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HCV-Related Cryoglobulinaemic Glomerulonephritis with Sustained Improvement in Renal Function after Combined Therapy

Glomerulonefrite Crioglobulinémica Associada ao VHC com Melhoria Sustentada da Função Renal após Terapêutica Combinada

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ABSTRACT

Introduction: Hepatitis C virus (HCV) infection remains a leading cause of secondary immune complex-mediated membranoproliferative glomerulonephritis (MPGN). Despite the efficacy of direct-acting antivirals (DAAs), severe cryoglobulinemic glomerulonephritis may require immunosuppression for rapid control of immune-mediated kidney injury. The optimal integration and timing of antiviral and immunosuppressive treatment remain clinically challenging.

Case Presentation: A 51-year-old man with chronic HCV infection presented with rapidly progressive kidney dysfunction, nephrotic-range proteinuria, microscopic haematuria, hypertension, arthralgia, and palpable purpura. Kidney biopsy showed diffuse MPGN with endocapillary proliferation, crescent formation, dominant IgM and C3 deposition, and subendothelial electron-dense deposits, consistent with HCV-associated cryoglobulinemic glomerulonephritis. Owing to the severity of renal involvement, high-dose intravenous methylprednisolone and rituximab were initiated, followed by an 8-week course of glecaprevir/pibrentasvir. The patient achieved sustained virological response, rapid improvement in kidney function, and a marked reduction in proteinuria, with stable serum creatinine (1.17 mg/dL) and a urine protein-to-creatinine ratio of approximately 1.0 g/g after one year of follow-up. Circulating cryoglobulins remained detectable despite sustained clinical and renal improvement.

Conclusion: This case supports a severity-based therapeutic approach to HCV-associated cryoglobulinemic glomerulonephritis. In patients presenting with rapidly progressive kidney injury and severe immune-mediated disease, early combined immunosuppressive and antiviral therapy may achieve sustained virological response while preserving kidney function. Persistent cryoglobulin positivity after viral eradication does not necessarily indicate treatment failure when accompanied by sustained clinical improvement.

Keywords: Hepatitis C virus; Cryoglobulinaemia; Membranoproliferative glomerulonephritis; Rituximab; Direct-acting antivirals; Kidney biopsy.

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RESUMO

Introdução: A infeção pelo vírus da hepatite C (VHC) continua a ser uma das principais causas de glomerulonefrite membranoproliferativa secundária mediada por imunocomplexos. Apesar da eficácia dos antivirais de ação direta, a glomerulonefrite crioglobulinémica grave pode requerer imunossupressão para o controlo rápido da lesão renal imunomediada. A integração e o momento ideais da terapêutica antiviral e imunossupressora permanecem um desafio clínico.

Descrição do Caso: Homem de 51 anos, com infeção crónica pelo VHC, apresentou deterioração rapidamente progressiva da função renal, proteinúria em intervalo nefrótico, hematúria microscópica, hipertensão arterial, artralgias e púrpura palpável. A biópsia renal revelou glomerulonefrite membranoproliferativa difusa, com proliferação endocapilar, formação de crescentes, depósitos predominantes de IgM e C3 e depósitos subendoteliais eletrodensos, compatível com glomerulonefrite crioglobulinémica associada ao VHC. Perante a gravidade do envolvimento renal, iniciou terapêutica com metilprednisolona em altas doses e rituximab, seguida de um esquema de oito semanas com glecaprevir/pibrentasvir. O doente atingiu resposta virológica sustentada, com melhoria rápida da função renal e redução significativa da proteinúria, mantendo creatinina sérica de 1,17 mg/dL e rácio proteína/creatinina urinária de aproximadamente 1 g/g após um ano de seguimento. As crioglobulinas permaneceram detetáveis apesar da resposta clínica e renal sustentada.

Conclusão: Este caso apoia uma abordagem terapêutica baseada na gravidade clínica da glomerulonefrite crioglobulinémica associada ao VHC. Nos doentes com lesão renal rapidamente progressiva e doença imunomediada grave, a associação precoce de terapêutica imunossupressora e antiviral pode permitir a obtenção de resposta virológica sustentada e preservar a função renal. A persistência de crioglobulinas após a erradicação viral não indica necessariamente falência terapêutica quando acompanhada de melhoria clínica sustentada.

