Genomic and clinical-pathological features of mucinous cystadenocarcinoma of the breast with HER2 amplification: A case report

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Abstract. Mucinous cystadenocarcinoma (MCA) of the breast is a rare, invasive carcinoma that resembles pancreatobiliary or ovarian MCA in terms of histological appearance. Most cases of MCA of the breast are negative for the estrogen receptor, progesterone receptor and ERBB2 (HER2). To the best of our knowledge, only five reports of HER2-positive MCA cases have been reported in the English language, and no reports focusing on the molecular characteristics of HER2-positive MCAs have been published. In the present study, a rare case of a 64-year-old woman with HER2-positive MCA who underwent long-term follow-up without recurrence or distant metastasis is reported. In addition, a detailed analysis of the genomic characteristics of the tumor is provided.

Introduction

Primary breast mucinous cystadenocarcinoma (MCA) is a rare and newly recognized entity according to the 5th edition of the World Health Organization classification of breast tumors (1). Since it was first reported by Koenig and Tavassoli in 1998 (2), only ~40 cases of primary breast MCA have been reported in the English language according to the PubMed database (https://pubmed.ncbi.nlm.nih.gov/). Most of these cases are case reports. Primary breast MCA, similar to pancreatic-biliary or ovarian variants, features cystic structures lined with tall columnar cells rich in intracytoplasmic mucin (1). Before the primary MCA of the breast is diagnosed, ovarian and pancreatic sources should be excluded. The entity is typically triple-negative breast cancer (TNBC), which is characterized by negative expression of HER2, progesterone receptor (PR) and estrogen receptor (ER) (1), but rare HER2-positive cases have been reported. To the best of our knowledge, only five cases of HER2-positive MCA have been reported in the English language (3-7). Due to the rarity of the disease, the clinical characteristics, molecular pathogenesis and prognosis of HER2-positive MCA are poorly understood, and the standard treatment regimen remains controversial.

In the present study, a HER2-positive primary breast MCA case is reported. Although the patient did not receive anti-HER2 targeted therapy after surgery, there was still no recurrence or distant metastasis after 104 months of follow-up. This unusual tumor was genetically profiled to provide an improved understanding of its molecular characteristics.

Case report

A 64-year-old woman was admitted to The Second Affiliated Hospital of Guangzhou University of Chinese Medicine (Guangzhou, China) on March 7, 2016, complaining of a left breast mass 1 week prior. Mammogram revealed a high-density mass measuring ~22x20 mm in the left breast, which had an irregular shape with some marginal burrs and no malignant calcification (Fig. S1). The mass was classified as Breast Imaging Reporting and Data System (BI-RADS) 5th Edition (2013) category 4C (8). The patient subsequently underwent left breast-conserving surgery and sentinel lymph node biopsy on March 11, 2016.

On gross examination, the tumor measured 2.2x1.8x1.7 cm and had well-defined boundaries. The cut surface appeared gray-white and gelatinous. The samples were sent for standard pathological analysis. The tissues were prepared as paraffin-embedded tissue blocks after being fixed in 10% neutral formalin fixative for 24 h at 25˚C. Sections that were 4-μm thick were produced for hematoxylin-eosin, Alcian blue and periodic acid-Schiff (AB-PAS) and immunohistochemical staining, as well as HER2 fluorescence *in situ* hybridization (FISH). The sections were deparaffinized with xylene and rehydrated with anhydrous ethanol, 95% ethanol, 80% ethanol, 70% ethanol and distilled water. Subsequently, the sections were stained with hematoxylin for 10 min and eosin for 4 min, both at room temperature. AB-PAS staining

