

Case Report

Mammary synchronous mucinous cystadenocarcinoma and columnar cell mucinous carcinoma: a case report

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Abstract: Mucin-producing carcinomas are unusual primary malignancies of breast, and constitute about 1-4 percent of total breast cancer. The mammary mucin producing carcinomas are divided into 4 histologic subtypes according to WHO classification, including mucinous carcinoma, mucinous cystadenocarcinoma (MCA), columnar cell mucinous carcinoma (CCMC), and signet ring cell carcinoma. However, the synchronous primary MCA and CCMC of breast is a very rare case presentation. The case reported a 56-year-old female, who presented with right mammary lumps and nipple discharge about 1 year. Imaging examinations revealed multiple cystic and solid nodules in upper outer quadrant of right breast, associated with ectatic ducts. Serum levels of tumor markers were normal. Right mammary lumpectomy revealed mucinous carcinoma, modified radical mastectomy, and lymph node dissection were carried out. For neoplastic cells, ER and PR were positive, HER2 (1+) was negative, Ki67 was low expression (3-5%). There was no metastatic carcinoma in lymph nodes (0/8). Modified radical mastectomy and lymph node dissections were carried out. Tamoxifen was chosen for adjuvant therapy. After a 3 month follow up, the patient survived without recurrences and distant metastasis. We report the first synchronous primary MCA and CCMC of breast with molecular subtype of Luminal A.

Keywords: Breast cancer, mucinous cystadenocarcinoma, columnar cell mucinous carcinoma, molecular subtype, case report

Introduction

Intracellular mucin producing carcinoma is extremely rare malignancies of breast, up to now, only 21 reports of single MCA or CCMC have been published. For mammary synchronous MCA and CCMC, it is the first time to describe this case in our literature. After reviewing all published reports about MCA and CCMC, we make a summary for epidemiological distribution and clinicopathological data of MCA and CCMC. We supplement the molecular subtype, histopathologic findings and prognosis for MCA and CCMC, and illustrate the essentiality of prospective anti-inflammatory therapy before the modified radical mastectomy of mammary malignancies with the feature of cystic hypersecretion. It is significant for pathologic diagnosis and clinical decision of MCA and CCMC.

Case presentation

A 56-year-old, postmenopausal female presented with lumps and nipple discharge of right

breast about 1 year. Mammography examination showed the abnormality high density shadow (**Figure 1A**). MRI revealed irregular masses and calcification (**Figure 1B**). Mammary ultrasound hinted the right cystic and solid masses (**Figure 1C**) with multiple ectatic ducts (**Figure 1D**). Serum levels of tumor markers (C12) were normal, leucocyte count $17.7 \times 10^9/L$ (normal $3.5-9.5 \times 10^9/L$), neutrophil count $15.6 \times 10^9/L$ (normal $1.8-6.3 \times 10^9/L$). Ceftriaxone and Levofloxacin were used for infection control. Right mammary lumpectomy revealed mucinous carcinoma, subsequent, modified radical mastectomy and lymph node dissection were carried out. After operation, incision was healing poorly with faint yellow discharge. The glycemic and glycosylated hemoglobin levels were normal, the cytological examination was implemented for incision exudation, lymphocytes and neutrophils were found, and the germiculture was negative. Strict anti-inflammatory therapy was carried out, 8 days later, the incision began to

