—**Report on Experiments and Clinical Cases**—

A Case Report of Metachronous Hepatocellular Carcinoma and Early Esophageal Cancer

Ken Takahashi, Hiroshi Yoshida, Yasuhiro Mamada, Nobuhiko Taniai, Yoshiharu Nakamura, Yoshiaki Mizuguchi, Masao Miyashita, Tsutomu Nomura, Hiroshi Makino and Takashi Tajiri

Surgery of Organ Function and Biological Regulation, Nippon Medical School Graduate School of Medicine

Abstract

We report a case of double cancer of the liver and esophagus, an extremely rare condition that can be very difficult to treat. A tumorous lesion was pointed out in segment 6 of the liver of a 69-year-old man under treatment for liver cirrhosis. Abdominal computed tomography and angiography revealed a hepatocellular carcinoma. The patient underwent transcatheter arterial embolization and partial resection of segments 5 and 6.

Fourteen months later, a small elevated lesion was detected in the esophagus during an endoscopic examination. The patient was treated by endoscopic mucosal resection and radiation therapy at a total dose of 50 Gy. Histological examination revealed a squamous cell carcinoma with cancer cells confined within the epithelium of the esophagus. Over the 6 years since the hepatectomy, there have been no signs of recurrence.

We report a successful curative resection in an extremely rare form of double cancer with a poor prognosis.

(J Nippon Med Sch 2005; 72: 187–190)

Key words: Hepatocellular carcinoma, Esophageal cancer

Introduction

Progress in diagnosis technologies, improved treatment outcomes, increased longevity, and other favorable changes in the healthcare environment have contributed to recent increases in the incidence of double cancers. We consider the case reported here significant in view of our success at curative resection in spite of the poor prognosis of this extremely rare form of double cancer.

Case Report

A 69-year-old man under treatment for alcoholic liver cirrhosis was admitted for an operation for hepatocellular carcinoma (HCC) in segment 6 which was post transcatheter arterial embolization (TAE) state. Physical examination on admission revealed a moderately nourished man with an impalpable liver and neither ascites nor jaundice. The results of blood tests were as follows: hemoglobin (Hb): 15.0 g/dl; white blood cell count (WBC): 3,900/mm^3; platelet count (Plt): 10.1 × 10^4/μl; glutamic oxaloacetic

Correspondence to Hiroshi Yoshida, The First Department of Surgery, Nippon Medical School, 1–1–5 Sendagi, Bunkyo-ku, Tokyo 113–8603, Japan
E-mail: hiroshiy@nms.ac.jp
Journal Website (http://www.nms.ac.jp/jnms/)

transaminase (GOT): 83 IU/*l*; glutamic pyruvic transaminase (GPT): 40 IU/*l*; total bilirubin (T-Bil): 1.3 mg/d*l*; and prothrombin time (PT): 92.9%. Alpha fetoprotein (AFP) and protein induced by vitamin K antagonists-2 (PIVKA-2) were both within normal limits (18 ng/m*l* and 38 mAU/m*l*, respectively). The indocyanine green (ICG) R15 level was elevated to 21.3%. Both HBs-antigen and anti-HCV antibody were negative. Abdominal ultrasonography revealed a tumor mass in segment 6 of the liver, 1.6×1.6 cm in size with hypo and hyperechoic components, and a hypoechoic margin. Abdominal computed tomography demonstrated a round mass measuring about 2 cm in the same liver segment (**Fig. 1**). Endoscopic examination revealed only gastric varices. These findings were consistent with a diagnosis of HCC.

The patient underwent a partial resection of segments 5 and 6 for HCC. The resected liver tumor was indistinctly bordered with normal tissue and measured less than 2 cm (**Fig. 2**). Histological examination revealed HCC with cirrhosis of the hepatic tissue (**Fig. 3**). The postoperative course was uneventful and the patient was discharged on the 25th postoperative day.

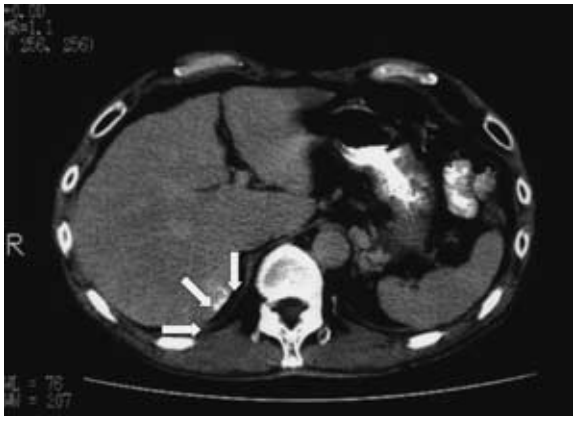

Fig. 1 Abdominal computed tomography post transcatheter arterial embolization state revealed hepatocellular carcinoma in segment 6 (arrows).

