8 mg/dL, serum albumin of 3.4 mg/dL, and total cholesterol of 290 mg/dL. After clinical diagnosis of nephrotic syndrome, she was closely followed-up without any additional treatment for her proteinuria.

About 8 months after nephrotic syndrome diagnosis, sCr rose to 4.7 mg/dL, whereby she was referred to our nephrology clinic. A review of her past medical history revealed that she had been diagnosed with hypothyroidism, hypertension, and hyperlipidemia 2 years ago. She had no history of smoking, travel, or infections.

Her physical examination showed body mass index (BMI) = 25, arterial blood pressure of 140/80 mm Hg and bilateral pitting edema (+) of the lower extremities was remarkable. For further evaluation of her renal dysfunction, she was admitted to hospital. Laboratory testing upon admission revealed: white blood count= 9300 µL, hemoglobin= 10.5 g/dL; platelet = $20.3 \times 10^4/mm^3$; blood urea nitrogen (BUN)= 44 mg/dL; sCr= 3.9 mg/dL; uric acid= 10.1 mg/dL; serum albumin = 3.5 g/dL; sodium = 134 mmol/L; potassium = 5 mmol/L; calcium= 8.7 mg/

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Implication for health policy/practice/research/ medical education

This case report highlights the following points:

1. Malignancies should be considered in adults presenting with nephrotic syndrome as well as other underlying renal diseases like polycystic kidney disease.
2. The association between glomerular disease and neoplasm has been established.
3. It is suggested that immune response influenced by neoplasm may lead to the development of nephrotic lesion in a patient with malignancy
4. FSGS is the most common idiopathic glomerular lesion causing End-stage renal disease.

dL; and phosphorus = 5.5 mg/dL. Urinalysis showed 4+ proteinuria and hematuria without any casts.

According to the results of 24-hour urine collection, urine creatinine and protein excretion were 1247 mL/min and 3.137 g, respectively. Secondary study for antinuclear antibody (ANA), anti-double-stranded deoxyribonucleic acid (ds-DNA), anti-glomerular basement membrane (GBM), cryoglobulins and cold agglutinins were negative. Serum complement (C3, C4, CH50), c-ANCA, p-ANCA and viral serological evaluations (HBs Ag, HCV Ab, HIV Ab) were almost within normal limits, through which secondary causes of the nephrotic syndrome were less likely and ultimately were excluded. Renal ultrasound scan showed normal-sized kidneys (L: 99 mm, R: 98 mm) with the increment of echogenicity. In addition, 3 cysts were detected in the upper pole of the left kidney with different sizes (2, 10, and 26 mm) which was indicative of polycystic kidney (Figure 1). Whereas polycystic kidney

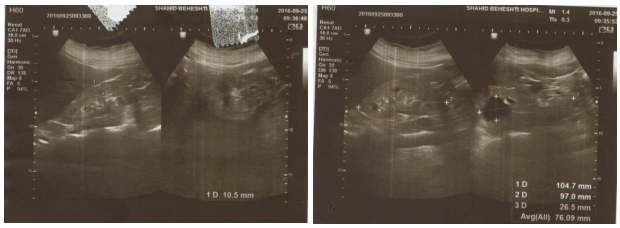

Figure 1. Sonographic view of kidneys. Renal ultrasound scan is indicative of normal sized kidneys (L: 99, R: 98) with 3 cysts in the upper pole of the left kidney with different sizes (2, 10, and 26 mm).

with three small cysts was unable to explain her heavy proteinuria, a kidney biopsy was performed to rule out her underlying renal disease. The specimen consisted of eight glomeruli, seven of which were globally sclerotic. The remaining glomeruli disclosed mesangial cell proliferation and thickening of the glomerular basement membranes. Focal and segmental sclerosis lesions along with the presence of synechiae were observed. Tubulointerstitial area examination showed 30% of the interstitium with tubular atrophic changes. Pathological findings of glomerulosclerosis with typical focal and segmental lesions were indicative of FSGS (Figure 2). Immunofluorescence revealed positive staining for C3 (3+), IgM (3+), IgG (2+), C1q (3+), kappa (2+), and lambda (1+); However, staining for IgA was negative in glomeruli.

Due to acute intestinal nephritis, prednisolone was administered at 30 mg/d dose for 10 days. Despite all therapeutic attempts, her renal function worsened gradually within 4 months, and the sCr had improved to 6.7 mg/dL approximately. Considering that sufficient improvement of renal function was not provided, prednisolone was tapered and discontinued over a period of 8 months subsequently.

