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REVIEW ARTICLE

## Challenges in Cholangiocarcinoma, Misdiagnosis with Hydatid Cyst Rupture: A Review

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**ABSTRACT:**

Cholangiocarcinoma, an adenocarcinoma arising from the epithelium of biliary ducts, is considered the second most common hepatic malignancy after hepatocellular carcinoma with increasing incidence over the past 3 decades. Many imaging modalities with correlation to clinical presentation are used for the diagnosis and staging of cholangiocarcinoma. However, the diagnosis of cholangiocarcinoma is still challenging due to the presence of some benign and malignant conditions that mimic the clinical presentation and radiological findings of this disease. One of those mimics is the condition of intrabiliary hydatid cyst rupture which can cause biliary obstructive symptoms over weeks with radiological findings that may be indistinguishable from those of cholangiocarcinoma and specifically klatskin tumor when found at the bifurcation of the common hepatic duct. In such a confusing situation, the correct preoperative diagnosis and potential treatment of the disease could both be made possible using Endoscopic Retrograde Cholangiopancreatography avoiding unrequired surgical interventions.

**Keywords:** Cholangiocarcinoma, Hydatid disease, Hydatid cyst rupture

## Introduction:

Cholangiocarcinoma (CCA), a diverse disease entity, is defined as an adenocarcinoma arising from the epithelium of biliary ducts, either intrahepatic or extrahepatic.<sup>1</sup> Many classifications have been developed in order to cover all the diversity of this tumor, either by its location, macroscopic and microscopic features and cell of origin.<sup>2</sup> Anatomically, the second order bile ducts separate intrahepatic (IH-CCA) and extrahepatic (EH-CCA) tumors, and by the separation of cystic duct insertion, the EH-CCA is subdivided into hilar (Klatskin) and distal.<sup>2,3</sup>

Cholangiocarcinoma is the second most common hepatic malignancy after hepatocellular carcinoma and represents 3% of all gastrointestinal malignancies.<sup>4</sup> The overall incidence of this fatal tumor has increased over the past 3 decades with persistent low 5 years survival percentage among patients diagnosed with it.<sup>5,6,7</sup>

The clinical presentation of CCA is usually non-specific, with symptoms of abdominal pain, nausea, weight loss and night sweats in some cases. Jaundice is a common symptom, especially in EH-CCA.<sup>8</sup> Some cases are asymptomatic and CCA is found incidentally by imaging<sup>[9]</sup>. Certain imaging modalities are used in correlation with the clinical presentation and labs tests for the diagnosis and staging of CCA such as Ultrasound (US), contrast enhanced ultrasound (CEUS), computed tomography (CT), Magnetic resonance imaging (MRI) and 18F-fluoro-2-deoxy-D-glucose positron emission tomography (18FDG PET), which show some typical and atypical features of CCA, and some ancillary finding according to the used imaging technique.<sup>8,10</sup> However some benign or malignant conditions could represent a challenge in the diagnosis of CCA by simulating the characteristic findings of it on imaging, those mimickers could be a focal confluent fibrosis, sclerosing hemangioma, organizing hepatic abscess, primary liver lymphoma, hemangioendothelioma, atypical forms of hepatocellular carcinoma (HCC) and certain forms of hydatid cyst.<sup>10</sup>

An additional condition that could mimic the imaging findings of CCA is intrabiliary hydatid cyst rupture that represents a specific entity not uncommon in occurrence.<sup>11</sup>

In this review, we will discuss the challenge that hydatid cyst and its rupture put on the diagnostic modalities of cholangiocarcinoma and how we could prevent such misdiagnosis.

