



## Original article

# Glomerular disease in chronic graft versus host disease

Leticia Peluffo<sup>a</sup>, Lucía Barceló<sup>b</sup>, Gabriela Otatti<sup>b</sup>, Andrés Urrestarazu<sup>b</sup>, Ruben Coitiño<sup>b</sup>, Cecilia Baccino<sup>a</sup>, Sofía San Román<sup>a</sup>, Agustín Noboa<sup>a</sup>, Jimena Cabrera<sup>c</sup>, Haydee Aunchaunya<sup>d</sup>, Fernanda Varela<sup>c</sup>, Cecilia Coelho<sup>e</sup>, Lucía Santini<sup>e</sup>, Eliana Cabrera<sup>e</sup>, Paula Gauronas<sup>e</sup>, Santiago Acle<sup>e</sup>, Oscar Noboa<sup>a</sup>, Ricardo Silvarino<sup>a,\*</sup>

<sup>a</sup> Unidad Académica de Nefrología y Centro de Nefrología, Hospital de Clínicas, Facultad de Medicina, Universidad de la República, Servicio de Nefrología, Cooperativa de Servicios Médicos (COSEM), Montevideo, Uruguay

<sup>b</sup> Unidad Académica de Nefrología y Centro de Nefrología, Hospital de Clínicas, Facultad de Medicina, Universidad de la República, Montevideo, Uruguay

<sup>c</sup> Servicio de Nefrología, Hospital Central de las Fuerzas Armadas, Montevideo, Uruguay

<sup>d</sup> Unidad Académica de Anatomía Patológica, Hospital de Clínicas, Facultad de Medicina, Universidad de la República, Montevideo, Uruguay

<sup>e</sup> Servicio de Nefrología, Cooperativa de Servicios Médicos (COSEM), Montevideo, Uruguay

## ARTICLE INFO

## Article history:

Received 2 December 2024

Accepted 2 February 2025

Available online xxx

## Keywords:

Allogeneic hematopoietic progenitor cell transplantation  
Graft-versus-host disease  
Nephrotic syndrome  
Renal biopsy  
Membranous nephropathy  
Rituximab

## ABSTRACT

Allogeneic hematopoietic progenitor cell transplantation is a widely used procedure, and graft-versus-host disease (GVHD) is a common complication. Glomerular involvement due to GVHD is exceptional. Objective: to describe the clinical and histopathological presentation of patients with glomerular disease secondary to GVHD. Materials and methods: a retrospective review of the Uruguayan registry of glomerulopathies was conducted to identify renal biopsies from patients with confirmed GVHD. Results: seven patients were identified, four male, with a median age of 41 years (range 8–58). The most common clinical and analytical presentation was nephrotic syndrome. Histopathological findings included membranous glomerulonephritis (4), segmental and focal sclerohyalinosis (1), membranoproliferative glomerulonephritis (1), and thrombotic microangiopathy (1). All patients were treated with corticosteroids in combination with immunosuppressors, most frequently mycophenolate mofetil and rituximab. Five patients achieved complete remission, one had partial remission, and one did not respond. The combination of corticosteroids with rituximab showed a good response rate in those presenting with podocytopathy in the renal biopsy.

© 2025 Published by Elsevier España, S.L.U. on behalf of Sociedad Española de Nefrología.

This is an open access article under the CC BY-NC-ND license (<http://creativecommons.org/licenses/by-nc-nd/4.0/>).

DOI of original article:

<https://doi.org/10.1016/j.nefro.2025.02.002>.

\* Corresponding author.

E-mail address: [rsilvarino@gmail.com](mailto:rsilvarino@gmail.com) (R. Silvarino).

2013-2514/© 2025 Published by Elsevier España, S.L.U. on behalf of Sociedad Española de Nefrología. This is an open access article under the CC BY-NC-ND license (<http://creativecommons.org/licenses/by-nc-nd/4.0/>).

## Enfermedad glomerular en enfermedad injerto versus huésped crónica

### R E S U M E N

#### Palabras clave:

Trasplante alogénico de  
progenitores hematopoyéticos  
Enfermedad injerto versus  
huésped  
Síndrome nefrótico  
Biopsia renal  
Nefropatía membranosa  
Rituximab

