Clinical Case Report

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Neoadjuvant modified-FOLFIRINOX followed by surgical resection of both the primary and metastatic tumors of a pancreatic hepatoid carcinoma with synchronous liver metastasis

A case report

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Abstract

Rationale: Pancreatic hepatoid carcinoma (PHC) is a rare form of pancreatic malignancy mimicking hepatocellular carcinoma (HCC) in morphology, immunohistochemistry, and behavior. PHC usually has an aggressive clinical course and poor prognosis. Effective treatment strategies are lacking due to poor understanding and extreme rarity of such kind of malignancy.

Patient concerns: we present the case of a 75-year-old man with tumors in the liver and the tail of pancreas that were detected in a routine health check-up.

Diagnoses: Pancreatic hepatoid carcinoma with liver metastasis

Interventions: The patient was treated by neoadjuvant modified-FOLFIRINOX (mFOLFIRINOX) chemotherapy and subsequent resection of both the primary pancreatic tumor and the sole liver metastasis.

Outcomes: Pathology findings confirmed complete pathological response of the liver metastatic tumor and partial response of the primary pancreatic tumor to neoadjuvant mFOLFIRINOX. Adjuvant chemotherapy with mFOLFIRINOX was given and until now the patient has a progression-free survival of 13 months after diagnosis.

Lessons: PHC are often associated with early liver metastasis and a poor prognosis, surgical resection combined with neoadjuvant and adjuvant FOLFIRINOX chemotherapy is proved to be efficient in such kind of malignancy, even with liver metastasis.

Abbreviations: AFP = alpha-fetoprotein, CEA = carcinoembryonic antigen, CT = computed tomography, GPC3 = glypican 3, HC = hepatoid carcinoma, HCC = hepatocellular carcinoma, mFOLFIRINOX = modified-FOLFIRINOX, MRI = magnetic resonance imaging, PHC = pancreatic hepatoid carcinoma.

Keywords: FOLFIRINOX, liver metastasis, neoadjuvant chemotherapy, pancreatic hepatoid carcinoma, surgery

1. Introduction

Hepatoid carcinoma (HC) is a group of malignant tumors arising from extrahepatic organs or tissues that typically comprising areas showing morphological and immunohistological evidence of hepatocellular differentiation. The first reported case of HC worldwide is in the stomach,[1] which is also the most frequent location. Only few cases of pancreatic hepatoid carcinoma (PHC) are available in the literature. The clinical behavior, prognosis, and effective treatment strategies remain unclear. Here, we report a case of PHC with synchronous liver metastasis that is successfully managed by neoadjuvant modified-FOLFIRINOX (mFOLFIRINOX) chemotherapy and complete resection of both the primary and the metastatic tumors.

2. Case report

A 75-year-old man was referred to our hospital because of tumors in the liver and the tail of pancreas detected in a routine health check-up. He did not have pain, anorexia, nausea, vomiting, or fever. He noticed a body weight loss of 5 kg in the recent 3 months. Physical examination on admission was unremarkable. Laboratory tests revealed the elevation of carcinoembryonic antigen (CEA) at 7.5 ng/mL (0–5 ng/mL, reference range in our hospital) and alpha-fetoprotein (AFP) at 1897.7 ng/mL (0–20 ng/mL, reference range in our hospital). He had no hepatitis B virus (HBV) or hepatitis C virus (HCV) infection. Other tests were all within normal ranges. Enhanced computed tomography (CT) and enhanced magnetic resonance imaging (MRI) showed a heterogeneous solid hypovascular mass (7.8 cm in the largest diameter) located in the tail of pancreas and an oval sharped mass (7.0 cm in the largest diameter) in segment IV of liver (Fig. 1). Ultrasound-guided biopsy of the liver and pancreatic masses was performed. The pathology of the pancreatic

