

Title: Gastric Metastasis before Diagnosis of Primary Invasive Lobular Breast Carcinoma: A Rare Case Presentation from Pakistan

Mashhood Ali¹, Shahid Aziz^{2,3}, Imran Ahmad⁴, Aiza Saadia⁵, Rabaab Zahra³, Felicity E B May⁶, David Mark Pritchard⁷, Faisal Rasheed²

Affiliations

¹Department of Gastroenterology, Pakistan Institute of Medical Sciences, Shaheed Zulfiqar Ali Bhutto Medical University, Islamabad, Pakistan.

²BreathMAT Lab, Pakistan Institute of Nuclear Science and Technology, Islamabad, Pakistan.

³Department of Microbiology, Faculty of Biological Sciences, Quaid-i-Azam University Islamabad, Islamabad, Pakistan.

⁴Department of Pathology, Shifa International Hospital, Islamabad, Pakistan.

⁵Department of Histopathology, Army Medical College, Rawalpindi, Pakistan.

⁶Department of Pathology, Northern Institute for Cancer Research, Newcastle University, Newcastle upon Tyne, UK.

⁷Gastroenterology Research Unit, Department of Cellular and Molecular Physiology, University of Liverpool, Liverpool, UK.

Abstract

Metastatic spread of invasive lobular breast carcinoma to stomach is rare especially before diagnosis of primary breast cancer. Incorrect diagnosis might result in delay of appropriate treatment for breast cancer. Recognition of this possibility enables better clinical management. A 62-year-old female presented with upper gastrointestinal symptoms and weight loss and was referred to a gastroenterologist for investigation. At the time of initial diagnosis of stomach cancer, patient was asymptomatic for breast cancer. Multiple gastric biopsies taken showed features suspicious of metastatic breast cancer. Consequently, the initial provisional diagnosis of stomach cancer changed into metastatic invasive lobular breast carcinoma. These findings were corroborated radiologically. The patient was treated with letrozole and zoledronic acid as first line therapy for one year. Residual metastatic breast cancer was present in the gastric mucosa. The patient was treated with endocrine therapy containing ribociclib and treatment was ineffective confirmed by PET-CT scan. But, her symptoms have resolved completely despite her presentation with stage IV. We present rare case of initial presentation of gastric metastasis before diagnosis of a primary invasive lobular breast carcinoma. Correct diagnosis and appropriate treatment was accomplished through initial clinical suspicion, accurate histological examination, and endoscopy together with analysis of disease specific biomarkers.

Background

Metastasis of invasive lobular breast carcinoma to the stomach occurs infrequently (Guler et al. 2018; Ma et al. 2018) and it can be diagnosed after a long period of time from primary tumor detection (Birla R et al. 2019). The rarity of metastasis from invasive lobular breast carcinoma to the stomach is occasionally confused with a primary stomach malignancy. However, discerning features with clinical implications may subsist (Hong J et al. 2019). Patients with gastric metastases from breast cancer sometimes experience nonspecific gastrointestinal symptoms (Kaneko Y et al. 2020).

The metastasis may be misdiagnosed and cause morbidity and possibly mortality. Therefore, earlier diagnosis would be helpful to avoid delay in appropriate treatment for breast cancer (Baa AK et al. 2020). Detection of gastric and breast cancer biomarkers such as transcription factor,

Globin Transcription Factor binding protein 3 (GATA3) by immunohistochemistry can assist a correct diagnosis of metastasis of mammary origin (Liu et al. 2012). We present a case of gastric metastasis of invasive lobular breast carcinoma and highlight the significance of its correct diagnosis for successful treatment of the secondary gastric metastasis and of the primary breast cancer.

Case Description

A 62-year-old female presented to her health care practitioner with hematemesis, loss of appetite and unintended weight loss of 20 lb over 2 months. On the basis of her clinical presentation, she was referred to a gastroenterologist for investigation and to a radiologist for computed tomography (CT) scan of her chest, abdomen, and pelvis. Gastroscopy revealed patchy erythema of the gastric mucosa, multiple erosions, and an ovoid lesion with a central depression in the distal gastric body and antrum (Figure 1). The gastroenterologist suspected the malignancy after hematemesis and representative gastric biopsies of the gastric lesion were taken for analysis. The histopathological examinations of the gastric biopsies diagnosed an adenocarcinoma with poorly differentiated signet ring type cell morphology. There was proliferation of atypical cells, forming groups and isolated cells with signet ring morphology in the lamina propria. Additionally, the nuclei were hyperchromatic and mitoses were also seen.

