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 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
### 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 microscopic 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
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. The factors that alter the risk of skin cancer are patient's age, skin type, lifetime sun exposure and male sex. 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.

Jain et al 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). 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 (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. 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.

### 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  | 6126 |
| Infection (bacterial, viral, fungal) | 372 | 66 | 113 | 76 | 45 | 10 | 9 | 3 | 1 | 2 | 14 | 16 |
| Malignancy (recurrent/de novo) | 42 | 45 | 28 | 18 | 11 | 19 | 12 | 6 | 3 | 1 | 2 | 190 |
| Cardiovascular         | 42 | 14 | 6 | 1 | 13 | 17 | 13 | 9 | 6 | 5 | 9 | 135 |
| Respiratory            | 37 | 20 | 14 | 7 | 8 | 3 | 3 | 4 | 5 | 4 | 9 | 114 |
| Intraoperative         | 50 | 4 | 1 | 2 | 4 | 2 | 1 | 1 | 1 | 1 | 1 | 113 |
| Multisystem organ failure | 45 | 16 | 9 | 5 | 6 | 9 | 7 | 3 | 1 | 3 | 1 | 109 |
| Liver failure (recurrent) | 21 | 15 | 15 | 7 | 10 | 6 | 3 | 2 | 1 | 2 | 1 | 82 |
| Gastrointestinal       | 31 | 6 | 2 | 4 | 5 | 1 | 1 | 1 | 1 | 1 | 1 | 52 |
| Central nervous system | 20 | 2 | 2 | 4 | 1 | 5 | 3 | 1 | 1 | 4 | 2 | 42 |
| PTLD                   | 8 | 5 | 6 | 2 | 3 | 1 | 1 | 1 | 1 | 2 | 18 | 11 |
| Renal failure          | 8 | 5 | 1 | 3 | 1 | 1 | 1 | 1 | 1 | 1 | 18 | 11 |
| Rejection (acute/chronic) | 4 | 2 | 1 | 1 | 1 | 2 | 2 | 1 | 4 | 18 | 11 |
| Primary nonfunction     | 13 | 1 | 1 | 1 | 1 | 1 | 1 | 1 | 1 | 1 | 14 | 11 |
| Miscellaneous           | 27 | 15 | 7 | 12 | 10 | 12 | 8 | 10 | 7 | 5 | 5 | 118 |
| Unknown                 | 55 | 20 | 18 | 5 | 5 | 7 | 4 | 5 | 4 | 1 | 11 | 135 |
| Total                   | 816 | 204 | 197 | 6.7 | 122 | 45 | 96 | 3.8 | 85 | 3.7 | 93 | 4.6 |

**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 acniform eruptions with pustules on his face, ears, and scalp.

**Clinical diagnosis**

Physical examination was normal for all systems except that the patient had acniform 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.

**REFERENCES**

1. Berg CL, Steffick DE, Edwards EB, Heimbach JK, Magee JC, Washburn WK, Mazarioges GV. Liver and intestine transplantation in the United States 1998-2007. *Am J Transplant* 2009; 9: 907-931 [PMID: 19341415 DOI: 10.1111/j.1600-6143.2009.02567.x]

2. Burra P, Senzolo M, Adam R, Delvart V, Karam V, Germani G. Liver transplantation for alcoholic liver disease in Europe: a study from the ELTR (European Liver Transplant Registry). *Am J Transplant* 2010; 10: 138-148 [PMID: 19951276 DOI: 10.1111/j.1600-6143.2009.02869.x]

3. Singal AK, Chaha KS, Rasheed K, Anand BS. Liver transplantation in alcoholic liver disease current status and controversies. *World J Gastroenterol* 2013; 19: 5953-5963 [PMID: 24106395 DOI: 10.3748/wjg.v19.i36.5953]

