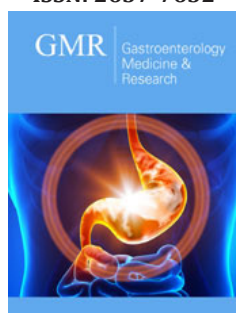


Gastric Metastasis at the First Presentation of Breast Cancer May Mimic Primary Carcinoma: A Case Report and Literature Review

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Abstract

Gastric metastasis from breast cancer is a rare phenomenon in clinical practice, of which the disease features and natural course could be insidious and undistinguished from primary gastric carcinoma. We reported a 37-year-old female patient newly diagnosed as endocrine-dependent breast cancer with synchronous the diffuse thickness of stomach and extensive metastases in the peritoneum as well as bilateral ovaries. The endoscopic view demonstrated a sign of linitis plastica. Histopathological results from gastric biopsy showed molecular features in favor of breast origin, which could be the major source of antidiastole. The prognostic outcomes were heterogeneous among patients with receipt of sequential therapy, where the molecular mechanisms remained to be elucidated.

Introduction

Over the recent decades, more than 90% breast cancer at newly diagnosed is early-stage disease due to the development and generalization of screening mammography [1]. De novo stage IV breast cancer is defined as the advanced disease with synchronous involvement of distant metastasis, which accounts for mere 6% proportions in female breast cancer [1,2]. The common metastatic sites from primary breast cancer are bone and lung, whereas the metastasis to gastrointestinal (GI) tract is not frequent. This involvement at the first presentation of primary disease, considering the reported length timeframe to secondary lesions, could be fairly rare and sticky for antidiastole, especially in company with diffuse abdominal metastases including ovaries and peritoneum [3]. Herein, we report a case of gastric metastasis at the first presentation of breast cancer followed by a literature review of disease characteristics and natural course in clinical practice.

Case report

A 37-year-old female presented to our department with a palpable lump in the left breast which was touched at incidence in April 2019. She complaint of no symptoms other than anorexia and maransis. On physical examination, a lump in around 5cm diameter, occupying the whole left breast, was detected with a crater nipple and locoregional skin ulcer, while a palpable mass was also detected in bilateral axillary and supraclavicular region. Ultrasonic examination showed a 5.9*1.8*5.3cm lump in the left breast with left axillary and supraclavicular adenopathy.

In August 2019, she underwent histopathological biopsy of puncture and the results confirmed invasive breast cancer with ipsilateral axillary nodal metastasis. The immunochemistry (IHC) of breast tissue was as follows: estrogen receptor (ER) (-), progesterone receptor (PR) (+,90%), HER2 (-), Ki67 (+,10%). Then, contrast-enhanced computed tomography (eCT) revealed that diffuse thickness of stomach fundus and corpora ventriculi (Figure 1), the mesentery, momentum majus and endometrium, in addition to the extensive metastases in bilateral ovaries, suspicious lung and pleura, bone and multiple lymph nodes. Serum biomarkers showed that CEA was 36.16ng per milliliter (normal rage, 0.0 to 5.0), CA125 175.60U per milliliter (normal rage, 0.0 to 35.0), CA15-3 1016.00 U per milliliter (normal rage, 0.0 to 25.0), CA72-4 40.36U per milliliter (normal rage, 0.0 to 6.9)

and CYFRA21-1 9.85ng per milliliter (0.0-3.3). Test for hepatitis B, hepatitis C, syphilis and human immunodeficiency virus were

negative. The genetic test from saliva demonstrated TP53 mutation c.1010G>A (p. Arg337His) missense mutation.

