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Case Report

Idiopathic Immune Complex-Mediated Membranoproliferative Glomerulonephritis: A Significant Cause of End-Stage Kidney Disease in Children

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Abstract

Introduction: Membranoproliferative glomerulonephritis (MPGN) is a significant cause of glomerulopathy and chronic kidney disease (CKD) or end-stage renal disease (ESRD) in children. The deposition of circulating immune complexes in the glomerulus and abnormal activation of the alternative complement pathway is believed to trigger the disease. However, there is limited knowledge regarding the optimal treatment and prognosis for children with immune complex-associated MPGN (IC-MPGN) and C3 glomerulopathy (C3G).

Case report: We report the case of a 14-year-old child admitted for rapidly progressive glomerulonephritis with anuria managed on haemodialysis. The kidney biopsy showed an appearance compatible with MPGN on light microscopy, with immunoglobulin and complement C3 deposits on direct immunofluorescence. The prognosis was poor, with rapid progression to ESRD despite treatment combining corticosteroid therapy and immunosuppressants.

Discussion and conclusion: Evaluating the effectiveness of different therapeutic approaches for MPGN in children is challenging due to the small sample sizes and the short duration of the published controlled studies. As a result, it is crucial to conduct more comprehensive trials that focus on both prognosis and treatment options.

More Information

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Keywords: Membranoproliferative glomerulonephritis; Chronic Kidney disease; Children

Abbreviations: ANCA: Anti Neutrophil Cytoplasmic Antigen; CKD: Chronic Kidney Disease; C3G: C3-glomerulopathy; C3GN: C3 Glomerulonephritis; DDD: Dense Deposit Disease; ESRD: End-Stage Kidney Disease; IC-MPGN: Immune-Complex-Membranoproliferative Glomerulonephritis; Ig-A: Immunoglobulin A; Ig-G: Immunoglobulin G; ISKDC: International Study of Kidney Disease in Children; MPGN: Membranoproliferative Glomerulonephritis

Introduction

Membranoproliferative glomerulonephritis (MPGN) is a type of glomerular damage marked by pathological features such as mesangial interposition and double contours of the capillary wall [1]. The diagnosis is confirmed through immunofluorescence imaging. Following this, patients with predominantly IgG staining were reclassified as having immune-complex MPGN (IC-MPGN), whereas those with dominant C3 deposition were reclassified as having C3 glomerulopathy (C3G) [2,3]. IC-MPGN typically manifests in children and young adults [4,5], although it can develop at any age [6,7]. Affected individuals have an estimated 9% to 41% risk of developing kidney disease within 10 years and face a significant risk of recurrence following kidney transplantation, with a reported recurrence rate of 43% [8,9].

We illustrate the case of a child from southern Morocco, in whom chronic end-stage kidney disease was secondary to immune-complex MPGN after a kidney biopsy.

Patient and observation

This concerns a 14-year-old child with a medical history devoid of notable incidents, admitted for severe kidney acute discovered during the biological test results when he presented with vomiting, diarrhoea, and an oedematous syndrome that had been evolving for 10 days, associated with anuria for 48 hours.

Upon admission, the clinical examination identified a conscious patient presenting with hypertension at 160/85 mmHg. Respiratory status remained stable, with anuria, lower limb oedemas and there were no signs of delayed growth and weight. The urinary sediment exhibited active glomerular proteinuria and microscopic hematuria.

Biologically, we observed a rapidly progressive glomerulonephritis with a serum creatinine level rising from 4 mg/dL to 11.5 mg/dL and then to 16,1 mg/dL [0,6 - 1,2 mg/dL], over a 96-hour period, along with a 24-hour proteinuria of 19 g/24h. The rest of the biological assessment showed an imbalance in the phosphocalcic profile, characterized by hypocalcemia at 64 mg/L [85 - 100 mg/L], hyperphosphatemia at 96 mg/L [25 - 45 mg/L], secondary hyperparathyroidism at 235 pg/mL [13 - 65 pg/mL], normochromic normocytic anemia and C3 hypocomplementemia.

Given the normal-sized kidneys on kidney ultrasound with good cortico-medullary differentiation, a kidney biopsy was performed. Optical microscopy showed features compatible with membranoproliferative glomerulonephritis with significant tubulointerstitial involvement (Figure 1). Direct immunofluorescence revealed mesangial deposits of immunoglobulin A (IgA), G (IgG), and complement C3 (Figure 2).

