

A Case Report of Intrahepatic Cholangiocarcinoma in a Young Male

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Abstract

Background: Cholangiocarcinoma (CCA) is a malignant epithelial cancer of the biliary tract characterized by late diagnosis and poor outcomes. We report the case of a young healthy caucasian male patient who presented with non-specific symptoms, normal blood tests and atypical radiological findings of CCA.

Case presentation: A 30-years-old Caucasian man, employed as welder in a yacht components factory, without known risk factor for CCA, was admitted because of acute upper abdominal pain, nausea and vomiting. Patient's medical history was significant only for heroin abuse treated with methadone maintenance therapy. Imaging findings on Computed Tomography and Magnetic Resonance of the abdomen showed multiple intrahepatic lesions of undetermined nature. The biopsy of hepatic lesions finally revealed an intrahepatic cholangiocarcinoma.

Conclusion: Although there is no case described in literature of CCA due to opioid consumption, hepatotoxic Heroin and Methadone exposition may have exerted a role on cholangiocytes proliferation, increasing proinflammatory and mutagenic stimuli and down-regulating local pro-apoptotic factors, leading ultimately to CCA development in this young patient.

Keywords: Cholangiocarcinoma; Opioids; Heroin; Methadone

Background

Cholangiocarcinoma (CCA) is a malignant epithelial cancer of the biliary tract characterized by late diagnosis and poor outcomes due to its anatomical, clinical and molecular heterogeneity. According to the World Health Organization (WHO) [1], current classification of CCA is based on different anatomical locations, including Intrahepatic CCA (IH-CCA, located proximally to the second degree bile ducts) and Extrahepatic CCA (EH-CCA), which is further divided in Perihilar-CCA (Klatskin tumour, the most frequent form, localized to the area between the second degree bile ducts and the insertion of the cystic duct into the common bile duct) and Distal-CCA (confined to the area between the origin of the cystic duct and ampulla of Vater) [2]. CCA is the second most common primary hepatic malignancy, accounting for 10-20% of primary liver cancers. The highest percentage of CCA incidence is reported in Hispanic and Asian populations (2,8-3,3 per 100 000) and the lowest in non-Hispanic white people and black people (both 2,1 per 100 000). Perihilar-CCA represents about 50%, Distal-CCA 40%, and Intrahepatic-CCA less than 10% of cholangiocarcinoma cases.

The highest age-adjusted mortality rate for IH-CCA is in American Indian and Alaska Native groups (1.3 per 100 000) and Asian populations (1.4 per 100 000) and the lowest in white people (0.8 per 100 000) and black people (0.7 per 100 000) [3]. Despite several epidemiologic studies [4], including data from Italy [5] and other western countries, reported a global increase in IH-CCA incidence and mortality over the past 30 years, it could result from a misclassification of perihilar tumors as IH-CCAs in International Classification of Disease for Oncology before 2001 [6]. Geographic variations in incidence rates of CCA are related to different risk factor [3,4]. In Asian countries, hepatobiliary parasites *Opisthorchis viverrini* and *Clonorchis sinensis*, *epatitis B* infection and *hepatolithiasis* are major risk factor for developing CCA (mainly IH-CCA).

Major risk factor associated with IH-CCA in western countries include primary sclerosing cholangitis, biliary-duct cysts disorders (including Caroli's disease), *hepatolithiasis*, *hepatitis C* infection, non-

alcoholic liver disease, cirrhosis, HIV infection, diabetes and metabolic syndrome. Data from smoking, alcohol use and obesity show weak association with development of CCA. With the exception of patients with primary sclerosing cholangitis, who develop CCA before age 40 years, the mean age of diagnosis is 65 years, with slight predominance among men. CCA is unusual in children. Typical symptoms and signs of CCA, such as jaundice, dyspepsia, and a palpable abdominal mass are inconstant, depending on the extension of the tumour mass in the intrahepatic area, hilar area, or extrahepatic area. Many patients with CCA often present with non-specific symptoms such as cachexia, abdominal pain, night sweats, and fatigue which can precede or follow altered hepatocellular and biliar function tests.

