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Synchronous Primary Tumors of the Extrahepatic Bile Duct and Gallbladder

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Background and Objectives: This study aims to clarify clinicopathologic characteristics of synchronous primaries of the extrahepatic bile duct and gallbladder. Understanding multiplicity and its histologic confirmation is an important step for successful surgical management.
Methods: Of the 190 cases of resection of biliary tract neoplasms in this study, 10 had two separate tumors in the extrahepatic bile duct and gallbladder, which were investigated by the microscopic mapping technique for tumor extent using serial stepwise sectioning of specimens.
Results: Clinical diagnosis was made successfully in only two cases. Detailed histologic examination revealed seven cases with synchronous primaries and three cases with metastatic tumors. Several microscopic parameters had additional diagnostic value. The presence of synchronous primaries is not necessarily associated with a poor prognosis, since we had four long-term survivors.
Conclusions: Diagnosis of synchronous extrahepatic biliary neoplasms is rarely made preoperatively. However, aggressive resection and careful microscopic examination are essential for the successful management and diagnosis of these special cases.
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KEY WORDS: multiple biliary tract neoplasms; metastatic bile duct tumor; microscopic mapping technique; survival

INTRODUCTION

Synchronous primary tumors of both the bile duct and gallbladder are a rare occurrence [1–4]. However, recent studies have demonstrated that they occur more frequently than previously thought [5,6].

When considering synchronous tumors of the bile duct and gallbladder, the first issue is what criteria can be used to prove or disprove this relatively rare situation, as the two sites have embryologic similarity and anatomic proximity. Recently, Gertsch et al. [5] have advocated three criteria: no direct continuity between the two tumors, a growth pattern typical of a primary tumor, and clear histologic differences between the two tumors. These criteria may be useful and practical for most situations; however, three of the four patients reported by Gertsch et al. [5] underwent only palliative cholecystectomies, and thus histologic examination of the entire bile duct was not performed.

This study focuses mainly on seven cases of resection of synchronous cancers and compares their clinicopathologic characteristics with three cases of metastatic bile duct tumors.

MATERIALS AND METHODS

From 1981 to 1994, 190 patients with biliary tract cancer (85 patients with cancer of the extrahepatic bile

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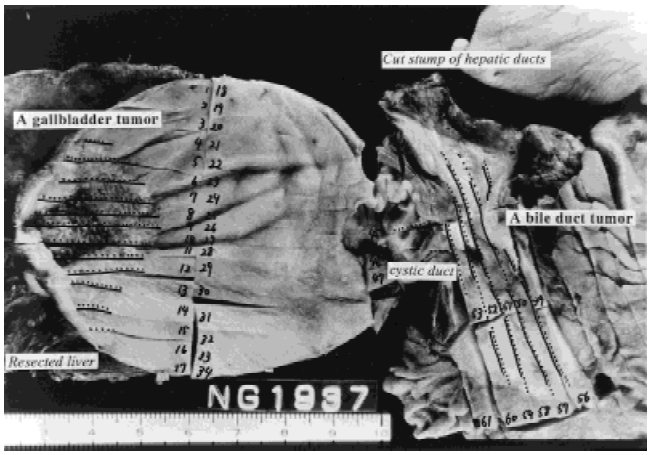

Fig. 1. A case of synchronous biliary primaries (patient #2). Microscopic mapping of tumor extent according to the depth of invasion. The tumor-free area in all layers of the wall of the gallbladder was also carefully investigated with multiple microscopic specimens (dotted lines, tumor located in superficial layer and black lines, tumor extending to subserosa or beyond serosa).

