



Treating Unresectable Intrahepatic Cholangiocarcinoma with Transarterial Chemoembolization and an Unusual Progression with Cardiac Involvement

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Abstract

Intrahepatic cholangiocarcinoma is a rare type of cancer that is usually discovered at an advanced stage where surgical treatment is not an option. When compared to standard systemic therapy, transarterial chemoembolization (TACE) can provide a survival benefit to unresectable patients. Extrahepatic tumor spread is not rare, but cardiac involvement is an unusual complication.

We present the case of a 56-year-old man with histologically proven intrahepatic cholangiocarcinoma. Oncologic risk factors include hepatitis B and liver cirrhosis. Being in an unresectable stage of the disease, three TACE procedures were performed. Partial response was achieved (according to RECIST) leading to a 16-month survival. However, disease progression was present, with unusual heart metastases.

TACE can bring a survival benefit to unresectable cholangiocarcinoma patients. Defining the best disease stages in which TACE can be implemented and introducing it as part of standard treatment guidelines still presents a challenge.

Keywords

cardiac metastases, intrahepatic cholangiocarcinoma, transarterial chemoembolization

INTRODUCTION

Cholangiocarcinomas (CCCs) are a rare type of malignancies with an incidence rate of 0.3–6 per 100,000 people that may originate from the biliary tree.^[1] They are nowadays divided into three different groups – intrahepatic (iCCA), perihilar (pCCA), and distal (dCCA). The rarest is iCCAs, comprising around 10%–20% of all cholangiocarcinomas,

and around 15% of the primary hepatic malignancies (the main one being hepatocellular carcinoma).^[1]

When discovered early, surgery is the treatment of choice. Most cases of iCCA (around 60%–88%) are often diagnosed at an advanced stage when surgery is not feasible. For these patients, systemic therapy is the standard practice.^[2] Alternatively, transarterial chemoembolization (TACE) may serve as an alternative treatment modality.

Some analysis even conveyed a survival benefit with an acceptable safety profile.^[3]

Oncologic progression is often defined by the appearance of distant metastases. Overall, cardiac involvement (when sought) is not that rare, accounting for 9% of all cancers.^[4] iCC, however, rarely involves the heart with only one case reported so far.^[5]

CASE REPORT

We present the case of a 56-year-old man who was admitted to the Gastroenterology Department complaining of jaundice and increasing waist circumference. The concomitant high blood pressure was treated adequately. The patient was neither smoker nor used excessive amounts of alcohol. Ultrasound examination of the abdomen revealed changes characteristic for hepatic cirrhosis (portal hypertension) - hepatosplenomegaly, ascites - and a hypoechoic nodule 5.7 cm in diameter in the right liver lobe (segments VII-VIII). The etiology of the disease was found to be hepatitis B - the patient was HBsAg (+) positive, anti-HBcore total (+) positive, anti-HCV(-) negative, anti-HDV (-) negative with a high HBV (hepatitis B virus) DNA load - 3 133 525 IU/ml. Significant portal hypertension was confirmed. An upper GI endoscopy showed esophageal varices grade II-III in the OMED classification. A CT scan of the abdomen with contrast characterized the liver nodule as a primary liver tumor, with nor-

mal Alpha-fetoprotein level and elevated level of the CA19-9 marker (166 IU/ml, normal ranges 0-39 IU/ml). At this point, the patient was classified as a newly-found cirrhotic. In Child score, he received 8 points (max. 15) - class B, while in MELD score he received 11 points. He started therapy with diuretics due to ascites and treatment of hepatitis B with nucleotide analogue (tenofovir, TDF).

Ascites was completely eliminated a month later, making a percutaneous liver biopsy feasible. The results of liver biopsy demonstrated an intrahepatic cholangiocarcinoma (immunohistochemical staining was positive for CK7 and CK 20). The disease stage was T1bN0M0 according to the 8th edition of the American Joint Cancer Committee (AJCC).^[6] Considering the size of the primary tumor and the underlying advanced hepatic disease (cirrhosis with previous episode of decompensation) resection was not an option. Additionally, since the risk for adverse effects of systemic therapy outweighs the benefits, TACE appeared to be much better therapeutic option. Three TACE procedures were performed, using biodegradable starch microspheres Emboccept S® (Figs 1C, 1D). No adverse events were reported. Four months post-TACE, we found no laboratory or imaging evidence of decompensation of the underlying cirrhosis. Due to the TDF therapy, HBV DNA was non-detectable in serum. The results of TACE for the iCCA were classified using the RECIST criteria as partial response. Shrinkage of the hepatic tumor from 66 to 36 mm was achieved with no signs of distant metastases (Figs 1A, 1B).

