IgA Nephropathy: A Rare Lesion in Renal Biopsy in Systemic Lupus Erythematosus: Case Reports and Review of Literature

Sistemik Lupus Eritematozusda Böbrek Biyopsisinde Nadir Görülen Bir Lezyon; IgA Nefropatisi: Olgu Sunumu ve Literatürün Gözden Geçirilmesi

Gürsel YILDIZ[1]
Emre ÇİÇEKLİ[2]
Mansur KAYATAŞ[1]
Abdulkerim YILMAZ[3]
Ferhan CANDAN[1]

1 Cumhuriyet University Faculty of Medicine, Department of Nephrology, Sivas, Turkey
2 Cumhuriyet University Faculty of Medicine, Department of Internal Medicine, Sivas, Turkey
3 Gaziosmanpaşa University Faculty of Medicine, Department of Internal Medicine, Tokat, Turkey

ABSTRACT

Lupus nephritis is an inflammation of the kidney caused by systemic lupus erythematosus (SLE). Lupus nephritis is a frequent complication of SLE that increases mortality and morbidity. Minimal glomerular lesions, mesangial proliferative, focal proliferative, membranous and diffuse glomerulonephritis can be seen in renal biopsies of patients with lupus nephritis. It has been reported that non-lupus nephritis can also rarely occur in SLE. While non-lupus nephritis cases usually manifest as focal segmental glomerulosclerosis, they have been seen rarely as IgA nephropathy. In this paper, we have represented a SLE case with IgA nephropathy on renal biopsy.

KEY WORDS: IgA nephropathy, Systemic lupus erythematosus, Renal biopsy

ÖZ

Sistemik lupus eritematozusta (SLE) morbidite ve mortaliteyi arttıran lupus nefritine (LN) sık olarak rastlanır. Lupus nefritinde böbrek biyopsisinde; minimal glomerüler lezyonlar, mezengioproliferatif, fokal proliferatif, membranöz ve diffüz proliferatif glomerülonefrit görülebilmektedir. Ancak SLE'de nadiren non-lupus nefritler de bildirilmiştir. Non-lupus nefritlerde en sık fokal segmental glomerüloskleroz görülmekle birlikte nadiren IgA nefropatiside (IgANP) bildirilmiştir. Bu yazıda böbrek biyopsisinde IgANP saptanan bir SLE olgusu sunulmuştur.

ANAHTAR SÖZCÜKLER: IgA nefropatisi, Sistemik lupus eritematozus, Böbrek biyopsisi

INTRODUCTION

SLE is an autoimmune disease characterized by the production of antibodies against cell nucleus fragments, in which immune complexes cause tissue damage. Symptomatic lupus nephritis rates in SLE are about 50%. When electron and immune fluorescent microscopic evaluations are performed, renal involvement is defined in almost all SLE patients(1). Lupus nephritis is the first sign in about 5% of the patients with SLE. The renal involvement in SLE manifests in the first five years and it is the first sign in about 5% of the patients with SLE. It is accepted that renal damage is caused by complement activation and deposition of immune complexes composed of DNA and other nuclear antigens in glomeruli(2). Histopathological findings in lupus nephritis are variable. Histopathological classification is made according to classification of World Health Organization (WHO) and International Society of Nephrology/Renal Pathology Society (ISN/RPS) that is based on light, electron and immunofluorescent microscopic findings (Table I).

When renal specimens of SLE patients are evaluated, differences not morphologically or pathogenetically related to SLE are occasionally seen. These lupus nephritis cases exert a wide morphological spectrum and FSGS is the most common lupus nephritis(4). IgA nephropathy is uncommonly seen in lupus nephritis. IgA nephropathy is the most common glomerulonephritis in the world. End stage renal failure is seen in 30 percent of patients with IgA nephropathy within 20 years. The

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Correspondence Address:
Gürsel YILDIZ
Yeşil Mahallesi, Akşemsettin Caddesi, Ada Sitesi, D-Blok, No:7, Zonguldak, Turkey
Phone : +90 372 252 19 00/3319
E-mail : drgursel@yahoo.com

Table I: WHO classification of lupus nephritis (3).

Class	Histopathological appearance	Incidence (%)
Class I	Normal glomerular structure	<10
Class II	Mesangial glomerulonephritis	10-20
Class III	Focal proliferative glomerulonephritis	15-20
Class IV	Diffuse proliferative glomerulonephritis	50
Class V	Membranous glomerulonephritis	15

histopathological changes in biopsy specimens of patients with IgA nephropathy are varied. Although there has been no national concern on pathologic or clinic classification of IgA nephropathy, it has been suggested that the Oxford classification, in which mesangial hypercellularity, segmental glomerulosclerosis, endocapillary hypercellularity and tubular atrophy/interstitial fibrosis are scored according to the clinical data, can be used in order to estimate progression risk(5). In this paper, a SLE patient with IgA nephropathy in renal biopsy is represented because of its low incidence.

