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Successful Treatment of Severe Refractory Hepatic Graft-Versus-Host-Disease by Cadaveric Liver Transplantation

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Keywords

Graft-versus-host-disease (GVHD); steroid-refractory; liver transplantation; allogeneic bone marrow transplantation (BMT)

Severe steroid-refractory hepatic graft versus host disease (GVHD) is a highly lethal complication of allogeneic bone marrow transplantation (alloBMT) with very few successful treatment options. Orthotopic liver transplantation (OLT) from a cadaveric or a living donor has been very rarely performed as a last-resort therapeutic option in patients with hematologic malignancies who develop refractory hepatic GVHD following alloBMT. Here we report a patient with acute lymphoblastic leukemia (ALL) who successfully underwent OLT for severe refractory hepatic GVHD post alloBMT and review relevant literature.

An asymptomatic 33-year old male was diagnosed with T-cell ALL after routine laboratory work showed a white blood cell count (WBC) of 31,900/μL with 28% blasts. The patient received induction chemotherapy with daunorubicin, vincristine, peg-asparaginase, prednisone, methotrexate, cyclophosphamide, cytarabine, and 6-mercaptopurine. A bone marrow (BM) evaluation showed complete remission (CR), but minimal residual disease

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was detectable by flow cytometry (1%). After additional chemotherapy, he underwent a myeloablative, HLA-matched related donor (MRD) alloBMT from his sister 5 months after diagnosis [Figure 1A]. The conditioning regimen consisted of busulfan and fludarabine, followed by post-transplant high dose cyclophosphamide (PTCy) 50 mg/kg IV on days 3 and 4 as sole graft-versus-host-disease (GVHD) prophylaxis on institutional protocol. Neutrophil engraftment occurred by day 22 and full donor chimerism was observed on the day +30.

On day 30, he developed a diffuse erythematous maculopapular rash and marked transaminitis. Imaging of the liver was unremarkable and viral hepatitis B and C, cytomegalovirus, and Epstein-Barr virus studies were all negative. A skin biopsy was consistent with acute GVHD (aGVHD). Treatment with high dose steroids (prednisone 2.5 mg/kg daily) and on a clinical trial mycophenolate mofetil versus placebo was initiated. The skin and hepatic GVHD was refractory to therapy and the liver enzymes continued to rise, so a transjugular liver biopsy was performed on day +42. Pathology showed patchy bile duct injury and apoptosis, consistent with hepatic GVHD, and moderate lobular spotty necrosis. Viral stains were negative, including CMV. He was switched to tacrolimus and steroids without improvement. Based on the diffuse skin involvement and markedly elevated bilirubin, the aGVHD was stage IV by the Keystone Criteria. On day +53 surveillance quantitative CMV polymerase chain reaction became positive and he developed CMV pneumonitis which was treated successfully with ganciclovir and anti-CMV immunoglobulin. There was no response to subsequent therapies for refractory GVHD with high dose cyclophosphamide, extracorporeal phototherapy, or sirolimus [Figure 1A].

Despite multiple infectious complications, he remained in complete remission from ALL with full donor chimerism. Another liver biopsy on day +170 showed a mild patchy portal chronic inflammation and reactive epithelial changes in the bile ducts with patchy inflammation and injury, consistent with active GVHD [Figure 1B]. The bilirubin level peaked at 53.3 mg/dL [Normal range (NR), 0.6-1.2 mg/dL], alanine transaminase (ALT) 2331 IU/L [NR, 12-40 IU/L), and prothrombin time (PT) of 75.7 seconds [NR, 10.7-13.8 seconds]. These abnormalities, in conjunction with the development of ascites, were all consistent with end-stage liver disease. Therefore, he was referred for evaluation for liver transplantation and underwent an OLT from a cadaveric donor on day +317, with prednisone and tacrolimus utilized for post-OLT immune suppression. Although the immediate postoperative course was complicated by multiple infections and persistent hemorrhagic cystitis, he fully recovered with normalization of liver function (albumin 3.9 g/dL, bilirubin 0.2 mg/dL, ALT 94 IU/L, PT of 11.1 seconds). Twenty-seven months after the BMT and 18 months after the OLT, he remains in CR with full donor chimerism, continues on tacrolimus with normal liver function, and returned to work.

