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CASE REPORT

특발성 간경변증 환자에서 발생한 남성 유방암

신수린, 이명석, 박상훈, 최종수, 이경민, 김진배, 김형수, 김정원[1]
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A Case of Breast Cancer in a Male Patient with Cryptogenic Cirrhosis

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Breast cancer is a rare disease in men. We report a case of 53-year-old obese male, with known cryptogenic cirrhosis and hepatocellular carcinoma, presenting a tender mass on left breast. He was diagnosed with invasive intraductal carcinoma, which was consistent with a sporadic lesion. On the basis of previous literatures, obesity can be regarded as a cause for breast cancer even in men. However, there has been inconsistent data about link between liver cirrhosis and male breast cancer, which can be due to heterogenity in the etiology of cirrhosis. Through this case, it can be postulated that the risk for male breast cancer may vary according to the etiology of cirrhosis. **(Korean J Gastroenterol 2012;60:182-185)**

Key Words: Breast cancer; Cirrhosis; Non-alcoholic fatty liver disease; Hepatocellular carcinoma

INTRODUCTION

Male breast cancer (BC) is a rare disease, which make up less than 1% of all breast malignancies in United States.[1] The incidence in Korea has been reported at about 0.2 per year/100,000 and its prevalence accounts for 0.6% of all BC in Korea (Korean Statistical Information Service, http://kosis.kr).

Because of the rarity, relatively little is known regarding the etiology of male BC and mostly depends on case-control studies. To date, several conditions to predispose BC in men were identified, which included family history of first-degree relative with BC, Klinefelter syndrome, mutations on breast cancer susceptibility gene (BRCA) 1 and 2, and obesity.[2-5] Relationships with other conditions in male BC, including low physical activity, alcohol ingestion, gynecomastia, history of bone fracture, liver cirrhosis, and diabetes were indicated in several studies, but not significant in other studies.

Obesity is well known for the cause of non-alcoholic fatty liver disease (NAFLD), represented by the more aggressive non-alcoholic steatohepatitis (NASH). NASH can progress to cirrhosis and its related complications including hepatocellular carcinoma (HCC). NASH accounts for a large proportion of cryptogenic cirrhosis, even though most of the histologic hallmarks of NASH are not present in cryptogenic cirrhosis.[6]

Here we report a case with BC in obese man after having cryptogenic cirrhosis with HCC. We believe this case is worthy of being discussed to speculate the effect of cirrhosis on male BC.

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CASE REPORT

A 53-year-old man, with known cryptogenic cirrhosis of the liver, presented a painful mass on left breast developed 3 months ago. He had undergone wedge resection of liver due to HCC 3 years ago. The following year, HCC recurred, and a total of 3 sessions of transarterial chemoembolization (TACE) were done over next 2 years. He has been treated with insulin for 3 years due to diabetes. Current medications included proton pump inhibitor with itopride for reflux symptom and ursodeoxycolic acid but not diuretics. He was a self-employed man and never drank or smoked. There was no family history of malignancy. The patient's height was 167 cm, body weight 81 kg, and body mass index 29.4 kg/m^2, and he weighted more than 100 kg during last 10 years. Physical examination revealed gynecomastia in both breasts and a tender mass on left one. He had Child-Pugh class A cirrhosis (score 5). On computed tomography, a mass of 3 cm in size showing speculation of the margin at left subareolar area was scanned (Fig. 1A). Breast ultrasonography depicted a hypoechoic mass containing uneven calcifications and a lymph node enlargement of 2 cm in size on left axilla (Fig. 1B). Since the lesion was highly suspicious of malignancy according to aforementioned findings, the modified radical mastectomy with axillary lymph node dissection including level I and II was performed. The final pathology showed invasive intraductal carcinoma of 3.5×3.0×2.0 cm invading skin and nipple (Fig. 2). Eight of 29 lymph nodes were confirmed as metastatsis,