## Cholangiocarcinoma diagnostic modalities and features:

All bile duct cancers, including intrahepatic, perihilar, and distal extrahepatic, are referred to as cholangiocarcinomas.<sup>12</sup> Usually patients with CCA presents late in an advanced stage of the disease with non-specific symptoms such as fatigue and weight loss, and this is especially true when one duct is blocked by more proximal intrahepatic and perihilar tumors. In case of perihilar or extrahepatic tumor, patients present commonly with biliary obstruction symptoms like jaundice, pale stools and dark urine.<sup>13</sup>

In order to diagnose Cholangiocarcinoma, several diagnostic tools come into play notably carbohydrate antigen 19-9 (CA 19-9) and carcinoembryonic antigen (CEA) which are the key blood biomarkers or tumors markers. On one hand as a diagnostic tool, its weakness lies in its limited sensitivity for detecting early-stage CCA and its possibility of being elevated by benign conditions such as peptic ulcer disease, gastritis, diverticulitis, and liver disease, in addition to various primary gastrointestinal cancers.<sup>14,15</sup> Therefore, It is possible to use CEA to evaluate the effectiveness of a treatment as a follow-up and to detect disease recurrence if CA19-9 levels were not elevated at the time of presentation.<sup>14</sup> On the other hand, Alpha-fetoprotein (AFP) is highly specific for identifying hepatocellular carcinoma so it can be helpful in differentiating intrahepatic CCA from hepatocellular carcinoma since intrahepatic CCA can present as a liver mass.<sup>14,15,16</sup>

Several imaging modalities can be used to diagnose cholangiocarcinoma. The first step in diagnosing biliary obstruction or suspected liver disease is usually to perform an ultrasound test. It has a sensitivity of up to 87-96 % in detecting ductal masses or mural thickening in hilar and extrahepatic cholangiocarcinoma. However, its specificity is unknown.<sup>17</sup> The ultrasound findings of cholangiocarcinoma includes the following: bilateral intrahepatic duct nonunion and segmental dilatation in Klatskin tumor ; polypoid masses inside the biliary tract in papillary tumors; isolated, smooth masses with mural thickening in nodular CCAs; mass with irregular margins in intrahepatic CCA.<sup>17,18</sup> However transabdominal US has the limitation that duodenal air may mask the distal common bile duct which makes biliary dilation an indicator of distal biliary obstruction.<sup>18</sup>

Multidetector-row CT (MDCT) scan can be used as alternative to ultrasound due to its wide availability. It can demonstrate a tumor mass with

bile duct dilation, wall thickening of bile duct, or intraductal tissue in exophytic, infiltrative, and polypoid cholangiocarcinoma, respectively.<sup>17</sup>

Magnetic resonance imaging Cholangiopancreatography (MRCP) is widely regarded as the preferred modality for the detection of cholangiocarcinoma due to its capacity to detect the parenchymal, biliary, and vascular extension, as well as its high contrast resolution and multiplanar capabilities.<sup>17</sup>

Another imaging modality to be mentioned is PET scan. In the study by Anderson et al., the sensitivity of PET was 85% in nodular cholangiocarcinoma, but only 18% in infiltrative cholangiocarcinomas.<sup>17,19</sup> Since most of hilar and extrahepatic cholangiocarcinoma are infiltrative in nature, these tumors cannot be easily detected with PET. However, the specificity of PET has been reported to be of 80%–100%.<sup>17</sup> The specificity of PET is limited because infectious and inflammatory lesions may show a high FDG uptake.<sup>20</sup> In order to differentiate between cholangiocarcinoma and inflammatory process, it is recommended to use delayed imaging 2 hours after injection of the tracer. In general, the use of PET scan didn't provide better accuracy than CT scan, but it can be helpful in detected distal metastasis.<sup>17</sup>

