Case Report

A case of membranous nephropathy as a manifestation of graft-versus-host disease

Jae Hyun Han1, Hyoung Rae Kim1, Gi Jeong Kim2, Beom Jin Lim2, Hyeon Woo Jeong2, Hyung Jung Oh1, Tae-Hyun Yoo1, Shin-Wook Kang1,3, Kyu Hun Choi1, Seung Yoo Han1,∗

1Department of Internal Medicine, Yonsei University College of Medicine, Seoul, Korea
2Department of Pathology, Yonsei University College of Medicine, Seoul, Korea
3Brain Korea 21 for Medical Science, Severance Biomedical Science Institute, Yonsei University, Seoul, Korea

A B S T R A C T

Nephrotic syndrome (NS) rarely occurs after hematopoietic stem cell transplantation (HSCT) as a late manifestation of graft-versus-host disease (GVHD). Herein, we report a case of HSCT-associated membranous nephropathy in a female patient with aplastic anemia. The patient received an allogeneic HSCT from her human leukocyte antigen-identical brother following myeloablative conditioning chemotherapy. NS occurred 21 months after HSCT without any concurrent features of chronic GVHD. The patient was treated with prednisolone and cyclosporine after renal biopsy confirmed membranous nephropathy, and achieved complete remission. Our report contradicts previous assumptions that concomitant chronic GVHD is responsible for the development of NS, suggesting that NS can develop as a new, independent manifestation of GVHD.

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Introduction

Allogeneic hematopoietic stem cell transplantation (allo-HSCT) is an established treatment for hematologic malignancy, and more than 15,000 procedures are performed worldwide each year [1]. After HSCT, chronic graft-versus-host disease (cGVHD) is the most common cause of morbidity and mortality. Indeed, the incidence of cGVHD is reported to be 60–80% during long-term follow-up [2], and the incidence has recently been increasing because of the extensive use of unrelated donor transplants, older donor age, increased use of donor leukocyte infusion, and peripheral blood stem cell transplantation (PBSCT) [3]. Symptoms of cGVHD can vary depending on the site of involvement, which may include the skin, eyes, oropharynx, or respiratory and gastrointestinal tracts. However, renal involvement associated with GVHD, particularly glomerulopathy, is very rare. In general, renal injury after HSCT occurs due to hemodynamic compromise, medications, radiation, or thrombotic microangiopathy [4], which manifests as tubulointerstitial nephropathy. Cases of nephrotic or nephritic syndrome after HSCT have recently been reported, and these glomerulopathies are presumably related to cGVHD. Herein, we report a case of membranous nephropathy (MN) in a patient who underwent HSCT 21 months before this unusual nephrotic syndrome (NS) developed.

Case report

A 39-year-old female patient was admitted to our hospital due to generalized edema and fatigue. The patient was diagnosed with aplastic anemia 3 years previously, and had no history of diabetes or hypertension. Most importantly, she had undergone allogeneic PBSCT from her human leukocyte antigen-identical brother 21 months before admission following myeloablative conditioning chemotherapy with cyclophosphamide and
anti-thymoglobulin. Grade IV acute gastrointestinal GVHD accompanied by diarrhea developed 12 days after transplantation despite GVHD prophylaxis with cyclosporine, methotrexate, and steroids, for which a continuous maintenance regimen of cyclosporine and prednisolone resulted in resolution. The patient also suffered from cytomegalovirus colitis 4 months after transplantation, and recovered after a 2-week administration of gancyclovir while cyclosporine was discontinued and prednisolone was tapered to 5 mg/day. Eighteen months after cytomegalovirus infection, the patient suddenly developed generalized edema and gained 5 kg of body weight over a 2-week period.

At this time physical examination revealed 3+ pitting edema of the lower extremities. Initial laboratory tests showed the following values: hemoglobin, 10.5 g/dL; platelets, 320 × 10^9/L; serum albumin, 0.77 g/dL; random urine protein-to-creatinine ratio (UPCR), 7.85 g/g; and 24-hour urinary protein excretion, 5.03 g/day. Hepatitis B surface antigen, hepatitis C antibody and anti-nuclear antibody titers were undetectable, and serum concentrations of C3, C4, and immunoglobulins G, A, and M were within reference range.

Renal biopsy was performed 3 days after admission. On light microscopy (Fig. 1A), eight nonsclerotic glomeruli were normocellular without mesangial expansion. The glomerular basement membrane was not thickened and double contours or subepithelial spikes were not noted. The interstitium was moderately infiltrated by mononuclear inflammatory cells, which immunohistochemical staining confirmed as CD3+ T cells (Fig. 1B). Immunofluorescence studies showed a granular pattern of IgG (2+) (Fig. 1C). Electron microscopy demonstrated numerous nodular electron-dense deposits that were mainly located in the subepithelial space along with diffusely effaced epithelial foot processes (Fig. 1D).

These pathologic findings were consistent with Grade II MN. As such, oral prednisolone at a dose of 1 mg/kg was immediately started, and an 8-week treatment resulted in partial remission with a UPCR of 1.9 g/g. Because the patient was intolerant to the side effects of corticosteroid treatment, prednisolone was tapered. Two weeks later, however, the random UPCR increased to 7.58 g/g; thus, cyclosporine at a dose of 5 mg/kg was added. Complete remission was achieved as demonstrated by a UPCR of 0.23 g/g 4 months after the combined treatment with cyclosporine and 10 mg/day of low-dose prednisolone.

**Discussion**

Acute kidney injury (AKI) is a common complication in patients with allo-HSCT. In general, AKI can be attributed to preexisting renal disease, underlying malignancy, previous chemotherapies, irradiation, and various nephrotoxic agents such as antimicrobials, antifungals, and antivirals [5]. Accordingly, acute tubular necrosis, hemolytic uremic syndrome, thrombotic microangiopathy, and radiation nephritis are the most common forms of AKI after HSCT. However, glomerulopathy such as NS or nephritis rarely occurs as a manifestation of cGVHD.

The notion that graft-versus-host reaction is directly related to glomerular injury has recently been gaining acceptance. However, the clinical characteristics of HSCT-associated glomerulopathy are not well defined. Several studies conducted comprehensive analyses of patients with postHSCT NS [1,6–9]. One of these reports showed that nine of 889 patients who

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**Figure 1. Pathologic findings in a patient with membranous nephropathy as a manifestation of graft versus host disease.** (A) Light microscopy shows normal appearance of glomeruli without thickened basement membrane (original magnification ×400). (B) Immunohistochemical staining identifies CD3+, suggesting infiltration of T cells in the interstitium (original magnification ×100). (C) Immunofluorescence staining shows granular pattern of IgG (2+) deposition along the peripheral capillary wall. (D) Electron microscopy shows numerous nodular electron-dense deposits in the subepithelial space.