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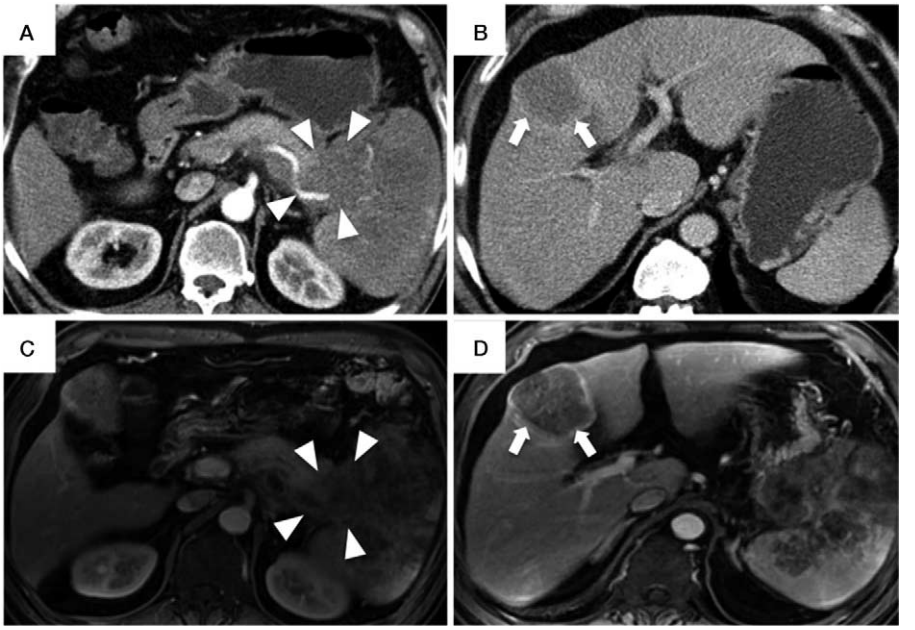

Figure 1. Image studies of the upper abdomen on admission. An abdomen CT (panels A and B) shows a hypovascular mass (arrowhead) located in the tail of pancreas that incased the splenic artery and invaded into the spleen, also shown is a hypovascular left liver mass (arrow), findings suggestive of a pancreatic cancer with liver metastasis. The abdominal MRI (panels C and D) shows similar findings that are suggestive of a pancreatic cancer in the tail of pancreas (arrowhead) with liver metastasis (arrow). CT = computed tomography, MRI = magnetic resonance imaging.

mass showed poorly differentiated adenocarcinoma with component of polygonal cells with a wide eosinophilic or clear cytoplasm, which are diffusely positive for AFP and glypican 3 (GPC3), and are weakly positive for HepPar-1 (Fig. 2). The pathology of the liver mass showed similar appearance and immunohistological characteristics with the pancreatic specimen (Fig. 3).

The diagnosis of pancreatic HC with liver metastasis was made after a multidisciplinary consultation. As there was only single metastasis in the liver, neoadjuvant mFOLFIRINOX was initiated in an attempt to control and to facilitate the possible resection of both the primary and the metastatic tumors. One cycle of mFOLFIRINOX regimen in our center consisted of intravenous

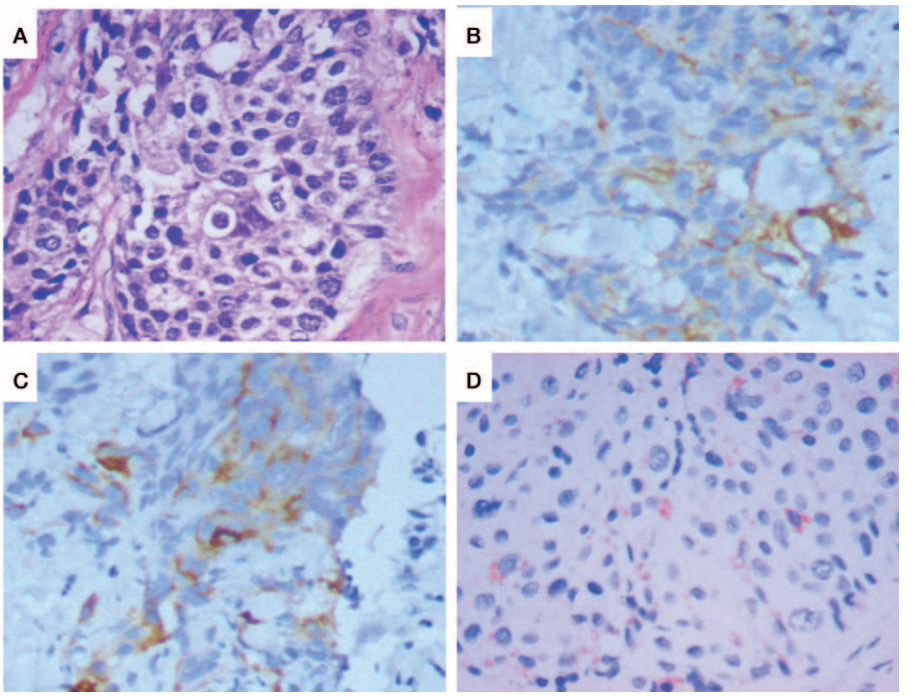

Figure 2. Pathological findings of the biopsy specimen of the pancreatic mass. Hematoxylin and eosin (H-E) staining of the specimen shows poorly differentiated adenocarcinoma with component of polygonal cells with a wide eosinophilic or clear cytoplasm (panel A). Immunohistochemical staining shows the specimen is diffusely positive for AFP (panel B) and GPC3 (panel C), and is weakly positive for HepPar-1 (panel D). AFP = alpha-fetoprotein, GPC3 = glypican 3.