El trasplante alogénico de progenitores hematopoyéticos es un procedimiento ampliamente utilizado y el desarrollo de enfermedad injerto versus huésped (EIVH) una complicación frecuente. El compromiso glomerular por EIVH es excepcional. Objetivo: describir la presentación clínica e histopatológica de pacientes con enfermedad glomerular secundaria a EIVH. Material y métodos: se revisó retrospectivamente el registro uruguayo de glomerulopatías en busca de biopsias renales de pacientes con EIVH demostrada. Resultados: se identificaron 7 pacientes, 4 de sexo masculino, edad 41 (8–58) años. La presentación clínica-analítica más frecuente fue el síndrome nefrótico. Los hallazgos histopatológicos fueron glomerulonefritis membranosa (4), esclerohialinosis segmentaria y focal (1), glomerulonefritis membranoproliferativa (1) y microangiopatía trombótica (1). La totalidad de pacientes se trataron con corticosteroides asociados con inmunosupresores, más frecuentemente micofenolato mofetilo y rituximab. Presentaron remisión completa 5 pacientes, remisión parcial 1 y no remisión 1. La combinación de corticoides con rituximab mostró una buena tasa de respuesta en quienes se presentaron con podocitopatía en la biopsia renal.

© 2025 Publicado por Elsevier España, S.L.U. a nombre de Sociedad Española de Nefrología. Este es un artículo Open Access bajo la CC BY-NC-ND licencia (<http://creativecommons.org/licencias/by-nc-nd/4.0/>).

## Introduction

Allogeneic hematopoietic stem cell transplantation (ASCT) is a widely used procedure for the treatment of multiple hematological diseases.<sup>1</sup> A complication of ASCT is graft-versus-host disease (GVHD), which can develop acutely during the first 100 days after ASCT (a-GVHD) or be a chronic complication (c-GVHD) when it occurs after this time period.<sup>2</sup> c-GVHD is the most common late complication in patients with ASCT, present in 40–80% of transplant recipients, and is responsible for high morbidity and mortality.<sup>3</sup> The most common manifestations of c-GVHD are cutaneous and mucosal (lichen planus, scleroderma-like lesions, mucosal erosions with ulcerated lesions), gastrointestinal, and hepatic.<sup>1</sup>

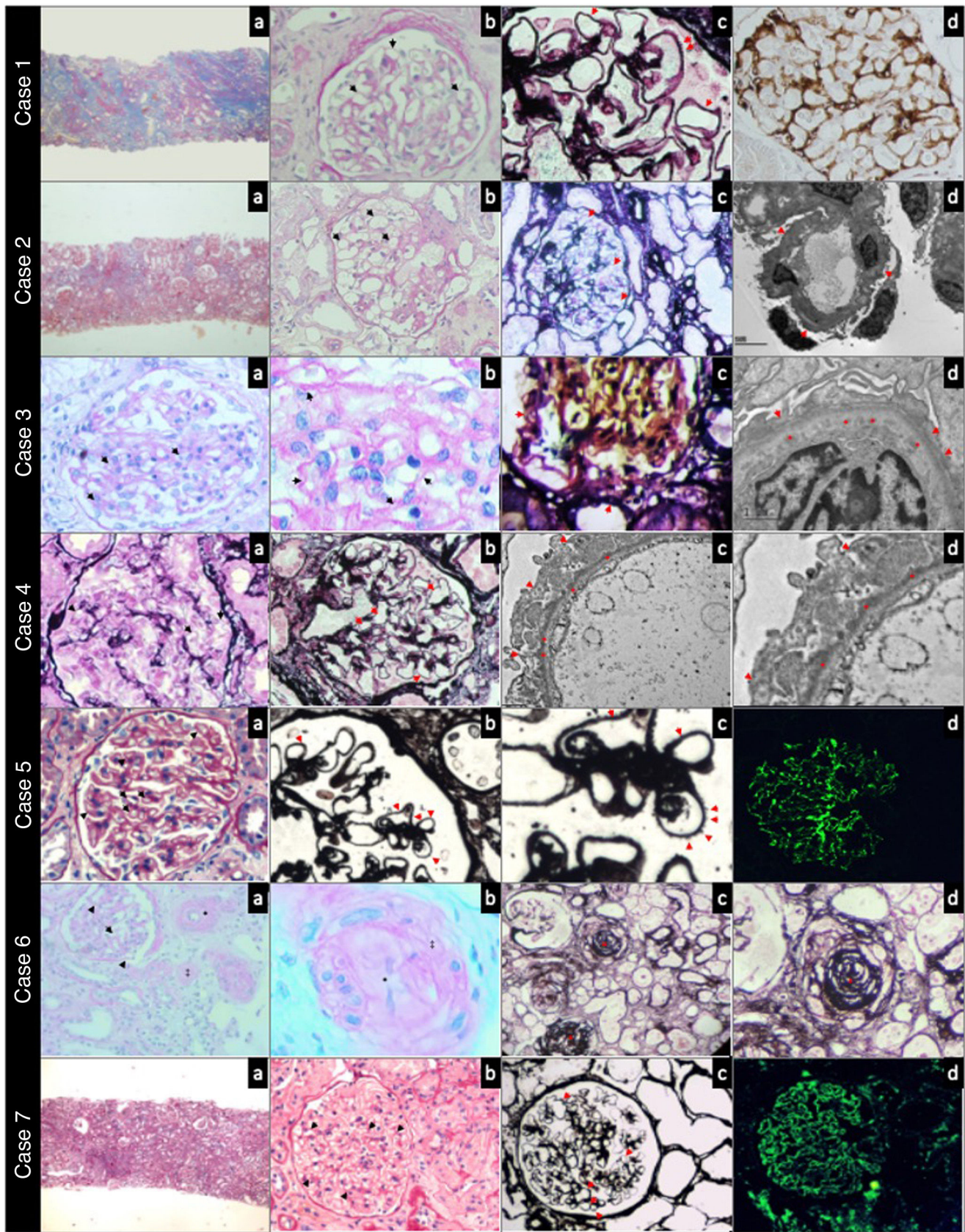
The kidney may be affected during the course of ASCT as a consequence of drug toxicity linked to pre-transplant conditioning, sepsis, or toxicity from calcineurin inhibitors used to prevent GVHD.<sup>4</sup> This involvement may be clinically expressed as acute kidney failure with an incidence of 50–75%,<sup>5</sup> or as chronic kidney disease with reported incidence that ranges between 7% and 66% depending on the series.<sup>6</sup> Glomerular involvement secondary to c-GVHD is a rare complication, with a prevalence of less than 2% in published series. The most frequent histopathological patterns are membranous nephropathy and minimal change disease, followed by much less frequent lesions such as focal segmental glomerulosclerosis, membranoproliferative glomerulonephritis, IgA nephropathy, crescentic glomerulonephritis, and lupus nephritis-like glomerular lesions.<sup>7</sup> The objective of this study is to describe the clinical and analytical characteristics of patients with c-GVHD who underwent renal biopsy due to manifestations of glomerular injury.

