

Metastatic Tumors to the Breast from Extramammary Malignancies

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Background : Metastases to the breast from extramammary malignancies are very rare. We describe here the clinicopathologic features of the metastatic breast tumors that were identified in Korean patients at a single institute. **Methods :** We analyzed the clinicopathologic data of the patients who were diagnosed between January 1989 and April 2009 at Asan Medical Center. **Results :** Only 31 (0.21%) patients with metastases to the breast from extramammary malignancies were diagnosed over a 20-year period, and 29 of them had available data. The mean time to the diagnosis of metastasis after the diagnosis of the primary malignancy was 21 months (range, 0 to 102 months). The most common primary site was the stomach, followed by the uterus and lung. The most common histologic type was adenocarcinoma. A common clinical presentation was a unilateral palpable mass. Most metastatic tumors had morphological features that were similar to those of their respective primary tumors. However, in situ carcinoma, microcalcification and desmoplastic reactions were rarely observed. **Conclusions :** Metastatic breast lesions from extramammary sites are extremely rare, and the stomach, uterus and lung could be considered as the common primary sites in Korean patients. The clinical history and comparing the morphology of the primary tumor with the morphology of the metastatic tumor are important for achieving the proper diagnosis.

Key Words : Breast; Neoplasms; Neoplasm metastasis; Carcinoma; Sarcoma

Breast carcinoma is the most common cancer in females, and there were an estimated 182,460 new cases and 40,480 deaths due to breast cancer in the United States in 2008.¹ Breast carcinoma is also the most common malignancy in Korean females.² Most breast carcinomas are primary tumors of the breast, and breast metastases from extramammary sites are very rare, with an incidence of 0.43% to 6.6%.³⁻⁵ There have been several case reports and reviews of extramammary breast metastases in the English-language literature, with most originating from the USA, the United Kingdom and Australia.⁴⁻⁶ Hematopoietic neoplasms, lung carcinoma and malignant melanoma are the most common primary tumors that metastasize to the breast.⁴⁻⁶ Although many metastatic breast cancers from extramammary malignancies are similar to their primary malignancies for the morphological features, some can simulate the features of a primary breast tumor. Therefore, making the diagnosis may be difficult without a prior history of non-mammary malignancy.⁷ We recently experienced a case with a metastatic breast lesion that simulated ductal carcinoma in situ, and this caused confusion when trying to make the proper diagnosis. Although the radiologic and histologic features of individual metastatic lesions

to the breast have been described, such breast lesions have no specific features.^{4,8-10}

In Korea, there have been a few cases of breast metastases from extramammary sites.¹¹⁻¹⁸ We retrospectively reviewed the surgical archives of Asan Medical Center to identify the patients who had histopathologically and clinically confirmed extramammary metastases to the breast and to analyze their clinicopathologic characteristics. To date, this is the largest series of metastatic lesions of the breast from extramammary malignancies to be described in Korea.

MATERIALS AND METHODS

We searched the clinical and pathological database of Asan Medical Center for the patients who were diagnosed with breast malignancies between January 1989 and April 2009. Of the 14,725 such patients, 31 of them had clinicopathologically confirmed metastases to the breast from extramammary malignancies. Two of these patients were excluded because their clinical and pathologic data was incomplete. Therefore, this study in-

cluded 29 patients with pathologically proven metastases to the breast from extramammary malignancies. The hematoxylin-and-eosin-stained slides and/or the immunostained slides were available for only 15 patients. The remaining 14 patients were evaluated based on only the pathology records and medical records. The clinical records of all 29 patients were retrospectively reviewed to obtain the demographic and clinical information, including age, gender, a history of primary malignancy, the time to presentation of breast metastasis, the mammographic findings and the presence of distant metastases to other sites.

