CASE REPORT

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Gastric cancer after cadaveric liver transplantation in a patient with autoimmune hepatitis: A case report and review of the literature

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The risk of malignancy in transplant patients is higher than in the general population. The risk is increased mostly due to immune alteration and viral infections. While the most common cancers following liver transplantation include skin cancers, lymphoma and Kaposi's sarcoma, gastric cancer is uncommon. Herein, we report a case of gastric adenocarcinoma developing three years after cadaveric liver transplantation in a patient with autoimmune hepatitis. The patient was successfully operated. The patient did not receive any adjuvant therapy, and is free of disease at 9 months' follow-up.

Key words: Gastric cancer, autoimmune hepatitis, liver transplantation, immunosuppressive therapy

Otoimmün hepatitli bir hastada kadavradan karaciğer nakli sonrasında gelişen mide kanseri: Olgu sunumu ve literatür derlemesi

Transplant hastalarında kanser genel popülasyona göre daha sık görülmektedir. Risk daha çok immün değişiklikler ve viral enfeksiyonlar ile artmaktadır. Karaciğer transplantasyonu sonrasında en sık cilt kanserleri, lenfoma ve kaposi sarkomu görülürken mide kanseri nadirdir. Bu yazıda otoimmün hepatitli bir hastada karaciğer transplantasyonundan 3 yıl sonra gelişen mide adenokarsinomunu rapor ettik. Hastaya başarılı bir cerrahi uygulandıktan sonra herhangi bir adjuvan tedavi verilmedi ve postoperatif dönemde 9. ayda hastalıksız olarak izlenmektedir.

Anahtar kelimeler: Mide adenokarsinomu, karaciğer tranplantasyonu, otoimmün hepatit

INTRODUCTION

The incidence of cancer in transplant patients in the years following transplantation tends to increase due to the use of immunosuppressive agents. The risk of malignancy after transplantation is about 20% (1). Although various cancers such as skin tumors, Kaposi's sarcoma and lymphoid malignancies have been reported in transplant recipients, gastric cancer is uncommon in these groups of patients (2).

In Turkey, the number of liver transplantations from cadaver or living donors is increasing each year (3). There are only a few studies about the risk of malignancies following liver transplantation (16-19). Herein, we report a case of gastric cancer occurring three years after cadaver-donated liver transplantation in a patient with autoimmune hepatitis.

CASE REPORT

A 51-year-old male was diagnosed to have chronic autoimmune hepatitis with positive anti-mitochondrial antibody, anti-LKM antibody and antinuclear antibodies (ANA) in 1993. Because of recurrent intractable variceal bleeding from the

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esophagus due to portal hypertension, a transhepatic portosystemic shunt was performed in 1998. At follow-up, the serum liver transaminases were increased and liver biopsy was performed. The pathological examination revealed cirrhosis. The patient was clinically classified as Child-Pugh A. In April 2005, liver transplantation from cadaver was performed because of chronic liver failure. The patient was put on a treatment with FK 506, azathioprine, methylprednisolone, and ursodeoxycholic acid after transplantation. In March 2008, the patient was admitted to hospital with abdominal pain, nausea and vomiting. His past medical history included type 2 diabetes mellitus and hypertension. His routine biochemistry, blood count and tumor markers including carcinoembryonic antigen and CA 19-9 were within normal ranges. Because of his gastric symptoms, upper gastrointestinal endoscopy was performed, which demonstrated an antral mass narrowing the passage at the pyloric canal. Endoscopic biopsy was performed and histopathological examination revealed adenocarcinoma, but *Helicobacter pylori (Hp)* was not detected. At pre-operative evaluation, abdominal computerized tomography (CT) showed multiple lymphadenopathies, the greatest diameter of which was 1 cm, near the pyloric canal and first part of the duodenum. In April 2008, a distal gastrectomy was performed. Pathological examination revealed good-moderately differentiated adenocarcinoma, invading the submucosal layer without any metastasis to the five resected lymph nodes (Figures 1A, B). The patient was diagnosed as stage IB gastric adenocarcinoma (pT2N0M0). No postoperative adjuvant treatment was given because of early-stage disease. The doses of immunosuppressive agents were reduced. In January 2009, the patient was alive without progression.

DISCUSSION

Organ transplant recipients are at increased risk for solid and hematological malignancies, making them the second most frequent cause of mortality in transplant recipients. Solid organ transplanted patients have three-to-four-fold higher lifetime risk of developing cancer when compared to the general population (1). The risk is increased several hundred-fold for virus- related cancers, such as Kaposi's sarcoma (4). In liver transplant recipients, the overall relative risk was 2 to 4.3-fold in comparison to the general population (5,16,17,19). The relative risk is 70.0 for non-melanoma skin cancer and 2.7 for non-skin solid cancer (5). In the study of Haagsma (5), age >40 years and immunosuppressive therapy were associated with significantly increased risk for cancer development. Aberg et al. (16) studied the risk of malignancies after liver transplantation in a Finnish population. Non-melanoma skin cancer and non-Hodgkin lymphoma were found to be the most frequent malignancies (38.5- and 13.9-fold increased risk compared to the general population, respectively) in parallel with the literature data. The risk of cancer was higher in males than females (4.16- vs 1.76-fold), in children than among adults (18.1- vs 5.77-fold for ages 17-39 years vs 2.46-fold for ages >39 years), and more elevated in the immediate posttransplant period compared to later periods (3.71-fold at <2 years vs 2.46-fold at 2-10 years, 1.53-fold at >10 years) (16).

