

## **The Gastric Metastasis in Breast Cancer: A Retrospective Study of Clinical Characteristics, Management and Review of Literature**

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### **Abstract**

Breast cancer is the most common malignant tumour in the female population, accounting for high morbidity and mortality worldwide. Breast cancer is known to spread to bone, lung and liver commonly. However, spread to gastrointestinal tract is rare. As compared to other parts of the gastrointestinal tract, stomach is the most commonly involved metastatic site. Primary gastric cancers must be differentiated from metastasis to stomach as the later condition is underdiagnosed and associated with poor prognosis. Information is very sparse regarding the management of patients with cancer breast metastasizing to stomach, as there are very few case series and reports that are available in literature. We

present a case series of nine patients of breast cancer with mixed pathology metastasising to stomach with review of literature.

**Keywords:** Breast Cancer, Gastric Metastasis, Immunohistochemistry, Stomach, Prognosis, Case Series.

### **Introduction**

Breast cancer is the most common malignant tumour in the female population. At presentation 6-10 % of women present with metastasis and 50% will have metastasis in lifetime. The sites most affected in decreasing order are bone, lung, liver and brain. Although breast cancer spreads to all most organs, uncommon sites include skin, kidney, spleen, thyroid, bronchus, ovary and GIT.

Among entire gastrointestinal tract, stomach is the most common site of from breast cancer followed by oesophagus and rectum (7%) (1). Gastric metastases from breast cancer are not common, but the autoptic incidence is not negligible, and varies from 5% to 18% (2,3). Gastric metastases are metachronous in most cases and even in patients with a known history of breast cancer it may be difficult to correlate the two diseases to a common cause, since the gastric disease often presents only several years after the treatment for the breast tumour [4,5]. Even though invasive ductal carcinoma is the most common histological type (80%) in primary breast cancer followed by lobular carcinoma 10-14%, reverse is true for metastasis as later the is most common type associated with metastases to the pleura, peritoneum and GIT. Patients present with varied symptomatology ranging from no symptoms to nausea, vomiting, pain, obstruction and bleeding. These symptoms may occur due to previous treatment, undetected gastrointestinal tract metastasis or late recurrence. Hence proper evaluation and diagnosis with pathology and immuno-histochemistry is essential to differentiate primary gastric cancer from the metastasis of breast primary, which will aid in adequate management.

### **Aims And Objectives**

This article aims to study of series of cases with breast cancer metastasing to stomach. Most interesting fact about these cases was they presented with gastro intestinal symptoms and the diagnosis of metastatic breast cancer to stomach was very unlikely as its incidence is extremely rare.

The diagnosis must be considered in the back ground of breast cancer.

### **Patients And Methods**

This is a retrospective observational study of 9 patients with metastatic breast cancer, who received treatment at our institute. All the clinical, investigational, operative, pathology details and follow-up data were collected from patient records. The diagnosis was confirmed based on histopathology, receptor status and most importantly immunohistochemistry with her2, GCDFP-15 and mammaglobin.

### **Case Description**

A 56-year-old female patient underwent breast conservation therapy in 2009 for invasive ductal carcinoma and her stage of the disease was pT2N2cM0. The histopathological examination revealed invasive ductal carcinoma grade III, oestrogen receptor (ER) positive, progesterone receptor (PR) negative and Her 2 neu positive disease with margins free of tumour. Adjuvant therapy with docetaxel, adriamycin and cyclophosphamide for 6 cycles followed by trastuzumab 3 weekly for 1 year was administered. She was later continued on anastrozole. In July 2011, she developed multiple skeletal and supraclavicular lymph node metastases. She was treated with 13 cycles of Trastuzumab, exemestane and zoledronic acid. She developed cardiac dysfunction and hence Trastuzumab was discontinued and was continued on exemestane alone. In January 2013, she presented with epigastric discomfort and non-bilious vomiting. She underwent upper gastrointestinal endoscopy (UGIE), which showed diffuse nodular lesions involving whole of the stomach with decreased distensibility. A biopsy was taken which showed infiltration of lamina propria and mucosa diffusely with small round cells as sheets and single neoplastic cells with surrounding normal glands (fig a,b). Immunohistochemistry (IHC) showed the tumour to

