Gastric Metastasis of Mammary Signet Ring Cell Carcinoma
- A Differential Diagnosis with Primary Gastric Signet Ring Cell Carcinoma -

Metastasis of breast carcinoma to the stomach is relatively uncommon, although metastasis to other organs such as lung, bone, and lymph nodes is not rare. It may cause difficulty in differentiating from primary gastric carcinoma. We report a case of signet ring cell carcinoma of the breast with metastasis to the stomach with illustrations of histologic findings of both lesions. The results of immunohistochemical stainining with GCDFP-15 (gross cystic disease fluid protein-15), that can be used to differentiate primary gastric signet ring cell carcinoma and metastatic mammary signet ring cell carcinoma, are described. (JKMS 1997;12:256~61)

Key Words : Signet ring cell carcinoma, Breast, GCDFP-15 (gross cystic disease fluid protein), Gastric metastasis

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INTRODUCTION

Metastasis of breast carcinoma is not uncommon and often involves multiple organs. The common metastatic sites are lung, bone, lymph nodes and liver. The incidence of metastasis to the gastrointestinal tract is relatively rare. Of the breast carcinomas, lobular carcinoma has a higher tendency to metastasize to stomach, which often manifests as linitis plastica, radiologically, grossly and histologically. When the breast carcinoma metastasize to the stomach, it can cause great difficulty to differentiate from gastric primary, especially in the cases of breast carcinoma showing signet ring cell features. Correct identification of mammary origin is important, because prolonged survival can be expected with anti-estrogenic therapy.

We report a case of signet ring cell carcinoma involving both stomach and breast with confirmation of breast primary. We illustrate the cytological, histological and immunohistochemical features that might be useful to differentiate primary lesion from metastatic signet ring cell carcinoma.

CASE REPORT

A 48 year-old housewife was admitted to the hospital with a huge palpable mass of left breast. She initially noticed the mass 3 or 4 years prior to admission, which had recently been increasing in tumor size and intensity of pain. She did not seek treatment until one month previously when she had an endoscopic biopsy because

of mild epigastric discomfort; signet ring cell carcinoma of the stomach was diagnosed at that time. There was no family history of breast cancer. On admission, the patient was found to have a huge, firm to hard left breast mass lesion. The nipple was markedly retracted and overlying skin had erythematous change with scale. The right breast also showed a small firm mass at subareolar area with mild retraction of the nipple (Fig. 1). There were no palpable lymph nodes of the axilla and the neck. Mammogram of the right breast revealed increased

Fig. 1. Left breast showed a huge, firm to hard mass. Overlying skin had erythematous change with scale and ulceration. Right breast reveled retraction of the nipple.
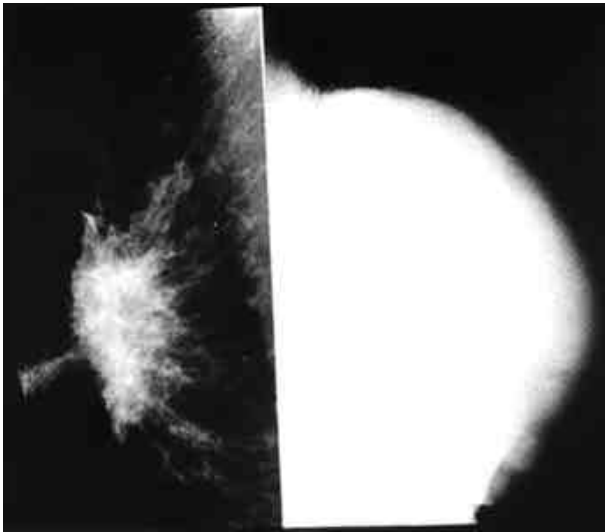
Fig. 2. Mammography of right breast also showed retroareolar mass with spiculation.

Fig. 4. There is erosive lesion of more deep excavation revealed on endoscopic findings.