CASE

A 22-year-old women was diagnosed SLE 4 months ago. She had been under treatment with 250 mg/day chloroquine and 100 mg/day salicylic acid. She has been referred to the nephrology clinic after detection of proteinuria on urinalysis. She had a history of venous thrombosis in the right lower extremity in 2006 and was using warfarin (5 mg/day for 3 months). There was no other significant past or family history. Physical examination was normal at the admission of the patient with BP: 100/60 mmHg and pulse: 68/min. Laboratory findings were BUN: 26 mg/dL, creatinine: 0.6 mg/dL, Na: 138 mEq/L, K: 4.1 mEq/L, P: 3.9 mg/dL, albumin: 4 mg/dL, total protein: 6.9 mg/dL, triglyceride: 34 mg/dL, cholesterol: 95 mg/dL, HDL-K: 27 mg/dL, LDL-K:52 mg/dL, AST: 18IU/L (15-41), ALT: 12 IU/L (14-54), LDH: 131IU/L, ALP: 66 IU/L, GGT: 19 IU/L, T.BIL: 0.9 mg/dl and 24 hour proteinuria: 0.88 g/day, ANA: 1/320 positive, (centromeres staining), anti-ds DNA: positive, anti-DNA: positive, anticardiolipin antibody IgM and IgG: positive, C3, C4, IgA ve IgM levels were normal. pANCA, cANCA and antiglomerular basement membrane antibody were negative. Microbiological findings were antiHCV: negative, HBsAg: negative, EBV EBNA IgM: negative, EBV EBNA IgG: positive, parvovirus B19 IgG and IgM: negative, mumps IgM: negative, mumps IgG: positive, measles IgM: negative, measles IgG: positive, toxoplasma IgG and IgM: negative, rubella IgM: negative, rubella IgG: positive. The tuberculin skin test was negative and AFP, CEA, CA 19-9, CA 15-3 tumor markers was identified to be within normal ranges. CBC values and the other parameters were normal. Thyroid function tests were normal. In urine analysis, protein was positive. There was no leukocyte, erythrocyte or cylinders on microscopy. The density of urine was 1020 and pH was 6. There was no growth on urine culture. Renal USG was reported as normal. On the renal biopsy performed with USG, the findings were as follows; LM: there was minimal segmental mesangial cell growth. There was no focal segmental or global sclerosis and the tubulointerstitial space was natural. IFM: dense diffuse mesangial staining for IgA was detected but no staining was detected for IgG, IgM, C3, C4, fibrinogen or C1q and IgA nephropathy was reported by the pathology department.

DISCUSSION

SLE is a systemic and autoimmune disorder. The kidney is the most commonly affected organ in SLE. Renal histological involvement commonly exists before onset of clinical symptoms of renal damage. Renal involvement in SLE can be detected on microscopic examination in almost all patients. Lupus nephritis is the most serious clinic form of SLE and lupus nephritis commonly onsets in the first 5 years of SLE. SLE commonly occurs between 20 and 40 years of age and it has a high incidence in women. It also has a bad prognosis in men(6).

Lupus nephritis is diagnosed by renal biopsy. Mesangial and sub-endothelial IgG, C_3, C_4 deposition, mesangial, endothelial proliferation, segmental necrosis and thickening in glomerular basal membrane are seen in renal biopsies of SLE patients.

The pathogenesis of lupus nephritis is not clear. Experimental studies or human studies have shown that there is an alteration in some of the mechanism in immune regulation. It is accepted that LN is the prototype of chronic immune complex glomerulonephritis even if the etiology could not be defined(7).

The mechanisms including cross-reaction of anti-dsDNA antibodies with glomerular basal membrane, the actions of auto antibodies like intravascular immune complexes deposits in glomeruli, high affinity of cationic auto antibodies to anionic glomerular basal membrane and activation of complement system by isotopic antibodies like IgG_1 and IgG_3 can play role in pathogenesis of LN(8). Glomerular thrombosis is one of the other mechanisms in pathogenesis of lupus nephritis in patients with antiphospholipid syndrome(9,10).

The clinical symptoms of lupus nephritis related to active nephritic or nephrotic syndrome may include peripheral edema, hypertension or hypoalbuminemia. Usually lower complement levels and high levels of a-dsDNA antibody accompany nephrotic syndrome. The proliferation of mesangial, endothelial, and epithelial cells and fibrosis caused by production of matrix proteins can leads to serious forms of lupus nephritis(11).

Getting easy of the early diagnose with the utilization of more sensitive and specific diagnostic tests, better following of the

physical course of disease and, SLE and treatment the symptoms of SLE, has been improved the renal survey significantly.

IgA nephropathy, also called Berger disease, was identified by Berger and Hinglais at the year of 1968(12). It is the most common primary glomerular disease of the world (13-14). IgA nephropathy can occurs in every decades, but typically commons secondary and third decades and %80 of patients are between the age of 16-35 and it has been seen men more common than women (Male/ Female:2-6/1)

The immunohistochemical analysis of renal biopsy, is the gold standard of the diagnose of IgA nephropathy. At the specimens of the renal biopsy of IgA nephropathy characterized by widespread mesangial IgA and C3 deposition. But couldn't settled with the clinical and pathological classification yet.

