

## CASE REPORT

# Intrahepatic cholangiocarcinoma with gastric infiltration misdiagnosed as gastric submucosal tumor

Shunichi Ito\*, Yutaka Takahashi, Takuji Yamada, Yosuke Kawai and Kei Ohira

Department of Surgery, Tama-Hokubu Medical Center, Tokyo, Japan

\*Correspondence address. Department of Surgery, Tama-Hokubu Medical Center, 1-7-1 Aoba-cho, Higashimurayama-shi, Tokyo, 189-8511, Japan.  
Tel: +81-42-396-3811; Fax: +81-42-396-3076; E-mail: shunichi\_itou@tokyo-htm.jp

## Abstract

Intrahepatic cholangiocarcinomas (ICC) are rare primary liver tumors. In few cases, they may invade nearby organs and present as extrahepatic growths, leading to poor prognosis. We report a case of a 78-year-old man who presented with fatigue. An upper gastrointestinal endoscopy was performed to find a cause for his anemia, which showed a submucosal tumor with dellen at the lesser curvature of the gastric cardia. A computed tomography revealed a low-density tumor of diameter 70 mm at the cardia. It appeared to infiltrate the liver directly. We performed lateral hepatectomy, proximal gastrectomy and lymphadenectomy. The pathological findings revealed an ICC with gastric infiltration. Although adjuvant chemotherapy was administered, 12 months postoperatively, the patient developed pain and multiple bone metastases for which palliative radiation was initiated. The guidelines for lymphadenectomy and adjuvant chemotherapy in such cases are unclear. Appropriate regional lymphadenectomy and adjuvant chemotherapy can improve the prognosis of such patients.

## INTRODUCTION

Intrahepatic cholangiocarcinoma (ICC) is a rare primary liver tumor, and accounts for 4.8% of all primary liver cancers in Japan [1]. Occasionally, an ICC presents as an extrahepatic growth. In few cases, ICC may invade nearby organs. Herein, we present a case of ICC with gastric infiltration that appeared like a submucosal tumor (SMT).

## CASE REPORT

A 78-year-old man visited a hospital for fatigue. He underwent an upper gastrointestinal (GI) endoscopy for anemia, and was diagnosed with a gastric SMT. He was referred to our hospital for further treatment. His family history was unremarkable. His past history included atrial fibrillation, right cerebral infarction and hypertension. His physical examination was unremarkable.

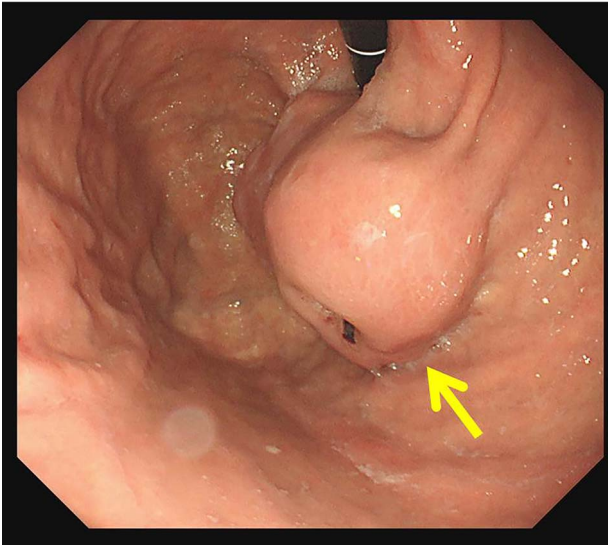
On investigating, his hemoglobin was 10 g/dl, and tumor markers, carcinoembryonic antigen and carbohydrate antigen 19-9 (CA 19-9), were elevated to 12.5 ng/ml and 94.3 U/ml, respectively. Tests for Hepatitis B and C viruses were negative. His upper GI endoscopy showed SMT with dellen at the lesser curvature of the cardia (Fig. 1). A computed tomography (CT) showed a slightly low-density tumor of 70 mm in diameter at the cardia (Fig. 2). It appeared to infiltrate into the liver directly. We diagnosed it as gastric SMT (suspected GI stromal tumor) with liver infiltration.

