CASE REPORT

Metachronous bile duct cancer nine years after resection of gallbladder cancer

Hye Jin Joo, Gi Hyun Kim, Won Joong Jeon, Hee Bok Chae, Seon Mee Park, Sei Jin Youn, Jae Woon Choi, Rohyun Sung

Abstract

We report a rare case of a 74-year-old man with metachronous gallbladder cancer and bile duct cancer who underwent curative resection twice, with the operations nine years apart. At the age of 65 years, the patient underwent a cholecystectomy and resection of the liver bed for gallbladder cancer. This was a well-differentiated adenocarcinoma, with negative resection margins (T2N0M0, stage I B). Nine years later, during a follow-up examination, abdominal computed tomography and MRCP showed an enhanced 1.7 cm mass in the hilum that extended to the second branch of the right intrahepatic bile duct. We diagnosed this lesion as a perihilar bile duct cancer, Bismuth type III a, and performed bile duct excision, right hepatic lobectomy and Roux-en-Y hepaticejunoanastomosis. The histological diagnosis was a well-differentiated adenocarcinoma with one regional lymph node metastasis (T1N1M0, stage III B). Twelve months after the second operation, the patient is well, with no signs of recurrence. This case is compared with 11 other cases of metachronous biliary tract cancer published in the world medical literature.

INTRODUCTION

The occurrence of two or more primary malignant tumors in a patient is regarded as uncommon. In 1889, Billroth documented several such cases as rare events. However, in recent years, several studies have noted multiple primary cancers frequently due to the prolonged survival of patients who have previously been cured of a primary cancer[1]. Multiple primary cancers are defined as either synchronous tumors or metachronous tumors, according to whether the diagnostic intervals of the lesions are shorter or longer than six months, respectively[2,3]. Synchronous multiple biliary cancers occur in 3.7%-7.4% of all surgically resected biliary tumors. Most of them develop in the gallbladder and bile duct[4-6]. On the other hand, metachronous multiple biliary cancers are rare, with only 11 cases reported in the world literature[7-17]. In Korea, one case was reported in 1997 when a 61-year-old man underwent curative resection for bile duct cancer 30 mo after a radical cholecystectomy to cure gallbladder cancer[17].

We report the case of a 74-year-old man with metachronous gallbladder cancer and hilar bile duct cancer, who underwent curative resection twice, with an interval of nine years separating the operations. We also refer to 12 cases of metachronous biliary tract cancer published in the world literature, including the present case.
of elevated serum alkaline phosphatase level. Nine years previously, he had undergone a cholecystectomy and resection of his liver bed for gallbladder cancer. The pathologic specimen revealed a well-differentiated adenocarcinoma with muscular invasion, no hepatic invasion, and with negative resection margins (T2N0M0, stage I B). He did not receive adjuvant therapy and was followed up periodically without evidence of tumor recurrence. However, nine years later, blood tests showed an elevated serum alkaline phosphatase level. He had been taking antihypertensive agents and oral hypoglycemic agents for ten years. He underwent splenectomy for idiopathic thrombocytopenic purpura 15 years ago. He is a nonsmoker and a farmer.

On admission, the patient complained of dyspepsia but physical examination revealed no abnormalities. Laboratory test results showed WBC 9010/mm³, hemoglobin 13.3 g/dL, hematocrit 41.3%, platelet 312 × 10⁹/L, AST 44 U/L, ALT 43 U/L, total bilirubin 0.5 mg/dL, alkaline phosphatase 975 IU/L, CEA 5.2 ng/mL (< 5 ng/mL), and CA 19-9 77.4 ng/mL (< 37 ng/mL). Abdominal CT and magnetic resonance imaging (MRI) revealed an enhanced 1.7 cm mass in the hilum that extended to the second branch of the intrahepatic bile duct on the right side of the liver, as well as diffuse dilated intrahepatic bile ducts (Figure 1). These findings suggested hilar bile duct cancer, Bismuth type IIIa. There was no evidence of peritoneal metastasis or enlarged lymph nodes. The patient underwent curative surgery comprising bile duct excision, right hepatic lobectomy and Roux-en-Y hepaticojunostomy (Figure 2). Pathologic specimens revealed a well-differentiated adenocarcinoma invading the entire thickness of the bile duct; one of seven lymph nodes was positive for malignant cells; and there was a high degree of dysplasia around the main lesion (T1N1M0, stage II B). We used genetic alterations in CA19-9, p53 gene, and k-ras as a means of distinguishing multi-centric primary cancers from primary cancer metastases. The tissues of the gallbladder cancer and the bile duct cancer were both positive for the p53 and k-ras gene. However, CA19-9 was negative in the tissue of the gallbladder cancer, but positive in the tissue of the bile duct cancer (Figure 3). Now, 12 mo after the second operation, the patient is doing well with no evidence of recurrence. These two cancers apparently occurred independently and each surgical treatment was successful.

