

# Bilateral breast cancer following augmentation mammoplasty with polyacrylamide hydrogel injection: A case report

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Received May 24, 2014; Accepted February 13, 2015

DOI: 10.3892/ol.2015.3116

**Abstract.** Breast cancer occurring following injection with polyacrylamide hydrogel (PAMG) for augmentation mammoplasty is rare. The present study reports the case of a 43-year-old female presenting with bilateral breast cancer 10 years after augmentation mammoplasty with PAMG injection and no family history of breast cancer. A 5.5x6.0-cm mass in the right breast with multiple intumescent axillary lymph nodes was revealed and a palpable mass of ~1.0 cm was identified in the outer upper quadrant of the left breast. Multiple smaller nodules were observed in the pulmonary field. Pathological examination revealed invasive lobular grade II carcinoma in both breasts with ER(+++), PR(+++), C-erbB2(-), Top-2(+), in the right breast and ER(++), PR(++), c-erb-B2(-), Top-2(+) in the left. Preoperative chemotherapy, modified radical bilateral mastectomy with axillary clearance, postoperative chemotherapy, and an oophorectomy were conducted, followed by treatment with Arimedex® until the present date. A number of valuable insights can be garnered from this case. First, close follow-up is required for female patients who receive an injection of PAMG for augmentation mammoplasty in order to achieve an early diagnosis and to intervene in any incidences of breast cancer. Second, the differential diagnosis of dual primary carcinoma versus metastatic breast cancer is important and may be aided by the use of molecular technology. Third, it remains difficult to determine gene expression values for the prediction of chemotherapy sensitivity. Thus, discrimination between primary and secondary carcinomas is the principle

barrier for identifying an appropriate treatment strategy when a patient is diagnosed with bilateral breast cancer.

## Introduction

Medical polyacrylamide hydrogel (PAMG), consists of polyacrylamide and nonpyrogenic water, is an extensively cross-linked polymeric soft tissue filler substance (1) that has been used in Ukraine, Russia and China in plastic and aesthetic surgical procedures for the past 15-20 years (2-4). However, different types of complications associated with PAMG injection have been reported, particularly in association with augmentation mammoplasty (5). For example, breast cancer has been identified as one type of serious complication (6-7). The Chinese State Food and Drug Administration (SFDA) has banned the production, sale and use of PAMG (8).

The incidence of synchronous bilateral infiltrating breast cancer, reported about 0.2-2%, is rare (9). The standard of definitive diagnosis and management of patients with this disease is not well established (10). The present study reports a rare case of bilateral breast cancer with common histologies following augmentation mammoplasty with PAMG injection. Furthermore, the current study provides a number of insights into the appropriate diagnostic and therapeutic approaches for bilateral breast cancer. Written informed consent was obtained from the family of the patient.

## Case report

A 43 year-old female received augmentation mammoplasty with a 100-ml PAMG injection 10 years previously. The patient had no family history of cancer and no acute complications following the PAMG injection. The patient was married at 22 years and, at the age of 24 years, gave birth to a child that was breast fed for ~10 months. The patient's hormonal profiles, including testosterone, prolactin and thyroid function tests, were normal.

On November 16th, 2010, the patient was admitted to the Breast Unit of Baoji Municipal Central Hospital (Baoji, China) with a 1-year history of a palpable, tender lesion of ~0.3x0.5 cm in diameter in the right breast, with sharp pain and a mild occasional cough. However, no additional symptoms, such as weight loss, fever or loss of appetite, were noted.

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**Key words:** bilateral breast cancer, polyacrylamide hydrogel injection, primary, metastatic, gene expression levels

Clinical examination revealed mastoptosis of the right breast, with edema, an orange peel-like appearance to the skin and a 5.5x6.0-cm mass. The mass was fixed to the underlying structure of the breast, was not tender and exhibited an obscure boundary. Furthermore, no bloody discharge developed upon palpation just under the right nipple, and the overlying skin of the breast, the nipple and the areola were not involved. Furthermore, multiple intumescent lymph nodes were felt in the right axilla, one of which was large in size (diameter, ~1.5 cm) and mobile. In addition, a palpable mass with a maximum diameter of ~1.0 cm was identified in the outer upper quadrant of the left breast, 3 cm away from the nipple; however, no lymph nodes were palpable in the left axilla.