## Methods

### Patients

The Uruguayan Registry of Glomerulopathies (RUG) was retrospectively reviewed searching for renal biopsies from patients receiving ASCT with a confirmed diagnosis of c-GVHD. Patients aged  $\geq 14$  years with biopsies obtained between 2000 and 2024 were included. The RUG was launched in 1970 at the Unidad Académica de Nefrología de la Facultad de Medicina, Universidad de la República, and gradually included data on patients with biopsy-confirmed glomerular disease. Since 2000, reporting of renal biopsies has been mandatory, and the RUG therefore collects information on all renal biopsies performed in the country. The medical records of the included patients were reviewed, obtaining epidemiological data, including the disease that led to the indication for ASCT, medications received during the pretransplant conditioning process, nephrological clinical presentation, and laboratory data before and after the renal biopsy.

To evaluate the renal response to established treatments, complete remission was defined as a reduction in proteinuria  $< 0.3$  g/day, a reduction in creatinine levels to baseline values prior to the development of renal impairment, and serum albumin levels  $\geq 3.5$  g/dL; partial remission was defined as a reduction in proteinuria  $< 3.5$  g/day and  $> 0.3$  m g/day, and stabilization at creatinine levels no greater than 25% above the baseline values prior to the development of renal impairment; and non-remission was defined as a failure to meet the above definitions.



**Figure 1** – Case 1. Panoramic view of a cortical fragment —Masson’s trichrome— (a). Glomerulus showing rigid capillary loops (arrows) —periodic acid-Schiff— (b). Capillary loops with microspicules (arrows) in the external sector of the glomerular basement membrane —methenamine silver— (c). Immunohistochemistry with intense positivity for antibodies (d).

**Table 1 – Population characteristics, ASCT, GVHD—nonrenal—and treatment received.**

|  | Case 1     | Case 2      | Case 3  | Case 4  | Case 5     | Case 6  | Case 7     |
|--|------------|-------------|---------|---------|------------|---------|------------|
| Age at ASCT (years)                    | 58         | 16          | 55      | 41      | 14         | 8       | 55         |
| Sex (M/F)                              | M          | F           | M       | F       | M          | M       | F          |
| Hematologic disease                    | AML        | ALL         | NHL     | AML     | AML        | ALL     | AML        |
| BM donor compatibility                 | I          | I           | I       | E       | E          | I       | I          |
| Conditioning treatment                 | FLU/MEL    | FLU/TBR     | FLU/MEL | CF/BU   | CF/BU/ETO  | CF/TBR  | ARA-C -DAU |
| GVHD prophylaxis                       | CsA        | CsA/MMF     | CsA/Mtx | CsA/MMF | CsA        | CsA/MMF | CsA        |
| Time from ASCT to start of GVHD (days) | 120        | 120         | 90      | 90      | 90         | 90      | 450        |
| Manifestations of GVHD (non-renal)     | C/G/H      | C/M/H/O/R/A | C/H     | C/M/H   | C/M/H/O/R  | C/R     | M/H/O      |
| Treatment of GVHD                      | CC/MMF/CsA | CC          | CC/CsA  | CsA     | CC/MMF/CsA | CC/MMF  | CC/CsA/Rtx |