be positive for gross cystic disease fluid protein (GCDFP-15), mammaglobin and human epidermal growth factor receptor 2/neu. A contrast enhanced computer tomography (CECT) scan showed diffuse thickening of gastric wall from esophagogastric junction until the pylorus with sclerotic lesion in left iliac bone. The right breast showed seroma which did not show an increased fluoro-deoxyglucose (FDG) uptake, whereas there was an increased FDG uptake of the stomach lesion. She was started on paclitaxel and anastrozole. She is doing well after 3 cycles of chemotherapy with partial response with clinical improvement.

A 61-year-old female patient was diagnosed with invasive ductal carcinoma in March 2010 with a clinical staging of T3N1M0. She underwent modified radical mastectomy of the left breast. Histopathological examination revealed a pT3N1 disease and a triple negative breast cancer. Patient was administered 5-fluorouracil, epirubicin and cyclophosphamide regimen followed by adjuvant radiotherapy. In August 2012, she presented with abdominal pain, melena and abdominal distension. A CECT scan showed a nodular thickening in the gastric wall involving the body of the stomach. An upper gastro intestinal endoscopy revealed a nodular growth involving the body and pylorus of stomach. Biopsy of the growth on histopathological examination depicted neoplastic cells infiltrating the stomach wall with normal mucosal glands in between. IHC showed the specimen to be positive for GCDFP-15. Patient was started on palliative chemotherapy with paclitaxel, but was succumbed to death after 6 months.

#### **Patient Characteristics**

A 51-year-old woman presented with history of right breast lump for period of 4 months in 2008. She was diagnosed with right breast cancer, stage T2N1M0

disease. Patient opted for breast conservation surgery. Pathology report showed invasive lobular carcinoma grade 2 with signet ring appearance and all margins were negative. Nine of the fourteen lymph nodes dissected were positive for metastasis with extra capsular spread. She was ER positive, PR negative and her 2neu positive. With pathological stage being pT2N2cM0. Adjuvant therapy with 6 cycles of docetaxel, adriamycin, cyclophosphamide and IMRT of 50.4 Gy and 18 cycles of herceptin given. Tamoxifen was given for hormonal therapy. Patient was on regular follow up. In 2011 patient had right supraclavicular node metastasis and investigation showed multiple bone metastases. Patient received 3 cycles of gemcitabine and carboplatin with monthly zoledronic acid. In 2013 patient developed pain abdomen and distension. On investigation erect x-ray abdomen suggestive of sub acute small bowel obstruction.

Gastric wall thickening and free fluid noted on ultra sound scan. OGD showed ulcer in greater curvature with reduced distensibility. Biopsy showed poorly differentiated signet ring carcinoma. IHC revealed Her2 =2+ve, mammaglobin +ve and GCDFP 15 +ve. Peritoneal fluid analysis was positive for malignancy. PET CT showed bone, liver, brain, and peritoneal carcinomatosis. Patient was given only supportive care in view of the poor performance status. She succumbed to the disease in a week's time.

A 63-year-old lady diagnosed with invasive lobular carcinoma in 2012, underwent modified radical mastectomy of right breast. Histopathological examination revealed a pT3N2M0 disease and ER positive, PR and Her2 negative breast cancer. Patient was administered 5-fluorouracil, epirubicin and cyclophosphamide regimen and adjuvant radiotherapy.

10 months later she presented with vomiting, abdominal pain and distension. Investigations revealed metastasis to lung and brain. A CECT scan showed gastric wall thickening and on upper gastro intestinal endoscopy, growth was seen in the body and pylorus of stomach. Endoscopic Biopsy revealed neoplastic cells infiltrating the stomach wall. IHC showed tissue positive for GCDFP-15 and mammaglobin. Patient was managed symptomatically and treated with palliative chemotherapy with paclitaxel, but died due to malignancy after 14 months.

