Primary mucinous cystadenocarcinoma of the breast: A case report and literature review

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Abstract. Mucinous cystadenocarcinoma (MCA) is a rare breast cancer. The present study reports a case of primary MCA of the breast with a comprehensive evaluation of this rare tumour. A 51-year-old woman sought medical attention for a mass in the left breast. A core needle biopsy revealed an infiltrating adenocarcinoma with mucus secretion and papillary formation. The macroscopic appearance was of a greyish-white, tough and well-circumscribed solid mass, without a notable cyst. Microscopically, the tumour consisted of ducts and cysts of varying sizes. Varying degrees of branching papillary structures were observed in the lumen and cyst cavities. The tumour cells were highly columnar in shape, with high-grade nuclei arranged in a single-layer. Immunohistochemistry revealed that the tumour was a basal-like triple-negative breast cancer with a high proliferation index and tumour protein p53 diffuse strong expression. Mutations in breast cancer 1-associated RING domain 1 (*BARD1*), kinase domain containing receptor (*KDR*), mucin-6 (*MUC6*), tumour protein 53 (*TP53)* and breast cancer 1-interacting protein C-terminal helicase 1 (*BRIP1*) were identified using DNA analysis. The patient was followed up for 26 months and showed no signs of recurrence or metastasis. In conclusion, the current study presents a case of MCA of breast accompanied by mutations in the *BARD1*, *KDR*, *MUC6*, *TP53* and *BRIP1* genes, with no recurrence after a 26-month follow-up. Combining this case with a review of the literature helps us to better understand the clinicopathological and genetic characteristics of MCA, and guide treatment.

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Introduction

Mucinous cystadenocarcinoma (MCA) is a rare malignant breast tumour, first reported by Koenig and Tavasoli in 1998 (1). MCA was first classified as a mucus-producing breast cancer, characterised by a cystic structure with columnar cells and abundant intra- and extracellular mucin, in 2003 (2). According to the 2019 World Health Organisation classification of breast tumours, it is recognised as an independent and specialised type of breast cancer (3). Most MCA cases present with a loss of oestrogen receptor (ER), progesterone receptor (PR) and human epidermal growth factor 2 (HER2) expression, and a better prognosis compared with other triple-negative breast cancer of no specific type. To date, only a limited number of MCA cases have been reported worldwide (1,4-38). Most reports of MCA show that the tumour is not usually accompanied by axillary lymph node metastasis, and the prognosis is good. MCA is also confused with other mucus-secreting breast cancers and metastases of ovarian or pancreatic cancers (9,16,39,40). Therefore, MCA diagnosis demands precision through a comprehensive evaluation of clinical, pathological, imaging and genetic characteristics. It is also necessary to give an individualized treatment plan for MCA.

The current study reports a case of primary MCA of the breast with complete clinicopathological features and genomic profiling using next-generation sequencing for a comprehensive evaluation of this rare tumour.

Case report

A 51-year-old premenopausal woman presented to the Peking Union Medical College Hospital (Beijing, China) in June 2022, due to a mass in the left breast that had been present for nearly 1 year. The patient had no history of breast surgery, hormonal treatment or malignant tumours; however, the patient's mother had ben diagnosed with lung cancer. A clinical examination confirmed a hard mass, with a diameter of 2 cm, which could be palpated at the 2 o'clock position in the left breast. No nipple discharge or enlarged lymph nodes in the axilla were observed. Ultrasound showed a 2.4-cm irregularly hypo-echoic mass with abundant blood flow signals 2 cm away from the nipple in the direction of the 2 o'clock position on the left breast (Fig. 1). The patient had undergone a mammography examination in

another hospital prior to attending the Peking Union Medical College Hospital for treatment, and the mammography had revealed an irregularly shaped high-density mass in the upper left breast. Analysis of peripheral blood tumour indicators included results for carcinoembryonic antigen (CEA), cancer antigen (CA)153 and CA125. The serum level of CEA was elevated to 60.1 ng/ml, which markedly exceeded the upper limit of the normal range (5 ng/ml). While both the CA153 and CA125 were within the normal levels.

