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Original Article

Bilateral male breast cancer: a case presenting with synchronous invasive lobular carcinoma and invasive ductal carcinoma

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Abstract: Synchronous bilateral male breast cancer is a very rare entity and invasive lobular carcinoma is less common in male breast cancer (MBC) than in female breast cancer (FBC). A 51-year-old man presented with a palpable mass in the left breast was finally diagnosed synchronous bilateral MBC, one an invasive lobular carcinoma and the other an invasive ductal carcinoma. It remains a matter of debate whether invasive lobular carcinoma has better or worse outcome than invasive ductal carcinoma, so that clinicopathological characteristics of tumors are used to evaluate the risk of recurrence. In our case, an unusually small invasive ductal carcinoma with a low level of proliferation had already developed many axillary lymph node metastases in spite of dire clinicopathological characteristics of the invasive lobular carcinoma of the left breast determined during the first treatment, while the invasive ductal carcinoma of the right breast was thought to have developed distant metastasis. We report the first case of synchronous bilateral MBC, one an invasive lobular carcinoma and the other an invasive ductal carcinoma, and discuss about the unusual clinicopathological characteristics of these two tumors.

Keywords: Male breast cancer, bilateral, invasive lobular carcinoma

Introduction

Male breast cancer (MBC) is an uncommon disease accounting for less than 1% of all breast cancer incidences [1, 2]. Synchronous bilateral male breast cancer is even more uncommon with an incidence of less than 1% of male breast cancers. Invasive ductal carcinoma, the most common histological subtype, accounts for approximately 85% of all male breast cancers, and the incidence of invasive lobular carcinoma is less common in male breast cancer (1.2%-1.5%) than in female breast cancer (11.8%) [3, 4]. There are several case reports of synchronous bilateral male breast cancer, including invasive ductal carcinoma and ductal carcinoma in situ or lobular carcinoma in situ [1, 5], but to the best of our knowledge, no cases have been reported of synchronous bilateral male breast cancer including invasive lobular carcinoma and invasive ductal carcinoma.

This is therefore the first reported case of synchronous bilateral male breast cancer, one an invasive lobular carcinoma and the other an invasive ductal carcinoma, and includes a discussion of the clinicopathological features which differs from the usual female breast cancers.

Case report

A 51-year-old Japanese male was referred to our hospital with a self-discovered left breast lump with tenderness which had been noticed for about one month. Physical examination revealed an elastic, hard, lobulated shape and smooth surface mass, about 4 cm in size, in the left breast lesion. In addition, an elastic hard and ill-defined lump, about 1.0 cm in size, was found in a right breast subareolar lesion. No nipple discharge or erosion of the nipple and areola was detected on either breast, nor was there any palpable lymphadenopathy in either axilla. The patient had a past history of dyslipidemia and medication with 2.5 mg of rosvastatin once a day. There was no history of Klinefelter syndrome, gynecomastia or other malignan-