Diagnosis [3] of CCA includes imaging techniques, such as Computed Tomography scan and Magnetic Resonance Imaging, and Biopsy of the intrahepatic lesion. Basing on imaging features, IH-CCA can be morphologically classified into three different types: intrahepatic mass forming cholangiocarcinoma (IMCC, the most common), periductal infiltrating cholangiocarcinoma and intraductal growth variants [7]. Common metastatic sites of CCA include locoregional lymph nodes and adjacent organs. Distant metastases are infrequent and usually involve bone, muscle, brain, and thyroid gland. Surgical resection is a first-line therapy in patients with early stage Intrahepatic or Perihilar-CCA. Liver transplantation coupled with neoadjuvant chemoradiation is recommended only for highly selected patients with Perihilar-CCA. Patients with unresectable tumor can be treated

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with palliative biliaryenteric bypass or endoscopic or percutaneous stent placement. For advanced disease, palliative chemotherapy with Gemcitabine and Cisplatin combination is an acceptable standard of practice but does not show significant benefits, as survival rates remain low [4]. Here, we report the case of a young male patient without known risk-factors who presented with non-specific symptoms, normal blood tests and atypical radiological findings of CCA.

Case Presentation

A 30-years-old Caucasian man with no significant medical history was admitted at the Emergency Department with acute upper abdominal pain, nausea and vomiting. The pain was localized in epigastric region, rated at 7 on a scale of 0 to 10 and not radiated. The patient reported no fever, diarrhea, weight loss, night sweats, dyspnea or thoracic pain and he didn't eat uncooked foods or travelled abroad recently. He lived with his family in Italy and he has worked as welder of yacht components for 10 years but he lost his job 9 months ago and he actually works as farmer. He smoked cigars occasionally and drank alcohol only in week end. He reported no allergies and took no regular medications, even though the patient was an heroin-inhaled addict, in treatment with methadone maintenance therapy.

On arrival in our Institution, the patient's vital sign were: temperature 37 °C, heart rate 58 beats per minute, blood pressure 120/80 mmHg, oxygen saturation 99% while the patient was breathing ambient air. On physical examination, cardiac and pulmonary function was normal; the abdomen was tender in the upper quadrant and revealed hepatomegaly (upon palpation liver inferior margin was 3 cm below the right costal margin on the midclavicular line, the liver surface regular, the consistency slightly increased). Blood test showed

moderate increase of neutrophils, mild elevation of serum C-Reactive Protein (CRP), and lactate dehydrogenase (LDH). Normal serum values of Bilirubin, Serum Glutamic Oxaloacetic Transaminase (SGOT) Serum Glutamic-Pyruvic Transaminase (SGPT), Gamma-Glutamyl Transferase (GGT), Alkaline Phosphatase (ALP), total protein and protein electrophoresis, glucose, total cholesterol and triglycerides. Renal function test, urinalysis and Arterial Blood Gas (ABG) was normal. Serum test for HIV, HBV, HCV were negative.

An Electrocardiogram (ECG) showed sinus rhythm at 60 beats per minute and was otherwise normal. Chest and abdomen X-Ray showed no pathological sign. Abdominal Ultrasound revealed multiple liver nodules of varying sizes with no evidence of biliary duct dilatation, cholecystitis sign, portal vein hypertension, splenic involvement or ascites. The abdominal Computed Tomography examination showed the presence of multiple nodular hypovascular lesions, partially confluent, involving almost all the segments II and III, with some lesions even in the context of all other liver segments. No infiltration of the segmental arteries and veins has been detected. Because of its undetermined meaning, Magnetic Resonance Imaging was performed. DWI sequences showed strong restriction of water mobility, as in the case of highly cellular lesions (Figure 1). After administration of hepato-specific contrast medium, these lesions showed hypovascular behavior and absent uptake in the hepato-biliary phases, as in the case of replacing disease (Figure 2).

Because of ambiguous imaging findings (primitive hepatic neoplasia? metastases? infectious foci?), we decided to perform a needle biopsy of hepatic lesions, which was positive for malignancy originating from the biliary tract. Histological analysis showed an intrahepatic malignant epithelial neoplasm, composed of cuboidal



Figure 1: Magnetic Resonance Imaging – DWI Sequences.

or columnar cells with hyperchromatic round or oval nucleus, often with prominent nucleolus, and weakly eosinophilic cytoplasm with indistinct edges, arranged in solid cords and pseudotubular structures, sometimes containing mucoid material (resulted PAS positive diastase resistant) and immersed in abundant desmoplastic reaction. The

immunohistochemical analysis showed that the neoplastic cells were positive for CK AE1/AE3, CK 7, CK 8/18 and CK 19 and negative for Heppar-1, CK20, CDX2, alphaFetoProtein (alphaFP) and CD45. The final histological diagnosis was cholangiocarcinoma (Figure 3). Total body Computed Tomography examination performed one