AlloBMT is the only known curative therapeutic modality for some high-risk and refractory hematologic malignancies. Despite recent improvements, alloBMT is still associated with a significant incidence of life-threatening complications including severe GVHD. Up to 60% of patients undergoing alloHSCT develop some form of GVHD, and those who suffer from aGVHD are at higher risk of developing chronic (c)GVHD [1–3]. High-dose steroids are the first line of therapy for severe GVHD, but steroids alone result in complete or partial

remission of GVHD in less than half of the cases1. Steroid-refractory severe GVHD is frequently refractory to subsequent therapies and is associated with dismal outcomes and very high mortality rates. It has been estimated that up to 10% of hepatic GVHD cases may become severe and can lead to hepatic cirrhosis [4].

Patients with significantly compromised liver function due to hepatic GVHD who fail to respond to steroids or immunosuppressive therapies (IST) have very limited options. Therefore, OLT has been proposed as a last resort for refractory severe liver GVHD with significant hepatic functional derangement. The rationale for this treatment is the removal of the antigenic targets on the native liver that are being targeted by the aberrant immune response [3]. Use of cadaveric donor liver transplantation (CDLT) has been reported very rarely in the literature but never received wide acceptance as a therapeutic modality for severe refractory hepatic GVHD [1, 3, 5–10]. This is most likely due to concerns of relapse of the underlying hematologic malignancy or hepatic GVHD, the scarcity of cadaveric liver grafts, and possibly the multiple medical and infectious complications common to patients with severe GVHD. To address the issue of the scarcity of cadaveric liver grafts, more recently several case reports were published describing successful living donor liver transplantation (LDLT) from the same HLA-identical related BM donor [11], the same HLA-haploidentical related BM donor [12, 13], the same HLA-matched unrelated BM donor [2], and from an HLA-haploidentical mother LDLT donor after a MUD BMT [14].

In our literature search, we found only 13 case reports of OLT performed for severe hepatic GVHD that occurred after alloBMT, in addition to our patient [Table 1]. The indication for alloBMT was a hematologic malignancy in 11 (most common indication was ALL). Eleven patients were 30 years old or younger at the time of alloBMT (age range at BMT, 0.5-34 years). The BM donor was MRD for 7 patients, matched unrelated donor (MUD) for 5 patients, and an HLA-haploidentical donor for 2 patients. Most OLT were performed a year or more after BMT (8), while only 3 were performed within the first 4 months (all 3 after 100 days post BMT). Our patient had CDLT 10 months after his BMT. Nine patients underwent cadaveric donor liver transplants [Table 1A], while the other 5 underwent LDLT [Table 1B]. Several patients, especially those who received the liver and the BM grafts from the same donor, eventually discontinued IST. Among the 14 patients, only one was reported to have developed liver graft rejection, and only 2 deaths were reported. After a follow-up period that varied between 23 days to 128 months post the LDLT (8 patients with follow-up of 2 years or longer), 12 of the 14 patients were still alive, with many having no evidence of GVHD or recurrence of malignancy, including our patient.

It is very likely that more cases of OLT for severe hepatic GVHD have been performed and not reported in literature, especially cases with worse outcomes. Therefore, the numbers might overestimate the success rates and underestimate the complications associated with OLT for hepatic GVHD. Barshes et al conducted a search of the UNOS Organ Procurement and Transplant Network database from 1988 to 2003 [1]. The authors reported 73 patients who received OLT for severe liver GVHD after a non-liver organ transplant (65 had alloBMT [89.1%]). The median age for the entire cohort was 35 years. Median waiting time from transplantation registration to OLT was 8.5 days, and most patients received a cadaveric whole liver transplant (85%) while 11% received cadaveric partial liver transplant.

At time of reporting with a median follow-up of 357 days after OLT, 25% of patients had died. Interestingly, none of these deaths were attributed to GVHD or graft rejection, and only 2 patients died from cancer (lymphoma-not clear if recurrent or secondary- and metastatic squamous cancer). The 5-year graft and patient survival rates of 57.3% and 69%, respectively, but the authors did not comment on malignancy relapse or GVHD recurrence [1].

A recently published questionnaire surveyed 67, 578 patients who underwent alloBMT in 107 European centers for performance of solid organ transplantation subsequent to alloBMT [15]. The authors documented only 45 solid organ transplants, of which 15 were OLT performed in 14 patients. Of the 14 patients who had OLT, the indication for OLT was refractory hepatic GVHD in six (3 acute and 3 chronic). The authors did not report characteristics and outcomes of the GVHD patients individually, but reported an overall 5-year survival rate of 71%. The authors noted that these patients were very carefully selected [15].