DISCUSSION

Synchronous multiple primary cancers of the biliary system occur in up to 7% of resected bile duct cancers. Most are found on removing the gallbladder during a resection for bile duct cancer[4-6]. However, metachronous multiple bile duct cancer is very rare. Because biliary tract cancers are usually advanced by the time of diagnosis, and surgery involves a broad bile duct resection with curative intent, the chances of developing a metachronous double biliary cancer are slim⁷-¹⁷.

In 1932, Warren and Gates proposed the three still generally accepted criteria that had to be met in order to consider malignant tumors as multiple primary tumors rather than recurrences: first, each of the tumors must present a definite picture of malignancy; second, each tumor must have a different histological appearance; third, the possibility that one might be a metastatic lesion from a former lesion must be excluded⁸. Gertsh also stated the criteria for double primary cancer in the biliary tract: first, each tumor must be distinct; second, each tumor must be separated from normal tissue; third, there should be no evidence of invasion to the submucosal layer and lymph nodes around the bile duct⁹. Bile duct
cancer often exhibits metastasis to the lymph node nearest the mass, or via the bile duct; therefore, spreading of micro-vessels and nerve system, depth of tumors and the possibility of peri-lymph node invasion must all be considered in discriminating between metastatic cancer and double primary cancer. When multiple cancers are identified, the distinction between multi-centric primary cancers and primary cancer metastases is often clinically difficult. Recent studies reported that analysis of loss of heterozygosity, point mutations of k-ras oncogene\(^1\), overexpression of the tumor suppressor gene \(p53\)\(^2\) and tumor marker CA19-9, and CEA in the cancers, may all play an important role in diagnosing the second cancer as primary or metastatic tumors\(^3,4,5\). Hori et al\(^6\) diagnosed four cases of double primary cancer of gallbladder and bile duct cancer by point mutation of k-ras and overexpression of \(p53\), CEA, and CA19-9 by immunohistochemistry. Ogawa et al\(^7\) reported metastatic bile duct cancer, located in both the upper and lower extrahepatic bile duct, which met the criteria of double primary tumors; then he revealed metastasis by analyzing the loss of heterozygosity, using microsatellite genetic markers on five arms. Therefore, it is not sufficient to diagnose double cancer only by means of pathologic examination. New diagnostic technology, such as genetic analysis, may be needed.

This case was diagnosed as metachronous double biliary cancer, which developed nine years after resection for gallbladder cancer, and was cured surgically. This case shows evidence to support a diagnosis of double primary cancers. First, both the gallbladder cancer and the bile duct cancer were malignant; however, there was no evidence of malignancy in the surgical stump, indicating there was no link between them. Second, advanced gallbladder cancers usually recur within five years of resection. The second bile duct cancer was detected nine years after the first operation, and so it would be extremely

![Image 3  Histopathological finding of hilar bile duct cancer. A: Histologic section of the gallbladder shows well-differentiated biliary-type adenocarcinoma infiltrating the entire thickness of the gallbladder wall (HE, × 100); B: None of the tumor cells expressed CA19-9 (immunoperoxidase method, × 100); C: Histologic section of the hepatic duct demonstrates severe epithelial dysplasia of the mucosa in the upper field (arrows) and invasive adenocarcinoma in the lower field (arrow heads) (hematoxylin and eosin, × 100); D: Most of the dysplastic epithelial cells in the upper field (arrows) and some of invasive tumor cells in the lower field express cytoplasmic CA19-9 (arrow heads). An invasive tumor gland is noted in the mid-left field (immunoperoxidase method, × 100).