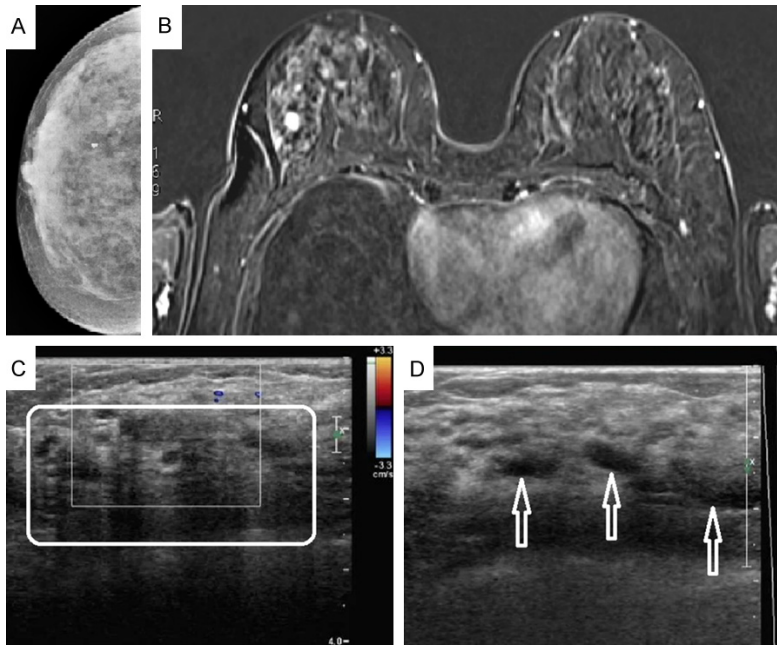


Figure 1. Mammary imaging examinations. (A) The irregular high density shadow in mammography. (B) MRI revealed the right mammary masses and calcification. Ultrasonograph showed the (C) cystic-solid nodules (square) and (D) multiple ectatic ducts (arrow).

heal. There was no history of family malignancy and hormone replacement therapy. Her menarche was on 12 years old, menopause was on 52 years old. Tamoxifen was chosen for adjuvant therapy, after following up 3 months, she was alive without recurrences and distant metastasis.

Macroscopically, 4 separate nodules were found in her right mammary upper outer quadrant, 1-2 cm in diameter, cut surfaces of nodules were cystic-solid structure, cyst walls were rough on palpation, which were full of light yellow and jelly-like substance. These nodules were surrounded by multiple ectatic ducts, honeycomb like, which were filled with dark red and soft materials, hemorrhage and necrosis were evident by naked eye.

Microscopically, the tumor mainly consisted of cystic and solid areas (**Figure 2A**). In the cystic parts, epithelium of the tumor was lined by a single layer of tall columnar cells with papillary or tufting protrusions as the feature of MCA, but there seemed to be different relationships between tall columnar cells and papillary or tufting protrusions. States of tight junction, gradual separation, and complete detachment

were seen. This suggests a dynamic process of separation (**Figure 2B**). For solid areas, 3 histopathologic patterns were observed, thready or cord-like structures consisted of low columnar cells with small and regular nuclei (**Figure 2C**), as the feature of CCMC. Pseudostratified tall columnar cells constituted the tumor parenchyma, nuclei of tumor cells were basally located without atypia or mitotic figures (**Figure 2D**). Thin and thick tubular malignant components lined by columnar cells were observed in mesenchymal tissue (**Figure 2E, 2F**). Noticeably, some atypical lobular appearances were more extended than the normal, and original epithelium were replaced by columnar cells with abundant intracellular mucin (**Figure 2G**).

It was obvious for aggregations of inflammatory corpuscle beside ectatic ducts (**Figure 2H**), lymphocyte and neutrophils were found in the cytological examination of incision exudation (**Figure 2I**). There was no lymphatic metastasis (0/8), and some components of carcinoma in situ were found. Skin, nipple, breast base were not invaded. The pathological TNM stage of tumor was pT1N0M0.

Alcian blue staining showed abundant intracellular and extracellular mucin (**Figure 3A**). In the tumor parenchyma, the immunohistochemical analysis revealed that ER had weakly nuclear positive staining with a single glandular strongly positive expression (**Figure 3B**). The nuclear staining of PR was blandly positive (**Figure 3C**), the result of HER2 was 1+ because of the incomplete and weak membrane positive reaction (**Figure 3D**), the Ki67 was low expression with an mean nuclear proliferative index of 3-5% in 10 random microscopic fields (**Figure 3E**), the molecular subtype of the tumor was compatible with Luminal A. The positive sites of E-Cadherin and p120 were located in membrane of neoplastic cells (**Figure 3F, 3G**), focal peritumoral myoepithelial cells presented with

