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CASE REPORT | BILIARY

Rapidly Fatal Metastatic Cholangiocarcinoma Associated With Metabolic Dysfunction–Associated Steatotic Liver Disease and Metabolic Syndrome: A Case Report Highlighting Emerging Risk Factors

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ABSTRACT

Cholangiocarcinoma (CCA), a rare biliary cancer, typically presents with nonspecific symptoms that hinder early diagnosis. Emerging metabolic risk factors are increasingly being recognized as contributors. We present the case of a 54-year-old woman with newly diagnosed metabolic dysfunction–associated steatotic liver disease and metabolic syndrome, who presented with acute abdominal pain and a subsequent liver biopsy-confirmed intrahepatic CCA. Despite chemotherapy and immunotherapy, rapid disease progression led to metastasis and systemic complications, resulting in death. This case highlights the aggressive nature of CCA and the importance of addressing modifiable metabolic risk factors to improve the outcomes.

KEYWORDS: intrahepatic cholangiocarcinoma; metabolic dysfunction–associated steatotic liver disease; obesity; diabetes and metabolic syndrome; palliative and supportive care

INTRODUCTION

Cholangiocarcinoma (CCA), a rare and aggressive bile duct cancer, affects approximately 1 in 100,000 individuals annually in the United States, and typically emerges in the sixth decade of life, accounting for less than 1% of all cancers.[1] Symptoms frequently manifest in advanced stages, underscoring the importance of prevention and early detection. Established risk factors include chronic biliary inflammation as seen in primary sclerosing cholangitis, liver fluke infections, and chronic viral hepatitis. However, emerging risk factors, including metabolic dysfunction–associated steatotic liver disease (MASLD), metabolic syndrome, diabetes, and obesity, are increasingly being recognized, as highlighted in this case. This report calls for heightened awareness of these contributors, timely identification of atypical presentations, and development of personalized treatment strategies. Finally, it highlights the importance of integrating early palliative care discussions in cases of advanced unresectable disease to improve outcomes and quality of life.

CASE REPORT

A 54-year-old woman presented to the emergency department in October 2023 with a 3-day history of intermittent, pressure-like epigastric and right upper quadrant abdominal pain alleviated by food intake. She denied any other symptoms including nausea, vomiting, jaundice, melena, hematochezia, or changes in bowel habits. She emigrated to the United States at age 16 and visited her family's farm in Mexico 3 months before presentation. She had no established primary care, no known medical or surgical history, and had experienced menopause 2 years prior. She denied current or past alcohol, tobacco, or drug use as well as exposure to cats, dogs, or cattle. Living with her daughter and being unemployed, she recalled no significant environmental exposure to toxic

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substances, including heavy metals. Her family history was negative for cancer or inflammatory bowel diseases. She reported no prescription, over-the-counter medications, or supplements.

Her body mass index was 36 kg/m^2, and vital signs were within normal limits. Physical examination revealed hepatomegaly and moderate tenderness in the epigastric and right upper quadrant regions without rebound tenderness or guarding. Electrocardiogram showed normal sinus rhythm with no ischemic changes.

Initial laboratory results showed a normal complete blood count, renal chemistry, coagulation studies, thyroid function, troponin, lipase, urinalysis, and urine drug screen but revealed findings consistent with hepatocellular injury, dyslipidemia, and new-onset diabetes (Table 1). Imaging studies suggested acute cholecystitis, hepatomegaly (23 cm), hepatic steatosis, multifocal liver abscesses, and mild common bile duct dilation (7.3 mm) without stones (Figure 1). Tumor marker analysis revealed elevated carcinoembryonic antigen and carbohydrate antigen levels. Differential diagnoses, including infectious, metabolic, and autoimmune disorders, were thoroughly investigated. This included extensive testing to rule out viral (Epstein-Barr virus, cytomegalovirus, herpes simplex virus, HIV), parasitic (ova and parasites, *Echinococcus*, *Entamoeba*), bacterial/mycobacterial (QuantiFERON tuberculosis), metabolic (ceruloplasmin, ferritin, iron profile), autoimmune (antinuclear antibodies, smooth muscle antibody, anti-LKM1, soluble liver antigen, antimitochondrial antibody, anti-tissue transglutaminase antibody, deamidated gliadin antibody, immunoglobulin classes), and hereditary/genetic (α-1 antitrypsin) etiologies. The above workup revealed no significant abnormalities. Due to the urgent need to exclude malignancy, and with a fibrosis-4 index score of 1.51 indicating low risk for advanced fibrosis, a FibroScan was not performed.

