

## A Patient with Gastric Metastasis of Lobular Breast Cancer with CDH1 Mutation: A Case Report

Wang H<sup>1</sup>, Li Z<sup>1</sup>, Zhang H<sup>2</sup>, Yang Z<sup>1\*</sup> and Nie J<sup>1\*</sup>

<sup>1</sup>Department of Breast Surgery, The Third Affiliated Hospital of Kunming Medical University, Kunming 650118, China

<sup>2</sup>The Medical Department, 3D Medicines Inc., Shanghai, 201114, P.R.China

### \*Corresponding author:

Zhuangqing Yang and Jianyun Nie,  
Department of Breast Surgery,  
The Third Affiliated Hospital of Kunming  
Medical University, Kunming 650118, China,  
Tel: +8613888293252,  
8613608815577,  
E-mail: 1790996705@qq.com and  
njyvip@sina.com

Received: 02 Nov 2020

Accepted: 18 Nov 2020

Published: 24 Nov 2020

### Copyright:

©2020 Yang Z et al. This is an open access article distributed under the terms of the Creative Commons Attribution License, which permits unrestricted use, distribution, and build upon your work non-commercially.

### Authors' contributions:

Wang H, Li Z, Zhang H, Yang Z and Nie J. These authors have contributed equally to this article.

### Keywords:

Invasive lobular carcinoma; Metastatic gastric cancer; Gene sequencing

### Citation:

Yang Z, A Patient with Gastric Metastasis of Lobular Breast Cancer with CDH1 Mutation: A Case Report. Clinics of Oncology. 2020; 3(3): 1-5.

### 1. Abstract

Gastric metastasis of breast cancer is extremely rare, diagnosed as breast cancer metastases to the stomach should distinguish between primary and metastatic tumors because of their differences in prognosis and management. Mutations in the CDH1 gene may increase the risk of this pathogenesis since E-cadherin plays a crucial role in both lobular breast cancer and gastric cancer.

### 2. Introduction

About 60% of breast cancer patients in face of metastasis problems during the initial diagnosis. Several case reports reported that metastatic lesions exist in the stomach after diagnosis as invasive lobular carcinoma (ILC), and differentiate metastatic or primary gastric cancer according to clinical history and pathological report. In addition, there are few similar cases reported, especially, CDH1 (cadherin-1) mutation related to gastric metastasis of invasive lobular carcinoma. The novelty of this case is that CDH1 mutation was detected in both breast and gastric tumors, which helps explain that invasive lobular carcinoma is more likely to metastasize to the stomach than other types of breast cancer.

