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(CASE REPORT)

Cholangiocarcinoma complicating primary sclerosing cholangitis: Case report and brief literature review

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Abstract

Cholangiocarcinoma (CCA) is an uncommon yet highly aggressive malignancy that arises from the biliary epithelium. It is frequently observed in the setting of chronic inflammatory disorders, where ongoing epithelial injury and regeneration predispose to malignant transformation.

We present a case of a 47-year-old man with longstanding ulcerative colitis and primary sclerosing cholangitis who presented with progressive fatigue, pruritus, jaundice, and unintentional weight loss. Laboratory evaluation and radiographic findings raised a strong suspicion of malignant transformation in the context of PSC.

Given the high pretest probability of perihilar cholangiocarcinoma (pCCA) and the inherent limitations of tissue acquisition in this anatomically complex region, a multidisciplinary consensus supported definitive surgical management. The patient underwent extensive hepatic resection with biliary reconstruction. Histopathologic analysis confirmed moderately differentiated CCA arising in a background of PSC, with high-risk features including perineural invasion and positive resection margins for invasive carcinoma. Loss of SMAD4 expression was observed, a finding associated with more aggressive tumor behavior and poorer prognosis.

The postoperative course was complicated by bile leak and cholangitis. Despite aggressive surgical intervention, early local recurrence occurred within one year, necessitating transition to palliative systemic therapy.

This case underscores the formidable diagnostic and therapeutic challenges inherent in PSC-associated cholangiocarcinoma and highlights its aggressive clinical trajectory and poor prognosis despite timely intervention.

Keywords: Primary sclerosing cholangitis; Cholangiocarcinoma; Perihilar cholangiocarcinoma; Cholangiopancreatography; Immunohistochemical; Malignant biliary epithelium

1. Introduction

PSC is a chronic, progressive cholestatic liver disease characterized by inflammation and fibrosis of the intrahepatic and extrahepatic bile ducts, ultimately leading to multifocal strictures and biliary cirrhosis. [1] It is a relatively uncommon condition, with an estimated prevalence of approximately 6–16 per 100,000 individuals, and occurs more frequently in

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men, with a strong association with inflammatory bowel disease, particularly ulcerative colitis, present in up to 70–80% of cases. [2] PSC is recognized as a premalignant condition, with patients carrying a lifetime risk of CCA estimated at 5–15%, making it one of the most serious complications of the disease. [3]

CCA is an aggressive biliary tract malignancy with poor overall prognosis, particularly when arising in the setting of PSC. Early detection remains challenging, as clinical manifestations, including jaundice, pruritus, abdominal pain, and weight loss, often overlap with symptoms of progressive PSC. Furthermore, diagnostic tools such as cross-sectional imaging and serum markers, including carbohydrate antigen 19-9 (CA 19-9), lack sufficient accuracy for distinguishing benign inflammatory strictures from malignant transformation in this high-risk population. [4,5] As a result, many cases are identified at advanced stages, limiting curative treatment options.

Given the significant diagnostic challenges and high morbidity associated with PSC-related CCA, case reports remain valuable in emphasizing clinical features that may prompt earlier suspicion. We report this case to highlight the diagnostic difficulty and rapid progression of CCA arising in a patient with PSC, emphasizing the importance of maintaining a high index of suspicion in patients with new or worsening symptoms.

2. Clinical Presentation

2.1. Clinical Presentation

A 47-year-old male with a 15-year history of extensive ulcerative colitis (pancolitis, in remission on mesalamine) presented with a three-month history of progressive fatigue, generalized pruritus, and intermittent right upper quadrant abdominal pain. He also had a 2-year history of PSC, managed with ursodeoxycholic acid (UDCA), and routine imaging demonstrating stable intrahepatic biliary strictures. His most recent magnetic resonance cholangiopancreatography (MRCP), performed six months prior to presentation, showed no interval change.

The patient sought medical evaluation due to worsening jaundice, dark urine, and an unintentional weight loss of approximately 10 pounds over the preceding month.

2.2. Physical Examination, Laboratory Findings, Imaging, and Differential Diagnosis

Physical examination revealed scleral icterus, diffuse jaundice, and excoriations over the extremities consistent with chronic pruritus. Abdominal examination demonstrated a firm, non-tender liver edge palpable 4 cm below the right costal margin. No asterixis was observed. Family history was non-contributory.