TABLE I. Clinical Characteristics of 10 Patients With Synchronous Primary Tumors of Extrahepatic Bile Duct and Gallbladder

Patient	Age (yr)/ gender	Initial symptoms	PTBD[a]	Operations[b]
1	72/M	Jaundice	(+)	PD + WHR + LN
2	62/F	Fever, fatigue	(+)	PD + WHR + LN
3	77/M	Abdominal pain	(+)	PD + C + LN
4	73/F	Jaundice	(+)	PD + C + LN
5	66/F	Liver injury	(−)	RBD + C + LN
6	56/M	Liver injury	(−)	ELH + RBD + LN
7	74/F	Abdominal pain	(−)	RC + RBD + LN
8	51/M	Jaundice	(+)	PD + C +LN
9	84/F	Body weight loss	(−)	ERH + RBD + LN
10	62/M	Jaundice	(+)	PD + ERH + LN

[a]Percutaneous transhepatic biliary drainage.
[b]PD = pancreaticoduodenectomy; WHR = cholecystectomy with wedge resection of the liver; LN = lymph node dissection; C = cholecystectomy; RBD = resection of the bile duct; ELH, ERH = extended left/right hepatectomy.

duct and 112 patients with cancer of the gallbladder) underwent surgery at Niigata University Hospital. Patients who received a bypass procedure or an exploratory laparotomy were excluded. After surgery, the gallbladder and bile duct were incised and opened for macroscopic examination, and the resected regional lymph nodes were separated from the specimen. The macroscopic features of the tumor were carefully described, and the specimen was fixed in 10% buffered formalin solution for several days. Serial partial incisions were made at 3–4-mm intervals through the resected gallbladder and bile ducts, and a color photograph of the specimen was taken. The specimen was sectioned along these incisions into 30–70 blocks, and all the sectioned specimens were embedded in paraffin and 4×10^{-3} mm deparaffinized sections were prepared. These deparaffinized sections were stained with hematoxylin and eosin for microscopic tumor mapping on the color photograph (Fig. 1). The local extent of the tumor and any residual tumor was determined microscopically by this mapping technique. The histopathologic features of the tumor were described based upon the American Joint Commission on Cancer (AJCC) TNM staging system [7], and microvascular involvement and perineural invasion were classified according to the ''General Rules for Surgical and Pathological Studies on Cancer of Biliary Tract'' [8].

Of the 190 surgical specimens investigated microscopically in this manner, 10 specimens contained two separate tumors with one located in the extrahepatic bile duct and the other in the gallbladder. The two lesions were not continuous in any layer of the biliary duct wall or extraductally.

Age, gender, initial symptoms, use of percutaneous transhepatic biliary drainage, and operations in the 10 patients are listed in Table I.

TABLE II. Macroscopic Comparison of Two Separate Tumors in 10 Cases on Synchronous Bile Duct and Gallbladder Tumors

	Bile duct tumor		Gallbladder tumor		
Patient	Gross type[a]	Tumor location	Gross type	Tumor	Stone
1	Nodular	Middle third	Nodular type	Fundus	(−)
2	Infiltrating	Middle third	Nodular	Fundus	(−)
3	Nodular	Distal third	Polypoid (8 mm)	Neck	(−)
4	Nodular	Distal third	Flat	Neck to body	(−)
5	Nodular	Middle third	Flat	Body to fundus	(−)
6	Nodular	Lt hepatic duct	Nodular	Neck to body	(+)[b]
7	Flat	Middle third	Nodular	Neck	(−)
8	SMT-like	Middle third	Nodular	Fundus	(+)[c]
9	SMT-like	Rt hepatic duct	Infiltrating	Body	(+)[c]
10	SMT-like	Proximal third	Nodular	Fundus	(+)[c]

[a]SMT = submucosal tumor.
[b]Gallstones in both bile duct and gallbladder.
[c]Gallstones in gallbladder only.