The block of gastric biopsy specimens were sent to the histopathologist for a second opinion. The microscopic examination revealed morphology consistent with invasive lobular carcinoma of breast. Moreover, sections showed gastric antral type mucosa with an infiltrative tumor composed of single and small clusters of atypical cells, showing intracytoplasmic mucin and eccentric hyperchromatic nuclei. Additionally, the immunohistochemical analysis of the gastric biopsy specimens showed positive expression of two of the breast cancer tumour markers such as CK7 and GATA3. In contrast, expressions of the CK20 and homeobox protein CDX2 were not detected (Figure 2).

The patient had a CT scan with oral and IV contrast one month after her initial presentation. An oval mass measuring 8-11 mm in short axis dimension was identified in the right breast with skin thickening and involvement of the ipsilateral axilla. Moreover, the CT scan showed an enlarged liver measuring 19 cm in the craniocaudal span, bones riddled with lytic lesions and a pathological fracture in the superior ramus of the left pubic bone.

Consequent to the findings of the CT scan, ultrasound-guided core biopsies of the right breast mass at 10 o'clock were taken for histopathology. The pathology report was indicative of invasive lobular breast carcinoma with a histopathological grade of 2. The patient had breast cancer clinical stage IV. Other microscopic descriptions were: total modified Nottingham's score, 5 out of 9; tubule formation <10% (score: 3 out of 3); nuclear polymorphism, mild (score: 1 out of 3) and mitotic figures, 1-2/10 HPF (score: 1 out of 3). The breast tumor was left *in situ*. The breast cancer tissue was analysed for expression of breast cancer biomarkers. High expression of both estrogen receptor (ER) and progesterone receptor (PgR) was detected; both were Allred score 8. Strong expression of Ki67 was also detected (Figure 3). Because the human epidermal growth factor receptor 2 (HER2) immune-reactions was considered intermediate, gene amplification was analysed by fluorescence in situ hybridization (FISH in 20 nuclei). The ratio of *ErbB2*-specific probe to general chromosome 17 probe fluorescence indicated that *ErbB2* was not amplified.

The possibility that malignant cells in the gastric lesion expressed the same biomarkers as the malignant cells in the primary breast tumour was investigated. Strong nuclear expression of estrogen receptor and membranous expression of HER2 were detected with moderate nuclear expression of PgR in the gastric biopsy specimens (Figure 2).

One month after the CT scan, a bone scan showed consistent widespread osseous metastases. Additionally, further analysis included x-ray of the lumbosacral spine, which demonstrated

heterogeneously lucent and sclerotic bone densities with metastasis, lumber spondylosis with Grade I with anterolisthesis of L4 over L5 vertebral body and left side nephrolithiasis and ureterolithiasis. The magnetic resonance imaging (MRI) of the lumbar spine suggested infiltrative metastasis in the vertebral bodies with spondylolisthesis at L4-5. Other routine tests included C reactive protein (25.4 mg/L) which was elevated (<5.0 normal), vitamin D3 (25-OH), (>160 ng/mL) which was found to be intoxicated (<20 deficiency, 20-29 insufficiency, >30 desirable and >100 intoxication). The complete blood picture showed leukocytosis, neutrophils: 66.0% (normal: 40-75%) and monocytes: 10.0% (normal: 02-12%), and anisocytosis with an increased erythrocyte sedimentation rate: 98 mm/1st hour (normal: 0-20).

Based on the overall diagnosis, the patient was prescribed letrozole (2.5 mg/*od*), zoledronic acid (4 mg/every month) and epoetin alfa (10,000 units/twice a week) to treat her advanced breast cancer and was given 1 unit of blood to treat her severe anemia (hemoglobin: 9.7 g/dl, RBC: 3.6 million/cmm, WBC: 10,800 /cmm). She was prescribed rebamipide (100 mg/*tid* for 6 weeks), pantoprazole (40 mg/*od* for 6 weeks) and feroglobin (*bid* for 12 weeks) to treat her benign gastric lesions. One year later, the patient was assessed to evaluate her condition and treatment response. A repeat gastroscopy showed that the gastric lesions had regressed and that only scar tissue was visible. Gastric biopsies were also taken to assess the treatment response. The histopathology report revealed residual metastatic invasive lobular breast carcinoma which indicates that the response was partial rather than complete. The patient was therefore prescribed endocrine therapy containing ribociclib (600 mg/*od* for 21 days) with letrozole (2.5 mg/*od*). Her symptoms had resolved completely and she was referred for a positron emission tomography (PET)-CT scan to assess the treatment response. The PET-CT scan showed fluorodeoxyglucose avid breast mass with hyper metabolic metastatic hepatic, osseous, muscular, and nodal involvements. She has survived her extensively metastatic stage IV of invasive lobular breast carcinoma for over one year.

