IJKD KIDNEY DISEASES

Immunoglobulin M Nephropathy in Adults
A Clinicopathological Study

Muhammed Mubarak,[1] Rubina Naqvi,[2] Javed I Kazi,[1] Shaheera Shakeel[1]

[1]Histopathology Department, Sindh Institute of Urology and Transplantation, Karachi, Pakistan
[2]Nephrology Department, Sindh Institute of Urology and Transplantation, Karachi, Pakistan

Keywords. adult, immunoglobulin M, glomerulonephritis, nephrotic syndrome, Pakistan

Introduction. There is no data specifically on the clinical and immunopathologic features of Immunoglobulin M nephropathy (IgMN) in adults with kidney diseases in Pakistan.
Materials and Methods. We retrospectively reviewed our adult native renal biopsy records from May 2001 to April 2010 and identified 57 cases out of a total of 1753 biopsies labeled as IgMN on final histopathological analysis. Among these, 41 cases were included in the present analysis. Their relevant data items were collected from the case files and biopsy reports.
Results. The mean age of this cohort was 30.21 ± 10.12 years. The male-female ratio was 1.15:1. The most common presentation was idiopathic nephrotic syndrome. Hematuria and hypertension at presentation were noted in 24 (58.5%) and 10 (24.4%) patients, respectively. The most common morphologic change was glomerular mesangial cell proliferation, found in 28 biopsies (68.3%). Mesangial matrix expansion was noted in 16 (39%). Minor glomerular alterations were noted in 5 cases (12.2%) and focal segmental glomerulosclerosis in 4 (9.8%). Immunofluorescence microscopy showed diffuse mesangial positivity of IgM in all specimens. Subdominant IgA was noted in 6 cases (14.6%). Complements C3 and C1q were found in 28 (68.3%) and 21 (51.2%) patients, respectively.
Conclusions. Our results show that IgMN is not very common in adults. Its clinicopathological spectrum is similar to that described from the neighboring countries, showing a spectrum of morphologic changes ranging from minor changes to focal segmental glomerulosclerosis.

IJKD 2013;7:214-9
www.ijkd.org

Original Paper

INTRODUCTION

Immunoglobulin (Ig) M nephropathy (IgMN) is a poorly understood and still largely controversial clinicoimmunopathologic entity, which presents predominantly as idiopathic nephrotic syndrome in both children and adults. The discovery of the disease in proteinuric patients is widely attributed to Cohen and colleagues[1] and Bhasin and coworkers[2] in 1978. However, a similar description of the predominant deposits of IgM immunoreactant in the glomeruli in patients presenting with recurrent or persistent hematuria was in fact first reported in renal biopsies in 1974 by van de Putte and colleagues.[3] The disease, like IgA nephropathy, is identified by its immunopathologic features: the presence of IgM as the sole or dominant immunoglobulin in the glomerular mesangium in a diffuse generalized distribution.[4-8] The light microscopic features are protean, ranging from minor changes in the glomeruli to variable degrees of mesangial proliferation to the lesion, resembling idiopathic focal segmental glomerulosclerosis (FSGS).[9-13]

The disease has been most well-studied in children than in adults, especially during the recent past years and is also more common in this age group.[14-18] We have also earlier characterized the disease in detail with respect to the presenting features and immunopathologic spectrum in children.[19] The frequency of IgMN reported in renal biopsy series in adults in the literature has varied from 2% to 45%.[1,20] We have earlier found a prevalence of IgMN of 2.9% in all primary glomerular diseases on native renal biopsies on adults in Pakistan.[21] However, there is still little information on the mode of presentation, clinical and laboratory features, immunopathologic findings, and the long-term prognosis of IgMN in adults from this country. This study attempts to determine the frequency and the demographic, clinical, and immunopathologic characteristics of this disease in adults undergoing renal biopsies for medical kidney diseases at our center and to compare our findings with those previously reported in the literature.

