ISSN: 2584-0355
DOI: doi.org/10.51219/MCCRJ/Hatem-Alnasser/249

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Medical & Clinical Case Reports Journal

https://urfpublishers.com/journal/case-reports

Vol: 3 & Iss: 2

Case Report

Remission by Plasmapheresis, in IgM Nephropathy, Refractory to Other Treatments: A Rare and Challenging Case

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Citation: Alnasser H, Muneif YB, Asiri M. Remission by Plasmapheresis, in IgM Nephropathy, Refractory to Other Treatments: A Rare and Challenging Case. *Medi Clin Case Rep J* 2025;3(2):957-960. DOI: doi.org/10.51219/MCCRJ/Hatem-Alnasser/249

Received: 26 May, 2025; **Accepted:** 06 June, 2025; **Published:** 09 June, 2025

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ABSTRACT

We report the rare and challenging case of a 22-year-old male patient from Saudi Arabia, suffering from Immunoglobulin M nephropathy (IgMN) since the age of two years. He underwent several cycles of remission followed by relapse and remained refractory to almost all corticosteroid and immunosuppressant regimens. This patient could finally achieve a sustainable remission when plasmapheresis was added to his ongoing treatment. The current case prompts clinicians to consider plasmapheresis, as an adjunct to ongoing steroid and immunosuppressants, to help IgMN patients achieve sustainable remission, especially in cases that are refractory to conventional treatment alone. Past evidence has demonstrated that plasmapheresis has the potential to remove autoantibodies and other deleterious primary circulating factors. It has been reported to be efficacious in addition to conventional treatment, in the management of immunologic kidney diseases. Although plasmapheresis has the ability to remove IgM autoantibodies, its utility in IgMN treatment remains largely unexplored and warrants further large-scale studies.

Keywords: Immunoglobulin M nephropathy; Plasmapheresis; Remission; Steroid resistance; Immunosuppressants; Nephrotoxicity

Introduction

Immunoglobulin M nephropathy (IgMN) was first described in the 1970s, as a distinct clinical entity, characterized by diffuse deposits of immunoglobulin M (IgM) in the glomerular mesangium. However, the precise definition of IgMN remains unclear and controversial, ever since its first description[1].

Varying histological patterns of IgMN have been shown by light microscopy, ranging from complete absence of glomerular abnormality to mesangial hyperplasia and extracellular mesangial matrix of varying degrees, accompanied by segmental or complete glomerular sclerosis. Due to such a wide range of histological presentations, IgMN could not yet be established as a single clinical entity. Past evidence presents a divergent view on the histological classification of IgMN, some past studies support the idea that IgMN resembles minimal change disease (MCD) and focal and segmental glomerulosclerosis (FSGS), while others have considered IgMN as a transitional entity between these two disorders. To further compound the problem, there are no widely accepted set of diagnostic criteria for IgMN, evidence from clinical trials is scarce and scanty. In the absence of any clear-cut definition, classification, diagnostic criteria and clinical trial evidence; no wonder that researchers and clinicians are often reluctant to include IgMN in their differential diagnosis or even make a reference to it[1,2].

The uncertainty surrounding IgMN extends to its treatment approaches as well. Due to its idiopathic nature, varying pathogenesis and paucity of clinical trial data; no consensus has been achieved yet regarding a recommended treatment protocol. So far, corticosteroids have been the mainstay of treatment. Immunosuppressants like cyclophosphamide and rituximab have been employed with varying degrees of success. The clinical journey of a patient with IgMN typically comprises of periods of remission alternating with frequent recurrence and relapse[1,2].

We report the challenging and interesting case of a 22-year-old male patient from Saudi Arabia, suffering from IgMN since the age of two years. He underwent several cycles of remission followed by relapse and remained refractory to all steroids and immunosuppressants employed to treat him over several years. This patient could finally achieve a sustainable remission when plasmapheresis was added to his ongoing treatment. To the best of our knowledge, this is the first reported case of the use of adjunctive plasmapheresis in the treatment of IgMN, leading to a long-lasting remission.

Case Presentation

A 22-year-old male patient presented to the nephrology unit of our hospital, with a past history of steroid-dependent MCD. He was diagnosed with MCD at the age of two years and had a frequently-relapsing disease course till adulthood.

At the age of two years (August 2002), the MCD was managed with high-dose steroids and helped the patient remain in remission for the next two years. As the steroids were tapered and then discontinued two years later (July 2004), he had a relapse and was started on a 6 months course of cyclophosphamide in addition to steroids. This was followed by another course of cyclosporine and steroids. Remission was achieved again and the patient continued on a tapering dose of steroids.