Palavras-Chave: Vírus da hepatite C; Crioglobulinemia; Glomerulonefrite membranoproliferativa; Rituximab; Antivirais de ação direta; Biópsia renal.

Introduction

Membranoproliferative glomerulonephritis (MPGN) is a histopathological pattern of glomerular injury characterised by mesangial hypercellularity, endocapillary proliferation, mesangial interposition, and duplication of the glomerular basement membrane. Rather than representing a single disease entity, MPGN encompasses a heterogeneous group of disorders currently classified according to the underlying pathogenic mechanism into immune complex-mediated and complement-mediated forms. Chronic hepatitis C virus (HCV) infection remains a leading cause of secondary immune complex-mediated MPGN worldwide and is most frequently associated with mixed cryoglobulinaemia[1–3].

Mixed cryoglobulinaemia represents the most common extrahepatic manifestation of chronic HCV infection and results from persistent stimulation of B lymphocytes by viral antigens, leading to the production of circulating cryoglobulins, rheumatoid factor, and immune complexes. Deposition of these complexes within small vessels and glomerular capillaries activates the classical complement pathway, promoting endothelial injury and the characteristic clinicopathological features of cryoglobulinemic glomerulonephritis. Renal involvement develops in approximately 20.0-–35.0% of patients with mixed cryoglobulinaemia and is associated with a poorer renal and overall prognosis.

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Patients may present with microscopic haematuria, proteinuria, hypertension, nephrotic syndrome, or rapidly progressive kidney dysfunction, frequently accompanied by systemic manifestations such as palpable purpura, arthralgia, peripheral neuropathy, and fatigue[2–4].

The introduction of direct-acting antivirals (DAAs) has transformed the management of chronic HCV infection, with sustained virological response rates at week 12 exceeding 95.0% and a substantial reduction in hepatic and extrahepatic complications. Nevertheless, viral eradication does not invariably translate into immediate immunological remission. Persistent B-cell clonal expansion and continued production of pathogenic immune complexes may sustain cryoglobulinemic vasculitis and glomerular injury despite successful clearance of HCV. Consequently, patients presenting with severe renal disease, including rapidly progressive glomerulonephritis, nephrotic-range proteinuria, or life-threatening systemic vasculitis, frequently require immunosuppressive therapy in addition to antiviral treatment[5–7].

Current Kidney Disease: Improving Global Outcomes (KDIGO) guidelines recommend a severity-based therapeutic approach for HCV-associated glomerular disease. Patients with stable kidney function and mild urinary abnormalities may respond to antiviral therapy alone, whereas those with severe cryoglobulinemic glomerulonephritis should receive combined treatment with direct-acting antivirals and immunosuppressive therapy, with or without plasma exchange, depending on the clinical presentation. Rituximab has become the preferred immunomodulatory agent because of its efficacy in controlling B-cell-mediated immune activation and its favourable safety profile compared with conventional cytotoxic therapy[6].

We report a case of severe HCV-associated cryoglobulinemic membranoproliferative glomerulonephritis presenting with rapidly progressive kidney dysfunction, nephrotic-range proteinuria, and crescent formation on kidney biopsy. The case illustrates the diagnostic challenges and therapeutic decision-making involved in managing severe immune-mediated kidney injury in the era of direct-acting antivirals and highlights the favourable renal and virological outcomes achieved with combined rituximab and glecaprevir/pibrentasvir therapy.

Case Presentation

A 51-year-old man with no previous history of kidney disease was admitted to the emergency department because of progressively worsening fatigue, symmetrical arthralgia, dyspnoea, bilateral lower-limb oedema, and non-pruritic palpable purpura involving both legs (figure 1). His medical history was otherwise unremarkable, and he was not receiving regular medication. On admission, his blood pressure was 191/112 mmHg. No previous laboratory results were available; therefore, baseline kidney function could not be determined.

