

Characteristics of Metastasis in the Breast From Extramammary Malignancies

SE KYUNG LEE, MD,¹ WAN WOOK KIM, MD,¹ SUNG HOON KIM, MD,¹ SUNG MO HUR, MD,¹
SANGMIN KIM, PhD,¹ JAE HYUCK CHOI, MD,¹ EUN YOON CHO, MD, PhD,² SOO YEON HAN, MD,³
BOO-KYUNG HAHN, MD, PhD,³ JUN-HO CHOE, MD, PhD,¹ JUNG-HAN KIM, MD, PhD,¹ JEE SOO KIM, MD, PhD,¹
JEONG EON LEE, MD, PhD,¹ SEOK JIN NAM, MD, PhD,¹ AND JUNG-HYUN YANG, MD, PhD^{1*}

¹Division of Breast and Endocrine Surgery, Department of Surgery, Samsung Medical Center, Sungkyunkwan University School of Medicine, Seoul, South Korea

²Department of Pathology, Samsung Medical Center, Sungkyunkwan University School of Medicine, Seoul, South Korea

³Department of Radiology, Samsung Medical Center, Sungkyunkwan University School of Medicine, Seoul, South Korea

Background and Objective: Breast metastasis from extramammary neoplasm is rare. We present the cases of metastasis to the breast after review of results in one institute and we want to show the difference of previous report.

Methods: The surgical and pathology databases of Samsung Medical Center from November 1994 to March 2009 were investigated to identify all patients with a diagnosis of metastasis to the breast.

Results: Thirty-three patients with breast metastases from extramammary neoplasm were studied. Gastric carcinoma was most common metastatic origin in this study. There were four cases with microcalcifications in their metastatic lesions. This is the first report of microcalcification of metastatic lesions to the breast from hepatocellular carcinoma and gastric cancer.

Conclusions: Pathologic examination and considering known clinical history may be helpful to differentiate the primary breast cancer and metastatic cancer. Metastasis to the breast from an extramammary neoplasm usually indicates disseminated metastatic disease and a poor prognosis. An accurate diagnosis of breast metastases, differentiating primary from metastatic breast carcinoma, is important for proper management.

J. Surg. Oncol. 2010;101:137–140. © 2010 Wiley-Liss, Inc.

KEY WORDS: breast; diagnosis; metastasis; neoplasm; secondary

INTRODUCTION

Breast cancer is a very common malignancy in women though metastases from extramammary malignant neoplasms to the breast are rare. It has been reported that metastases from extramammary malignant neoplasms to the breast account for approximately 0.3–2.7% of all malignant mammary tumors [1–5]. To date, the cases of less than 500 patients with secondary involvement of the breast by extramammary primary tumors have been reported [6,7]. Some authors have suggested that this rarity is caused by the characteristics of breast tissue [8,9]. Other authors have suggested that hormonal status has a role in cancer predisposition, based on the high occurrence of breast metastases in pubescent, lactating, and pregnant females [10–12]. Other hypotheses for these metastases to unexpected and anatomically non-connected locations have also been proposed. One such theory suggests that micrometastatic foci arise from dissemination of clonogenic cells (or stem cells) that spread by systemic, lymphatic or transcoelomic migration. Another hypothesis proposes a transfection phenomenon of the cancer genome [7,13].

The major problem in establishing such a diagnosis is to differentiate primary from metastatic extramammary neoplasms. Misdiagnosis as a primary breast cancer even in cases with a medical history of another primary cancer is common. Many authors have reported the differential diagnostic point to distinguish metastatic extramammary neoplasms from primary breast cancer, therefore, we want to know the characteristics of metastatic neoplasms to the breast by reviewing our cases and published article.

After reviewing of the 14 years of surgical and pathologic databases from a single institute, we found 33 cases of metastases to the breast. In this article, we report these cases with a review of the English published literature on this subject.

MATERIALS AND METHODS

During the past 15 years (November 1994 to March 2009), 7,511 patients underwent operation for breast cancer. Our data was retrospectively obtained from these patients' medical records. The surgical and pathology databases of Samsung Medical Center from November 1994 to March 2009 were investigated to identify all patients with a diagnosis of metastasis to the breast.

