

Case Report

Breast Metastasis of Gastric Signet Ring Cell Carcinoma: A Case Report and Literature Review

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Keywords

Breast metastasis · Signet ring cell · Gastric carcinoma · Chemotherapy

Abstract

Breast metastasis from gastric signet ring cell carcinoma is extremely rare in clinical practice. The estimated incidence is 0.5–1.3%. There are few cases reported in the literature (approx. less than 60) of breast metastasis from gastric signet ring cell carcinoma, and due to the rare association between gastric cancer and its extension to the breast, it is difficult to establish the diagnosis. Clinical history, histological findings, and immunohistochemical markers are helpful in distinguishing primary breast cancer from breast metastasis of gastric cancer. The treatment for breast metastasis from gastric carcinoma remains controversial. The prognosis of breast metastasis from gastric carcinoma is generally poor. We report a case of breast metastasis of gastric signet ring cell carcinoma in a 38-year-old woman. She started chemotherapy with ramucirumab, paclitaxel, and irinotecan. Three months later, a combined 2-[¹⁸F]-fluoro-2-deoxy-D-glucose positron emission tomography/computed tomography showed a complete response. This is the first reported case of breast metastasis from gastric signet ring cell carcinoma with a complete response.

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Published by S. Karger AG, Basel

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Introduction

Mammary metastases from extramammary neoplasms are infrequent, even more so in the case of gastrointestinal tumors as the origin. The estimated incidence is 0.5–1.3%, and up to 6.6% in autopsy series [1, 2]. They represent a diagnostic challenge, where clinical examination is not enough and additional tools are required, such as performing immunohistochemistry on the pathology specimen, to establish a definitive diagnosis [1].

Approximately less than 500 cases of metastasis of solid tumors to the breast have been described so far [3]. Gastric cancer has been reported as the cause in the scarce literature, being the main association with the signet ring cell subtype in young women, and mainly on the left side [1, 3]. In previous decades, reports on this subject were minimal and primarily limited to case reports. At present, little is known about the clinicopathological features and prognosis of this condition, and breast metastasis remains a challenging clinical problem. Previous studies have demonstrated treatment strategies including intensive multiagent chemotherapy, surgery, radiation, and targeted therapy; however, the treatment strategies for achieving complete remission or partial remission remain controversial [1–4].

As breast metastasis from gastric carcinoma is rare, increased awareness is necessary, and this possible diagnosis should be considered when patients with a history of gastric cancer detect a new breast mass. We present the case of a patient in the fourth decade of life with breast metastasis due to gastric signet ring cell carcinoma, an interesting and unusual presentation of gastric cancer.

Case Report

A 38-year-old woman with no relevant history started in June 2018 with intense left flank pain, dyspepsia, early satiety, and bloating, without improvement with medical management. Due to the persistence of the symptoms, she went to a gastroenterologist, who performed an endoscopy. It showed the presence of an ulcer in the gastric antrum, without active bleeding. Biopsies were taken during the procedure. The pathology report demonstrated a moderately differentiated gastric adenocarcinoma with signet ring cells and a test positive for *Helicobacter pylori*. The molecular analysis showed a HER2-negative and mismatch repair-proficient tumor (Fig. 1).

An additional work-up included a transthoracic echocardiogram that demonstrated a preserved left ventricular ejection fraction and a 2-¹⁸F-fluoro-2-deoxy-D-glucose positron emission tomography/computed tomography (¹⁸F-FDG-PET/CT) showed evidence of retroperitoneal and left supraclavicular lymphadenopathy (Fig. 2A, B). An ultrasound-guided fine-needle aspiration biopsy of the left supraclavicular node was carried out and resulted positive for malignancy. According to the results, the disease was unresectable and port catheter placement was decided.

The patient received first-line chemotherapy for advanced disease with epirubicin, oxaliplatin, and capecitabine (EOX) for 4 cycles until December 2018. Afterward, the response was evaluated at the end of the fourth cycle, showing a partial response (Fig. 2C). In February 2019, she developed a right breast lump of approximately 3 cm, in the absence of inflammatory changes, which was mobile and tender on physical examination and without palpable lymphadenopathy. Renewed ¹⁸F-FDG-PET/CT showed progression of the disease with retroperitoneal and right iliac lymphadenopathy, as well as evidence of a right breast tumor (Fig. 2D–F). Subsequently, a breast ultrasound was performed, which classified the lesion as BI-RADS 4C, so a biopsy was taken, with a pathology report of poorly differentiated carcinoma with signet ring cells, metastatic to the breast, compatible with gastric carcinoma (HER2 negative and with a Ki-67 proliferation index of 50%) (Fig. 3).