Initial laboratory investigations demonstrated normocytic anaemia (haemoglobin 9.2 g/dL), normal C-reactive protein (0.4 mg/dL), hypoalbuminemia (1.8 g/dL), hypercholesterolemia (total cholesterol 351 mg/dL; low-density lipoprotein cholesterol 227 mg/dL), and severe kidney dysfunction with a serum creatinine of 3.7 mg/dL and urea of 94 mg/dL. Urinalysis revealed dysmorphic microscopic haematuria (75 red blood cells/high-power field) and nephrotic-range proteinuria, with a urine protein-to-creatinine ratio (UPCR) of 9.2 g/g, consistent with active glomerular disease.

Immunological evaluation showed positive serum cryoglobulins and rheumatoid factor (22 IU/mL). The laboratory reported the cryoglobulins qualitatively as positive, but no immunochemical characterisation, cryocrit determination, or subtype classification (type II or type III) was available. Serum complement concentrations (C3 and C4) were within the normal range. Antinuclear antibodies, anti-double-stranded DNA antibodies, antineutrophil cytoplasmic antibodies, and anti-glomerular basement membrane antibodies were negative. Serological tests for human immunodeficiency virus and syphilis were negative. Hepatitis B virus serology showed negative HBsAg, anti-HBc, and anti-HBs, indicating no evidence of cur-

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rent or previous Hepatitis B virus (HBV) infection and absence of protective immunity. Interferon-gamma release assay (IGRA) was also negative.



Figure 1. Patient's lower limbs showing non-pruritic palpable purpura consistent with cryoglobulinemic vasculitis.

During the diagnostic work-up for rapidly progressive glomerulonephritis and positive circulating cryoglobulins, HCV infection was identified as the underlying cause. Virological testing confirmed active HCV infection, with an HCV RNA level of 1,030,000 IU/mL (genotype 1a). Serum immunoglobulin concentrations were as follows: IgG 507 mg/dL, IgA 79.9 mg/dL, and IgM 180 mg/dL, with a free κ/λ light-chain ratio of 2.18. Abdominal ultrasonography revealed mild hepatomegaly (16.7 cm) with regular contours and homogeneous parenchyma, without imaging features suggestive of cirrhosis. Transient elastography was not performed. The aspartate aminotransferase-to-platelet ratio index (APRI) and Fibrosis-4 Index (FIB-4) were 0.8 and 0.2, respectively; despite an intermediate APRI, the low FIB-4 was overall consistent with a low likelihood of advanced liver fibro-

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sis. Renal ultrasonography demonstrated normal-sized kidneys with preserved corticomedullary differentiation and no structural abnormalities.

Given the combination of rapidly progressive kidney dysfunction, nephrotic-range proteinuria, active urinary sediment, and cutaneous vasculitic manifestations, a kidney biopsy was performed. Light microscopy demonstrated ten glomeruli showing a diffuse membranoproliferative pattern characterised by lobular accentuation, mesangial expansion with mesangial interposition, duplication of the glomerular basement membrane, and marked endocapillary hypercellularity with prominent neutrophilic infiltration. Crescent formation was identified in three glomeruli (two cellular and one fibrocellular crescents). Additional findings included interstitial oedema with mononuclear inflammatory infiltrates, acute tubular necrosis, and intimal thickening of medium-sized arteries.

Immunofluorescence microscopy demonstrated dominant mesangiocapillary IgM (+++) deposition associated with C3 (++), κ light-chain (++), faint λ light-chain (+/−), and weak C1 (+/−) staining. Congo red staining was negative. Electron microscopy revealed abundant amorphous electron-dense subendothelial deposits without the organised microtubular substructure classically described in cryoglobulin deposits (figure 2). Although the ultrastructural findings were not specific, the overall clinicopathological picture strongly supported immune complex-mediated membranoproliferative glomerulonephritis associated with HCV-related cryoglobulinaemia.