RESULTS

Clinical findings

Of the 14,725 patients who had breast malignancies diagnosed and treated at our institution over a 20-year period, only

31 (0.21%) had been diagnosed with metastatic breast lesions. The clinicopathologic features of the 29 evaluable patients are summarized in Table 1. All 29 patients were women, with a mean age of 51 years (range, 27 to 77 years). The sites of the primary tumors varied, with the most common being the stomach (7 patients, 24%), followed by the uterus (5 patients, 17%) and the lung (4 patients, 14%). The other primary sites included the soft tissue, head and neck, ovary, thyroid and kidney. The most common histologic type was adenocarcinoma, with the metastases from stomach cancer being poorly differentiated carcinomas including signet ring cell carcinoma, and lung cancer. The other tumor histologies included squamous cell carcinoma, serous papillary carcinoma, rhabdomyosarcoma, leiomyosarcoma and malignant melanoma. Six patients presented with metastases from hematologic malignancies, including acute myelomonoblastic leukemia (AML), diffuse large B cell lymphoma, natural killer T cell (NK-T cell) lymphoma and multiple myeloma.

Table 1. The clinicopathologic features of 29 patients with metastases to the breast from extramammary malignancies

Case	Age (yr)	Sex	Primary site	Histology	Time after primary malignancy Dx (mo)
1	41	F	Stomach	SRCCa	1
2 ^a	46	F	Stomach	Adenocarcinoma, PD	1
3 ^a	39	F	Stomach	Adenocarcinoma, PD	^b
4 ^a	42	F	Stomach	SRCCa	0
5	46	F	Stomach	SRCCa	26
6	56	F	Stomach	Adenocarcinoma, PD	4
7	42	F	Stomach	SRCCa	0
8	73	F	Uterus	Squamous cell carcinoma	NA
9	38	F	Uterus	Squamous cell carcinoma	8
10	57	F	Uterus	Squamous cell carcinoma	47
11	57	F	Uterus	Small cell carcinoma	3
12 ^a	54	F	Lung	Adenocarcinoma	30
13 ^a	68	F	Lung	Adenocarcinoma	40
14 ^a	32	F	Lung	Adenocarcinoma	0
15	68	F	Lung	Adenocarcinoma	1
16 ^a	45	F	Ovary	Serous papillary carcinoma	17
17 ^a	45	F	Maxillary sinus	Embryonal rhabdomyosarcoma	NA
18 ^a	53	F	Uterus	Leiomyosarcoma	NA
19	63	F	Thyroid	Anaplastic carcinoma	0
20 ^a	46	F	Kidney	Papillary RCC	44
21 ^a	27	F	Soft tissue	Alveolar rhabdomyosarcoma	3
22 ^a	37	F	Soft tissue	Embryonal rhabdomyosarcoma	4
23 ^a	44	F	Soft tissue	Malignant melanoma	18
24	70	F	Gingiva	AML	1
25 ^a	77	F	Lung	Diffuse large B cell lymphoma	102
26	57	F	Nasal cavity	NK-T cell lymphoma	7
27 ^a	43	F	Systemic	AML	9
28	53	F	Bone	Multiple myeloma	24
29	56	F	Spleen	Diffuse large B cell lymphoma	NA

^aHistological review is available; ^bMetastatic breast tumor detected before the primary tumor.

Dx, diagnosis; F, female; SRCCa, signet ring cell carcinoma; PD, poorly differentiated; NA, not accessible; RCC, renal cell carcinoma; AML, acute myelomonocytic leukemia; NK-T cell, natural killer T cell.

The time to the diagnosis of breast metastases after the diagnosis of the primary malignancy ranged from 0 to 102 months (mean, 21.1 months). Of the 29 patients, only one (case 3) presented with metastatic breast cancer prior to the detection of the extramammary primary malignancy. In four patients (cases 4, 7, 14, and 19), the metastatic breast tumor was detected simultaneously with the primary tumor.

