CASE REPORT

Breast cancer metastases to the stomach and colon mimicking primary gastrointestinal cancer: Four cases and literature review

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Abstract: Intraluminal gastric and colonic metastases of the breast cancer are very rare and may sometimes prove a diagnostic dilemma to distinguish from primary gastric and colonic cancers. It is important to make the distinction in order to navigate the proper treatment approach, which is a systemic treatment rather than surgery if the disease is metastatic. The spread to the gastrointestinal (GI) tract is more frequent in lobular histology and according to a number of investigators, it is related to a particular tropism of lobular cells toward gastrointestinal mucosa. Any region of GI tract may be involved, from the tongue to the anus. Over the last decade, among the 1,100 breast cancer cases registered at our institutions, we diagnosed four patients with breast cancer who had metastases to the stomach and/or colon and presented symptoms that simulated primary gastrointestinal cancer. A total of 84 out of the 1,100 patients experienced invasive lobular histology. Among the four patients with GI tract metastases, three were diagnosed with lobular histology – two of whom had the signet ring cell subtype. The remaining patient was diagnosed with triple negative invasive ductal carcinoma; however, it clinically resembled invasive lobular carcinoma. Clinical and pathological features of these cases, as well as the review of related literature are discussed in this report.

Keywords: gastric and colon metastasis of breast cancer; triple negative; invasive lobular carcinoma


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Introduction

The most common sites of breast cancer metastasis are bones, lungs, soft tissues, and the liver, depending on the biology of the tumor. Hormone receptor-positive tumors tend to spread to the skeleton whereas hormone receptor-negative tumors, including triple negatives, preferentially invade visceral organs such as liver and lungs. Gastrointestinal tract metastases of breast origin are very rare in clinical practice and most series reported a greater propensity for lobular carcinoma, although other histological features such as invasive ductal carcinoma and signet ring cells have also been reported. In a retrospective study at a single institution in Italy, a total of 5 out of 980 patients (0.5%) with breast cancer showed gastrointestinal metastases. By reviewing medical literature published in English, 206 patients affected by gastrointestinal metastases from breast cancer were identified. The most frequent site of metastasis was the stomach (60%) [1]. Mayo Clinic previously reported 32 cases out of 1,169 breast cancers metastasizing to the gastrointestinal tract and peritoneum [2]. Breast cancer
histological features included 47% lobular, 31% ductal, 13% mixed, and 9% unknown. Metastatic spread to the GI tract may occur many years after the initial diagnosis and affects both the colon and stomach (as in Case 1); or it can be the first manifestation of breast cancer metastases, mimicking primary gastric cancer (as in Case 4). Herein, we report four breast cancer cases manifesting gastric and colonic metastasis, which mimicked second primary gastrointestinal cancer.

Materials and methods

The Institutional Review Board of Ethical Committee granted approval for this study, and clinical records of primary breast cancer metastasizing to the gastrointestinal (GI) tract were reviewed retrospectively. From December 2005 to January 2016, a total of 84 out of 1,100 patients with invasive lobular cancer (ILC) were diagnosed with metastatic breast cancer and registered at Anadolu Health Science Center and Istanbul Bilim University’s Florence Nightingale Hospital. Among them, four cases of breast cancer metastasizing to the stomach and colon were identified. Their medical records were reviewed for demographic information, which included dates of primary diagnosis and relapses, presenting symptoms at recurrence, sites of metastases, pathology of the GI involvement, as well as the primary tumor, its treatment, and outcome. A review of the literature was performed using a computerized literature search via PubMed, Medline, Cancerlit, Embase, and National Citation Index databases.

