Breast Metastasis from Gastric Cancer Mimicking Benign Breast Mass

Youn Ju Lee, M.D., Ph.D.¹, Jin Uk Na, M.D.¹, Bo Bae Choi, M.D., Ph.D.², Song Yi Choi, M.D., Ph.D.³,
Jin Sun Lee, M.D., Ph.D.¹

¹Department of Surgery, ²Department of Radiology, ³Department of Pathology, Chungnam National University School of Medicine, Daejeon, Korea

Breast metastases from extra-mammary malignancies are unusual. In particular, the characteristics of breast metastasis from gastric cancer are rarely reported and there is no common specific finding among the reported cases. Breast metastases from extra-mammary malignancies are often misdiagnosed as benign lesions due to the absence of characteristic finding in imaging studies; however, they also resemble inflammatory breast cancer clinically sometimes. Therefore, differential diagnosis between the primary breast cancer and the metastatic disease is considered difficult. In order to hasten the diagnosis, to avoid unnecessary mastectomy, and to determine appropriate options of treatment, it is important that physicians understand the clinicopathological and radiologic features of breast metastases and consider its possibility in patients with a history of extra-mammary malignancies. Herein, we report a case of breast metastases from gastric cancer.

Key Words: Breast neoplasms, Differential diagnosis, Stomach neoplasms, Metastases

INTRODUCTION

Breast metastases from extra-mammary malignancies are rare [1], and in particular, breast metastases from gastric cancer are even rarer. The common symptoms in all reported cases of breast metastases, including from gastric cancer, are a non-tender palpable mass, diffuse edema of the skin, or erythema. However the radiologic features of secondary breast malignancies tend to indicate a benign tumor [2,3]. Therefore even though there are no typical malicious imaging findings of palpable breast masses, clinicians should consider the possibility of breast metastases and perform a histological examination in patients with a history of extra-mammary malignancies.

CASE REPORT

A 41-year-old female asymptomatic patient was on annual follow-up since February 2014 for a non-palpable right breast nodule that was detected on a screening mammography. One year after the first visit, a hypoechoic mass was found in the 10 o'clock position at a 4cm distance from the nipple. The ultrasonographic feature of the mass

seemed benign because it was well-circumscribed and the architectural structure was preserved. In mammography, a new isodense mass was found in left breast upper-inner quadrant. A ultrasound-guided core needle biopsy of the mass was performed and it was later confirmed as an malignancy and positron emission tomography/computed tomography (PET/CT) and breast magnetic resonance imaging (MRI) were performed for initial staging. On PET/CT, there was no evidence of hypermetabolism around the proven malignant mass. Instead, a new mass-like consolidation was observed at the 5 o'clock position of the left breast. In addition, the malignant mass in the left breast was not noted on MRI (Figure 1). The breast surgeon planned to perform a left mastectomy with ipsilateral sentinel lymph node biopsy. Intraoperative frozen biopsy for the left axillary sentinel lymph nodes was positive for malignancy; thus, a left modified radical mastectomy was performed in April 2015. Multifocal metastatic adenocarcinomas were detected in the mastectomy specimen, and the largest one measured 4.3 × 2.2 cm. Eighteen out of the 19 dissected axillary lymph nodes were positive for malignancy. On immunohistochemistry, the tumor cells were negative for estrogen receptor, progesterone receptor, and HER-2, but positive for p53, CK7, and E-cadherin (Figure 2). The patient previously underwent surgery for advanced gastric cancer in October 2013. The stage of gastric cancer was IIa (pT1b-N2M0). The cell type was tubular adenocarcinoma, poorly differentiated. She completed 6 cycles of adjuvant chemotherapy with the

Correspondence: Jin Sun Lee, M.D., Ph.D.

Department of Surgery, Chungnam National University School of Medicine,
228 Munhwa-ro, Jung-gu, Daejeon 35015, Korea

Tel: +82-42-280-7175; Fax: +82-42-257-8024, E-mail: jinsunlee@cnuh.co.kr

Received: May 31, 2018 **Revised:** Aug 3, 2018 **Accepted:** Oct 13, 2020

Figure 1. Imaging findings for Case. (A) Ultrasonogram of left breast demonstrates an about 0.7cm sized oval circumscribed hypoechoic mass in 10 o'clock direction. (B) Mammograms of left breast show a small oval high density mass in upper inner quadrant (arrow). This mass was not seen on contrast enhanced MRI (C) and 18-FDG PET/CT (D). MRI = magnetic resonance imaging; PET/CT = positron emission tomography/computed tomography.