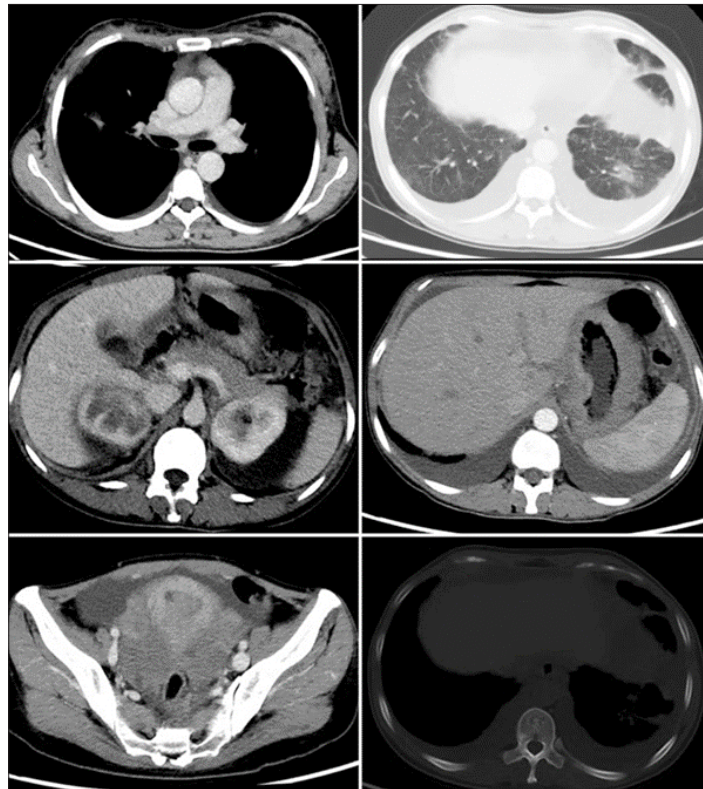


Figure 1: Computed tomography (CT) scan showing widespread metastases in stomach, ovary, diffused peritoneum and pleura, lung and bone.

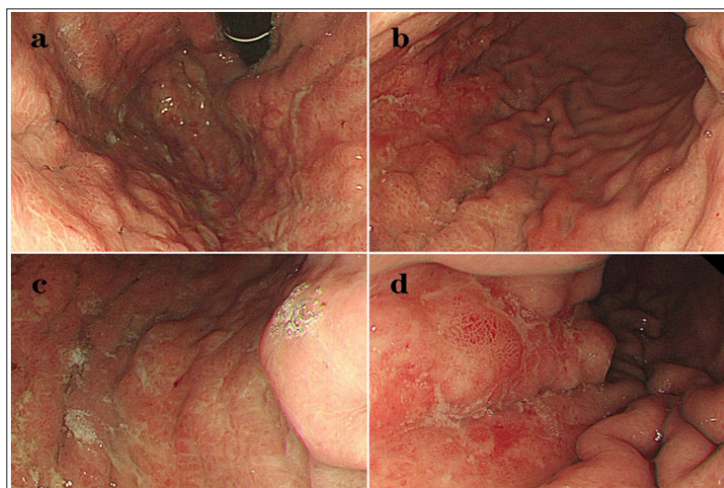


Figure 2: Endoscope showing the hypertrophic gastric folds, swelling and scattered erosion in the fundus with infiltrative appearance mimicking primary linitis plastica (a-d).

With the aim of antidiastole on gastric origin, an endoscopy examination was performed in September 2019. The endoscopic view showed a linitis plastica lesion with swelling, hyperemia, enlarged folds in the mucosa of gastric fundus and body (Figure 2). Histological results from multiple biopsies indicated a poorly differentiated carcinoma with no specific reference, while the

IHC was as follows: CK7 (3+), CDX-2 (-), CK20 (-), GATA3 (+), Mammaglobin (2+), GCDFP15 (-), ER (-), PR (+, 90%), HER2 (2+) (Figure 3). Furthermore, the HER2 amplification was confirmed by Fluorescence in Situ Hybridization (FISH), which the ratio of HER2 to CEP17 was 6.6 and the ratio of average HER2 copies to cell was 1.9.

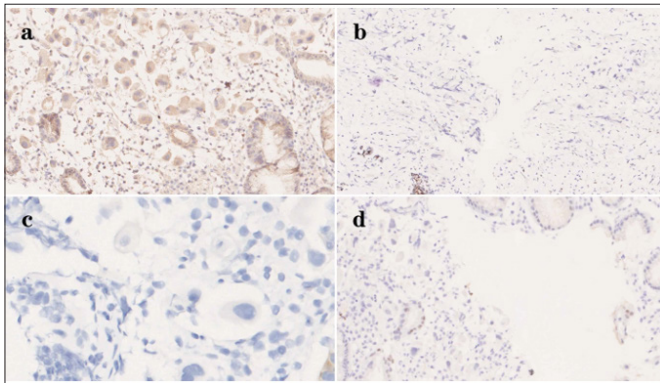


Figure 3: Immunohistochemistry results revealing gastric metastasis from breast cancer: Mammaglobin positivity (a) (×20), GATA3 partially positivity (b) (×10), CK20 negativity (c) (×20) and CDX-2 negativity (d) (×10).

