Original contribution

Hepatocyte nuclear factor 4A expression discriminates gastric involvement by metastatic breast carcinomas from primary gastric adenocarcinomas

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Summary Breast carcinomas sometimes metastasize to the stomach, and the histopathologic distinction of such metastases from primary gastric adenocarcinomas is often difficult. We characterized the clinicopathologic features of 21 breast carcinomas that had metastasized to the stomach and examined the use of a panel of antibodies, including hepatocyte nuclear factor 4A, for distinguishing the metastases from primary gastric diffuse-type adenocarcinomas. Histologically, all the metastatic breast carcinomas showed a poorly differentiated and/or signet ring cell morphology. Although most metastatic breast and primary gastric carcinomas contained signet ring cell components, the cases that were predominantly or exclusively composed of univacuolated-type signet ring cells were limited to metastatic breast carcinomas. Immunohistochemically, hepatocyte nuclear factor 4A was expressed in all 33 primary gastric carcinomas that were examined but was never expressed in metastatic breast carcinomas. Previously reported markers for breast and gastric carcinomas also showed a high specificity, but their sensitivities were quite variable. Estrogen receptor α, progesterone receptor, mammaglobin, and gross cystic disease fluid protein 15 were expressed in 76%, 33%, 52%, and 62%, respectively, of the metastatic breast carcinomas, whereas none of the primary gastric carcinomas expressed these antigens. CDX2, MUC5AC, MUC6, and CK20 were expressed in 36%, 85%, 27%, and 55%, respectively, of the primary gastric carcinomas. All the metastatic breast carcinomas were negative for these antibodies except for 1 case that expressed MUC5AC. Overall, the use of immunohistochemistry efficiently discriminated metastatic breast carcinomas from primary gastric carcinomas. In particular, the present study identified hepatocyte nuclear factor 4A as an excellent marker for differentiating the 2 lesions.

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1. Introduction

In surgical pathology practice, we sometimes encounter breast cancer metastases to the gastrointestinal tract, especially to the stomach. Interestingly, most previous
studies agree that invasive lobular carcinomas are more common than invasive ductal carcinomas among breast cancers that metastasize to the stomach [1-5]. The distinction of metastatic breast carcinomas from primary gastric carcinomas is clinically important because these lesions require different treatment strategies. Patients with metastatic breast carcinomas are usually treated with chemotherapy; on the other hand, if the lesion is a primary gastric carcinoma, further evaluation of the clinical stage is required before determining an appropriate therapeutic management. However, the histologic diagnosis of metastatic breast carcinomas is sometimes problematic because the typical histologic features of invasive lobular carcinomas, for example, linear, dissociated, and a single-file growth pattern, are similar to those of diffuse-type gastric carcinomas. In particular, invasive lobular carcinomas frequently show a signet ring morphology that can be easily confused with that of primary signet ring cell–type gastric carcinomas [2,5-8]. Furthermore, the stomach is the initial site of presentation of advanced breast cancers in some instances [1,5,9-11]. Immunohistochemistry using a panel of antibodies has been reported to be capable of differentiating metastatic breast carcinomas from primary gastric carcinomas [6,12,13]. Estrogen receptor (ER) α, progesterone receptor (PR), mammaglobin, and gross cystic disease fluid protein 15 (GCDFP-15) have been used as markers of breast carcinomas [6,8,12-20], whereas CDX2, MUC5AC, MUC6, and CK20 are highly specific to gastric carcinomas [6,13,15,21-27]. However, these antibodies have limitations in their sensitivities; thus, the use of multiple antibodies is often required.