MATERIALS AND METHODS

Patients

We retrospectively reviewed for this cross-sectional survey our 10 years' native renal biopsy record (May 2001 to April 2010) and identified 57 cases (3.25%) of IgMN in adults (≥ 18 years) out of a total of 1753 renal biopsies performed for the established indications at the Department of Nephrology of Sindh Institute of Urology and Transplantation. Among these, 16 patients were excluded on the account of incomplete data and 41 cases were included in the present study for detailed analysis. Their biopsy reports and case files were reviewed and relevant data items were recorded. Systemic diseases causing IgM deposition in the kidney, such as systemic lupus erythematosus, rheumatoid arthritis, diabetes mellitus, and paraproteinemia, were excluded. Hypertension was defined as blood pressure exceeding 140/90 mm Hg. Elevated serum creatinine at presentation was defined as a serum level greater than 1.4 mg/dL in men and greater than 1.2 mg/dL in women.[22]

Histopathologic Study

Percutaneous renal biopsies were studied by light microscopy and immunofluorescence microscopy as described in detail in our previous studies.[19,21,22] In brief, 2 cores of renal biopsy specimens were obtained in each patient. One core was fixed in 10% buffered neutral formalin and processed for paraffin embedding and examination by light microscopy. The other core was divided into 2 pieces; one of these was processed for immunofluorescence and the other was preserved for later electron microscopic study.

The definition of IgMN used in this study was a diffuse and global mesangial positivity of IgM (either as sole Ig or predominant) of 2+ or higher intensity on immunofluorescence on a scale of zero to 3+ (where zero is absent, 1+ is mild, 2+ is moderate, and 3+ is marked).[19]

Statistical Analyses

Data were analyzed using the SPSS software (Statistical Package for the Social Sciences, version 10.0, SPSS Inc, Chicago, Ill, USA). Descriptive statistics of mean ± standard deviation were used for continuous variables, and numbers (percentages) for categorical variables.

RESULTS

Demographic, Clinical, and Laboratory Findings

A total of 41 cases were included in the present study. Their demographic, clinical, and laboratory findings at the time of presentation are shown in Table 1. The mean age of this cohort was 30.21 ± 10.12 years. They were 22 men (53.7%) and 19 women (46.3%). The male-female ratio was 1.15:1. The majority of the patients presented with idiopathic nephrotic syndrome. Other indications

Table 1. Patients' Demographic and Clinical Findings at the Time of Presentation in 41 Adults With IgM Nephropathy*

Characteristic	Value
Number of patients	41
Sex	
Male	22 (53.7)
Female	19 (46.3)
Mean age, y)	30.21 ± 10.12
Hematuria	24 (58.5)
Hypertension	10 (24.4)
Renal dysfunction	13 (31.7)
Clinical presentation	
Idiopathic nephrotic syndrome	34 (82.9)
Acute nephritic syndrome	3 (7.3)
Non-nephrotic proteinuria	2 (4.8)
Isolated hematuria	2 (4.8)

*Values in parentheses are percents.

were less frequent. Hematuria was found in 42 patients (31.2%) and hypertension in 10 (24.4%). The mean serum creatinine level was 1.19 ± 0.74 mg/dL (range, 0.3 mg/dL to 3.3 mg/dL). There were 13 (31.7%) adults with kidney dysfunction, most probably of hemodynamic origin, at the time of presentation, which later improved with steroid therapy in the majority of cases.

Immunopathologic Findings

The detailed morphological and immunofluorescence microscopy findings are shown in Table 2. Regarding light microscopy findings, the total number of glomeruli per biopsy specimen included was 16.14 ± 8.02 (range, 6 to 36). The most common morphologic change consisted of mesangial cell proliferation of the glomeruli, found in 28 biopsies (68.3%), mostly of mild to moderate degree. Minor glomerular alterations were seen in 5 patients (12.2%). Variable numbers of globally sclerosed glomeruli were found in 12 renal biopsy specimens (29.2%). The morphological pattern of FSGS was found in 4 cases (9.8%). All cases with FSGS morphology showed diffuse mesangial positivity of IgM in contrast to the nonspecific segmental trapping of IgM in idiopathic FSGS, and hence, were included in the IgMN category. The vascular changes of arteriolosclerosis and fibrointimal thickening of arteries were less frequent, seen in 2 (4.9%) and 3 (7.9%), respectively. Tubular atrophy and interstitial scarring was found in 22 cases (53.6%). These chronic changes were mostly mild, seen in 18 cases (43.9%), and moderate in 4 (9.8%). No tubular atrophy was seen in 19 patients (46.3%).

Immunofluorescence microscopy showed diffuse mesangial positivity of IgM in all cases, the defining criterion for the inclusion of IgMN cases in this study. The intensity was 2+ in 28 cases (68.3%) and 3+ in 13 (31.7%), as shown in the Figure. In 35 cases (85.3%), IgM was the sole localizing immunoglobulin, and it was the predominant globulin in 6 cases (14.6%). Concomitant but not dominant deposits of IgA were found in 6 (14.6%) cases. Complement fragments of C3 and C1q were found in 28 (68.3%) and 21 (51.2%), respectively.

