A Case of Gastric Cancer Following Living Donor Liver Transplantation

Hiroki TAKEHARA[1,2], Kazuaki TANABE[1,*], Nobuaki FUJIKUNI[1], Hiroyuki TAHARA[1],
Kentaro IDE[1], Yuka TANAKA[1], Wataru YASUI[3] and Hideki OHDAN[1]

1) *Department of Gastroenterological and Transplant Surgery, Hiroshima University, Hiroshima, Japan*
2) *Department of Artificial Organs and Radiology, Akane-Foundation, Tsuchiya General Hospital, Hiroshima*
3) *Department of Molecular Pathology, Hiroshima University Institute of Biomedical and Health Sciences, Hiroshima, Japan*

ABSTRACT

Only a few cases of *de novo* malignancy, especially gastric cancer after living donor liver transplantation (LDLT), have been reported. We report a case of gastric cancer following LDLT, after which immunosuppressants were minimized in accordance with the results of the mixed lymphocyte reaction (MLR) assay. A 65-year-old woman had previously undergone LDLT for hepatocellular carcinoma associated with hepatitis B virus infection. The liver graft had been donated by her son. During the course of postoperative surveillance with the MLR assay in order to minimize immunosuppressants, she was incidentally found to have gastric cancer during an endoscopic examination, 8 years after the liver transplantation. She underwent total gastrectomy with lymph node dissection. In this case, gastric cancer was detected 8 years after LDLT, which is longer than previously reported intervals between LDLT and malignancy detection. The number of patients undergoing LDLT is increasing, and the prognosis after liver transplantation has improved. Therefore, endoscopic surveillance programs are important for detecting malignancies in the early stages in liver transplant recipients.

Key words: *Liver transplantation, Gastric cancer, Immunosuppression*

As the availability of organs from deceased donors is limited in Japan, living donor liver transplantation (LDLT) has become the main treatment for end-stage liver diseases. According to the Japanese Liver Transplantation Society, 6195 LDLT procedures were performed by the end of 2010[17].

The prognosis after liver transplantation has significantly improved with the use of newer immunosuppressive regimens. Conversely, *de novo* malignancies after transplantation have become an important cause of death. Liver transplant recipients are at some risk for the development of cancers such as skin tumors, Kaposi sarcoma, and lymphoid malignancies. However, the risk of gastric cancer development has not yet been established[5]. With regard to *de novo* malignancies after transplantation, early detection and treatment, including surgery, are essential for long-term survival[15]. In accordance with the increase in the number of individuals undergoing LDLT,

the incidence of *de novo* malignancy in transplant recipients is anticipated to increase. However, to date, only a few cases of *de novo* malignancy, especially gastric cancer after LDLT, have been reported in the literature. Herein, we report a case of gastric cancer occurring 8 years after LDLT.

CASE REPORT

The patient was a 65-year-old woman who was diagnosed with gastric cancer. She had undergone LDLT for hepatocellular carcinoma associated with hepatitis B virus infection 8 years previously. The graft was donated by her son. The postoperative course was uneventful. The patient was administered a treatment regimen with an immunosuppressive agent, tacrolimus, after undergoing transplantation. The results of the mixed lymphocyte reaction (MLR) assay, performed to monitor the patient's course, were unremarkable[20]. She

*Corresponding author: Kazuaki Tanabe, M.D.; Department of Gastroenterological and Transplant Surgery, Hiroshima University
1-2-3 Kasumi, Minami-ku, Hiroshima 734-8551, Japan
Tel: +81 82 257 5222   Fax: +81 82 257 5224   E-mail: ktanabe2@hiroshima-u.ac.jp

did not experience graft rejection or infection episodes and was discharged 30 days after the surgery. Follow-up evaluations included laboratory data measurement, including tumor marker level measurement every month; computed tomography (CT) once a year; and gastrointestinal endoscopic examination before and 3 years after LDLT.

