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Bilateral breast lesions mimicking metastases of hepatocellular carcinoma in a male patient



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Bilateral breast lesions mimicking metastases of hepatocellular carcinoma in a male patient

Hepatocellular carcinoma metastases to the breast have been reported only rarely.

A 63-year-old male patient with metastatic hepatocellular carcinoma presented with a lump in his left breast. On physical examination, there was a hard, well-circumscribed, and partially mobile mass of 2 cm in diameter in the lower middle quadrant of the left breast. Breast ultrasound revealed a hypoechoic solid lesion of 1.8 cm × 1.9 cm in diameter in the lower middle quadrant of the left breast. F-18 FDG PET/CT imaging revealed bilateral subcutaneous nodular lesions of anterior chest wall that were adjacent but not invasive to the glandular tissues of the breasts, with high SUVmax values. Tru-cut biopsy result of the mass in the left breast region was reported as hepatocellular carcinoma metastasis. Positive immunohistochemical staining for Hep Par 1 and glypican-3 were detected. While the patient was on sorafenib therapy, he died 6 months later.

Hepatocellular carcinoma is a common malignancy for which chronic hepatitis B infection has been defined as the most common etiologic factor. The most frequent metastatic sites are the lung, bone, lymphatics, and brain, respectively, and metastases to the breast have been reported extremely rarely. Breast metastasis from non-mammary malignant neoplasm is rare, accounting for approximately 2% of breast tumors. Metastasis to the breast from an extramammary neoplasm usually indicates disseminated metastatic disease and a poor prognosis.

It should be borne in mind that a mass lesion detected in the breast region by physical examination and imaging methods may be a hepatocellular carcinoma metastasis in male or female patients with hepatocellular carcinoma.

KEY WORDS: Breast, Hepatocellular carcinoma, Metastasis

Introduction

Hepatocellular carcinoma (HCC) is the most common primary malignant tumor of the liver ¹, and causes approximately 600.000 deaths every year in the world ². Chronic liver disease and cirrhosis developing secondary to chronic hepatitis B and C infections are predisposing factors for HCC ³. HCC is a highly invasive tumor and usually has distant metastases at the time of diagnosis 4,5 . HCC most often metastasizes to the lungs, lymph nodes, bones and adrenal glands 1,5,6 . Brain, gallbladder, gastrointestinal tract, pancreas, seminal vesicles, diaphragm, kidney and splenic metastases are rarely encountered, and they almost never appear as the first metastatic site of HCC ⁷. A few cases of HCC with breast metastasis have been reported in the literature $^{2,6,8-10}$. Metastatic lesions of the breast are generally single, round, hard, painless, properly limited, fast growing, and mobile 4,11 . Unilateral left-sided and upper outer quadrant of the breast is the most frequently metastatic location 12 .

A breast metastasis from a non-mammary malignancy is rare, accounting for approximately 2% of breast tumors ⁴. Metastatic breast tumors usually do not invade the skin

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and pectoral muscle ¹¹. Ultrasonography (US), mammography (MMG), magnetic resonance imaging (MRI), fine needle aspiration biopsy (FNAB), tru-cut biopsy or excisional biopsy can be used to distinguish primary breast cancer and metastatic breast tumor ¹³. The treatment of HCC breast metastasis is not well defined because of its extremely rarity ⁴. Breast metastasis is an indicator of advanced disease stage and survivors are generally in poor condition ⁴.

This report presents unusual metastatic lesions of HCC which mimic bilateral breast metastases in a 63-year-old male patient.

