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## Case Report

# Multifocal pancreatobiliary malignancies: A diagnostic and therapeutic challenge

Ruhaid Khurram<sup>a,\*</sup>, Rahul Khamar<sup>a</sup>, Aatif Amir Husain<sup>b</sup>, Zohaib Khawaja<sup>c</sup>, Raees Lunat<sup>a</sup>

<sup>a</sup> Royal Free Hospital, Royal Free London NHS Foundation Trust, Pond St, Hampstead NW3 2QG, London, UK

<sup>b</sup> St Mary's Hospital, Imperial College Healthcare NHS Trust, Praed St, Paddington W2 1NY, London, UK

<sup>c</sup> Salford Royal Hospital, Salford Royal NHS Foundation Trust, Stott Lane M6 8HD, Salford, UK

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## ABSTRACT

The synchronous presentation of multifocal pancreatobiliary tumors is a rare occurrence and can prove to be a significant diagnostic and therapeutic challenge. We describe the case of a 70-year-old female who presented with a 2-week history of jaundice, reduced appetite, and mild epigastric discomfort of insidious onset. Radiological evaluation with computed tomography and magnetic resonance imaging demonstrated features consistent with a hilar cholangiocarcinoma, also known as a Klatskin tumor, involving both the cystic duct and gallbladder neck. In addition to this, a pancreatic neoplasm with associated splenic vein occlusion and metastatic deposits in the liver and lung were identified. The patient was managed with percutaneous transhepatic external biliary drainage and stenting by interventional radiology. Cytology results from the brushings obtained from the aforementioned procedure were nondiagnostic. Core biopsies were performed of the pancreatic lesion; the histopathological results of which were in keeping with pancreatic ductal adenocarcinoma. The patient was scheduled for chemotherapy however unfortunately deteriorated clinically prior to commencement. This case highlights the diagnostic and management challenges of synchronous pancreatobiliary malignancies.

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## Introduction

Cholangiocarcinoma (CCs) constitute a rare spectrum of malignancies arising from the biliary epithelium. They are best classified as intrahepatic, hilar or distal tumors [1]. Hilar CCs originate from the hepatic duct confluence and constitute 60%-80% of all CCs [2]. Pancreatic ductal adeno-

carcinoma (PDACs) are 1 of the most aggressive solid organ malignancies and are the fourth leading cause of cancer related deaths in the modern world [3]. Their poor prognosis is related to vague, nonspecific symptoms as well as aggressive metastatic potential, with approximately 50% of cases presenting with established metastatic disease [4]. Both of these cancers carry a poor prognosis. Synchronous pancreatobiliary cancers are rarely reported in literature and can pose significant diagnostic challenges to oncologists and the cancer multidisciplinary team. This is further complicated by the his-

\* Corresponding author.

E-mail address: [ruhaidk@gmail.com](mailto:ruhaidk@gmail.com) (R. Khurram).

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tological and anatomical similarities of biliary and pancreatic malignancies which hinders the identification and distinguishability of the clonal origin of these tumors [5]. Understanding the origin of synchronous tumors is essential as it has an impact on surgical and oncological treatment and follow-up strategies. We present the case of a 70-year-old patient who was diagnosed with synchronous hilar CC and PDAC with lung and liver metastases and discuss the challenges in the diagnosis and management.

## Case presentation

A 70-year-old female presented to the emergency department with nonspecific abdominal discomfort for 2 weeks situated in the epigastric region. She described signs of obstructive jaundice for example yellow sclera, dark urine, pale stools, and had significantly reduced appetite. She denied any weight loss. The patient had no past medical history or medication history however, had a family history of gastrointestinal malignancy. Her sister was diagnosed with gastric cancer and mother suffered from colorectal cancer. She is a nonsmoker, does not consume alcohol, and works as a paralegal.

On examination: she was visibly jaundiced and a palpable epigastric mass was noted. Her abdomen was otherwise soft, nontender and there were no clinical features suggestive of peritonism. There were no peripheral stigmata of chronic liver disease. Her cardiovascular, respiratory, and neurological systems were unremarkable.

