

Single Case

Clinical and Pathological Course of Recurrent C3 Glomerulonephritis from Onset to Graft Loss: A Case Report

Azusa Kobayashi^a Asami Takeda^b Shoji Saito^a Hibiki Shinjo^a
Daiki Iguchi^a Kenta Futamura^c Manabu Okada^c Takahisa Hiramitsu^c
Shunji Narumi^c Yoshihiko Watarai^c

^aNephrology, Japanese Red Cross Aichi Medical Center Nagoya Daini Hospital, Nagoya, Japan; ^bNephrology, Masuko Memorial Hospital, Nagoya, Japan; ^cTransplant Nephrology and Surgery, Japanese Red Cross Aichi Medical Center Nagoya Daini Hospital, Nagoya, Japan

Keywords

Recurrent C3 glomerulonephritis · Allograft kidney · Pathology · Case report

Abstract

Introduction: Complement 3 glomerulonephritis (C3GN) has a high recurrence rate after kidney transplantation. Before the disease became well understood, kidney transplantation was performed without a diagnosis of C3GN. This report describes a case of recurrent C3GN diagnosed using allograft biopsy and evaluates its long-term clinical and pathological course. **Case Presentation:** A 35-year-old man with membranoproliferative glomerulonephritis underwent an ABO-compatible living-donor renal transplantation. Three weeks post-transplantation, an allograft biopsy showed prominent granular C3 deposits. One year after transplantation, an allograft biopsy revealed slight mesangial expansion with C3 deposits and a few urinary proteins. Recurrent C3GN was diagnosed based on similar C3 deposition in the native kidney. Eight years post-transplantation, urinary protein levels began to increase and renal function gradually declined. Approximately 10 years after transplantation, an allograft biopsy revealed severe secondary focal segmental glomerulosclerosis and arteriolopathy with no active C3GN lesions. Ten months later, deteriorating kidney function necessitated hemodialysis. **Conclusion:** In this case, C3GN recurred early after transplantation, but its activity did not increase for 8 years. The causes of chronic allograft dysfunction vary among cases. More cases and detailed observational studies are needed to determine treatment strategies for recurrent C3GN and graft prognosis.

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Published by S. Karger AG, Basel