Retrospectively analyzing the data obtained from the patients' records and the histology reports of the excised breast lesions, we found that 33 patients had metastases to the breast from extramammary neoplasms.

Tumors were classified as genuine secondary neoplasms if a primary site outside of the breast could be established and the histology of the breast lesion was consistent with the primary tumor. The tumors were also considered genuine secondary neoplasms if there was evidence of systemic disease with coincidental involvement of the breast, and histology of the breast lesion was not consistent with that of a primary breast cancer.

Se Kyung Lee and Wan Wook Kim contributed equally to this work as first co-author.

*Correspondence to: Jung-Hyun Yang, MD, PhD, Division of Breast and Endocrine Surgery, Department of Surgery, Samsung Medical Center, Sungkyunkwan University School of Medicine, 50 Irwon-dong, Gangnam-gu, Seoul 135-710, South Korea. Fax: +82-2-3410-6982. E-mail: drjh.yang@samsung.com

Received 19 August 2009; Accepted 19 October 2009

DOI 10.1002/jso.21453

Published online in Wiley InterScience (www.interscience.wiley.com).

RESULTS

Thirty-three patients presented with metastases to the breast from extramammary neoplasms. Females were more frequently affected (3 males, 30 females). Mean age of onset for breast metastasis was 46 years with a wide range of ages (25–76 years old). Mean time interval from diagnosis of a primary extramammary neoplasm to breast metastases was 13.9 months. The most common symptom was a palpable breast mass. In three cases, the breast was the only metastatic site from primary extramammary neoplasms.

In 24 of all 33 patients, there was a known history of a primary extramammary neoplasm and they had taken operation and/or chemotherapy, radiotherapy previously. One of these 24 patients underwent modified radical mastectomy for a breast mass as regard of double primary cancer after 20 months to the gastric cancer operation. For the remaining 9 patients, the breast lesions were diagnosed as simultaneous metastasis from other extramammary origin malignancy. In two of these cases, the primary extramammary neoplasm was not found. Two patients presented with a palpable breast mass as the initial symptom, the breast lesions were eventually diagnosed as metastases from extramammary neoplasms. One patient was initially diagnosed with a double primary tumor (hepatocellular carcinoma and breast cancer). However, after operation (partial mastectomy with sentinel lymph node biopsy), her breast mass was ultimately diagnosed as a metastatic lesion from the hepatocellular carcinoma (Table I).

Among 30 patients who had radiologic imaging done, 28 patients underwent breast ultrasonography and 22 patients took a mammography. Three patients did not have radiologic imaging done because definitive pathologic diagnoses of breast metastases had already been established. Unilateral, left sided and upper outer quadrant of the breast were more frequently affected. On mammographic findings, four patients showed calcifications (gastric carcinoma, two cases; HCC, one case; ovarian cancer, one case) (Fig. 1). Enlarged axillary lymph nodes were common (Table II).

Core needle biopsy was performed in 24 patients, and was diagnostic in 22 cases. Two patients were diagnosed with a breast cancer (invasive ductal carcinoma and invasive lobular carcinoma) on core biopsy, and they underwent breast cancer surgery (partial mastectomy and modified radical mastectomy). Postoperatively, the diagnosis of metastatic carcinoma from another origin (liver and stomach) was established. Among nine patients who did not undergo the core biopsy, four patients were diagnosed by fine needle aspiration and the rest by excisional biopsy.

The histologic diagnosis of metastasis to the breast can be more difficult than that of primary breast cancer. Immunohistochemical staining was performed in 15 patients. Breast cancer specific markers like ER/PR/BRST-2 were the most commonly used in immunohisto-

TABLE I. Clinical Characteristics of Patients With Metastatic Lesions From Extramammary Neoplasms (Total n = 33)

Mean age	46 (25–76)
Male/female	3/30
Mean time from diagnosis to breast metastasis (in months)	13.9
History of primary extramammary carcinoma	
Known history	24
Unknown history	9
Presenting symptom(s) of the breast metastatic lesions	
Palpable mass	20
Found during work-up for other primary cancer	5
Inflammatory breast symptoms (redness, pain, edema)	5
Found during follow-up of known primary carcinoma	3
Presence of other metastases	
Breast only	3
Cases of other metastases before breast metastasis	25
Simultaneous other metastases	5

