Case Report

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Gastrointestinal Tract Metastases of Invasive Lobular Carcinoma of the Breast: An Immunohistochemical Survey Algorithm

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ABSTRACT

Invasive lobular carcinoma (ILC) accounts for almost 15% of all breast carcinomas. The potential of ILC to metastasize to the gastointestinal system is significantly greater than that of invasive ductal carcinoma. Gastric metastasis occurred in the ninth year of the follow-up in a patient who was operated on the right breast due to ILC. The patient was investigated for simultaneous masses in the stomach and colon, and a random mass was found in her right breast.

Keywords: Breast cancer; colonic metastasis; gastric metastasis; gastrointestinal tract metastasis; invasive lobular carcinoma

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Key Points

- The histopathological findings are similar in invasive lobular carcinoma of the breast and poorly cohesive carcinoma of the stomach. Therefore, the possibility of metastasis should be kept in mind in multiple erosions or linitis plastica type gastric lesions.
- In breast cancer patients who develop gastrointestinal tract metastases, determining the nature of the tumor (primary or metastatic) is extremely important in terms of treatment.
- The importance of histopathological examination is critical and is highlighted in this report.
- Possible diagnostic errors can be avoided by making immunophenotypic evaluation of endoscopic biopsy material with an appropriate immunohistochemical panel.

Introduction

Invasive lobular carcinoma (ILC) accounts for almost 15% of all breast carcinomas (1, 2). Since the 1960s, many case reports about gastrointestinal tract (GIT) metastases of ILCs have been reported (3-6). The susceptibility of ILC to metastasize to GIT is many times greater than invasive ductal carcinoma (IDC) (4.5% *versus* 0.2%, respectively, $p<0.05$) (1).

Isolated GIT metastasis of ILC is extremely rare and at least 60% of ILC patients with GIT metastases have had concurrent bone (7,8) and, less frequently, other organ metastasis (5, 9-11). The pattern of metastasis is often diffuse and infiltrative so that it essentially presents as multiple erosions (7, 8) or often linitis plastica type in the stomach (6, 7, 12). Since molecular profiling and immunophenotyping methods were not available in the past, the diagnosis of GIT metastases of ILC was based almost entirely on histological evaluation (3, 13). However, in the recent literature, there are few case reports in which differential diagnosis was made by immunohistochemical (IHC) methods (8, 10).

In this study, we evaluated two patients treated in our clinic. The first had ILC in the breast and subsequently developed gastric metastasis (Case 1). In the second patient, an incidental mass was found in the right breast while investigating simultaneous masses in the stomach and colon (Case 2).

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In addition, using current and specific immunohistochemical methods, we examined the staining pattern of poorly cohesive carcinoma of the stomach (PCCS), including signet ring cell carcinoma and gastric metastasis of ILC.

Case Presentations

Case 1: A 76-year-old female patient was admitted to our service nine years previously, due to a mass in her right breast. The tru-cut needle biopsy was reported as ILC. Following radiodiagnostic studies, the patient underwent right mastectomy and axillary dissection upon detection of carcinoma metastasis in the sentinel lymph node (1/3). Histological examination of the breast revealed two separate tumor foci (3.0 and 1.8 cm) with signet-ring cell component. The number of metastatic lymph nodes was 1/12.

Immunohistochemistry showed positive estrogen receptor (ER) and negative progesterone receptor (PgR), human epithelial growth factor receptor type 2 protein (Cerb-B2), p53 and e-cadherin staining.

The patient had had T2N1M0 Stage 2B tumor. She received six courses of adjuvant consisting of tri-weekly TEC regimen (75 mg/m^2 docetaxel + 75 mg/m^2 epirubicin + 600 mg/m^2 cytoxan) followed by radiotherapy.

