



RESEARCH ARTICLE

METASTATIC BREAST CANCER TO STOMACH: MANAGEMENT AND REVIEW OF THE LITERATURE

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ABSTRACT

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 gastro intestinal 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 five patients of breast cancer with mixed pathology metastasising to stomach with review of literature.

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INTRODUCTION

Breast cancer is most common cancer in women worldwide and India (http://www.breastcancerindia.net/statistics/stat_global.html; <http://www.wcrf.org/int/cancer-facts-figures/world-wide-data>). At presentation 6-10 % of women present with metastasis and 50% will have metastasis in life time. The exact incidence of metastatic recurrences is not known, but range between 20-30% (Harris et al., 1984; Lamovec, 1991). The sites most commonly 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. Gastrointestinal tract metastasis from breast cancer is very rare and the, exact incidence is not known.

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The reported incidence according to autopsy series ranged from 8 to 35 % (Washington, 1995; Caramella et al., 1983). Among entire gastrointestinal tract, stomach is the most common site of metastasis (60%) from breast cancer followed by esophagus (12%), colon (11%) and rectum (7%) (Ambroggi et al., 2012). 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 serosal metastases to the pleura, peritoneum and GIT. The exact reason for this is not known. 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 gastro intestinal 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.

Aim 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.

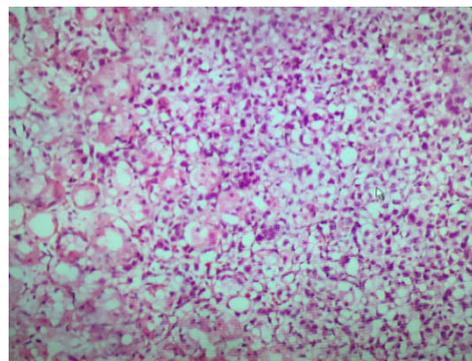
Patients & Methods

This is a retrospective observational study of 5 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.

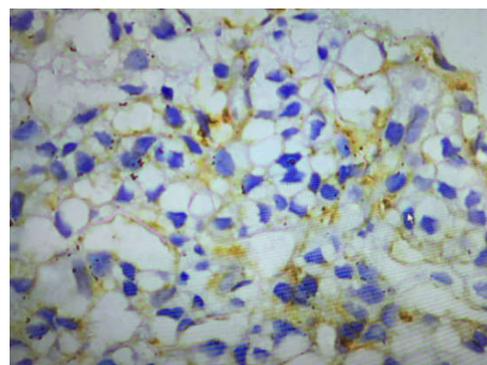
Case description

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, estrogen 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 tumor 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.



(a)



(b)

Figure (a) Gastric mucosa and lamina propria infiltrated by invasive breast cancer with small discohesive tumor 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

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.

Age	Pathology	TNM	Other Metastasis	Receptor status			IHC			Treatment	Survival after metastasis (months)
				ER	PR	HER2	her2	GCD FP-15	mammaglobin		
56	IDC	pT2N2M0	Bone, liver	+ ve	- ve	+ ve	+ ve	+ ve	+ ve	Sx,CT,RT,HT	18
61	IDC	pT3N1M0	Bone, Lung	- ve	- ve	- ve	- ve	+ ve	+ ve	Sx,CT,RT	6
51	ILC	pT2N2M0	Bone, Liver, brain, Peritoneal carcinomatosis	+ ve	- ve	+ ve	+ ve	+ ve	+ ve	Sx,CT,RT,HT	16
63	ILC	pT3N2M0	Lung, Brain	+ ve	- ve	- ve	-ve	+ ve	+ ve	Sx,CT,RT	14
48	ILC	pT3N1M0	Bone, lung, skin	+ ve	+ ve	+ ve	+ ve	+ ve	+ ve	Sx,RT,HT	11

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, mamoglobin +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, GCDFP-15 and mammaglobin positive disease. Due to poor performance status, was put only on hormonal therapy and she succumbed to death in 11 months time.

DISCUSSION

Breast cancer being the most common malignancy in females has varied presentations ranging from asymptomatic breast lump to metastasis. At presentation the disease is limited to breast and axilla in most women. Even though breast cancer can involve any organ in the body, it commonly spreads to bone, lungs, liver, brain, adrenals. Rarely, it also involves skin, thyroid, spleen, bronchus, GIT, kidney, uterus and ovary. Spread to GIT is rare. In GIT, stomach is most commonly affected. But gall bladder, pancreas and small bowel involvement also have been reported. Reports on GI metastases in the clinical literature are scarce and are mainly limited to case reports or case series. The incidence of a breast cancer metastasis to the stomach has been found to vary according to the study. The incidence of gastric metastases in post-mortem varied from 2–18% (Schwarz *et al.*, 1998; Taal *et al.*, 1992; Cormier *et al.*, 1980; Klein and Sherlock, 1972; Raju *et al.*, 1993; Davis *et al.*, 1968)

