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CASE REPORT

A case of extrahepatic bile duct cancer with distant metastases showing pathological complete response to treatment combining gemcitabine and cisplatin

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Abstract
The patient was a 69-year-old female with a chief complaint of yellow staining of her urine. A detailed physical examination and laboratory tests were carried out, and as a result, her condition was diagnosed as unresectable advanced extrahepatic cholangiocarcinoma with liver metastases. Chemotherapy using gemcitabine + cisplatin was initiated, and computed tomography after six cycles revealed that the liver metastases had disappeared, and that a partial response was achieved in the primary tumor. After tan cycles, a pylorus-preserving pancreaticoduodenectomy was performed as conversion surgery, and as a result, a pathological complete response was achieved in the primary tumor. After the primary lesion was resected, we were able to start an adjuvant chemotherapy immediately. Approximately 19 months have passed since the surgery, and the patient is currently alive and recurrence-free. If an improvement of the outcomes of chemotherapy in unresectable advanced biliary tract carcinomas is achieved in the future, there could be an increase in the number of treatment-responsive cases like the one reported in this study. Accumulating a large number of cases successfully treated by conversion surgery, and conducting a detailed analysis of the postoperative course, may help design adequate treatment strategies.

Keywords Biliary tract cancer · Chemotherapy · Conversion surgery · Pathological complete response

Introduction

Surgical resection is the only therapeutic method that can offer hope for radical cure of biliary tract cancers. The curative resection rate of patients diagnosed with biliary tract cancer differs according to the site of onset. However, more than 30% of patients with extrahepatic biliary tract cancer or gallbladder cancer are not diagnosed until after curative resection becomes an impossibility [1]. In these cases, chemotherapy is the treatment of choice. Based on the results of the ABC-02 study [2], treatment combining gemcitabine and cisplatin (GC therapy) has been used as the standard treatment regimen for unresectable advanced biliary tract cancers, but the outcomes have not been favorable. In recent years, there have been occasional reports of a small number of cases that responded effectively to chemotherapy, as well as cases that were subsequently subjected to conversion surgery [3, 4]. We experienced one case of advanced extrahepatic cholangiocarcinoma with liver metastases which responded favorably to GC therapy, which was consequently subjected to conversion surgery and showed a pathological complete response (pCR). While cases with a complete response (CR), based on findings from diagnostic imaging, have occasionally been reported, cases with confirmed pCR, like in the one reported in this study, are rare; that is why we report it in this communication [5–8].

Case report

The patient was a 69-year-old female with a chief complaint of yellow staining of her urine. She had no particular medical history, family history or daily living-related

