

Invasive lobular breast carcinoma metastatic to the colon: a case report of a rare condition and its challenges

Carcinoma lobular invasivo de mama metastático para o cólon: relato de caso de uma condição rara e seus desafios

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ABSTRACT

The most common sites for metastatic breast neoplasm are the bones, lungs, liver, and central nervous system. Metastases to the gastrointestinal tract are rare and especially involve the stomach, more than to the colon. The clinical and radiological presentation of the metastatic disease usually does not aid in making the differential diagnosis between primary neoplastic lesions of the colon or rectum and metastases from breast cancer. This often results in inadequate initial treatment. The clinical, radiological and histopathological diagnoses are challenging, and immunohistochemical analyses become necessary in most cases. Therefore, publication in the medical literature of more cases like this one should be stimulated, with the aim of gaining more data on treatments that are used and hence to clarify what the best approach is, focusing especially on better quality of life and survival for these patients.

Keywords: Lobular breast carcinoma; Breast neoplasm; Neoplasm metastasis; Gastrointestinal cancer.

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RESUMO

Os locais mais comuns de neoplasia metastática da mama são os ossos, pulmões, fígado e sistema nervoso central. As metástases do trato gastrointestinal são raras e envolvem especialmente o estômago, mais do que o cólon. A apresentação clínica e radiológica da doença metastática geralmente não ajuda a fazer o diagnóstico diferencial entre lesões neoplásicas primárias do cólon ou reto e metástases de câncer de mama. Isso geralmente resulta em tratamento inicial inadequado. Os diagnósticos clínico, radiológico e histopatológico são desafiadores, e análises imunohistoquímicas tornam-se necessárias na maioria dos casos. Portanto, deve-se estimular a publicação na literatura médica de mais casos como este, com o objetivo de se obter mais dados sobre os tratamentos que são utilizados e, assim, esclarecer qual é a melhor abordagem, com foco principalmente na melhor qualidade de vida e sobrevida destes pacientes.

Descritores: Carcinoma lobular da mama; Neoplasia da mama; Metástase de neoplasia; Câncer gastrointestinal.

INTRODUCTION

The types of neoplasia that most commonly metastasize to the gastrointestinal tract are melanoma, epithelial ovarian, kidney, and bladder neoplasia. Breast cancer is generally not associated with metastasis to the digestive tract and this is considered to be a rare event, although the incidence rate may be underestimated, as seen from autopsy series. When metastases to the gastrointestinal tract occur, the stomach, small intestine and colon are the sites most involved, in this order.^[1] Infiltrating lobular carcinoma (ILC) represented some cases of the gastrointestinal metastases.^[2] Usually, metastasis to the colon occurs as part of widely disseminated disease, and for it to appear as the first manifestation of metastatic disease is unusual.^[1] The clinical and radiological presentation of the metastatic disease usually does not aid in making the differential diagnosis between primary neoplastic lesions of the colon or rectum and metastases from breast cancer.

The clinical, radiological and histopathological diagnoses are challenging, and immunohistochemical analyses become necessary in most cases.^[3] Nonetheless, even though it is a rare event, it should always be a hypothesis to be considered in cases of women with personal histories of breast cancer and persistent gastrointestinal symptoms. This often results in inadequate initial treatment. Although the optimal treatment for these patients remain to be elucidated. An appropriate systemic therapeutic strategy that includes chemotherapy and hormonal therapy may be beneficial for this group of patients. Palliative surgical intervention in did not affect overall survival but some survival benefit may have accrued to select patients with gastrointestinal metastasis who underwent surgical palliation.^[2]

After reviewing the literature, reports on this subject are poor and often limited to single case reports. This review has an objective to report an interesting case, review the literature and to draw attention to the