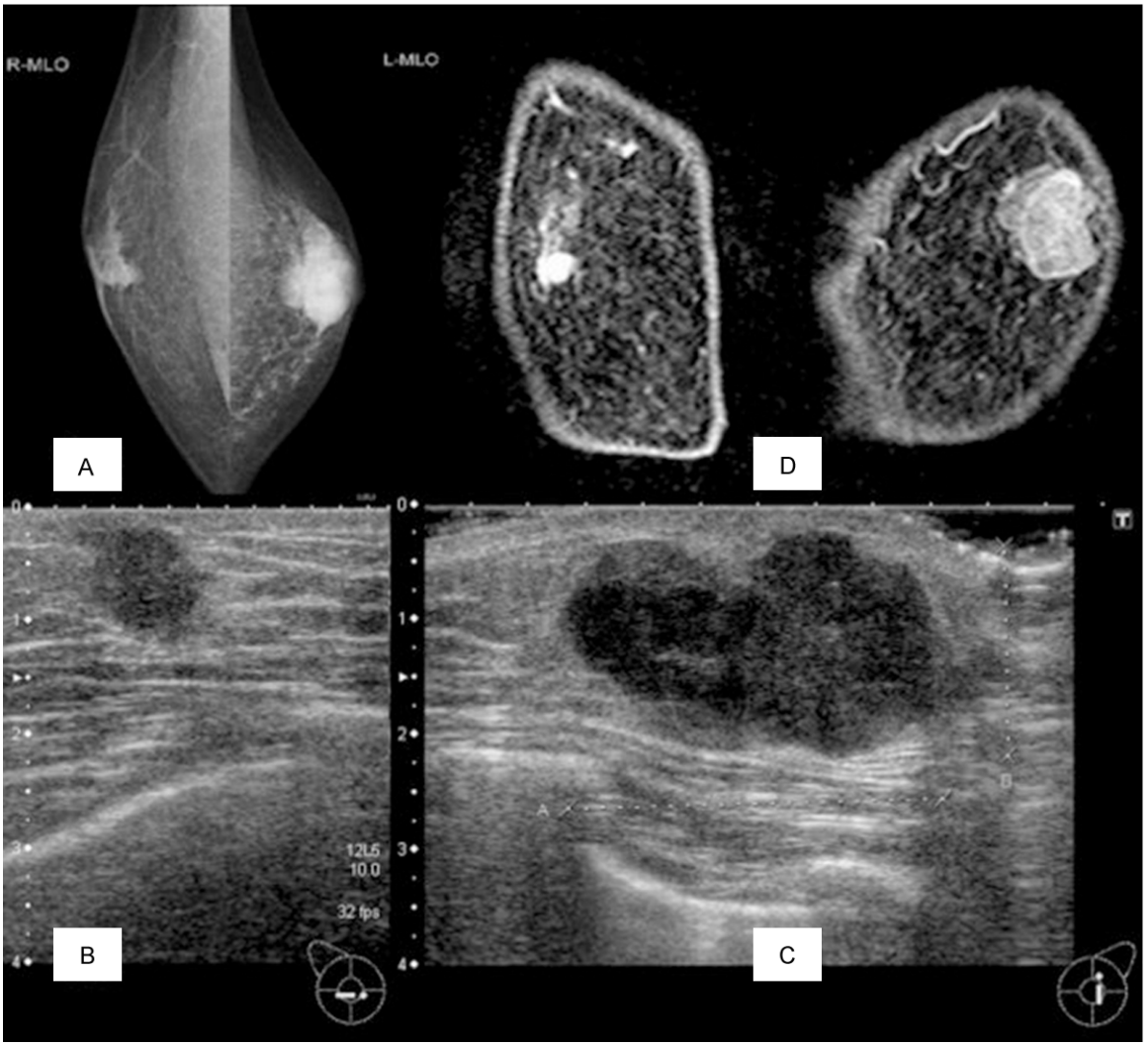

Figure 1. A. Mammography showed a well-defined and lobulated high density mass without any calcification in the left breast, and focal asymmetric density in the sub-areolar area while no calcification was found in the right breast. B. Ultrasound revealed a 1.0 cm hypoechoic mass with an indistinct border and a low and heterogeneous internal echo level in the subareolar lesion of the right breast. C. Ultrasound confirmed the presence of a well-defined, lobulated, hypoechoic and heterogeneous mass, 3.2 cm × 1.8 cm in size, in the left subareolar lesion. D. MRI showed a well-defined and lobulated mass, 4.2 cm in size, which was heterogeneously enhanced with contrast medium in the left breast, and a 1.0 cm mass with an indistinct border and slow/persistent kinetics in the right breast.

cies, or of hormonal treatment. The patient had no first-degree relatives with a history of cancer except for his father who had esophageal cancer. His paternal second-degree relatives had prostate cancer (uncle) and breast cancer (aunt), and a paternal third-degree relative had breast cancer (female cousin). This patient had a 30-year history of tobacco chewing and was not a drinker.

Images of the breast

Mammography showed a well-defined and lobulated high density mass without any calcification in the left breast (**Figure 1A**). Ultrasound confirmed the presence of a well-defined, lobulated, hypoechoic and heterogeneous mass, 3.2 × 1.8 cm in size, in the left subareolar lesion (**Figure 1C**). There was no lymph node swelling in the left axilla. MRI showed a well-defined and lobulated mass, 4.2 cm in size, which was heterogeneously enhanced with contrast medium (**Figure 1D**).

Mammography showed focal asymmetric density in the sub-areolar area while no calcification was found in the right breast (**Figure 1A**).

