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CASE REPORT

Liver transplantation for chronic graft-versus-host disease: case report with 10-year follow-up

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Summary

Graft-versus-host disease (GVHD) is a frequent complication of bone marrow transplantation (BMT). Chronic GVHD (cGVHD) may lead to irreversible liver failure. We report a case of successful liver transplantation (LT) for end-stage liver failure because of cGVHD that had developed 22 months after BMT in a 24-year-old male. Re-transplantation was necessary 6 months later because of intrahepatic ischaemic type biliary tract lesions. He is now in excellent condition 10 years after the first transplant. This experience and the review of literature indicate that LT can cure GVHD-related chronic liver failure. Recurrent GVHD in the allograft has not yet been reported.

Introduction

Although liver transplantation (LT) is the accepted therapy for the treatment of chronic end-stage liver disease, there is as yet no consensus that chronic graft-versus-host disease (cGVHD) complicating bone marrow transplantation (BMT) and causing irreversible hepatic failure is a validated indication for LT.

Since the first report of successful LT performed for cGVHD [1], only three other cases have been reported [2–4].

The authors report a successful case of LT for this indication whose follow-up is the longest reported (10 years).

Case report

In March 1990, a 24-year-old man developed chronic myeloid leukaemia. BMT was proposed. The pretransplant conditioning regimen consisted of cytosine arabinoside (4 g/m^2), cyclophosphamide (120 mg/kg) and total body irradiation (10 Gy). In October 1990, human leucocyte antigen (HLA) identical BMT from an unrelated donor was performed. HLA typing was as follows: A1,2; B8,14; DR1,13. Cyclosporine A (CyA; 3 mg/kg/day) and methotrexate (15 mg/m^2 at day +1, and 10 mg/m^2 at day +3, +6 and +11) were administered for GVHD prophylaxis.

At day 51, he complained of fatigue, nausea and anorexia. Aspartate aminotransferase [AST; 10× normal) and gamma glutamyl transferase [GGT; 12× normal) were both raised. GVHD was suspected on diagnostic work-up [not including liver biopsy (LB)]. The CyA dose was increased so as to achieve whole trough blood levels of 600 ng/ml and steroids – 0.5 mg/kg methylprednisolone – introduced. He recovered, CyA therapy was continued and steroids were stopped. At day 109 bone marrow biopsy showed chromosome-rich Ph-negative BM with 100% chimaerism.

In the fall of 1992, his condition again deteriorated; he developed cutaneous lichenoid papules nearby areas of local erythema, oropharyngeal lichen planus-like striae and plaques in the absence of intestinal symptoms. Skin biopsy confirmed cGVHD. Liver tests were severely deranged (AST 6×; ALT 10×; GGT 11× normal). He deteriorated further and developed extensive GVHD despite restart of steroids and increase in CyA (3 mg/kg every other day). In January 1993, LB showed severe epithelial necrosis of bile ducts associated with lymphoid infiltration and cholestasis, a pattern consistent with hepatic cGVHD. Liver tests continued to deteriorate further (total bilirubine 4×, ALT 8×, AST 19× and GGT 30× normal). In March 1993, he became severely jaundiced (total bilirubine 15× normal) and the oral lesions did not improve. Thalidomide (400 mg/day) was added but did not improve the GVHD. As LB had confirmed the progressive cGVHD, he was listed for transplantation. The bone marrow showed a donor karyotype (46 XX) in all lines.

In January 1994, he received an ABO-identical whole liver allograft. Donor HLA was A2,24; B7,27,BW4; CW1; DR1, 3; HLA sequencing was not available at that time. Three HLA antigens were shared between donor and recipient. The graft was implanted with preservation of the recipient inferior caval vein; biliary reconstruction was a choledochocholedostomy protected by a T-tube. Native liver pathology showed severe degenerative atrophic changes in the bile ducts associated with cholestasis; in some portal tracts, bile ducts were absent. Immunoperoxidase staining for cytokeratine 7 confirmed atrophic bile duct damage (Fig. 1). Immunosuppression consisted of CyA, azathioprine and low-dose steroids.

After an uneventful postoperative course he was discharged on day 16. From the fourth post-transplant month onwards, cholestasis developed (GGT 22× normal). Percutaneous transhepatic cholangiography revealed diffuse intrahepatic ischaemic type biliary tract lesions. Interventional biliary radiology was judged to be impossible because of the extension of the lesions, so it was decided to re-transplant the patient.

A second successful LT was carried out in August 1994. Donor HLA typing was A2,9,(A24); B13,40,60; Bw4,6; Cw3,6; DR7,6(DR13)DR52,53; DQ1,2,6. Donor and recipient thus shared A2 and DR13; cross-match was negative. Immunosuppression consisted of CyA and short-term steroids.