Ultrasonography of the breasts identified a dark region in each of the interspaces of the mammary glands. Additionally, an ill-defined, inhomogeneous, low echo level lesion measuring 5.0x5.0x4.0 cm was identified in the root of the right nipple. The lesion was non-enveloped and irregular in appearance (similar to the foot of a crab). Sufficient blood flow signals were recorded using color Doppler ultrasonography. Multiple intumescent lymph nodes were detected in the right axilla, one of which was large in size (diameter, ~1.9 cm) and exhibited sufficient blood flow signals. Additionally, a low echo level nodule measuring ~0.8x0.6x0.8 cm was observed in the upper outer quadrant of the left breast, with an obscure boundary and uneven internal echoes. Multiple oval nodes were clearly visible in the left axillary cavity, the largest of which (diameter, ~1.9 cm) exhibited sparse blood flow signals. A computed tomography (CT) scan performed in November 2010 demonstrated the presence of a soft-tissue mass around the root of the right nipple, localized conglutination of the bilateral pleura, a narrow band shadow of water in the bilateral pleural cavity, and lesser tubercles in the field of the lung and pleura. Furthermore, nodosity was identified in the right axillary space and multiple lesser nodules were observed in the pulmonary field (Fig. 1). Additional scans, including abdominal ultrasonography SPECT, revealed no other metastases.

Fine-needle aspiration cytology confirmed the malignancy of the breast masses and the two lesions were diagnosed as invasive ductal carcinoma (grade II according to the WHO Classification of Oncopathology and Genetics of Mammary Glands and Female Genital Organs). Immunohistochemical staining of the right breast lesion revealed the following: Estrogen receptor (ER)(+++), progesterone receptor (PR)(+++), c-erbB2(-), Top-2(+), cytokeratin 5 (CK5)(-) and E-cadherin(+) (Fig. 2). Immunohistochemical staining of the right breast lesion revealed the following: ER(++), PR(++), c-erb-B2(-), Top-2(+), CK5(-) and E-cadherin(+) (Fig. 3). A multiplex branched DNA (bDNA) liquidchip technology was developed for the quantitative measurement of gene mRNA levels. bDNA is a non-PCR-based technology. It is a nucleic acid sandwich hybridization platform in which the targets are captured through the cooperative hybridization of multiple probes which are conjugated with a fluorescence signal amplification system. The fluorescence value of each sample was analyzed using the Luminex 200 system (Luminex, Austin, TX, USA). SPSS 18.0 (SPSS Inc., Chicago, IL, USA) was used to analyze data in this study. Furthermore, gene mRNA expression levels, which were detected by Guangzhou SurExam Bio-Tech Co., Ltd. (Guangzhou, China),

