

Case Report

Synchronous primary breast cancer and hepatocellular carcinoma in a male patient: a case report

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Abstract: Male breast cancer is a rare malignant disease characterized by hormonal imbalance. Hepatocellular carcinoma (HCC) is the most common neoplasm of the liver, and is generally correlated with hepatitis B or C virus-related cirrhosis. While to our knowledge a case with these two malignant diseases in a same male patient in the concomitant period is an exceptional event, rarely reported in literature. In this report, we present a case in which a Chinese patient with hepatitis B developed a tumor mass that originated from segment V of the liver and presented with right breast nodules at the same time. Synchronous mastectomy and hepatectomy were performed, and standard endocrine therapy and chemotherapy as adjuvant treatment were therefore followed. The diverse histogenesis of the two kinds of cancers highlights the need for us to investigate any common physiopathogenetic elements.

Keywords: Male breast cancer, hepatocellular carcinoma, synchronous resection

Introduction

In the worldwide, male breast cancer (MBC) is an uncommon disease, accounting for approximately 1% of all cases of breast cancer and only 0.85-1.3 per 100000 men population [1, 2]. Compared with female breast cancer, a large proportion of them probably be associated with higher ratio of positive hormone receptor (estrogen receptor ER, progesterone receptor PR) expression [3]. However, by contrast, epidermal growth factor receptor (HER2) over-expression is a relatively rare event. Age, BRCA2 mutations, altered ratio of estrogen to androgen and lack of exercise have been the mostly studied risk factors in the literature. The treatment therapy for female breast cancer has been proposed as standard principles for breast cancer in men [4]. Hepatocellular carcinoma (HCC) is a tumor mostly born in developing countries and the sixth most frequent cause of cancer related death worldwide [5]. The dominant risk factor for HCC is chronic infection with HBV, which accounts for 52% of all HCC and virtually all from eastern Asia and sub-Saharan Africa [6]. In the opposite, the hepatitis C virus (HCV) and alcohol abuse were the

main risk factors in the United States. During the past two decades, the incidence of new occurrence has increased to three times while cumulative 5-year overall survival rate was still less than 12% [6]. Surveillance with ultrasonography and serum alpha-fetoprotein allows early stage diagnosis when curative treatment is feasible by resection, transplantation, or ablation, and median survival beyond 5 years may be achieved [7].

Until recently, there is a rare reported case of concomitant MBC and HCC in the general literature. If the mass is not diagnosed correctly, it can be mistaken for metastatic breast cancer to the liver and result in a very different treatment therapy. Therefore, appropriate investigation and proper management at an early stage of illness is very important. In this case report, we describe an early staged HCC patient with synchronous extrahepatic tumor mass in upper outer quadrant of the right breast. The tumor nodule was punctured and a core needle biopsy was confirmed as malignant. Afterwards, concomitant surgical extirpation of segment V of the liver and right modified radical mastectomy was performed.

