Successful Long-term Graft Survival of a Renal Transplantation Patient with Wiskott-Aldrich Syndrome

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Abstract

Wiskott-Aldrich syndrome, a rare X-linked hereditary syndrome, is characterized by immunodeficiency, thrombocytopenia, and eczema. The underlying T-cell defect renders renal transplantation and immunosuppressive treatments uncertain. The present case exhibited the mild clinical manifestation, regarded as X-linked thrombocytopenia. He successfully underwent a living-donor ABO-compatible renal transplantation and splenectomy in 2002, and thereafter experiencing no severe rejection, serious infection, or malignancy for more than 10 years. Though IgA nephropathy was detected 8 months after transplantation, the patient’s renal function and proteinuria were stable without any treatment. The present case showed a successful long-term graft survival and the importance of splenectomy added to renal transplantation.

Key words: renal transplantation, Wiskott-Aldrich syndrome, X-linked thrombocytopenia, splenectomy, IgA nephropathy

(Intern Med 55: 1761-1763, 2016)

DOI: 10.2169/internalmedicine.55.6337)

Introduction

Wiskott-Aldrich syndrome (WAS) is a rare X-linked hereditary syndrome characterized by immunodeficiency, thrombocytopenia, and eczema (1). Although typical cases of WAS have this full triad of clinical manifestations, others have a milder phenotype (2). A defect of the cellular and humoral immune system renders patients with WAS more vulnerable to infections, autoimmune diseases, and malignancies.

Immunoglobulin A (IgA) nephropathy is occasionally found in WAS patients, which often causes end-stage renal disease (ESRD) (3).

The underlying T-cell defect renders renal transplantation (RTx) and the immunosuppressive regimen uncertain. Only four such cases have been reported in the literature (4-7). Only one report described a successful long-term outcome (7). These cases showed that the risk of complications attributable to RTx remained during the perioperative term and afterward in WAS patients. It is important to assess the patient’s manifestations before operation and to determine whether or not the regimen of immunosuppressive agents should be modified. Because IgA nephropathy might develop in grafts, careful monitoring is needed.

We herein report a successful long-term follow-up case with WAS who underwent living donor RTx and splenectomy.

Case Report

A 25-year-old man who was genetically diagnosed as having WAS visited our outpatient office in 2001 for an evaluation before RTx. Since early childhood, he developed thrombocytopenia, eczema, recurrent nasal hemorrhage, and purpura, two intracranial hemorrhages requiring platelet transfusion, and abscesses of the thigh and cheek. When he was 16 years of age, proteinuria was detected. His renal
function deteriorated gradually. A renal biopsy was not conducted because of the risk of hemorrhaging with a low platelet count. Hemodialysis was initiated five years later.

The result of a genetic analysis showed a known WAS mutation, c. 168C>T p. Thr45Met, which corresponds to an X-linked thrombocytopenia (XLT) phenotype. Chronic thrombocytopenia, transient eczema, and minor infection without autoimmune disease or malignancy and genetic testing suggested the diagnosis of XLT, a mild form of WAS. One HLA-AB mismatch was found, and another in HLA-DR. A lymphocyte cytotoxicity test was negative. The patient was negative for anti-cytomegalovirus IgG antibody, anti-herpes simplex virus IgG antibody, anti-variella zoster virus IgG antibody, anti-Epstein-Barr virus IgG antibody, anti-adenovirus antibody, anti-mumps virus IgG antibody, anti-measles virus IgG antibody and anti-rubella virus IgG antibody. A defect of CD43 expression was not found.

After a careful evaluation, we decided to perform RTx. He received platelet transfusion on the day prior and the day of surgery because his platelet count was 1.0×10^9 mm^-3. A living-donor ABO-compatible RTx from his mother was conducted and splenectomy was undertaken simultaneously for thrombocytopenia in 2002. Since our case was considered to be a mild form of WAS, our standard immunosuppressive regimen for ABO-compatible RTx was applied: 20 mg basiliximab was administered on day 0 approximately 2 hours before transplantation with a second course on postoperative day (POD) 4. An infusion of 250 mg methylprednisolone (MP) was initiated on the transplant day, which was tapered to achieve the dose of 20 mg/day by POD 10. The MP infusion was then changed to oral administration and tapered gradually to a maintenance dose (4-6 mg/day). The patient’s MP dose was decreased to 8 mg/day on discharge. An oral dose of cyclosporine (CsA) microemulsion (8 mg/kg/day) was started 2 days before RTx. The patient received continuous infusion of CsA (3 mg/kg/day) after the operation, and was switched to oral administration at 4 mg/kg/day. The dose of CsA was decreased to 3 mg/kg/day at discharge, which was adjusted with monitoring of the CsA level at 2 hours (C2) or the area under the time-concentration curve (AUC). Mycophenolate mofetil at a dose of 2 g/day was commenced 2 days before RTx and continued thereafter.

