CLINICAL CASE
doi: 10.35366/109317

Cirujano General
January-March 2022
Vol. 44, no. 1 / p. 34-39

Cholangiocarcinoma. Case report on the diagnostic approach

Colangiocarcinoma. Caso clínico a propósito del abordaje diagnóstico

José Luis Maldonado-Calderón,* Antonio Urbina-Zeglen,*
Edwin Leopoldo Maldonado-García*

Keywords:
cholangiocarcinoma, perihilar, Klatskin, cholestasis, CA 19-9.

Palabras clave:
colangiocarcinoma, perihiliar, Klatskin, colestasis, CA 19-9.

ABSTRACT

Cholangiocarcinomas are tumors derived from the biliary epithelium, both intrahepatic and extrahepatic. They constitute the second most frequent primary tumor of the liver. Their presentation in advanced stages characterizes them. There are different important risk factors for developing this pathology; however, up to 50% of cases are reported without an associated risk factor. Diagnosis requires a combination of clinical findings, imaging studies, biopsy or brushing, and tumor markers. The only treatment with curative intent is surgical resection.

RESUMEN

Los colangiocarcinomas son tumores derivados del epitelio biliar tanto intrahepático como extrahepático; constituyen el segundo tumor primario más frecuente de hígado; se caracterizan por su forma de presentación en estadios avanzados. Existen diferentes factores de riesgo importantes para el desarrollo de esta patología; sin embargo, hasta 50% de los casos se reportan sin un factor de riesgo asociado. Para su diagnóstico se requiere del conjunto de clínica, estudios de imagen, biopsia o cepillado, así como de marcadores tumorales. El único tratamiento con intención curativa es la resección quirúrgica.

INTRODUCTION

Cholangiocarcinomas (CCa) are tumors derived from the biliary epithelium, both intrahepatic and extrahepatic.[1] They are the second most frequent primary tumor of the liver.[2,3] They are characterized by their presentation in the advanced stages of the disease. There are different important risk factors associated with the development of this pathology; however, up to 50% of cases are reported without an identifiable risk factor.[3-7] Diagnosis requires a combination of clinical findings, imaging studies, biopsy or brushing, and tumor markers. The only treatment with curative intent is surgical resection of the tumor. We present the case of a 77-year-old man with typical manifestations suggestive of cholangiocarcinoma.

PRESENTATION OF THE CASE

We present the case of a 77-year-old male patient who reports the removal of nasal polyps 40 years ago as the only relevant history.

His condition began approximately two months earlier with abdominal discomfort, which progressively increased until he presented abdominal pain in the right hypochondrium radiating to the back as a hemi belt and weight loss in recent months. An abdominal ultrasound was performed, and the patient was started on analgesics without achieving total remission of the symptoms. The patient reported choluria, acholia of one month of evolution, and generalized pruritus. One week before, he started with jaundice reflected in his skin and sclerae. He came to the Emergency Department of our institution due to worsening of the symptoms described

* General Surgery Service of the University Hospital of Torreón. Torreon, Coahuila, Mexico.

Received: 16/04/2021
Accepted: 15/07/2022

How to cite: Maldonado-Calderón JL, Urbina-Zeglen A, Maldonado-García EL. Cholangiocarcinoma. Case report on the diagnostic approach. Cir Gen. 2022; 44 (1): 34-39. https://dx.doi.org/10.35366/109317

above, accompanied by anorexia and nausea without vomiting.

Physical examination revealed icteric staining of the skin, oral mucosa, and sclerae. Flat abdomen with traces of scratching, soft and depressible, painful on deep palpation in the right hypochondrium, positive Murphy's sign, with a palpable gallbladder under tension, slightly painful on palpation, with no evidence of peritoneal irritation.