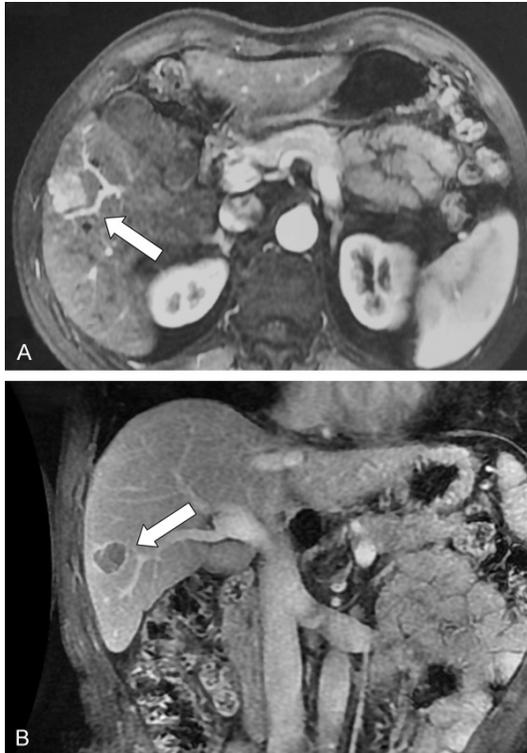


Figure 1. A. Enhanced magnetic resonance imaging (MRI) of the liver revealing an irregular 22 × 20 mm lesion within the segment V, approaching the right anterior branch of hepatic portal vein and the liver capsule. B. Sagittal section of enhanced MRI scan showing the primary lesion in the T1WI delayed phase.

Case presentation

A 60-year-old man who had been diagnosed with liver cirrhosis type B seven years ago presented to Cancer Institute and Hospital affiliated to Chinese Academy of Medical Science in July 2014 because of an elevation of serum alpha fetoprotein (AFP). The patient had been seen regularly and was generally healthy until his AFP level began to rise to 163.4 ng/mL. In the meanwhile, no specific symptom concerning malaise, weakness, anorexia, weight loss and upper abdominal pain was complained. An immediate color Doppler ultrasonic scanning (US) of his upper abdomen showed an uneven surface of the liver along with a nodule of hypoecho pattern in the segment V, 2.3 × 1.9 cm in diameter. Computed tomography (CT) of the liver revealed multiple foci of heterogeneous mass lesions. Only the largest mass roughly 1.9 cm × 2.0 cm located in segment V was enhanced. This irregular mass was also

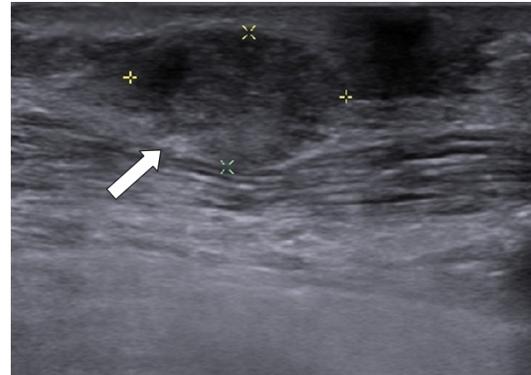


Figure 2. An ultrasonogram showing a well boundary inhomogeneous hypoechoic mass located in upper outer quadrant of the right breast.

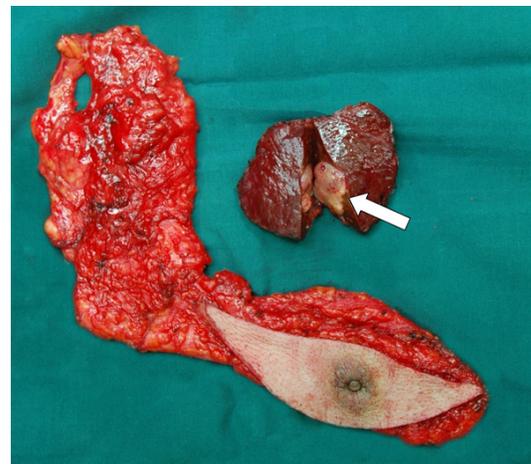


Figure 3. Resected specimen of liver tumor (arrow), right breast and subaxillary nodes. The HCC tumor is tan-white, firm and covered with a pseudocapsule.

showed with T1WI low signal, T2WI/FS high signal, restricted diffusion in DWI and early enhancement after injection of gadolinium-diethylenetriaminepentaacetic acid (Gd-DTPA) in magnetic resonance imaging (MRI) (**Figure 1**). Laboratory findings were normal: serum aspartate aminotransferase (ALT), 10 IU/L; alanine aminotransferase (AST), 12 IU/L; bilirubin, 10.1 μmol/L; creatinine, 0.8 mg/dL. We made diagnosis of primary HCC depending on the two kinds of positive imaging findings and elevated AFP. The patient was a non-smoker, however, occasionally consumed alcohol. In the past seven years, he had regularly taken oral adefovir dipivoxil to combat HBV propagation. No history of portal hypertension, splenomegaly and other concurrent disease had been identified.