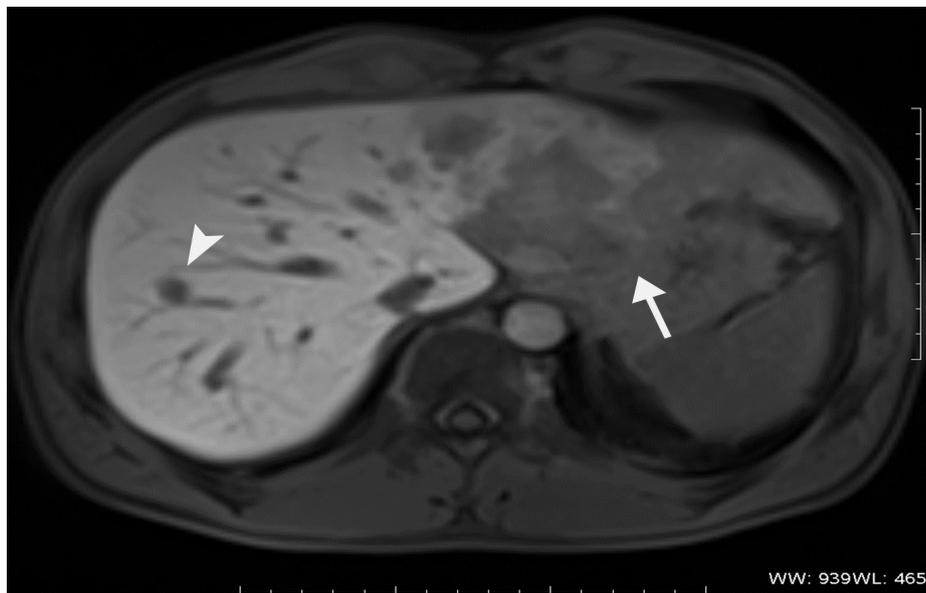


Figure 2: Magnetic Resonance Imaging – Hepatobiliary phase after contrast medium.

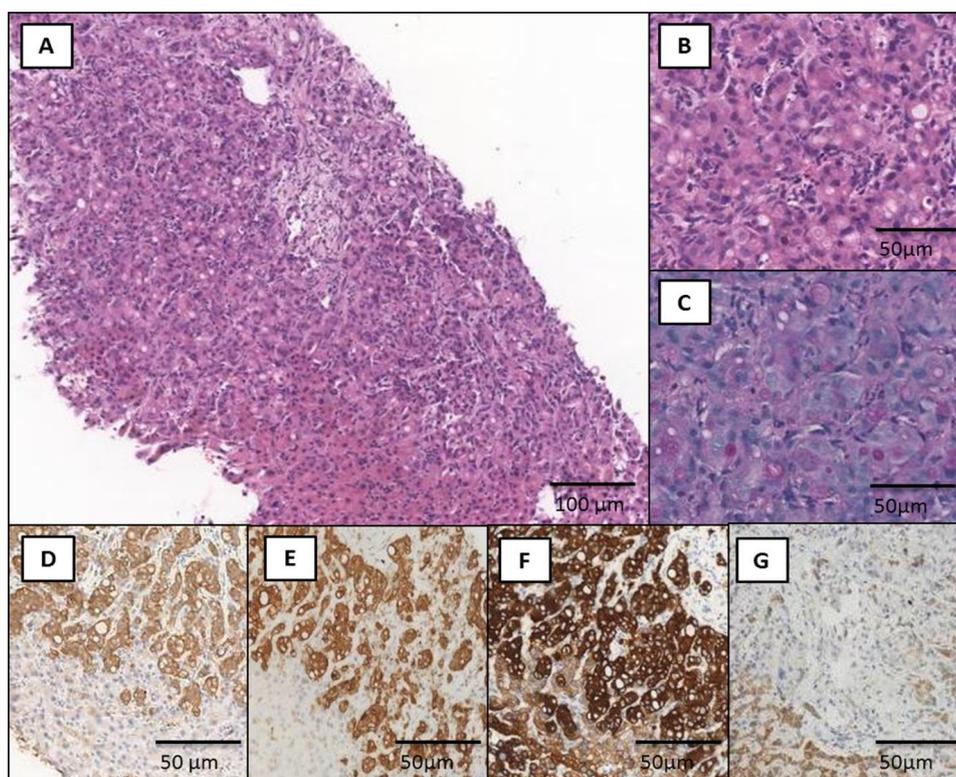


Figure 3: Histological analysis.

month later showed a significant disease progression with peritoneal carcinomatosis, lung and cerebral lesions. The patient was taken care of by oncologists for the follow-up and polichemiotherapy. After 6 months, the patient died.