Fig. 3. Radiological findings reveal multiple mottled osteolytic lesions on right clavicle, humerus and scapula.

opacitiy in the subareolar area with spiculation, suspicious for malignancy (Fig. 2). Chest X-ray revealed multiple mottled osteolytic lesions on the right clavicle, humerus, scapula, and ribs (Fig. 3). Multiple hot uptakes at skull, scapula, humerus, rib, sternum, ischium and tibia were found on whole body bone scans. Incisional biopsy of left breast mass with overlying skin was done. Gastrofiberscopy revealed multiple small erosive lesions on prepylorus and body of the stomach. The largest of them, which was located on the greater curvature of midbody,
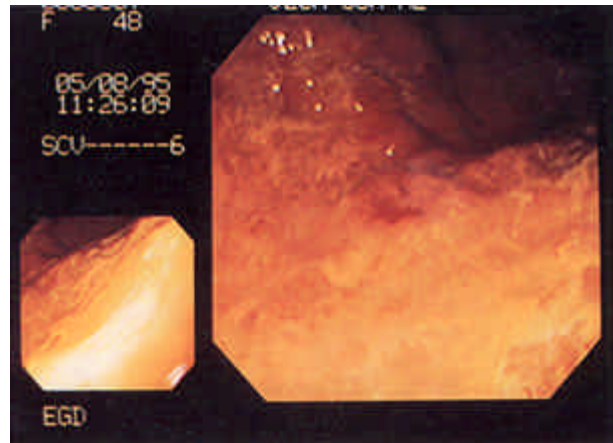
showed deep excavation (Fig. 4) from which an endoscopic biopsy was performed.

Histologically, the mass of the left breast was composed of diffuse sheets of uniform tumor cells, arranged in irregular solid nests surrounded by thin fibrovascular tissue (Fig. 5A). Focal coagulative necrosis of the tumor was found. At the overlying dermis, there were minor foci of tumor cells arranged in single linear fashion resembling an "Indian file" pattern (Fig. 5B). Individual tumor cells had round to ovoid nuclei with frequent wrinkling and indentation, and one or more conspicuous small nucleoli ; nuclei were vesicular to hyperchromatic. Mitotic figures were numerous. Tumor cells had relatively well defined cellular margin with a modest amount of eosinophilic cytoplasm. Intracytoplasmic lumina were frequently observed with eosinophilic inclusion-like secretory material within them. Signet ring cells showing distended bubbly cytoplasms and displacing nuclei, that occupied about 50% of tumor cells, were found to be admixed with non-signet ring round tumor cells (Fig. 5C). Many signet ring cells were positive for alcian blue-PAS stain. Nonneoplastic breast parenchyma and *in situ* ductal or lobular carcinoma were not included in the biopsied specimen. Biopsied gastric tissue revealed interstitial infiltration of signet ring cells between gastric glands (Fig. 6). Dysplastic change of gastric glandular epithelium was not seen. Alcian blue-PAS also stained signet ring cells in stomach.

Immunohistochemically, neoplastic cells of the breast and the stomach were negative for estrogen receptor (DAKO, Denmark) and progesterone receptor (Immunotech, France). BRST-2 (gross cystic disease fluid protein (GCDFP)-15, Signet Lab, USA) was positive in the breast tumor; but only a few tumor cells showed characteristic paranuclear dot-like pattern (Fig. 7A). Signet ring cells in
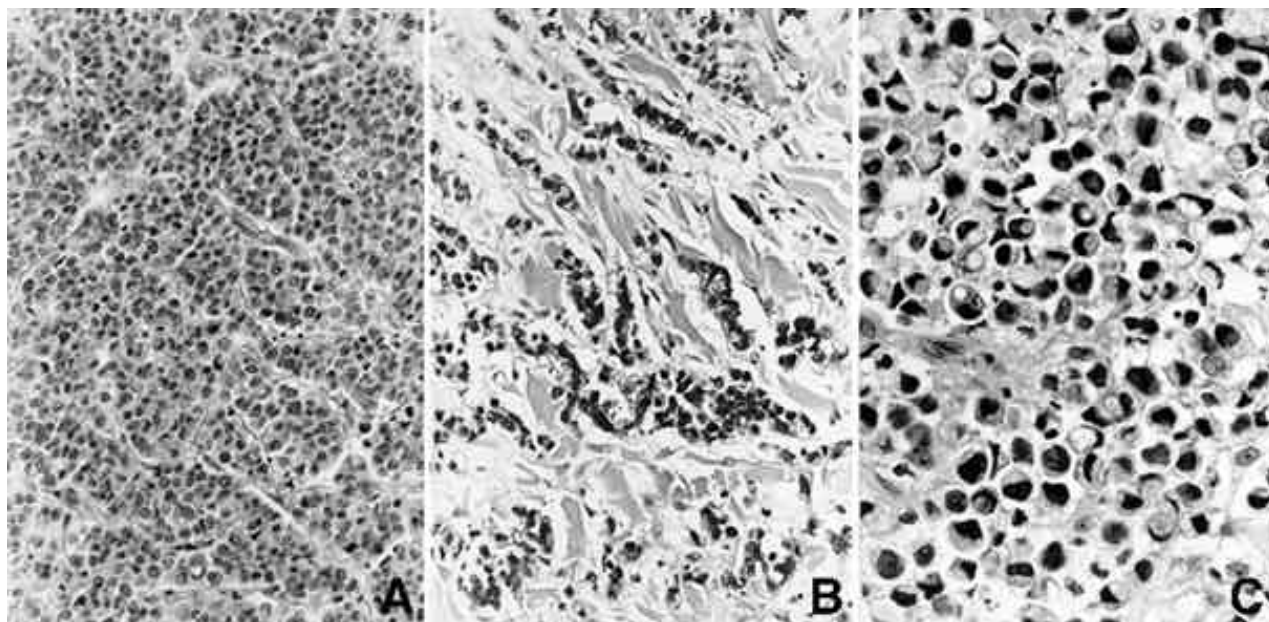
Fig. 5. A : Solid variant of invasive lobular carcinoma nested by thin fibrovascular tissue (×200). B : Typical arrangement of tumor, "indian file" in the dermis (×200). C : Signet ring cells with distended bubbly cytoplasms and distinct intracytoplasmic lumens (×400).

