

Isolated Colonic Metastasis from Carcinoma of the Breast: An Unusual Site of Metastasis

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ABSTRACT

Gastrointestinal (GI) metastasis is very rare in patients with breast cancer. This study reports a case with colon metastasis originated from breast cancer. A 52 year old female presented with abdominal pain and Left axillary mass. Immunohistochemistry (IHC) results done on breast showed positive for CK 7 and BRST and negative for CK 20 ER and PR positive and Her 2 neu negative. Colon biopsy was also positive for IHC markers CK 7 and BRST and E cadherin patchy positive, CK 20 negative. The pathologist reported metastatic breast carcinoma spread to the colon. Patient was managed on lines of breast cancer and underwent local surgery and metastasectomy as was taken as oligometastatic breast cancer. But as no formal guidelines are there, so treatment plan is individualized depending upon number and site of metastases and treatment is not uniform.

Keywords: Colon, Breast carcinoma, Oligometastatic, Unusual Sites.

INTRODUCTION

Metastatic breast cancer is a heterogeneous disease, which includes both single metastatic lesions and diffuse involvement of multiple organs. Breast cancer subtypes show a strong correlation to site-specific metastasis patterns. Patients with all subtypes were most prone to bone metastases, and Her 2 neu amplified subtype patients had a higher probability of brain and liver metastases. While patients with triple negative breast cancer primarily presented with lung metastasis [1]. Unusual sites of metastases are frequently seen in breast cancer with increased propensity in lobular carcinoma [2].

CASE PRESENTATION

52 years old female presented in Oncology OPD with complains of dyspepsia, vomiting and constipation since 4 to 5 months, associated with abdominal pain and weight loss. Upon inquiring further she also complained of Left axillary lump.

On examination she had Left axillary tail firm swelling mx 3 x 2 cm. On abdominal examination no mass was palpable but gut sounds were sluggish. Rest of systemic examination was normal. Investigations were carried to make diagnosis.

RADIOLOGY DETAILS

Patient had bilateral mammogram done which showed multiple soft tissue density areas in left axillary tail region,

matted together and was labelled as Birads IV (**Fig. 1**). Right breast was Birads III. In her metastatic workup, bone scintigraphy was negative but CT scan Chest and abdomen showed bowel wall thickening and luminal



Fig. (1): Mammogram (Medial-Lateral) view showing multiple soft tissue density areas in left axillary region.

narrowing involving distal descending colon (**Fig. 2**) and proximal ascending colon also demonstrating similar lesion. No other metastases were found.

ENDOSCOPIC FINDINGS

Patient then underwent colonoscopy which showed mass lesion at 52 cms from anal verge, causing luminal narrowing and scope could not be negotiated beyond this lesion. Biopsy was taken.

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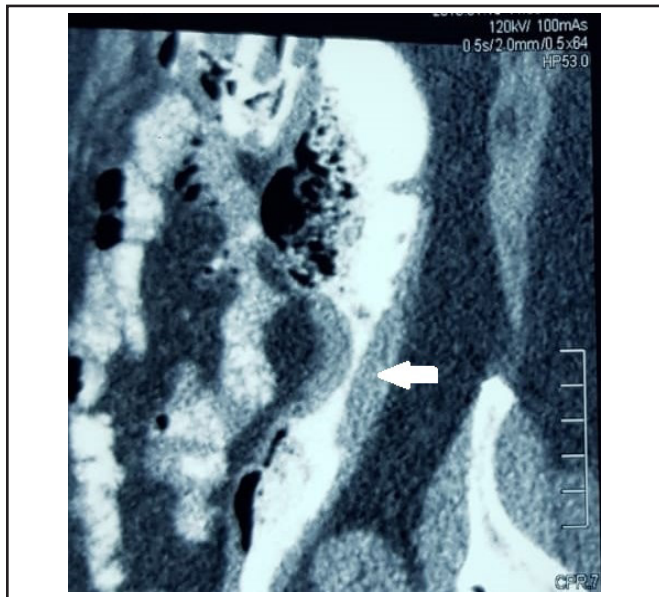


Fig. (2): Contrast-enhanced computed tomography (CT). A contrast-enhanced CT image reveals bowel wall thickening of colon and luminal narrowing.

HISTOPATHOLOGY DETAILS

Axillary Lymph Node Biopsy:

Left axillary mass was biopsied which was a lymph node on gross examination and microscopically showed sheets and clusters of neoplastic cells having vesicular pleomorphic nuclei with coarse chromatin variably prominent nucleoli and moderate pale staining cytoplasm with distinct cell borders and on IHC positive for CK 7 and BRST and negative for CK 20 favoring breast primary which is estrogen and progesterone receptor positive and Her 2 neu negative.