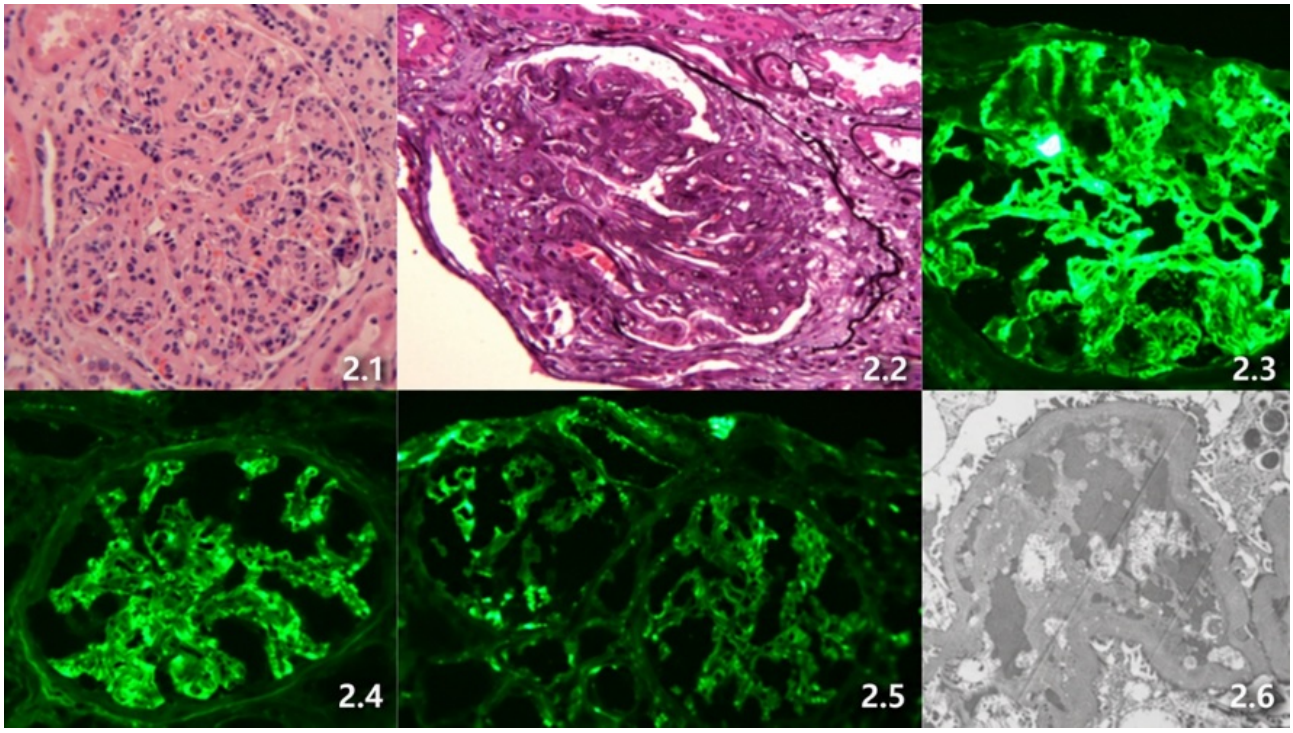


Figure 2. 2.1 – Light microscopy (haematoxylin and eosin stain) showing glomerular lobulation and double contouring of the glomerular basement membrane, with endocapillary hypercellularity and neutrophil infiltration (original magnification ×400). **2.2** – Silver stain highlighting mesangial expansion and duplicated basement membranes characteristic of a membranoproliferative pattern (original magnification ×400). **2.3** – Immunofluorescence microscopy demonstrating intense mesangiocapillary IgM deposition (+++) (original magnification ×200). **2.4** – Immunofluorescence microscopy demonstrating moderate C3 deposition (++) (original magnification ×200). **2.5** – Immunofluorescence microscopy showing κ light-chain deposition (++) with faint λ staining (+/−) (original magnification ×200). **2.6** – Electron microscopy revealing amorphous, strongly electron-dense subendothelial deposits within capillary loops and occasional luminal aggregates, surrounded by newly formed basement membrane, consistent with cryoglobulinemic membranoproliferative glomerulonephritis (scale bar: 1 μm).

