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Case Report

Acute myeloid leukemia of a primary hepatic carcinoma patient after liver transplantation: a case report and literature review

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Abstract: Living donor liver transplantation (LDLT) is an important means to treat end-stage liver disease. Although effective immunosuppressant medication greatly assists the survival of patients, it is likely to promote infections and cancer. Acute leukemia (AL) is a rare complication after LDLT and up to now only 1 case of post-transplantation AL has occurred in our liver transplantation center after more than 1,600 LDLT interventions since 1993. In the present report, we describe a rare case of subsequent acute myeloid leukemia (AML), 27 months after LDLT and review the literature of this infrequent complication.

Keywords: Acute myeloid leukemia, liver transplantation, hepatic carcinoma, alpha-fetoprotein, metastases

Introduction

Due to advances in the development of solid organ transplantation and the increased long-term survival of recipients, the issue of secondary malignancies after transplantation has become a matter of concern. The incidence of *de novo* tumors after liver transplantation has been reported to be in the range of 2.6% to 11.5% [1], with the majority being non-Hodgkin's lymphomas, non-melanoma skin cancers, cancer of the lip and oral cavity, as well as squamous cell carcinoma of the oropharynx and esophagus [2, 3]. However, AL is an extremely rare complication after liver transplantation with an incidence estimated at 0.2-2.5% [4]. Here we present a case of AL after liver transplantation and compare its characteristics with 28 previously reported cases in the literature.

Case report

The ethics committee of The First Affiliated Hospital of Medical College, Zhejiang University approved the study. In 2008, a male patient aged 50 years with a history of hepatitis B came to our hospital because of right upper quadrant pain. An abdominal ultrasound examination revealed multiple, right hepatic occupancy, suggesting the presence of liver cancer. The serum concentration of alpha-fetoprotein (AFP) was 6,416 ng/mL and an enhanced computer tomography (CT) scan revealed an occupying lesion in the V segment of the liver, indicative of a hepatoma. No metastases were detected by bone emission CT and systemic positron emission tomography/CT examinations. In May 2008, the patient accepted a LDLT in the hepatobiliary and pancreatic surgery center of our hospital. A biopsy of hepatic segment VI revealed a poorly differentiated hepatocellular carcinoma, but no metastatic nodules were found in the pelvic cavity or the abdominal viscera. The immunosuppressive therapy comprised glucocorticoids, FK 506 (tacrolimus) and mycophenolate mofetil (MMF), and prophylactic systemic chemotherapy with gemcitabine and oxaliplatin was administered 4 times. During the follow up examinations, lung metastases were detected in December 2008, February 2009 and December 2009, which were resected and confirmed as previous hepatocellular

Table 1. Characteristics of liver transplant patients with postoperative *de novo* AML occurrence