Laboratory evaluation demonstrated a cholestatic pattern of liver injury, with a total bilirubin of 8.2 mg/dL (direct bilirubin 6.5 mg/dL) and a markedly elevated alkaline phosphatase level of 1,200 U/L, significantly increased from a baseline of 320 U/L. The carbohydrate antigen 19-9 (CA 19-9) level was elevated to 450 U/mL. Contrast-enhanced computed tomography (CT) of the abdomen identified a new dominant stricture with a characteristic shouldered morphology at the confluence of the right and left hepatic ducts, accompanied by prestenotic intrahepatic biliary ductal dilation.

The primary clinical differential diagnosis included progression of PSC with development of a dominant stricture versus cholangiocarcinoma. Radiologic considerations similarly included benign PSC-related stricture, cholangiocarcinoma, and, less likely, ampullary pathology.

2.3. Multidisciplinary Tumor Board Discussion and Management

The case was reviewed at a multidisciplinary tumor board comprising specialists in hepatology, interventional radiology, hepatobiliary surgery, pathology, and oncology. The principal diagnostic challenge involved distinguishing a high-risk benign biliary stricture from early-stage pCCA in the context of PSC, a recognized premalignant condition.

The patient's clinical course, characterized by rapid functional decline, worsening cholestasis, and markedly elevated CA 19-9, raised significant concern for malignancy. Given the Bismuth–Corlette type II location of the dominant stricture and the absence of metastatic disease on staging CT, the consensus recommendation was surgical resection as the best potentially curative intervention.

Although proceeding to surgery without histopathologic confirmation carries inherent risk, the decision was deemed justified due to the technical challenges of obtaining a reliable, uncontaminated biopsy at this anatomical location. The

recommended surgical approach consisted of en bloc resection with left trisegmentectomy and caudate lobe resection, followed by Roux-en-Y hepaticojejunostomy.

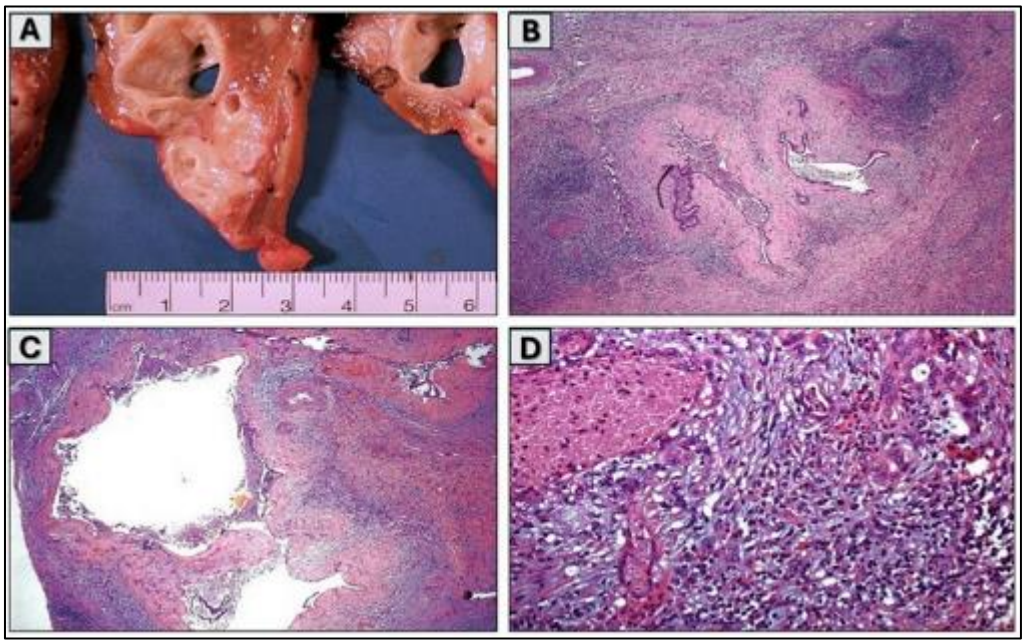
2.4. Special Studies, Ancillary Testing, and Pathology Diagnosis

Intraoperative frozen section analysis of proximal bile duct margins was performed to guide the extent of resection. The resected liver tissue showed thickened, indurated major intrahepatic bile ducts exhibiting a "pipestem" appearance due to extreme, dense concentric fibrosis. Final histopathologic evaluation demonstrated malignant biliary epithelium, infiltrative glands, and dense fibrous stroma, all set against the chronic sclerosing/inflammatory background of PSC. The tumor measured 3.5 cm and exhibited perineural invasion. Histomorphology was consistent with a moderately differentiated perihilar intrahepatic cholangiocarcinoma arising in a background of large-duct PSC (Figure 1, A, B, C, D) and (Figure 2 A, B).