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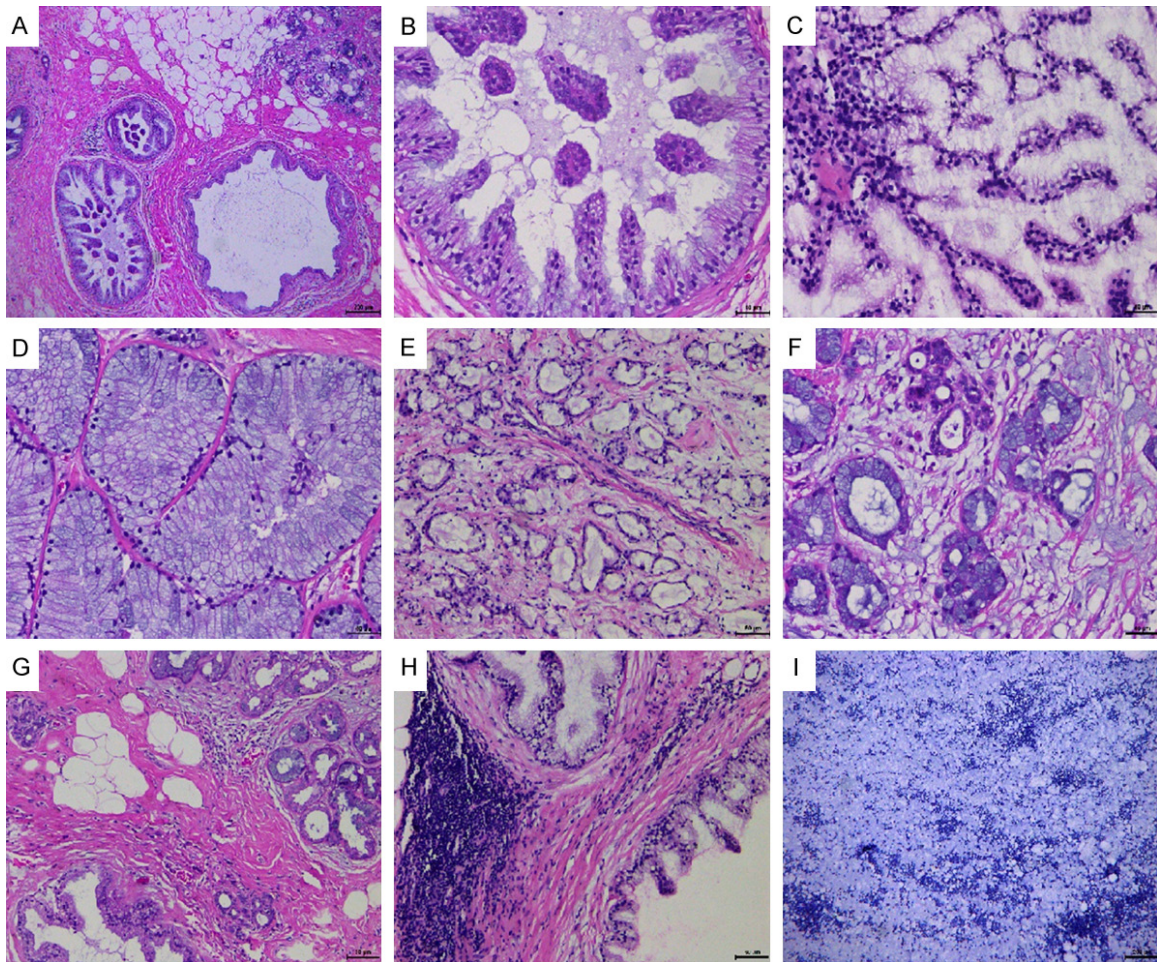


Figure 2. Histological findings (H&E staining). A. Cystic and solid areas of tumor. B. The relationships between columnar cells and papillary or tufting protrusions. C. Thready or cord-like structures consisted of low columnar cells with small and regular nuclei. D. The pseudostratified tall columnar cells constituted the tumor parenchyma, nuclei of tumor cells were basally located without atypia or mitotic figures. E, F. Tubular malignant components lined by columnar cells. G. Atypical lobular appearances were more extended than the normal and original epithelial cells were replaced by columnar cells. H. Obvious aggregations of inflammatory cells beside ectatic ducts. I. The cytologic examination of incision exudation.

positive test for p63 (**Figure 3H**) and Calponin. The neoplastic cells expressed positive reaction for Mammaglobin (**Figure 3I**), EGFR and CK19, but were negative for AR, GATA3, GCDPF-15, CDX2, MUC2, MUC5AC, CK7, CK20, TTF-1, TG, NapsinA, WT1, SOX10, PAX-8 and PD-L1. The basal cells showed positive staining for CK5/6.