This is a case report of 48-year-old female who presented with lump in the left breast which on work up was found to be invasive lobular carcinoma. Patient underwent modified radical mastectomy and final pathology revealed pT3N2cM0 disease and ER positive, PR positive and Her2 neu positive disease. She was subjected to adjuvant chemotherapy by Adriamycin, cyclophosphamide followed by docetaxel, radiotherapy and hormonal therapy. 14 months later patient had low backache, vomiting and cough, investigations revealed spread to bone, lung, stomach and skin. CT scan revealed diffuse thickening of stomach and ascites. UGIE revealed poorly differentiated carcinoma, IHC revealed HER2, GCDFP15 and mammaglobin positive disease. Due to poor performance status, was put only on hormonal therapy and she succumbed to death in 11 months' time.

A 54-year-old female was diagnosed with invasive ductal carcinoma left breast. Patient underwent Modified radical mastectomy followed by adjuvant chemotherapy consisting of doxorubicin and cyclophosphamide, followed by paclitaxel. Subsequently she received adjuvant hormonal therapy with tamoxifen due to positive hormone receptor status. Approximately two

years after completing her adjuvant therapy, she presented with complaints of persistent epigastric pain, early satiety, and unintended weight loss. Physical examination revealed mild tenderness in the epigastric region. CECT abdomen and pelvis revealed nodular lesion measuring 3 cm in the posterior wall of the stomach. Upper gastrointestinal endoscopy reveals a raised, ulcerated lesion in the body of the stomach. Histopathological examination of the gastric biopsies reveals metastatic adenocarcinoma consistent with the primary breast tumour. Immunohistochemical staining confirms the tumour to be ER, PR- positive, consistent with the primary breast cancer. It was also positive for GCDFP-15 and mammaglobin. Patient was managed symptomatically and treated with palliative chemotherapy with paclitaxel but succumbed to malignancy in 10 months.

A 49-year-old female presented with lump in left breast and was diagnosed to have invasive lobular carcinoma left breast without any metastasis. She underwent modified radical mastectomy and histopathology revealed pT3N1M0 disease with ER +, PR Negative, and Her2 neu Negative disease.

She was subjected to chemotherapy by Adriamycin, cyclophosphamide followed by docetaxel, RT. After 16 months, she presented with back ache. On investigation, she was found to have metastasis to lumbar vertebra and nodular lesion in near body of stomach. On upper GI endoscopy, there was ulcer proliferative lesion over the body of stomach which on biopsy revealed round cells with ER positive and mammaglobin positivity. Patient was

given palliative chemotherapy, but she died after 12 months.

A 57-year-old female presented with lump in breast and diagnosed to have invasive lobular carcinoma, with negative metastatic workup. She underwent modified radical mastectomy. HPE revealed pT2N2M0 disease with ER+, PR+, Her 2 neu+ disease. She was subjected to chemotherapy, radiotherapy, hormonal therapy. After 22 months, she presented with appetite loss, early satiety, vomiting. On investigating, she was found to have liver and lung metastasis. Upper GI endoscopy showed changes suggestive of linitis plastica which on biopsy and IHC was found to have triple positive disease positive for mammaglobin and GCDFP-15. She was given just symptomatic management because of poor performance status and succumbed to death in 4 months.

RT: Radiotherapy

Sx: Surgery

HT: Hormonal therapy

This is a case report of 62-year-old female who presented with lump in the left breast which on work up was found to be invasive lobular carcinoma. Patient underwent modified radical mastectomy and final pathology revealed pT3N2M0 disease and ER positive, PR positive and Her 2 neu positive disease. She was put on adjuvant chemotherapy by Adriamycin, cyclophosphamide followed by paclitaxel, radiotherapy and hormonal therapy. 1year later patient had low backache, loss of weight vomiting, abdominal distention, investigations revealed spread to bone, liver, stomach and peritoneum. CT scan revealed diffuse thickening of stomach with peritoneal deposits and ascites. UGIE revealed poorly differentiated carcinoma, IHC revealed HER2, GCDFP15 and mammaglobin positive disease. Due to poor performance status, was put only on hormonal therapy and she succumbed to death in 5 months' time.