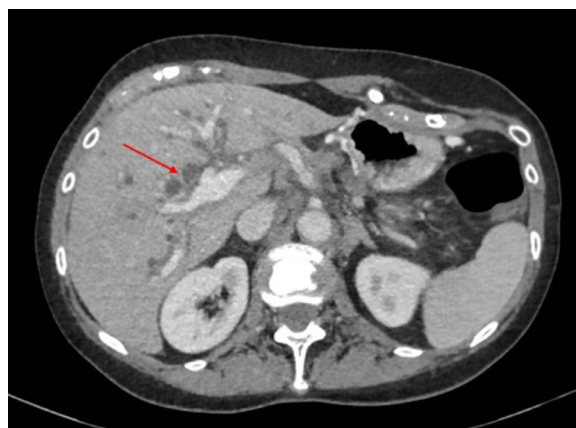
The biochemical investigations depicted obstructive cholestasis with a raised CA-19.9 level. The results were as follows: hemoglobin 148 g/L (110-150), white cell count  $7.0 \times 10^9/L$  (3.5-11), platelets  $258 \times 10^9/L$  (140-400), Na 138 mmol/L (135-145), K 4.0 mmol/L (3.5-5.1), urea 3.5 mmol/L (2.5-7.1), creatinine 71  $\mu\text{mol/L}$  (74-107), bilirubin 84  $\mu\text{mol/L}$  (1.7-20.5), alanine aminotransferase 793 units/L (<50), aspartate aminotransferase 523 units/L (<50), alkaline phosphatase 968 units/L (50-150), albumin 31 g/L (35-50), C-reactive protein 5 mg/L (0-5), INR 1.1, alpha-fetoprotein 7.9k units/L (0-6), CA-19.9 1818 units/ml (0-34), carcinoembryonic antigen 1.8 (0-4) and CA125 67 units/ml (0-34).

A computed tomography thorax, abdomen, and pelvis scan with contrast was performed on admission in the portal venous phase and demonstrated a spectrum of pathologies. There was evidence of gallbladder wall thickening, mural enhancement, and hypodensity of the walls (Fig. 1). Furthermore, the gallbladder neck and cystic duct demonstrated thickening and contrast enhancement. There was presence of significant intrahepatic biliary duct dilatation (Fig. 2). These findings were indicative of either a primary hilar CC or gallbladder carcinoma with local invasion. Hypodense, heterogenous foci were noted in the pancreatic distal body and tail with surrounding peripancreatic fat stranding suspicious for a primary pancreatic tumor, associated with local tumor invasion causing splenic vein thrombosis (Fig. 3). Hepatic and lung metastatic deposits were also demonstrated (Fig. 4).

The patient subsequently underwent magnetic resonance cholangiopancreatography (MRCP) which identified a



**Fig. 1 – Coronal computed tomography (CT) demonstrating an abnormal gallbladder appearance, associated with thick hypodense walls, intramural enhancement and thickening of the gallbladder neck, and cystic duct (red arrows). There is an enhancing lesion causing bilateral hepatic duct dilatation (green arrow). These findings were suggestive of either a primary hilar cholangiocarcinoma or gallbladder carcinoma with local invasion.**



**Fig. 2 – Axial CT in portal venous phase showing evidence of significant intrahepatic biliary duct dilatation (red arrow).**

