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# Membranous nephropathy associated with graft-versus-host disease in allogeneic bone marrow transplantation successfully treated with rituximab: A case report.

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## Abstract

**Introduction:** The incidence of renal disease in patients who have received a hematopoietic stem cell transplant is relatively low. However, nephrotic syndrome occurs in some patients, and membranous nephropathy is the most common cause.

**Clinical case:** A 58-year-old woman diagnosed with chronic myeloid leukemia was treated with nilotinib. She underwent allogeneic bone marrow transplantation with 100% HLA compatibility. Six months after the bone marrow transplant, the patient developed graft-versus-host disease affecting the mouth and salivary glands. She received tacrolimus at therapeutic doses. Without improvement, she developed nephrotic syndrome and anasarca.

**Diagnostic workshop:** Serum creatinine 0.64 mg/dl, albumin 3.58 g/dl, cholesterol 689 mg/dl, positive antinuclear antibodies. C3 and C4 were standard; ANCA C, P, and anti-DNA were negative; viral serologies for hepatitis B, C, and HIV were negative; 24-hour urine proteinuria was 4.9 g; and urine sediment: eumorphic micro hematuria (20–30 red blood cells/field) was detected. Renal biopsy was conclusive of membranous glomerulopathy. PLA2R staining (phospholipase A2 receptor type M), which was positive, was performed.

**Evolution**: The patient received oral prednisone at 1 mg/kg/day for two weeks without remission. Four doses of rituximab (375 mg/m2/week) were added. The nephrotic syndrome gradually improved until it wholly resolved after treatment without any sign of chronic myeloid leukemia relapse.

## Keywords:

Membranous nephropathy, Hematopoietic stem cell transplantation, Graft-versus-host disease.

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The incidence of kidney disease in patients who have received a hematopoietic stem cell transplant is relatively low. However, nephrotic syndrome occurs in some patients, and membranous nephropathy is the most common cause. Membranous nephropathy can be classified into two types: idiopathic, when there is no underlying disease, and secondary, when it is associated with a causal systemic disease. This nephropathy can develop in association with graft-versus-host disease and is considered secondary. Twenty percent of patients do not respond to standard therapy and can progress to end-stage kidney disease. Since glucocorticoid monotherapy is generally not effective in primary membranous nephropathy, the use of rituximab is considered a therapeutic alternative based on currently published evidence from case reports [1,2 ].

# Clinical case

### Case summary

A 58-year-old female patient diagnosed with chronic myeloid leukemia was treated with nilotinib as a first-line treatment. She underwent a 100% HLA-compatible allogeneic bone marrow transplant. At 6 months postbone marrow transplantation, he developed graft-versus-host disease affecting the mouth and salivary glands, which is why it was classified as GVHD-oral. He received tacrolimus at therapeutic doses.

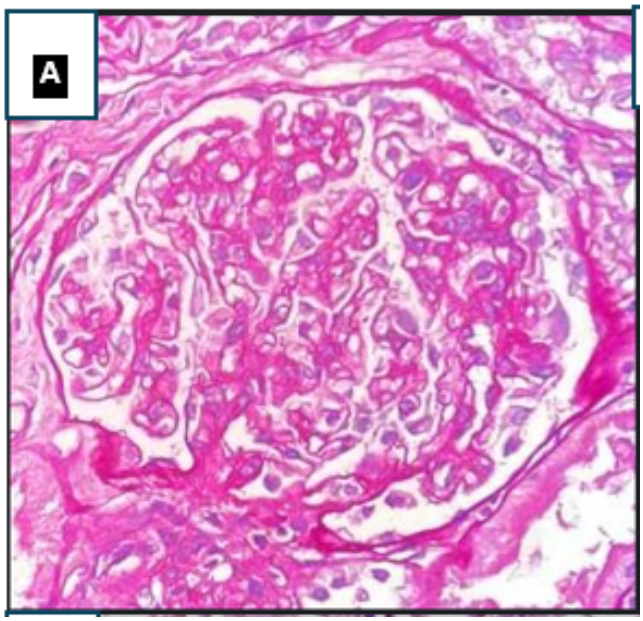
### Evolution

The patient was admitted due to the development of nephrotic syndrome with generalized edema, and in the previous week, she presented with anasarca. On admission, the following laboratory studies were performed: serum creatinine 0.64 mg/dl; albumin 3.58 g, cholesterol 689 mg/dl; triglycerides 295 mg/dl; positive antinuclear antibodies; standard C3 and C4 levels; ANCAs C, P and anti-DNA negative; viral serologies of hepatitis B, C and HIV-negative; proteinuria in urine of 24 hours, 4.9 g; and urine sediment: eumorphic hematuria (20–30 red blood cells/field) without acanthocytes, casts or crystals.