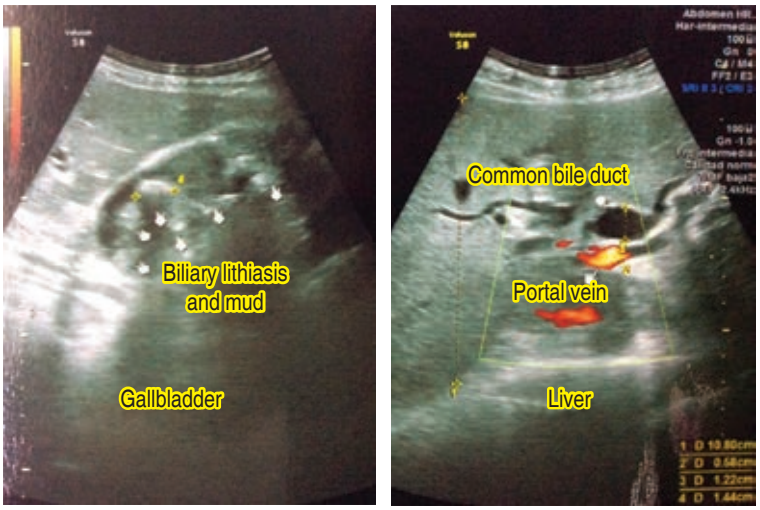

Figure 1: *Ultrasound scan of the liver and biliary tract demonstrating dilatation of the hepatic and biliary ducts. Gallbladder with multiple lithos and biliary sludge with a common bile duct of 12 mm in diameter is shown.*

Laboratory studies: hemoglobin 13.9 g/dl, hematocrit 46.2%, platelets 234 K/µl, leukocytes 8.7 K/µl, glucose 151 mg/dl, creatinine 0.8 mg/dl, sodium 147 mmol/l, potassium 4.1 mmol/l, calcium 9.5 mg/dl, phosphorus 4.2 mg/dl, magnesium 2.4 mg/dl, alkaline phosphatase (ALP) 370 U/l, gamma-glutamyl-transpeptidase (GGT) 369 U/l, total bilirubin (BT) 13.7 mg/dl, direct bilirubin (BD) 11.8 mg/dl, indirect bilirubin (BI) 1.9 mg/dl, TGO 68 U/l, TGP 160 U/l, DHL 205 U/l, albumin 4.1 g/dl, prothrombin time 10.8 seconds, INR 0.87, partial thromboplastin time 29.8 seconds, amylase 204 U/l, lipase 207 U/l.

Previously performed abdominal ultrasound reported *(Figure 1)*: *"dilatation of the hepatic and biliary ducts. Gallbladder with multiple lithos, as well as biliary mud. Common bile duct: 12 mm in diameter (normal up to 4 mm). No obstructive process (litho) can be identified. Conclusion: data compatible with cholelithiasis with associated choledocholithiasis and cholangitis"*.

Due to the obstructive pattern in the liver function tests (LFTs), together with the weight loss, it was necessary to rule out tumor pathology, so a computed tomography (CT) scan was requested, and prophylactic antibiotic treatment with a fluoroquinolone (ciprofloxacin 400 mg every 12 hours for seven days) was started. Hospital admission was also decided.

