Case Report

Distal cholangiocarcinoma: case report and brief review of the literature✩✩

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Article history:
Received 6 October 2022
Revised 17 October 2022
Accepted 23 October 2022

Keywords:
Cholangiocarcinoma
Pancreatobiliary type
Common bile duct
Metastatic disease

Abstract

Adenocarcinomas of the distal bile duct are traditionally classified as either pancreatobiliary or intestinal type, with pancreatic adenocarcinoma and cholangiocarcinoma included within the former classification. Cholangiocarcinoma is a rare and deadly malignancy that occurs within three clinically defined regions: intrahepatic, perihilar, and in the distal bile duct. We present a 68-year-old male with a past medical history of human immunodeficiency virus, hepatitis B, hypertension, and hyperlipidemia who presented to the emergency department with a 3-week history of diarrhea, diffuse abdominal pain, malaise, and nausea. Contrast enhanced CT of the abdomen and pelvis revealed a peripancreatic mass. Endoscopic ultrasound biopsy was performed, with histopathology suggestive of distal cholangiocarcinoma. Endoscopic retrograde cholangiopancreatography was utilized for palliative stent placement until patient received pancreaticoduodenectomy (ie, Whipple procedure). In this case, we highlight the imaging presentation and histopathology of a distal cholangiocarcinoma.

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✩ Competing Interests: The authors have declared that no competing interests exist.
✩✩ Acknowledgements: This work was supported by Resident managed peer-mentorship program at West Virginia University. Lakhani DA, Swaney KJ, Hogg JP. "Resident Managed Peer-Mentoring Program": A Novel Way to Engage Medical Students and Radiology Residents in Collaborative Research. Acad Radiol. 2021 Dec 1:S1076-6332(21)00531-6. doi: 10.1016/j.acra.2021.11.004.
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https://doi.org/10.1016/j.radcr.2022.10.072
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Background

Cholangiocarcinoma belongs to a group of molecularly heterogeneous adenocarcinomas that can exist anywhere along the biliary tract [1–3]. Cholangiocarcinoma accounts for approximately 2% of all malignancies in the United States, representing 15%-20% of all primary liver malignancies and 3% of gastrointestinal malignancies ([1,4]). While the site of malignancy is generally very broad, it is clinically divided into regions including the intrahepatic, perihilar, and distal [2]. Most malignancies are perihilar (~60%), with distal and intrahepatic manifestations comprising a much smaller population of patients at 30% and 10%, respectively [3].

Between 1995 and 2016, global mortality rates of intrahepatic cholangiocarcinoma were seen to rise (likely due to increases in risk factors and enhanced diagnosis techniques) while mortality rates of extrahepatic cholangiocarcinoma, both perihilar and distal, were seen to decrease (likely due to increasing access to laparoscopic cholecystectomy interventions) [5]. Across all cancer groups, the percent increase in intrahepatic cholangiocarcinoma in the United States was the highest for all cancers between 1999 and 2014 [6]. Additionally, this increase was shown to be disproportionately spread across racial/ethnic groups, including the highest rates among Blacks/African Americans (45%), followed by American Asians (22%) and Caucasians (20%) [6].

In patients with nonresectable cholangiocarcinoma, the 1-year (35.4%), 3-year (16%), and 5-year (0%) survival rates are very low [7]. Generally, 5-year survival rates in surgically resectable cases range from 10% to 40%, depending on the studied population and procedure [4]. Surgical treatment options are dependent on the cholangiocarcinoma site. For intrahepatic cholangiocarcinoma, hepatectomy with regional lymphadenectomy and liver transplantation may be considered [2]. For perihilar disease, hepatectomy with en-bloc resection of the extrahepatic bile duct and regional lymphadenectomy could be performed, while pancreaticoduodenectomy is reserved for distal disease [2]. Following pancreaticoduodenectomy, 5-year survival rates in patients with distal cholangiocarcinoma (45%) are higher than all resectable cases of cholangiocarcinoma (10%-40%) [4,8]. Prognosis following surgical intervention is decreased when lymph nodes are involved [9], there are positive post-surgical margins [10], or multifocal disease is present [11].