Hepatoctye nuclear factor (HNF) 4A is a member of the nuclear receptor superfamily and is a critical developmental regulator of the visceral endoderm [28]. Recent studies have shown that HNF4A is expressed in an organ-specific manner in normal as well as neoplastic tissues [28-30]. Among nonneoplastic tissues, HNF4A is expressed in epithelial cells of the gastrointestinal tract, liver and pancreas, and the proximal tubules of the kidney but not in most other organs including mammary glands [28]. The expression of HNF4A in neoplastic lesions has not been extensively studied, but previous reports imply that tumors originating from HNF4A-positive organs generally retain HNF4A expression [28-30]. This suggests that HNF4A might be useful for determining the primary sites of metastatic tumors. Here, we tested the use of HNF4A, in addition to a previously tested panel of antibodies, for the diagnosis of metastatic breast carcinomas in the stomach.

2. Materials and methods

2.1. Study group

Endoscopic biopsy specimens of 21 metastatic breast carcinomas were included in the present study. All the cases were retrieved from the surgical pathology files of the National Cancer Center Hospital, Tokyo, Japan, between 1997 and 2010. Patients with metastatic breast carcinomas involving the stomach had been diagnosed in cases that (1) had a history of surgical treatment of primary breast cancer or concurrent gastric and breast tumors of identical histologic type and (2) were immunohistochemically consistent with metastatic breast carcinomas using 1 or more of the following antibodies: ERα, PR, GCDFP-15, mammaglobin, CK20, MUC5AC, MUC6, and CDX2. Paraffin-embedded specimens of the corresponding primary lesions were available in 12 cases of metastatic breast carcinomas, and these specimens were also subjected to immunohistochemical analysis for comparison with the metastatic lesions.

For histologic and immunohistochemical comparisons, endoscopic biopsy samples of primary gastric cancers were also examined. A consecutive series of 33 poorly differentiated and/or signet ring cell adenocarcinomas of the stomach were retrieved from our case files without taking age and sex into account. These patients were clinically confirmed not to have any breast tumors.

This study was approved by the Ethics Committee of the National Cancer Center, Tokyo, Japan.

2.2. Histologic evaluation

The histology of breast carcinomas involving the stomach was classified into poorly differentiated adenocarcinoma, signet ring cell carcinoma, or others. Both metastatic breast and primary gastric carcinomas were histologically examined for the presence of signet ring cell components. The cytologic features of signet ring cells, with either univacuolated or multivacuolated cytoplasms, were further classified as previously described [7]. Briefly, the univacuolated type is characterized by a single well-circumscribed intracytoplasmic lumen with/without a central eosinophilic inclusion. The multivacuolated type is characterized by foamy cytoplasm with an abundance of mucin-filled vesicles.

2.3. Immunohistochemistry

Deparaffinized 4-μm-thick sections from each paraffin block were exposed to 0.3% hydrogen peroxide for 15 minutes to block endogenous peroxidase activity and then washed in deionized water for 2 to 3 minutes. For heat-induced epitope retrieval, the sections were subjected to citrate buffer (pH 6.0) at 121°C for 10 minutes. The primary antibodies that were used are monoclonal and listed in Table 1. For staining, we used an automated stainer (Dako, Glostrup, Denmark) according to the vendor’s protocol. ChemMate EnVision (Dako) methods were used for detection. Appropriate positive and negative controls were used for each antibody.
The extent of positive staining was graded semiquantitatively as follows: − (negative), ± (1%-10% positive cells), + (11%-50% positive cells), and ++ (>51% positive cells). To determine the specificity and sensitivity of each antibody, cases with completely negative staining were regarded as negative, whereas cases with any positive staining were considered positive. Two observers (T. K. and S. S.) evaluated the immunohistochemical results. Discrepant cases were reviewed using a multiheaded microscope to achieve consensus.

2.4. Statistical analysis

The Fisher exact test was used to analyze each 2-by-2 table of discrete data. $P < .05$ was considered statistically significant.

3. Results

3.1. Clinicopathologic features

The clinicopathologic features of metastatic breast carcinomas are summarized in Table 2. All the patients with metastatic breast carcinomas to the stomach were women, with a mean age of 59.6 years (range, 43-77 years). The mean interval between the diagnosis of primary breast carcinomas and the detection of gastric metastases was 65.8 months (range, 0-270 months). In 4 cases (cases 1, 8, 9, and 19), gastric metastasis was pointed out concurrently with or before the detection of the primary lesions.