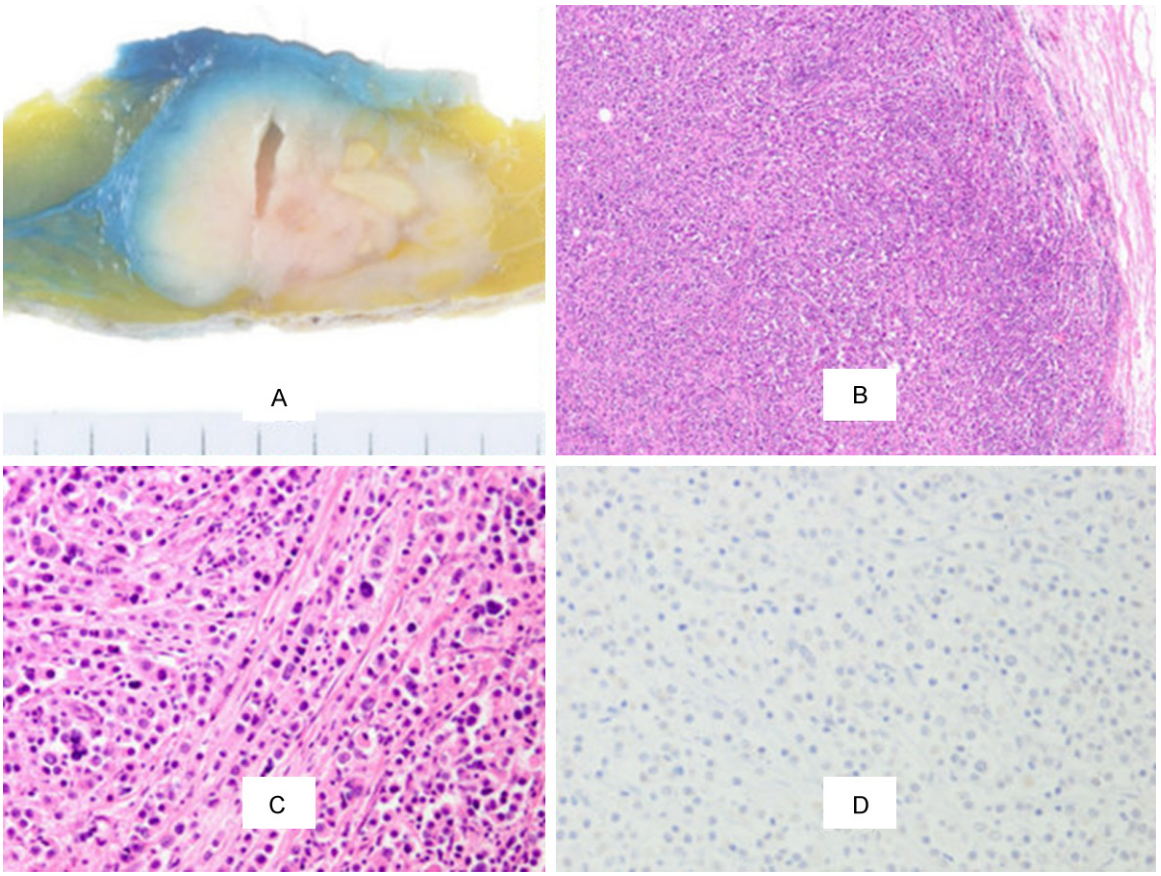

Figure 2. A. The left mastectomy specimen showed a subareolar and subdermal tumor mass measuring 3.3 × 2.2 × 4.0 cm. The cut section showed a lobulated, whitish tumor mass with a clear border. The tumor was partially dyed blue with indigo carmine injected into the subareolar lesion for sentinel lymph node biopsy. B. The tumor had a relatively clear invasive border covered with collagenous fiber, which may have resulted in the clear borders seen in the clinical images (× 4). C. The tumor cells were characterized by non-cohesive and small cells with bland nuclei and intracytoplasmic lumina. The tumor cells showed a lobular morphology, but were arranged in a nodule rather than having infiltrated in a single file growth pattern. The nuclei were moderately pleomorphic and included some mitotic figures (× 20). D. The tumor cells showed loss of E-cadherin expression, immunohistochemically (× 20).

Ultrasound revealed a 1.0 cm hypoechoic mass with an indistinct border and a low and heterogeneous internal echo level in the subareolar lesion of the right breast (**Figure 1A**). No evidence of axillary lymphadenopathy was observed in the right axilla. MRI showed a 1.0 cm mass with an indistinct border and slow/persistent kinetics in the right breast sub-areolar lesion (**Figure 1D**).

Core needle biopsy and surgery

Core needle biopsies (CNB) were performed for diagnosis of the bilateral breast tumors. Pathological CNB diagnosis for the left breast tumor was invasive lobular carcinoma, and invasive ductal carcinoma for the right breast tumor. Bilateral mastectomy and sentinel lymph node biopsy was performed as well as an additional right axillary lymph node dissection because intra-operative frozen section revealed a metastatic tumor in a sentinel lymph node resected from the right axilla.

