Sarcoidosis Presenting with Membranous Nephropathy in a Patient with Hypertensive Nephropathy: Case Report

Hipertansif Nefropatili bir Hastada Membranöz Nefropati ile Prezente Olan Sarkoidoz Olgusu

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ABSTRACT

Sarcoidosis is a systemic granulomatous disease that primarily involves the lung but may also have renal involvement. We present a hypertensive nephrosclerosis case found to have sarcoidosis after membranous nephropathy was diagnosed. A 57-year-old female patient was admitted due to nephrotic syndrome. She had a history of hypertension for 5 years. Fundus examination was consistent with grade 2 hypertensive retinopathy. Kidney biopsy was performed because of nephrotic syndrome and impaired renal function and revealed membranous nephropathy. Sarcoidosis was diagnosed while secondary causes of membranous nephropathy were investigated. Nephrotic syndrome was improved with steroid treatment in 6 months. In conclusion, a sarcoidosis case initially presenting with membranous nephropathy is an uncommon manifestation. Secondary causes of membranous nephropathy must be carefully investigated.

KEY WORDS: Sarcoidosis, Nephrotic syndrome, Membranous nephropathy, Hypertensive nephropathy

ÖZ

Sarkoidoz başlıca akciğerler olmak üzere böbrek tutulumunun da görülebildiği granümatöz bir hastalıktır. Burada hipertansif nefrosklerozu olan, membranöz nefropati tanısı alıp sonradan sarkoidoz saptanan bir olgunun sunulması amaçlandı. 57 yaşında kadın hasta nefrotik sendrom kliniğiyle başvurdu. Hastanın öz geçmişinde 5 yıldır hipertansiyon öyküsü mevcuttu. Hastanın göz dibi bakısı grade II hipertansif retinopati ile uyumluydu. Nefrotik sendrom ve bozulmuş böbrek fonksiyonu nedeniyle yapılan böbrek biyopsisinde membranöz nefropati saptandı. Membranöz nefropatinin sekonder sebepleri araştırılırken hastaya sarkoidoz tanısı konuldu. Steroid tedavisiyle hastada 6 ayda tam remisyon sağlandı. Sonuç olarak, membranöz nefropati ile prezente olan sarkoidoz oldukça nadirdir. Her ne kadar membranöz nefropati sıklıkla idiopatik olsa da sekonder nedenler ısrarla araştırılmalıdır.

ANAHTAR SÖZCÜKLER: Sarkoidoz, Nefrotik sendrom, Membranöz nefropati, Hipertansif nefropati

INTRODUCTION

Sarcoidosis is a noncaseating granulomatous disease that can affect many organs. Renal involvement is commonly seen in sarcoidosis. Renal manifestations of the disorder include nephrolithiasis due to hypercalciuria and hypercalcemia, granulomatous interstitial nephritis, glomerular disease and obstructive uropathy (1-3). Sarcoidosis may rarely cause end-stage renal disease (4,5).

Although association of membranous nephropathy (MN) with sarcoidosis has been reported in the literature (6,7), we reported this case due to a rare form of presentation before the diagnosis of sarcoidosis: nephrotic syndrome presentation accompanying impaired renal function due to hypertensive nephropathy.

CASE

A 57-year-old female patient was admitted to the hospital with peripheral

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edema for two months in February 2012. She had a history of hypertension and dyslipidemia for 5 years and hypothyroidism for 4 years. She was receiving treatment with valsartan 160 mg per day, amlodipine 10 mg per day, furosemide 40 mg per day, atorvastatin 20 mg per day and levothyroxine sodium 200 mcg per day. On physical examination, blood pressure was 150/100 mmHg and three positive (+3) pretibial edema was detected. There were no crackles or rhonchi on pulmonary auscultation. Fundus examination revealed grade 2 hypertensive retinopathy.

