CASE REPORT
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BREAST METASTASIS OF GASTRIC SIGNET RING CELL CARCINOMA MIMICKING BREAST LYMPHANGITIC CARCINOMATOSIS

Metástase mamária de carcinoma gástrico em anel de sinete simulando linfangite carcinomatosa da mama

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ABSTRACT

Introduction: The incidence of breast metastasis from gastric adenocarcinoma is extremely low. Since 1908, 44 cases have been reported in the literature, of which 30 are signet ring cell type. **Case report:** A 49-year-old patient being investigated for digestive bleeding was found to have left axillary lymphadenopathy, associated with breast asymmetry, associated with breast asymmetry, edema and thickening of the skin. Breast ultrasonography showed a heterogeneous lesion in the left breast. Core biopsy histology was compatible with Lauren diffuse gastric adenocarcinoma with signet ring cells. There was positive immunohistochemical staining for CK7, CK20 and CDX2 and negative for RE, RP and ERB2. Our findings were compatible with gastric adenocarcinoma (lymphatic embolism), favoring the possibility of a secondary neoplasm. At the time of diagnosis, the patient already had radiological signs of multiple metastases. **Discussion:** Breast metastases of gastric carcinoma differ from primary breast cancer in histopathological features. The clinical manifestations of gastric cancer metastasis vary, but it is known that there is a greater tendency for inflammatory disorders compared to primary tumors. In the metastatic process, breast involvement may be the first event or occur in a context of multiple metastases. Most patients have a one-year survival after diagnosis. There is no gain in survival with breast surgery, but it can alleviate the symptoms in some cases. **Conclusion:** Gastric cancer with breast metastasis is a rare condition associated with poor prognosis. The diagnosis is based on clinical history, histological findings and immunohistochemical markers, differing from primary tumors of the breast, to provide patients with adequate treatment.

KEYWORDS: breast neoplasm; metastasis; stomach neoplasms; carcinoma, signet ring cell; immunohistochemistry.

RESUMO

Introdução: A incidência de metástase mamária de adenocarcinoma gástrico é extremamente baixa. De 1908 até o momento, 44 casos foram relatados na literatura, dos quais 30 são do tipo em anel de sinete. **Relato do caso:** Paciente de 49 anos em propedêutica de sangramento digestivo alto. Apresentava linfadenomegalia axilar esquerda, associada a assimetria mamária, edema e espessamento de pele. Ultrassonografia mamária evidenciou lesão heterogênea em mama esquerda. Histologia de *core biopsy* da área compatível com adenocarcinoma gástrico tipo difuso de Lauren, com células em anel de sinete. Imuno-histoquímica positiva para pancitoqueratinas CK7, CK20, CDX2 e negativa para RE, RP e ERB2. Achados compatíveis com adenocarcinoma gástrico (embolia linfática), favorecendo a possibilidade de neoplasia secundária. Ao momento do diagnóstico, a paciente já apresentava sinais radiológicos de múltiplas metástases. **Discussão:** As metástases mamárias do carcinoma gástrico diferem do câncer de mama primário nas características histopatológicas. As manifestações clínicas das metástases de câncer gástrico são variadas, mas é sabido que há tendência maior de alterações inflamatórias que nos tumores primários. No processo metastático, o envolvimento mamário pode ser o primeiro evento ou ocorrer em um contexto polimetastático. A maioria dos pacientes tem sobrevida inferior a

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um ano. Não há ganho de sobrevida com a cirurgia de mama, mas ela pode aliviar os sintomas em alguns casos. **Conclusão:** O câncer gástrico com metástase na mama é uma condição rara associada a mau prognóstico. O diagnóstico é baseado em história clínica, achados histológicos e marcadores imuno-histoquímicos, o que diferencia a metástase de um tumor primário da mama, a fim de oferecer aos pacientes o tratamento adequado.

PALAVRAS-CHAVE: neoplasias da mama; metástase neoplásica; neoplasias gástricas; carcinoma de células em anel de sinete; imuno-histoquímica.

INTRODUCTION

Breast metastases of gastric carcinoma are extremely rare events. Forty-four cases of this condition are described in the literature. Clinically and radiologically, metastatic tumors resemble primary breast tumors. The correct diagnosis of breast metastasis is of fundamental importance for the proper treatment of the disease. Lymphatic dissemination is the likely mechanism of metastasis.

