Case Series

IgM Nephropathy, A Question of Existence in the Domain of Glomerular Diseases: A Case Series

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Abstract

Introduction: Immunoglobulin M nephropathy (IgMN) is a rare glomerular disease characterized by isolated IgM deposits in the glomeruli. Its clinical presentation and prognosis remain controversial, often overlapping with other glomerular diseases like minimal change disease (MCD). Objectives: This is a case series describing the clinical and pathological features of patients diagnosed with IgMN at our tertiary care center. Methods: A retrospective review of renal biopsies performed between January 2023 and December 2023 was conducted. Patients diagnosed as IgMN were included. Clinical data, laboratory parameters, histopathological findings, immunofluorescence results, treatment regimens, and follow-up data were collected. Results: Five patients (four females, one male) were diagnosed with IgMN. The majority presented with nephrotic syndrome with frequent relapses, and steroid dependence. Histopathological examination revealed mesangial hypercellularity and matrix expansion. Immunofluorescence staining showed diffuse 2+/3+ mesangial IgM deposits. Treatment with corticosteroids and rituximab resulted in clinical improvement and stabilization of renal function. Conclusion: IgMN is a distinct clinical entity with a variable clinical course. Early recognition and appropriate treatment, including immunosuppressive therapy, are crucial for achieving remission and preventing disease progression. Further research is needed to better understand the pathogenesis and optimal management of IgMN.

Keywords: Renal biopsy; glomerulus; Immunofluorescence; nephropathy

Introduction

IgM nephropathy (IgMN) is a clinicopathologic entity characterized by isolated IgM deposition in the glomeruli and clinically presenting as nephrotic syndrome, especially in the pediatric population or as isolated hematuria more commonly in adults. It was first described in the 1970s, yet its classification within glomerular diseases remains debated even today. Pathologically, IgMN is characterized by diffuse or granular deposits of IgM, typically exhibiting a 2+/3+ intensity in the mesangium in immunofluorescence (IF) microscopy.[2] Light microscopy findings vary significantly, from no observable glomerular abnormalities to mild to moderate increase in mesangial cellularity and matrix expansion. There should be no evidence of systemic disease (e.g., systemic lupus erythematosus, rheumatoid arthritis, diabetes mellitus, and paraproteinemia) for the diagnosis of primary IgMN.

However, recognizing this as a specific entity became a matter of debate because IgM is frequently seen in biopsies as a nonspecific finding. Further, a lack of consensus on the definition of significant IgM deposits also gave rise to controversy. According to many authors immunofluorescence staining of IgM deposits with an intensity of 2+ or more was required to diagnose IgM nephropathy. However, Dr. Jean L. Olson specifies the diagnosis of IgM nephropathy as "those cases with bright staining (at least two positives out of three) and with demonstrable mesangial deposits on electron microscopy".[11]

Some authors consider IgMN and MCD as clinically indistinguishable entities. Some researchers propose that it represents a transitional state between minimal change disease (MCD) and focal segmental glomerulosclerosis (FSGS). However, the poor response to conventional steroid therapy and worsening of renal functions in a few patients as opposed to MCD warrants further study into the entity and placing it as a distinct entity in the domain of glomerular diseases. [9, 10]

The present study describes the clinical and pathological features of five cases of IgMN diagnosed at a tertiary care centre in South Kerala over one year. This case series aims to contribute to the understanding of IgM nephropathy by presenting clinical data alongside relevant literature to facilitate further research into this complex condition.

Materials and Methods

This is a series of five cases of renal biopsies diagnosed as IgMN from January 2023 to December 2023. Renal biopsies were performed with 18-gauge needle. Two cores were taken, of which one was sent in formalin for routine H&E staining and special stains. The second core was sent in normal saline for IF studies. Immunofluorescence staining was done with reagents from Nanda Biotech in 1:30 dilution and intensity was evaluated under Leica microscope with mercury lamp using blue filter with green emission. The study analyzed clinical presentations, laboratory parameters (at the time of biopsy and after initiation of treatment), indications for renal biopsy, histopathological findings, immunofluorescence results, treatment regimens, and patient responses. The cases were followed up till the last documented clinical visit.

The diagnosis of primary IgM nephropathy was based on the currently accepted guideline which specifies diffuse 2+/3+ intense IgM deposition in the glomeruli as evidenced by immunofluorescence microscopy and after ruling out all secondary causes of IgM deposition.