In the ninth year of follow-up, an increase in tumor markers was detected (CEA = 29.7 U/mL, CA15-3 = 1019 U/mL). The abdominal ultrasound and computed tomography revealed free intraperitoneal fluid accumulation, hypermetabolic implants in the peritoneum (peritoneal carcinomatosis) and a diffuse but asymmetric gastric wall thickening reaching 17 mm. The patient underwent gastroduodenal endoscopy. There were numerous infiltrative nodular lesions in the gastric corpus and antrum mucosa and multiple biopsies were taken. On positron emission tomography/computed tomography (PET/CT), a possibly metastatic lymph node in the left axillary region with a size of 16x13 mm [(maximum standardized uptake value (SUV_{max}: 4)] was seen and a tru-cut biopsy was performed. Endoscopic gastric biopsies and left axillary lymph node biopsies were evaluated together with previous right mastectomy and axillary dissection material for pathological evaluation.

The endoscopic biopsy sample of the stomach revealed a non-cohesive tumor with an infiltrative pattern between the normal gastric glands in the lamina propria. Considering the medical history of the patient, an IHC panel was simultaneously applied to primary breast adenocarcinoma and gastric endoscopic biopsy specimen in order to rule out possible metastasis.

In the breast biopsy samples, tumor cells were ER 100% (3+), GATA 3 (+), PR (-), CerbB2 score 1, Ki-67 25% (+), e-cadherin (-), mammoglobulin (+), GCDFP15 focal (+), CDX2 (-). In the stomach biopsy samples, tumor cells were ER 100% (3+), GATA 3 (+), PR (-), e-cadherin (-), mamoglobulin (+), GCDFP15 focal (+), CDX2 (-). CerbB2 and Ki-67 assessments were suboptimal (Figure 1).

A sample of primary malignant gastric carcinoma and its staining pattern for comparison with metastatic gastric carcinoma is shown in Figure 2. With histological and immunohistochemical findings, both breast mass and infiltrative nodular gastric lesions were evaluated as "infiltrating lobular carcinoma".

First line endocrine therapy (aromatase inhibitor) was started. The patient died 11 months after metastasis was detected.

Case 2: A 65-year-old female patient was admitted to our clinic in December 2020 with nausea, vomiting and intermittent colic abdominal pain, resembling incomplete mechanical bowel obstruction. On abdominal CT, an irregular wall thickening in an approximately 8 centimeters long segment of the proximal transverse colon was observed. Chest CT revealed multiple lymph nodes in the right axillary region with a maximum dimension of 30x24 mm and diffuse sclerotic metastatic lesions in the bony structures.

