Case Report
Breast metastasis from hepatocellular carcinoma: a case report and literature review

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Abstract: The incidence of breast metastasis from extramammary malignancy was rare. A case of breast metastasis from hepatocellular carcinoma (HCC) after partial hepatectomy and radical lymphadenectomy in a 49-year-old woman was reported. The breast metastasis from HCC was confirmed by immunohistochemistry. Therefore, metastatic breast HCC as end stage should be considered for patients who had liver cancer history and newly diagnosed breast lesions. And pre-operative biopsy was recommended to avoid unnecessary hepatectomy, as the patient attenuated quickly after surgery.

Keywords: Hepatocellular carcinoma (HCC), breast metastasis

Introduction
The incidence of intramammary metastasis from extramammary malignancy was rare, and the most common metastatic origins were melanoma and gastric carcinoma while pathological and clinical features may be helpful for the differential diagnosis [1, 2]. Metastases from extramammary malignancies to breast encounter 0.5% of all breast tumors [3]. Besides, the incidence of extrahepatic metastasis of HCC was approximately 13% at 5 years after medical treatment, and the most common extrahepatic metastatic site was lung [4, 5]. Herein, a rare case of breast metastasis from HCC was presented and related literatures were reviewed.

Case presentation
A 49-year-old woman was admitted for a focal liver lesion detected by the ultrasound. Routine tests for hepatic, renal and coagulation functions were normal. Besides, the HBV test revealed positive serum HBsAg, HBeAg and HBeAb. HBV-DNA copies was $2.3 \times 10^6$ IU/ml. In addition, the serum level of alpha-fetoprotein (AFP) was slightly elevated as 21.9 ng/ml (normal AFP < 10.9 ng/ml), and the other tumor markers such as CA125, CA199 and CEA were normal. In addition, dynamic enhanced CT scan of the upper abdomen showed single lesion in the right anterior lobe of the liver. The image characters of hyper-attenuation in arterial phase and washout in the late phase met the diagnosis of HCC. Multiple isolated enlarged lymph nodules were found in the hepatoduodenal ligament, and the formatted mass behind the head of pancreas was fused lymph nodes. The maximum lymph nodule was 6.0 centimeters in diameter (Figure 1).

The entecavir (0.5 mg, once a day) was administrated every day after she was enrolled, followed by partial hepatectomy and radical lymph node dissection 5 days later. Histopathological examination confirmed the HCC (poor differentiation) with neural invasion and tumor thrombus in portal vein, and the cut surface revealed a well-defined tumor of 6.0 cm × 5.0 cm × 5.0 cm. The surgical margin was negative. Microscopically, hepatic parenchyma around the tumor revealed liver cirrhosis. The tumor specimen featured cells growing in solid nests, and individual cells showed marked nuclear pleomorphism and prominent nucleoli with abundant eosinophilic granular cytoplasm and fre-
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Figure 1. Dynamic enhanced CT scan of the upper abdomen showed single lesion in the right anterior lobe. The mass behind the head of pancreas was fused lymph nodes. The chest CT scan showed no lesion in mediastinum and breast.

quent mitotic figures (Figure 2). Besides, the immunohistochemical analysis indicated positive Ki67 (>80%), VEGF, EGFR, VILLIN, CK19, and negative CK7, CK20, CD34, Hep-1 and GPC-3. The lymph nodules behind the head of pancreas were metastatic HCC; however, lymph nodes in the hepatoduodenal ligament were negative. Then she was discharged 14 days after operation, and Sorafenib (400 mg, twice a day) was administrated 21 days after the surgery.

Furthermore, she was re-admitted 1 month later because of aggravated backache. Her serum level of AFP was 24 ng/ml, and the CT scan showed no mass except multiple enlarged retroperitoneal lymph nodes (Figure 3A). Local three-dimensional conformal radiotherapy (linear accelerator 6MV photons, 36 Gy/18 times) was adjusted, and then the back pain of the patient was relieved gradually. Additionally, 4 months after the surgery, a breast mass was indicated by CT scan. Routine blood test was normal, and the liver function tests showed ALT 35.5 IU/L, AST 52.0 IU/L, TBL 29.3 µmol/L, DBIL 12.0 µmol/L, GGT 277.5 U/L, ALB 27.6 g/L, and the Child-Pugh grade of hepatic reserve was B (8 points), and the serum level of AFP was 31.7 ng/ml. The chest CT scan indicated multiple mediastinal lymph nodes under the left clavicle and around the parasternal, additionally, small amount of pericardial effusion and a mass about 2.0 cm × 2.0 cm × 1.5 cm in the upper inner quadrant of the left breast was also indicated (Figure 4). Besides, abdominal CT scan showed multiple new masses in the liver and small amount of ascites (Figure 4), and retroperitoneal lymph nodes were shrunk obviously (Figure 3B). The breast mass was resected for biopsy, and the pathological examination showed metastatic cancer invasion and the cytology revealed poorly differentiated carcinoma. Immunohistochemical analysis indicated positive C-erbB-2, Villin, AE1/AE3, and negative CK7, CK20, ER, PR, CA125, TTF-1, Naspin A, GATA-3, GPC-3, Arg-1 and GCDFP15. The tumor was similar to the HCC microscopically. As the immunohistochemical tests did not indicate primary breast cancer, a clinical diagnosis of metastatic HCC was made. The liver function of the patient was deteriorated gradually, and she received only supportive treatment. Then the patient was died from hepatorenal syndrome five month after the operation.