Pathological findings in resected tumor specimens

The left mastectomy specimen showed a subareolar and subdermal tumor mass measuring 3.3 × 2.2 × 4.0 cm. The cut section showed a lobulated, whitish tumor mass with a clear border. The tumor was partially dyed blue with indigo carmine injected into the subareolar lesion for sentinel lymph node biopsy (**Figure 2A**). The tumor had a relatively clear invasive border covered with collagenous fiber, which

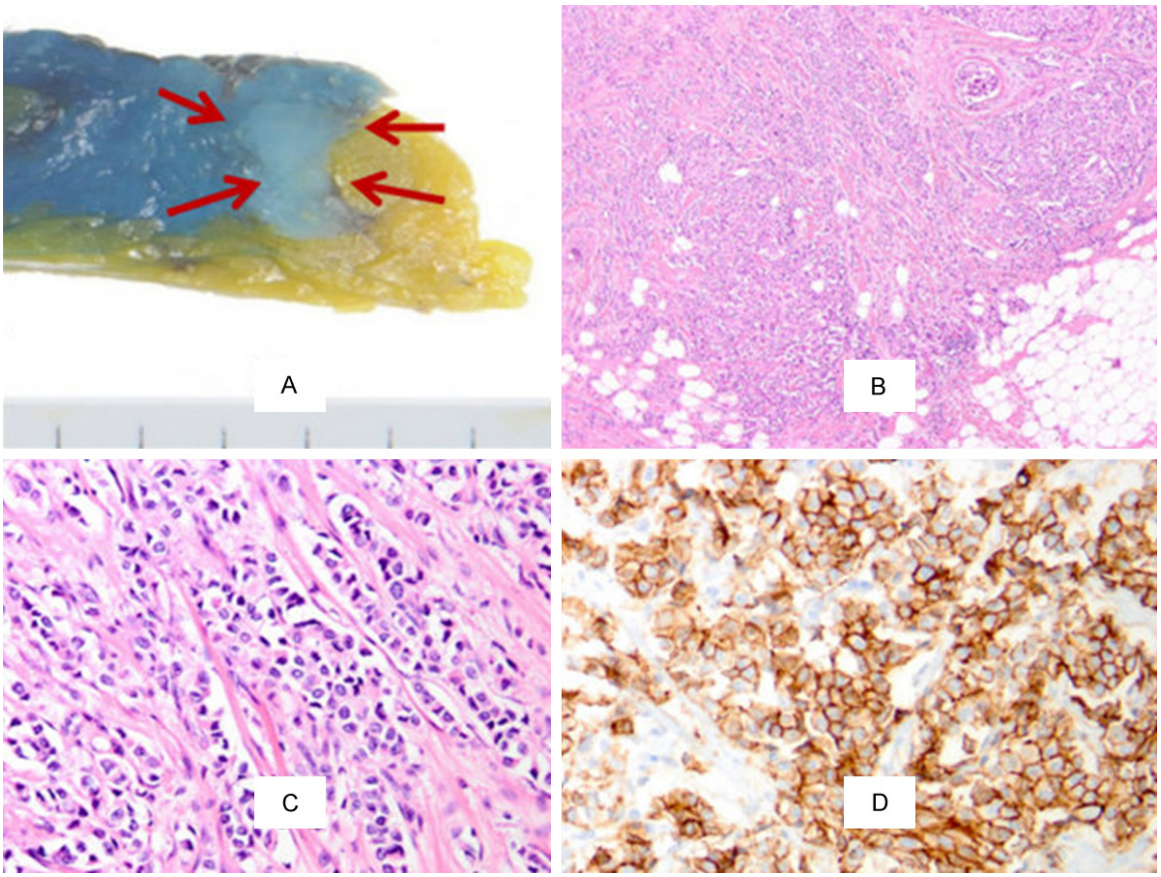

Figure 3. A. The right mastectomy specimen showed a subareolar tumor mass measuring 1.3 × 1.0 × 1.1 cm. Tumor had an irregular border and a whitish cut surface. B. The tumor cells had infiltrated in cords and clusters and produced a desmoplastic stromal response (× 4). C. Tumor cells had distinct cell borders, the nuclei were enlarged with a variety of sizes and shapes and the mitotic count was less than four per 10 HPF and there were no lymphatic invasion (× 20). D. Right breast tumor cells were positive for E-cadherin, immunohistochemically (× 20).

may have resulted in the clear borders seen in the clinical images (**Figure 2B**). Under higher power microscopy, the tumor cells were characterized by non-cohesive and small cells with bland nuclei and intracytoplasmic lumina. The tumor cells showed a lobular morphology, but were arranged in a nodule rather than having infiltrated in a single file growth pattern. The nuclei were moderately pleomorphic and included some mitotic figures (**Figure 2C**), while the tumor cells showed loss of E-cadherin expression, immunohistochemically (**Figure 2D**). On the basis of these findings, the diagnosis was "invasive lobular carcinoma, solid variant". No cancer metastasis was detected in the resected sentinel lymph node.