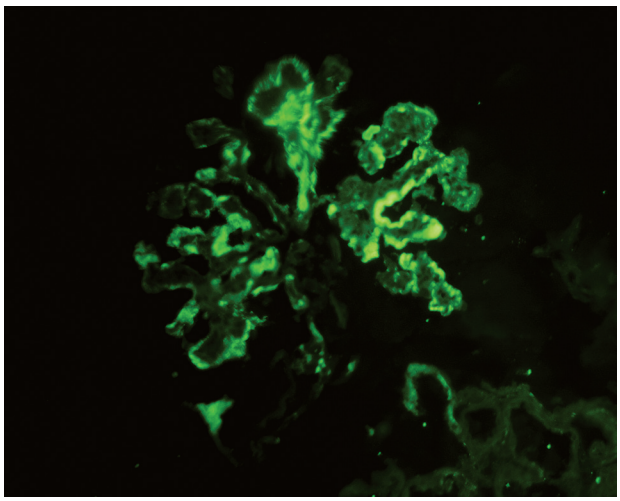
Table 2. Morphological and Immunoflourescent Microscopy Findings in 41 Biopsies of Adults With IgM Nephropathy*

Characteristic	Value
Mean number of glomeruli	16.14 ± 8.02
Light microscopic alterations	
Glomerular alterations	
Minor changes	5 (12.2)
Mesangial proliferation	28 (68.3)
Mild	15 (36.6)
Moderate	11 (26.8)
Focal segmental glomerulosclerosis	4 (9.8)
Tubulo-interstitial alterations	
Tubular atrophy/interstial fibrosis	22 (53.6)
Mild	18 (43.9)
Moderate	4 (9.8)
No tubular atrophy	19 (46.3)
Vascular alterations	
Arteriolosclerosis	2 (4.9)
Fibrointimal thickening of arteries	3 (7.3)
Immunofluorescence findings	
IgM	41 (100)
2+ positivity	28 (68.3)
3+ positivity	13 (31.7)
IgA (trace/minimal)	6 (14.7)
C3	28 (68.3)
C1q	21 (51.2)

*Values in parentheses are percents.

DISCUSSION

There is relatively scant information in the literature on the detailed clinicopathological characterization of IgMN in adults. The majority of the published studies on this disease date back to late 1970s and early 1980s or are related to the pediatric population. To our knowledge, this is the first and the largest study published to date on the clinical and immunopathologic characteristics at the time of presentation of IgMN in adults from



Medium-power view showing global, bright, predominantly mesangial positivity of IgM (intensity 3+, on a scale of zero to 3+) on immunofluorescence microscopy (IgM, × 200)

Pakistan. We also acknowledge that there are certain limitations in the present study. It is a retrospective analysis of cases of IgMN in adults from a single center in Pakistan. There is no information in this study on the treatment or long-term prognosis of the disease. We are, however, following these patients and the treatment and prognostic aspects of the study will be reported in the near future.

We have earlier found a frequency of IgMN of 2.9% in all primary glomerular diseases undergoing renal biopsies in adults. The reported frequency of this disease has varied widely among the studies.[1,2,4,20,21] The first two pioneering studies observed prevalence rates of IgMN of 2% and 6.1% in their biopsy series.[1,2] Soon thereafter, a series by Lawler and colleagues from the United Kingdom observed a frequency of 11.7% of IgMN.[4] The highest prevalence of this disease has been reported from Thailand, where it was the most common glomerular disease in adolescents and adults, constituting 45% of all diagnoses on renal biopsies.[19] The explanation for this wide variation in the prevalence of IgMN is not yet clear, but it most probably reflects varying biopsy indications, varying definitions used for the diagnosis of this lesion, and genetic or environmental factors.[23-26] In this study, IgMN constituted 3.25% of all renal biopsies in adults. This is very close to the figure reported by Singhai and colleagues from the neighboring India.[25] However, another study, also from India, found an incidence of 12.3% in adults.[26]