Importantly, the bile duct transection margin was positive for invasive carcinoma (R1 resection). Immunohistochemical (IHC) analysis revealed tumor cell positivity for cytokeratin 7 (CK7) and cytokeratin 19 (CK19), supporting biliary epithelial origin. Loss of SMAD4 expression was observed, a finding associated with more aggressive tumor behavior and poorer prognosis. Next-generation sequencing (NGS) identified an IDH1 mutation (p.R132C), with no evidence of FGFR2 fusions. A bile leak and subsequent cholangitis complicated the postoperative course.

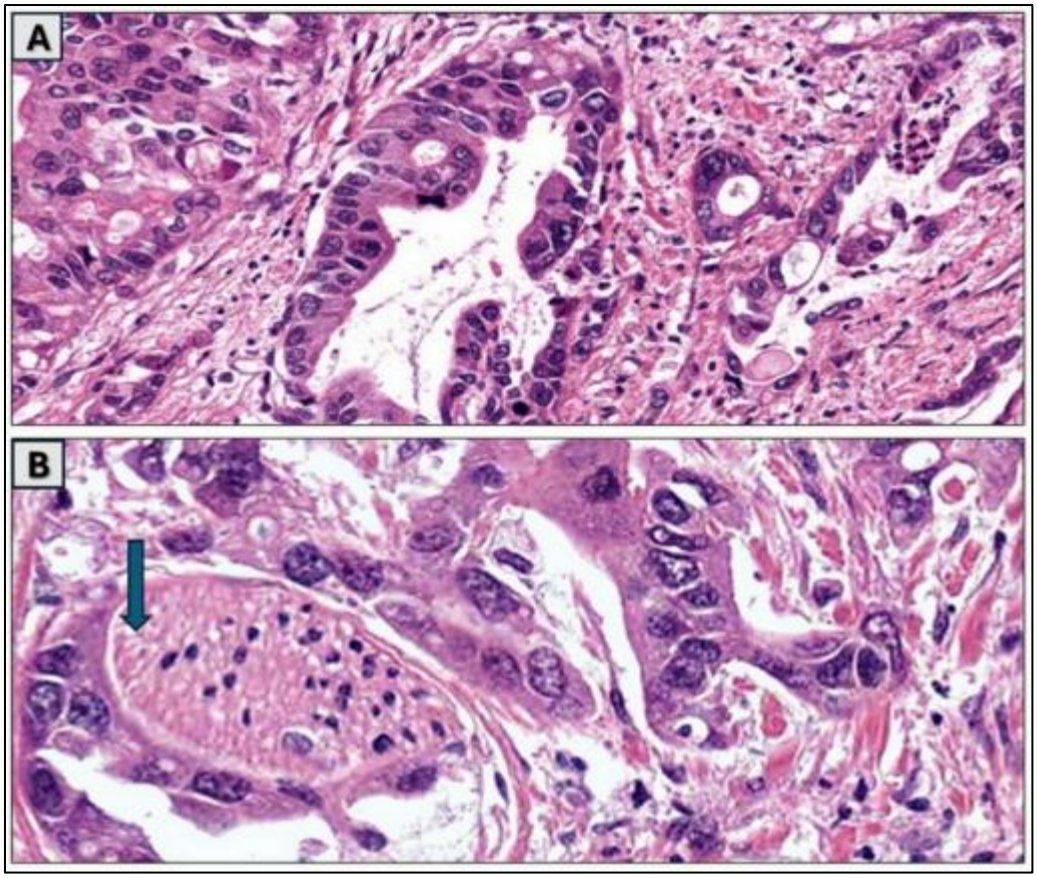
2.5. Follow-up and Outcome

Despite undergoing technically complex surgical resection, the patient developed locally recurrent disease within 12 months and was ultimately transitioned to palliative systemic therapy. This case highlights the poor prognosis associated with cholangiocarcinoma arising in the setting of PSC, reflecting both the underlying field defect and the high rate of disease recurrence, even following surgical intervention.



