Pattern of renal pathology among renal biopsy specimens in Eastern Saudi Arabia

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ABSTRACT

Objectives: To identify the pattern of renal pathology among renal biopsy specimens, and to study the clinical correlation in a general hospital in the eastern region of the Kingdom of Saudi Arabia.

Methods: All patients who underwent native kidney biopsy by the author at Dhahran Health Center (DHC) between June 1998 and April 2005 were included and prospectively followed-up.

Results: One hundred native kidney biopsies were performed on 95 patients with a mean age of 40.8 ± 18 years, and a glomerular filtration rate of 57 ± 42 ml/min/1.73 m^2. Patients were followed up for a mean of 28 ± 22.5 months. Primary renal pathology was identified in 72 specimens and secondary in 28. Primary renal pathologies included focal and segmental glomerulosclerosis (FSGS) (35%), immunoglobulin A nephropathy (IgAN) (14%), tubulo-interstitial nephritis (12%), minimal change disease (10%), membranous nephropathy (4%), mesangioproliferative glomerulonephritis (6%), mesangiocapillary glomerulonephritis (4%), thin glomerular basement membrane disease (8%), and miscellaneous (7%). Secondary lesions included lupus nephritis (LN) (36%), sickle cell nephropathy (SCN) (18%), diabetic nephropathy (14%), hypertensive nephrosclerosis (11%), Henoch Schönlein purpura (7%), and miscellaneous (14%). Obesity was particularly prevalent among patients with FSGS. Among the entire group, 12 patients (13%) progressed to end stage renal disease (ESRD) at a mean of 17.6 ±17 months (range, 1- 45 months), and the overall mortality rate was 5.3%.

Conclusion: At DHC, FSGS was the most common primary renal pathology, followed by IgAN. There was an association between FSGS and obesity. Lupus nephritis was the predominant secondary renal pathology followed by SCN. Within the time of follow up, primary renal lesions were associated with a low rate of progression to ESRD.

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Dhahran Health Center (DHC) is the main hospital that serves the employees of Saudi Aramco (SA) (the Saudi Arabian American Oil Company, Saudi Arabia), and their dependents. The main bulk of these employees are stationed in the eastern region, where oil production takes place. Saudi Aramco employees are of multi-nationalities, with Saudi citizens representing the majority (90%). Approximately 400,000 individuals (employees and dependents) are eligible for medical care at SA. One-half of these individuals (200,000) are treated at DHC, and the rest are contracted for treatment at private hospitals distributed across the Kingdom of Saudi Arabia (KSA). We have previously reported that diabetic nephropathy is the major cause of end stage renal disease (ESRD) at DHC, and may be in the eastern region of KSA.[1] However, the data on the nature of renal pathology confirmed by renal biopsy in this part of the country is very limited. In this article, we report our finding of renal pathology among renal biopsy specimens obtained from patients who were suspected to have primary or secondary renal diseases. The clinical outcome of these patients was prospectively followed up and correlated with the pathological findings.

Methods. All adult patients (age ≥14 years) who underwent native kidney biopsy by the author between July 1998 and April 2005 were included and prospectively followed up. Patients were classified as adults ≥14 years, ≤65 years or ≥65 years. Detailed clinical data was collected at baseline including renal function tests, urinalysis and urine microscopy, quantitation of proteinuria, blood pressure (BP), and body mass index (BMI). Serological markers including antinuclear antibodies, rheumatoid factors,