A core needle biopsy (CNB) of the breast mass was performed. The specimens were sent for routine pathological examination. The tissue were fixed in 10% formalin neutral fixative for at least 6 h at 25˚C and then made into paraffin-embedded tissue blocks. Sections (4-μm thick) were prepared for further haematoxylin-eosin (H&E) staining and immunohistochemical staining. After being deparaffinized with xylene and rehydrated with a series of anhydrous ethanol, 95% ethanol, 70% ethanol and PBS, some of the sections were stained with haematoxylin for 3 min and eosin for 45 sec at room temperature. All immunohistochemical staining (Table SI) was performed using a Ventana Benchmark XT Autostainer (Ventana Medical Systems, Inc.) according to the manufacturer's protocols. Finally, visualization was performed using a DAB color development kit, followed by counterstaining using haematoxylin for 3 min at 25˚C. All sections were sealed with neutral resin. Tumour morphology of H&E staining and immunohistochemical results were observed using Olympus light microscope BX53. Images were captured by a microscope camera (BASLER, acA1920-150uc).

The pathological diagnosis was a high-grade infiltrating adenocarcinoma with mucus secretion and papillary formation. Immunohistochemical markers of biopsy included ER, PR, HER2, androgen receptor (AR), cytokeratin (CK)7, CK14, CK20, CK5/6, epidermal growth factor receptor (EGFR), tumour protein p53 (p53), p63, GATA-binding protein 3 (GATA3), paired box 8 (PAX-8), special AT-rich sequence-binding protein 2 (SATB2), homeobox protein CDX-2 (CDX-2) and Ki-67 (Fig. S1). No *in situ* carcinoma was found on needle biopsy, and the tumours were ER-, PR-, AR- and HER2-negative. The neoplastic cells showed diffused strong expression of p53 and a high Ki-67 index of 70%, indicating their highly aggressive nature. The neoplastic cells were CK7-positive, and both CK20- and SATB2-negative, which excluded the possibility of a gastrointestinal origin. PAX-8 negativity excluded a gynaecological origin. The neoplastic cells were GATA3-negative, which is common in triple-negative breast cancer and is consistent with the lack of ER, PR and HER2 expression. The tumour was negative for CK5/6, CK14, p63 and CDX-2 expression, and positive for EGFR expression. Other tumours, including mucinous adenocarcinoma of the lungs and pancreatic or biliary tract cancers, should be excluded; however, the biopsy tissues were limited. Further clinical examinations are also required to distinguish metastatic adenocarcinomas from primary breast lesions. Positron emission tomography (PET)/computed tomography (CT) examination only showed a lesion with increased radioactive uptake in the upper quadrant of the left breast, measuring 1.5x1.2 cm, with a maximum standardised uptake value of 10.5 and no other lesions, confirming that it was a primary tumour (Fig. S2).

The patient underwent a left mastectomy and sentinel lymph node biopsy, and the absence of lymph node metastasis was confirmed. The surgical specimens were fixed in 10% formalin neutral fixative for at least 12 h at 25˚C and then made into paraffin-embedded tissue blocks. Sections (4-μm thick) were prepared for further H&E staining and immunohistochemical staining as aforementioned. The macroscopic appearance was a greyish-white tumour with a maximum diameter of 2.4 cm, a tough texture and a relatively well-circumscribed mass without obvious cysts. A mucous-like lustre was observed on the cut surface of the tumour (Fig. S3). Microscopically, the tumour consisted of different sizes of irregular cysts and ducts (Fig. 2A and B). Varying degrees of branching papillary structures were observed in the lumen and the cyst cavity (Fig. 2C and D). The tumour cells were highly columnar in shape, with high-grade nuclei arranged in a single or layered manner. There was a large amount of mucus both inside and outside the cells. When the tumour cells were arranged in a single layer, the intracellular mucus was more prominent and the nuclei were often located at the base (Fig. 2C). Extracellular mucus filled the lumen and cyst, and overflowed into the tumour stroma. Carcinoma *in situ* with similar morphology was observed around the invasive tumour (Fig. 2E and F).

The immunohistochemistry (IHC) staining, performed as aforementioned, and the results of the surgical specimens were similar to those of the needle biopsy. Quadruple-negative breast cancer (ER-, PR-, AR- and HER2-negative) (Fig. S1), with diffuse and strong positive expression of p53 (Fig. 3A) and a high Ki-67 index (Fig. 3B), was diagnosed, which was different from mucinous carcinoma or encapsulated papillary carcinoma that typically expresses hormone receptors. Additional markers of breast cancer, such as mammaglobin and gross cystic disease fluid protein 15 (GCDFP-15), were identified. Mammaglobin was partially positive (Fig. 3C) and GCDFP15 was focal and weakly positive, indicating that the tumour was a primary breast lesion. The absence of the myoepithelium also excluded the possibility of benign breast mucinous lesions. Papillary formation and abundant intra/extracellular mucus excluded the possibility of invasive papillary carcinomas. Finally, the patient was diagnosed with primary MCA of the breast based on these morphological and immunohistochemical features. Mucus subtype-related immunohistochemistry showed that the tumour cells mainly expressed mucin (MUC)1 and MUC6 (Fig. 3D and E), with partial expression of MUC5AC (Fig. 3F) and no expression of MUC2. DNA mismatch repair protein Msh2 (MSH-2) (Fig. 3G), MSH-6 (Fig. 3H), DNA mismatch repair protein Mlh1 (Fig. 3I) and PMS-2 were also expressed, indicating microsatellite stability. A sentinel lymph node biopsy did not reveal any metastatic tumours. For this patient, the left breast tumour had a maximum diameter of 2.4 cm, so the T stage was T2. An axillary sentinel lymph node biopsy showed no metastatic cancer, so the N stage was N0. No hypermetabolic lesions other than that in the left breast were found on the whole-body PET/CT scan, so the M stage was M0. The TNM stage (41) was therefore determined to be T2N0M0.

