Primary mucinous cystadenocarcinoma of the breast with amplification of the *HER2* gene confirmed by FISH – case report and review of the literature

Betul Bolat Kucukzeybek[1], Seyran Yigit[1], Ayşegul Akder Sari[1], Turkan Rezanko[1], Evren Durak[2], Canan Sadullahoglu[1]

[1]Department of Pathology, İzmir Katip Celebi University Atatürk Training and Research Hospital, Turkey
[2]Clinic of General Surgery, İzmir Katip Celebi University Atatürk Training and Research Hospital, Turkey

Fifty five-years-old woman was presented to the general surgery upon the palpation of a mass in her left breast. In the excisional biopsy performed, partially cystic tumor of 2 × 1 cm with solid areas was macroscopically observed. After through microscopic examination, the patient was diagnosed as invasive mucinous cystadenocarcinoma and the tumor was found to be ER- and PR-negative and C-erbB2 (2+). In the fluorescent *in situ* hybridization, *HER2/neu* gene amplification was observed. Here, we present the clinical, cytological, morphological and immunohistochemical features of a very rare type of breast carcinoma, mucinous cystadenocarcinoma of the breast, with the review of the relevant literature.

Key words: breast, mucinous cystadenocarcinoma, FISH.

Introduction

Mucinous cystadenocarcinoma (MCA) is a rare variant of the primary breast carcinomas [1-5]. It is strikingly similar to ovarian and pancreatic counterparts [1, 2, 5]. To our knowledge only 15 cases of primary breast MCAs have been reported up to date in the English literature. Here, we present the clinical, cytological, morphological and immunohistochemical (IHC) features of MCA of the breast in a case of a 55 year old woman, with the review of the relevant literature.

Case report

55-years-old woman was presented to the general surgery department of our hospital upon the palpation of a mass in her left breast. Fine needle aspiration biopsy (FNAB) revealed only a cystic content which was composed of histiocytes. In the FNAB repeated in our department, we observed atypical epithelial cells which tended to form isolated or small groups, with irregular nuclear contours, hyperchromatic nuclei, eosinophilic cytoplasms and few big vacuoles on a basis of debris and bleeding, containing macrophages (Fig. 1A). The patient was suspected to have a malignancy and confirmation with tissue biopsy was recommended. In the excisional biopsy performed, partially cystic irregular tumor in dimensions of 2 × 1 × 1 cm with solid areas was macroscopically observed. Upon microscopic examination, we observed a cystic tumor composed of papillary structures with thin fibrovascular cores that were lined with columnar mucinous cells (Fig. 1B-D).

Histochemically, Alcien Blue positive, dense extracellular and intracellular mucin content was present. Tumoral cells were quite atypical and had prominent nucleoli (Fig. 2A, B). In focal areas, some cells appeared to have decreased content of cytoplasmic mucin and to have large eosinophilic cytoplasma (Fig. 2C).

Around the periphery of the tumor high nuclear grade ductal carcinoma in situ with solid morphology and comedonecrosis was present (Fig. 2D).

Among myoepithelial markers, P63 and smooth muscle actin were negative. Tumoral cells were diffusely positive with cytokeratin 7 (Fig. 3A), whereas