Case presentations

Patient 1 (Protocol No.: 18632, Anadolu Health Science Center)

A 41-year-old Caucasian female of Turkish nationality underwent left breast mastectomy in May 2004 for invasive lobular carcinoma, Stage IIIA, pT2N2M0, axilla 16/20 positive, both estrogen receptor (ER) and progesterone receptor (PR) 90% positive, human epidermal growth factor receptor 2 (HER-2) negative, a Ki-67 score of 30%, Grade III. She received adjuvant 5-fluorouracil (5FU), epirubicin, and cyclophosphamide (FEC) chemotherapy for six courses, followed by adjuvant radiotherapy (XRT), and was put on tamoxifen of 10 mg b.i.d (twice a day) for five years. In June 2007, positron emission tomography-computed tomography (PET-CT) scan revealed bone metastasis in the left ninth rib and L3 vertebra corpus, which was confirmed through biopsy. Zometa (4 mg) for every four weeks was added to the treatment protocol. The patient did not receive radiotherapy for bone metastases as she was asymptomatic and there was no imminent collapse. She had been diagnosed as clinically well and symptomless until June 2013 when, for the first time, the Ca-15-3 and Ca-125 tumor markers were found to be high and she started to complain about bloating. PET-CT scan did not reveal any pathological metabolic activity anywhere in the body.

The blood work-up revealed mild iron deficiency anemia, which led us to perform total colonoscopy and esophagogastroduodenoscopy on the patient. There was a diffuse intramural infiltration of the stomach by the tumor, appearing as ‘limitis plastica’. Multiple biopsies from the stomach, the ascending colon, near the hepatic flexure, in the transverse colon, and from the rectum (5–10 cm from anal margin) also revealed GATA3 and GCDFP15 immunoreactive breast cancer in the lobular signet ring cell phenotype (Figure 1). Further immunohistochemistry (IHC) stains confirmed the primary breast cancer. Multiple genetic analyses by Foundation One (USA) showed CDH1 and K-ras mutations, and MEK amplification. Treatment attempts using carboplatin + docetaxel, followed by eribulin and genomic-guided treatment with trametinib (MEK-1 inhibitor), only resulted in temporary responses. Eventually, the disease progressed to the peritoneum, which caused intestinal obstruction and surgical interventions were futile; the patient died in June 2015.

Figure 1. Tumor cells revealing GATA3, cytoplasmic mamoglobin, and GCDFP15 protein expressions (brown in color) without CDX2 immunoreactivity

Patient 2 (Protocol No.: 256904, Anadolu Health Science Center)

A 43-year-old white female from Bulgaria was diagnosed with stage IV multifocal invasive lobular cancer of the left breast (in April 2012), True-cut Bx, ER/PR positive, HER-2 negative, a Ki-67 score of 60%, axilla clinically positive, and multiple bone metastases in the
dorsolumbar vertebrae. The patient received multiple courses of chemo- and radiotherapies for the bone metastases, and was put on tamoxifen + zoladex (3.6 mg monthly). In March 2014, re-evaluation with PET-CT scan did not reveal any metabolic activity in the skeletal metastasis and she underwent bilateral mastectomy with left sentinel lymph node dissection. Pathology showed invasive lobular carcinoma in both breasts. Both tumors were staged as PT2N0/AJCC-2010 and graded as III, with ER positivity (60%, strong), PR negativity (<1%, normal limits), and negative HER-2 immunoreexpression. Endocrine treatment was resumed postoperatively. In March 2015, re-evaluation revealed progression in skeletal metastasis, left supraclavicular, and axillary lymph nodes.

A biopsy of the left supraclavicular recurrence disclosed triple negative lobular breast cancer metastasis. Endocrine treatment was stopped and she was put on a denosumab (X-Geva) + capecitabine treatment. In August 2015, a PET-CT control confirmed good partial response in the bones and nodes. During a routine outpatient control on November 16th 2015, the patient was clinically symptomless; however, the CA 19-9 tumor marker was found to be high at 397%. Other markers and biochemical test results were within normal limits. Colonoscopy was carried out, which showed a 2 cm fragile, hemorrhagic mass lesion in the hepatic flexure, encircling a quarter of the lumen, and another 1.5 cm polypoid mass in the sigmoid colon. A biopsy of the fragile, easily bleeding lesions revealed triple negative breast cancer metastasis; PanCK, E-cadherin, and GATA3 immunoreactivities were also found to be positive, whereas ER, PR, and HER-2 immunoreactivity were not detected (negative). Meanwhile, the Ki-67 index was 30%. Pathological findings were analogous to the previous left supraclavicular lymph node biopsy findings performed in March 2015. A repeated PET-CT scan did not show any hypermetabolic activity anywhere in the body including the colon. The patient was subsequently scheduled for systemic chemotherapy.