The patient was taken up for surgery. Intraoperatively, the tumor was located in the stomach wall at the cardia and was invading the liver directly (Fig. 3). We performed a lateral hepatectomy by the Glissonian pedicle ligation method, proximal gastrectomy and lymphadenectomy. The operation time was

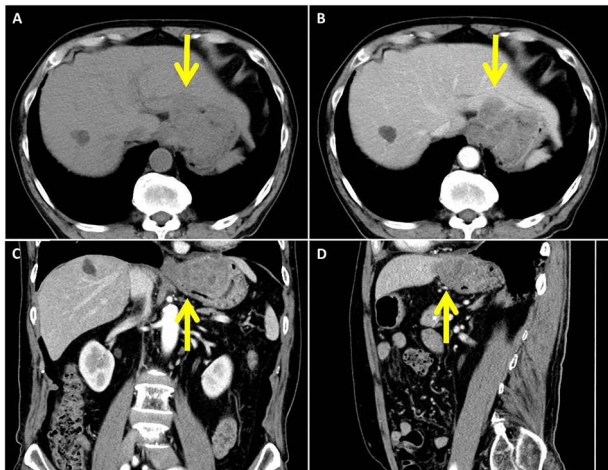
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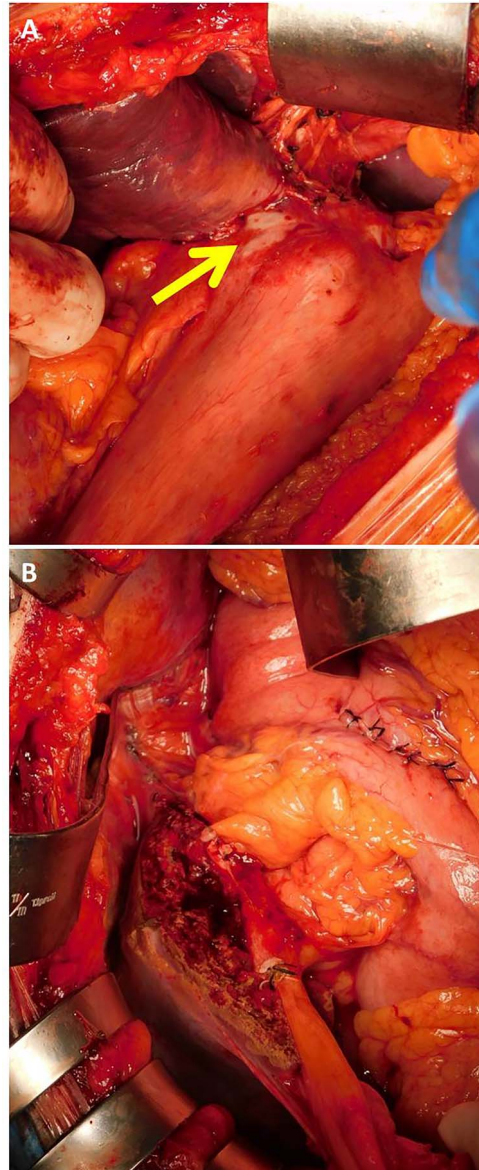


**Figure 1:** In upper gastrointestinal endoscopy, the tumor looked like a submucosal tumor with dells at the lesser curvature of the cardia (arrow).



**Figure 2:** In abdominal enhanced computed tomography, a slightly low-density tumor of about 70 mm in diameter at the cardia (arrow) was seen. It appeared to infiltrate into the liver directly. (A: plane; B: axial image in the artery phase; C: coronal image in the artery phase; D: sagittal image in the artery phase)

3 h and 19 min, and intraoperative blood loss was 260 ml. The resected specimen showed a white solid tumor of dimensions 80 mm × 55 mm × 44 mm. It showed a little ulcerative change in the mucosal layer (Fig. 4). Most of the tumor originating from the liver was found under the gastric mucosa (Figs 4 and 5). Microscopically, a poorly differentiated adenocarcinoma with unclear duct formation was detected (Fig. 6). The non-tumor area of the liver was normal. Immunostaining showed that the tumor was positive for AE1/AE3 and negative for CK20, CK7, CD34, c-kit, CD56, synaptophysin and chromogranin A (Fig. 6). Based on these findings, our diagnosis was ICC with gastric infiltration, and we categorized it as pT4, pN0, cM0, Stage IIIB as per the eighth edition of the American Joint Committee on Cancer (AJCC)/Union for International Cancer Control (UICC) [2]. The immediate postoperative course was uneventful, and the patient was discharged on postoperative Day 16. Three months after the surgery, he was administered S-1 orally as adjuvant chemotherapy. However, 12 months after the surgery, multiple

