Clinical Case Report

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Iodine-125 seed implantation for synchronous pancreatic metastases from hepatocellular carcinoma

A case report and literature review

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Abstract

Rationale: The image-guided iodine-125 seed implantation has been widely used for a variety of tumors, including prostatic cancer, pulmonary cancer, hepatocellular carcinoma and pancreatic cancer. However, the clinical value of iodine-125 seed implantation for the treatment of pancreatic metastasis from hepatocellular carcinoma has not been reported. We presented the first case with ultrasound-guided iodine-125 seed implantation for this disease.

Patient concerns: We presented the case of a 48-year-old man patient with primary hepatocellular carcinoma and pancreatic metastasis who was managed with ultrasound-guided iodine-125 seeds implantation.

Diagnoses: She was diagnosed with synchronous pancreatic metastases from hepatocellular carcinoma.

Interventions: Puncture biopsy and ultrasound-guided iodine-125 seeds implantation.

Outcomes: The hepatic and pancreatic tumors were obviously reduced after 15 months. Moreover, the liver function test was mildly abnormal in glutamic-oxalacetic transaminase and glutamic-pyruvic transaminase.

Lessons: The image-guided iodine-125 seeds implantation was an important therapeutic approache to unresectable hepatocellular carcinoma with pancreatic metastasis. However, more related cases should be reported for further evaluating the value of the way.

Abbreviations: AFP = alpha-fetoprotein, ALB = albumin, ALT = glutamic-pyruvic transaminase, APTT = activated partial thromboplastin time, AST = glutamic-oxalacetic transaminase, CA19-9 = carbohydrate antigen 19-9, CEA = carcinoembryonic antigen, CT = computerized tomographic scanning, GGT = glutamyl transpeptidase, GPC3 = glypican 3, HbcAB = hepatitis B core antibody, HbeAg = hepatitis B e antigen, HbsAg = hepatitis B surface antigen, HBV-DNA = hepatitis B virus deoxyribonucleic acid, HCC = hepatocellular carcinoma, HCV = hepatitis C virus, HE = hematoxylin-eosin, HGB = hemoglobin, INR = International Normalized Ratio, NEUT = neutrophil, PD = prescription dose, PLT = blood platelet, WBC = white blood cell, PT = prothrombin time, PV = portal vein, RFA = radiofrequency ablation, SMA = superior mesenteric artery, SV = splenic vein, TACE = transcatheter arterial chemoembolization.

Keywords: hepatocellular carcinoma, iodine-125, metastasis, pancreas

1. Introduction

Hepatocellular carcinoma (HCC) is one of the most common malignant tumors in the world. Among primary liver cancers, HCC is the major histological subtype and ranks fourth among the organ-specific causes of cancer related deaths worldwide.[1] Extrahepatic metastases are commonly found during the diagnosis of HCC. The most common sites of extrahepatic metastatic HCC are the lungs, lymph nodes, bones, and adrenal glands, respectively.[2] However, metastasis to the pancreas occurs in only <1% of patients with HCC.[3] Currently, image-guided iodine-125 seed implantation can achieve a necrotizing dose of irradiation within the target volumes with a very sharp falloff outside the implanted area, thus sparing the normal tissues around the lesion. It has been widely used for a variety of tumors, including prostatic cancer,[4] pulmonary cancer,[5] HCC,[6] and pancreatic cancer.[7] However, the clinical value of iodine-125 seed implantation for the treatment of pancreatic metastasis of HCC has not been reported. To the best of our knowledge, this is the first report of iodine-125 seed implantation as the treatment of pancreatic metastasis from HCC. Using our experience, a world literature review of all such cases was performed in order to better recognize this rare pathology.

2. Case presentation

A 48-year-old man was admitted to West China Hospital of Sichuan University as result of abdominal pain in the right upper quadrant. He suffered from hypertension for 1 year and was

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The authors have no conflicts of interest to disclose.