Case Presentation

A 63-year-old male patient had cirrhosis due to chronic hepatitis B virus (HBV) infection for 13 years. In the 7th year of the routine follow-up of the patient, a mass lesion of approximately $3.5 \text{ cm} \times 3 \text{ cm}$ in liver segment 7 was detected and the biopsy result was reported as HCC. Initially, transarterial chemoembolization (TACE) was applied to the patient. Then, radiofrequency ablation (RFA) was applied to a lesion of $1.5 \text{ cm} \times 1.2 \text{ cm}$ in diameter in liver segment 8 approximately 1 year later. RFA therapy was applied to the patient 4 times totally in the 1st year (the diameter of liver lesion: $1.5 \text{ cm} \times 1.2 \text{ cm}$), 3rd year (the diameter of liver lesion: $1.9 \text{ cm} \times 1.5 \text{ cm}$), 4th year (the diameter of liver lesion: $2.0 \text{ cm} \times 1.0 \text{ cm}$), and 5th year (the diameter of liver lesion: $1.5 \text{ cm} \times 1.5 \text{ cm}$), 4uring the follow-up, respectively.

¹⁸F-2-fluoro-2-deoxyglucose positron emission tomography/computed tomography (¹⁸F-FDG PET/CT) revealed multiple lesions in the liver, and multiple metastases in the brain, bones, lungs, spleen and adrenal glands were also detected. Then, a systemic agent, sorafenib, which is a multikinase inhibitor with antiangiogenic and antiproliferative action, and cranial radiotherapy were planned for the patient. However, a mass lesion developed in the lower middle quadrant of the left breast 2 months later. On physical examination, there was a hard, well-circumscribed, and partially mobile mass of 2 cm in diameter in the lower middle quadrant of the left breast. Breast ultrasound revealed a hypoechoic solid lesion of 1.8 cm × 1.9 cm in diameter in the lower middle quadrant of the left breast. ¹⁸F-FDG PET/CT revealed bilateral subcutaneous nodular lesions of anterior chest wall that were adjacent but not invasive to the glandular tissues of the breasts, with high maximum standardized uptake values (SUVmax) (SUVmax: 7.01 for lesion in the right breast region, and SUVmax: 14.03 for lesion in the left breast region) (Figs. 1, 2). Tru-cut biopsy result of the mass lesion in the left breast region was reported as HCC metastasis (Fig. 3). Positive immunohistochemical staining for Hep Par 1 and glypican-3 were detected (Fig. 4). The patient was focally positive for keratin immunostain. However, stains for CD38, CD56, kappa, lambda and arginase-1 were all negative. The patient's alpha-fetoprotein (α FP) value was 2.71 ng/mL (normal range: 0-6 ng/mL) at the time of diagnosis of HCC, and was not elevated until recurrence that developed 3 years later (α FP value in 2015:



Fig. 1: F-18 FDG PET/CT images of the patient; A) coronal PET image; B) coronal CT image; C) coronal fused PET/CT image (white and black arrows indicate bilateral breast lesions).



Fig. 2: F-18 FDG PET/CT images of the patient; A) axial PET image; B) axial CT image; C) axial fused PET/CT image (white and black arrows indicate bilateral breast lesions).

Fig. 4: Glypican-3 staining of the tumor tissue by immunohistochemical method confirms that the tumor was compatible with HCC metastasis.

10.27 ng/mL, and α FP value in 2016: 126 ng/mL). The levels of α FP of the patient were always high after the 3rd year of follow-up. While he was on sorafenib therapy, the patient died approximately 2 months after the diagnosis of HCC metastasis to the left breast region.

Discussion

Hepatocellular cancer is a tumor caused by malignant transformation of the hepatocyte epithelium. It is the most common primary malignancy of the liver and is characteristically seen as a complication of chronic liver disease and cirrhosis ³. The purpose of HCC treatment is to improve survival and maintain quality of life. The development of procedures (ablation, chemo/radioembolization) that can induce tumor necrosis and positively affect survival, and the efficacy of sorafenib for patients in the advanced disease stage changed the old limited therapeutic landscape 14-16.

Although recurrence varies depending on the primary cause and treatment methods of HCC, the rate of recurrence after ablation is the same with surgical resection, but anatomical resection may provide better local control. Unfortunately, there is no effective approach to reduce the risk of recurrence. Antiviral therapy may decrease the rate of development of metachronous HCC in HBV patients 14-18.