As part of the etiological investigation of immune-complex MPGN, the entire requested assessment, including the immunological workup (antinuclear antibodies, anti-DNA antibodies, Anti Neutrophil Cytoplasmic Antigen (ANCA), anti-GBM antibodies), serological testing (HIV, Hepatitis B, Hepatitis C, syphilis), infectious workup (C-reactive protein, procalcitonin, urine cytobacteriological examination, abdominal-pelvic CT scan, transthoracic ultrasound), and liver function tests, showed no abnormalities.

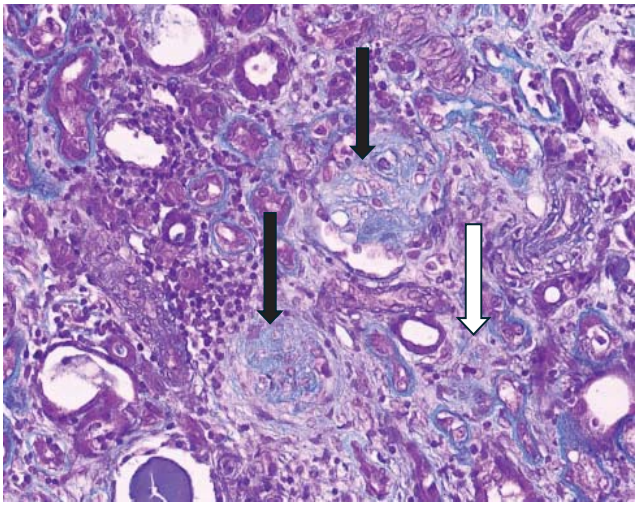

Figure 1: Fragment of renal parenchyma, in optical microscopy stained with Masson's Trichrome, showing a morphological aspect compatible with membranoproliferative glomerulonephritis (black arrows) with significant tubulointerstitial involvement (white arrow). (× 400).

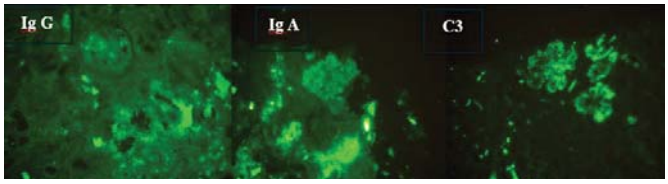

Figure 2: Direct immunofluorescence revealed mesangial deposits of immunoglobulin A (IgA), G (IgG), and complement C3 (× 400).

The management involved urgent initiation of haemodialysis due to this severe presentation, along with the introduction of corticosteroids and immunosuppressants based on cyclophosphamide, combined with close monitoring of urine output and renal function. The progression was marked, one month later, by the absence of urine output recovery and no improvement in the serum creatinine level.

The diagnosis of End-Stage Chronic Kidney disease secondary to Idiopathic Immune-Complex MPGN was confirmed, and our patient was managed with chronic haemodialysis and registered on the waiting list for potential kidney transplantation.

Discussion

Membranoproliferative glomerulonephritis (MPGN) can be categorized into immune-complex MPGN (IC-MPGN) and C3 glomerulopathy (C3G), which encompasses dense deposit disease (DDD) and C3 glomerulonephritis (C3GN). These conditions arise from abnormalities in distinct complement pathways and may result in varying prognoses. However, there is a lack of extensive studies outlining the specific clinical courses of these conditions [10].

The pathophysiological mechanisms of MPGN remain poorly understood. IC-MPGN is believed to result from the formation of antigen-antibody immune complexes, which activate the classical complement pathway in the presence of persistent antigenemia [11]. In adults with IC-MPGN, the most commonly identified antigens are associated with infections, autoimmune diseases, or monoclonal gammopathies [11]. However, in children, antigenemia in IC-MPGN is most often idiopathic [12].

In contrast, C3G is a disorder characterized by primary dysregulation of the alternative complement pathway. The constant activation of the alternative complement cascade results from impaired regulatory mechanisms, ultimately leading to the downstream activation of the terminal complement cascade and the formation of the membrane attack complex.

Membranoproliferative glomerulonephritis primarily affects children and young adults, with no particular sex preference. In children, MPGN is often idiopathic, whereas in adults, it is commonly associated with cryoglobulinemia and HCV infection. Patients with MPGN may present in one of four ways: nephrotic syndrome (40% - 70%), acute nephritic syndrome (20% - 30%), asymptomatic proteinuria and hematuria detected through routine urinalysis (20% - 30%), or recurrent episodes of gross hematuria (10% - 20%) [13].