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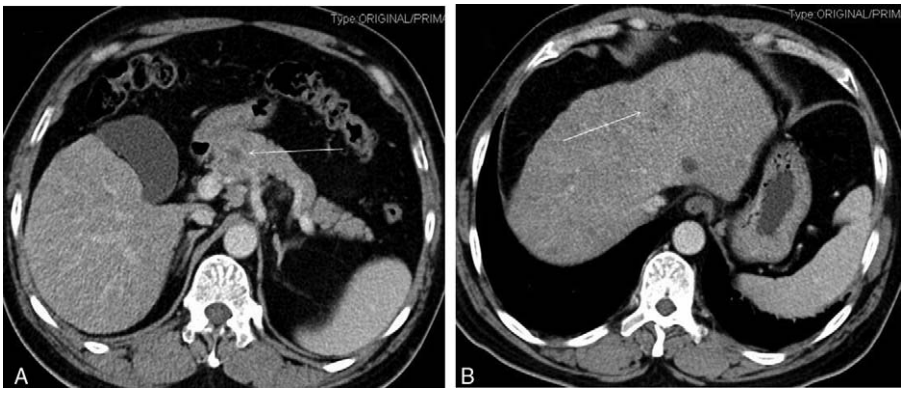

Figure 1. CT scan suggested a heterogeneous enhanced mass in the pancreatic head (A: white arrow) and an unobvious mass in the left of the liver (B: white arrow). CT = computerized tomographic scanning.

given oral medication. There was no remarkable family history. On admission, the vital signs of the patients were within the normal limits. On physical examination, the abdomen was soft, but tender in the right upper quadrant. The blood examination showed the following: hemoglobin (HGB) was 149 g/L (reference range: 135–175 g/L), blood platelet (PLT) was 134×10^9/L (reference range: $100–300 \times 10^9$/L), white blood cell (WBC) was 4.99×10^9/L (reference range: $3.5–9.5 \times 10^9$/L), percentage of neutrophil (NEUT) was 62.6% (reference range: 40–75%). The prothrombin time (PT) was 14.0 seconds (reference range: 9.6–12.8 seconds), activated partial thromboplastin time (APTT) was 28.1 seconds (reference range: 20–40 seconds), international normalized ratio (INR) was 1.24 seconds (reference range: 0.86–1.14 seconds). The patient's liver function tests showed the albumin (ALB) was 36.6 g/L (reference range: 40–55 g/L), A/G was 1.12 (reference range: 1.2–2.4), and glutamyl transpeptidase (GGT) was 176 IU/L (reference range: <60 IU/L). The hepatitis serology was positive including hepatitis B surface antigen (HbsAg), hepatitis B e antigen (HbeAg), and hepatitis B core antibody (HbcAB). Hepatitis B virus deoxyribonucleic acid (HBV-DNA) was 1.31E+05 copies/mL (reference range: <1.00E +03 copies/mL). Tumor marker assays showed raised alpha-fetoprotein (AFP) with 96.43 ng/mL (reference range: <8 ng/mL) and carbohydrate antigen 19–9 (CA 19–9) with 34.54 IU/mL (reference range: <22 IU/mL). However, carcinoembryonic antigen (CEA) was 1.93 ng/mL (reference range: <5 ng/mL). Furthermore, the abdominal enhanced computerized tomographic scanning (CT) scans found that there was a 4×3 cm mass in the head of the pancreas (Fig. 1A). However, the imaging specialist suspected the presence of a tumor in the left lobe of the cirrhosis liver (Fig. 1B) which was confirmed by subsequent intraoperative exploration. The chest x-ray scan was normal.

When all the preoperative examinations were completed, the patient underwent exploratory laparotomy. We found a mass of about 4×4 cm in the nodular cirrhosis liver, which was located in segment IV, and a mass of about 4×3 cm in the pancreatic head. The pancreatic neoplasm had broken through the capsule of the pancreas, and invaded the superior mesenteric artery (SMA), portal vein (PV), and splenic vein (SV). However, the main pancreatic duct had no dilatation, and the duodenum had neither invasion nor stricture. Therefore, primary pancreatic cancer with hepatic metastasis was suspected. We conducted the puncture, with 18-gauge needles, for hepatic and pancreatic masses under ultrasonic guidance for frozen section. After that, considering the liver cirrhosis and the patient's condition, ultrasound-guided iodine-125 seeds were implanted into the hepatic and pancreatic tumors. The ethics committee of West China hospital approved this study and the patient signed the informed consent form.