In conclusion, liver transplantation, whether from a cadaveric or living donor, can be an effective therapeutic modality for refractory hepatic GVHD after alloBMT. Acknowledging the retrospective nature of the available literature and the associated selection and publication biases, the literature suggests low rates of recurrent hepatic GVHD, graft rejection, and favorable survival in stringently selected patients. Careful selection of patients based on the underlying malignancy, risk of relapse, and medical co-morbidities are all very important considerations for candidacy for liver transplantation and the choice of the graft source.

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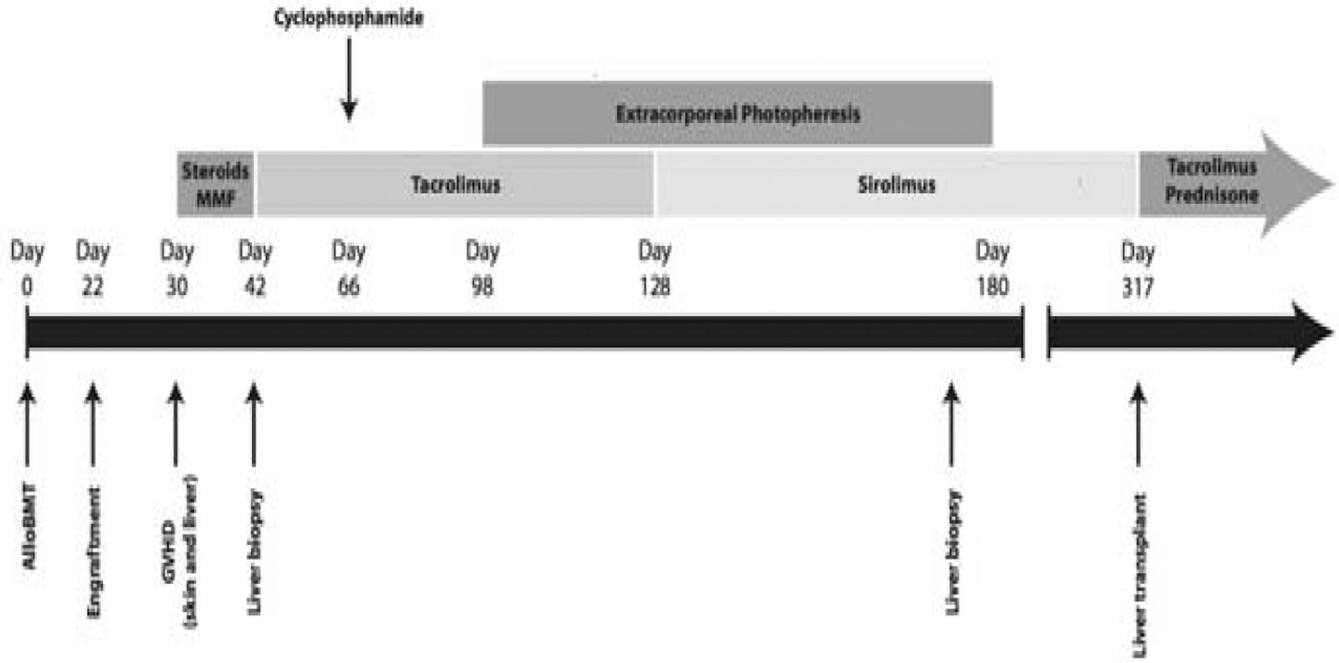
A