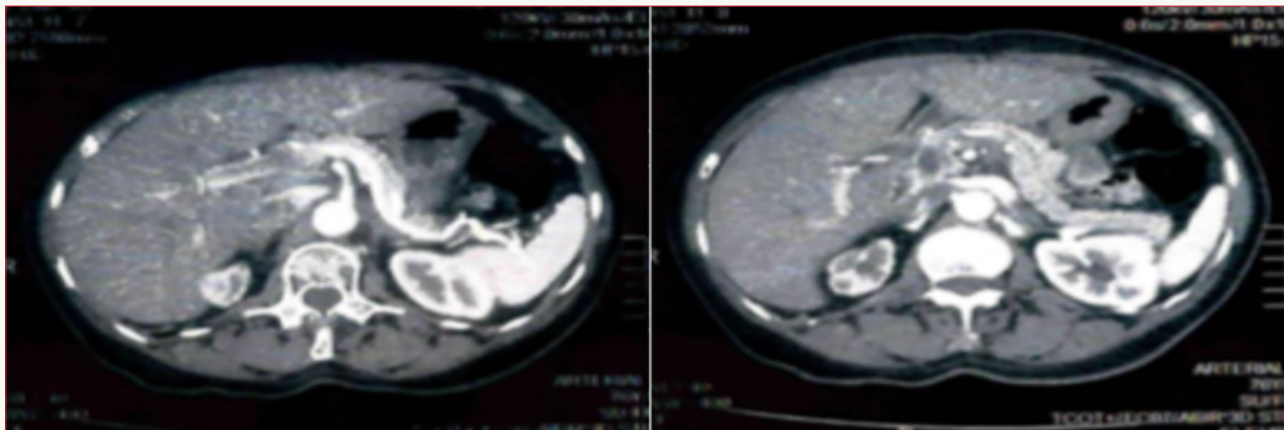
possibility of breast cancer metastases in patients with gastrointestinal disease symptoms.

CASE REPORT

A 76-year-old female patient was assessed in an outpatient consultation and right-side axillary lymph node enlargement was diagnosed. Histopathological analysis on a previous biopsy had revealed a diagnosis of metastatic carcinoma, and immunohistochemical evaluation on the material showed that it was strongly positive for estrogen and progesterone receptors and negative for HER-2/neu.

The patient had a previous history of breast cancer. She had undergone left-side mastectomy with removal of ipsilateral axillary lymph nodes more than seven years earlier, in May 2011, because of an occurrence of pleomorphic infiltrating lobular breast carcinoma. The histopathological report on that surgical specimen stated that the tumor measured 7 x 5cm and that 14 of the 16 axillary lymph nodes were compromised. At that time, the patient underwent adjuvant chemotherapy and radiotherapy and started to be medicated with tamoxifen, since she was positive for estrogen and progesterone receptors.

In 2018, the patient relapsed from the breast cancer with palpable contralateral axillary lymph node, confirmed with biopsy. Several staging examinations were requested. Magnetic resonance imaging on the breast revealed a nodule of irregular shape, measuring 1.4 x 0.7 x 1.2cm, in the posterior third of the lower quadrant of the right breast, of suspect appearance (BI-RADS 4). Computed tomography on the chest did not show any notable alterations and bone scintigraphy showed low likelihood of metastatic disease. Computed tomography on the entire abdomen showed accentuated concentric parietal thickening of the ascending colon, with heterogeneous highlighting through contrast medium, measuring around 27 mm in thickness (Figures 1 and 2), without any description



Figures 1 and 2. Tomographic alterations seen in the ascending colon.

of hepatic or peritoneal alteration. Colonoscopy confirmed the presence of a lesion in the region of the ascending colon and cecum. A biopsy was performed on this and it was found histopathologically to be an undifferentiated adenocarcinoma.

The patient was referred to an oncological surgeon. Right-side hemi-colectomy with primary anastomosis was performed in January 2019, and this operation was considered to be R0. The patient then evolved with intestinal sub-occlusion due to adhesions. On the 12th postoperative day, she successfully underwent a second operation, and subsequently was discharged from hospital.

Macroscopic analysis on the resected colon showed the presence of a vegetative tumor growth of 4cm that occupied the ileocecal valve and infiltrated the entire wall as far as the pericolic fat. Under a microscope, an undifferentiated carcinoma was observed, which diffusely infiltrated the entire thickness of the wall. It was formed by isolated pleomorphic cells, with somewhat eosinophilic cytoplasm. The lesion occupied the region of the ileocecal valve and seemed not to have originated from the intestinal mucosa. It infiltrated as far as the subserosa, with mucosal ulceration. The surgical margins were free, and 15 lymph nodes were evaluated, among which three were found to be compromised by disease.