Discussion

The diagnosis rate of early HCC was low because of its ambiguous symptoms, and extrahepatic metastases may be presented as the initial manifestation [6]. Metastatic tumor in breast was usually single, round and painless [1]. It can be misdiagnosed as benign tumor. Unilateral left-sided and upper outer quadrant of the breast was the most frequently metastatic location [2]. Similarly, the breast lesion in this case was located in the upper inner quadrant of left breast.

Intrahepatic lymph drainage into hepatic portal lymph node via the portal triads was the usual pathway of local regional spread of HCC. And treatment of extrahepatic metastases in selected HCC patients who have good hepatic reserve, intrahepatic tumor stage (TO-T2), and are free of portal venous invasion may improve survival [7]. In this case, the peripancreatic lymph nodes were involved synchronously with HCC. The exact metastatic pathway to breast from HCC is still unknown, and more studies are needed. The prognosis of patients with lymph nodes involvement was poor, and the median survival time was 7.4 months even after hepatic resection and radical lymphadenectomy [7].
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Accurate diagnosis of metastatic breast cancer is important for selection of appropriate treatment to avoid unnecessary or even harmful therapy. Routine pathologic examination and immunohistochemical study may be helpful to confirm the diagnosis in most cases. The tumor markers such as AFP for HCC, CK7/20 for gastric carcinoma, thyroid transcription factor (TTF-1) for lung cancer, ER/PR/BRSR-2 for breast cancer and PSA for prostate cancer were helpful in differential diagnosis [2]. If immunohistochemical study showed negative breast cancer marker and positive extramammary cancer marker, the diagnosis of metastatic breast carcinoma should be considered.

In this case, the immunostaining of breast mass showed negative AFP, ER/PR and slightly positive C-erbB-2. Pathological comparison of the mass and the personal family history, clinical medical history was useful to differentiate primary and metastatic cancer. The value of AFP declined after the surgery, and 4 month later, it was elevated after the breast mass, multiple enlarged lymph nodules and recurrent HCC was detected. The breast mass showed histological structural resemblance to HCC, and the diagnosis of breast metastasis from HCC was confirmed through pathological comparison of previously diagnosed cancer and metastatic lesion.

There were significant differences in proportions of patients with invasion of the portal vein, hepatic vein, or inferior vena cava, intrahepatic metastases, and tumor stage between patients with intra- and extrahepatic metastases [8]. Metastasis to the breast from an extramammary neoplasm usually indicates disseminated metastatic disease and a poor prognosis [2]. It was reported that the frequent metastatic sites from HCC were lung, bone and lymph node. The median survival time and 1-year survival rate of HCC with extrahepatic metastases were 7 months and 24.9% [9]. Surgical resection (SR) for metastatic lesions can provide survival benefits for carefully selected patients with 1 or 2 isolated extrhepatic metastases and successful treatment of intrahepatic HCC, in addition, surgical intervention was shown to lead to relative prolongation of the survival time for HCC patients with brain metastasis, especially in those with preserved hepatic function [10, 11]. Control of intrahepatic tumor and good hepatic reserve function were the only two sig-

Figure 2. The breast mass showed pathological resemblance of the liver cancer. A. Primary HCC (hematoxylin-eosin, × 400); B. Metastatic HCC in the breast (hematoxylin-eosin, × 400); C. Specimen of metastatic breast mass from HCC.

Figure 3. Multiple enlarged lymph nodes in retroperitoneal were detected one month later after she was discharged from hospital (A). The lymph nodes were shrunk obviously after local three-dimensional conformal radiotherapy (B).
significant predictors of survival in patients with extrahepatic metastases from HCC, and therapeutic approaches to control intrahepatic tumors were important for survival improvement [12]. A variety of interventional-based liver-directed therapies and more recently systemic therapy with sorafenib are available to treat unresectable tumors, and long-term survival may be achieved from resecting metastasis at sites of the abdominal lymph node, adrenal gland, lung, and peritoneum for selected cases with limited isolated metastasis, preserved liver function and the primary tumor has been adequately controlled [13]. However, only 1 month was indicated for the presenting patient due to poor hepatic function reserve, as the patient attenuated quickly after surgery regardless of best supportive treatment. On the other hand, the therapeutic role of mastectomy for patients with breast metastasis from HCC was unknown [10, 11].

In conclusion, metastatic breast cancer should be considered when a patient had liver cancer history and newly diagnosed breast mass and pre-operative fine needle biopsy of metastatic foci was recommended, because the patient might not benefit from radical hepatectomy and mastectomy, then personalized multidisciplinary therapy should be critically selected according to the general status and hepatic reserve of the patients.

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Disclosure of conflict of interest

None.

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