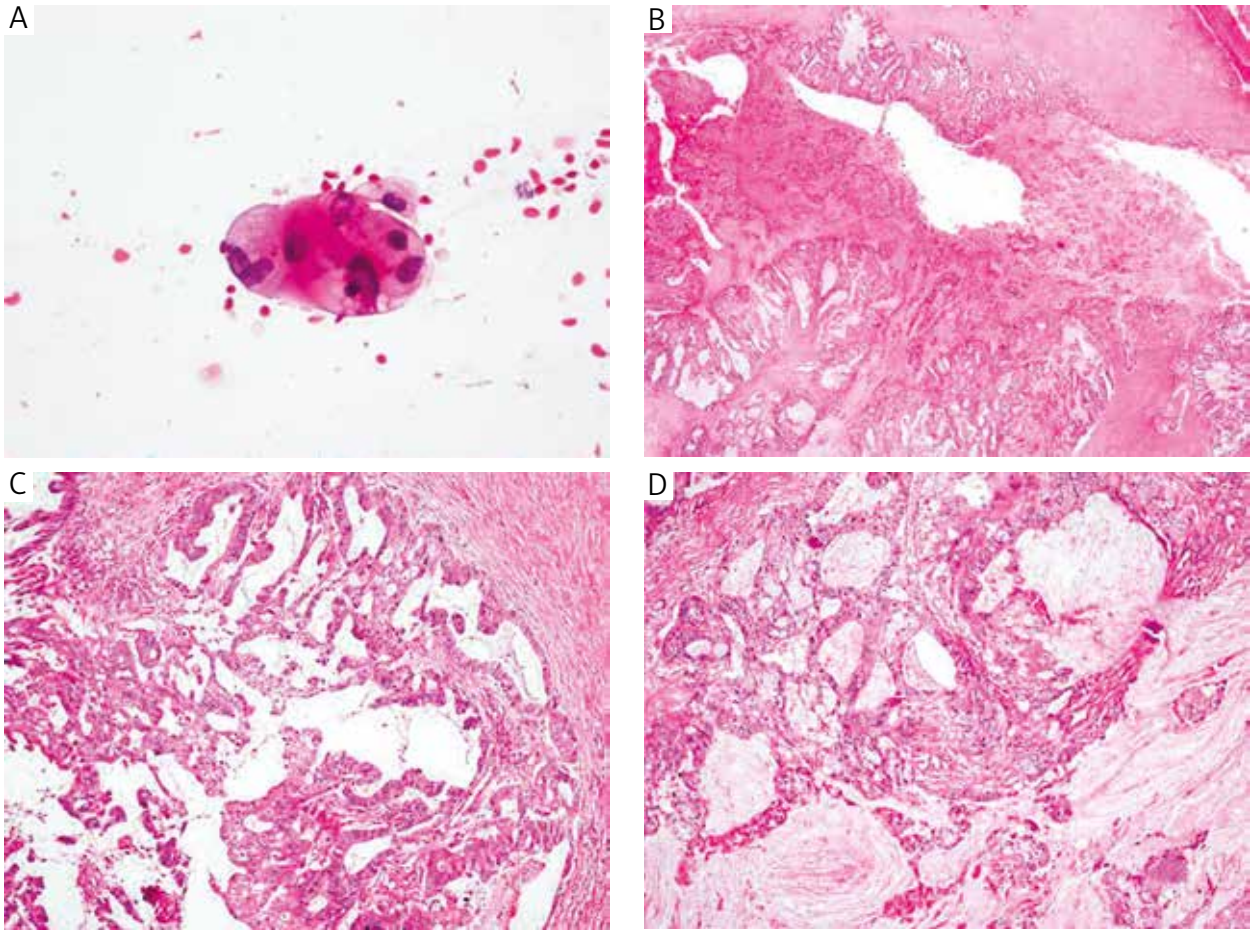

Fig. 1. A) Atypical epithelial cells tended to form small groups, with irregular nuclear contours, hyperchromatic nuclei, eosinophilic cytoplasms and few big vacuoles on a basis of debris and bleeding. **B–D)** Cystic tumor paved with columnar mucinous cells with papillary structure that contains partially thin fibrovascular cores

cytokeratin 20 (Fig. 3B), p53, ER and PR were all negative. C-erbB2 showed a moderate membranous positivity which was scored as 2 (+) (Fig. 3C). Fluorescent in situ hybridization (FISH) method revealed *HER2* gene amplification (Fig. 3D). Ki67 proliferation index of the tumor was 30%. All the 3 sentinal lymphe nodes were free of tumor, therefore axillary dissection was not performed. Upper and lower abdominal CT scans and detailed clinical examination did not reveal any additional pathology. The patient received adjuvant chemotherapy and adjuvant trastuzumab and radiotherapy. During 10-month follow-up, the patient revealed neither recurrence nor metastasis.