The immunohistochemical analysis on the lesion in the colon showed that it was positive for mammaglobin and negative for E-cadherin. The final report, based also on the morphological findings, was that this was a case of pleomorphic infiltrating lobular carcinoma that originated from the breast, presenting infiltration of the intestinal wall (Images 1, 2, 3 and 4).

Treatment for the right breast, with its suspicious magnetic resonance imaging, was postponed so as to prioritize surgical treatment of the colon. However, medication with tamoxifen was replaced by anastrozole, at that time of the relapsed in August 2018. The patient started the aromatase inhibitor that continued until the first disease progression in July 2019. Subsequently, capecitabine was introduced for a short time when occurred the new disease progression, and the therapy was replaced

by docetaxel. The patient developed severe diarrhea and this chemotherapy was replaced by paclitaxel. After, she has a reduction of the contralateral axillary lymph node. Meanwhile, in April 2020, the patient presented an intestinal sub-occlusion once more. Unfortunately, after admission at the hospital, she presented intestinal complications resulting in death.

Epidemiology

Breast carcinoma is the most common malignant neoplasm in women. According to the Brazilian National Cancer Institute (INCA), the estimate for each year of the three years 2020-2022 will be about 66,000 new cases, in Brazil.^[4] The most common sites for metastases are the lungs, liver and central nervous system. Metastatic lesions in the gastrointestinal tract are rare. In a large series in which more than 2,600 cases of metastatic breast cancer that occurred over an 18-year period were analyzed, only 17 patients (less than 1%) were documented as having metastatic disease in the gastrointestinal tract. This demonstrates the rarity of metastases to this site. In this same series, it could be seen that invasive lobular carcinoma (ILC) and infiltrating ductal carcinoma of the breast displayed different patterns of metastatic dissemination. Whereas the rates of metastases to the lymph nodes, liver and central nervous system did not differ, the rates of metastases to the gastrointestinal tract were substantially different: 4.5% for the infiltrating lobular subtype and 0.2% for the infiltrating ductal subtype.^[5]

Metastatic pattern

Metastases to the stomach^[2] and to the small intestine^[6] have been documented more frequently than those to the colon or rectum,^[7,8] although there have been some divergences in the data. In autopsy series, the incidence of metastases to the gastrointestinal tract was found to be greater than expected, with rates ranging from 6% to 35%.^[2,9] In a retrospective series at the Mayo Clinic, 23 cases of metastasis to the gastrointestinal tract were recorded, and the most frequent sites were the colon/rectum (45%), stomach (28%), small intestine (19%), and esophagus (8%).^[2]

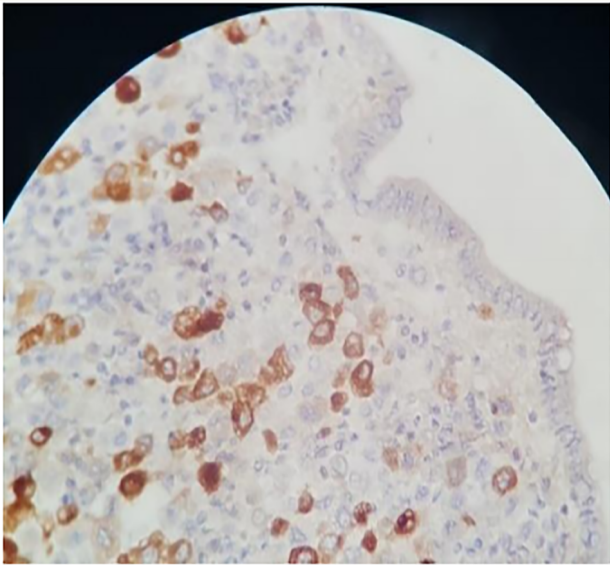


Image 1. Immunohistochemical analysis for mammaglobin. This is a specific marker for the breast and has slightly higher sensitivity for invasive lobular carcinoma. It marks the cytoplasm of neoplastic cells with brown staining. In this photo, at a magnification of approximately 200 X, many invasive lobular carcinoma cells can be seen in the mucosal chorion, while the cells of the epithelium coating the intestinal crypts as negative.

