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Case Report

Real-World Experience with Iptacopan Treatment in a Case of C3 Glomerulonephritis in a Native Kidney

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Introduction

C3 glomerulopathy (C3G) is an ultra-rare kidney disease caused by dysfunction of the alternative complment pathway. The prognosis of this glomerular disorder is very poor, with up to 50% of patients requiring renal replacement therapy within 10 years of diagnosis [1, 2].

Therapeutic approaches employed in clinical practice to date have not conclusively demonstrated a significant modification in the natural course of the disease. Immunosuppressive therapy with corticosteroids (CS) and mycophenolate mofetil (MMF) has been proposed. However, the evidence supporting its efficacy is limited and restricted to specific patient subgroups [3, 4]. Other agents targeting the terminal complement pathway, such as eculizumab or avacopan, have likewise failed to yield encouraging results [5-7].

Novel inhibitors acting at more proximal levels of the complement cascade appear to offer new hope for this form of glomerulopathy [8]. In particular, Iptacopan, an oral Factor B inhibitor, has shown promising results for C3G in both phase II and phase III clinical trials [9, 11]. This drug has been recently approved for the treatment of C3G. However, real-world evidence in this setting remains scarce and is mainly limited to reports of recurrent C3G in kidney transplantation [12,13].

Case Presentation

We report the case of a 59-year-old woman with C3G in a native kidney. Informed consent was obtained from the patient, authorizing the anonymized disclosure of her clinical data. The diagnosis was established by renal biopsy in November 2023.

Light microscopy revealed a morphological pattern consistent with membranoproliferative glomerulonephritis. Immunofluorescence studies demonstrated intense and exclusive C3 deposition. No deposits of light chains or immunoglobulins were detected by direct immunofluorescence or following enzymatic digestion.

Electron microscopy confirmed these findings, showing basement membrane reduplication without evidence of deposits suggestive of dense deposit disease (Figure 1).

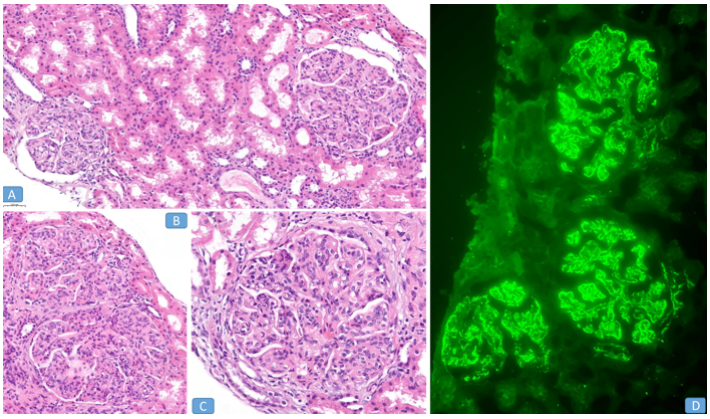

Figure 1: Renal biopsy: A) Renal glomeruli (5x) showing global and diffuse glomerular involvement with isolated interstitial lymphocytic infiltrate, without interstitial fibrosis or tubular atrophy. **B and C)** Renal glomeruli (20x and 40x) with a membranoproliferative pattern: glomerular lobulation, mesangial and endocapillary hypercellularity, glomerular basement membrane thickening with areas of splitting, and focal neutrophilic infiltration. **D)** Direct immunofluorescence (5x) for C3 showing mesangial and glomerular basement membrane deposition with focal involvement of Bowman's capsule.

The patient had no concurrent infections. Serum C3 was reduced (60–70 mg/dL), while the remainder of the immunologic work-up including monoclonal gammopathy screening (serum and urine electrophoresis and immunofixation) and serum free light chains was unremarkable. Complement functional and genetic testing excluded nephritic factors or other relevant abnormalities. By late February 2024, despite therapy with an angiotensin receptor blocker and an SGLT2 inhibitor, she exhibited proteinuria of 3.5 g/day, microhematuria (40 RBCs/HPF), serum creatinine 1.2 mg/dL, and an eGFR of 50 mL/min/1.73 m². Immunosuppressive therapy with prednisone and mycophenolate mofetil (MMF) was initiated; MMF was discontinued after three doses due to gastrointestinal intolerance, and treatment with Iptacopan 200 mg every 12 hours was started under compassionate use (Novartis).

Treatment response was excellent, with progressive reduction of proteinuria, ultimately achieving complete remission of proteinuria and albuminuria at 15 months. Microhematuria resolved, C3 normalized, and eGFR remained stable at 47 mL/min/1.73 m² (May 2025). No drug-related adverse events occurred during follow-up. (Figure 2, 3)