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was carried out using the AB-PAS Stain Kit (cat. no. G1285; Beijing Solarbio Science and Technology Co., Ltd.), following the manufacturer's instructions. All immunohistochemical staining was performed using the antibodies listed in Table SI and a Ventana BenchMark ULTRA immunostainer (Roche Tissue Diagnostics) according to the manufacturer's protocols. Chromogenic detection was performed using the OptiView DAB IHC Detection Kit (cat. no. 760-700; Roche Tissue Diagnostics), which contains biotinylated secondary antibody, streptavidin-HRP conjugate and DAB substrate. Histopathological features (H&E staining), immunohistochemical profiles and AB-PAS staining results were analyzed using an Olympus BX46 brightfield microscope. All images of H&E staining, immunohistochemical staining and AB-PAS staining were captured using an Olympus DP27 digital camera (Evident Corporation) mounted on either a BX46 microscope or a NanoZoomer 2.0 HT (Hamamatsu Photonics K.K.). The HER2 FISH assay was performed using a HER2 gene detection kit (cat. no. F.01359; Guangzhou LBP Medicine Science & Technology Co., Ltd.) according to the manufacturer's protocols. HER2 FISH photomicrographs were collected using a fluorescence microscope (BX51; Olympus Corporation) and a ProgRes MF cool CCD (Jenoptik).

Microscopic examination revealed a cystic solid mass within the breast tissue, which had relatively clear boundaries but no capsule (Fig. 1A). The cystic spaces were lined with tall columnar tumor cells arranged in a complex pattern, including multilayered, papillary, small-cluster and scattered configurations (Figs. 1B and S2). The tumor cells exhibited moderate-to-severe nuclear atypia (grades 2-3; Fig. 1C) according to the Nottingham grading system (1). A small focus of high-grade ductal carcinoma *in situ* (DCIS) was observed adjacent to the tumor, and the diagnosis was further confirmed by the presence of intact myoepithelial cells demonstrated through immunohistochemical staining for p63 (Fig. 1D). Immunohistochemistry revealed that the tumor cells were positive for CK7, E-cadherin, GATA-3, mammaglobin, mucin (MUC)1, MUC2 and MUC5AC (Figs. 2A, 2B and S3A-E). p53 protein showed strong diffuse nuclear immunoreactivity in ~90% of the tumor cells (Fig. S3F). The Ki-67 labeling index was ~50% (Fig. S3G). ER, PR, GCDFP15, CK5/6, EGFR, CK20, CDX2, SATB2, paired box 8 (PAX8), WT1 and transcription termination factor 1 expression was negative (Figs. 2C and S4). Calponin, smooth muscle myosin heavy chain and p63 staining revealed that myoepithelial cells were absent both at the periphery and in the inner part of the tumor (Fig. S5). HER2 immunohistochemical staining was positive (score 3+; Fig. 2D) and HER2 FISH revealed a clustered amplification pattern (Fig. 2E). AB-PAS staining confirmed that the tumor had abundant, blue-stained acidic intracellular and extracellular mucin (Fig. 2F). The surgical margins were negative and the sentinel lymph node biopsy results were negative (0/9).

To exclude the possibility of metastatic spread of MCA from other organs, which are more commonly associated with MCA occurrence, to the breast, a comprehensive physical examination and a series of imaging investigations were conducted. The pelvic ultrasound examination showed no abnormalities in both ovaries, the abdominal ultrasound did not detect any abnormal changes in the pancreatic region and chest radiography demonstrated normal pulmonary findings. In the present case, positive immunohistochemical staining for GATA-3 and mammaglobin suggested a primary breast origin, whereas positive CK7 and negative PAX8, CK20 and CDX2 helped to exclude the possibility of the MCA originating from the ovaries, pancreas and gastrointestinal tract. In addition, the presence of a small focus of DCIS around the tumor further suggested a primary breast origin.

Primary MCA of the breast also needs to be distinguished from other primary breast tumors with mucin secretion, including mucinous carcinoma of the breast and encapsulated papillary carcinoma. Primary MCA of the breast typically displays multilocular cystic architecture lined by columnar epithelial cells containing abundant intracellular mucin and often shows ER/PR negativity. By contrast, mucinous carcinoma features tumor cell clusters suspended in extracellular mucin pools, demonstrating low-to-moderate nuclear atypia and is strongly associated with ER/PR positivity and HER2 negativity (1). Encapsulated papillary carcinoma presents as a well-demarcated lesion with papillary proliferations surrounded by a fibrous capsule, showing minimal mucin production and typically expresses ER/PR positivity but lacks HER2 amplification (1). Integrated evaluation of clinical, radiological and histopathological features revealed the following diagnostic findings: i) A patient-reported palpable mass in the left breast; ii) mammographic identification of a high-density lesion (BI-RADS 4C) with no metastatic evidence on other imaging tests; iii) histological confirmation of a 2.2-cm cystic tumor lined by tall columnar cells with abundant intracytoplasmic mucin, accompanied by adjacent DCIS and negative sentinel lymph node biopsy (0/9); and iv) immunohistochemical profiling demonstrating GATA-3 and mammaglobin co-expression with concurrent negativity for ER, PR, CK20, CDX2 and PAX8. These cumulative findings conclusively established the diagnosis of primary breast MCA as pT2pN0cM0 on March 19, 2016, based on the American Joint Committee on Cancer Staging Manual (7th edition) (9).

