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ORIGINAL ARTICLE

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Rapid development of esophageal squamous cell carcinoma after liver transplantation for alcohol-induced cirrhosis

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Abstract Liver transplant recipients have an increased risk of developing de novo malignancies. It is generally accepted that chronic alcohol abuse is a contributive factor in the pathogenesis of several malignancies, in particular, of oropharyngeal squamous cell carcinoma (SCC). Thus, patients with end-stage alcohol-induced cirrhosis could be at risk of esophageal SCC following orthotopic liver transplantation (OLT). From January 1986 to December 1997 a total of 313 patients underwent OLT for various indications. Of these patients, 72 had alcohol-related cirrhosis. Oropharyngeal and esophageal malignancies after OLT were not observed in non-alcoholic patients. In contrast, these malignancies were diagnosed in three male patients who underwent transplantation for alcohol-induced cirrhosis (incidence 4.2%). Furthermore, all patients had a history of tobacco abuse. The tumors were located in the tongue of one patient and in the esophagus of two patients. While SCC of the tongue became apparent 5 years after OLT, esophageal SCC was detected 8 and 16 months after transplantation. Shortly before transplantation, endoscopy of the esophagus had not revealed evidence of pre-malignant dysplastic lesions in any of these patients. Thus, esophageal SCC may develop rapidly in patients undergoing transplantation for alcohol-related cirrhosis with a history of tobacco abuse before liver transplantation, which warrants careful post-transplant screening of these patients.

Keywords Alcohol-induced cirrhosis · De novo malignancy · Esophageal and oropharyngeal squamous cell carcinoma · Immunosuppression · Liver transplantation

Introduction

The risk of de novo malignancies after kidney transplantation is well documented [12]. In the kidney-recipient population, the most frequent tumors are B-cell lymphoproliferative disorders, which are most common in the first year after transplantation, and skin, lips and perineal cancers, with an increasing incidence with duration of follow up [11]. Several risk factors for de novo tumors after renal transplantation have been identified, including induction immunosuppression with antilymphocyte antibodies [12], length of exposure to immunosuppressive drugs [10], age over 50, and male gender [1].

An increased risk of de novo malignancies after liver transplantation has recently been reported [4, 7, 8, 9, 13]. The cumulative risk of de novo malignancies was found to rise from 6% to 55% at 15 years after liver transplantation and to account for a significant risk of late death [5]. Skin cancers account for 30–70% of all tumors after liver transplantation [5, 7, 13]. Interestingly, there is high incidence of lymphoproliferative disorders in

patients who underwent transplantation for HCV-related cirrhosis [6]. Furthermore, a recent study demonstrated an overall incidence of oropharyngeal squamous cell carcinoma (SCC) of 17% in alcohol-induced cirrhosis transplant patients, suggesting specific risk factors in liver transplant recipients [2]. This view is supported by the present study. Here, we report the rapid development of esophageal SCC after liver transplantation for alcohol-related cirrhosis and provide further evidence of a high incidence of oropharyngeal SCC in former alcohol and nicotine abusers.

Case reports

Case 1

A 60-year-old man with liver cirrhosis secondary to hepatitis C and chronic alcohol abuse (approximately 60 g daily for 20 years) suffered several times from recurrent esophageal bleeding. Several endoscopic examinations of the esophagus in bleeding-free intervals revealed no signs of pre-existing dysplastic lesions. He had been a heavy smoker (60 pack years).

Four months after the last elective endoscopy the patient underwent liver transplantation. He was maintained on standard immunosuppression therapy (cyclosporin A, prednisone) and antithymocyte globulin (ATG) for 9 days (cumulative dose 270 mg). He did not receive azathioprine because of thrombocytopenia. One week later he had a severe episode of liver rejection. High-dose prednisone therapy (500 mg for 5 days) together with cyclosporin A was not effective, therefore, cyclosporin-based immunosuppression was converted to tacrolimus. After conversion, the rejection disappeared, and liver function rapidly recovered. Long-term immunosuppression comprised tacrolimus and prednisone.

Six months after liver transplantation, the patient developed a cytomegalovirus-retinitis, which was successfully treated with long-term therapy with ganciclovir (300 mg daily for 6 months). Sixteen months after liver transplantation the patient was admitted to our hospital with progressive dysphagia and weight loss. Endoscopy showed an exophytic-growing tumor in the proximal esophagus. Biopsy specimens obtained from this area established the diagnosis of SCC of the esophagus with low-grade differentiation. There was no evidence of metastasis. The patient was treated with polychemotherapy comprising a single dose of mitomycin (10 mg/m^2) for 1 day and 5-fluoruracil (500 mg/m^2) over 4 days. The chemotherapy was accompanied by local irradiation. After two cycles of chemotherapy and a total radiation dose of 50 Gy, a complete remission of the tumor was obtained. Meanwhile, more than 5 years after transplantation, there is no evidence of cancer recurrence.

Case 2

A 57-year-old male patient with alcohol-induced liver cirrhosis was admitted to our hospital for ascites and frequent episodes of hepatic encephalopathy. The patient had consumed more than 150 g of alcohol daily for more than 10 years. He continued smoking until transplantation (more than 10 pack years). Two months before transplantation, endoscopy in the absence of bleeding showed esophageal varices but no mucosal lesions. The patient underwent successful liver transplantation without acute rejection or significant complications. He was maintained on long-term immunosuppression with cyclosporin A and prednisone and, additionally, received ATG for 9 days (cumulative dose 360 mg) and azathioprine for 13 days (cumulative dose 650 mg).