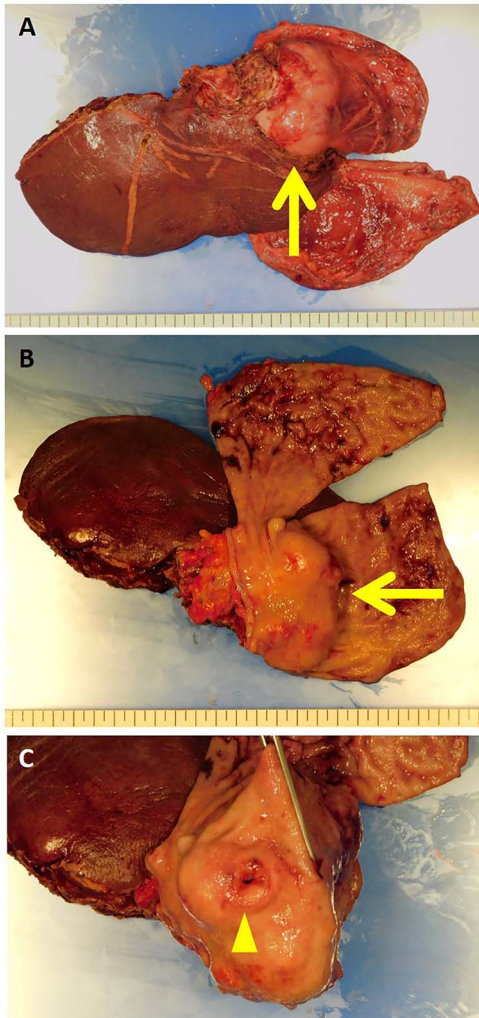


**Figure 3:** Intraoperative findings showed that the tumor was located in the stomach wall of the cardia and was invading into the liver directly (A, arrow). Lateral hepatectomy, proximal gastrectomy, and lymphadenectomy were performed (B).

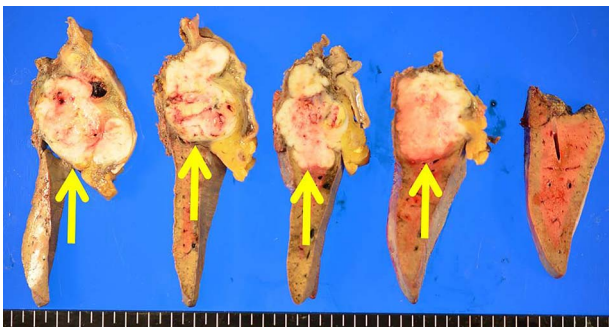
bone metastases were detected on CT. He underwent palliative radiation to relieve pain and prevent pathological fractures.

## DISCUSSION

ICC has a poor prognosis and an overall 5-year survival of <10% for all patients [3]. Unfortunately, 80–85% of patients with ICC present at an unresectable stage of the disease, with no potential for cure [4]. Kang et al. [5] indicated in a multivariate analysis that independent risk factors for tumor recurrence and patient survival were multiple tumors; CA, 19-9 > 200 U/mL; tumor size, > 5 cm; direct invasion to extrahepatic structures; and lymph node metastases. Although a surgery, such as hepatectomy, is considered the first option of treatment for ICC, the role of lymph node excision is still unclear, with no clear guidelines [6]. Giorgio et al. [6] report that routine regional lymphadenectomy is the

