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Bilateral Invasive Lobular Cancer Presenting with Multiple Gastro-Intestinal and Disseminated Metastasis

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Abstract

Invasive Lobular Cancer (ILC) of the breast accounts for about 15% of breast malignancies and tend to present as multiple lesions and involve bilateral breasts compared to Invasive Ductal Cancer (IDC). Because of its subtle symptoms, ILC would present late in terms of age and disease stage. This is a case of an otherwise healthy, middle aged women presenting with progressive abdominal distention and dyspepsia. Later she was found to have multiple widespread malignancies originating from the breast. Breast cancer metastasis to Gastrointestinal Tract (GIT) occurrence is rare and is more commonly observed among ILCs. There are few cases reported of ILC with GIT metastasis and even less with multiple GIT metastasis. Here we report a case with multiple GIT, and other site of metastasis with initial presentation of late stage breast cancer disease.

Keywords: Cancer; Breast malignancy; Gastroduodenoscopy

Introduction

Among the commonest malignancy in women is Breast Cancer (BC), Invasive Lobular Carcinoma (ILC) is the second common type of breast malignancy, after Invasive Ductal Carcinoma (IDC), accounting for about 5-16% of all breast malignancies [1]. BC commonly metastasize to regional lymph node, bone, lung, liver and brain. Metastases from BC to the Gastrointestinal Tract (GIT) are rare and occurs in less than 1% [2]. However, when considering ILC cases alone, GIT metastases occurs in as high as 6% [1]. Incidence of GIT metastasis in BC patients may be rare in clinical practice but in autopsy series, the incidence of GI metastasis in BC patient varied between 8-35% [3]. Diagnosing GIT metastasis is of importance, as their presence alters the treatment plan and modality; however, it remains a diagnostic challenge as it is rare and present with nonspecific vague GIT symptoms [3].

Case Report

A 43-year-old women who was otherwise healthy, presented with persistent dyspepsia and abdominal distention for 2 months. She had distended abdomen with fluid shifting on physical examination. After initial investigations with endoscopic Gastroduodenoscopy (EGD) and abdominal CT, she was found to have massive ascites, bilateral ovarian enlargement with irregular mass like lesion, bilateral hydronephrosis and peritoneal deposit giving the impression of ovarian cancer with peritoneal and periuretral metastasis, suggested due to hydronephrosis (Figure 1). Other primaries such as colon cancer were also considered. Her endoscopic findings showed a gastric lesion at the lower body (Figure 2). Biopsy was taken and sent for histopathological study and showed signet ring cell carcinoma which directed the provisional diagnosis towards gastric cancer as the primary disease. Afterwards, she underwent a diagnostic laparoscopy which showed a left pelvic wall mass which was histopathologically confirmed as metastatic invasive lobular carcinoma. Subsequently both mammogram and breast ultrasound were per-formed and displayed left breast mass, and a suspicious right upper central lesion in addition to prominent left axillary lymph nodes which correlated with her physical examination of left palpable mass (Figure 3). Core needle biopsy of both lesions revealed to be invasive lobular cancer (Figure 4).

After reassessment of histopathology samples of gastric, peritoneal mass and left breast, it was concluded that the gastric and peritoneal malignancies were metastatic lesions originating from primary invasive lobular cancer, supported by the strong positivity of estrogen receptor. As part of her full workup due to the peritoneal deposit and to investigate the possibility of colonic involvement, the patient underwent colonoscopy which showed multiple colonic polyps. Biopsies of two polyps turned out to be metastatic poorly differentiated carcinoma. Her bone scan showed multiple disseminated bone metastases. Genetic

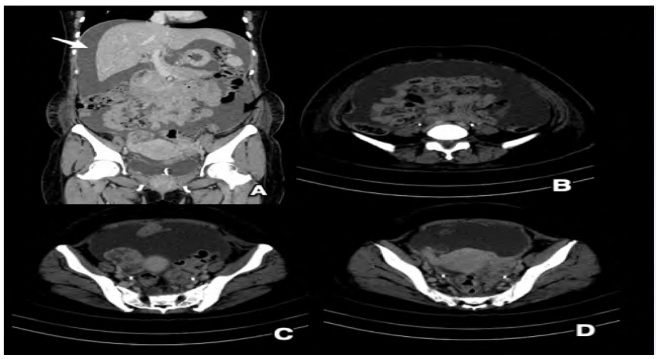

Figure 1: CT scan of the abdomen showing: (A) Coronal view, white arrow showing diffuse massive Ascites, black arrow showing diffuse peritoneal thickness and peritoneal carcinomatosis (B) Axial view showing Peritoneal deposits with, (C, D) Axial view showing irregular contoured masses and enlarged bilateral ovaries.