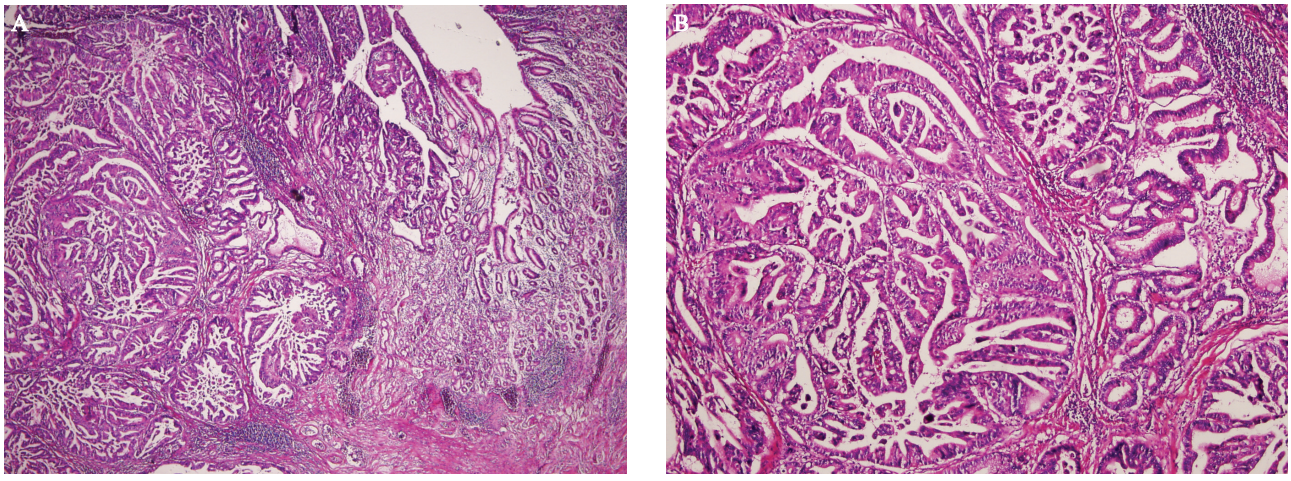


Figure 1. A, B: Hematoxylin-eosin staining of well-moderately differentiated gastric adenocarcinoma.

A variety of action mechanisms may account for cancer development after transplantation. Firstly, most of the cancers in this population are often associated with oncogenic viruses such as Epstein-Barr virus and herpes virus and/or with the immunosuppressive therapy used for transplantation (6). Epstein-Barr virus often causes lymphoproliferative disorders in transplant recipients, while human herpes virus 8 accounts for skin cancer and Kaposi's sarcoma (7-9). However, the role of infectious agents is not clear for gastrointestinal cancer. Immunosuppressive treatment might predispose to *Hp* infection, which plays an important role in developing gastric cancer (10). In this setting, *Hp* eradication treatment might be an important point in *Hp*-positive transplant recipients. Secondly, inhibition of T cell-induced immunity and suppression of interleukin (IL)-2 may take a role in carcinogenesis and tumor growth in patients receiving immunosuppressive treatment (11,12). Furthermore, many immunosuppressive drugs increase the risk of cancer after transplantation without known mechanisms. Long-term use of thiopurines in transplant patients has been shown to be associated with a significantly increased risk for various types of cancer (13). Tacrolimus was also shown as an independent risk factor for malignancy in renal transplant patients (4). Benlloch et al. (18) reported an increase in the frequency of *de novo* malignancies after liver transplantation in recent years (before vs after 1995). The time interval between liver transplantation and diagnosis of de novo malignancy was shorter (58 vs 22 months, before and after 1995, respectively) (18). They hypothesized that these findings were attributable to immunosuppression in association with the recent introduction of novel and potent immunosuppressive drugs. Thus, lowering the dose of immunosuppressive drugs or using new agents such as sirolimus and everolimus with anti-proliferative effect in immunosuppressive therapy after transplantation might help in reducing the risk of posttransplant malignancy.

To date, fewer than 10 cases of gastric cancer after liver transplantation have been published (14,15-19). In these cases, patients generally had received living donor liver transplants in contrast to the present case, who received a cadaveric liver transplant for liver failure due to autoimmune hepatitis. Immunologic stimulation in autoimmune diseases may promote carcinogenesis, i.e. some autoimmune diseases such as systemic lupus and rheumatoid arthritis are associated with lymphoproliferative malignancies but not with gastric cancer. However, no data exist about the risk of cancer in transplant patients with a history of an autoimmune disease.

The prognosis of patients with post-transplant tumors is worse than in the normal population, and systemic treatment options are limited in this group because of their immunocompromised status. Therefore, early detection and treatment of malignant diseases might be more crucial in transplant patients. Patients with increased risk deserve more aggressive investigation and meticulous therapy, because of the considerably high cancer mortality rate after liver transplantation. There is no standard screening procedure for solid tumors described for transplant patients. Transplant patients with gastric symptoms should be carefully evaluated, and endoscopic evaluation should be considered for early diagnosis.

In conclusion, with the increasing population and surveillance, malignancies are forthcoming health problems in transplant patients. In these patients, early diagnosis of malignancy after transplantation is very important because of the toxicity of chemotherapy agents and the increased risk of morbidity and mortality. A higher attention should be taken with respect to post-transplant patients with a history of autoimmune disease. Although gastric cancer is one of the infrequent tumors in transplanted patients, physicians should be aware of the risk.

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