A Hematopoietic Stem Cell Transplant Recipient with Nephrotic Syndrome and Immune Complex Deposits in Tubular Basement Membrane: A Rare Case Report

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Following allogenic hematopoietic stem cell transplantation (HSCT), graft-versus-host disease (GVHD) may develop which may affect several organs. Although the presence of nephrotic syndrome after HSCT is rare, sometimes it occurs in the setting of GVHD. The most common histological finding on kidney biopsy of patients with proteinuria owing to GVHD is membranous glomerulonephritis (MGN). However, reports of immune complex deposition in the tubular basement membrane (TBM) and glomerular basement membrane (GBM) are extremely rare. Herein we present a 65-year-old female with a history of HSCT at six years ago who was referred to Dr.Shariati Hospital in Tehran with nephrotic syndrome. Secondary serologic laboratory tests were all normal. The histopathologic study indicated diffuse GBM and TBM thickening, spike formation, infiltration of inflammatory mononuclear cells in tubulointerstitial area and acute tubular injury in light microscopy. Immunofluorescence staining showed immune complex deposits in GBM, mesangial cells, and TBM.

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Case Report

INTRODUCTION

Following allogenic hematopoietic stem cell transplantation (HSCT), graft-versus-host disease (GVHD) may develop which may affect several organs. About 50% of patients with HSCT suffer from chronic GVHD (cGVHD). It may occur within a few months to a few years after HSCT.[1] The nephrotic syndrome after HSCT as a rare complication sometimes occurs in the setting of GVHD.[2] Membranous glomerulonephritis (MGN) is the most common histological finding on kidney biopsy of the patients with proteinuria owing to GVHD. The complication is similar to what is seen in secondary membranous nephropathy due to autoimmune diseases.[3]

Immune complexes seldom deposit in both the tubular basement membrane (TBM) and the glomerular basement membrane (GBM). We present a case of membranous nephropathy with the immune complex deposits in both GBM and TBM following allogenic HSCT.

CASE PRESENTATION

A 65-year-old female with edema, weight gain, and nephrotic range proteinuria was referred to Dr. Shariati Hospital in Tehran for further evaluation. The patient had a history of HSCT due to acute myeloid leukemia six years ago. The physical examination revealed a diffuse edema in lower extremities. The body mass index (BMI) was 28.5 kg/m^2. The laboratory findings showed serum creatinine 2.3 mg/dL, blood urea nitrogen (BUN)

66 mg/dL, abnormal lipid profile, proteinuria of 3 g/d, without hematuria in urine analysis (UA) (Table 1). Cell blood count (CBC), serum electrolytes, liver and thyroid function tests were normal. The patient 's glomerular filtration rate (GFR) on admission day was 23 mL/min /1.73 m^2 based on CKD-EPI equation. Further workup to find of secondary causes of nephrotic syndrome, such as hepatitis B, hepatitis C, cytomegalovirus, human immunodeficiency virus, urine culture, blood culture, anti-streptolysin antibody, antinuclear antibody (ANA), anti-double stranded DNA antibody, rheumatoid factor, cryoglobulin antibodies, antibody against phospholipase A2 receptor, anti-glomerular basement membrane, anti-neutrophil cytoplasmic antibodies, serum indices of complement activity (C3, C4, CH50) revealed normal results. A percutaneous kidney biopsy was performed. The histopathologic study indicated diffuse GBM and TBM thickening, spike formation, mild mesangial expansion (Figure 1-A, C), infiltration of inflammatory mononuclear cells in tubulointerstitial space and acute tubular injury in light microscopy (Figure 1-B). Immunofluorescence staining showed granular deposits of C3 and IgG in GBM and mesengial cells, linear deposits of C3 and IgG in TBM which were suggestive of TBM deposits (Figure 1-D).

Based on the clinical, laboratory and histopathologic evaluation, chronic GVHD was diagnosed. Tacrolimus was started with a dose of 2 mg per day in addition to other supportive treatments (Losartan, Rosuvastatin, Calcitriol), Prednisolone and diuretics to control edema. After three months, the rate of protein excretion in 24-hour urine collection decreased and GFR improved. The patient achieved partial and complete response, within 3 and 6 months, respectively and was followed for 2 years (Table 1).

DISCUSSION

There are some reports of nephrotic syndrome after HSCT in the literature since 1988 that indicate different histological involvements in kidney biopsy, mostly MGN, (70%) and minimal change disease (MCD) in about 20% of patients.[4] Most nephrotic syndromes due to MGN were successfully treated with corticosteroids and calcineurin inhibitors.[5] However, in resistant cases, the rate of successful treatment was considerably increased with Rituximab. The incidence of renal involvement, several years after HSCT, due to chronic GVHD is rare.[6]

The case of this study who was suffering from nephrotic syndrome six years after HSCT was referred to Dr. Shariati Hospital in Tehran. MGN was confirmed by kidney biopsy. In addition to presence of immune complex deposits in GBM and mesangial area in immunofluorescent staining, we also discovered C3 and IgG deposits in the TBM. Considering the association of these tubular deposits with interstitial inflammation and tubular injury, reduced kidney function could be expected. On the other side, immune complex deposits in TBM were exclusively reported by Ohsawa I, *et al*.[7] The report of five cases of membranous nephropathy with deposits in TBM following HSCT was recently published by Nasr SH, *et al*.[8] Based on the histological findings of the above-mentioned two studies and our study, it seems that occurrence of immune complex deposits in TBM and GBM due to cGVHD following HSCT is rare.