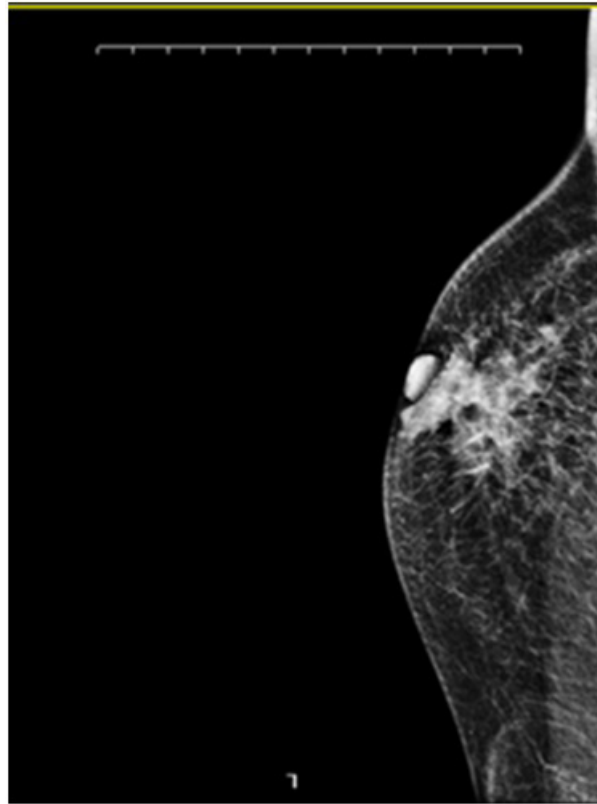
### 3. Case presentation

A 56-years-old woman, was found a small lump in her left breast in

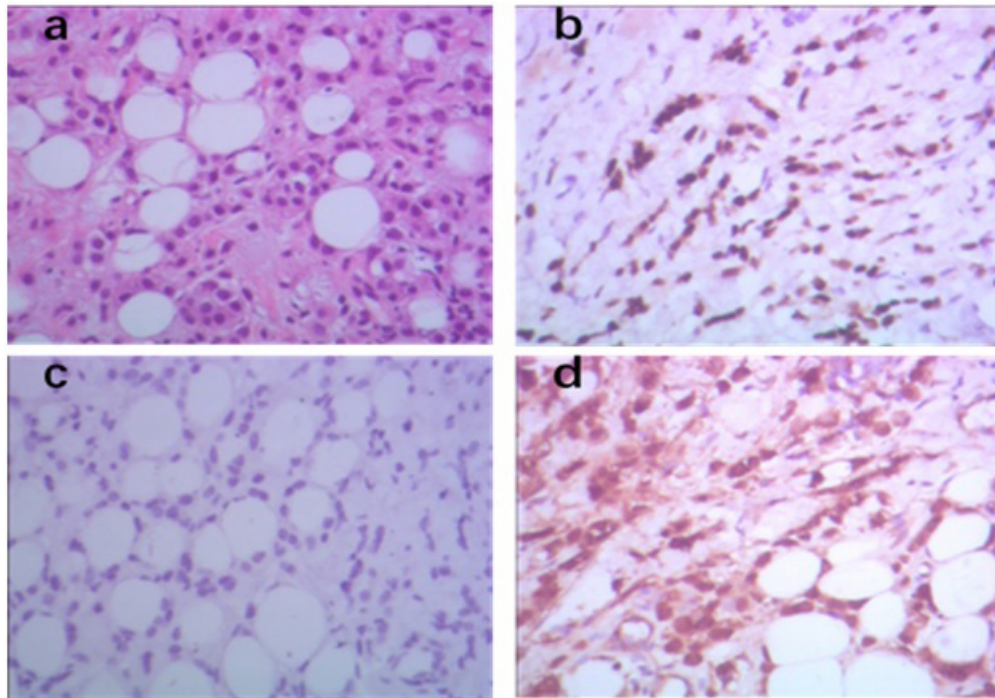
Yunnan Cancer Hospital on 2016, she was diagnosed as "cervical cancer in situ" in the outer court on December 8, 2016, and she refused to take the second biopsies to assess the pathologic change during this time. An examination of the biopsy specimen and Immunohistochemistry analysis revealed evidence of invasive lobular carcinoma, it was negative for Cerb-B2, positive for ER (about 70%) and progesterone receptor (PR, about 10%); Ki-67 expressed about 2% (Figure 1 and 2).

During the time of the patient's hospitalization, she complained of "upper abdominal pain", the competent doctor checked the computed tomography and electronic gastroscopy found the existence of extensive invasive ulceration lesion in small curvature of stomach anterior and posterior wall, the subsequent biopsy specimen confirmed the carcinoma in small curvature of the stomach (Figure 3). Whole-body bone scan showed multiple bone site metastasis.

