Primary Mucinous Cystadenocarcinoma of the Breast: Cytologic Finding and Expression of MUC5 Are Different from Mucinous Carcinoma

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Mucinous cystadenocarcinoma (MCA) in the breast is a rare neoplasm. There have been 13 cases of primary breast MCA reported. The MCA presents as a large, partially cystic mass in postmenopausal woman with a good prognosis. The microscopic findings resemble those of ovarian, pancreatic, or appendiceal MCA. The aspiration findings showed mucin-containing cell clusters in the background of mucin and necrotic material. The cell clusters had intracytoplasmic mucin displacing atypical nuclei to the periphery. Histologically, the tumor revealed an abundant mucin pool with small floating clusters of mucin-containing tumor cells. There were also small cysts lined by a single layer of tall columnar mucinous cells, resembling those of the uterine endocervix. The cancer cells were positive for mucin (MUC) 5 and negative for MUC2 and MUC6. This mucin profile is different from ordinary mucinous carcinoma and may be a unique characteristic of breast MCA.

CASE REPORT

Clinical summary

A 59-year-old postmenopausal woman presented with an ill-defined, hard mass in her left breast for a year. Radiologic evaluations demonstrated a hypo-echoic mass (14 mm) with a speculated margin in ultrasonography and a focal asymmetric density in the upper medial portion by mammography. Fine needle aspiration followed by needle biopsy was performed with the di-

in situ hybridization.9

In the case being reported here, the mass was only 9 mm, though the size before core biopsy was assessed to be 14 mm by ultrasound examination. Other characteristics of this new case share those clinical, cytological, and histopathological findings described in previously published cases (Tables 1, 2). In this paper, we present a rare cytologic finding of primary MCA in the breast and the characteristics of mucin (MUC).
agnosis of MC and invasive carcinoma with abundant mucin pool formation, respectively. She underwent partial mastectomy with sentinel lymph node biopsy. The sentinel lymph node was free from metastasis. She has been followed for 3 months with chemotherapy for adjuvant treatment and remains disease-free.

**Pathologic findings**

The aspiration showed a few scattered, variably sized, irregular clusters of columnar cells in the greenish blue mucinous background with necrotic debris. The columnar cells contained abundant mucin vacuoles in cytoplasm which had displaced their nuclei. The nuclear membrane was irregular and sharply angulated and the nuclei revealed a coarse chromatin pattern with prominent nucleoli (Fig. 1).

On gross examination, the cut surface showed an irregular, white to tan, solid and firm mass (9×7 mm), with a glistening appearance. Most MCAs in previous reports have demonstrated grossly cystic cut surfaces, except one case of MCA reported from Koenig and Tavassoli in 1998. The case in 1998 was small in size (8 mm) and had a grossly solid appearance. The present case was 9 mm in maximal diameter and did not contain a macroscopic cyst. It is assumed that the small size of the MCA meant that it did not produce enough mucin to fill out and dilate cysts and ductal structures. The microscopic findings revealed a few cysts and ductal carcinoma in situ, adjacent to the invasive carcinoma. The cysts were lined by a single layer of tall columnar mucinous cells with focal areas of micropapillary structures, resembling those of the uterine endocervix. The luminal

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**Table 1. Clinical feature of mucinous cystadenocarcinoma in the breast**