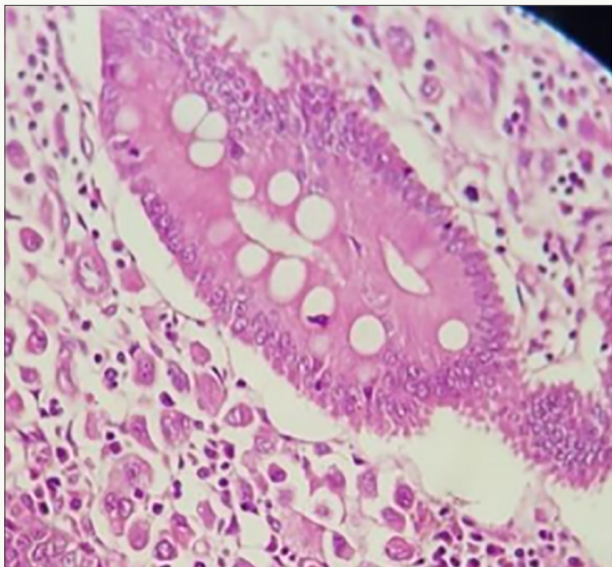


Image 2. Hematoxylin-eosin (HE), magnification of 400X. At the center of the section, a normal intestinal crypt can be seen, but all the remainder are invasive lobular carcinoma cells infiltrating the chorion. The main morphological characteristic that can be noted is the cells without cohesion (without forming tubules or glands), with accentuated pleomorphism and nuclear atypias.

Most metastases to the gastrointestinal tract from breast cancer result from the histological subtype of infiltrating lobular carcinoma, even though the prevalence of infiltrating ductal carcinoma is much higher (90%) among women with breast cancer. [3,6,7,9] McLemore et al. (2005)^[2] documented that ILC accounted for 34 out of 53 (64%) of their cases of metastases to the gastrointestinal tract.^[2] It has also been documented that even in patients with primary breast lesion who present both subtypes (ductal and lobular), the lobular type predominates

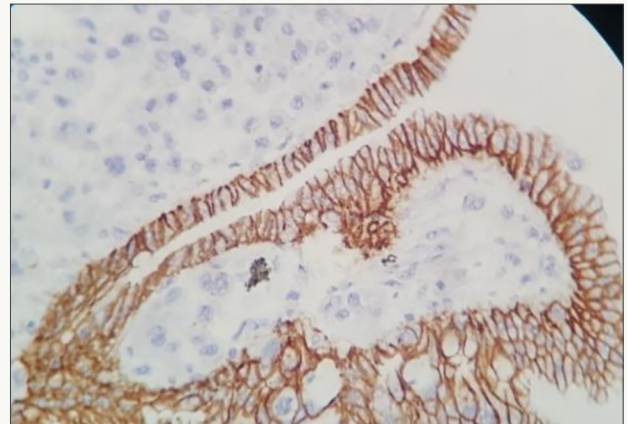


Image 3. Immunohistochemical analysis for E-cadherin. E-cadherin is a protein with intercellular adhesive properties that is lost in invasive lobular carcinoma. It is used for various purposes and among these, it differentiates between invasive lobular carcinoma and infiltrating ductal carcinoma of the breast. Note that the normal intestinal epithelium preserves positivity for this marker. Magnification of approximately 200X

