BREAST CANCER METASTASIS FROM PRIMARY GASTRIC CARCINOMA: CASE REPORT

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ABSTRACT

This case report aims to raise awareness of metastatic malignant tumor in the breast as the initial presentation of the occult non-mammary primary tumor. Embarking on radical surgical treatment for such metastatic tumors on the assumption of primary breast malignancy would have grave consequences for the patient and results in delayed treatment of the primary extra-mammary malignancy. The distinction is easier in patients with previously known malignancy in the contralateral breast or non-mammary malignancy.

There are no consensuses about clinical, radiological, and histological features to distinguish primary from metastatic breast neoplasm due to the rarity of the condition. The case below is a young woman with a diagnosis of diffuse-signet ring cell gastric cancer. The first presentation was in form of rapid diffuse painless swelling of the right breast accompanied by abdominal distention, with the finding of ascites, peritoneal nodules, and enlarged enhancing ovaries on imaging. Biopsy from multiple sites confirmed involvement by metastatic adenocarcinoma with signet ring pattern. Her condition progressed after the 5th cycle of EOX.

INTRODUCTION

Gastric cancer at young ages is rare. The median age at diagnosis is 71 years and is the second most common cause of death worldwide [(1)]. Incidence of signet ring cell gastric cancer ranges from 3.4% in Japan to 39% in western countries [(2,3)] and accounts for 29% of gastric cancers, it occurs most commonly in women and mainly younger age groups, it is less chemo-sensitive with poor prognosis than intestinal type.[(4,5)] Diffuse-signet ring cell type exhibits very little cell cohesion with a predilection for the extensive sub-mucosal spread and early metastasis, [(6)] diffuse form's main carcinogenic event is the loss of E-cadherin expression through mutation of CDH1 gene [(7).] Carcinoma of the stomach can spread by local extension, hematogenous spread, lymphatic dissemination or seeding of peritoneal surface, widespread metastasis may involve any organ, especially liver, lung, and peritoneum,[(8, 6 ,9)] while signet ring cell subtype's main metastatic sites are peritoneum and lymph nodes rather than the liver [(10)].

Metastatic lesions to the breast from the extra-mammary primary site are unusual with a poor prognosis. The most commonly reported sources are malignant melanomas, lymphoma/leukemia group, contralateral breast carcinoma, lung carcinoma, and carcinoid tumors [(11,12)]. There is no consensus on a distinct radiologic and clinical presentation [(12,13)]. Diagnosis of primary malignancy usually precedes the detection of the metastatic breast lesion but in some cases may have no history of the primary malignancy [(13)].

Keywords: *Gastric cancer; Breast metastasis; Young age.*

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CASE PRESENTATION

A 32-year-old married lactating woman, mother of 3 children presented to the breast clinic with a rapid painless diffuse swelling of the right breast over few weeks, not associated with redness, she had also mild diffuse abdominal pain, but a good appetite with no vomiting, no weight loss or change in bowel habit. Her review of systems was otherwise negative, and there was no family history of cancer.

An ultrasound of the right breast revealed an enlarged breast with moderately heterogeneous tissue texture, multiple well defined hypoechoic cystic lesions, largest one measures 14*9mm at 10 o'clock with multiple duct dilatation and periductal thickening. In the right axilla a slightly enlarged lymph node of 13*5mm was detected that had a cortex of 3 mm in thickness and echogenic hilum. Both left breast and left axilla were reported as normal. Mammography in both CC and MLO views showed right breast composition of ACR 4, with a single superficial well-defined dense lesion at superolateral aspect was seen; normal left breast, clear both axillae (Fig.1).

Histopathological examination of percutaneous core biopsy from the mass was reported as metastatic mucin secreting adenocarcinoma (Fig.2). The results of the immunohistochemical study of biopsy with positive controls were reported as follows:

Negative immunoreactivity for ER, PR, HER2, CA125, mammaglobin, and WT1.