Case report

Here we present a 68-year-old man with a past medical history of human immunodeficiency virus (HIV), hepatitis B, hypertension, and hyperlipidemia who presented to the emergency department with a 3-week history of diarrhea, diffuse abdominal pain, malaise, and nausea. The patient had a 12-hour history of increasing jaundice. In the emergency department laboratory work revealed an elevated alkaline phosphatase of 548 IU/L (reference range = 44-147 IU/L), total bilirubin of 8.4 mg/dL (reference range = 0.1-1.2 mg/dL), conjugated bilirubin of 5.4 mg/dL (reference range = 0.1-0.3 mg/dL), aspartate transaminase of 92 U/L (reference range = 8 to 33 U/L), alanine transaminase (ALT) of 183 U/L (reference range = 4-36 U/L), and lipase of 1502 U/L (reference range = 0 to 160 U/L), suggesting a cholestatic pattern of liver injury. Initial assessment with right upper quadrant ultrasound showed intra- and extra-hepatic bile duct dilation. The common bile duct measured up to 18 mm in diameter (Figs. 1A and B). Follow-up CT abdomen and pelvis with intravenous contrast revealed a 2.0 cm × 2.7 cm hypo-attenuating periampullary mass with associated abnormal dilation of the pancreatic and biliary ducts (Figs. 2A and B).

Gastroenterology was consulted, and the patient underwent endoscopic ultrasound (EUS). There was an ill-defined, obstructing hypoechoic distal common bile duct mass measuring 2.0 cm × 2.7 cm, resulting in pancreatic and biliary ductal dilation (Fig. 3). A transduodenal EUS-guided fine needle biopsy was subsequently performed. Preliminary on-

![Fig. 1 – Transabdominal ultrasound of the abdomen showed abnormal dilation of extrahepatic (A) and intrahepatic (B) bile ducts (yellow arrows).](image-url)
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Fig. 2 – Coronal (A) and axial (B) CT abdomen and pelvis, showed an ill-defined 2.0 cm × 2.7 cm hypoattenuating periampullary mass (yellow arrows) with intra- and extrahepatic biliary ductal dilation (red arrows). Pancreatic ductal duct dilation (green arrow) was also present. Incidental note of duodenal diverticulum was made (orange arrows).

Fig. 3 – Endoscopic ultrasound revealed an erythematous, edematous, and indurated periampullary region. There was an ill-defined, obstructing hypoechoic periampullary mass measuring 2.7 cm × 2.0 cm (white box).

site cytopathology revealed malignancy (Fig. 4). Endoscopic retrograde cholangiopancreatography revealed an erythematous, edematous, and indurated periampullary region (Fig. 5A) with a severe distal common bile duct malignant stricture. Small biliary endoscopic sphincterotomy was performed and a transpapillary biliary stent was placed across the common bile duct stricture (Figs. 5B and C). Both Papanicolaou (Pap) (Fig. 6A) and hematoxylin and eosin (H&E) (Fig. 6B) staining revealed malignant transformation of the distal common bile duct biopsy. Immunohistochemical staining of the periampullary mass revealed aberrant p53 expression (loss of nuclear expression) (Fig. 6C), cytokeratin 7 (CK7) gain of function (Fig. 6D), and retained SMAD Family Member 4 (SMAD4) (Fig. 6E) expression.

The patient was discharged and outpatient follow-up scheduled with surgical oncology to assess candidacy for intervention. Pancreateicoduodenectomy (ie, Whipple resection) was performed revealing metastatic disease with 4 of 22 nodes positive and staging of pT3b N2. Primary tumor resection revealed a moderately to poorly differentiated adenocarcinoma (2.7 cm), centered near the ampulla, with invasion into the duodenum, pancreas, and peri-pancreateicoduodenal soft tissue. Final pathology of the tumor cells revealed diffusely positive mucin 1 (MUC-1) and negative immunostaining for mucin 2 (MUC-2), caudal type homeobox 2 (CDX2), CK20, MutL protein homolog 1 (MLH1), MutS homolog 2 (MSH2), MSH6, and PMS1 homolog 2 (PMS2). The cell surface markers confirm a pancreatobiliary immunophenotype and support a diagnosis of distal cholangiocarcinoma.

Postoperative course complicated by pancreatic leak, right pleural effusion requiring pigtail placement, and failure to thrive.
Fig. 4 – Diff-Quik-stained slides (100X magnification) with rapid on-site evaluation/adequacy assessment (ROSE). The specimen was cellular and showed an admixture of benign ducts (yellow arrow) and malignant ducts (red arrows). Benign ducts are a flat sheet of ductal cells arranged with a “honeycomb” appearance, while malignant ducts are three dimensional and crowded with irregular nuclear membranes, prominent nucleoli, and anisonucleosis.