Colon Biopsy:

To clarify colon mass, biopsy showed tumor cells having vesicular nuclei and moderate cytoplasm, IHC showing CK 7 and BRST and E cadherin patchy positive, CK 20 negative, metastatic carcinoma favoring breast primary.

TREATMENT COURSE

She was diagnosed as Left Ca breast with oligometastases in colon. As there was suspicion of bowel obstruction thus she underwent elective defunctioning ileostomy and started on docetaxel. Patient responded to treatment and after 18 weeks of docetaxel, clinically the axillary lump became impalpable. Oncologist planned to continue chemotherapy for 6 more weeks and then re-evaluate but as patient was reluctant for further chemotherapy thus her case was kept in Breast tumor board where it was decided to get a Pet scan and case to be kept in multidisciplinary meeting.

PET Scan:

Pet scan was done which showed mild soft tissue thickening seen over cecum with nonhomogeneous FDG uptake, representing residual disease and no other hypermetabolic disease.

TUMOR BOARD DECISION

Participants included medical oncologists, breast surgeon, general surgeon, gastroenterologist, histopathologist, radiologist and radiation oncologist.

Question: how should this patient be managed further?

In tumor board it was decided to get colonoscopy through ileostomy till the stricture until the scope could not be passed any further. If no evidence of disease is found then options are to do modified radical mastectomy and resection of stricture followed by ileocolic anastomosis or the other option can be stenting and closure of ileostomy. Thus multidisciplinary decision was to proceed for oncological surgical management.

TREATMENT COURSE

Surgical Intervention:

Patient opted for conservation surgery so had left breast conservation surgery and sentinel lymph node biopsy. Almost 4 sentinel lymph node were sent for frozen section which were negative for malignancy thus axillary clearance was not done.

For resection of colonic mets, preoperatively there was mass at splenic flexure with disease extending up to descending colon with no distant metastasis seen. No ascites or any mass palpable at transverse and ascending colon so underwent subtotal colectomy.

Subsequent Histopathology:

On microscopic examination there was a residual breast primary T1b lesion with negative sentinel nodes with positive margins.

Colectomy specimen showed multiple foci of invasive tumor (**Fig. 3**) with IHC marker GATA 3 positive (**Fig. 4**) and CDX 2 negative (**Fig. 5**). Omentum was positive and 3 LN positive out of 14 resected lymph nodes were also positive.

SYSTEMIC TREATMENT

Patient was advised for re-shaving or mastectomy but patient was reluctant for further resection and even

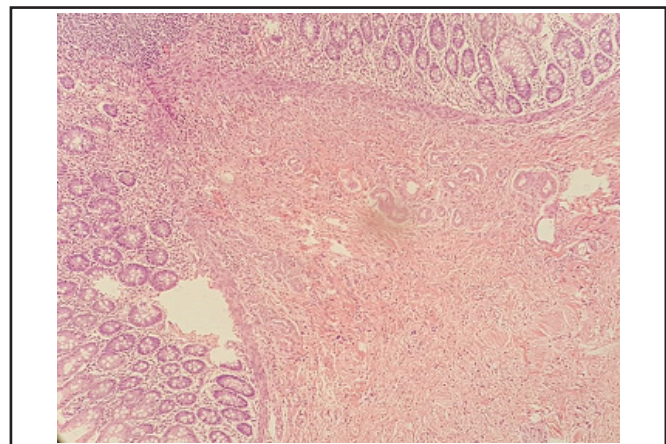


Fig. (3): Hematoxylin and eosin staining of colon (x20 magnification).

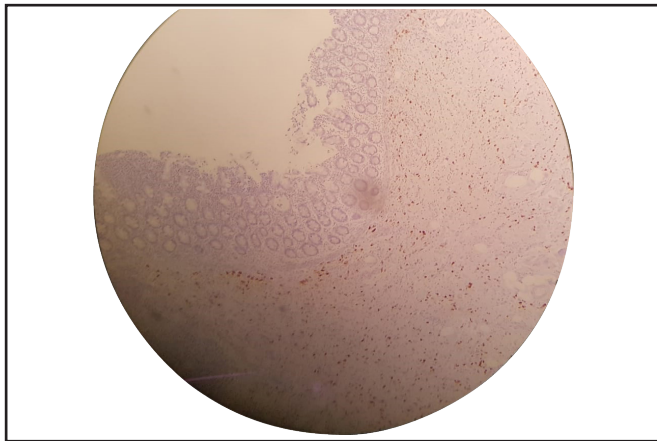


Fig. (4): Immunohistochemical stain gata performed on colon biopsy and it is positive in tumor cells.