Manifestations of GVHD: cutaneous (C), mucosal (M), gastrointestinal (G), hepatic (H), ocular (O), respiratory (R), osteoarticular (A).

ARA-C: cytosine arabinoside; BU: busulfan; CC: corticosteroids; CF: cyclophosphamide; CsA: cyclosporine A; DAU: daunorubicin; E: related donor; GVHD: graft-versus-host disease; ETO: etoposide; I: identical donor; F: female; FLU: fludarabine; AML: acute myeloblastic leukemia; ALL: acute lymphoblastic leukemia; NHL: non-Hodgkin lymphoma; M: male; MEL: melphalan; MMF: mycophenolate mofetil; Mtx: methotrexate; TBR: total body irradiation; Rtx: rituximab; ASCT: allogeneic hematopoietic stem cell transplant.

### Ethical aspects

The study protocol was approved by the Research Ethics Committee of the Hospital de Clínicas, Facultad de Medicina (No. 55-24). In Uruguay it is mandatory to report the Glomerular diseases, and an informed consent is obtained by which Patients agree that the data obtained from the renal biopsy, as well as the clinical data collected, may be used for research purposes.

## Results

### Population

Seven patients biopsied during the study period were included. Four were male, and the age was 41 (8–58) years. [Table 1](#) shows patient characteristics and data related to hematologic disease, ASCT, and the development of GVHD.

### Graft-versus-host disease

Four of the seven patients presented extrarenal manifestations of GVHD before the first 100 days after ASCT. The most frequent manifestations were cutaneous, presented as hyperpigmented lesions, lichen planus on the oral mucosa, and hepatic, primarily as elevated liver transaminases. GVHD prophylaxis was prescribed in all cases, with cyclosporine A being the most commonly used drug. None of the patients initially presented renal manifestations attributable to GVHD. Immunosuppressive treatment for the manifestations of GVHD included corticosteroids in all cases, with varying frequencies of cyclosporine A, mycophenolate mofetil, and rituximab ([Table 1](#)).

### Glomerular disease associated with GVHD

[Table 2](#) shows the most relevant histopathological findings of patients of the present study. The age at the time of developing renal manifestations was 42 (17–60) years. The

against phospholipase A2 in the glomerular basement membrane (d). **Case 2.** Panoramic view of a cortical fragment—Masson's trichrome— (a). Glomerulus showing rigid capillary loops (arrows)—periodic acid-Schiff— (b). Thin basement membranes (arrows) without spicules or double contours—methenamine silver— (c). Electron microscopy showing a glomerular capillary loop without deposits and diffuse pedicellar fusion (arrows) (d). **Case 3.** Glomerulus with segmental intracapillary hypercellularity (arrows)—periodic acid-Schiff— (a). Capillary loops at higher magnification, with occasional double contour images (arrows)—periodic acid-Schiff— (b). Glomerulus with segmental double contour images in the glomerular basement membrane (arrows)—methenamine silver— (c). Electron microscopy showing diffuse subendothelial deposits (\*) and pedicellar fusion (arrows) (d). **Case 4.** Glomerulus showing rigid capillary loops (arrows)—periodic acid-Schiff— (a). Rigid glomerular capillary loops (arrows)—methenamine silver— (b). Electron microscopy showing regular and diffuse subepithelial deposits (\*) in the external sector of the glomerular basement membrane, and diffuse pedicellar fusion (arrows) (c and d). **Case 5.** Glomerulus showing thickened and rigid capillary loops (arrows)—periodic acid-Schiff staining— (a). Diffuse spicules on the outer slope of the glomerular basement membrane (arrows)—methenamine silver staining— (b and c). Direct immunofluorescence with IgG staining showing a fine granular pericapillary pattern (d). **Case 6.** Glomerulus with infolding of the basement membranes (arrows); interlobular artery with myointimal fibrosis (\*) and arteriole with luminal thrombosis (‡)—periodic acid-Schiff staining— (a). Arteriole at higher magnification, with complete occlusion of the lumen (\*) and collagenization of the arteriolar wall (‡)—periodic acid-Schiff staining— (b). Vessels of different calibers with complete occlusion of the vascular lumen (\*)—methenamine silver staining— (c and d). **Case 7.** Panoramic view of a cortical fragment—periodic acid-Schiff— (a). Glomerulus showing regular thickening (arrows) of the glomerular basement membrane of the capillary loops—periodic acid-Schiff— (b). Glomerulus with rigid capillary loops (arrows)—methenamine silver— (c). Direct immunofluorescence staining for IgG with a fine granular pericapillary pattern (d).