Fig. 5 – Endoscopic retrograde cholangiopancreatography (ERCP) revealed an enlarged and edematous periampullary region when visualizing the major papilla (white box) (A). Fully covered self-expanding metal stent (FCSEMS) placement in the common bile duct (CBD) (B). Intraoperative fluoroscopic images during ERCP shows a high-grade short segment common bile duct stricture from obstructing distal common bile duct mass (yellow arrow), with upstream dilation of intra- and extrahepatic duct dilation. Biliary stent across the stricture was subsequently placed (C).
Fig. 6 – Papanicolaou (Pap) stain (200X magnification) revealing an admixture of benign ducts (yellow arrow) and malignant ducts (red arrows). Benign ducts are a flat sheet of ductal cells arranged with a “honeycomb” appearance, while malignant ducts are three dimensional and crowded with irregular nuclear membranes, prominent nucleoli, and anisonucleosis (A). Hematoxylin and eosin (H&E) stain (100X magnification) revealing malignant ducts (red arrows) infiltrating the stroma with a desmoplastic response. A few benign ducts (yellow arrows) and duodenal epithelium (blue arrow) are seen in the background (B). p53 stain (400X magnification) showing a loss of nuclear stain (aberrant p53 expression suggestive of p53 gene mutation). The brown stain shows retained p53 in stromal cells (C). Cytokeratin 7 (CK7) stain (400X magnification) with malignant ducts positive (dark brown stain) (D). SMAD Family Member 4 (SMAD4) stain (400X magnification) with malignant ducts showing retained nuclear and cytoplasmic expression (light brown stain) (E).

**Discussion**

Clinical and laboratory assessments generally comprise the first steps in diagnosing pancreatic and biliary tract cancers. These tests include assessments of biliary obstruction, abnormal liver function tests, and elevated tumor markers [12]. In our patient, presenting with malaise, abdominal pain, and jaundice, assessments of his liver function were made and revealed a cholestatic pattern of liver injury (ie, increased alkaline phosphatase and bilirubin, with slight increases in alanine transaminase and aspartate aminotransferase). Additionally, he presented with an elevated carbohydrate antigen 19-9 (CA 19-9). Such as the current case, when clinical suspicion of biliary obstruction is high, ultrasonography can be applied as a first-line imaging modality [13].

On initial assessment, the presence of intrahepatic bile ducts and common bile duct dilation were present, but visualization of the periampullary tumor was not achieved, which can occur due to variations in presentation of the malignancy [14]. While magnetic resonance cholangiopancreatography is considered the gold standard for diagnosing distal bile duct adenocarcinomas [15] and can achieve up to 88% sensitivity and 95% specificity [12], CT abdomen was employed in our case due to an undefined primary source. Other imaging modalities can also be used in the diagnosis and staging of distal bile duct adenocarcinomas. These include EUS, endoscopic retrograde cholangiopancreatography, intraductal ultrasound, cholangioscopy, optical coherence tomography, and fluorodeoxyglucose positron emission tomography [12,16–19].

Risks factors associated with cholangiocarcinoma include genetic, congenital, environmental, and parasitic factors. Familial adenomatous polyposis is specifically linked to distal cholangiocarcinoma through the adenomatous polyposis coli gene [20]. Because of the heterogenous nature of dis-
tal cholangiocarcinoma, further research is needed to assess new genetic markers for characterizing the malignancy and predicting survival. In a study of 46 patients, genetic markers cytokeratin 7 (CK7), cytokeratin 17 (CK17), cytokeratin 20 (CK20), CDX2, mucin 1 (MUC1), mucin 2 (MUC2), and mucin 5AC (MUC5AC) were assessed. CK17 was shown to be useful in separating pancreaticobiliary adenocarcinomas from extra-pancreatic non-malignant adenocarcinomas [21]; this is important, as pancreaticobiliary types of ampullary carcinoma have worse survival outcomes compared to intestinal ampullary carcinoma or mixed types [22]. In our study, CK7 upregulation was used in aiding the diagnosis, as it can be aberrantly upregulated in up to 96% of cholangiocarcinomas [23].

Additionally, like our case presentation, loss of p53 expression is associated with cholangiocarcinoma development [24]. Dietary and other environmental causes that increase inflammation, through Interleukin (IL)-6 and tumor necrosis factor (TNF)-α, also predispose to malignancy development [25,26]. Disease and congenital malformation of the biliary system can predispose to cholangiocarcinoma, including pancreaticobiliary maljunction, choledochal cysts, primary sclerosing cholangitis, and adenomyomatosis [20]. Finally, *Opisthorthix viverrini* and Clonorchis sinensis, 2 liver flukes, can lead to cholangiocarcinomas and are a major contributor in the increased rates if cholangiocarcinoma observed in East and Southeast Asia [27,28].

**Patient consent**

Written consent was obtained for the publication of the current case. No patient identifiers disclosed.

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