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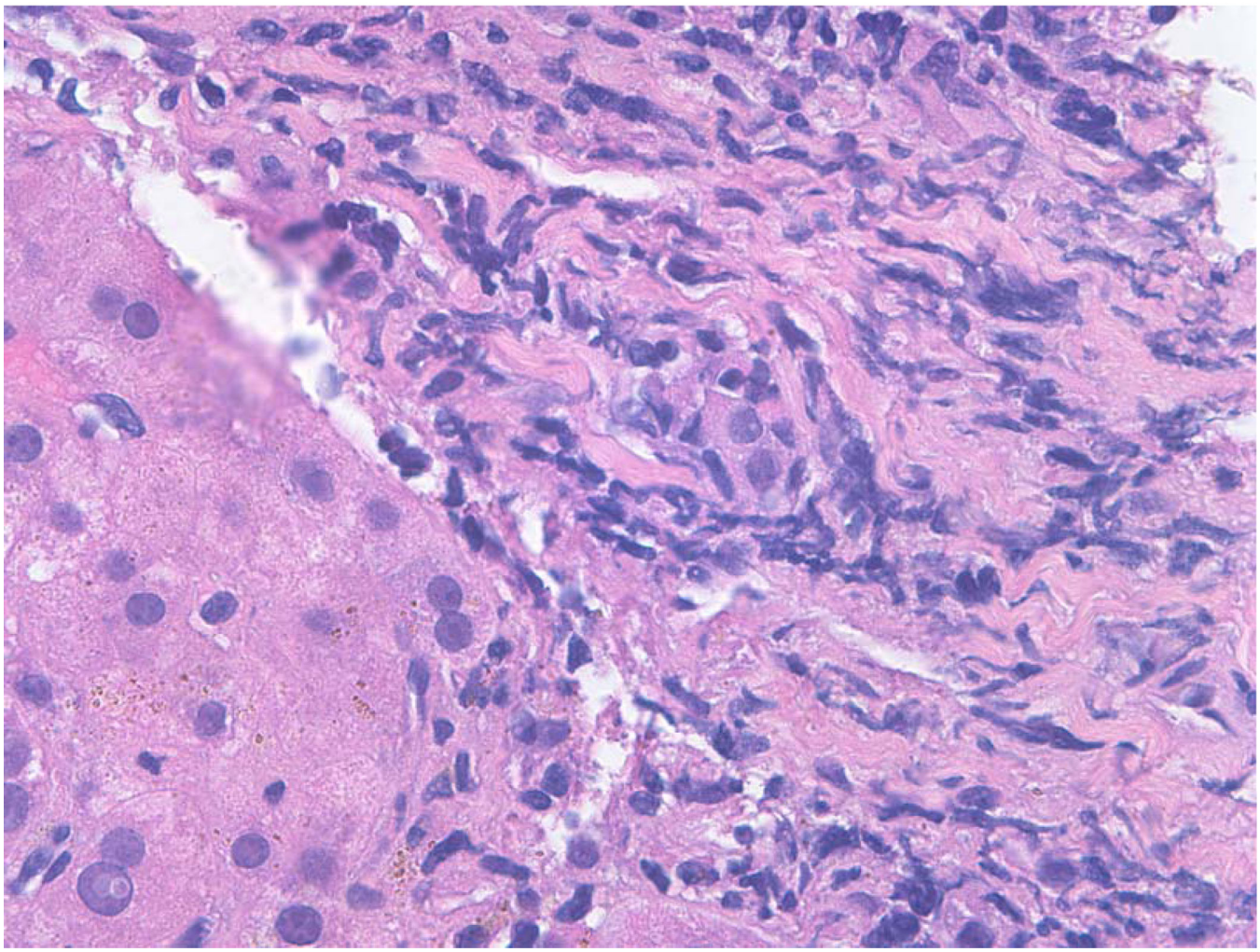

Figure 1.

A Timeline of clinical course of the patient.

B Liver biopsy showing active graft versus host disease (GVHD). H&E, original magnification 260X. A portal tract shows mild chronic inflammation with bile duct injury.

Table 1

Reported cases of orthotopic liver transplantation (OLT) for treatment of refractory severe hepatic graft versus host disease (GVHD) following blood and bone marrow transplantation (BMT).