The results from our study are more or less concordant to those previously published in the literature on IgMN in adults, especially from the Asia.[1,2,4,23-26] The mean age of patients is almost similar to that reported from the neighboring India.[25] As in previous studies from this part of the world, we found no gross gender predilection.[25] The clinical presentation is also more or less similar, although the biopsy indications were not clearly stated in the study from India.[25] Hypertension was also less prevalent. On the other hand, there are some major differences from the studies published from the developed parts of the world.[7,16,24] The main difference relates to the generally restrictive renal biopsy criteria in our patients, comprising mainly idiopathic nephrotic syndrome. Isolated hematuria and asymptomatic proteinuria are very rare indications for renal biopsy in this study; these indications constituted almost half of biopsy indications in some reports from developed countries.[24] This can obviously affect the clinicopathological spectrum of the disease and the subsequent long-term outcome of these patients. It is also apparent from the later studies that IgMN commonly presents in adults as asymptomatic urinary abnormalities. We strongly believe that the true prevalence of IgMN is higher than what is apparent from the present study, as many patients with hematuria or non-nephrotic proteinuria go undetected and even if picked up by urine analysis, they are not biopsied.

The histopathological findings observed in our study are also more or less concordant to those observed by other investigators from different parts of the world.[1,2,4,24-26] The predominant glomerular change consisted of mesangial cell proliferation, mostly of mild degree. Almost similar frequencies of mild mesangial proliferation were also seen in the studies by Myllimaki and colleagues[24] and Singhai and colleagues.[25] Minor structural alterations in the glomeruli were seen in a small minority of cases. This pattern also constituted a minority of lesions in the majority of previously reported studies.[4,23,24,25] The morphological lesions of FSGS were also noted in only a minority of cases. There is controversy in the literature on the inclusion of this pattern in IgMN category. However, we and other investigators have found cases of FSGS with diffuse global positivity of IgM on immunofluorescence microscopy as opposed to segmental positivity of IgM in sclerosed regions of the glomeruli in idiopathic FSGS.[25] Due predominantly to definitional problems, the previously reported prevalence of this morphologic pattern in biopsies of IgMN shows wide variation.[4,23-25] A few authors have entirely excluded this lesion; while, others have included cases of FSGS showing diffuse mesangial positivity of IgM in this disease category of IgMN, as in our study. Due to aforementioned reasons, the reported rates of this lesion have varied from 9% to 65.2%.[2,4] Still other researchers have reported progression of IgMN cases with minor changes or mesangial proliferation into FSGS-like lesions on repeat renal biopsies.[24] Similar to the glomerular changes, the involvement of tubulointerstitial compartment was also minimal to mild in the majority of cases. This is also concordant with previous studies on

IgMN in adults.[24,25] Similarly, the vascular changes of arteriolosclerosis and fibrointimal thickening of arteries were rare in our series as in previous reports of IgMN in adults.[24,25]

The scoring of immunofluorescence findings in renal biopsies are also more or less concordant with those reported previously by other investigators.[1,2,4,7,16,25] However, it is worth stating that there is marked interobserver variability in the reporting of immunofluorescence results and the minimum intensity score used to diagnose IgMN has varied among these studies. Some authors have included patients with trace IgM positivity on immunofluorescence as the inclusion criteria for IgMN, while others have included cases with +1 or greater positivity of IgM.[4] We and some others have used higher intensity score of IgM positivity ($\geq$ 2+) to homogenize the cases of IgMN.[19,25] This may be partly responsible for the concordance of clinicopathological presentation of this disease in these studies.[27]

CONCLUSIONS

The results from this study show that IgMN is a less common cause of renal diseases in adults in Pakistan. It shows a spectrum of morphologic changes ranging from minor changes to FSGS.

CONFLICT OF INTEREST

None declared.