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history. Blood tests conducted in another hospital had shown elevated levels of total bilirubin; computed tomography (CT) revealed the presence of a mass in the extrahepatic bile duct; thus, the patient was referred to our hospital for a detailed physical examination and laboratory tests. Physical findings on the skin revealed the presence of jaundice. Blood tests showed a total bilirubin level of 10.6 mg/dL and a direct bilirubin of 8.0 mg/dL; therefore, obstructive jaundice was suspected. The blood levels of tumor markers were elevated; namely the level of carcinoembryonic antigen was 124.8 ng/mL and the carbohydrate antigen (CA) 19-9 was 94 ng/mL. Abdominal contrast-enhanced CT revealed a relatively well-circumscribed, faint contrast-enhanced tumor mass measuring 45 × 30 mm in size in the extrahepatic bile duct (distal bile duct), and the intrahepatic and extrahepatic bile ducts on the hepatic side of tumor mass were diffusely dilated. The tumor mass had directly invaded the pancreas and the duodenum. In addition, a low-density tumor mass measuring 10 mm in size was found in the S4 segment of the liver, and metastasis was suspected (Fig. 1). In magnetic resonance imaging (MRI), the tumor mass in the liver showed a low signal in T1-weighted images, a faint high signal in T2-weighted images; in the diffusion weighted imaging (DWI), from the apparent diffusion coefficient (ADC) map that was constructed using the DWI images with *b* factor = 100 s/mm^2 and *b* factor = 800 s/mm^2, which are high signals, the ADC value of the same site was 1.09×10^{-3} mm^2/s, and in T1-weighted hepatocyte phase images from a dynamic MRI using gadolinium ethoxybenzyl diethylenetriamine pentaacetic acid (Gd-EOB-DTPA), the tumor mass was depicted as a nodule with a low signal measuring 13 mm in size, leading to the diagnosis of liver metastasis (Fig. 2). Endoscopic retrograde cholangiopancreatography (ERCP) findings revealed that the distal bile duct was severely stenosed over a distance of 45 mm; therefore, endoscopic biliary drainage was performed (Fig. 3). A bile duct biopsy was performed, and the results revealed that the tumor was an adenocarcinoma (Fig. 4). Based on the test results, the condition was diagnosed as an extrahepatic cholangiocarcinoma T3N0M1 (HEP) Stage IV (UICC eighth edition), and GC therapy was started [1000 mg/m^2 gemcitabine and 25 mg/m^2 cisplatin administered on days 1 and 8 of a 21-day cycle]. After six cycles of GC therapy were carried out, CT was performed for the assessment of treatment efficacy, and the findings revealed that both the primary tumor and the metastatic foci in the liver had decreased in size, showing a partial response (PR). Findings from a CT performed after ten cycles of GC therapy (Fig. 5) revealed that the primary tumor had further diminished in size, and that the metastatic foci in the liver had disappeared, showing a PR. Findings from a fluorodeoxyglucose-positron emission tomography (FDG-PET) performed after ten cycles of GC therapy revealed an increased accumulation of FDG in the distal bile duct, but there was no apparent increased accumulation of FDG in the liver metastases (even in the S4 segment of the liver where accumulation was found at the time of the diagnosis); thus, there was no suspicion of distant metastasis (Fig. 6). Based on the above results, our choice of treatment was conversion surgery. Pylorus-preserving pancreatoduodenectomy (D2 lymphadenectomy) was performed approximately 7 months after introduction of GC therapy. During operation, intraoperative ultrasonography was performed. However, liver tumor was not detected. Macroscopic findings from surgical specimens showed only a scar-like membrane in the distal bile duct, and there was no apparent tumor mass (Fig. 7). Histological findings showed ulcerations and erosions over an extensive area on the bile duct mucosa, but there were no tumor cells. The findings also showed an accumulation of macrophages in the subserosal layer. Findings showed only fibrosis in the excised lymph nodes; and there were no tumor cells (Fig. 8). The histological response was Evans grade IV [9].

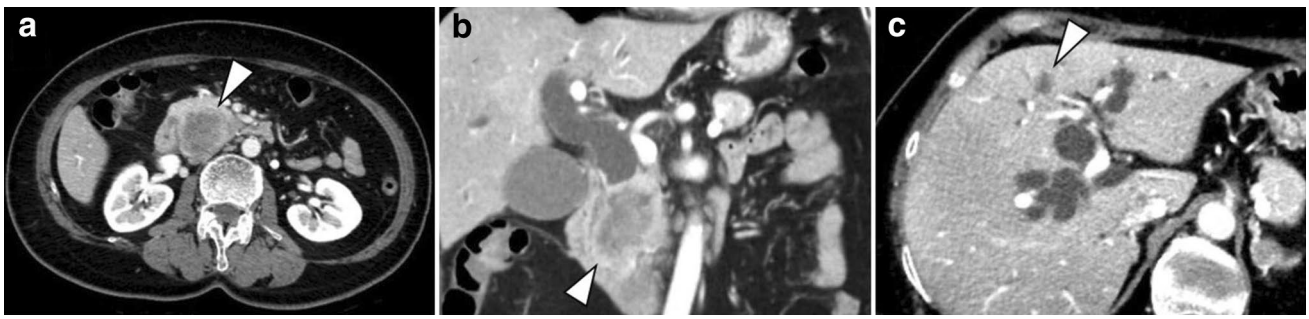

Fig. 1 Computed tomography at first diagnosis. Contrast-enhanced CT findings revealed that a relatively well-circumscribed faint contrast-enhanced tumor mass (arrow) measuring 45 × 30 mm in size was present in the distal bile duct. The tumor was found to directly infiltrate the pancreas and the duodenum (**a**, **b**). A low-density tumor mass (arrow) measuring 10 mm in size was found in the S4 segment of the liver (**c**)