complement levels, hepatitis B and C serologies, cryoglobulins, antineutrophil cytoplasmic antibodies (ANCA), anti glomerular basement membrane antibodies (anti-GBM) were checked as indicated by the clinical setting. Kidney imaging was performed using ultrasonography (US) and nuclear medicine imaging if indicated. Indications for renal biopsy were: 1. nephrotic range proteinuria (P) with or without nephrotic syndrome; 2. chronic kidney disease (CKD); 3. acute renal failure (ARF); 4. hematuria with or without nephritic sediment; 5. systemic diseases with renal involvement such as systemic lupus erythematosus (SLE). Diabetic and hypertensive patients underwent biopsy only if a primary disease was suspected. Nephrotic syndrome was defined as proteinuria ≥3.5 gm/day/1.73 m^2 or a urine protein/creatinine ratio of ≥3.5 associated with hypoalbuminemia, limb edema and hyperlipidemia. Nephritic syndrome was defined as hematuria, hypertension, and proteinuria, with or without renal impairment. Acute renal failure was defined as a rapid deterioration of renal function with a rise of serum creatinine of >0.5 mg/dl (above baseline). Glomerular filtration rate (GFR) was calculated using the Cockcroft-Gault method.[2] Chronic kidney disease was considered when GFR levels were persistently lower than 60 ml/min/1.73 m^2. Hypertension was defined as a BP of ≥140/90 mm Hg. Overweight was considered when BMI was ≥25 kg/m^2, while obesity was defined as a BMI of ≥30 kg/m^2. Informed, written consent was obtained prior to renal biopsy. All biopsies were performed either using US or computer tomography (CT) scanning. On average, 2 cores were obtained, and biopsy was considered adequate if at least 5 glomeruli were obtained. All biopsy specimens were processed and examined by light microscopy (LM), and stained for immunohistochemistry (IF) using polyclonal anti sera against human IgG, IgM, IgA, C3, C1q, kappa, lambda, light chain and albumin. Electron microscopy (EM) studies were performed on all specimens as well. Light microscopy was performed at DHC, while EM and IF were sent to the pathology laboratory at the Mayo Clinic (Rochester, the United States) for processing. Following the procedure, the patients were instructed to stay in bed until next morning for observation of vital signs, and development of hematuria as well as monitoring of hemoglobin. A drop in hemoglobin of ≥1.0 gm/dl from baseline was considered as indication of a significant bleed. Primary renal pathology was classified into: focal and segmental glomerulosclerosis (FSGS), immunoglobulin A nephropathy (IgAN), tubulo-interstitial nephritis (TIN), minimal change disease (MCD), membranous nephropathy (MN), mesangioproliferative glomerulonephritis (MP), mesangiocapillary glomerulonephritis (MCGN), thin glomerular basement membrane disease (TGBM), crescentic glomerulonephritis (CGN), non-IgA mesangioproliferative glomerulonephritis (non-IgAN), and acute tubular necrosis (ATN). Secondary renal pathology was classified into: lupus nephritis (LN), sickle cell nephropathy (SCN), diabetic nephropathy (DN), hypertensive nephrosclerosis (NS), Henoch Schonlein purpura (HSP), post infectious GN (PIGN), amyloidosis, scleroderma, and fibrillary GN. Steroids ± immunosuppressive agents such as cyclosporine A, or alkylating agents were used to treat primary and secondary GN as clinically indicated. All patients who had proteinuria received antiproteinuric agents, either angiotensin converting enzyme inhibitors (ACE-I) or angiotensin receptor blockers (ARB), unless prohibited by side effects. Complete response (CR) was considered when proteinuria disappeared and or renal function returned to baseline values, while partial response (PR) was defined as incomplete resolution of proteinuria and or partial improvement of renal function. This study was approved by the Advisory Group at Saudi Aramco.

The data was analyzed when a total number of 100 renal biopsies were obtained. Patients were followed up until the end of May 2005, development of major events such as ESRD, loss of eligibility of treatment at DHC, or death, whichever occurred first. Statistical analysis was performed using Microsoft Excel 2003 and Graph Pad Instat Version 2. Numerical data was expressed as mean ± SD. Probability values of ≤0.05 were considered statistically significant.