The right mastectomy specimen showed a subareolar tumor mass measuring 1.3 × 1.0 × 1.1 cm. Tumor had an irregular border and a whitish cut surface (**Figure 3A**). None of the resected lymph nodes was swollen but palpation revealed them to be rather hard. The tumor cells had infiltrated in cords and clusters and produced a desmoplastic stromal response (**Figure 3B**). Tumor cells had distinct cell borders, the nuclei were enlarged with a variety of sizes and shapes (**Figure 3C**) and immunohistochemistry showed them to be positive for E-cadherin (**Figure 3D**). The diagnosis was "invasive carcinoma of no special type". Cancer cells showed moderate pleomorphism, the mitotic count was less than four per 10 HPF and there was no lymphatic invasion. Although the largest of the resected axillary lymph nodes was less than 1.0 cm in size, cancer cells had metastasized to 24 of 35 resected lymph nodes.

ER, PgR, HER2, Ki-67 immunostaining

The tumor cells in the left breast were strongly positive for estrogen receptor expression and weakly positive for progesterone receptor ex-

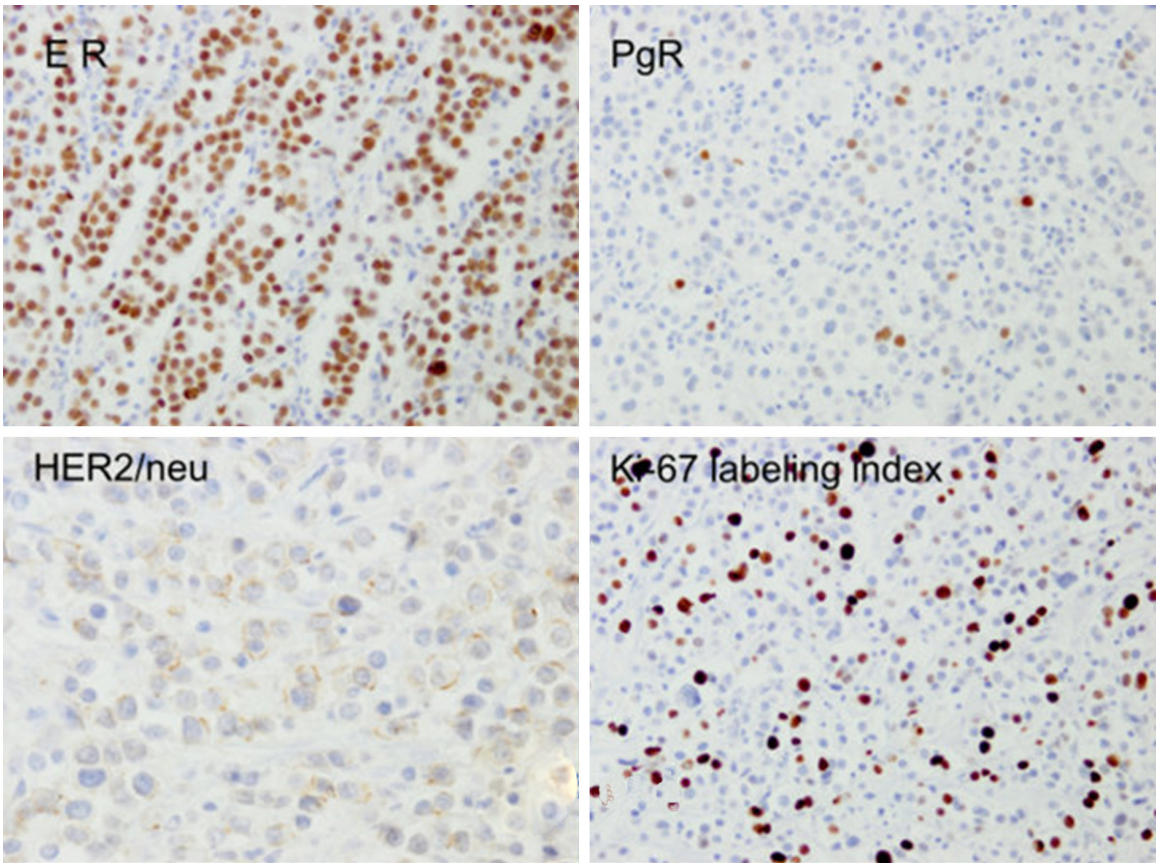

Figure 4. The tumor cells in the left breast were strongly positive for estrogen receptor expression and weakly positive for progesterone receptor expression. The immunohistochemical HER2/Neu staining score was 1+, and the Ki-67 proliferative index was 25% (× 20).

pression. The immunohistochemical Her2/Neu staining score was 1+, and the Ki-67 proliferative index was 25% (**Figure 4**).