Discussion

The microscopic features of intracellular mucin producing carcinomas, especially synchronous primary MCA and CCMC of breast, were described first in our report. Except for components of carcinoma in situ and positive expres-

sion of Mammaglobin for tumor parenchyma, imaging examinations also supported this neoplasm arising from breast rather than metastatic carcinoma. In a part of the tumor parenchyma, the histopathological pattern was compatible with reported cases of MCA or CCMC, being characterized as tall columnar cells with basally located bland nuclei and abundant intracellular mucin. The structures of flat, intracapsular, papillary and thready are regarded as the common morphological features of MAC and CCMC. However, well-differentiated and open tubular glands lined by a single layer of columnar cells with abundant intracellular mucin were found in this case, as the character of mammary tubular carcinoma, which has rarely been reported.

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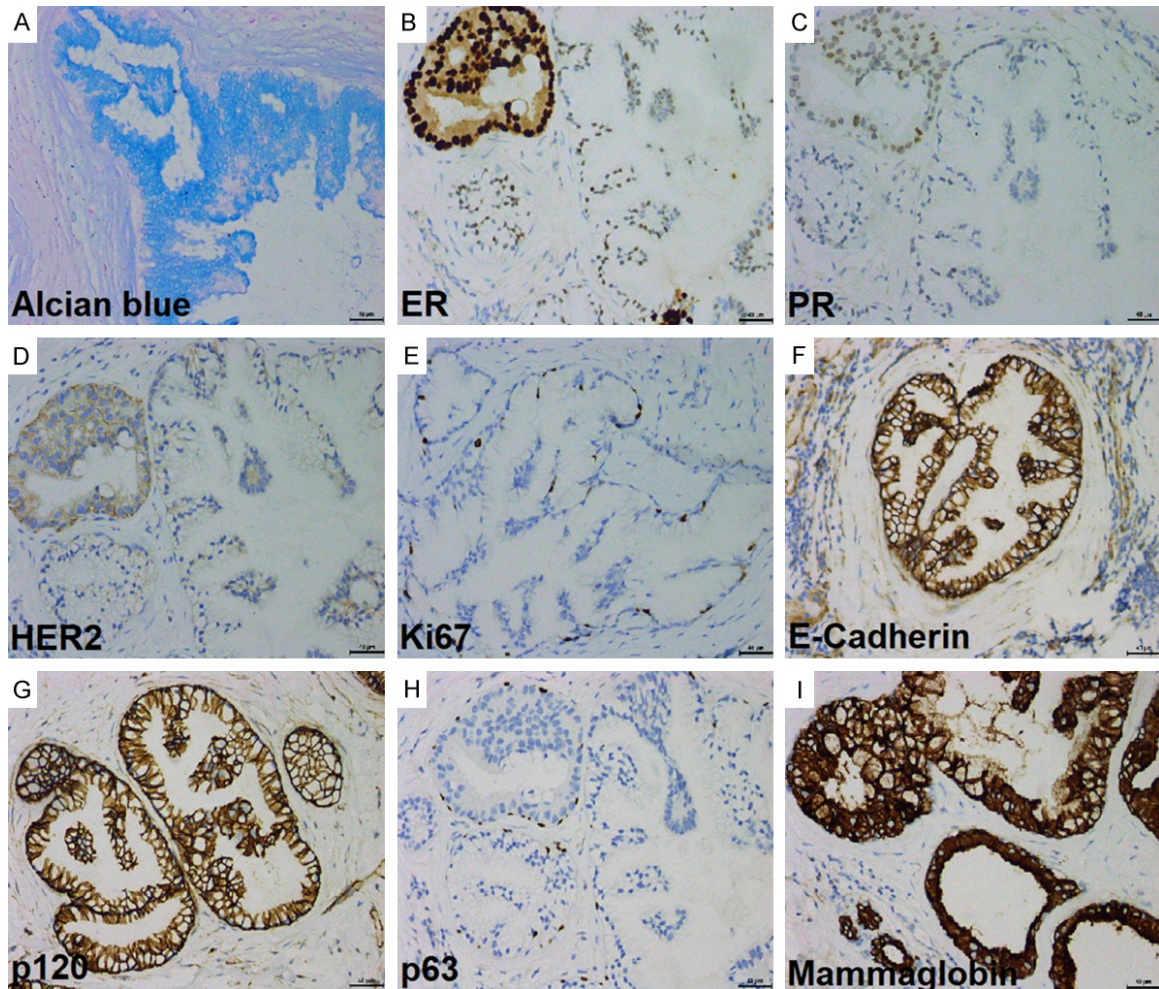