TABLE III. Microscopic Comparison of Two Separate Tumors in 10 Cases of Synchronous Bile Duct and Gallbladder Tumors

	Bile duct					Gallbladder					
Patient	Histologic type/grade[a]	Tumor extent[b]	ly[c]	v[d]	pn[e]	Histologic type/grade[a]	Tumor extent[b]	ly[c]	v[d]	pn[e]	n[f]
1	ad-sq	T3 (pancreas)	3+	1+	3+	por	T3 (serosa)	1+	–	–	(+)
2	pap to well	T3 (duodenum)	2+	–	2+	mod to por	T3 (liver)	1+	–	1+	(+)
3	mod to por	T3 (pancreas)	2+	2+	2+	mod	T1	–	–	–	(+)
4	well to mod	T3 (duodenum)	2+	–	–	well	T1	–	–	–	(+)
5	mod	T2	2+	–	–	well	T1	–	–	–	(−)
6	mod	T3 (liver)	1+	–	–	pap to well	T3 (liver)	1+	1+	–	(+)
7	pap to well	T1	–	–	–	well	T2	–	–	–	(−)
8		(metastatic tumor)				well to mod	T2	1+	3+	1+	(+)
9		(metastatic tumor)				mod to por	T3 (liver)	–	1+	2+	(+)
10		(metastatic tumor)				well	T3 (liver)	1+	–	–	(+)

[a]ad-sq = adenosquamous carcinoma; pap to well = papillomatous to well differentiated; mod/por = moderately/poorly differentiated tubular adenocarcinoma; ly, lymphatic permeation; v, venous permeation; pn, perineural invasion; n, lymph nodal metastasis.
[b]Determined according to AJCC TNM classification.
[c]Lymphatic permeation.
[d]Venous permeation.
[e]Perineural invasion.
[f]n = lymph nodal metastasis.

RESULTS

Histopathologic Discrimination Between Synchronous Primaries and Metastatic Tumor

Macroscopic and microscopic features are shown in Tables II and III, respectively.

Of the 10 patients with two separate tumors, seven were identified as synchronous primaries. In four cases (patients #3, 4, 5, and 7), three gallbladder tumors and one bile duct tumor were pT1 tumors without lymphatic, venous, or perineural invasion (Table III). These pT1 tumors were judged to be primary tumors without metastasis to other organs. In the remaining three patients (#s 1, 2, and 6), the two tumors were pT2 or pT3 with lymph node involvement. However, tumors differed in histologic type and in degree of microvascular or perineural invasion (Table III). One bile duct and two gallbladder superficial tumors were not detected macroscopically (Table II).

In contrast, in three patients (patients # 8–10), the bile duct lesions were diagnosed as metastatic tumors from occult gallbladder cancers, via a lymphatic or intramural route. Each metastatic lesion had a submucosal tumorlike appearance with choledochal stenosis or obstruction. In one, obstruction of the common bile duct at the superior border of the head of the pancreas was ascribed to metastatic pericholedochal lymph nodes. In the remaining two, metastatic tumors involving the common and right hepatic bile ducts were located predominantly in the outer layer of the bile duct.

Accordingly, synchronous primaries accounted for 8.2% of bile duct tumors (n = 85) and 6.3% of gallbladder tumors (n = 112). Metastatic bile duct tumors were detected in 3.5% of the 112 cases of gallbladder cancer.

Retrospective Evaluation of Imaging Diagnosis

Multiple diagnostic modalities, including ultrasonogram of the biliary tree, abdominal computed tomography, visceral angiography, and cholangiogram (percutaneous transhepatic cholangiogram and/or endoscopic retrograde cholangiogram), were performed on all patients prior to operation. No patient had an anomalous junction of the pancreaticobiliary duct system.

Preoperative diagnoses were made in only two of the seven patients (patients # 1 and 6) with two primaries. In the remaining five patients, preoperative diagnoses were bile duct cancer in four patients and gallbladder cancer in one. In one of these five patients (patient #2), retrospective review of computed tomography and cholangiography revealed evidence of a lesion that was missed preoperatively and was first detected intraoperatively. The second tumor that was demonstrated by diagnostic imaging examinations in three patients (patients #1, 2, and 6), were all advanced cancers: two pT3 tumors of the gallbladder and one pT3 tumor of the bile duct. Three pT1 tumors of the gallbladder and one pT1 tumor of the bile duct could not be demonstrated by any imaging technique.