After surgery, considering that the patient had no lymph node metastasis or distant metastasis and the TNM stage was pT2pN0cM0, the patient received chemotherapy and radiotherapy according to the National Comprehensive Cancer Network guidelines for breast cancer version 2.2015 (10). Chemotherapy was initiated on March 24, 2016 using an EC-T regimen: Four cycles of epirubicin (60 mg/m^2 intravenous on day 1) combined with cyclophosphamide (600 mg/m^2 intravenous on day 1) administered every 21 days, followed by four cycles of docetaxel (100 mg/m^2 intravenous on day 1) every 21 days. Radiotherapy commenced on August 31, 2016 with breast-conserving intensity-modulated radiotherapy, delivering 29 fractions comprising 52.2 Gy to clinical target volume (CTV) 2 (ipsilateral breast) and 63.8 Gy to CTV1 (tumor bed and 1 cm surrounding tissue). No chemotherapy- or radiotherapy-related adverse events were documented. Although anti-HER2 targeted therapy was recommended as part of the treatment plan, the patient declined this intervention due to economic limitations.

To further investigate the genetic profile of HER2-amplified breast MCA, additional next-generation sequencing (NGS) analysis was performed on May 23, 2022. Genetic profiling

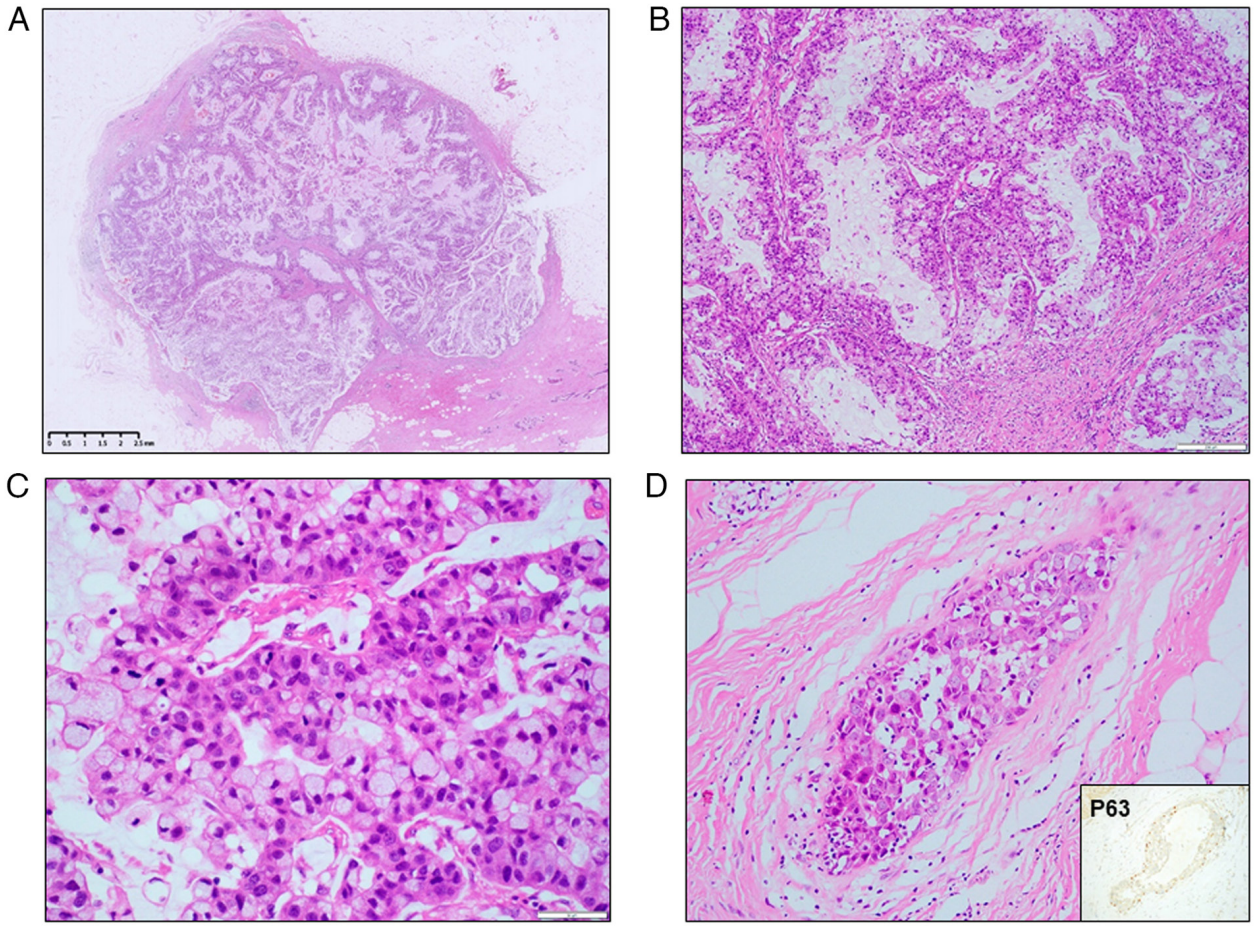

Figure 1. Hematoxylin-eosin staining images. (A) Overview of the tumor. (B) Some tumor cells were arranged in a papillary pattern inside the cyst (magnification, x100). (C) Tumor cells exhibited moderate-to-severe nuclear atypia (magnification, x400). (D) A high-grade ductal carcinoma *in situ* was observed (magnification, x200). p63 staining revealed the presence of myoepithelium (magnification, x200).