Figure 3. Alcian blue and immunohistochemical staining. (A) Alcian blue staining showing abundant mucin. Immunohistochemical staining showing neoplastic cells were positive for ER (B) and PR (C), incomplete and weak membrane positive for HER2 (D), low expression (3-5%) for Ki67 (E). Positive expressions of E-Cadherin (F) and p120 (G) were observed on the membrane of tumor cells, p63 (H) positive staining revealed existences of focal peritumoral myoepithelial cells. Cytoplasm of tumor cells expressed positive reaction for Mammaglobin (I).

Some solid cancer nests consisted of pseudostratified columnar cells, small and regular nuclei without mitotic figures were observed just above basal position, the 2 histologic findings were poorly expounded in the published literature [1-18].

We found some abnormal lobular structures. The lobular original epithelia were replaced by intracellular mucin producing columnar cells, and immunohistochemical analysis revealed that E-Cadherin and p120 had membranous positive expression; together with morphologic character, it is reasonable to consider cancerization of lobules. In addition, there is another possibility, simultaneous appearance of MAC and CCMC may suggest that the two tumors have some identical pathogenesis, lobular orig-

inal ductal epithelia have the differentiation potentiality to become malignant intracellular mucin producing cells.

After reviewing all published relevant reports of MAC and CCMC, we found the common character of these tumor was multiple cystic spaces lined by columnar cells with abundant intracellular and extracellular mucin. The clinicopathologic data of published reports of MAC and CCMC are summarized in **Table 1**. There are differences between this case and previous reports. On clinical features, nipple discharge and inflammatory hemogram (leucocyte count $17.7 \times 10^9/L$, neutrophil count $15.6 \times 10^9/L$) were showed. Macroscopically, large amounts of ectatic ducts were filled with dark red and soft materials, which was accordant with imaging examinations. Histologically, obvious aggrega-

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Table 1. Clinicopathologic data of mammary primary MCA and CCMC (n=22)

Case no.	Tumor type	Age (years)	Tumorsize (cm)	TNM	ER	PR	HER2	Molecular subtype	Treatment	Follow up (months)
1 [1]	MCA	41	7.0, 5.0, 2.5	T3N1M0	-	-	-	TNBC	MRM/LND	Alive, 24
2 [2]	CCMC	49	8.5	T3NOM0	-	-	-	TNBC	MRM/LND +Chm+RT	Alive, 11
3 [3]	MCA	51	4.0	T2NOM0	-	-	N/A	N/A	Lumpectomy	N/A
4 [4]	MCA	52	10.0	T3NOM0	+	-	-	Luminal	MRM +Tamoxifen	Alive, 24
5 [5]	MCA	52	6.5	T3NOM0	-	-	-	TNBC	N/A	N/A
6 [2]	MCA	54	19.0	T3N2M0	-	-	-	TNBC	MRM/LND	Alive, 24
7 [6]	MCA	55	2.5	T2NOM0	-	-	-	TNBC	Lumpectomy	Alive, 6
8 [7]	MCA	55	2.0	T1NOM0	-	-	+	HER2	Lumpectomy +Chm+RT	Alive, 24
9 [8]	MCA	59	0.9	T1NOM0	-	-	+	HER2	PM/LND +Chm	Alive, 3
10 [2]	MCA	61	0.8	T1NOM0	-	-	-	TNBC	Lumpectomy/LND	N/A
11 [9]	MCA	61	3.0	T2NOM0	-	-	-	TNBC	MRM/LND	Alive, 6
12 [10]	MCA	62	5.6	T2NOM0	-	-	-	TNBC	MRM	Alive, 5
13 [11]	MCA	65	3.0	T2NOM0	-	-	-	TNBC	MRM/LND	Alive, 8
14 [12]	MCA	65	3.0	T2NOM0	-	-	N/A	N/A	PM/LND	Alive, 6
15 [2]	CCMC	67	2.3	T2NOM0	-	-	-	TNBC	MRM/LND	Alive, 22
16 [13]	MCA	73	4.5	T2NOM0	-	-	+	HER2	MRM/LND	N/A
17 [14]	MCA	74	10.0	T3NOM0	-	-	-	TNBC	MRM/LND	Alive, 24
18 [15]	CCMC	74	8.0	T4N3M0	-	-	-	TNBC	MRM/LND +Chm+RT	Died with other reason, 16
19 [16]	MCA	79	6.0	T2NOM0	N/A	N/A	N/A	N/A	MRM	Died with other reason
20 [17]	MCA	91	7.5	T3NOM0	-	-	-	TNBC	MRM/LND +RT	Died for stroke
21 [18]	MCA	96	2.0	T2N2M0	-	-	-	TNBC	Lumpectomy/LND	Died with other reason, 46
Presentcase	MCA CCMC	56	1.0, 1.2, 1.52.0	T1NOM0	+	+	-	Luminal	MRM/LND+ Tamoxifen	Alive, 3 and following up

