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Rituximab in IgM Nephropathy Resistant to Multiple Immunosuppressives: A Case Report

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Abstract **Case Report**

Immunoglobulin M (IgM) Nephropathy is a primary glomerulonephritis, characterized by predominant IgM deposition on direct immunofluorescence (DIF) microscopy. Long considered to be similar to minimal change disease (MCD) or focal segmental glomerulosclerosis (FSGS), it is now considered to be a separate entity with unique epidemiology, clinical presentation, biopsy findings, treatment response and prognosis. Although steroid is the first line treatment, there is a high degree of steroid resistance. Other immunosuppressive egents have not been quite effective. Rituximab is an emerging treatment option. We present a 40-year-old man with IgM Nephropathy in whom Rituximab proved to be a highly effective treatment.

Keywords: Immunoglobulin M (IgM), glomerulonephritis, direct immunofluorescence (DIF), epidemiology.

INTRODUCTION

IgM Nephropathy is a form of glomerulonephritis that was first described in 1978 [1]. Since then, there has been much debate regarding whether it should fall somewhere in between the MCD-FSGS spectrum or be considered as a separate entity [2]. Owing to its unique DIF findings, presentation, higher steroid resistance and worse prognosis compared to MCD or FSGS, it is now considered as a different disease [3]. No unifying guideline has been published so far regarding its management. Despite high chances of resistance, steroid still remains the first line treatment [4]. Other immunosuppressives have been tried with varying degrees of success [5]. In recent years, Rituximab has emerged as a promising treatment option [6]. Here we present a 40-year-old male with IgM Nephropathy, who was refractory to most immunosuppressives for several years and was successfully treated with Rituximab.

CASE REPORT

Mr. Fazlul Karim, a 40-year-old non-diabetic businessman, presented to us with a history of generalized swelling and hypertension for two years. He was diagnosed as a case of nephrotic syndrome one and a half years back based on a Urinary Total Protein (UTP) of 3.8 grams per day associated with bland urine and normal renal function.

Secondary causes of glomerulonephritis were excluded based on absence of relevant positive clinical features and negative laboratory investigations. He then underwent renal biopsy. Biopsy yielded 21 glomeruli, revealing mesangial proliferation and matrix expansion, with normal basement membrane and 1 segmental and 1 global sclerosis on light microscopy. DIF showed granular deposition of IgM in a focal and segmental pattern with 2+ intensity. A mesangial proliferative glomerulonephritis was the primary diagnosis suggested by the histopathologist, keeping FSGS as a differential. Correlating these biopsy findings with clinical presentation, a diagnosis of IgM Nephropathy was made.

He was started on high dose oral Prednisolone (1 mg/kg/day). It was continued for 10 weeks, but he failed to achieve remission. UTP remained at 2.5 g/day at the end of the course and steroid was gradually tapered over a period of 10 weeks. He was then put on

Mycophenolate Mofetil 1.5 g/day for 6 months. This treatment failed to achieve remission as well, UTP remaining at 3.5 g/day. After adequate counseling, oral Cyclophosphamide was started at 2 mg/kg/day. It was continued for 4 months, failing to achieve remission. Although he was co-prescribed antiproteinuric drugs as well over the course of these 15 months, UTP failed to fall to below 50% of the baseline values, rather went up to 9.7 g/day.

His renal function remained noraml during this period. He was explained that this unremitting proteinuria is a poor prognostic indicator and that most conventional, well studied treatment options were exhausted. The option of Rituximab was presented, since it showed promise in several studies.

After excluding possible underlying sub-clinical infections, 1 gram of IV Rituximab was administered, followed by another dose of 1 gram after 4 weeks. The patient did not appear to have any obvious side-effects with either of the 2 doses. During the first follow up after 2 weeks, his proteinuria came down to 2.5 gram per day from 9.7 gram per day, but went up to 4 gram per day before the next dose. After the second dose his proteinuria gradually came down to 0.6 gram per day and maintained at that level for the next year. Anti-proteinurics were continued and regular follow-ups were ensured.