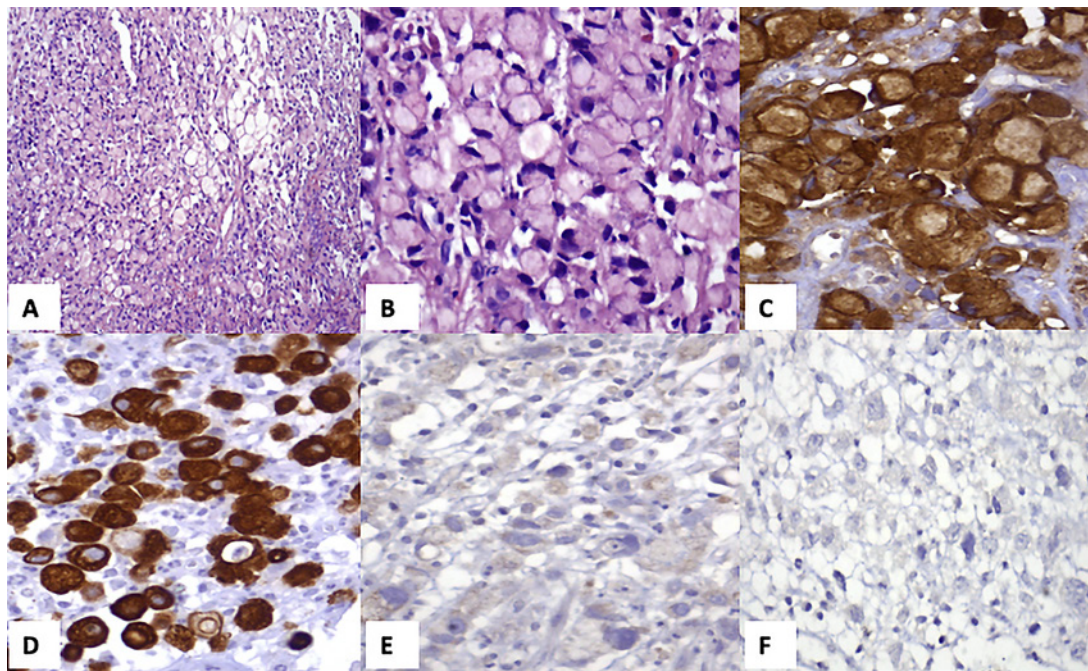


Fig. 1. **A, B** Hematoxylin and eosin stains. **A** Medium magnification ($\times 20$). **B** High magnification ($\times 40$). Infiltrating malignant neoplasm composed of signet ring cells, with the nucleus rejected to the periphery and the cytoplasm with a single vacuole of mucin. **C–F** Immunohistochemistry. **C, D** Positive for ACE and CK20. **E, F** Negative for GATA3 and estrogen receptors.

