Gastric metastasis from breast carcinoma. Report of three cases, diagnostic-therapeutic critical close examination and literature review.

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Although the use of newer therapies in patients affected by breast cancer has led to an increase in median survival rates, it has also given rise to an increased risk of developing metastases, often after a prolonged disease-free interval varying from 2 to 104 months 1.

Organs most commonly affected by secondary localization (bones, lungs and pleura, liver and central nervous system) are extra-hepatic; in particular, gastrointestinal (stomach and colon) metastases have been described with increasing frequency 2-4.

A frequency of 0.3% of breast cancer patients with secondary localization in the stomach is reported 11,27.

We describe three cases of gastric metastases from breast cancer that have come under our observation in the last few years, all occurring long after the onset of the first malignancy, with differing clinical and histopathological pathways, but unfortunately associated with extensive spreading of the disease and a bad prognosis.

Case report

CASE N. 1

In 1980, patient A.D. (female), aged 59, had undergone Halsted’s mastectomy of the left breast associated with...
ipsilateral axillary lymphadenectomy, for infiltrating lobular carcinoma.

Definitive histological examination showed 3/20 lymph node metastases (pT3N1M0). Receptor status was positive for both ER and PG. The patient was treated with endocrine therapy (tamoxifen); she refused to undergo adjuvant systemic therapy or radiotherapy. There were no distant localizations of the disease at staging examinations.

In 1990 the patient underwent a Patey's modified radical mastectomy for infiltrating ductal carcinoma of the right breast. There were 2/18 lymph node metastases, which were treated with endocrine therapy (tamoxifen). Also in this case, the patient refused to undergo other therapies.

In 1993, vertebral bone metastases appeared at CT and they were treated with locoregional radiotherapy and with anastrozole (endocrine therapy), achieving remission of the clinical features.

The patient was asymptomatic and self-sufficient until April 1998, when she began to present vague dyspeptic disorders such as nausea, anorexia and weight loss; thus she was subjected to esophagus-gastro-duodenoscopy, which showed a picture of plastic linitis of the gastric mucosa; antral, corpus and fundus mucosa biopsies were done, resulting in a suspected neuroendocrine “small cell” carcinoma.

Given these histological features and because of the occurrence of important transit disorders, we decided to perform an explorative laparotomy. Intraoperative exploration of the abdomen confirmed the diagnosis of plastic linitis of the stomach, and so we decided to perform a total gastrectomy with Roux esophagus-jejunal anastomosis. The patient had a good postoperative course with a good recovery of nutrition. The definitive histological examination showed a diagnosis of gastric localization of breast cancer. The patient began hormone therapy and she was asymptomatic until the end of 1999.

In 2000, about 2 years after surgery, the patient died of advanced disease and cachexia.

### CASE N. 2

Patient B.L. (female), aged 68, had undergone Patey's radical right mastectomy with ipsilateral axillary lymphadenectomy for infiltrating lobular carcinoma of the breast in 1986.

There were 2/20 lymph node metastases and receptor status was positive for both ER and PG. There were no distant metastases (pT3 N1M0).

The patient was treated with adjuvant systemic chemotherapy (CMF) and with endocrine therapy (tamoxifen).

### Table 1 - Immunohistochemical diagnosis: Comparison between metastatic breast cancer and primary gastric cancer.

<table>
<thead>
<tr>
<th>Neoplastic markers</th>
<th>Metastatic carcinoma of the breast</th>
<th>Primary gastric cancer</th>
</tr>
</thead>
<tbody>
<tr>
<td>ER</td>
<td>72%</td>
<td>0%</td>
</tr>
<tr>
<td>PR</td>
<td>33%</td>
<td>0%</td>
</tr>
<tr>
<td>GCDFP</td>
<td>78%</td>
<td>0%</td>
</tr>
<tr>
<td>CK 5/6</td>
<td>61%</td>
<td>14%</td>
</tr>
<tr>
<td>CK 7</td>
<td>++</td>
<td>+/-</td>
</tr>
<tr>
<td>CK 20</td>
<td>–</td>
<td>++</td>
</tr>
<tr>
<td>E-cadherin</td>
<td>Absent (positive only in lobular type breast cancer)</td>
<td></td>
</tr>
</tbody>
</table>

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Intraoperative exploration of the abdomen confirmed the diagnosis of plastic linitis of the stomach, and so we decided to perform a total gastrectomy with Roux esophagus-jejunal anastomosis. The patient had a good postoperative course with a good recovery of nutrition. The definitive histological examination showed a diagnosis of gastric localization of breast cancer.