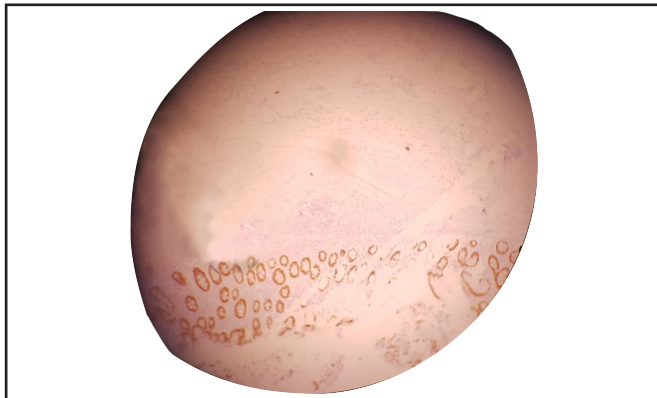


Fig. (5): Immunohistochemical stain cdx2 performed on colon specimen and it is interpreted as negative.

radiotherapy and as it was metastatic disease so decision was left upon patient and Aromatase Inhibitor was started as she was hormone positive and remained well for 18 months after which she came with obstructive symptoms.

RELAPSE

On restaging she was found to have recurrent disease in colon. She underwent colonoscopy in which a tight stricture was found at 15 cm from anal verge. For palliation of symptom patient was advised for stenting and an uncovered colonic stenting was done and started on Fulvestrant and CDK4/6 Inhibitor but after 1 month patient came with bowel perforation and she was treated conservatively but as not a surgical candidate and later she succumbed to death.

SURGEON'S PERSPECTIVE

The role of surgery in metastatic breast cancer has been under debate in the last many years. There are many studies that support the surgery and one of the reason being reducing tumor burden does have an influence on tumor growth [3-5]. It has been recommended to operate when metastatic disease is treated by systemic therapy [6]. Our patient was treated with systemic therapy first with good response. After that one can do only breast surgery

if there is no systemic residual disease. However, even if there is residual metastatic focus that can be treated locally by appropriate modality. In our patient because of colonic obstruction decision of colonic resection was made. One may do mastectomy or breast conservation, but margins must be tumor free as complete resection has been shown to have better survival [7, 8]. Our patient had margin positive disease and she refused to have further surgical intervention. Our patient had abdominal disease recurrence and reason could be extensive disease seen abdominally involving omentum even after systemic therapy. So we recommend systemic therapy in metastatic setting and operate on breast with clear margins once systemic disease is fully treated. Residual focus of systemic disease can be treated by appropriate modality including surgery, radiotherapy or RFA.

ONCOLOGIST PERSPECTIVE

Metastatic breast cancer is a heterogeneous disease, which includes both single metastatic lesions and diffuse involvement of multiple organs. Oligometastatic disease refers to one or few detectable metastases, usually less than 5 and smaller than 5 cm. The incidence of oligometastatic breast cancer is unknown, and it is estimated at 1%-10% of newly diagnosed metastatic disease. The incidence of extrahepatic gastrointestinal tract metastases observed in autopsy studies varies from 4% to 18%, with the most commonly affected organ being the stomach, followed by colon and rectum [9] and overall survival from the diagnosis of metastases was 5.8 months in patients with peritoneal metastases as compared to 22.6 months in metastatic breast cancer patients with no peritoneal involvement [10].

Prospective studies evaluating the effect of surgical resection of the primary lesion have yielded somewhat mixed results, possibly because of differences in the patient populations evaluated. In a trial from India, 350 previously untreated patients (≤ 65 years of age with an estimated remaining life expectancy of at least 1 year) presenting with de-novo metastatic breast cancer from Tata Memorial Centre, who achieved a partial or complete response to anthracycline-based chemotherapy were randomly assigned to surgery and standard postoperative radiation versus no locoregional treatment [11]. There was no difference between the two groups in regards to overall survival (19.2 versus 20.5 months in the control group). Locoregional treatment resulted in improvement in locoregional progression-free survival (median not attained versus 18.2 months) but worsened distant progression-free survival (11.3 versus 19.8 months in the control group). In this study, endocrine therapy and HER2-directed therapy were permitted when clinically appropriate; however, most eligible women did not receive these treatments. It is unclear whether locoregional therapy would have improved survival in these women if these systemic treatments had been administered.

For patients with oligometastatic breast cancer undergoing local therapy, surgery, stereotactic body radiation therapy (SBRT), or both are primarily employed according to the involved site. As breast cancer with colonic metastases is a rare occurrence thus no formal guidelines are available. Systemic therapy is the first option, and surgical treatment can be considered in patients who have limited metastatic disease and have responded well.

Our patient was found to have omentum positive in addition to disease in colon thus it was not oligometastases and hence prognosis was not as good as was expected at the time of diagnosis. Literature shows surgical cytoreduction and HIPEC with encouraging results among selected patients treated in specialized centers in patients with peritoneal carcinomatosis [12] and have prognosis equivalent to patients having oligometastatic disease. Larger and more robust studies are needed in order to determine their impact on breast cancer-specific survival.