Meanwhile, systemic therapy based on epirubicin 90mg/m² and paclitaxel liposomes 175mg/m² every 21 days was administrated on September 20th, 2019. In November 2019, the therapeutic evaluation suggested that the tumor burden was significantly shrinking through eCT imaging, whereas left strabismus and instability of gait were detected on physical examination. Further, brain magnetic resonance imaging (MRI) revealed multiple metastasis in the right parietal lobe, left occipital lobe and cerebellum. This disease progression was followed by a protocol based on docetaxel 75mg/m² and carboplatin AUC=5 plus trastuzumab every 21 days in combination with planned simultaneous radiotherapy on December 18th, 2019 (Table 1). Unfortunately, the symptoms, including bilateral visual loss and instability of gait, were increasingly deteriorating during this time, and they chose best supportive care (BSC) instead of any medical therapeutics and examinations in January 2020. She was alive in a poor performance status and the follow-up was terminated on August 1st, 2020.

Table 1: Clinical characteristics and disease course of the reported patient.

Gender	Female
Race	Asian Chinese
Age at diagnosis	37 years old
Type of cancer	Invasive ductal breast cancer
Clinical stage	cT4N3M1 Stage IV
IHC	
Primary disease	ER (-), PR (+,90%), HER2 (-), Ki67 (+,10%)
Secondary disease	ER (-), PR (+, 90%), HER2 (2+)
FISH	
the ratio of HER2 to CEP17	6.6
the ratio of average HER2 copies	1.9
Metastatic sites	Multiple viscera, bone and soft tissue
Molecular feature	TP53 mutation c.1010G>A (p. Arg337His)
First-line therapy	Epirubicin 90mg/m ² , paclitaxel liposomes 175mg/m ² , intravenously, every 21 days, 4 cycles
Therapeutic evaluation	Progression disease, newly diagnosed brain metastasis
Second-line therapy	Docetaxel 75mg/m ² , carboplatin AUC=5, trastuzumab, intravenously, every 21 days, 2 cycles
Therapeutic evaluation	Recognized as progression disease, deteriorating symptoms

Discussion

This is a 37-year-old woman who was newly diagnosed as de novo stage IV breast cancer with synchronous metastases to stomach and bilateral ovaries. No apparent Initial symptoms were exposed other than anorexia and weight loss. Endoscopic biopsy confirmed the appearance of linitis plastica in addition to the integrity of mucous, whilst HER2 status conversed to amplification in the secondary lesion. Genomic profiles test showed TP53 germline mutation c.1010G>A (p. Arg337His). The overall clinical

response to chemotherapy plus anti-HER2 targeted therapy, from this patient, was poor for rapid brain metastasis with the loss of vision and locomotion and the descending performance status.

Gastric metastasis from breast carcinoma is not a common phenomenon in clinical practice. On the basis of literature review [4-25], an incidence ranging from 1.7% to 6% was reported in the involvement of gastrointestinal metastases from primary breast cancer [26]. The average age of patients was 53 years (ranging, 38 to 84). Invasive lobular breast cancer occupied a higher risk, than

that of ductal subtype, to metastasize in stomach with incidence of 69.1%. The luminal subtype was supposed to hold the foremost rate of 92.1% and triple-negative (TN) also had a risk of 7.9%, while gastric metastasis was not documented to occur in HER2 enriched subtype (Table 2).

Table 2: Clinical Characteristics of breast cancer and gastric metastasis from literature review.

Characteristics	No. of Patients (N=46)
Age at primary diagnosis (average, yr)	53(ranging, 38 to 84)
Breast cancer	
Pathology	
IDC	13(30.9)
ILC	29(69.1)
Subtype	
Luminal	35(92.1)
HER2 enriched	0
Triple-negative	3(7.9)
Gastric metastasis	
Abdominal symptoms	
Weight loss	7(15.2)
Abdominal pain	14(30.4)
Dysphagia	6(13.0)
Nausea	6(13.0)
Vomit	5(10.9)
GI bleeding	8(17.4)
Anemia	6(13.0)
Asymptomatic	17(36.9)
Others	7(15.2)
Subtype	
Luminal	27(90.0)
HER2 enriched	0
Triple-negative	3(10.0)
Subtype status	
Consistency	16(72.3)
Inconsistency	6(27.7)
Comitant metastasis	
None	23(50.0)
Yes	
Visceral	
Gastrointestine	5(10.9)
Ovaries	2(4.3)
Lung	5(10.9)
Liver	6(13.0)
Brain	2(4.3)
Bone	11(23.9)
Soft tissue	8(17.4)
Others	3(6.5)