Results. One hundred native kidney biopsies were performed on 95 patients with a male to female ratio of 1.2:1. Eighty-six patients were Saudi citizens (90%), and 9 patients were expatriates (10%). The patients had a mean age of 40.8 ± 18 years (range, 14-90 years), a mean BMI of 24.9 ± 5.6 kg/m^2 (range, 16.5-39.7 kg/m^2), a mean creatinen of 2.64 ± 2.7 mg/dl (range, 0.6-10.6 mg/dl) corresponding to a mean GFR of 57 ± 42 ml/min/1.73 m^2 (range, 9.5-125) (**Table 1**). Ultrasound was used in 53 cases (53%) while CT was used in 47 cases (47%). The main indication for renal biopsy was proteinuria followed by CKD (**Table 2**). The main reason to use CT guidance was overweight followed by structural abnormalities of the kidneys such as small sized kidneys and horseshoe kidneys. Four patients had a drop in hemoglobin of ≥1.0 gm/dl, one patient required blood transfusion, and none required radiological or surgical intervention. Patients were followed for a mean of 28 ± 22.5 months (range, 2-82 months). Primary and secondary renal pathologies were identified in 72 and 28 specimens respectively as shown in **Tables 3 and 4**. Focal and segmental glomerulosclerosis was the most common primary GN followed by IgAN. The

Table 1 - Patients' characteristics (n=95).

Patients' characteristics	n	(%)
No. of patients	95	
No. of biopsies	100	
Male	52	(55.0)
Female	43	(45.0)
Mean age (years)	40.8 ± 18	
Age >65	7	(7.2)
Saudis	86	(90.0)
Non-Saudis	9	(10.0)
Serum creatinine (mg/dl)	2.64 ± 2.7	
Glomerular filtration rate (ml/min/1.73 m^2)	57 ± 42	
Body mass index (kg/m^2)	24.9 ± 5.6	
Follow up (months)	28 ± 22.5	
Primary renal disease	72	(72.0)
Secondary renal disease	28	(28.0)

Table 3 - Primary renal pathology.

Diagnosis	n	(%)
Focal and segmental glomerulosclerosis	25	35
Immunoglobulin A nephropathy	10	14
Tubulo-interstitial nephritis	9	12
Minimal change disease	7	10
Thin glomerular basement membrane disease	6	8
Membranous nephropathy	3	4
Mesangiocapillary glomerulonephritis	3	4
Mesangioproliferative glomerulonephritis	4	6
Miscellaneous	5	7
Total	**72**	**100**

Table 2 - Indication for renal biopsy.

Indication	n	(%)
Proteinuria	45	(45)
Acute renal failure/rapidly progressive glomerulonephritis	12	(12)
Chronic kidney disease	17	(17)
Hematuria	7	(7)
Systemic lupus erythematosus	10	(10)
Sickle cell disease	6	(6)
Miscellaneous	3	(3)
Total	**100**	**(100)**

Table 4 - Secondary renal pathology.

Diagnosis	n	(%)
Lupus nephritis	10	(36)
Sickle cell nephropathy	5	(18)
Diabetic nephropath	4	(14)
Hypertensive nephrosclerosis	3	(11)
Henoch schönlein purpura	2	(7)
Miscellaneous	4	(14)
Total	**28**	**(100)**

Table 5 - Main clinical presentations of primary renal lesions at the time of biopsy and risk of developing ESRD in percentage.

Clinical presentations	Proteinuria	Nephrotic syndrome	CKD	ARF/RPGN	Hematuria	ESRD rate
Focal and segmental glomerulosclerosis	48	32	20			12
Immunoglobulin A nephropathy	30		20	20	30	20
Minimal change disease		85		15		0
Tubulo-interstitial nephritis	12		55	33		22
Thin glomerular basement membrane disease	66	17		17		0
Membranous nephropathy	66	34				0
Mesangiocapillary glomerulonephritis	34	66				0
Mesangioproliferative glomerulonephritis	75	25				0

CKD - chronic kidney disease, ARF - acute renal failure,
RPGN - rapidly progressive glomerulonephritis, ESRD - end stage renal disease.