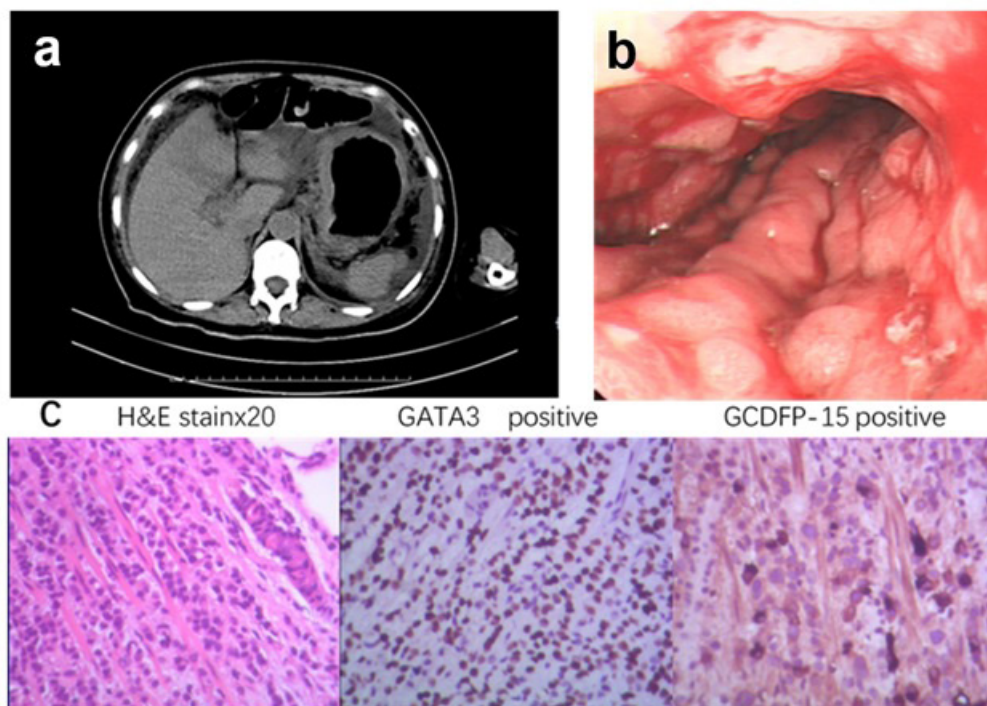
She is diagnosis as breast cancer (lobular carcinoma, cT2, N1, M1, Stage 4, estrogen and progesterone receptor-positive, Her-neu negative). On October 22, 2019, we conduct 20,000 exon sequencing by "WES", CDH1 mutations were detected in breast and gastric tissue (Table 1 and 2). She was married and had a daughter, menarche at 25-years-old, menopause at 53-years-old.



**Figure 1.** Mammography image. A lump in the central of left breast, about the size of 2.5 x 4.3 x 3.5cm, consider breast cancer, lesions may involve nipples.



**Figure 2:** Pathological diagnosis of the tumor tissue sample. (a). Hematoxylin-eosin staining (x20), immunohistochemical analysis of estrogen receptor (b), E-cadherin negative (c); P120 cytosolic positive (d)



**Figure 3.** (a). CT Scan of Abdomen Plain and enhanced CT of the upper and middle abdomen. (b). Gastroscopy displayed the antrum and body of the stomach nodular mucosal thickening with a thickened gastric fold. (c). Hematoxylin-eosin staining of the left breast specimen (x20).

**Table 1:** Whole exome sequencing (WES) of tumor samples and matched normal DNA

**Table 1 Breast lesion tissues of the 20,000 exon sequencing**

	PI3KCA	CDH1
mutation site	p.E726K Exon14 p.H1047R Exon21	p.K608Sfs x5 Exon12
copy number	13.95% 11.83%	12.26%

**Table 2:** Next-generation sequencing findings for the primary breast tumor tissue samples.

**Table 2. Breast lesion tissues of the next-generation gene sequencing**

	PI3KCA	CDH1
mutation site	p.H1047R Exon21 p.E726K Exon14	p.K608Sfs x5 Exon12
copy number	11.34% 8.13%	13.68%

On examination of the breasts and axillae, the central area of the left breast can touch the size of about 3.5 x 2.5cm lump, the size of left armpit lymph nodes was 2.0 x 1.5cm probably, the neck lymph did not touch the swollen lymph nodes.

This patient at high recurrence risk for she had multiple metastases, and we consider she exists a visceral crisis, according to NCCN

guidelines, she should receive chemotherapy at first. Chemotherapy don't recommend either due to she ECOG scores 3 points, we recommended endocrine treatment for the expression of ER was positive, endocrine drugs for metastatic breast cancer include aromatase inhibitors, fulvestrant, and CDK4/6 inhibitors. Finally, she was referred for palliative treatment with everolimus and CDK4/6 inhibitors. She had been detected PI3KCA gene mutation, suggests that the patient may be resistant to endocrine therapy. Some studies showed that PI3KCA may lead to secondary drug resistance to anti-estrogens treatment [1], P13K/mTOR is a reasonable target to improve the efficacy of endocrine therapy [2].