In December 2017, she was readmitted to our hospital for further follow-up evaluation. During hospital admission, her vital signs were stable. On physical evaluation, right thyroid lobe swelling was found clinically, as well as evidence of a heterogeneous solid nodule with fine calcification foci ultrasonically. Subsequently, fine needle aspiration was performed and PTC was reported (Bethesda V). Thyroid function tests (TSH = 3.1 mIU/L, T3 = 1.5 nmol/L, T4 = 7.9 µg/dL) and thyroid antibodies (thyroglobulin 14.8) were normal. She had no family history of thyroid disease. The patient had been on medical treatment for hypothyroidism with no history of radiation. For further investigation, she was referred to the surgical division; however, the patient was reluctant to have surgery at that time.

Six months after the initial diagnosis of FSGS, the patient presented to the emergency department because of nausea, vomiting, decreased appetite and oliguria. Initial laboratory studies revealed improved sCr to 9.9 mg/dL. Other significant laboratory studies included BUN 79

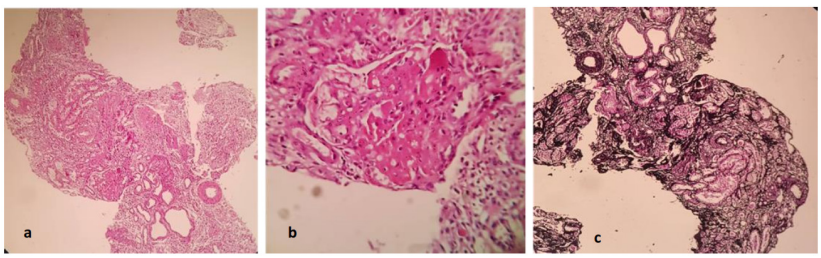

Figure 2. Microscopic appearance of focal segmental glomerulosclerosis (FSGS). (A) Light microscopy of a renal biopsy specimen containing 8 glomeruli reveals global sclerosis of 7 of them. The tubules show focal atrophy, thickening of the glomerular basement membrane with increased mesangial matrix in the interstitial areas ((a,b) Periodic acid–Schiff stain; (c) Silver Methenamine–Masson trichrome stain with original magnification, 10X, 40X).

mg/dL, hemoglobin 7.5 g/dL, calcium 7.9 mg/dL and phosphorus 6.1 mg/dL. Due to renal failure progression, hemodialysis was started. Maintenance hemodialysis was continued 3 times weekly for 3.5 hours per session. After a few days, the patient was recovered and discharged with decreased creatinine to 4.99 mg/dL and BUN 29 mg/dL.

A week later, for the third time, she was readmitted to hospital with the symptoms of nausea, loss of appetite and dysuria. At this hospitalization, swelling was noted in the right lobe of the thyroid. Repeated ultrasonic examination showed right lobe enlargement than normal size (44×32×29 mm, volume: 22 cc) with no change in the rest of the thyroid compared to the first ultrasound study (Figure 3). She was transferred to surgical for thyroidectomy surgery as soon as possible. Finally, three months later, total thyroidectomy was performed followed by one session of radioactive iodine therapy. The pathological specimen confirmed FNAB result which was coupled with PTC (Figure 4). In the next 7 months, complete remission of PTC was noted. Hemodialysis has been continued under nephrology follow-up.

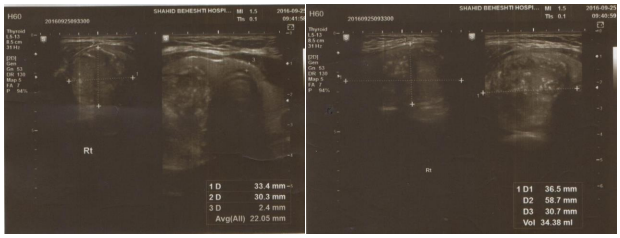

Figure 3. Ultrasonographic view of thyroid. Thyroid ultrasound scan showed the right lobe with the bigger size than normal one (44×32×29 mm, volume: 22 cc). in addition, heterogeneous solid nodule with fine calcification foci was also found.

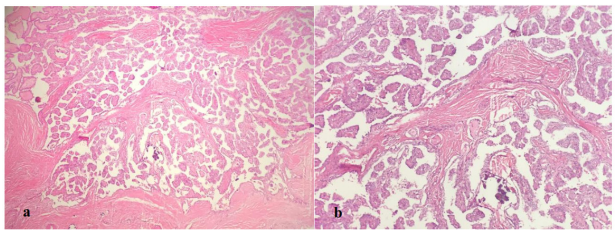

Figure 4. Microscopic views of papillary thyroid carcinoma (PTC). Photomicrograph of the classical papillary carcinoma is showing with overlapping nuclei and ground-glass appearance. Pseudo-inclusion with occasionally nuclear groove are also present (Periodic acid–Schiff stain with original magnification, a; 10X, b; 40X).