Results and Observations

During the study period of one year from January 2023 to December 2023 we received 52 renal biopsies among which 5 cases were diagnosed as IgMN, the frequency was 9.6%.

Patient Demographics: The cohort consisted of four females and one male, with three pediatric cases ($\leq$15 years) and two young adults.

Table 1: Patient clinical details and laboratory parameters at the time of biopsy.

S.No	Age	Sex	Clinical Diagnosis	Indication for Renal Bopsy	Urine albumin	Serum albumin(g/dl)	Urine P/Cr ratio	Serum creatinine
1	9yrs	F	Nephrotic syndrome diagnosed at 10 months of age	Steroid dependent-4th relapse	3+	1.9	10.7:1	0.6
2	12yrs	M	Nephrotic syndrome diagnosed at 2.5yrs of age	Steroid dependent-3rd relapse	3+	1.9	15:1	0.3
3	15yrs	F	Nephrotic syndrome diagnosed at 7yrs of age	Steroid dependent-2nd relapse	4+	1.4	11.7:1	0.4
4	23yrs	F	Sub nephrotic proteinuria	Persistent frothuria	1+	2.9	0.69:1	0.8
5	42yrs	F	Adult Nephrotic syndrome	Relapse	4+	2.3	8.9:1	0.8

Clinical details Of the five cases, four were already diagnosed cases of nephrotic syndrome at a very young age and presenting with frequent relapse and steroid dependence. One was a case of a young female with persistent frothuria despite steroid

treatment and no cause identified on various investigations including those for autoimmune disorders.

In all 4 cases of nephrotic syndrome renal biopsy was done in view of frequent relapses and steroid dependence.

Laboratory Parameters at the time of Biopsy: Urine albumin levels were predominantly in the nephrotic range (except one case). Serum albumin levels were low. Urine protein-to-creatinine ratio was elevated. Serum creatinine levels remained normal.

Indications for Renal Biopsy: Frequent relapses and persistent symptoms prompted the need for renal biopsy in all the cases.

Histopathology Findings: All the cases showed similar findings on histopathological examination which included intercapillary matrix expansion and mild to moderate mesangial hypercellularity.

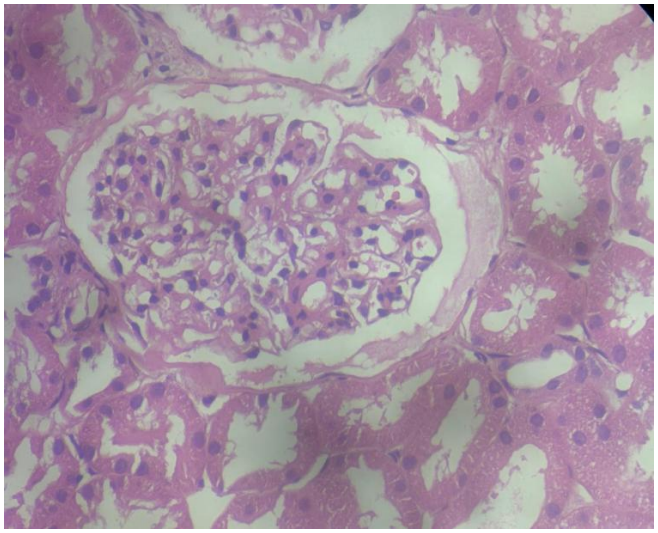

Figure 1: H & E figure mesangial hypercellularity (40x).

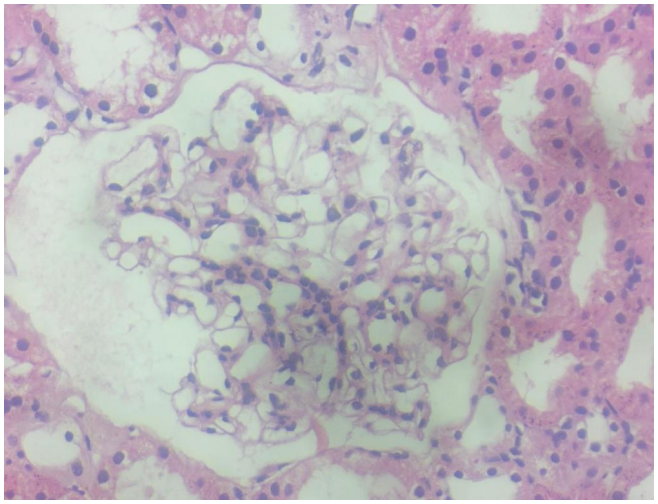

Figure 2: H& E figure matrix expansion (40x).