DNA was extracted from formalin-fixed paraffin-embedded (FFPE) tissues using FFPE tissue genomic DNA one-step extraction kit (cat. no. RC1004; Kaishuo Biotech (Xiamen) Co., Ltd.). Samples were quantified using the Qubit dsDNA

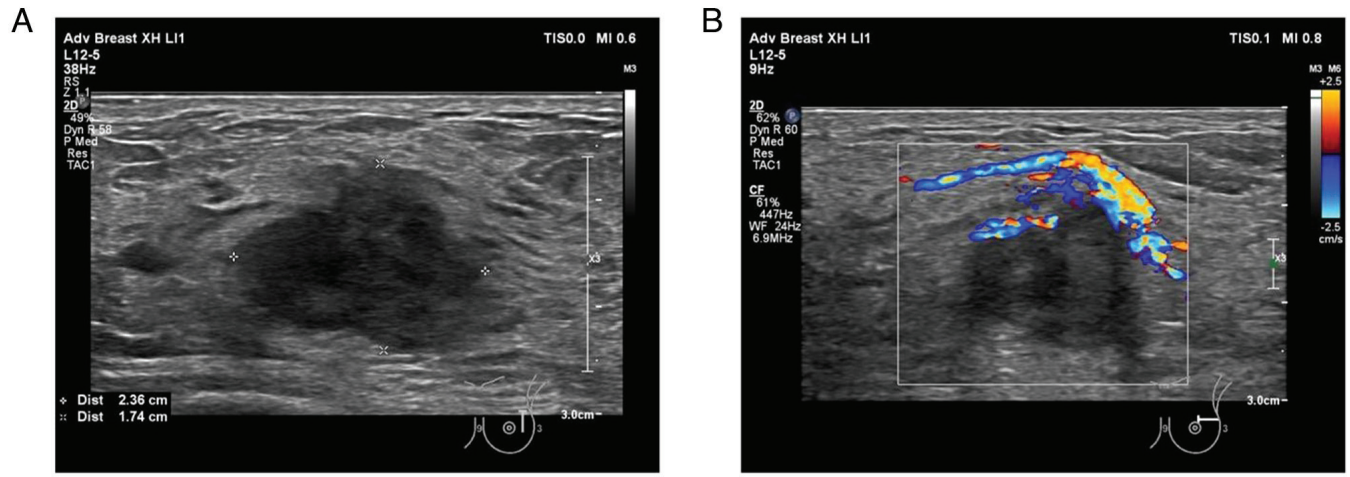

Figure 1. Ultrasound images. (A) A hypo-echoic lesion with an irregular shape and small lobulated visible, and with (B) rich and large blood flow signals around the periphery.