**Table 2 – Clinical presentation, histopathology, treatment, and outcome of glomerular disease associated with GVHD (GVHD-G).**

|                                 | Case 1                                   | Case 2                       | Case 3                                       | Case 4                         | Case 5  | Case 6                         | Case 7                                      |
|---------------------------------|--|------------------------------|--|--------------------------------|---|--------------------------------|---|
| Age at diagnosis GVHD-G (years) | 60                                       | 18                           | 56   | 42                             | 20  | 17                             | 57  |
| Time from ASCT to GVHD-G (days) | 630                                      | 690                          | 480  | 360                            | 2160  | 3240                           | 450   |
| Nephrological manifestation     | NS                                       | NS                           | NS   | NS                             | NS  | RPRF                           | NS  |
| Creatinine (mg/dL)              | 1.1                                      | 0.5                          | 1.4  | 0.8                            | 0.5   | 3.1                            | 0.4   |
| Proteinuria (g/day)             | 2.54                                     | 11                           | 16   | 7.68                           | 11.7  | SD                             | 2.2   |
| Histopathology: OM pattern      | MG (E1)                                  | FSGS                         | MPGN   | MG(E1)                         | MG (E2)                                       | MAT                            | MG (E1)                                     |
| Histopathology: Indirect IF     | IgG+/K+/L+/Pla2r+<br>/IgM-/IgA-/C1q-/C3- | IgG-/IgM-IgA-/C1q-/C3-/K-/L- | C3+(pc)/IgG-/IgM-/IgA-/C1q-/K-/L-            | IgG+ /IgM-/IgA-/C1q-/C3-/K-/L- | IgG+<br>+(pc)/IgM+/IgA-/C1q-/C3-/K-/L-/Pla2r- | IgG-/IgM-/IgA-/C1q-/C3-/K-/L-/ | IgG+++ (pc)/IgM-/IgA-/C1q-/C3-/K-/L-/Pla2r- |
| Histopathology: EM              | ND                                       | ND                           | Diffuse PF, DC in GBM ND, Sn and IM deposits | Diffuse PF, Sp deposits        | ND  | ND                             | ND  |
| Treatment                       | CC/Rtx                                   | CC/Rtx                       | CC/MMF                                       | CC/CsA/Rtx                     | CC  | CC/MMF/EVE                     | CC/CsA/Rtx                                  |
| Follow-up (months)              | 15                                       | 14                           | 100  | 72                             | 96  | 24                             | 34  |
| Treatment response              | CR                                       | CR                           | PR   | CR                             | CR  | NR <sup>a</sup>                | CR  |

C1q: complement fraction C1q; C3: complement fraction C3; CC: corticosteroids; CsA: cyclosporine A; DC: double contour; E1: stage 1; E2: stage 2; FSGS: focal segmental GS; GVHD-G: graft-versus-host disease (GVHD); EVE: everolimus; PF: pedicellar fusion; MG: membranous glomerulonephritis; MPGN: membranoproliferative glomerulonephritis; IF: indirect immunofluorescence pattern on histopathology; IgA: immunoglobulin A; IgG: immunoglobulin G; IgM: immunoglobulin M; IM: intramembranous deposits; RPRF: rapidly progressive renal failure; K: kappa light chain; L: lambda light chain; TMA: thrombotic microangiopathy; GBM: glomerular basement membrane; EM: histopathological findings on electron microscopy; MMF: mofetil mycophenolate; BM: histopathological pattern on light microscopy; NR: non-remission; PR: partial remission; pc: pericapillary deposits; Pla2r: phospholipase A2 receptor; CR: complete remission; RT: rituximab; ND: no data; Sn: subendothelial deposits; Sp: subepithelial deposits; NS: nephrotic syndrome; ASCT: autologous hematopoietic progenitor cell transplant.