In three patients with a metastatic bile duct tumor from gallbladder cancer, the preoperative diagnosis was middle bile duct cancer in one patient (Fig. 2) and gallbladder cancer in two patients. In the latter patients, bile duct lesions in the hepatic hilum were believed to be due to the direct involvement from a tumor in the neck of the gallbladder. Actually, two occult gallbladder tumors were located in the body or fundus of the gallbladder. Multiple gallbladder calculi were found in all three patients (Table II).

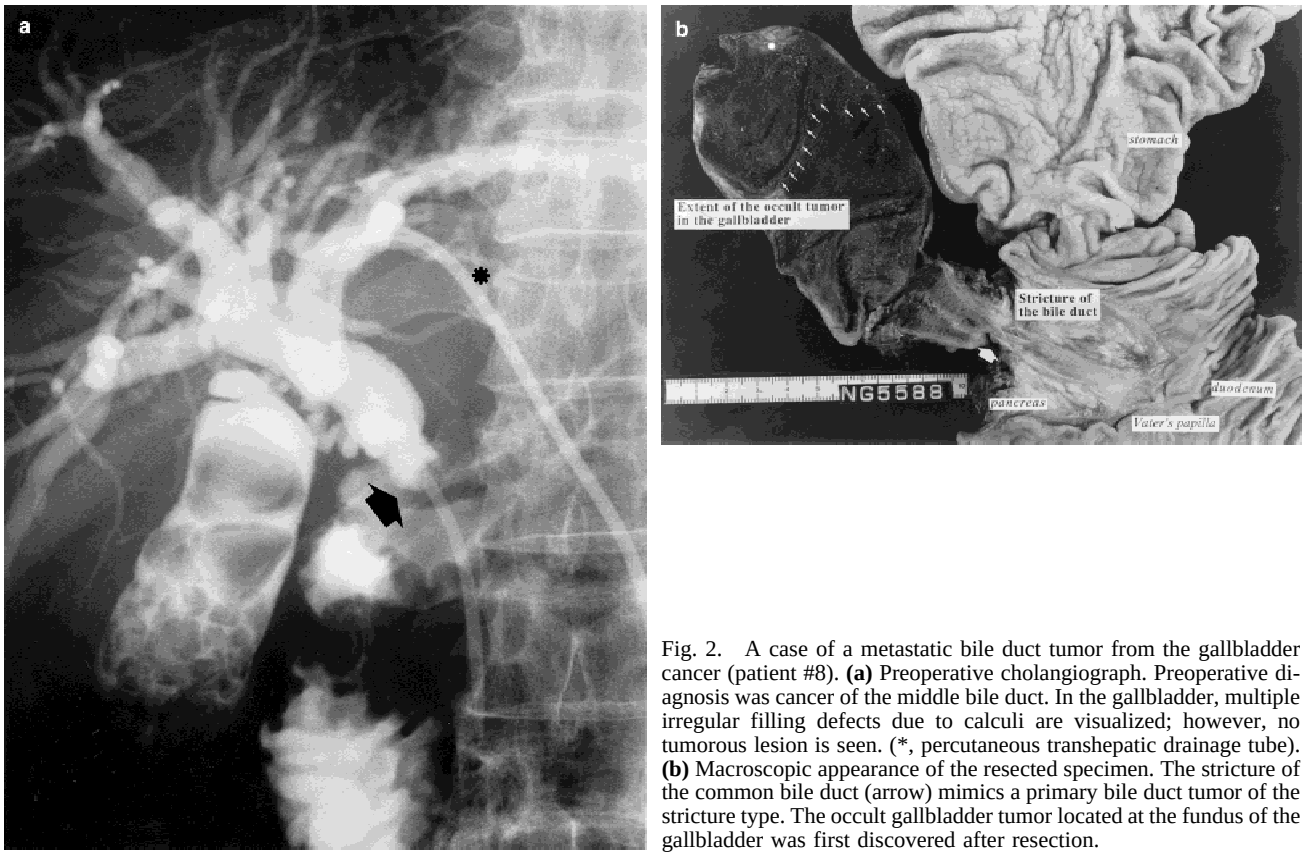

Fig. 2. A case of a metastatic bile duct tumor from the gallbladder cancer (patient #8). **(a)** Preoperative cholangiograph. Preoperative diagnosis was cancer of the middle bile duct. In the gallbladder, multiple irregular filling defects due to calculi are visualized; however, no tumorous lesion is seen. (*, percutaneous transhepatic drainage tube). **(b)** Macroscopic appearance of the resected specimen. The stricture of the common bile duct (arrow) mimics a primary bile duct tumor of the stricture type. The occult gallbladder tumor located at the fundus of the gallbladder was first discovered after resection.

Prognoses

Four patients (patients #2, 4, 5, and 6) in the synchronous primary group survived more than 59 months, and three are currently alive without recurrent disease. In two (patients # 2 and 6) of the four long-term survivors, the tumors in both the bile duct and gallbladder were advanced lesions classified as pT2 or greater. Patient #2 died of recurrent disease in the peritoneum 59 months after surgery. Two patients (patients # 1 and 3), who had histologically positive margins of resection of the bile duct, died of acute purulent cholangitis 3 months after operation and of recurrent disease 5 months after operation, respectively. The remaining patient (#7) committed suicide 2 months after operation. All three patients in the metastatic group died of recurrent disease between 1 to 2 years post-operatively.

DISCUSSION

Although more than half of the gallbladder tumors associated with synchronous primaries are early tumors that involve only mucosa or muscularis propria [4], both small [5] or superficial tumors and advanced tumors [6] of the gallbladder can escape preoperative detection, even with multiple imaging modalities. In our series, three of the seven gallbladder tumors were at an early stage and were not detected preoperatively. One advanced gallbladder cancer was undiagnosed even though it could be seen on preoperative imaging studies. In contrast, some occult tumors of the gallbladder cause discontinuous metastatic lesions of the wall of the bile ducts or near the bile ducts, which can mimic a primary bile duct tumor [9,10]. Careful clinical examination of the biliary tree is necessary both pre- and intraoperatively for successful management of these patients [11]. In addition, careful microscopic evaluation of tumors in the bile duct and gallbladder is essential to determine the precise relationship between the two tumors.

