

Case Report

## Chronic graft-versus-host disease complicated by nephrotic syndrome

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### Abstract

Chronic graft-versus-host disease (cGVHD) is one of the most frequent and serious complications of allogeneic hematopoietic stem cell transplantation (HSCT). Nephrotic syndrome (NS) is an uncommon and underrecognized manifestation of cGVHD. We report a patient who developed NS 18 months after allogeneic bone marrow transplantation. The onset of NS was accompanied by active manifestations of cGVHD, and immunosuppressants had not been tapered recently. Renal biopsy revealed membranous nephropathy. The patient failed to improve with three combined immunosuppressants (prednisolone, cyclosporine, and mycophenolate mofetil), but achieved partial remission after intravenous immunoglobulin (IVIG) infusion. Twenty-four months after the diagnosis of NS, the patient was still in hematological remission, with normal serum creatinine level, urinary protein loss of 0.7–1.9 g/day and mild oral mucositis. Our report suggests that NS can be a cGVHD-related immune disorder in HSCT patients. Monitoring of renal parameters, especially proteinuria, is important in cGVHD patients. Our case indicated that post-transplant NS, occurring without history of tapering or following immunosuppressant withdrawal, presents a more severe activity of cGVHD and a relatively severe clinical course. IVIG may modify and control the refractory GVHD-related NS, and can be one of the choices of treatment.

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**Keywords:** graft-versus-host disease; intravenous immunoglobulin; membranous nephropathy; nephrotic syndrome

### 1. Introduction

Chronic graft-versus-host disease (cGVHD) is one of the most serious and common late complications of allogeneic hematopoietic stem cell transplantation (HSCT). It occurs in 20–70% of patients surviving >100 days after HSCT, and

causes significant morbidity and mortality.<sup>1</sup> cGVHD develops at least 2–3 months after transplantation, presenting as a systemic autoimmune disorder.<sup>2</sup> It frequently affects the skin, eyes, mouth, serous membranes, liver, gastrointestinal and respiratory tract.<sup>3</sup> Despite increasing knowledge about cGVHD, nephrotic syndrome (NS) following HSCT remains an ill-defined entity. It is reported as an uncommon and underrecognized complication and is usually associated with cGVHD.<sup>4</sup> A close temporal relationship between NS, tapering or discontinuation of immunosuppressants and simultaneous cGVHD is observed. The majority of reported cases respond to immunosuppressive therapy. Here, we present a patient with

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cGVHD-related NS, who responded poor to prednisolone, cyclosporine (CsA), and mycophenolate mofetil (MMF) therapy. Partial remission was achieved following treatment with intravenous immunoglobulin (IVIG). To the best of our knowledge, this is the second case of IVIG used in cGVHD-related NS.<sup>5</sup>

## 2. Case report

An 8-year-old boy was diagnosed with acute lymphoblastic leukemia (ALL). Surface marker examination of the leukemic blasts showed MY7 = 4%, MY9 = 2%, B1 = 93%, B4 = 97%, HLADR = 95%, Leu4 = 2%, Leu9 = 2%, T11 = 3%, TDT = 94%, CALA = 97%, CD5 = 1%, CD22 = 97%, and CD34 = 76%. Karyotypic analysis demonstrated 46,XY,t(9;22)(q34;q11.2)/46, idem, t(7;9)(q11.2;p23)/46,XY, and molecular analysis showed bcr-abl fusion gene positive. The patient received induction, consolidation, and maintenance chemotherapy, and remission was achieved. Sixteen months later, ALL relapse was diagnosed. The patient received another course of chemotherapy, and then bone marrow aspiration revealed remission status. Two months after the second remission, he received an allogeneic bone marrow transplantation from his HLA-identical brother. However, second relapse was diagnosed 1 month later and he received another course of chemotherapy and imatinib mesylate treatment. Donor lymphocyte transfusion was given after remission was achieved again. Four months after allogeneic bone marrow transplantation, oral mucosal ulceration and maculopapular skin rash were observed. cGVHD was diagnosed on the basis of clinical findings, and prednisolone and CsA were prescribed for treatment. The patient had normal pre- and post-transplant renal function and was without proteinuria.

