Successfully-treated Advanced Bile Duct Cancer of Donor Origin After Hematopoietic Stem Cell Transplantation by Pancreaticoduodenectomy: A Case Report

KOICHIRO HARUKI, HIROAKI SHIBA, YASURO FUTAGAWA, SHIGEKI WAKIYAMA, TAKEYUKI MISAWA and KATSUHIKO YANAGA

Department of Surgery, The Jikei University School of Medicine, Tokyo, Japan

Abstract. *Secondary malignancies are one of the late complications observed in long-term survivors of allogeneic hematopoietic stem cell transplantation (HSCT). However, reports on secondary non-hematopoietic solid tumors derived from donor cells is extremely rare. We herein report a successfully-treated case of advanced bile duct cancer of donor-origin after allogeneic HSCT. A 44-year-old man was diagnosed with acute myeloid leukemia. When he achieved the third complete response, allogeneic hematopoietic stem cells of one-mismatch female donor were transplanted at the age of 50 years. Post-transplant acute and chronic graft-versus-host disease was treated by increased immunosuppression. At the age of 59, the patient was diagnosed with lower bile duct cancer and underwent pancreaticoduodenectomy with lymph node dissection. Pathological findings revealed a well-differentiated adenocarcinoma of the bile duct. Additional fluorescence in situ hybridization analysis revealed female patterns of the tumor cells, which suggested that the tumor cells originated from the donor. The patient had a satisfactory recovery, and received adjuvant chemotherapy with S-1. He remains well with no evidence of tumor recurrence as of one year after resection.*

In long-term survivors of allogeneic hematopoietic stem cell transplantation (HSCT), secondary malignancies, including post-transplant lymphoproliferative disorders, hematological disorders, and non-hematological solid tumors, are late complications (1). Although these secondary malignancies are generally considered to be derived from the recipient cells, sporadic cases of donor-cell derived leukemias have been reported since the original description of a case in 1971 (2).

In contrast, report of secondary non-hematopoietic solid tumors derived from donor cells are extremely rare. Houghton *et al*. reported for the first time in 2004 that bone marrow-derived cells play an important role in the re-generation of inflammatory tissue and in carcinogenesis (3). There have been limited reports on the involvement of bone marrow cells in human cancers after allogeneic HSCT (4-6). We report a patient that developed bile duct cancer of donor-origin after allogeneic HSCT. To the best of our knowledge, such a case has not been reported in the English literature.

Case Report

A 44-year-old man, post-cholecystectomy for gallstones, was diagnosed with acute myeloid leukemia. He was treated with chemotherapy and achieved the first complete response (CR). The relapse in the bone marrow was confirmed twice and he achieved the third CR at the age of 47 years. After nine courses of consolidation chemotherapy to prepare for transplantation, he underwent allogeneic hematopoietic stem cells from bone marrow of a one-mismatch female donor at the age of 50 years. Acute and chronic graft-*versus*-host disease (GVHD) developed post-transplant, which was successfully treated by increased immunosuppression.

At the age of 59 years, the patient was noted to have elevated liver and biliary enzymes. Computed tomography (CT) showed a nodule in the lower bile duct, which was slowly enhanced by dynamic CT (Figure 1A). Magnetic resonance cholangiopancreatography (MRCP) revealed post-cholecystectomy state, dilatation of intra- and extra-hepatic bile duct (Figure 1B) and a space-occupying lesion which showed slight high intensity on fat suppression T1-weighted images (Figure 1C). Endoscopic retrograde cholangiopancreatography (ERCP) showed stenosis and a mass in the lower bile duct (Figure 2A), which was diagnosed as tubular adenocarcinoma by biopsy. With a diagnosis of lower bile duct cancer, the patient

Correspondence to: Koichiro Haruki, MD, Ph.D., Department of Surgery, The Jikei University School of Medicine, 3-25-8, Nishi-Shinbashi, Minato-ku, Tokyo 105-8461, Japan. Tel: +81 334331111 ext. 3401, Fax: +81 354724140, e-mail: haruki@jikei.ac.jp

Key Words: Hematopoietic stem cell transplantation, bile duct cancer, carcinogenesis, secondary malignancies.