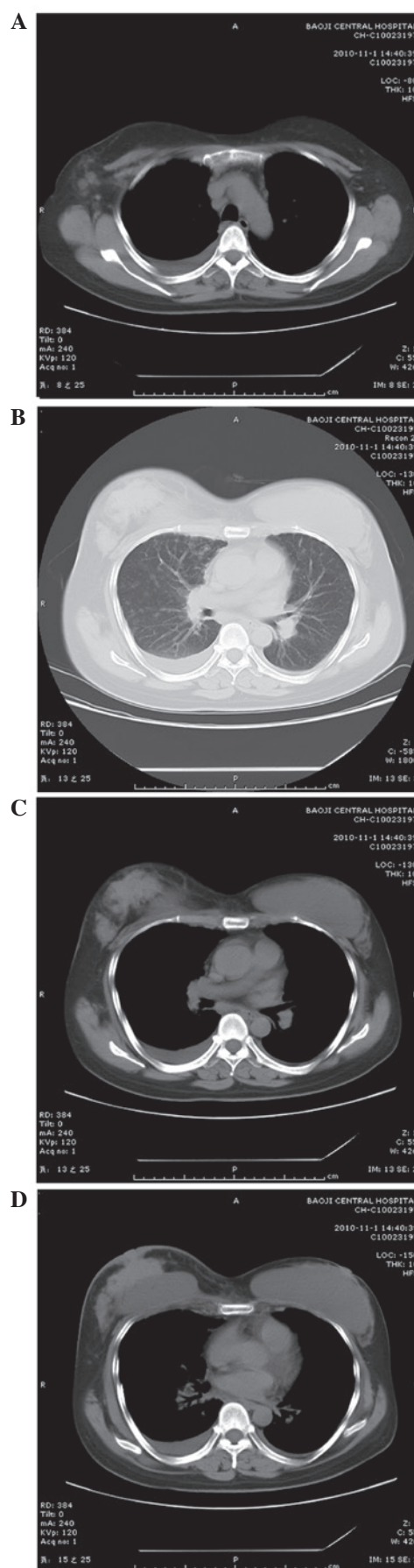


Figure 1. Computed tomography scan of the chest identifying (A) intumescent lymph nodes in the right axilla and (B) multiple lesser nodules in the pulmonary field and on the pleura. (C and D) Soft-tissue masses around the root of the right nipples are clearly visible.



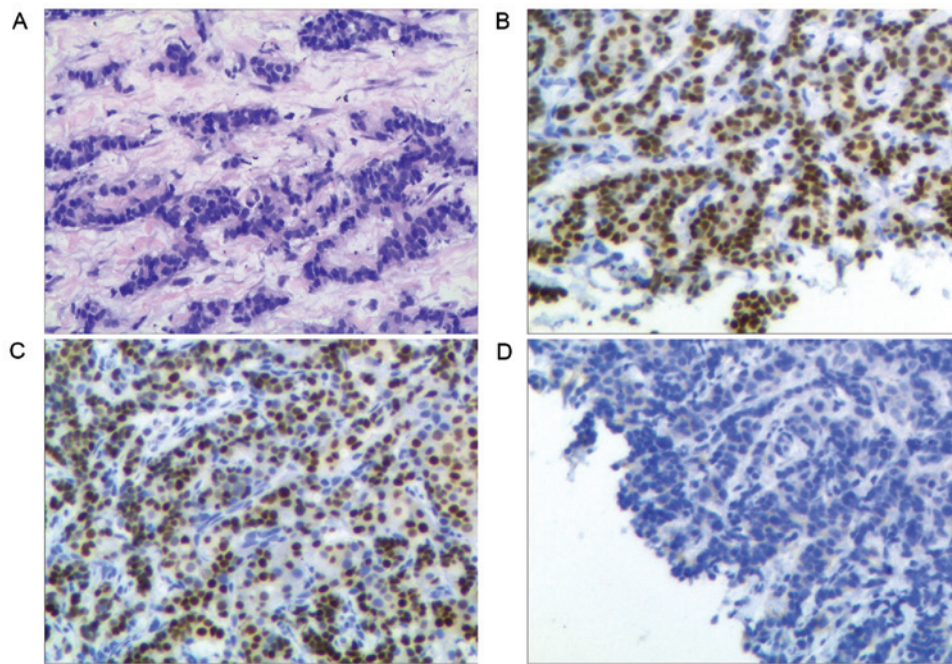


Figure 2. Histopathological features of the right breast mass. (A) The mass was pathologically diagnosed as invasive ductal carcinoma (grade II; hematoxylin and eosin staining). Immunohistochemical staining identified (B) estrogen receptor(+++), (C) progesterone receptor(+++) and (D) c-erbB2(-) (magnification, x10).