Discussion

Primary MCAs of the breast which was first described by Tavassoli and Koenig in 1998 [1] is a very rare variant of breast tumor. MCA of the breast is histopathologically very similar to its ovarian and pancreatic counterparts [1, 3, 4, 6] and contains both extracellular and intracellular mucin.

Since it is a very entity, differential diagnosis should consider the likelihood of metastasis from other organ tumors [1, 2]. The presence of cytokeratin 7 and cytokeratin 20 in the IHC panel and detailed clinical evaluation are useful for the differential diagnosis of the primary and metastatic mucinous tumors [1, 2, 4]. Ovarian and pancreatic MCAs are cytokeratin 7 (+)/cytokeratin 20 (+), whereas breast MCAs are cytokeratin 7 (+)/cytokeratin 20 (–) [2, 4]. In our case tumoral cells were also cytokeratin 7 (+), cytokeratin 20 (–) which supports that the breast is the primary site of the tumor. In addition, no pathological findings were detected by CT scans or by clinical examination.

Reported cases of MCA of the breast in the literature were all female ranged in age from 41 to 96 years. However most cases were diagnosed during the post-menopausal period.

Tumor diameters ranged between 0.8 cm and 19 cm [1, 2, 4]. Our case was also a 55-years-old woman who was diagnosed during the post-menopausal period and the tumor diameter was 2 cm.

Except one ER positive tumor, all reported cases of MCA were hormone status negative [1, 2, 4, 7-13]. Based on this immunohistochemical finding, primary MCAs of the breast were thought to occur regardless of the estrogenic stimulation [2, 4, 10].