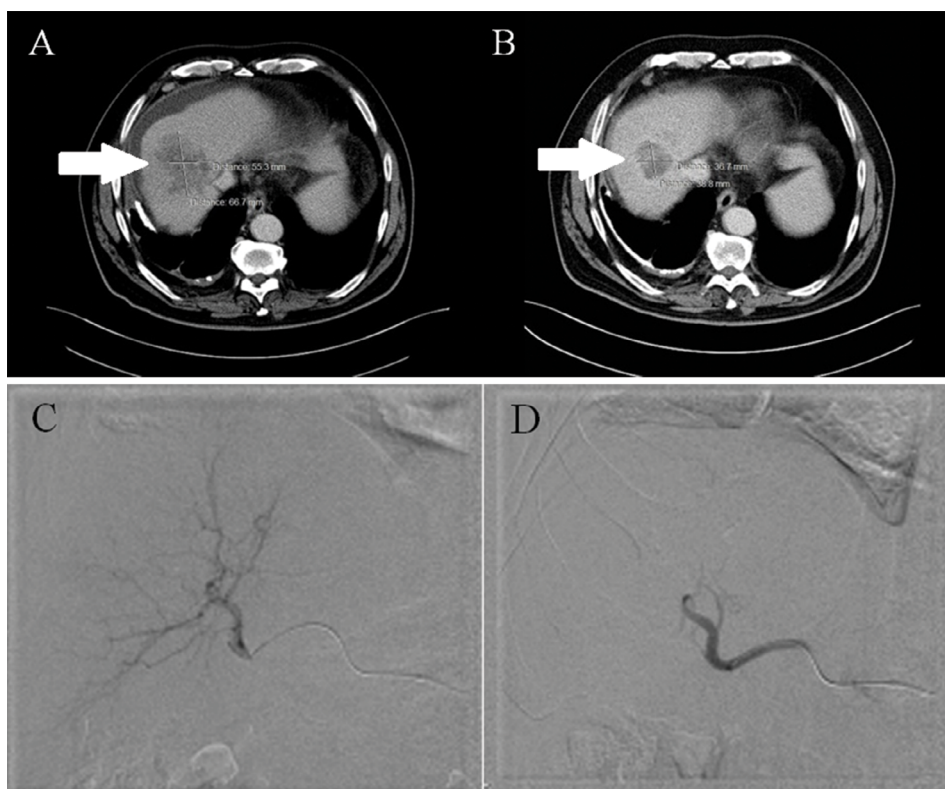


Figure 1. A. Pre-TACE CT image of the CCC; **B.** CT image – a post-TACE shrinkage in tumor size, white arrows mark the liver tumor; **C.** angiographic image of the involved hepatic vessels pre-TACE; **D.** Post-TACE occlusion of the involved vessel.

With the outbreak of the COVID-19 pandemic, the patient ceased to attend the follow-ups for eight months. He presented to the Department with signs of ascites and shortness of breath. The ultrasound of the abdomen revealed multiple enlarged abdominal lymph nodes in addition to the ascites. Pericardial effusion was visible on ultrasound in subxiphoid view with a large mass protruding into the right ventricle. Contrast CT of the chest and abdomen verified multiple pulmonary metastases, severely enlarged (metastatic) lymph nodes in the mediastinum and abdominally (**Fig. 2**). Pericardial effusion was evident with a mass originating from the apex and the free wall of the right ventricle, protruding into the ventricular cavity (**Fig. 2**). Progression of the oncologic disease was present. The patient received palliative care. He died a few months after hospitalization.

DISCUSSION

The risk factors for intrahepatic cholangiocarcinoma seem to differ between perihilar and distal cholangiocarcinoma. Chronic ductal inflammation from flukes, primary sclerosing cholangitis (PSC), biliary cysts, or hepatolithiasis is not a crucial risk factor for iCCA. As acknowledged lately (and as in the presented case), the risk factors of iCCA seem to be the same as the ones for HCC, that is, hepatitis B or C, cirrhosis, alcohol consumption and obesity.^[1,2] Diffuse hepatic injury often renders the patient's tumor unresectable. Therefore, new staging systems that can take into account liver function tests (perhaps similar to those for HCC) might prove more valuable than the typical TNM classification. In them, loco-regional therapies can easily find a place in order to be correctly evaluated.

Transarterial therapies aim to deliver a high load of chemotherapeutic agents in the tumor while sparing other organs; they are often combined with embolization of the tumor-feeding arteries. Several modalities exist – hepatic artery infusion (HAI), conventional TACE (cTACE), TACE with eluting drug beads (deb-TACE), selective internal ra-