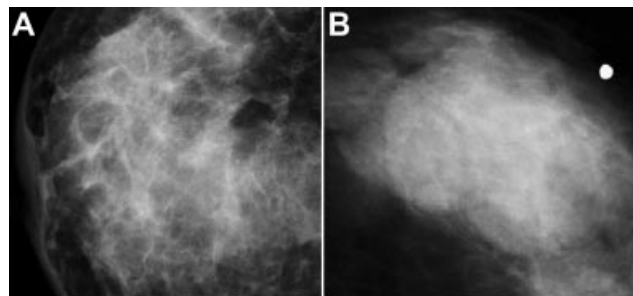


Fig. 1. Calcifications in metastatic tumors on mammography (**A:** metastatic gastric carcinoma, **B:** metastatic hepatocellular carcinoma).

chemical staining (10/15 patients) and tumor specific markers such as PSA for prostate cancer, α FP for HCC, TTF-1 for lung cancer and CK7/20 for gastric carcinoma were helpful to diagnosis (Fig. 2).

There was a wide range of the metastases from a variety of organs. Unlike other reports, metastasis from hematologic origin was uncommon. The most common primary malignancies were gastric carcinoma, lung cancer and skin cancer. Gastric carcinoma was most common metastatic origin in this study, however, the rate of melanoma and malignant thymoma was significantly higher compared with that of gastric carcinoma ($P = 0.02$ and $P = 0.009$, respectively) (Table III). Among eight patients who had a breast metastasis from gastric carcinoma, five patients were previously diagnosed with high stage gastric carcinoma (more than stage IIIA).

Survival was traced through medical records and phone-interviews. Follow-up was possible in 29 patients. Twenty-four patients died; median survival period from diagnosis of metastasis to death was 13.9 months. Five patients survived; two with gastric carcinoma, two with thymic cancer and one with tracheal cancer. Two cases of gastric carcinoma of these survivors were diagnosed 2 and 8 months before

TABLE II. Radiologic Findings of Metastatic Lesions From Extramammary Neoplasms (Total n = 30)*

Location	
Right/left/both	7/20/3
Quadrant	
Inner	
Upper	2
Lower	1
Outer	
Upper	8
Mid	4
Lower	4
Subareolar	2
Diffuse/multiple	7/2
Multiplicity	
Single lesion	21
Multiple lesions	
Unilateral	6
Bilateral	3
Presence of calcification ^a	
Yes	4 ^b
No	18
Presence of enlarged axillary lymph node	
Yes	13
No	17

*Three patients did not have radiologic imaging done because definitive pathologic diagnoses of breast metastases had already been established.

^aEight patients who did not undergo mammography were excluded.

^bOne hepatocellular carcinoma, one ovarian cancer, two gastric carcinomas.

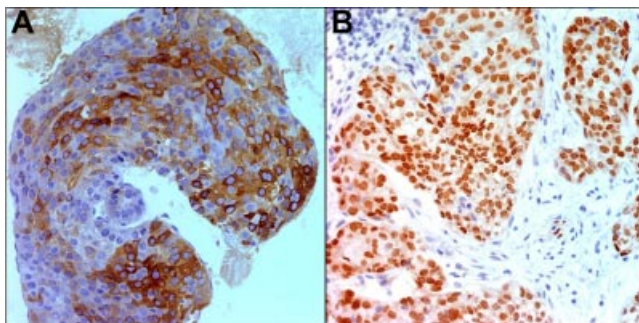


Fig. 2. Immunohistochemical staining with tumor specific markers (A: α FP for HCC, B: TTF-1 for lung cancer). [Color figure can be viewed in the online issue, available at www.interscience.wiley.com.]

inquiry. Two thymic carcinoma patients and one tracheal cancer patient survived more than 30 months after diagnosis of secondary breast metastasis (32, 34, and 49 months, respectively) without any recurrence of disease after breast surgery.

DISCUSSION

The breast is an uncommon site for metastasis from other malignancies. To date, the cases of less than 500 patients with secondary involvement of the breast by extramammary primary tumors have been reported [6,7].