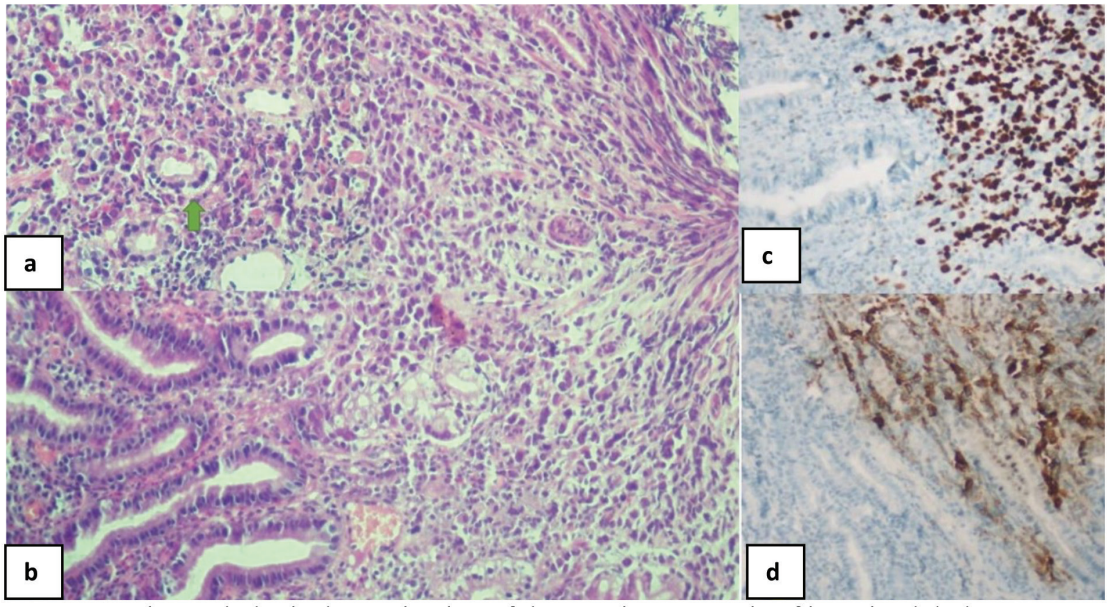

Figure 1. Histopathological examination of the gastric metastasis of invasive lobular carcinoma of the breast. **a)** Tumoral infiltration in the lamina propria of stomach (H&E, x200). **b)** Dyscohesive tumor cells (H&E, x400) around the usual stomach glands (arrow). **c)** GATA3 nuclear positivity in tumor cells and gland epithelium without staining (IHC, GATA3). **d)** Tumor cells with Mammoglobin staining and gastric gland epithelium without staining immunohistochemical (IHC, Mammoglobin)

H&E: hematoxylin and eosin stain; ICH: immunohistochemical

In the colonoscopic examination of the patient, there was an ulcerovegetan mass encircling the lumen and multiple biopsies were taken. In the same session, upper GI tract endoscopy was also performed and a few biopsies were taken from erosive lesions in the stomach.

In the histopathological examination, there was atypical tumoral infiltration showing loss of cohesion in the lamina propria of both colon and gastric epithelium. In tumor cells, ER was 80% (3+), PR (-), GATA3 (+), CK7 (+) Pancytokeratin diffuse (+), CD20 (-), CD3 (-) and CDX-2 (-), LCA (-), Synaptophysin (-), Chromogranin (-), Vimentin (-), OCT3 (-), SOX10 (-), PAX8 (-), CK20 (-), S100 (-) (Figure 3).

With the described IHC findings, metastasis of breast carcinoma to the colon and stomach was strongly considered. Afterwards, breast

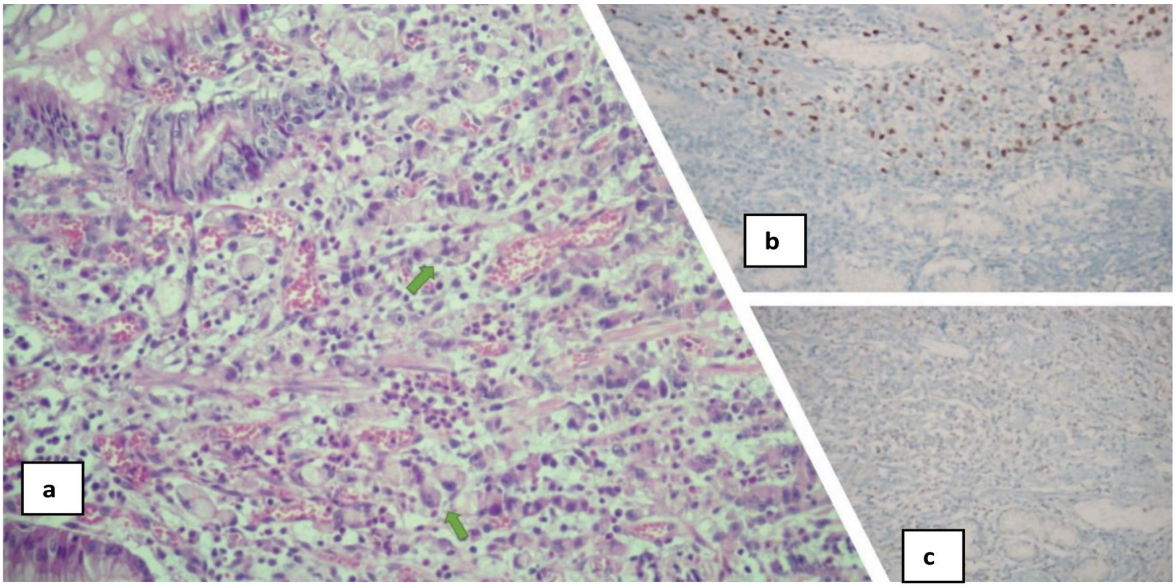

Figure 2. The histology of primary malignant (poorly cohesive) gastric carcinoma and its' immunohistochemical (IHC) staining pattern. **a)** Cohesive carcinoma cells between gastric glands (arrow) (H&E, x200). **b)** CDX2 positivity in tumor cells (IHC, CDX2). **c)** GATA3 negativity in both stomach gland epithelium and tumor cells (IHC, GATA3)