Patient 3 (Protocol No.: 477214, Anadolu Health Science Center)

A 47-year-old Caucasian female from Romania (without a family history of cancer) was diagnosed in February 2015 with a clinical stage T3N2M0, triple negative type tumor – an invasive ductal carcinoma with high Ki-67 immunoreactivity (<40%). The primary tumor (6 cm in diameter) was located in the left outer quadrant. Lymph node packs measuring 5 cm were palpable in the axilla. The PET-CT result was negative for any distant metastases. Following six courses of docetaxel + carboplatin neoadjuvant chemotherapy, a left modified radical mastectomy was performed on July 14th 2015, which showed pT1aN0/AJCC-2010 invasive ductal carcinoma, with ER, PR, and HER-2 negative immunophenotype. Axillary dissection material revealed 21 lymph nodes with no tumor burden. The patient was followed up without any further treatment. In mid-October 2015, she was seen at an outpatient clinic with complaints of bloating, nausea, and vomiting.

On physical examination, she was found to have a 3 × 2 cm mass in the right breast, right axillary and supraclavicular lymph node enlargements, and a palpable 5 × 6 cm mass in the epigastrium. Biopsies from the right breast mass, as well as right axilla and supraclavicular lymph nodes showed triple negative invasive ductal carcinoma, a compatible histology with the left breast carcinoma. Thorax and abdominal CT results revealed multiple masses in the transverse mesocolon, the gastric wall of the minor curvature, multiple peritoneal implants, and para-aortic/caval lymph node metastasis. The patient was started on the TAC (docetaxel, doxorubicin, cyclophosphamide) regimen, which then shifted to a paclitaxel (175 mg/m²) + gemcitabine (1,250 mg/m²) protocol owing to the lack of response. Progressive disease caused intestinal and bilateral urethral obstruction, which prompted several stenting procedures. On December 21st 2015, she was found to have leptomeningeal involvement and subsequently scheduled for radiotherapy and intrathecal treatment with Ommaya reservoir.

Patient 4 (Florence Nightingale Hospital, Bilim University)

A 54-year-old Turkish female was admitted to the Department of Gastroenterology in early November 2015 with complaints of abdominal swelling, lack of appetite, nausea, and vomiting. Gastroscopy revealed diffuse tumoral infiltration in the corpus of the stomach and the biopsy result was compatible with signet ring cell carcinoma (Figure 2). Staging work-up with PET-magnetic resonance (MR) tomography showed hypermetabolic lymph nodes (SUV Max: 5.7), diffuse hypermetabolic gastric wall thickness in both antrum and corpus, as well as bilateral adnexal masses of 39 × 34 mm and 24 × 19 mm in size.

A biopsy from the left breast mass showed invasive lobular carcinoma with strongly positive ER (95%) but was weakly (5%) PR positive, HER-2 negative, and a luminal tumor with 20% Ki-67 score. Further immunophenotyping studies confirmed the lobular type by mammaglobin, whereas GCDFP15 positivity and E-cadherin negativity were validated through signet ring cell
morbidity’s appearance. The primary site-histology grouping was compatible with gastric and adnexal metastasis. As of current, the patient has received four courses of docetaxel, cisplatin, and 5-fluorouracil (DCF) chemotherapy, with partial responses in the breast and all primary sites.