majority of patients who had FSGS were males 18/25 (72%) (male to female ratio was 3:1), and a substantial number were overweight or obese with a mean BMI of 28.4 ± 6.3 kg/m^2 (range, 17.3-39.7 kg/m^2), compared to a BMI of 22.4 ± 3.4 kg/m^2 (range, 16.5-31.1 kg/m^2) in the rest of the group (p=0.0002). Twenty patients (80%) had nephrotic range proteinuria, of whom 8 (32%) had nephrotic syndrome, while 5 patients (20%) had CKD as their initial presentation. Only 7 patients (28%) were treated with prednisone ± immunosuppressive agents for up to 9 months. Four patients (57%) had CR, while 3 patients (43%) had PR or no response. The decision to treat patients who had FSGS with prednisone ± immunosuppressive agents was based on clinical grounds whether they had a primary or secondary disease. Patients who were suspected to have secondary FSGS such as obese patients were treated with ACE-I or ARB. Among the 10 patients who had IgAN, 3 (30%) were expatriates, and 8 (80%) were males. Three (30%) patients presented with hematuria, 2 (20%) had rapidly progressive renal failure, 3 (30%) had proteinuria and 2 (20%) had CKD as their initial presentations. All patients with IgAN received non-specific treatment with ACE-I or ARB, and only one was treated with steroids for rapidly progressive renal failure with good response. The various clinical presentations and outcome of the primary renal lesions are shown in **Table 5**. Crescentic glomerulonephritis (CGN) was rare, and found in only one specimen, associated with myeloperoxidase positive ANCA. None of the patients had proteinase 3 positive ANCA or anti GBM antibodies. Cryoglobulins were found in two diabetic patients who had hepatitis C liver disease. In both cases the biopsy revealed DN. Among the secondary lesions, LN accounted for 36% of the cases, and 50% of the specimens were classified as WHO class IV. Out of all patients with LN 70% were females, owing to the high female to male ratio of SLE. Sickle cell nephropathy was found to be the second common cause of secondary lesions in 18% of the cases (**Table 4**). The pathology of SCN was characterized by focal and global glomerulosclerosis, glomerular enlargement, intimal thickening, medial hypertrophy, and interstitial fibrosis. Four diabetic patients underwent renal biopsy for suspected non-diabetic lesions, and all were found to have DN. Nephrosclerosis was the fourth cause of secondary lesions. The other lesions were HSP (2 patients), amyloidosis, presumably secondary to pulmonary tuberculosis, post infectious GN, scleroderma, and fibrillary GN associated with colon cancer (one patient each). Among the entire group, 12 patients (13%) progressed to ESRD at a mean of 17.6 ± 17 months (range, 1- 45 months). Of those patients, 3 had FSGS, 2 had IgAN, 2 had TIN, and the rest had either SCN, amyloidosis, CGN, LN or DN as the underlying disease. A total of 5 patients (5.3 %) died, 3 of them following the development of ESRD.

Discussion. Due to better job opportunities, SA has attracted a large group of the Saudi population from all over the country to come to the eastern region of KSA for employment. All major tribes of the Saudi population are well represented in SA, and that makes the finding of this study fairly applicable to the whole country. In this series, primary renal diseases constituted the majority of the renal biopsy specimens. There was only a slight, statistically not significant male predominance, and this may indicate that females and males have an equal access to medical care in this part of the Kingdom. Similar to earlier reports, FSGS was found to be the predominant form of primary renal lesions.[3-6] However, others have reported membranoproliferative GN/(MCGN) to be the predominant renal pathology.[7,8] The majority of patients with FSGS were obese, and had proteinuria without nephrotic syndrome as their initial presentation. Among these patients, there was no correlation between BMI and the presence or absence of nephrotic syndrome. It is rather difficult to dissociate primary FSGS from secondary FSGS due to lack of sensitive and specific tests that can differentiate between both entities. The observation that obesity was more prevalent among patients with FSGS as compared to the rest of the study group indicates that a substantial proportion of the patients had secondary FSGS. Obesity has become a major health problem in all parts of the kingdom including the eastern region.[9-12] Therefore, a sharp increase of FSGS in KSA may soon be encountered. Only little more than a quarter of patients with FSGS (28%) received specific treatment with prednisone ± immunosuppressive agents, while all received nonspecific treatment with ACE-I or ARB. The decision to treat patients with specific agents was based on the clinical suspicion of whether FSGS was a primary or secondary in nature. The relatively high response rate to treatment with prednisone ± immunosuppressive agents indicates that most treated patients had primary/ immunologically mediated lesions. The collapsing variety of FSGS was not found in any of the biopsy specimens. Immunoglogulin AN was found to be the second most common primary lesion. Among the 10 patients who had IgAN, 3 (30%) were Asians. In comparison, only 10% of patients who underwent renal biopsy were non-Saudis. This correlates well with the observation of the high prevalence of IgAN among Asian populations.[13-15] Similar to FSGS, there was a clear male gender predominance with a male to female ratio of 4:1. Proteinuria and hematuria were the most common indications for biopsy. The true prevalence