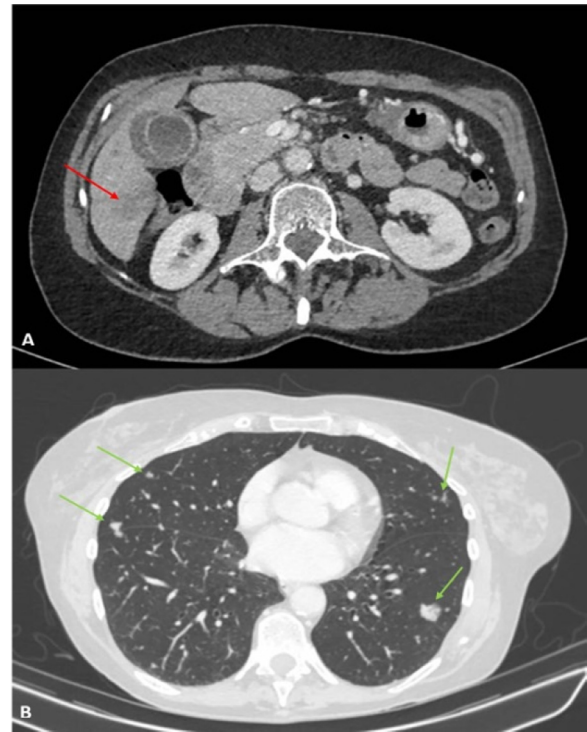
16mmx15mm mass at the bifurcation of the left and right intrahepatic bile ducts. There was also contiguous proximal, abnormally enhancing tissue within the cystic duct and gallbladder neck, causing moderate gallbladder distension. These features were consistent with a hilar CC involving the cystic duct and gallbladder neck (Fig. 5). A mixed signal, 5.2cm x 2.6cm predominantly cystic mass affecting the body and tail of the pancreas was also visible, causing secondary splenic vein occlusion. This mass was independent from the liver hilar pathology, hence raising the suspicion of a synchronous pancreatic malignancy (Fig. 6).



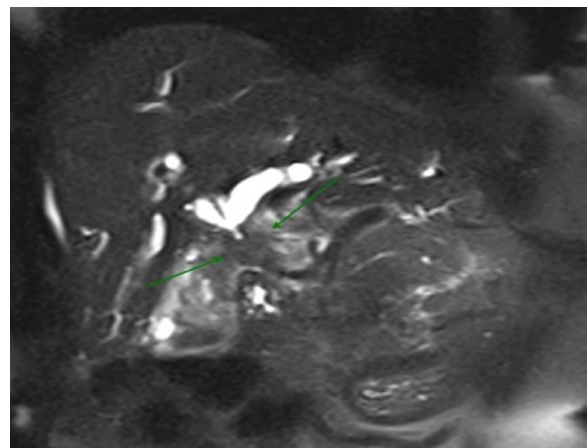
**Fig. 3 – (A) Axial CT slice showing multiple hypodense heterogeneous foci within the distal pancreas and/or tail with surrounding peripancreatic fat stranding, suspicious for a primary pancreatic neoplasm (red arrow). (B) Direct local invasion of the pancreatic tumor into the splenic vein causing a tumor thrombus (green arrow).**

The patient was initiated on subcutaneous low molecular weight heparin for the treatment of splenic vein thrombosis. Following extensive radiological evaluation, the patient was discussed in a hepato-pancreato-biliary multidisciplinary team meeting. Since the patient was unsuitable for endoscopic retrograde cholangiopancreatography (ERCP) with brushings and/or biopsy, percutaneous transhepatic external biliary drainage, and subsequent internalization of biliary stents were decided to manage the patient's symptoms of obstructive jaundice (Fig. 7). Unfortunately, cytology obtained from brushings of the aforementioned procedure were non-diagnostic. Ultrasound guided core biopsies of the pancreatic lesion were performed for histopathological and immunohistochemical analysis. Histopathological evaluation of the core biopsy specimens showed features of adenocarcinoma. The immunoprofile of this tumor favored the diagnosis of a primary PDAC.