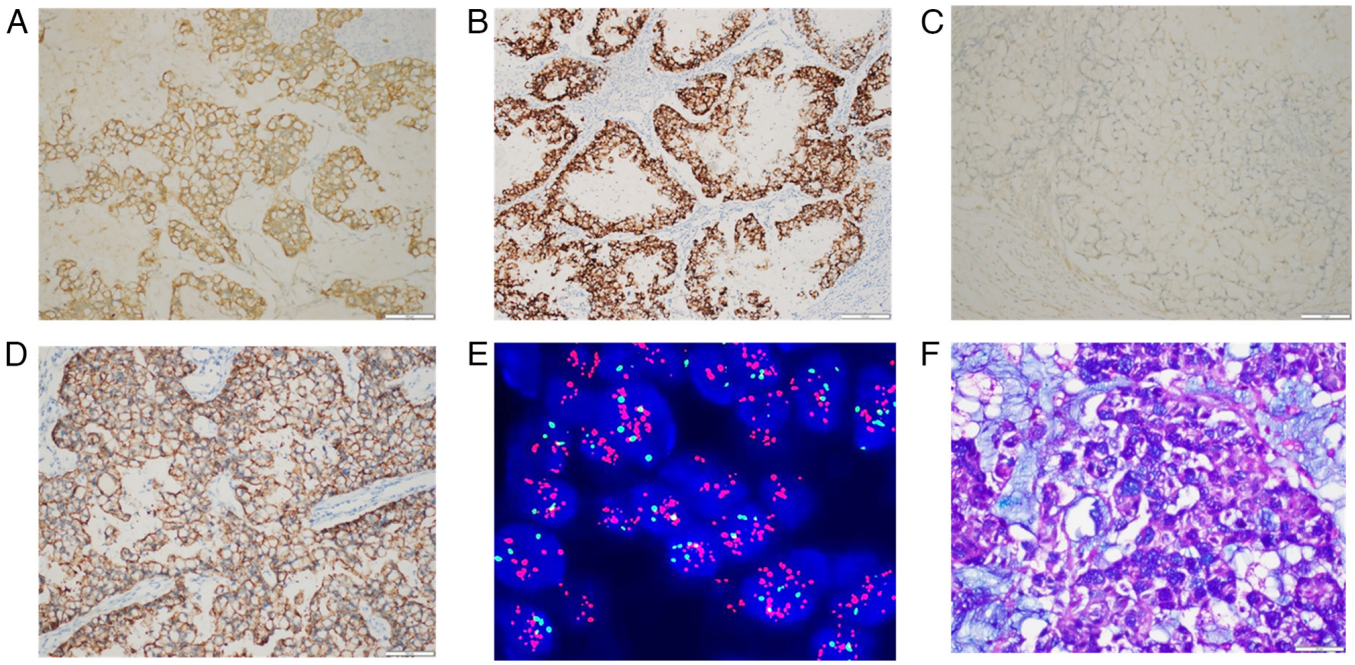

Figure 2. IHC, FISH and AB-PAS staining images. (A) Positive staining for CK7 (IHC magnification, x200). (B) Positive staining for mammaglobin (IHC magnification, x200). (C) Negative staining for CK20 (IHC magnification, x200). (D) Positive staining for HER2, score 3+ (IHC magnification, x200). (E) FISH showed clustered amplification of the HER2 gene (magnification, x1,000). (F) AB-PAS staining showed blue-stained intracellular and cystic mucin (magnification, x400). IHC, immunohistochemical; FISH, fluorescence *in situ* hybridization; AB-PAS, Alcian blue and periodic acid-Schiff.

Table I. Somatic variants detected by next-generation sequencing.

Gene	Result	Allele frequency or copy Number
ERBB2	Copy number gain	15.14
TP53	p.F134I	51.86%
	c.400T>A	
LATS1	p.H820Y	
	c.2458C>T	34.48%
NFE2L2	p.V319A	17.53%
	c.956T>C	
CDK12	Copy number gain	12.60
GRB7	Copy number gain	16.01
RARA	Copy number gain	12.09
AXIN2	Copy number gain	9.68
PRKAR1A	Copy number gain	18.74
SOX9	Copy number gain	10.31
ZNF217	Copy number gain	9.13
GNAS	Copy number gain	6.42

was conducted on formalin-fixed paraffin-embedded (FFPE) tumor samples using the Solid Tumor Multi-gene Combined Detection Kit (cat. no. MFG030041; BGI group), which comprehensively analyzes a panel of 688 cancer-associated genes (Table SII). DNA was extracted from FFPE tissues with a nucleic acid extraction kit (cat. no. MFG010019; BGI Group). DNA concentration was measured by a Qubit fluorometer (Invitrogen; Thermo Fisher Scientific, Inc.) in conjunction with the Qubit dsDNA HS (High Sensitivity) Assay Kit (cat. no. Q32854; Invitrogen; Thermo Fisher Scientific, Inc.). Library construction was performed following the protocols recommended