The iodine-125 seeds were provided by the Beijing ZHIBO BioMedical Technology Company, China. Each particle was 0.8 mm in diameter and 4.5 mm in length, with a radioactivity of 0.6 to 0.8 mCi, radioactive half-life of 60.2 days, and radiation energy of 28 keV. Pre-procedural planning was conducted. Tumor volume was measured during laparotomy by intraoperative ultrasonography. The procedure for iodine-125 seed implantation was carried out under the guidance of ultrasound. 18-gauge needles were inserted into the tumor mass at intervals of 1.0 cm in a parallel array, extending at least 0.5 to 1.0 cm beyond

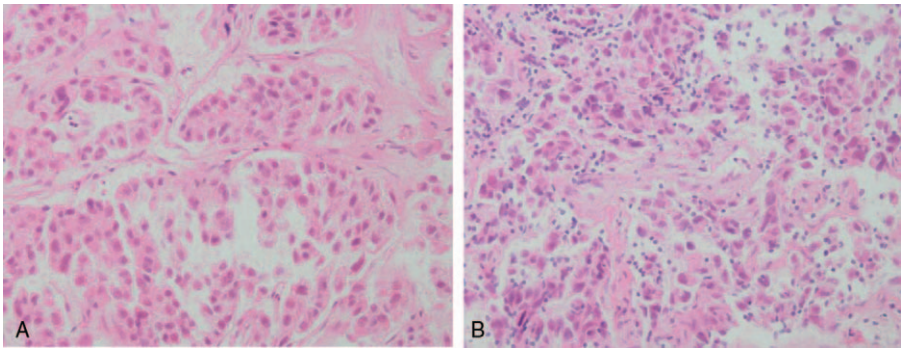

Figure 2. Hematoxylin and eosin stains showed poorly differentiated malignant cells in the hepatic (A) and pancreatic masses (B) (×400).

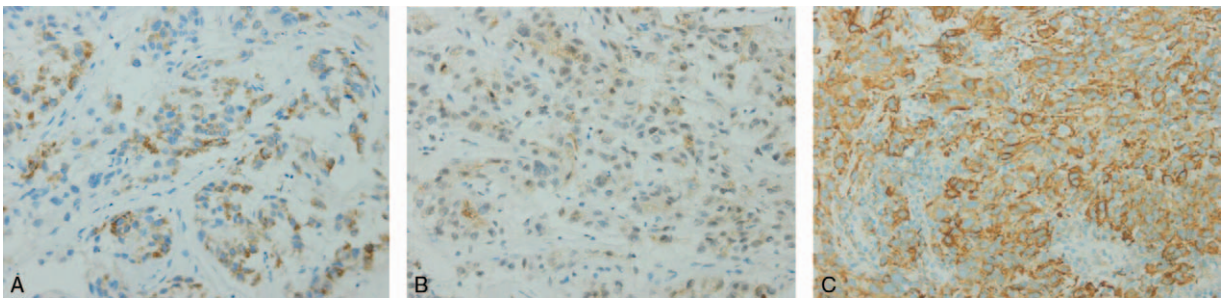

Figure 3. Immunohistochemical stains showing positive staining of the tumor cells for HepPar1 (A), GPC3 (B), and CK8 (C) (×400).

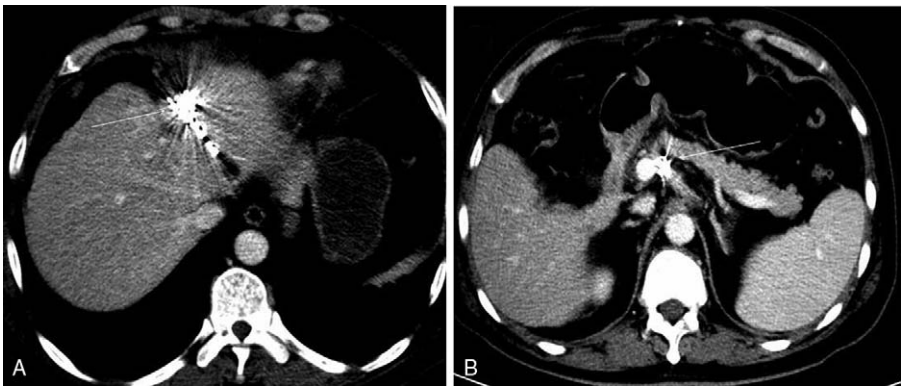

Figure 4. CT images at 15 months after I-125 seed implantation suggested that the tumors were largely reduced (A: hepatic tumor [white arrow], B: pancreatic tumor [white arrow]). CT = computerized tomographic scanning

the margins of pancreatic lesions. Penetration of the pancreatic duct, small blood vessels, and adjacent transverse colon was avoided. After the needles were placed, iodine-125 seeds were implanted using a Mick applicator and the spacing was maintained at 1.0 cm intervals. The prescription dose (PD) was set to 140 Gy.