Because of its invasiveness, ERCP is usually replaced by MRCP and other imaging modalities in suspected patients.<sup>17,21</sup> However tissue samples can be obtained during ERCP using a variety of techniques, such as brush cytology, fine-needle aspiration, and transpapillary biopsy. These sample techniques have a poor sensitivity of 46%–73% but a high specificity of 100% for identifying malignant tumors. Combining the sample techniques can boost sensitivity, but doing so comes with longer procedure times and higher skill requirements.<sup>17</sup> Thus, a significant number of patients remain non diagnostic after obtaining tissue sampling via bile duct brushing during ERCP with low cytology and FISH sensitivity. Therefore, endoscopic ultrasound (EUS) with fine needle aspiration (FNA) can improve the diagnosis of extrahepatic cholangiocarcinoma as the cause of extrahepatic biliary strictures as it has a sensitivity of 66% and specificity of 100% for detecting cholangiocarcinoma.<sup>18,22</sup> Intraductal ultrasound (IDUS) can distinguish between malignant and benign strictures. Additionally, IDUS can be used for the early detection of tumors and can enhance the accuracy of the local staging of CCA.<sup>18,23</sup> It cannot be used for FNA, but it is more effective than EUS at assessing the proximal biliary system and surrounding structures. On the other

hand, it has a limited ability of assessing distal structures due to its limited penetration.<sup>18</sup>

Cholangioscopy can be used to evaluate ambiguous findings during fluoroscopy in ERCP and to assess the extent of CCA before surgery and for the presence of biliary stones. In addition, it allows direct visualization of biliary tissue which allows for targeted biopsy of bile duct lesion. Cholangioscopy with biopsy has an accuracy of 85 % in diagnosing intermediate strictures compared with cytology (34%) and ERCP-guided biopsy (54%).<sup>18</sup>

### Hydatid cyst diagnostic features:

Echinococcosis or Hydatid disease, is a parasitic disease that occur in humans by the ingestion of dog's taenia egg, *Echinococcus granulosus* or *Echinococcus alveolaris*.<sup>24</sup> The liver is the most commonly affected site, followed by lungs, but peritoneum, kidneys, muscles, brain, and heart, although rare, have been also described.<sup>25</sup> The diagnosis of Hydatid liver disease may occur incidentally during a work-up prompted by pain in the area or a sensation of heaviness, or after the occurrence of complications.<sup>26</sup> Complications include compression of surrounding structures (bile ducts, duodenum) because of increase in the cyst's volume, in addition to rupture of the cyst in the bile ducts, and superinfection with bacteria.<sup>26</sup>

Ultrasound is usually the first modality to use in front of suspected intraabdominal hydatid cyst.<sup>27,28</sup>

The basic sonographic features of hydatid cyst are almost the same whenever the cyst is localized, with some variation according to the stage of the disease. In hepatic hydatidosis, characteristics can vary from homogenous anechoic space, or hydatid sand with multiple echogenic foci in the early stages (honeycomb pattern), to multivesicular cysts see as well-defined fluid collections with multiple septa, during the process, and it ends with a calcification of the cystic wall.<sup>29</sup>

Computed tomography and MRI are more helpful in case of complications such as abscess or rupture, or in case of recurrence of the disease and when planning for surgery with superiority of MRI in better visualization of liquid area within the matrix.<sup>28</sup>

### Hydatid cyst rupture:

- PATHOPHYSIOLOGY AND CLINICAL MANIFESTATIONS: Intrabiliary rupture of hepatic hydatid cyst is one of the most common and life-threatening complications of the disease, it is reported in about 6.1 to 7% of the cases.<sup>30</sup>

Rupture commonly occurs when the intracystic pressure rises up to 80 cm H<sub>2</sub>O. The high pressure inside the cysts causes leakage into small and perforation into large bile ducts. About 55 to 60 % of rupture occur in the right duct, 25 to 30% in the left duct, and rarely in the confluence or gallbladder.<sup>31</sup>

Cyst rupture, according to Lewall and McCorkell, is classified into 3 types: contained, communicating and direct. Contained rupture happens when the host-derived pericyst keeps the cyst contents contained and only the parasitic endocyst bursts. The rupture is communicating when the cyst's contents leak out through biliary or bronchial radicles that are embedded in the pericyst. When both the endocyst and the pericyst tear, a direct rupture takes place, causing the cyst's contents to leak directly into the peritoneal or pleural cavities or other structures.<sup>32</sup>