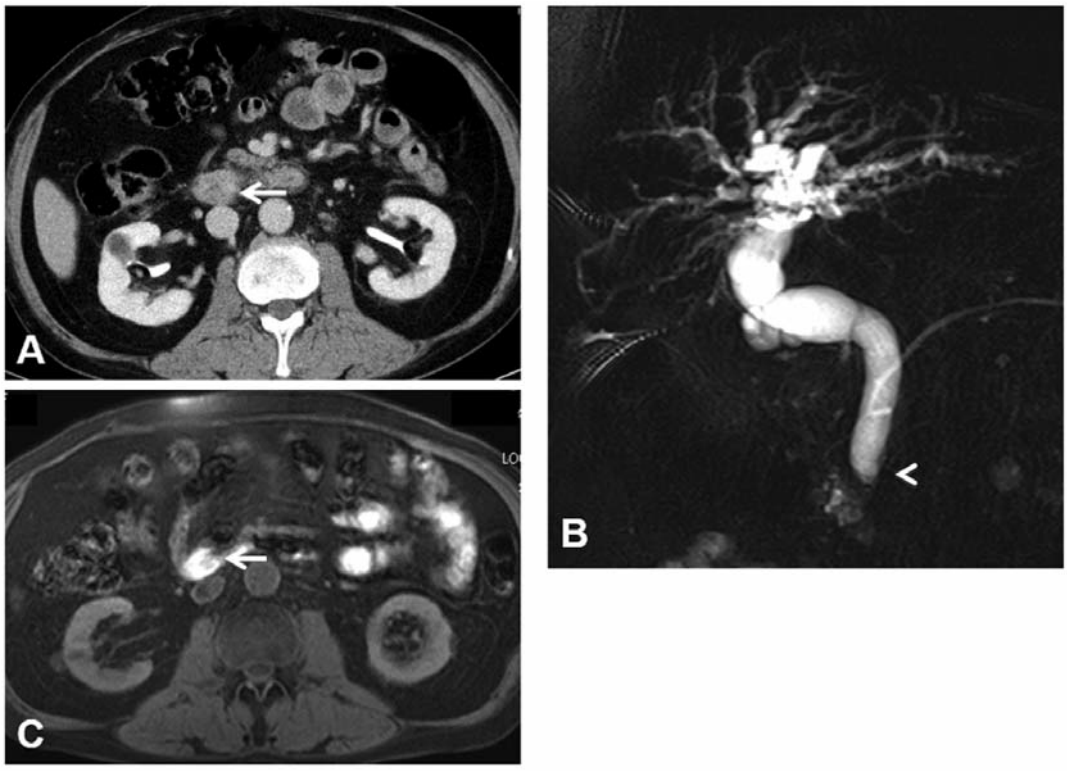

Figure 1. *Computed tomography (CT) showed a nodule in the lower bile duct, which was slowly enhanced on dynamic CT (A, arrow). Magnetic resonance cholangiopancreatography (MRCP) revealed post-cholecystectomy state, dilatation of intra- and extra- hepatic bile duct (B, arrowhead) and a space-occupying lesion, which showed slight high intensity on fat suppression T1-weighted images (C, arrow).*

underwent pancreaticoduodenectomy with lymph node dissection. In the resected specimen, histological findings demonstrated lower bile duct cancer (Figure 2B). Pathological findings revealed a well-differentiated adenocarcinoma of the bile duct (Figure 3A-B). Postoperative pancreatic fistula classified a grade B by the ISGPF criteria (7) was treated by US-guided drainage and antibiotics. Thereafter, the patient made a satisfactory recovery, and was discharged on postoperative day 33, and received adjuvant chemotherapy with S-1. He remains well with no evidence of tumor recurrence 1 year after resection.

