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CASE REPORT

# A case of concomitant colitic cancer and intrahepatic cholangiocarcinoma during follow-up for ulcerative colitis

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**Abstract** Colitis-associated colorectal cancer (CAC) is known to occur in long-standing and extensive ulcerative colitis (UC). Furthermore, UC is known to complicate primary sclerosing cholangitis (PSC), which subsequently results in an increased risk of developing cholangiocarcinoma. We report a case of colitis-associated rectal cancer (CARC) accompanied by intrahepatic cholangiocarcinoma (ICC) based on UC and PSC. A 73-year-old man had suffered from UC for 19 years. During surveillance colonoscopy, a tumor was found in the rectum that was pathologically diagnosed as CARC from the resected specimen. Abdominal computed tomography also revealed a localized dilation of the intrahepatic bile duct, and endoscopic retrograde cholangiography revealed a band-like stricture. This remarkable tumor lesion was not observed in the hepatic duct. Left hepatectomy was performed because of the suspicion of possible ICC at the stenosis of the hepatic duct. The presence of ICC was confirmed at the lesion causing the stricture. The pathological diagnosis from the resected specimen was ICC based on PSC. Adjuvant chemotherapy for ICC was performed for 6 months. Neither cancer has recurred for 2.5 years after hepatectomy. Patients with PSC concomitant with UC should be considered a high-risk group for CAC and ICC.

**Keywords** Colitic cancer · Cholangiocarcinoma · UC · PSC

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## Introduction

Colitic cancer is appreciated as a colitis-associated colorectal cancer that develops in long-standing and extensive ulcerative colitis (UC). The number of patients with colitic cancer has increased recently along with increased morbidity from UC in Japan [1]. The risk factors for colitic cancer are considered to be long disease duration, extensive lesions, family history of colon cancer, and additionally, the complication of primary sclerosing cholangitis (PSC) [2, 3]. Patients with PSC are also at increased risk of developing cholangiocarcinoma [4], which is known as a disease with poor prognosis in terms of the difficulty in making an imaging diagnosis and the involvement of lymph nodes [4, 5].

We report a patient with concomitant UC and PSC who developed colitis-associated rectal cancer (CARC) and intrahepatic cholangiocarcinoma (ICC), which we successfully cured by surgery. This is a rare case of CARC and ICC complicating these diseases in Japan.

## Case report

A 73-year-old man with a 19-year history of UC was referred to our hospital. He had undergone colonoscopy every year at a previous outpatient clinic. The patient had extensive colitis and had been treated with aminosalicylate

for low disease activity without corticosteroid administration. After several years of asymptomatic UC, a 10-mm tumor was observed in the upper rectum. Under a diagnosis of dysplasia-associated lesion or mass, the patient underwent endoscopic mucosal resection (EMR) at the previous outpatient clinic. Histopathological findings after EMR revealed focal adenocarcinoma with tubulovillous adenoma, with tumor cells remaining in the resected margin. Re-examination with colonoscopy after EMR revealed residual tumor at the resected site (Fig. 1a); however, the macroscopic margin of the tumor was unclear. A biopsy from the site of the erosive margin of the tumor revealed high-grade dysplasia (Fig. 1b). Considering that this patient with UC and CARC was elderly, laparoscopic total proctocolectomy combined with abdominoperineal resection and ileostomy was performed to avoid the risk of residual cancer and fecal incontinence.

The resulting resected specimen showed well-differentiated tubular adenocarcinoma with a component of mucinous adenocarcinoma (Fig. 2a, b), and dysplastic epithelium was observed in the area surrounding the cancer lesion. Furthermore, abnormal p53 accumulation was found by immunohistochemical examination (Fig. 2c–e), which was compatible with CARC. The cancer invaded the muscular layer without node metastasis, and therefore was eventually diagnosed as pT2 and pN0, Stage I according to the Union for International Cancer Control (UICC) 7th edition [6].