Blood chemistry tests revealed serum creatinine 2 mg/dl, urea 54 mg/dl, albumin 3.2 g/dl, total cholesterol 293 mg/dl, low-density lipoprotein 219 mg/dl, triglycerides 221 mg/dl, and calcium 8.5 mg/dl. The blood cell count was normal. The erythrocyte sedimentation rate was 71 mm/hour. Urine sediment analysis showed 2 leukocytes, rare red blood cells and granular casts in every field. Proteinuria was 7.47 g in 24-hour urine collection. Thyroid function tests were consistent with subclinical hypothyroidism (TSH 13.72 μIU/ml, FT4 0.99 ng/dl, FT3 2.38 pg/ml). The size, parenchyma and echogenicity of the kidneys were normal on ultrasonography of the urinary system. Kidney biopsy was performed because of the nephrotic syndrome and impaired renal function. Light microscopy examination showed marked thickening of the glomerular basement membrane in all glomeruli, with global sclerosis in 4 of 17 (23.5%) glomeruli and segmental sclerosis in one glomerulus (0.6%). Mild interstitial fibrosis, tubular atrophy and prominent communities of foam cell histiocytes were seen in the interstitium. Marked intimal fibrosis and intimal hyalinosis were detected in the arterioles. Immunofluorescence microscopy showed granular membranous positivity (++) with IgG, kappa and lambda staining. The final pathological diagnosis was membranous glomerulonephritis with focal segmental sclerosis (FSGS) (Figure 1A,B).

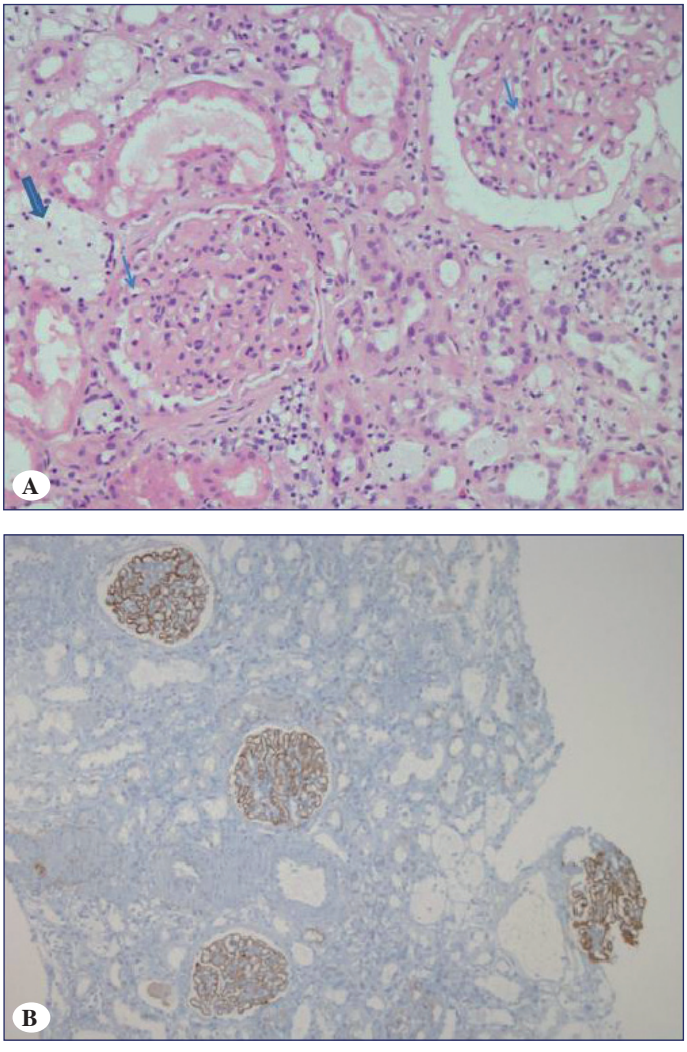

Figure 1: A) *Magnification of a renal biopsy specimen (Hematoxylin-eosin stain, x200) showing marked thickening of the glomerular basement membrane (small arrow) and foam cell histiocytes (thick arrow).* ***B)*** *Immunopathologic evidence of glomerular basement membrane thickening is demonstrated by the presence of staining with C4d (immunohistochemical stain, x100).*

