



Antineutrophil Cytoplasmic Antibody–Associated Glomerulonephritis in Chronic Graft-Versus-Host Disease After Allogenic Hematopoietic Stem Cell Transplantation

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ABSTRACT

Graft-versus-host disease (GVHD) is one of the most frequent complications that occur after hematopoietic stem cell transplantation (HSCT). Recently, renal involvement, including membranous nephropathy, focal segmental glomerulosclerosis, and minimal change disease, has been described as a manifestation of chronic GVHD. This case report describes a patient who developed antineutrophil cytoplasmic antibody (ANCA)–associated glomerulonephritis after HSCT. Following preparation with chemotherapy, a 29-year-old man with chronic myeloid leukemia underwent allogenic peripheral blood stem cell (PBSC) transplantation, after which first acute and then chronic GVHD developed. Treatment with prednisone resulted in improvement in the patient's GVHD. After the termination of steroid therapy and about 10 months after PBSC transplantation, nephritic syndrome appeared and the patient's serum creatinine value increased to 1.7 mg/dL. Laboratory evaluation revealed perinuclear antineutrophilic cytoplasmic antibody (p-ANCA) in the serum. Histological examination of renal biopsy tissue showed focal segmental proliferative glomerulonephritis with glomerulosclerosis in 20% of available glomeruli, large cellular crescents in 6% of glomeruli, and no staining of immunoglobulins or complement along the capillary walls. Electron microscopy revealed no immune deposits. After treatment with prednisone 60 mg/d, diltiazem 120 mg/d, and enalapril 10 mg/d, the proteinuria gradually decreased, and p-ANCA was undetectable. These findings suggest that in this patient the ANCA-associated glomerulonephritis was associated with renal involvement that occurred during the course of chronic GVHD.

GRAFT-versus-host disease (GVHD) is a serious complication that can develop during allogenic hematopoietic stem cell transplantation (HSCT). GVHD occurs in 50% of patients who have undergone bone marrow transplantation. Although the clinical manifestations of acute GVHD appear during the first few weeks after bone marrow transplantation, the chronic form of the disease may persist for several months to a year after that procedure. Many of the features of chronic GVHD are similar to those of various immune system disorders such as collagen vascular disease. In humans, glomerulonephritis is rarely associated with chronic GVHD. Recently, however, renal involvement, including (membranous nephropathy, focal segmental glomerulosclerosis, and minimal change disease), has been described as a manifestation of that disease.

CASE REPORT

In March 1999, a 29-year-old man was diagnosed as having Philadelphia chromosome (PH¹)-positive chronic myeloid leukemia. After receiving hydroxyurea, the patient underwent allogenic peripheral blood stem cell (PBSC) transplantation after conditioning with busulphan (16 mg/kg total dose) and cyclophosphamide (200 mg/kg). In April 2000, the patient received 7.5×10^8 mononuclear cells/kg and 7.5×10^6 CD34+ cells/kg from his

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human leukocyte antigen (HLA)-identical sibling. Skin and gastrointestinal manifestations of GVHD, which were treated with prednisolone and cyclosporine, occurred on the ninth day after transplantation. Twenty days after transplantation, the patient complained of itching. Laboratory evaluation revealed hepatic manifestations of chronic GVHD that have persisted: alkaline phosphatase (ALP), 910 U/L; alanine transaminase (ALT), 50 U/L; aspartate transaminase (AST), 60 U/L; and γ -glutamyltransferase (GGT), 607 U/L. After the termination of prednisone and cyclosporine therapy at about 10 months after transplantation, the patient presented with bilateral pedal edema.

The patient's blood pressure was 120/85 mm Hg, and laboratory analyses showed the following values: white blood cell count, 9600/mm³; hemoglobin level, 14 g/L; platelet count, 215,000/mm³; and sedimentation rate, 90 mm/h. Proteinuria was detected with a 24-hour urinary albumin loss of 7 g. Microscopic examination of a urine sample revealed an active urinary sediment. The following values were also identified: serum albumin, 2 g/dL; total protein, 4 g/dL; blood creatinine, 1.7 mg/dL; blood urea nitrogen, 97 mg/dL; AST, 55 U/L; ALT, 65 U/L; and ALP, 710 U/L. The values for serum bilirubin, prothrombin time (PT), and partial thromboplastin time (PTT) were within the normal range. The patient's total cholesterol level was 516 mg/dL, and his triglyceride level was 244 mg/dL.