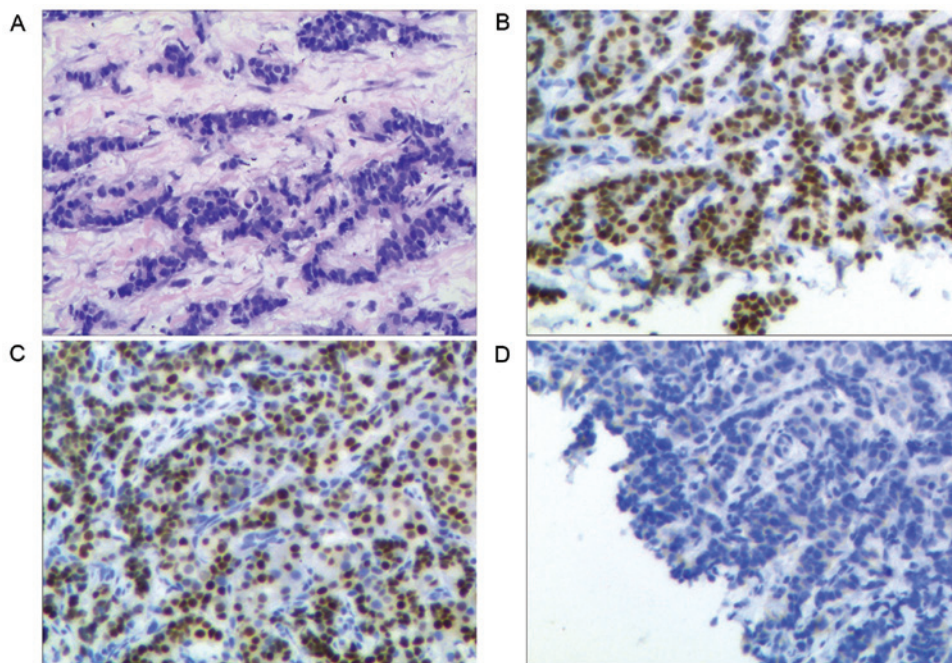


Figure 3. Histopathological features of the left breast mass. (A) The mass was pathologically diagnosed as invasive ductal carcinoma (grade II; hematoxylin and eosin staining). Immunohistochemical staining identified (B) estrogen receptor(++) (C) progesterone receptor(++) and (D) c-erbB2(-) (magnification, x20).

were compared to that of a database of Chinese Breast Cancer patients (Guangzhou SurExam Bio-Tech Co., Ltd.) to obtain relative mRNA expression levels (%). The results were as follows: Thymidylate synthetase,  $\geq 67.3\%$  [increased versus control; expression level is inversely correlated with fluorine/pemetrexed/capecitabine treatment (11,12)]; ribonucleotide reductase M1,  $\geq 86.7\%$  [increased versus control; expression level is inversely correlated with gemcitabine (GEM) treatment (13)]; tubulin  $\beta 3$  class III (TUBB3),  $\geq 21.2\%$  [decrea

sed versus control; expression level is inversely correlated with anti-microtubule agent treatment (14)]; and topoisomerase (DNA) II $\alpha$  (TOP2A),  $\geq 70.0\%$  [increased versus control; expression level is directly correlated with etoposide and anthracycline treatment (15,16)].

Following six cycles of post-operative epirubicin plus docetaxel (TA) chemotherapy (100 mg/m<sup>2</sup> epirubicin and 75 mg/m<sup>2</sup> docetaxel every 3 weeks, supported by G-CSF), <sup>18</sup>F-fluorodeoxyglucose positron emission