in the aforementioned Solid Tumor Multi-gene Combined Detection Kit. Final library DNA quantification was measured by Qubit fluorometer in conjunction with the Qubit dsDNA HS (High Sensitivity) Assay Kit. The DNA concentration must exceed 16 ng/μl, with a total yield >320 ng. The sequencing reactions were performed in accordance with the instructions of the General Sequencing Kit (cat. no. 940-001802-00; Shenzhen MGI Technology Co., Ltd.) and the gene sequencer (MGISEQ-2000) manufactured by BGI Group. The sequencing type was 100 bp for length and paired end for the direction of sequencing. Data analysis was conducted using Solid Tumor Multi-Gene Detection and Analysis Software (oseq_T-v1.4.5.0; BGI Group). Table I summarizes the identified missense mutations (TP53, LATS1 and NFE2L2) and copy number gains (ERBB2, CDK12, GRB7, RARA, AXIN2, PRKAR1A, SOX9, ZNF217 and GNAS). The microsatellite status of the tumor was stable, and no clinically significant germline mutations were detected.

After the completion of treatment, the patient underwent 6-monthly assessments for suspicious symptoms, combined with ultrasonographic examinations of the breasts and axillary lymph nodes, cervical and supraclavicular lymph nodes, abdominal region and gynecological system, along with annual chest CT surveillance. The most recent breast ultrasound and chest CT (November 22, 2024) show no discernible abnormalities (Fig. S6). The patient achieved a disease-free survival of >104 months (from March 2016 resection to November 2024 follow-up), with no evidence of recurrence or metastasis throughout this period. All critical time points throughout the clinical course of the patient have been systematically summarized in Table SIII.

