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Membranous Nephropathy after Allogeneic Hematopoietic Stem Cell Transplantation in a Patient with Aplastic Anemia
: A Case Report

Nephrotic syndrome has been described as one of the clinical forms of chronic graft-versus-host disease (cGVHD), but a limited number of cases have been described. We experienced a young female patient with nephrotic syndrome developed 22 months after allogeneic hematopoietic stem cell transplantation (HSCT) for severe aplastic anemia. She had been well after successful management for gut-limited cGVHD until she developed a clinical nephrotic syndrome with hypoalbuminemia of 2.0 g/dL and 24-hr urine protein of 6.88 g/dL. On physical examination and laboratory findings, there was no other evidence of cGVHD. Clinical and renal biopsy findings were consistent with cGVHD-related membranous nephropathy, and immunosuppressive agents with cyclosporine and prednisone were prescribed. After 3 month of treatment, the proteinuria decreased to normal range; and the patient from nephrotic syndrome nearly recovered. We recommend cGVHD-related glomerulonephritis should be considered in all patients with hypoalbuminemia following allogeneic HSCT, even if there is no other evidence of clinical GVHD.

Key Words : *Graft vs Host Disease; Nephrotic Syndrome; Glomerulonephritis*

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INTRODUCTION

Chronic graft-versus-host disease (cGVHD) occurs in approximately 50-60% and is a major cause of morbidity and mortality of long-term survivors of allogeneic hematopoietic stem cell transplantation (1, 2). Most of clinical manifestations seen in cGVHD are similar to those in various immune complex disorders such as collagen vascular diseases with involvement of oral mucosa and gastrointestinal track, skin and soft tissue, eye, liver, lung, etc. Although the mechanisms are not well elucidated, the involvement of the kidney and central nervous system seems unusual. Nephrotic syndrome has been described as one of the clinical forms of cGVHD, but a limited number of cases with nephrotic syndrome after allogeneic HSCT has been described (3-13).

We report a patient with nephrotic syndrome that developed 22 months after allogeneic HSCT for severe aplastic anemia with a review of the literature. According to our literature review, this is the first case of nephropathy after allogeneic HSCT in Korea.

CASE REPORT

A 21-yr-old female was admitted to the hospital in September 2001 because of the abrupt development of a nephrotic syndrome. She was diagnosed as severe aplastic anemia in April 1998 and received immunosuppressive therapy with ATG, cyclosporine, and glucocorticoid. Complete remission was attained after the immnosuppressive therapy, but the aplastic anemia relapsed after 16 months.

In November 1999, she underwent an allogeneic peripheral HSCT from an HLA-identical sibling donor. She received ATG 90 mg/kg and cyclophosphamide 200 mg/kg as conditioning regimen and cyclosporine, methotrexate, and glucocorticoid as prophylaxis of GVHD. Engraftment was sustained and there was no acute GVHD. Cyclosporine was tapered and finally withdrawn after 6 months. After 1 month, she developed a grade IV cGVHD of gastrointestinal track with diarrhea and a grade II skin disease with diffuse erythema requiring the cyclosporine again. After 3 months, the diarrhea and erythema were subsided and cyclosporine was gradually tapered off. In February 2001, she never needed any medications.

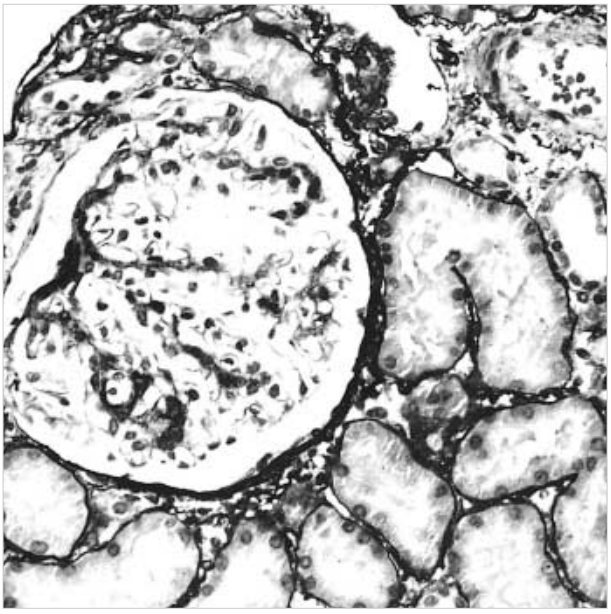

Fig. 1. Renal biopsy shows mild thickening of the glomerular capillary walls. Mesangial cellularity is not increased (PA-silver stain, ×200).

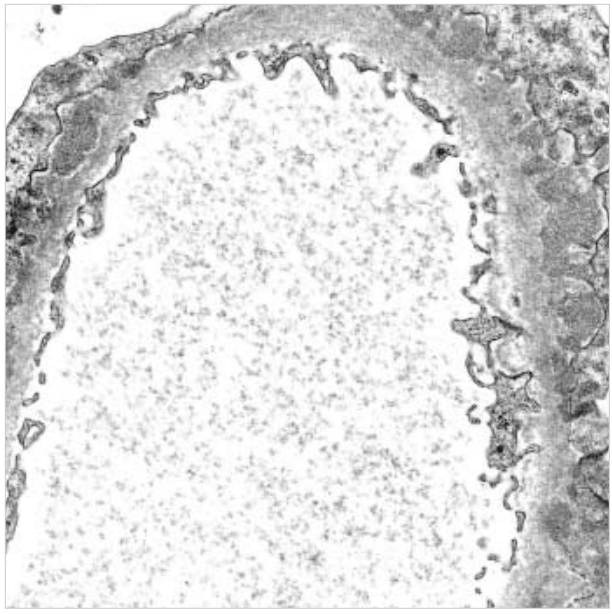

Fig. 2. Electron microscopy shows epimembranous electron-dense deposits along the glomerular basement membrane (×11,200).