Immunofluorescence Results: All the cases showed Diffuse 2+/3+ mesangial deposits of IgM. Focal capillary wall deposits were observed in two cases and co-localization of C1q and kappa/lambda light chains was noted in one case.

Treatment and Follow-Up: The treatment protocols varied among patients but included corticosteroids initially, followed by Rituximab in cases demonstrating steroid resistance. The patients were followed up for a minimum period of period of one year or till the last documented clinical visit whichever came later. Absence of urine albumin with normalised urine protein creatinine ratio was taken as in remission. Reappearance of urine albumin was considered as criteria for relapse. Follow-up assessments indicated a good response with Rituximab showing normalization of urine albumin levels, urine protein creatinine ratio and serum albumin levels.

Discussion

Among the five cases we received in a span of one year there was a male predominance and except 2 cases all were pediatric patients who had to undergo renal biopsy for a frequently relapsing steroid resistant nephrotic syndrome. Clinically all of the

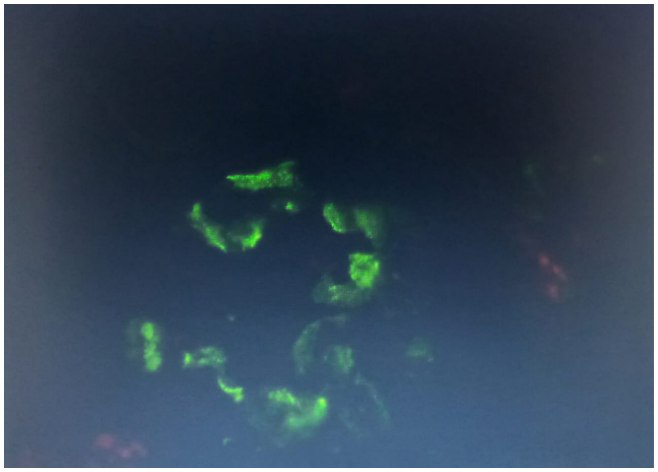

Figure 3: IF showing IgM deposits.

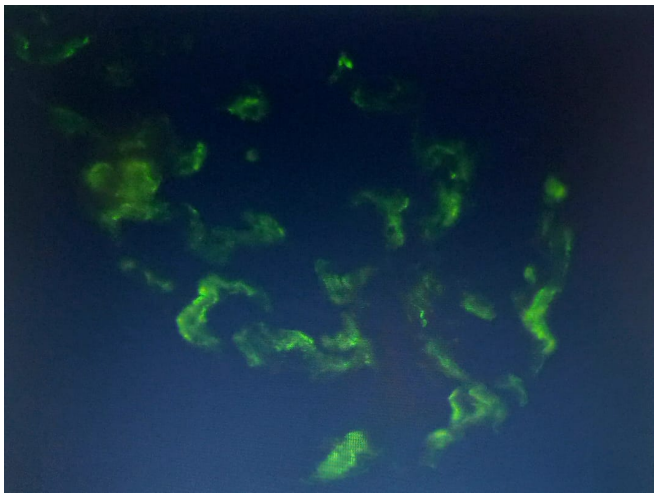

Figure 4: IF showing IgM deposits.

Table 2: Treatment details and follow-up parameters.

S.no	Treatment given	Current status	Urine albumin	Serum albumin(g/dl)	Urine P/Cr ratio	Serum creatinine
1	2 doses of Rituximab infusion+steroids	Tapering steroid dose	Nil	3.9	0.07:1	0.6
2	2 doses of Rituximab infusion+steroids	Steroids stopped(on remission)	Nil	3.6	0.08:1	0.5
3	2 doses of Rituximab infusion+steroids	Steroids stopped(on remission)	Nil	4.5	0.09:1	0.4
4	Wysolone+tacrolimus	Tapering steroid dose	Nil	3.3	0.1:1	0.7
5	Wysolone	Steroids stopped(on remission)	2+	3.7	1.2:1	0.69

patients had nephrotic range of proteinuria. In our study the frequency was around 9.6% of the renal biopsies received over a period of one year. The reported frequency of IgMN in literature ranges from 2% to 18.5% with a rising trend since its recognition[1]. Studies by Cohen etal and Bhasin et al reported an incidence of 2% and 6.1% respectively in their biopsies [2, 3].