What's more, other accompanying diagnostic tests about FDA-approved targeted drugs were negative.

The level of breast cancer biomarker CA15-3(289Ku/L, normal<=25u/L), and reduce to normal range on March 24, 2020, she feels the abdominal distention relived. We don't recommend the patient take surgery for she had advanced body multi-metastasis. McLemore et al reported that surgery did not have a significant impact on the overall survival of metastatic breast cancer [3], hormonal therapy has proven efficient for gastric lesion caused by gastric metastasis of ILC, especially when it was positive for hormone receptors [4]. There was a literature report that metal stents can be placed in the patient's Pylorus to relieve her symptoms [5]. Zoledronic acid in the treatment of breast cancer bone metastasis would recommend regardless of surgical treatment

#### 4. Discussion

Breast cancer gastric metastasis is extremely rare, the rate in clinical was only 0.2%-0.7%, account for about 1-5% in all types of breast cancer metastasis, the mostly pathology type was invasive lobular carcinoma [6, 7]. Diagnosed as Breast cancer metastasis to the stomach, should distinguish between primary and metastatic tumors, from the medical history of development, breast ultrasound found a malignant lump in her left breast in 2016, she appeared with gastrointestinal symptoms in 2019, pathology data of gastric tissue also support our diagnosis. We also rule out the possibility of cervical cancer transfer to the stomach, the incidence of cervical cancer metastasis to the stomach is lower compared to breast cancer gastric metastasis [8, 9], what's more, there are differences in the speed of disease progression between cervical cancer and ILC, ILC has the characteristics of strong invasiveness, the majority of patients have made significant progress when diagnosed [10], only a few intraepithelial neoplasias of the uterus can progress from precancerous lesions to invasive cancer within 8-15 year [11].

Patient's CDH1 mutation can support the diagnosis, CDH1 is associated with ILC, the mechanism of ILC transfer to the stomach is not entirely clear, but the absence of cell adhesion molecule is involved in this clinical behavior [12]. A study found that E-cadherin protein expression loss accounted for 84% in ILC (32/38), which can lead to E-cadherin loss of gene amputation accounted for 55% in shorter mutations (21/38) [13].

At present, the research on CDH1 mutation mainly focuses on the family history of diffuse stomach cancer (HDGC), separation of cadherin catenin complex on cell membrane more likely to occur in ILC compared to HDGC [14], which indicated that there was a high probability of stomach metastasis source of breast cancer. There was not hot-spot CDH1 mutations study in metastatic breast cancer, other studies found that the mutation of E-

cadherin mRNA exon 9 can be used as a marker for patients with HDGC [15], gene test report in this patient: mutation of E-cadherin mRNA exon 12. Although there is no FDA-approved CDH1 targeted drug currently, some studies have found that target in molecules associated with abnormal changes in E-cadherin can reactivate E-cadherin to inhibit tumor metastasis in HDGC. In the process of pre-mRNA conversion to mature mRNA, the abnormal shearing process is associated with E-cadherin mutation [16], thus the abnormal shearing mutants can be used as molecular targets. Studies have suggested that aspirin can reduce the high methylation ratio of the CDH1 gene in HDGC and reactivate E-cadherin to inhibit tumor metastasis [17, 18].

In general, the prognostic significance of CDH1 mutation on gastric metastasis and molecular target research is still lacking, the patient's genetic test data could provide a reference value for breast cancer gastric metastasis screening and diagnostic consultation.

#### 5. Acknowledgements

This work was supported by the National Natural Science Foundation of China (Grant No. 81760480;81360392;81960479) and Science and Technology Innovation Team of Yunnan Province (Grant No.2018HC002).

#### 6. Disclosure statement

All authors declare that they have no conflict of interest.