Conclusions

In conclusion, we describe a rare case of invasive lobular carcinoma with metastases to the stomach and bones that was considered initially to be a gastric cancer. The microscopic study of gastric biopsies indicated the morphology consistent with invasive lobular carcinoma of the breast. This lead to the search of immunohistochemical markers (CK7 and GATA 3) to diagnose the breast origin of the lesion. Moreover, the expression of the breast tissue biomarker GATA3 in the gastric tissue and of ER, PgR, and HER2 in both breast and gastric tissue allowed conclusive diagnosis of breast cancer metastasis to the stomach. The immunohistochemical analysis helped to differentiate between a primary gastric cancer and metastatic breast cancer. Notably, endocrine treatment for estrogen responsive breast cancer with letrozole induced a substantial regression of the secondary gastric lesion in which ER and PgR expression had been detected. The consultants should evaluate every patient for gastric lesions with the utmost care during endoscopic procedures. In case of oozing of blood, gastric biopsy specimens should be collected for histopathological examinations in order to assess the presence of malignancy. The histological findings should be clinically correlated to manage and treat gastrointestinal malignancies especially gastric cancer. Additionally, special stains should be advised for immunohistochemical analysis in order to identify the metastatic spread and primary origin of cancer.

Disclosure of Interest

Authors have no conflicts to declare.

References

1. Baa, A. K., R. D. Naik, I. Vanidassane, S. Arora, S. A. Shamim, S. Mallick, and A. Batra.

2020. Unusual gastric metastasis in triple-negative (estrogen receptor/progesterone receptor/HER2neu negative) GATA-binding protein 3-positive breast cancer. *Indian Journal of Nuclear Medicine: IJNM: The Official Journal of the Society of Nuclear Medicine, India*, 35(1): 82.
2. Birla, R., D. Dinu, C. Iosif, and S. Constantinoiu. 2019. Gastric metastasis of invasive lobular breast carcinoma, a current diagnostic and treatment challenge—a review. *Chirurgia (Bucur)*, 114(5): 571-8.
3. Guler, S. A., T. Simsek, G. Posteki, A. Guresin, S. Cinar, U. Onbasilar, and N.Z. Canturk. 2018. A very rare reason for gastric perforation, caused by gastric metastasis of breast cancer: case presentation. *Eur J Breast Health* 15: 59-62.
4. Hong, J., Y. Kim, J. Cho, S.W. Lim, S.E. Park, H.K. Kim, and Y.H. Im. 2019. Clinical features and prognosis of breast cancer with gastric metastasis. *Oncology Letters*, 17(2): 1833-1841.
5. Kaneko, Y., K. Kajitani, M. Ohara, and Y. Daimaru. 2020. Asymptomatic solitary metastasis to the stomach from breast cancer: A case report. *Molecular and Clinical Oncology*, 13(6): 1-1.
6. Liu, H., J. Shi, M.L. Wilkerson, and F. Lin. 2012. Immunohistochemical evaluation of GATA3 expression in tumors and normal tissues: a useful immunomarker for breast and urothelial carcinomas. *Am J Clin Pathol*, 138: 57-64.
7. Ma, Y., W. Liu, J. Li, Y. Xu, and H. Wang. 2018. Gastric cancer with breast metastasis: clinical features and prognostic factors. *Oncol Lett*, 16: 5565-74.

Figure Titles and Legends

Figure 1: Gastroscopy reveals ovoid lesion with central depression along the distal stomach (distal body/antrum)

Figure 2: Expression of breast cancer biomarkers in gastric lesion. The gastric biopsy showed adenocarcinoma with poorly differentiated signet ring type cell morphology and intact normal gastric mucosa (2A H&E: 40×). Immunohistochemical staining of gastric tissue demonstrated membranous and cytoplasmic positive staining of CK7 (2B: 40×). Positive nuclear staining of GATA3 (2C: 400×), negative for CK20 (2D: 400×) and CDX2 (2E: 400×).