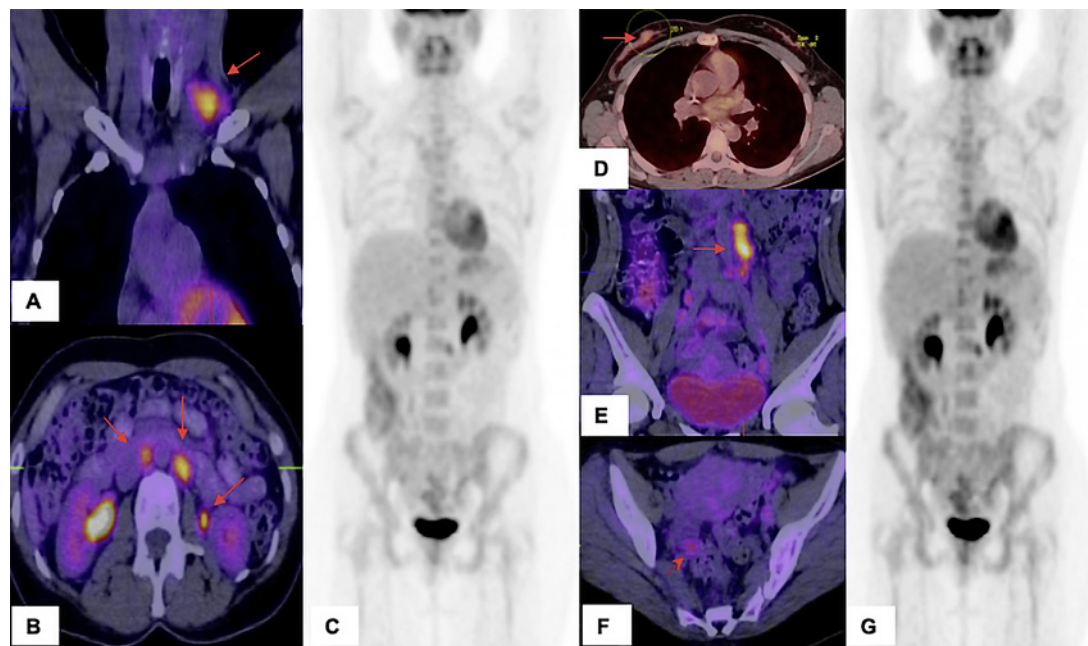


Fig. 2. Combined 2- ^{18}F -fluoro-2-deoxy-D-glucose positron emission tomography/computed tomography showed: increased uptake in retroperitoneal and left supraclavicular lymphadenopathy (**A, B**, arrows); partial response with chemotherapy (**C**); progression of the disease with retroperitoneal and right iliac lymphadenopathy, as well as evidence of a right breast tumor (**D–F**, arrows); and a complete response to second-line chemotherapy (**G**).