### Table 1  Clinicopathological characteristics of the 12 reported cases with metachronous cancers of the biliary tract

| Yr   | Sex | Interval (yr) (1st-2nd cancers) | Site | Pathology          | Type of surgery                      | 2nd cancer | Site | Pathology          | Type of surgery   |
|------|-----|---------------------------------|------|--------------------|--------------------------------------|------------|------|--------------------|-------------------|
| 1987 | F   | 3.5                             | GB   | Tub, ss            | Chole                                | CBD        | Pap, ss | PD\(^7\)           |                   |
| 1997 | M   | 4                               | GB   | Pap, mp            | Chole                                | HBD        | Tub, ss | Excision HBD       | [1, 14]           |
| 1999 | F   | 7                               | LHBBD| Tub, mp, WD        | LH extended                          | CBD        | Tub, MD-PD\(^3\), si | PD\(^2\)          |                   |
| 1999 | M   | 7                               | GB   | Pap, mp            | Chole                                | CBD        | Pap, fm | PD\(^2\)           |                   |
| 2001 | F   | 4                               | CBD  | Tub, ss            | Chole+ liver resection + resection extrathepatic BD | LHBBD     | Tub, si | LH extended       | Liver resection    |                   |
| 2001 | F   | 7                               | GB   | Muc, mp            | Chole+ liver resection + resection extrathepatic BD | CBD        | Pap,mur | HBD              |                   |
| 2004 | M   | 4                               | GB   | Pap,mp             | Chole                                | CBD        | Pap, mp | HBD              |                   |
| 2003 | M   | 4                               | GB   | CIS with adenoma   | Chole                                | CBD        | CIS     | Excision CBD       | [14]              |
| 2004 | F   | 10                              | GB   | Ss, WD             | Chole+ liver resection               | CBD        | WD      | PD\(^2\)           | [15]              |
| 2007 | M   | 2.3                             | CBD  | fm                 | Resection middle third extrathepatic BD + chole | CBD        | fm      | PD\(^2\)           | [16]              |
| 1997 | M   | 2.5                             | GB   | Ss, MD-PD\(^3\)    | Chole+ liver resection               | CBD        | Ss, MD  | PD\(^2\)           |                   |
| 2009 | M   | 9                               | GB   | mp                 | Chole+ liver resection               | HBD        | ss      | RH               |                   |

\(^1\)PD: Poorly differentiated; \(^2\)PD: Pancreaticoduodenectomy; CIS: Carcinoma in situ; CBD: Common bile duct; Chole: Choledectomy; fm: Fibromuscular layer; GB: Gallbladder; HBD: Hilar bile duct; HPD: Hepaticopancreatic duodenectomy; LH: Left hepatectomy; m: Mucosal layer; LHBD: Left hepatic bile duct; MD: Moderately differentiated; mp: Proper muscle layer; muc: Mucinous adenocarcinoma; pap: Papillary adenocarcinoma; RH: Right hepatectomy; si: Serosal invasion; ss: Subserosal layer; tub: Tubular adenocarcinoma; WD: Well differentiated.

---

www.wjgnet.com
unlikely for the second cancer to be a remnant tumor from the first operation. Third, although both tumors of the gallbladder and the bile duct showed the same histological differentiation and positive k-ras and p53 immunohistochemistry, the expressions of CA19-9 were different: CA19-9 expression was negative in the gallbladder cancer and positive in the bile duct cancer. Lastly, the bile duct cancer resembled a primary tumor from evidence of dysplastic changes near the main mass which would not be found in metastatic cancer.