At the same time of admission for surgery for CARC, the patient's laboratory data revealed elevated γ-glutamyltransferase and alkaline phosphatase levels of 133 and 371 IU/L, respectively. The aspartate transaminase and alanine transaminase levels were normal, and the carbohydrate antigen 19-9 (CA19-9) level was 32.3 U/mL. Abdominal enhanced CT revealed partial intrahepatic bile duct dilation in the left lateral section of the liver (Fig. 3a), and endoscopic retrograde cholangiography demonstrated stenosis and dilation of the bile duct in the left lateral sector (Fig. 3b). At the same time, cholangiography demonstrated a pruned-tree appearance in the bile duct of the right lobe which led to a suspicious diagnosis of primary sclerotic cholangitis. However, brush cytology of the stenotic site revealed no malignancy. At 6 months after the total proctocolectomy, the patient's laboratory data revealed elevation of his CA19-9 level to 56.4 U/mL. Although a malignant tumor of the bile duct could still not be observed, the possibility of ICC at the stenosis in the hepatic duct was suspected because biliary stenosis with atrophy of the left lateral section had not changed. Therefore, we decided to perform a left hepatectomy and to attempt intraoperative pathological diagnosis in the cut edge of the bile duct to determine whether to add extrahepatic bile duct resection.

After the left hepatectomy, an intraoperative diagnosis of adenocarcinoma in the liver was made, and abnormal cells were observed in the left bile duct at the first resected site. An additional resected specimen of the left bile duct and caudate branch revealed no malignant tumor. The resected specimen showed a bile duct carcinoma of 2 cm in diameter and stenosis of the hepatic duct wall, which represented an ICC of the periductal infiltration invading the left branch of the portal vein (Fig. 4a). The primary well-differentiated tubular adenocarcinoma infiltrating the liver parenchyma was diagnosed histologically (Fig. 4b). In addition, an onion-skin appearance indicating PSC was found in the non-cancerous region of the liver (Fig. 4c). Finally, the periductal infiltration type was classified as T4, and was diagnosed as pT4 and pN0, Stage IVa according to the UICC classification 7th edition [6].

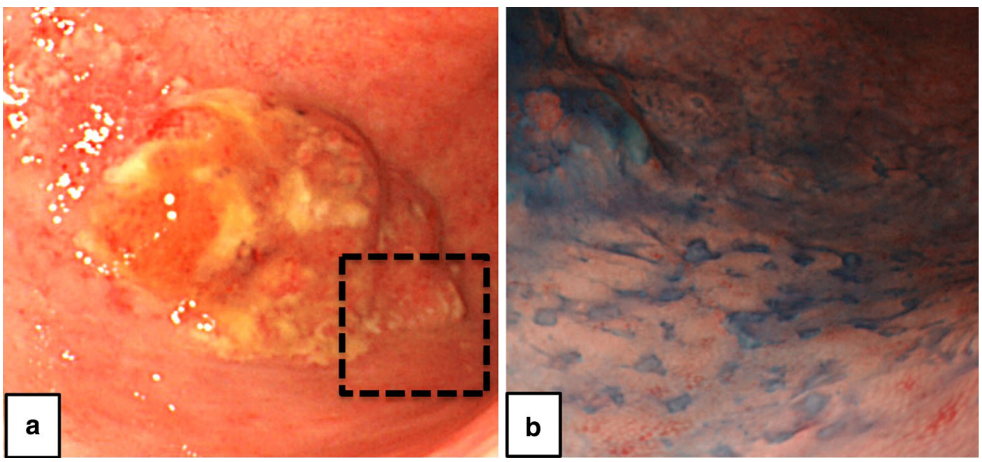


**Fig. 1** Colonoscopy findings. **a** An elevated lesion with coarse margin covered with mucin-like secretion was detected in the upper rectum. The rectal mucosa adjacent to the elevated lesion was associated with coarse and erosive change (area surrounded by the *dashed line*). **b** Chromoendoscopy with indigo carmine staining clarified the extent of the lesion (magnification of the area demarcated by *dashed lines* in **a**)