Fourteen months after diagnosis of cGVHD the patient presented with symptoms of NS, including scrotum swelling, severe bilateral leg, and eyelid edema. In the recent 9 months, prednisolone and CsA had not been tapered or withdrawn. He was afebrile, with blood pressure 112/73 mmHg, pulse of 75/minute, with no respiratory distress. Relapse of ALL was excluded by confirming a 100% donor chimerism, and conventional cytogenetics revealed absence of the Philadelphia chromosome. The patient had oral mucosal ulceration and maculopapular skin rash consistent with active manifestations of cGVHD (Fig. 1). Laboratory tests showed that his white cell count was 6500/cumm, hemoglobin 7.76 mmol/L, and platelet 318,000/cumm. Serum albumin was 21 g/L, total protein 42 g/L, blood creatinine 70.72  $\mu$ mol/L, blood urea nitrogen 7.50 mmol/L, aspartate transaminase 19 U/L, alanine transaminase 7 U/L, alkaline phosphatase 82 U/L, and  $\gamma$ -glutamyltransferase 35 U/L. Serum immunoglobulin (Ig) levels were IgG 3.62 g/L, IgA 0.39 g/L, and IgM 1.64 g/L. Total cholesterol was 12.82 mmol/L and triglyceride 2.75 mmol/L. Urine test revealed proteinuria 4+ and 24-hour urinary protein loss was 6.2 g. Search for antinuclear antibody and anti-double-stranded DNA was negative, and serum complement levels (C3, C4) were within the normal range. Tests for hepatitis B virus antigen, hepatitis C,



Fig. 1. Skin lesion of chronic graft-versus-host disease. The maculopapular skin rash over the face is compatible with chronic graft-versus-host disease.

cytomegalovirus IgM, and Epstein–Barr virus IgM were negative. Renal venous Doppler ultrasonography, abdominal sonography, and chest X-ray were normal.

A percutaneous renal biopsy was performed, and membranous glomerulonephropathy (MGN) was diagnosed on the basis of light, immunofluorescence and electron microscopy (Fig. 2). There was diffuse global thickening and rigidity of glomerular capillary walls. Mild diffuse segmental expansion of mesangial matrix was also noted. No interstitial infiltration, fibrosis, or vascular abnormalities, which may be evidence for CsA toxicity, were found. Immunofluorescence analysis showed diffuse granular immune deposition for IgG and mild deposition for C3 along the capillary loops. Immunofluorescence staining was negative for IgA, IgM, C4, and C1q antibodies. Electron microscopy showed moderate global subepithelial deposition of electron-dense material with frequent intramembranous extension. The glomerular basement membrane showed prominent thickening up to 804 nm. The visceral epithelial foot process showed extensive global effacement.

The patient was treated with methylprednisolone pulse therapy for 3 consecutive days, followed by oral prednisolone (1 mg/kg/day). The dosage of CsA was increased to 4 mg/kg/day. However, hypoalbuminemia, proteinuria, and edema did not improve. Owing to resistance to prednisolone and CsA treatment, MMF was added. One month later, edema had not resolved, and hypoalbuminemia and heavy proteinuria were persistent. Very low serum IgG level of 0.97 g/L was noted, and IVIG with 400 mg/kg was administered. After the IVIG infusion, edema resolved and serum albumin returned to a normal level gradually. Partial remission was achieved 2 weeks later with 24-hour urinary protein loss being 1.48 g. Evolution of NS was in parallel with the evolution of cGVHD. Twenty-four months after the diagnosis of NS, the patient was still in hematological remission, with normal serum creatinine level, urinary protein loss of 0.7–1.9 g/day, and mild oral mucositis. The patient is still on immunosuppressive therapy with prednisolone, CsA, and MMF.

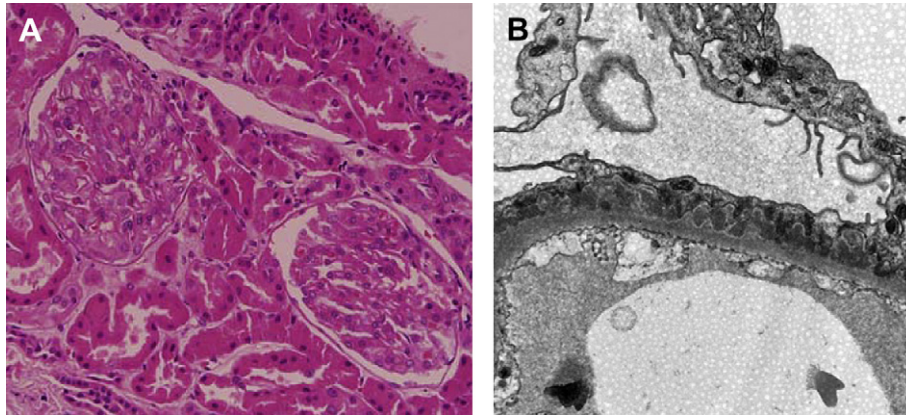


Fig. 2. Renal biopsy findings showing membranous glomerulonephropathy. (A) Hematoxylin and eosin stain: diffuse global thickening and rigidity of glomerular capillary walls. (B) Electron microscopy: moderate global subepithelial deposition of electron-dense material, prominent thickening of the glomerular basement membrane, and extensive global effacement of visceral epithelial foot processes.