The etiology of double biliary tract cancer has not been defined, but it is generally accepted that the anomalous union of the pancreaticobiliary duct (AUPBD) plays an important role in the development of multiple biliary tract cancers. Kaneko et al.\(^8\) and Fujii et al.\(^8\) reported that 50%-62.5% of cases of synchronous double biliary tract cancers were associated with AUPBD. A close relationship is known to exist between cancer of the bile duct system and AUPBD. In most patients with AUPBD, there is a long common channel between the junction of the pancreatic and common bile ducts and the sphincter of Oddi. We also know that the risk of bile duct carcinoma increases with age. Continuous reflux of the pancreatic juice into the bile duct induces chronic inflammation and metaplastic epithelial changes in the biliary tree.\(^30\) Despite more than half of synchronous double biliary cancers having AUPBD as a risk factor, none of the twelve metachronous cases was associated with AUPBD (Table 1). Also, bile duct cancer is associated with AUPBD, almost middle and inferior regions of the bile duct and none of superior part of the bile duct cancer are associated with AUPBD.\(^16\) This would reinforce the idea, suggested by other investigators, that upper biliary tract cancers and metachronous double biliary cancers have a strong genetic predisposition, or oncogenic susceptibility, irrespective of the presence of AUPBD. Although most metachronous double cancers have no obvious cause, several predisposing factors have been identified including: previous treatment of cancer, environmental factors, race, genetic factors, and long-term survival.\(^5\) Although this case shows no evidence of AUPBD, double cancer of the gallbladder and bile duct is associated with expression of k-ras oncogene and the p53 tumor suppressor gene. Thus, we can guess which oncogenes were responsible for both biliary systems forming a malignant lesion simultaneously.

Table 1 illustrates all twelve cases of metachronous biliary tract cancer (including this case) previously described in the literature. There were six male and six female patients, ranging in age from 12-83 years (mean, 63 years). One patient developed metachronous biliary double cancer aged 21 years.\(^10\) The three cases of a second cancer in the upper bile duct and six cases of a second cancer in the lower bile duct were detected at a mean age of 5.7 years after a first operation for gallbladder resection. Three second cancers developed in the remnant bile duct at 7, 4, and 2.3 years after the first operation for bile duct resection. There was no definite cause identified in the 12 cases of metachronous bile duct cancer, including this case. None of them has AUPBD as etiology. Also, the criteria for double primary cancer are based solely on pathologic evidence: with the exception of this case, no previous cases have used gene expression as a diagnostic tool.

There is no clear evidence about follow-up intervals and diagnostic methods during postsurgical monitoring. Takai et al.\(^12\) reported that magnetic resonance cholangiography and gadolinium enhanced dynamic MRI were useful in the diagnosis of a bile duct cancer that developed seven years after resection for gallbladder cancer, in the anatomically rearranged structure following gallbladder resection. Merenda et al.\(^24\) suggested a potential role for PET-CT to detect metachronous bile duct cancer in the postsurgical monitoring of bile duct cancer when abdominal CT did not reveal any lesions. However, metachronous bile duct cancer is very rare, so it is not cost-effective to routinely provide expensive procedures, such as MRI or PET-CT, during the postoperative period. Further studies are needed to facilitate the cost-effective early detection of metachronous double cancers.

In conclusion, we present a rare case of advanced metachronous double cancer of the gallbladder and bile duct cancer, separated by a period of nine years. We enhance our report with a review of the relevant literature.

REFERENCES

1. Travis LB, Rabkin CS, Brown LM, Allan JM, Alter BP, Ambrosone CB, Begg CB, Caporaso N, Chanock S, DeMichele A, Figg WD, Gospodarowicz MK, Hall EJ, Hisada M, Inskip P, Kleinerman R, Little JB, Malkin D, Ng AK, Offit K, Pui CH, Robison LL, Rothman N, Shields PG, Strong L, Taniguchi T, Tucker MA, Greene MH. Cancer survivorship—genetic susceptibility and second primary cancers: research strategies and recommendations. J Natl Cancer Inst 2006; 98: 15-25

2. Eom BW, Lee HJ, Yoo MW, Cho JJ, Kim WH, Yang HK, Lee KU. Synchronous and metachronous cancers in patients with gastric cancer. J Surg Oncol 2008; 98: 106-110

3. Mortel CG, Dokerty MB, Baggenstoss AH. Multiple primary malignant neoplasms. I. Introduction and presentation of data. Cancer 1961; 14: 221-230

4. Horii H, Ajiki T, Fujita T, Okazaki T, Suzuki Y, Kuroda Y, Fujimori T. Double cancer of gall bladder and bile duct not associated with anomalous junction of the pancreaticobiliary duct system. Jpn J Clin Oncol 2006; 36: 638-642

5. Kurosaki I, Watanabe H, Tsukada K, Hatakeyama K. Synchronous primary tumors of the extrahepatic bile duct and gallbladder. J Surg Oncol 1997; 65: 258-262