H&E: hematoxylin and eosin stain; ICH: immunohistochemical

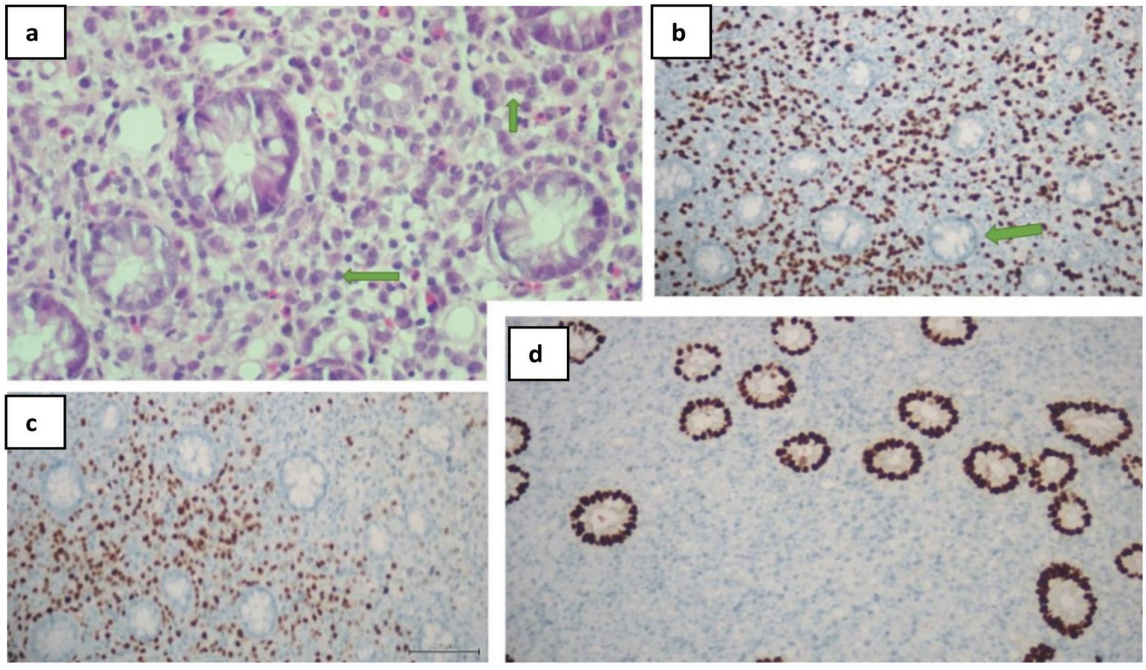

Figure 3. Breast carcinoma metastasis to the colon.

a) Poorly cohesive carcinoma cells (arrow) between the glands of colonic epithelium (H&E, x200). **b)** GATA3 stained tumor cells and unstained glandular epithelium of the colon (arrow) (IHC, GATA3). **c)** ER positivity in tumor cells in the lamina propria (IHC, ER). **d)** CDX2: Negative staining in tumor cells and positive nuclear staining in colonic epithelial cells (IHC, CDX2)

H&E: hematoxylin and eosin stain; ICH: immunohistochemical; ER: estrogen receptors

magnetic resonance imaging (MRI), mammography and breast ultrasonography (USG) examinations were performed. On ultrasound examination, there was an irregularly circumscribed area in the right breast that did not show a clear mass formation. MRI examination revealed an irregular and spicular mass located in the retroareolar and mid-quadrant area of the right breast, with a size of 16x11 mm. The mass was classified as Breast Imaging Reporting and Data System (BI-RADS) 4-C. The MRI images of the right axilla was compatible with adjacent and numerous pathological lymph nodes ≤33 mm in size. Ultrasound guided tru-cut biopsy and fine needle aspiration biopsy (FNAB) was performed from the mass in the right breast and the axillary lymph node, respectively.