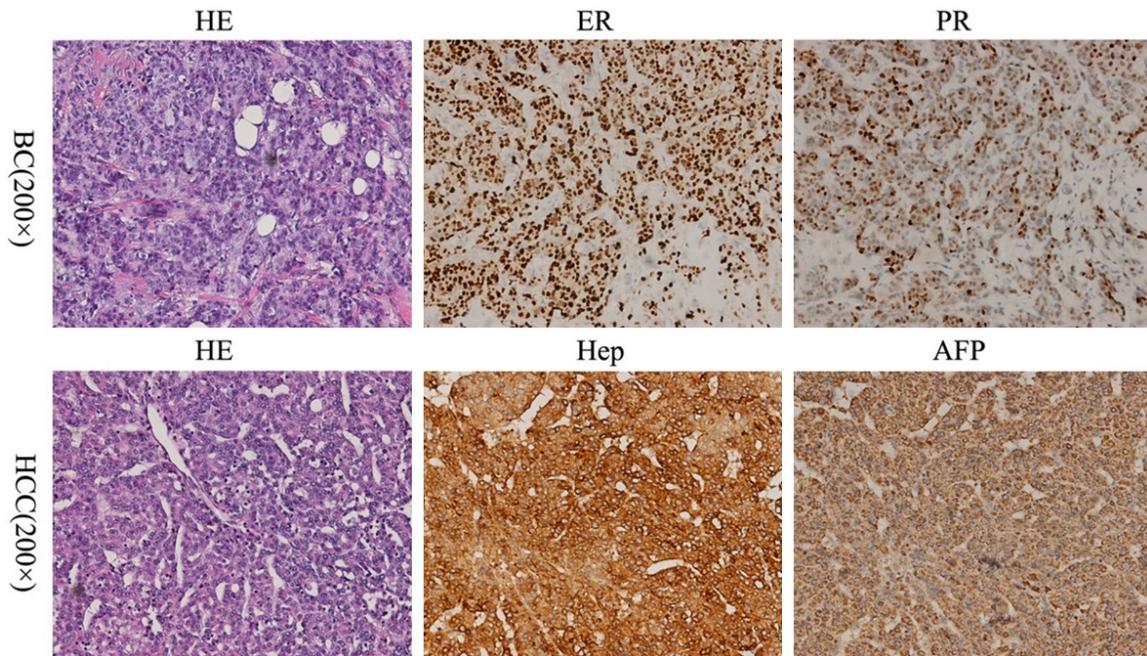


Figure 4. Pathologic findings for breast invasive ductal carcinoma (upper) and hepatocellular carcinoma (lower). The invasive ductal carcinoma comprised of concentrated mitotic cells (stain, hematoxylin and eosin; magnification, $\times 200$). Immunohistochemical staining for PR expression were weaker than ER. No microvascular invasion were observed in the microscopic findings of primary HCC tumor (magnification, $\times 200$). Immunohistochemical analysis demonstrated that Hepatocyte Specific Antigen antibody and α -fetoprotein were positive in the cytoplasm.

Then this patient was admitted to the hospital prepared for surgical intervention. However, on physical examination, a roughly 2 cm nontender mass was detected in upper outer quadrant of his right breast, while the other breast was normal. The mass was firm, round, and not fixed to the underlying structure. There was no bloody discharge from the right breast nipple or skin dimple and no lymph node enlargement in the axillary and supraclavicular regions. Ultrasonography displayed an inhomogeneous hypoechoic nodule measuring 1.5 cm \times 1.0 cm with a regular boundary (**Figure 2**). Serum carcinoembryonic antigen (CEA) and carbohydrate antigen 15-3 (CA15-3) were in the normal ranges (3.7 ng/mL and 17.9 U/mL, respectively). A percutaneous ultrasound guided core needle biopsy was then performed and pathological diagnosis of invasive ductal carcinoma was obtained. Afterwards, a positron emission tomography (PET) was decided to carry out to confirm whether the tumor mass located in the liver is a metastatic nodule originated from the breast and if there are new metastatic masses which have not been detected. Consequently, an affluent solitary uptake of 2-deoxy-2-(18) fluoro-D-glucose (FDG) was observed in the right