Clinically, IgMN primarily presents with proteinuria—often in the nephrotic range—or hematuria, particularly in young adults and children This condition is associated with frequent relapses, steroid dependence, and resistance to conventional treatment protocol of nephrotic syndrome [1]. Some authors have reported frequent presence of haematuria in the clinical

presentation as well as a less responsive result to therapy. All our cases showed steroid dependence/resistance with nephrotic range of proteinuria as the major presentation.

Histopathological examination in all cases uniformly showed increase in mesangial cellularity of varying degrees and mesangial matrix expansion. There was no evidence of tubular changes or interstitial fibrosis. According to literature mesangial hypercellularity and matrix expansion constitute the major histological changes. Some authors have described tubular atrophy and interstitial fibrosis especially in cases which progressed to end stage renal failure. These findings were considered to be indicative of bad prognosis. Al-Eisa et al. showed more frequent mesangial expansion, more tubular atrophy, and more frequent hypertension in children with IgM nephropathy.[8] In many cases with bad outcome typical morphological characteristics of focal and segmental glomerulosclerosis can be seen. But none of our cases showed features of FSGS.

Immunofluorescence in all the cases uniformly showed diffuse 2+/3+ intense deposition of IgM in the glomeruli, consistent with the definition of the entity as accepted in literature.

With reference to the acceptance of IgMN as a distinct entity, when there are intense and diffuse mesangial deposits of IgM, associated to NS, many authors consider that it is a disease different to MCD and FSGS; nevertheless, others consider that it is a variant of MCD or FSGS

The pathogenesis of IgMN may involve classical immune complex-mediated activation of the complement cascade, with abnormalities in T-lymphocyte regulation also suggested as contributing factors. Hsu et al put forward the above concept with reference to the co-localization of C3, C1q and C4 along with IgM [15]. In our case series one of the cases showed co-localization of C1q in immunofluorescence. IgM deposition in the glomeruli may be seen in a variety of systemic diseases, such as systemic lupus erythematosus (SLE), rheumatoid arthritis, diabetes mellitus, paraproteinemia, and Alport's syndrome. [1, 4, 5] The above conditions must be ruled out by clinical and laboratory tests to diagnose primary IgMN. All the three pediatric cases were administered 2 doses of rituximab infusion along with steroids. Adult cases were treated with wysolone and tacrolimus. All the cases are under remission and the cases who were given rituximab showed a better improvement of laboratory parameters including urine albumin and urine protein to creatinine ratio as documented according to the last follow up visit. Prognosis varies; without prompt recognition and treatment, patients can have worsening renal function. Recent advancements have shown promising results with monoclonal antibodies like Rituximab in achieving remission and stabilizing renal function in our case series.

Another study by Myllymäki J et al in 110 patients with 15-year follow-up showed that 22.7% progressed to end-stage renal disease with another 13.7% manifesting renal insufficiency; half of the patients became hypertensive. Other authors also had reported worse prognosis in IgM Nephropathy compared to MCD. [11, 16, 17]

The clinical presentation is very similar to that of MCD, but it seems that there is minor response to steroids and the prognosis can be worse.

Conclusion

Immunoglobulin M nephropathy (IgMN), known since 1978, is a very controversial clinicopathological entity characterized by IgM diffuse deposits in the mesangium at immunofluorescence whereas light microscopy identifies minimal glomerular lesion, hypercellularity and expansion of the mesangium or sclerotic focal segmental lesion. Clinically, it is a nephrotic syndrome, especially in paediatric patients, or asymptomatic proteinuria and/or isolated haematuria. These characteristics narrowly define IgMN between minimal change disease and focal segmental glomerulosclerosis, so it is not often recognized as a separate pathology. Over the recent years IgM nephropathy is increasingly recognized as a distinct clinicopathologic entity presenting as idiopathic nephrotic syndrome in both children and adults. The diagnosis relies heavily on thorough pathological evaluation via light microscopy (LM) and immunofluorescence (IF). While steroid therapy often yields poor responses, newer therapeutic agents like Rituximab have demonstrated significant efficacy. Risk factors associated with end-stage renal disease (ESRD) in IgMN include hypertension, proteinuria, interstitial fibrosis, and positivity for glomerular C1q. Further research is essential to elucidate the distinctiveness of IgMN with emphasis on a scoring system based on prognostic histopathologic variables and to better understand long-term renal outcomes and patient prognosis

Limitation Electron microscopy could not be performed in any of the cases due to lack of availability

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