EXPERT COMMENTS

This case of a 52 years old female clearly highlights a small sub group of breast cancer patient who will present with a breast mass that is clearly malignant however does not conform to the usual presentation of garden variety Breast cancer patients. The case also demonstrates metastases to unusual sites especially multifocal gastrointestinal and genitourinary serosal surfaces [13]. It is this very mode of presentation that clinicians are faced with when patients are diagnosed with Invasive lobular carcinoma (ILC) breast, also referred to as the evasive cancer.

My current literature search shows that ILC is still the second most common breast cancer that we see accounting for 5-15% of all cases. In the last two decades the incidence of ILC has demonstrated a rise however IDC incidence has stayed the same. Increased use of hormonal replacement therapy may be the inciting factor however enhanced awareness and improved diagnostic finesse may also have contributed to the rise in numbers.

As in the case being discussed, ILC has a distinct presentation in terms of its mammographic, histologic as well as clinical characteristics. It evades detection on routine mammogram and may present with subtle architectural distortion rather than the typical microcalcification. It requires specific additional modalities like tomosynthesis, 3D mammogram, sonogram and MRI as further aids to elucidate the abnormality.

The histologic hallmark is the functional loss of E Cadherin on Immunostaining seen by the pathologist. An astute pathologist will identify the splintered single cell infiltrative morphology of ILC that stands out as compared to IDC that demonstrates a cohesive, glued ductal pattern. E Cadherin is a transmembrane cell-cell

adhesion molecule that typically glues breast cancer cell together. By its absence in ILC the cells are separated as single cells the so called Indian filing pattern. The E Cadherin gene is mutated in ILC and could become a potential target not only therapeutically but also for early detection as in cell free DNA on liquid biopsy. LobSig is a multigene predictor of ILC and although in its early stage may become a tool to dissect out patients with ILC who can be categorized to need lesser or more intensive management. It is a field of great evolving interest.

In the clinics, patients with ILC present with multifocal, more often bilateral and advanced disease which opens door for multifaceted disease management incorporating discussion on bilateral mastectomy, hormonal therapy, chemotherapy as well as surgery for sites of metastatic disease especially involving the gastrointestinal tract when they present with obstruction or evidence of carcinomatosis [14, 15]. Initial surgical guidelines in early stage patients are along the same line as IDC, based upon traditional dogma taking into account disease extent at time of surgical visit. ILC typically presents as ER positive, grade 2 disease with low KI67 index that portends a favorable short term prognosis. However late relapses are seen commonly, hence consideration for extended hormonal manipulation or participation into clinical trials based upon gene profiling. Data from BIG 1-98 suggests that Letrozole could be superior to Tamoxifen in such patients. Generally it is felt that these patients respond poorly to chemotherapy. However guidelines for chemotherapy continue to be extrapolated from experience treating IDC patients.

It may be time to see ILC patients differently than IDC patients as they appear different entities and diseases. They present sneakily and relapse covertly and late. Their patterns of spread are entirely different as compared to the garden variety IDC. Their genomic imprints are also different. E Cadherin again highlights as the critical molecular event that may be the hallmark of its evasive potential. While IDC classically spreads to Liver, Lung and Bones. ILC has a predilection for serosal surfaces of the gastrointestinal and genitourinary tract. Metastases are commonly seen involving stomach, colon, rectum, ovaries, peritoneal/retroperitoneal spaces as well as lacrimal gland [16]. Bone spread is also seen. The etiology remains a mystery. Pet scan may not be as sensitive because of the cancer's propensity for a low proliferative index hence low SUV values on FDG which may escape metastatic sites as false negative. CT with contrast as well as bone scan is generally preferred with special emphasis on abnormal soft tissues lining serosal surfaces. PET could be exploited as a modality in addition to traditional scans.

Despite the clinical and biological differences, the broader treatment guidelines for IDC and ILC remains the same. The future holds promise regarding gene profiling and targeted therapy. A small cohort of ILC and a larger cohort of the pleomorphic variant will harbor

ERBB2 and ERBB3 mutation in the order of 5-25% with higher grade histology showing the greatest cluster of patients. ILC typically shows CDH1 and PTEN loss along with enhanced AKT activation, mutation in TBX3, FOXA1 as well as amplification of ESR1. ROS1 gene may be closely involved in loss of E Cadherin function and all of these genes may become potential targets along with attempts to recover E Cadherin function.

SUMMARY

1. It should be remembered that in patients with malignancy, a second tumor of a different origin should be considered in systemic physical examination and in all laboratory tests and imaging performed.
2. There is no definitive guideline for the treatment of synchronous tumors. The treatment plan should be planned specifically for each patient with a multidisciplinary approach.
3. Studies regarding surgical cytoreduction and HIPEC are needed to ascertain management of breast ca with peritoneal carcinomatosis.

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