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In 2000, about 2 years after surgery, the patient died of advanced disease and cachexia.
In 1991, (5 years from diagnosis of breast cancer), after the appearance of neurological disturbances, the patient underwent brain CT revealing a single metastasis of the right frontal lobe, which was treated with radiotherapy, with good results. Apparently there were no other distant locations. The patient went on with only hormonal treatment without evident problems.

In 1997, 11 years after the mastectomy, because of the occurrence of dyspeptic disorders such as nausea and anorexia with weight loss, the patient underwent esophago-gastro-duodenoscopy, which yielded a picture of suspected lymphoma of the gastric corpus-fundus. Multiple biopsies were done, and the histological finding was “carcinoma, probably from the breast”.

The patient were subjected to exploratory laparotomy, with intraoperative features of plastic limitis of the stomach and peritoneal carcinomatosis.

The patient started postoperative chemotherapy with no significant results and she died 3 months after surgery.

CASE N. 3

Patient S.T., (female), aged 61, underwent Patey’s right radical mastectomy with ipsilateral axillary lymph node dissection (to third level) for a 2.5 cm infiltrating ductal carcinoma, locally advanced (infiltration of the breast skin), in February 1991.
Histological examination showed 2/21 axillary lymph node metastases. 

Erika and PGrica status was positive. The patient had been subjected to 6 cycles of neoadjuvant chemotherapy with CMFV.

The patient refused postoperative chemotherapy, and she began endocrine therapy with tamoxifen for 5 years until 1996.

The patient was asymptomatic until March 2001, when she was admitted for bone metastases in the spine; because of this, the patient was treated with radiation therapy and was prescribed letrozole and diphosphonates.

In July 2001, the bone scan showed a progression of the disease and the therapy was suspended; the patient began hormone therapy with tamoxifen, which was replaced with exemestane in November 2002.

In May 2003, because of the progression of the disease the patient was subjected to 8 cycles of chemotherapy with fluorofolate and vinorelbina (FNL) and diphosphonates, with good results.

In March 2005, 14 years from the initial diagnosis, the patient presented epigastric pain associated with dyspepsia, and was consequently subjected to esophagous-gastro-duodenoscopy.

Histological examination of the gastric walls showed neoplastic infiltration compatible with breast origin. Erika and PGrica receptors were positive, and Herb2 was unamplified. Surgery was not considered as being indicated in this case, so the patient began chemotherapy with epirubicin. In June 2007, brain metastases appeared; the patient underwent brain radiotherapy and she was treated with fulvestrant. The patient died in July 2007.

Discussion

Gastric metastasis is defined as a secondary invasion of the submucosa, which extends from the mucosa layer to the muscle layer (Fig. 1) 5.

In our cases we could talk about " Cormier's Phase III" (Mayo Clinic), that is, the infiltration of all layers of the gastric wall, from the mucosa to the muscle, with rigidity of the gastric wall, as in plastic linitis.

Sometimes, the metastasis is single, infiltrating the submucosa and the gastric mucosa (Phase II).

Together with malignant melanoma and lung cancer, breast cancer seems to have the greatest capacity to metastasize in the stomach 6.

Both of the most frequently occurring histological types - infiltrating ductal and infiltrating lobular types - seem to be able to metastasize in the stomach; however, the lobular type, which constitutes 10-15% of all breast cancers and which is frequently bilateral or multifocal-multicentric, is certainly the most frequently involved in gastric metastases (in at least 83-85% of cases) 7,9, as in the case of 2 of our patients. Also in the mixed histological type, lobular and ductal, it is the lobular component that tends to metastasize in the stomach.

In Case No. 1, the preoperative histological biopsy diagnosis was "neuroendocrine tumor" with signet-ring cells, especially in lobular carcinoma 10.

The symptoms are usually nonspecific (anorexia in 71% of cases, dyspepsia in 50%, nausea and vomiting in 15% to 41% of cases, epigastric pain in 53% of cases, abdominal distension in 21% of cases, dysphagia in 11% of cases and weight loss in 11% of cases) 11, while sometimes the diagnosis is made during surgery for a perforated ulcer 12. In Case No. 1 and 2, subocclusion was the indication for surgery.

Some cases are clinically advanced, with peritoneal and retroperitoneal carcinomatosis by permeabilization of the serosa, from infiltrating lobular type breast carcinoma 11.

The endoscopic exploration is the test of choice for obtaining a diagnosis of malignancy 13.