Discussion

CCA is a heterogeneous group of tumours with different topographic site of growth, clinical features and specific treatments, usually diagnosed in 6th to 7th decade of life. In western countries, occurrence of CCA is uncommon among young caucasian people without known risk factor. CCA with typical imaging features can be easily diagnosed. The imaging features of IMCC are an irregularly shaped solid mass with peripheral rim enhancement and incomplete concentric pooling of contrast material on dynamic contrast material-enhanced CT or MR images. In addition, frequently noted ancillary findings of IMCC include capsular retraction, bile duct dilatation distal to the tumor, central scar, satellite nodules, vascular encasement and hilar adenopathy [7,8]. However, unusual manifestations and mimics can get the scenario complicated, as in this case report. Several neoplastic and non-neoplastic biliary tract diseases may complicate the management of patients suspected to have CCA. Mimics of CCA include non-neoplastic conditions such as autoimmune disorders of pancreatic and biliary tract (autoimmune pancreatitis, primary sclerosing cholangitis), flogistic and infectious disease (cholangitis, xanthogranulomatous cholangitis, recurrent piogenic cholangitis, inflammatory pseudotumour), traumatic and iatrogenic sequelae (chemotherapy-induced sclerosis), confluent fibrosis in cirrhotic patients and obstructive disease (Mirizzi syndrome, papillary stenosis) [9]. Conversely, neoplastic biliary tract mimics are represented by lymphoproliferative disease, some variants of hepatocellular carcinoma (sclerosing, fibrolamellar and hepatocholangiocellular carcinoma) and metastasis. Moreover, unusual neoplastic presentation (mucin hypersecreting cholangiocarcinoma, squamous adenocarcinoma, biliary cystadenocarcinoma and mucinous carcinoma) show different growth pattern compared to typical ones. The imaging findings of these several conditions may be indistinguishable from the typical imaging presentation of CCA and a definitive diagnosis can be achieved only with a biopsy specimen.

A plausible explication to the occurrence of a highly aggressive metastatic IH-CCA in this young male patient without relevant medical history (absence of hepatotropic viruses infection or HIV infection, cirrhosis, primary pathologies of biliary duct, gallstones or chronic cholangitis) may derive from the patient's voluptuary habits. He has been a strong consumer of heroin by inhalation for many years. He's currently attending Substance Abuse Treatment Center for Methadone maintenance therapy. Opioidergic system activation is related to hepatic and biliary damage. Previous studies showed hystological finding of hepatotoxicity, including active hepatitis, microvesicular and macrovesicular steatosis, hemosiderosis, cholestasis and lymphocytic cholangitis in opium addicts [10]. Hepatotoxicity induced by synthetic opioids (Morphine, Heroin, Meperidine, and Methadone) was also indirectly observed through a depression of hepatic glutathione antioxidant system in treated mice [11].

It was also recently demonstrated that the increase in opioidergic tone by the central administration of Morphine, binding to the mu-Opioid Receptor, is associated with pruritus (classical sign of cholestasis) in patients with primary biliary cirrhosis [12]. Administration of Naltrexone (an opioid receptor antagonist) and derivatives exerted anti-inflammatory activity through decreased hepatic stellate cell activation, preventing liver fibrogenesis [13] and promoting angiogenesis [14,15].

Curiously, morphologic evidence of cholestasis opioid drug-induced was often not related to serum increasing of serum GGT in heroin addicts [16], as in our patient. Despite at the present time cholangiocarcinoma opioid drugs-related has not yet been described, recent study have demonstrated that human cholangiocarcinoma development is associated with dysregulation of endogenous opioidergic system involved in modulation of cholangiocyte growth [17]. Cholangiocyte proliferation occurs in all pathologic conditions of liver injury [18], including cholestasis, leading to bile ductular proliferation which can be complicated by malignancy. Proliferating cholangiocytes acquire the phenotype of neuroendocrine cells secreting diverse substances like endogenous opioids [19]. Endogenous opioids are known to have an autocrine effect on cell growth, in order to limit the cholangiocyte hyperplastic response to cholestasis [20].

As it is reported both in human with primary biliary cirrhosis and in cholestatic liver mice, proliferating cholangiocytes produce higher quantity of Met-enkephalin and express all opioid receptors, involved in different functions: delta opioid receptor (δ OR) reduces biliary cell proliferation, whereas mu opioid receptor (μ OR) increases cell proliferation [21,22]. It was observed in preliminary studies [22,23] that malignant cholangiocytes altered their capability to modulate cell growth, losing susceptibility to the growth-inhibitory effect of δ OR and enhancing cell proliferation response to μ OR activation.

Conclusion

CCA in this young healthy patient probably occurred due to hepatotoxic consequence of Heroin addiction and Methadone consumption, which exerted chronic proinflammatory and mutagenic stimuli to cholangiocytes, leading to failure of local pro-apoptotic factors and amplificating pro-proliferative stimuli, causing ultimately CCA.

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