The tumor cells in the right breast were positive for estrogen receptor expression but negative for progesterone receptor expression. The immunohistochemical Her2/Neu staining score was 2+ and the FISH test result was negative for HER2-gene expression. The Ki-67 proliferative index was 10% (**Figure 5**).

Therapeutic process after operation

The patient was given adjuvant systemic therapy and radiation therapy, which is similar to the adjuvant treatment for female breast cancer. After completion of 4 cycles of triweekly doxorubicin (60 mg/m^2) and cyclophosphamide (600 mg/m^2) followed by 12 cycles of weekly paclitaxel (80 mg/m^2), the patient started 5 years of tamoxifen with concurrent post-mastectomy radiation therapy for the right chest wall and supraclavicular area (total 50 Gy). These adjuvant therapies were well tolerated. No symptoms related to breast cancer recurrence had been detected by 39 months after the operation, but the serum CEA level had increased and PET-CT revealed LN metastasis (in the right axilla and mediastinum) and multiple bone metastases (**Figure 6**). He started oral endocrine therapy (letrozole 2.5 mg/day) for breast cancer recurrence complied with the treatment for metastatic female breast cancer.

Discussion

Breast cancer in men is an uncommon disease, which represents less than 1% of all breast cancers, and bilateral occurrence of this disease is even rarer and reportedly account for only 1.4% of all male breast cancers. Moreover, the incidence of lobular neoplasms in men is less common (1.5%) than in females (11.8%) [4]. Recent reports indicate that the incidence of male breast cancer is increasing, but there