Fluorescence in situ hybridization analysis. To determine whether donor-derived cells were involved in the bile duct cancer, fluorescence *in situ* hybridization (FISH) analysis was performed. Three-μm thick paraffin sections were cut from formalin-fixed paraffin-embedded sample of the tumor, and stained using sex chromosome probes. The Y chromosomes are stained bright green and the X chromosome are stained red.

Based on the result of FISH analysis, female patterns were observed in the tumor (Figure 3C). These results suggested that the tumor cells originated from the donor.

Discussion

With improved outcome of allogeneic HSCT, the development of secondary malignancies becomes one of the serious late complications, which is associated with considerable morbidity and mortality. Several studies have reported that the incidence of secondary solid tumors in recipients aged 10 years or older range from 2.2 to 6.1%, and that total body irradiation (TBI), T-cell depletion, GVHD and immunosuppressive therapy may be the important risk factors (1, 8, 9).

In patients who have undergone allogenetic HSCT, chronic GVHD is associated with chronic inflammation and serves as a risk factor for the development of secondary cancers. Oral mucosa, gastrointestinal tract, and skin are well-known target organs of chronic GVHD, which are also frequent sites of secondary cancers (1, 10). Chronic inflammation causes the damage of tissue and reported to trigger carcinogenesis (11). Okamoto *et al*. reported that bone marrow-derived cells were involved in the repair of damaged epithelium in the gastrointestinal tract (12). Regeneration and tissue repair of the human epithelium can occur by proliferation and differentiation of human adult bone marrow-derived stem

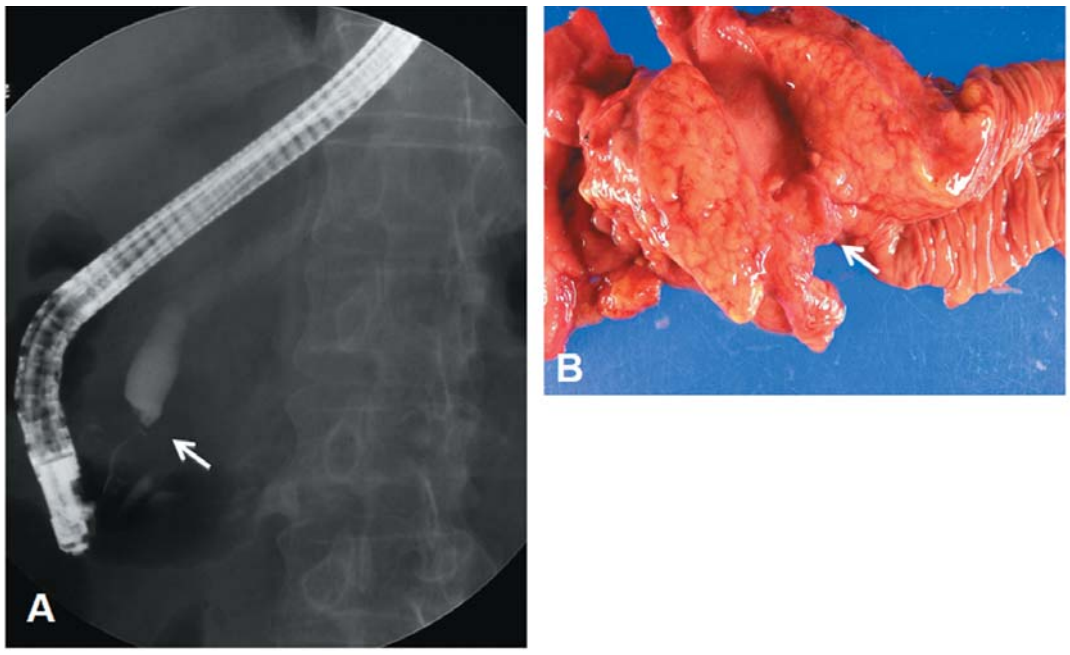

Figure 2. *Endoscopic retrograde cholangiopancreatography (ERCP) showed stenosis and a mass shadow in the lower bile duct (A, arrow). In the resected specimen, histological findings showed lower bile duct cancer (B, arrow).*