Table 1. Initial laboratory results

Laboratory tests	Results	Normal range
Aspartate aminotransferase	85 U/L	≤35 U/L
Alanine aminotransferase	113 U/L	≤35 U/L
Alkaline phosphatase	303 U/L	35–104 U/L
γ-Glutamyl transferase	344 U/L	6–42 U/L
Total bilirubin	0.5 mg/dL	≤1.2 mg/dL
Direct bilirubin	<0.2 mg/dL	≤0.3 mg/dL
Total cholesterol	284 mg/dL	≤200 mg/dL
HDL cholesterol	28 mg/dL	≥60 mg/dL
LDL cholesterol	202 mg/dL	≤99.9 mg/dL
Triglycerides	267 mg/dL	≤150 mg/dL
Hemoglobin A1C	9.1%	4%–5.6%
α-Fetoprotein	5.2 ng/mL	≤8.3 ng/mL
Carcinoembryonic antigen	50.3 ng/mL	0.0–3.8 ng/mL
CA 19-9	38,892 U/mL	≤35 U/mL

CA, Carbohydrate Antigen; HDL, high-density lipoprotein; LDL,low-density lipoprotein .

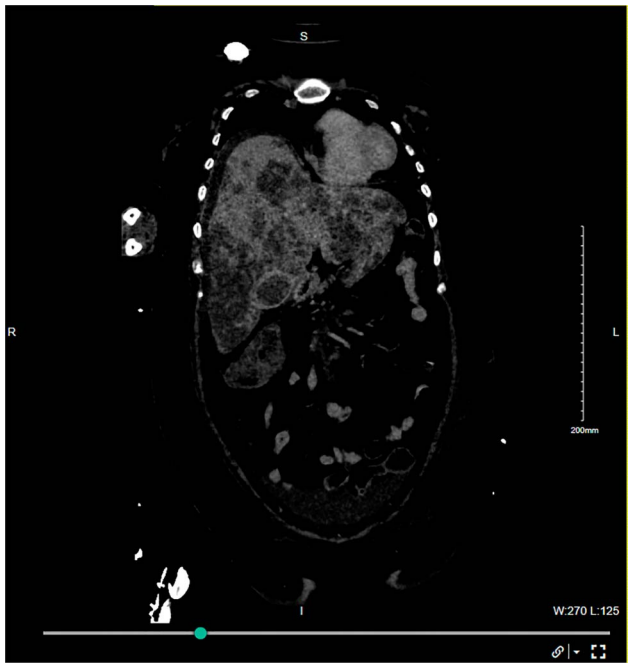

Figure 1 Contrast-enhanced abdominal computed tomography scan (coronal section, liver window) showing gallbladder wall thickening, hepatomegaly and multiple hypodense hepatic lesions.

A computed tomography-guided liver biopsy was conducted, and the pathology was not exact but suggested metastatic adenocarcinoma of pancreaticobiliary origin and intrahepatic CCA. Immunohistochemistry (cytokeratin 7 and 19 positivity, weak cytokeratin 20 positivity, Special AT-rich sequence-binding protein 2 negativity, and stable mismatch repair) and the irregular gallbladder findings on imaging favored CCA over pancreaticobiliary cancer. The patient was managed with insulin for diabetes and referred to oncology. Unresectable disease precluded surgery, and she commenced systemic therapy with gemcitabine, cisplatin, and durvalumab, receiving 2 cycles. Disease progression included pulmonary embolism, thoracic metastases, renal vein thrombosis, worsening jaundice requiring anticoagulation, and a biliary stent. Second-line therapy with trastuzumab-anns and pertuzumab was initiated; however, her condition deteriorated, culminating in brain metastases. In February 2024, she presented with shock and her family opted for comfort care. The patient died the following day.

DISCUSSION

Although most CCA in Western countries are considered sporadic, several well-described risk factors involving chronic inflammation and cholestasis are recognized contributors, initiating a cycle of reactive cell proliferation, genetic mutations, and eventual cholangiocarcinogenesis.[1] In this patient, the

primary identified risk factors were diabetes, obesity, metabolic syndrome, and phenotypically diagnosed MASLD, a fatty liver disease associated with metabolic dysfunction. The role of these emerging metabolic conditions in CCA development is still being researched, and the literature contains conflicting data.