CASE REPORT

A female patient, 49 years old, was hospitalized for the diagnosis of digestive hemorrhage, where gastric malignancy was suspected, and she was still awaiting anatomopathological confirmation. She had axillary lymphadenomegaly, so a lymph node biopsy was requested. On examination, there was breast asymmetry (left breast larger than right) and edema in the lateral third to the left breast nipple-areola complex, without hyperemia or palpable nodules (Figure 1). Left axillary lymphadenomegaly with hardened and fixed lymph nodes was observed. There were free supra- and infraclavicular fossa and absence of nipple discharge. Imaging examinations were requested.

Chest, abdomen and pelvic tomography yielded multiple findings: cervical lymphadenomegaly, bilateral and axillary inferior paratracheal; paramediastinal septal thickening in right upper pulmonary lobe suspected of carcinomatous lymphangitis; massive bilateral pleural effusion; nonocclusive thrombosis of the left subclavian vein; stenosing concentric parietal thickening, ulcerated in antrum and gastric pylorus; atypical lymphadenomegaly in portal hepatic, infrapyloric and mesenteric chain; sclerotic nodules in the bone marrow of the T6 and T11 vertebrae and in the right iliac bone, and the possibility of secondary neoplasia needed to be considered.

A mammogram showed skin thickening and predominance of dense fibroglandular tissue, without other relevant findings — CAT 2 Breast Imaging Reporting and Data System (BI-RADS®) (Figure 2).

Breast ultrasound revealed a heterogeneous area with poorly defined margins in the upper left breast quadrant junction, measuring 13 × 19 × 0.9 mm, with posterior acoustic shadow, and pathological left axillary lymph nodes — CAT 4 BI-RADS® (Figure 3).

A core biopsy from a suspected area was performed and histology was consistent with diffuse gastric adenocarcinoma

Figure 1. Clinical presentation: breast edema and skin thickening.

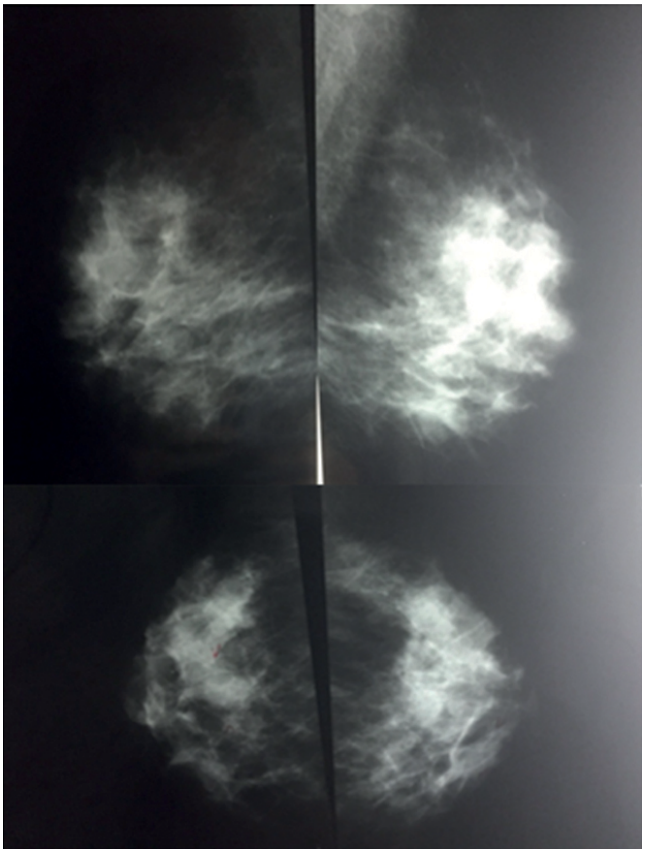


Figure 2. Mammogram.

according to Lauren, with signet ring cells (Figures 4A and 4B). An immunohistochemical study revealed immunopositivity for pancytokeratins CK7, CK20 CDX2 (Table 1, Figures 5A and 5B). Findings were compatible with gastric adenocarcinoma (lymphatic embolism). Negativity for RE and PR favored the possibility of secondary neoplasia, with the stomach being a possible primary site.

The anatomopathological examination of the gastric biopsy confirmed diffuse gastric adenocarcinoma Lauren of the signet ring cell type. The patient had poor performance status and was referred to oncology for consideration of palliative chemotherapy.

DISCUSSION

Breast metastases from non-breast sites are rare events, accounting for 0.3–2.7% of all malignant breast tumors[1-3]. Melanomas and lymphomas are the main sources of breast metastases, followed by lung, ovarian, kidney, stomach, oropharynx and carcinoid tumors[4]. Regarding breast metastasis from gastric cancer, including the present report, there are only 44 cases reported in the literature, as described in Table 2. Of these, 66.6% (30) are signet ring cell type, which corresponds to only 10% of all gastric cancers. The median age of presentation of this rare condition is 46 years, younger than the average diagnosis of primary breast cancer (which is 56 years[21]).