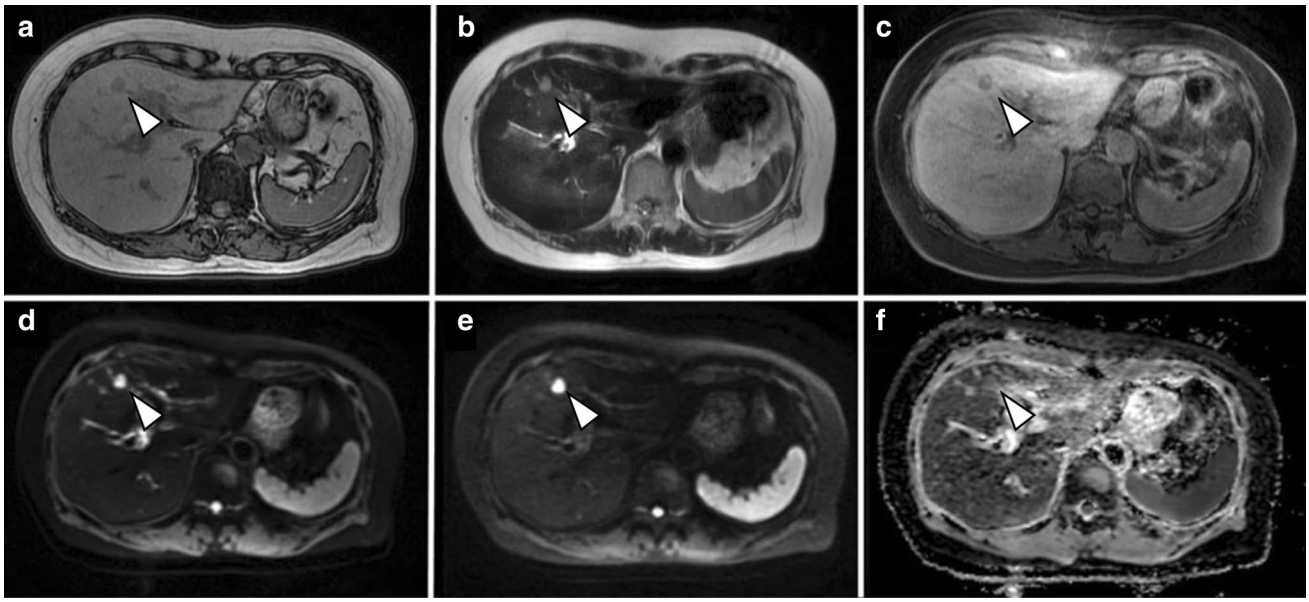

Fig. 2 Gd-EOB-DTPA enhanced magnetic resonance imaging for the diagnosis of metastatic liver tumor. MRI T1-weighted images showed the presence of a low signal area (arrow) **a** measuring 13 mm in size in the S4 segment of the liver; T2-weighted images showed a faint high signal (arrow) (**b**); dynamic MRI using Gd-EOB-DTPA of the hepatocyte phase showed a low signal (arrow) (**c**); DWI showed high signals (arrow) [*b* factor = 100 s/mm^2 (**d**)], [*b* factor = 800 s/mm^2 (**e**)]; and an ADC map showed a nodule at the lesion site with ADC value = 1.09×10^{-3} mm^2/s (**f**) that was consistent with liver metastasis. *DWI* diffusion weighted images, *Gd-EOB-DTPA* gadolinium ethoxybenzyl diethylenetriamine pentaacetic acid, *MRI* magnetic resonance imaging, *ADC* apparent diffusion coefficient

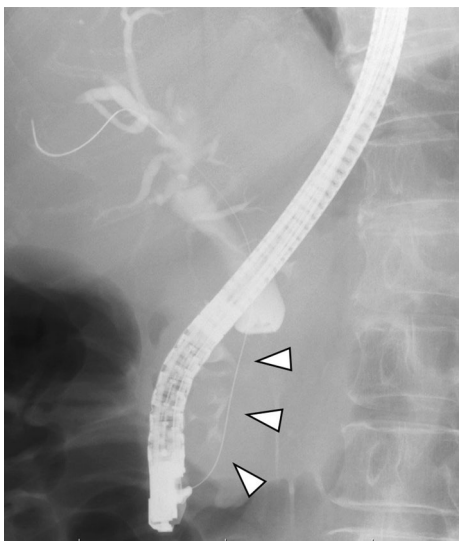

Fig. 3 Endoscopic retrograde cholangiopancreatography for the diagnosis of the primary tumor. Cholangiography revealed a stenosis over a distance of 45 mm in the distal bile duct (arrow)