Intrabiliary rupture of hydatid cyst was classified into two categories by John R. Hankins in 1963: frank rupture and occult rupture. Frank rupture was defined as the overt passage of hydatid material into the biliary tree, whereas occult rupture occurs when the hydatid cyst itself becomes infected with bacteria (suppurating hydatids) through very small cysto-biliary communications.<sup>11</sup>

The clinical presentation of intrabiliary rupture of the hydatid cyst depends mostly on the size of the cystobiliary communication, patient could be asymptomatic, or having biliary obstructive symptoms, such as right upper quadrant pain and jaundice and in severe cases he could have cholangitis and septicemia, moreover the incidence of complications is increased in cases with large size of cystobiliary communication.<sup>33,34</sup>

#### - DIAGNOSTIC MODALITIES AND FEATURES:

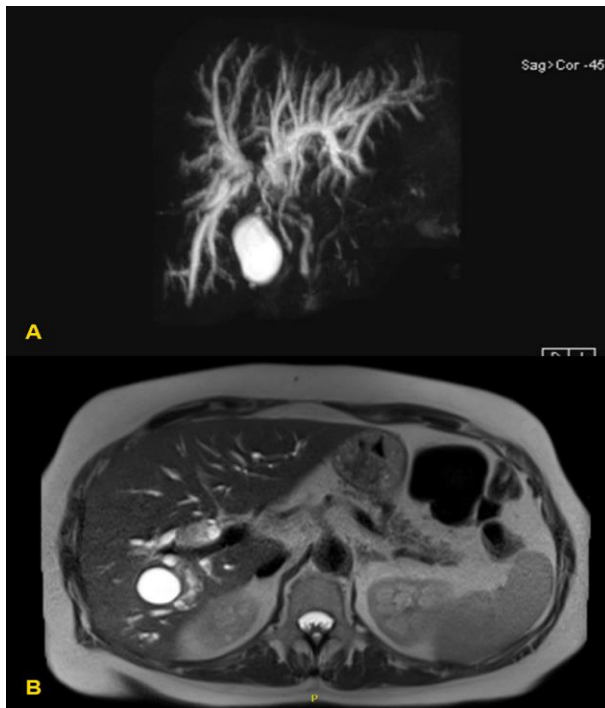
In clinically suspected patients, laboratory results are frequently nonspecific, which makes radiological imaging use important to make the diagnosis. Patients with rupture into the bile ducts may have leukocytosis and elevated levels of alkaline phosphatase, direct bilirubin, and liver enzymes. The combination of CT scan with ultrasound showed near 100% accuracy in cases with uncomplicated intrabiliary rupture.<sup>31</sup> Ultrasonography can show irregular cystic lesions, loss of wall integrity and internal distention in the liver in addition to echogenic material within an enlarged main biliary canal with no posterior

acoustic shadowing.<sup>31</sup> Abdominal CT can detect the location and morphological characteristics of a cyst along with less dense intraluminal material in a dilated bile duct.<sup>35</sup> Cyst wall discontinuity, which is a direct sign of rupture, is present in only 75% of cases on abdominal CT.<sup>31</sup> Magnetic resonance cholangiopancreatography(MRCP) can facilitate the diagnosis of hydatid cyst complications as it can visualize daughter cysts, separation of the membranes, a dilated biliary tree, and hydatid cyst material in the biliary system. Endoscopic Retrograde Cholangiopancreatography (ERCP) is the gold standard in confirming rupture into the biliary tract, either by seeing the signs of radiolucent filling defect of daughter cyst in the dilated biliary ducts or a swollen ampulla of Vater with hydatid material protruding out.<sup>31</sup> Moreover, this condition can be distinguished from other causes of obstructive jaundice on ERCP by the presence of irregular leaf-like material that changes shape with variation in pressure.<sup>36</sup> However, small cystobiliary communication cannot always be ruled out by ERCP and it must be sought out during surgery.<sup>31</sup>

