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Membranous Glomerulopathy After Autologous Hematopoietic Stem Cell Transplant in a Patient With Multiple Myeloma

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INTRODUCTION

Autologous hematopoietic stem cell transplant (HSCT) is a standard treatment for multiple myeloma (MM).[1] It is well known that kidney dysfunction related to MM, either acute or chronic, may be multifactorial, with factors including cast nephropathy and other paraprotein-associated renal diseases, nephrotoxicity owing to chemotherapy, immunosuppressive agents, and direct infiltration of neoplastic cells, among others. Furthermore, HSCT *per se* adds additional risks of developing kidney dysfunction with issues related to nephrotoxicity from medications, thrombotic microangiopathy, graft-versus-host disease (GVHD), and increased risk of infectious diseases.[2] There were 2 different studies that aimed to characterize renal biopsy findings in patients who underwent HSCT, either autologous or allogenic, for various indications, including MM, which have described membranous glomerulopathy (MGN), thrombotic microangiopathy, focal and segmental glomerulosclerosis, minimal change disease, acute tubular injury, tubulointerstitial nephritis, and another less common diagnosis.[3,4]

We present a case of MGN after autologous HSCT in a patient with MM. Unique histologic features are highlighted, and the issue of whether a MGN can be a manifestation of autologous GVHD is discussed.

CASE PRESENTATION

A 61-year-old man with a history of IgA lambda MM diagnosed in 2018, who was treated with 5 cycles of bortezomib, thalidomide, and dexamethasone, followed by autologous hematopoietic progenitor transplantation in March 2019 achieving a complete response. Subsequently, he was given 5 mg/day lenalidomide for maintenance, with adequate control of his underlying disease. In December 2019, the patient presented to the emergency department with acute polyuric renal failure and proteinuria in the nephrotic range. Laboratory studies revealed serum creatinine levels of 3.44 mg/dl, serum albumin of 1.30 g/dl, nephrotic range proteinuria (15.196 g/24 h), and urinalysis with no active sediment. The patient had no signs or symptoms of an active or chronic infection, and pretransplant workup examination results did not reveal infectious diseases. Pretransplant serology results ruled out cytomegalovirus, hepatitis B, toxoplasma, varicella-zoster, and human T cell lymphotropic virus. Results of a bone marrow biopsy revealed changes in the monoclonality of the initial light chain, with 10% of CD138-positive plasma cells having the kappa phenotype. Serum electrophoresis results revealed a monoclonal peak of 0.23 g/dl, and those of serum immunofixation revealed IgG kappa monoclonal paraprotein. Urine immunofixation result was negative, and positron emission tomography-computed tomography result was negative for bone neoplastic lesions.

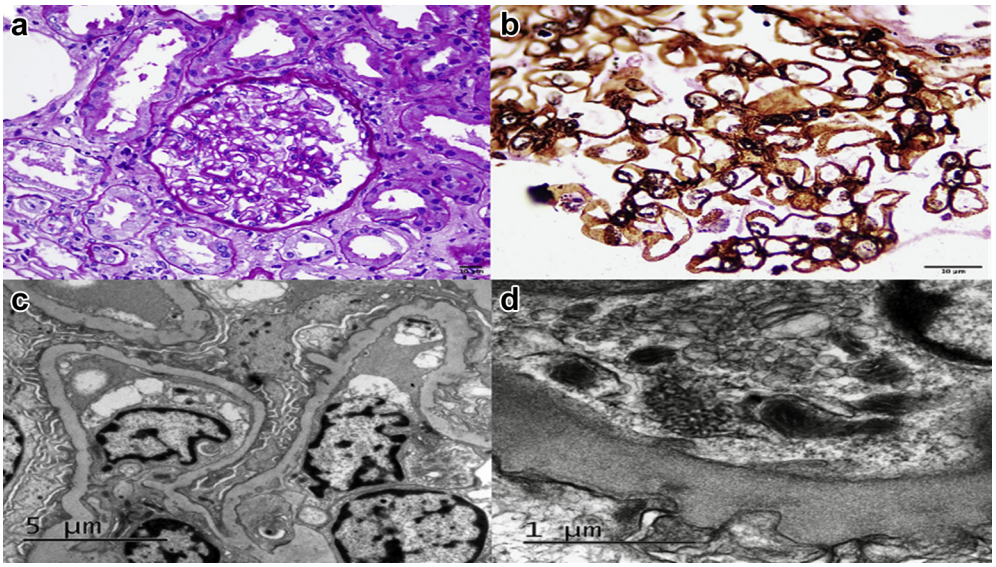

Figure 1. The kidney biopsy result revealed glomeruli with mild thickening of the capillary walls (a: periodic acid-Schiff stain, original magnification ×400) and the GBM having a vacuolated appearance (b: Jones silver stain, original magnification ×100). Electron microscopy images revealed an irregular and thickened GBM with scattered subepithelial and intramembranous immune-complex–type electron-dense deposits. There was extensive podocyte foot process effacement with infolding and invagination into the GBM and entrapment of microtubular structures in the GBM (c: electron microscopy, original magnification ×5000). Tubuloreticular inclusions were identified in endothelial cells (d: electron microscopy, original magnification ×10,000). GBM, glomerular basement membrane.