Gastric cancer metastases in the breast are mostly of the signet ring cell type and should be distinguished from primary breast signet ring cell carcinomas, which were first described as a subtype of lobular tumors by Steinbrecher and Silverberg in 1976[5]. Primary breast signet ring cell carcinomas have aggressive biological behavior and a higher tendency for metastasis to the abdomen. Still, cases of metastasis to the stomach have been described[6-8].

Breast metastases from gastric carcinoma differ from primary breast cancer in histopathological features. Immunohistochemical findings are generally negative for estrogen and progesterone receptors, and for c-erbB-2 as well. There are no signs of *in situ* component or loss of desmoplastic response. In contrast, lymphatic emboli and epithelial markers such as CK7, CK20 and CEA are usually present[9,10].

The clinical manifestations of gastric cancer metastases reported in the literature are varied. Of the 44 cases described, 22 were clinically palpable nodules and 11 had inflammatory changes. Chang et al.[11] reported that the incidence of inflammatory changes (local redness, swelling, bumps or warmth)

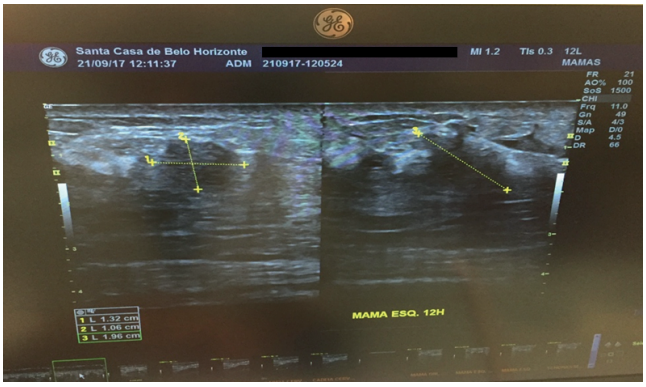
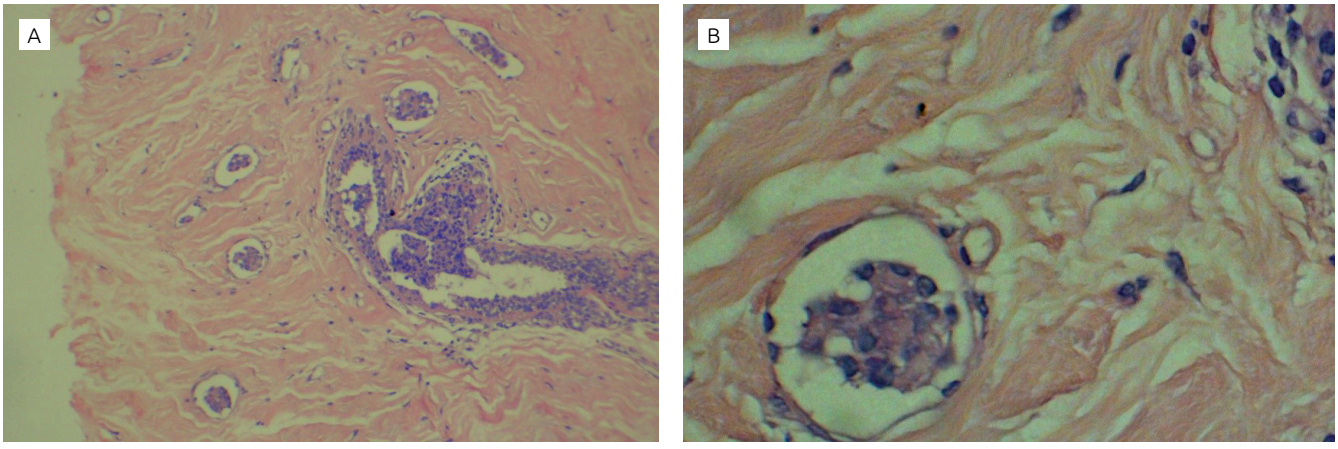


Figure 3. Breast ultrasound.

Table 1. Immunohistochemical study of core biopsy fragment.

