BANTAO Journal 2023; 22(2): 37-40

BJ
BANTAO Journal

Case Report

A Case of Persistent Microscopic Hematuria with Associated Proteinuria - Not Your Usual Suspect

Gabriela Fibia Chichinesdi[1], Iulia Grosu[1,2], Adrian Vaduva[3], Felix Maralescu[1,2], Madalina Bodea[1,2] and Flaviu Raul Bob[1,2]

[1]Department of Internal Medicine II -Nephrology University Clinic, "Victor Babes" University of Medicine and Pharmacy Timisoara, County Emergency Hospital Timisoara, [2]Centre for Molecular Research in Nephrology and Vascular Disease, Faculty of Medicine, "Victor Babes" University of Medicine and Pharmacy, Timisoara, [3]Department of Microscopical Morphology-Morphopathology ANAPATMOL CMC, "Victor Babes" University of Medicine and Pharmacy, Timisoara, Romania

Abstract

IgM nephropathy has been described as a distinct glomerulopathy characterized by the presence of IgM deposits in immunofluorescence. Its presentation is usually associated to nephrotic syndrome, and not so often with subnephrotic proteinuria or hematuria. Most often it affects children and young adults. This clinical case outlines the evaluation of a nephritic syndrome - a 51-year-old woman with essential hypertension for 30 years and persistent microscopic hematuria for 6 months. Besides the complete laboratory workup specific for glomerulopathies, the case required a kidney biopsy in order to establish the etiology of the nephritic syndrome. After confirming the diagnosis of IgM nephropathy, an angiotensin 2 receptor blocker and a sodium-glucose cotransporter-2 inhibitor (SGLT2i) were introduced for symptom control, with a favorable outcome and complete remission of proteinuria and albuminuria. The particularity of the case is that even if clinical presentation suggested an IgA nephropathy (the most frequent presentation with a similar clinical picture), kidney biopsy eventually indicated an IgM nephropathy, a much rarer entity.

Keywords: nephritic syndrome, IgM nephropathy, microscopic hematuria

Introduction

From an epidemiological point of view, the prevalence of IgM Nephropathy (IgMN) ranges from 2% to 18.5% [1]. It is often associated with systemic disorders including systemic lupus erythematosus, rheumatoid arthritis, diabetes mellitus, Sjogren syndrome, Alport's syndrome etc. [2].

The pathogenesis of IgM nephropathy is still uncertain, most theories advocating T-cell abnormalities with stimulation of cytotoxic T-cells and down-regulation of regulatory T-cells [1] or an ineffective clearance by mesangial cells [3]. Others propose the hypothesis of an immune complex disease with activation of the immune complement pathway [4], as suggested by the consistent appearance of C1q, and C4 in the glomerular mesangium [5]. Antigens that trigger immune complex formation are thought to be specific antigens found in food or the environment [1]. Certain studies indicate that the female gender and those presenting with hematuria tend to have a more favorable outcome, suggesting that genetic factors may play a role in the development of this pathology. [6].

Regarding IgM deposits at IF, the distribution is present in all glomeruli in a diffuse manner and it affects the whole glomerulus in a global disposition [7]. This particular pathological aspect can be found in minimal change disease (MCD), focal segmental glomerulosclerosis (FSGS), and mesangial proliferative glomerulonephritis [8], however, it is now agreed that it represents a distinct entity with a greater resistance to steroids and worse prognosis compared with MCD [3]. Compared to FSGS, which usually recurs early in the renal graft, there are fewer cases of IgM nephropathy recurrence post-transplantation [9].

To diagnose IgM nephropathy on kidney biopsy, Connor *et al*., proposed a number of criteria: prevalent staining for IgM by immunofluorescence, with an intensity more than trace, distributed in the mesangium; IgG and IgA should not be equal or higher in intensity than IgM-i.e. IgM should be dominant; with obvious mesangial deposits on EM [10]. In their study, Connor *et al*., concluded that the histological finding most often linked with progressive renal impairment was segmental sclerosis affecting >20% of glomeruli. Interstitial fibrosis and

Correspondence to: Gabriela Fibia Chichinesdi, Department of Internal Medicine II -Nephrology University Clinic, "Victor Babeș" University of Medicine and Pharmacy Timisoara, County Emergency Hospital Timisoara, Romania; E-mail: fibia.chichinesdi@yahoo.com

tubular atrophy involving more than 20% of the biopsy specimen are also associated with kidney dysfunction [10]. IgM nephropathy often presents with nephrotic syndrome. A study by Ghadeer A Mokhtar found that, from a total of 36 patients examined, the initial presentation was nephrotic syndrome in 32 patients, proteinuria in two, and hematuria coupled with proteinuria in 16 [3]. Rarely, IgM nephropathy can display as rapidly prog ressive glomerulonephritis (RPGN).