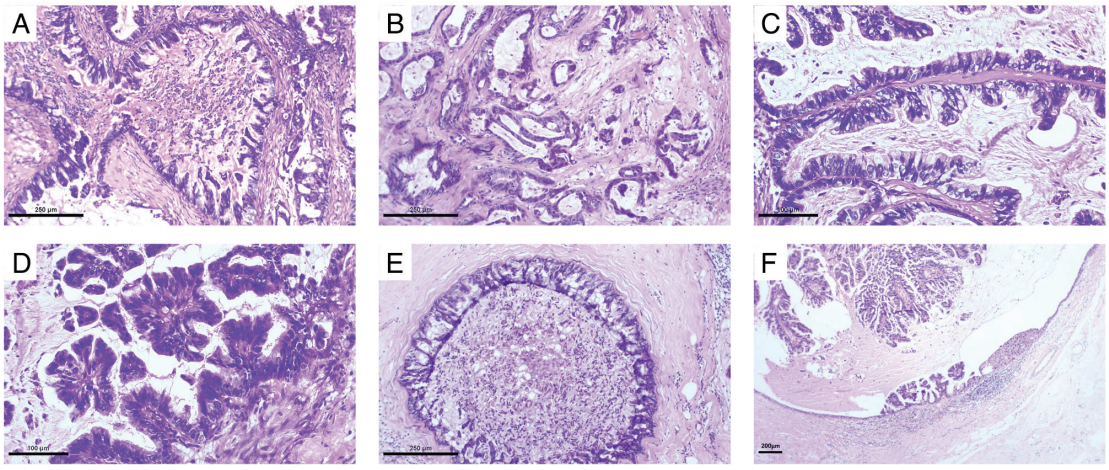

Figure 2. Histological findings. The infiltrating part of mucinous cystadenocarcinoma may present as (A) cystic spaces, lined with tumour cells forming small papillae and mucus visible both in the cytoplasm and cystic spaces (H&E; x100 magnification), as (B) glandular ducts of varying sizes and irregular small cell nests, with visible mucus broken into the stroma (H&E; x100 magnification), and as (C and D) a complex branching papillary structure with high columnar cells and abundant mucus inside and outside the cells, as shown in high magnification (H&E; x200 magnification). (E) *In situ* lesions of mucinous cystadenocarcinoma showing similar morphology with invasive lesions of this case, the duct also being lined by high columnar cells rich in mucus and having a papillary formation (H&E; x100 magnification). (F) A duct containing both normal ductal epithelium and numerous columnar cells rich in mucus with a complex papillary structure (H&E; x40 magnification). [Images (A) and (C) are images of the present case from different fields of view, with different magnifications]. H&E, haematoxylin and eosin.

BR Assay Kit (cat. no. Q32853; Thermo Fisher Scientific, Inc.), and DNA integrity was evaluated with 1% agarose gel electrophoresis. Library Preparation was performed with the Twist Human Core Exome EF Multiplex Complete Kit, 96 Samples (cat. no. PN100803; Twist Bioscience) and library concentration was quantified using the Qubit dsDNA BR Assay Kit (cat. no. Q32853; Thermo Fisher Scientific, Inc.). Library length was evaluated on an Agilent 2100 Bioanalyzer (Agilent Technologies, Inc.). Concentration in moles was calculated according to library length, and the concentration of final library was 6.8 pM and sequenced using whole-exome sequencing. The sequencing type was 150 bp for length and paired end for direction of sequencing with the NovaSeq 6000 S4 Reagent Kit v1.5 (300 cycles; cat. no. 20028312; Illumina Inc.). Two variant callers, MuTect2 (v4.1.0.0) (42) for SNV and indels, and Strelka (v2.9.10) (43) for indels, were used to call somatic variants annotated by ANNOVAR (Version: 2023Jan05) (44). CNVkit (v 0.9.11) (45) analysis was used to evaluate copy number alterations. Mutations inbreast cancer 1-associated RING domain 1 (BARD1), kinase domain-containing receptor (KDR), mucin-6 (MUC6), tumour protein 53 (TP53) and breast cancer 1-interacting protein C-terminal helicase 1 (BRIP1) were identified, and are summarized in Table I.

After surgery, considering that the patient had no distant metastasis and the TNM stage was T2N0M0, according to the Chinese Society of Clinical Oncology Breast Cancer Guidelines 2022 (46), the patient received eight cycles of chemotherapy (75 mg/m^2 intravenous doxorubicin on day 1 and 600 mg/m^2 intravenous cyclophosphamide on day 1, cycled every 21 days for 4 cycles; and sequential 85 mg/m^2 intravenous docetaxel on day 1, cycled every 21 days for 4 cycles), followed by sequential

Table I. Genetic profile identified in the present case of primary mucinous cystadenocarcinoma of the breast.

Gene	Chromosome	Exon	Type of mutation	DNA sequence change	Amino acid change	Allele frequency, %
BARD1	2	6	Missense	c.1518_1519delinsCA	p.V507M	99.4
KDR	4	24	Missense	c.G3207C	p.L1069F	11
MUC6	11	31	Missense	c.C5146T	p.P1716S	16.1
TP53	17	10	Missense	c.T1013G	p.F338C	29.6
BRIP1	17	6	Missense	c.A587G	p.N196S	32.3

BARD1, breast cancer 1-associated RING domain 1; *KDR*, kinase domain-containing receptor; *MUC6*, mucin-6; *TP53*, tumour protein 53; *BRIP1*, breast cancer 1-interacting protein C-terminal helicase 1.