Correspondence to:
Azusa Kobayashi, akobayashi@nagoya2.jrc.or.jp

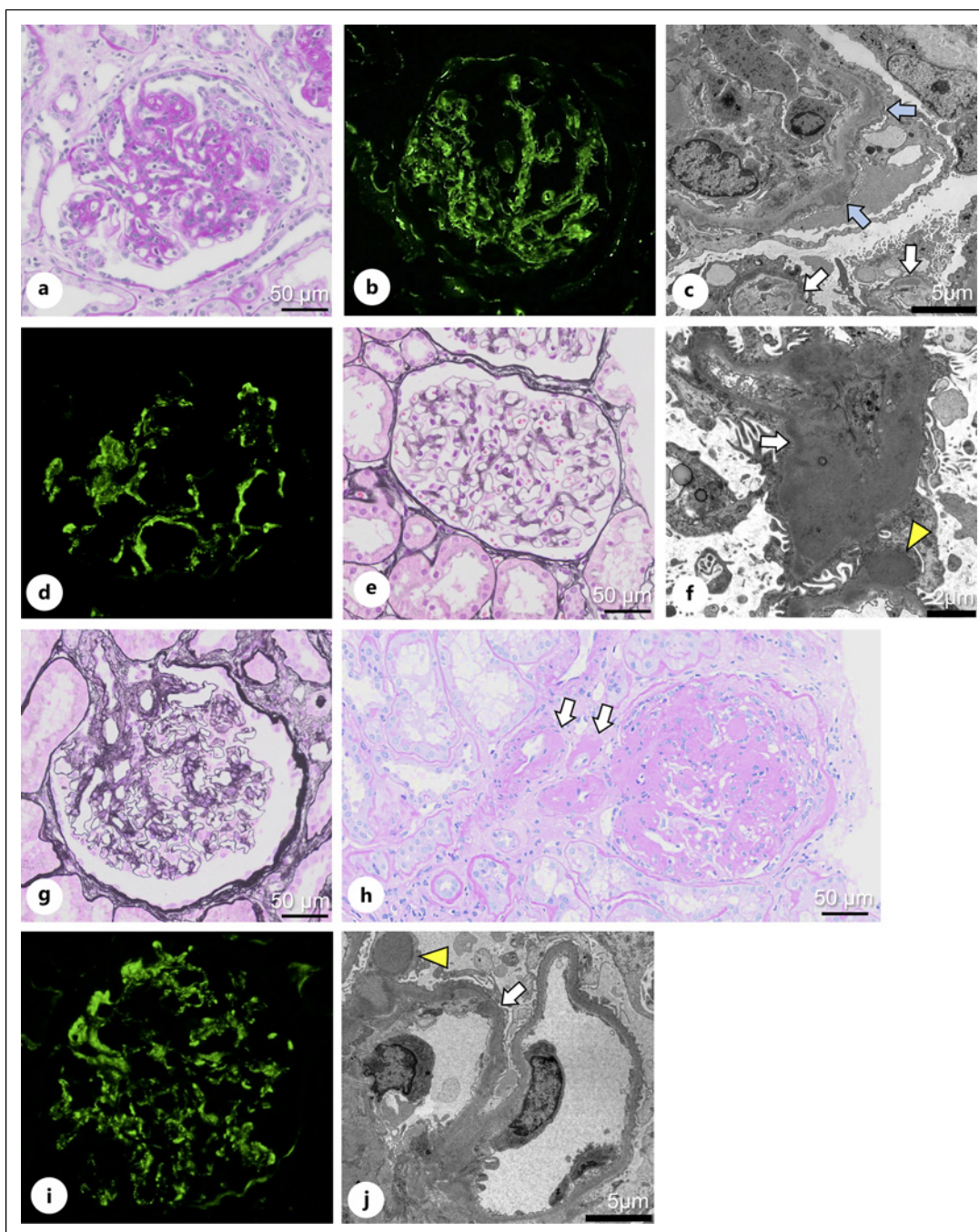
Introduction

Complement 3 glomerulonephritis (C3GN) is a form of glomerulonephritis caused by dysfunction of the alternative complement pathway (AP) and is characterized by C3 deposits in the glomeruli, as confirmed by immunofluorescence (IF) [1]. In a previous report, the recurrence rate of C3GN post-kidney transplantation ranged from 60 to 86%, and the 10-year transplant kidney failure rate was approximately 50% [2]. Renal biopsies (RBx) performed before 2010 resulted in renal transplantations (RTx) without a diagnosis of C3GN, as the concept of C3GN was proposed in 2010 [3]. No previous reports have described the renal pathology of post-transplant C3GN, including that of the native kidney, from onset to graft loss. This case report describes recurrent C3GN diagnosed through allograft biopsy and evaluates its long-term clinical and pathological course. The CARE Checklist has been completed by the authors for this case report, attached as online supplementary material (for all online suppl. material, see <https://doi.org/10.1159/000545853>).

Case Presentation

A 28-year-old man with no significant medical history underwent RB for nephrotic syndrome and low serum C3 levels. The glomeruli showed mesangial hypercellularity and glomerular basement membrane duplication with endocapillary hypercellularity and cellular crescents (Fig. 1a). The IF indicated intense granular deposition of C3 in the mesangium and glomerular capillary loops (Fig. 1b). Electron microscopy (EM) revealed electron-dense deposits in the mesangial, subendothelial, and subepithelial-to-intramembrane areas (Fig. 1c). He was diagnosed with membranous proliferative glomerulonephritis (MPGN) as it was pre-2010. Despite receiving prednisolone (PSL) and cyclosporine therapies, his renal function progressively deteriorated. The patient's clinical course is shown in Figure 2. Seven years later, he received an ABO-compatible kidney transplant from his sister. An immunosuppressive regimen comprising of tacrolimus, mycophenolate mofetil (MMF), and PSL was administered. Renal function was restored to a serum creatinine level of 1.2 mg/dL, and the proteinuria disappeared. Three weeks post-transplantation, allograft biopsy revealed deposition of only C3 in the mesangium on IF (Fig. 1d) (Banff classification: i0, t0, g0, v0, ptc0, ci0, ct0, cg0, cv0 ah0, aah0). One year post-transplantation, allograft biopsy revealed slight mesangial expansion with mesangial deposits without endocapillary hypercellularity or cellular crescents (Fig. 1e) (Banff classification: i0, t0, g0, v0, ptc0, ci0, ct1, cg0, cv0 ah2, aah0). EM revealed mesangial-to-subendothelial and hump-shaped subepithelial deposits (Fig. 1f). Recurrent C3GN was diagnosed based on similar C3 deposits in the native kidney.