REFERENCES

1. Cohen AH, Border WA, Glassock RJ. Nephrotic syndrome with glomerular mesangial IgM deposits. Lab Invest. 1978;38:610-9.
2. Bhasin HK, Abeulo JG, Nayak R, Esparza AR. Mesangial proliferative glomerulonephritis. Lab Invest. 1978;39:21-9.
3. Van de Putte LBA, DeLaRiviere GB, Van Breda Vriesman PJC. Recurrent or persistent hematuria, sign of mesangial immune-complex deposition. N Engl J Med. 1974;290:1165-70.
4. Lawler W, Williams G, Tarpey P, Mallick NP. IgM associated primary diffuse mesangial proliferative glomerulonephritis. J Clin Pathol. 1980;33:1029-38.
5. Mampaso F, Gonzalo A, Ternel J, et al. Mesangial deposits of IgM in patients with the nephrotic syndrome. Clin Nephrol. 1981;16:230-4.
6. Cavalo T, Johnson MP. Immunopathologic study of minimal change glomerular disease with mesangial IgM deposits. Nephron. 1981;27:281-4.
7. Helin H, Mustonen J, Pasternack A, Antonen J. IgM associated glomerulonephritis. Nephron. 1982;31:11-6.
8. Hsu HC, Chen WY, Lin GJ, et al. Clinical and immunopathologic study of mesangial IgM nephropathy: report of 41 cases. Histopathology. 1984;8:435-46.
9. Pardo V, Riesgo I, Zilleruelo G, Strauss J. The clinical significance of mesangial IgM deposits and mesangial hypercellularity in minimal change nephrotic syndrome. Am J Kidney Dis. 1984;3:264-9.
10. Ji-Yun Y, Melvin T, Sibley R, Michael AF. No evidence for a specific role of IgM in mesangial proliferation of idiopathic nephrotic syndrome. Kidney Int. 1984;25:100-6.
11. Kopolovic J, Shvil Y, Pomeranz A, Ron N, Rubinger D, Oren R. IgM nephropathy: morphological study related to clinical findings. Am J Nephrol. 1987;7:275-80.
12. Border WA. Distinguishing minimal change disease from mesangial disorders. Kidney Int. 1988;34:419-24.
13. Habib R, Girardin E, Gagnadoux M-F, Hinglais N, Levy M, Broyer M. Immunopathological findings in idiopathic nephrosis: clinical significance of glomerular “immune deposits”. Pediatr Nephrol. 1988;2:402-8.
14. Mokhtar GA. IgM nephropathy: clinical features and pathological findings in 36 patients. Saudi J Kidney Dis Transpl. 2011;22:969-75.
15. Al Eisa A, Carner JE, Lirenman DS, Magil AB. Childhood IgM nephropathy: comparison with minimal change disease. Nephron. 1996;72:37-43.
16. Saha H, Mustonen J, Pasternack A, Helin H. Clinical follow up of 54 patients with IgM nephropathy. Am J Nephrol. 1989;9:124-8.
17. Kishimoto H, Arakawa M. Clinico-pathological characterization of mesangial proliferative glomerulonephritis with predominant deposition of IgM. Clin Exp Nephrol. 1999;3:110-5.
18. Donia AF, Sobh MA, Moustafa FE, Bakr MA, Foda MA. Clinical significance and long term evolution of minimal change histopathologic variants and of IgM nephropathy among Egyptians. J Nephrol. 2000;13:275-81.
19. Mubarak M, Kazi JI, Malik S, Lanewala A, Hashmi S. Clinicopathologic characteristics and steroid response of IgM nephropathy in children presenting with idiopathic nephrotic syndrome. APMIS. 2011;119:180-6.
20. Parichatikanond P, Chawanasuntorapoj R, Shayakul C, et al. An analysis of 3555 cases of renal biopsy in Thailand. J Med Assoc Thai. 2006;89:S106-11.
21. Mubarak M, Kazi JI, Ahmed E, et al. Pattern of renal diseases in native renal biopsies in adults from Pakistan. Nephrology. 2011;16:87-92.
22. Jafry N, Ahmed E, Mubarak M, Kazi J, Akhter F. Raised serum creatinine at presentation does not adversely affect steroid response in primary focal segmental glomerulosclerosis in adults. Nephrol Dial Transplant. 2012;27:1101-6.
23. Chan YH, Wong KM, Choi KS, Chak WL, Cheung CY. Clinical manifestation and progression of IgM mesangial nephropathy: a single center perspective. Hong Kong J Nephrol. 2000;2:23-6.
24. Myllymaki J, Saha H, Mustonen J, Helin H, Pasternack A. IgM nephropathy: clinical picture and long term prognosis. Am J Kidney Dis. 2003;41:343-50.
25. Singhai AM, Vanikar AV, Goplani KR, et al.

Immunoglobulin M nephropathy in adults and adolescents in India: a single center study of natural history. Indian J Pathol Microbiol. 2011;54:3-6

26. Bhowmik D, Chitale A, Bulchand S. IgM nephropathy in adults: incidence and correlation with electron microscopic features. Indian J Pathol Microbiol. 2007;50:511-4.
27. Mubarak M. Immunoglobulin M nephropathy in adults and adolescents in India: a single center study of natural history. Indian J Pathol Microbiol. 2012;55:126-7.

Correspondence to:
Muhammed Mubarak, MD
Histopathology Department, Sindh Institute of Urology and Transplantation, Karachi-74200, Pakistan
Tel: +92 21 921 5752
Fax: +92 21 272 6165
E-mail: drmubaraksiut@yahoo.com

Received June 2012
Accepted October 2012