Eight years after LDLT, the patient was admitted to the hospital because of appetite loss for 3 months. Physical examination did not reveal any characteristic abnormalities. No hematologic abnormalities were noted, nor were elevations in the levels of tumor markers such as carcinoembryonic antigen and carbohydrate antigen 19-9. Upper gastrointestinal endoscopy revealed a non-dilated stomach with a giant fold, and gastric scirrhous carcinoma was strongly suspected. Histological examination revealed poorly differentiated adenocarcinoma. Endoscopic ultrasonography revealed muscularis propria invasion by the tumor. Abdominal CT did not indicate regional lymph node metastasis or distant metastasis.

Total gastrectomy and regional D2 lymph node dissection plus Roux-en-Y reconstruction was performed for the gastric scirrhous carcinoma (Fig. 1). Pathological examination revealed a poorly differentiated adenocarcinoma partially invading the serosa, with 1 metastasis in the 20 resected lymph nodes (Fig. 2). The neoplastic and non-neoplastic gastric mucosa both showed chronic atrophic gastritis. The patient was diagnosed with stage IIIA (T4aN1M0) gastric adenocarcinoma according to the Union for International Cancer Control (UICC) guidelines[16]. During the patient's postoperative course, minor leakage occurred but was effectively managed with conservative therapy. Administration of the immunosuppressive agent, tacrolimus, was resumed just after operation. The patient is currently being treated with adjuvant chemotherapy with S-1, and no recurrence has been observed 1 year after gastrectomy.

DISCUSSION

The use of newer immunosuppressive agents has reduced the incidence of acute rejection, resulting in the improved prognosis of transplant recipients. However, the increasing incidence of malignancy after transplantation, first reported by Murray et al in 1968[8], has become an important issue. Some studies have reported a 3−4-fold increase in the incidence of cancer in transplant recipients[10]. Malignancy after transplantation may be an important prognostic factor for recipients in the near future.

With regard to ethnic and environmental factors, Aberg et al reported an incidence of malignancy of 9.2% among 540 Finnish liver transplant recipients. In this group, the most frequent malignancies were non-melanoma skin cancer (20.0%), non-Hodgkin lymphoma (16.0%), and gastric cancer (4.1%)[1]. Sanchez et al created a single-institution prospective database of 1421 liver transplant recipients in the United States; the incidence of malignancy among these patients was 8.8%. The most frequent malignancy was skin cancer (32.8%), followed by lymphoma (28%). Gastric cancer is rarely reported in transplant recipients in Western countries[11]. In South Korea in Asia, Park et al reported that the incidence of malignancy in transplant recipients was 2.3% among 1952 liver transplant recipients, with gastric cancer being the most frequent malignancy (25.0%), followed by colorectal cancer (20.5%)[9].

The types of de novo malignancies after liver transplantation differ between Western and Asian countries. In 2008, approximately 1 million people were newly diagnosed with gastric cancer worldwide; 74% of these patients were from Asia. More-
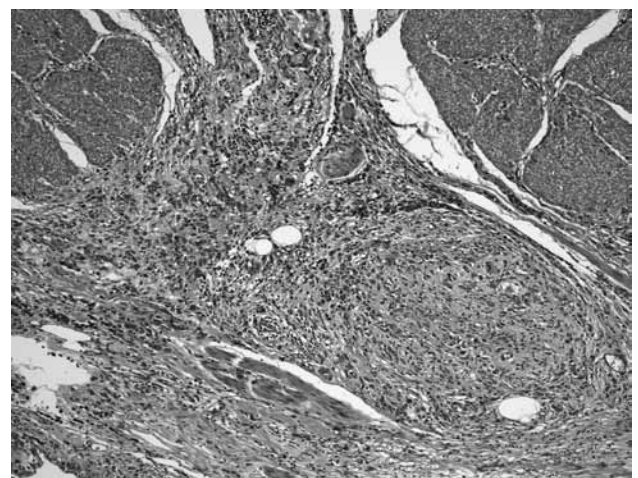

Fig. 1. Macroscopic observation showed a scirrhous carcinoma in the fundus and body of the stomach, with loss of distensibility and a thickened wall.