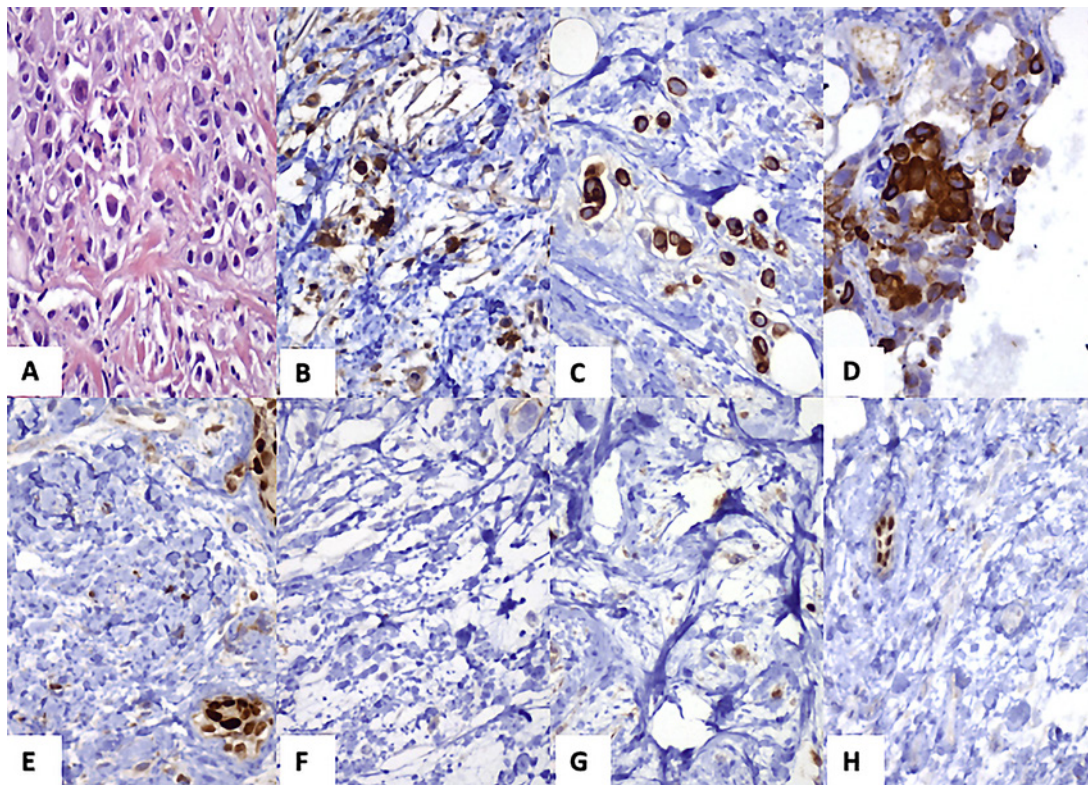


Fig. 3. **A** Hematoxylin and eosin stain. High magnification ($\times 40$). Neoplastic cells with the nucleus rejected to the periphery and with a single vacuole cytoplasm with mucin in a signet ring aspect. Nuclear atypia with hyperchromatism. **B–H** Immunohistochemistry. **B–D** Positive for ACE, CK7, and CK20. **E–H** Negative for GATA3, Her2/Neu, mammaglobin, and estrogen receptors.

The patient started second-line treatment with ramucirumab, paclitaxel, and irinotecan. Three months later, ^{18}F -FDG-PET/CT showed a complete response (Fig. 2G). In July 2019, she was rushed to the emergency room because of severe incoercible headache associated with confusion and daytime sleepiness. A thoracoabdominal CT was performed, without evidence of disease, as well as skull MRI, which displayed two intra-axial lesions of less than 2 cm. They were treated by Gamma knife without complications. It was decided to continue with the same chemotherapy regimen for clinical benefit.

However, a month later, she presented palpitations and dyspnea at rest. She was taken again to the emergency department, where she suffered cardiorespiratory arrest and died.

Discussion

According to the World Health Organization, breast cancer is one of the most common neoplasms worldwide, affecting 2.1 million women each year [5]. In contrast, the spread of another solid tumor to this location is very unusual. It is calculated that between 0.5 and 2% of patients will present metastasis to the breast, mainly originating from melanoma, lymphoma, and lung and ovarian cancer, and the estimated rate of occurrence in autopsy series is 1.7–6.6%. Gastrointestinal tumors are among the least frequent causes. Common sites of distant metastasis of gastric cancer include the peritoneum, liver, lymph nodes, and lungs [6–9].

The mechanism through which gastric cancer has the ability to metastasize to the breast is unknown. A role for estrogens, which could promote tumor cell proliferation in an extramammary region, mediated through ER- β , has been proposed as a possible mechanism, especially in patients with signet ring cell adenocarcinoma [10, 11]. Likewise, the abundant blood flow to breast tissue has been described as part of the pathogenesis, mostly in premenopausal women [12–14].

There are few cases reported in the literature (approx. less than 60) of breast metastasis from gastric signet ring cell carcinoma, and due to the rare association between gastric cancer and its extension to the breast, it is difficult to establish the diagnosis. Most of the patients are from Asian countries and the published case reports are observational in nature, focusing principally on the clinical presentation and immunohistochemical characteristics [14–16].

According to available data, the majority of cases are women between 22 and 70 years old, with a mean age of 46 years; in a review of 54 patients, they were even younger, around 43 years old. The same review exposed a relationship between age and overall survival, the prognosis being better if patients were younger than 45 years with statistical significance ($p = 0.001$) [1, 7]. Comparatively, the average age with the highest incidence of breast cancer is usually 62 years in the USA and between 50 and 59 years in Mexico, representing 45% of all cases, so it seems that patients with gastric cancer metastatic to the breast are affected at younger ages [1, 7, 17, 18] and most of them are premenopausal women [19]. Approximately 40% of cases are diagnosed in the first year after the identification of the primary tumor [7], within an average time of 1.25 months [1], showing that the disease has an aggressive behavior.

In regard to the clinical manifestations, the data are less precise. Invasion of the breast as an initial presentation occurs in 25–40% of cases, with a palpable, mobile, well-defined, and solitary mass being found in more than half of the patients, followed by inflammatory changes in the affected breast [1, 14, 20, 21], the latter with a calculated incidence at least 4 times higher than in patients with primary breast tumors [20]. Likewise, it has been reported that more than 50% of patients with this pathology have greater involvement of the left side, and up to 60% are located in the upper external quadrant of the breast [1, 22]. There is a hypothesis that the preference of the tumor for this site may be due to a higher incidence of invasion of breast tissue through the left supraclavicular nodes [1, 6, 7, 19]; however, the mechanism is not well understood. The preference for laterality has also been related to prognosis [1].