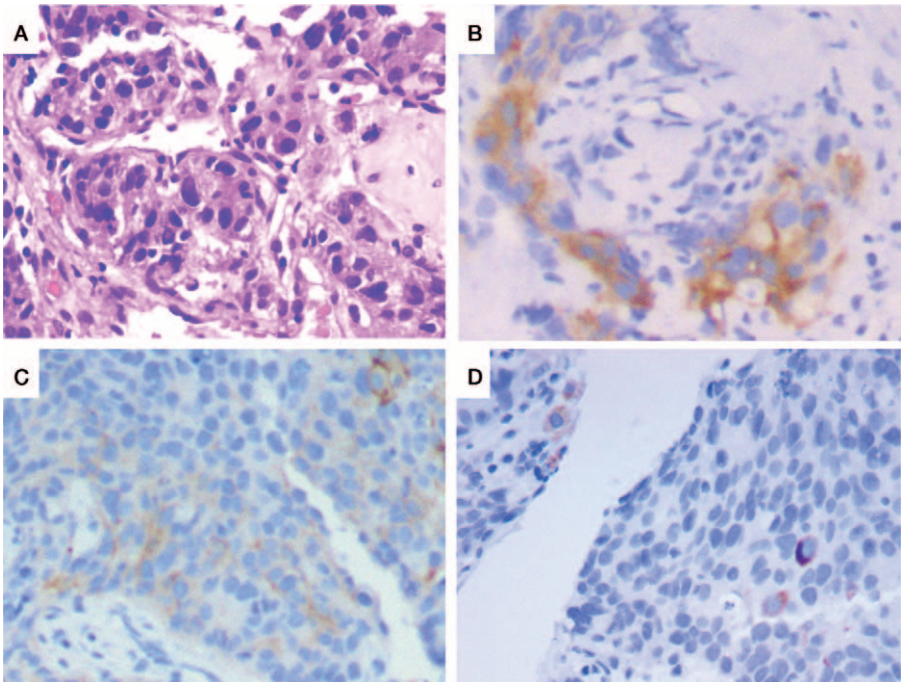

Figure 3. Pathological findings of the biopsy specimen of the Liver mass. H-E staining of the specimen shows poorly differentiated adenocarcinoma with component of polygonal cells with a wide eosinophilic or clear cytoplasm (panel A). Immunohistochemical staining shows the specimen is diffusely positive for AFP (panel B) and GPC3 (panel C), and is weakly positive for HepPar-1 (panel D). AFP = alpha-fetoprotein, GPC3 = glypican 3.

infusion of oxaliplatin (68 mg/m^2) followed by leucovorin (400 mg/m^2) concomitantly with infusion of irinotecan (135 mg/m^2), followed by a 46-hour continuous infusion (2400 mg/m^2) of 5-fluorouracil. The regimen was delivered every 2 weeks for a total of 16 weeks before re-evaluation of the tumor. During chemotherapy, the patient tolerated well to this regimen and there were no grade 3 or 4 toxicity and dose reduction associated with adverse events. After finishing 8 cycles of mFOLFIRINOX, the serum CEA and AFP had dropped to normal ranges, and abdominal CT and MRI were performed again to evaluate the tumor response.

Abdominal enhanced CT and MRI after chemotherapy showed both tumors in the pancreatic tail, and liver shrank