In the right breast tru-cut biopsy specimen, an invasive tumor was observed that developed as individual cells and short cell lines with scanty cytoplasm. In the tumor cells, ER was 100% (+++), PR 40% (++++), cerbB2 (-), Ki-67 5%, p53 (-), e-cadherin (-), P63 (-). Findings were consistent with "invasive lobular carcinoma" as the most likely diagnosis. In addition, cytomorphological and immunocytochemical findings (GATA 3 positivity in tumor cells) in axillary lymph node FNAB were interpreted as breast carcinoma metastasis. In the light of IHC findings, it was reported that the tumor was not primary colon carcinoma and the primary focus was most likely the breast. Thus, in this case, the diagnosis of ILC of the breast was reached based on the GI tract metastases.

In terms of treatment, the patient had first-line systemic hormonotherapy; + CDK4-6 inhibitor treatment was started in January 2021. The patient is still using palbociclib 125 mg/d for 21 days in combination with letrozole 2.5 mg/d. In addition, she is regularly receiving Denosumab 60 mg (recombinant human monoclonal IgG2 antibody) subcutaneously every 6 months.

Discussion and Conclusion

In our clinic, the number and percentage of patients with ILC (excluding mixed-type tumors) among 2000 patients with primary breast carcinoma was 162 and 8.1%, respectively. Among these, the number of ILC patients with gastrointestinal organ metastasis was only two (1.2%). In patients dying of breast carcinoma, gastric metastasis was found in 6–18% at autopsy. This might be due to the diffuse nature of the disease (ILC) and some predilection for gastric involvement (3, 14, 15). In one study, metastatic disease secondary to breast cancer was detected in 12,000 patients over a 15-year period. The number of patients with GIT metastases in this series was only 23 (0.2%). In this series, the prevalence of ILC was 12 percent, however it was significantly increased (54%) in patients with GIT metastases and carcinomatosis ($p<0.001$) (16). The metastasis of ILC to the colon is less common compared to the stomach, and it is frequently encountered in the literature as single case reports (4, 10, 17, 18).

In published breast cancer patient series, when the surviving patients are compared to those deceased and autopsied, a significant difference was observed in the frequency of GIT metastasis. This suggests that clinicians failed to notice the GI tract metastases during the follow-up of these patients. Patients with breast cancer very rarely have isolated GIT metastases. On the contrary, in almost all of them, multiple metastases are observed, most commonly in the bone (about 60%) before or simultaneously with the GIT metastasis (5, 7-11, 17). This perhaps causes clinicians to focus on the more common metastases with more prominent symptoms and may result in failure to recognize possible GIT metastases.

In our study, in the first patient who had gastric metastasis after ILC, there were simultaneous metastasis in the locoregional lymph nodes, and in the second case, multiple bone metastases were demonstrated concurrently with colon metastasis.

In breast cancer patients who develop GI tract tumors, histopathological examination is extremely important in determining the nature of the tumor and for optimal treatment planning. In this study, direct histopathological examination of H&E stained specimens of metastatic ILC were characterized by poorly cohesive tumor cells around the epithelial glands located in the lamina propria. This infiltration was sometimes patchy or diffuse. Poorly cohesive ILC cell infiltration in the lamina propria has also been reported in different studies (11, 19). In these cases, the use of immunomarkers, alone or in combination, significantly increased the sensitivity and specificity for diagnosing metastatic ILC in the GIT. We used CDX2 to differentiate adenocarcinoma of intestinal or breast epithelial origin. *CDX2* gene encodes a nuclear transcription factor relatively specific for the development of intestinal epithelium from duodenum to rectum (20). In an immunohistochemical survey study, CDX2 monoclonal antibody was expressed uniformly in 76%–100% of tumor cells in 183 of 184 tumors originated from esophagus to the colon (21). However in our patients, tumor cells from gastric and colon biopsies were CDX2-negative, thus effectively excluding primary GI adenocarcinomas.