The clinical presentation and radiologic findings are summarized in Table 2. Breast involvement was unilateral in 20 patients (74%), whereas 7 patients presented with bilateral, multiple breast lesions. Clinically, the breast lesions in 14 patients (52%) presented as palpable masses, whereas 3 patients (11%) presented with skin thickening and nipple retraction. In seven patients (24%), the breast lesions were suspected during the follow-up clinical examinations for the primary tumors by the findings of computed tomography or whole body positron emission tomography, and the breast lesions were pathologically confirmed as breast metastases from primary extramammary tumors. The mammography results were available for 27 of the 29 patients (93%). Some of these patients presented with mass-like lesions that had slightly indistinct, speculated or irregular margins, and 12 presented with multiple nodules. In six patients, mammography showed diffuse edematous changes of the breast parenchyma and irregular increases of the parenchymal density. Distortion of the parenchymal architecture and calcification were infrequently seen.

Pathologic findings

Metastasis from gastric carcinoma

The metastatic tumors from stomach cancers showed a diffuse infiltration of poorly differentiated adenocarcinoma cells or

Table 2. The clinical and radiological findings of breast metastases

Characteristics	No. of patients
Clinical presentation	
Unilateral involvement	20
Bilateral involvement	7
Palpable mass	14
Skin change with thickening and nipple retraction	3
Mammographic findings	
Single mass	15
Multiple nodules	12
Diffuse increase of parenchymal density	6
Parenchymal architecture distortion	3
Calcification	1

Mammography results were available for 27 patients.

typical signet ring cells without desmoplastic reaction (Fig. 1). The tumor cells were negative for gross cystic disease fluid protein-15 (GCDFP-15), estrogen receptor (ER) and progesterone receptor (PR). In case 3, the tumor cells showed diffuse, strong positivity for carcinoembryonic antigen. The lobules or ducts of the benign breast parenchyma were embedded in fibrotic stroma and they had minimal or the usual ductal hyperplasia without associated carcinoma in situ. Many of the lobular units and ducts were surrounded by infiltrating tumor cells. No microcalcification was seen.

Metastasis from lung carcinoma

The metastatic tumors from lung adenocarcinomas showed micropapillary features (Fig. 2A). Desmoplastic reaction around the tumors was rare. The tumors had relatively well demarcated margins and mainly dilated duct-like structures lined with atypical tumor cells with abundant eosinophilic cytoplasm and prominent nucleoli (Fig. 2B). The tumor cells showed papillary proliferation with micropapillary clusters in the lumen, and so this resembled the micropapillary pattern of ductal carcinoma in situ of the breast, although myoepithelial cells were not present in these areas that were confirmed by immunonegativity for the myoepithelial cell markers smooth muscle myosin heavy chain and cytokeratin 5/6. Several residual normal ducts of the breast were scattered around the metastatic tumor portion. Neoplastic changes of the adjacent ducts or associated carcinoma in situ were rare. Microcalcifications were identified. The tumors involved dilated lymphatic spaces. The tumor cells were strongly positive for thyroid transcription factor-1 (Fig. 2C), but they were negative for ER and PR.

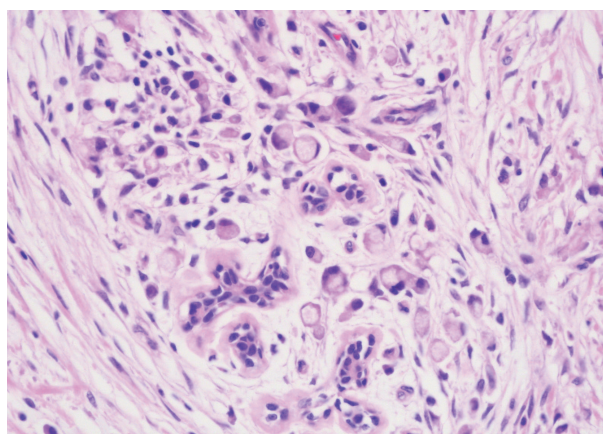


Fig. 1. The histological appearance of a metastatic breast carcinoma arising from stomach cancer. The tumor shows diffuse infiltration of tumor cells with signet ring cell features, but there is no desmoplastic reaction.