While secondary causes of MN were investigated, an increase in density at the perihilar areas was detected on chest X-ray. High resolution computed tomography was performed and showed multiple lymphadenopathies at the subcarinal and both hilar areas (Figure 2). The serum angiotensin converting enzyme (ACE) level was 57 U/L (8-52 U/L). Bronchoscopy was performed. Acido-resistant bacilli (ARB) were not seen in bronchoalveolar lavage (BAL) fluid and no microorganisms were detected in BAL fluid cultures. Bronchoscopic aspiration cytology was benign. Fine needle aspiration biopsy from subcarinal region via endoscopic bronchial ultrasonography was performed and numerous noncaseating epithelioid granulomas were seen in the microscopic examination of the cell block. The final pathological diagnosis was granulomatous lymphadenitis

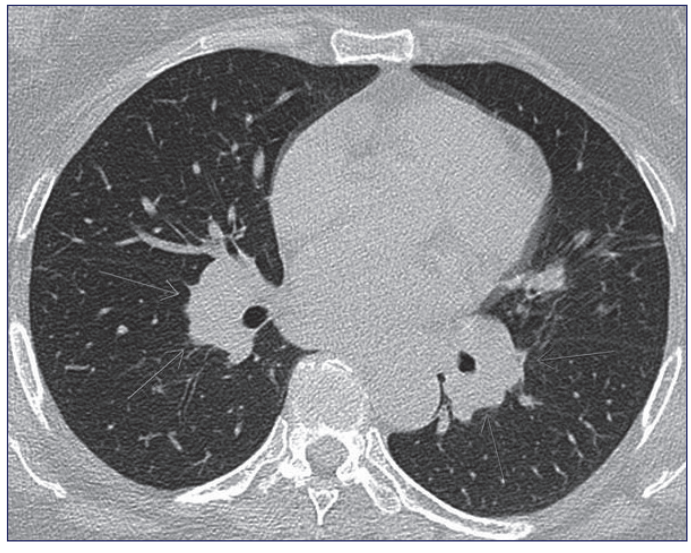

Figure 2: *Bilateral hilar lymphadenopathies in HRCT (arrows).*

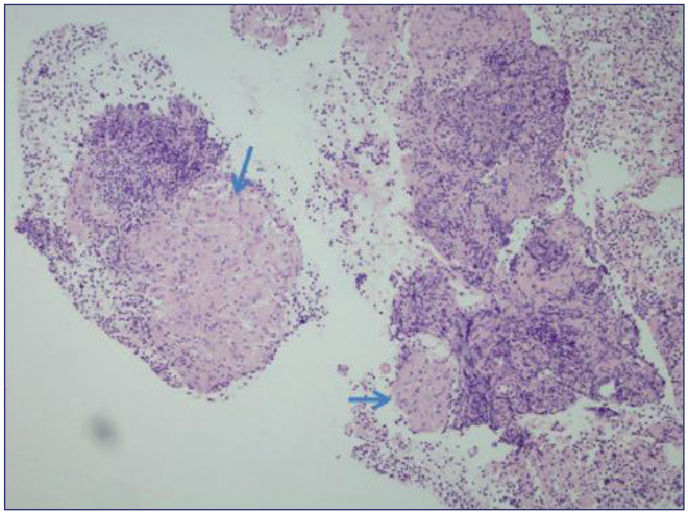

Figure 3: *The noncaseating epithelioid cell granulomas (arrows) (Hematoxylin-eosin stain, x100).*

(Figure 3). Bacilli were negative with the method of Ziehl Neelsen histochemical staining in the cell block. Taking into consideration the clinical, radiological and pathological findings of the patient, stage 1 sarcoidosis was diagnosed.

In addition to the strict salt restriction, valsartan 160 mg per day, nifedipine 60 mg per day and furosemide 80 mg per day were prescribed for the control of blood pressure. In May 2012, proteinuria was 11 g/day and 0.8 mg/kg/day methyl prednisolone was started. The steroid dose was gradually reduced to 4 mg/day by the 9th month of treatment. Proteinuria had decreased to 1.48 g/day in the 3rd month follow-up. Complete remission was achieved in the 6th month. At the latest outpatient follow-up, proteinuria, serum albumin and creatinine levels were 0.29 g/day, 4.6 g/dl and 1.52 mg/dl, respectively. The blood pressure of the patient was also normal.

DISCUSSION

Sarcoidosis affects many organs including the lung, eye, heart, skin, kidney and nervous system. Different forms of renal involvement have also been reported in the literature. Our case was admitted to our clinic because of nephrotic syndrome and the renal biopsy revealed MN. Sarcoidosis was diagnosed after further investigations.

