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CASE REPORT

Skin cancer in immunosuppressed transplant patients: Vigilance matters

Ozan Unlu, Emir Charles Roach, Alexis Okoh, May Olayan, Bulent Yilmaz, Didem Uzunaslan, Abdullah Shatnawei

Ozan Unlu, Didem Uzunaslan, Department of Pathobiology, Cleveland Clinic, Cleveland, OH 44106, United States
Emir Charles Roach, Abdullah Shatnawei, Department of Gastroenterology, Cleveland Clinic, Cleveland, OH 44106, United States
Alexis Okoh, Department of Endocrine Surgery, Cleveland Clinic, Cleveland, OH 44106, United States
May Olayan, Department of Internal Medicine, Fairview Hospital, Cleveland Clinic, Cleveland, OH 44106, United States
Bulent Yilmaz, Department of Gastroenterology, Hacettepe University School of Medicine, 06230 Ankara, Turkey
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Correspondence to: Emir Charles Roach, MD, Department of Gastroenterology, Cleveland Clinic, 9500 Euclid Avenue, Cleveland, OH 44106, United States. roache@ccf.org
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Abstract

Liver transplantation (LT) is a widely-accepted, definitive therapy of irreversible liver diseases including hepatitis C, alcoholic liver disease and metabolic liver disease. After transplantation, patients generally use a variety of immunosuppressive medications for the rest of their lives to prevent rejection of transplanted liver. Mortality after LT is mainly caused by recurrence of alcoholic hepatitis which is mostly seen in the patients who resume heavy drinking. On the other hand, *de-novo* malignancies after LT are not seldom. Skin cancers make up 13.5% of the *de-novo* malignancies seen in these patients. Malignancies tend to affect survival earlier in the course with a 53% risk of death at 5 years after diagnosis. We aimed to report a case who underwent LT secondary to alcoholic liver disease and developed squamous cell carcinoma of the skin eighteen years after transplantation. In summary, transplant recipients are recommended to be educated on self examination for skin cancer; health care providers should be further suspicious during routine dermatological examinations of the transplant patients and biopsies of possible lesions for skin cancer is warranted even many years after transplantation.

Key words: Alcoholic liver disease; Skin cancer; Non-squamous; Liver transplantation; Sirolimus

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Core tip: We presented a case who underwent liver transplantation due to alcoholic liver disease and developed a skin cancer after 18 years of follow-up, which is exceptionally rare as malignancies tend to

affect survival earlier in the course with a 53% risk of death at 5 years after diagnosis.

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INTRODUCTION

Alcoholic liver disease (ALD) is known to be the number one cause of cirrhosis in western countries. Twenty percent of the liver transplants in United States and forty per-cent in Europe are performed due to ALD which makes it the second most common indication for liver transplantation (LT), a definitive treatment option for patients with cirrhosis and end stage liver disease[1-3].

Patient survival rates after LT for alcoholic cirrhosis have been reported to be 73%-86% at 5 years after diagnosis[4,5]. Mortality after LT is mainly caused by recurrence of ALD and alcoholic hepatitis which are mostly seen in the patients who resume heavy drinking. Other causes of mortality in patients who stay abstinent are cardiovascular diseases or events, infection and malignancies. Of note is the high incidence of *de-novo* malignancies after LT. This has been associated with the use of post LT immunosuppressants and the history of heavy alcohol use. Other reported risk factors for *de-novo* malignancies include older age, male gender, and Epstein Barr virus reactivation or infection for lymphoproliferative malignancy, and exposure to sun for non-melanoma skin cancer. Skin cancers make up the 13.5% of the *de-novo* malignancies seen in the patients with LT[6-8]. Malignancies tend to affect survival early after LT with a 53% risk of death at 5 years after diagnosis[9].

Herein, we present a case underwent LT (ALD etiology) who is followed up for 18 years without development of any malignancy. The patient consequently developed skin cancer at different sites 7 years after change of immunosuppressive regimen.

A high index of clinical suspicion together with routine dermatological examinations and biopsies of possible lesions for skin cancer is warranted in LT patients even eighteen years after transplant.