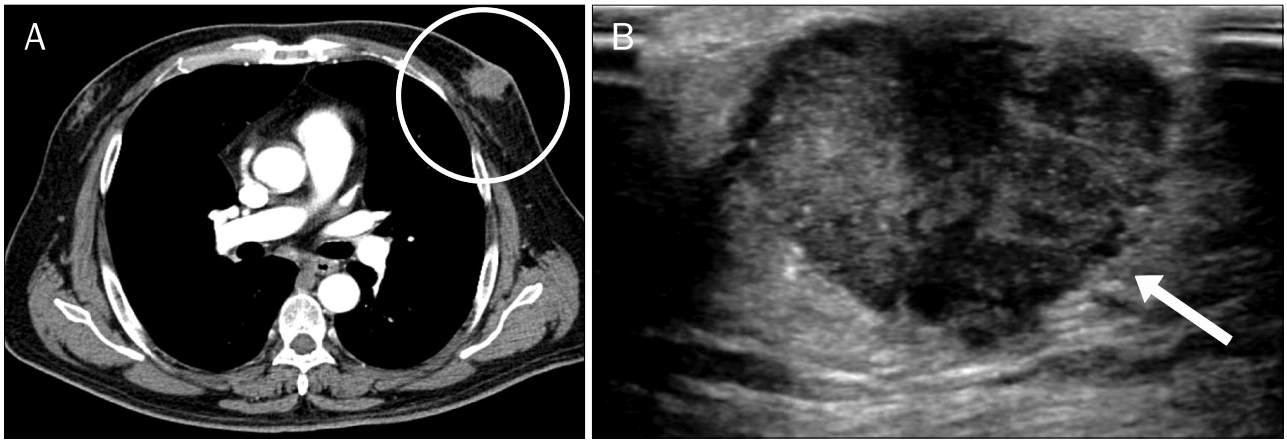

Fig. 1. Radiologic findings of the patient. (A) Computed tomography showed low attenuated lesion with spiculated margin in the left breast (white circle). (B) Ultrasonographic scanning shows lobular hypoechoic mass of 3.2 cm in size including calcification on the left subareolar area (white arrow).

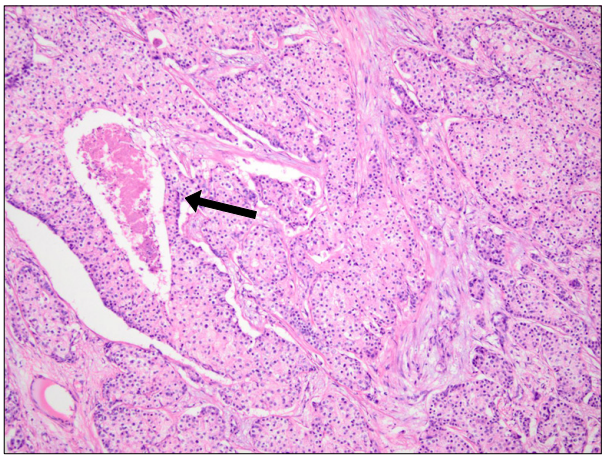

Fig. 2. Microscpic image of H&E (×100). Invasive ductal carcinoma with prominent desmoplastic response and comedo necrosis was present (arrow). There was a lack of glandular differentiation.

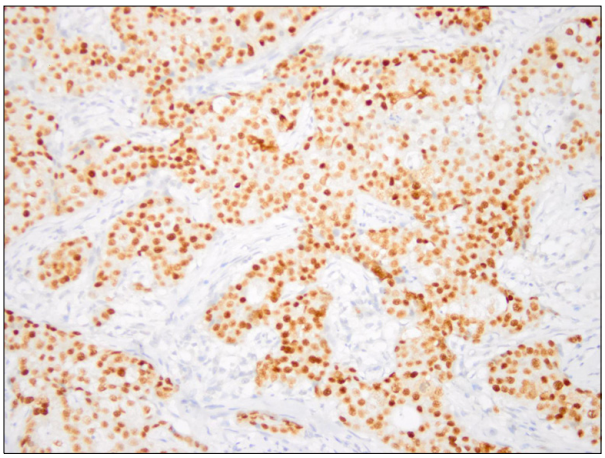

Fig. 3. Representative immunohistochemical staining (×200). The tumor cells stained with brown color represented strong and diffuse positivity for estrogen receptor.

and the final stage was pT2N2M0, stage IIIA. Immunohistochemical staining showed positivity for c-erbB2, and strong positivity for estrogen and progesteron receptors (Fig. 3). Serum estrogen level was 237 pg/mL, which was more than 2 times of upper normal limit in men. He received radiotherapy following adjuvant chemotherapy. Since then, tamoxifen combined with herceptin has been administered till now, 14 months after the operation. In addition, 4 sessions of TACE were done for HCC concomitantly with the BC treatment. At present, there is no evidence of recurrence of either HCC or BC.

DISCUSSION

Similarly to female, predisposing factors for male BC are divided into genetic and hormonal factors. The former is related with hereditary BC and identified risks include germline BRCA1 and BRCA2 mutations, and Klinefelter syndrome. The latter is called sporadic BC, caused by acquired condition with high circulating estrogen level.[7] As results, the sporadic BCs tend to be positive for estrogen receptor. Albeit poorly developed ducts without lobule formation, male breast is also influenced by estrogen. Estrogen exposure can increase the number of potential target cells by stimulating breast growth and drive cycles of proliferation that promote DNA damage. Once premalignant or malignant cells are present, hormones can stimulate their growth as well as the growth of normal epithelial and stromal cells that may aid tumor development. In addition, estrogen may also play a more direct role in carcinogenesis through its metabolites.[8] Abnormal circumstances of hyperestrogenism was maintained for a long time without any genetic risk factor related BC in our case. Increased serum estrogen level was ascertained and estrogen receptor was positive in histology as like other male BC. These findings strongly suggest that BC in this patient is most likely sporadic disease.