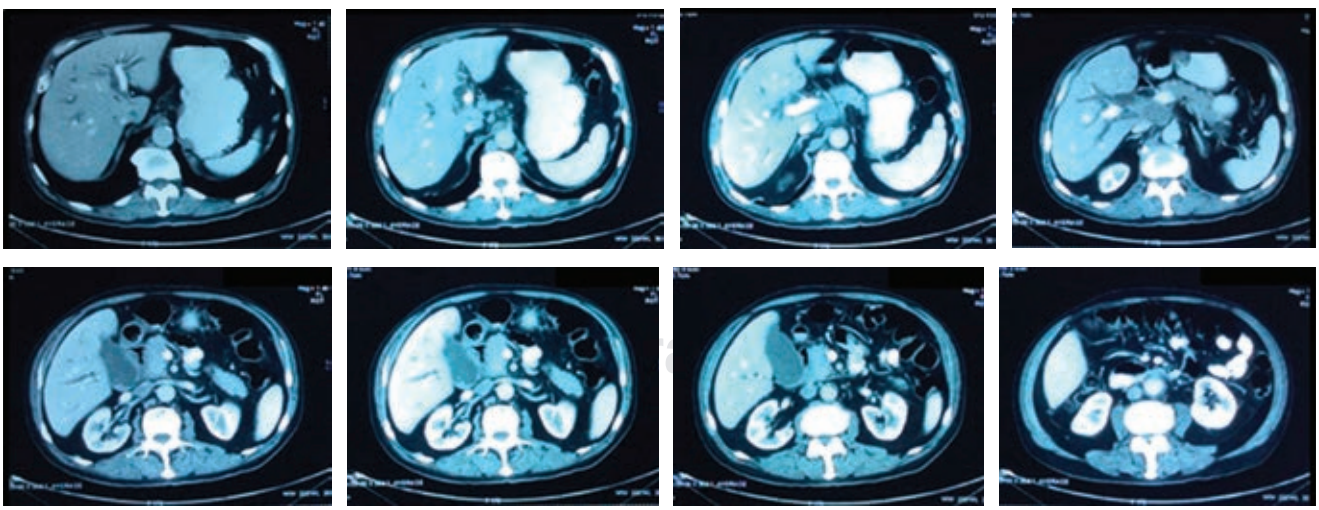

Figure 2: *CT scan showing data suggestive of a neoplastic process at the level of the hepatic hilum, which conditions intrahepatic cholestasis, and may correspond to a Klatskin's tumor without being able to rule out an inflammatory process.*

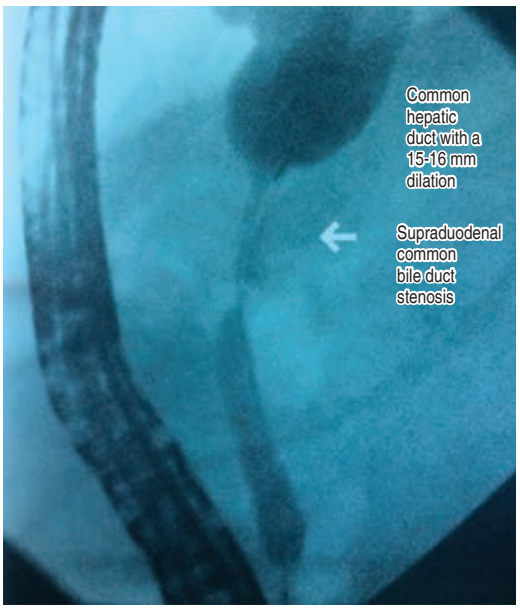

Figure 3: *Cholangiography showing a dilated intrahepatic and extrahepatic biliary tract, with a pencil-point narrowing at the supraduodenal level.*

A CT scan was performed and reported *(Figure 2)*: *"...marked dilatation of the intrahepatic biliary tract, left hepatic of 13 mm, right hepatic of 14 mm, common hepatic duct of 16 mm and cystic duct of 9 mm. There is apparent stenosis of the common hepatic and cystic ducts. No common bile duct is observed; in topography, there is an irregular image of solid appearance, with partially defined contours, with heterogeneous intensification after the administration of contrast medium, which measures 61 × 30 mm and is accompanied by lymphadenopathy at the level of the hepatic hilum. Diagnostic impression: tomographic data suggestive of neoplastic process at the level of the hepatic hilum, which conditions intrahepatic cholestasis, and may correspond to Klatskin's tumor without being able to rule out an inflammatory process"*.

Due to the CT scan findings, it was decided to perform an endoscopic retrograde cholangiopancreatography (ERCP), which reported the following *(Figure 3)*: *"small ampulla of Vater, with ectropion of the ampulla, null biliary drainage. Intrahepatic biliary tract with severe dilatation. Extrahepatic bile ducts with dilatation of the common hepatic duct between 15-16 mm, pencil point narrowing zone at the level of the supraduodenal portion of approximately 2 cm in length, null biliary drainage. Selective sphincterotomy of the biliary tract was performed, obtaining abundant purulent material and cellular detritus*. An endoprosthesis *is placed. Conclusion: intrahepatic bile duct dilatation, Klatskin tumor type IV, cholangitis"*.

Three smears were sent to pathology.