CASE REPORT

This is a 74-year-old male patient, who was under follow up for LT due to ALD at our center for 18 years. He was first diagnosed with cirrhosis secondary to ALD in 1993 and had a liver transplant two years later. Early post-transplant immunosuppressive treatment regimen included mycophenolate and tacrolimus for which he showed moderate clinical response. Afterwards, he developed calcineurin inhibitor induced end stage renal insufficiency and switched to sirolimus from tacrolimus in 2003 and a combination therapy with mycophenolate was continued.

Previous medical and surgical history included uncomplicated diabetes mellitus, hyperlipidemia and hypertension for 15 years and aortic valve replacement due to vascular thrombosis that occurred over the course of treatment. His co-morbidities were under control with antihypertensives and lipid lowering statins and his renal insufficiency related anemia was managed with erythropoietin.

Two years after treatment with sirolimus was started, the patient had recurring acneiform eruptions with pustules on his face, ears, and scalp. He was therefore referred to a dermatology unit for further evaluation and follow up.

A definitive diagnosis consistent with squamous cell carcinoma of the skin was made five years later. In September 2010, the patient underwent a resection of a tumor from his left temple, sacrificing the frontal branch of left facial nerve. He had multiple surgeries including left superficial parotidectomy due to relapses at different sites such as left auricle, preauricular area and occipitofrontal region of the scalp. Histological evaluations after each surgery revealed surgical margins wider than 6 mm. Identification of atypical tumor cells and keratinous pearls in microscopical evaluation supported the diagnosis. Despite multiple surgeries, chemotherapy and radiotherapy, patient was diagnosed with stage 4 squamous cell carcinoma due to metastatic lesions in his brain in 2012, and died in February 2013.

DISCUSSION

Patient survival rates after LT for alcoholic cirrhosis have been reported to be 81%-92%, 78%-86%, and 73%-86% at 1, 3, and 5 years respectively[4,5]. In an European Liver Transplant Registry which enrolled patients between 1988 and 2009, survival rates were reported as 73% and 59% for 5 and 10 years of follow-up respectively. These rates were shown to be higher compared to non-alcoholic etiology associated liver transplants, thus confirming ALD as an acceptable indication for LT[4,5,10].

Malignancy has been shown to significantly affect survival in LT patients with about 38% and 53% risk of death at 1 and 5 years after diagnosis[9]. Among LT recipients who survive the first year after transplantation, *De novo* malignancy is reported to account for 30%-40% of all deaths[9,11]. Although, intensive surveillance protocols in the post-transplant period have been shown to improve survival by detection of malignancy, clear guidelines including the frequency of work-up have not been developed yet. In this report, we describe the case of an LT patient who was followed up for 18 years after LT due to ALD. Renal insufficiency that occurred secondary to immunosuppressive therapy with

Table 1 Causes of death after liver transplantation *n* (%)

Years postimplantation	1	2	3	4	5	6	7	8	9	10	> 10	Total
Patient at risk (*n*)	4000	2940	2665	2478	2261	2018	1732	1511	1238	958	735	
Infection (bacterial, viral, fungal)	372	38	13	16	4	6	8	1	3	1	2	464 (28.4)
Malignancy (recurrent/*de novo*)	42	45	28	18	11	19	12	6	3		6	190 (11.6)
Cardiovascular	42	14	6	1	13	17	13	9	6	5	9	135 (8.3)
Respiratory	37	20	14	7	8	3	3	4	5	4	9	114 (7.0)
Intraoperative	99	4	1	2	4	2		1				113 (6.9)
Multisystem organ failure	45	16	9	5	6	9	5	7	3	1	3	109 (6.7)
Liver failure (recurrent)	21	15	15	7	10	6	3	2	1	2		82 (5.9)
Gastrointestinal	31	6	2	4	5	1		1	1		1	52 (3.2)
Central nervous system	20	2	2	4	1	5	3		1		4	42 (2.6)
PTLD	8		5	6	2	3	1	1	1		2	29 (1.8)
Renal failure				8	5	1		3			1	18 (1.1)
Rejection (acute/chronic)	4	2	1	1	1	2	2		1		4	18 (1.1)
Primary nonfunction	13		1									14 (1.1)
Miscellaneous	27	15	7	12	10	12	8	10	7	5	5	118 (6.1)
Unknown	55	20	18	5	5	7	4	5	4	1	11	135 (8.3)
Total	816 (20.4)	197 (6.7)	122 (4.5)	96 (3.8)	85 (3.7)	93 (4.6)	62 (3.5)	50 (3.3)	36 (2.9)	19 (1.9)	57 (7.7)	1633

PTLD: Posttransplant lymphoproliferative disease.

tacrolimus required a switch to sirolimus. Unfortunately, the patient consequently developed squamous cell carcinoma of the skin at multiple sites. In spite of surgical, chemo and radiation therapy, the patient died due to metastatic lesions in the brain.