### Renal pathology

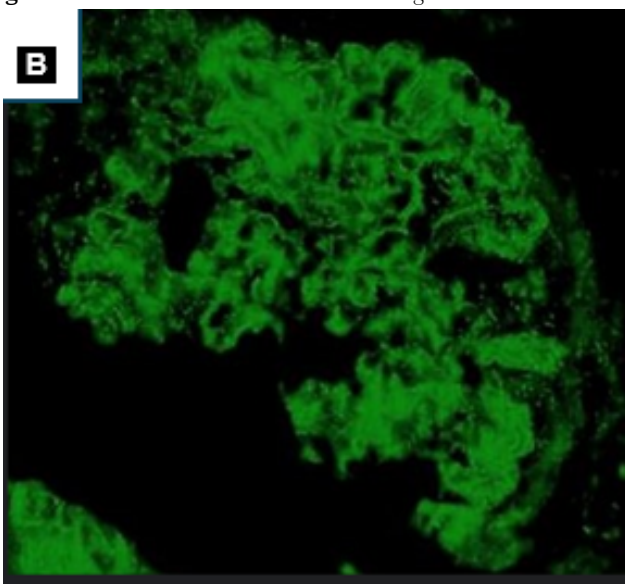
The renal biopsy revealed the following via light microscopy: 7 glomeruli, without global or segmental sclerosis, all with global and diffuse thickening of the glomerular basement membranes, with filling defects and spicules, preserved mesangial cellularity, and no endocapillary hypercellularity or extracapillary lesions. Tubules with atrophy ranging from 15–20%. The interstitium showed foci of fibrosis between 15% and 20%. Direct immunofluorescence revealed the following: IgG with fine granular deposits in the glomerular basement membrane and focal mesangium; C3, kappa, and lambda with fine granular deposits in the glomerular basement membrane; and IgA, IgM, and C1q negative. Staining was performed with PLA2R (phospholipase A2 receptor type M), which was positive (Figure 1, Figure 2 and Figure 3).

**Figure 1.** PAS staining.



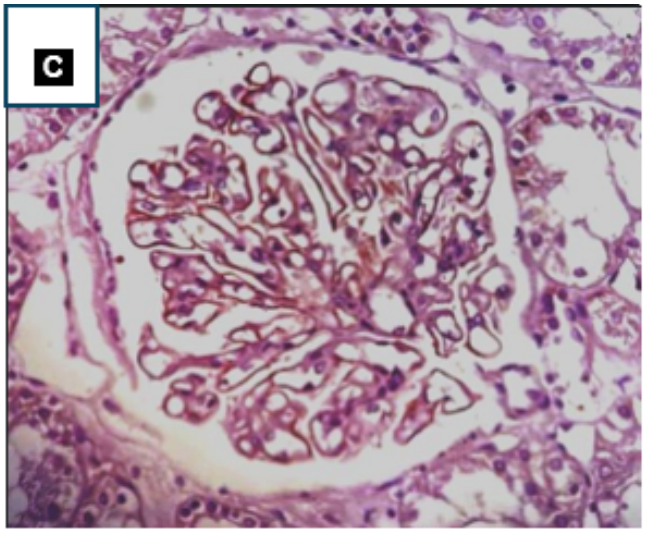

Basal and diffuse thickening of the basement and glomerular membranes.

**Figure 2.** Immunofluorescence for immunoglobulin G.




Fine granular deposits of immunoglobulin G +++/+++ in the glomerular basement membrane.

**Figure 3.** PLAR 2 staining was positive.




### Treatment

Initially, the patient received oral prednisone at 1 mg/kg/day for two weeks without remission. Rituximab (375 mg/m2/week) was added at four doses (Figure 4 and Table 1). The nephrotic syndrome gradually improved until its complete resolution after treatment without any sign of chronic myeloid leukemia relapse. The protein levels in the urine and serum albumin remained less than 1 g/day and greater than 3 g/dl during the 6-month follow-up period.