the stomach showed strong positivity for GCDFP-15 (Fig. 7B) ; primary gastric signet ring cell carcinoma from another case used as control was negative for GCDFP-15.

The patient received chemotherapy with the regimen of intravenous 5-FU 750 mg (day 1 and day 8), adriamycin 60 mg (day 1) and cytoxan 750 mg (day 1) every 3 weeks. The size of the tumor has been decreased gradually from 20 cm to 8 cm after 5 cycles of chemotherapy.

DISCUSSION

Metastatic breast carcinoma to the stomach is relatively uncommon (1) compared to that of metastasis to other viscera (2). The incidence mainly based on autopsy is reported to be from 2.1 to 15.2% (3, 4). A patient with breast carcinoma has increased susceptibility to second primary malignancy, especially cancer of the
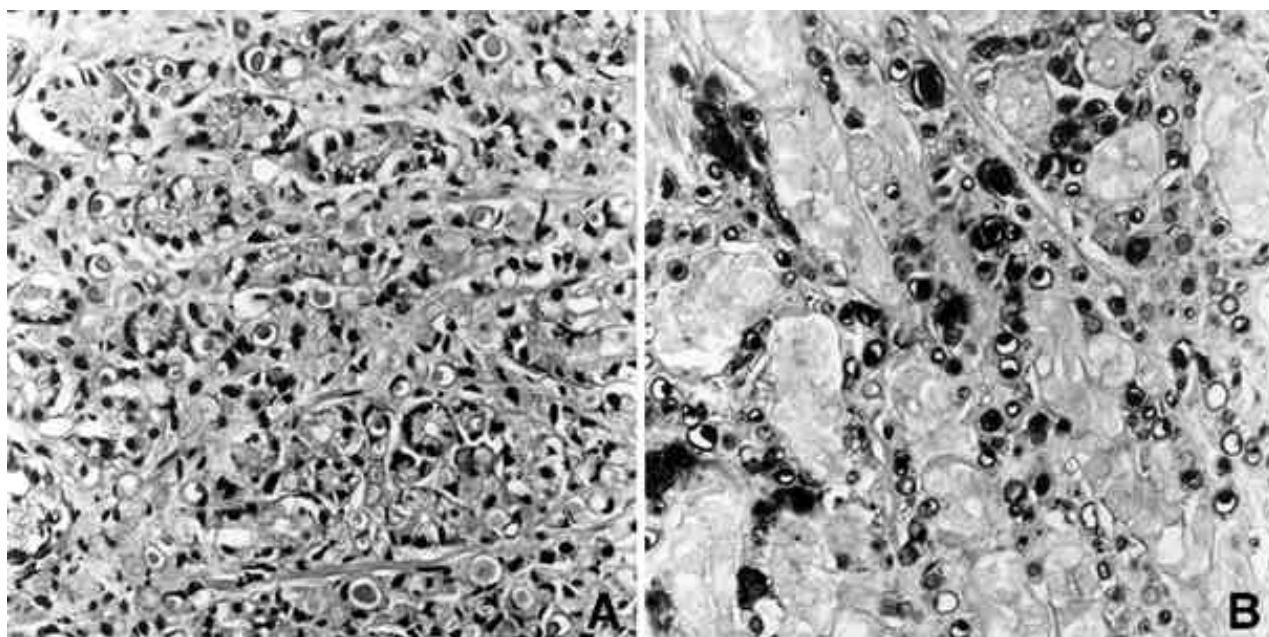