4. Adam R, Karam V, Delvart V, O’Grady J, Mirza D, Klemmnauser J, Castaing D, Neuhaus P, Jamieson N, Salizzoni M, Pollard S, Lerut J, Paul A, Garcia-Vädeccas J, Rodríguez FS, Burroughs J. Evolution of indications and results of liver transplantation in Europe. A report from the European Liver Transplant Registry (ELTR). *J Hepatol* 2012; 57: 675-688 [PMID: 22609307 DOI: 10.1016/j.jhep.2012.04.015]

5. Singal AK, Guturu P, Hmoud B, Kuo YF, Salameh H, Wiesner RH. Evolving frequency and outcomes of liver transplantation based on etiology of liver disease. *Transplantation* 2013; 95: 755-760 [PMID: 23370710 DOI: 10.1097/TP.0b013e31827af3a]

6. Chandok N, Watt KD. Burden of de novo malignancy in the liver transplant recipient. *Liver Transpl* 2012; 18: 1277-1289 [PMID: 22887956 DOI: 10.1002/lt.23531]

7. Ducroux E, Boillot O, Ocampo MA, Decullier E, Roux A, Dumortier J, Kanitakis J, Julienn D, Euvrard S. Skin cancers after liver transplantation: retrospective single-center study on 371 recipients. *Transplantation* 2014; 98: 335-340 [PMID: 24621534 DOI: 10.1097/TP.0000000000000051]

8. Iruzubieta P, Crespo J, Fábrega E. Long-term survival after liver transplantation for alcoholic liver disease. *World J Gastroenterol* 2013; 19: 9198-9208 [PMID: 24409408 DOI: 10.3748/wjg.v19.i48.9198]

9. Aberg F, Pukkala E, Höckerstedt K, Sinka R, Isoniemi H. Risk of malignant neoplasms after liver transplantation: a population-based study. *Liver Transpl* 2008; 14: 1428-1436 [PMID: 18825704 DOI: 10.1002/lt.21475]

10. Varma V, Webb K, Mirza DF. Liver transplantation for alcoholic liver disease. *World J Gastroenterol* 2010; 16: 4377-4393 [PMID: 20845504]

11. Herrero JJ, España A, Quiroga J, Sando ro B, Pardo F, Álvarez-Cienfuegos J, Prieto J. Nonmelanoma skin cancer after liver transplantation. Study of risk factors. *Liver Transpl* 2005; 11: 1100-1106 [PMID: 16123952]

12. Mitlohefer AB, Supran S, Freeman RB. Risk factors associated with the development of skin cancer after liver transplantation. *Liver Transpl* 2002; 8: 939-944 [PMID: 12360438]

13. Alberú J, Pascoe MD, Campistol JM, Schena FP, Rial Mdel C, Polinsky M, Neylan JF, Korth-Bradley J, Goldberg-Alberts R, Müller ES. Lower malignancy rates in renal allograft recipients converted to sirolimus-based, calcineurin inhibitor-free immunotherapy: 24-month results from the CONVERT trial. *Transplantation* 2011; 92: 303-310 [PMID: 21792049 DOI: 10.1097/TP.0b013e3182247a2e]

14. Mathew T, Kreis H, Friend P. Two-year incidence of malignancy in sirolimus-treated renal transplant recipients: results from five multicenter studies. *Clin Transplant* 2004; 18: 446-449 [PMID: 15233824]

15. Jain A, DiMartini A, Kashyap R, Youk A, Rohl S, Fung J. Long-term follow-up after liver transplantation for alcoholic liver disease under tacrolimus. *Transplantation* 2000; 70: 1335-1342 [PMID: 11087149]

16. Kashyap R, Jain A, Reyes J, Demetris AJ, Elmagd KA, Dodson SF, Marsh W, Madariaga V, Mazariogies G, Deller D, Bonham CA, Cacciarelli T, Fontes P, Staral TE, Fung JJ. Causes of death after liver transplantation in 4000 consecutive patients: 2 to 19 year follow-up. *Transplant Proc* 2001; 33: 1482-1483 [PMID: 11267383]

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