IgA occasionally deposits at the capillary wall of mesangium at the form of granular. Rarely IgG and frequently C3 deposition may attends(15). Also The pathogenesis of the deposition of glomerular IgA couldn't be illuminated well. However the observing glomerular changings alters, mesangial proliferation and IgA deposition has been projected in, almost the whole biopsy specimens. The deposit of IgA is predominantly IgA1. Although has been seen the focal and diffuse mesangial proliferative disease at most of the patients, normal or close to normal glomerul, focal sclerosis, membranoproliferative GN, membranous GN, acute GN, end stage chronic GN or interstitial GN can also occur in. And also the crescentic form of IgA nephropathy has been identified(16-17).

The characteristic pathological findings are the granular IgA and C3 deposition at the glomerular mesangium, while monitoring with the immunofluorescent microscopy. This situation preoccupies that, the originate of IgA nephropathy are the deposition of immune complex at the circulation and result of activated complement systems. The role of the complement system in the pathogenesis of IgA nephropathy. Because the antibodies of IgA can not activate the system of complement by classically way. Studies shows that they activate by the alternative way. İt is suggested that deposition of the immune complexes of IgA at the circulation, on the glomerular mesangium, has becomes the disorder. High levels of the relaps in the IgA nephropathy and renal transplant clients, is supports this prediction. IgA levels are high in almost 50 percent of patients with IgA nephropathy. It is not likely that increase in IgA levels play role in pathogenesis of disease. Forasmuch IgA levels are significantly high in IgA nephropathy negative AIDS patients. In the other hand mesangial IgA deposition can be determined in much systemic disease sporadically including SLE, hepatitis, dermatitis, herpetiformis and ankylosing spondylitis.

The clinic progress of IgA nephropathy is highly variable. The most common clinic sign is recurrent microscopic hematuria attacks in which there is no proteinuria(14). Although clinic progress of IgA nephropathy is slow rapidly progressive glomerulonephritis may accompany with IgA nephropathy. In a period of 20 years, the risk of end stage renal failure in patients with IgA nephropathy is 14 to 39 percent(18). Although IgA nephropathy and Lupus nephritis have common physiopathological feature, these diseases has different laboratory, histopathological and non-renal clinical findings. Also pathogenesis of these two diseases is different too(19). In that respect renal symptoms of Lupus nephritis and IgA nephropathy are not diagnostic in differential diagnosis. Nevertheless glomerular lesion in diagnosis of IgA nephropathy is almost consisting of deposition of IgA and C3, hypercellularity and sclerosis(20). These biopsy findings are not expected in SLE. Although non-lupus nephritis can be defined in biopsies of patients with SLE. Therefore to define non-lupus nephritis in patients with SLE accompany with IgA nephropathy is interesting pathological event and reported rarely(21). In a study in which renal biopsies were evaluated between 1975 and 1998 in 224 SLE patients, Beranowska et al. defined 6 cases with focal segmental glomerulosclerosis, 2 cases with hypertensive nephrosclerosis, a case with IgM nephropathy, a case with thin basal membrane disease, a case with acute allergic tubulointerstitial nephritis and a case with amiloidosis(4).

The question that "how can be explained the existence of non-lupus nephritis in SLE patients?" is an important research subject. Because although either IgA nephropathy and Lupus nephritis are immune complex mediated diseases, each has different pathogenesis even if the pathogenesis is not clear. Highly different clinic and histological features of two diseases including cross allograft recurrence may support the idea that they have different pathogenesis(22, 23). In the other hand laboratory and clinic except renal involvement are important for diagnosis of SLE. Histological diagnosis of SLE is ignored in the absence of clinical history and also even if patient is clinically SLE, histological findings can not confirm atypical form or lupus nephritis. Although SLE is an autoimmune disease, relationship between IgA nephropathy and autoimmünity is controversial. But the lacks of important antibodies are defined in IgA nephropathy(24). Although IgA nephropathy is a non-systemic disease just involved in kidney, in many systemic diseases including SLE mesangial IgA deposition can be seen. It is not clear that if renal mesangial IgA deposition is cause of SLE or just a coincidence situation. It has been suggested that lupus nephritis is a subtype of SLE in which IgA immune complex deposition is dominant.

In brief, diagnosis of glomerular disease is based on clinic manifestation of disease, presence or absence of systemic findings and laboratory findings. The renal biopsy is needed for exact diagnosis and disease is named according to the histopathological view. But same histopathological views may belong to different diseases. Renal biopsies in SLE patients may be different from biopsies in patients with lupus nephritis. While focal segmental glomerulosclerosis is the most common type in

non-lupus nephritis, IgA nephritis cases are also reported. For this reason renal biopsy is important to make a correct diagnosis, start appropriate cure, select patients need aggressive treatment, evaluate responds to treatment, predict prognosis and avoid unnecessary immünosuppressive treatment.

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