Case	Gender	Age	Primary disease	IST	Onset time since LDLT (month)	FAB type	WBC (/μL)	Chromosome	Gene	Chemotherapy regimen	Outcome
1 [17]	F	57	PBC	PDN, CsA	24	M3	5200	T (15; 17)	Short PML-RARa	ATRA	Death during induction chemotherapy
2 [18]	M	46	CHB	FK506, CsA	3	MDS-CMML-M5	14000	46XY/47XY, + (8)	NK	(Hom-Ara-C)	PR
3 [19]	M	28	AHB	FK506, PDN, MMF	4	M5	13100	No split phase	NK	Ida	CR
4 [20]	F	12	OTCD	FK506, azathioprine	23	M3	77500	T (15; 17)	PML/RAR a	ATRA, D-Ara-C	CR
5 [20]	F	4	CBA	FK506	46	M3	3300	T (15; 17)	PML/RAR a	ATRA, D-Ara-C	CR
6 [21]	M	61	HCC	CsA, PDN	1	M0	2200	Normal	NK	Ida	CR, recurrence 2 months later
7 [21]	M	41	Alcoholic cirrhosis	CsA, PDN	24	M3	1800	T (15; 17)	NK	ATRA+CT	CR
8 [21]	M	51	HC	CsA, PDN	42	M1	1800	Normal	NK	IDAE	CR, recurrence 2 months later
9 [4]	M	34	Cirrhosis	FK506, PDN	19	M4	3500	NK	NK	D-Ara-C+G-CSF	CR
10 [4]	F	14	FHF	FK506, MTX, CsA	10	B-ALL	5300	Normal	NK	Ara-C	CR
11 [4]	F	48	Alcoholic cirrhosis	FK506, PDN, MMF	18	M3	1000	T (15; 17)	NK	NO	Death
12 [22]	M	72	Cirrhosis after CHB	PDN, CsA, azathioprine	76	M4	187000	Normal	NK	Ida-Ara-C	Death
13 [4]	M	48	HC & alcoholic cirrhosis	FK 506, PDN	NK	M3	1000	46XY, t (15; 17); (q22; 14)	NK	ATRA, D-Ara-C	Death
14 [23]	M	41	CHB	CsA	14	NK	NK	NK	NK	NK	Death
15 [23]	F	60	CHB	FK	28	NK	NK	NK	NK	NK	PR
16 [24]	M	16	EBA	CsA, PDN	242	ALL (T-cell)	40400	NK	bcr-abl	NK	ALLO-BMT; Death
17 [21]	M	51	Cirrhosis after HC	PDN, CsA	42	M1	NK	Normal	NK	IDAE	CR
18 [24]	M	43	NTC	FK 506	36	M4 (Extramedullary)	9000	NK	NK	D-Ara-C	Death
19 [25]	M	49	Subacute severe hepatitis	FK 506	26	ATL	NK	NK	NK	VDCP	Death (hepatic failure)
20 [26]	M	62	HBV associated cirrhosis	FK 506	52	M3	NK	T (15; 17)	NK	ATRA, Ida	R
21 [26]	F	64	HBV associated cirrhosis	FK 506	40	M7	NK	NK	NK	Ida-Ara-C	R
22 [27]	M	69	HBV associated cirrhosis	CsA	36	AML	NK	45, X, -Y, t (8; 21) (q22; q22)	NK	MAE	Death (pneumonia)
23 [7]	M	42	Cirrhosis, CHB, HCC	CsA, FK 506	38	M2	NK	T (8; 21), -3	AL1/ETO	Ida-Ara-C	R
24 [19]	M	28	Cirrhosis after CHB	FK 506	4	M5	13100	NK	NK	NK	NK
25 [28]	F	7	Hepatic failure	FK 506	79	M4	NK	NK	NK	Ida	NK
26 [29]	M	59	Cirrhosis, HCC	MMF, FK 506, rapamycin	96	NK	NK	NK	NK	Ida	NK
27 [9]	M	50	Cirrhosis after CHB	FK 506	84	APL	85000	46XY, t (15; 17) (q22; q12)	PML/RAR	RAD	CR
28 [30]	M	53	Cirrhosis after CHB	FK 506, MMF, steroids	36	AML	7260	48XY, +21, +21 [2]/46, XY [50]	NK	NK	Death
29	M	50	Primary HCC	PDN, FK 506, MMF	27	M2	92200	Normal	Normal	Hom-Ara-C Ida-Ara-C, AAE	Death (recurrence)

NK = not known. IST = Immunosuppressive therapy; F = female; M = male; PBC = primary biliary cirrhosis; CHB = chronic hepatitis B; AHB = acute hepatitis B; OTCD = ornithine transcarbamylase deficiency; CBA = congenital biliary atresia; HCC = hepatocellular carcinoma; HC = hepatitis c; FHF = fulminant hepatic failure; EBA = extrahepatic biliary atresia; NTC = nutrition toxic cirrhosis; HBV = hepatitis B virus; PDN = prednisolone; CsA = cyclophosphamide; FK 506 = tacrolimus; MMF = mycophenolate mofetil; ATRA = all-trans-retinoic acid; Hom = homoharringtonine; Ara-C = cytarabine; Ida = Idarubicin; ICE = ifosfamide + carboplatin + etoposide; D-Ara-C = daunorubicin + Ara-C; CT = cytoxan + taxotere; idea = ida + daunorubicin + Ara-C + etoposide; G-CSF = granulocyte colony-stimulating factor; VDCP= vincristine + daunorubicin + cyclophosphamide + prednisone; MAE = mitoxantrone + Ara-C + etoposide; RAD = ramosetron + aprepitant + dexamethasone; AAE = aclacinomycin + Ara-C + etoposide; CR = complete remission; PR = partial remission; R = remission.

carcinoma metastases after postoperative pathology analyses.