<sup>a</sup> Admission to a chronic dialysis program.

time between ASCT and the development of manifestations attributable to glomerular disease was 1144 (360–3240) days. The most frequent clinical presentation was nephrotic syndrome (6/7), with proteinuria 8.58 (2.2–16) g/day, creatinine 1.1 mg/dL, and a median creatinine level of 0.8 mg/dL. The most frequent histopathological pattern was membranous glomerulonephritis (MG) (4/7); less frequently, findings were compatible with focal segmental glomerulosclerosis (FSGS), membranoproliferative glomerulonephritis (MPGN), and thrombotic microangiopathy (TMA). One of the MG cases (case 1) was positive for Pla2r by immunofluorescence in the tissue sample, with negative plasma anti-Pla2r antibodies. Fig. 1 shows the most relevant histopathological findings in each case.

Treatment included corticosteroids in all cases, with bolus of methylprednisolone followed by prednisone, combined with rituximab (3/7), mycophenolate mofetil (2/7), or cyclosporine (2/7).

The response to the treatment was satisfactory, with complete remission in 5/7 cases and partial remission in

1/7. There was no response in only one case (case 6). This patient presented with rapidly progressive renal failure, with histopathological findings consistent with thrombotic microangiopathy, which necessitated the initiation of chronic dialysis.

## Discussion

We present a group of patients with glomerular disease associated with chronic GVHD. In all cases, glomerular involvement occurred in patients with other manifestations of GVHD. The most frequent clinical presentation was NS in the context of MG and, less frequently, FSGS, consistent with other reports shown in Table 3. The finding of TMA, present in our group and also in other series (Table 3), may be a consequence of the immunological activity of GVHD or of treatment with calcineurin inhibitors used as prophylaxis. In our case (case 6), TMA appeared after the development of GVHD in a patient with multiple extrarenal manifestations of the disease, suggesting that it may be a direct consequence of the disease. In

**Table 3 – Case series of glomerular disease associated with graft-versus-host disease in allogeneic hematopoietic stem cell transplant recipients published between 2014 and 2024.**

| Author (year)                               | Patients (n) | Reason for ASCT                        | Conditioning         | Presentation GVHD-G | Histopathological pattern                 | Treatment                       | Outcome                             |
|---|--------------|--|----------------------|---------------------|---|---------------------------------|-------------------------------------|
| Chanswangphuwana et al. (2014) <sup>7</sup> | 4            | CML                                    | ND                   | NS                  | MG  | MMF                             | CR                                  |
|   |              | FGCL                                   | CyA + MMF + TBR      | NS                  | FSGS (RB-1)/MG (RB-2)                     | CC (RB-1)/CC + CyA + MMF (RB-2) | NR (RB-1)/RC (RB-2)                 |
|   |              | AA                                     | CyA + MMF + CF + TBR | NS                  | MG + LN class III-IV                      | CC + CyA + MMF + Rtx            | CR(1)                               |
| Elghawy et al. (2022) <sup>14</sup>         | 2            | CML                                    | ND                   | NS + RPRF           | MGD                                       | CC + CyA + MMF                  |                                     |
|   |              | MDS                                    | ND                   | NS                  | MGL                                       | CC + TAC                        | CR                                  |
| Wong et al. (2016) <sup>15</sup>            | 4            | MDS                                    | ND                   | NS                  | MGL                                       | CC + TAC                        | CR                                  |
|   |              | AML                                    | FLU + MEL            | NS                  | MG  | CC                              | PR                                  |
|   |              | AML                                    | FLU + MEL            | NS                  | MG  | CC + MMF + Rtx                  | PR(2)                               |
| Mii et al. (2018) <sup>16</sup>             | 4            | FGCL                                   | FLU + MEL            | NS                  | MGL                                       | CC + CyA                        | CR                                  |
|   |              | ALL                                    | TBR + ETO            | NS                  | MG  | CC + TAC                        | CR(3)                               |
|   |              | MDS                                    | FLU + CF             | AUA                 | TMA                                       | Reduction of TAC                | NR                                  |
|   |              | NHL                                    | CF + ETO             | AKI                 | TMA                                       | CC                              | PR                                  |
| Guillaume et al. (2023) <sup>17</sup>       | 17           | AA                                     | FLU + CF + TIM       | AKI                 | TMA                                       | CC                              | ND                                  |
|   |              | AML                                    | CF + CIT             | AKI                 | TMA                                       | CC + reduction of CyA           | PR                                  |
|   |              | AML(5p)<br>CLL(3p)                     | ND                   | ND                  | TMA(4p)<br>ATN (5p)                       | ND                              | NR in TMA<br>CR in MGN and MGL(4)   |
| Hirokazu et al. (2000) <sup>18</sup>        | 51           | HL(3p)<br>NHL(2p)<br>MDS(1p)<br>ND(3p) | ND                   | AKI and NS          | MG(4p)<br>FSGS(1p)<br>ATN(2p)<br>MGL(1p)  | ND                              |                                     |
|   |              | AML (10p)                              | ND                   | AKI and NS          | TMA(2p)<br>MG(3p)<br>FSGS(1p)<br>MPGN(3p) | ND                              | CR if absence of TMA<br>NR with TMA |

- Initial complete response (CR) with CC + CyA; relapse treated with RTx + MMF with sustained CR.

