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IgM nephropathy; can we still ignore it

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ABSTRACT

Context: IgM nephropathy (IgMN) is a relatively less recognized clinico-immunopathological entity in the domain of glomerulonephritis, often thought to be a bridge between minimal change disease and focal segmental glomerulosclerosis.

Evidence Acquisitions: Directory of Open Access Journals (DOAJ), Google Scholar, Pubmed (NLM), LISTA (EBSCO) and Web of Science has been searched.

Results: IgM nephropathy can present as Nephrotic syndrome or less commonly with subnephrotic proteinuria or rarely hematuria. About 30% patients respond to steroids whereas others are steroid dependent / resistant. They should be given a trial of Rituximab or stem cell therapy.

Conclusions: IgM nephropathy (IgMN) is an important and rather neglected pathology responsible for renal morbidity in children and adults in developing countries as compared to developed nations with incidence of 2-18.5% of native biopsies. Abnormal T-cell function with hyperfunctioning suppressor T-cells are believed to be responsible for this disease entity. Approximately one third of the patients are steroid responders whereas the remaining two thirds are steroid resistant or dependent. Therapeutic trials including cell therapies targeting suppressor T-cells are required.

Implication for health policy/practice/research/medical education:

IgM nephropathy (IgMN) is an important and rather neglected pathology responsible for renal morbidity in children and adults in developing countries as compared to developed nations with incidence of 2-18.5% of native biopsies. Abnormal T-cell function with hyperfunctioning suppressor T-cells are believed to be responsible for this disease entity. Approximately one third of the patients are steroid responders whereas the remaining two thirds are steroid resistant or dependent. Therapeutic trials including cell therapies targeting suppressor T-cells are required.

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1. Context

IgM nephropathy (IgMN) is a relatively less recognized clinico-immunopathological entity in the domain of glomerulonephritis

(GN), often thought to be a bridge between minimal change disease (MCD) and focal segmental glomerulosclerosis (FSGS).

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2. Evidence Acquisition

Directory of Open Access Journals (DOAJ) Google Scholar, Pubmed (NLM), LISTA (EBSCO) and Web of Science were searched with key words relevant to IgM nephropathy, proteinuria, minimal change disease, focal segmental glomerulosclerosis and hypertension.

3. Results

IgM nephropathy was first described independently by two groups; Cohen and Border et al, and Bhasin et al, in 1978 (1-2). Their series of native renal biopsies displayed mesangial hypercellularity on light microscopy, diffuse granular mesangial IgM and C3 deposits on immunofluorescence (IF), and on electron microscopy (EM) generalized foot process effacement with mesangial electron dense deposits in about 50% of the patients. Early avalanche of these reports from Finland, US, UK and other developed countries receded only to be taken up by developing countries. Since then many papers related to IgMN from developing and occasionally developed nations are being published every year.

3.1. Epidemiology

Most of the studies have reported on prevalence of IgMN as frequency/ percentage of renal biopsies with diagnosis of IgMN reported from 2 % to 18.5 % in native biopsies (3-13). Occasional cases of IgMN in transplant biopsies have also been reported (14). The etiology of IgMN like IgA nephropathy/C1q nephropathy is largely unknown. However common denominator in all these studies is exclusion of systemic diseases like lupus nephritis, rheumatoid arthritis, diabetes and diabetic nephropathy, Alport's syndrome and paraproteinemias.

3.2. Pathogenesis

The pathogenesis of this disease entity still remains elusive. Classical immune complex medi-

ated activation of complement system leading to mesangial injury and reaction has been observed. Majority of the cases show associated presence of C1q and C4 deposits along with IgM in glomerular mesangium whereas properdin and factor B are conspicuous by their absence (6,15,16). C3 deposits are more common accompaniments rather than C1q deposits in these biopsies. Thus classical complement pathway appears to play a major role in the evolution of this disease. The source of antigens triggering immune complex formation is still unknown, but it is hypothesized that certain antigens in the environment (or food) which preferentially elicit IgM responses may be responsible for the genesis of this disease (11,17-20). Abnormalities of T-lymphocyte function with stimulation of cytotoxic T-cells and down-regulation of natural suppressor/ regulatory T-cells may be an integral factor in the causation of this disease and inability for clearance of immune complexes by mesangial cells (15, 21). Reports on increased serum IgM/ IgM-immune complex concentration in patients with IgMN are available in literature (16, 17). However there are no studies reporting on abnormalities of IgM molecule in these patients.