Figure 2. Immunohistochemical staining findings of Case. The immunohistochemical staining for ER, PR, HER-2 and CK-7 were performed in both breast metastases from gastric cancer (A–D) and primary stomach cancer (E–H). Both tumors showed a consistent staining pattern. The tumor cells demonstrated negative immunoreactivity for ER and PR. The tumor cells showed weak staining (1+ intensity score) for HER-2 and strong positive reactivity for CK-7. ER = estrogen receptor; PR = progesterone receptor; HER-2 = human epidermal growth factor receptor 2; CK-7 = cytokeratin-7.

capecitabine plus oxaliplatin (XELOX) regimen approximately 1 year before the breast surgery. Multiple metastatic skin masses were found 2 months after the modified radical mastectomy of the left breast. She

received palliative chemotherapy with 6 cycle of fluorouracil plus irinotecan (FOLFIRI) and 3 cycle of Paclitaxel/carboplatin. She died in August 3, 2016. Progression free survival was 14 months. The char-

Table 1. Data of a case of breast metastases from gastric cancer

Characteristic	
Sex	Female
Age at diagnosis (yr)	41
Multiplicity	Yes
Clinical presentation	Palpable mass
location	Left
Mammography findings	New isodense mass
Ultrasound findings	Well-circumscribed hypoechoic mass without posterior acoustic shadow
MRI findings	No abnormal findings
PET/CT findings	Discordance with ultrasound findings No hypermetabolic masses
Metastases except breast	Skin, Axillary lymph node
Time to breast metastases (mo)	16
Follow up period after diagnosis (mo)	18
Operation	Modified radical mastectomy

MRI = magnetic resonance imaging; PET/CT = positron emission tomography/computed tomography.

Table 2. Ultrasonographic features of the metastatic lesion of the breast

Classifications	Sonographic findings
Typical hematogenous	Similar with benign breast mass like fibroadenoma
	Single or multiple
	Round to oval, hypoechoic
	Well-circumscribed or microlobulated
	Lack of speculation, calcifications, architectural distortion, retrotumoral acoustic shadowing, echogenic halo
Typical lymphatic	Less axillary lymph node involvement
	Similar with inflammatory breast cancer
	Skin thickening, obliteration of subcutaneous fat without evidence of definitive mass
	Microcalcification is not common, but in some cases
Atypical mass	More lymph node involvement compared to the hematogenous metastasis
	Variable (like primary breast cancer or benign)
	Spiculation, calcification, and surrounding parenchymal distortion
	Heterogeneous hyperechoic masses with indistinct margins
Atypical non-mass	Intratumoral cystic lesion – few cases
	Similar with ductal carcinoma <i>in situ</i>
	Multiple small hypoechoic non-mass lesions with segmental, ductal distribution without definitive mass

acteristics of the case is summarized in Table 1. This case study was approved by our Institutional Review Board, and the requirement for written consent was waived (IRB No. 2020-10-087).

DISCUSSION

The first case of breast metastasis from gastric cancer was reported by Reitmann et al. in 1908, but since then, only 45 cases (including ours) have been reported. Moreover, only one patient was a male [4-6]. The most common symptom among all reported cases of breast metastases from any malignancy is a non-tender palpable mass [3]. Simi-

larly, most cases of breast metastases from gastric cancer initially presented as a palpable lesion of the breast [2,4-11]. Except for the 12 cases with inconclusive symptoms, 22 of the 33 reported cases (66.6%), including our case, had palpable lesions. Meanwhile, the remaining 33.4% have similar symptoms of inflammatory breast cancer such as diffuse edema of the skin or erythema.