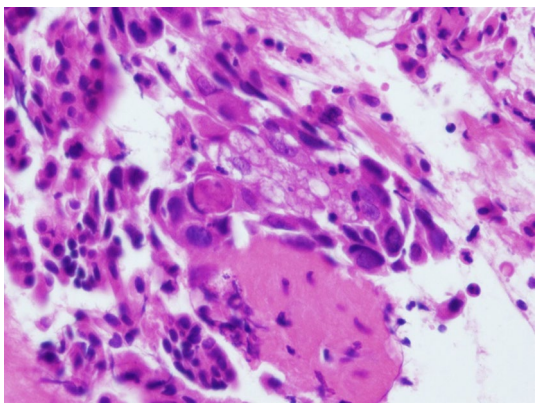

Fig. 4 Bile duct biopsy for the definitive diagnosis. Bile duct biopsy findings showed a high nuclear/cytoplasmic ratio, and adenocarcinoma cells with increased chromatin content and nuclear shape irregularity were found accumulated as agglomerates (Hematoxylin and Eosin staining, ×400)

The postoperative diagnosis was T0N0M0 stage 0 according to the TNM classification, and the pathological diagnosis of the primary tumor was pCR. After consultation with the patient, ten cycles of a postoperative adjuvant chemotherapy consisting of tegafur + gimeracil + oteracil potassium [S-1 (100 mg/m^2/day) on days 1–28, every 42 days] were carried out. At 31 months after the initial diagnosis, and at approximately 19 months after surgery, the patient is alive and recurrence-free.