Although early evidence suggested a clearer association between both intrahepatic and extrahepatic CCA (iCCA and eCCA) and nonalcoholic fatty liver disease, now termed MASLD, recent studies present a complex and nuanced picture of this relationship.[2] Meta-analyses by Xiao et al and Corrao et al indicate a statistically significant, albeit moderate, increased risk of overall CCA in the context of MASLD.[3,4] These analyses suggest a nearly twofold increased likelihood. Corrao's analysis further suggests that this association might be specific to iCCA, with less conclusive evidence for eCCA.[4] Adding further complexity, a large-scale cohort study by Villard et al using Swedish national registry data found a surprisingly low incidence of CCA in patients with MASLD, comparable to the general population.[5] This study, employing the updated MASLD definition, suggests that routine screening for CCA may not be warranted in all patients with MASLD. Furthermore, De Lorenzo et al highlight the importance of histological subclassification, indicating that metabolic dysfunction–associated steatohepatitis, the more aggressive inflammatory form of MASLD, may be a more pertinent risk factor for iCCA and impact prognosis, rather than just hepatic steatosis alone.[6]

Several mechanisms may explain the link between MASLD/metabolic syndrome and CCA. These include leptin overexpression, low-grade systemic inflammation driven by adipose tissue–derived cytokines (interleukin-6 and tumor necrosis factor-α), and insulin resistance. These factors can converge to increase hepatic insulin-like growth factor-1, which in turn promotes cell proliferation and survival.[7]

Intrahepatic CCAs, like in our patient, represent a minority (15%) of cases and are often asymptomatic until late stages, frequently discovered incidentally on imaging.[8] Perihilar (60%–70%) and distal extrahepatic tumors (15%–25%), more common, often present with obstructive jaundice symptoms, including pruritus, jaundice, and clay-colored stools.[1,8–10] The Courvoisier sign may appear with distal common bile duct stenosis but is less common in perihilar tumors. Symptoms, such as abdominal pain and weight loss, usually indicate advanced, unresectable disease, highlighting the importance of early detection.[1,9]

Imaging plays a pivotal role in the diagnosis. Transabdominal ultrasound is the initial modality that is highly sensitive in detecting lesions but is operator-dependent.[1,8] Magnetic resonance cholangiopancreatography offers superior detail without the invasiveness of endoscopic retrograde cholangiopancreatography. However, magnetic resonance cholangiopancreatography has limitations, including understaging and susceptibility to artifacts.[1,8] Biopsy may not always be required when imaging findings are favorable for the resectability of the lesion.[11] In our case, the unresectability of the lesion necessitated computed tomography-guided live rbiopsy for histopathological confirmation.

Pathologists face difficulties in establishing exact diagnosis, partially due to limited exposure to these tumors but also due to overlapping morphological features between iCCA and pancreatic ductal adenocarcinoma.[12] In our case, as expected, the pathology could not definitively differentiate between the 2, and immunohistochemical testing along with imaging features were key in distinguishing between the diagnoses.

The prognosis is dismal, with late-stage diagnoses limiting surgical resection, the only curative option. Five-year survival rates for iCCA range from 16% to 44% after resection.[13,14] In unresectable cases, gemcitabine and cisplatin combination chemotherapy provides a modest survival benefit compared with gemcitabine alone.[15] Early initiation of palliative care in these tumors has been proven to improve symptom control, enhance quality of life, better align care with patient values, and reduce aggressive end-of-life interventions.[16]

This report underscores the need to raise awareness of modifiable metabolic risk factors for CCA, such as diabetes, obesity, MASLD, and metabolic syndrome, and advocates for lifestyle modifications as a cornerstone of primary prevention. Physicians should maintain a high index of suspicion for CCA, particularly in at-risk populations. Finally, it emphasizes the importance of initiating early palliative care discussions in advanced, unresectable cases to enhance patient outcomes and improve the quality of life.

DISCLOSURES

Author contributions: All authors critically reviewed the manuscript for intellectual content, reviewed the final version to be published, and agreed to be accountable for all aspects of the work. Concept and design: J. Konlack, Akil Olliverrie, N. Pendyala, JY Bena, GL Nguefang, C. Chum. Acquisition, analysis, or interpretation of data: J. Konlack, A. Olliverrie, N. Pendyala, N. Pandya, C. Chum. Drafting of the manuscript: J. Konlack, N. Pendyala, JY Bena, GL Nguefang, N. Pandya. C. Chum is the article guarantor.

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