Positive immunoreactivity for E-cadherin, and CDX2 with moderate nuclear staining. (Fig3) The Proliferative activity of the tumor was reported as (KI 67: 60%).

Dynamic staging computed tomography (CT) scan of chest, abdomen, and pelvis reported both abdominal and pelvic ascites, diffuse infiltration of the peritoneum with omental cake, stranding of pelvic fat, enlarged and enhanced right and left ovary, and diffuse gastric wall thickening.

Tumor markers were reported as follows:

CEA: 1.2 ng/ml, AFP: 2.23 IU/ml, CA 19.9: 0.62 u/ml, CA 125: 62.6 u/ml, CA 15.3: 19.7 u/ml.

Upper gastrointestinal endoscopy reported easily bleeding ulcers over great curvature from mid-body to the antrum (Fig 4).

Histopathology of endoscopic mucosal biopsy from the gastric lesion was reported as poorly differentiated adenocarcinoma of diffuse signet ring subtype (Fig 5). Immunohistochemical study of the gastric biopsy was reported as positive immunoreactivity of tumor cells to AE1/AE3 and negative HER2/neu status.

With the collaboration of our oncologist, pathologist, and radiologist we diagnosed and managed our case as primary signet ring cell gastric cancer with multiple site metastasis, and she was started on EOX (EPIrubicin 50mg/m2, OXALIplatin 130mg/m2, Capecitabin 625mg/m2), on fifth cycle there was progression on image study, and unfortunately, we lost her after 2 weeks.

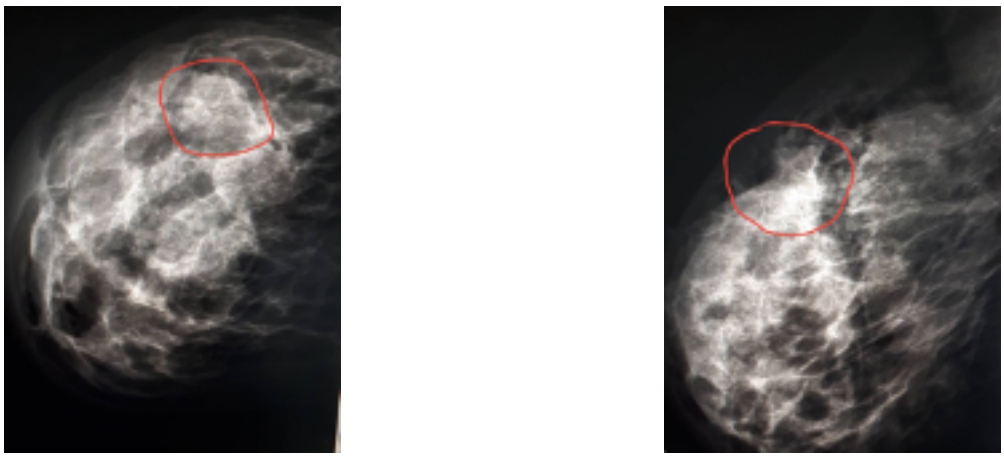

Figure 1. Mammography.

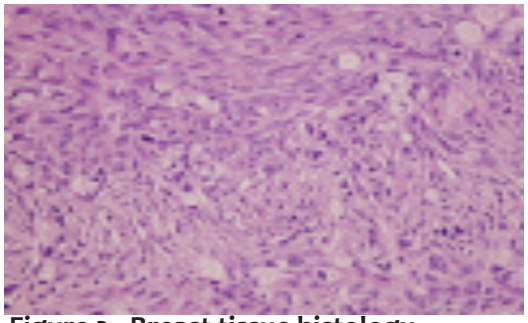

Figure 2 . Breast tissue histology.

