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Graft-vs-host disease after small bowel transplantation in children

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Abstract

Purpose: Graft-vs-host disease (GVHD) is a rare complication of transplantation of organs rich in immunocompetent cells. The goal of this study was to report the features of GVHD after small bowel transplantation (SBTx) in children.

Methods: The study involved a retrospective review of patients undergoing SBTx between 1999 and 2009 who had GVHD.

Results: Of 46 children receiving 52 intestinal grafts (2 liver-intestine and 3 multivisceral), 5 (10%) developed GVHD. Median age at transplant was 42 (19-204) months. Baseline immunosupression consisted of tacrolimus and steroids supplemented with thymoglobulin (n = 2) or basiliximab (n = 3) for induction. Median time between transplantation and GVHD was 47 (16-333) days. All patients had generalized rash, 2 had diarrhea, and 2 had respiratory symptoms. Other symptoms were glomerulonephritis (n = 1) and conjunctivitis (n = 1). Four developed severe hematologic disorders. The diagnosis was confirmed by skin biopsy in 4 patients and supported by chimerism studies in two. Colonoscopy and opthalmoscopic findings were also suggestive in one. Treatment consisted of steroids and decrease of tacrolimus, with partial response in four. Other immunosuppressants were used in refractory or recurrent cases. Three patients died within 4 months after diagnosis.

Conclusion: Graft-vs-host disease is a devastating complication of SBTx, with high mortality probably associated with severe immunologic dysregulation.

Graft-vs-host disease (GVHD) is a rare complication of transplantation of organs rich in immunocompetent cells and consists of a reaction of donor immune cells against host tissues. The 3 main tissues involved in acute GVHD are skin, liver, and gastrointestinal tract, and the diagnosis is based on symptoms and laboratory evidence of disease in these

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organs. Both inflammatory cytokines and cells from both the donor and the host contribute to tissue damage of GVHD. It is a common cause of significant morbidity and mortality after transplantation, especially in patients in whom first-line treatment with high-dose steroids fails.

Graft-vs-host disease is a major concern after hematopoietic stem cell transplantation (HSCT), where it is considered the primary risk factor for morbidity and mortality [1]; however, it has rarely been addressed in small bowel transplantation (approximately 10%) [2]. Although some reports regard this as a benign disease with favorable outcome after treatment with high-dose steroids, it can also be a devastating complication leading to death [3,4]. Steroids remain the cornerstone of treatment of severe GVHD, and the prognosis worsens dramatically for nonresponders (eg, >2 mg/kg of methylprednisolone) [1]. Empirical treatments that have been occasionally useful in HSCT may have value in intestinal transplantation, but the evidence seems weak. The aim of this study was to report our experience on GVHD after small bowel transplantation (SBTx) in children.

1. Methods

All children undergoing SBTx from October 1999 to March 2009 at Hospital Universitario La Paz (Madrid, Spain) were retrospectively reviewed (institutional review board 0147/08). Those with evidence of GVHD form the study group. Data included underlying disease, type of graft, inmunosuppression regimen, concomitant infections, and immunologic features were described.

The diagnosis of GVHD was suspected on the basis of clinical symptoms, according to the Consensus Conference on Acute GVHD grading [5]. Patients were divided into 4 stages depending on the degree of involvement of 3 organs: skin, liver, and intestine. Clinical features of GVHD were described, as well as time elapsed between transplantation and diagnosis, organs involved, severity of the symptoms, and other pathologic conditions.

The skin or intestinal pathologic examination confirmed the diagnosis. The histologic features and diagnostic criteria were similar to those used for GVHD occurring after HSCT as follows: lymphocytic infiltrate of the epithelium, lymphocytic exocytosis, apoptotic bodies, and cellular vacuolization in the native involved organs. If necessary, peripheral blood chimerism was examined by flow-polymerase chain reaction (PCR) to confirm the diagnosis. In cases of a sex mismatch between donor and recipient, donor cells were identified by fluorescence in situ hybridization for X and Y chromosomes.

Baseline immunosupression at our institution consisted of tacrolimus and steroids (6-methylprednisolone beginning with 10 mg/kg per day on postoperative day 0, and tapering until 0.5 mg/kg per day by the eighth month after transplant). Tacrolimus was administered orally at 0.2 to 0.3 mg/kg per day in 2 daily doses starting on the transplant day and adjusting for maintaining optimal blood levels (15-20 ng/mL during the first month, 12-15 ng/mL between the first and third month, and between 8 and 12 ng/mL after the third month). Mycophenolate mofetil was also administered in one case because of renal insufficiency. Immunosupression was supplemented with an induction regimen starting after reperfusion, which was different depending on the year of the transplant: Thymoglobulin (5 mg/kg in 2 doses, one after reperfusion and the second on postoperative day 1) or basiliximab (12 mg/m^2 at day 0, 4, and 8 after transplant). Wisconsin preservation solution was used in all cases.

The initial treatment of GVHD consisted of methylprednisolone, 2 mg/kg, and reduction of tacrolimus, adjusting the dose of steroids according to the response of the patient in refractory cases. Other immunosuppressants were occasionally introduced, according to the symptoms and associated pathologic conditions.

This protocol and its efficacy were reviewed. Outcome was considered good when the patient survived and the symptoms disappeared. Response to treatment was defined as complete if stage 0 in all involved organs was achieved and as partial if a reduction by at least one stage in at least one organ system was achieved without worsening of other organs.

Data are described as medians (range).

2. Results

Forty-six children received 52 intestinal grafts and 5 patients (3 boys) developed acute GVHD (11%). The main features are summarized in Table 1. Median age at transplant was 42 (19-204) months. Type of transplant was liver-intestine in 2 and multivisceral in 3 (one was modified multivisceral, including small bowel, duodenum, pancreas, and spleen). No GVHD was observed after an isolated bowel graft. No patient had known immunologic disorders before transplantation except for one patient (no. 2) in whom the GVHD appeared after retransplantation for severe acute rejection refractory to steroids, mycophenolate mofetil, monoclonal antibodies anti-CD3 (OKT3), and antitumor necrosis factor (anti-TNF) (infliximab) of a first combined liver-intestinal graft carried out 4 months before. Cytomegalovirus and Epstein-Barr virus (EBV) serologies were positive in 1 and 2 patients respectively before transplantation.

Median time elapsed between transplantation and the onset of GVHD was 47 (16-333) days. All patients had cutaneous symptoms manifested as generalized maculopapular rash beginning anywhere in the body, with palm and sole involvement, sometimes pruritic or even painful. As the rash progressed, it used to become confluent with blisters in severe cases (no. 2, 3, and 4) (Figs. 1 and 2). Drug toxicity was ruled out in all cases.

Two children had gastrointestinal involvement in the form of diarrhea (Fig. 2B) and 3 had respiratory symptoms (bronchiolitis obliterans, n = 1) (Figs. 1 and 2B). One patient developed membranous glomerulonephritis, and another one had conjunctivitis. Four developed severe hematologic