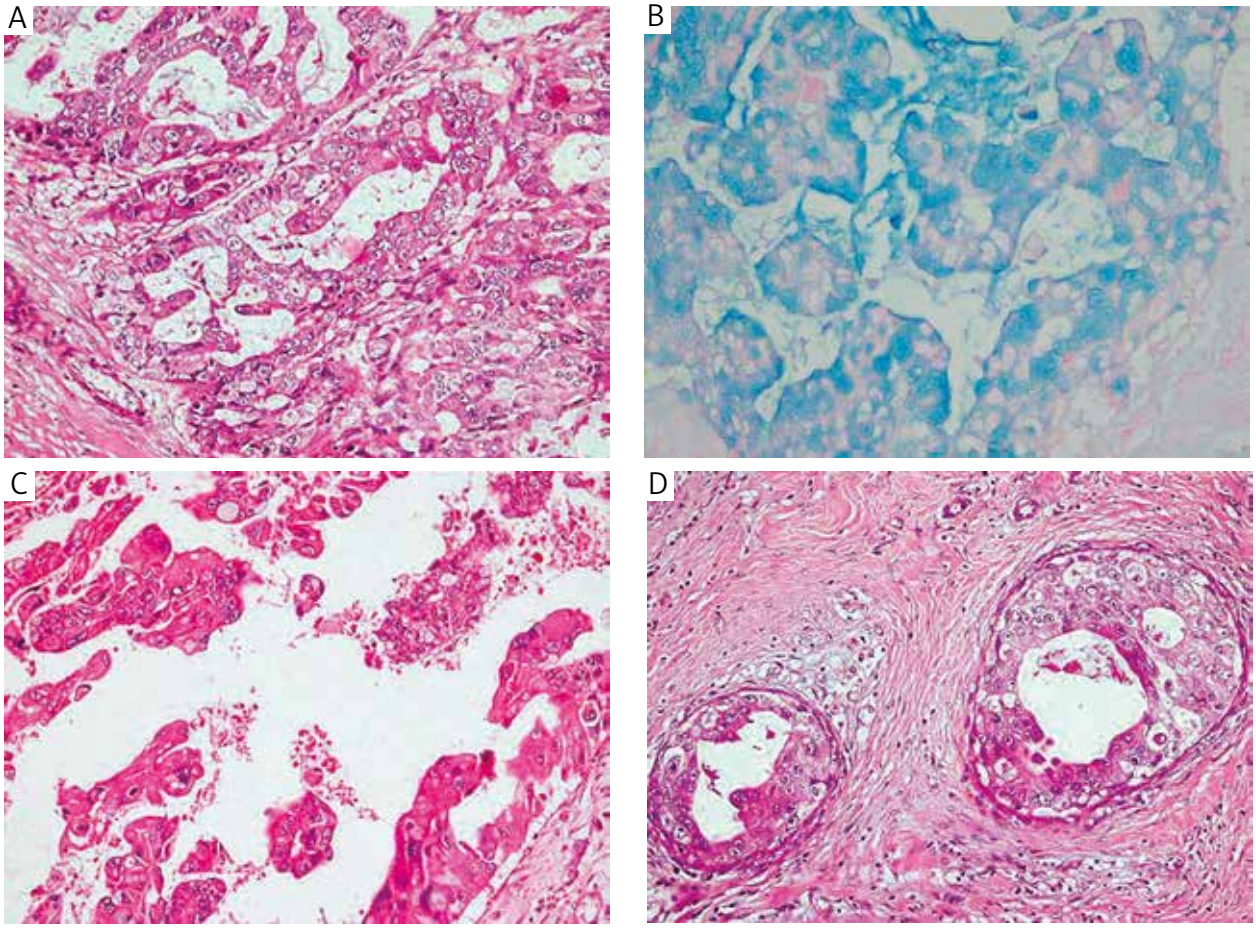

Fig. 2. A, B) Tumoral cells were quite atypical and had prominent nucleoli. Histochemically Alcien Blue positive, dense extracellular and intracellular mucin content was present. **C)** Some cells appeared to have decreased content of cytoplasmic mucin and to have large eosinophilic cytoplasma. **D)** High nuclear grade ductal carcinoma *in situ* that showed comedonecrosis

In one case [9], HER2 protein expression and, *HER2* gene amplification with FISH method were demonstrated, whereas all other cases were found to have no HER2 protein expression based on IHC [1, 2, 4, 8, 10, 12]. In our case ER and PR were negative and C-erbB2 was 2(+).

FISH method revealed *HER2* gene amplification. This is the second case that was detected to have *HER2* gene amplification in the literature. Among all the cases reported, Ki-67 proliferation index of the tumor was generally high [1, 2]. In our case, Ki-67 proliferation index was 30% and p53 was negative.

Although majority of the reported cases were hormone receptors negative and had high Ki-67 proliferation index [1, 2, 7, 8, 10-12] which indicate poor prognosis, no recurrences and no disease-related death were detected in the follow-ups [2]. Lymph node metastases was only found in three cases [1, 2, 12]. Our case also had no lymph node metastasis and free of disease at 10-months follow-up.

In some cases, DCIS and/or invasive ductal carcinoma were reported in the tissue surrounding the tumor [3, 8, 11]. In our case high nuclear grade DCIS with comedonecrosis was also present in some foci around the periphery of the tumor.

Although the cases of MCA which were reported to be ER, PR and CerbB2 negative and which had a high Ki-67 index were not followed-up long-term, they showed good prognosis [2, 3, 7]. MCA of the breast with different pathogenesis and biological behavior should be differentiated from other histological subtypes of the primary breast cancers and from the metastases of the other organ tumors. The determination of the prognostic features of this very rarely seen variant warrants more case reports with long-term follow-up.

Mucinous cystadenocarcinoma was mentioned as a distinct variant in the 2003 WHO classification of breast tumors. However it was rejected from the classification in WHO 2012 [14]. Although it is rare tumor, owing to the problems in the differential diagnosis and its distinct biological behavior, we think that MCA of the breast merits to take part in the breast tumor classification.