**Figure 4.** Evolution with the use of Rituximab.

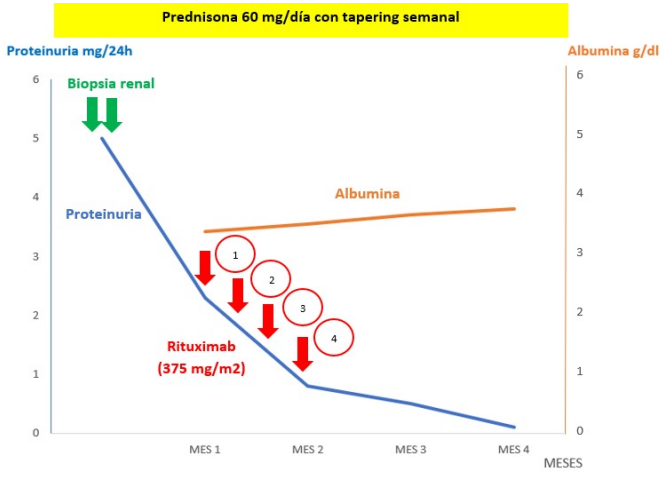



**Table 1.** Evolution in proteinuria and serum albumin.

| Time | Proteinuria | Serum albumin |
|---|---|---|
| Month 1 | 2,3 g/24 horas | 3,42 g/dL |
| Month 2 | 0,8 g/24 horas | |
| Month 3 | | 3,71 g/dL |
| Month 4 | 0,1 g/24 horas | 3,8 g/dL |

# Discussion

One of the most important causes of nephrotic syndrome in the population with autologous hematopoietic cell transplantation is graft-versus-host disease, which is related to the suspension or reduction of the dose of immunosuppressants [3,4].

Membranous nephropathy is the most common cause of nephrotic syndrome in cancer patients, accounting for approximately two-thirds of affected patients, followed by minimal change disease [5,6]. Although the precise pathogenetic mechanism underlying graft-versus-host disease-associated membranous nephropathy remains unclear, protocadherin FAT1 was recently identified as the primary target antigen. It was less frequently associated with PLA2R and NELL1. On the other hand, alloreactive B cells that produce antibodies with antigens in organs or tissues play essential roles.

In primary membranous nephropathy, exclusive corticosteroid therapy is inefficient; therefore, rituximab, a monoclonal antibody directed against B cells, has been used as a reasonable therapeutic option [7 -9]. Significantly few reported cases of secondary membranous nephropathy are associated with graft-versus-host disease treated with rituximab [9,10]. In the present clinical case, the response to using the monoclonal antibody was evaluated.

Although more studies are needed to understand the mechanisms involved fully, it is suggested that rituximab could improve nephrotic syndrome in patients with graft-versus-host disease through the following mechanisms:

Reducing humoral activity: by decreasing the number of B cells, the production of antibodies decreases, which modulates the immune response in graft-versus-host disease. Importantly, although isolated reports, such as the one presented in this report, suggest a potential benefit of rituximab in this population, the evidence still needs to be provided. More research is required to confirm its efficacy and safety. Treatment with rituximab should be individualized and considered in conjunction with other factors, such as the severity of the disease, possible side effects, response, and combination with other treatments and potential side effects.

# Conclusions

In this case study, we present a patient who, after a bone marrow transplant and the development of graft-versus-host disease (GVHD), developed membranous nephropathy. Treatment with rituximab has proven to be effective in managing this renal complication, significantly improving clinical markers and a favorable evolution of the disease.

# Patient perspective

I never imagined that after a bone marrow transplant, I would have to face such a great challenge again. When I was diagnosed with nephrotic syndrome, I felt like the world was falling on me. The thought of losing my bone marrow transplant and having to rely on dialysis

was overwhelming. However, owing to my medical team's and my family's support, I decided to face this new battle with optimism. The rituximab treatment was long and sometimes difficult, with some side effects that bothered me. However, I always keep in mind that it was a necessary step to regain my health. I remember feeling great emotion when the tests began improving, and the doctors confirmed that I was responding to the treatment. Today, I can say with joy that I have passed this stage. I have an everyday life again; I can enjoy the things I love the most, and I am deeply grateful for the opportunity to move on. This process has taught me the importance of resilience, hope, and the value of life. I want other patients to know that although the road may be difficult, there is hope. Medicine has rapidly advanced, and there are effective treatments for many diseases. The most important thing is to stay positive and trust the medical team. My experience has shown me that it is possible to overcome any obstacle with the proper support and a fighting spirit."

### Abbreviations

GVHD: graft-versus-host disease.
PLA2R phospholipase A2 receptor type M,.
C3: Complement 3.

### Supplementary information

The supplementary materials have not been declared.

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Does not apply.

### Authors' contributions

Jorge Quinchuela, conceptualization, data curation, formal analysis, fund acquisition, research, methodology.
Ricardo Mosquera, Project Administration, Resources, Software, Supervision.
Karla Arcentales, Validation, Visualization, Writing - original draft.
Genesis Velastegui, Drafting - review and editing, research, methodology.
Nicolás Larrea, conceptualization, methodology, research, writing - original draft.
Verónica Remache: Conceptualization, methodology, research, writing - original draft, project management, supervision, validation, visualization, writing - review and edition.

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### Availability of data or materials

Does not apply.

## Declarations

### Ethics committee approval and consent to participate

It does not apply to clinical cases.

### Consent for publication

The authors have permission from the patient to publish this manuscript in writing.

### Conflicts of interest

The authors declare that they have no conflicts of interest.

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