With a clinical impression of nephrotic syndrome and acute renal failure, a renal biopsy was performed. Light microscopy results revealed a total of 7 glomeruli, of which 1 had global sclerosis. The peripheral glomerular capillary walls were mildly thickened and had a vacuolated appearance on the silver Jones stain. No mesangial expansion or mesangial hypercellularity was noted. In addition, the glomeruli had no evidence of endocapillary hypercellularity, fibrinoid necrosis, or crescent formation. Less than 25% of the renal cortex had interstitial fibrosis and tubular atrophy. Furthermore, there was interstitial edema with patchy mononuclear inflammation. The tubules had signs of injury with detachment and flattening of tubular cells and loss of brush border. The arterioles were unremarkable and the arteries had mild intimal sclerosis.

Immunofluorescence microscopy results revealed a total of 6 glomeruli. There was diffuse granular staining along the glomerular capillary wall with IgG (1/4+), IgM (1/4+), C3 (1/4+), C1q (1/4+), kappa light chain (1/4+), and lambda light chain (1/4+). IgA was negative. No extraglomerular deposits were detected. Ultrastructural evaluation of 3 glomeruli revealed an irregularly thickened glomerular basement membrane with scattered subepithelial and intramembranous electron-dense, immune-complex–type deposits. No mesangial or subendothelial deposits were found. There was widespread effacement of the overlying foot processes. Endothelial cytoplasmic tubuloreticular inclusions were noted. Light microscopy and electron microscopy images of the kidney biopsy are found in Figure 1. A diagnosis of MGN and acute tubular injury was made in the renal biopsy results.

After obtaining the results from the bone marrow and renal biopsy, the patient received treatment with cyclophosphamide, dexamethasone, bortezomib, and daratumumab. After which, improvement of proteinuria (617 g/24 h) and creatinine levels (0.98 mg/dl) was observed. Nevertheless, cyclophosphamide was discontinued owing to pancytopenia after 2 doses. After 1 month, the patient was readmitted owing to anasarca, creatinine levels of 4.9 mg/dl, and proteinuria of 23 g/24 h, in which hemodialysis was started and oral cyclophosphamide was added. The patient was discharged with a modified Ponticelli regimen achieving creatinine levels of 0.9 mg/dl and proteinuria of 0.162 g/24 h after 1 month of treatment.

DISCUSSION

Membranous glomerulopathy is one the of most common diagnosis in renal biopsies from patients with HSCT and has been acknowledged as a manifestation of GVHD.[4] A clear-cut distinction between a primary and a secondary membranous glomerulonephritis is difficult to establish in this case because the results of anti-PLA2R serology performed after initiating treatment were negative. Nevertheless, considering that the patient was postautologous bone marrow transplant, including the presence of tubuloreticular inclusions in endothelial cells and C1q in immunofluorescence, a secondary etiology can be favored.

In theory, patients who undergo autologous HSCT should not be at risk of GVHD; nonetheless, it has been reported that up to 10% of these patients can have GVHD involving the skin, gastrointestinal tract, and liver.[4] It has been hypothesized that autologous GVHD is due to an autoimmune mechanism in which autoreactive T cells recognize self-major histocompatibility complex class II antigens and B cells produce autoantibodies.[5] In addition, there is evidence that interferon gamma may be a critical mediator for the development of autologous GVHD.[6]

Furthermore, few case reports have documented kidney involvement in patients with autologous HSCT in the form of MGN.[3,5,7] To the best of our knowledge, a total of 4 cases of MGN developing after autologous HSCT have been reported in the literature.[3,5,7]

Interestingly, in this case, tubuloreticular inclusions in endothelial cells were observed. These inclusions are subcellular organelles related to the biological activity of interferons and have been detected in patients with autoimmune disorders, viral infections, and systemic interferon treatment.[8] When found in the context of MGN, they suggest a secondary etiology. Although there are no data on the prevalence of tubuloreticular inclusions in patients who had received autologous HSCT, it is plausible that they can be related to an underlying autoimmune mechanism, which is also supported by the documented role of interferon gamma as a mediator in autologous GVHD. This unique ultrastructural finding warrants further studies, because to the best of our knowledge, this is the first case that describes tubuloreticular inclusions in a case of MGN after autologous HSCT.

Patients with MM are at risk of developing spontaneous autologous GVHD, with predisposing factors including dysregulation of the immune response from the disease *per se* or to the immunomodulatory treatment used for managing MM.[9] A renal biopsy can be a helpful tool to establish a diagnosis and guide treatment, please see the teaching points in Table 1.

Table 1. Teaching points

Teaching points
Membranous glomerulopathy can be a manifestation of GVHD after autologous hematopoietic stem cell transplant.
Autologous GVHD is likely due to an autoimmune mechanism, and interferon gamma may be a mediator for its development.
The ultrastructural finding of tubuloreticular inclusions is indicative of interferon activity and in the context of membranous glomerulopathy after autologous HSCT may serve as evidence of GVHD by an autoimmune mechanism.

GVHD, graph-versus-host disease; HSCT, hematopoietic stem cell transplant.

DISCLOSURE

All the authors declared no competing interests.

PATIENT CONSENT

Reporting of this case was approved by the local ethics review committees at the Hospital Universitario Fundación Santa Fe de Bogotá and the patient provided written informed consent.

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