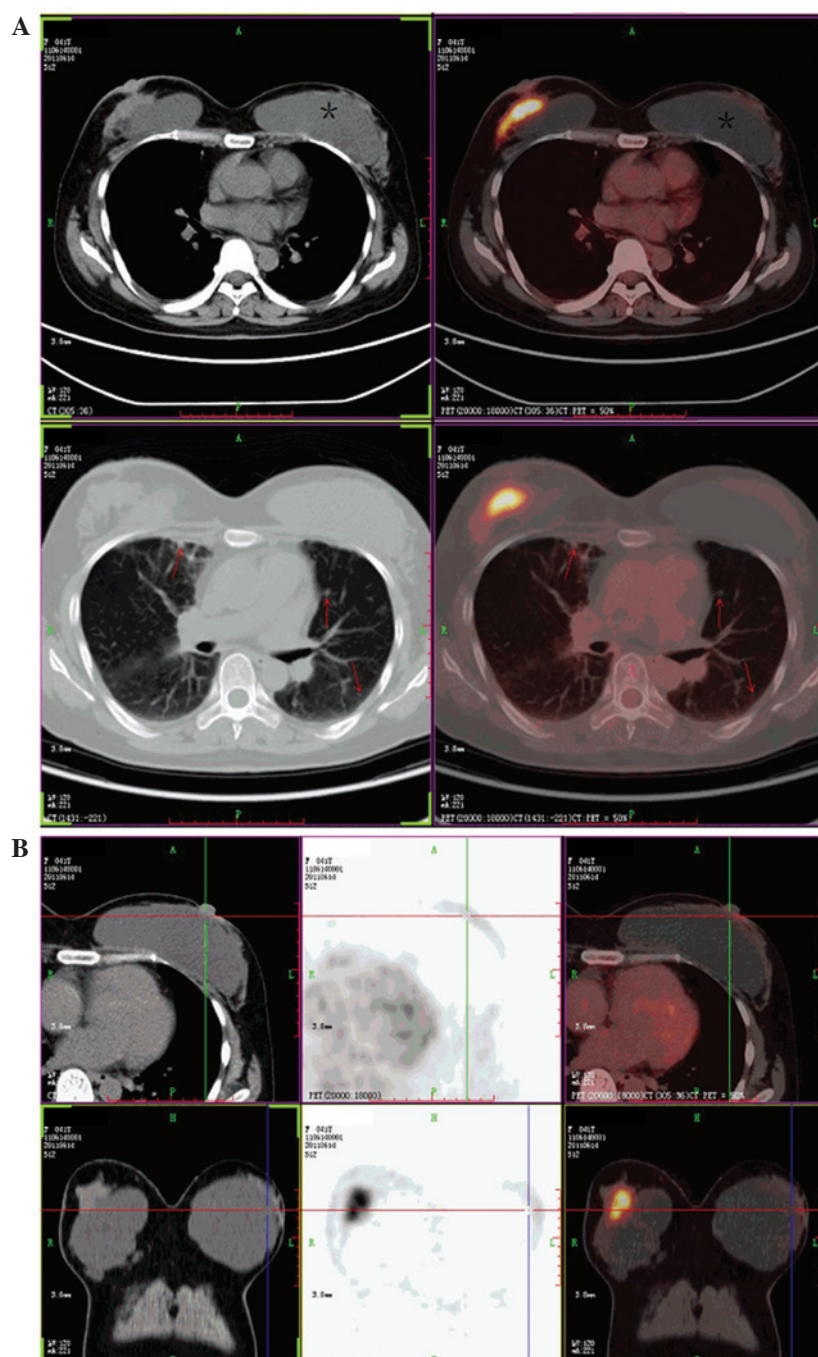


Figure 4. Positron emission tomography-computed tomography scan following six cycles of epirubicin plus docetaxel chemotherapy revealing (A) a high maximum standardized uptake value of the mass in the right breast and nodules in the fields of the lung, with no abnormal metabolic activity. (B) The left breast was almost normal.

tomography (PET)/CT identified a 5.4x1.2x4.3-cm lump in the root of the right nipple, with a high maximum standardized uptake value of 6.5, and pachyderma around the nipple. By contrast, the left breast was almost normal. Multiple nodes of the bilateral lung fields exhibited no abnormal metabolic activity, and the metabolic activity of the intumescent lymph nodes in the neck and armpit exhibited close to normal values (Fig. 4).

Due to the only minor to partial remission identified by PET/CT evaluation, a modified radical bilateral mastectomy with axillary clearance was performed. Pathological examination of the two specimens determined a diagnosis

of invasive ductal lobular mixed carcinoma of the mammary gland. However, the incised margins of the two breasts and the substrate of the left nipple were negative. Furthermore, the lower region of the right nipple was invaded by carcinoma. Cancer metastasis was observed in the axillary lymph nodes (8/13 and 11/11 lymph nodes were positive for metastasis in the left and right breasts, respectively).