Discussion

Invasive lobular carcinoma of the breast accounts for 6%–10% of all mammary carcinomas and exhibits unusual clinicopathological, radiological, histological, and metastatic patterns. Unlike invasive ductal carcinoma (IDC), lobular carcinoma exhibits a distinct metastatic pattern. Invasive ductal carcinoma tends to metastasize more commonly to the liver, lung, and brain, while lobular carcinoma metastasizes more to the bones, peritoneum, retroperitoneum, gastrointestinal tract, and genitourinary tract[3]. The exact mechanism for this unusual metastatic pattern is currently unknown. The loss of E-cadherin expression on tumor cell membrane is a characteristic feature of ILC. E-cadherins are epithelial-specific, cell-to-cell adhesion molecules that are responsible for the maintenance of differentiation and prevention of cellular invasion. In normal glands, these molecules are well expressed at the borders of epithelial cells and the loss of these molecules, a result of the inactivation of the CDH1 gene at 16q22, has been implicated in lobular breast carcinomas. The loss of E-cadherin expression is associated with abnormalities in catenin expression, leading to the loss of cell-to-cell adhesion and facilitates tumor cell migration, as well as intra- and intercellular signaling. In addition, the loss of CDH1 expression is also believed to confer the highly dis cohesive morphology characteristic of this tumor subtype, and is often associated with tumor invasion and metastasis, which rarely occurs in other tumor types[4-5].

Therefore, ILCs form irregularly bordered tumors with diffuse infiltration in comparison to IDCs, which form discrete masses. This is postulated as the mechanism for the unusual metastatic pattern of ILC[6]. However, this does not explain why ILCs spread specifically to the GI system. A number of investigators believed that ILCs’ growth is strongly dependent on estrog enic stimulation. Anatomical sites associated with ILC metastases such as the ovaries, abdominal cavity, skin, and gastrointestinal tract consist of tissue compartments with favorable steroid hormone supply. Estrogens are produced by mesenchymal cells of the dermis and bones. Estrogen concentrations are up to 1,000-fold higher in ovarian tissue and peritoneal cavity when compared to body circulation[7]. Lobular cancers are usually hormone receptor-positive. However, triple negative cases have been reported in the literature[8]. Other theories on the predilection for the GI tract argued that the unique microenvironment of the gastrointestinal tract potentially allows the proliferation of tumor cells by providing the necessary building blocks for their survival, and the morphology of the tumor cells’ shape might cause them to be favorably trapped in the microanatomy of the GI tract[9].

To investigate the molecular process that drives the development of ILC, Michaut et al. performed a comprehensive genomic, transcriptomic, and proteomic analyses of a large ILC patient cohort[10]. Mutations in CDH1 and in the phosphoinositide 3-kinase (PI3K) pathway are the most frequent molecular alterations in ILC. They identified two main subtypes of ILCs: an immune-related subtype with mRNA up-regulation of PD-L1, PD-1, and CTLA-4; and a hormone-related subtype, associated with epithelial to mesenchymal transition (EMT), and gaining chromosome 1q and 8q while losing chromosome 11qA. They suggested that this molecular characterization might help to tailor the treatment of ILC through the application of specific targeted chemo- and/or immunotherapies. Radiologically, lobular carcinomas are more difficult to detect via mammogram. This is because lobular tumors tend to grow as sheets of cancer cells rather than discrete masses and induce less desmoplastic reaction. ILCs often fail to form a distinct mass in the breast. A similar diffuse spreading pattern is also common at the metastatic sites[11].

Gastrointestinal metastases of breast cancer are rather uncommon occurrences, although they are well described in the literature and exist mostly as case reports and small series. Mayo Clinic has previously reported a total of 32 cases out of 1,169 metastatic breast cancer incidences, metastasizing to the gastrointestinal tract and peritoneum[2]. Breast cancer histological features included 47% lobular, 31% ductal, 13% mixed, and 9% un-
known. The most common sites of metastasis were peritoneum at 46%, followed by stomach (17%), colon (15%), and small bowel (15%). Receptor status in the patients was ER+ (91%), PR+ (62.5%), and HER2– (90%). Switzer et al. found 6% of GI metastases in a retrospective chart review, which included 343 consecutive cases of lobular breast cancer\textsuperscript{12}. They concluded that approximately 1 in 20 patients diagnosed with ILC would have the ILC spread to the GI tract, manifesting 4–5 years after the initial primary diagnosis.