During a clinic visit in May 2006, he was challenged with stopping cyclosporine for three months while maintaining on a small dose of steroids (5 mg every other day). However, three months later, he had a relapse and restarted on cyclosporine and steroids, again achieving remission for 3 years. While remaining on the same medications, he had another relapse. He was started on rituximab, of which he received five doses and continued on the previous regimen of cyclosporine 100 mg twice daily and steroid 40 mg daily. The initial plan was to keep him on rituximab therapy every 6 months, however he continued on it for another 3 years. Throughout this period, he was on remission and his medications included cyclosporine, steroids and rituximab every six months.

In April 2014, he experienced another relapse, prompting the switch of cyclosporin to tacrolimus 4mg twice daily; however, remission was not achieved. In June 2015 mycophenolate mofetil (MMF) 750 mg BID was added. He was maintained on a regimen of MMF, Tacrolimus, steroids, the last dose of rituximab (10th dose) and lisinopril, resulting in the achievement of remission.

Around six months later, as he experienced another relapse in January 2016, it was decided to repeat the kidney biopsy, however, it showed no significant pathology under light microscopy. Occasional glomeruli showed minimal mesangial proliferation. Immunofluorescence studies showed IgM 2+diffuse mesangial positivity. Based on these findings, the diagnosis of IgM nephropathy was made with mild acute tubular injury (Tubular atrophy and interstitial fibrosis, [IF/TA]: less than 10%).

Eight months later, in September 2016 he experienced another relapse while on MMF, tacrolimus and prednisolone. He was managed with increasing the dose of prednisolone to 80 mg daily, continued on tacrolimus and given a total of six doses of rituximab. Despite this regime, complete remission was achieved four years later, in October 2020, when was seen in the clinic and was continued on a tapering dose of steroids and tacrolimus.

In April 2021 he experienced a relapse again. At this juncture, the renal biopsy was repeated again, as his relapse persisted for six months, along with 9 gm of proteinuria per day. The biopsy revealed focal podocytopathy, interstitial fibrosis and tubular atrophy involving approximately 35% of the sampled cortex. Along with negative immunofluorescence, the features resembled FSGS (tip variant). Hence, it was resolved to stop tacrolimus, as he was unresponsive to the drug with a risk of increasing nephrotoxicity. He was continued on high dose steroid and received a single dose of rituximab. In spite of this, the patient could not achieve remission and hence, in November 2021, he was admitted again. He received two doses of cyclophosphamide, 1 gm each. In addition to the drug therapy, he also received 10 sessions of plasmapheresis, five sessions each in November and December 2021. Concurrently, he was started on dapagliflozin 10 mg daily, azathioprine 100 mg BID and continued on oral steroid 20 mg every alternate day. The patient could achieve remission within 10 days of undergoing the plasmapheresis.

In November 2022, during a clinic visit, he was on remission for more than 12 months, with proteinuria of 1.3 gram per day. He was receiving azathioprine 150 mg daily, prednisolone 10 mg every alternate day, lisinopril 10 mg and dapagliflozin 10 mg. The patient's last follow-up visit was in November 2023 and the remission obtained with the addition of plasmapheresis was yet sustained.

Discussion

IgMN presents quite a complex clinical conundrum. Though it was first described in the 1970s, the medical fraternity yet does not have a universally approved clinical and histopathological definition of this disorder. Whether or not it can be considered as a distinct stand-alone clinical entity or is part of a larger cluster of disorders like MCD and FSGS, has also long been a matter of debate. The etiology, pathogenesis, natural history of progression and prognostic factors of the disease have also not yet been clearly understood. Moreover, no globally accepted clinical guidelines have been promulgated to streamline the diagnosis and treatment protocol for this disorder. Evidence from clinical trials and published literature is sparse and scanty. Clinicians often hesitate to include it in their differential diagnoses, most likely due to the multiple uncertainties surrounding this disorder[1,2]. Hence, we believe, that it is imperative to report cases like ours, to help clinicians understand the clinical journey of patients with IgMN and the treatment modalities that can be explored. This, we believe, will help plug the existing evidence gap on this subject. The history of multiple remissions and relapses experienced by our patient and the use of multiple drug therapies, over several years, adds to the rarity of this case.