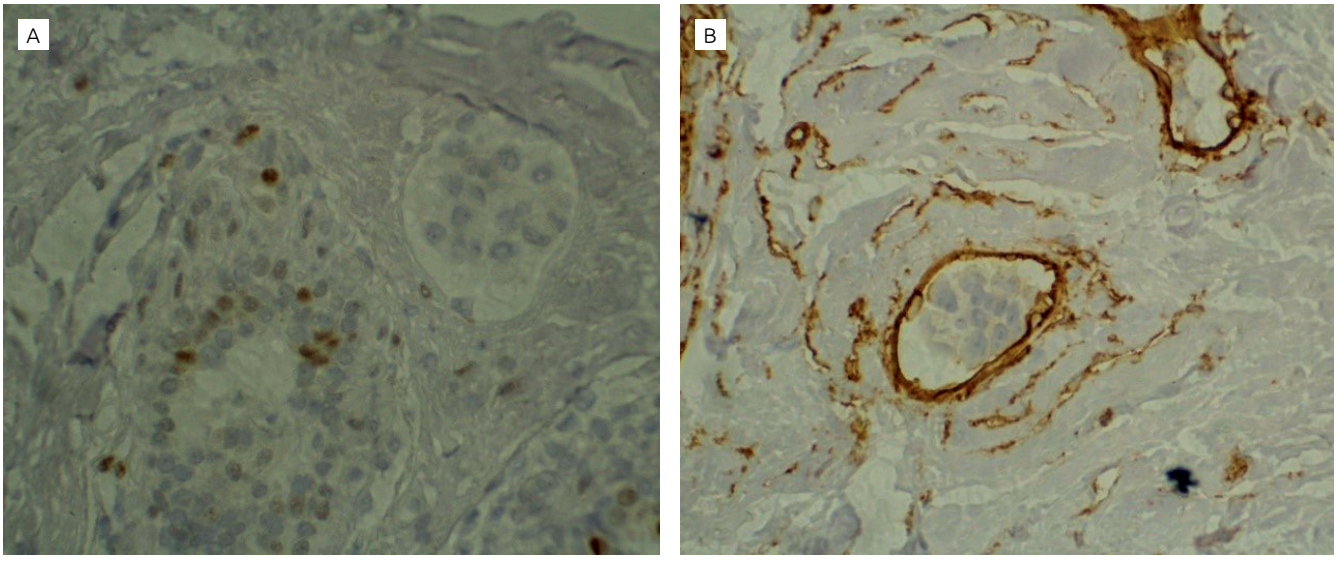
Antibody	Result	Antibody	Result
Pancytokeratins	+	CDX2	+
KI67	+ (30%)	RE	-
CK7	+	RP	-
CK20	+	HER-2/neu	-
CD34	+		

Source: Dr. Maurício Buzzellin of the Pathological Anatomy Laboratory, Santa-Casa de Belo Horizonte.



Source: Dr. Maurício Buzzellin of the Pathological Anatomy Laboratory, Santa-Casa de Belo Horizonte.

Figure 4. (A) Anatomopathological examination of core biopsy fragment; (B) Anatomopathological examination of core biopsy fragment at higher magnification. Note lymphatic embolism with signet ring cell.



Source: Dr. Maurício Buzzellin of the Pathological Anatomy Laboratory, Santa-Casa de Belo Horizonte.

Figure 5. (A) Immunohistochemical staining. Note the immunonegativity for RE; (B) Immunohistochemical staining. Note the immunopositivity for CD34.

Table 2. Forty-four cases of breast metastasis from gastric cancer reported in the literature*.

Authors	Sex	Age	Histological type	Clinical presentation of breast lesion
Reitmann[a]	F	33	Scirrhous carcinoma	–
Kreibich[a]	F	65	Scirrhous carcinoma	–
Mourier et al.[a]	F	31	Mucinous carcinoma	–
Stahr[a]	M	46	Anaplastic carcinoma	–
Dawson[a]	F	25	Mucinous carcinoma	–
Abrams et al.[a]	F	–	–	–
Sandison[a]	F	56	Signet ring cell carcinoma	–
Nance et al.[a]	F	59	–	Inflammatory
Hajdu et al.[a]	F	–	Adenocarcinoma	–
Schmutzer et al.[a]	F	22	Poorly differentiated adenocarcinoma	Nodules
Silverman et al.[a]	F	–	Mucin-producing carcinoma	–
Toombs et al.[a]	F	–	–	–
Satake et al.[a]	F	39	Signet ring cell carcinoma	Nodule
Togo et al.[a]	F	70	Signet ring cell carcinoma	Nodule
Nielsen et al.[a]	F	59	Mucinous carcinoma	Nodules
Champault et al.[a]	F	65	Adenocarcinoma	Nodule
Kasuga et al.[a]	F	48	Signet ring cell carcinoma	Nodules
Tachibana et al.[a]	F	46	Signet ring cell carcinoma	–
Alexander et al.[a]	F	28	Mucinous carcinoma	Nodules
Hamby et al.[a]	F	31	Signet ring cell carcinoma	Nodule
Mishina et al.[a]	F	36	Signet ring cell carcinoma	–
Cavazzini et al.[a]	F	50	Signet ring cell carcinoma	Inflammatory
Domanski[a]	F	48	Signet ring cell carcinoma	Nodule
de la Cruz Mera[a]	F	61	Signet ring cell carcinoma	Nodule

Continue...