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Because of the severity of renal involvement, including rapidly progressive kidney dysfunction, nephrotic-range proteinuria, and crescentic glomerulonephritis, treatment was initiated with three consecutive daily pulses of intravenous methylprednisolone (1 g/day), followed by rituximab (1 g on days 0 and 14). Two weeks after the first rituximab infusion, antiviral therapy with glecaprevir/pibrentasvir was initiated and continued for eight weeks. A third 1-g rituximab infusion was administered three months after the second dose because of persistent immunological activity.

Adjunctive nephroprotective therapy with ramipril (5 mg once daily) and dapagliflozin (10 mg once daily) was subsequently introduced; concomitant atorvastatin therapy was also prescribed. Kidney function improved rapidly after treatment. Three weeks after the second rituximab infusion, serum creatinine had decreased to 1.7 mg/dL, accompanied by a marked reduction in microscopic haematuria. During follow-up, proteinuria progressively declined to approximately 1 g/g, while serum creatinine stabilised at 1.2 mg/dL after one year (figure 3 and table I). Treatment with glecaprevir/pibrentasvir achieved a sustained virological response 12 weeks after treatment, with undetectable HCV RNA during follow-up. No adverse events related to immunosuppressive or antiviral therapy were observed.

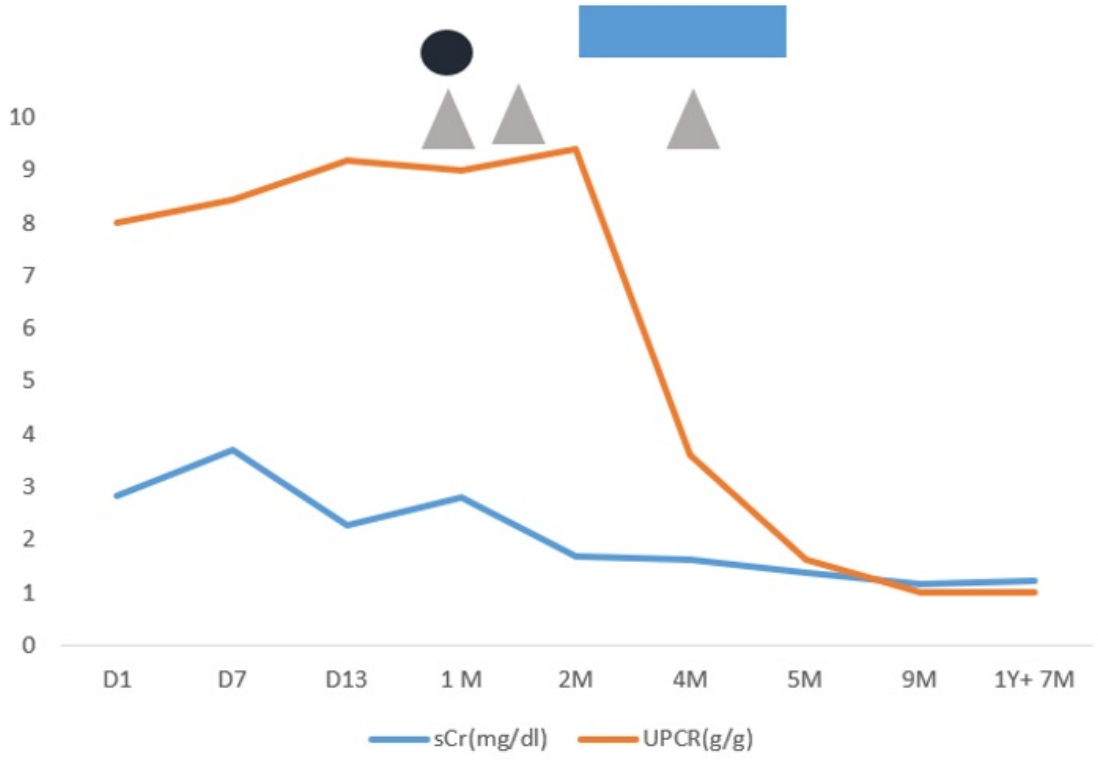


Figure 3. Evolution of kidney function and other laboratory parameters.