The definitive diagnosis of MPGN is made through a kidney biopsy. Morphologically, MPGN is characterized by diffuse proliferation of mesangial cells and thickening of the capillary walls, which occurs due to the subendothelial

extension of the mesangium. This is why it is also referred to as "mesangiocapillary glomerulonephritis" [13].

The effectiveness of various therapeutic regimens for MPGN in children is challenging to assess due to the small sample sizes and the short duration of published controlled trials. Additionally, the larger studies conducted so far have been uncontrolled [14]. Moreover, most trials include patients with both types of MPGN in varying proportions, which complicates the analysis of treatment outcomes. Treatment strategies for idiopathic MPGN remain controversial and have included corticosteroids, immunosuppressive drugs, antiplatelet therapies, plasma exchange, and biologic agents.

Both retrospective and prospective studies have shown the beneficial effect of alternate-day steroid therapy on renal survival in pediatric patients with MPGN. Among these, a prospective, multicenter, randomized trial was conducted by the International Study of Kidney Disease in Children (ISKDC) [15]. In one study, 19 pediatric and adult patients with MPGN were treated with an intensive and prolonged regimen of pulse methylprednisolone plus oral prednisone and cyclophosphamide. Of these 19 patients, 15 achieved complete remission, and three achieved partial remission. Based on these findings, the researchers concluded that cyclophosphamide is effective in inducing remission and preventing the progression of MPGN to ESRD. However, in our case, the progression of renal function following the administration of corticosteroids and cyclophosphamide was unfavorable [16].

Iptacopan (LNP023) is an oral, groundbreaking medication that acts as a potent inhibitor of the proximal complement pathway. It specifically targets and binds to factor B, effectively blocking the alternative pathway (AP) (Figure 3) [17]. By inhibiting factor B, iptacopan disrupts the activity of the AP-related C3 convertase, preventing the subsequent formation of the C5 convertase. While it does not interfere with the activation of the classical or lectin pathways, iptacopan does hinder its ability to recruit the AP amplification loop. Clinical trials have demonstrated that iptacopan is well-tolerated in first-in-human studies [18,19].

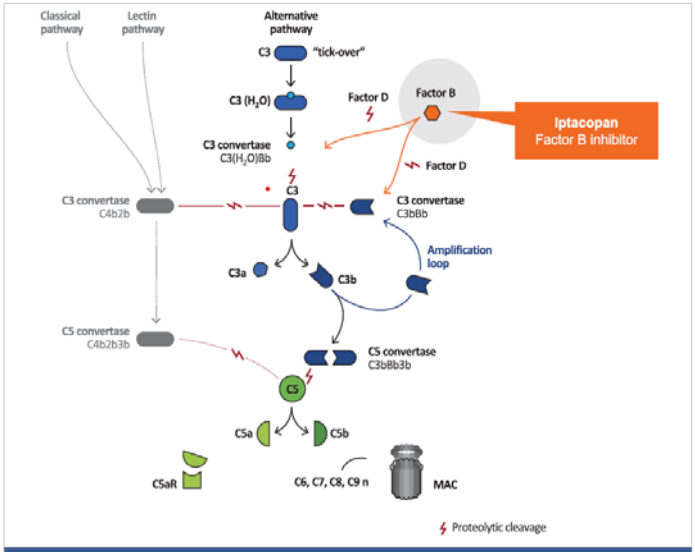

Figure 3: Targeting complement in IC-MPGN. Iptacopan, a factor B inhibitor, specifically binds to factor B and efficiently blocks the alternative pathway [17].

The prognosis of MPGN in children is generally poor, with a high frequency of progression to chronic renal failure, even after kidney transplantation. A study involving pediatric patients with C3G or IC-MPGN revealed a high risk of disease recurrence post-transplant (55%) and significantly lower 5-year graft survival compared to matched controls with other primary kidney diseases. These findings highlight the need for effective and specific post-transplant therapies that target the underlying disease mechanisms [20].

Conclusion

In summary, in the light of our clinical case, we have found that pediatric patients with IC-MPGN appear to have a poor prognosis and progression to advanced CKD appears to be notable in children. This underscores the importance of early diagnosis through immediate renal biopsy to initiate appropriate treatment and improve renal prognosis. Further studies appear necessary to better understand the pathophysiology of MPGN in order to establish universal management strategies for children.

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Patient consent statement

For the purpose of scientific research, I freely consent to the use of my personal and clinical data by the editorial team to publish this case report in your journal.

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