Among his characteristics, obesity appears to play major etiologic role because body mass index of the patient had been approximately 36 kg/m^2 during more than 10 years. Obesity has been relatively well-documented as an implication in male BC. Though variable definitions of obesity were used, risk for BC in obese men is reported about 1.6-2.6 times compared to non-obese men.[2-5] In obese men, plasma testosterone and sex hormone-binding globulin levels are decreased but estrogen production, metabolism, and bioavailability are enhanced by peripheral conversion of testosterone to estradiol and androstenedione to estrone. Obesity is also associated with an increased risk and poor prognosis of postmenopausal female BC, presumably through peripheral conversion of androgens to estrogens.

Cirrhosis has been proposed as a possible risk factor for male BC.[9-11] The hypothesis is based on the hormonal imbalance occurs in cirrhotic patients. A combined testicular and pituitary abnormality in cirrhosis leads to decreased testosterone production and impaired hepatic extraction of adrenal androstenedione induces the extraglandular conversion to estrone and estradiol, which partially suppresses luteinizing hormone and results in hyperestrogenism. However, in spite of high plausibility, the cases of male BC in cirrhotic patients have been rarely documented, and only few case-control studies revealed significant association (Table 1). Although authors postulate the link of cirrhosis with male BC suggest that the reason for the lack of association is that cirrhotic patients do not live long enough to develop BC, it has been only hypothesis yet.[12]

Given that the patient had been overweighed during more than 10 years and had late-onset diabetes, cryptogenic cirrhosis is supposed to be induced by NASH.[6] As mentioned above, despite cirrhosis can lead hyperestrogenic condition, there is insufficient evidence that cirrhosis predisposes male BC. Through our case, authors suggest that the inconsistent results of previous studies about relation between liver cirrhosis and male BC may be due to different etiologies of cirrhosis, because patients with NASH-associated cirrhosis inevitably have increased risk for male BC compared to cirrhosis from other causes. Unfortunately, most case-control studies about cirrhosis and male BC did not determine the etiology of cirrhosis. There is an unique report to classify liver disease, in which the type of liver disease did not affect the incidence of male BC.[13] However, they included patients with non-cirrhotic liver disease, did not distinguish cirrhosis from other liver disease, and the etiologies of liver disease was poorly categorized except alcohol. Even in case reports described the details of subjects, the physical measurements were mostly omitted and cryptogenic cirrhosis was verified in only one case report.[14] Lack of understanding about NASH than now may contribute the insufficient etiologic evaluation of cirrhosis in previous studies.

Table 1. Summary of Reports Assessing the Link between Liver Cirrhosis and Male Breast Cancer

Author	Country	Type of publication	Material and method	Etiology	Association with LC	Other risk factors	Remark
Yoneda et al.[14]	Japan	Letter	55 yr	Undetermined	-	-	Multiple HCCs
Mohan et al.[12]	India	Letter	65 yr	Alcohol	-	-	-
Misra et al.[15]	India	Case report	47 yr	Viral hepatitis	-	-	
Rubino et al.[16]	Italia	Case report	61 yr	Alcohol & chronic hepatitis B	-	-	Bilateral BC HCC
Lenfant-Pejovic et al.[9]	France-Switzerland	Case-control study	91 male BC *vs.* 255 male cancer control	No comment	No	Bachelor Family history Digitalis/isoniazid Hyperthyroidism Tuberculosis	LC was more prevalent but not statistically significant.
Sørensen et al.[11]	Denmark	Prospective follow-up study	11,642 men with LC	2: alcoholic 1: non-alcoholic	Yes		3 occurred *vs.* 0.75 expected
Liukkonen et al.[10]	Finland	Descriptive study	58 male BC	No comment	Probable	Obesity Family history High alcohol drink	Prevalence of LC: 7%
Brinton et al.[13]	United States	Case-control study	642 male BC among 26 million discharge records		No	Kleinfelter syndrome Gynecomastia Obesity Orchitis/epididymitis	Poorly categorized

LC, liver cirrhosis; HCC, hepatocellular carcinoma; BC, breast cancer.

This is a first case report of BC developed in obese man with cirrhosis and HCC. On the basis of reviewing previous literatures, the causative role of cirrhosis is not clear and it can be postulated that the risk for male BC varies according to the etiology of cirrhosis. This presumption must be noticeable with a growing concern about obesity and NAFLD these days.

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