The endoscopic appearance of gastric lesions was linitis plastica-like in 8 cases (38%), multiple erosions in 6 cases

<table>
<thead>
<tr>
<th>Case no.</th>
<th>Age/sex</th>
<th>Primary histology</th>
<th>Interval $^d$ (mo)</th>
<th>Endoscopic finding</th>
<th>Histology</th>
<th>Signet ring cells</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>43/F</td>
<td>ILC $^a$</td>
<td>0 $^e$</td>
<td>SMT with ulceration</td>
<td>POR &gt; SIG</td>
<td>UNI</td>
</tr>
<tr>
<td>2</td>
<td>45/F</td>
<td>NA</td>
<td>76</td>
<td>SMT</td>
<td>SIG &gt; POR</td>
<td>UNI &gt; MULTI</td>
</tr>
<tr>
<td>3</td>
<td>46/F</td>
<td>IDC</td>
<td>45</td>
<td>Linitis plastica</td>
<td>POR</td>
<td>–</td>
</tr>
<tr>
<td>4</td>
<td>49/F</td>
<td>ILC</td>
<td>18</td>
<td>SMT with erosion</td>
<td>SIG = POR</td>
<td>UNI &gt; MULTI</td>
</tr>
<tr>
<td>5</td>
<td>51/F</td>
<td>ILC</td>
<td>87</td>
<td>SMT</td>
<td>POR</td>
<td>–</td>
</tr>
<tr>
<td>6</td>
<td>52/F</td>
<td>ILC</td>
<td>62</td>
<td>Linitis plastica</td>
<td>SIG = POR</td>
<td>MULTI</td>
</tr>
<tr>
<td>7</td>
<td>53/F</td>
<td>ILC</td>
<td>54</td>
<td>Multiple erosions</td>
<td>POR &gt; SIG</td>
<td>UNI &gt; MULTI</td>
</tr>
<tr>
<td>8</td>
<td>54/F</td>
<td>ILC</td>
<td>0 $^a$</td>
<td>Multiple SMTs</td>
<td>SIG &gt; POR</td>
<td>MULTI &gt; UNI</td>
</tr>
<tr>
<td>9</td>
<td>54/F</td>
<td>ILC</td>
<td>0</td>
<td>Multiple erosions</td>
<td>SIG &gt; POR</td>
<td>MULTI &gt; UNI</td>
</tr>
<tr>
<td>10</td>
<td>55/F</td>
<td>NA</td>
<td>17</td>
<td>Multiple erosions</td>
<td>POR</td>
<td>–</td>
</tr>
<tr>
<td>11</td>
<td>55/F</td>
<td>ILC</td>
<td>7</td>
<td>Multiple SMTs</td>
<td>POR &gt; SIG</td>
<td>MULTI &gt; UNI</td>
</tr>
<tr>
<td>12</td>
<td>55/F</td>
<td>ILC</td>
<td>145</td>
<td>Linitis plastica</td>
<td>SIG &gt; POR</td>
<td>UNI &gt; MULTI</td>
</tr>
<tr>
<td>13</td>
<td>59/F</td>
<td>ILC</td>
<td>1</td>
<td>Linitis plastica</td>
<td>SIG = POR</td>
<td>UNI</td>
</tr>
<tr>
<td>14</td>
<td>62/F</td>
<td>ILC</td>
<td>107</td>
<td>Linitis plastica</td>
<td>SIG &gt; POR</td>
<td>MULTI &gt; UNI</td>
</tr>
<tr>
<td>15</td>
<td>70/F</td>
<td>IDC</td>
<td>270</td>
<td>SMT with erosion</td>
<td>POR</td>
<td>–</td>
</tr>
<tr>
<td>16</td>
<td>71/F</td>
<td>Mixed $^b$</td>
<td>183</td>
<td>Multiple erosions</td>
<td>POR &gt; SIG</td>
<td>MULTI &gt; UNI</td>
</tr>
<tr>
<td>17</td>
<td>73/F</td>
<td>IDC</td>
<td>30</td>
<td>Linitis plastica</td>
<td>SIG &gt; POR</td>
<td>MULTI</td>
</tr>
<tr>
<td>18</td>
<td>73/F</td>
<td>ILC</td>
<td>121</td>
<td>Multiple erosions</td>
<td>POR &gt; SIG</td>
<td>MULTI</td>
</tr>
<tr>
<td>19</td>
<td>76/F</td>
<td>IDC</td>
<td>0</td>
<td>Multiple erosions</td>
<td>POR &gt; SIG</td>
<td>MULTI</td>
</tr>
<tr>
<td>20</td>
<td>77/F</td>
<td>ILC + IDC $^c$</td>
<td>109</td>
<td>Linitis plastica</td>
<td>SIG</td>
<td>UNI</td>
</tr>
<tr>
<td>21</td>
<td>77/F</td>
<td>ILC</td>
<td>39</td>
<td>Linitis plastica</td>
<td>SIG</td>
<td>MULTI</td>
</tr>
</tbody>
</table>