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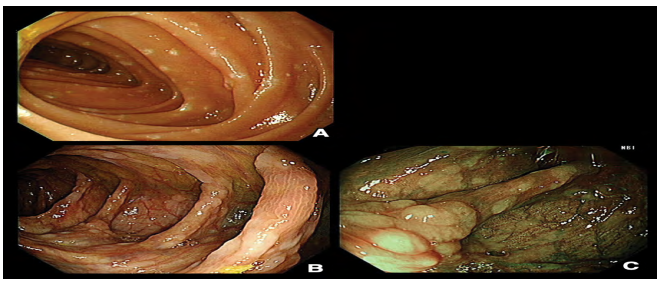

Figure 2: Upper and lower endoscopy of the patients A of the stomach, B and C of the colon showing multiple polpoyed lesions throughout the stomach and the colon.

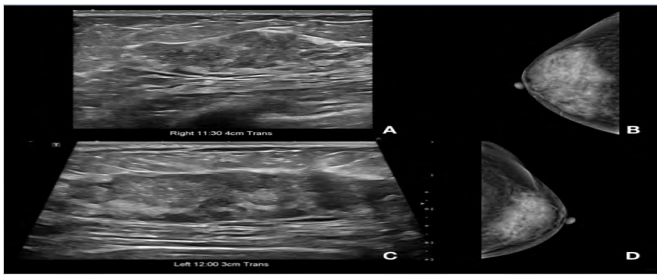

Figure 3: Ultrasound (US) and Mammogram (MMG) of Both Right and Left breast showing: (A) US Rt 2.6 mm hypo echoic mass at 11 o'clock direction 4 cm from the nipple. (B) Craniocodal MMG view of right breast showing 2.5 cm irregular isodense lesion in upper central portion (C) US Lt 50.3 mm hypo echoic mass at 12 o'clock direction 3 cm from the nipple (D) Craniocodal MMG view of left breast showing 4.8 cm irregular isodense lesion in the upper outer quadrant with calcification and architectural distortion.

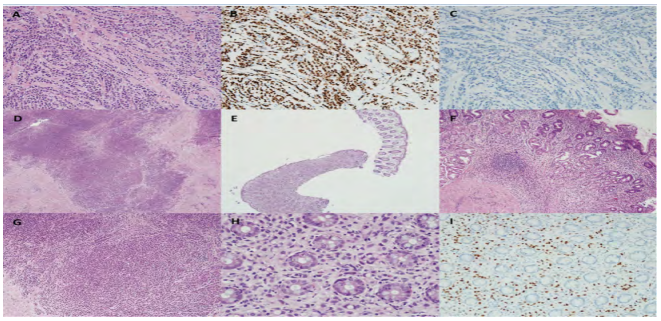

Figure 4: Invasive lobular carcinoma with multiple metastasis. (A) The tumor cells invade the stroma in linear strands in breast (Original magnification, 100x). (B) Estrogen receptor immunostain showing strong nuclear staining of the tumor cells (200x). (C) E-cadherin immunostain of invasive lobular carcinoma showing loss of expression in the tumor cells (200x). Tumor cells invade pelvic wall (D) (100x), descending colon (E) (40x), and stomach (F) (100x). Tumor cells infiltrate the stroma in linear strands in pelvic wall (G) and singly between colonic crypts (H), showing positivity for estrogen receptor (I) (200x).

testing for BRCA 1 and 2 mutations done and turn out to be negative. As a whole, the patient was concluded to have bilateral ILC, with gastric, colonic, ovarian, peritoneal, periuretral and multiple bone metastasis. She is under palliative chemotherapy along with supportive management.

Discussion

Recently, with improved screening protocols and advances in comprehensive treatment for breast cancer, more cases are detected early and managed properly. However, ILC remains a challenge owing to several issues. Due to lack of some radiological features that are frequently seen in IDC such as microcalcification, architectural distortion and desmoplastic reaction, detecting ILC in early stage is rather difficult. This explains the greater size of ILC tumors at time of diagnosis compared to IDCs, as only 3% of IDC tumors sized more than 5 centimetres at time of diagnosis whereas 6% of ILC diagnosed at the size range [4,5]. ILC also display a distinct biological behaviour, an indolent infiltration into stromal tissue, that may explain the usual clinical image of late presentation and larger tumor size. Also, the infiltrative growth of ILC contribute greater chance to metastasis to GI tract. Stomach is the commonly involved site which mimic primary gastric malignancy as in linitis plastica in case of diffuse infiltration, or as small polyp or Gastrointestinal Stromal Tumor (GIST) in case of localized infiltration [1-6].

There is a difference in the pattern of metastatic spread between the ILC and IDC. IDC spreads more to lung (46%), liver (49.1%); whereas ILC spreads more to GIT (9.7%) and ovaries (8.1%). It also demonstrates greater preference for bone involvement especially as initial site of metastasis compared to IDC as bone involvement observed in 56.8% of patients with ILC compared to 37.7% in patients with IDC [6]. Among GIT metastasis, breast is known as the second most common site of origin after melanoma, and some other reports described breast cancer as the most common cancer of origin, specifically to stomach [7,8]. Of the GIT, breast metastasize most commonly to stomach (60%), followed by oesophagus (12%), colon (11%), small bowel (8%) and rectum (7%) [9,10].