Fib. 6. A : Interstitial infiltration of signet ring cells between gastric glands. B : Alcian blue-PAS stain showed target like mucin globules in intracytoplasmic lumen (×200).
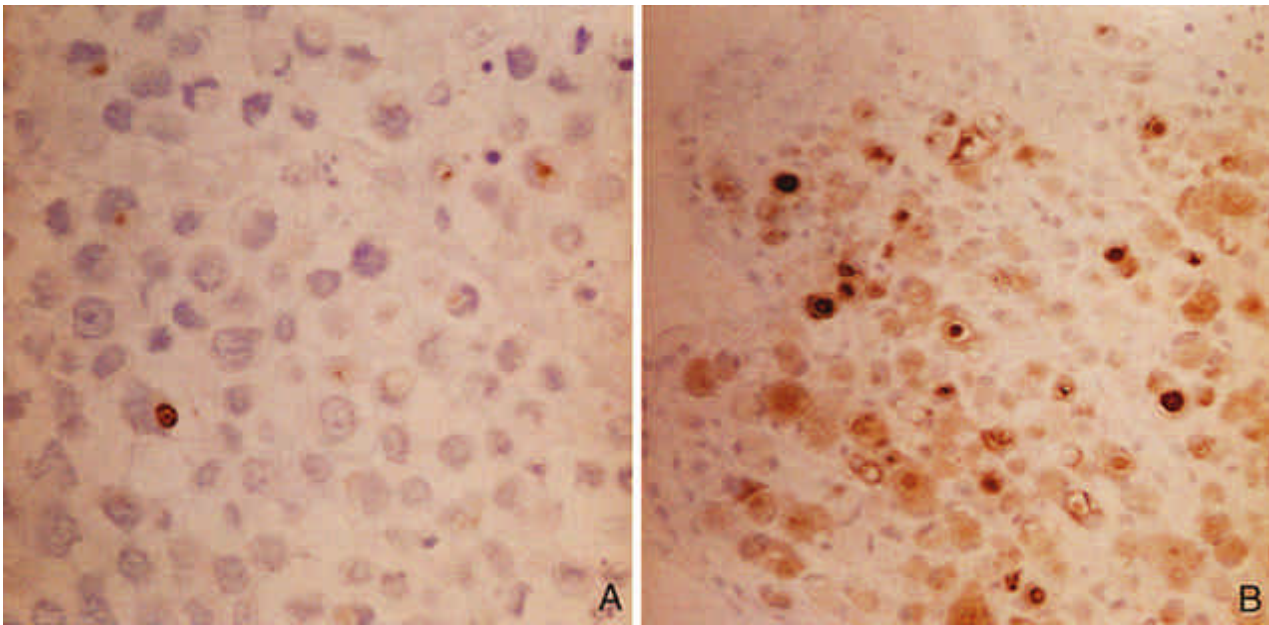
Fig. 7. Immunohistochemical stain of GCDFP-15. **A** : Breast (×400) **B** : Stomach (×200)

stomach and colon (5, 6). Gastric lesion of a patient who has history of breast carcinoma can be considered as either metastatic from breast carcinoma or primary gastric carcinoma. Differentiation of two possibilities is often difficult, but very important with regard to the responsiveness to endocrine ablation and prognosis.

Clinically, the patients with gastric metastasis of breast carcinoma may not have gastric symptom and most of the primary breast tumor is already in advanced stage with widespread dissemination. Of breast carcinomas, lobular carcinoma has higher tendency to metastasize to the gastrointestinal tract and only half of lobular carcinomas metastatic to stomach has initial manifestation by metastatic lesion (7). When there is a gastric symptom, it has a similar clinical manifestation as that of primary gastric carcinoma (8). The present case had breast mass for at least 3 or 4 years without any treatment and gastric symptom developed recently. In view of the long duration of breast carcinoma and presence of multiple bony metastases, it is reasonable to consider the gastric tumor as metastasis from breast primary.

Radiologically, gastric metastasis of breast carcinoma usually manifests as extrinsic mass without involving mucosa or as multiple masses. But, "linitis plastica" pattern involving whole layer of gastric wall can also occur (8). So, when it comes to the pattern of linitis plastica, it becomes particularly difficult to differentiate metastatic tumor from primary gastric carcinoma.