Eight months after liver transplantation, the patient presented with dysphagia. Endoscopy showed a tumor in the distal esophagus. Histological examination of biopsy specimens revealed SCC with low-grade differentiation. At this time, computed tomography showed pulmonary metastasis. The patient underwent combined radiotherapy–chemotherapy comprising a single dose of mitomycin (10 mg/m^2) for 1 day and 5-fluoruracil (500 mg/m^2) over 4 days, and local irradiation (50 Gy). Unfortunately, the carcinoma did not respond to these therapeutic regimes. Twenty months after liver transplantation, the patient died. At autopsy, an advanced local SCC with tumor spread into the lungs and the heart was found.

Case 3

A 43-year-old male patient with liver cirrhosis secondary to chronic alcohol abuse (approximately 100 g daily for more than 15 years) was admitted to our hospital for recurrent life-threatening bleeding from esophageal varices. After successful liver transplantation, induction immunosuppressive regimen was based on cyclosporin A and prednisone in combination with ATG for 5 days (cumulative dose 240 mg) and azathioprine for 21 days (cumulative dose 1,320 mg). Thereafter, the patient was maintained on long-term immunosuppression with cyclosporin A and prednisone. The patient had been a heavy smoker (40 pack years) and continued smoking after undergoing transplantation. Five years after transplantation, the patient developed SCC of the tongue. Treatment comprised surgery and irradiation. One year later the patient died of mechanical small-bowel obstruction resulting from adhesive bands. Autopsy revealed no evidence for tumor recurrence.

Discussion

SCC of the esophagus is a very rare complication that can occur after solid-organ transplantation. Only two cases have been reported in patients who have undergone renal transplantation [3, 14]. These patients had none of the more commonly recognized risk factors, in particular, heavy tobacco or alcohol abuse, which seemed to implicate immunosuppressive therapy as a possible cause of esophageal SCC.

Recently, an increased incidence of oropharyngeal SCC after liver transplantation for alcohol-related cirrhosis has been observed [2]. SCCs were located in the uvula and the tongue, and, in one case, in the esophagus. The high incidence of these tumors (16.7%) found in recipients with alcohol-induced cirrhosis [2] is supported by our observation: oropharyngeal SCC appeared in three of 72 patients who underwent liver transplantation for alcohol-related cirrhosis (incidence 4.2%), but not in patients with non-alcohol-related cirrhosis ($n = 241$).

In all patients, the occurrence of oropharyngeal SCC seems to be related to a concomitant chronic exposure to alcohol and tobacco. These well-established risk factors for oropharyngeal SCC seem to be less important in patients undergoing liver transplantation for non-alcohol-related liver diseases. Although immunosuppressive regimes were similar between both groups, immunosuppression may enhance the oncogenic effects of pre-transplant alcohol and tobacco consumption. Due to the lack of control groups in the present and

earlier study [2], it still remains unclear whether the development of SCC was influenced by immunosuppression, or might have occurred in the same percentage of at-risk patients without liver transplantation and immunosuppression. In agreement with earlier observations [2] oropharyngeal SCC was diagnosed exclusively in men. However, this finding must be interpreted with caution, since there was a high ratio (8.0) of male/female patients who underwent transplantation for alcohol-induced cirrhosis in our center, as well as in the study by Duvoux et al. [2].

All patients who were considered in the present report underwent liver transplantation between 1985 and 1997, thus providing a follow-up period of at least 4 years after transplantation. However, esophageal SCC appeared in both patients 8 and 16 months after transplantation, respectively, whereas tongue SCC was diagnosed after 60 months. In both patients with esophageal SCC, endoscopy revealed no evidence of mucosal dysplastic lesions 2 and 4 months before transplantation. Therefore, it seems likely that the carcinomas developed rapidly after transplantation. Consistent with our observation, Duvoux et al. reported similar rapid development of oropharyngeal SCC 10 to 48 months after liver transplantation for alcohol-related cirrhosis [2]. Thus, careful screening for esophageal and oropharyngeal SCC can be suggested in this risk group and should be started early after transplantation. The same post-transplant screening has recently been recommended for patients with Barrett's esophagus, which is detected in up to 2% of candidates for liver transplantation [16]. Importantly, high-grade dysplasia may develop rapidly in these patients, following liver transplantation, suggesting an increased risk of adenocarcinoma arising from Barrett's esophagus [15].

Diagnosis of esophageal SCC as early as possible is pivotal. In one patient pulmonary metastasis was found at diagnosis and showed rapid progress, despite radio-chemotherapy. In the other patient tumor growth was limited to the esophagus. In this patient radio-chemotherapy was effective, and long-term remission has now been achieved for more than 4 years. This case shows for the first time that successful treatment of esophageal SCC in a liver transplant recipient can be achieved by radio-chemotherapy when tumor growth is still limited to the esophageal wall.

In conclusion, esophageal SCC may develop rapidly in patients who undergo transplantation for alcohol-induced cirrhosis with a history of tobacco abuse before liver transplantation, which warrants careful post-transplant screening of these patients.

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