Case presentation

A 51-year-old female patient known with essential hypertension for 30 years and treated with lercanidipine and nebivolol was recently diagnosed with a left adrenal adenoma, hepatomegaly, and a bicornuate uterus, otherwise no other known pathologies, presented at the Nephrology outpatient clinic for persistent microscopic hematuria for six months. Three months prior to the presentation, she underwent blood and urine tests with the following results (Table 1).

Table 1. Laboratory parameters before presentation

Parameters	May	June
\Creatinine (mg/dl)	1.13	
eGFR (ml/min/1.73 m^2)	59	
24h proteinuria (g/24h)	1.1	0.67
Addis sediment count Leukocytes (/min)	3878	
Addis sediment count RBCs (/min)	28254	

Abbreviation: eGFR - estimated glomerular filtration rate; RBCs - red blood cell count

On admission, clinical examination revealed light pitting edema, blood pressure 140/80 mmHg, and a heart rate of 80 bpm. To establish the cause of the nephritic syndrome, an extensive panel of laboratory tests was performed, including serum total protein, serum albumin, UACR, complement levels (normal levels), and serum immunoglobulin levels (normal values). Viral markers and anti-nuclear antibodies (ANA) for infectious and immunological causes, respectively, were ordered-normal results. Urinalysis and Addis sediment count were also repeated. The most relevant results are shown below (Table 2).

Table 2. Laboratory parameters at the time of presentation

Parameters	August
Creatinine (mg/dl)	1.07
eGFR (ml/min/1.73 m^2)	63
24h proteinuria (g/24h)	0.34
Addis sediment count Leukocytes (/min)	900
Addis sediment count RBCs (/min)	900
UACR (mg/g)	340

Abbreviation: UACR - urine albumin-creatinine ratio

A kidney biopsy was performed. Out of 13 glomeruli examined, the kidney biopsy depicted one glomerulus with segmental sclerosis and two with complete sclerosis. Minimal expansion of the mesangial matrix was detected, along with red blood cell casts, interstitial hemorrhage, rare atrophic tubules, and small areas of interstitial fibrosis. Immunofluorescence studies showed strong granular staining for IgM within the mesangial area and some minimal deposits of IgA, establishing the diagnosis of IgM nephropathy.

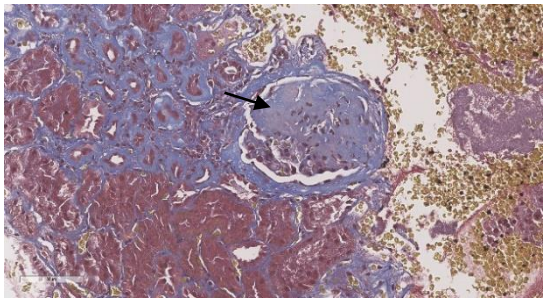

Fig. 1. Masson's trichrome showing segmental sclerosis

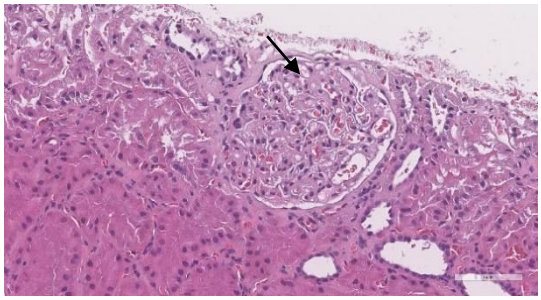

Fig. 2. Hematoxylin and eosin revealing minimal expansion of the mesangial matrix