The median age of patients with breast metastases from gastric cancer is relatively younger than that of patients with primary breast cancer [5]. Given the relatively young age of premenopausal patients, it can be inferred that hormonal factors may influence the pathogenesis of the breast metastasis [12]. Estrogen affects tumor metastasis in two

ways: (1) direct effect on the tumor cell cycle and (2) modulation of the peritumoral microenvironment. While it is inconclusive and we do not know the exact mechanisms, substantial evidence supports that an elevation of the level of circulating bioactive estrogen can directly affect carcinogenesis and tumor cell growth in patients with hormone receptor-positive cancer. However, the histological type of our case is signet ring cell carcinoma, and the estrogen receptor is not expressed in this case; therefore, there is no evidence for a direct effect of estrogen in breast metastasis from gastric cancer in this case.

In the previously reported 42 cases of metastatic breast cancer from gastric cancer, excluding three cases of no site information, 54.7% (23/42) were located in the left side of the breast. As such, some authors suggested retrograde lymphatic spread hypothesis, i.e., cancer cells spread from regional lymph nodes to the breast via specific lymphatic pathways that extend from the extra-mammary organs to the breast such as the left supraclavicular lymph node [2]. However breast metastases from extra-mammary malignancies and from gastric cancer develop in the both side of breast. Regional lymph node metastases in left breast metastasis from gastric cancer is rare, accounting for only 26.0% (6/23) of all reported cases; moreover, lymph node involvement is even rarer in metastatic breast cancer from extra-mammary malignancies [13].

It is challenging for radiologists to distinguish between primary breast cancer and breast metastasis. The ultrasonographic features of breast metastases from extra-mammary malignancies vary considerably. Breast metastases from extra-mammary malignancies are classified into four categories, namely, typical hematogenous, typical lymphatic, atypical mass lesion, and atypical non-mass lesion, and described the ultrasonographic features of each category [2,3]. The features of each group are summarized in Table 2. In the 45 reported cases of breast metastases from gastric cancer, including ours, 29 cases have no records of ultrasonographic features. Only 10 cases were described as indistinct hypoechoic masses ($n=5$), diffuse hypoechoic non-mass lesions ($n=2$), hypoechoic mass ($n=2$, no record about the margin), well-circumscribed hypoechoic mass ($n=1$, our case), and skin thickening ($n=3$). There are no specific ultrasonographic findings for breast metastases from gastric cancer, and similar findings were obtained from other imaging modalities such as mammography, MRI, or PET/CT. In our female patient, PET/CT and MRI findings did not coincide with the ultrasonographic findings.

Diagnosing breast metastasis from gastric cancer is difficult due to the similar pathology between the primary breast cancer and the primary gastric cancer. The unusual type of invasive lobular carcinoma have signet ring cells and 20%–40% of gastric cancer stain positively for the estrogen receptor on immunohistochemistry. Although most reports discussed the absence of in-situ components and the periductal location of tumor cell as hallmarks of metastatic cases, it does not accurately exclude primary breast cancer. Most cases of breast metastasis from gastric cancer are signet ring cell carcinoma, and it is hard to distinguish the metastatic mammary signet ring cell carcinoma from the primary gastric cancer on hematoxylin and eosin staining. There is no single conclusive method for diagnosing breast metastasis; thus, it is useful to compare the biopsy slide of the breast lesion with that of the primary site, and an integrative decision should be made with clinical, radiological, and pathological data [14]. In our case, the preoperative diagnosis of core needle biopsy specimen was intraductal carcinoma, which was misdiagnosed because the pathologist had no clinical information and primary breast cancer cells also have both glandular or ductal differentiation.

Similar to conventional markers for primary breast cancer, several tumor markers could assist the pathologic diagnosis of breast metastases from gastric cancer. Breast metastasis tumors usually stain positively for CEA, CK7, CK20, or E-cadherin on immunohistochemistry, similar to gastric signet ring cell carcinoma. The tumor markers specific to gastric cancers such as HIK1083 or MUC families could also be used for diagnosis [5]. Our female patient stained positively for CK7 and E-cadherin, and the mastectomy specimen had extensive tumor emboli in the lymphovascular spaces without *in situ* components and was similar to the primary gastric cancer slide on H&E staining. As such, we concluded that the breast lesion was a metastatic lesion.