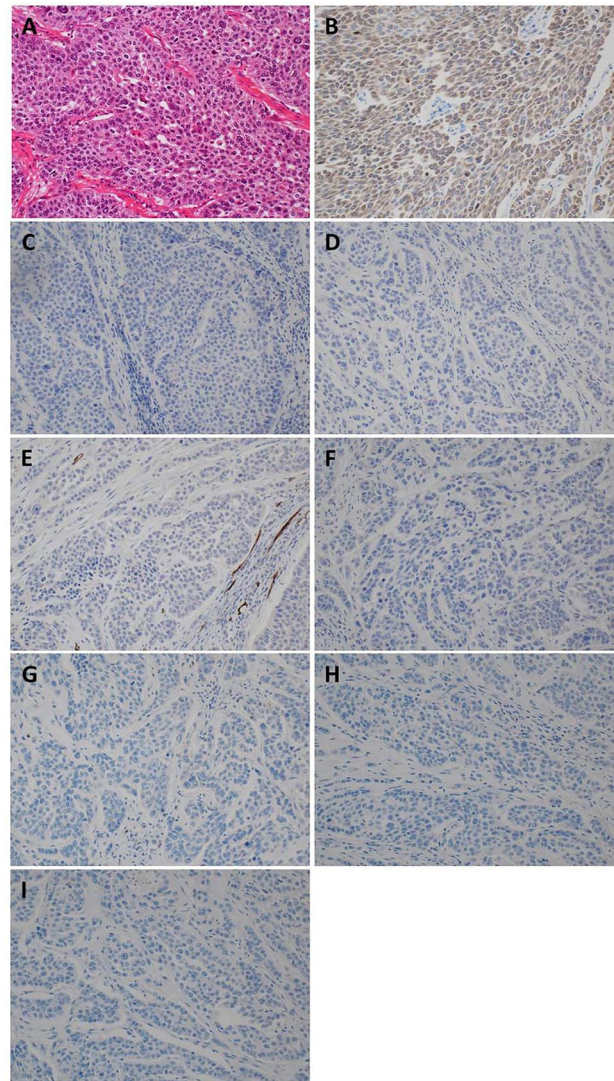


**Figure 4:** The resected specimen showed a white solid tumor continued from the left lateral liver to the stomach wall (A, arrow). Most of the tumor was found under the gastric mucosa (B, arrow). The tumor looked like a submucosal tumor with dells (C, arrowhead).



**Figure 5:** The tumor originated from the liver and showed extrahepatic growth (arrow).

most recent therapeutic strategy for ICC because the incidence of lymph node metastases is 40% for ICC. Nozaki et al. [7] suggested that regional lymphadenectomy should be performed in consideration with tumor location and the two main lymphatic drainage routes: one through the hepatoduodenal ligament and other through the cardiac portion of the stomach. If the tumor is



**Figure 6:** Pathological and immunostaining findings. (A) Hematoxylin–Eosin staining (×20): A poorly differentiated adenocarcinoma with unclear duct formation was detected. (B) AE1/AE3 staining (×20): positive. (C) CK20 staining (×20): negative. (D) CK7 staining (×20): negative. (E) CD34 staining (×20): negative. (F) c-kit staining (×20): negative. (G) CD56 staining (×20): negative. (H) synaptophysin staining (×20): negative. (I) chromogranin A staining (×20): negative.

located in the right lobe, lymphadenectomy in the former route may be necessary, and if it is located in the left lobe such as in our case, lymphadenectomy in both routes may be necessary. However, since our case was misdiagnosed as gastric SMT, we performed lymphadenectomy only in one route. Bartsch et al. [8] studied 102 cases of hepatectomy for ICC in a single center. Out of these 102, six had visceral infiltration—two in the diaphragm, one in adrenal gland, one in pericardium, one in duodenum and one in colon. They also reported that patients with visceral infiltration had a significantly shorter overall survival than patients without it (14.9 vs. 23.1 months) [8].

In the eighth edition of the AJCC/UICC, T4 is defined as ‘tumor involving local extrahepatic structures by direct invasion’ [2]. To the best of our knowledge, resected ICCs with visceral infiltration have been reported only in three cases in English literature and in 14 cases in Japanese literature (Table 1). The median age of these patients was 63.5 years (range: 41–85). The median size of

Table 1. Clinicopathological features of resected intrahepatic cholangiocarcinoma with visceral infiltration reported in the literature