Table 2. Continuation.

Authors	Sex	Age	Histological type	Clinical presentation of breast lesion
Briest et al.[a]	F	46	Signet ring cell carcinoma	Inflammatory
Kudo et al.[a]	F	46	Signet ring cell carcinoma	Nodule
Kwak et al.[4]	F	41	Signet ring cell carcinoma	Inflammatory
Kwak et al.[4]	F	23	Signet ring cell carcinoma	Inflammatory
Madan et al.[a]	F	39	Signet ring cell carcinoma	Nodule
Di Cosimo et al.[a]	F	39	Signet ring cell carcinoma	Nodule
Boutis et al.[13]	F	37	Signet ring cell carcinoma	Inflammatory
Qureshi et al.[a]	F	34	Signet ring cell carcinoma	Nodule
Isobe et al.[a]	F	48	Signet ring cell carcinoma	Nodule
Hasegawa et al.[a]	F	61	Signet ring cell carcinoma	Nodule
Makni et al.[12]	F	40	Signet ring cell carcinoma	Nodule
Gugić et al.[a]	F	43	Signet ring cell carcinoma	Nodule
Sato et al.[19]	F	67	Signet ring cell carcinoma	Inflammatory
Cil et al.[a]	F	63	Signet ring cell carcinoma	Inflammatory
Cil et al.[a]	F	65	Signet ring cell carcinoma	Inflammatory
Iesato et al.[10]	F	41	Signet ring cell carcinoma	Inflammatory
Iesato et al.[10]	F	34	Signet ring cell carcinoma	Nodule
He et al.[20]	F	48	Signet ring cell carcinoma	Nodule
Wei et al.[17]	F	49	Signet ring cell carcinoma	Nodule
Tian et al.[5]	F	39	Signet ring cell carcinoma	Nodule

*Clinical information is given in in the table only if available from the authors. Inflammatory: indicating redness, swelling, tightness or warmth in the chest; - not described; [a]references included in [10]; F: females; M: male.

in gastric carcinoma breast metastasis was at least four times higher than in primary breast cancer.

Imaging diagnosis of breast metastasis from gastric carcinoma can be flawed. Mammograms can show circumscribed nodules and skin thickening, and ultrasound can identify irregular hypoechoic nodules, diffuse irregular areas, and skin thickening, but none of the examinations can show significant changes.

In this case, the patient had left breast edema associated with skin edema (*peau d'orange*) without hyperemia or palpable nodules. Tomography revealed left subclavian vein thrombosis, which could be one of the differential diagnoses of clinically noted breast asymmetry.

Usually about 40% of breast metastases are found during or up to one year after the diagnosis of the primary site[10]. In the metastatic process, breast involvement could be the first event or occur in a polymetastatic manner[12]. In a literature review covering 41 cases of gastric cancer metastasis to the breast, 28 patients had other metastasis sites, including axillary, supraclavicular, ovarian, peritoneal, pleural, hilar lymph nodes and liver, among others[10].

Selective invasion of hormone-dependent organs (ovaries, breast) especially in premenopausal women is intriguing[9]. Some authors propose that breast blood supply is the mechanism for the increased incidence of breast metastasis in premenopausal women[13,14]. However, another explanation may be the fact that gastric cancer has a more aggressive biological behavior in younger groups[15]. The appearance of breast metastases in men with gynecomastia supports the latter hypothesis[16].

The prognosis of patients with breast metastases from gastric carcinoma is quite poor. Most patients survive less than one year after the diagnosis of breast metastasis[1]. Systemic treatments include neoadjuvant chemotherapy appropriate for the primary tumor and curative or palliative surgery for the primary cancer or breast metastasis[17]. There is no survival gain with breast surgery, but it can alleviate symptoms in some cases[18,19].

CONCLUSION

The present case represented an extremely rare condition, with few cases reported in the literature, usually associated with poor prognosis. In cases of breast tumors showing the presence of signet ring cells without associated *in situ* lesions, the possibility of gastric cancer should be considered. Clinical history and anatomopathological and immunohistochemical examinations are important to distinguish metastatic cancer from primary breast cancer, allowing patients to receive appropriate treatment.

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