To select the appropriate treatment modality for the patients with metastatic breast cancer from gastric cancer, it is necessary to understand that these patients have poor prognosis. Most cases of metastatic breast cancer from gastric cancer are advanced. Despite the absence of extra-mammary metastases, there is a high potential for systemic dissemination of the primary cancer. The overall 1-year survival rate is less than 20% [1,7]. Thus, radical operation should not be performed except for the relief of symptoms such as continuous nipple discharge or severe pain. Iesato et al. [4] reported a case of combination chemotherapy of S-1 and cisplatin that was tolerable and effective for the re-

duction of the breast mass. However, in most cases, chemotherapy was ineffective because of disseminated metastatic disease and poor general condition. Meanwhile, hormonal therapy is rarely performed due to an absence of hormone receptor in immunohistochemical stains.

Breast metastases from gastric cancer might be a heterogeneous disease entity based on the clinical, radiological, and histopathological inconsistencies. Because of its rarity, a multicenter study is necessary to obtain more data and to increase the statistical power of findings. Currently, there is no standard and accurate diagnostic modality for breast metastases, and patients are diagnosed based on the clinician's suspicion and combination of objective findings.

CONFLICT OF INTEREST

The authors declare that they have no competing interests.

REFERENCES

1. Toombs BD, Kalisher L. Metastatic disease to the breast: clinical, pathologic, and radiographic features. *AJR Am J Roentgenol* 1977;129:673-6.
2. Lee SK, Kim WW, Kim SH, Hur SM, Kim S, Choi JH, et al. Characteristics of metastasis in the breast from extramammary malignancies. *J Surg Oncol* 2010;101:137-40.
3. Lee JH, Kim SH, Kang BJ, Cha ES, Kim HS, Choi JJ. Metastases to the breast from extramammary malignancies—sonographic features. *J Clin Ultrasound* 2011;39:248-55.
4. Iesato A, Oba T, Ono M, Hanamura T, Watanabe T, Ito T, et al. Breast metastases of gastric signet-ring cell carcinoma: a report of two cases and review of the literature. *Onco Targets Ther* 2015;8:91-7.
5. He CL, Chen P, Xia BL, Xiao Q, Cai FL. Breast metastasis of gastric signet-ring cell carcinoma: a case report and literature review. *World J Surg Oncol* 2015;13:120.
6. Hamby LS, McGrath PC, Cibull ML, Schwartz RW. Gastric carcinoma metastatic to the breast. *J Surg Oncol* 1991;48:117-21.
7. Hajdu SI, Urban JA. Cancers metastatic to the breast. *Cancer* 1972;29:1691-6.
8. Madan AK, Ternovits C, Huber SA, Pei LA, Jaffe BM. Gastrointestinal metastasis to the breast. *Surgery* 2002;132:889-93.
9. McCrea ES, Johnston C, Haney PJ. Metastases to the breast. *AJR Am J Roentgenol* 1983;141:685-90.
10. Canda AE, Sevinc AI, Kocdor MA, Canda T, Balci P, Saydam S, et al. Metastatic tumors in the breast: a report of 5 cases and review of the literature. *Clin Breast Cancer* 2007;7:638-43.
11. Yan Z, Hummel P, Waisman J, Newstead GM, Chachoua A, Chhieng D, et al. Prostatic adenocarcinoma metastatic to the breasts: report of a case with diagnosis by fine needle aspiration biopsy. *Urology* 2000;55:590.
12. Boutis AL, Andreadis C, Patakiouta F, Mouratidou D. Gastric signet-ring adenocarcinoma presenting with breast metastasis. *World J Gastroenterol* 2006;12:2958-61.
13. Tian Q, Zeng J, Tao X, Zhang Z, Zhou X, Wang Y. Clinical pathology of metastatic gastric carcinoma to the breast: a report of two cases and a review of literature. *Oncol Lett* 2016;11:3081-4.
14. Péqueux C, Raymond-Letron I, Blacher S, Boudou F, Adlanmerini M, Fouque MJ, et al. Stromal estrogen receptor-alpha promotes tumor growth by normalizing an increased angiogenesis. *Cancer Res* 2012;72:3010-9.