In July 2010, 27 months after LDLT, the patient came to our hospital because of unexpected fever. The patient's hemoglobin (Hb) level was 72 g/L and the white blood cell and platelet counts were 92.2 × 10^9/L and 11 × 10^9/L, respectively. His blood HBV-DNA concentration was below the detection limit. Of the serum blood cells, 82% were found to be abnormal, while bone marrow aspiration showed that 71.5% of bone marrow cells were promyelocytic and according to the FAB guidelines [5] acute myeloid leukemia with maturation (AML-M2a) was considered. Immunophenotyping revealed that the abnormal cells were positive for CD117, CD71, CD13, CD33 and myeloperoxidase, while myeloblasts represented approximately 79.3% of all non-erythroid cells. Chromosome analysis showed 46, XY and fluorescence *in situ* hybridization (FISH) evidence that translocation t (15; 17) was negative. In addition, a polymerase chain reaction analysis did not detect a promyelocytic leukemia/retinoic acid receptor alpha (PML/RARα) chimeric gene, findings which confirmed the AML-M2a diagnosis. The patient was started on a omacetaxine mepesuccinate (previously termed homoharringtonine (Hom)), and cytarabine (Ara-C) chemotherapy regimen on 8th July 2010 (Hom 2 mg bid d1-6, Ara-C 150 mg d1-6) and complete remission (CR) was achieved, with a minimal residual disease of 0.83%. In August 2010, a second Hom/Ara-C chemotherapy regimen was administered to the patient (Hom 2 mg bid x d1-7, Ara-C 150 mg d1-7). In the following 6 months, the patient was given 2 cycles of Hom/Ara-C (Hom 4 mg bid d1-5, Ara-C 150 mg d1-7) and 2 cycles of idarubicin (Ida)/Ara-C (Ida 10 mg d1-3, Ara-C 170 mg d1-7). During the chemotherapy, the patient remained in a CR state with stable liver function and continued FK506 medication as antirejection therapy with a plasma concentration adjusted dose. On 11 April 2011, the patient came to our hospital again due to cryptogenic fever. His white blood cell, hemoglobin and platelet values were 89.4 × 10^9/L, 72 g/L and 9 × 10^9/L, respectively. Because of an assumed AML-M2a relapse, a chemotherapy regimen was initiated using aclacinomycin, cytarabine and etoposide. The following morning, the patient was unconscious and an emergency head CT revealed multiple bleeding in both cerebral hemispheres (intracranial cerebral hemorrhages). Although treatments such as intravenous mannitol for dehydration were administered, the patient died on the 15 April 2011.

Discussion

The incidence of *de novo* AML in our LDLT patients is 0.06%, which is lower than the previously reported values of 0.2-2.5% [4], but higher than the rate of 0.0013% in the general Chinese population [6]. We analyzed 29 reported cases of AL after liver transplantation (including the present case) and the characteristics are listed in **Table 1**. The average age of the patients (22 men, 8 women, and 3 children) was 48 years and the mean time from transplant surgery to the occurrence of AL was 56.2 months. The main cause of primary liver disease was cirrhosis followed by liver cancer, but the disease spectrum was not correlated with the patients' prognosis. The CR rate after chemotherapy was 56.7% (**Table 1**), suggesting that LDLT patients could tolerate standard doses of chemotherapy. Some patients were treated with high doses of Ara-c and hematopoietic stem cell transplantation as consolidation therapy, and exhibited good chemotherapy tolerance. Our patient also tolerated standard chemotherapy doses well and his liver function was stable without obvious abnormalities. Unified guidelines have not yet been established on how to adjust the dosage of immunosuppressant drugs during AL chemotherapy. Some authors reduce tacrolimus to the minimum dosage needed to maintain normal liver function and stop tacrolimus if a fungal infection is detected, and also the courses of intensification therapy [7]. Our patient was medicated and maintained with an effective concentration of FK506 during the entire chemotherapy treatment but no serious complicating infections occurred. Effective immunosuppressant usage on the one hand greatly reduces the incidence of transplant rejection and improves survival in transplant patients. On the other hand, cancer may develop as result of immunosuppressive drug therapy [8]. Liu et al. posited that MMF and sirolimus might be suitable antitumor immunosuppressant therapies after transplantation [9], because inosine monophosphate dehydrogenase (IMPDH) is abundantly expressed in leukemia and solid tumor cells, and MMF acts as an inhibitor of IMPDH [10, 11]. Sirolimus has been used as an anti-