The existing knowledge deficits in understanding the etiopathogenesis of IgMN and the lack of evidence regarding the disease, have in turn, limited the treatment options available. So far, only corticosteroids have largely remained the most frequently employed treatment of IgMN. However, the use of corticosteroids comes with its own systemic adverse effects and contraindications. Past studies have reported a response rate ranging between 20%-30%, with the use of corticosteroids. The use of steroids is further complicated by the need for tapering and the need to intermittently pause the steroids to reduce their toxicity. The chances of relapse and recurrence are increased during these periods of tapering and pause, as evident by the many relapses suffered by our patient[2-4].

Due to the autoimmune nature of IgMN, immunosuppressants have also been frequently used in its treatment, albeit with varying degrees of success. Available clinical data is insufficient to support the use and response rates of immunosuppressants in IgMN. Past studies have described the use of oral cyclophosphamide with response rates reaching up to a maximum of 50%. Cyclophosphamide resistance has also been a frequent problem that further complicates the use of this agent. On the other hand, data regarding the use of cyclosporine is also scanty and insufficient, with only a handful of studies reporting its use[2]. Tacrolimus and rituximab have been employed in a few studies, with good short-term results. However, the use of these immunosuppressive agents too, has been limited due to their nephrotoxicity in the long run[5-7]. In the case of our patient too, we did achieve short-term remissions with rituximab and tacrolimus.

Finally, our patient started suffering from tacrolimus-induced nephrotoxicity and relapsed in spite of receiving rituximab. At this juncture, we realized that throughout his clinical journey, ever since his first diagnosis of IgMN in 2002, he had been exposed to almost all available therapeutic drugs including steroids and different immunosuppressants. Despite this, he had repeatedly relapsed. This clearly implied that he was refractory to most drug therapies and the situation presented a need to consider additional or complementary modalities of treatment, in order to improve his prognosis. Hence, we chose to add plasmapheresis to his ongoing drug treatment.

Plasmapheresis has been employed for treating a wide variety of disorders, especially autoimmune diseases. It involves extracorporeal removal of plasma from other components of blood, followed by discarding and replacing plasma with physiological fluids. It targets removal of high molecular weight substances, reduces the concentration of target molecules, thereby providing a therapeutic window for drugs to act. It is an optimal choice if the pathogenic substance cannot be removed by routine therapy, requires rapid removal has a relatively long half-life, undergoes slow re-synthesis and has intravascular distribution. Therefore, ever since its introduction in 1952, plasmapheresis has been used as an adjunct to standard care, in the clinical management of various disorders, with appreciable safety and efficacy[8].

The underlying rationale for this use has been that plasmapheresis has the potential to remove autoantibodies and any deleterious primary circulating factors that could be responsible for the disease. Plasmapheresis has been reported to be efficacious in addition to immunosuppressive drugs, in the management of immunologic kidney diseases, since the 1970s. It has been employed in a variety of renal diseases in which there is evidence for the role of circulating factors such as autoantibodies or immune complexes in pathogenesis. Past evidence favors the use of plasmapheresis, as an adjunct to drug treatment, in the management of FSGS. Previous reports also highlight successful use of plasmapheresis in the treatment of MCD[8-11].

Our patient who was refractory to multiple drug combinations earlier, could achieve a long and sustained remission with the addition of plasmapheresis, to his ongoing regime of steroids and immunosuppressants. His proteinuria had stabilized, with no signs of relapse or recurrence. While plasmapheresis has been incorporated in the treatment of different types of immunological nephropathies, it has not yet been employed widely for IgMN, although the features of plasmapheresis are applicable to the removal of IgM autoantibodies, along with IgG and other immune complexes[8].

As evident from the case presented here, the patient who was refractory to multiple drug combinations and relapsed multiple times, could finally achieve a sustainable remission with ten rounds of plasmapheresis being added to his standard drug regime. To the best of our knowledge, this is the first such case of remission achieved by plasmapheresis in a patient of IgMN, especially from Saudi Arabia. We believe this case will prompt clinicians to include adjunctive plasmapheresis as a modality in the treatment plan for IgMN patients, especially those who are refractory to ongoing drug regimens. We opine that large scale controlled clinical studies should be conducted to establish the clinical utility and benefit of adjunctive plasmapheresis, in the treatment of IgMN. This will help widen the currently limited treatment options of this rather neglected and poorly understood autoimmune disorder.

Conclusion

Plasmapheresis has been previously used as an adjunct to drug therapy in the management of immunologic kidney disease; however, its use has not yet been extended to patients of IgMN. The current case report shows that addition of plasmapheresis to ongoing steroid and immunosuppressive treatment, can help IgMN patients achieve sustainable remission, even in cases that are refractory to conventional treatment alone.

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