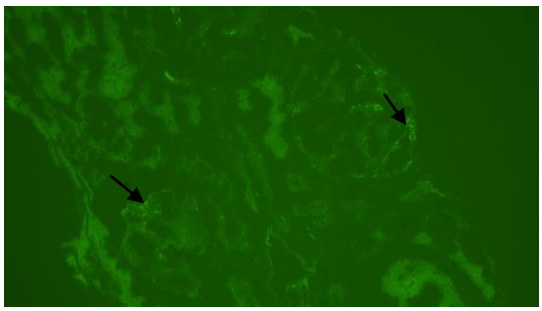

Fig. 3. Immunofluorescence with IgM deposits

There are no specific guidelines yet regarding the treatment of IgM nephropathy. The management of the case was to introduce an angiotensin 2 receptor blocker and a sodium-glucose cotransporter-2 inhibitor (SGLT2i) in order to control hypertension and elevated proteinuria. As recommended, the first approach to management is to treat the underlying pathology (which is not really feasible in this case with an unknown etiology) and then control risk factors for the progression of CKD, especially hypertension, which causes glomerular hyperfiltration and proteinuria [11]. Four months later, serum creatinine was 1.08 mg/dl, with proteinuria levels decreased to 0,26 g/24h. The urine albumin-creati-

nine ratio dwindled from 340 mg/g in August to 77 mg/g in December.

Apart from the antihypertensive effect, angiotensin 2 receptor blockers have a number of benefits. The renal vasodilatation they produce can help prevent renal ischemia and hypoxia; by lowering intraglomerular pressure, they lower urinary albumin excretion [12]. As for SGLT2i, the DAPA-CKD trial showed reduced albuminuria by 26% and a diminished risk by 71% of major adverse kidney events with dapagliflozin compared to the control group in patients with IgA nephropathy [13]. It has been demonstrated that SGLT2i, through increased delivery of sodium, chloride, and water to the macula densa, causes vasodilation in the afferent arterioles, reducing intraglomerular pressure and thus decreasing urinary protein excretion [13].

If the patient does not respond to the above treatment, other treatment options would be glucocorticoids and immunosuppressive agents. Studies have shown a mean resistance of 28% at corticosteroids, proving that IgM nephropathy has a less effective response to steroids than MCD (minimal change disease) [6]. Among the immunosuppressive agents, cyclosporine and anti-CD antibodies (rituximab) could constitute a treatment option. IgM nephropathy can also present as an immune complex-mediated crescentic GN, with nephrotic-range proteinuria, as reported by Park K *et al*., In such cases, much more aggressive treatment is needed, such as Rituximab [14].

Table 3. Laboratory parameters after treatment

Parameters	August	December
Creatinine (mg/dl)	1.07	1.08
eGFR (ml/min/1.73 m^2)	63	62
24h proteinuria (g/24h)	0.34	0.26
Stansfeld Webb -urine Leukocytes (/μL)		0
Stansfeld Webb -urine RBCs (/μL)		7.5
UACR (mg/g)	340	77

Discussion

Most cases of IgMN documented until now are associated with nephrotic syndrome, many of them resistant to steroids. However, this type of pathology may present with hematuria coupled with proteinuria, as is the case described above. The proteinuria level of our patient was not extremely high at presentation-1.1 g/24h-however it responded well to the antiproteinuric treatment, falling to 0.26 g/24h six months later. Another presentation is with hematuria as the only sign-described mainly in female patients [3].

In rare cases, IgM nephropathy can present with rapidly progressive glomerulonephritis (RPGN) as descrybed by Kazi and Mubarak in the case of an 11-year-old female who presented with sudden generalized body swelling, anorexia, and moderate hearing loss. Her blood and urinary tests revealed 1+ albumin, 15-20 white blood cells (WBCs)/HPF and 6-8 red blood cells (RBCs)/HPF, blood urea 198 mg/dL and serum createnine 4.5 mg/dL. She was treated with three pulses of methylprednisolone followed by oral steroids, her serum creatinine falling to 2.3 mg/dl [16].

Though the studies regarding IgM nephropathy treatment are not so many, Bagchi *et al*., studied the RAS (renin-angiotensin system) blockade with an ACEi (angiotensin-converting enzyme inhibitor) or an ARB (angiotensin receptor blocker) in IgMN with a follow-up of 6 months, to investigate on proteinuria remission. Remission was obtained in 36.5% of patients at 3 months and 55.2% at 6 months [15].

As for the natural history of the pathology, up to 25% of followed-up cases progressed to end stage renal disease (ESRD) [17]. It is also frequent for IgM nephropathy to develop in later stages into FSGS [6], as many repeated biopsies done in patients with worsening kidney function or recurrence of nephrotic syndrome had typical histological aspects of FSGS [14]. In the study done by Myllymäki *et al*., 36% of patients progressed to renal failure, 23% advanced to ESRD, and from the 35% with hypertension at the time of biopsy, the percentage rose up to 45% at the end of the study [6].