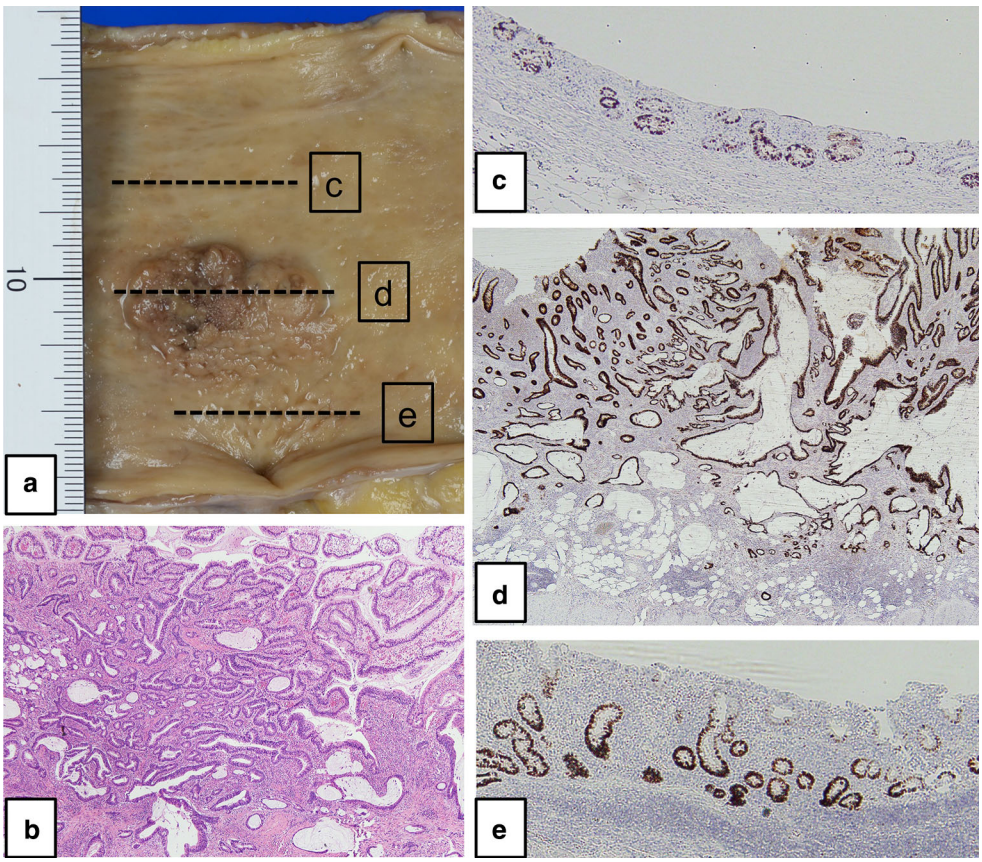


**Fig. 2** Macroscopic and microscopic findings of the resected specimen of the rectum. **a** Magnification of the lesion in the upper rectum. **b** H&E stain revealed well-differentiated adenocarcinoma and mucinous adenocarcinoma in the area in **a** marked by *dashed line d*. Original magnification ×200. **c–e** Immunohistochemistry by p53 staining. Microscopic findings of **c**, **d**, and **e** correspond to the *dashed lines* at the locations *c*, *d*, and *e* in the panel **a**. In addition to the staining of the main lesion, the surrounding mucosa was stained by p53 although no lesion appeared to be present in the macroscopic lesion in **a**. In the area marked by *dashed line e*, strong p53 expression is identified in the lower two-thirds of the crypts. Original magnification ×200

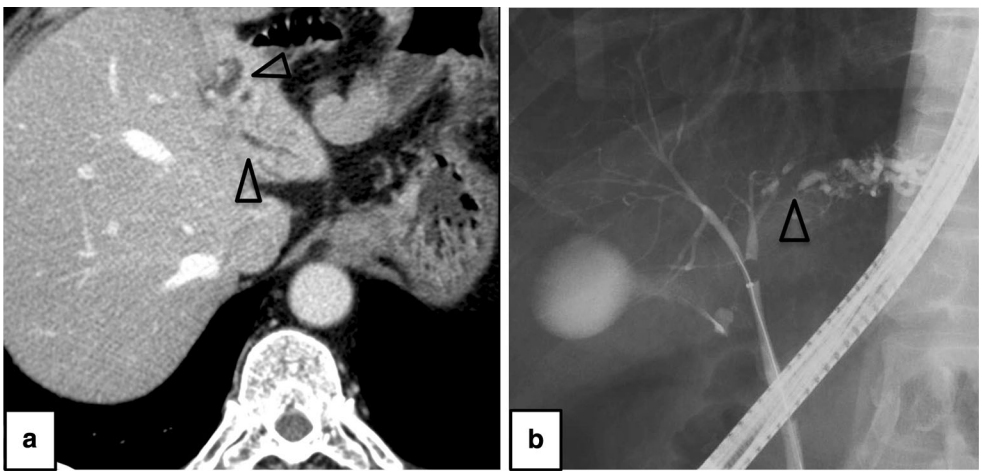


**Fig. 3** Findings of computed tomography and endoscopic retrograde cholangiography (ERC). **a** Computed tomography revealed limited dilation of the intrahepatic bile duct in the lateral segment of the liver (*arrowheads*), although no tumor was detected. **b** ERC demonstrated a pruned-tree appearance in the bile duct of the right lobe, which was compatible with primary sclerosing cholangitis. A band-like stricture of 5 mm in length in the left lateral sector (*arrowhead*) and dilation of the bile duct suggested a malignancy