of IgAN is not clear as patients who had isolated microscopic hematuria were not routinely subjected to renal biopsy. MCD was found to be the third cause of primary GN in 10% of the cases. Minimal change disease is known to have a relatively high prevalence in the pediatric age group as shown in previous studies from the same region.[16,17] Although patients as young as 14 years were included in this study, the mean age of patients with MCD was 28 ± 14 years. Crescentic GN was diagnosed in only one patient who had myeloperoxidase positive ANCA. None of the patients tested positive for proteinase 3 ANCA or anti GBM antibodies. These tests were performed at the pathology laboratory of the Mayo clinic, a very reputable facility, which makes false negative results an unlikely possibility. Among the secondary renal lesions, LN stood out as the predominant. This is similar to earlier reports from the same region and neighboring countries.[4,7,18] Sickle cell nephropathy was found in 18% of the cases of secondary lesions. The pathology of SCN was characterized by focal and global glomerulosclerosis, glomerular enlargement, intimal thickening, medial hypertrophy, and interstitial fibrosis in disproportion to the degree of renal failure. Significant intimal thickening and medial hypertrophy was found even in patients with SCD who had normal or only mildly elevated BP. This indicates that patients with SCD are prone to develop hypertensive vascular changes at a lower range of BP as compared to patients with normal hemoglobin. For these patients, aggressive BP control targeting low values may be of significant benefit. Similarly, the BP threshold for pharmacological intervention in patients with SCD should be lower than the recommended value of 140/90 mm/Hg. SCD is epidemic in this part of KSA, and therefore, the figure stated in this study may very well underestimate the true magnitude of SCN. Renal biopsy was performed only in cases of nephrotic range proteinuria, renal impairment or both, while patients with non-nephrotic range proteinuria and normal renal function were not subjected to renal biopsy. The true prevalence of nephropathy related to SCD in this area remains to be determined. However, in our experience, SCN is not a common cause of ESRD. One explanation may be related to the benign nature of SCD in this area as compared to SCD in other regions.[19] Another explanation is the short life span of patients with SCD compared to the rest of the population. Most patients who develop SCN die from other complications of SCD such as acute chest syndrome, before they progress to ESRD. Tuberculosis is still a common diagnosis in the eastern region of KSA, however the development of amyloidosis related to tuberculosis seems to be an uncommon event. In this series, there was only one case of secondary amyloidosis attributed to old pulmonary tuberculosis. Similarly, crescentic GN was very rare and found only in one patient (1%) who had myeloperoxidase positive ANCA. In this series, the development of ESRD was not high, and that might be due to the benign nature of renal pathology identified, and the relatively short time of follow up. In addition, diabetics with renal impairment and proteinuria were excluded except if a primary renal disease was suspected. We have previously documented that the main cause of ESRD among our population is diabetic nephropathy accounting for 60% of all causes of ESRD, followed by hypertensive nephrosclerosis and primary GN in 11% and 10% respectively.[1]

This study sheds some light on the nature of renal pathology in this part of KSA, however it has several limitations. First, all the patients were evaluated by a single physician, who performed all the biopsies. Personal bias about timing of and indication for renal biopsy may have influenced the results. Similarly, the decision to use steroids or immunosuppressive agents in the treatment of glomerulonephritis may have had a subjective element to it. The second limitation is the small size and relatively short time of follow up. Due to the relative rarity of glomerulonephritis, larger multi-center studies with longer follow up are needed to further explore the nature of renal pathology in this area.

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