### 3. Discussion

Here, we have described a case of NS, which developed 16 months after HSCT and was found to be associated with cGVHD. Renal biopsy revealed MGN. In previous reported cases, the majority of patients had evidence of cGVHD, had recently changed immunosuppressant doses, and responded well to immunosuppressive medications.<sup>4,6</sup> Our case developed NS without clear-cut relationships with medication change, but had active manifestations of cGVHD at MGN diagnosis and responded poorly to three combined immunosuppressant treatments. Our case indicates that post-transplant NS, occurring without history of tapering or following immunosuppressant withdrawal, shows a more severe activity of cGVHD. It presents a relatively severe clinical course and poor clinical response to treatment. IVIG, with immunomodulatory efficacy, was effective in this refractory GVHD-related NS. To the best of our knowledge, this is the second case to show that IVIG is effective in reducing proteinuria in patients with cGVHD-related NS.<sup>5</sup>

Renal involvement is an uncommon and underrecognized manifestation during the course of cGVHD. MGN has been found in two-thirds of patients with GVHD-related NS.<sup>6</sup> Other renal diseases, such as minimal change disease, focal segmental glomerulonephritis, diffuse proliferative glomerulonephritis, IgA nephropathy, membranoproliferative glomerulonephritis, and antineutrophil cytoplasmic antibody-associated glomerulonephritis, have also been described.<sup>7</sup> Many features seen in cGVHD are similar to those of autoimmune diseases, such as systemic lupus erythematosus, systemic sclerosis, Sjögren's syndrome, primary biliary cirrhosis, myasthenia gravis, and polymyositis.<sup>8,9</sup> Because circulating or *in situ* immune complexes are responsible for the features of MGN, post-HSCT MGN may represent another consequence of this graft-versus-host conflict. In experimental studies, lupus nephritis was induced by murine GVHD models.<sup>7,8</sup> These findings support that an immune complex-mediated mechanism during the course of GVHD may have a role in the pathogenesis of MGN.

The most used treatment options include prednisolone and CsA in post-HSCT MGN patients. Other agents have been used in the past for GVHD-related glomerular disease, such as cyclophosphamide, tacrolimus, MMF and rituximab, and clorambucil.<sup>4,6</sup> However, the appropriate treatment, dose, and duration of immunosuppressive medication is still unknown. Response of post-HSCT MGN to treatment with prednisolone and immunosuppressant is variable: 27% showed complete and 62% showed partial remission.<sup>9</sup> Furthermore, chronic immunosuppressant therapy has multiple toxicities. Prolonged exposure to immunosuppressive medication facilitates the development of new cancers or relapse of disease.<sup>1</sup> Stevenson et al<sup>10</sup> reported two cases of NS after HSCT: relapsed solid organ and bone marrow leukemia were diagnosed following reintroduction of CsA. Therefore, the prescription of immunosuppressive medication should be very cautious, and new approaches to treating cGVHD is an emerging approach.<sup>1</sup>

IVIG is a complex product that has been used as an adjunct to antibacterial and antiviral therapy. IVIG, with the effects of anti-idiotypic regulation and inhibition of cytokines, has also been hypothesized to modulate or reduce the severity of acute GVHD.<sup>11</sup> In clinical studies, the role of IVIG therapy in prevention and treatment of GVHD is vague.<sup>12</sup> Several large controlled trials showed that administration of IVIG prevented infection in patients undergoing HSCT and reduced the incidence of acute GVHD,<sup>13</sup> and other studies failed to show a statistically significant benefit.<sup>12</sup> Sullivan et al demonstrated that passive immunotherapy with IVIG had immunomodulatory and antimicrobial efficacy in HSCT patients.<sup>14</sup> Furthermore, the use of IVIG is standard in HSCT patients with severe hypogammaglobulinemia in many centers.<sup>2,13,15</sup> In our case, IVIG infusion accompanied partial remission of proteinuria and regression of edema in immunosuppressant-refractory NS. The prompt clinical response suggested the role of immunomodulation of IVIG in post-HSCT NS. Combined or coincident response with other immunosuppressive therapy is another consideration. In a previously reported case, immunosuppressant, IVIG, and plasma exchange were prescribed to achieve partial remission.<sup>5</sup> Unlike previous reports, recent studies show

that post-HSCT MGN treatment is burdened by high morbidity and mortality rates.<sup>5,6</sup> According to our report, IVIG may be one of the choices to modify GVHD when patients do not respond to multiple immunosuppressive interventions.

In conclusion, our report supports that NS can be a cGVHD-related immune disorder in HSCT patients. Monitoring of renal parameters, especially proteinuria, is important in cGVHD patients. Although the pathogenesis of GVHD-related glomerular disease after HSCT remains elusive, our case underlines the possible importance of IVIG in modifying and controlling GVHD-related NS. Further study of larger cohorts is mandatory to delineate the therapeutic benefits of IVIG in NS associated with cGVHD.

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