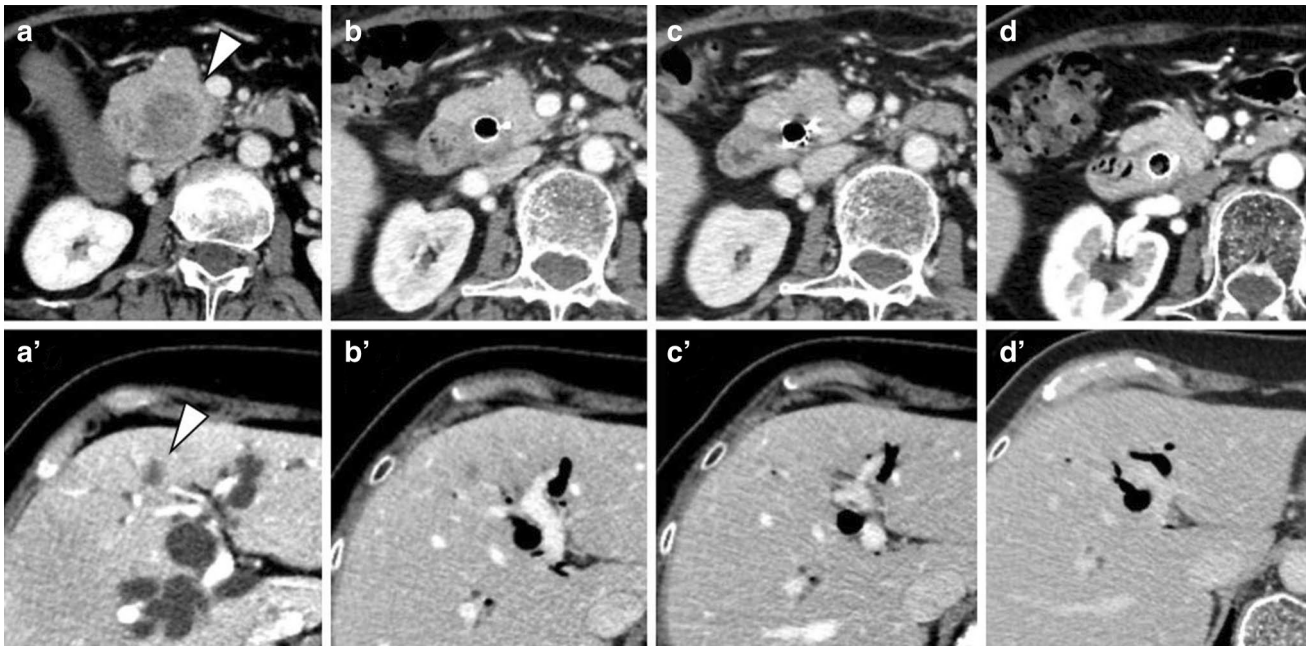

Fig. 5 Computed Tomography for the assessment of treatment efficacy after 1, 3, 6, and 10 cycles of GC therapy. Primary tumor (arrow) (**a**) and liver metastases (arrow) (**a′**) after 1 cycle of GC therapy. After three cycles, both the primary tumor (**b**) and the liver metastases (**b′**) decreased in size, showing a PR. After six cycles, both the primary tumor (**c**) and the liver metastases (**c′**) decreased in size, showing a PR. Findings after ten cycles of GC therapy also revealed that the primary tumor (**d**) had decreased in size, and that the liver metastases (**d′**) had disappeared, showing a PR. *GC* gemcitabine + cisplatin, *PR* partial response

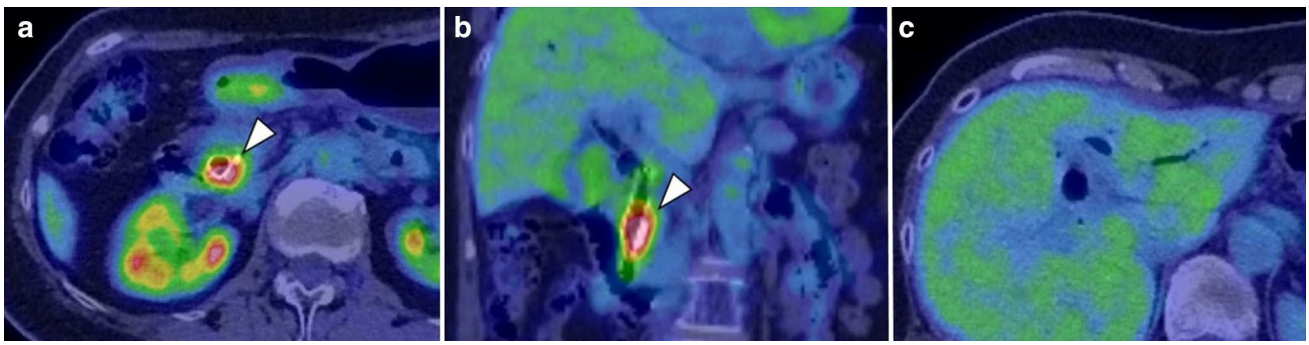

Fig. 6 Assessment of the effect of treatment on the liver metastases, using FDG-PET after ten cycles of GC therapy. After ten cycles of GC therapy, findings from a fluoro-deoxyglucose positron emission tomography (FDG-PET) showed an increased accumulation of FDG in the distal bile duct (arrow) (**a**, **b**), whereas the increased accumulation which was found in areas comprising the S4 segment of the liver at the time of diagnosis, and which had led to the suspicion of distant metastases, was no longer found (**c**). *GC* gemcitabine + cisplatin, *FDG* fluorodeoxyglucose, *FDG-PET* fluorodeoxyglucose-positron emission tomography

Discussion

A previous report on the results of a nationwide counting of biliary tract cancer cases in Japan (over the years 1998 through 2004) showed that the resection rates of biliary tract cancers were as follows: 68.8% for gallbladder cancers, 70.2% for extrahepatic cholangiocarcinomas, 89.4% for carcinomas of the papilla of Vater, and that the rates of curative resection were as follows: 68.7% for gallbladder cancers, 68.1% for extrahepatic cholangiocarcinomas, and 93.0% for carcinomas of the papilla of Vater [1]. Meanwhile, unresectable advanced biliary tract carcinomas have a poor prognosis, with a 1-year survival rate of 8% and a 5-year survival rate of approximately 2%; thus, an increase in the resection rate is an important factor for the improvement of outcomes in the treatment of biliary tract cancers. Based on the results of the ABC-02 study (response rate: 25.7%, median progression-free survival period: 8 months, median survival time: 11.7 months)