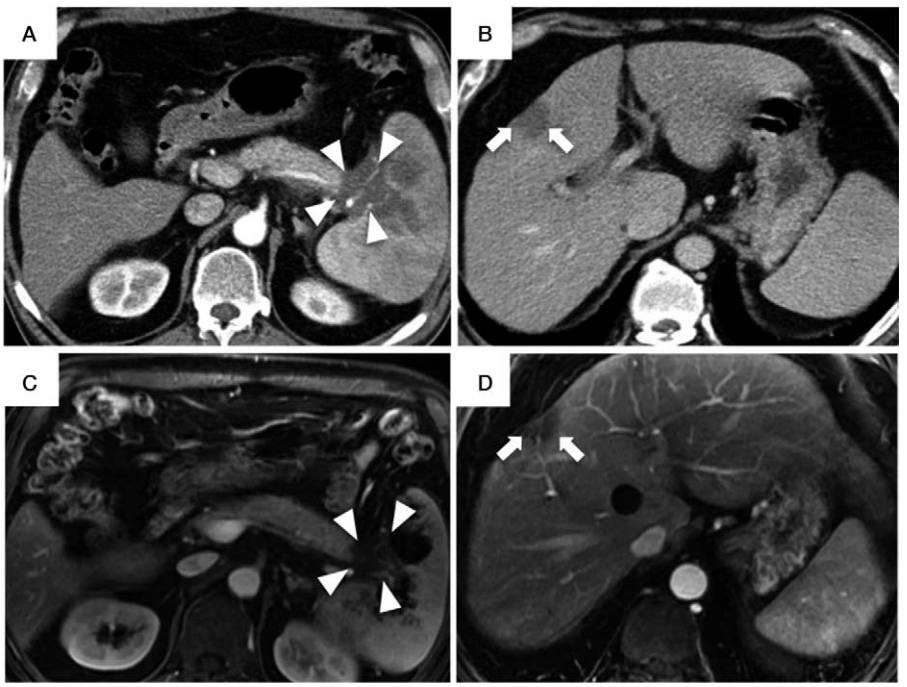

Figure 4. Image studies of the upper abdomen after neoadjuvant chemotherapy. An abdomen CT (panels A and B) and MRI (panels C and D) shows masses in the tail of pancreas (arrowhead) and in the left liver (arrow) shrank dramatically, findings suggestive of a good response to chemotherapy. CT = computed tomography.

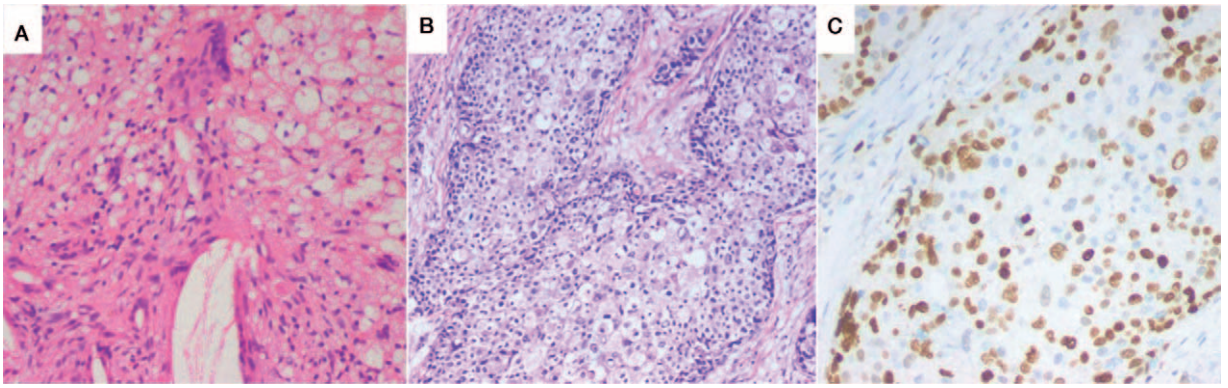

Figure 5. Pathological findings of the resected specimens of the liver metastatic tumor and the pancreatic tumor. No tumor cell is visible in the resected specimen of the liver metastatic tumor (panel A). H-E staining of the pancreatic specimen shows clusters of residential hepatoid carcinoma cells that characterized as polygonal cells with a wide eosinophilic or clear cytoplasm (panel B). Immunohistological staining of Ki 67 in the pancreatic specimen shows a 50% to 60% positive rate (panel C).

dramatically (Fig. 4). The liver metastatic tumor appeared roughly being not enhanced at all, suggesting a complete response to mFOLFIRINOX. After reviewing the imaging, the normalization of serum CEA and AFP, and the patient's performance score, resection of tumors was suggested by the multidisciplinary board. Curative-intended distal pancreatectomy with splenectomy and wedge resection of the metastatic tumor in the liver was performed. The recovery was uneventful. Postoperative pathology revealed there was a complete pathological response to chemotherapy in the liver metastatic tumor, and scattered residential HC cells remained in the specimen of the distal pancreas (Fig. 5A and B). Additional immunohistochemical stains for synaptophysin, chromogranin, CD56, neuron-specific enolase, trypsin, and CK7 were all negative. The Ki-67 mitotic index in the specimen of the pancreatic tumor was around 50% to 60% (Fig. 5C). Adjuvant chemotherapy using mFOLFIRINOX followed by oral S-1 was initiated 2 months after operation. The patient tolerated well and remained tumor-free on follow-up visits 6 months after operation.

