RECURRENCE OF HEMOLYTIC-UREMIC SYNDROME FOLLOWING LIVE RELATED RENAL TRANSPLANTATION

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There is a significant risk of disease recurrence in patients with diarrhea-negative hemolytic-uremic syndrome undergoing renal transplantation. Considering the low frequency of hemolytic-uremic syndrome among adults with end-stage renal disease, only a few reports are available on the outcome of these patients after renal transplantation. It has been suggested, though not proven, that living related transplant recipients are at increased risk of recurrence of hemolytic-uremic syndrome.

We report a 23-year-old woman with end-stage renal disease, owing to postpartum hemolytic-uremic syndrome and the recurrence of the disease following live related renal transplant. Investigators believe that some cases of atypical hemolytic-uremic syndrome are familial and related donors may have a genetic susceptibility to develop hemolytic-uremic syndrome. In addition, recurrence of hemolytic-uremic syndrome in the allograft is associated with a very poor prognosis. Therefore, at present, many clinicians are reluctant to recommend live related transplantation in any forms of diarrhea-negative hemolytic-uremic syndrome.

Keywords: End-stage renal disease • hemolytic-uremic syndrome • renal transplant

Introduction

Hemolytic-uremic syndrome (HUS) is a clinical syndrome characterized by presence of hemolytic anemia with schistocytosis, thrombocytopenia, and renal failure. The pathologic hallmark of this syndrome is the thrombotic microangiopathy (TMA) that can be seen on renal biopsy.1–3

Clinically, HUS can be classified as the classic form, also known as the diarrhea positive (D’) or epidemic, and the atypical form, also known as the diarrhea negative (D–) or sporadic HUS.1–3

Classic or typical HUS is associated with prodromal diarrhea. This form occurs mainly in young children and is the most common cause of acute renal failure in children under the age of three years.4 In more than 80% of the pediatric cases, HUS complicated the course of an infection with verotoxin- (VT), and shiga toxin- (ST) producing Escherichia coli (VTEC or STEC).1–3,5 These bacterial toxins can induce endothelial cell lesions, which are supposed to induce TMA.1–3 TMA in the classic form of the disease is most often confined to the glomeruli, with a consequent good prognosis.

Atypical form of HUS presents without prodromal diarrhea in both children and adults, and in various reports accounts for approximately 5–12% of all cases.1 The onset is usually insidious, and marked proteinuria and hypertension are characteristic features.1

While D’ cases are mostly associated with VTEC infection, D cases have numerous causes; it can be associated with systemic diseases including systemic lupus erythematosus (SLE), systemic sclerosis (scleroderma), and malignant hypertension and may also be related to pregnancy, as well as the use of various drugs including oral contraceptives, cyclosporine or FK506, and antineoplastic drugs such as mitomycin.1–3,6

Patients with D’ form of HUS may also be familial. Both autosomal dominant and recessive
forms of inheritance have been described in familial HUS. 1, 2 Some cases are associated with intrinsic causes, including hypocomplementemia.

Recent studies have shown that approximately 20% of sporadic cases of HUS have mutations in the gene responsible for the complement regulator protein factor H. 2, 7

HUS is an uncommon cause of end-stage renal disease (ESRD) in adults. Renal transplantation is the treatment of choice for these patients; nonetheless, recurrence of HUS in the allograft has been reported, which is associated with a very poor prognosis. 8, 9 A diagnosis of ESRD, owing to HUS, was the strongest risk factor for incident HUS. 10

The case presented here underlines the risk of disease recurrence in recipients associated with live related renal transplantation, in keeping with previous reports.

Case Report

In April 2004, a 23-year-old woman was admitted to receive a kidney transplant from a living related donor. In 2003, she had developed renal failure, one week after her first delivery. Her child was normal. She had laboratory evidence of microangiopathic hemolytic anemia and her plasma creatinine reached 6.4 mg/dL. She underwent hemodialysis. Serum levels of C3 and C4 were normal. Antinuclear antibody (ANA), anti-ds-DNA, antineutrophil cytoplasmic antibody (ANCA), HBsAg, and HCV Ab were all negative. A renal biopsy showed changes compatible with HUS.