Presentation of ILC metastasis to GIT varies from synchronously with the primary tumor, to as late as 30 years after diagnosis and treatment of ILC, while a study of 21 case series had a mean interval time for the development of GIT metastasis from ILC to be 4 years [1,7]. There are several reported cases where the patient presented initially with symptoms of metastasis and were not known to be diagnosed with breast cancer prior to their presentation; one patient presented with GIT related complaints and found to have colon and gastric metastatic ILC [5]. Another patient presented with lower gastrointestinal bleeding found to have colonic metastatic ILC, with pathology showing signet ring poorly differentiated adenocarcinoma [7]. Lonzetta Neal et al., have reported a case of primary breast lobular carcinoma diagnosed after gastric metastatic lesion. The patient underwent an EGD for anorexia and fatigue, and gastric lesions exhibiting linitis plastica appearance was confirmed metastatic carcinoma from mammary origin. Her mammogram showed negative other than minimal architectural distortion at the left upper breast which was similar to subsequently performed bilateral breast MRI showing no defiant lesion. She was diagnosed to have occult breast cancer with gastrointestinal metastasis [11-15]. In our case, the patient initially presented symptoms from GIT metastasis rather than palpable mass of primary breast tumor; and was initially considered to have an ovarian primary with peritoneal metastasis. Or, a double primary of ovarian and gastric origin. The patient could have been diagnosed of breast tumor before metastasis if she has had undergone mammogram screening. There are difficulties to differentiate between primary gastric tumor and ILC metastasis especially during examining a gastro-duodenoscopy evaluation when immunohistochemistry is most likely to be absent yet. With higher incidence of primary gastric tumors in Asia, the initial diagnosis is primary gastric cancer before final diagnosis after IHC of the biopsy lesion. Immunohistochemistry staining for Cytokeratin Expression (CK) of the breast shows CK7 positive without CK20 expression, whereas gastric cancer shows high expression of CK20; which is a critical finding for differential diagnosis. Also, IHC analysis of Estrogen

Receptors (ER) and Progesterone Receptor (PR) would be of great help for diagnosis, which are essential prognostic, predictive biomarkers and a therapeutic target [1-8].

The main histologically distinguishable feature of ILC from IDC is the loss or inactivation of E-cadherin. This is assumed to be the reason for the high propensity for peritoneal and visceral metastasis of ILC compared to IDC; this inactivation is a result of mutation to *CDH1* gene. In the absence of diffuse gastric cancer, it is observed that the presence of bilateral ILC at early age is highly associated with *CDH1* germline mutation [6-13]. Presence of CHD1 mutation implies high cumulative risk for developing Diffuse Gastric Cancer (DGC), and ILC. As by age of 80 years, 70% of men and 56% of women with *CDH1* mutation will develop DGC and 42% of women will develop ILC [14]. *CDH1* mutation testing is recommended in 1st patient with two or more family member with gastric cancer one of them DGC, 2nd patient with DGC before the age of 40 years, 3rd patient with a family history of DGC and ILC, one diagnosed before the age of 50 years [14]. Also, in patient with/or family member with bilateral ILC before the age of 50 years. For unaffected *CDH1*germline mutation carrier, prophylactic gastrectomy is recommended, as well as annual breast screening with MRI starting at the age of 30 years [14]. In case gastrectomy was refused or not carried for other reason, annual gastroscopy is recommenced.

The prognosis of metastatic ILC is rather poor with median Overall Survival (OS) of 2.5 years especially in the presence of peritoneal metastasis the OS of metastatic ILC drops to 19 ± 9 months [6,10]. While there are limited large prospective data regarding the best treatment option for these cases; surgical treatment is not initially recommended for GI tumors unless in case of complications resulting from metastasis, such as obstruction or bleeding [9]. Radiotherapy for rectal bleeding due to ILC metastasis could be considered for supportive management [3]. The main treatment remains palliative systemic therapy mostly chemotherapy or combined with hormonal therapy, since most of ILC are highly express ER and or PR, as 80% of ILC metastatic group was hormone positive in comparison to 69.3% of IDC group [6]. When comparing chemotherapy to hormonal therapy, the survival analysis of a report of 78 cases by Xu et al., showed extended Overall Survival (OS) with hormonal therapy than with chemotherapy [9-15].

Conclusion

Considering the biological behaviours of ILC, clinicians should always keep high index suspicion for any nonspecific symptoms complained by patients with history of ILC and investigate the possibility of GIT and visceral metastasis. The challenge comes when the patient presents with metastatic disease and without prior diagnosis of ILC, it might be worth considering immunohistochemical staining of ER/PR when examining a patient with multiple metastasis especially when GIT, ovaries and peritoneum are involved. Early diagnosis and management would help prolong patient survival.

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