Due to an increase in beta-D glucan on POD 4, fluconazole was administered orally. On POD 15 he sustained a high fever with a C-reactive protein level up to 11.19 mg/dL, along with cytomegalovirus viremia. Because an abdominal CT scan image revealed cellulitis of the left internal oblique muscle of the abdomen, 2.5 g of gamma globulin was administered for three days with ganciclovir. The fever subsequently subsided within three days. Severe infection and perioperative bleeding did not develop during the hospital stay. The serum creatinine level was 0.9-1.1 mg/dL without proteinuria on discharge. The platelet count was also elevated to approximately 15×10^9 mm^-3. Anti-herpesvirus prophylaxis with acyclovir (600 mg/day, twice a week), anti-pneumocystis prophylaxis with sulfamethoxazole-trimethoprim (3 g/day, twice a week), antibiotics in general with sulfamethicillin tosil late (750 mg/day), and 2.5 g of gamma globulin for 3 days per month were continued until 5 months after RTx for the prevention of severe infection. At eight months after transplantation, his serum creatinine level had increased to 1.3-1.4 mg/dL, accompanied with mild proteinuria (0.15 g/gCr) and hematuria (10-19/HPF). A renal biopsy demonstrated mild IgA nephropathy which was not found in his 0-hour biopsy on transplantation. It showed a mild mesangial matrix expansion with mild infiltration of monocytes and neutrophils. Neither mesangial cell proliferation nor membranous change was detected. Immunofluorescence revealed mesangial IgA deposition. There was no evidence of rejection. Without any treatment, the patient’s serum creatinine level declined to 1.05 mg/dL 2 months after the renal biopsy. Although 20-29/HPF hematuria remained, proteinuria disappeared.

The patient has maintained a stable graft function (Cre 1.2 mg/dL, eGFR 57.8 mL/min) with no severe rejection, serious infection, bleeding, or malignancy during the more than 10-year follow-up in our outpatient office.

**Discussion**

In 1973, Alfred Wiskott described a clinical entity characterized by thrombocytopenia, eczema, bloody diarrhea, and recurrent otitis media. In 1954, Robert Aldrich reported a similar clinical phenotype, which was named as WAS. WAS results from mutations in the gene encoding for Wiskott-Aldrich syndrome protein (WASP), a key regulator of signaling and cytoskeletal reorganization in hematopoietic cells (1, 2). Mutations in WASP produce wide clinical manifestations ranging from mild XLT to the classic WAS phenotype characterized by thrombocytopenia, immunodeficiency, eczema, and high risk of developing severe infections and malignancies (8). Currently, the only curative therapy is hematopoietic stem cell transplantation (HSCT) (1). Splenectomy is occasionally conducted for thrombocytopenia.

The first WAS case for RTx was reported in 1993 (4). Though that patient unfortunately died due to coronary artery disease, the clinical course after transplantation had been successful. The second patient also underwent transplantation successfully with reversible cellular rejection (5). Subsequently, Fischer et al. reported the fatal outcome of WAS with severe complications, including viral and bacterial infections, cellular rejection, subdural hematoma, and malignant non-Hodgkin lymphoma, which are common among WAS patients. Their patient died on POD 98 (6). According to the findings of these cases, RTx for WAS patients became controversial.

In 2014, Garnier et al. first reported a long-term successful case for RTx in a XLT patient who was genetically diagnosed (7). They concluded that RTx was suitable for XLT patients. Our case presented a similar clinical course to that
of their case, except for his history of splenectomy. Our case suffered from thrombocytopenia with a platelet count of $1.0 \times 10^4 \text{ mm}^3$, which was lower than that of the patient reported by Garnier et al. We recommend splenectomy with RTx for WAS/XLT patients to alleviate thrombocytopenia and prevent postoperative severe bleeding. This report strengthens the evidence that RTx can be beneficial for XLT patients and the need for simultaneous splenectomy for the management of severe thrombocytopenia.

IgA nephropathy often occurs in WAS/XLT patients (3). Some hypotheses including abnormalities in IgA glycosylation and deficiency in reticuloendothelial phagocytosis of IgA-containing immune complex have been proposed to explain why WAS/XLT patients are vulnerable to IgA nephropathy (9). In fact, IgA nephropathy is expected to be difficult to prevent unless HSCT is completed before transplantation. Because the patient’s clinical phenotype was mild and he was genetically diagnosed with XLT, we decided not to conduct HSCT.

Compared with the case of Garnier et al., the present patient did not require steroid treatment for IgA nephropathy. Since his primary kidney disease is unknown, it is unclear whether his IgA nephropathy is due to the de novo or recurrent type. Careful monitoring is necessary for preventing the deterioration of IgA nephropathy.

In conclusion, RTx should be considered for WAS patients, in addition to splenectomy to alleviate thrombocytopenia.

The authors state that they have no Conflict of Interest (COI).

References