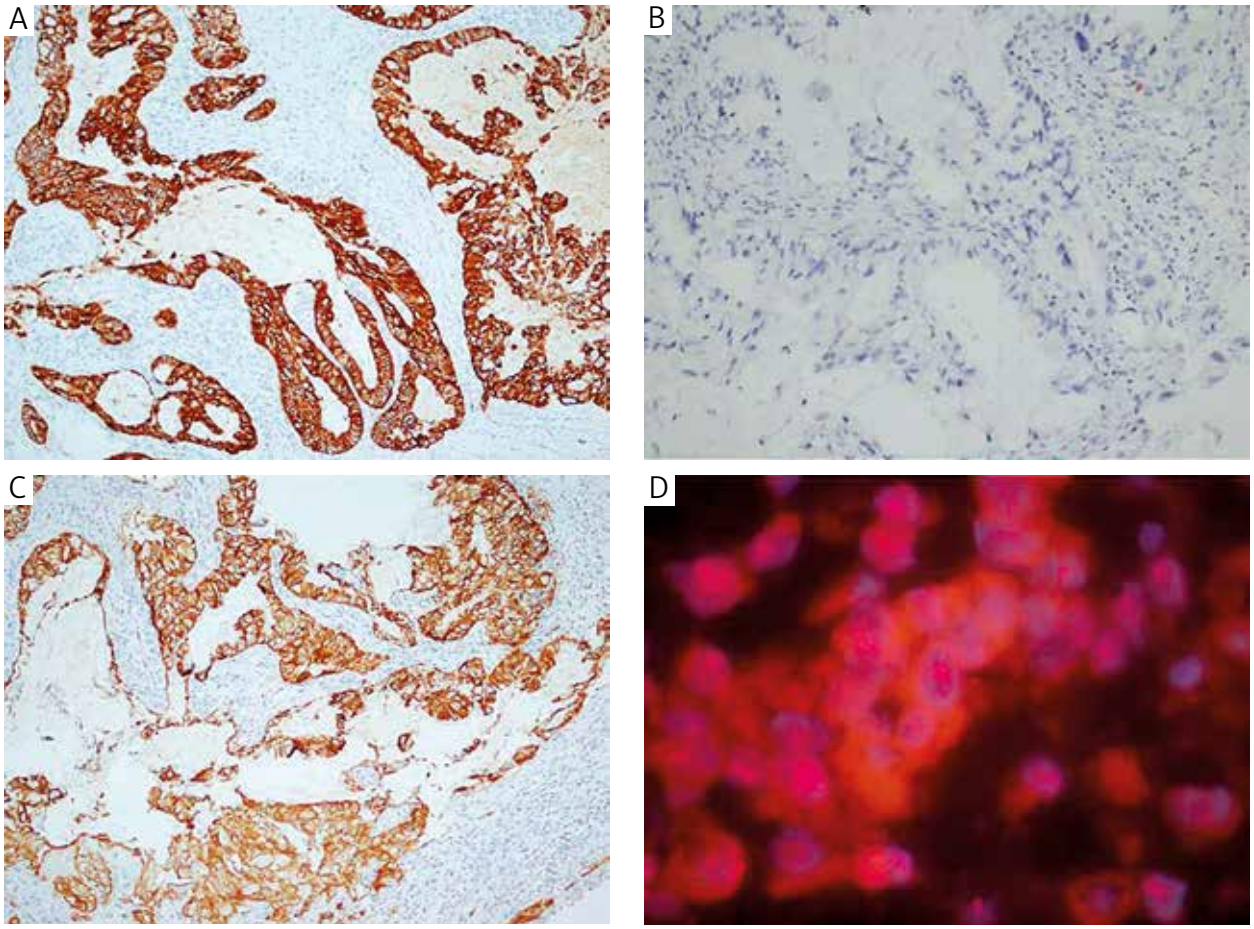

Fig. 3. A) Immunohistochemically tumor cells were cytokeratin 7 diffuse (+). **B)** Immunohistochemically tumor cells were cytokeratin 20 (–). **C)** Immunohistochemically CerbB-2 showed a moderate membranous positivity. **D)** Fluorescent *in situ* hybridization (FISH) method revealed *HER2* gene amplification

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Address for correspondence

Betul Bolat Kucukzeybek
Department of Pathology
İzmir Katip Celebi University Atatürk Training and Research Hospital
Basinsitesi-Karabaglar-Izmir, Turkey 35360
e-mail: bbkzeybek@yahoo.com