The serum monoclonal immunoglobulin test results were negative. Genetic variants and autoantibodies linked to AP hyperactivity were not assessed. Only methyl PSL pulse therapy was added, and transplant immunosuppressive therapy was not altered as renal function remained stable, with minor proteinuria (up to 0.3 g/day) and no microscopic hematuria. The patient's blood pressure averaged 130/80; therefore, angiotensin receptor blocker therapy was initiated. After treatment, proteinuria became negative, and no signs of hematuria or proteinuria were observed, even when the patient had a cold. Eight years after transplantation, urinary protein levels began to increase and renal function gradually declined. An allograft biopsy was performed 9 years and 10 months post-transplantation as the serum creatinine (2.3 mg/dL) and urine protein creatinine ratio (1.1 g/gCre) increased. Serum C3 levels did not decrease. Allograft biopsy showed that 25% of the glomeruli had developed global glomerulosclerosis, and 20% of the areas had interstitial fibrosis and tubular atrophy. Twenty percent of the glomeruli showed mesangial expansion with deposits, without signs of



(For legend see next page.)

mesangial or endocapillary proliferation (Fig. 1g). Sixty percent of the glomeruli showed advanced focal segmental glomerulosclerosis (FSGS). Some arterioles showed severe arteriolar hyalinosis and replacement of degenerated smooth muscle cells with hyaline deposits (Fig. 1h). No rejection was observed. Granular mesangial and glomerular capillary loop staining was observed for C3 only on IF (Fig. 1i). EM showed intermediately dense deposits from the paramesangium to the subendothelial area and within the glomerular basement membrane; however, there was no increase compared to 1 year post-transplant (Fig. 1j)

(Banff classification: i0, t0, g0, v0, ptc0, ci1, ct1, cg0, cv0, ptcbm0, ah3, aah2). The renal function decline was considered to be primarily due to severe secondary FSGS lesions and arteriopathy; immunosuppressive therapy was not administered, and the transplant immunosuppressive regimen remained unchanged. His kidney function declined rapidly, leading him to undergo hemodialysis 10 years and 8 months after RTx.

Discussion

Here, we report a case of recurrent C3GN diagnosed using allograft biopsy and evaluate its long-term clinical and pathological course. This report is valuable for the long-term observation of the renal pathology of recurrent C3GN, from onset to graft loss, including in the native kidney. Although C3 glomerulopathy frequently recurs after transplantation, this concept was introduced relatively recently in 2010 [3]. This classification demonstrates that C3 glomerulopathy often appears in cases previously classified as MPGN. Initially, the patient was diagnosed with MPGN after a native kidney biopsy was performed before 2010. However, an allograft biopsy conducted after 2010 revealed histopathological similarities with the original kidney, resulting in a diagnosis of recurrent C3GN.

Graft loss frequently occurs in patients with C3GN owing to recurrence [4]. A previous study reported that 57% of patients with recurrent disease experience graft loss [5]. A histopathological index was created to evaluate the prognosis of patients with C3 glomerulopathy and assess RB disease activity and chronicity [6]. Activity scores originate from various criteria, including mesangial hypercellularity, endocapillary proliferation, membranoproliferative morphology, leukocyte infiltration in glomeruli, presence of cellular and fibrocellular crescents, fibrinoid necrosis, and interstitial inflammation, each scored from 0 to 3. The chronicity score assessed factors such as glomerulosclerosis (both segmental and global), percentage of cortical area with tubular atrophy, interstitial fibrosis (each rated from 0 to 3), and arteriosclerosis (rated from 0 to 1). Total disease activity (total score of 21) and chronicity (total score of 10) were identified as strong independent predictors of the progression of C3 glomerulopathy. In this case, a native kidney biopsy showed high disease activity (score 13) and no chronicity (score 0). The patient developed end-stage kidney