Despite treatment with methylprednisolone pulse, cyclophosphamide pulse, plasma exchange, and IV Ig, kidney function did not reverse and after 43 days, she was discharged from the hospital on maintenance hemodialysis.

Fourteen months after the onset of the disease, she received a live related transplant from her brother. The initial course was uncomplicated, with immediate graft function. A urinary tract infection, after one month, was accompanied by an increased serum creatinin. After recovery, the patient’s condition deteriorated rapidly, with declining graft function, hemolytic anemia, and thrombocytopenia.

She received methylprednisolone pulse and antithymocyte globulin (ATG) with no response. A renal biopsy was performed. The specimen contained 11 glomeruli, which showed widespread thickening and occasional double-contour of the capillary walls. There was endothelial cell swelling, without increased glomerular cellularity. Some glomeruli contained red blood cells and fibrin thrombi. Fibrin was present in tuft and also seen in the arteriolar wall (Figure 1).

Fibrillar appearance of the glomerular mesangium was noted in four glomeruli. Interstitium showed edema with mononuclear and polymorphonuclear cells infiltration. There was focal tubular necrosis and regeneration. Some tubes contained polymorphonuclear leukocytes. Small arteries showed fibrinoid necrosis (Figure 2). Transplant biopsy confirmed the recurrence of HUS.

Plasma exchange began daily, with no benefit. Several days later, she developed a high-grade fever, severe graft tenderness, and pain. After 60 days, she underwent graft nephrectomy. The final pathological diagnosis was consistent with recurrence of HUS.

Six months after nephrectomy, she was admitted for her severe dyspnea, severe anemia, and thrombocytopenia. Plasma exchange was started again. She was discharged following recovery of all her signs and symptoms on maintenance plasma exchange and hemodialysis.

Discussion

HUS may occur in renal transplant recipients, either as a recurrent disorder or as a de novo disease. The diagnosis of posttransplant recurrent HUS is difficult, because the histological features could be similar to those seen in acute humoral allograft rejection and HUS induced by cyclosporine or FK-506 nephrotoxicity. 1, 11

The clinical signs of microangiopathic hemo-
lytic anemia and thrombocytopenia, when present, are helpful to distinguish graft rejection from disease recurrence, because they are not typical of acute allograft rejection.1

De novo HUS has been described in patients undergoing renal transplantation, as a manifestation of humoral rejection.1 De novo HUS is uncommon and may occur later, after renal transplantation. Risk factors for de novo HUS included younger recipient age, older donor age, female recipient, and initial use of sirilimus.7, 10, 12

The recurrence of HUS after renal transplantation has been reported by a number of authors. Reports on the overall risk of recurrence in renal allograft are contradictory.13 In a study from the United States, 29.2% of patients with ESRD owing to HUS developed HUS later while only 0.8% of those with ESRD owing to other causes did so. The risk of HUS was highest within the first three months posttransplantation. They found no significant relationship between the donor subtype (living related vs. living unrelated donor).10

From other reports, it is apparent that the risk of recurrence ranges from 10 to 50% and that the risk is greatest in patients who received allografts from living related donors.2, 3, 8, 14, 15

By reviewing of the literature and in agreement with previous studies, we conclude that the recurrence of HUS in adult kidney recipients is a frequent early and severe complication with a poor graft prognosis. However, it should not be considered as a contraindication for retransplantation.8

It is suggested that renal transplantation from living related donors should be avoided in patients with a past history of HUS. It is also suggested that bilateral nephrectomy, prior to transplantation, may decrease the recurrence rate.1 Large multicentric prospective studies would help to verify this hypothesis and other strategies for the prevention of recurrence of HUS.

References