6. Gertsch P, Thomas P, Baer H, Lerut J, Zimmermann A, Blumgart LH. Multiple tumors of the biliary tract. Am J Surg 1990; 159: 386-388

7. Hachiya KU, Yamaguchi A, Isogai M, Yasui A. Metachronous multiple primary cancer of the biliary tract, a case of long-term survival (in Japanese). Tan to Suii (J Bil Pancre) 1987; 8: 1217-1221

8. Kaneko H, Haruyama T, Ogata H, Tamura A, Waki K, Hashimura C, Shiba T. A case of metachronous double cancer of the gallbladder and superior bile duct (in Japanese). Nihon Gekakeiryo Gakkaiishi (J Jpn Coll Surg) 1997; 1: 114-117

9. Saiura A, Takayama T, Sano K, Toyoda H, Abe H, Kubota K, Mori M, Makuchi M. Metachronous bile duct cancer in a patient surviving for a decade and undergoing curative surgery twice. Jpn J Clin Oncol 1999; 29: 353-355

10. Yodonawa S, Yamabe K, Ogawa I, Fujiwara A, Hirano M,
Goto Y, Takahashi M, Nishida K. A case of metachronous double cancer of the biliary tract (in Japanese with English abstract). *Gan No Rinsho* (Jpn J Cancer Clin) 1999; 45: 1202-1207

Nakakubo Y, Kondo S, Omi M, Hirano S, Ambo Y, Morikawa T, Okaushiba S, Kato H, Shimizu M. A case of heterochromic development of extrahepatic bile duct carcinoma and cholangiocellular carcinoma (in Japanese with English abstract). *Nihon Syokakigeka Gakkaisshii* (Jpn J Gastroenterol Surg) 2001; 34: 1429-1432

Takai S, Shiratori Y, Kanematsu M, Yamazaki K, Naiki T, Yasuda I, Nagaki M, Murakami N, Kato T, Takao H, Shimokawa K, Hoshi H, Saji S, Moriwaki H. Usefulness of MR imaging in the postsurgical monitoring of gallbladder cancer in a patient with bile duct cancer that developed 7 years after resection of mucinous adenocarcinoma of the gallbladder. *J Gastroenterol* 2001; 36: 787-789

Fujii T, Kaneko T, Sugimoto H, Okochi O, Inoue S, Takeda S, Nagasaka T, Nakao A. Metachronous double cancer of the gallbladder and common bile duct. *J Hepatobiliary Pancreat Surg* 2004; 11: 280-285

Goh J, Kelleher B, Clarke E, O'Keane JC, MacMathuna P. Early neoplasias of the gallbladder and bile duct: an "unstable" biliary epithelium? *Endoscopy* 2003; 35: 538-541

Yuzawa H, Ikematsu Y, Ito Y, Nishiwaki Y, Kida H, Uchimura M, Ozawa T, Kanematsu T, Waki S. Successful surgical treatment for metachronous advanced cancers of the gallbladder and the common bile duct--case report. *Hepatogastroenterology* 2001; 48: 664-667

Merenda R, Portale G, Sturniolo GC, Marciani F, Faccioli AM, Ancona E. A rare surgical case of metachronous double carcinoma of the biliary tract. *Scand J Gastroenterol* 2007; 42: 1265-1268

Ahn CJ, Lee JR. Primary double cancer metachronously occurred in the biliary system. *J Korean Surg Soc* 1997; 52: 299-304

Warren S, Gates O. Multiple primary malignant tumors: survey of the literature and a statistical study. *Am J Cancer* 1932; 16: 1358-1414

Ogawa A, Sugo H, Takamori S, Kojima K, Fukasawa M, Beppu T, Futagawa S, Fujii H. Double cancers in the common bile duct: molecular genetic findings with an analysis of LOH. *J Hepatobiliary Pancreat Surg* 2001; 8: 374-378

Funabiki T, Matsubara T, Miyakawa S, Ishihara S. Pancreaticobiliary maljunction and carcinogenesis to biliary and pancreatic malignancy. *Langenbecks Arch Surg* 2009; 394: 159-169

S- Editor Li LF  L- Editor Webster JR  E- Editor Lin YP