diation therapy (SIRT), and transarterial radioembolization (TARE). Each has provided survival advantages, but TACE seems to be the most practiced.^[7,8] In the presented case, a TACE modality was implemented using biodegradable starch microspheres (EmboSept S[®]). Biodegradability achieves a temporary stop in the blood flow, thus allowing chemotherapeutic load, while reversal of the blood flow makes follow-up TACE procedures feasible. This temporary ischemia expresses the idea of better outcomes and tolerability compared to conventional TACE, especially in patients with liver dysfunction.^[9] In a meta-analysis, Ray et al. found that the median general survival was 15.7 ± 5.8 months after TACE for unresectable iCCA (from the time of diagnosis).^[3] Our case also supports this finding with the patient surviving for 16 month post-diagnosis. Current systemic therapy comprises gemcitabine/cisplatin and has a median overall survival of 11.7 months.^[2] Biomarker-driver therapy (which will probably be crucial in the coming years) improves prognosis even further for advanced metastasis iCA. The survival benefit of TACE (nearly five months) and the different safety profiles make it an alternative area and approach to be looked in.^[3] Moreover, as in our case, TACE can downstage a disease (partial response according to the Response Evaluation Criteria in Solid Tumors (RECIST criteria)).^[3] According to Burger et al., two patients achieved resectability after TACE.^[10] The beneficial effect from TACE is estimated to be even more remarkable when using modified RECIST, the latter taking into consideration the tumor size and vitality.

Tumor metastasis to the heart is an uncommon finding. However, when searched for systemically in autopsies, they can be found in up to 9% of all autopsies for malignancy.^[4] Often, as in our case, they are associated with widespread metastatic disease.^[11] Cardiac metastases can be pericardial/ epicardial, myocardial and endocardial, with each type having different pathophysiology (origin) and clinical symptoms. We only found a few cases of heart metastases from intrahepatic cholangiocarcinoma.^[5,12,13] Our patient had a mass infiltrating the myocardium which was

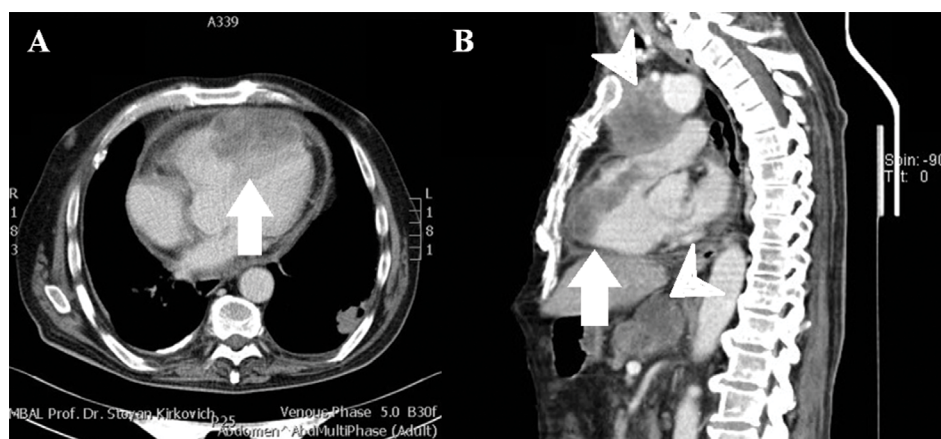


Figure 2. A. CT image - transversal view, B. CT image - sagittal view. The arrows point to the heart metastasis protruding through the right atrium into the truncus pulmonalis. The arrowheads mark the enlarged mediastinal and perihilar lymph nodes.

protruding into the ventricular cavity. Additionally in our case, there was an insignificant pericardial effusion. How to properly address such a complication as metastases to the myocardium is a relatively unknown area.

CONCLUSION

TACE with biodegradable starch microspheres can be used as an alternative to standard chemotherapy in unresectable intrahepatic cholangiocarcinoma. Progression of the disease (CCC) can include atypical metastases such as myocardial involvement.

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Лечение нерезектабельной внутрипечёночной холангиокарциномы с трансартериальной химиоэмболизацией и необычным прогрессированием с вовлечением сердца

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Резюме

Внутрипечёночная холангиокарцинома – это редкий тип рака, который обычно обнаруживается на поздних стадиях, когда хирургическое лечение невозможно. По сравнению со стандартной системной терапией трансартериальная химиоэмболизация (ТАСЕ) может повысить выживаемость нерезектабельных пациентов. Внепечёночное распространение опухоли не является редкостью, но поражение сердца является необычным осложнением.

Мы представляем случай 56-летнего мужчины с гистологически подтверждённой внутрипечёночной холангиокарциномой. Онкологические факторы риска включают гепатит В и цирроз печени. На нерезектабельной стадии заболевания выполнено 3 процедуры ТАСЕ. Был достигнут частичный ответ (согласно RECIST), что привело к 16-месячной выживаемости. Однако имело место прогрессирование заболевания с необычными метастазами в сердце.

ТАСЕ может повысить выживаемость пациентов с нерезектабельной холангиокарциномой. Определение наилучших стадий заболевания, на которых можно применять ТАСЕ, и включение её в стандартные руководства по лечению по-прежнему представляет собой сложную задачу.

Ключевые слова

метастазы в сердце, внутрипечёночная холангиокарцинома, трансартериальная химиоэмболизация