1A: Gross appearance of the resected liver tissue with thickened, indurated major intrahepatic bile ducts exhibiting a "pipestem" appearance due to extreme, dense concentric fibrosis; **1B:** Low power view showing bile ducts proliferation, prominent periductal fibrosis, and adjacent ducts with moderate chronic inflammation (H&E stain X20); **1C:** Low power view showing portal tracts enlargement due to inflammation and fibrosis. (H&E stain X20); **1D**: High power view showing periportal inflammation and fibrosis, and bile ducts nuclear disarray (H&E stain X40)

Figure 1 Gross features and microscopic findings of primary sclerosing cholangitis (PSC)



2A: High power view showing infiltrating cholangiocarcinoma. Large nuclear cytoplasmic ratio, irregular hyperchromatic nuclei, and abnormal mitosis (H&E stain X40); **2B:** High power view showing malignant infiltrating glands of cholangiocarcinoma and perineural invasion (Blue arrow) (H&E stain X60)

Figure 2 Microscopic findings of Cholangiocarcinoma

3. Discussion

3.1. Background (History, epidemiology, risk factors, and WHO classification)

PSC was historically described as a chronic fibroinflammatory cholangiopathy affecting the intrahepatic and extrahepatic bile ducts, and it has remained an uncommon but clinically important premalignant disorder because of its strong association with hepatobiliary cancer. [5,6] Population-based syntheses estimated PSC incidence at approximately 0.5-0.9 per 100,000 person-years and prevalence at roughly 6-14 per 100,000 persons, with a male predominance and frequent coexistence with inflammatory bowel disease, particularly ulcerative colitis. [4,6]

CCA, the second most common primary liver cancer, has been anatomically classified into intrahepatic, perihilar, and distal subtypes; contemporary guidance recommended that cases be recorded in this tripartite manner because these entities differ in biology, presentation, and management. [5,7] In Western populations, PSC has been the strongest established risk factor for CCA, and the lifetime incidence of CCA in PSC cohorts has been reported at 6%-36%, with many tumors detected within the first year after PSC diagnosis and at a younger age than sporadic CCA. [5,7]

Most PSC-associated tumors have arisen in the large ducts and have therefore been presented as perihilar or distal disease, often creating a difficult distinction from dominant benign strictures. [5] This background has made vigilant surveillance, multidisciplinary assessment, and early recognition of clinical red flags essential in PSC patients who develop worsening cholestasis, jaundice, weight loss, or rising CA 19-9 levels. [5,6,7]

3.2. Pathogenesis, Pathophysiology

PSC is a common comorbidity of ulcerative colitis and can be complicated by CCA. Biliary tree stem progenitor cells (BTSCs) within the peribiliary glands undergo malignant transformation and proliferation, leading to CCA. [8] Sustained exposure to inflammatory mediators such as IL-6, TNFα, IL-17, and COX-2, as well as bile acid activation of ERK1/2, Akt,

and NF-kB pathways driven by chronic inflammation and cholestasis, encourages carcinogenesis. [9] This inflammation promotes epithelial-to-mesenchymal transition (EMT), loss of primary cilia in BTSCs, and autophagy. [8]

In PSC-CCA, copy number variations (i.e., loss of FGFR1 or CDKN2A) lead to a stepwise progression in which dysplastic lesions accumulate, culminating in high-grade dysplasia and invasive carcinoma involving TP53 (30-36%), KRAS (16-28%), ERBB2, GNAS, and PIK3Ca mutations. [10,11] Additionally, mutations in RTK/RAS, PI3K, and TP53 pathways often correlate with increased mortality. [12] A proliferative, tumorigenic environment with increased angiogenesis, driven by VEGF upregulation and extracellular matrix remodeling, is created by stromal remodeling and by cancer-associated fibroblasts and macrophages. [9]

Biliary obstruction due to strictures presents with jaundice, pruritus, and cholangitis. [13] PSC-CCA exhibits a uniform extrahepatic morphology-molecular phenotype, which often presents as mucin-producing tumors with intraductal papillary features. [11] Therapeutic opportunities include targeting ERBB2 mutations, FGFR3 amplifications, and MDM2. [11,12]

3.3. Comparative Analysis of Our Case with Existing Literature. (Clinical, radiology, pathology, Lab, diagnosis, management, and outcome)

3.3.1. Clinical Presentation

Clinical features of the present case reveal significant agreement with the findings of CCA related to PSC, except for a few disparities. Typically, CCA occurring due to PSC presents with symptoms such as progressive jaundice, pruritus, weight loss, and impaired cholestatic liver functions. [5,14] In the current case, the patient's rapid progression of the disease, along with these symptoms, fits better with a malignant scenario. The rapid onset of symptoms over about 1 month is not characteristic of stable PSC and is an indication of serious progression with complications, here, in the form of malignant progression.