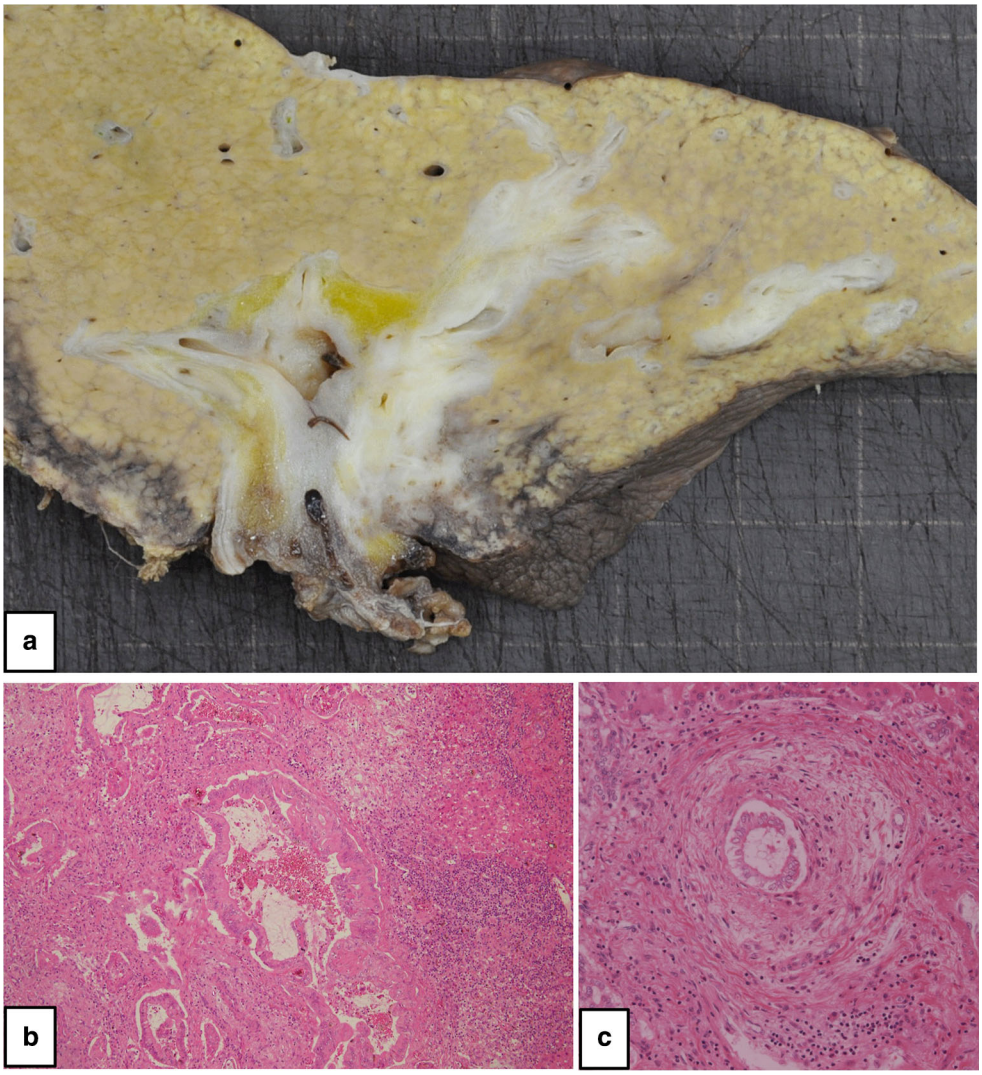


**Fig. 4** Resected specimen of the liver and microscopic findings. **a** Macroscopic findings of the resected liver specimen showing bile duct carcinoma spreading along the left side of the umbilical portion of the portal vein, B2 and B3. **b** Histological findings demonstrated tubular adenocarcinoma infiltrating into the surrounding liver parenchyma. H&E stain, original magnification ×100. **c** A normal area of the liver specimen showed concentric periductal fibrosis, the so-called onion-skin appearance. H&E stain, original magnification ×200

The patient was discharged after an uneventful postoperative period. A month after the hepatectomy the patient's CA19-9 level returned to normal (14.1 U/mL). Adjuvant therapy for ICC consisting of combination therapy of gemcitabine and S-1 was administered for 6 months. The patient remains alive and has been followed-up for 2.5 years after hepatectomy with no recurrence of ICC or colitic cancer observed.