The early postoperative course was uneventful, but 2 months later, he again developed cholestasis (GGT 5×, ALT 6× normal). LB showed bile duct proliferation with pericholangitis and transhepatic cholangiography revealed two ischaemic biliary strictures, one located at the confluence of the right posterior and anterior sectorial branches, the other at the left hepatic duct. The former stenosis was successfully dilated and stented, whereas the latter was initially left untreated because contrast medium passed

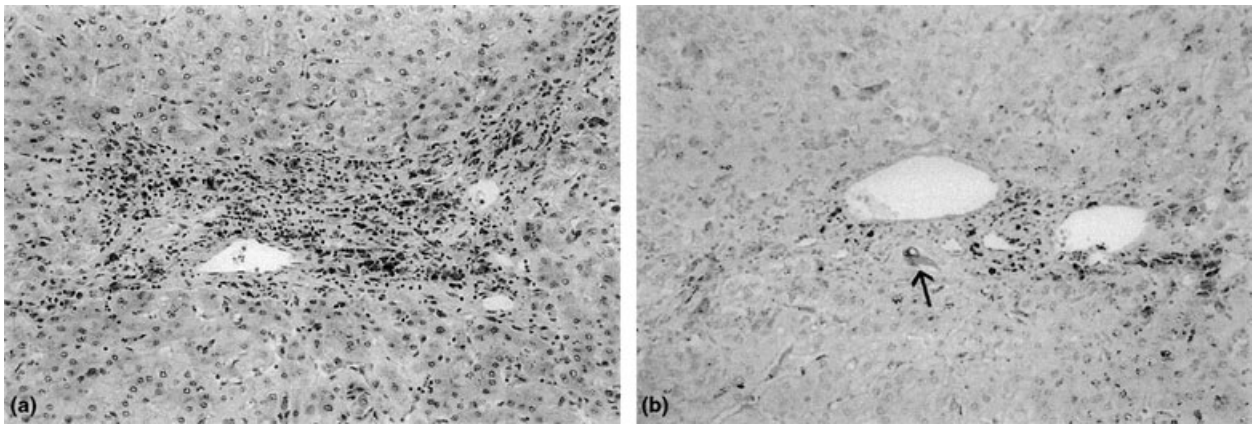

Figure 1 (a) Histological H&E sections of native liver (×400) showed mild lymphocytic infiltration in parenchyma and in portal tracts, focal acidophilic hepatocyte necrosis and severe degenerative atrophic changes of bile ducts associated with cholestasis; in some portal tracts, bile ducts were absent. Others findings included large iron deposits and moderate fibrosis. (b) Immunoperoxidase staining for cytokeratine 7 confirmed atrophic bile duct damage (arrow).

easily in the absence of proximal biliary tree dilation. In September 1995, dilatation of the right biliary stent was performed for cholangitis; in May 1996 the left bile duct required stenting because of another incidence of cholangitis in the presence of progressive stenosis. LB was almost normal except for the presence of bile duct proliferation. The patient is now well and alive 128 months after the first and 120 months after the second transplant, with infratherapeutic, spaced, CyA monotherapy (25 mg CyA three times a week; CyA whole trough level is around 25 ng/ml). All liver tests and liver biopsy are normal and he has remained free from cholangitis. He had no episodes of rejection so the process of immunosuppression withdrawal is continued.

Discussion

Despite advances in histocompatibility matching and immunosuppressive drugs, GVHD continues to be a common and often lethal complication of BMT, which subjects the liver to numerous potential toxic, infectious and immunological insults [5]. The latter play a major role in the clinical syndrome of GVHD. GVHD can be acute (aGVHD) or chronic, this means occurring beyond 100 days after BMT. Thirty to 60% of BMT recipients experience cGVHD. Acute GVHD increases the probability of cGVHD. Chronic GVHD may develop as a prolongation of aGVHD (progressive form) or, as showed in this case report, after a disease-free interval following an episode of aGVHD (quiescent). Finally it may develop *de novo* without any antecedent [6]. In the presented case, suspicion of previous aGVHD was based on the fact that the patient recovered after adaptation of immunosuppressive regimen and therefore, the histologically confirmed cGVHD was interpreted as a quiescent form.

The mainstay of diagnosis of GVHD is epithelial damage of different target organs. Skin, intestine and liver represent anatomical districts functioning as barriers to environmental pathogens and featuring a fast cell turnover [7].

The skin is the most common organ involved in cGVHD [8]. Our patient simultaneously developed skin lesions and progressive end-stage liver damage. The mechanisms by which hepatocytes are attacked in the disease course remain largely unexplored. It is likely that several conditions are necessary to develop GVHD including infusion of immunocompetent cells, major histocompatibility between donor and recipient, identification of liver antigens as foreign by immunocompetent cells and finally inability of the recipient to destroy donor cells [5]. The fact that this process also occurs after HLA-identical BMT indicates that minor histocompatibility differences play an important role.