Fig. 2. Histological findings of the resected gastric specimen

Poorly differentiated adenocarcinoma and tubular adenocarcinoma penetrated the muscularis propria but not the serosa (hematoxylin and eosin staining, 100 ×).

over, in South Korea, China, and Japan, gastric cancer is a common cancer ($\geq$ 30 cases per 100,000 person-years)[14]. Therefore, the type of malignancy that occurs after liver transplantation may be influenced by ethnicity and environmental factors.

Cancer development after transplantation may be owing to a variety of mechanisms. First, some types of cancers are often associated with oncogenic virus infection such as Epstein- Barr virus (EBV) or *Helicobacter pylori* (Hp) infection after immunosuppressive therapy[7]. EBV often causes lymphoproliferative disorders and gastric cancer in transplant recipients[12]. Furthermore, recipients might have increased susceptibility to Hp infection because of the effect of immunosuppressive therapy. Treatment for Hp eradication might be important for gastric cancer prevention in Hp-positive recipients. In the case reported here, immunostaining of the pathologic sample revealed no EBV or Hp infection. To evaluate T-cell proliferation against the donor liver in liver transplant recipients, we employ the established MLR assay using a carboxyfluorescein diacetate succinimidyl ester (CFSE)-labeling technique with flow cytometry[20] in our department. The CFSE-MLR assay allows phenotypic analysis of proliferating T-cells in response to allostimulation, enabling the determination of whether the patient's immune status is optimal. According to the results of the MLR assay, the immune status of the patient reported here was optimal during the post-transplantation course. An anti-donor-specific immunosuppressive status achieved by minimizing immunosuppression could have prevented EBV infection in the patient.

Second, inhibition of T-cell-induced immunity and suppression of interleukin-2 might play a role in carcinogenesis and tumor growth in immunosuppressive recipients[18,19]. However, in this patient, the risk of *de novo* malignancy due to immuno- suppression might have been low because the patient was not over-immunosuppressed, according to the results of the MLR assay. Additionally, some immunosuppressive drugs increase the risk of cancer after transplantation. Treatment with tacrolimus is known to be an independent risk factor for malignancy in renal transplant recipients[6]. Benlloch et al reported that the time interval between liver transplantation and the diagnosis of *de novo* malignancy was getting shorter after 1995 (58 months vs. 22 months, before and after 1995, respectively); tacrolimus therapy was not introduced in their department before 1995[2].

In this case, *de novo* malignancy was diagnosed long after LDLT; this duration was 96 months, regardless of the use of tacrolimus for immunosuppression. The incidence of gastric cancer after liver transplantation in our department is 0.46% (1/217), which is lower than that previously reported[9]. The lower rate could be partly explained by the optimally controlled immune status, as moni-

tored using the MLR assay. In this case, the cancer could have developed *de novo* or by other alternative mechanisms.

In Japan, LDLT has become the standard therapy for advanced-stage liver disorders over the past 10 years, and patient prognosis after transplantation has been improving. Attention should now be focused on *de novo* malignancies after liver transplantation. Post-transplantation malignancies have become an important cause of mortality in the United States[3]. The 5-year survival rate was clearly worse for gastric cancer in liver transplant recipients[13]. This is probably because 60% of gastric cancers after liver transplantation were detected at UICC stage IV[2,16].

Shen et al reported that > 70% of countries have a mortality-to-incidence ratio of > 0.8; however, Japan, which provides a government-sponsored screening program for gastric cancer, has a high incidence but a low mortality-to-incidence ratio (0.43), highlighting the benefit of population-based screening in regions with a high prevalence[14]. However, Buell et al reported that gastric malignancies in transplant recipients were identified on the basis of either the symptoms (36%) or the results of follow-up endoscopy (55%) or CT (9%)[4].

In conclusion, to our knowledge, this is the first reported case of gastric cancer after LDLT, the postoperative course of which was managed by minimizing immunosuppressants in accordance with monitoring via the CFSE-MLR assay. The number of patients undergoing LDLT is increasing, and the incidence of gastric cancer is high in Asia. Accordingly, endoscopic screening programs are necessary to improve post-transplantation prognosis in transplant recipients in Asia.

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