

Treatment of graft-*versus*-host disease with mesenchymal cells as a complication of a liver transplantation

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ABSTRACT

We present the case of a liver transplant (LT) recipient donor who developed graft *versus* host disease (GVHD). The main features were cutaneous rash, diarrhea and pancytopenia. Mesenchymal cells were administered as part of the treatment. This is the first case of a patient with GVHD after LT reported to date. Despite the treatment, there was no improvement in aplasia or gastrointestinal symptoms and the patient died due to a disseminated infection.

Key words: Orthotopic liver transplantation. Graft *versus* host disease. Mesenchymal cells.

INTRODUCTION

Acute graft-*versus*-host disease (GVHD) is a rare complication of liver transplantation (LT) due to the reaction of the lymphoid tissue associated with the transplanted organ against the receptor tissue (1-3). The incidence is 0.5-2% according to a recently published article (3). Thus, a high clinical suspicion is important for early diagnosis, since the symptoms are usually nonspecific (diarrhea, fever, rash) and the liver tests are normal. It may be useful to perform endoscopy with a biopsy of the gastrointestinal tract in cases of digestive symptoms and/or a biopsy of skin lesions in the case of a rash.

There are several therapeutic options. Some studies propose to decrease or even withdraw immunosuppression in order to restore the immune system of the recipient. Other studies suggest to enhance it, by increasing basal immunosuppression, adding corticosteroid therapy or using monoclonal antibodies such as basiliximab. However, the results are very poor and the mortality rate is greater than 75%. In spite of this, there is no case described in the literature of a rescue treatment with the administration of mesenchymal cells in this scenario.

CASE REPORT

We present the case of a 60-year-old male with alcoholic cirrhosis, Child-Pugh C10, MELD 23, who received a LT from a donor after cardiac death. Anti-HLA antibodies class I and II were negative. The patients' HLA was A2 A3, B7 B44, DRB1 10 DRB1 15 and the donors' HLA was A2 A29, B7 B44, DRB1 7 DRB1 13. He received immunosuppressive treatment with basiliximab and mycophenolate mofetil during the immediate postoperative period, initiating tacrolimus on postoperative day 6.

During the immediate postoperative period, he presented a retrohepatic intra-abdominal hemorrhage that required blood transfusion and surgical drainage of the hematoma on postoperative day 4. The patient was discharged the 10th day post LT with tacrolimus and mycophenolate mofetil and prophylaxis of a cytomegalovirus infection with valganciclovir.

On postoperative day 17, he was admitted to the hospital due to a low-grade fever and generalized maculo-papular rash, non-pruritic, which affected the trunk, abdomen and extremities, including the hands and palms. He had no other infectious focality. The skin biopsy showed a vacuolar degeneration of the basal lamina with apoptotic keratinocytes and a lymphocytic inflammatory infiltrate of T cells in the dermis, all suggestive of GVHD. In addition, the patient had anemia (Hb 6.5 g/dl) and lymphopenia (0.1 10E9/l). Upper gastrointestinal endoscopy did not find evidence of bleeding lesions and mycophenolate mofetil was reduced from 2,000 to 1,000 mg/day. He also presented tremors and myoclonus. Thus, tacrolimus was replaced by everolimus

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and methylprednisolone (40 mg /day) due to a suspected pharmacological neurotoxicity.

On postoperative day 25, he presented with liquid diarrhea of up to eight daily stools, without pathological products. On day 29, he presented a fever of up to 38 °C and persisting pancytopenia (Hb 6.1 g/dl platelets 72 10E9/l leukocytes 0.1 10E9/l). Broad spectrum antibiotic therapy was started with fluconazole + meropenem + vancomycin + metronidazole. Furthermore, HLA typing was performed using peripheral blood T lymphocytes of the patient (A2 A29, B7 B44, DRB1 7 DRB1 13), which was consistent with the HLA type of the donor, demonstrating the presence of chimerism.

Treatment with corticosteroids (methylprednisolone 2 mg/kg/day), cyclosporine and basiliximab was started due to the diagnosis of GVHD and the poor clinical and laboratory evolution. In the absence of a response and after receiving the consent of the patient, treatment with mesenchymal cells was initiated on the 5th day, with a dose of approximately 1 million/kg (days 35, 38, 42 and 47 post-LT). The patient continued with pancytopenia that required high transfusion support and profuse diarrhea. He finally developed fungemia secondary to *Candida krusei* and pneumonia due to *Stenotrophomonas* and *Enterococcus faecium* and he died on the 51st day post-LT.