In about 25–40% of breast metastases from extramammary carcinoma patients, the breast lesion is the initial manifestation of the disease [5,7,14–16]. In our study, most patients presented with a history of loco-regional and wide spread metastases of extramammary neoplasms; a breast lesion was the initial manifestation of disease in only two cases. The mean time interval from diagnosis of primary extramammary neoplasm to the breast metastasis was 13.9 months. A previous study reported that the time from initial diagnosis to development of breast metastasis averaged 2 years in cases with a known primary carcinoma [17].

Some authors have suggested various differential diagnostic points on radiologic images to distinguish metastatic extramammary neoplasms from primary breast cancer. Metastatic carcinomas to the breast have relatively well-circumscribed and freely movable masses [11,18,19]. In present study, two patients had lesions classified to BI-RADS category 3 lesions by ultrasonography, and the others had lesions categorized to BI-RADS category 4B or greater. A solitary lesion was the most common presentation in our study. Among

30 patients, 21 radiologically available patients presented with a solitary lesion. The upper outer quadrant was the most commonly involved breast quadrant. This result corresponds with other reports [11,14,19,20]. However, Akcay reported that metastatic lesions are more likely to be multiple and are frequently bilateral [21]. Enlarged axillary lymph node is commonly encountered. In our report, 13 (43.3%) of 30 cases showed enlarged axillary lymph node. This rate is consistent with previous results [9,11,14,18,20,22,23]. The left breast was the most commonly involved site. This laterality may suggest the possibility of the presence of other lymphatic pathway or lymphatic preponderance to the breast from other organ such as left supraclavicular lymph node metastasis from both side lung or gastric carcinoma. However, we could not find any relation between this preference and primary site or other clinicopathologic features. More study and observation about this phenomenon will be necessary. Absence of microcalcifications is considered a characteristic of metastatic lesions to the breast with the exception of ovarian cancer [15,24–26]. McCrea et al. [18] even suggested that the presence of recognizable calcification in a mass on a mammogram virtually excludes metastatic disease to the breast. However, in our study, there were four cases with microcalcifications in their metastatic lesions: one hepatocellular carcinoma, two gastric carcinomas and one ovarian cancer (Fig. 1). This is the first report of microcalcification of metastatic lesions to the breast from hepatocellular carcinoma and gastric cancer.

Core needle biopsy was performed in 24 patients and was diagnostic in 22. Unnecessary breast cancer surgery was performed in the two patients, where core biopsy was not diagnostic. Among 9 patients who did not take the core biopsy, 4 patients were diagnosed by fine needle aspiration (FNA) and the rest by excisional biopsy (Table III). Some authors have suggested that fine needle aspiration of the breast is the best approach to tumor diagnosis, and offers the most appropriate and as well as cost-effective patient management [21,27,28]. According Smymiotisto et al. [23], preoperative FNA is invaluable because most cases in their report were indistinguishable from primary breast cancer by FNA findings. In our study, the specimens obtained by core biopsy were the more effective for differentiation in cases which needed immunohistochemical staining for accurate diagnosis.

The pathologic findings of metastatic breast lesions include atypical histologic features, the presence of many lymphatic tumor emboli, periductal and perilobular distribution without signs of hyperplasia or atypia, a lack of desmoplastic response and absence of ductal in situ and elastosis [11,15,29]. Comparison of previously diagnosed neoplasms and metastatic breast lesions is a very important factor in establishing a diagnosis of metastasis. Immunohistochemical studies

TABLE III. Site of Primary Carcinoma in Patients With Breast Metastases

Primary site	No. of metastasis	Total no. ^a	Incidence (%)	P-value
Stomach	8	2,1008	0.038	
Lung	5	12,305	0.041	
Liver (hepatocellular carcinoma)	2	10,432	0.019	
Biliary (cholangiocarcinoma)	1	595	0.168	
Skin				
Melanoma	2	479	0.42	0.02 ^b
Squamous cell carcinoma	1	260	0.385	
Colon	2	7,260	0.028	
Hematologic (lymphoma)	2	3,306	0.061	
Thymus	2	322	0.621	0.009 ^b
Unknown primary carcinoma	2	—	—	
Others (heart, ovary, prostate, thyroid, trachea, soft tissue)	6	—	—	
Total	33	—	—	—

^aNumber of patients diagnosed with each carcinoma during a single period in our institute.