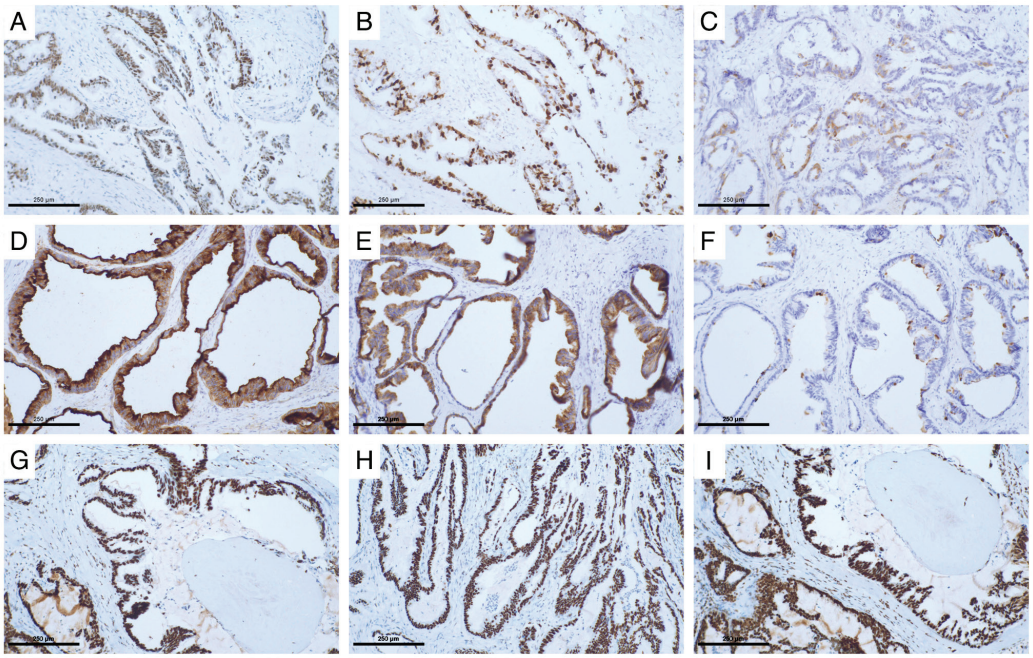

Figure 3. Immunohistochemical features of the lesion. (A) Tumour protein p53 expression was diffuse and strongly positive in the tumour cells. (B) The Ki-67 index of the tumour cells was 70%. (C) Mammaglobin was partially positively expressed. Mucus subtype-related immunohistochemistry showed that the tumour cell mainly expressed (D) MUC1 and (E) MUC6, with (F) partial expression of MUC5AC. The mismatch repair proteins (G) MSH-2, (H) MSH-6 and (I) DNA mismatch repair protein Mlh1 were all expressed (all x100 magnification). MUC, mucin; MSH-2, DNA mismatch repair protein Msh2.

capecitabine (650 mg/m^2 orally twice daily for 6 months). The patient was followed up every 6 months, including an assessment of any abnormal signs, ultrasound examinations of breast and axillary lymph nodes, neck and supraclavicular lymph nodes, abdomen and gynecological regions, chest CT and contralateral breast mammogram once a year. No recurrence was evident during 26 months of follow-up. The serum CEA level markedly decreased to 3 ng/ml 16 months after surgery.

Written informed consent was obtained from the patient and all procedures followed the ethical standards of the Declaration of Helsinki.

Discussion

Primary MCA of the breast is a rare invasive breast cancer that is characterised by a cystic structure lined with tall columnar cells and abundant intra-and extracellular mucus, and is similar to pancreatic or ovarian mucinous cystadenocarcinoma. According to the PubMed database (https://pubmed.ncbi.nlm.nih.gov/), a literature review with key words including 'primary', 'breast' and 'mucinous cystadenocarcinoma', and excluding any metastatic lesions of breast cases, revealed that 40 cases were reported by December 2023, as shown in Table II. Primary MCA of the breast predominantly occurred in postmenopausal women, with a median age of 59 years (range, 33-96 years) (1,4-38). The tumour size ranged from 0.8 to 19 cm and 95% were single lesions. Among the reported 35 cases with known lymph node status, 26 cases had no lymph node metastasis, 1 case showed isolated tumour cells, 8 cases had lymph node metastasis and 5 cases had >3 lymph nodes involved. In the present case, the patient was 51 years old with a 2.4-cm tumour and no lymph node metastasis. In the present case, the CEA level was significantly elevated at diagnosis and decreased to normal after surgery. In previous research, it

Table II. Comparison of the clinicopathological features of the present case with the other cases reported in the literature.