3. Discussion

To date, only about 20 cases of PHC are reported worldwide. PHC usually has an aggressive clinical course and extremely poor prognosis.[2,3] In a review conducted by Marchegiani et al,[4] half of the PHC cases (n = 22) presented with metastatic disease, most commonly to the liver. The presenting case is a PHC with a solitary liver metastasis, which is more rare. However, the single metastasis, on the contrary, may facilitate en bloc surgical resection of the primary and metastatic tumors.

It is important to exclude metastatic HCC before diagnosing primary pancreatic HC, by clinical and pathological features. Serum AFP is well-established marker for HCC and was found to be elevated in most cases of PHC, like in this case. It can be used to evaluate the completeness of surgical resection and response to systemic therapies. However, AFP can be detected in other pancreatic tumors like ductal, acinar cell, neuroendocrine, and undifferentiated carcinomas. Characteristic pathological features and immunohistochemical markers play a key role in diagnosing PHC. PHC resembles HCC in terms of morphology and immunohistochemistry. For the morphology, PHC cells are polygonal with a wide eosinophilic or clear cytoplasm, large ovoid nuclei, and large central nucleoli. Bile production may present and is a strong evidence of hepatocyte linage differentiation. For the immunohistochemistry, PHC is usually positive for liver-synthesized proteins, such as HepPar 1 and AFP, or proteins of canaliculi formation, such as polyclonal CEA or CD10. In this case, even though the tumor is generally poorly differentiated, the residual tumor after neoadjuvant chemotherapy was composed of polygonal cells with a wide eosinophilic or clear cytoplasm, which is positive for HepPar-1 and GPC3. GPC3 is another recently identified tumor marker that is exclusively overexpressed in HCC. Its expression in this case further confirmed hepatoid linage differentiation.

It was considered that PHC can present in pure form or in mixed form that with histologically different components such as adenocarcinoma or neuroendocrine tumors.[5] The prognosis of the pure form of HC is reported to be superior to mixed form.[3] This case is a pure form, without expression of specific markers of neuroendocrine tumor, acinar cell tumor, or ductal adenocarcinoma. This may partially explain the good response to treatments and long survival.

The prognosis of PHC is extremely poor, and effective treatment strategies are lacking due to poor understanding and extreme rarity of such kind of malignancy. In most reported cases, surgery remains the best choice of treatment whenever possible. Chemotherapy is seldom applied for unresectable metastatic tumors or in adjuvant setting. However, the treatment response varies with some reports of no additional benefit. Sorafinib, a multitarget tyrosine kinase inhibitor, which has been widely used in metastatic or advanced HCC, has been shown to possibly benefit patients with advanced HC.[6,7] Surgical resection is usually contraindicated in case of pancreatic ductal adenocarcinoma (PDAC) with liver metastasis. As that indicates a systematic disease and only systematic treatments are reliable. However, surgical resection remains to be the only potentially curative treatment for most kinds of malignancy, especially in PHC, a rare type of pancreatic cancer that behaves different with PDAC. Natsume et al[8] reported 1 case of PHC with a metachronous solitary liver metastasis that had survived for more than 8 years after resection of the primary tumor and subsequent resection of the metachronous liver metastasis, suggesting surgery may be a treatment of choice for patients with liver metastasis from PHC, particularly for those with a solitary tumor. In this case, there is a solitary liver metastasis

that responded well to mFOLFIRINOX, and no new lesion emerged after neoadjuvant chemotherapy. The primary tumor also shrank significantly. All of these make curative-intended surgical resection the best choice.

The patient in the present case survived more than 13 months and is still in good condition without signs of tumor recurrence. The use of mFOLFIRINOX chemotherapy may play a pivotal role both in the neoadjuvant and adjuvant settings. There is complete response in the liver metastasis and partial response in the primary pancreatic tumor after 8 cycles of mFOLFIRINOX, facilitating the curative-intended surgical resection. Also, its use as adjuvant chemotherapy might have prevented early recurrence of tumor postoperatively. FOLFIRINOX is 1 of recent milestones in the field of chemotherapy for pancreatic cancer. It has a response rate as high as 31.6% and can prolong the median overall survival as long as 4.3 months in metastatic pancreatic cancer.[9] The use of FOLFIRINOX in PHC has never been reported to date. The dramatic response to FOLFIRINOX regimen in this case might improve the understanding of such kind of malignancy and highlight the possible usefulness of FOLFIRINOX in rare types of pancreatic cancer.

4. Conclusions

In summary, we present a case of PHC with a solitary liver metastasis. Although PHCs are often associated with early liver metastasis and a poor prognosis, in this case, the patient has a progression-free survival of 13 months to date and is still doing well. Surgical resection combined with neoadjuvant and adjuvant FOLFIRINOX chemotherapy is proved to be efficient in such kind of malignancy, even with liver metastasis.

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