The postoperative hematoxylin-eosin (HE) staining suggested that the hepatic tumor was poorly differentiated HCC, and the pancreatic tumor was a metastasis of the HCC (Fig. 2). The above diagnosis was further supported by immunohistochemical staining. The immunocytochemical panel consisted of HepPar1, glypican 3 (GPC3), AFP, CK8, CK18, CK7, and CK19. Of these, the hepatic neoplastic cells were strongly and diffusely positive for HepPar1, GPC3, CK8, and CK18 (Fig. 3). All other immunocytochemical stains were negative. In comparison, the GPC3, CK8, CK18, and CK19 were positive in the pancreatic neoplastic cells. The final diagnosis was pancreatic metastatic tumor from HCC. The patient's immediate postoperative course was uneventful. A medical oncologist did not recommend adjuvant systemic chemotherapy. After the operation, the patient was followed up with routine CT scans performed every 3 months. Based on this, 15 months after the initial operation of the patient, the CT examination suggested that the tumor size of the hepatic and pancreatic tumors were obviously reduced (Fig. 4). Moreover, the liver function test was mildly abnormal except for only a slight elevation in glutamic-oxalacetic transaminase (AST, 65 IU/L) and glutamic-pyruvic transaminase (ALT, 60 IU/L).

3. Discussion

HCC is one of the most common and fatal cancers in the world.[1] It is a disease that is much more common in the Eastern world. In China, most of the patients have underlying cirrhosis associated with HBV or hepatitis C virus (HCV) viral hepatitis. Currently, the symptoms of metastases confined to the pancreas at the time of diagnosis are diagnostically unspecific, and imaging also rarely

Table 1

Literature review for pancreatic metastasis from HCC.

Author	Year	Country	Tumor location	Diagnostic method	Therapy	Survival
Lowe	1997	USA	Pancreatic head	FNA	Palliative surgery (Roux-en-y cholecystojejunostomy, gastrojejunostomy)	Unknown
Texler	1998	Australia	Pancreatic tail	Postoperative pathological examination	Surgical excision (hepatectomy, distal pancreatectomy, splenectomy)	More than 16 months
Sugai	1999	Japan	Pancreatic tail	FNA	TACE (HCC) and PEI (pancreatic metastasis)	Unknown
Thirabanjasak	2009	Thailand	Pancreatic body	FNA	Chemotherapy	More than 9 months

FNA = fine needle aspiration, HCC = hepatocellular carcinoma, PEI = percutaneous ethanol injection, TACE = transcatheter arterial chemoembolization.

shows abnormalities seen only in primary neoplasms. In our patient, the metastatic pancreatic tumor originating from the HCC was a solitary tumor located in the pancreatic head. However, the primary HCC was not clearly seen in the preoperative CT. Therefore, pancreatic non-functioning neuroendocrine tumors with liver metastasis were also suspected. Finally, the laparotomy was performed.

