Use of GCDFP-15 (BRST-2) as a Specific Immunocytochemical Marker for Diagnosis of Gastric Metastasis of Breast Carcinoma

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Metastasis of breast cancer to the stomach is relatively uncommon and typically occurs in patients with disseminated diseases. This may cause difficulty in differentiating it from primary gastric carcinoma. The correct diagnosis of the primary source is important, since the treatment and prognosis of metastatic breast cancer is quite different from those of metastatic gastric cancer. Immunohistochemical staining with GCDFP-15 (gross cystic disease fluid protein-15) can be used to differentiate primary gastric carcinoma and gastric metastasis from breast cancer. We report two cases of gastric metastasis of breast cancer by describing their clinical course, illustrating the histologic findings, and showing the results of immunohistochemical staining with GCDFP-15. (Cancer Research and Treatment 2003;35:460-464)

Key Words: Breast neoplasm, Gastrointestinal metastases, Gross cystic disease fluid protein-15

INTRODUCTION

Breast carcinoma is one of the most common malignancies in women in Korea (1). Common metastatic sites of breast cancer are the bones, lung, liver, lymph node, and brain. Metastases to the gastrointestinal tract are infrequent and are usually underestimated by most clinicians due to its rarity (2). An accurate diagnosis of gastric metastasis from breast carcinoma is imperative due to different treatment modalities. However, the nonspecific symptoms, as well as the nonspecific radiologic or endoscopic findings of gastric metastasis, are the obstacles to correct diagnosis (3). GCDFP-15, a glycoprotein isolated from human gross cystic disease fluid present in breast carcinomas, is known as a highly specific and sensitive breast carcinoma marker that may effectively differentiate breast tissue origin from others (4,5). We report here two cases of gastric metastases from breast cancer using GCDFP-15 as an immunohistochemical marker.

CASE REPORT

Case 1

A 49-year old woman was admitted for an evaluation of a palpable right breast mass. She had complained of epigastric discomfort for the past 2 months. A physical examination revealed pale conjunctivae. A firm, 4×4 cm sized mass was palpated at the upper outer quadrant of the right breast. An ipsilateral axillary lymph node was also detected. Her hemoglobin was 6.6 g/dL, her white blood cell count was 6,880/mm³, and her platelet count was 162,000/mm³. The initial CEA was 163 ng/ml, and CA 15-3 was 820 U/ml. Mammography showed a spiculated mass measuring 5 cm in diameter. The endoscopy revealed a 0.2 cm sized polypoid lesion at the gastric fundus, on which a biopsy was performed (Fig. 1A). There were numerous hot uptakes on whole body bone scan (Fig. 2A). Histologic examination of breast and stomach tissues showed infiltrating lobular carcinoma (Fig. 3A, B). Bone marrow aspiration and biopsy showed metastatic lobular carcinoma. Immunohistochemically, the tumor cells of the breast and the stomach were both positive for GCDFP-15 (Fig. 3C, D), estrogen, and progesterone receptor, and negative for S-100 protein. Under the diagnosis of breast cancer with stomach, bone, and bone marrow metastases, she received six cycles of cyclophosphamide and doxorubicin, and six additional cycles of taxol and carboplatin. As the breast mass had grossly

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disappeared with residual skin dimpling, CA 15-3 and CEA markers were normalized. Furthermore, multiple hot uptakes on whole body bone scan were markedly reduced in size and number (Fig. 2B). Gastric metastatic lesions were not found on follow-up endoscopy (Fig.1B) and anemia had improved.

Case 2

A 67-year old woman was admitted for the evaluation of palpable masses on both breasts. She had complained of epigastric pain for the past 3 months. A firm, 8 x 6 cm sized mass was palpated in the right breast, and a 7 x 7 cm mass in the left breast. There were no palpable lymph nodes. Mammographic findings showed asymmetric opacities with spiculation in both breasts. The endoscopy showed a 0.8 cm sized mucosal depressed lesion at the greater curvature side of the gastric fundus (Fig. 4A). Multiple hot uptakes were found on whole body bone scan (Fig. 5A). The pathologic findings of breast and gastric tissues were consistent with signet ring cell carcinoma (Fig. 6A). Immunohistochemically, both tissues were positive for GCDFP-15 (Fig. 6B) and estrogen receptor, and negative for S-100 protein and progesterone receptor. The patient also received six cycles of cyclophosphamide and doxorubicin, and six additional cycles of taxol and carboplatin. The mass on the left breast decreased in size to 3 x 2 cm while the mass on the right reduced to a non-detectable mass. Furthermore, gastric metastatic lesions disappeared on follow-up endoscopy (Fig. 4B). Moreover, multiple hot uptakes on whole body bone scan were reduced in size and number (Fig. 5B) after chemotherapy.