3.3. Pathology

3.3.1. Light microscopy:

Light microscopy and IF are mandatory for diagnosis of IgMN. The spectrum of morphological changes in glomerular pathology range from mild to moderate mesangial proliferation in majority of the cases involving about 70-75%, followed by FSGS in 15-20% and unremarkable morphology/ MCD in 5-10% biopsies (11, 20-25). (figure 1a). Tubular and interstitial injuries are manifested as secondary pathology associated with primary glomerular pathology. Tubular and interstitial injury including chronic changes in the form of tubular atrophy and interstitial fibrosis

correspond with progression in glomerular lesion however fibrointimal proliferation of vessel wall is not significant in these biopsies (26-30). A comparison of some studies from different geographical regions is presented in the table 1.

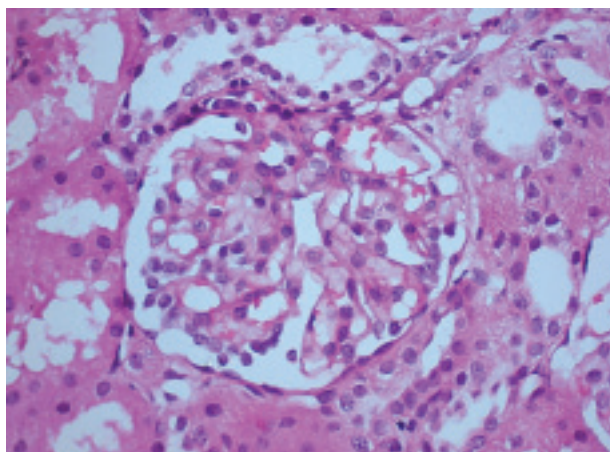


Figure1 (a). Photomicrograph showing glomerulus with mild mesangial prominence, (H & E stain, x 400)

3.3.2. IF findings

IgM deposits with intensity of $\geq 2+$ in more than 50% mesangial regions of non-sclerotic glomeruli are predominant features. The associated immune deposits are C3 in 15-20% followed by IgG and IgA. These immune complexes may also be noted across capillary membranes. The intensity of other immune deposits is usually less than that of IgM deposits (figure 1b) (20-31).

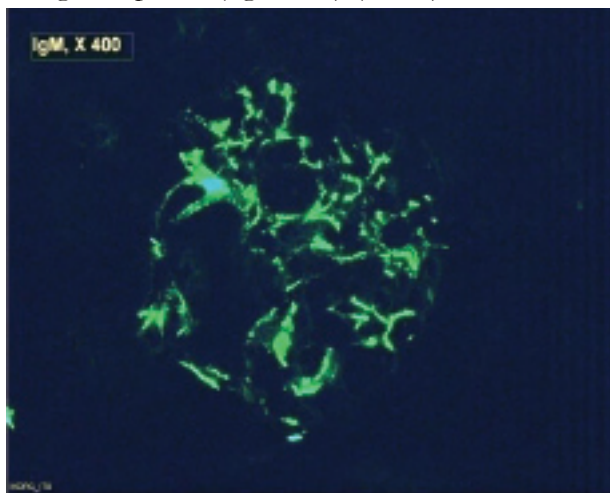


Figure1 (b). Immunofluorescence study showing glomerulus with IgM deposits in mesangial regions and capillaries (3 + to 4 +), anti-human IgM antiserum, x 400

3.3.3. Electron microscopy (EM)

Few reports on EM findings in these biopsies have shown small, granular electron dense deposits in mesangium and para-mesangium accompanied by mesangial hypercellularity and widening of mesangial regions, variable degrees of foot process effacement correlating with extent of proteinuria have also been observed. The deposits are typically of low volume and density (7, 8).

3.4. Clinical presentation

IgMN presents in the age group of 13 to 78 years in adults and adolescents, and in the age group of 2 to 12 years in children. In children the common age of presentation is about 6 years whereas in adults it is usually in late thirties to late fifties. Some studies have reported male predilection and others have reported female predilection. However it has been noted that males are more commonly affected than females when the presentation is Nephrotic syndrome (NS), whereas females usually present with hematuria or sub-nephrotic proteinuria. Hypertension is roughly noted in up to 30% of the patients (8, 11, 20, 23, 32-33) (table 2).