Non melanoma skin cancer is the most common malignancy (NMSC) among the LT recipients with an overall incidence of 16% to 22.5%. Previous studies have shown NMSC as a factor effecting mortality[9,11]. The factors that alter the risk of skin cancer are patient's age, skin type, lifetime sun exposure and male sex[12]. Immunosuppressant agents were shown to increase the risk of skin cancers, with no evidence of superiority over one another. On the other hand, there are randomized controlled trials suggesting antitumor effects of sirolimus on skin cancer in renal transplant patients. Although studies on sirolimus in LT recipients had high discontinuation rates, similar results with studies on renal transplant patients are anticipated[13,14].

Jain *et al*[15] demonstrated that LT recipients with non-alcoholic liver disease had significantly longer survival rates compared to those with an ALD history. Moreover, another review suggested that while 5 year survival rates in ALD patients were similar between the ones who resumed drinking and those who didn't, 10 year survival rates were significantly different (45.1% *vs* 85.5%, respectively)[8]. In these studies, mortality was mainly caused by cardiovascular events and *de novo* neoplasms. This may indicate that there are factors causing malignant changes other than immunosuppressants.

Management of short and long term complications of LT is challenging and the choice of immunosuppressant agent is controversial. The causes of mortality may alter in short and long term follow-up after LT[16] (Table 1). In order to decide which immunosuppressant should be used as a first choice, further controlled randomized data are needed.

LT recipients are recommended to be educated on self examination for skin cancer and health care providers should be further suspicious during patients' routine dermatological examinations even many years after transplantation[6].

ALD is a good indication for LT. In the long term follow up, *de novo* malignancies and particularly skin cancer are long term complications of LT. Therefore, there is a need for particular vigilance of LT recipients. Further investigation into effects of immunosuppressant agents on *de novo* malignancies after LT is warranted to clarify the first choice of therapy.

COMMENTS

Case characteristics

This is a 74-year-old male patient, who was under follow up for 18 years for liver transplantation due to alcoholic liver disease. He presented with recurring acneiform eruptions with pustules on his face, ears, and scalp.

Clinical diagnosis

Physical examination was normal for all systems except that the patient had acneiform eruptions with pustules on his face, ears, and scalp.

Differential diagnosis

Keratoacanthoma, Basal Cell Carcinoma, Malignant melanoma, Solar (actinic) keratosis. A definitive diagnosis of squamous cell carcinoma was made with an excisional biopsy.

Laboratory diagnosis

Laboratory diagnosis was not necessary for the definitive diagnosis of squamous cell carcinoma.

Imaging diagnosis

Computed tomography scan revealed multiple metastatic lesions in the brain.

Pathological diagnosis

Pathology revealed atypical tumor cells, keratinous pearls and surgical margins wider than 6 mm.

Treatment

He took sirolimus and a combination therapy with mycophenolate for immunosuppression. His co-morbidities were under control with antihypertensives and lipid lowering statins. His renal insufficiency related anemia was managed with erythropoietin. After the definitive diagnosis of squamous cell carcinoma, he

had multiple surgeries and took chemotherapy and radiotherapy.

Related reports

De novo malignancies and non melanoma skin cancers were shown to develop in liver transplant patients under immunosuppressive therapy. However, the case is highly unique to develop a squamous cell carcinoma after 18 years of follow up.

Term explanation

A focus of central keratinization found within concentric layers of abnormal squamous cells, occurring in squamous cell carcinoma. Also called epithelial pearl.

Experiences and lessons

Transplant recipients are recommended to be educated on self examination for skin cancer; health care providers should be further suspicious during routine dermatological examinations of the transplant patients and biopsies of possible lesions for skin cancer is warranted even many years after transplantation.

Peer-review

The article reports a case of a patient who developed a squamous cell carcinoma 7 years after liver transplant following the change of immunosuppressive therapy. It is interesting.

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