-, negative; N/A, not available; +, positive; MRM, modified radical mastectomy; LND, lymph node dissection; PM, partial mastectomy; RT, radiation therapy; Chm, chemotherapy; TNBC, triple negative breast cancer.

tions of inflammatory cells beside ectatic ducts were observed. For reviewing above-mentioned clinicopathological presentation, the cause of poor healing with discharge can be appropriately analyzed, the multiple ectatic ducts and nipple discharge are caused by abundance of tumor secretion, which create a condition for the aggregations of inflammatory corpuscle beside ectatic ducts. So, it is hard for incision to heal well in an inflamed microenvironment, cytological examination of incision exudation and healing well after strict anti-inflammatory therapy can indirectly demonstrate this opinion. In summary, mammary cystic hypersecretion tumor is considered after core biopsy or lumpectomy, present with nipple discharge and multiple ectatic ducts, before modified radical mastectomy, it is essential to execute prospective inflammation control for healing well.

The age distribution of MCA and CCMC ranges from 41 to 96 (median age: 60 years old); the majority are old and postmenopausal. of them

have definite molecular subtype; the proportions of Luminal, HER2, and TNBC subtypes are 10.5% (2/19), 15.8% (3/19) and 73.7% (14/19), the phenomenon is not compatible with natural distribution of invasive breast cancer (Luminal-70%, HER2-15% and TNBC-15%), it could be related to histopathological type and small amount of cases. The feature of age distribution and low proportions of luminal (10.5%) may suggest that occurrence of this tumor is irrelevant to estrogenic stimulation. The molecular subtype mainly distribute in TNBC (73.7%) that has a poor prognosis; however, the extremely low fatality rate of these cases perhaps suggest that prognosis of this tumor is independent of molecular subtype. We believe extracellular mucin arises from disruption of columnar cells, which could restrain the development of tumor [19]. Papillary protrusions may be an indication that neoplastic cells have character of cohesion [20]. In addition, extracellular mucin could have adhesive ability, which restrict tumor metastasis.

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In conclusion, we report one case of mammary primary synchronous MAC and CCMC in a 56-year-old postmenopausal Chinese female. The tumor expressed ER, PR, HER2 (1+) and Ki67 (3-5%), displayed a molecular subtype of luminal A. For mammary cystic hypersecretion tumor with nipple discharge and multiple ectatic ducts, prospective anti-inflammatory therapy before modified radical mastectomy may be a significant clinical decision. We supplement the histopathologic findings, molecular subtype and prognosis for MCA and CCMC. Currently, the molecular subtype of this tumor is mainly distributed in TNBC and the occurrence may be irrelevant to estrogenic stimulation. The prognosis is independent of molecular subtype.

Disclosure of conflict of interest

None.

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