DISCUSSION

The diagnosis of GVHD post-LT is complex and requires a high diagnostic suspicion. The first symptoms usually start between two and eight weeks after LT (4) and may include a rash (which is usually maculo-papulose, pruritic and affects palms and plants), low-grade fever/fever, diarrhea and pancytopenia. Characteristically, the liver function remains normal. A biopsy of the affected tissues and organs (usually the gastrointestinal tract and skin) is recommended if there is a clinical suspicion. The demonstration of chimerism (when the phenotype of circulating leukocytes coincides with that of the liver donor) strongly supports the diagnosis.

Currently, there is no therapeutic consensus (3,5,6) for the treatment of the GVHD after LT. Immunosuppression is increased in most published cases, although some studies recommend reducing it or even interrupting it completely. In addition, broad-spectrum antibiotics are usually started empirically. However, the results are very poor, with a high mortality rate, mainly due to infectious complications.

The administration of mesenchymal cells is used as a rescue treatment for GVHD after bone marrow transplantation (7). According to a meta-analysis (8) published in 2015, treatment with mesenchymal cells in GVHD resistant to corticosteroid treatment seems to be more effective in patients with low GVHD grade compared to those with high grade (OR = 3.22; IC 95%: 1.24-8.34). This was only in cases with skin involvement and was less effective when the liver (OR = 2.30; IC 95%: 1.12-4.69) or gastrointestinal tract were involved (OR = 1.93; IC 95%: 1.05-3.57). Age could be a prognostic factor, as children seem to show a better response than adults (OR = 2.41, 95% CI: 1.01-5.73). However, more research and studies are needed to define its role in the treatment of GVHD.

In conclusion, GVHD is an infrequent complication of LT and the mortality is very high. We present the first case described in the literature of GVHD after LT treated with an infusion of mesenchymal cells. The treatment was not effective.

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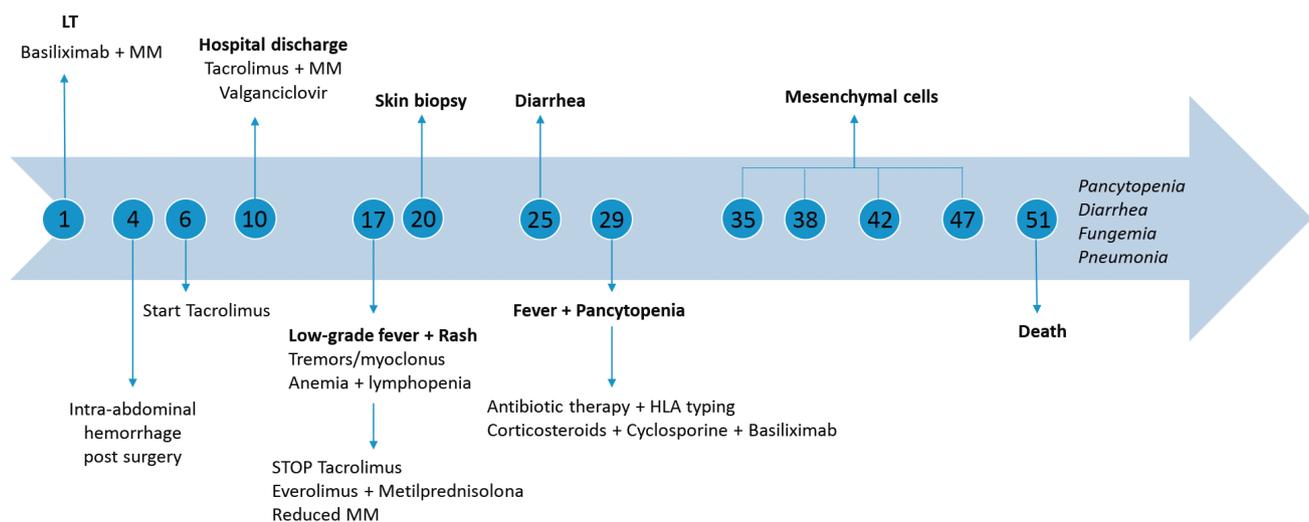


Fig. 1. Evolution after liver transplant (LT: liver transplant; MM: mycophenolate mofetil).

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