Grossly, gastric metastasis of breast carcinoma can assume single sessile ulcerated tumor, multiple nodules or ulcerated plateau-like tumor; metastatic breast cancer to the stomach microscopically do not have transitional dysplastic zone (6). The absence of dysplastic change in gastric biopsy as in the present case is not critical for the differentiation of primary gastric carcinoma and gastric metastasis of breast carcinoma, because primary gastric signet ring cell carcinoma usually does not show transitional dysplastic zone. Battifora (7) described two types of signet ring cells in his report on metastatic breast carcinoma to the stomach resembling linitis plastica, i.e. intracytoplasmic lumen type (ICL-SRCs) with one or more sharply demarcated thick walled vacuoles with occasional target like appearance, which are not mucicarminophilic and the gastrointestinal type (GI-SRCs) with abundant mucin-filled vesicles, which is mucinocarminophilic with foamy appearance. And he stated that the metastatic breast carcinoma to the stomach did not have GI-SRCs. However, the present case showed both types of signet ring cells. Therefore, the type of signet ring cells may not be able to differentiate gastric metastasis of breast carcinoma from primary gastric carcinoma.

Estrogen receptor (ER) is known to be found in hormone-dependent tumors, such as breast cancer, endometrial cancer, and prostatic cancer (9). However, since the present case did not reveal ER positivity in either breast or gastric tumor, ER status was not helpful to differentiate primary gastric from metastatic breast cancer. Furthermore Kojima et al. (9) recently reported

that 23% of primary gastric carcinoma was ER positive.

Gross cystic disease fluid protein-15 (GCDFP-15) is a protein of 15,000~44,000 Da and is mainly present in normal apocrine gland and metaplastic apocrine cells of the breast (10, 11). Overall 55% of breast cancers were positive for GCDFP-15 (12). Positivity was higher in cases with apocrine feature (75%) than those without apocrine features (23%), and was not correlated with nuclear grade, mitosis, ER status and risk of recurrence or survival (12). Overall positivity in invasive ductal carcinoma (57%) was higher than invasive lobular carcinoma (35%). Interestingly, invasive lobular carcinoma with signet ring cell differentiation had higher positivity (90%) of GCDFP-15 in spite of lack of the apocrine features. Experimental study revealed that estrogen inhibited production of GCDFP-15 and stimulated the division of cells (13). So it was hypothesized that the activation of selector gene for apocrine metaplasia may involve the oncogenesis of breast cancer. As expected, GCDFP-15 can be a useful marker to differentiate metastatic breast cancer from primary tumor in some organ. In Monteagudo's study (14), 71% of metastatic breast carcinoma to the ovary were positive for GCDFP-15 in comparison with none of the primary ovarian neoplasm and ovarian metastasis from other organs. So they claimed GCDFP-15 was a highly specific and sensitive marker for tumors of breast origin (14). Gastric tumor of the present case showed strong GCDFP-15 positivity in intracytoplasmic lumens and bubbly cytoplasms of signet ring cells, as well as characteristic paranuclear pattern.

Signet ring cell carcinoma of the breast was first reported by Saphir (15). He first thought that it was a variant of mucinous (colloid) breast carcinoma with multiple cell clusters in large mucin lakes and it soon was classified as a variant of colloid or mucinous carcinoma by others (16). But Foote and Stewart (17) described signet ring cells in lobular carcinoma of the breast. Recently signet ring cell carcinoma is defined by more than 20% of neoplastic cells containing intracytoplasmic vacuoles, which have mucin positive, PAS positive, and diastase resistant mucin (18). Lobular histogenesis of signet ring cell carcinoma also has been confirmed (19, 20). Signet ring cell carcinoma has more aggressive clinical behavior than colloid carcinoma, which is thought to have relatively better prognosis than usual breast carcinoma (21). Signet ring cell carcinoma of the breast is a unique variant of invasive lobular carcinoma and occurs as a pure lesion or in conjunction with invasive lobular carcinoma as in the present case or rarely with colloid or ductal carcinoma (22). Solid variant of invasive lobular carcinoma in the present case is known to have a poorer prognosis than classical invasive lobular

carcinoma (23). The presence of 10% or more signet ring cells in invasive lobular carcinoma represents a poor prognostic factor in stage I invasive lobular carcinoma (24). Signet ring cell carcinoma occurs more commonly in postmenopausal women and reveals high incidence of positivity for estrogen and progesterone receptors, and a good response to hormonal therapy is expected.

In conclusion, immunohistochemical expression of GCDFP-15 might be useful for confirmatory diagnosis of metastatic signet ring cell carcinoma of the breast to the stomach.

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