Ambroggi et al. reviewed literature published from 1943 to June 2012 and found that only 206 patients were affected by gastrointestinal metastases from breast cancer. In their review, the most common sites of gastrointestinal metastasis of breast cancer were the stomach (60%), followed by esophagus (12%), colon (11%), and small intestine (8%)\textsuperscript{13}. They also conducted a retrospective analysis at their institution and reported five cases of GI tract metastases out of a total of 980 patients. Among them, two were invasive ductal, another two were lobular cancer, and the remaining one was a signet ring cell type carcinoma. ER’s status was positive in all five cases and that of PR was negative in two cases, while all cases were negative for the HER-2 receptor\textsuperscript{14}.

Among the unusual metastatic sites of lobular breast cancer are orbital metastasis of breast carcinoma\textsuperscript{15} and uterus (including cervix)\textsuperscript{14,15}. Authors have claimed that there is indirect evidence that the orbital fat pad produces steroid hormones to regulate tear film composition, forming a suitable microenvironment for cancer cells. An alternative explanation is a direct extension to the orbit, either from the nearby bone metastases or from occult meningeal metastases. Metastases of non-gynecological tumors to the cervix are also rare events. Out of 325 metastatic female genital neoplasms, Mazur et al. found only 3.7% involved cervix and none of them originated from primary breast cancer\textsuperscript{16}. The cervix, with its limited blood supply and only with afferent lymphatic drainage, is a less favorable site for metastasis. The most common tumors metastasizing to the cervix and uterus are gastrointestinal tract and ovarian cancers\textsuperscript{17}.

Among secondary metastatic tumors to the gastrointestinal tract, breast is the second most common source when benchmarked against melanoma\textsuperscript{18}. In an autopsy study performed on 707 patients of metastatic breast cancer, the GI tract was involved in 16% of the cases\textsuperscript{19}. In Borst and Ingold’s study, which looked at the patterns of metastasis between lobular and ductal carcinoma, invasive lobular carcinoma only accounted for 14% of the cases but significantly metastasized to the gastrointestinal tract compared to invasive ductal carcinoma (4.5% versus 0.2%), with stomach and small bowel being the most common locations\textsuperscript{20}.

**Unique features and case analysis**

**Case 1**

The patient’s initial tumor diagnosis was strongly positive for ER and PR. Gastric and colonic metastases occurred simultaneously nine years after the initial diagnosis. Metastases were confined to the gastric and colonic mucosa (Figure 3). Multiple colonic sites were involved (ascending colon, transverse colon, and rectum). There were no liver, lung, or bone metastases at the time of recurrence. She was diagnosed to have limited bone metastases in 2007, which was stabilized with hormonal treatment and denosumab. Subsequently, she remained asymptomatic. The first symptoms at relapse mimicked gastrointestinal primary cancer. Although tumor markers were elevated (Ca-15-3: 500), the result of PET-CT and abdominal MR scans did not show any pathological findings. She was only found to have multiple sites of gastric and colonic metastases involvement after undergoing colonoscopy and gastroscopy. The pathology at the time of recurrence was lobular breast cancer of signet ring variant and negative for ER, PR, and HER-2 status; unlike the ER and PR status of the primary tumor (both positive) in 2004. Genomic study conducted by Foundation One (USA) revealed CDH1 and K-ras mutations, as well as MEK amplification in the subject.

Figure 3. Colonoscopic view of metastases from primary breast cancer

**Case 2**

The special aspect of this case lies with it being symptomless at the time of recurrence. Re-evaluation of the patient was initiated after an elevated tumor marker (CA 19-9: 397) was observed during her routine follow-up.
visit. Colonoscopy revealed isolated tumor metastases in the ascending colon near the hepatic flexure and in the sigmoid colon. Tumor histology of the triple negative invasive ductal carcinoma was different from the initial diagnosis of the primary tumor (bilateral lobular invasive carcinoma). The expressions for PanCK, E-cadherin, and GATA3 were all positive whereas the ER, PR, and HER-2 status were negative, with a Ki-67 value of 30%.

**Case 3**

The unique aspect of this case is that the metastasis was clinically mimicking invasive lobular carcinoma, with radiological appearance and failing to form a distinct mass in the breast and bilateral breast, along with peritoneal and colonic involvement as well as early leptomeningeal involvement. All of these are clinical features of lobular carcinoma. However, the primary and metastatic disease pathologies were compatible with triple negative cancer.