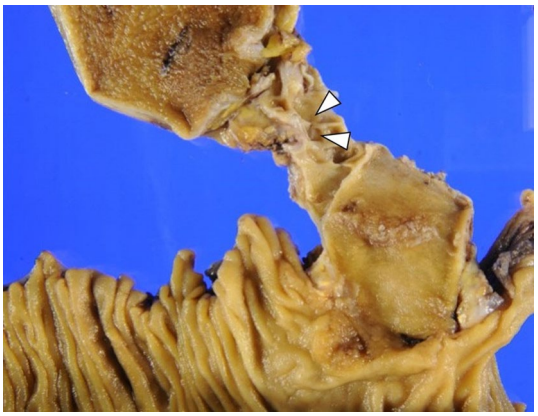

Fig. 7 Macroscopic findings in the pylorus-preserving pancreaticoduodenectomy specimen. The macroscopic findings of the surgical specimen showed only a scar-like membrane in the distal bile duct, and there was no apparent tumor mass (arrow)

[2] and the BT-22 study (response rate: 19.5%, median progression-free survival period: 5.8 months, median survival time: 11.2 months) [10], GC therapy has been considered the standard chemotherapy for unresectable advanced biliary tract carcinoma. In addition, a previous report on the treatment outcome of a combination therapy using gemcitabine + S-1 (GS therapy), as a regimen that does not use cisplatin, has also been shown to be a valid treatment (response rate: 36.4%, median progression-free survival period: 7.1 months, median overall survival period: 12.5 months) [11]. The results of a phase III study (JCOG1113) conducted in Japan that compared the GC therapy and GS therapy were reported at the Gastrointestinal Cancers Symposium, which was held in 2018 in San Francisco, USA, and the non-inferiority of GS therapy compared to GC therapy was demonstrated [12]. In recent years, various clinical trials mainly using molecular-targeted drugs have been carried out on unresectable advanced biliary tract carcinomas. Findings from a phase III study comparing gemcitabine + oxaliplatin (GEMOX) therapy combined or not combined with erlotinib showed that while the response rate was high in the erlotinib combination group (30% vs. 16%, $p = 0.005$), the findings did not show any superiority in terms of progression-free survival (PFS) (5.8 months vs. 4.2 months, $p = 0.08$) and overall survival (OS) (9.5 months vs. 9.5 months, $p = 0.61$) [13]. In addition, randomized phase II studies using medications composed of anti-epidermal growth factor receptor antibodies and vascular epidermal growth factor-receptor inhibitors have also been reported [14, 15], but hitherto none of the reported efficacies have exceeded that of the standard treatment. Currently ongoing studies include the following, and reports on their results are being awaited: a randomized phase II study which examines the effect of adding ramucirumab to GC therapy (NCT02711553), a phase I and II studies which examine the effect of adding regorafenib to GEMOX therapy (NCT02386397), a phase II study which examines the effect of a combination therapy using pazopanib and gemcitabine (NCT01855724), and a randomized phase II study which examines the effect of adding selumetinib (using two different methods of administration) to GC therapy (NCT02151084). In addition, expectations are being placed on the validation of the effect of fibroblast growth factor receptor 2 (FGFR2) inhibitors [16, 17] targeting the FGFR2 fusion gene, which is a driver gene believed to be involved in the development of 5% of biliary tract cancers and reported to be highly involved in the development of 10–45% of intrahepatic cholangiocarcinoma.

GC therapy is currently considered as the standard chemotherapy for the treatment of unresectable advanced biliary tract carcinoma; and in recent years, cases subjected to conversion surgery have occasionally been reported [3,