- If no response (NR) with CC, RTx was added and partial response (PR) was achieved.

- If PR with CC, TAC was added and CR was achieved.

- They were treated with a combination of CC, CyA, and RTx.

AA: aplastic anemia; AUA: asymptomatic urinary abnormalities; RB: renal biopsy; CC: corticosteroids; CF: cyclophosphamide; CIT: cytarabine; CyA: cyclosporine A; FSGS: focal segmental sclerosing glomerulonephritis; G-GVHD: glomerular damage due graft-versus-host disease; ETO: etoposide; FLU: fludarabine; MG: membranous glomerulonephritis; MPGN: mesangial proliferative glomerulonephritis; AKI: acute kidney injury; RPRF: rapidly progressive renal failure; ALL: acute lymphoblastic leukemia; AML: acute myeloblastic leukemia; FGCL: follicular giant cell lymphoma; MGL: minimal glomerular lesion; HL: Hodgkin lymphoma; CML: chronic myeloid leukemia; NHL: non-Hodgkin lymphoma; CLL: chronic lymphoid leukemia; TMA: thrombotic microangiopathy; MEL: melphalan; MMF: mycophenolate mofetil; AIN: acute interstitial nephritis; LN: lupus nephritis; NR: no response; ATN: acute tubular necrosis; ITN: tubulointerstitial nephropathy; CR: complete response; TBR: total body irradiation; PR: partial response; RTx: rituximab; ND: no data; SIR: sirolimus; MDS: myelodysplastic syndrome; NS: nephrotic syndrome; TAC: tacrolimus; ASCT: allogeneic hematopoietic progenitor transplant; TIM: thymoglobulin.

other series, the finding of TMA (Table 3) is primarily associated with the use of calcineurin inhibitors. One case of MG in our series (case 1) was tissue-positive for the phospholipase A2 receptor (immunohistochemistry) without detecting anti-phospholipase A2 receptor (Pla2r) antibodies in plasma. This situation, that has been described in isolated cases,<sup>8,9</sup> may be explained in the context of GVHD by the production of donor-derived antibodies in response to allovariants of podocyte antigens (Plar2) from the recipient.<sup>10</sup> Other podocyte antigens identified in MG from patients with GVHD were NELL-1 (neural epidermal growth factor-like protein 1),<sup>11</sup> described in primary MG (without identified underlying disease), malignant diseases, drugs, autoimmune diseases, and solid organ and hematopoietic organ transplantation.<sup>12</sup> In a recent report,

Sethi et al. identified the procadherin FAT1 in 5 of 9 patients who developed MG in the context of GVHD.<sup>13</sup> In most of our patients with MG, we did not study the antigen involved in basement membrane deposition. The increased use of laser microdissection and mass spectrophotometry may allow for greater understanding of the antigens involved in MG development in patients with GVHD. The treatments prescribed in our patients varied (Table 2), with a notable favorable response in those presenting with podocytopathies (MG/FSGS) compared to those with TMA or MPGN. In our series, three patients were treated with rituximab, achieving complete remission in a short period of time. In other series (Table 3), treatment with rituximab was associated with complete remission in a high number of cases, which may be explained by the involvement

of B lymphocytes in the pathogenesis of GVHD, particularly in late stages (chronic GVHD).<sup>2,3</sup> In our patients the prognosis of renal function was good; only one patient (case 6) with rapidly progressive renal failure and TMA lesions in the renal biopsy required chronic dialysis. The strength of this study is that it captures all patients with chronic GVHD biopsied in the country. Its weakness is the retrospective nature of the analysis, which can lead to the loss of relevant information.

## Conclusions

Glomerular involvement secondary to chronic GVHD is rare. The most common histopathological pattern in renal biopsy is MG, followed by FSGS, MPGN, and TMA. Treatment based on corticosteroids combined with other immunosuppressants achieves adequate response rates. Rituximab appears to have a prominent place in the treatment of patients presenting with podocytopathy (MG, FSGS) in this context. The more extended use of mass spectrophotometry may allow identification of antigens associated with membrane deposits in those who develop MG in the context of GVHD secondary to ASCT.

## Funding

This research has not received specific grants from public, commercial, or non-profit agencies.

## Declaration of competing interest

The authors declare no conflict of interest.

## Acknowledgments

To all the nephrologists reporting to the Glomerulopathies Prevention and Treatment Program of Uruguay.