Abbreviations: D, day; DAA, direct-acting antiviral; M, month; sCr, serum creatinine; UPCR, urine protein-to-creatinine ratio; Y, year.

Treatment symbols: blue bar, DAA therapy; black circle, methylprednisolone (three 1-g pulses); grey triangle, rituximab (1 g).

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Table I. Evolution of laboratory parameters.

Lab tests	D1	D7	D13	1M	2M	4M	5M	8M	9M	1Y+7M
HCV antibody	+	—	—	—	—	—	—	—	—	—
HCV RNA, IU/mL	—	1,030,000	—	—	—	—	ND	ND	—	—
HCV genotype	—	—	1a	—	—	—	—	—	—	—
Total cholesterol, mg/dL	351	—	457	—	—	—	280	—	—	260
LDL cholesterol, mg/dL	227	—	322	—	—	—	213	—	—	173
Albumin, g/dL	1.8	1.8	—	1.2	—	—	4.1	—	4.2	4.7
Cryoglobulins	—	+	—	—	+	+	—	—	+	+
Rheumatoid factor, IU/mL	—	—	22	—	17	—	—	—	—	—
Urinary erythrocytes	—	75	—	31	32	23	13	—	16	—
Urinary leukocytes	—	7	—	3	3	1	3	—	1	—

Note: Urinary erythrocytes and leukocytes are expressed as cells per high-power field.

Abbreviations: D, day; HCV, hepatitis C virus; IU, international units; LDL, low-density lipoprotein; M, month; ND, not detected; RNA, ribonucleic acid; Y, year; +, positive; —, not assessed.

Because the patient had no serological evidence of previous hepatitis B virus infection or protective immunity, the case was discussed by a multidisciplinary team involving nephrologists and infectious disease specialists. Given the severity of the renal disease, rituximab treatment was not delayed to allow completion of hepatitis B vaccination. Instead, a short-course hepatitis B vaccination schedule was initiated nine months after the last rituximab infusion.

Discussion

Mixed cryoglobulinaemia is the most common extrahepatic manifestation of HCV infection and remains the leading cause of secondary immune complex-mediated MPGN worldwide. Chronic viral antigenic stimulation promotes expansion of B-cell clones producing rheumatoid factor and cryoglobulins, resulting in circulating immune complexes that activate the classical complement pathway and deposit within glomerular capillaries. This process leads to endothelial injury, mesangial proliferation, and the characteristic histopathological features of cryoglobulinemic glomerulonephritis[1–4].

Kidney involvement represents one of the most severe complications of HCV-associated mixed cryoglobulinaemia and is associated with increased morbidity and a higher risk of chronic kidney disease progression. The spectrum of renal manifestations ranges from isolated urinary abnormalities to nephrotic syndrome and rapidly progressive glomerulonephritis[2,3]. Our patient presented with several features associated with severe disease, including rapidly progressive kidney dysfunction, nephrotic-range proteinuria, active urinary sediment, palpable purpura, and crescent formation on kidney biopsy, all of which indicated extensive immune-mediated renal injury requiring prompt intervention.

Kidney biopsy remains essential for establishing the diagnosis and determining disease severity. In the present case, light microscopy demonstrated diffuse immune complex-mediated MPGN with marked endocapillary hypercellularity, neutrophilic infiltration, and crescent formation, reflecting active inflammatory injury. Immunofluorescence showed dominant IgM and C3 deposition, consistent with immune complex-mediated disease. Although electron microscopy did not demonstrate the organised microtubular structures classically

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described in cryoglobulin deposits, the presence of abundant amorphous subendothelial electron-dense deposits, together with the clinical presentation, positive circulating cryoglobulins, active HCV infection, and characteristic immunofluorescence findings, strongly supported the diagnosis of HCV-associated cryoglobulinemic glomerulonephritis. Similar ultrastructural variability has been described in previous pathological series, emphasising that the diagnosis should rely on clinicopathological correlation rather than on a single ultrastructural feature[2].