Immunohistochemical analyses of gastric tissue (2F: H&E 400×). Membranous and cytoplasmic positive staining of CK7 (2G: 400×) nuclear immunoreaction for GATA3 (2H: 100×), ER (2I: 100×), PgR (2J: 100×) and circumferential membrane immunoreaction for HER2 (2K: 400×). All these findings demonstrate that the gastric lesions represented metastases from breast carcinoma

Figure 3: The expression of histological markers in breast core biopsies. Breast core biopsy revealed invasive lobular breast carcinoma (3A: H&E 40×). Indian Filing Pattern of tumor cells was suggestive of invasive lobular breast carcinoma (3B: H&E 400×). Positive nuclear immunoreaction for ER (3C: 100×), PgR (3D: 400×), proportion + intensity scores: 5 + 3 = 8. Detection of HER2/neu (3E: 400×) shows positive circumferential membrane intermediate strength immunoreaction and strong expression of Ki67 (3F: 400×).

Figure 1



Figure 2

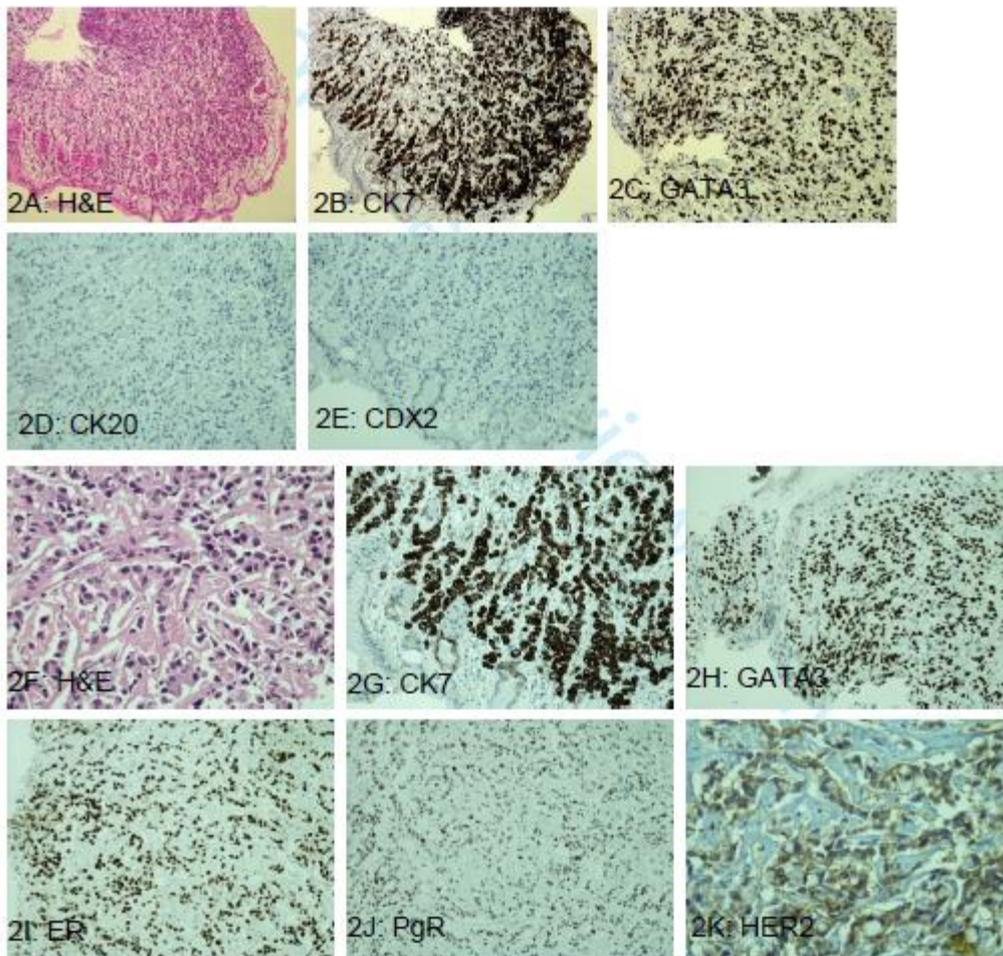


Figure 3