Abbreviations: F indicates female; ILC, invasive lobular carcinoma; IDC, invasive ductal carcinoma; SMT, submucosal tumor; POR, poorly differentiated; SIG, signet ring cell; UNI, univacuolated; MULTI, multivacuolated; NA, not available.

$^a$ Diagnosis was made by axillary lymph node biopsy.

$^b$ Mixed invasive ductal lobular carcinoma.

$^c$ Bilateral tumors, invasive lobular in the right breast, and invasive ductal in the left breast.

$^d$ Interval between diagnosis of primary breast carcinomas and the detection of gastric metastases.

$^e$ Gastric lesions were detected before the primary lesions.
(28%), a submucosal tumor with a central ulceration/erosion in 3 cases (14%), solitary submucosal tumor in 2 cases (10%), and multiple submucosal tumors in 2 cases (10%).

The histologic subtypes of the primary lesions of the metastatic breast carcinoma cases were invasive lobular in 13 cases (62%), invasive ductal in 4 cases (19%), and mixed invasive ductal lobular in 1 case (5%). One case had bilateral tumors, with an invasive lobular carcinoma in the right breast and an invasive ductal carcinoma in the left breast (case 20).

Detailed information on the histology of the primary lesions was not available in 2 cases (cases 2 and 10).

Histologically, all the gastric involvements by metastatic breast carcinomas showed a poorly differentiated morphology. None of the cases showed gland formation. Signet ring cell components were identified in 17 cases (81%). In 11 cases, signet ring cell components were predominant or equal to the poorly differentiated components; and in the other 6 cases, the signet ring cell components were only minor. In 4 cases (19%), the entire biopsy specimen was composed of poorly differentiated components.

Among the 17 cases with signet ring cells, all the signet ring cells were a univacuolated type in 3 cases (Fig. 1A), whereas all the signet ring cells were a multivacuolated type in 5 cases. The other cases had both univacuolated and multivacuolated signet ring cell components.

With regard to the primary gastric carcinoma cases used as a control, the male-female ratio of the patients was 19:14; and their mean patient age was 65.5 years (range, 42-85 years). Histologically, signet ring cells were present in 31 of the 33 cases. In all the patients, signet ring cells were predominantly or exclusively the multivacuolated type (Fig. 1B), whereas minor components of univacuolated signet ring cells were observed in 13 (39%) of the 31 cases with signet ring cells.

### 3.2. Immunohistochemistry

The results of the immunohistochemical analysis are summarized in Tables 3 and 4. In 21 gastric lesions of metastatic breast cancers as well as 12 primary sites of the breast cancers, HNF4A was consistently negative (Fig. 2A). In contrast, in the 33 primary gastric cancers, HNF4A was diffusely positive in 31 cases and focally positive in 2 cases (Fig. 3A). HNF4A was consistently expressed in nonneoplastic gastric epithelium but was negative in stromal cells in all the cases that were examined. For the discrimination of these 2 entities, the sensitivity and specificity of HNF4A were both 100%.