After 6 months, in August 2001, she developed a clinical nephrotic syndrome with hypoalbuminemia of 2.0 g/dL and 24-hr urine protein of 6.88 g/dL. She never had renal problems with routine laboratory findings. On physical examination, the vital signs were normal and no skin lesion was observed. Laboratory examination showed normal CBC, CRP, liver enzymes, renal function, cholesterols, and electrolytes. Serum immunoglobulin G, A, M and C3, C4 levels were normal. Urinalysis showed proteinuria and microscopic hematuria. Tests for hepatitis B antigen and antibody, hepatitis C, and antinuclear antibody were all negative.

The renal biopsy contained a total of 12 glomeruli, three of which were globally sclerotic. The remaining tufts showed mild thickening of capillary walls. Mesangial cellularity was not increased. There were patchy foci of tubular atrophy and striped interstitial fibrosis with a moderately dense mononuclear cell infiltrate. Mild arteriolar thickening was present (Fig. 1). Immunofluorescence study showed diffuse granular deposits of IgG along the capillary walls. IgA, C1q, C3, IgM, and fibronogen were negative (rabbit anti-human, FITC, DAKO). Electron microscopy revealed diffuse thickening of glomerular basement membranes by epimembranous electron-dense deposits. These deposits were separated by spike-like processes or occasionally surrounded by a thin membrane. The epithelial foot processes were diffusely effaced. There observed no mesangial deposits (Fig. 2). These clinical and renal biopsy findings were consistent with chronic GVHD-related membranous nephropathy, and she was treated with cyclosporine and prednisone, which has greatly improved her symptoms and signs related with nephrotic syndrome. After 3 month of treatment, the proteinuria decreased to normal range and the nephrotic syndrome nearly recovered.

DISCUSSION

The occurrence of GVHD-related nephropathy after allogeneic HSCT is a rare event (14). HSCT-related nephropathy includes hemolytic uremic syndrome, acute renal failure, nephrotic syndrome, and chronic renal failure. The main patterns of the early-onset nephropathy after HSCT are known to be acute renal failure and hemolytic uremic syndrome related to drugs including cyclosporine or infections. Conversely, GVHD-related nephrotic syndrome, chronic renal failure, and sometimes irradiation-related nephropathy are the main patterns of the late-onset nephropathy. The most common type of the late-onset nephropathy after HSCT is nephrotic syndrome, and the most common pathologic finding of nephrotic syndrome is membranous nephropathy (12, 13). But other nonspecific findings, such as mesangiolysis, tubulointerstitial nephritis, and focal segmental glomerulonephritis have been reported.

It is not uncommon that a late-onset nephropathy simultaneously develops with other GVHD symptoms and signs after insufficient immunosuppression. Therefore the renal damage seems to be caused by the effects of antibodies induced by GVHD. Glomerular immune complex formation in chronic GVHD, similar with lupus nephritis, can be caused by immune complex trapping from the circulation, by binding of autoantibodies to antigens deposited in the glomerulus,

by direct binding of autoantibodies to intrinsic glomerular antigens, or by a combination of these mechanisms. The possible etiologic factors of membranous nephropathy include infection, autoimmune disorders, cancer, drugs, etc. Ohsawa et al. (11) reported a glomerular and tubular immune complex deposits in a HSCT recipient and suggested that the renal deposition of immune complex seemed to be caused by lodging of circulating immune complex to the glomeruli and tubules. But the precise mechanisms are still controversial and direct GVHD-mediated renal injury cannot be completely excluded. Occasionally de novo cases of nephrotic syndrome in renal allografts have been found and these suggest that cellular alloreactivity could induce the membranous nephropathy (15). Experimental data showed that in situ immune complex formation caused by alloreactive T cells could be associated with the glomerulonephritis (16). Also, Müller et al. (6) reported that the presence of interstitial CD8+ T lymphocytes infiltration indicated a GVHD-mediated renal injury. In our case, glomerular IgG desposits and patchy interstitial fibrosis with moderate-degree mononuclear cell infiltrates were observed. And there were no endothelial tubuloreticular inclusions or mesangial or tubulointerstitial electron-dense deposits. Cyclosporine has withdrawn for 6 months. These findings may be encountered in the advanced stages of membranous nephropathy, but also suggest a direct GVHD-mediated renal injury. More interestingly, our case showed only nephrotic syndrome without other evidence of GVHD-related symptoms or signs. On our literature review, there are a few cases with nephrotic syndrome without other evidence of GNHD-related symptoms or signs (4, 11, 12). Further investigation on these rare cases may provide valuable insight into the immunopathogenesis of membranous nephropathy in allogeneic HSCT recipients.

In conclusion, we recommend cGVHD-related glomerulonephritis should be considered in all patients with hypoalbuminemia following allogeneic HSCT, even if there is no evidence of clinical GVHD.

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