One month after surgery, imaging evaluation identified disease progression, as shown in Fig. 5. Following the completion of two regimens of post-operative vinorelbine plus cisplatin chemotherapy (25 mg/m<sup>2</sup> vinorelbine, days 1 and 8; and 25 mg/m<sup>2</sup> cisplatin, days 1-3) and GEM



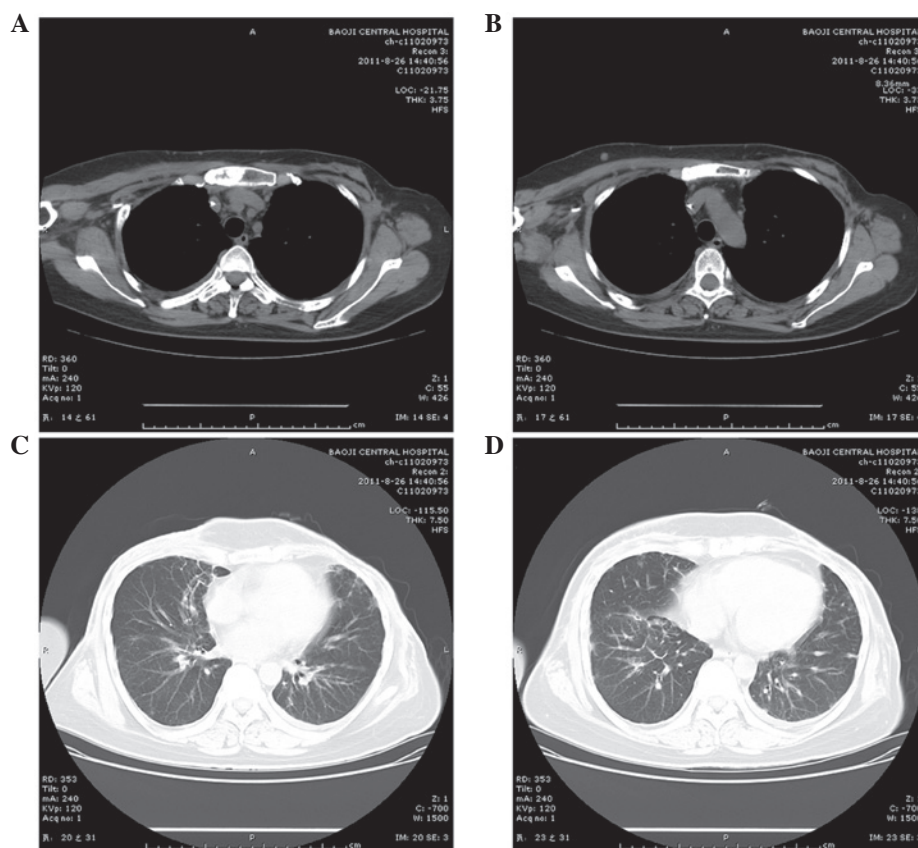


Figure 5. Computed tomography scan of (A) the chest one month after surgery indicating intumescent lymph nodes in the armpit and (B) multiple small subcutaneous nodes around the incised opening. (C and D) An increase in the number and size of nodules in the lung field was identified.

plus capecitabine (1,000 mg/m<sup>2</sup> GEM, days 1 and 8; and 1,000 mg/m<sup>2</sup> capecitabine, days 1-14), a metastatic tumor of ~2 cm in diameter was detected in the liver by abdominal ultrasonography. Therefore, the patient underwent an oophorectomy, followed by treatment with Arimedes<sup>®</sup> (Letrozole, 2.5 mg/d) until the present date.

## Discussion

PAMG is a type of polymer composed of acrylamide monomers. Based on its theoretical safety, PAMG has commonly been applied as a body filler in esthetic surgical procedures for a number of years. However, as an increasing number of complications have been reported (5-7), the safety of PAMG has been called into question. Therefore, the injection of PAMG for augmentation mammoplasty was discontinued in 2006 in China.