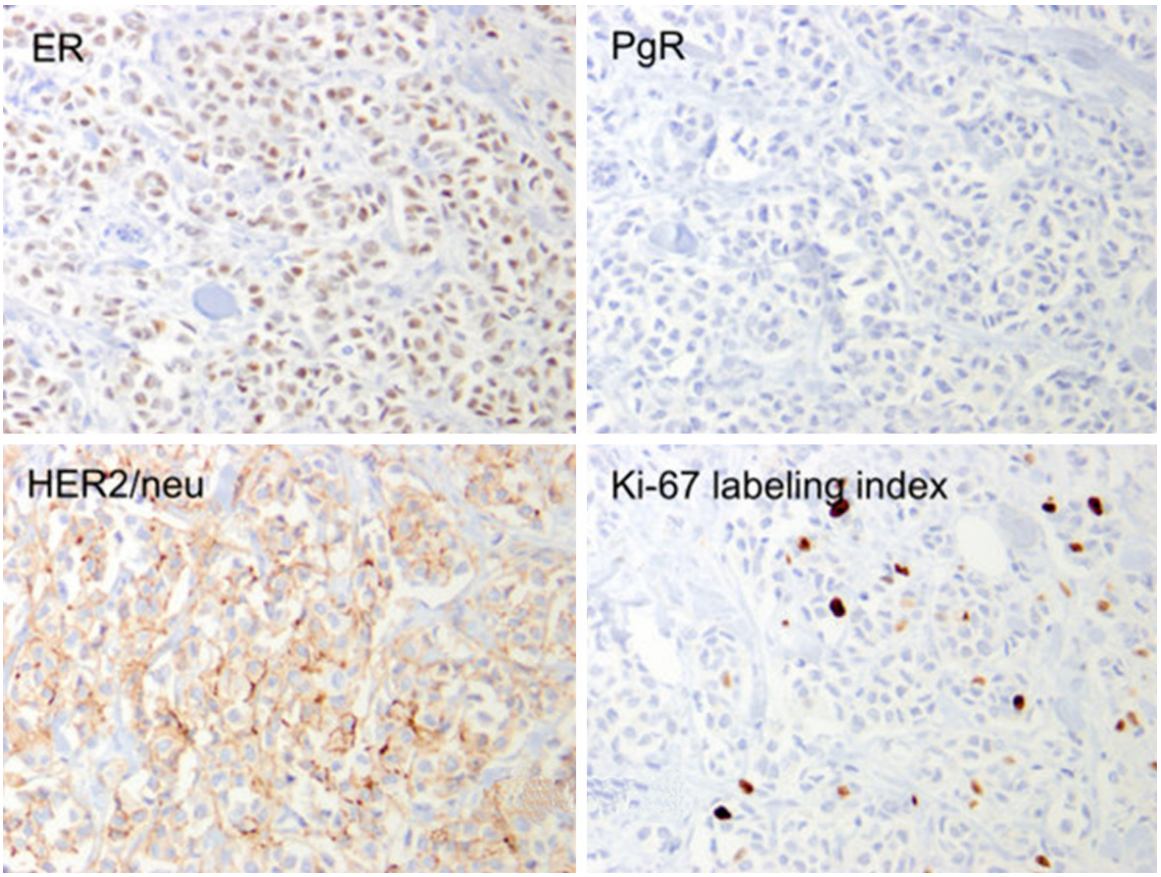

Figure 5. The tumor cells in the right breast were positive for estrogen receptor expression but negative for progesterone receptor expression. The immunohistochemical Her2/Neu staining score was 2+ and FISH test resulted in negative for HER2-gene expression (date is not shown). The Ki-67 proliferative index was 10% (× 20).

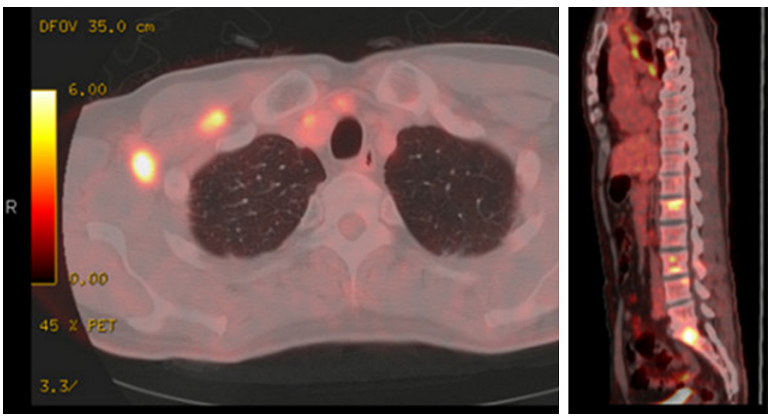

Figure 6. PET-CT shows lymph node metastasis in the right axilla and mediastinum, and multiple bone metastasis of spine.

have been only a few case reports of synchronous bilateral male breast cancer, especially of different types of breast cancer [1, 6]. To the best of our knowledge, this is the first report of synchronous bilateral male breast cancer, one an invasive lobular carcinoma and the other an invasive ductal carcinoma.

The patient first noticed his left breast tumor, which was about 4 cm in size and was eventually diagnosed as synchronous bilateral breast cancer. Despite its poor histopathological characteristics such as large tumor size, being an E-cadherin negative invasive lobular carcinoma [7], thus not a classic variant of invasive lobular carcinoma [8], and high Ki-67 LI, the left tumor showed no axillary metastasis. The right breast cancer, on the other hand, with some better histopathological characteristics such as small tumor size, no lymphatic invasion and low Ki-67 LI, was found to contain a great deal

of axillary lymph node metastasis at the time of operation. The aggressive proliferation of the right breast cancer may well have resulted in tumor recurrence in the right axilla and mediastinum lymph nodes and bone metastases. For these reasons, the pathological characteristics and clinical course of male breast cancer are different from those of the typical female breast cancer. Moreover it is not clear whether being an invasive lobular carcinoma affects the tumor's aggressiveness in MBC. Other morphological factors or genetic factors [9] may be related to tumor aggressiveness or a tendency to metastasize to axillary lymph nodes, but they have no yet been definitively identified.

The prognosis of male breast cancer is worse than that of its female counterpart (not matched for age and stage) and one of the reasons is thought to be that there is less awareness at an early stage of male breast tumor [3]. Our patient thought that the right breast tumor might have been there for a long time without becoming enlarged and staying asymptomatic. It was finally detected during a physical examination for the left breast cancer which had unexpectedly enlarged but without lymph node metastasis despite of its worse pathological characteristics than those of the tumor in the right breast. Because of the rarity of male breast cancer, breast screening for men is not adequate, which makes it difficult to detect such a small and asymptomatic breast cancer in men. It is therefore important to be aware of the risk factors for male breast cancer and identify men at high risk for breast cancer at an early stage.

Adjuvant treatment of male breast cancer is extrapolated from female breast cancer because the rarity of the former and paucity of randomized trials. Medical hormonal treatment is preferable to orchidectomy for adjuvant hormone treatment for men and retrospective comparison suggest that adjuvant tamoxifen can be beneficial [10, 11]. In fact, a population-based study reported that tamoxifen was superior to aromatase inhibitors in an adjuvant setting [12], but this finding is not definitive yet, because no randomized trial has been performed to compare the effect of adjuvant tamoxifen and aromatase inhibitors on male breast cancer. Since there is not enough evidence to determine the optimal adjuvant chemotherapy for male breast cancer, practitioners usually use treatment similar to that for female patients. The effectiveness of adjuvant chemotherapy for men is dealt with in only one retrospective single-institution review [13], but most guidelines recommending adjuvant chemotherapy for men are based on the results of clinical trials performed for women. To gain a better understanding of more appropriate treatment for male breast cancer, prospective randomized trials are needed to determine the effect and safety of adjuvant therapy specifically for male breast cancer patients.