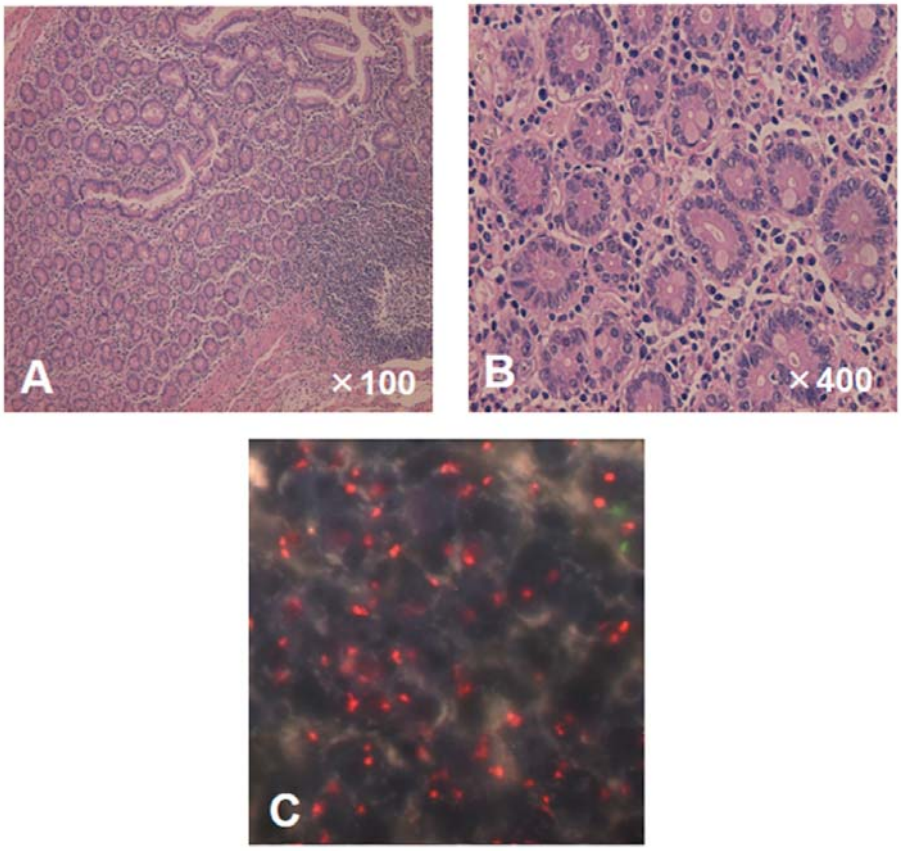

Figure 3. *Pathological findings demonstrated well-differentiated adenocarcinoma of the bile duct (A-B). Fluorescence in situ hybridization analysis revealed female patterns of the cancer cells (C).*

cells (13). Several reports showed that secondary cancers were derived from donor cells after HSCT (5, 14). These reports suggested that bone marrow-derived stem cells have a role in solid organ cancer's carcinogenesis. Total-body irradiation (TBI) is also reported to be a risk factor of secondary malignancies. TBI may induce DNA damage and mutations, which increase the risk of thyroid and brain cancer (9). Furthermore, immunosuppressive treatment among patients who had chronic GVHD and prolonged immunosuppressive treatment increases cutaneous and mucosal neoplasms (15).

Regarding risk factors of secondary malignancies in the current case, chronic GVHD, immunosuppressive agents and TBI at the time of the transplantation apply. However, there have been no reports of bile duct cancer after HSCT. Furthermore, the current case of bile duct cancer contained donor-derived cells, which to our knowledge is extremely rare. The factor that affected the process of carcinogenesis in the current case is unclear. Further analysis is required to clarify the mechanisms of secondary malignancies after HSCT.

Conflicts of Interest

The Authors declare that they have no conflicts of interest.

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