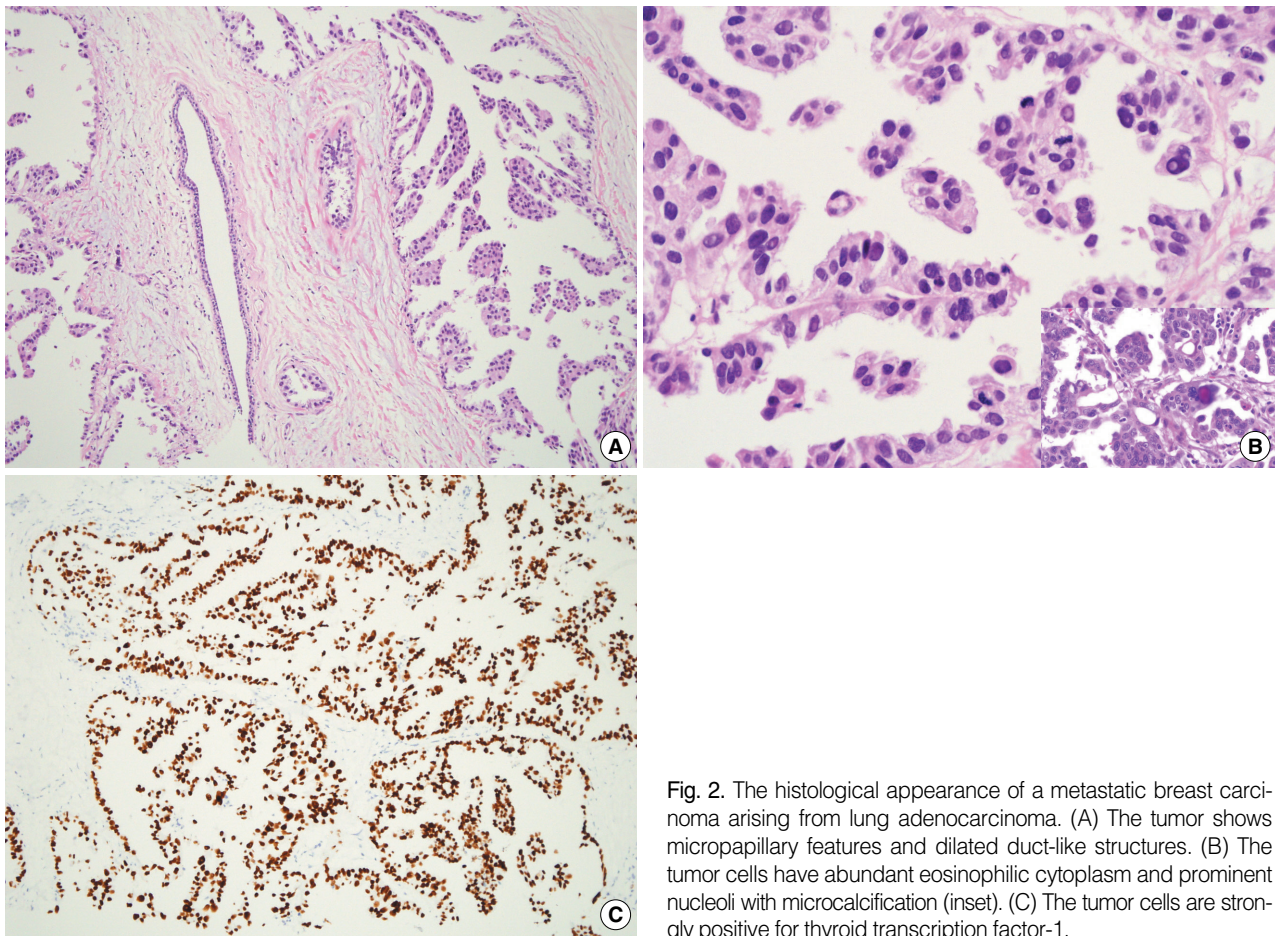


Fig. 2. The histological appearance of a metastatic breast carcinoma arising from lung adenocarcinoma. (A) The tumor shows micropapillary features and dilated duct-like structures. (B) The tumor cells have abundant eosinophilic cytoplasm and prominent nucleoli with microcalcification (inset). (C) The tumor cells are strongly positive for thyroid transcription factor-1.