First author, year	Age, years	Tumour size, cm	pN stage	ER	PR	HER2	Ki-67 %	CK7	CK20	Associated findings	Surgery; CT/RT/HT	Follow-up time, status	(Refs.)
Koenig and Tavasolli,	54	19.0	N2	-	-	NA	40	+	-	None	M, LND	24 months, ANED	(1)
1998	67	2.3	N0	-	-	NA	30	+	-	DCIS	M, LND	22 months, ANED	
	49	8.5	N0	-	-	NA	70	+	-	DCIS	M, LND, CT + RT	11 months, ANED	
	61	0.8	N0	-	-	NA	50	+	-	None	L, LND	NA	
Rosen and Scott, 1984	79	6.0	NA	-	-	NA	NA	NA	NA	NA	M, LND	108 months, DOD	(4)
Domoto *et al*, 2000	74	10.0	N0	-	-	-	22	+	-	NA	M, LND,	24 months, ANED	(5)
Honma *et al*, 2003	96	2.0	N1	-	-	-	35	NA	NA	None	L, LND	46 months, DOD	(6)
Chen *et al*, 2004	65	3.0	N0	-	-	-	20.5	+	-	IDC, DCIS	M, LND, CT	8 months, ANED	(7)
Coyne and Irion, 2006	51	4.0	NA	-	-	NA	NA	+	-	None	L	NA	(8)
Lee and Chaung, 2008	55	2.5	N0	-	-	-	10	+	-	IDC, DCIS	M, LND	6 months, ANED	(9)
Rakici *et al*, 2009	52	10.0	N0	+	-	-	NA	-	-	ADH	M, LND, CT	24 months, ANED	(10)
Gulwani and Bhalla, 2010	61	3.0	N0	-	-	-	NA	NA	-	None	M, LND	6 months, ANED	(11)
Petersson *et al*, 2010	73	4.5	N0	-	-	2+ ($FISH^+$)	NA	+	-	DCIS	M, LND	NA	(12)
Sentani *et al*, 2012	65	3.0	N0	-	-	-	NA	+	-	DCIS	L, LND	6 months, ANED	(13)
Deng *et al*, 2012	41	7.0, 5.0, 2.5	N3	-	-	-	50	+	-	DCIS	M, LND	24 months, ANED	(14)
Li *et al*, 2012	52	6.5	N0	-	-	-	10	+	-	None	M, LND, CT	12 months, ANED	(15)
Kim *et al*, 2012	59	0.9	N0	-	-	2+ ($FISH^-$)	5	+	-	IDC, DCIS	L, SLNB, CT	3 months, ANED	(16)
Witherspoon *et al*, 2015	91	7.5	N0	-	-	-	40	+	-	IDC, DCIS	L, LND, RT	14 months, DOD	(17)
Lin *et al*, 2013	62	3.2	N0	-	-	-	NA	+	-	None	M, LND	5 months, ANED	(18)
Kucukzeybek *et al*, 2014	55	2.0	N0	-	-	2+ ($FISH^+$)	30	+	-	DCIS	L, SLNB, CT, RT, H	10 months, ANED	(19)
Seong *et al*, 2016	59	2.0	NA	-	-	3+	NA	NA	NA	NA	NA	NA	(20)
	50	2.2	NA	-	-	-	NA	NA	NA	NA	NA	NA	
Koufopoulos *et al*, 2017	63	1.6	N1	-	-	-	NA	+	-	None	L, LND, CT, RT	48 months, ANED	(21)
Nayak *et al*, 2018	68	6.2	N0	-	-	-	NA	+	-	DCIS	L, SLNB	3 months, ANED	(22)
	51	2.0	N0	-	-	-	NA	+	-	DCIS	L, LND	96 months, recurrence	
Kaur *et al*, 2019	45	12.0	NA	-	-	-	NA	+	-	NA	M	NA	(23)
Sun *et al*, 2020	56	2.0	N0	+	+	-	3-5	-	-	Atypical lobular lesion	M, LND, HT	3 months, ANED	(24)
Wang *et al*, 2020	66	2.5	N0	-	-	-	60	+	-	DCIS	M, LND	13months, ANED	(25)
Hu *et al*, 2020	50	5.8	N0	-	-	-	70	NA	NA	NA	L, SLNB	NA	(26)
Jain *et al*, 2021	45	4.3	N0	-	-	-	45-50	+	+	DCIS	M, LND, CT	6 months, ANED	(27)
Lin *et al*, 2021	72	0.9	N0	-	-	-	30	+	-	None	L, SLNB, RT	16 months, ANED	(28)
Kamrani *et al*, 2021	69	2.0	N0	+	+	-	NA	NA	NA	DCIS	M, LND	NA	(29)
Zuo *et al*, 2022	61	2.1	N1	-	-	-	40	+	-	DCIS	M, SLNB, LND, CT	10 months, ANED	(30)
Kaur *et al*, 2022	65	18.0	N0	-	-	3+	90	+	Focal +	None	M	6 months, ANED	(31)

Table II. Continued.