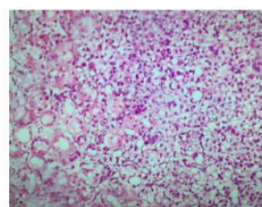
| Age | Pathology | TNM     | Other metastasis                              | Receptor status |    |      | IHC  |          |             | Treatment      | Survival after metastasis (months) |
|-----|-----------|---------|---|-----------------|----|------|------|----------|-------------|----------------|------------------------------------|
|     |           |         |   | ER              | PR | HER2 | her2 | GCDFP-15 | Mammaglobin |                |                                    |
| 56  | IDC       | pT2N2M0 | Bone, liver                                   | +               | -  | +    | +    | +        | +           | Sx, CT, RT, HT | 18                                 |
| 61  | IDC       | PT3N1M0 | Bone, lung                                    | -               | -  | -    | -    | +        | +           | Sx, CT, RT     | 6                                  |
| 51  | ILC       | PT2N2M0 | Bone, liver, brain, peritoneal carcinomatosis | +               | -  | +    | +    | +        | +           | Sx, CT, RT, HT | 0.25                               |
| 63  | ILC       | PT3N2M0 | Lung, brain                                   | +               | -  | -    | -    | +        | +           | Sx, CT, RT     | 14                                 |
| 48  | ILC       | PT3N1M0 | Bone, lung, skin                              | +               | +  | +    | +    | +        | +           | Sx, RT, HT     | 11                                 |
| 54  | IDC       | PT2N1M0 | Bone, lung                                    | +               | +  | +    | +    | +        | +           | Sx, CT, RT, HT | 10                                 |
| 49  | ILC       | PT3N1M0 | Bone  | +               | -  | -    | -    | +        | +           | Sx, CT, RT     | 12                                 |
| 57  | ILC       | PT2N2M0 | Liver, lung,                                  | +               | +  | +    | +    | +        | +           | Sx, CT, RT, HT | 4                                  |
| 62  | ILC       | PT3N2M0 | Liver, bone, Peritoneal carcinomatosis        | +               | +  | +    | +    | +        | +           | Sx, CT, RT, HT | 5                                  |

Table 1: Summary of Patient characteristics, treatment modalities and survival period

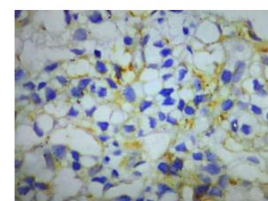
IDC: Invasive ductal carcinoma

CT: Chemotherapy

ILC: Invasive lobular carcinoma



(a)



(b)

Figure (a) Gastric mucosa and lamina propria infiltrated by invasive breast cancer with small discohesive tumour cells located between normal gastric glands; (b) Immunohistochemical staining showing sheets of cells and single neoplastic cells with surrounding normal glands positive for gross cystic disease fluid protein-15.

Discussion

Breast cancer metastasis rarely occurs in the gastrointestinal tract, with the majority of cases

involving invasive ductal carcinoma (IDC) representing approximately 80% of all breast carcinomas. However, gastric metastasis primarily arises from invasive lobular carcinomas (ILCs) at a rate of 65.4%, while IDC accounts for only 24.4% (6-12). In some instances, gastric metastasis may manifest as primary or peritoneal carcinomatosis, affecting the peritoneum, adrenals, and lung pleura (7,13).

Several studies have identified three primary mechanisms through which malignant breast cells disseminate to the upper gastrointestinal (GI) tract: lymphatic spread, hematogenous route, and direct invasion from adjacent organs. Among these mechanisms, lymphatic spread is more commonly observed in esophageal metastasis. The typical presentation involves strictures or submucosal nodules with an intact mucosal layer, making it challenging to diagnose using endoscopic methods.

Additionally, infiltration of paraesophageal lymph nodes can lead to the compression of the esophageal lumen, resulting in intramural infiltration. Hematogenous spread, on the other hand, is characteristic of metastasis to the esophagus, stomach, or duodenum. This type of spread often leads to stenosis or the formation of localized masses within the intramural or submucosal layers, which may eventually ulcerate (25, 26, 27).

Chemokines play a crucial role in the metastatic process. Breast cancer cells express two main chemokine receptors, CXCR4 and CXCR7, which are involved in trans endothelial migration (TEM) and guide the cells towards specific target organs (28). Tumours that express CXCR4+ have a higher tendency for distant metastasis compared to CXCR4- tumours, although this association lacks statistical significance [29]. The ligands for these receptors are CXCL12 and CCL21.