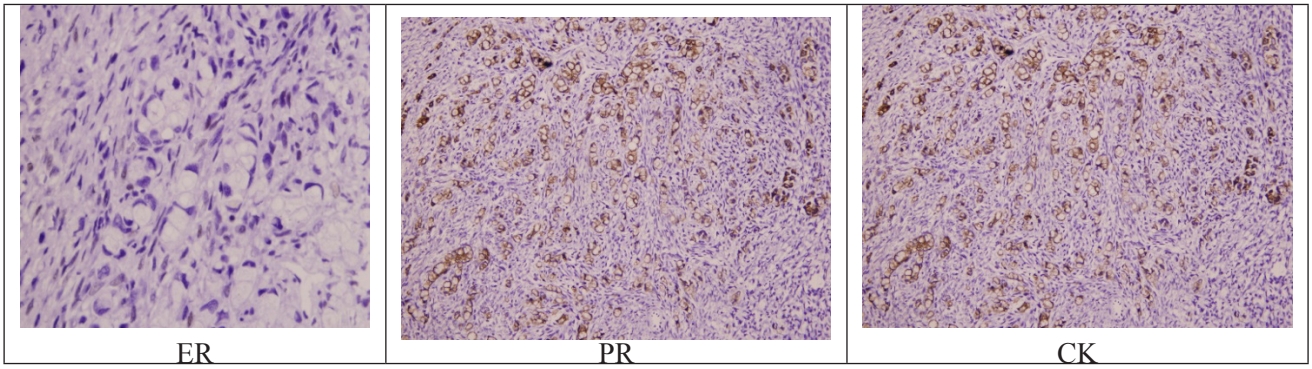

Figure 3 .Immunohistichemistry.

Figure 4. Gastric endoscopy.

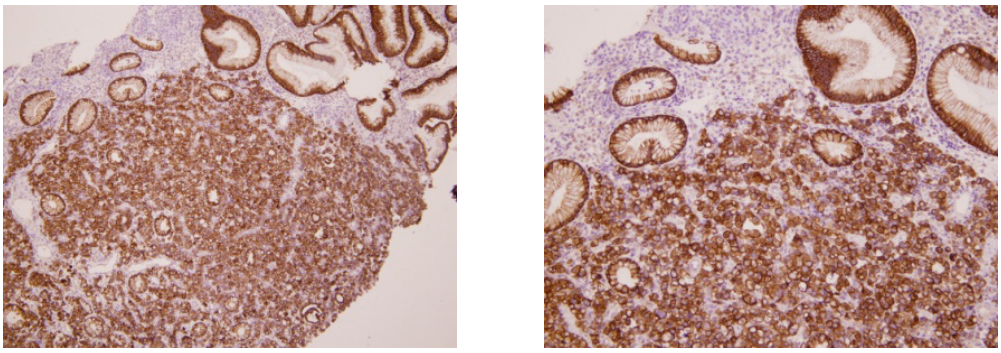

Figure 5. Histopathology of a gastric tissue sample.

DISCUSSION

Breast cancer accounts for the most common malignancies, but metastasis to the breast from extramammary malignancies is a rare condition and comprising around 3% of breast malignancies, the majority are from the contralateral breast, less than 0.5% resulted from extra mammary sites [14]. In 25% of cases, breast involvement is bilateral [15]. Prognosis is poor, according to reported cases overall survival ranged from 12 days to 18 months [16].

Around 400 cases have been reported to have breast metastasis from extra-mammary sides, their incidence ranged from 1.7%-6.6%, 1.2%-2%, 2.7% in (autopsy, clinical, and cytological reports), [17]. Slightly more than half of these are from hematolymphoid malignancies[1] and the most common solid organ sites from highest to lowest rate were from melanoma, lung, ovary, prostate, kidney, stomach, ileum, thyroid, cervix, squamous cell carcinoma of the tongue and floor of the mouth, fibrosarcoma of the nasal septum and pancreatic adenocarcinoma.

With our case, another 38 cases have been reported so far in English language pathology literature and 16 cases in Chinese language pathology literature [16, 2] to have metastatic disease from the stomach, 22 of them had the histological feature of signet ring cell carcinoma [16].

Unlike our case that had synchronous multiple metastasis at presentation, breast metastases appear on the average 1.9-2.0 years after the discovery of the primary lesion, [12, 13, 18] and usually signifies disseminated metastatic gastric tumor [15, 19], while in some cases there may be no history of neoplasm [14].