The initial symptoms of gastric metastasis tend to be unspecific. Furthermore, except for 30.4% proportions appeared abdominal pain, the initial symptoms tend to be far from recognition with the incidence of 36.9% obtained for asymptomatic patients. The average time from primary disease to gastric metastasis was 6.6 years, of which 39.5% cases occurred within 5 years after the diagnosis of breast cancer and 18.6% proportions presented at diagnosis of

de novo stage IV breast cancer. Of note, a long term was suggested that around one-third patients confirmed metastasis to stomach above ten years after the completion of adjuvant therapy for breast cancer (Figure 4). The distance interval beyond maybe 10 years, in addition to the imperceptible emergence, could further lead to the difficulty of diagnosis and therapy delay.

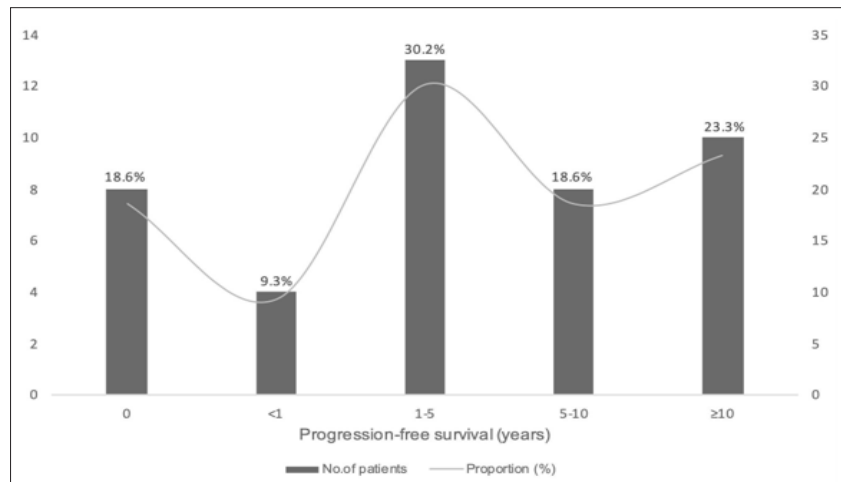


Figure 4: Time from primary breast cancer to gastric metastasis.

The diagnosis of gastric metastasis is dependent on endoscopic biopsy and histopathological examination. The most common endoscopic view is linitis plastica with the rate of 78.7%, whereas the evident ulcer or polypus lesions occupy 19.3%. However, linitis plastica is also a common endoscopic sign of primary gastric carcinoma at the advanced stage, which further increase the difficulty in antidiastole. Under this circumstance, more significance should be attached to the solid evidence acquired from immunochemistry analysis. GATA binding protein gene 3 (GATA3), gross cystic disease fluid protein-15 (GCDFP-15) and mammaglobins are the main

diagnostic markers for primary breast cancer with the sensitivity of 32%-100%, 5%-74%, 7%-84%, and the specificity of 71%-93%, 85%-100%, 9%-100%, respectively [3,27]. Cytokeratin 7 (CK7) is estimated to entirely express positive in breast epithelial cells, which are negative, by contrast, in the primary carcinoma of the stomach. Conversely, CK20 is a fairly specific marker for gastrointestinal epithelial cells, yet with absence of expression in breast cancer. Combining the aforementioned markers could favor the clarification of the gastric origin.