| Case No. | Age (yr) | Size (mm) | TNM   | Duration | Operation          | Adjuvant treatment | Follow-up     |
|----------|----------|-----------|-------|----------|--------------------|--------------------|---------------|
| 1        | 79       | 60        | T2N0M0| N/A      | MRM                | No                 | Died with other reason | 9 yr         |
| 2        | 54       | 190       | T3N2M0| N/A      | MRM/LND            | No                 | Alive with no evidence of disease | 24 mo        |
| 3        | 67       | 23        | T2N0M0| N/A      | MRM/LND            | No                 | Alive with no evidence of disease | 22 mo        |
| 4        | 49       | 85        | T3N0M0| N/A      | MRM/LND            | Chm+RT             | Alive with no evidence of disease | 11 mo        |
| 5        | 61       | 8         | T1N0M0| N/A      | Lymphectomy/LND    | No                 | N/A           | Recent        |
| 6        | 74       | 100       | T2N0M0| 2 yr     | MRM/LND            | No                 | Alive with no evidence of disease | N/A          |
| 7        | 96       | 20        | T2N2M0| 5 yr     | MRM/LND            | No                 | Died with other reason | 46 mo        |
| 8        | 65       | 30        | T2N0M0| >3 mo    | MRM/LND            | No                 | Alive with no evidence of disease | 8 mo         |
| 9        | 51       | 40        | T2N0M0| N/A      | Lymphectomy        | N/A                | N/A           | N/A           |
| 10       | 55       | 25        | T2N0M0| N/A      | Lymphectomy        | No                 | Alive with no evidence of disease | 6 mo         |
| 11       | 52       | 100       | T3N0M0| N/A      | Excision           | Tamoxifen          | Alive with no evidence of disease | 24 mo        |
| 12       | 73       | 45        | T2N0M0| Few months | MRM/LND       | N/A                | N/A           | N/A           |
| 13       | 65       | 30        | T2N0M0| N/A      | PM/LND             | No                 | Alive with no evidence of disease | 6 mo         |
| Present case | 59   | 9         | T1N0M0| 1 yr     | PM/LND             | Chm                | Alive with no evidence of disease | 3 mo         |

TNM, tumor-node-metastasis; N/A, not acquired; MRM, modified radical mastectomy; LND, with lymph node dissection; Chm+RT, chromatography+radiation therapy; PM, partial mastectomy.

**Table 2. Immunohistochemical feature of mucinous cystadenocarcinoma in the breast**

| Case No. | ER | PR | c-erbB2 | CK7 | CK20 | CDX-2 | Ki-67 (%) | p53 (%) |
|----------|----|----|---------|-----|------|-------|-----------|---------|
| 1        | N  | N  | P       | N   | N    | 40    |           |         |
| 2        | N  | N  | P       | N   | N    | 30    |           |         |
| 3        | N  | N  | P       | N   | N    | 70    |           |         |
| 4        | N  | N  | P       | N   | N    | 50    |           |         |
| 5        | N  | N  | P       | N   | N    | 21.80 | N         |         |
| 6        | N  | N  | N       | N   | N    | 35    | P (5)     |         |
| 7        | N  | N  | N       | P   | 2+++ | Focal | N         | 20.50   |
| 8        | N  | N  | N       | P   | N    | 50    |           |         |
| 9        | N  | N  | P       | N   | N    | 90    |           |         |
| 10       | N  | N  | N       | P   | N    | N     |           |         |
| 11       | P  | N  | N       | N   | N    | N     |           |         |
| 12       | N  | N  | 2++     | P   | N    | N     |           |         |
| 13       | N  | N  | P       | N   | N    | N     |           |         |
| Present case | N  | N  | 2++     | P   | N    | N     | 5         | P (5)   |

ER, estrogen receptor; PR, progesterone receptor; CK7, cytokeratin 7; CK20, cytokeratin 20; N, negative; P, positive.
space contained mucin (Fig. 2). The invasive cancer area contained an abundant mucin pool in stroma with floating cell clusters. The floating cells contained mucin vacuoles in cytoplasm displacing atypical nuclei to the periphery.

Special staining and IHC on paraffin embedded tissue were performed. Both intracytoplasmic and extracytoplasmic mucin were stained by periodic acid-Schiff with diastase, alcian blue, and mucicarcine, representing the acidic and neutral nature of mucin. The tumor cells were positive for CK7 and negative for CK20 and CDX-2. The IHC for MUC proteins was performed. The cancer cells were positive for MUC5 and MUC1 and negative for MUC2 and MUC6. Mucin of the intracytoplasm and stroma revealed positivity for MUC5 and negativity for the other MUC proteins (MUC1, MUC2, and MUC6). The hormone receptors, ER and PR, were negative. The c-erbB2 was 2-positive (Fig. 3), but silver in situ hybridization demonstrated no amplification of the HER-2 gene.

**DISCUSSION**

In the breasts, mucin-producing tumors are classified as MC, signet ring cell carcinoma (SRC), or mucocele-like tumors. The differences among mucin-containing tumors in the breast are shown in Table 3. MC and mucocele-like tumors are characterized by abundant extracellular mucin with floating neoplastic cells that do not contain intracytoplasmic mucin. The mucocele-like tumor is benign and the floating tumor cells are very rare. MC is specific type of invasive ductal carcinoma. The cytologic features show tight clusters of bland looking cells with moderate cellularity in the mucinous background. SRC demonstrates mucin only in the cytoplasm. The aspiration reveals a cellular smear of pleomorphic and plasmacytoid cells with intracytoplasmic mucin in the bloody or necrotic background. MCA has similar characteristics to both MC and SRC. The aspiration smears reveal tight clusters of mucin-containing cells of low to moderate cellularity in the background of mucinous and necrotic material. The histopathologic findings confirm both, intracytoplasmic and extracytoplasmic mucin.