Discussion

Primary MCA of the breast is rare, with only ~40 cases documented in the English language according to the PubMed database (https://pubmed.ncbi.nlm.nih.gov/). Notably, HER2-positive MCAs are considerably rarer and, to the best of our knowledge, only five individual case reports have been reported prior to the present case (3-7). Table II presents the clinicopathological characteristics of the present patient and the previously documented patients with HER2-positive breast MCA. All 6 patients with HER2-positive MCA were female, and their ages ranged from 55-73 years. The tumor size varied from 2 to 18 cm. In total, 4 patients (3 of whom had confirmed HER2 FISH amplification) were reported to have a HER2 IHC 3+ score, and the other 2 cases had a HER2 IHC 2+ score with HER2 FISH amplification. All published cases of HER2-positive MCA were ER- and PR-negative. All patients underwent surgical treatment: 2 underwent partial mastectomy and the others underwent radical mastectomy. In total, 5 patients underwent lymph node evaluation, of whom 2 had lymph node metastases. Notably, among the 2 patients with lymph node metastases, 1 case showed discordant histology: The primary tumor was mixed MCA and invasive lobular carcinoma, whereas the metastasis was exclusively lobular carcinoma. Some patients received chemotherapy and radiotherapy: 3 patients received postoperative radiotherapy and chemotherapy and 1 patient received only chemotherapy. Notably, although these cases were HER2-positive, only 2 cases eventually received anti-HER2 targeted therapy. The present case did not receive anti-HER2 targeted therapy for economic reasons. The follow-up time ranged from 10 to 104 months, and the present case had the longest follow-up of 104 months. The follow-up data demonstrated that no recurrence or distant metastasis occurred in any of the 6 patients, regardless of whether they received anti-HER2 targeted therapy. Data from these limited cases suggest that HER2 positivity does not appear to alter the favorable prognosis of MCA (on the basis of the current understanding of triple-negative MCA). Given the limited number of cases, the potential benefit of anti-HER2 targeted therapy in this patient population requires validation through larger prospective studies.

At present, little is known about the genetic background of MCA. Lin *et al* (11) discovered mutations in TP53, RB1 and BAP1 in a 72-year-old woman with breast MCA, indicating abnormalities in tumor suppressor genes. Lei *et al* (12) discovered pathogenic mutations in the PIK3CA, KRAS, MAP2K4, RB1, KDR, PKHD1, TERT and TP53 genes after reporting a case of breast MCA in a 59-year-old woman. The genetic profile closely resembled that of typical high-grade TNBC, which frequently has PIK3CA, TP53, KRAS and RB1 mutations (13). Chen *et al* (14) discovered a PIK3CA hotspot mutation in a

Table II. Summary of the clinical features of previously reported HER2-positive cases and the present case.

First author, year	Age, years	Size, cm	Treatment	LNM	Immunohistochemistry	HER2 FISH	Follow-up data	(Refs.)
Petersson *et al*, 2010	73	4.5	Mastectomy and LND	-	+ve: CK7 and HER2 (3+) -ve: ER, PR, CK20 and CDX2	A	NA	(3)
Kucukzeybek *et al*, 2014	55	2	Partial mastectomy, LND, chemo trastuzumab and rad	-	+ve: HER2 (2+) CK7 and Ki-67 (30%) -ve: ER, PR and CK20	A	ANED, 10 months	(4)
Seong *et al*, 2016	59	2	Partial mastectomy	NA	+ve: HER2 (3+) -ve: ER and PR	NA	NA	(5)
Kaur *et al*, 2022	65	18	Mastectomy, LND and chemo	+	+ve: HER2 (3+), CK7, GATA3, mamaglobin, MUC1, CK20 (focal) and Ki-67 (90%) -ve: ER, PR, CDX2, SATB2, TTF1, PAX8, WT1, MUC2 and MUC5AC	A	ANED, 46 months	(6)
Guzelis *et al*, 2024	68	5	Mastectomy, LND, chemo trastuzumab and rad	+[a]	+ve: HER2 (2+), CK7 and p53 (10%) -ve: ER, PR and CK20	A	ANED, 72 months	(7)
Present case	64	2.2	Mastectomy, LND, chemo and rad	-	+ve: HER2 (3+), CK7, E-cadherin, GATA3, mammaglobin, MUC1, MUC2, MUC5AC, p53 and Ki-67 (50%) -ve: ER, PR, GCDFP15, CK5/6, EGFR, CK20, CDX2, SATB2, PAX8, WT1 and TTF1	A	ANED, 104 months	