4. Treatment modalities

Corticosteroids remain the mainstay of therapeutic strategies in these patients. Unfortunately only one third of the patients, mainly with MCD/unremarkable glomerular morphology respond to steroids. Calcineurin inhibitors and Rituximab have been tried in limited studies and have shown favorable short term response (8, 11, 31-35). However therapeutic strategies targeting suppressor T-cells and cell therapies should be tried in these patients.

4.1. Prognostic indicators

Women with hematuria have been found to

Table 1. Histopathology findings of IgM nephropathy in different geographical regions and age groups

Study	Total patients	Unre-markable/ MCD (%)	MePGN (%)	FSGS (%)	Others (%)	Steroid response (%)
O'Donoghue et al, 1991	54	0(0)	47 (87)	6 (11.1)	Crescentic GN-1(1.9)	5 out of 18 responded
Zeis PS et al 2001	64	20 (31.3)	37 (57.8)	7 (10.9)	Nil	14(21.9)-Responders, 50(78.1)-Resistant
Myllymäki et al, 2003	110	38 (34.5)	33 (30.0)	39 (35.5)	Nil	47(42.7)-Responders, 50(45.5)-Dependent, 13(11.8)-Resistant
Singhai et al, 2011	117	11 (9.4)	87 (74.4)	19 (16.2)	Nil	42(40.2)- Responders, 75(59.8)- Resistant/ dependent
Vanikar et al, 2011	28	8 (28.6)	17 (60.7)	3 (10.7)	Nil	7(25.0)-Responders, 21(75.0)-Dependent/resistant

Key to table 1. MCD: Minimal change disease, ESRD: End stage renal disease, GN: Glomerulonephritis, MePGN: Mesangial proliferative glomerulonephritis, FSGS: Focal and segmental glomerulosclerosis

Table 2. Clinical presentation of IgM nephropathy in different geographical regions and age groups

Study	Total patients	Males: Females	Mean Age in years (range)	Presentation	Hypertension (%)	Mean Serum creatinine (mg/dL)
O'Donoghue et al, 1991	54	35:19 (64.8:35.2)	31 (14-69)	NS-31 (57.4), PU-19 (35.2), HU-4 (7.4)	15 (27.8)	1.07 (median)
Chan YH et al, 2000	39	28:11 (71.8:28.2)	35 ±2	NS-18(46.2), PU-11(28.2), PHU-9 (23.1), HU- 1 (2.5)	7 (17.9)	1.14 (median)
Zeis PS et al 2001	64	33:31 (51.6:48.4)	2-14	NS-20 (31.2), PU-14 (21.9), HU-18 (28.1), PHU-12 (18.8)	3 (4.7)	Not mentioned
Myllymäki et al, 2003	110: 36-children 74-adults	63:47 (57.3: 42.7)	6 (1-15) 29 (17-75)	NS-50 (45.5), others-60 (54.5)	55 (50)	Not mentioned
Singhai et al,	117	62: 55 (53: 47)	29 (13-78)	NS (100)	12 (10.3)	1.46 ±1.6
Vanikar et al, 2011	28	24:4 (85.7: 14.3)	10 (2-12)	NS (100)	2 (7.1)	0.7 ±0.3

Key to table 2. NS- Nephrotic syndrome, HU: Hematuria, PU: Proteinuria, PHU: Proteinuria and hematuria

have better prognosis than all other patients. Hypertension and proteinuria are poor prognosticators whereas age has no role in prognosis. In the largest reported series of 110 patients with 15 years follow-up, Myllymäki et al state that clinically hypertension and steroid resistance are bad prognosticators (8). Steroid resistant cases were found to have FSGS on re-biopsy. In histologi-

cal criteria, interstitial fibrosis was the most important marker for poor prognosis. FSGS lesions have worst prognosis with high probability of progression to end stage renal disease within 5 years as compared to FSGS without IgM deposits (8,11,20, 35). Similarly MCD with IgM deposits has worse prognosis than MCD without IgM deposits (11, 20, 35).

5. Conclusions

IgMN is an important and rather neglected pathology responsible for renal morbidity in children and adults in developing countries as compared to developed nations with incidence of 2-18.5% of native biopsies. Abnormal T-cell function with hyperfunctioning suppressor T-cells are believed to be responsible for this disease entity. Approximately one third of the patients are steroid responders where as the remaining two thirds are steroid resistant or dependent. Therapeutic trials including cell therapies targeting suppressor T-cells are required.

Conflicts of interest

I declare that I have no conflict of interest regarding this article.

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