A number of cases of sporadic breast cancer following PAMG injection have been reported (6,7). Although there is no direct evidence with regard to the carcinogenicity of PAMG in humans, doctors should carefully consider the use of the agent, as various studies have indicated that PAMG exhibits cytotoxicity, inhibits the growth of human fibroblasts and causes the apoptosis of human fibroblasts. Additionally, PAMG appears to induce the mRNA expression levels of specific genes, for example, c-myc (17).

Breast cancer following the injection of PAMG is typically diagnosed 5-10 years after surgery (2,3). This extended period of time often results in the patient neglecting to

consider the history of augmentation mammoplasty and patients rarely visit the doctor or self-examine for health check-ups, as with the patient in the current study. Thus, if the injection of PAMG is a high risk factor for breast cancer, missed and delayed diagnoses will occur. Furthermore, in incidences of self-examination of the breast, it is difficult for patients to discriminate a breast mass from filler hardening in the breast and subcutaneous tissue. For example, it was reported that the patient in the present study mistook the cancerous lesion as deformed or displaced packing material upon initial self-examination. Therefore, despite the lack of definitive evidence that PAMG injection is associated with a high risk of breast cancer, close follow-up is recommended for those who have received augmentation mammoplasty with PAMG to allow an early diagnosis and intervention in incidences of breast cancer.

Bilateral breast carcinomas exist in two forms: Synchronous primary, in which the two tumors occur concurrently (within 1-12 months of each other); and metachronous, in which the carcinomas occur at different times (>12 months apart) (18). In the present case, cancerous lesions with the same pathological morphology were simultaneously detected in the bilateral breast upon initial diagnosis. However, it was unknown whether the tumor was a secondary primary cancer or a metastatic spread from the contralateral breast cancer. It is biologically and therapeutically important to make this differentiation, however, it is difficult to definitively determine the origin from the clinical features of an individual patient alone (19-22).

According to Chaudary *et al* (23), the pathological criteria of synchronous primary breast cancer is as follows: i) An *in situ* change in the contralateral tumor; ii) a histologically different tumor in the second breast compared with the first; iii) a distinctly greater degree of histological differentiation than in the first breast; and iv) no evidence of local, regional or distant metastases in the ipsilateral breast. Thus, the female patient reported in the present study appears to have exhibited metastatic disease. However, these pathological criteria are basic, and alternative studies have concluded that *in situ* lesions should no longer be considered as a criterion for *de novo* carcinogenesis (24). Furthermore, a number of cases exist that have been verified as bilateral primary cancer despite exhibiting the same pathology as the initial breast cancer (25) or the metastatic carcinoma of an axillary lymph node. This indicates that a reevaluation of the histological criteria commonly used to differentiate between primary and metastatic lesions is required (26).

Genetic and molecular pathologic features should also be considered during the differential diagnosis between a secondary or a metastatic breast carcinoma from the contralateral breast. In the present case, distinguishing simultaneous bilateral breast cancer from primary and secondary cancer was difficult using molecular pathology data alone. An accumulating number of studies, including a small number of genetic studies, are presenting contradictory results with regard to whether the molecular pathology alone is sufficient to make this distinction. Determining the hormone receptor status by immunohistochemistry has almost no discriminatory value, as no conclusive differences in hormone receptor status have been reported between primary breast cancer and its metastases (27-29), for example, with regard to HER-2 expression status (19,30). An alternative study revealed that a greater number of DNA copy number changes occur in metachronous compared with synchronous bilateral breast cancer (31). However, it has also been reported that distinct, characteristic genetic alterations could not be detected using the comparative genomic hybridization method (32). By performing loss of heterozygosity studies, Saad *et al* (26) identified discordant mutations in synchronous bilateral breast carcinoma patients, supporting the diagnosis of *de novo* bilateral primary breast carcinoma. This indicated that the application of molecular technology may be important in the differential diagnosis of dual primary carcinoma versus metastatic breast cancer from the contralateral breast. However, additional studies with expanded sample sizes are required to clarify this proposal.