In both of our patients, an immunohistochemical survey with ER and GATA3 was used in all biopsies obtained from the breast, axillary lymph nodes, stomach and colon to prove that tumors were of breast origin. GATA3 is a transcription factor important in the differentiation of breast epithelia and urothelia. As expected, ER expression in tumor cells was 100% positive in breast, axillary lymph node and stomach biopsies and 80% in colon biopsy while GATA3 was strongly and uniformly expressed in all four biopsy specimens. Several case series have been reported about high ER-positivity (5, 10, 12, 17, 22) and GATA3 expression (11, 23) in both primary and metastatic tumor foci of ILC of the breast. In one study GATA 3 was immunohistochemically examined in 268 patients with primary or metastatic IDC and ILC of the breast. GATA3 positivity was observed in 97.3% (251 of 268 tumors) and was strongly expressed in 100% of primary ILC cases (23). In another study, primary breast and gastrointestinal carcinomas showing signet ring features were reviewed with respect to expression patterns of several immunohistochemical markers. The specificity of ER and GATA3 expression was 100% and 98% in primary breast carcinomas and the specificity of CDX2 was 100% for tumors of gastrointestinal origin. Thus, these markers successfully discriminated ILC and gastric signet ring carcinomas (24). These findings were supported in a different study in which ER and GATA3 expression were positive in 82% of the patients with metastatic ILC (mILC) and were helpful in distinguishing mILC from primary diffuse gastric adenocarcinoma (25).

Estrogen receptor expression in gastric carcinoma may sometime lead to misdiagnosis. It has been reported that some isoforms of ER-alpha (ERα) are highly expressed in cases with gastric cancer. Furthermore, the incidence of ER-alpha 66 isoforms is significantly higher, especially in diffuse type and poorly differentiated gastric adenocarcinomas (26). However, there are still inconsistencies regarding the effects of estrogen receptors on the development and/or progression of gastric cancer (27).

In our study, as a comparison group, we immunohistochemically surveyed the pathological specimens of five malignant (poorly

cohesive) gastric adenocarcinoma cases operated in our clinic. As seen in Figure 2, CDX2 was positive and GATA3 expression was negative in gastric tumor cells in all cases. In addition to the IHC stains presented above, we also used mammoglobin and GCDFP15 molecular markers in our first patient. Mammoglobin was reported to have higher expression, particularly in ILC and ER-positive tumors than IDC (28). These two markers were expressed both in primary breast tumor (50%–70%) and its gastric metastasis and this strengthened our diagnosis of gastric metastasis of primary ILC of the breast. Here, we do not intend to specifically recommend these last two molecular markers to be routinely used in differential diagnosis of GI tract metastasisof ILC of the breast. However, there are publications stating that these two markers are very useful to distinguish primary GI tract adenocarcinomas from gastrointestinal metastases of ILC (5, 9).

As a result, ER-α positivity can be reliably used to diagnose gastric metastasis of hormone receptor positive ILC of the breast. Simultaneous GATA3 positivity in both primary and metastatic foci significantly increases diagnostic accuracy. Negative CDX2 staining in gastrointestinal tumor cells fairly specifically excludes GI origin.

Also, in our second case presentation, the malignant primary focus was elucidated during the investigation of the metastatic masses. Therefore, since the histopathological findings are similar in ILC of the breast and poorly cohesive carcinoma of the stomach, the possibility of metastasis should definitely be kept in mind in cases with multiple erosions or linitis plastica type gastric lesions, even if there is no history of breast carcinoma in the medical records of the patient. Possible diagnostic errors can be avoided by implementing immunophenotypic evaluation in endoscopic biopsies with the IHC panel described above.

Informed Consent: Written informed consent was obtained from patients who participated in this study.

Peer-review: Externally peer-reviewed.

Authorship Contributions

Surgical and/or Medical Practices: B.Z., D.Ç., Ö.Ö., F.T., M.K., C.Ş.; Concept: B.Z., D.Ç., A.U.; Design: B.Z., D.Ç., F.T., A.U.; Data Collection and/or Processing: B.Z., D.Ç., Ö.Ö., F.T., M.K., C.Ş.; Analysis and/or Interpretation: B.Z., D.Ç., Ö.Ö., F.T., A.U.; Literature Search: B.Z., D.Ç., Ö.Ö., F.T., A.U.; Writing: B.Z., A.U.

Conflict of Interest: No conflict of interest was declared by the authors.

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