In a retrospective study by McLemore *et al.*, estimated incidence rate of GI tract metastasis from breast was 0.3% (Davis *et al.*, 1968). Another study by Taal *et al.*, gastric metastases were found in approximately 0.3% of patients with a breast carcinoma (Taal *et al.*, 1992). Spread to the gastro intestinal tract (GIT) is of special mention due to its uncommon spread and diagnostic dilemma. The presenting symptoms may be from the absence of symptoms to non specific abdominal pain, nausea, vomiting and obstruction. The treatment can be curative or palliative, in the form of chemotherapy, surgery or best supportive care. Infiltrating or invasive ductal cancer is the most common breast cancer histologic type and comprises 70% to 80% of cases. Spread to GIT can occur from any breast cancer pathology, due to unknown reasons infiltrating lobular cancer is the predominant type to metastasize (Borst and Ingold, 1993); mixed type and infiltrating ductal cancer are rarely the source for GI metastasis. For reasons unknown, Lobular carcinoma are more often associated with serosal metastases to the pleura and abdomen (Chow, 2003). The classical presentation of stomach involvement is the linitis plastica appearance due to diffuse infiltration of the gastric wall by the neoplastic cells leading to narrowed gastric lumen and decreased distensibility that can be seen on upper gastro intestinal endoscopy. It can be typically diagnosed by CECT scan or barium meal. Microscopically, the "signet ring" appearance found in lobular carcinoma closely resembles primary gastric carcinoma (Taal *et al.*, 2000); hence correct interpretation of "signet ring" cells is a must for appropriate diagnosis and management.

IHC may be the only way of differentiating between a primary and a metastatic gastric carcinoma. Metastatic breast carcinomas are usually positive for gross cystic disease fluid protein-15 (GCDFP-15), mammaglobin, cytokeratin 7, carcinoembryonic antigen, estrogen receptor, and progesterone receptors, and negative for cytokeratin 20 and CA19-9 (Chu, 2004; Tot, 2000). CK20 has been found to be positive in gastric, colorectal, pancreatic and in transitional cell carcinomas, but negative in breast cancer (Tot, 2000). CK7 in contrast is widely expressed in 90% of breast carcinomas, but less frequently in primary gastric adenocarcinoma (O'Connell et al., 2005).

The presence of ER and PR receptors in gastric biopsy is suggestive of breast cancer metastasis. Its positivity rate in patients with gastric cancer is 32% and 12%, respectively (Jones et al., 2007). Her 2 is found in 20-30 % of patients with gastric cancer and 5-10% of patients with ILC (Bilous et al., 2003). GCDFP-15 is the most important marker to distinguish primary from metastatic carcinoma. This is a monoclonal antibody which is detected in macroscopic cyst fluid in breast and plasma of breast cancer patients. It has been found to be sensitive (55-76%) and specific (95-100%) marker to accurately diagnose a malignant lesion as metastatic breast carcinoma (Honma et al., 2006). Mammaglobin is another important marker which is expressed in 80-90% of breast tumors. It is more specific than GCDFP-15 to identify breast cancer but lacks specificity (Bhargava et al., 2007). The presence of CK7 and GCDFP-15 along with hormone receptors and absence of CK20 and CA19-9 were of great value in differentiating lobular breast carcinoma from a gastric carcinoma.

As with other metastatic breast cancer sites the principles of management remains same. The choice of therapy depends on age, performance status, symptoms and previous treatments. The survival differs in each series, the reported median survival in series by Taal et al. was 10 months (Taal et al., 2000), by McLemore et al. was 28 (McLemore et al., 2005) months and by Ayantunde et al. was 20 months (Ayantunde et al., 2007) as compared to 16 months in our series. In majority of patients the treatment was either in form of palliative chemotherapy or hormonal therapy. In our series 4 out of 5 patients received chemotherapy and 4 patients received hormonal treatment but overall response was poor. Surgical intervention is needed only in cases of obstruction, bleeding or perforation. Hence in our series none underwent surgical intervention.

Conclusion

Gastric metastasis from breast cancer is very rare. Due to its non specific symptoms it poses a challenge to treating surgeon both in making a correct diagnosis and planning treatment. A high index of suspicion must be maintained while treating a patient with gastric symptoms, especially with history of previous breast cancer. Clinical expertise along with endoscopic, radiological and pathological evaluation with IHC is essential to discriminate primary gastric cancer from breast cancer metastasis to the stomach which will result in optimal outcome in such cases.

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