The day after the ERCP was performed, hospital discharge and outpatient management were decided, having remained in the hospital for three days and pending the results of cytology and cytochemistry. Eight days later, he was evaluated in the outpatient clinic with the pathology report: *"inconclusive suspicion of malignancy"*. CA 19-9 marker and liver function tests (LFTs) were requested. Two weeks later, the patient was seen at the outpatient clinic, and the results were reviewed: FA 368 U/l, BT 7.5 mg/dl, BD 5.1 mg/dl, BI 2.4 mg/dl, TGO 62 U/l, TGP 64 U/l, albumin 4 g/dl, and CA 19-9: 1,611 U/ml (normal ranges 0-34).

Since this hospital does not have medical or surgical oncology, the patient moved to another medical facility to receive an oncological evaluation.

DISCUSSION

Cholangiocarcinomas are tumors derived from the epithelium of the bile ducts, which can appear anywhere in the biliary tree.[1] They are classified, anatomically, into intrahepatic (defined as those located proximal to the second-degree bile ducts), perihilar (located in the area between the second-degree bile ducts and the insertion of the cystic duct into the common hepatic, also known as Klatskin's tumors) and distal (those located in the area between the confluence of the cystic to the common hepatic and the ampulla of Vater) *(Figure 4)*.[2]

They represent 3% of all gastrointestinal tumors and are the second most common primary hepatic tumor after hepatocellular

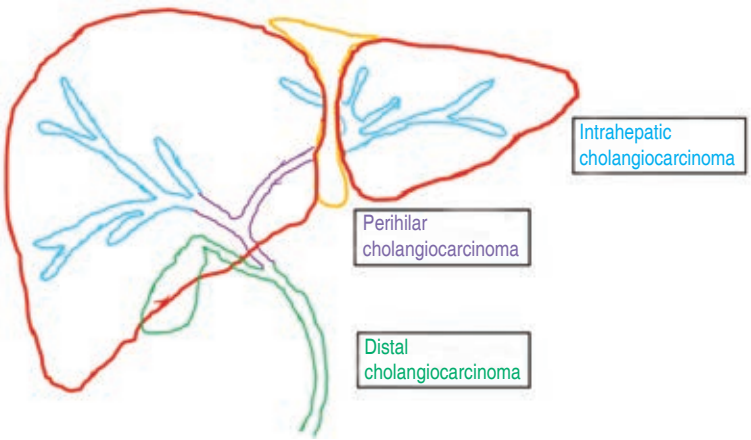

Figure 4: *Anatomical classification of bile duct tumor lesions.*

carcinoma. Intrahepatic cholangiocarcinomas account for 5-10% of all cholangiocarcinomas, hilar cholangiocarcinomas 60-70% and distal cholangiocarcinomas 20-30%.[3]

Several risk factors have been established, such as bile duct cysts, Caroli's disease, cholangitis, primary sclerosing cholangitis, hepatolithiasis, cholelithiasis and choledocholithiasis, parasitic infections (by *Opisthorchis viverrini* and *Clonorchis sinensis*), among others.[3-7]

However, most cholangiocarcinomas occur sporadically, and about 50% of cases are still diagnosed without any identifiable risk factor.[3,7]

In this article, we present the case of a 77-year-old male patient who presented to the Emergency Department of our hospital with vague symptoms that, nevertheless, were indicative of cholangiocarcinoma, namely: weight loss, abdominal pain, fatigue, nausea, pruritus, and a cholestatic pattern in the LFTs.[8] Because early in the disease, the signs and symptoms are unclear and nonspecific, typically patients with cholangiocarcinoma present with cachexia, fatigue, and jaundice, reflecting locally advanced disease or metastasis.[9] Non-painful jaundice is the most common presenting symptom in 90% of patients with hilar cholangiocarcinoma.[10]

Regarding diagnosis, abdominal ultrasound is the initial study of choice since it accurately detects obstruction, extension, and location within the biliary tree. It is also helpful to rule out the presence of etiologies such as choledocholithiasis or Mirizzi's syndrome.[11] The typical findings are dilatation of the intrahepatic biliary tract without dilatation of the gallbladder or common bile duct.[9] However, it continues to be an operator-dependent technique in which several factors influence an excellent result, such as the operator's experience, the equipment's quality, and the tumor's characteristics.[12]