^bBy Fisher's exact test (comparison of melanoma and thymic cancer with gastric carcinoma).

help to confirm the diagnosis in some cases. Expression of C7 and CK20 for adenocarcinoma, PSA for prostate cancer, α FP for HCC, TTF-1 for lung cancer and ER/PR and BRST-2 for breast cancer is well-known markers for differentiating the origin of metastatic lesions whose morphological features do not specify the initial origin. We did immunohistochemical studies in 15 cases with breast specific markers (ER/PR and BRST-2) and all cases except one from lung cancer were negative to these markers. In the cases of prostate cancer (PSA), lung cancer (TTF-1) and HCC (α FP), these immunohistochemical studies were very helpful for definitive diagnosis, and it also did in other cases with breast specific markers. Routine pathologic examination and clinical history consideration may also be helpful to differentiate primary breast cancer from metastatic cancer.

In our study, most common cause of metastasis to the breast was gastric carcinoma (8/33). The most common tumors to metastasize to the breast from extramammary sites are malignant melanoma, lymphoma, lung cancer, ovarian cancer, soft tissue sarcoma, gastrointestinal and genitourinary tumors, followed by sporadically reported tumors, for example, osteosarcoma, thyroid neoplasm and cervical, vaginal and endometrial carcinoma [2,6,9,21,29–31]. This discordance with previously published studies may be due to a difference in disease prevalence. Gastric carcinoma is the most common cancer and the 3rd most common carcinoma in women, followed by breast and thyroid carcinoma in Korea [32]. In our institute, a total of 21,008 patients were diagnosed with gastric carcinoma during the same period. However, by a rate comparison, the rates of melanomas and malignant thymomas were higher than that of gastric carcinoma ($P=0.02$ and $P=0.009$, respectively) (Table III).

Among the reports of breast metastases from extramammary origin, metastases from gastric cancer are extremely rare. Five of our eight gastric origin breast metastases were diagnosed with gastric carcinoma before diagnosis of breast metastases. Most cases were at a high stage (greater than AJCC stage III). By Bormann's classification, type IV (linitis plastica) was the most common type. The stomach and breast specimens showed similar morphology, especially in the case of lobular carcinoma, as lobular breast carcinoma can have signet ring features. In these cases, immunohistochemical staining patterns and negative staining for breast carcinoma markers (ER, PR, c-erbB2 and BRST-2) can be helpful in the differential diagnosis. However, though ER is often present in breast cancer, but more than 20% of primary gastric cancers also have evidence of ER [33]. There were no positive staining of breast specific markers in our gastric carcinoma cases.

Early and accurate diagnosis of secondary breast involvement is important for appropriate management and for avoiding unnecessary and potentially harmful treatments in these patients. Microscopic, pathologic, immunohistochemical and radiologic findings in conjunction with the patient's clinical history should be considered in differentiating a secondary mass from a primary breast carcinoma. A breast mass in a patient with a history of cancer (especially high stage cancer), even if clinically or mammographically benign, should make suspicion for a possible metastasis.