Discussion

The association between glomerular disease and neoplasm has been established earlier by Lee et al in 1966 (7,8). They demonstrated that 10.9% of patients with the nephrotic syndrome had a neoplasm concomitantly and approximately 40% of the patients had nephrotic syndrome prior to detection of a tumor which may occur with variant time onset (7,9). In our patient, the diagnosis of nephrotic syndrome was documented 13 months prior to diagnosis of the tumor. Considering the cases of nephrotic syndrome and non-hematologic malignancies, the most common histological finding was the membranous glomerulonephritis variant, whereas FSGS disease associated with carcinoma has rarely been reported (6,10). In our previous case report, we reported the renal involvement due to FSGS in a patient with multiple myeloma which was uncommon. However, to the best of our knowledge, this is the first documented case of PTC-associated FSGS and ADPKD in English literature (11).

The pathogenesis of renal injury in patients with cancer-nephrotic syndrome remains unclear. Some studies have been done with the main interest in investigating the association between NS and cancer etiologically. Investigations have provided direct evidence of abnormality of the immune response which may evoke anti-tumor antibody that reacts with normal tissues like renal tissue (9,12,13). Formation of the immune complexes composed of the tumor-associated antigen and antibody can induce the renal lesion (3). Costanza et al also studied the development of NS in a patient with colon carcinoma by immunofluorescent technique. The findings indicate the deposits of granular immune complexes consisting of cell-surface antigens and tumor antibodies on the granular basement membrane which led to granular nephritis (13).

Therefore, it is suggested that immune response influenced by neoplasm may develop nephrotic lesion in patients with malignancy. A review of cases reported that the nephrotic syndrome might successfully regress by the excision of the tumor (12, 14), but Revol et al reported no resolution of nephropathy despite the underlying tumor complete resolution (15). It is also recognized that malignancies can indirectly effect the kidney through renal amyloidosis, intravenous thrombosis or neoplastic infiltration (12, 14). In our case, nephrotic syndrome occurred in the absence of these renal complications. It is also probable that she was a case of spontaneous thyroid neoplasm that was recognized with the nephrotic syndrome due to FSGS.

FSGS is the most common idiopathic glomerular lesion causing end-stage renal disease (ESRD) which accounts for about 20% of cases of adult nephrotic syndrome (2). FSGS is complicated by primary and less commonly secondary forms with different etiologic associations. The primary (idiopathic) form typically manifests with nephrotic range proteinuria. The severity of nephrotic proteinuria along with the degree of interstitial fibrosis appears to be the best predictor of poor outcome in primary FSGS. On the other hand, sub-nephrotic range proteinuria and usually lack of hypoalbuminemia support the diagnosis of secondary form of FSGS. Since the therapeutic implications differ significantly between the primary and secondary forms of FSGS, it is essential to discriminate between these two forms (16-18). Otherwise, treatment failure and

the progression of renal function impairment can occur especially in its idiopathic forms. Immunosuppressive agents with prednisone play a critical role in treatment of idiopathic nephrotic syndrome which is suggestive of the involvement of immunologic mechanisms (16). In our case, the FSGS was not responsive to standard steroid therapy which led to insufficient improvement of renal function and ultimately hemodialysis was started to manage her renal function.

Considering literature, an untreated form of idiopathic FSGS is progressive and up to half of the patients develop to ESRD over 5-8 years (3,17). Our case progressed to ESRD about 1 year after diagnosis which noted the poor prognosis and aggressive manner of FSGS in this patient. The presented patient had unusual association of FSGS and PTC. Clearly, the available evidence was not sufficient to confirm the association of renal dysfunction and thyroid carcinoma; therefore, the exact causal relationship between the two conditions remains unproven.

Except for minimal change nephritis (MCN) with hematological malignancies, most cases of glomerular disease associated with malignancy occur in older patients (19), while our patient was a young woman. Hence, underlying malignancy should be considered in young adult patients presenting with nephrotic syndrome.

As a conclusion, we presented the first case of a co-incidence between PTC and FSGS in a female patient who eventually reached ESRD over a short time. No particular mechanisms seemed to be causative in the evolution of both conditions. Therefore, further studies are required to elucidate the mechanism linking renal lesion and cancer pathologically. It is also suggested that an adult patient presenting with nephrotic syndrome be evaluated for the malignancies accompanying, as well as other underlying renal diseases like polycystic kidney disease.

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Authors' contribution

All the authors were involved in conception, drafting/revising the article and final approval of the version to be published. RA, FE, AF and HF, read and signed the final manuscript.

Conflicts of interest

The authors declare that they have no competing interests.

Ethical issues

Ethical issues (including plagiarism, data fabrication, double publication) have been completely observed by authors. Written informed consent was obtained from the patient.

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