First author, year	Age, years	Tumour size, cm	pN stage	ER	PR	HER2	Ki-67 %	CK7	CK20	Associated findings	Surgery; CT/RT/HT	Follow-up time, status	(Refs.)
Moatasim and Mamoon, 2022	61	3.5	N2	+	+	-	<10	NA	NA	DCIS	M, LND,	NA	(32)
Lei *et al*, 2023	59	3.0	N0	-	-	-	40	+	-	None	M, LND, CT	108 months, ANED	(33)
Gong *et al*, 2024	54	4.2	N2	-	-	-	70	+	-	None	Salvage CT	6 months, PR	(34)
Vegni *et al*, 2023	41	3.0	N0 (i+)	+	-	-	35	Focal +	Focal +	PILC	L, LND, CT, RT	12 months, ANED	(35)
Xiao *et al*, 2021	58	3.0	N0	-	-	-	70	+	-	IDC	L, SLNB, CT	6 months, ANED	(36)
Yao *et al*, 2022	45	4.0	N2	-	-	-	60	+	-	IDC, DCIS	M, LND, CT, RT	36 months, recurrence	(37)
Luo *et al*, 2023	33	3.7	N0	+	+	-	70	-	-	None	M, LND, CT	8 months, ANED	(38)
Present case	51	2.4	N0	-	-	-	70	+	-	IDC	M, SLNB, CT	26 months, ANED	

pN, pathology lymph node; M, metastasis; ER, oestrogen receptor; PR, progesterone receptor; HER2, human epidermal growth factor 2; FISH, fluorescence *in situ* hybridization; CK, cytokeratin; CT, chemotherapy; RT, radiotherapy; HT, hormonotherapy; H, trastuzumab; NA, not available; M, mastectomy; L, lumpectomy; LND, lymph node dissection; SLNB, sentinel lymph node biopsy; ANED, alive with no evidence of disease; DOD, died of other disease; PR, partial response; IDC, invasive ductal carcinoma; DCIS, ductal carcinoma *in situ*; ADH, atypical ductal hyperplasia; i+, isolated tumour cells; PILC, pleomorphic invasive lobular carcinoma.

has been reported that both CA153 and CA125 are elevated at diagnosis and decreased after surgery (26). However, there is no previous report on the elevation of CEA in MCA.

Among the previously reported cases (1,4-38), 19 cases exhibited MCA with ductal carcinoma *in situ* (DCIS) and/or invasive ductal carcinoma (IDC), 1 case exhibited pleomorphic invasive lobular carcinoma, 1 case exhibited atypical ductal hyperplasia and 13 cases exhibited pure MCA. A previous report suggested that MCA accompanied with DCIS indicated that MCA cells were derived from the mucinous metaplasia of epithelial cells of DCIS, accompanied with loss of ER and PR expression (7). It is difficult to diagnose primary MCA of the breast and exclude metastatic cancers when the breast lesions only present with MCA, without other characteristic lesions of the accompanying breast epithelial cells. Primary pancreatic and ovarian MCA were positive for both CK7 and CK20, while gastrointestinal carcinoma was CK7-negative and CK20- and CDX-2-positive (25), and nearly all the cases of primary MCA of the breast were CK7-positive and CK20-negative, as summarized in Table II. In the present case, CK7 positivity and CK20, CDX-2 and PAX-8 negativity, and positive expression of breast origin-related markers, such as GCDFP15 and mammaglobin, supported the diagnosis of primary MCA of the breast. In the present study, four mucin glycoprotein markers were analysed. The tumour mainly expressed MUC1 and MUC6, and partially expressed MUC5AC, but not MUC2. In a previous case of MCA (30), IHC staining for mucin glycoprotein showed positive results for MUC1 and MUC5AC, but no staining for MUC2, which was similar to the present case. The lack of expression of MUC2 in the present case was different from the expression status in ovarian mucinous carcinoma, which is mainly positive for MUC2 (39,40). In the present case, MUC6 was mainly expressed and there was also a mutation in the *MUC6* gene in the molecular analysis. This was different from previous reports (16,35,37), which showed a negative expression status for MUC6 in breast MCA. This may be related to the mutation of the *MUC6* gene in the present case and deserves further investigation. Therefore, when considering the literature and the present case, it is necessary to distinguish MCA from other breast diseases. Both MCA and mucinous carcinoma of the breast have abundant extracellular mucus, but the latter has no intracellular mucus (47,48). Both MCA and encapsulated papillary carcinoma have a papillary structure and lack myoepithelium, but the latter has no intracellular mucus and strongly diffused expression of ER and PR (47,48). Mucocele-like lesions are benign mucinous cysts with uniformly arranged flat or cuboidal epithelium, mostly accompanied by mucin exudation into the surrounding stroma, and have a myoepithelium but no heterologous cells, unlike MCA (4,49).