#### - MISDIAGNOSIS WITH CHOLANGIOCARCINOMA:

A typical hydatid cyst is usually easy to diagnose, especially when characteristic imaging features on MRI or CT scan are present.<sup>37</sup>

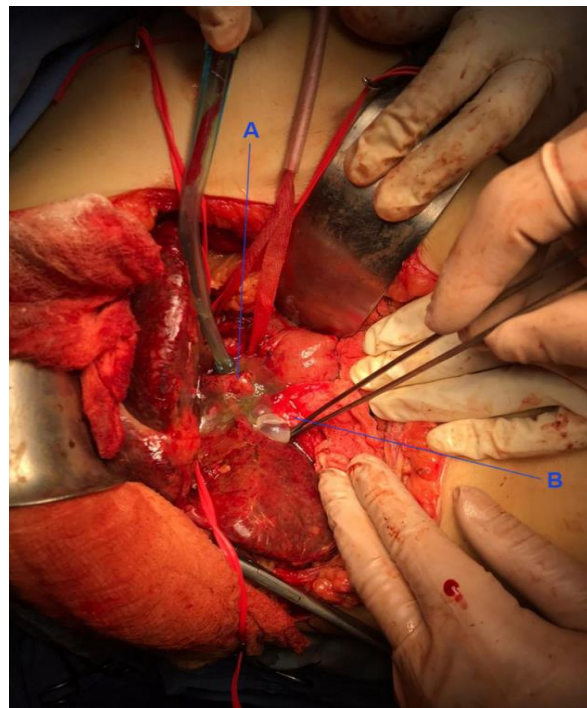
When frank rupture occurs, it leaves hydatid material in the biliary tree, and that is interpreted clinically by biliary obstruction symptoms over weeks.<sup>11-38</sup> Radiologically, those hydatid material can mimic a CCA and more specifically a klatskin tumor when found in the bifurcation of the common hepatic duct, and that is due to the lack sometimes of specific radiological signs of hydatid material while using MRCP or CT scan such as cyst's intense rim, detachment of the membrane and daughter cysts (Figure 1).<sup>11</sup> The combination of non-specific clinical and radiological findings in addition to the lack of history of hydatid disease in the patient lead to a misdiagnosis of intrabiliary hydatid cyst rupture as a CCA that is discovered during the surgery while trying to remove it (figure 2).<sup>11</sup> Thus, this represents a challenging differential diagnosis that physicians should take into consideration during the investigatory process of CCA and should encourage the use of further diagnostic methods like ERCP which would be helpful in establishing an accurate diagnosis before more invasive investigations, and eventually could provide treatment of the condition.



**Figure 1.** Hydatid cyst material in the hepatic duct mimicking cholangiocarcinoma in a 64-year-old lady.<sup>11</sup> MRI of the abdomen showing a  $30 \times 17.5$  mm intraluminal lesion in the right hepatic duct extending to the hepatic bifurcation (A and B), suggestive of a type 3A klatskin tumor. A simple 3 cm biliary cyst in segment V close to the right hepatic duct is also noted (B).

### Conclusion:

Despite the variety of modalities used for the diagnosis of cholangiocarcinoma, differentiating it from some conditions is still challenging during the investigatory process. Intrahepatic hydatid cyst rupture could represent a radiological mimicker of cholangiocarcinoma that should be considered as a differential diagnosis even in the absence of hydatid disease history and considering the use of a helpful diagnostic modality such as ERCP in this



**Figure 2.** Multiple daughter hydatid cysts, cystic fragments, and whitish fluid ejected from the proximal part of the hepatic duct ruling out the presence of CCA.<sup>11</sup> The proximal (A) and distal (B) parts of the bile duct are seen.

situation, would prevent any misinterpretation, and possibly treating the condition before any invasive surgical procedure.

### Conflict of interest:

The authors have no conflicts of interest to declare.

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All authors contributed equally to this work.

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