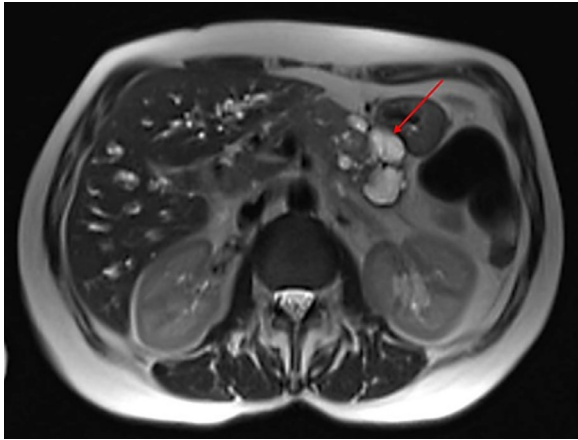
The patient was consented for chemotherapy with Gemcitabine and Abraxane (2-weekly dosing). Unfortunately, she had rapid clinical deterioration causing her to be unfit for treatment. A decision was made to provide supportive, palliative care in the community in her best interests.



**Fig. 4 – (A) Axial CT slice demonstrating a 2 cm metastatic deposit in segment VI of the liver (red arrow) (B) Multiple pulmonary metastatic deposits noted on lung windowing of CT thorax (green arrows).**



**Fig. 5 – Coronal T2 weighted slice on magnetic resonance cholangiopancreatography demonstrating with arrows, a 16 mm x 15 mm mass at the bifurcation of the left and right intrahepatic ducts with enhancing cystic duct and gallbladder neck. Radiologically, this was consistent with a hilar cholangiocarcinoma (green arrow).**



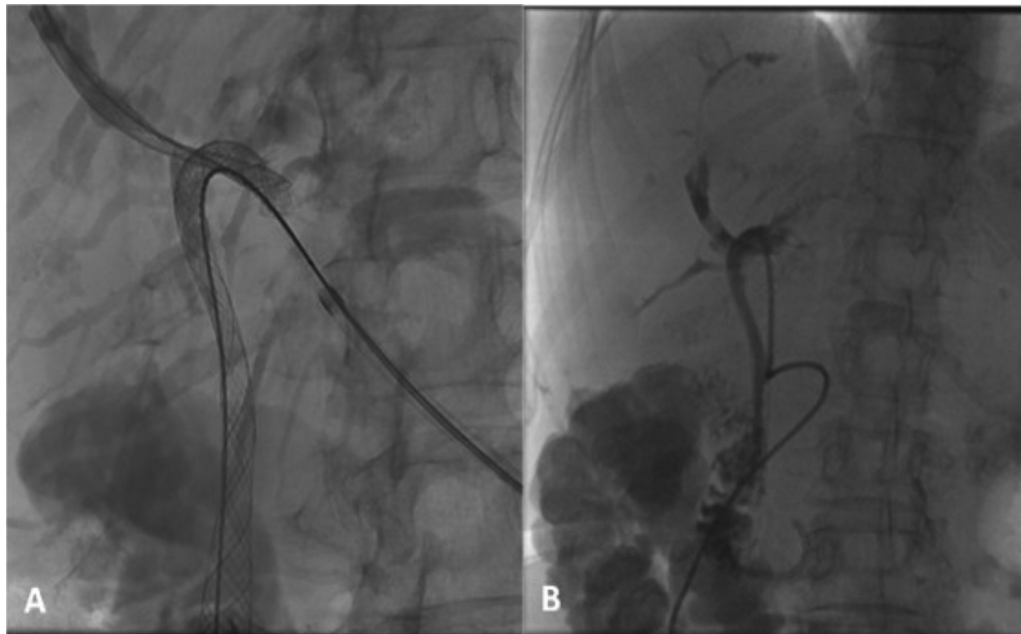
**Fig. 6 – A 5.2 cm x 2.6 cm cystic mass affecting the body and tail of the pancreas visualized on this axial T2 weighted image, causing secondary splenic vein occlusion (red arrow). This mass was discontinuous from the liver hilar pathology, thus raising the suspicion of co-existent pancreatic neoplasm.**

## Discussion

Synchronous tumors of the biliary system and pancreas are rare, with fewer than ten cases reported in the literature

[6–12]. Notably, the majority of these cases were geographically confined to Asia and involved the head of the pancreas. Abnormalities at the pancreato-biliary junction are postulated to be a significant contributor to the carcinogenesis of both metachronous and synchronous pancreatobiliary tumors, likely mediated through chronic biliary and ductal inflammation secondary to a pancreatic secretion reflux [13]. The finding of CC with pancreatic metastasis is even more uncommon than 2 distinct carcinogenic processes and gives rise to a significant diagnostic dilemma. In such cases where the histological and immunophenotypical similarities between CC and pancreatic carcinoma render it difficult to make a clinical distinction between the 2 pathologies, next generation sequencing can play an important role in the determination of aetiology and subsequent therapeutic options [14].