Metastases from other sites

Eighteen patients had metastatic tumors to the breast from other extramammary malignancies, and all of the metastatic tumors showed histological and immunohistochemical features that were identical to those of the primary neoplasm.

The metastatic carcinoma to the breast from an ovarian serous papillary carcinoma was diagnosed by comparing the breast tumor with the primary ovarian tumor. The breast tumor had a typical papillary architecture, along with high-grade nuclear atypia with mitoses and several microcalcifications (Fig. 3A).

The metastatic tumor from anaplastic carcinoma of the thyroid showed single scattered atypical cells or clusters with pleomorphic, hyperchromatic, elongated nuclei and abundant cytoplasm. The tumor cells were negative for thyroglobulin, calcitonin, ER and PR. The metastatic papillary renal cell carcinoma of the breast had papillae with a delicate fibrovascular core, along with a high nuclear grade and eosinophilic or clear cytoplasm. Uninvolved breast parenchyma was identified and no microcalcification or necrosis was noted.

Five patients had metastases from sarcomas or malignant mel-

anomas, and all of which showed histological and immunohistochemical features that were identical to those of the primary neoplasm. The metastasis from a rhabdomyosarcoma of the maxillary sinus and soft tissue was a primitive malignant round-cell neoplasm. The alveolar-type tumor was well circumscribed from the adjacent breast parenchyma in the excised specimen (case 21) (Fig. 3B). The embryonal-type cells were found to have infiltrated diffusely without a specific pattern, with many rhabdomyoblasts scattered throughout the stroma (Fig. 3C). Immunohistochemical staining showed that the tumor cells were positive for desmin and myoglobin. In the metastatic tumor of the breast from the uterus leiomyosarcoma, plump and pleomorphic spindle cells with frequent mitoses and necrotic foci were arranged in bundles or fascicles. These tumor cells were positive for desmin and smooth muscle actin, but no microcalcification was observed.

The metastatic malignant melanoma was well demarcated from the remaining adjacent breast parenchyma. The tumor cells were spindle cells with cytoplasmic melanin pigment and prominent nucleoli. HMB-45 immunostaining showed strong