In gastric lesions of metastatic breast carcinomas, ERα, PR, mammaglobin, and GCDFP-15 were expressed in 16 (76%), 7 (33%), 11 (52%), and 13 (62%) cases, respectively (Fig. 2B-E). One case (case 15) was negative for all these antibodies. None of the primary gastric carcinomas expressed any of these 4 antibodies.

Primary lesions of metastatic breast carcinomas were also stained for the same panel of antibodies in 12 cases. ERα, PR, mammaglobin, and GCDFP-15 were positive in 10 (83%), 9 (75%), 6 (50%), and 4 (33%) cases, respectively. The immunophenotypes were entirely concordant between the primary and metastatic lesions in only 1 of the 12 cases, but the other cases showed some differences. In 3 cases, ERα was positive in the primary lesions but negative at metastatic sites. Similarly, the loss of PR expression at the metastatic sites was observed in 6 cases. Mammaglobin expression was lost in the metastatic lesions in 3 cases. On the other hand, mammaglobin expression was observed only in the metastatic lesions in 3 cases. In 4 cases, GCDFP-15 was negative in the primary lesions but positive in metastatic lesions of the stomach.
In primary gastric carcinomas, CDX2, MUC5AC, MUC6, and CK20 were expressed in 12 (36%), 28 (85%), 9 (27%), and 18 (55%) cases, respectively (Fig. 3B-E). These 4 markers were negative in all the metastatic and primary breast carcinomas except for 1 metastatic breast carcinoma (case 2) that stained positive for MUC5AC and 1 primary breast carcinoma (case 6) that stained positive for MUC6.

With regard to the reactivity of these antibodies in nonneoplastic gastric mucosa, CDX2 was expressed in metaplastic epithelium, MUC5AC was expressed in foveolar epithelium, MUC6 was expressed in pyloric glands and mucous neck cells of the fundic glands, and CK20 was expressed in metaplastic and foveolar epithelium. The expressions of ER$\alpha$, PR, mammaglobin, and GCDFP-15 were completely absent in nonneoplastic gastric mucosa.

The sensitivity and specificity of each antibody for metastatic breast and primary gastric carcinomas are summarized in Table 4. ER$\alpha$, PR, mammaglobin, and GCDFP-15 were 100% specific to metastatic breast carcinoma; but the sensitivities were variable, ranging from 33% to 76%. CDX2, MUC5AC, MUC6, and CK20 were highly specific to primary gastric carcinomas. Their sensitivities varied from 27% for MUC6 to 85% for MUC5AC.

4. Discussion

Gastric metastases of breast carcinomas can be clinically confused with primary gastric carcinomas, particularly linitis plastica, because of the similarity of their endoscopic and histologic findings. In agreement with previous studies, a linitis plastica–like gross appearance was the most common endoscopic finding for metastatic breast carcinoma [1,2,6]. However, metastatic breast carcinomas can also present with various gross appearances, including submucosal tumor–like, erosive, and ulcerated lesions [1,5,10]. In the present study, we confirmed these results and showed that metastatic tumors frequently occur as multiple lesions.

The histologic subtypes of the primary breast lesions were predominantly invasive lobular carcinomas, as previously reported [1-5]. All metastatic breast carcinomas showed a poorly differentiated morphology; and none of the cases exhibited gland formation. Signet ring cells were identified in most of the metastatic breast carcinomas, including some of the metastatic invasive ductal carcinomas.

Previous studies have suggested that metastatic breast and primary gastric carcinomas can potentially be differentiated based on morphology using hematoxylin and eosin–stained sections [7,26,31]. These previous studies suggested that the signet ring cells of lobular carcinoma are of a univacuolated type, which is characterized by a single, well-circumscribed intracytoplasmic lumina. On the other hand, signet ring cells of gastric carcinomas usually have multivacuolated cytoplasm with foamy and abundant mucin-filled vesicles.