Mucin is a high molecular weight glycoprotein that consists of one protein core and O-linked carbohydrate side chains attached. Epithelial cells produce two types of mucin. One is secretory mucin (MUC2, MUC5, and MUC6) and the other is trans-membrane mucin (MUC1, MUC3, MCU4, MUC12, and MUC17). They are expressed differently according to the types of organs and tumors. For example, MC of the colon shows high positivity for MUC2. SRC of the colon shows MUC2 and MUC4 positivity. Among breast cancers, MC expresses mainly MUC2 along with a low level of MUC1, while SRC of the
breast has a high level of MUC1 expression with a variable level of MUC2. In the breasts, MUC5 is not frequently observed. MCs of the breast express MUC5 in only small proportions (less than 5%). In our case of MCA reported here, the MUC IHC demonstrates a high level of expression of MUC5 and no expression of MUC2 or MUC6. This mucin profile is different from ordinary mucinous carcinoma arising in the breast and other organs. MUC5-positive and MUC2-negative immunoprofiles have not been reported before, in breast carcinoma.

Because of the rarity of mammary MCA, the diagnosis has to be made cautiously. Thus metastasis from distant organs should be initially considered. The usual immunoprofiles to rule out
Fig. 3. Immunohistochemical staining of mucinous cystadenocarcinoma. The tumor cells are positive for cytokeratin 7 (A) and negative for cytokeratin 20 (B). The hormone receptors, estrogen receptor and progesterone receptor, are negative and the c-erbB2 is 2-positive (C). The tumor cells are positive for mucin (MUC) 1 (D) along the cytoplasmic membrane and negative for MUC2 (E). Mucin of the intracytoplasm and stroma reveal positivity for MUC5 (F).

Table 3. Comparison of mucin-producing tumors in the breast

|                         | Mucocle-like tumor | Mucinous carcinoma | Signet ring cell carcinoma | MCA          |
|-------------------------|--------------------|--------------------|---------------------------|--------------|
| Cytologic feature       | Presence of mucin  | Presence of mucin  | Bloody, necrotic, clear   | Mucin, necrotic |
|                         | N/A                | Tight cluster      | Loosely cohesive group    | Tight cluster |
|                         | Scant              | Moderate           | High                      | Low to moderate |
|                         | Monolayered        | Monolayered, 3-D   | Plasmaoctoid, pleomorphic | 3-D |
| Cellularity             | Lack of cytologic atypia | Absent | Mucin, necrotic | Mucin, necrotic |
| Arrangement             | Absent             | Absent             | Present                   | Present |
| Cohesiveness            | Present            | Present            | Absent                    | Present |
| Cohesiveness            | Flat or low cuboidal cells | Rarely present | N/A                      | N/A |
| Histologic feature      | ADH, DCIS, IDC     | Present            | N/A                      | Tall columnar cells |
| Extracellular mucin     | Rarely present     | Present            | IDC                      | IDC |
| Lining cells            | ADH, DCIS, IDC     | Present            | IDC                      | IDC |
| Floating tumor cells    | ADH, DCIS, IDC     | Present            | IDC                      | IDC |
| Associated lesion       | ADH, DCIS, IDC     | Present            | IDC                      | IDC |

MCA, mucinous cystadenocarcinoma; N/A, not available; ADH, atypical ductal hyperplasia; DCIS, ductal carcinoma in situ; IDC, invasive ductal carcinoma; ILC, infiltrating lobular carcinoma.

metastasis from distant MCA are following: CK7 positive, CK20 negative, and CDX-2 negative. These results can help to exclude the possibility of metastatic MCA from the ovary, pancreas, and gastrointestinal tract. Being MUC5 positive and MUC2 negative may be the unique characteristics of MCA in the breast, together with the immunoprofiles of being CK7 positive, CK20 negative, CDX-2 negative, ER negative, and PR negative.