## Discussion

In this report, we presented a case of CARC and ICC that developed after a 19-year follow-up of UC associated with PSC. A search of the Japanese literature found only one previous case report of CARC and ICC complicating UC, indicating the rarity of the present case [7]. A PubMed search revealed no other reports like our case diagnosed definitely as CARC-complicated cholangiocarcinoma in UC and PSC.

Colitic cancer was first reported by Crohn and Rosenberg in 1925 as colitis-associated cancer [8]. Following this, Morson and Pang reported that surveillance for dysplasia would lead to the identification of colitic cancer [9]. In recent years, colonoscopic surveillance for long-standing UC patients is generally accepted to avoid unnecessary prophylactic colectomy and to reduce mortality due to colitic cancer [10]. As the prognosis of Stage III colitic cancer is worse than that of sporadic cancer in Japan [11], the early detection of cancer by careful surveillance is

important. In the present case, annual colonoscopy was able to detect colitic cancer at the early stage. The European guidelines recommend surveillance involving high-quality visual inspection of the mucosa, using chromoendoscopy and target biopsy with endoscopic recognition of colorectal dysplasia in patients with inflammatory bowel disease (IBD) [12]. In our case, chromoendoscopic examination revealed an elevated lesion surrounded by erosion with unclear margins, indicating a dysplasia-associated lesion or mass for which we performed surgery. Eventually, the surgically resected specimen showed invasive adenocarcinoma with the coexistence of dysplasia as indicated by p53 staining. In colitic cancer, p53 immunoreactivity is useful to confine the basal half of the glands associated with early neoplastic lesions [13]. With these detailed findings, we finally diagnosed our patient as having colitic cancer, not sporadic cancer.

The risk of a patient with UC developing PSC is between 2.5 and 5% [14]. Conversely, the prevalence of IBD in Swedish patients with PSC is reported to be higher (69%) than in Japan (32%) [15, 16]. Furthermore, cholangiocarcinoma developed in 22.5% of Swedish patients with a history of PSC with IBD, as opposed to only 1.6% in Japanese patients [15, 16]. Patients with UC and PSC are at a greater risk of developing colorectal cancer or dysplasia (25%) than patients with UC without PSC (5.6%) [17], although we could not find specific morbidity data for patients with colitic cancer with UC and PSC in Japan. Taking these reports into consideration, our case which was also complicated by colitic cancer and ICC would appear to be a quite rare in Japan.

Broomé et al. reported patients with UC and PSC who have colorectal neoplasia to be more prone to developing cholangiocarcinoma than those with UC and PSC only. In contrast to the 17.5% of the patients with UC and PSC who had colorectal neoplasia and cholangiocarcinoma, only 5% of these patients without colorectal neoplasia developed cholangiocarcinoma in Sweden [15]. The development of colitic cancer in our patient might be a risk factor for the complication of cholangiocarcinoma.

A previous report showed that the period between the detection of colorectal neoplasia and the diagnosis of cholangiocarcinoma ranges from 0−22 years [15]. In the present case, PSC, ICC and colitic cancer were concomitantly found at the same time. Careful examination is needed to discover PSC or ICC in UC patients with colitic cancer.

It is difficult to make an imaging diagnosis of ICC at an early stage, especially in ICC of the periductal infiltration type, which infiltrates along the portal pedicle surrounding large vessels or metastasizes to lymph nodes, resulting in a poor prognosis [5]. Uchiyama et al. reported the 5-year survival rate of patients with intrahepatic cholangiocarcinoma to be 19.4%, indicating the poor prognosis of this disease [18]. In the present case, with the abnormal level of CA19-9 as the first indicator, ICC was diagnosed at surgery. However, the serum level of CA19-9 is not sensitive enough to allow for the early detection of localized disease of cholangiocarcinoma [19]. The diagnostic value and potential of biomarkers using microRNAs might be highlighted in the future [20].

We eventually succeeded in curing our patient through careful management and the appropriate decision to perform surgery that has resulted in a long period of tumor-free survival.

In recent years, as the number of patients with long-standing UC has increased, the incidence of colitic cancer has also risen. In this situation, we stress that it is necessary to consider the possible presence of PSC or ICC in patients with UC.

**Compliance with ethical standards**

**Conflict of interest** All authors declare no conflict of interest.

**Human rights** All procedures followed have been performed in accordance with the ethical standards laid down in the 1964 Declaration of Helsinki and its later amendments.

**Informed consent** Informed consent was obtained from the patient in this report.

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