Fig. 1. Pathological findings. **a** In the native kidney, the glomerulus exhibited mesangial hypercellularity, GBM duplication with endocapillary hypercellularity, and a cellular crescent. **b** In the native kidney, IF for C3 exhibited granular mesangial and glomerular capillary loop staining. **c** In the native kidney, EM revealed mesangial and subendothelial (white arrow) EDD as well as subepithelial-to-intramembranous (blue arrow) EDD. Endocapillary hypercellularity with subendothelial widening and foot process effacement of podocytes was observed. **d** At 3 weeks post-transplant, IF for C3 demonstrated granular mesangial staining. **e** At 1 year post-transplant, the glomerulus displayed slight mesangial expansion with deposits. **f** At 1 year post-transplant, EM showed mesangial-to-subendothelial (white arrow) and hump-shaped subepithelial (yellow arrowhead) deposits. **g** At 9 years and 10 months post-transplant, the glomerulus showed mesangial expansion with deposits without endocapillary proliferation or GBM duplication. **h** At 9 years and 10 months post-transplant, severe arteriole hyalinosis and arteriolar replacement of degenerated smooth muscle cells with hyaline deposits (white arrow) were observed. **i** At 9 years and 10 months post-transplant, IF for C3 exhibited granular mesangial and glomerular capillary loop staining. **j** At 9 years and 10 months post-transplant, EM revealed paramesangial and subendothelial-to-intramembranous intermediately dense deposits (white arrow) along with peeled-off hump-shaped subepithelial deposits (yellow arrowhead). **a, h** Periodic acid-Schiff stain. **e, g** Periodic acid methenamine silver stain. GBM, glomerular basement membrane; EDD, electron-dense deposit.

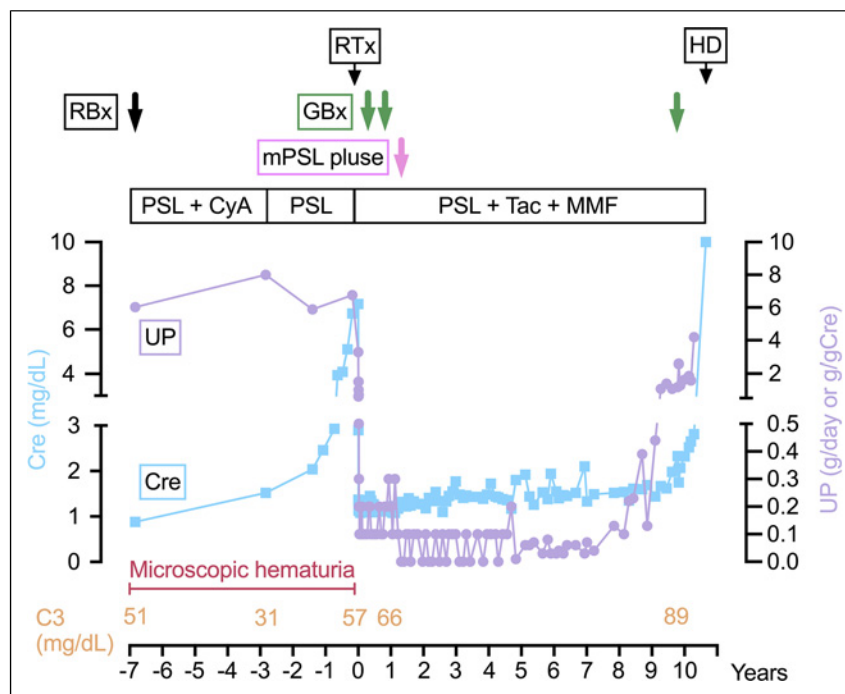


Fig. 2. Clinical course. RTx, renal transplantation; HD, hemodialysis; RBx, renal biopsy; GBx, graft biopsy; mPSL, methylprednisolone; PSL, prednisolone; CyA, cyclosporine; Tac, tacrolimus; MMF, mycophenolate mofetil; Cre, serum creatinine; UP, urine protein.