While CCA develops between the fourth and fifth decades of life, predominantly in males, the critical point is the timing of disease manifestation. In this case, CCA developed after only two years of PSC, which is shorter than the typically reported duration. This finding reinforces emerging evidence that malignancy can occur early in PSC and supports the need for vigilant surveillance regardless of disease duration. [5]

3.3.2. Diagnostic Workup

Imaging revealed a dominant stricture at the hepatic duct confluence with "shouldered" morphology, a feature strongly associated with pCCA. [14] The rapid increase in bilirubin and the markedly elevated CA 19-9 (450 U/mL) further heightened suspicion of malignancy, consistent with thresholds reported in recent studies. [15]

However, no preoperative tissue diagnosis was obtained. Studies confirm that ERCP brush cytology has a low sensitivity (45-60%) and that FISH has a higher sensitivity (70-80%) among patients with PSC. [10] The histopathological analysis revealed moderately differentiated CCA with perineural invasion and PSC background. Notably, the current patient showed IDH1 (p.R132C) mutation and SMAD4 loss (Section 2.4). Although only a small number of patients with PSC-associated CCA harbor an IDH1 mutation, IDH1 mutations confer therapeutic benefit, as the inhibitor Ivosidenib is efficacious in advanced tumors. [17] In contrast, SMAD4 loss is associated with malignancy and poor prognosis, which explains the early recurrence.

3.3.3. Management

Surgical resection remains the primary curative option for localized pCCA, and the decision to proceed with extended hepatectomy was appropriate given the absence of metastatic disease (Section 2.3). [5,14] However, the case resulted in an R1 resection, indicating microscopic residual disease. Importantly, PSC-associated CCA is known to have lower R0 resection rates (approximately 40–60%) compared to sporadic CCA, due to multifocal disease and the “field defect” of chronic inflammation. [18] The R1 margin in this case is therefore consistent with known surgical challenges.

In the patient's management, there was no inclusion of neoadjuvant treatment or liver transplantation (LT). Recent protocols that include both the LT and neoadjuvant chemoradiation have shown 5-year survival rates of up to 70%-80% among selected patients. [19] The patient had no neoadjuvant treatment before surgery, which may have contributed to the positive margin. Although the tumor was surgically resectable (type II Bismuth), transplant approaches such as LT could be essential.

3.3.4. Outcome and Follow-up

The patient showed signs of recurrence within 12 months after the surgery (Section 2.5). The median RFS is 9–14 months, while overall survival (OS) is 18–24 months for R1 resection cases, whereas R0 resections show significantly better results [18,19,20]. In this case, only 1 year of follow-up after the resection was available; subsequently, disease recurrence was diagnosed. The long-term survival information has not been provided. Nevertheless, even with imaging surveillance, aggressive behavior of PSC-related CCA is noted, but follow-up mechanisms are limited.

Additionally, despite routine surveillance prior to diagnosis, including MRCP imaging six months earlier, the tumor developed rapidly. Current guidelines recommend six-monthly surveillance in high-risk PSC patients using MRI/MRCP and CA 19-9 trends. [5] The present case demonstrates that even guideline-concordant surveillance may fail to detect early malignant transformation.

3.3.5. Literature Summary and Lessons Learned

The current case is largely consistent with the contemporary literature on PSC-associated CCA regarding its presentation, difficulty of diagnosis, and poor prognosis. First, malignant transformation can arise early in PSC patients, therefore requiring close monitoring of their condition. Secondly, the diagnostic challenges have persisted despite advances in radiological and cytological techniques. Third, prognostic and therapeutic guidance on molecular characterization is useful. Finally, R1 resection has a poor prognosis, and considering LT or preoperative therapy is crucial.

Abbreviations: Primary sclerosing cholangitis (PSC); Cholangiocarcinoma (CCA); perihilar cholangiocarcinoma (pCCA); Cholangiopancreatography (MRCP), Immunohistochemical (IHC)

4. Conclusion

This case illustrates the aggressive clinical course of cholangiocarcinoma arising in the setting of primary sclerosing cholangitis, a premalignant biliary disorder in which malignant transformation may occur early. It may closely mimic the progression of benign dominant strictures. In our patient, worsening jaundice, weight loss, rising cholestatic indices, and marked CA 19-9 elevation signaled a malignant process despite previously stable imaging, underscoring the limited sensitivity of routine surveillance and the persistent diagnostic difficulty of PSC-associated perihilar disease. The case also reinforced the importance of multidisciplinary decision-making when tissue confirmation is technically challenging and curative-intent surgery must be weighed against the risks of advanced local disease, positive margins, and early recurrence.

For the medical community, the principal lesson was that new or rapidly progressive biliary obstruction in PSC should prompt urgent reassessment for cholangiocarcinoma, because early recognition remains central to timely intervention, prognostic stratification, and selection of appropriate oncologic or transplant-based strategies.

Compliance with ethical standards

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Data access statement

All relevant data are included in the paper.

Author contributions

All authors contributed equally to producing this manuscript.

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