Factors which cause male breast cancer include genetics, lifestyle, work and other diseases [14, 15]. The only identifiable causes of male breast cancer for our patient were genetic factors. As our patient was a candidate for human hereditary ovarian and breast cancer (HBOC) syndrome, we recommended gene testing, but no gene test was performed. There seemed to be several reasons for this, one being that the patient had no living first-degree female relatives and also that he thought testing him and his sons for gene mutation would not have many advantages. Other possible reasons are that the importance of the HBOC syndrome is still not widely recognized, and that gene testing is not covered by national health insurance in Japan.

Disclosure of conflict of interest

None.

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References

[1] Sun WY, Lee KH, Lee HC, Ryu DH, Park JW, Yun HY, Song YJ. Synchronous Bilateral Male Breast Cancer: A Case Report. J Breast Cancer 2012; 15: 248.

[2] Giordano SH. A review of the diagnosis and management of male breast cancer. Oncologist 2005; 10: 471-9.

[3] MacGregor MC, Clarke CA, Lichtensztajn D, Hortobagyi GN, Giordano SH. Male breast cancer according to tumor subtype and race: a population based study. Cancer 2013; 119: 1611-7.

[4] Giordano SH, Cohen DS, Buzdar AU, Perkins G, Hortobagyi GN. Breast carcinoma in men: A population-based study. Cancer 2004; 101: 51-7.
[5] Qureshi K, Athwal R, Cropp G, Basit A, Adjogatse J, Bhogal H. Bilateral synchronous ductal carcinoma in situ in a young man: case report and review of the literature. Clin Breast Cancer 2007; 7: 710-2.
[6] Hoque HM, Kothari A, Hamed H, Fentiman IS. Synchronous bilateral breast cancer in a patient with Klinefelter's syndrome. Int J Gen Med 2010; 3: 19-21.
[7] Engstrøm MJ, Opdahl S, Vatten LJ, Haugen OA, Bofin AM. Invasive lobular breast cancer: the prognostic impact of histopathological grade, E-cadherin and molecular subtypes. Histopathology 2015; 66: 409-19.
[8] Orvieto E, Maiorano E, Bottiglieri L, Maisonneuve P, Rotmensz N, Galimberti V, Juini A, Brenelli F, Gatti G, Viale G. Clinicopathologic characteristics of invasive lobular carcinoma of the breast: Results of an analysis of 530 cases from a single institution. Cancer 2008; 113: 1511-20.
[9] Ottini L, Silvestri V, Rizzolo P, Falchetti M, Zanna I, Saieva C, Masala Giovanna, Bianchi S, Manoukian S, Barile M, Peterlongo P, Varesco L, Tommasi S, Russo A, Giannini G, Cortesi L, Viel A, Montagna M, Radice P, Palli D. Clinical and pathologic characteristics of BRCA-positive and BRCA-negative male breast cancer patients: Results from a collaborative multicenter study in Italy. Breast Cancer Res Treat 2012; 134: 411-8.
[10] Goss PE, Reid C, Pintilie M, Lim R, Miller N. Male breast carcinoma: a review of 229 patients who presented to the princess Margaret hospital during 40 years: 1955-1996. Cancer 1999; 85: 629-39.
[11] Digenis AG, Ross CB, Morrison JG, Holcomb GW 3rd, Reynolds VH. Carcinoma of the male breast: a review of 41 cases. South Med J 1990; 83: 1162-7.
[12] Eggemann H, Ignatov A, Smith B, Altmann U, Minckwitz G, Röhl FW, Jahn M, Costa SD. Adjuvant therapy with tamoxifen compared to aromatase inhibitors for 257 male breast cancer patients. Breast Cancer Res Treat 2013; 137: 465-70.
[13] Giordano SH, Perkins GH, Broglio K, Garcia SG, Middleton LP, Buzdar AU, Hortobagyi GN. Adjuvant Systemic therapy for male breast carcinoma. Cancer 2005; 104: 2359-64.
[14] Weiss JR, Moysich KB, Swede H. Epidemiology of male breast cancer. Cancer Epidemiol Biomarkers Prev 2005; 14: 20-6.
[15] Khan MH, Allerton R, Pettit L. Hormone Therapy for Breast Cancer. Clin Breast Cancer 2015; 15: 245-50.