[a]This case was diagnosed as primary mucinous cystadenocarcinoma of the breast coexisting with invasive lobular carcinoma, and the LNM was invasive lobular carcinoma. LNM, lymph node metastasis; LND, lymph node dissection; NA, not available; chemo, chemotherapy; rad, radiation therapy; A, amplification; and ANED, alive with no evidence of disease; +ve, positive; -ve, negative; ER, estrogen receptor; PR, progesterone receptor; PAX8, paired box 8; TTF1, transcription termination factor 1.

breast MCA case, but whole-genome NGS revealed no alterations in KRAS, NRAS, BRAF or AKT. Cao *et al* (15) used DNA analysis to detect mutations in BARD1, KDR, MUC6, TP53 and BRIP1 in a 51-year-old woman with breast MCA. All 4 cases of MCA that underwent genomic analysis were triple-negative. Based on a literature review and to the best of our knowledge, there have been no reports of genetic profiling for HER2-positive breast MCA to date. Although the present case shares similar clinical and histomorphological features with previously reported triple-negative MCA cases (15,16), their genetic profiles show distinct differences. In the present case, the NGS test revealed that most of the mutated genes were located on chromosome 17. Notably, ERBB2 exhibited amplification of up to 15 copies. Additionally, a series of concomitant amplifications of HER2-associated genes, including CDK12 and GRB7, were detected. According to existing knowledge, co-amplification of CDK12 and GRB7, along with ERBB2, is a common molecular event in HER2-positive breast cancer (17,18). As a transcriptional regulator, CDK12 is involved primarily in the maintenance of genomic stability; its amplification and upregulation can increase the genomic stability of cancer cells, leading to resistance to chemotherapy or targeted therapy (19). Moreover, the upregulation of GRB7, which acts as a linking molecule of HER2, strengthens the HER2 signaling process and can also promote the malignant growth of tumor cells and drug resistance (20). However, the present patient did not harbor a PIK3CA gene mutation, unlike previously reported patients with triple-negative MCA (12,14). Therefore, we consider that the present case represents a relatively typical type of breast cancer driven by the amplification of chromosome 17, resulting in the amplification of HER2 and a series of other oncogenes. A comparison of the results from the present case with those of previously reported cases revealed the heterogeneity of genomic alterations among the different MCA cases. Hence, we hypothesize that, on the basis of differences in the molecular expression profiles of tumors, it may be possible to categorize breast MCAs into two distinct subgroups, namely, the 'HER2-driven' and 'non-HER2-driven' subgroups. This hypothesis awaits further research and validation with the accumulation of more cases.

In addition, the present case harbored LATS1 mutation, NFE2L2 gene mutation and TP53 gene mutation. The downregulation of LATS1 and NFE2L2 expression serves a vital role in the carcinogenesis and progression of breast cancer (21,22). This may be one of the reasons for the favorable prognosis of the present case. However, the roles of these genes in primary breast MCA require further study, and the lack of investigations into these genes is a limitation of the present case report.

In conclusion, the present study reports a rare case of a primary breast MCA with concomitant HER2 amplification. NGS testing revealed that the tumor had the typical genomic features of HER2-driven breast cancer. Although the patient did not receive anti-HER2 targeted therapy, no recurrence or metastasis was observed after 104 months of follow-up, suggesting that HER2-positive breast MCA may have a favorable prognosis, similar to triple-negative breast MCA.

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Availability of data and materials

The NGS data generated in the present study may be found in the SRA under accession number PRJNA1229825 or at the following URL: https://www.ncbi.nlm.nih.gov/bioproject/PRJNA1229825.

Authors' contributions

LL, HY, GZ contributed to study design. ML, XQ, XZ contributed to data acquisition. LL wrote the manuscript. LL and HY confirm the authenticity of all the raw data. All authors read and approved the final version of the manuscript.

Ethics approval and consent to participate

Not applicable.

Patient consent for publication

The patient provided written informed consent for the case study to be published.

Competing interests

The authors declare that they have no competing interests.

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