In the present study, the cases in which all or most of the signet ring cells were univacuolated were limited to metastatic breast carcinomas. However, significant proportions of metastatic breast and primary gastric carcinomas contained both univacuolated and multivacuolated signet ring cells. Thus, a definitive diagnosis of metastatic breast carcinomas based solely on their histologic features may be difficult, whereas lesions predominantly composed of univacuolated signet ring cells are suggestive of metastatic breast carcinomas, rather than primary gastric carcinomas.

Immunohistochemically, all the primary gastric carcinomas but none of the metastatic breast carcinomas were positive for HNF4A. Thus, the use of this antibody alone allowed metastatic breast carcinomas to be discriminated from primary gastric carcinomas. The expression of HNF4A has not been extensively studied in tumors. Remarkably, however, all the primary gastric carcinomas that have been previously examined (total of 49 cases) were uniformly positive for HNF4A [28,29]. Moreover, the staining for HNF4A was mostly diffuse and strong, which is a major advantage for its use in the diagnosis of biopsy specimens, where only a limited amount of tissue is available.

### Table 3 Results of immunohistochemical staining

<table>
<thead>
<tr>
<th>Antibody</th>
<th>Breast carcinoma</th>
<th>Primary lesion</th>
<th>Primary gastric carcinoma</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Metastasis to the stomach</td>
<td>Primary lesion</td>
<td>Primary gastric carcinoma</td>
</tr>
<tr>
<td>HNF4A</td>
<td>− 0 0 0 0</td>
<td>12 0 0 0 0</td>
<td>0 0 0 2 31</td>
</tr>
<tr>
<td>ER$\alpha$</td>
<td>5 1 7 8 8</td>
<td>2 2 0 8 8</td>
<td>33 0 0 0 0</td>
</tr>
<tr>
<td>PR</td>
<td>14 1 3 3 3</td>
<td>3 4 3 2 2</td>
<td>33 0 0 0 0</td>
</tr>
<tr>
<td>Mammaglobin</td>
<td>10 3 3 5 6</td>
<td>6 3 3 0 0</td>
<td>33 0 0 0 0</td>
</tr>
<tr>
<td>GCDFP-15</td>
<td>8 1 4 8 8</td>
<td>8 2 2 2 0</td>
<td>33 0 0 0 0</td>
</tr>
<tr>
<td>CDX2</td>
<td>21 0 0 0 0</td>
<td>12 0 0 0 0</td>
<td>21 5 4 3 3</td>
</tr>
<tr>
<td>MUC5AC</td>
<td>20 0 1 0 0</td>
<td>12 0 0 0 0</td>
<td>5 1 9 18 18</td>
</tr>
<tr>
<td>MUC6</td>
<td>21 0 0 0 0</td>
<td>11 1 0 0 0</td>
<td>24 3 5 1 1</td>
</tr>
<tr>
<td>CK20</td>
<td>21 0 0 0 0</td>
<td>12 0 0 0 0</td>
<td>15 4 7 7 7</td>
</tr>
</tbody>
</table>

NOTE. −, negative; ±, 1% to 10% positive cells; +, 11% to 50% positive cells; and ++, more than 51% positive cells.
Our study also confirmed that previously reported markers could differentiate metastatic breast carcinomas and primary gastric carcinomas with a high specificity. ERα, PR, mammaglobin, and GCDFP-15 were specific markers of breast carcinomas. Although several older studies have reported that up to 28% of gastric carcinomas expressed ER [32,33], these findings were based upon studies using a particular antibody against ER, clone H222, which is no longer used in standard practice. Similarly, 1 study reported that mammaglobin was expressed in 13% of gastric carcinomas that had metastasized to the lymph nodes; however, they used a polyclonal mammaglobin antibody, which is not widely used [18]. Overall, these previous reports and the present study indicate that these 4 markers can specifically detect metastatic breast carcinomas when appropriate antibodies are used. On the other hand, their sensitivities for the identification of metastatic breast carcinomas were variable. ERα was the most sensitive marker for breast carcinomas, followed by GCDFP-15, mammaglobin, and PR.

