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

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

Gastric metastases of breast cancer represent a not so rare event in patients affected. In fact, it occurs in 0.3% of cases.
Although the introduction of new adjuvant therapies has given rise to an increase in disease free survival and overall survival rates, it has also led to more frequent occurrences of breast cancer metastatic lesions localized in bone, lung/pleura and liver, but above all in the stomach.
The authors present three cases of patients suffering from breast cancer with secondary gastric neoplastic lesions from lobular and infiltrating ductal breast cancer. Lobular breast cancer is the histological type mostly involved in disseminated disease, with an incidence of 85% of cases.
A review of the literature reveals that authors address the clinical and diagnostic problems of differentiating between a breast cancer metastasis to the stomach and a primary gastric cancer using recent diagnostic strategies to make an early diagnosis. Today practitioners have specific tests to detect early gastric cancer metastases of breast cancer such as endoscopic ultrasound, which provides a better endoscopic definition of the lesions, and immunohistochemical markers, able to distinguish the primary lobular histological type from ductal cancer.
Besides, an early diagnosis associated with the latest adjuvant systemic therapies and hormonal treatment, alone or in combination, may grant affected patients a remission with a survival rate of 10-28 months, and a reasonable quality of life. At present the surgical approach should be reserved for selected cases and/or complications.

KEY WORDS: Breast, Gastric cancer, Metastasis.

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].

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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

TABLE I - *Immunohistochemical diagnosis: Comparison between metastatic breast cancer and primari gastric cancer.*

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

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).

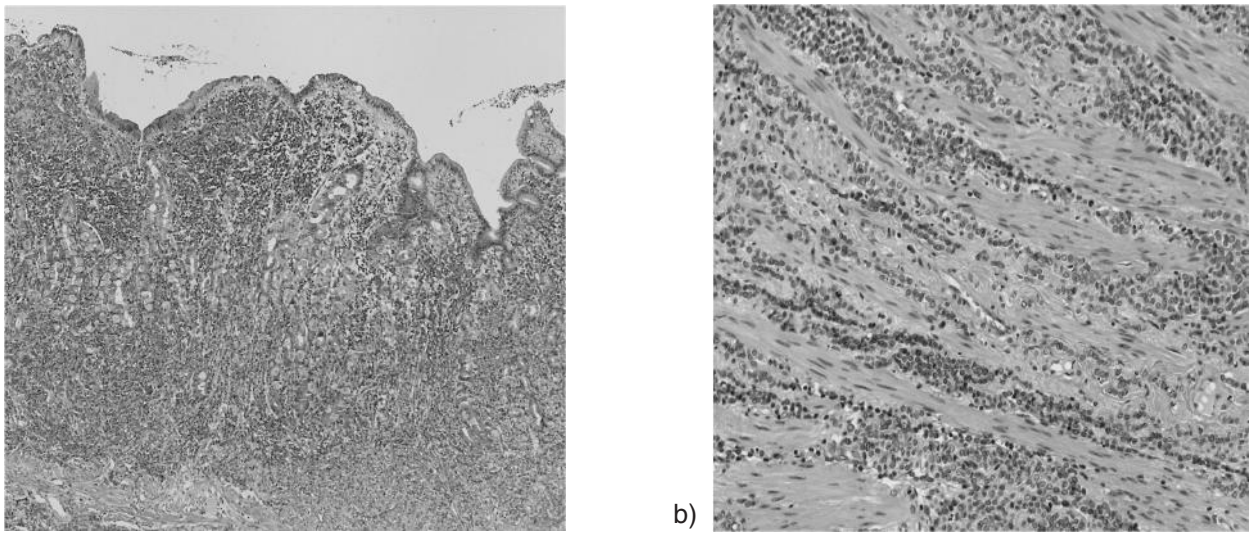

Fig. 1 : a) Infiltration of the gastric mucosa and submucosa (EE), magnification 10X; b) Tumor infiltration of the muscle tunica of the gastric wall (EE), magnification 20X.

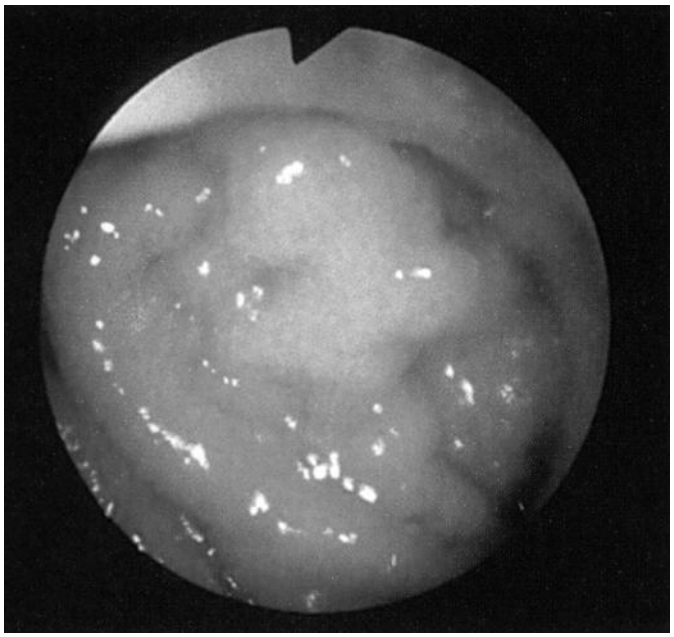

Fig. 2: Gastric breast cancer metastasis with the appearance of plastic linitis.