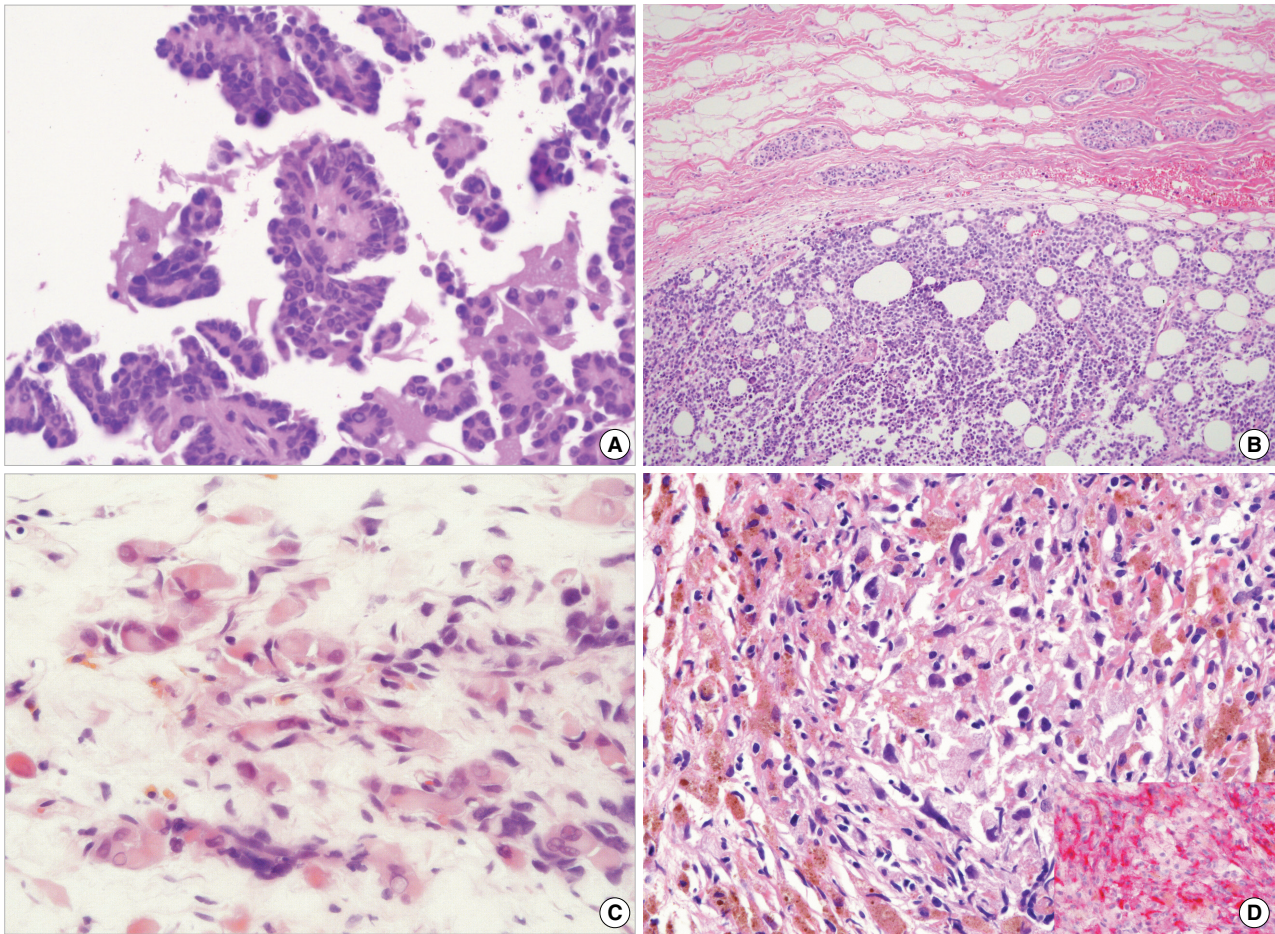


Fig. 3. (A) The metastatic breast carcinoma arising from an ovarian serous papillary carcinoma shows typical papillary proliferation with high-grade nuclear atypia and microcalcifications. (B) The metastatic breast cancer arising from a rhabdomyosarcoma is well demarcated from the adjacent breast parenchyma and (C) many rhabdomyoblasts are present in the stroma. (D) The metastatic breast cancer arising from a malignant melanoma is composed of atypical spindle cells with cytoplasmic melanin pigments and prominent nucleoli, and the tumor cells are strongly positive for HMB-45 (inset).

positivity in both the primary tumor and the breast metastases (Fig. 3D).

Six patients had metastatic tumors from hematologic malignancies with systemic manifestations. The metastatic tumor from AML showed that blastic cells had infiltrated diffusely without the recognizable breast parenchyma. The tumor cells were positive for myeloperoxidase. The metastatic NK-T cell lymphoma of the breast showed histological features that were similar to those of the primary tumor. The tumor cells, which were positive for CD56 and CD3, had infiltrated and involved the entrapped breast ducts.

DISCUSSION

Breast carcinoma is the most common tumor among women

in the United States and throughout the Western world,¹ and the incidence of breast carcinoma in Korean women is increasing.¹⁹ In contrast, metastases to the breast from extramammary malignancies are very rare, with a reported incidence in Western countries of only 0.43% to 6.6%.³⁻⁵ In our institute, the incidence over the past 20 years has been 0.21%, and so this incidence is much lower than that in Western countries. These metastases most frequently arise from carcinoma of the lung, including adenocarcinoma and small-cell carcinoma, malignant melanoma of the skin and hematologic malignancies.^{4,5,8} We found that the most common metastatic tumors to the breast were stomach cancer, including poorly differentiated adenocarcinoma and signet ring cell carcinoma, squamous cell carcinoma of the uterine cervix and adenocarcinoma of the lung. In addition, several other sites of origin were observed, including the soft tissue, ovary, kidney and the nasal cavity. The discrepancies be-

tween our findings and those from Western countries may reflect differences in the incidence of primary tumors. For example, stomach cancer and uterine cervix cancer are more common in Korea than in Western countries and so they may more frequently give rise to breast metastases in Korea, as compared to that in Western countries.