Most cases of primary MCA of the breast are negative for ER, PR and HER2 expression; in the literature review, only 4 cases presented with HER2 amplification and 6 cases were hormone receptor-positive. The median Ki-67 index was 40% (range, 5-90%). Among the 41 reported cases (including the present case), of which 32 had follow-up information (median follow-up time, 12 months; range, 3-108 months), 2 had recurrence (7,22). One of these cases (22) was of a 51-year old female diagnosed with T1N0 triple-negative MCA accompanied by DCIS, who underwent local surgical treatment and

experienced local recurrence after 96 months of follow-up. The other case (37) was of a 45-year old female diagnosed with T2N2 triple-negative MCA accompanied by IDC and DCIS, with a high Ki-67 index of 60%. This patient received chemotherapy and radiotherapy after modified radical surgery for breast cancer and was followed up for 36 months with local recurrence. There were 2 cases of recurrence among the 23 triple-negative MCA cases with follow-up information. In previous case reports and systematic reviews of primary MCA of the breast, researchers generally reported that MCA was a triple-negative subtype with a high Ki-67 index and a good prognosis. However, with an increasing number of case reports, it was found that the recurrence risk of triple-negative MCA was not significantly lower than that of triple-negative non-specific breast cancer. However, the number of known cases of primary MCA of the breast remains limited. In the present case, the patient underwent eight cycles of chemotherapy followed by 6 months of oral capecitabine and showed no evidence of recurrence at 26 months of follow-up; however, the risk of MCA recurrence should not be underestimated.

Next-generation sequencing revealed *TP53* missense mutations, similar to those in previous cases (28,33). As a tumour suppressor gene, *TP53* may cause abnormal protein expression and function when mutated, resulting in tumour development (50). A missense mutation was also found in *KDR* in the present study, which was similar to the result in a previous case (33). *KDR* mutations tend to occur frequently in advanced gastric cancer (51) and renal/adrenal angiosarcomas (52), suggesting that they might be related to the occurrence and development of carcinoma, although this requires further research. In the present case, MUC6-positive expression was found, along with a missense mutation in *MUC6*, which seemed to suggest an association between these two results. Research on colon adenocarcinoma revealed that the mutation of *MUC6* was associated with a high tumour mutation burden and microsatellite instability (53). Research on *MUC6* mutations is limited, but the findings of the present study warrant further investigation. The *BARD1* gene is structurally similar to *BRCA1*; these two genes can form dimers and play important roles in DNA repair and apoptosis (54). *BARD1* is a moderate-risk gene for hereditary breast cancer, particularly triple-negative breast cancer (55). In the present case, there was a high frequency of missense mutations in *BARD1*, which are related to tumour development and the immunohistochemical characteristics of triple-negative breast cancer. Further research on this gene may be important to further distinguish between common triple-negative breast cancer and breast MCA.

In summary, MCA is a rare breast cancer, with only 41 reported cases. The present study reports a case of MCA accompanied by mutations in the *TP53*, *KDR*, *MUC6* and *BARD1* genes, which mainly act as tumour suppressor genes and affect DNA repair, with no recurrence after 26 months of follow-up. Combining this case with a review of the literature helps us to better understand the clinicopathological and genetic characteristics of MCA, and guide treatment.

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Availability of data and materials

The data generated in the present study may be found in the SRA under accession number PRJNA1171987 or at the following URL: https://www.ncbi.nlm.nih.gov/sra/PRJNA1171987.

Authors' contributions

XC and XYR designed the report of this case. XC , YCL and SJS collected the clinical information and imaging examination data of this case, and participated in the literature search. XYR performed the pathological data. XYR and XC analyzed the datasets. XC drafted the manuscript and all authors discussed the results and commented on the manuscript. XC and XYR 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

Written informed consent was obtained from the patient, and all the procedures followed the ethical standards of the Helsinki Declaration.

Patient consent for publication

The patient provided written informed consent for the publication of this study.

Competing interests

The authors declare that they have no competing interests.

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