Fig. 3: Intragastric breast cancer metastasis with the appearance of a sessile polypoid lesion.

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 linitis of the stomach and peritoneal carcinomatosis.
The patient started postoperative chemotherapy with no significant results and she died 3 months after surgery.

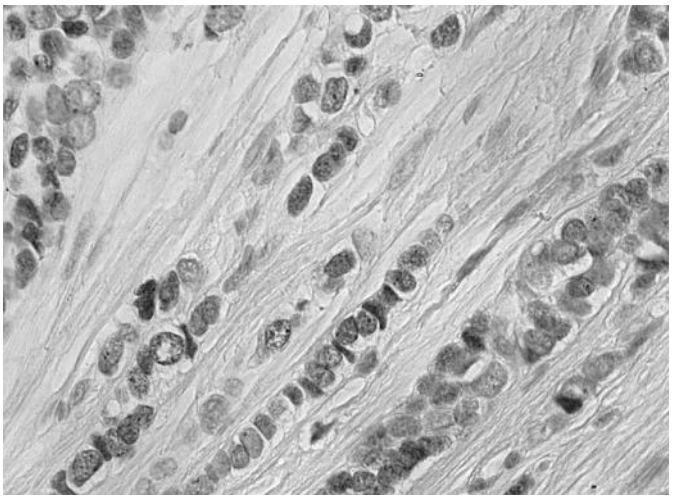

Fig. 4: Estrogen receptors (gastric mucosa), magnification 40x.

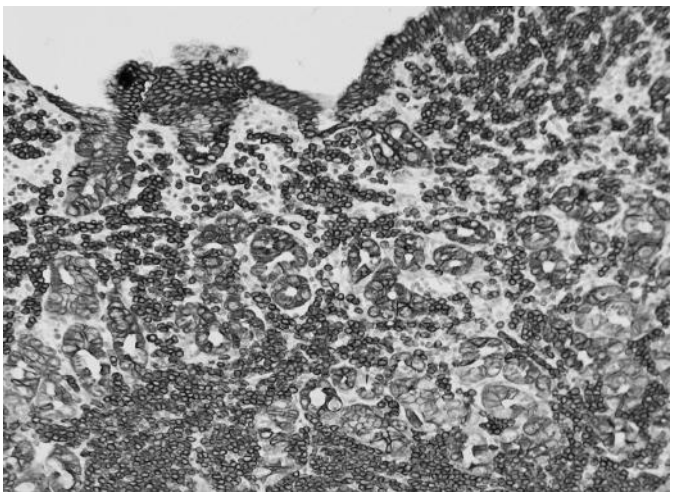

Fig. 5: Cytocheratin receptors (gastric mucosa) magnification 20x.

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.
Erica 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 vinerelbina (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. Erica 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 gastrointestinal tract [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), progestin 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.

Riassunto

Gli Autori presentano tre casi clinici di metastasi allo stomaco di cancro della mammella. Questo tipo di lesioni secondarie ha un'incidenza dell'0.3%, senza sintomi specifici nei soggetti colpiti. Possiamo trovare lesioni metastatiche allo stomaco nel 2-18% delle pazienti che sono decedute per un cancro della mammella.Non ci sono differenze nel tasso di incidenza nei diversi sottotipi istologici di cancro della mammella, sebbente il tipo di cancro lobulare infiltrante è quello più frequentemente coinvolto, con un'incidenza del 83-85% dei casi. Lo scopo che gli Autori si propongono nell'analizzare i casi clinici osservati, come è anche affermato nella letteratura, è di mettere in risalto l'importanza estrema di una distinzione precoce tra le lesioni secondarie allo stomaco di un cancro della mammella e le lesioni primitive proprie dello stomaco, facendo uso delle moderne tecniche endoscopiche (ecografia endoscopica) ed dei metodi immunoistochimici per evidenziare i marker neoplastici specifici.Infatti con una appropriata terapia adiuvante sistemica ed un trattamento ormonale di recente introduzione, si ottiene una sopravvivenza di 10-28 mesi con una ragionevole qualità di vita. L'impiego del trattamento chirurgico come approccio iniziale è controverso in casi del genere. La chirurgia andrebbe utilizzata solo in selezionati casi complicati, a scopo palliativo oppure nei casi in cui le metastasi sul tratto intestinale siano resecabili.

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