The therapeutic approach to HCV-associated cryoglobulinemic glomerulonephritis has evolved considerably following the introduction of DAAs, which achieve sustained virological response in more than 95.0% of patients and have dramatically improved both hepatic and extrahepatic outcomes. Nevertheless, viral eradication alone may not immediately suppress the immune-mediated process because persistent B-cell activation and autonomous B-cell clones may continue to produce pathogenic cryoglobulins even after successful HCV clearance[5,6]. Consequently, treatment should be individualised according to disease severity rather than based solely on virological status.

Current KDIGO guidelines recommend a severity-based strategy for HCV-associated glomerular disease. In patients with stable kidney function and mild urinary abnormalities, DAA therapy alone is generally appropriate. In contrast, patients presenting with rapidly progressive glomerulonephritis, nephrotic syndrome, or severe cryoglobulinemic vasculitis should receive combined antiviral and immunosuppressive therapy, with or without plasma exchange according to the clinical presentation. Rituximab is currently recommended as the preferred immunosuppressive agent because it selectively depletes CD20-positive B lymphocytes, rapidly suppresses cryoglobulin production, and has demonstrated superior efficacy and safety compared with conventional cytotoxic therapy[6].

Current recommendations from the European Association for the Study of the Liver (EASL) further support the use of DAA therapy in patients with HCV infection and advanced kidney disease. Approved DAA regimens can be used without dose adjustment in patients with severe renal impairment, including those with an estimated glomerular filtration rate < 30 mL/min/1.73 m^2 and those receiving haemodialysis. Glecaprevir/pibrentasvir is a recommended pangenotypic regimen in this setting, with high sustained virological response rates and a favourable safety profile. In our patient, the marked reduction in kidney function at presentation, together with the antiviral efficacy, renal safety profile, and 8-week treatment duration, supported the choice of glecaprevir/pibrentasvir[7].

EASL recommendations also emphasise the need for multidisciplinary management of patients with severe HCV-associated immune complex-mediated extrahepatic manifestations. In patients with severe cryoglobulinemic vasculitis, particularly when there is significant renal involvement, rituximab may be considered in addition to antiviral therapy, with treatment decisions individualised according to disease severity and clinical presentation. In the present case, the rapidly progressive kidney dysfunction, nephrotic-range proteinuria, active urinary sediment, and crescent formation on kidney biopsy prompted multidisciplinary discussion between Nephrology and Infectious Diseases and supported the early use of rituximab alongside antiviral therapy[7].

The efficacy of rituximab in severe cryoglobulinemic vasculitis has been established by two landmark randomized controlled trials. De Vita *et al.* demonstrated significantly greater treatment retention and disease control with rituximab compared with conventional immunosuppressive therapy, while Sneller *et al.* confirmed its efficacy in patients with HCV-associated cryoglobulinemic vasculitis who failed to achieve remission after antiviral therapy[8,9]. Subsequent observational studies consistently reported improvement in kidney function, reduction of proteinuria, resolution of active urinary sediment, and better control of systemic vasculitic manifestations following B-cell depletion[10–12].

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An important aspect of the present case is the therapeutic sequencing. Because the patient presented with rapidly progressive kidney dysfunction, nephrotic-range proteinuria, active urinary sediment, and crescentic glomerulonephritis, immediate suppression of immune-mediated inflammation was considered essential to minimise irreversible nephron loss. High-dose methylprednisolone and rituximab were therefore initiated promptly, followed shortly thereafter by glecaprevir/pibrentasvir to eradicate the underlying viral trigger. Although current guidelines recommend combined immunosuppressive and antiviral therapy for severe disease, they do not define the optimal sequence or interval between these treatments. Therefore, therapeutic decisions should be individualised according to disease severity, clinical stability, and multidisciplinary assessment. In our patient, early control of the immune-mediated process followed by definitive antiviral therapy resulted in sustained virological response and marked, lasting improvement in kidney function[6].