**Case 4**

An interesting feature of this case is that the initial diagnosis was primary gastric cancer, and it was only after a gastroscopic biopsy and an extensive work-up that the primary cancer in the breast and metastases in the adnexa and uterus were confirmed. Metastatic carcinoma in the stomach was strongly positive for ER (95%), weakly positive for PR (5%), negative for HER-2, and a 20% Ki-67 score. Further immunohistochemistry tests confirmed a lobular histology with signet ring cell variant. Mammaglobin was positive diffuse, focal positive GCDFP-15, and negative E-cadherin. Primary site-histology grouping was compatible with gastric and adnexal metastasis. During the follow-up visit, the patient developed leptomeningeal metastases.

**Conclusion**

At our institutions, we diagnosed four cases of invasive breast cancer metastasizing to the stomach and colon within the last decade. During this period, a total of 84 out of 1,100 (13%) registered invasive lobular cancer patients were diagnosed with metastatic breast cancer. As depicted in Table 1, three of them had lobular histology: two with signet ring variant and one with a classical ILC histology. Hormone receptors were triple negative at the site of GI tract metastases in three out of four cases. Each case is clinically unique, as outlined in the aforementioned discussion. Although there are reported cases of triple negative lobular cancers in the literature, those cases are usually in the pleomorphic form.[8,21,22] All of our cases were negative for HER-2.

Gastrointestinal tract metastases originating from the breasts are rare in clinical practice. Colonic involvement has a greater propensity for lobular carcinoma. We believe that it is due to the loss of cell adhesion molecule (E-cadherin) expression on primary tumor cell membranes. The loss of cell-to-cell adhesion is accompanied by increased mobility, migration, and invasiveness of the tumor cells. All these are the consequences of reduced intercellular adhesion. In patients with a history of breast cancer, especially when it is of a lobular histology, a high index of suspicion for potential breast cancer metastasis to unexpected sites such as stomach, colon, cervix, and orbit has to be considered.

**Table 1. Characteristics of patients with GI tract metastases**

<table>
<thead>
<tr>
<th>Patient</th>
<th>Age</th>
<th>Histology</th>
<th>TNM at Onset</th>
<th>ER/PR at Onset(%)</th>
<th>Ki-67 at Onset(%)</th>
<th>HER-2 at Onset</th>
<th>Time to GI Metastasis</th>
<th>Metastatic Site</th>
<th>Site of GI Metastasis</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>50</td>
<td>ILC/Signet</td>
<td>T2N2M0</td>
<td>90/90</td>
<td>30</td>
<td>(-)</td>
<td>9 years</td>
<td>Triple (-)</td>
<td>Stomach Colon</td>
</tr>
<tr>
<td>2</td>
<td>46</td>
<td>ILC</td>
<td>T2N2M0</td>
<td>60/1</td>
<td>60</td>
<td>(-)</td>
<td>3 years</td>
<td>Triple (-)</td>
<td>Colon</td>
</tr>
<tr>
<td>3</td>
<td>47</td>
<td>IDC</td>
<td>T3N2M0</td>
<td>0/0</td>
<td>40</td>
<td>(-)</td>
<td>8 months</td>
<td>Triple (-)</td>
<td>Colon Stomach Peritoneal</td>
</tr>
<tr>
<td>4</td>
<td>54</td>
<td>ILC/Signet</td>
<td>T2N3M2</td>
<td>95/5</td>
<td>20</td>
<td>(-)</td>
<td>Synchronous</td>
<td>90/5</td>
<td>Stomach Uterus Cervix</td>
</tr>
</tbody>
</table>

*Age at which GI metastasis was first diagnosed
Author contributions

Sezer Saglam and Ulkuhan Koksal provided the medical record of the patient from Bilim University Hospital and contributed to the retrospective chart review. All pathology slides were reviewed by Huseyin Baloglu. Necdet Uskent reviewed the literature and prepared the manuscript. Patients number 2 and 3 were operated by Metin Cakmakci.

Conflict of interest

The authors declare no potential conflict of interest with respect to the research, authorship, and/or publication of this article.

References