Endoscopic pictures are characterized by extremely variable aspects 14, ranging from diffuse forms, such as the plastic linitis type, as in Case No.1 (Fig. 2) 8,15,16 to submucosal solitary nodular lesions, as in Case No. 2; these nodular lesions can also be multiple 17 (Fig. 3).

However, precisely because infiltration is often localized in the deep layers of the gastric wall, biopsy is not significant in 50% of cases 18.

In particular, the stomach can sometimes be the first site of presentation of lobular breast carcinoma metastasis 9, which may be mistaken for undifferentiated medullary gastric cancer with focal neuroendocrine differentiation or for signet ring cell carcinoma.

Currently, because of the need to achieve broad and deep biopsies in suspected breast cancer metastases to the stomach, endoscopy with mucosectomy 19, and in particular echo-endoscopy, seems to be the best diagnostic test 20,21.

The conventional diagnostic tests, such as upper gastrointestinal radiography 22 or CT, because of the nonspecific findings of thickening gastric wall 23, can give only a suspicion of disease. Best results seem to be obtained with MRI 24 or PET CT 16.

Regarding histopathology, the advent of immunohistochemistry has enabled us to distinguish a primary gastric cancer from a metastatic gastric cancer 17.

A high percentage of metastatic breast carcinomas are positive for estrogen receptors- ER (72%) (Fig. 4), progesterin receptors- PG (33%), for Gross Cystic Disease Fluid Protein GCDFP 15 (78%) and for cytokeratin 5/6 (61%) (Figure 5), whereas primitive gastric cancers are negative for all these biological markers. 25 (Table I).

Furthermore, primary breast tumors and their metastases are phenotypically similar 25.

Therefore we can say that primary gastric carcinoma is more frequently positive for CK20 (50%), MUC 2 (54%), MUC5AC (71%), MUC 6 (39%) DAS-1 (43%) and CDX2 (67%) compared with metastatic breast cancer, which shows negativity for all these markers except MUC2, which is positive in 25% of cases.
No other difference was observed for immunohistochemical markers such as the Human Epidermal Growth Factor Receptor 2 protein, CK7, and MUC3. In essence, we can say that primary gastric cancer may also sometimes express hormone receptors for ER and PG, but no primary gastric cancer expresses Er-alpha, and this marker can be used for differential diagnosis (28). Besides, the absence of E-cadherin is associated with lobular carcinoma of the breast (Table I) 28.

Finally, reactivity to CK7 and GCDFP15 expression of hormone receptors, E-cadherin negativity and CK20 and CA 19-9 negativity appear to enable the differentiation between primary gastric cancer and gastric metastasis of lobular carcinoma of the breast.

Our patients No. 1 and 2 were subjected to surgery because immunohistochemical methods were not available, the histological diagnosis was uncertain and also because of their occlusive symptoms. We performed a total gastrectomy and an exploratory laparotomy for the extension of the disease. In Case No. 3, the preoperative diagnosis, which was already a very accurate histopathological and immunohistochemical diagnosis because of the introduction of a new test, did not suggest the need for any surgical measure.

In fact, there is an ongoing debate regarding the indications of the surgical approach and the extent of any resection 26,27. The current approach is to reserve surgery for cases of solitary nodular lesions or in cases of urgency, such as bleeding, obstruction or perforation, in any case without performing widely demolitive surgery. Sometimes we have to effect a jejunostomy to feed the patient.

Radiotherapy is little used on account of the poor results it yields, with responses in about 32% of cases 26; endocrine-therapy and chemotherapy, alone or in combination, seem to allow for the remission of the disease for 10 to 28 months in patients who respond to therapy, with a decent quality of life 11. In conclusion we can say that distant metastatic disease from breast cancer is extremely varied and subtle, and that it often appears after a long disease-free interval, often associated with a wider dissemination in bone, lung or liver.

Sometimes metastatic disease from breast cancer may occur with the histological features of the primary gastric cancer (a diagnosis obtained in the past only by histological examination of the final specimen). Besides, we have to say that in several autopsy studies of patients with disseminated disease, gastrointestinal extrahepatic locations are extremely common, representing 2-18% of postmortem investigations 29.

The advent of immunohistochemistry has enabled a more accurate and reliable preoperative histopathological differential diagnosis that is able to confirm the clinical and endoscopic suspicion. The recent discovery of new cytotoxic drugs, new combinations and optimization of the dosing schedule seem to lengthen the disease free survival (DFS) and to improve the overall survival of these patients, reserving surgery for selected cases, especially those with complications.

**References**


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