REFERENCES

- Rubio IT, Korourian S, Brown H, et al.: Carcinoid tumor metastatic to the breast. *Arch Surg* 1998;133:1117–1119.
- Cangiarella J, Symmans WF, Cohen JM, et al.: Malignant melanoma metastatic to the breast: A report of seven cases diagnosed by fine-needle aspiration cytology. *Cancer* 1998;84:160–162.
- Canda AE, Sevinc AI, Kocdor MA, et al.: Metastatic tumors in the breast: A report of 5 cases and review of the literature. *Clin Breast Cancer* 2007;7:638–643.
- Di Cosimo S, Ferretti G, Fazio N, et al.: Breast and ovarian metastatic localization of signet-ring cell gastric carcinoma. *Ann Oncol* 2003;14:803–804.
- Hamby LS, McGrath PC, Cibull ML, et al.: Gastric carcinoma metastatic to the breast. *J Surg Oncol* 1991;48:117–121.
- Alva S, Shetty-Alva N: An update of tumor metastasis to the breast data. *Arch Surg* 1999;134:450.
- Mihai R, Christie-Brown J, Bristol J: Breast metastases from colorectal carcinoma. *Breast* 2004;13:155–158.
- Jochimsen PR, Brown RC: Metastatic melanoma in the breast masquerading as fibroadenoma. *JAMA* 1976;236:2779–2780.
- Yeh CN, Lin CH, Chen MF: Clinical and ultrasonographic characteristics of breast metastases from extramammary malignancies. *Am Surg* 2004;70:287–290.
- Baranzelli MC, Granier AM, Cornillot M, et al.: Five cases of breast metastases in children. Cytologic aspects. *Arch Anat Cytol Pathol* 1986;34:58–61.
- Vergier B, Trojani M, de Mascarel I, et al.: Metastases to the breast: Differential diagnosis from primary breast carcinoma. *J Surg Oncol* 1991;48:112–116.
- Nayar M, Chandra M, Aggarwal R, et al.: Carcinoma cervix presenting as primary breast malignancy. *Indian J Pathol Microbiol* 1987;30:283–286.
- Baum M, Colletta A: Breast cancer: A revolutionary concept. *Breast Cancer* 1995;2:9–18.
- Toombs BD, Kalisher L: Metastatic disease to the breast: Clinical, pathologic, and radiographic features. *Am J Roentgenol* 1977;129:673–676.
- Alexander HR, Turnbull AD, Rosen PP: Isolated breast metastases from gastrointestinal carcinomas: Report of two cases. *J Surg Oncol* 1989;42:264–266.
- Hajdu SI, Urban JA: Cancers metastatic to the breast. *Cancer* 1972;29:1691–1696.
- McIntosh IH, Hooper AA, Millis RR, et al.: Metastatic carcinoma within the breast. *Clin Oncol* 1976;2:393–401.
- McCrea ES, Johnston C, Haney PJ: Metastases to the breast. *Am J Roentgenol* 1983;141:685–690.
- Madan AK, Ternovits C, Huber SA, et al.: Gastrointestinal metastasis to the breast. *Surgery* 2002;132:889–893.
- Bohman LG, Bassett LW, Gold RH, et al.: Breast metastases from extramammary malignancies. *Radiology* 1982;144:309–312.
- Akcy MN: Metastatic disease in the breast. *Breast* 2002;11:526–528.
- Chung SY, Oh KK: Imaging findings of metastatic disease to the breast. *Yonsei Med J* 2001;42:497–502.
- Smymiotis V, Theodosopoulos T, Marinis A, et al.: Metastatic disease in the breast from nonmammary neoplasms. *Eur J Gynaecol Oncol* 2005;26:547–550.
- Paulus DD, Libshitz HI: Metastasis to the breast. *Radiol Clin North Am* 1982;20:561–568.
- Moncada R, Cooper RA, Garces M, et al.: Calcified metastases from malignant ovarian neoplasm. Review of the literature. *Radiology* 1974;113:31–35.
- Royen PM, Ziter FM, Jr.: Ovarian carcinoma metastatic to the breast. *Br J Radiol* 1974;47:356–357.
- Gupta D, Merino MI, Farhood A, et al.: Metastases to breast simulating ductal carcinoma in situ: Report of two cases and review of the literature. *Ann Diagn Pathol* 2001;5:15–20.
- Domanski HA: Metastases to the breast from extramammary neoplasms. A report of six cases with diagnosis by fine needle aspiration cytology. *Acta Cytol* 1996;40:1293–1300.
- Georgiannos SN, Chin J, Goode AW, et al.: Secondary neoplasms of the breast: A survey of the 20th Century. *Cancer* 2001;92:2259–2266.
- Sandison AT: Metastatic tumours in the breast. *Br J Surg* 1959;47:54–58.
- Amichetti M, Perani B, Boi S: Metastases to the breast from extramammary malignancies. *Oncology* 1990;47:257–260.
- Adamovich TL, Simmons RM: Ductal carcinoma in situ with microinvasion. *Am J Surg* 2003;186:112–116.
- Kojima O, Takahashi T, Kawakami S, et al.: Localization of estrogen receptors in gastric cancer using immunohistochemical staining of monoclonal antibody. *Cancer* 1991;67:2401–2406.