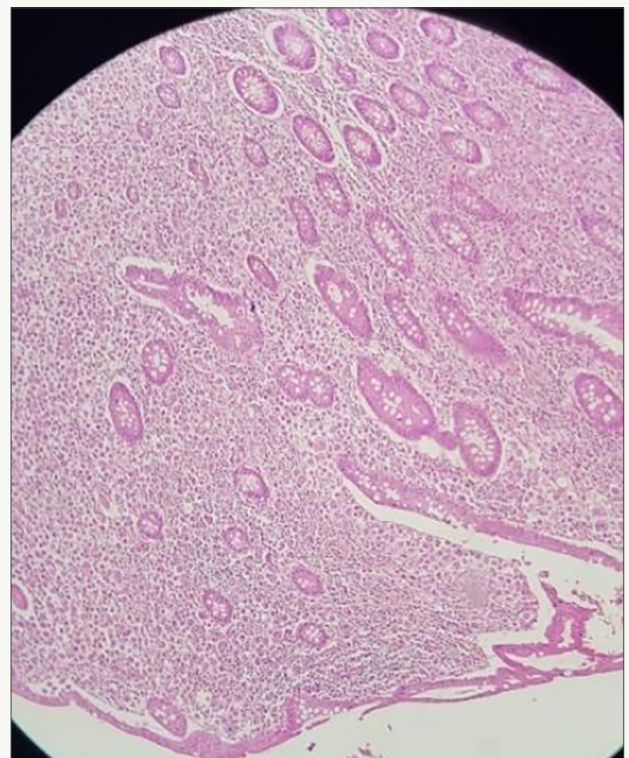


Image 4. HE, magnification of 100X. This is a lower magnification in comparison with Image 2. It shows several glands of the normal intestinal mucosa and dense proliferation of neoplastic cells of invasive lobular carcinoma in the mucosal chorion.

among cases of metastatic lesions.^[6] These tumors are characterized microscopically by small cells that insidiously infiltrate the mammary stroma and adipose tissue individually and in a single file pattern, often growing in a target-like configuration around normal breast ducts, frequently inducing only minimal fibrous reaction.^[10] This fact may be related to the phenotypic trait of incohesive small cells which characterizes ILC. EC loss, observed in most cases of

ILC, may result in alterations in cell-cell adhesion and a preferential growth at metastatic sites.^[11]

It has been estimated that the incidence rate of metastases to the gastrointestinal tract is 8.0% among cases of infiltrating lobular carcinoma versus 0.6% among cases of infiltrating ductal carcinoma. In the rare situations in which the gastrointestinal tract is the primary site for metastatic disease, the infiltrating lobular subtype also predominates over the infiltrating ductal subtype: 5.7% versus 0.3%, respectively.^[12] The reason is unknown, but some authors think that it could be related to a particular tropism of lobular cells. The fact that certain tumors exhibit a predilection for metastasis to specific organs has been noted through over the years. According to Langley et al. (2011), the "seed and soil" hypothesis was considered by Paget's (1989)^[13] and showed that the organ-preference patterns of tumor metastasis are the product of favorable interactions between metastatic tumor cells (the "seed") and their organ microenvironment (the "soil"). Others hypothesis were developed to explain this fact. Greene and Harvey (1964), mentioned by Langley et al.^[13], demonstrated that the adhesive interaction that occurred between tumor cells and the luminal surface of the microvascular endothelium might be liable for determining the localization of metastasis. A body of evidence also supports the proposition that anatomical and mechanical factors are important considerations in determining the metastatic patterns of several types of tumors.^[13]

The clinical presentation of metastatic disease in the gastrointestinal tract is diverse and non-specific, going from asymptomatic or oligosymptomatic cases,^[14] like in the present case, to situations in which the patient has a clinical condition of intestinal obstruction or manifestations reminiscent of idiopathic inflammatory disease.^[9] The imaging and endoscopic characteristics are also nonspecific and not very useful for establishing a more precise diagnosis. These lesions in the gastric commonly present an appearance of linitis.^[15,16] There is an association between mutations in the cadherin (*CDH1*) gene and invasive lobular breast cancers. Lobular breast cancers have been observed to occur in 20 to 54 percent of women from families with hereditary diffuse gastric cancer who carry germline mutations in the *CDH1* gene. However, germline *CDH1* mutations can also be co-segregated with invasive lobular breast cancer in the absence of diffuse gastric cancer, suggesting that gastric cancer is not an obligatory hallmark of families with *CDH1* mutations. Approximately 50 percent of sporadic lobular breast cancers contain E-cadherin mutations.^[17,18]

The importance of immunohistochemistry

The initial histopathological diagnosis is also difficult. In a series at the Memorial Sloan-Kettering Cancer Center involving seven cases between 1993 and 1996, all the patients had a diagnosis of undifferentiated adenocarcinoma from endoscopic biopsy samples.^[3] These samples need to be deep, given that metastatic

lesions ordinarily spare the mucosal layer. In all series, it has been recommended that samples from the digestive tract lesion should be compared with samples from the breast. Presence of cells of signet ring type in endoscopic biopsy samples should raise suspicion of a primary breast tumor.