## REFERENCES

- Socié G, Stone JV, Wingard JR, Weisdorf D, Henslee-Downey PJ, Bredeson C, et al. Long-term survival and late deaths after allogeneic bone marrow transplantation. *N Engl J Med*. 1999;341:14–21.
- Williams KM, Inamoto Y, Im A, Hamilton B, Koreth J, Arora M, et al. National Institutes of Health Consensus Development Project on criteria for clinical trials in chronic graft-versus-host disease: I. The 2020 etiology and prevention working group report. *Transplant Cell Ther*. 2021;27:452–66.
- Pérez-Simón JA, Encinas C, Silva F, Arcos MJ, Díez-Campelo M, Sánchez-Guijo FM, et al. Prognostic factors of chronic graft-versus-host disease following allogeneic peripheral blood stem cell transplantation: the national institutes health scale plus the type of onset can predict survival rates and the duration of immunosuppressive therapy. *Biol Blood Marrow Transplant*. 2008;14:1163–71.
- Ganguli A, Sawinski D, Berns JS. Kidney diseases associated with haematological cancers. *Nat Rev Nephrol*. 2015;11:478–90.
- Renaghan AD, Jaimes EA, Malyszko J, Perazella MA, Sprangers B, Rosner MH. Acute kidney injury and CKD associated with hematopoietic stem cell transplantation. *Clin J Am Soc Nephrol*. 2020;15:289–97.
- Hingorani S. Chronic kidney disease in long-term survivors of hematopoietic cell transplantation: epidemiology, pathogenesis, and treatment. *J Am Soc Nephrol*. 2006;17:1995–2005.
- Chanswangphuwana C, Townamchai N, Intratumornchai T, Bunworasate U. Glomerular diseases associated with chronic graft-versus-host disease after allogeneic peripheral blood stem cell transplantation. In: *Transplantation Proceedings*. Elsevier; 2014. p. 3616–9.
- Byrne-Dugan CJ, Collins AB, Lam AQ, Batal I. Membranous nephropathy as a manifestation of graft-versus-host disease: association with HLA antigen typing, phospholipase A2 receptor, and C4d. *Am J kidney Dis*. 2014;64:987–93.
- Huang X, Qin W, Zhang M, Zheng C, Zeng C, Liu Z. Detection of anti-PLA2R autoantibodies and IgG subclasses in post-allogeneic hematopoietic stem cell transplantation membranous nephropathy. *Am J Med Sci*. 2013;346:32–7.
- Ronco P, Debiec H. Target antigens and nephritogenic antibodies in membranous nephropathy: of rats and men. In: *Seminars in immunopathology*. Springer; 2007. p. 445–58.
- Kudose S, Sekulic M, Mehring CJ, Santoriello D, Batal I, Stokes MB, et al. NELL1-associated membranous glomerulopathy after hematopoietic stem cell transplantation. *Kidney Int Reports*. 2021;6:1992–5.
- Sethi S. The many faces of NELL1 MN. *Clin Kidney J*. 2023;16:442–6.
- Sethi S, Madden B, Moura MC, Nasr SH, Klomjit N, Gross LA, et al. Hematopoietic stem cell transplant-membranous nephropathy is associated with protocadherin FAT1. *J Am Soc Nephrol*. 2022;33:1033–44.
- Elghawy O, Wang JS, Hafey AC, Renaghan AD, Whitehair RM, Kindwall-Keller TL. Minimal change disease secondary to graft-versus-host disease after allogeneic hematopoietic cell transplant for myelodysplastic syndrome. *Case Reports Nephrol Dial*. 2022;12:31–7.
- Wong E, Lasica M, He SZ, Bajel A, Roberts AW, Mason KD, et al. Nephrotic syndrome as a complication of chronic graft-versus-host disease after allogeneic hematopoietic stem cell transplantation. *Intern Med J*. 2016;46:737–41.
- Mii A, Shimizu A, Kaneko T, Nakayama K, Yamaguchi H, Tsuruoka S. Renal thrombotic microangiopathy after hematopoietic stem cell transplantation: involvement of chronic graft-versus-host disease. *Kidney Int Rep*. 2018;3:743–7.
- Roy G, Iordachescu I, Royal V, Lamarche C, Ahmad I, Nadeau-Fredette A-C, et al. Kidney biopsy findings among allogeneic hematopoietic stem cell transplant recipients with kidney injury: a case series. *Kidney Med*. 2023;5:100674.
- Imai H, Oyama Y, Miura AB, Endoh M, Sakai H. Hematopoietic cell transplantation-related nephropathy in Japan. *Am J kidney Dis*. 2000;36:474–80.