#### References

1. Ma CX, Reinert T, Chmielewska I, Ellis MJ. Mechanisms of aromatase inhibitor resistance. *Nature reviews. Cancer.* 2015; 15(5): p. 261-275.
2. Bosch A, Li Z, Bergamaschi A, Ellis H, Toska E, Prat A, et al., PI3K inhibition results in enhanced estrogen receptor function and dependence in hormone receptor-positive breast cancer. *Sci Transl Med.* 2015; 7(283): p. 283ra251.
3. McLemore EC, Pockaj BA, Reynolds C, Gray RJ, Hernandez JL, Grant CS, et al. Breast cancer: presentation and intervention in women with gastrointestinal metastasis and carcinomatosis. *Ann Surg Oncol.* 2005; 12(11): p. 886-894.
4. Ciulla A, Castronovo G, Tomasello G, Maiorana AM, Russo L, Daniele E, et al., Gastric metastases originating from occult breast lobular carcinoma: diagnostic and therapeutic problems. *World J Surg Oncol.* 2008; 6: 78.
5. Trindade AJ, Hung CK, Zimmerman HM, Benias PC. Placement of a lumen-apposing metal stent for palliation of malignant pyloric stenosis. *Endoscopy.* 2018; 50(8): E210-E211.
6. Borst MJ, Ingold JA. Metastatic patterns of invasive lobular versus invasive ductal carcinoma of the breast. *Surgery.* 1993; 114(4): p. 637-641; discussion 641-632.
7. De Palma GD, Masone S, Rega M, Simeoli I, Donisi M, Addeo P, et al., Metastatic tumors to the stomach: clinical and endoscopic features. *World J Gastroenterol.* 2006; 12(45): p. 7326-7328.
8. De Lima VA and Cavalcanti AR, [Uterine cervix carcinoma with metastases to the stomach; case report]. *Rev Bras Gastroenterol.* 1956; 8(6): 357-360.
9. Ivan'ko AI and Moloshok AA, [Metastasis of a cervical cancer to the gastrointestinal tract (1 case)]. *Vopr Onkol.* 1982; 28(3): p. 99-100.
10. Thomas M, Kelly ED, Abraham J, Kruse M. Invasive lobular breast cancer: A review of pathogenesis, diagnosis, management, and future directions of early stage disease. *Semin Oncol.* 2019; 46(2): p. 121-132.
11. Schiffman M, Castle PE, Jeronimo J, Rodriguez AC, Wacholder S. Human papillomavirus and cervical cancer. *Lancet.* 2007; 370(9590): p. 890-907.
12. Keller G, Vogelsang H, Becker I, Hutter J, Ott K, Candidus S, et al. Diffuse type gastric and lobular breast carcinoma in a familial gastric cancer patient with an E-cadherin germline mutation. *Am J Pathol.* 1999; 155(2): p. 337-342.
13. De Leeuw WJ, Berx G, Vos CB, Peterse JL, Van de Vijver MJ, Litvinov

- S, et al., Simultaneous loss of E-cadherin and catenins in invasive lobular breast cancer and lobular carcinoma in situ. *J Pathol.* 1997; 183(4): p. 404-411.
14. Morrogh M, Andrade VP, Giri D, Sakr RA, Paik W, Qin LX, et al., Cadherin-catenin complex dissociation in lobular neoplasia of the breast. *Breast Cancer Res Treat.* 2012; 132(2): p. 641-652.
  15. Karl-Friedrich B, Kremmer E, Eulitz M, Becker I, Handschuh G, Schuhmacher C, et al. Analysis of E-cadherin in diffuse-type gastric cancer using a mutation-specific monoclonal antibody. *Am J Pathol.* 1999; 155(6): p. 1803-1809.
  16. Miura K, Fujibuchi W and Sasaki I, Alternative pre-mRNA splicing in digestive tract malignancy. *Cancer Sci.* 2011; 102(2): p. 309-316.
  17. Tahara T, Shibata T, Nakamura M, Yamashita H, Yoshioka D, Okubo M, et al., Chronic aspirin use suppresses CDH1 methylation in human gastric mucosa. *Dig Dis Sci.* 2010; 55(1): p. 54-59.
  18. Tahara T, Shibata T, Yamashita H, Nakamura M, Yoshioka D, Okubo M, et al. Chronic nonsteroidal anti-inflammatory drug (NSAID) use suppresses multiple CpG islands hyper methylation (CIHM) of tumor suppressor genes in the human gastric mucosa. *Cancer Sci.* 2009; 100(7): p. 1192-1197.