DISCUSSION

Since it was first described in the literature in 1978, IgM nephropathy has not received much attention from researchers. An absence of a clear pathophysiological mechanism, wide variety in light microscopy features and lack of clear definition regarding the degree of IgM deposition on DIF may have played a role. Recent years have evidenced an increase in an interest and concurrent publications related to this topic [3]. A consensus definition, diagnostic criteria and management guideline are still lacking.

IgM Nephropathy is used to describe a specific form of glomerulonephritis, where there is predominant, usually isolated deposition if IgM, seen in DIF microscopy. The intensity of deposition varies widely among reported cases, ranging from 1+ to 3+. IgG, IgA, C3 and C1q depositions may coexist, usually in trace amount [5]. In our case, the intensity was 1+. The light microscopy features vary widely. Mesangial proliferation is found in most cases. Focal and segmental glomerulosclerosis, tubular atrophy, interstitial fibrosis and mild fibrointimal thickening of arteries may be seen [7]. Although our biopsy report showed 1 segmental sclerosis, among 21 glomeruli the mesangial proliferation predominated. Electron microscopy [8] usually shows fusion of foot process along with ill-defined electron dense deposits in the mesangial and para-mesangial area [9]. Since EM was not available at our center, we cannot report on that aspect.

IgM Nephropathy is seen more commonly in adolescents and young adults, but it can occur in any age group [4]. Familial predisposition has been reported in rare cases [10]. Nephrotic syndrome is the most frequent presentation. But coexistent or isolated hematuria is not uncommon. Hypertension is found in a selected minority at presentation, but its prevalence increases with the duration of the disease to reach 50% at 15 years [5, 7, 8, 11]. Rate of development of end stage kidney disease [12] was slow and varied widely between studies. One study reported 23% over a follow-up period of 15 years [5]. However, full-blown crescentic glomerulonephritis has also been reported [13, 14]. Hypertension and degree of proteinuria seemed to be the predictors of decline of renal function [5, 7, 11]. Our patient presented with nephrotic syndrome and hypertension. His renal function remained normal throughout the period of observation despite very high levels of proteinuria.

Despite high chances of resistance, steroid remains the cornerstone of management in IgM Nephropathy. Steroid resistance ranges from 25% to 66% across studies, which is higher than MCD or FSGS [2, 5, 7, 11]. Other immunosuppressives have been used, with varying effect. Cyclophosphamide, Cyclosporine and Mycophenolate Mofetil were some of them [5, 15, 16].

Rituximab has emerged as a promising treatment option in both childhood and adult nephrotic syndrome with good response and few side-effects [17, 18]. It has showed promise in both MCD and FSGS [19]. Since IgM Nephropathy is predominantly seen in childhood and young adults and has a higher steroid resistance, trial of Rituximab in these cases were justified. As in other cases of nephrotic syndrome, Rituximab has shown promising results in the treatment of IgM Nephropathy as well. There have been several reported cases where Rituximab was able to achieve and maintain long term remission [6, 16, 20]. It has also been used successfully in post-transplant recurrence of IgM nephropathy, along with plasma exchange [21, 22]. Usual dose was 1 gram intravenously 1 month apart, which was the same dose that we used in our patient. Although we did not achieve remission right away, his proteinuria gradually came down to 0.6 gram/day 6 months after 2nd dose of Rituximab. Now after 18 months, he is maintaining proteinuria around 0.5 gram/day with normal renal function. Considering his unremitting proteinuria of around 10 gram per day despite several immunosuppressives, we consider this a huge success.

CONCLUSION

IgM Nephropathy has been around for a long time now. Lack of proper guidelines makes it difficult

to diagnose and treat this condition. Studies so far have been largely observational. No randomized controlled trials (RCTs) have been designed so far to look into its treatment options. Rituximab has emerged as a promising treatment. Future RCTs should look into its role in IgM Nephropathy.

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