CXCL12 is involved in modulating integrin expression, metalloproteinase production, tumour angiogenesis, tumour cell adhesion, and apoptosis [30]. Metalloproteinases play a critical role in breaking down the extracellular matrix, enabling the invasion of cells attracted to metastatic sites by chemokines from the bloodstream [30]. CXCL12 facilitates the homing of tumour cells to secondary sites and recruits endothelial stem cells for blood vessel formation and subsequent proliferation. Additionally, chronic inflammation induced by *Helicobacter pylori* infection leads to increased expression of chemokines and interleukins, which can attract tumour cells to the gastric or colon mucosa, promoting proliferation and the development of metastatic disease.

The endoscopic characteristics of metastatic breast cancer in the gastrointestinal tract can vary widely, ranging from benign-appearing lesions resembling gastritis to diffuse or ulcerated tumours that mimic primary gastric carcinoma or lymphoma (14,15,16). Lesions are typically classified into three main categories: localized tumour deposition (18%), diffuse infiltration (such as linitis plastica type or gastritis) (57%-73%), and external compression (25%) (14,15,17,18). Microscopically, lobular carcinoma with its "signet ring" appearance closely resembles primary gastric carcinoma (19), emphasizing the importance of accurately interpreting "signet ring" cells for proper diagnosis and management. Immunohistochemistry (IHC) is often necessary to differentiate between primary and metastatic gastric carcinoma. Metastatic breast carcinomas typically exhibit positive staining for gross cystic disease fluid protein-15 (GCDFP-15), mammaglobin, cytokeratin 7, carcinoembryonic antigen,

estrogen receptor (ER), and progesterone receptors, while showing negative staining for cytokeratin 20 and CA19-9 (20). External compression can occur when a ring-like tumour forms around the cardia or pylorus, potentially leading to pseudoachalasia or gastric outlet obstruction. As external metastatic invasion often spares the superficial mucosal layer, endoscopic biopsies may have an elevated false-negative rate (21, 22). A distinct feature of well-defined univacuolated cytoplasm is relatively specific for metastasis of invasive lobular carcinoma (23). Estrogen receptor protein (ER) is a highly influential and well-known marker for distinguishing metastatic breast cancer, as it is expressed in 72%-90% of breast tumour cells. Progesterone receptor protein (PR) is present in approximately 33% of cases [23]. However, relying solely on testing for ER and PR biomarkers is not sufficient, as not all breast cancer cells express these hormone receptors.

Additional breast-specific markers include gross cystic disease fluid protein (GCDFP-15) and mammaglobin. GCDFP-15 is a secretory protein produced by the breast, particularly in cases of apocrine metaplasia [24]. It exhibits high specificity for mammary differentiation, with a specificity range of 93% to 100% and a sensitivity range of 11% to 76%. Mammaglobin, a gene specific to mammary gland tissue, is overexpressed in breast cancer and shows expression rates of 47.8% to 80% in primary and metastatic breast carcinomas. The combination of CK7 and GCDFP-15, along with hormone receptor positivity and the absence of CK20 and CA19-9, proves valuable in differentiating lobular breast carcinoma from gastric carcinoma.

As with other metastatic breast cancer sites the principles of management remain same. The choice of

therapy depends on age, performance status, symptoms and previous treatments.

Once the metastasis was diagnosed, the mean survival in our study was 9 months.

### **Conclusion**

Metastasis of breast cancer to the stomach is an infrequent yet significant occurrence. This collection of case studies enhances our comprehension of the clinical features, diagnostic approaches, treatment choices, and outcomes linked to this phenomenon. Given its vague symptoms, it presents a dilemma for surgeons in terms of accurate diagnosis and treatment planning. Swift diagnosis, precise staging, and tailored treatment approaches, encompassing systemic therapy and supportive care, play a vital role in managing these patients and enhancing their quality of life. Surgical intervention is reserved for instances involving obstruction, bleeding, or perforation. Therefore, none of the cases in our series required surgical intervention.

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