Operative procedure	LD	Visceral infiltration	Pathological diagnosis	Tumor size (cm)	CA19-9 (U/ml)	Adjuvant chemotherapy	Survival after surgery
Left hepatectomy, Caudate lobectomy	+	Stomach	Well differentiated	5.5 × 5	7510	+	Not described
Total gastrectomy, Partial diaphragmectomy	+	Stomach	AC	7.7	WNL	Tegafur	Dead due to metastases
Hemigastrectomy			with sarcomatous elements			ND	5 months
Right hepatectomy, Right adrenalectomy	ND	Right AG	Moderately differentiated	6.5 × 5.5	WNL	ND	Alive without recurrence
Caval resection and reconstruction			AC				22 months
Right hepatectomy	-	Diaphragm	Poorly differentiated	7 × 6 × 3	23	ND	Alive without recurrence
Partial diaphragmectomy			AC				24 months
Left hepatectomy, Caudate lobectomy	+	Stomach	Moderately differentiated	6.4 × 5.8 × 5	17	ND	ND
Partial gastrectomy			AC				
Right hepatectomy, Partial diaphragmectomy	ND	Lung	Adenosquamous	11 × 8	ND	ND	Dead due to metastasis
Right lower partial pneumonectomy		Diaphragm	cell carcinoma				6 months
Right hepatic trisegmentectomy	+	Gallbladder	Well differentiated	11 × 9 × 6	>12000	ND	Alive without recurrence
			AC				7 months
Left hepatectomy, Caudate lobectomy	+	Stomach	Moderately differentiated	5	151.7	+	Alive without recurrence
Distal gastrectomy			AC			GEM	18 months
Right hepatectomy	+	TC	Poorly differentiated	12 × 10	WNL	+	Alive after treatment for
Right hemicolectomy			AC			Tegafur- urasil	brain metastasis
						ND	84 months
Right hepatectomy, Partial diaphragmectomy	ND	Lung	AC	9 × 6.5 × 6	1518	ND	Alive with recurrence
Right lower partial pneumonectomy		Diaphragm					3 months
Right hepatectomy, Partial diaphragmectomy	ND	Diaphragm, Right	Poorly differentiated	9 × 7.2	15.9	ND	Dead due to recurrence
Right adrenalectomy, Right nephrectomy		AG	AC				6 months
		Right kidney					
Extended right hepatectomy, Caudate lobectomy	+	Right AG	Moderately differentiated	10	222	+	Alive without recurrence
Partial diaphragmectomy, Right adrenalectomy			AC			GEM	12 months
Lateral hepatectomy, Total gastrectomy	+	Stomach	Moderately differentiated	9	9899	-	Alive with recurrence
Partial pancreatectomy		Pancreas	AC				8 months
Central bisegmentectomy	ND	Diaphragm	Poorly differentiated	4	WNL	ND	Alive after treatment for
Partial diaphragmectomy			AC				diaphragm recurrence
							29 months
Partial resection of the S4	+	Duodenum	Moderately differentiated	3.3	WNL	+	Alive after treatment for
Partial duodenectomy			AC			GEM	liver recurrence
							21 months
Subsegmentectomy of the S4 and S5	+	TC	Moderately differentiated	7 × 4.8 × 4	3605.5	+	Alive without recurrence
Partial colectomy		Gallbladder	AC			GEM	9 months
Extended cholecystectomy, Partial gastrectomy	+	Stomach,	Poorly differentiated	9	38	+	Dead due to recurrence
Partial duodenectomy, Partial colectomy		Duodenum	AC			GEM/Cisplatin	9 months
		TC, Gallbladder					
Lateral hepatectomy	+	Stomach	Poorly differentiated	8 × 5.5 × 4.4	94.3	+	Alive with recurrence
Proximal gastrectomy			AC			S-1	12 months

AC: adenocarcinoma, AG: adrenal gland, GEM: gemcitabine, LD: lymph node dissection, ND: not described, RFA: radiofrequency ablation, TACE: transcatheter arterial chemoembolization, TC: transverse colon, WNL: within normal limit

the tumor was 7.9 cm (range: 3.3–12), and except for one case, the size of the tumor was larger than 5 cm (94%). In six cases, CA 19-9 was over 200 U/L. In eight cases, adjuvant chemotherapy was administered—four, used gemcitabine; one, gemcitabine and cisplatin; one, tegafur; one, tegafur-uracil; and one, S-1. Visceral infiltration was noted for seven in the diaphragm; five, stomach; three, duodenum; three, transverse colon; three, gallbladder; three, lung; two, right adrenal gland; one, right kidney; and one, pancreas (some patients had visceral infiltration in more than one organ). Among the five cases of stomach infiltration, two showed SMT with dellen on upper GI endoscopy. Lymphadenectomy was performed in 11 cases (61%). Within 6 months after surgery, three patients died from recurrence.

Like for lymph node excision, no clear guidelines exist for administration of adjuvant chemotherapy for such cases. However, adjuvant chemotherapy with Capecitabine can improve the overall survival in patients with resected biliary tract cancer [3].

Only a few cases of resected ICCs with visceral infiltration have been reported in the literature. Therefore, we believe, our case report can help to understand the characteristic features of these rare cases and, as a result, improve their prognosis.

## CONFLICTS OF INTEREST STATEMENT

None declared.

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