Immunohistochemical analyses will be necessary in the majority of cases. Various markers are usually tested. Estrogen and HER-2/neu receptors are frequently used, but their expression is only identified in 30-56% and 4-14% of cases of neoplasia of the colon, respectively. Thus, their specificity is too low to establish the differential diagnosis. CK7 is commonly observed in the epithelial layers of the mammary ducts, while the intestinal tissue does not show expression of this protein. On the other hand, CK20 is usually expressed in the colon and rarely in the breast. Thus, metastatic disease that originated in the breast is revealed to be positive for CK7 and negative for CK20. GCDF-15 and mammaglobin are widely used. GCDF-15 is present in 32% to 47% of metastatic lesions from breast cancer. Mammaglobin, which is expressed only in breast and skin tissues, is present in 42% to 87% of cases of metastatic breast cancer.^[19] Other markers that are useful in making immunohistochemical evaluations include CK18, TSP, alpha-V integrin, cathepsin B, HLA-G, and CHC1.^[20]

Elucidation of rare cases and its difficulties

In addition to what is stated above, the differential diagnosis between primary lesions of the colon or rectum and metastases from the breast may also be made difficult because of the long disease-free interval that is frequently observed in relation to breast cancer. In many series, the median interval between making the diagnosis of breast cancer and the emergence of the metastasis is six to eight years.^[2,3,6,8,15] Intervals greater than ten years have only rarely been observed.^[20-22] In addition, even in women with a history of breast cancer, the diagnosis of a primary tumor of the colon or benign disease is still more common than is metastasis from breast cancer.^[23]

All these difficulties in making the differential diagnosis between primary lesions of the colon and metastatic disease from the breast may lead to inadequate initial treatment. Some authors do not recommend surgical treatment, except in situations of clinical emergency.^[20] This recommendation is made because in most cases, the metastatic lesion in the colon suggests that a systemic disease is present. Thus, the lesion would form part of a disseminated disease. Consequently, systemic treatment might produce better results with less morbidity. To illustrate this, in a series at the Mayo Clinic, gastrointestinal metastases were associated with peritoneal carcinomatosis in 25% of the cases, and 24% of the patients had metastases in two or more sites of the gastrointestinal tract.^[6] Nonetheless, in cases in which the disease is clearly limited to the gastrointestinal and is resectable, some authors would indicate surgery. McLemore et al. (2005)^[2] did not show that surgery had any

impact on median survival for the whole group (28 months for the surgical group versus 26 months for the systemic treatment group), but there was a tendency towards longer median survival for the surgical group, among patients whose metastases were exclusively to the gastrointestinal tract (44 months versus 9 months).^[2]

It needs to be emphasized again that metastasis to the colon or to any other site in the digestive tract is only rarely the first manifestation of metastatic disease, which makes the present case absolutely intriguing.

CONCLUSION

Breast carcinoma with metastasis to the colon or rectum is a very rare event. However, the real incidence may have been underestimated, given that necropsy series have revealed higher incidence rates. Many cases evolve without clinical symptoms.

Clearly, this diagnosis should be suspected when the patient has a personal history of breast cancer, even if there has been a long disease-free interval, and presents any persistent symptom relating to the gastrointestinal tract, albeit vague and non-specific and/or any radiological alteration of any importance. Making a clinical, radiological or histopathological diagnosis is challenging, and immunohistochemical analysis is invariably required.

Metastasis to the colon is mostly part of greater dissemination of the disease and only rarely occurs as the first manifestation of metastatic disease. An adequate initial diagnosis may avoid unnecessary surgical treatments, given that that surgery does not clearly prolong overall survival in the entire group and should only be considered for selected patients.

Therefore, publication in the medical literature of more cases like this one should be stimulated, with the aim of gaining more data on treatments that are used and hence to clarify what the best approach is, focusing especially on better quality of life and survival for these patients.

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