Regarding tomography, its usefulness lies in categorizing and staging the lesions since its diagnostic certainty in the evaluation of the biliary extension of the tumor is 85%. Additionally, tomography has reasonable certainty in evaluating the severity of portal vein and hepatic artery invasion; however, it is unsatisfactory in evaluating lymph node involvement.[13-15]

Cholangioresonance imaging is considered by many to be the study of choice since it can evaluate the extension of the biliary tract, vascular invasion, local lymphadenopathy, intrahepatic dissemination, and distal metastases. Its positive and negative predictive values for detecting the location and degree of bile duct involvement are comparable to ERCP's.[13]

In this case, it was decided not to perform cholangioresonance imaging since an imaging study already demonstrated and suggested the presence of a tumor, as did the CT scan. It was decided to perform an ERCP instead since the latter being therapeutic and allowing drainage of the biliary tract, benefitted the patient better.

Regarding ERCP, it has a sensitivity and certainty of 91 and 69%, respectively.[14] But in addition, its role in evaluating and managing cholangiocarcinoma is essential since it allows obtaining biliary brushings for cytological evaluation and serves as a therapeutic tool since it can dilate and drain the biliary tract by placing *stents*.[14,15]

Of the tumor markers, CA 19-9 and carcinoembryonic antigen (CEA) are the most commonly used markers in diagnosing cholangiocarcinomas. However, CA 19-9 levels show a wide variation in sensitivity

(38-90%) and specificity (50-98%).[12] This marker can also be elevated in patients with cholestasis, liver injury, benign biliary obstruction, and gastric, pancreatic, colorectal, and gynecologic cancers.[16] Obtaining baseline levels of tumor markers helps monitor response to treatment, disease recurrence, and progression.[9]

Brush cytology during ERCP is the most common technique for tissue sampling in patients with suspected malignant biliary strictures. The sensitivity of this technique for diagnosing cholangiocarcinomas is estimated at only 30-60%, in addition to presenting a high proportion of false negatives, which is consistent with what happened in the evaluation of the patient presented in this case. Because of this, a negative brushing should not rule out the diagnosis of perihilar cholangiocarcinoma or delay its treatment.[11,16] However, fluorescence *in situ* hybridization analysis for chromosomal aberrations associated with perihilar cholangiocarcinoma can significantly increase the sensitivity of brushing up to 90%.[9]

The diagnosis of hilar cholangiocarcinoma requires the presence of a malignant-appearing stenosis in the hepatic hilum and at least one of the following features:[11]

1. Biopsy or cytology positive for cancer cells.
2. Fluorescence polysomy due to in *situ* hybridization (FISH).
3. Mass-forming lesion in the stenosis seen by tomography or cholangioresonance.
4. CA 19-9 elevation above 100 U/ml

The diagnosis, in most cases, must be inferred by the sum and integration of clinical and imaging studies. Differential diagnoses include choledocholithiasis, benign focal stenosis of the hepatic ducts, Mirizzi syndrome, gallbladder cancer, primary sclerosing cholangitis, autoimmune cholangitis, metastatic disease to the bile ducts or hepatoduodenal lymph nodes (e.g., colorectal cancer).[11]

Surgical resection is the best available treatment for perihilar cholangiocarcinoma. The type of resection depends on the tumor's location and the anatomy of the bile duct at the confluence of the hepatic ducts;[17] However, this information is beyond the scope of this article.

An accurate diagnostic approach was performed in time and form in this case. Although a satisfactory sample was not obtained by brushing for cytology, this agrees with the literature reviewed. Despite this, the diagnosis of cholangiocarcinoma could be established when the patient presented a malignant-appearing stenosis in the hepatic hilum and CA 19-9 levels above 100 U/ml.

The "urgency" was resolved by draining the biliary tract by placing a stent through ERCP to reduce the risk of cholangitis associated with the stasis produced by the tumor occlusion.

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Ethical considerations and responsibility: the authors declare that they followed the protocols of their work center on the publication of patient data, safeguarding their right to privacy through the confidentiality of their data.
Funding: no financial support was received for this work.
Disclosure: the authors declare no conflict of interest in carrying out the work.

Correspondence:
José Luis Maldonado-Calderón
E-mail: jose.jlmc92@gmail.com