Wesphal S *et al*., describe the recurrence of nephrotic syndrome in a transplanted 15-year-old boy, with proteinuria levels at 20 g/L after three days and doubled values of serum creatinine from baseline. The treatment consisted of plasma exchanges, thymocyte globulin, steroids, and also a dose of rituximab. After 5 months, proteinuria was resolved, and the serum creatinine level normalized. [9]

Among histological data, Connor *et al*., identified glomerular sclerosis and tubular atrophy as factors contributing to kidney dysfunction, with focal segmental glomerulosclerosis present in 80% of individuals who underwent another kidney biopsy [10].

Conclusions

This report highlights a clinical and biological presentation of a primitive IgMN with a favorable response to a conservative therapy and no need for immunosuppressive treatment. This is particularly relevant given the heterogeneous case presentations described in the available literature.

Conflict of interest statement. None declared.

Reference

1. Vanikar A. IgM nephropathy; can we still ignore it. *J Nephropathol* 2013; 2: 98-103.
2. Zabaneh I, Bandak D, Thammineni V. IgM glomerulonephritis. *Biomedical Research and Clinical Practice* 2018; 3(2): 1-2.

3. Mokhtar G. IgM Nephropathy-Clinical Picture and Pathological Findings in 36 Patients. *Saudi Journal of Kidney Dis and Transpl* 2011; 22(5): 969-975.
4. Hsu H, Chen W, Lin G, *et al*. Clinical and immunopathologic study of mesangial IgM nephropathy: report of 41 cases. *Histopathology* 1984; 8: 435-446.
5. Mubarak M, Kazi JI. IgM nephropathy revisited. *Nephrourol Mon* 2012; 4: 603-608.
6. Myllymaki J, Saha H, Mustonen J. IgM nephropathy: Clinical picture and long-term prognosis. *Am Journ of Kid Dis* 2003; 41: 343-350.
7. PubMed Central. Available online: https://pmc.ncbinlm.nih.gov/articles/PMC3614302/#A2805R1.
8. Meyrier A, Radhakrishnan J. Minimal change disease: Etiology, clinical features, and diagnosis in adults. https://www.uptodate.com/contents/minimal-change-disease-etiology-clinical-features-and-diagnosis-in-adults?search=igm%20nephropathy&source=search_result&selectedTitle=1%7E7&usage_type=default&display_rank=1#H263816993.
9. Westphal S, Hansson S, Mjörnstedt L, *et al*. Early recurrence of nephrotic syndrome (immunoglobulin M nephropathy) after renal transplantation successfully treated with combinations of plasma exchanges, immunoglobulin, and rituximab. *Transplant Proc* 2006; 38: 2659-2660.
10. Connor TM, Aiello V, Griffith M, *et al*. The natural history of immunoglobulin M nephropathy in adults. *Nephrol Dial Transplant* 2017; 32: 823-829.
11. Burnier M, Lin S, Ruilope L, *et al*. Effect of angiotensin receptor blockers on blood pressure and renal function in patients with concomitant hypertension and chronic kidney disease: a systematic review and meta-analysis. *Blood Pressure* 2019; 28: 358-374.
12. Kobori H, Mori H, Masaki T, Nishiyama A. Angiotensin II Blockade and Renal Protection. *Curr Pharm Des* 2013; 19: 3033-3042.
13. Dong Y, Shi S, Liu L, *et al*. Effect of SGLT2 inhibitors on the proteinuria reduction in patients with IgA nephropathy. *Front Med (Lausanne)* 2023; 10: 1242241.
14. Park K, Kang E, Kie J. A case report of immunoglobulin M nephropathy manifesting as crescentic glomerulonephritis and nephrotic syndrome in an adult. *BMC Neph* 2019; 20: 335.
15. Bagchi S, Mani K, Swamy A, *et al*. Supportive Management of IgA Nephropathy With Renin-Angiotensin Blockade, the AIIMS Primary IgA Nephropathy Cohort (APPROACH) Study. *Kidney International Reports* 2021; 6: 1661-1668.
16. Mubarak M, Kazi JI. IgM nephropathy presenting as full blown crescentic glomerulonephritis: first report in the literature. *Nefrologia* 2014; 34: 423-424.
17. O'Donoghue DJ, Lawler W, Hunt LP, *et al*. IgM-associated primary diffuse mesangial proliferative glomerulonephritis: natural history and prognostic indicators. *Q J Med* 1991; 79: 333-350.