During follow-up 14 months after his operation for HCC, he was diagnosed with esophageal carcinoma by endoscopic examination and readmitted. The result of blood tests were as follows: Hb: 12.6 g/d*l*; WBC: 4,400/mm^3; Plt: 9.6×10^4/μ*l*; GOT: 37 IU/*l*; GPT: 27 IU/*l*; T-bil: 1.4 mg/d*l*; and PT: 81.4%. AFP and PIVKA-2 were both within normal limits (1.9 ng/m*l* and 0.8 mAU/m*l*, respectively). Squamous cell carcinoma antigen was also normal (0.8 ng/m*l*). The ICG R15 level was elevated to 20.1%. A double-contrast study of the esophagus did not show remarkable abnormalities. Endoscopic examination revealed a small 0-IIc type tumor with erosion located approximately 30 cm from dental line (**Fig. 4**). The biopsied tumor tissue was histologically diagnosed as squamous cell carcinoma. With the iodine preparation, the cancerous lesion was not revealed as a remarkable unstained area. Chest and abdominal computed tomography showed no sign of metastasis or recurrence in any other organs. These findings were consistent with a diagnosis of early esophageal carcinoma. The patient underwent endoscopic mucosal resection (EMR). The tumor had invaded no deeper than the mucosal epithelium and was histologically diagnosed as a poorly differentiated squamous cell carcinoma (**Fig. 5**). Distance from the line of resection to carcinoma was unclear. So radiation therapy at a total dose of 50 Gy was performed after the EMR as an adjuvant

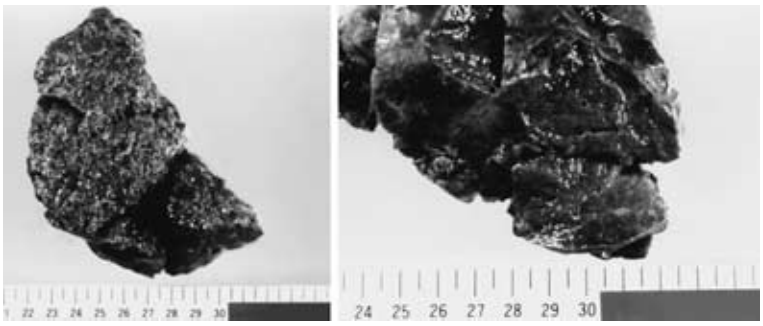

Fig. 2 Resected specimen.

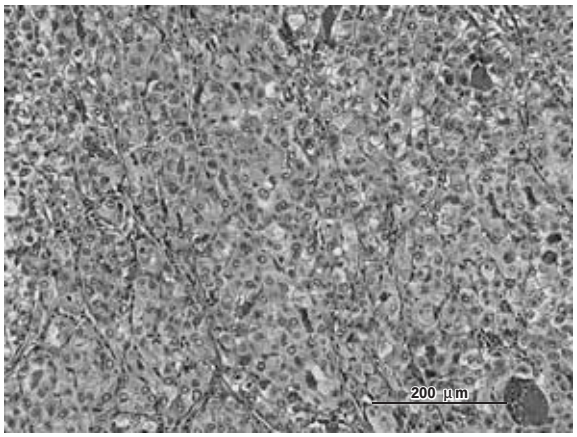

Fig. 3 Microscopic finding showed HCC. (H.E. stain)

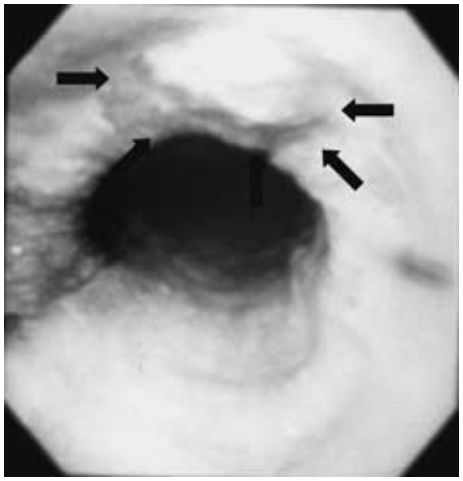

Fig. 4 Endoscopic examination revealed a 0-IIc type tumor located approximately 30 cm from dental line (arrows).

therapy. Over the 6 years since the hepatectomy, there have been no signs of recurrence.