Although metastases to the breast have been observed in males, the incidence is much lower than that in women.^{4,5,8} We did not observe any metastatic lesions to the male breast.

Metastatic breast tumors have been reported to show unilateral breast involvement with palpable masses; moreover, these tumors have been rarely associated with diffuse skin involvement or skin change.^{4,8} Radiologically, metastatic tumors of the breast frequently show multiple well-defined or relatively ill-defined masses without speculation,^{9,10} and similar results have been observed on mammography.^{4,8} We found that most metastatic breast tumors consisted of ill-defined masses with slightly irregular margins, and these features were suggestive of primary breast cancer. Furthermore, three lesions showed diffuse increases of the parenchymal density and edematous changes with skin thickening, and this all suggested inflammatory breast carcinoma. Only one of our patients showed evidence of microcalcification.

Clinically and radiologically, metastatic lesions may mimic primary breast carcinomas, making it difficult to distinguish such lesions from primary breast carcinoma. This is especially true if the metastatic breast lesions show diffuse breast involvement with skin changes, which are features indicative of inflammatory carcinomas of a breast origin.

Several attempts have been made to describe the histological features distinguishing metastatic tumors to the breast from those to other sites.^{4,5,8} For example, rare elastosis and the absence of ductal carcinoma in situ have been suggested as being useful in diagnosing metastatic lesions.^{5,8} We found that most metastatic tumors to the breast showed morphological features similar or identical to those of their respective primary tumors. Desmoplastic reaction and elastosis of the stroma are rarely found. Neoplastic changes such as carcinoma in situ in the adjacent ducts or lobules of the breast parenchyma are also rare.

The metastatic tumor cells were found to have diffusely infiltrated the stroma and the entrapped residual lobules or ducts were surrounded by tumor cells without architectural distortion. Only one patient, with a metastasis from an NK-T cell lymphoma of the nasal cavity, showed destruction of the involved ducts of the breast parenchyma. In agreement with previous reports,^{5,8} microcalcification was infrequently observed in

our study. Only two patients, one with a metastatic tumor from a micropapillary adenocarcinoma of the lung and one with a serous papillary carcinoma of the ovary, had microcalcifications in the tumor component.

In this study, the immunohistochemical profiles of the metastatic tumors to the breast from extramammary malignancies showed identical features to those of the primary tumor. In addition, the metastatic tumors cells were usually negative for ER and PR, as well as GCDFP-15. An immunohistochemical comparison with an extramammary primary tumor was helpful in confirming the diagnosis of metastatic tumor from an extramammary site.

In summary, metastases to the breast from extramammary malignancies are extremely rare. Although these metastases arise from primary tumors of several organs, the most common primary sites in Korean patients were the stomach and uterus. Making the diagnosis can be difficult in the absence of relevant clinical information because these metastatic tumors may have features simulating a primary breast cancer. In addition, it may be difficult to histologically diagnose a metastatic tumor to the breast because the breast metastasis may be detected before the primary tumor.³ Early recognition of secondary involvement is important for the appropriate patient management and to avoid offering unnecessary and potentially harmful treatment to patients.⁵ Therefore, the clinical history of patients who present with breast tumors of an unusual histology is important and the histology of their breast tumors should be compared with that of the primary tumor types. Some histological features, including the absence of ductal carcinoma in situ, the presence of multiple lymphovascular emboli and rare desmoplastic reactions, can be helpful to distinguish the metastatic breast lesions that develop from extramammary malignancies from the primary breast tumors. Immunohistochemical staining may be needed for making an accurate diagnosis.

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