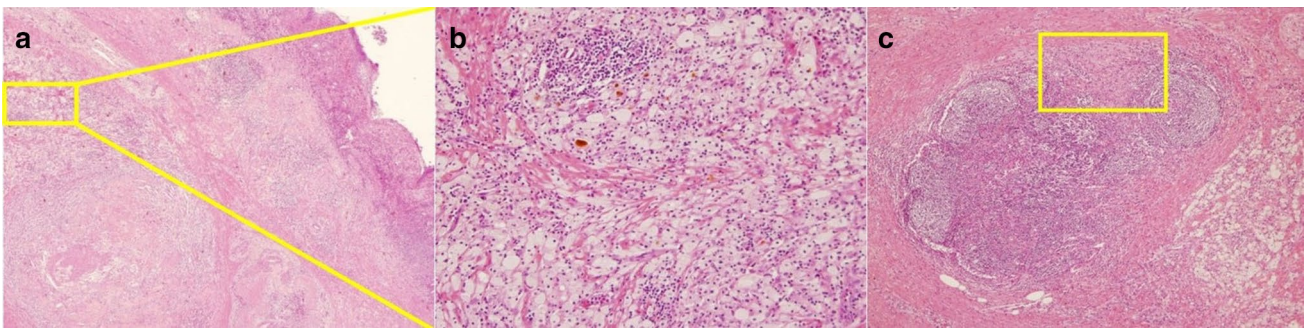

Fig. 8 Pathological findings of the pylorus-preserving pancreaticoduodenectomy specimen. The bile duct mucosa showed erosion and ulceration over an extended area. The findings only showed a bile duct epithelium with regenerative properties and with mild nuclear enlargement; and there were no atypical cells [Hematoxylin and Eosin staining, ×20 (**a**), Hematoxylin and Eosin staining, ×100 (**b**)]. Emergence of macrophages was found over an extensive area, from the submucosal layer all the way to the serosal membrane. Findings in the lymph nodes showed fibrosis [Hematoxylin and Eosin staining, ×40 (**c**)]

4]. However, CR has only been achieved in a small number of cases; and in the ABC-02 study, CR accounted for only 1 out of 200 cases (0.5%). In the future, when improvements are achieved in the outcomes of chemotherapy for the treatment of unresectable advanced biliary tract carcinoma, cases responsive to treatment like the one described in our study may increase in number, and particularly in patients with distant metastases. No consensus has yet been reached for a number of issues, such as the timing for performing conversion surgery and the necessity or non-necessity of surgical intervention to treat the metastatic tumors. In the case reported in our study, reducing surgical invasiveness to a minimum was considered a priority after the issue was fully discussed with the patient herself and her family; thus, hepatectomy was not performed; only the primary tumor was resected, and adjuvant chemotherapy was started immediately after surgery. The aforementioned report by Kato et al. [4] also mentioned that in addition to the treatment, segmental hepatectomy and partial hepatectomy were occasionally performed in some cases of intrahepatic cholangiocarcinomas as well as carcinomas of the upper bile duct. However, as far as we know from the literature, there has been no previous report of cases of concurrent hepatectomy in patients in need of pancreaticoduodenectomy as a method for the radical resection of the primary tumor of an extrahepatic cholangiocarcinoma like in the case reported in our study. For pancreatic cancers, which are refractory cancers such as biliary tract cancers, new regimens such as FOLFIRINOX [18, 19] and gemcitabine + nab-paclitaxel [20–22] have been developed, and the number of treatment-responsive cases have increased compared to those treated with gemcitabine monotherapy, and conversion surgery has finally been performed on some cases. A previous report has shown that in pancreatic cancers, the prognosis after tumor resection was favorable in patients whose serum levels of CA 19-9 decreased markedly or returned to normal levels after chemotherapy or after chemoradiotherapy [23]; and another report has shown that a significantly higher histological curative resection rate was achieved in patients with a 50% or greater rate of decrease of maximum standardized uptake value (SUV_{max}) in FDG-PET performed after the preoperative chemoradiotherapy (CRT) [24], however, in cholangiocarcinoma, indicators for determining whether to perform conversion surgery have not yet been fully studied. In the case reported in our study, CA19-9 levels returned to normal after initiation of chemotherapy, and the FDG-PET showed no accumulation of FDG in the liver metastases; therefore, it was presumed that the liver metastases had gone into complete remission. Thus, hepatectomy was not performed, and reducing surgical invasiveness to the minimum was considered as priority. We were able to start adjuvant chemotherapy immediately after resection of the primary tumor.

We experienced a case of advanced extrahepatic cholangiocarcinoma with liver metastases, which was very responsive to GC therapy and was subsequently treated by conversion surgery, and pCR of the primary lesion was achieved. Cases with confirmed pCR, like the one reported in this study, are rare. If an improvement of the outcomes of chemotherapy in the treatment of unresectable advanced biliary tract carcinoma can be successfully achieved, cases responsive to treatment may increase in number in the future. Accumulating cases successfully treated by conversion surgery like this case, and conducting a detailed analysis of the postoperative course, may help design adequate treatment strategies.

Compliance with ethical standards

Conflict of interest The authors state that they have no conflict of interest.

Human and animal rights All procedures followed were in accordance with the ethical standards of the responsible committee on human experimentation (institutional and national) and with the Helsinki Declaration of 1964 and its later amendments.

Informed consent Written informed consent was obtained from the patient for publication of this case report and accompanying images.

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