Extrahepatic metastasis of HCC occurs in about 30-50% of patients, and it depends on HCC stages ¹⁹. The incidence rate of extrahepatic metastasis, as detected during the lifetime after medical treatment of HCC, has been reported to be approximately 13% at 5 years ²⁰. The most common sites of extrahepatic involvement are the

lungs, lymph nodes, adrenal glands, and bones ^{19,20}. 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 intrahepatic and extrahepatic metastases²¹. Breast metastasis from extramammary malignancies is very rare and its incidence is 6 times higher in women than in men 6-10. Metastasis to the breast from an extramammary neoplasm usually indicates disseminated metastatic disease and a poor prognosis ¹². The exact metastatic pathway to breast from HCC is still unknown. However, metastasis of HCC occurs frequently by way of intrahepatic blood vessels, lymphatic permeation, or direct infiltration. Hematogenous spread occurs with the involvement of hepatic or portal veins or the vena cava. Metastases have also been found in collaterals and varices, and this appears to have been the route of metastasis in the patient reported here. Tumor cells might have passed through the thoracic wall via portosystemic collaterals, the azygous system and finally intercostal veins. Another possible route is through subcutaneous collaterals communicating to thoracoepigastric veins and draining into the axillary vein. Metastatic lesions in the breast are generally fast growing, hard, mobile, and well-circumscribed lesions ^{4,11}. Breast metastases of extramammary malignancies frequently locate on the left side and upper outer quadrant of the breast ⁴⁻¹¹. In our patient, the metastatic lesion was situated in the lower middle quadrant of the left breast.

A tumor specific marker, α FP, if elevated, often correlates with liver tumor size. α FP doubling time is also closely related to tumor doubling time. A rapidly growing breast mass, diffuse tumoral infiltration of the liver and a high level of α FP in our patient are consistent with these observations. However, nearly one-fourth of patients with HCC may have normal α FP values ²². Primary breast cancer and metastasis to the breast can be distinguished by imaging methods such as US, MMG, MRI, and PET/CT, and FNAB, tru-cut biopsy or excisional biopsy must be performed ¹³. Rubino et al. described a case of 61-year-old male patient with HCC who presented with swelling of both breasts with palpable axillary adenopathy 23. The patient was an ex-drinker and had suffered previously from hepatitis B infection. Due to the clinical characteristic of the bilateral breast mass a diagnosis of bilateral breast cancer was made. Abdominal computed tomography (CT) scan showed a non-capsulated area of 6 cm within liver segment VII. To resolve diagnostic doubt between hepatic metastasis from breast cancer and HCC in a cirrhotic liver, an echo-guided needle biopsy was performed. The histologic diagnosis was HCC. They treated HCC with multiple TACE applications and hepatic surgeries during a 5-year follow-up period. The patient was submitted to simultaneous bilateral mastectomy according to Patey shortly after the first TACE application. The histologic examination of the two breast tumors showed: 1) infil-

lar carcinoma with metastasis at two lymph nodes at right axillary level I and II; 2) infiltrating lobular carcinoma on the left side. Because of metastatic right axillary lymph nodes, six cycles of adjuvant systemic chemotherapy were administered. The patient underwent hormone treatment with tamoxifene. Patient died for progression of disease and liver failure 5 years after the diagnosis of both bilateral breast cancer and HCC. When we reviewed our patient's management progress, we found that initial chest CT scan did not report any lesion in the breast regions of our patient. However, on physical examination, a hard breast lump was palpated in the left breast. ¹⁸F-FDG PET/CT revealed bilateral subcutaneous nodular lesions of anterior chest wall that were adjacent but not invasive to the glandular tissues of the breasts, with high SUVmax values. Moreover, breast US showed a hypoechoic solid lesion of 1.8 cm × 1.9 cm in diameter in the lower middle quadrant of the left breast, and then tru-cut biopsy was performed, which revealed a HCC metastasis. Han et al. reported that thoracic CT imaging revealed a mass about 2.0 cm \times 2.0 cm \times 1.5 cm in the upper inner quadrant of the left breast in a 49-year-old woman with high α FP level in the 4th month after resection for HCC 9. Excisional biopsy of the breast mass was compatible with HCC metastasis. This patient developed HCC because of her chronic HBV infection, and she had multiple liver metastases and small amount of ascites in the abdomen. Similarly, our patient developed HCC on the background of chronic HBV infection, while his therapy was continuing for chronic HBV infection. Then, multiple HCC recurrences developed, and HCC metastasized to bilateral breast regions while he had already distant metastases.