Conflicts of Interest

No potential conflict of interest relevant to this article was reported.
REFERENCES

1. Rosen PP, Scott M. Cystic hypersecretory duct carcinoma of the breast. Am J Surg Pathol 1984; 8: 31-41.
2. Koenig C, Tavassoli FA. Mucinous cystadenocarcinoma of the breast. Am J Surg Pathol 1998; 22: 698-703.
3. Domoto H, Terahata S, Yamazaki T, Sato K, Takeo H, Tamai S. Mucinous cystadenocarcinoma of the breast showing sulfomucin production. Histopathology 2000; 36: 567-9.
4. Honma N, Sakamoto G, Ikenaga M, Kuroiwa K, Younes M, Takubo K. Mucinous cystadenocarcinoma of the breast: a case report and review of the literature. Arch Pathol Lab Med 2003; 127: 1031-3.
5. Chen WY, Chen CS, Chen HC, Hung YJ, Chu JS. Mucinous cystadenocarcinoma of the breast coexisting with infiltrating ductal carcinoma. Pathol Int 2004; 54: 781-6.
6. Coyne JD, Irion L. Mammary mucinous cystadenocarcinoma. Histopathology 2006; 49: 659-60.
7. Lee SH, Chaung CR. Mucinous metaplasia of breast carcinoma with macrocystic transformation resembling ovarian mucinous cystadenocarcinoma in a case of synchronous bilateral infiltrating ductal carcinoma. Pathol Int 2008; 58: 601-5.
8. Rakici S, Günülü G, Gürsel SB, Yıldız L, Bayrak IK, Yücel I. Mucinous cystadenocarcinoma of the breast with estrogen receptor expression: a case report and review of the literature. Case Rep Oncol 2009; 2: 210-6.
9. Peterson F, Pang B, Thamboo TP, Putti TC. Mucinous cystadenocarcinoma of the breast with amplification of the HER2-gene confirmed by FISH: The first case reported. Hum Pathol 2010; 41: 910-3.
10. Sentani K, Tashiro T, Uraoka N, et al. Primary mammary mucinous cystadenocarcinoma: cytological and histological findings. Diagn Cytopathol 2012; 40: 624-8.
11. Rosen PP. Rosen’s breast pathology. 3rd ed. Philadelphia: Wolters Kluwer/Lippincott Williams & Wilkins, 2009; 515-34.
12. Cheng L, Lee WY, Chang TW. Benign mucocele-like lesion of the breast: how to differentiate from mucinous carcinoma before surgery. Cytopathology 2004; 15: 104-8.
13. Lau, R, Bentz JS, Khalbuss WE, Clayton AC, Souers RJ, Moriarty AT. Performance characteristics of mucinous (colloid) carcinoma of the breast in fine-needle aspirates: observations from the College of American Pathologists Interlaboratory Comparison Program in Nongynecologic Cytopathology. Arch Pathol Lab Med 2011; 135: 1533-8.
14. Kelten C, Akbulut M, Zekioglu O, Kapkac M, Erhan Y, Ozdemir N. Signet ring cells in fine needle aspiration cytology of breast carcinomas: review of the cytological findings in ten cases identified by histology. Cytopathology 2009; 20: 321-7.
15. Lau SK, Weiss LM, Chu PG. Differential expression of MUC1, MUC2, and MUC5AC in carcinomas of various sites: an immunohistochemical study. Am J Clin Pathol 2004; 122: 61-9.
16. Nguyen MD, Plasil B, Wen P, Frankel WL. Mucin profiles in signet-ring cell carcinoma. Arch Pathol Lab Med 2006; 130: 799-804.
17. Chu PG, Chung L, Weiss LM, Lau SK. Determining the site of origin of mucinous adenocarcinoma: an immunohistochemical study of 175 cases. Am J Surg Pathol 2011; 35: 1830-6.
18. Hanski C, Hofmeier M, Schmitt-Gräff A, et al. Overexpression or ectopic expression of MUC2 is the common property of mucinous carcinomas of the colon, pancreas, breast, and ovary. J Pathol 1997; 182: 385-91.
19. Matsukita S, Nomoto M, Kitajima S, et al. Expression of mucins (MUC1, MUC2, MUC5AC and MUC6) in mucinous carcinoma of the breast: comparison with invasive ductal carcinoma. Histopathology 2003; 42: 26-36.