The age at diagnosis ranges from 22-70 years (mean 46 years; median 46.5 years) [16, 20, 21]. Breast metastasis from gastric carcinoma more common in female (95%) than male (5%), Georgiannos et al [14] attributed the reason behind this phenomena to differences in size and vascularity between two gender's breast, hormonal factors, endothelial cell adhesion molecule, angiogenic factors, immunologic determinants, hormone receptor, or other cellular components also may play a role since they are expressed differently in the male and female breast.

Secondary involvement of breast occurs mainly in elderly patients while lung and gastric cancer particularly signet ring cell variant of stomach develop in younger age group and anticipate more aggressive nature [22,23].

The clinical manifestations are quite similar to primary breast cancer which make suspicion of elsewhere primaries unusual but essential to avoid; unnecessary radical operation and providing optimal treatment reported cases in literature had a different presentation, from inflammatory breast cancer [18, 24, 25] to painful/painless lumps and often occur in the upper outer quadrant with the presence of axillary lymphadenopathy [12,13].

Radiological findings are not specific which makes the diagnosis quite difficult, they may present as solitary or multiple lesions, well-demarcated or poorly marginated masses, diffuse hypoechoic lesions, diffuse involvement of skin or parenchyma or both [12, 20] and sometimes there is no any radiologic findings [26, 27].

Kawak et al reported that for those with clinical features suggesting inflammatory breast carcinoma after confirmation of signet ring cell breast carcinomas has been made, metastatic signet ring carcinomas should be considered if there is no micro-calcification or masses on radiographic findings [13, 18], but metastasis from ovarian carcinoma may demonstrate microcalcification with psammoma bodies [28, 29].

Pathologically it's hard to differentiate between primary breast cancer and metastasis, breast cancer can have an ambiguous histological feature that can be easily mistaken for extramammary cancers [14]. Some histologic features may help in recognizing secondary from the primary like the absence of elastosis which is found in primary and indicating a slow growth and rarely found in secondary tumors [30]. A sharp transition at the border of the tumor gives clue for metastasis [31]. Tumors in subcutaneous rather than parenchymal or the breast tissue and absence of in situ component support extramammary origin [14].

Tumor metastasizes to the breast by unexplained pathway, this intriguing situation has been attributed to estrogen and high blood supply of breast in premenopausal women [32, 33].

Unlike our case in most of the reported cases, breast metastasis from gastric cancer has happened in the left breast although there is no consistent explanation Lee et al [19] reported that this laterality may suggest the presence of a lymphatic pathway or higher incidence of breast invasion from the stomach via left supraclavicular lymph node.

With our case another 5 cases have been reported to have breast and ovarian metastasis, it is uncommon to have an invasion of hormonal –dependent organs especially in premenopausal women[26].

Immunohistochemistry of breast metastasis from the stomach is usually positive for CK7, CEA, and GATA3 but negative for GCDFP-15(gross cystic disease fluid protein-15), ER, PR, and CK20 [34, 35]. What supported our case to have breast metastasis from gastric cancer was having positive CDX2, CK7 and negative CK20, ER, PR, CA125, WT1, Mammaglobin, HER2 status.

IHC can differentiate metastatic signet ring cell carcinoma from primary signet ring cell carcinoma of the breast, the latter one is a variant of invasive lobular carcinoma of the breast and accounts for 14% of breast cancer [36], its incidence is increasing among postmenopausal women and has aggressive nature with a tendency for early metastasis to abdomen and GIT tract, on IHC they demonstrate positive ER, PR, and GCDFP [34, 37].

In conclusion, breast metastasis from extra-mammary sites is uncommon with poor prognosis; clinical presentation might be quite misleading to primary breast cancer. Confirmation through the clinical presentation, clinical history, histopathology, Immunohistochemistry, and radiological examinations is crucial to ensure the appropriate therapy and avoiding unnecessary surgical treatment

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