In this study, synchronous primaries accounted for 8% of bile duct cancer and 6% of gallbladder cancer, comparable to 5–7.4% as previously reported [5,6,12]. Furthermore, all cases underwent resection, and metastatic lesions were excluded by the mapping technique. The basic rationale discriminating synchronous primaries from metastatic lesions is criteria proposed by Warren and Gates [13] and by Gertsch et al. [5]. However, true synchronous tumors and metastatic lesions originating from the biliary system cannot always be clearly distinguished. In these complicated situations, detailed histopathologic analyses to clarify the mode of tumor spread, such as microvessel invasion, perineural invasion, depth of tumor invasion, and lymph node involvement, are also important for producing an accurate diagnosis. Although

there may be no specific way directly to prove this rare condition, these careful microscopic investigations using the mapping technique appear greatly to reduce the likelihood that one tumor be regarded as a metastasis of the other.

The pathogenesis of synchronous primaries of the extrahepatic bile duct and gallbladder is not known; however, multiplicity is one of the characteristic features of biliary tract neoplasms [14,15]. It is generally accepted that an anomalous junction of the pancreaticobiliary duct system plays an important role in the development of biliary tract cancer [16–18]. Ikoma et al. [3] have stated that in an analysis of 32 reported cases of synchronous primaries of the bile duct and gallbladder, 12 cases were associated with that anomaly. However, that anomaly was not found in our series.

The prognosis of patients with synchronous biliary primaries has been reported to be poor [5,6,19]. However, four of the seven patients in this series survived for >59 months, even though two of these patients had advanced tumors of both the bile duct and the gallbladder. In addition, it appeared that recurrence was unrelated to the nature of the synchronous primaries. The presence of synchronous primaries itself does not always signify a poor prognosis. There is a lower likelihood of surgical cure in patients with gallbladder cancer metastasizing to the bile ducts, despite the fact that in most cases true synchronous primaries cannot be determined until the lesion is resected and examined histologically. Accordingly, an aggressive resection should be recommended in cases lacking widely disseminated tumor.