A current topic in the field of cancer treatment involves detecting the expression levels of genes in tumor tissues to screen out patients sensitive to specific chemotherapeutic agents, to thus determine the most appropriate type of neoadjuvant and adjuvant chemotherapy on an individual basis (26-28). Two such genes determined in the present case were TUBB3 and TOP2A.

The protein TUBB3 is reported to promote cell survival and represents an endogenous element of an inherent drug-resistance mechanism for counteracting the activity of microtubule-interacting agents (33). For example, the overexpression of TUBB3 was associated with the resistance to taxane-based chemotherapy and may be a predictive marker

for chemoresistance to docetaxel in patients with post-operative recurrent disease (34). Additionally, *in vitro* studies have reported that the sensitivity to TOP2 inhibitors is dependent on the expression levels of TOP2A in target cancer cells. Cells with a low concentration of TOP2A protein are less sensitive to TOP2-inhibiting agents compared with cells containing a high concentration of TOP2A (35). Numerous retrospective studies have investigated the predictive value of TUBB3 and TOP2A using different methods, occasionally resulting in contradictory data. In the present case, TUBB3 mRNA expression levels were <21.2% and TOP2A was expression was >70%, possibly indicating that the tumor may be sensitive to taxane- and anthracycline-based chemotherapy regimens. However, following six cycles of TA chemotherapy, the patient only exhibited minor remission. Furthermore, it remains difficult to determine gene expression values for predicting drug sensitivity; therefore, additional prospective randomized clinical trials should be performed.

Once a diagnosis was established in the present study, the patient received chemotherapy. Following six cycles of TA, PET-CT identified that the growth of the lesion was somewhat controlled as a minor to partial remission, predominantly observed by the negative metabolic activity of the internal organs. At that time, the patient was eager to undergo surgery due to concern that the PAMG present in the breasts would continue to contribute to the severity of the disease. However, following evaluation, systemic chemotherapy was considered to be the most appropriate response. A number of physicians considered that the patient should be diagnosed with a systemic disease due to the metastasis to the left breast, in which case surgery is not advised according to evidence-based medical guidelines and an alternative treatment strategy may be ovarian ablation plus endocrine therapy.

However, an alternative view was put forward that systemic chemotherapy was the most appropriate response in such circumstances, as a diagnosis of bilateral primary cancer could not be definitively excluded. Instead, the patient could receive surgery if the lesion was technically resectable. In consideration of the possible treatment strategies, the patient underwent a modified radical bilateral mastectomy with axillary clearance, and it was subsequently determined that the pathological margin was negative. However, one month later, after two cycles of post-surgery chemotherapy, the patient was admitted with a mild discontinuous cough without signs of infection. Physical examination identified multiple small nodules around the incision opening. Furthermore, a CT radiograph demonstrated that the lung nodules had increased in number and size by August 26th 2011, compared with those observed on presentation (July 27th; Fig. 5), and the cancer antigen (CA)125 (58.64 U/ml; normal range, 0-35 U/ml) and CA15-3 (220.30 U/ml; normal range, 0-25 U/ml) concentrations had increased. These observations indicated that the disease had progressed; the progression-free survival time was <2 months. Therefore, it is important to discriminate between primary and second carcinomas when a patient is diagnosed with bilateral breast cancer, as it is the basis of determining an appropriate treatment strategy.

In conclusion, although definite evidence that PAMG injection is associated with a high risk of breast cancer was not identified in the present study, close follow-up is required for female patients who have received injections of PAMG.

Second, the differential diagnosis of dual primary carcinoma versus metastatic breast cancer is important, and molecular technology may be important for this differentiation. Third, the determination of gene expression values for the prediction of chemotherapy sensitivity remains challenging. Thus, the discrimination between primary and secondary carcinomas is the basis of determining an appropriate treatment strategy when a patient is diagnosed with bilateral breast cancer.

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