The most common cause of the nephrotic syndrome in adults is MN. Although MN is most often idiopathic, secondary causes must be carefully investigated. Drugs, malignancies, infections, multisystem diseases are among other causes of secondary MN (8). When potential causes of MN were investigated in our patient, hepatitis serology was negative, and there was no clinical history of infection, malignancy or drug usage. She was diagnosed with stage 1 sarcoidosis.

Sarcoidosis is a systemic inflammatory disease characterized by accumulation of T lymphocytes. Although the etiology is not known clearly, genetic factors and immunity are thought to be responsible. It is seen more common in women and around 20-40 years of age. In addition to systemic symptoms such as fatigue, weight loss, and fever, other symptoms are usually associated with respiratory system (9). However, approximately half of sarcoidosis patients are asymptomatic. Diagnosis usually depends on the clinical findings, pulmonary imaging (X-ray and computed tomography), and pulmonary function tests and biopsy. The mortality rate is 5%. Corticosteroids are still the main treatment (10).

Renal involvement in sarcoidosis is clinically important. Sarcoidosis can rarely cause end-stage renal disease (4,5). Hypercalcemia and hypercalciuria are factors responsible for nephrolithiasis (11). Increased urinary excretion of beta-2 microglobulin may cause tubular damage (7). Although various types of glomerulonephritis are less commonly observed in patients with sarcoidosis, the disorder may present with symptoms and signs of MN, FSGS, diffuse mesangial proliferative glomerulonephritis, mesangio-capillary glomerulonephritis, IgA nephropathy, or crescentic glomerulonephritis.

In a retrospective study by Kaaroud et al., renal biopsies were performed in 12 patients with sarcoidosis. Tubulointerstitial nephritis, extra-capillary proliferative glomerulonephritis and MN were observed in a total of 10, 1 and 1 patients, respectively (12). Toda T et al. detected hypercalcemia and renal dysfunction in a patient with sarcoidosis at follow-up, and found MN by renal biopsy (7). Jones B et al. reported a MN case 5 years after the diagnosis of sarcoidosis at follow-up (13). Increased production of immunoglobulins may be responsible for the pathogenesis of MN in sarcoidosis. Suggestive findings for idiopathic MN rather than secondary MN such as phospholipase A_2 receptor in glomerular immune deposits, IgG4 staining in renal biopsy, and phospholipase A_2receptor antibodies in the serum were not evaluated in our case and it is therefore difficult to definitely state that the MN was related to sarcoidosis. However a case of phospholipase A_2 receptor-positive membranous nephropathy preceding sarcoid-associated granulomatous tubulointerstitial nephritis has been reported in the literature (14).

We also detected FSGS in our case. FSGS can be seen in sarcoidosis. Altiparmak et al. (15) and Hakaim et al. (16) have reported FSGS cases associated with sarcoidosis. It is thought that T-cell dysfunction could play a role in the pathogenesis of FSGS. However we thought that the FSGS in our patient was due to hypertension rather than sarcoidosis. The history of hypertension, presence of grade 2 hypertensive retinopathy and prominent intimal fibrosis and intimal hyalinosis of arterioles were suggestive of secondary FSGS due to hypertension.

Renal biopsy showed MN in our case. Interstitial nephritis or granulomas were not observed. Sarcoidosis was detected after subsequent evaluations. In patients with MN associated with sarcoidosis, steroid therapy has been tried and successful results have been reported in the literature (7,12). While the treatment

is not usually recommended for stage 1 sarcoidosis, we started steroid treatment taking into account the clinical and kidney biopsy findings of the patient. At follow-up, the patient's renal function had improved and the proteinuria disappeared in the 6th month of treatment.

In conclusion, renal involvement has usually been detected in patients diagnosed with sarcoidosis during follow-up. A sarcoidosis case initially presenting with nephrotic syndrome due to MN is an uncommon manifestation and must be kept in mind. Taking into account the potential progression of renal impairment due to hypertensive nephropathy and MN, and the possible renal involvement of sarcoidosis we believe that the diagnosis and treatment of sarcoidosis, MN and hypertensive nephropathy are important in such patients.

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