CK20, MUC5AC, MUC6, and CDX2 were confirmed to be useful for identifying primary gastric carcinomas. In our study, 1 case of metastatic breast carcinoma expressed MUC5AC. Indeed, O’Connell et al [6] also reported a similar

<table>
<thead>
<tr>
<th>Antibody</th>
<th>Metastatic breast carcinoma</th>
<th>Primary gastric carcinoma</th>
<th>P</th>
<th>Sensitivity</th>
<th>Specificity</th>
</tr>
</thead>
<tbody>
<tr>
<td>HNF4A</td>
<td>0/21 (0%)</td>
<td>33/33 (100%)</td>
<td>1.9 × 10^-15</td>
<td>100%</td>
<td>100%</td>
</tr>
<tr>
<td>CDX2</td>
<td>0/21 (0%)</td>
<td>12/33 (36%)</td>
<td>1.6 × 10^-3</td>
<td>36%</td>
<td>100%</td>
</tr>
<tr>
<td>MUC5AC</td>
<td>1/21 (5%)</td>
<td>28/33 (85%)</td>
<td>3.0 × 10^-9</td>
<td>85%</td>
<td>95%</td>
</tr>
<tr>
<td>MUC6</td>
<td>0/21 (0%)</td>
<td>9/33 (27%)</td>
<td>2.0 × 10^-2</td>
<td>27%</td>
<td>100%</td>
</tr>
<tr>
<td>CK20</td>
<td>0/21 (0%)</td>
<td>18/33 (55%)</td>
<td>6.0 × 10^-5</td>
<td>55%</td>
<td>100%</td>
</tr>
</tbody>
</table>

NOTE. P values indicate the significance of the difference between gastric involvement by metastatic breast cancer and primary gastric carcinoma.

Fig. 2 Immunohistochemical staining of metastatic breast carcinoma to the stomach. HNF4A is expressed in nonneoplastic gastric epithelium but is negative in metastatic breast carcinoma cells infiltrating the lamina propria (A). A metastatic breast carcinoma to the stomach shows the nuclear expression of ERα (B) and PR (C) and the cytoplasmic expression of mammaglobin (D) and GCDFP-15 (E) (original magnification ×200).
result: 1 of the 19 breast carcinomas that had metastasized to the gastrointestinal tract expressed MUC5AC in their study. In addition, studies on primary breast carcinomas have shown that minor subsets of breast carcinomas express CK20, MUC5AC, or MUC6 [15,26,27,34,35]. Thus, although our study showed that these gastric carcinoma markers are quite specific, the expression of CK20, MUC5AC, or MUC6 may not completely exclude the possibility of a metastatic breast carcinoma. The expression of CDX2 has never been reported in breast carcinomas, but its sensitivity for the identification of gastric carcinomas was relatively low in the present study.

In summary, breast carcinomas that metastasize to the stomach consistently show a poorly differentiated or signet ring cell morphology, regardless of the histology of the primary lesion. A predominance of univacuolated signet ring cells favors a diagnosis of metastatic breast carcinoma, but it may be difficult to conclusively differentiate these lesions from primary gastric carcinomas based solely on morphology. The use of immunohistochemistry is effective for the diagnosis of gastric metastases of breast carcinomas. ERα, PR, mammaglobin, and GCDFP-15 are specific markers for breast carcinomas, whereas HNF4A, CK20, MUC5AC, MUC6, and CDX2 are useful for identifying primary gastric carcinomas. Remarkably, HNF4A was able to distinguish all primary gastric carcinomas from metastatic breast carcinomas. We suggest that HNF4A may be a highly useful marker for excluding metastatic breast carcinomas in the diagnosis of gastric biopsy specimens.

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**References**