The result of antinuclear antibody testing was negative. Serum immunoglobulin levels and complement levels (C3 and C4) were within the normal range. The results of testing for hepatitis B surface antigen and hepatitis C antibody were negative. Perinuclear antineutrophilic cytoplasmic antibody (p-ANCA) identified using indirect immunofluorescence, showed specificity for myeloperoxidase (value, 8.7 U/mL; normal range, <3.1 U/mL). The result of testing for cytoplasmic ANCA (c-ANCA) was negative. Chest radiography and renal ultrasonography revealed no abnormalities. The results of renal venous Doppler ultrasonography were within normal parameters, which excluded renal venous thrombosis.

Light microscopy of renal biopsy tissue showed focal segmental proliferative glomerulonephritis with glomerulosclerosis in 20% of available glomeruli and large cellular crescents in 6% of glomeruli. No staining of immunoglobulins or complements along the capillary walls was revealed by immunofluorescence microscopy, and electron microscopy showed no immune deposits. The results of bone marrow biopsy were within the normal range; the result of testing for PH¹ was negative.

Treatment was initiated with prednisone 60 mg/d, diltiazem 120 mg/d, and enalapril 10 mg/d. After 3 months, the proteinuria gradually resolved, the serum creatinine level returned to the normal range, and the results of testing for ANCA were negative. Treatment with corticosteroids was tapered for 12 months. At the time of this writing, 24 months after the diagnosis of ANCA-associated glomerulonephritis, the patient's level of albuminuria was 1 g/d, and his treatment regimen consists of prednisone 2.5 mg alternate day, diltiazem 60 mg/d, and enalapril 10 mg/d.

DISCUSSION

The manifestations of chronic GVHD, which involve the skin, liver, eyes, and gastrointestinal and upper respiratory systems, resemble those of a variety of immune complex diseases.¹ Renal involvement is a rarely seen manifestation during the course of GVHD. The few cases reported to date have involved²⁻⁸ membranous nephropathy,²⁻⁴ minimal change disease,^{5,6} or focal segmental sclerosis.^{6,7} In this case report, ANCA-associated glomerulonephritis was di-

agnosed in a patient with hepatic manifestations of chronic GVHD. In the single reported case⁸ of vasculitis that developed after autologous PBSC transplantation, a 47-year-old man with non-Hodgkin's lymphoma exhibited ANCA-associated pulmonary and renal vasculitis (antineutrophil cytoplasmic antibody, MPO-ANCA) at 2 years after transplantation. When the patient's lymphoma recurred, so did his ANCA-associated vasculitis. Treatment consisted of prednisolone, cyclophosphamide, and plasma exchange. The patient profiled in this case report, however, demonstrated no pulmonary involvement or recurrence of chronic myeloid leukemia after transplantation, and his ANCA-associated glomerulonephritis improved only after corticosteroid therapy.

Immune-complex-mediated injury plays a key role in the pathogenesis of renal GVHD. In experimental studies, lupus nephritis was induced extensively in murine models of GVHD, which supports the theory that an immune-complex-mediated mechanism during the course of GVHD may have a role in the pathogenesis of membranous glomerulonephritis.⁹ The development of autoantibodies including ANCA has been reported after both allogeneic and autologous bone marrow transplantation.¹⁰ ANCA detected using immunofluorescence may not be recognized using antigen-specific enzyme-linked immunosorbent assay (ELISA) for the identification of antibodies against the neutrophil antigens myeloperoxidase and proteinase 3.¹⁰

Helper T cells play a crucial role in the initiation of ANCA production. One possibility is that donor helper T cells act against host leukocytes to cause production of ANCA by B cells during the course of GVHD, a role in the pathogenesis of ANCA-associated glomerulonephritis. However, other factors, such as postgraft bacterial and viral infections, may contribute to immune dysregulation, development of autoreactivity, and production of ANCA.⁸

In summary, ANCA-associated glomerulonephritis may be a new type of chronic GVHD-related immune disorder in patients who have undergone bone marrow or PBSC transplantation. Additional studies are needed to clarify this association.

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