Some authors have suggested various differential diagnostic features on radiologic images to distinguish metastatic extramammary neoplasms from primary breast cancer. Metastatic carcinomas to the breast have relatively well-circumscribed and freely movable masses. In the available imaging studies, mammography has usually been performed. The lesions tend to be heterogeneous and without specific findings that suggest a diagnosis. The mass is usually round, well defined, and in some cases presenting with calcifications. It may also resemble a benign breast lesion [13, 23, 24]. Ultrasound results including skin thickening and breast nodules, indistinguishable from those of primary breast cancer, were unassociated with overall survival time ($p > 0.05$), which suggests that it is difficult to diagnose metastatic breast cancer by clinical presentation or diagnostic imaging [1].

The definitive diagnosis is complicated, being established based on the immunohistochemical characteristics and similarities between the primary gastric tumor and the breast lesion under study, although with limited sensitivity. Differentiation between a primary breast neoplasm and a metastatic tumor is extremely important, since the treatment approach may impact the prognosis [1, 3].

The pathologic findings of metastatic breast lesions include atypical histological features, the presence of many lymphatic tumor emboli, a periductal and perilobular distribution

without signs of hyperplasia or atypia, lack of a desmoplastic response, and absence of ductal carcinoma in situ and elastosis [13, 25, 26].

The most reported stains show positivity for carcinoembryonic antigen, CK7, and CK20, and the absence of markers such as hormone receptors and GCDFP15 (gross cystic disease fluid protein-15) [1, 12, 14]. Nevertheless, cytokeratins alone are not sufficient to make the differential diagnosis of primary metastatic tumors [11, 23–28], while special stains particularly for hormonal receptors (estrogen and progesterone receptors) and GCDFP15 are considered specific for metastatic breast carcinomas [11, 24]. The presence of signet ring cells in a breast specimen forces one to rule out a primary gastric tumor as the origin [10], although the possibility of a primary breast tumor with signet ring cells is possible [21]. Histologically, approximately 66% of cases of breast metastases have shown signet ring cell carcinoma, a type that accounts for approximately 10% of gastric cancers [29]. Other frequently related characteristics that increase the risk of metastasis to the breast are T4 tumors, lymph node involvement, primary lesions of the antrum, and stage IV disease at diagnosis [1].

Ma et al. [1] reported that the median interval between diagnosis of the primary disease and identification of the metastatic lesion was only 1.25 months. This result indicates that gastric carcinoma with breast metastasis progresses rapidly and that the potential for metastasis from gastric carcinoma is high, even in patients with no history of gastric cancer.

Its treatment is controversial, even though systemic treatment is being considered the priority. However, previous advances in the development of anticancer agents, including trastuzumab and apatinib, have improved the prognosis of patients with unresectable advanced or recurrent gastric cancer [12, 30]. Although there are no current clinical case reports to confirm this, to the best of our knowledge, these novel drugs may be effective in treating this rare disease.

In contrast, the role of surgery is not well defined, and surgery may not impact survival and rather have a palliative role [21, 28, 31]. The prognosis is usually poor, with the mortality rate greater than 80% in the first year [7]. The reported median overall survival is about 8.6 months [1], with a range of 12 days to 18 months [12]. Early and accurate diagnosis of secondary breast involvement is important for appropriate management and for avoiding unnecessary and potentially harmful treatments of these patients [31–33].

Conclusions

Breast metastasis from gastric cancer is a very rare pathology with a poor prognosis in the short term. Its diagnosis is difficult, and clinical and histological findings are useful to differentiate a primary breast tumor from metastatic disease.

Acknowledgments

Thanks are due to the Southern Medical Hospital for their support in data collection.

Statement of Ethics

The patient gave informed written consent to publish her case (including the publication of images).

Conflict of Interest Statement

The authors have no conflicts of interest to declare.

Funding Sources

No funding was received.

Author Contributions

H.H. Buerba-Vieregge and R. Fernández-Ferreira contributed to the conception of the case report, the analysis and critical revision of the content, and the final approval of the version to be published. P.D. Soberanis-Piña, I.R. De la Peña-López, and L.M. Navarro-García contributed to critical revision of the content, as well as the final approval of the version to be published. A. Macari-Jorge carried out the exhaustive review of the histopathological characteristics of the cancer and an analysis of the article. All authors agree to be responsible for all aspects of the work to ensure that questions related to the accuracy or completeness of any part of the work are properly investigated and resolved.

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