breast (SUV, 3.7) but not in the right anterior lobe of liver (SUV, 2.6) or other body areas. Therefore, the overall presentation of the nodule located in segment V was not a typical pattern of metastasis. In view of the discrepant CT and PET findings, we suspected that synchronous primary breast cancer and primary liver cancer concurrently emerged.

After discussion by multidisciplinary treatment group, the most reasonable therapy for this individual patient was recommended. As maximum diameter of the breast tumor was < 2 cm and no metastatic lymph node was observed, the preoperative clinical staging for breast tumor is cT1N0M0 by American Joint Committee on Cancer (AJCC) guidelines. In the meanwhile, the Barcelona Clinic Liver Cancer (BCLC) staging system for the liver tumor was classified as A1. Synchronous surgical treatment without preoperative neoadjuvant chemotherapy was advised. Modified right mastectomy and hepatic segmentectomy was performed concomitantly one week after initial diagnosis.

The postoperative histopathological examination of the resected breast tumor tissue showed

invasive ductal carcinoma, unspecified type, G2, and no nerve infiltration or intraductal tumor embolus. The tumor mass was found to be $1.5 \times 1 \times 1$ cm in diameter, and the cut surface was gray-white colored (**Figure 3**). The nipple, skin, pectoral fascia and resected lymph nodes (0/25) were not found with massive metastatic invasive ductal carcinoma cells microscopically. Immunohistochemical studies (**Figure 4**) revealed that: ER(80%+), PR(60%+), HER2(++), Ki67(40%), TOP2A(20%+), CK5/6(-), EGFR(1+), E-cadherin(3+). In situ hybridization assay did not show amplified results in assessment of HER2 tumor status. The resected liver specimen revealed a well-defined, tan-white, firm tumor measuring $2.3 \times 2 \times 1$ cm with a slightly cirrhotic background (**Figure 3**). Microscopic findings showed moderately differentiated HCC which directly invaded the liver capsule but not involved a major branch of the portal vein or hepatic vein and adjacent organs. No microvascular invasion or microsatellites were observed and the minimum resection margin was 1.5 cm. Immunohistochemical test (**Figure 4**) were featured of AFP(2+), Hepatocyte(3+) and the patient's pTNM stage according to the AJCC Cancer Staging Manual (7th Edition) was pT1NOMO (solitary tumor without vascular invasion). The histological diagnosis was reviewed by three independent pathologists.

Following postoperative recovery, the patient was discharged on the ninth postoperative day and referred to the department of internal medical oncology. Combined adjuvant chemotherapy of epirubicin (160 mg), cyclophosphamide (1000 mg) for four cycles and endocrine treatment of tamoxifen were added for breast cancer. Only close examination was recommended for HCC. At follow-up two months after surgery, no signs of cancer relapse were observed. The patient had a normal CT and alpha-fetoprotein level had markedly decreased to 16.5 ng/mL.

Discussion

Breast cancer is the most frequent cancer in females, with an estimated more than 229 000 new cases of this malignant disease diagnosed in 2011 alone and 39 000 died in the United States [8]. By contrast with other highly prevalent cancers, breast cancer has been incredibly difficult for both patients and health care pro-

viders in view of its complexity and high morbidity rates in many years. Over the past decade, the mortality rates of breast cancer is declining in most developed areas, suggesting a benefit from improved diagnostic capacity and the availability of effective treatment. However, despite the increased incidence of female breast cancer over the last 25 years, male breast cancer is still a rare disease [8]. In a previously reported study, the greatest proportional cases of MBC are about ten years older than that of female breast cancer in China (median age at 61 years) [9]. Compared with breast cancer in women, MBC patients are more likely to present with pathological or immunohistochemical features of invasive ductal carcinoma, higher rates of hormone receptor (HR) expression and a rare HER2 overexpression [10]. For this reason, the prognosis of MBC may be better than that of female breast cancer as women with HER2 overexpression have a significantly shortened disease-free survival and overall survival [11].