A: Reports of cadaveric OLT.									
Reference And Year	**Age (years) at BMT, gender**	**Indication for BMT**	**Donor**	**GVHD timing, location**	**HSCT-OLT interval**	**IST regimen after OLT**	**Rejection**	**Post-OLT outcome**	**Follow-up Post OLT**
Rhodes et al. 1990 [5]	19, F	AML	MRD	23 days: acute: liver and skin; chronic: cirrhosis	37 months	CyA, S	No	Alive, no recurrence	2 years
Marks et al. 1992 [6]	21, M	CML	MRD	20 days: skin and liver	104 days	CyA, S	No	Alive, no recurrence	6 months
Dowlati et al. 1995 [7]	4, M	ALL	MRD	10 days: skin and gut, 82 days: liver	107 days	CyA, S	Yes	Death, DIC and GIB	23 days
Figuera et al. 1996 [8]	31, M	MDS	MRD	25 days: skin and liver	109 days	CyA, S	No	Death , disseminated aspergillosis	129 days
Rosen et al. 1996 [9]	32, M	ALL	Matched donor (not specified)	120 days: skin and liver	330 days	CyA, S, Azathio	No	Alive, no recurrence, rejection or liver GVHD	2.5 years
Urban et al. 2002 [10]	0.5, M	Sideroblastic anemia	MRD	27 days: skin, gut and liver. Chronic hepatic GVHD	5 years	CyA, S, Azathio	No	Alive, no recurrence	8.5 years
Current Case	33, M	ALL	MRD	30 days: skin and liver. Chronic hepatic GVHD.	305 days	S, Tacrolimus	No	Alive, no recurrence	18 months
Orlando et al. 2005 [3]	27, M	CML	MUD	51 days: skin and liver	39 months	CyA, S	No	Alive, no liver GVHD	128 months
Barshes et al. 2005 [1]	15, M	Idiopathic aplastic anemia	MUD	"several months": skin and liver	10 months	S, Tacrolimus	No	Alive, no recurrence or liver GVHD	3 years
Summary of 9 cases of cadaveric OLT	Median age 21 years (range, 0.5–33 years) M(8) F(1)	ALL (3) CML (2) AML (1) MDS (1) Aplastic anemia (1) Sideroblastic anemia (1)	MRD (6) MUD (2) Matched unspecified (1)	Median time 27 days (range, 10–120 days)	Median 10 months (range, 3.5–60 months)	CyA, S (5) CyA, S, Azathio (2) S, tacrolimus (2)	No (8) Yes (1)	Alive (7) Death (2)	Median 24 months (range, 0.8–102 months)

B: Reports of living OLT.

Reference And Year	Age (years) at BMT, gender	Indication for BMT	Donor	GVHD timing, location	HSCT-OLT interval	Donor living OLT	IST regimen after OLT	Rejection	Post-OLT outcome	Follow-up Post OLT
Shimizu et al. 2006 [12]	4, M	ALL	Haplo (Mother)	"after engraftment": skin and liver. Chronic hepatic GVHD	3 years	Mother	S, Tacrolimus*	No	Alive, no recurrence or liver GVHD	8 months
Yokoyama et al. 2008 [14]	10, M	CGD	MUD	"after engraftment": skin, gut and liver. Chronic hepatic GVHD	3 years	Mother	S, Tacrolimus*	No	Alive, no recurrence or liver GVHD	12 months
Mori et al. 2009 [11]	30, F	ALL	MRD (sibling)	Day 22: skin, day 41: gut. Day 356: chronic hepatic GVD.	421 days	Same sibling	S, Tacrolimus	No	Alive, no recurrence or liver GVHD	18 months
Englert et al. 2012 [2]	2, M	ALL	MUD	Chronic skin, gut and liver GVHD-cirrhosis.	4 years (from same MUD)	Same MUD donor	S, CyA	No	Alive, no recurrence or liver GVHD	3 years
Granot et al. 2012 [13]	2.5, M	ALL	Haplo (father)	Acute severe gut and hepatic GVHD. Chronic hepatic GVHD	6.5 years	Father	None	No	Alive, no recurrence or liver GVHD	7 years
Summary of 5 cases of living OLT	Median age 4 years (range, 2–30 years) M (4) F (1)	ALL (4) CGD (1)	MRD (1) MUD (2) Haplo (2)	N/A	Median 36 months (range, 14–78 months)	Parent (3) Sibling (1) MUD(1)	S, Tacrolimus (3) S, CyA (1) None (1)	No (5) Yes (0)	Alive (5) Death (0)	Median 18 months (range, 8–84 months)

IST: immunosuppressive therapy. C: Cadaveric. L: Living donor. AML: Acute myeloid leukemia. ALL: Acute lymphoblastic leukemia. MDS: Myelodysplastic syndrome, CML: Chronic myeloid leukemia. CGD: Chronic granulomatous disease. HLA: Human leukocyte antigen. MRD: HLA-matched related donor. MUD: HLA-matched unrelated donor. Haplo: HLA-Haploidentical donor.

*Hepatic artery and portal veins of hepatic graft flushed with the antibody muromonab-CD3. CyA: Cyclosporine, S: steroids, Azathio: Azathioprine.