REFERENCES

1. Schleifer D, Stohr U, Amann P, Plock D: Doppelkarzinom der Gallenwege. Bruns' Beitr Klin Chir 1974;4:297–300.
2. Kimura W, Miyata R, Takahashi T, Yamashiro M: Simultaneous development of gallbladder and bile duct carcinomas with atypical epithelium intervention: A case report. Jpn J Clin Oncol 1989;19: 287–293.
3. Ikoma A, Nakamura N, Miyazaki T, Maeda M: Double cancer of the gallbladder and common bile duct associated with anomalous junction of pancreaticobiliary ductal system. Surgery 1992;111: 595–600.
4. Miyakawa S, Horiguchi A, Hayakawa M, et al.: Multiple bile duct cancers presenting 3 years after resection of early gallbladder cancer. J Hep Bil Pancr Surg 1994;1:419–423.
5. Gertsch P, Thomas P, Baer H, et al.: Multiple tumors of the biliary tract. Amer J Surg 1990;159:386–388.
6. Chijiiwa K: Synchronous carcinoma of the gallbladder in patients with bile duct carcinoma. Aust NZ J Surg 1993;63:690–692.
7. American Joint Commission on Cancer: ''Manual for Staging of Cancer,'' 4th ed. Philadelphia: J.B. Lippincott, 1991.
8. Japanese Society of Biliary Surgery: ''General Rules for Surgical and Pathological Studies on Cancer of Biliary Tract,'' 3rd ed. Tokyo: Kanehara-shuppan, 1993.
9. Fahim RB, McDonald BC, Richards JC, Ferris DO: Carcinoma of the gallbladder: A study of its modes of spread. Ann Surg 1962; 156:114–124.
10. Kanai M, Yamamoto H, Shichino S, et al.: A case report of protruding type of gallbladder cancer, diagnosed by PTCCS and PTCS. Gastroenterological Endoscopy 1984;11:1987–1995 (in Japanese with English abstract).
11. Tompkins RK, Johnson J, Storm FK, Longmire WP: Operative endoscopy in the management of biliary tract neoplasms. Amer J Surg 1976;132:174–182.
12. Kozuka S, Tsubone M, Hachisuka K: Evolution of carcinoma in the extrahepatic bile duct. Cancer 1984;54:65–72.
13. Warren S and Gates O. Multiple primary malignant tumors: A survey of the literature and a statistical study. Am J Cancer 1981; 16:1358–1414.
14. Helpap B: Malignant papillomatosis of the intrahepatic bile ducts. Acta Hepato-Gastroenterol 1977;24:419–425.
15. Kinami Y, Miyazaki I: A study on multiple bile duct carcinoma. Nippon Ganchiryo-gakkaishi (J Jpn Soc Cancer Ther) 1981;16: 26–34 (in English).
16. Todani T, Tabuchi K, Watanabe Y, Kobayashi T: Carcinoma arising in the wall of congenital bile duct cysts. Cancer 1979;44: 1134–1141.
17. Nagata E, Sakai K, Kinoshita H, Kobayashi Y: The relation between carcinoma of the gallbladder and an anomalous connection between the choledochus and the pancreatic duct. Ann Surg 1985; 202:182–190.
18. Kimura K, Ohto M, Saisho H, et al.: Association of gallbladder carcinoma and anomalous pancreaticobiliary ductal union. Gastroenterology 1985;89:1258–1265.
19. Kato G, Nakai T, Ohba K, et al.: A resected case of middle bile duct carcinoma, associated with superficial-spreading type gallbladder carcinoma. Nippon Shokakigeka-gakkaishi (Jpn J Gastroenterol Surg) 1987;20:2229–2232 (in Japanese).