HCC, as a prevalent malignancy in Asia and Africa, has shown an increased incidence and mortality rates in North America and Europe [12, 13]. As the most common primary liver neoplasm, it is an epithelial tumor arising from malignant transformation of benign hepatocytes and often develops within a cirrhotic background. AFP, an alpha-1 globulin born in fetal, proliferating, and malignant hepatocytes, is often recommended for surveillance of HCC and > 400 ng per milliliter is highly predictive. To our knowledge, a case with these two malignant diseases concomitantly in a same male patient is an exceptional event and rarely reported in the literature. By comparison, metastatic breast cancer to the liver is more common, even in patients who have not a history of cancer.

This patient's presentation with a solitary nodule in upper outer quadrant of the right breast strongly suggested metastatic breast cancer to the liver. However, in light of the patient's cirrhotic liver and hepatitis B virus (HBV) infection background combined with elevated AFP, there is also an incidence of a HCC tumor mass metastasizing to the breast. Previous studies reported that metastasis to breast by nonmammary malignancy is approximately 1.3-2.7% [14]. Although theoretically any malignant tumor has a probability of metastasizing to the

breast, the most common primary tumors are lymphoma, melanoma, rhabdomyosarcomas and lung cancer [15, 16]. Metastasis to breast arising from liver has rarely been reported as the liver tumor preferentially metastasizes to the lungs, the other parts of the liver, the bone, adrenal glands, and regional lymph nodes [17]. Ji YR et al. [17] previously reported a case of 41-year-old woman diagnosed by HCC who underwent a left lobectomy of the liver, and three years later presented with a rapidly growing breast metastasis. Therefore, it is challenging to differentiate metastasis of HCC to the breast or metastasis of the breast cancer to the liver from synchronous double primary carcinoma of breast and liver. Afterwards, a core needle biopsy was performed to obtain pathological diagnosis. As the fine needle aspiration is often difficult to distinguish primary from metastatic disease in instances when cells are highly anaplastic, the core needle biopsy is usually associated with a higher diagnostic accuracy.

When the punctured pathological examination of invasive ductal carcinoma had been established, both the surgeon and pathologist suggested a whole-body PET/CT evaluation, which was widely applied for cancer staging, including malignancies of head/neck, lung cancer, breast, colon/rectum, lymphoma, etc. Although PET/CT is relatively more limited in the evaluation of primary HCC than the above mentioned cancers because of its relatively low uptake of FDG [18], it still plays an important role in the evaluation of tumor aggressiveness and detection of extrahepatic metastatic lesions. Therefore, our patient underwent PET/CT, a routine in our hospital, to be differentiated furthermore. Unexpectedly, unfamiliar pattern of low FDG uptake was found and primary HCC had a higher probability but metastatic breast cancer to the liver could not be eliminated completely.

In such a situation, a percutaneous needle biopsy of the liver tumor, as in the present case, may clinch the diagnosis. Some authors had asserted that percutaneous liver biopsy under radiological guidance presented a relatively high sensitivity and specificity, with 90%, 91% for US and 92%, 98% for CT scan guidance respectively [19]. However, a negative biopsy result, although highly suggestive, could not completely rule out malignant disease, and the

nodule should be further analyzed after 3- to 6-month intervals. In the meanwhile, the growth and development of HCC is so rapid that even after resection the incidence of recurrence is still up to 70% at 5 years and 15-30% after liver transplantation, ultimately leading to tumor related death [20]. For this reason, there is an urgency of exact diagnosis and standard treatment. In the present dilemma, surgical resection for segment V and modified radical mastectomy at the same term was recommended by a group of experts in oncology.