Extensive cGVHD carries a poor prognosis with fatal infection and terminal (multi-)organ failure. Death from hepatic failure is however rare [9–11]. As the main target of the process, bile duct epithelial cells must expose antigens that are recognized as foreign by immunological cell mediators, the nature of which is still unknown; they could be native (normal or aberrant) or external (derived from viruses, bacteria or tissue damage triggered by conditioning regimens or concomitant events). It is likely that this antigen presentation is associated with MHC class II antigens, which are normally not expressed in bile duct epithelium, but may become upregulated in the course of GVHD [5]. Once recognized as foreign, donor T cells, donor and host macrophages and natural killer cells, as well as inflammatory substances related to foreign pathogens and/or preparatory regimen, seem to interact in a self-perpetuating cycle, characterized by continuous changes of the microenvironment rather than continued exposure to fixed antigenic differences [7]. Although hepatic cGVHD is initiated by alloreaction to host antigens, it seems that its progression also relates to dysregulation of the immune system, with disruption of both peripheral and central mechanisms governing self-tolerance. There is evidence that CyA plays a role in the onset of this phenomenon by altering the thymic architecture and inhibiting lymphocytic clonal selection processes. This would lead to abnormal intrathymic T-cell differentiation and abrogation of normal clonal deletion, permitting the persistence of autoreactive T cells.

The rationale of performing an LT for cGVHD is to eliminate those antigens that are the target of the aberrant immune response by removing the native liver. Consequently, the new allograft antigens, unknown to the autoreactive T-cell clones, would abrogate any immunological attack and stop the ongoing immunological cascade, once the aberrant clones have been cleared after ending their natural cycle.

The first LT shared three HLA antigens with the recipient and bone marrow donor (A2, DR1, DR13); it means that there were no mismatches for HLA class II antigens at the generic level. The second liver had one HLA class I (A2) and one class II (DR13) similar to the recipient and former donors. BMT could of course induce tolerance to HLA compatible antigens present in the liver graft but they were already shared by the recipient. Minor antigens could be tolerated if bone marrow and liver were from the same donor which was not the case.

Liver destruction caused by GVHD was generated by allelic or minor antigen incompatibilities. The same incompatibilities were not present with second liver graft (provided by another donor) but others might have been recognized. However, at the time of LT, the BMT was functioning well, therefore giving the recipient a normal

Table 1. Literature review: LT for GVHD after bone marrow transplantation.

Reference	Patient Sex	Age	Indication BMT	GVHD delay and localization	Delay BMT-LT	IS	Rejection	Outcome	Follow-up
Rhodes *et al.* [1]	F	19	AML	23 days: acute liver and skin; chronic: cirrhosis	37 months	CyA, St	No	Alive	24 months
Rosen *et al.* [2]	M	32	ALL	120 days: skin and liver	330 days	CyA, St, Aza	No	Alive	29.3 months
Marks *et al.* [3]	M	21	CML	20 days: skin and liver	104 days	CyA, St	No	Alive	6 months
Figuera *et al.* [4]	M	31	MS	25 days: skin and liver	109 days	CyA, St	No	Aspergillosis	+4.4 months
Dowlati *et al.* [5]	M	4	ALL	10 days: skin and intestine 82 days: liver	107 days	CyA, St	Yes	Diffuse intravascular coagulopathy and GI bleeding	+23 days
Present case	M	27	CML	51 days: skin and liver	39 months	CyA, St	No	Alive	128 months

MS, myelodysplastic syndrome; AML/CML, acute/chronic myeloid leukaemia; ALL, acute lymphoblastic leukaemia; CyA, cyclosporine A; St, steroids; Aza, azathioprine; IS, immunosuppression; GI, gastrointestinal.

immune ability to fight against donor lymphocytes if necessary; moreover, lymphocytes coming from the bone marrow donor were not able to induce GVHD in the new transplanted liver.

Five cases of LT for cGVHD have been published. Three had a good outcome, at days 180, 730 and 880, respectively, without any episode of rejection [1–3]. One patient died 130 days after BMT and 23 days after LT because of gastrointestinal haemorrhage due to disseminated intravascular coagulopathy complicating a severe acute rejection [5]. The fifth patient died 238 days after BMT and 129 days after LT because of disseminated aspergillosis [4] (Table 1).

The main concern about the indication of LT for GVHD after BMT is the risk of allograft recurrence. It is supposed that heavy pre-LT immunosuppression facilitates graft acceptance (explaining the low incidence of rejection), that GVHD regresses with therapy and/or evolves with time to an inactive state and that prolonged immunosuppression could be the 'ideal' preparation for the solid organ transplant [7].

The experience of LT for chronic GVHD after BMT is scarce. As the mechanisms of GVHD are still unclear, definitive guidelines for management of patients developing this syndrome cannot yet be provided. The clinical experience obtained indicates that LT should be considered in the case of GVHD-related chronic liver failure, given the irreversibility of lesions and the lack of alternative approaches. Recurrent GVHD allograft disease has not been reported and allograft acceptance seems to be rendered easy probably as a consequence of the pre- and post-BMT conditioning and immunosuppression. These patients might be good candidates for immunosuppression withdrawal, once stable allograft function has been obtained.

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