Discussion

The current definition of double cancer was proposed by Warren[1]: each of the tumors must present a definite picture of malignancy, each must be distinct, and the probability of one being a metastasis of the other must be excluded. Double cancer is classified as either synchronous or metachronous, depending on the interval of appearance. The interval used to draw this distinction varies, however: Moertel et al.[2], for example, set the interval at 6 months, while

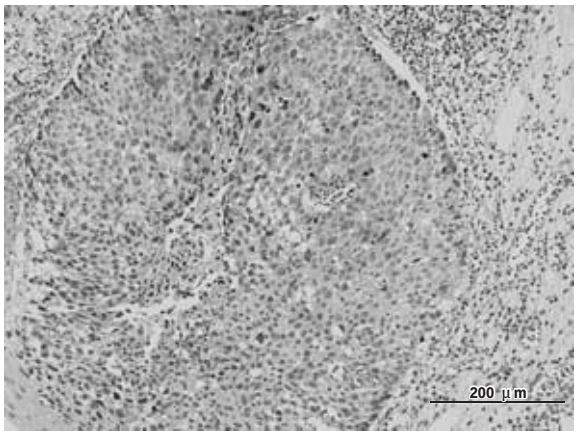

Fig. 5 Microscopic finding showed poorly differentiated squamous cell carcinoma and tumor had invaded no deeper than the mucosal epithelium. (H.E. stain)

Kitabatake et al.[3] set it at 1 year. In any event, the present case can be definitively categorized as a metachronous double cancer since the second diagnosis was made 14 months after the first. Warren reported only 1 case of double cancer of the liver and esophagus out of 306 double cancer cases (0.33%). Likewise, Nakamura et al.[4] reported only 6 out of 1,121 cases (0.54%). Jeger et al.[5] calculated that probability of HCC and esophageal cancer in the same patient as follows: 7.48 people/10×10^9 people/year. Among the 10,617 double cancer cases reported in Japan between 1998 and 2002, only 50 cases (0.47%) were double cancers of the liver and esophagus by Annual of the pathological autopsy cases in Japan[6]. The above-mentioned reports are all based entirely on autopsy examples. Yamamoto et al. are the only other investigators to publish a clinical report on double cancer of the liver and esophagus in Japan[7]. On these grounds, we can safely assert that this form of double cancer is extremely rare.

The treatment of double cancers involving the liver and a second organ is beset with difficulty. Among the synchronous cases, for example, many patients have degraded liver function due to liver cirrhosis or chronic hepatitis. This is thought to produce greater surgical stress in such patients, and even to rule out surgery in some cases. Among cases with metachronous double cancers who undergo operations for liver cancer first, the

adhesion in the abdomen following the operation is thought to significantly increase the risk of the operation for the second cancer. Our case initially underwent a partial resection of the liver based on a diagnosis of HCC, followed by EMR for esophageal cancer 14 months later. Over the 6 years since the hepatectomy, there have been no signs of recurrence.

Given the recent increase in the indications for endoscopic surgery, we think that it is very important to consider the possibility of double cancer and to aim for the early diagnosis of second cancers after operations for initial malignancies.

References

1. Warren S, Gates O: Multiple primary malignant tumors a survey of the literature and a statistical study. Am J Cancer 1932; 16: 1358–1415.
2. Moertel CG, Dockerty MB, Baggenstoss AH: Multiple primary malignant neoplasms. Introduction and presentation of data. Caner 1961; 14: 221–230.
3. Kitabatake T, Kaneko A, Kido T: Investigation on double cancer with case reports and statistic consideration. Jpn J Cancer Clin 1960; 6: 337–345.
4. Nakamura K, Aizawa K: Investigation on double cancer with special reference to the combination. Jpn J Cancer Clin 1972; 18: 662–666.
5. Jeger RM, Max MH: Association of squamous carcinoma of the esophagus with a synchronous primary hepatocelluler carcinoma. J Clin Gastroenterol 1981; 3: 73.
6. Annual of the pathological autopsy cases in Japan. Edited by The Japanese Society of Pathology; Vol 41–45.
7. Yamamoto T, Shinjo Y, Habukawa M, Seyama K, Hasegawa H, Miyashita H, Tatebayashi K: A case report of metachronous small live cancer and early esophageal cancer. J Jpn Surg Assoc 1995; 56: 160–164.

(Received, January 7, 2005)
(Accepted, February 2, 2005)