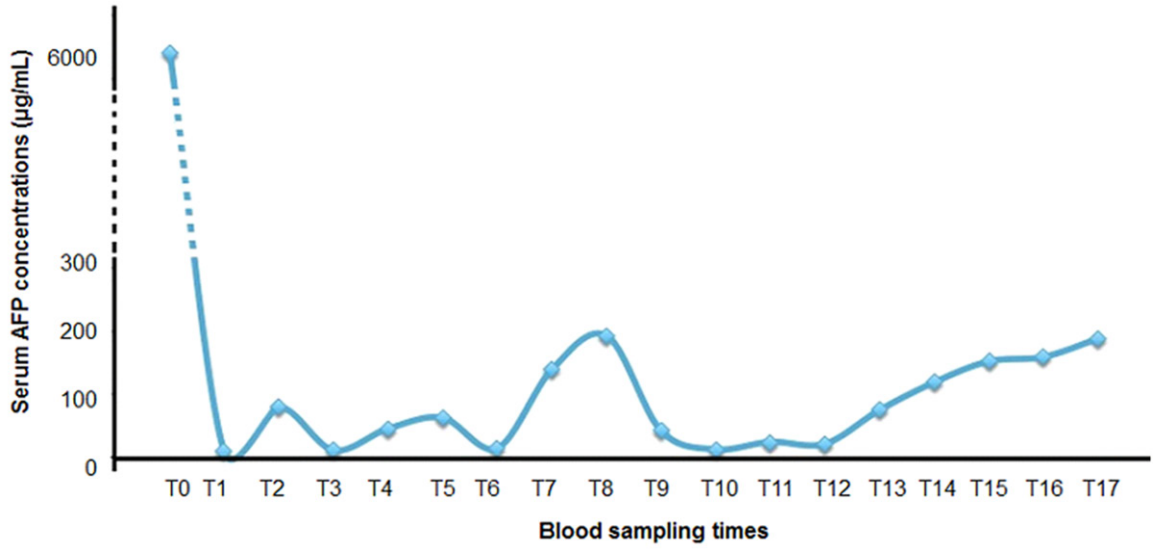

Figure 1. Scheme of AFP serum concentrations of the LDLT patients from pre-operation time until AML recurrence. T0 = the time before transplantation; T1 = the first day after transplantation; T2 (December 2008) = the first time we detected lung metastasis; T3 = the time after first pneumoresection; T4 (February 2009) = the second time we detected lung metastasis; T5 (May 2009) = several days after the second time we detected lung metastasis; T6 = time after the second pneumoresection; T7 (December 2009) = the third time we detected lung metastasis; T8 (May 2010) = time before the third pneumoresection; T9 = time after the third pneumoresection; T10 (July 2010) = time after the initial diagnosis of AML; T11 (2010-8-20), T12 (2010-9-1), T13 (2010-11-29), T14 (2011-1-7), T15 (2011-1-17), T16 (2011-2-16) are the times during CR; T17 (April 2011) = first day after the recurrence of AML.

cancer drug and later as a post-transplant immunosuppressive agent [12, 13]. Also, adjuvant chemotherapies might be the reason for the development of *de novo* acute leukemia [14, 15]. The serum AFP concentration was up to 6,146 ng/mL when liver cancer was first detected in the patient but returned to a normal level after liver transplantation. Thereafter, AFP rose slightly accompanied by the emergence of lung metastases and returned to a normal concentration after pneumoresection, which indicated that the lung tumors were derived from hepatocellular carcinoma cells. In the course of AML therapy, the serous AFP concentration was initially maintained at a low level after AML diagnosis and treatment, but then continued to increase to a high level after the recurrence of AL (**Figure 1**), which is unusual since AFP is not considered to be a marker for AL [16]. Other characteristics were also unusual in our patient. The cases of AL after liver transplantation reported internationally were mainly AML-M3, whereas the diagnosis of our case was AML-M2a and is only the second case of AML-M2a reported according to published clinical and international data (**Table 1**). In addition, in our patient repetitious occurrence of metastatic lung lesions developed during the first 20 months after liver transplantation, but no emerging liver metastases appeared during the entire postoperative period. In summary, the occurrence of leukemia after liver transplantation is rare, but higher than in the general population. Its pathogenesis, risk factors, treatment and prognosis are unclear. Therefore, further analysis of additional cases will be of great importance in order to develop suitable measures for the prevention and treatment of this infrequent complication of organ transplantation.

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Disclosure of conflict of interest

None.

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