Table 1. Results of Laboratory Findings

Serum Biochemistry	First	After 3 months	After 6 months	After 1-year	After 2-year
BUN, mg/dL	34	26	15	16	12
Creatinine, mg/dL	2.3	1.6	1.1	1.2	0.98
Sodium, meq/L	137	136	135	134	135
Potassium, meq/L	4.29	4.6	5.1	4.8	4.3
Urinary Protein, mg/d	3000	980	560	216	192
Urinary Creatinine, mg/d	680	656	675	650	672
Serum Albumin, g/dL	2.3	3.7	4	4.9	5
Cholesterol, mg/dL	406	225	119	152	147
Triglyceride, mg/dL	289	190	160	178	162
LDL, mg/dL	271	150	53	62	76

Abbreviations: BUN, blood urea nitrogen; LDL, low density lipoprotein.

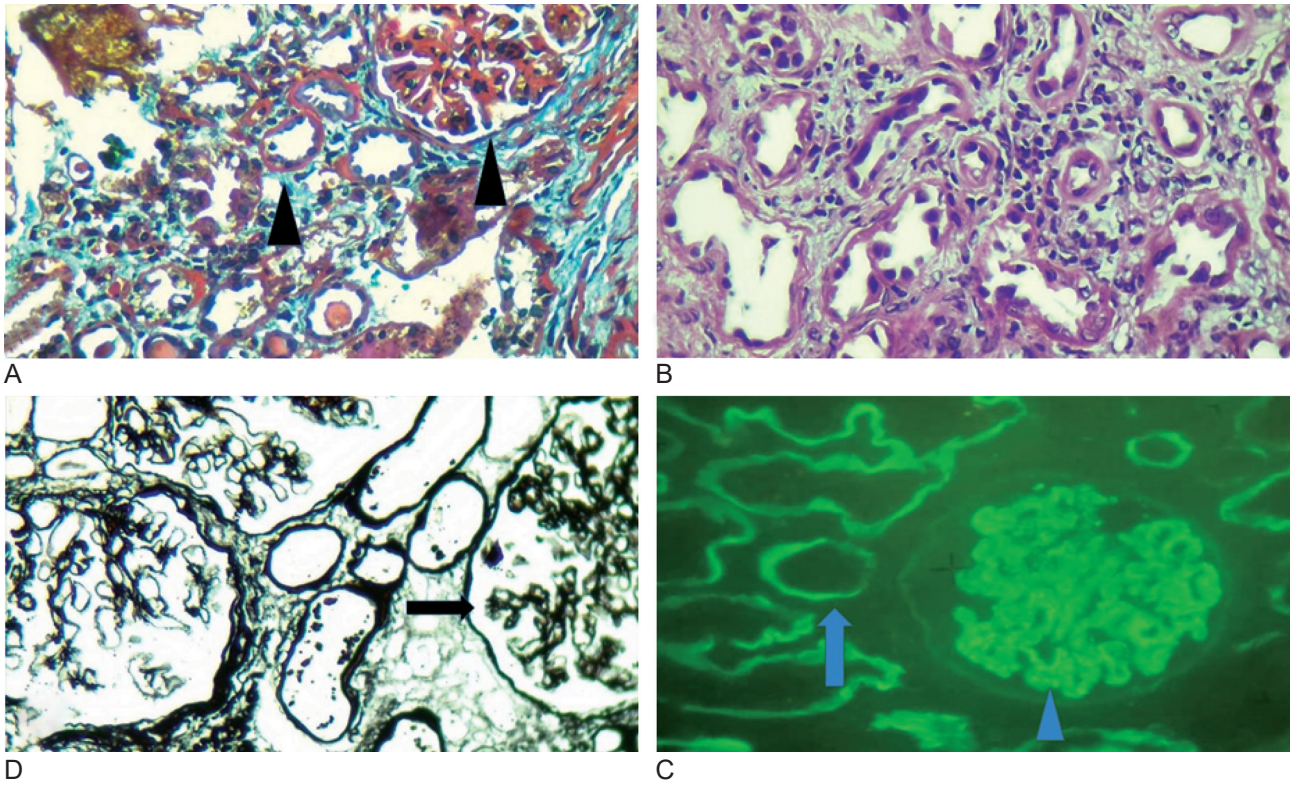

Figure 1. Histopathologic study of kidney biopsy in a 65-year-old female with acute nephrotic syndrome 6 years after HSCT [A: Masson's trichrome stain shows diffuse thickening of GBM and TBM (black arrow heads) with fuschinophilic deposits, B: H&E-stained sections show interstitial inflammation, C: Methenamine Silver stains reveal subepithelial spikes (black arrow), and D: Immunofluorescence study shows linear IgG deposits along the TBM (arrow) and granular deposits along the GBM and mesangial (arrow head)]

In this regard, to find immune complex deposits in patients with nephrotic proteinuria due to GVHD after HSCT, we emphasize evaluating non-glomerular and glomerular areas.

CONFLICT OF INTEREST

The authors declare that they have no conflict of interests.

ETHICAL CONSIDERATIONS

This case report was conducted in accord with the World Medical Association Declaration of Helsinki. This case report was approved by the Ethics Committee of Tehran University of Medical Sciences approved this study (Ethical code #IR.TUMS.SHARIATI.REC.1402.102). Written informed consent was obtained from the patient for publication of this report and permission to use the figures. Moreover, ethical issues (including plagiarism, data fabrication, double publication) have been completely observed by the authors.

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