disease (ESKD) after approximately 7 years. Allograft biopsy 1 year post-transplant revealed no disease activity (score 0) or chronicity (score 0). Renal function remained stable without urinary protein for nearly 8 years. Nine years and 10 months after the transplant, the biopsy showed high chronicity (score 6) but low disease activity (score 1). Previous studies indicated that the chronicity index is a more dependent predictor of outcomes [6]. After 10 months, the patient progressed to ESKD, supporting the finding that chronic lesions are correlated with a higher risk of ESKD.

However, in the case of recurrent C3 nephritis in allograft kidneys, the development of chronic lesions requires consideration of factors other than glomerulonephritis. Chronic allograft dysfunction can result from immunologic or non-immunologic graft injuries [7]. Non-immunologic causes include calcineurin inhibitor toxicity, hyperfiltration, and allograft aging [8]. Approximately 10 years post-transplantation, the patient presented with severe FSGS, severe arteriosclerosis, and alternative arteriolar hyalinosis without active lesions of C3GN. Therefore, this case was considered to have progressed to ESKD owing to non-immunological allograft dysfunction rather than the progression of chronic C3GN lesions. Allograft biopsy is a reliable method for differential diagnosis of silently progressive chronic allograft dysfunction [8].

The etiology of C3GN includes genetic variants and autoantibodies associated with AP hyperactivity, and monoclonal gammopathy [9]. Patients with C3GN are more likely to test positive for autoantibodies than for pathogenic gene variants, with C3 nephritic factor (C3NeF) being the most commonly identified autoantibody. Previous studies indicate that C3NeF positivity is linked to better patient outcomes and a greater response to immunosuppressive therapies, including MMF-based treatment [10]. In the present case, PSL and cyclosporine therapy were ineffective at the initial onset, leading to ESKD. After RTx, the patient experienced an early relapse but subsequently achieved

long-term remission and normalized serum C3 levels owing to transplant immunosuppressive therapy, including MMF. This clinical course indicates that MMF effectively suppressed the disease activity of C3GN. Therefore, we consider this case to be classified as C3GN with autoantibodies, including C3NeF, although autoantibodies could not be measured.

Here, we report the clinical and pathological course of recurrent C3GN, including that of the native kidney, from onset to graft loss. In this case, recurrent C3GN appeared early post-transplantation, but disease activity did not increase over an extended period, suggesting that the graft developed ESKD owing to non-immunologic graft dysfunction rather than the chronic progression of C3GN. Although C3GN recurrence is common early after transplantation, even with immunosuppressive treatment, graft loss may not only be due to C3GN progression. Treatment approaches for recurrent C3GN may require a closer examination of multiple cases.

Acknowledgments

We would like to thank Editage (www.editage.com) for English language editing.

Statement of Ethics

The study was conducted in accordance with the Declaration of Helsinki of the World Medical Association. This article does not include any study with human participants performed by any of the authors. The Institutional Review Board of the Japanese Red Cross Aichi Medical Center Nagoya Daini Hospital determined that ethical approval was not required for this case report. All efforts were made to protect patients' identities. Written informed consent was obtained from the patient to publish this case report and the accompanying images.

Conflict of Interest Statement

The authors declare no conflicts of interest.

Funding Sources

The authors did not receive any funding for this study.

Author Contributions

Azusa Kobayashi and Asami Takeda made substantial contributions to the study concept, data analysis, and interpretation; wrote the manuscript's first draft; approved the final version of the manuscript to be published; and agreed to be accountable for all aspects of the work. Shoji Saito, Hibiki Shinjo, Daiki Iguchi, Kenta Futamura, Manabu Okada, Takahisa Hiramitsu, Shunji Narumi, and Yoshihiko Watarai contributed to the data acquisition, revised the manuscript, approved the final version of the manuscript to be published, and agreed to be accountable for all aspects of the work.

Data Availability Statement

All data generated or analyzed during this study are included in this article and its online supplementary material files. Further inquiries can be directed to the corresponding authors.

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