Another noteworthy finding was the persistence of circulating cryoglobulins despite sustained virological response and marked clinical improvement. The laboratory reported cryoglobulins qualitatively as positive throughout follow-up but did not perform cryocrit determination or immunochemical characterisation. Recent studies have demonstrated that persistence of cryoglobulins after viral eradication is not uncommon, particularly in patients with long-standing disease or persistent B-cell clonal expansion, and does not necessarily indicate ongoing clinically significant vasculitis. Instead, clinical response, renal function, urinary findings, and viral clearance should guide therapeutic decisions and long-term monitoring[5,13–15].

This case also illustrates an important practical issue regarding HBV prevention in patients requiring urgent B-cell depletion. Although HBV vaccination before rituximab administration is desirable whenever feasible, delaying immunosuppressive therapy was considered inappropriate because of the severity of the renal disease. Following multidisciplinary discussion, rituximab was initiated without delay, and HBV vaccination was performed after completion of B-cell depletion. This individualised strategy balanced the immediate need to preserve kidney function against the potential reduction in vaccine immunogenicity associated with rituximab therapy[16].

Several limitations should be acknowledged. Cryoglobulins were reported only qualitatively as positive, without cryocrit measurement, immunofixation, or classification into cryoglobulin subtypes. Consequently, correlation between immunological activity and clinical evolution could not be fully assessed. In addition, electron microscopy lacked the classical organised microtubular appearance described in some cases of cryoglobulinemic glomerulonephritis. Nevertheless, the convergence of clinical manifestations, positive circulating cryoglobulins, active HCV infection, characteristic immune complex-mediated MPGN on kidney biopsy, and the favourable response to combined immunosuppressive and antiviral therapy strongly supports the diagnosis.

Overall, this case highlights the importance of integrating clinical, serological, virological, and pathological findings when managing HCV-associated cryoglobulinemic glomerulonephritis. More importantly, it illustrates that in patients presenting with severe immune-mediated renal injury, prompt initiation of closely sequenced immunosuppressive and antiviral therapy may preserve kidney function while achieving sustained virological response. Persistent cryoglobulin positivity should be interpreted cautiously and always within the context of the patient's overall clinical evolution rather than as an isolated marker of treatment failure.

Conclusion

This case highlights the diagnostic and therapeutic challenges of HCV-associated cryoglobulinemic glomerulonephritis in the era of direct-acting antivirals. Although viral eradication remains the cornerstone of treatment, patients presenting with rapidly progressive kidney dysfunction, nephrotic-range proteinuria, or crescentic glomerulonephritis require prompt recognition and a severity-based

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therapeutic approach to prevent irreversible kidney injury.

Our patient achieved sustained virological response together with marked and durable improvement in kidney function following combined immunosuppressive and antiviral therapy, supporting the role of early B-cell depletion in carefully selected patients with severe immune-mediated renal disease. The persistence of circulating cryoglobulins despite sustained clinical and renal remission further emphasises that virological, immunological, and renal responses may follow different trajectories and should be interpreted within the overall clinical context rather than as isolated markers of treatment success or failure.

Finally, this case underscores the importance of integrating clinical, serological, virological, and histopathological findings in the management of HCV-associated cryoglobulinemic glomerulonephritis and highlights the value of a multidisciplinary, individualised treatment strategy. Further prospective studies are needed to better define the optimal integration and timing of immunosuppressive and antiviral therapies in patients with severe HCV-associated glomerular disease.

Author Contributions

Francisca Fonseca: Conceptualisation; Data Curation; Formal Analysis; Writing – Original Draft.

Beatriz Mendes: Formal Analysis; Writing – Original Draft; Data Curation.

Patrícia Domingues: Data Curation; Formal Analysis; Writing – Original Draft.

Elsa Lourenço: Data Curation; Formal Analysis.

Elsa Soares and Karina Soto: Writing – Review & Editing; Supervision.

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Ethics Statement

This study was conducted in accordance with the ethical principles of the Declaration of Helsinki.

Written informed consent was obtained from the patient for publication of clinical details and images.

Conflicts of Interest

The authors declare no conflicts of interest.

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