Although remote metastasis of HCC accounts for two-thirds of cases, metastatic HCC to the pancreas is distinctly rare. Only 4 studies[8–11] have reported synchronous pancreatic metastases from the HCC as a literature review (Table 1). However, only this case was treated with iodine-125 seed implantation. Previously, HCC had been confirmed to be a radiosensitive tumor. With the development of new radiotherapy technology and facilities, the iodine-125 seed implantation therapy has provoked more interest throughout the world. The iodine-125 seed implantation is an ideal technique that combines the ability to target tumor cells under direct visualization and spare uninvolved liver parenchyma due to the sharp dose falloff outside of the implanted volume. Moreover, because of the liver's natural regenerative capabilities, a high dose of radiation can be delivered to restricted volumes by brachytherapy. With the property of local conformal radiotherapy, normal liver is spared. Hence, a potentially tumoricidal dose of radiation can be administered with acceptable complications. In 2009, Lv et al[12] reported that for patients with unresectable HCC, 48 patients who had failed transcatheter arterial chemoembolization (TACE) underwent iodine-125 seed implantation. The patients' survival rates at 1, 2, and 3 years were 75%, 45.8%, and 27.1%, respectively, with a median survival time of 15.5 months. The complications were acceptable and could be managed with conservative treatment. One randomized controlled trial study[6] suggested that iodine-125 seed implantation plus radiofrequency ablation (RFA) could obtain better local and intrahepatic tumor control as well as better long-term survival compared with treatment with RFA alone. Furthermore, for advanced tumors, Zhang et al[13] showed that CT-guided iodine-125 implantation may be a safe and effective treatment option for HCC patients with multiple pulmonary metastases. Their results suggested that the rate of complete response and partial response were 14.8% and 55.56%, respectively. The survival rates at 1 and 2 years were 67.0% and 30.8%, respectively, with a median survival of 13.5 months. However, to our knowledge, this is the first case of pancreatic metastases of HCC treated with ultrasonic guidance iodine-125 seed implantation. At 15 months follow-up, the tumor size of the hepatic and pancreatic metastasis was largely reduced. No complications occurred except for mild abnormal liver function. The iodine-125 seed implantation has some advantages, such as high-dosage in targeted organs, minimal damage to normal tissue, and avoidance of organ motion. It is a minimally invasive and accurate treatment method. Therefore, image-guided iodine-125 seed implantation may be a safe and effective treatment option for HCC patients with pancreatic metastases.

In conclusion, this is the first report with iodine-125 seed implantation for the treatment of pancreatic metastasis from HCC. Although there is presently no consensus on the optimal treatment strategy for this rare disease, image-guided iodine-125 seed implantation has been regarded as an important therapeutic approach to unresectable HCC or pancreatic tumor. For this patient, ultrasound-guided iodine-125 implantation provided an appropriate strategy for the patient with unresectable HCC accompanied with pancreatic metastasis, and can be considered by other hepatopancreatobiliary teams.

References

[1] Torre LA, Bray F, Siegel RL, et al. Global cancer statistics, 2012. CA Cancer J Clin 2015;65:87–108.

[2] Uchino K, Tateishi R, Shiina S, et al. Hepatocellular carcinoma with extrahepatic metastasis: clinical features and prognostic factors. Cancer 2011;117:4475–83.

[3] Katyal S, Oliver JH3rd, Peterson MS, et al. Extrahepatic metastases of hepatocellular carcinoma. Radiology 2000;216:698–703.

[4] Dickinson PD, Malik J, Mandall P, et al. Five-year outcomes after iodine-125 seed brachytherapy for low-risk prostate cancer at three cancer centres in the UK. BJU Int 2014;113:748–53.

[5] Wang ZM, Lu J, Liu T, et al. CT-guided interstitial brachytherapy of inoperable non-small cell lung cancer. Lung Cancer 2011;74:253–7.

[6] Chen K, Chen G, Wang H, et al. Increased survival in hepatocellular carcinoma with iodine-125 implantation plus radiofrequency ablation: a prospective randomized controlled trial. J Hepatol 2014;61:1304–11.

[7] Yu YP, Yu Q, Guo JM, et al. Effectiveness and security of CT-guided percutaneous implantation of (125)I seeds in pancreatic carcinoma. Br J Radiol 2014;87:20130642.

[8] Lowe CJJr, Riepe SP, Wood WC. Hepatocellular carcinoma presenting as a pancreatic head mass: report of an unusual case. Am J Clin Oncol 1997;20:509–10.

[9] Sugai Y, Watanabe Y, Hasoya T, et al. Pancreatic metastasis from hepatocellular carcinoma. AJR Am J Roentgenol 1999;172:839–40.

[10] Texler ML, Pierides J, Maddern GJ. Case report: a hepatocellular carcinoma metastasis in the distal pancreas. J Gastroenterol Hepatol 1998;13:467–70.

[11] Thirabanjasak D, Sosothikul D, Mahayosnond A, et al. Fibrolamellar carcinoma presenting as a pancreatic mass: case report and review of the literature. J Pediatr Hematol Oncol 2009;31:370–2.

[12] Lv J, Cao XF, Zhu B. 125I radioactive seeds implantation therapy for hepatocellular carcinoma. Gastroenterology Res 2009;2:141–7.

[13] Zhang L, Chen LH, Wang J, et al. CT-guided radioactive ^{125}I seed implantation treatment of multiple pulmonary metastases of hepatocellular carcinoma. Clin Radiol 2014;69:624–9.