trating ductal carcinoma associated with infiltrating lobu-

The correct 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 hepatocellular markers used for diagnosis of HCC in liver biopsies and surgical specimens vary widely. Hepatocyte paraffin antigen 1 (Hep Par 1), polyclonal antibody directed against carcinoembryonic antigen (p-CEA), glypican-3 (GPC-3), arginase-1 (Arg-1), bile salt export pump (BSEP), glutamine synthetase (GS), heat shock protein-70 (HSP70), enhancer of zeste homologue 2 (EZH2), aldehyde dehydrogenase 1A1 (ALDH1A1), golprotein-73 (GP73), des-α-carboxy prothrombin gi (DCP), keratin 19 (K19), α -fetoprotein (α FP), villin, reticulin, CD10, CD31, and CD34 are among the hepatocellular markers used for differential diagnosis ²⁴⁻²⁹. If immunohistochemical study showed negative breast cancer marker and positive extramammary cancer marker, the diagnosis of metastatic breast carcinoma should be considered. In the presented case, positive immunohistochemical staining for Hep Par 1 and GPC-3 were

detected. The patient was focally positive for keratin immunostain. However, stains for CD38, CD56, kappa, lambda and Arg-1 were all negative.

Conclusion

In conclusion, it should be borne in mind that a mass lesion detected in the breast region by physical examination and imaging methods may be a HCC metastasis in male or female patients with HCC. Fine needle or tru-cut biopsy of metastatic focus was recommended because the patient might not benefit from mastectomy. Then, personalized multidisciplinary therapy should be critically selected according to the general status of the patient.

Riassunto

Le metastasi di carcinoma epatocellulare al seno sono un reperto molto raro.

Un paziente maschio di 63 anni con carcinoma epatocellulare metastatico presentava un nodulo al seno sinistro. All'esame obiettivo, c'era una massa dura, ben circoscritta e parzialmente mobile di 2 cm di diametro nel quadrante medio inferiore del seno sinistro. L'ecografia mammaria ha rivelato una lesione solida ipoecogena di 1,8 cm × 1,9 cm di diametro nel quadrante medio inferiore del seno sinistro. L'imaging F-18 FDG PET / CT ha rivelato lesioni nodulari sottocutanee bilaterali della parete toracica anteriore che erano adiacenti ma non invasive ai tessuti ghiandolari del seno, con valori di SUV massimo elevati. Il risultato della biopsia tru-cut della massa nella regione del seno sinistro ha diagnosticato trattarsi di una metastasi del carcinoma epatocellulare. Sono state rilevate colorazioni immunoistochimiche positive per Hep Par 1 e glypican-3.

Il decesso del paziente si è verificato 6 mesi dopo, nel corso di trattamento con sorafenib.

Il carcinoma epatocellulare è un tumore maligno noto per essere l'infezione da epatite B cronica il suo fattore eziologico più comune. I siti metastatici più frequenti sono rispettivamente il polmone, l'osso, i linfatici e il cervello; le metastasi al seno sono state riportate molto raramente.

La metastasi al seno da neoplasia maligna non mammaria è rara e rappresenta circa il 2% dei tumori al seno. Le metastasi al seno dovute a una neoplasia non della mammella di solito indicano l'esistenza di una disseminazione di malattia metastatica e una prognosi sfavorevole.

Alla luce di questa esperienza va tenuto presente che una massa rilevata nel contesto della ghiandola mammaria con esame fisico e strumentali di imaging in pazienti di maschi o femmine portatori di un carcinoma epatocellulare, può esserne una manifestazione metastatica.

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