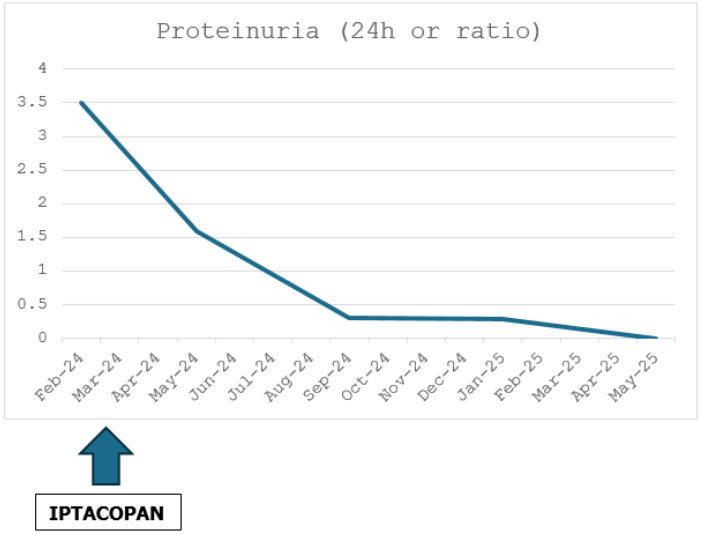

Figure 2: Proteinuria progression

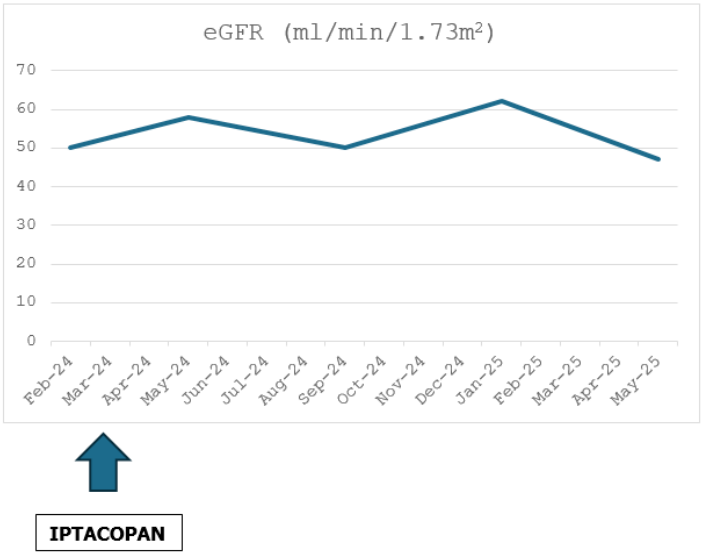

Figure 3: Estimated glomerular filtration rate (eGFR) progression.

Discussion

This is the first documented case in the literature of a patient with C3 glomerulopathy (C3G) in a native kidney treated with Iptacopan in a real-world clinical setting. The favorable response ob-

served in our patient adds to the emerging evidence on the efficacy of Iptacopan in C3G, previously demonstrated in clinical trials and in the few real-world cases reported, which have mainly focused on disease recurrence after kidney transplantation [9-13] .These findings further support the central role of the alternative complement pathway in C3G pathophysiology.

A phase 2 clinical trial, which included both patients with native kidney C3G (n = 16) and patients with post-transplant recurrence (n = 11), demonstrated a significant reduction in proteinuria at week 12 of treatment in the native kidney group, as well as a marked decrease in histologic C3 deposits by day 84 in transplant recurrence cases. Additionally, most treated patients showed normalization of serum C3 levels.9 Results from the 12-month extension study confirmed these findings and further demonstrated a significant improvement in eGFR in the native kidney cohort [10].

Preliminary results from the phase 3 APPEAR-C3G trial are consistent with the phase 2 findings. Among 43 patients who completed 12 months of treatment (out of 74 total), the 22 patients receiving Iptacopan achieved a 35% reduction in proteinuria compared with 21 patients receiving placebo ($p < 0.0014$). Additionally, 43% of treated patients met the study's primary endpoint: a ≥50% reduction in proteinuria with a decline in eGFR of no more than 15% at 12 months of follow-up [11].

To date, no real-world cases of Iptacopan use in patients with native kidney C3G have been reported. Only three clinical cases in kidney transplant recipients with recurrent C3G have been documented. Two of these were severe cases requiring renal replacement therapy. Nevertheless, all patients demonstrated a favorable renal response to Iptacopan, both clinically and histopathologically [12,13].

In our patient, the drug was well tolerated, and no treatment-related adverse events were observed, consistent with prior literature. Most adverse events associated with Iptacopan in this patient population have been mild to moderate. More severe adverse events have primarily been reported in kidney transplant recipients, likely related to concomitant immunosuppressive therapy required in that setting.

In conclusion, we report the first case of native kidney C3G treated with Iptacopan in a real-world clinical setting, achieving an excellent treatment response with clinical remission after 15 months of follow-up. This case provides additional real-world evidence of the positive impact of Iptacopan on C3G prognosis and further highlights the key role of the alternative complement pathway in its pathogenesis.

Conflict of Interest: AH has received consulting fees from Novartis and Sobi, as well as honoraria for scientific lectures from AstraZeneca. This article was prepared independently and is not related to the activities mentioned above. MM has received honoraria for teaching, training, and/or scientific advisory roles from Alexion, Amgen, AstraZeneca, Bayer, Boehringer Ingelheim, CSL Vifor, Esteve, GSK, Janssen Cilag, Mundipharma, Novartis, and Novo Nordisk.

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