Fig. 1. (A) Endoscopy revealed a 0.2 cm sized polypoid lesion at the gastric fundus. (B) On follow-up endoscopy, gastric polypoid lesion was not found after chemotherapy.

Fig. 2. Whole body bone scan (A) before chemotherapy (B) after chemotherapy.

**DISCUSSION**

Metastasis of breast cancer to the stomach is uncommon. In autopsy series, the overall incidence of gastric metastases from breast carcinoma was 2.1 to 15.2% (6,7). The differentiation of gastric metastasis of breast cancer from primary gastric cancer is clinically important since treatment options are different.
Clinical diagnosis of gastric metastases is difficult. Symptoms are often nonspecific, such as anorexia, epigastric pain, and vomiting (3,8). The nonspecific endoscopic features may be hard to distinguish from primary gastric carcinoma or gastric lymphoma. The endoscopic patterns of gastric metastasis from breast cancer were categorized as large ulceration, multiple small erosions, gastritis, linitis plastica, external compression, and polypoid masses. The most common endoscopic finding was linitis plastica (57%), with thickened folds and tumor infiltration in the deep layers, thus, frequently yielding negative
biopsy results (9). A retrospective study of 51 cases of gastric metastases showed that the most common histology was lobular carcinoma (70.6%), followed by ductal carcinoma (19%) and undifferentiated carcinoma (9.8%) (9).

The diagnosis of metastatic breast cancer by solely morphologic criteria can be a difficult challenge to pathologists. Estrogen receptor (ER)/progesterone receptor (PR) positivity is not useful for distinguishing primary gastric cancer from gastric metastasis of breast cancer because ER/PR can be positive in primary gastric cancer. It was reported that 23% of primary gastric carcinoma was ER positive (10). Therefore, the use of immunohistochemical markers, such as GCDFP-15, is often applied these days for a more accurate pathologic diagnosis of metastatic breast carcinoma.

GCDFP-15 is a glycoprotein isolated from human gross cystic disease fluid present in normal apocrine glands, in metaplastic apocrine epithelium of the breast, and in breast carcinomas (4,11). It is expressed in glands that have phylogenetic origins in common with apocrine glands and some with eccrine cutaneous glands. In normal adult tissues, GCDFP-15 expression was found in all apocrine, lacrimal, ceruminous, and Moll’s glands and in numerous serous cells of submandibular, sublingual, and minor salivary glands (12). There are no reports of GCDFP-15 positivity in gastric tissues. A retrospective analysis of 562 primary breast carcinomas revealed that the percentage of carcinomas that were stained positively was closely related to histologic subtypes: intraductal carcinoma (70%), infiltrating lobular carcinoma with signet-ring cell differentiation (90%), and medullary carcinomas (5%) (4). Furthermore, this study reported that only 23% of breast carcinomas without apocrine features stained positively for GCDFP-15. Thus, the use of this marker may be limited to breast carcinomas with apocrine features, and further investigations is needed to identify a specific marker that can differentiate metastatic tissues from non-apocrine breast carcinomas, such as medullary carcinoma. Monteagudo reported

Fig. 5. Whole body bone scan (A) before chemotherapy and (B) after chemotherapy.

Fig. 6. The H & E staining of (A) stomach tissue show signet ring cell carcinoma (×400). Immunohistochemical staining with BRST-2 in cytoplasm with paranuclear accentuation of (B) stomach tissue (×400).
that GCDFP-15 was a highly specific and sensitive immunohistochemical marker for breast metastases and demonstrated 71% positivity of ovarian metastases from breast cancer (5). The gastric metastases in our case showed strong GCDFP-15 immunoreactivity in the cytoplasm with a characteristic paranuclear pattern, which was consistent with the breast origin. Furthermore, the two patients received palliative chemotherapy in the setting of metastatic breast carcinoma and responded well as described.

REFERENCES