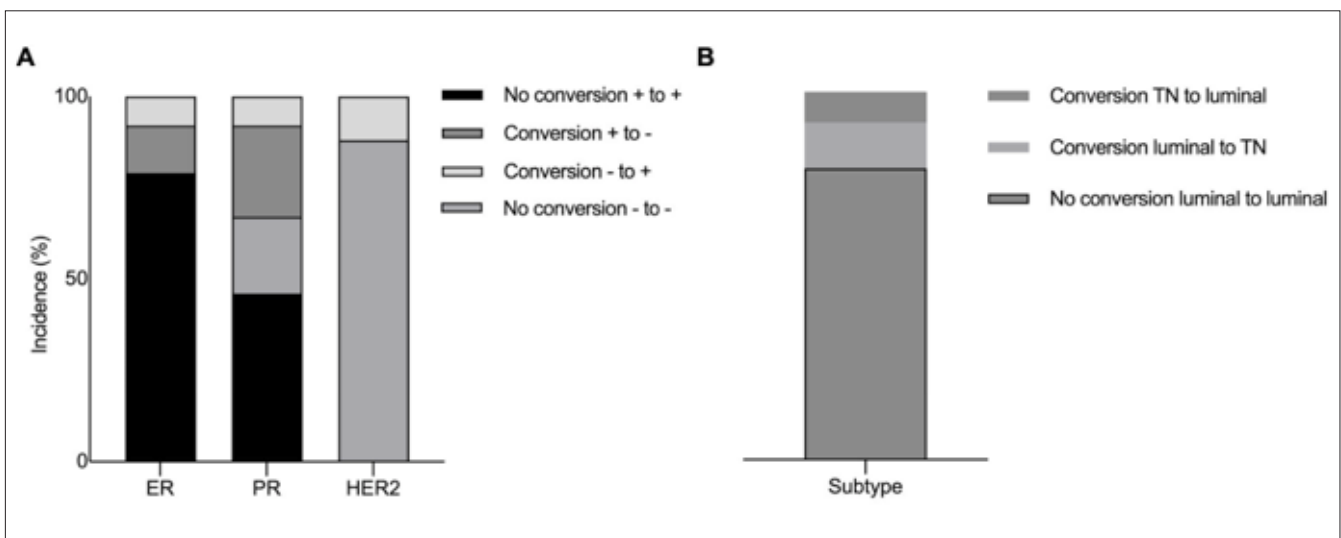


Figure 5: The conversion of ER, PR, HER2, and subtype in gastric lesions.

The decisive role of hormonal receptors in the treatment for breast cancer could not be applicable to antidiastole, since a total of 72.3% proportion of gastric carcinoma remained in accordance with primary breast cancer in terms of endocrine-dependent subtype. Notably, the conversion of molecular receptors occupied a substantial incidence during the metastasis, with overall rate of 21%, 33%, and 12% obtained for ER, PR and HER2 (Figure 5). Although the primary breast cancer was entirely HER2-negative, a 12% proportion of gastric lesion with HER2 expression conversed to positive, which enable the application of anti-HER2 targeted therapy and promise more survival benefit. In this respect, the test of hormonal receptors and HER2 expression were more meaningful to sequential therapy for metastatic disease. Moreover, in this report, the patient was first presented with breast cancer and synchronous gastric as well as ovarian and peritoneum disease, which was mimicking primary gastric carcinoma biological behaviors of implantation metastasis. Re-biopsy of secondary disease should be attached with more importance for not only differential diagnosis but also therapeutic chances.

Data on the following treatment were relatively consistent, which the entirety of patients received systemic treatment after the diagnosis of gastric metastasis, and chemotherapy, in combination with endocrine agents, was administrated for the aim of anti-cancer efficacy. Previous study suggested that surgical performance, rather than palliative surgical resection, could not significantly improve survival of patients [28]. However, there were significant differences in the prognosis of patients, which the time from gastric metastasis to death was ranging from one months to more than 42 months. No apparent factors from disease characteristics could account for the heterogeneity of survival, while more reasons could lie in the molecular mechanisms. The hallmarks of cancer are reflected in several aspects, where TP53 mutation plays a crucial role in the dysfunction of proliferation, metabolism and apoptosis, and could attribute to the poor prognosis of patients [29-31]. In this patient, saliva genetic test showed a missense mutation of TP53 with c.1010G>A (p. Arg337His). Although no genetic analysis was undergone due to the pessimistic economic conditions, this result could offer a solid clue to the aggressiveness of disease behaviors, especially of such an explosive progression at diagnosis. The intricate of malignant behaviors and the behind driving factors remains to be elucidated in this precision era.

Conclusion

Gastric metastasis from breast cancer is not common and may mimic primary gastric carcinoma, especially at the first presentation of primary disease with synchronous extensive abdominal metastases. The antidiastole mainly relies on the histopathological tests through re-biopsy, and the initial symptoms and endoscopic views tend to be unspecific in clinical observation. The conversion of molecular features should be focused and used to optimize therapeutic protocol. With the in-depth exploration of the molecular mechanisms, increasing biomarkers should be confirmed and contribute to clinical practice in the future.

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