The malignant forms of CC and PDAC arise from their pre-malignant counterparts; namely, biliary intraepithelial neoplasia and pancreatic intraepithelial neoplasia [5]. The molecular and phenotypical similarity between extrahepatic CCs and PDAC is likely to be related to their shared embryological origin, with both the proximal pancreatic and distal biliary ducts arising from a common endodermal structure: the ventral foregut [15]. The 2 most common mutations implicated in the carcinogenesis of PDAC (p53 and KRAS) have been found to play a similar role in the progression of biliary intraepithelial neoplasias to CCs [16,17]. Unsurprisingly, both share a similar growth pattern, are poorly responsive to conventional chemotherapy and are seldom associated with a good prognosis [5,15].



**Fig. 7 – (A) Percutaneous transhepatic cholangiogram guided external biliary drainage with deployment of biliary stents. A catheter wire was initially traversed across the hilar occlusion into the duodenum. A second catheter wire was traversed from the left to the right hepatic duct. A 10 mm x 9 cm stent was deployed from the left duct across the ampulla and dilated. A cholangiogram demonstrated contrast flow through the stent. An internal external drain was left in situ through the left-sided hepatic duct stent and left on free drainage. (B) Three days following the primary procedure, the external drains were removed, following a repeat cholangiogram demonstrating excellent patency of the biliary tree and contrast flowing freely into the duodenum.**

Even with cross-sectional imaging, discerning between extrahepatic ductal CCs and PDAC can pose a significant challenge, particularly if detected in later tumor stages when there is malignant invasion of local structures. Given that both neoplasms arise from ductal epithelia and grow longitudinally, mass formation occurs late which limits the use of imaging in screening [15]. The CASPS3 study which evaluated the role of computed tomography, MRI, MRCP and endoscopic ultrasound (EUS) concluded that MRCP and endoscopic ultrasound (EUS) enabled best visualization of small pancreatic lesions [18]. This is likely due to ductal obstruction occurring relatively early in the carcinogenic processes, prior to a tumor becoming radiologically identifiable. Furthermore, EUS enables samples to be obtained via fine-needle aspiration (FNA) or brush cytology, facilitating a histological and cytological diagnosis.

Despite the similarities between both of these malignancies, they are distinct entities and oncological treatment paradigms cannot be extended from 1 to another. Large multi-centered studies have shown that whilst CC is associated with a relatively more favorable prognosis, adjuvant therapy regimes are only associated with improved survival in patients with PDAC [19]. A recent adjuvant chemotherapy approach to treat PDAC that has gained traction involves a combination of gemcitabine, an agent already proven to increase survival alone [20], with a protein-bound form of paclitaxel: nab-paclitaxel. In a phase III study, this combination (compared against gemcitabine monotherapy) resulted in a higher median overall survival [21]. Whilst there is insufficient data from clinical trials regarding the successful use of adjuvant chemotherapy for CC, a single-institution case series reported that nab-paclitaxel may offer a therapeutic avenue [22].

There remains only 1 curative option for both malignancies: radical surgical resection with microscopic tumor-free resection margins [23]. Thus, the procedure of choice for cases such as hilar CCs, as described here, is an extended hemi-hepatectomy with hilar en bloc resection [15]. The procedure has been found to improve prognosis, offering a 29% greater 5-year survival rate than curative conventional major hepatectomy for hilar CCs [24].

## Consent statement

The authors of this manuscript have obtained written, informed consent from the patient to write up the case report and for the use of images pertinent to the case. We have ensured anonymity of all clinical and graphical data used.

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