Although a history of previous intake of estrogen and existence of gynecomastia was not observed in our patient, liver cirrhosis was considered to be a risk factor for male breast cancer [4], which might result in an underlying hormonal imbalance. Owing to its rarity, specific treatment guidelines for MBC are lacking. Treatment of male breast cancer generally follows the same principles as female breast cancer therapy [21]. Combination chemotherapy regimens administered as postoperative adjuvant therapy are integrated parts of the multidisciplinary curative treatment for primary breast cancer and often give rise to significant reduction of recurrence rate and better over survival [22]. Overexpression of HER2 occurs in 25 to 30 percent of breast cancers and in these cases patients are usually correlated with significantly shortened disease free survival and overall survival [23, 24]. Addition of trastuzumab to conventional chemotherapy for HER2-positive patients significantly reduces the risk of recurrence and death [25]. In the present case, in situ hybridization assay did not show amplified results, hence, trastuzumab was not added postoperatively. Prognostic factors predicting for future recurrence of breast cancer is highly variable, depending on race distribution and geographic diversity. Major risk factors include patient age, comorbidity, tumor size, tumor grade, number of involved axillary lymph nodes, and possibly HER2 tumor status [25]. Although there are certain characteristics shared by both genders, conspicuous differences still exist concerning incidence, age distribution, sex hormone receptor expression, prognosis and survival [4, 10]. A recent study has showed that even in the same extent of adjuvant treatment, males were inclined to have a poorer long term outcome compared with females [21]. Mitra Tewes et al. [26] found that the detection rate of disseminated and cir-

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culating tumor cells in MBC is comparable with the rate obtained in female breast cancer. Patten et al. [27] demonstrated a survival advantage for MBC patients given tamoxifen after mastectomy and asserted that positive hormone receptor status seemed to be a benefit factor.

Nowadays, treatment of hepatocellular carcinoma has changed greatly within the past decade. Potentially curative therapies (resection, transplantation, ablation) can improve survival in patients diagnosed at an early HCC stage (BCLC stage 0 or A) and offer a possibility of long-term cure [20]. In the present case, this solitary tumor was 2.3 cm and staged by pT1N0M0 with compensated Child-Pugh class A. For Child-Pugh class A patients with small HCC, surgical resection is the first treatment choice to consider [7]. Anatomical resection is preferred to non-anatomical resection and often associated with a favorable 5-year overall survival rate [6]. There is also no consensus for a minimum resection margin. Some authors demonstrated lower recurrence rate and longer overall survival with a 2 cm margin compared to a 1 cm margin, as a wider margin is likely to dissect the adjacent satellitosis which may prevent early recurrence [28]. Whereas other authors have not found significant differences between margin \leq and $>$ 1 cm [29, 30]. They suggested that intrahepatic recurrence was mostly multifocal recurrence but not marginal recurrence.

In conclusion, we believe this is the first case involved the coincident occurrence of primary male breast cancer and HCC which underwent surgical resection at the same term. Although it is a rare phenomenon, clinicians may encounter many similar conditions. Our case highlights the need to consider multi-primary malignant diagnoses in those with prior malignancies, and to combine their respective standard treatment tactics. We recommend performing biopsy sampling to rule out metastatic disease in addition to imaging studies and multidisciplinary treatment group to supervise the most appropriate therapy.

Disclosure of conflict of interest

None.

Abbreviations

MBC, Male breast cancer; ER, Estrogen receptor; PR, Progesterone receptor; HCC, Hepa-

tocellular carcinoma; AFP, Serum alpha fetoprotein; US, Ultrasonic scanning; CT, Computed tomography; MRI, Magnetic resonance imaging; PET, Positron emission tomography.

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