Editorial

Primary breast mucinous cystadenocarcinoma—histopathological analysis

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Breast cancer is the most prevalent invasive female cancer affecting around 14% of women during their lifetime worldwide and causing approximately 500,000 deaths yearly. Actually, breast cancer is a heterogeneous group of tumours consisting of different histological subtypes, characterized by various biology, clinical course and prognosis. Among them there are some rarely diagnosed subtypes, including mucinous cystadenocarcinoma (MCA), occurring as a pure form or mixed with foci of other histological types of breast cancer.

The primary MCA of the breast is an exceedingly uncommon tumour that has been distinguished as an individual breast cancer subtype in the recent 5th edition of WHO classification of breast tumours (1). It was firstly described in 1998 by Koenig and Tavassoli, who reported 4 cases (2). MCA is more commonly seen in the sites as ovary, pancreas and appendix. Thus, the final diagnosis cannot be made before the metastatic origin of the lesion is excluded. For the diagnosis of primary breast MCA, it is crucial to combine all proved clinical, pathological along with immunohistochemical (IHC) staining and radiological features of the tumour to exclude the most prevalent sites of primary MCA: the ovary, gastrointestinal tract and pancreas.

MCA of the breast is usually diagnosed in postmenopausal women and presents as a large, cystic mass. In a microscopic examination, the cysts are lined by tall columnar mucinous cells, which are similar to those of endocervical glands, with abundant extracellular and intracellular mucin. IHC shows consistent results with negative steroid hormone receptors status [estrogen (ER–) and progesterone receptor (PR–)], positive cytokeratin 7 (CK7+), negative cytokeratin 20 (CK20–) while various HER2 status (3,4). CK7/CK20 IHC combination is applicable as both primary ovarian and pancreatic MCA are positive for both cytokeratins whilst primary breast MCA shows no expression of cytokeratin 20 (CK20–). However, results presented by Chen *et al.* [2004] (5) and Kaur *et al.* [2022] (6) showed focal CK20 positivity of primary breast MCA.

MCA of the breast must be differentiated from other breast tumours characterized by the production of mucin, especially from mucinous breast cancer, signet ring cell carcinoma and columnar cell mucinous carcinoma. Typically, MCA doesn't form cystic conformations rather just conglomerations of epithelial cells suspended in extracellular mucin "lakes". In some cases, mucoid secretion spills into the surrounding stroma forming a "mucous lake" in which single cells or small clusters of tumour cells are floating, similarly to mucinous breast cancer (gelatinous cancer). There is no myoepithelial cell layer and desmoplastic stroma might be observed.

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Nuclear grade in MCA is usually low to intermediate. However, the positive rate of Ki-67 in most tumour cells is high, reaching the value up to 90% (7). This proves that the vast majority of the MCA cells show high proliferative index, regardless their degree of atypia.

As mentioned, MCA is typically ER- and PR-negative while mucinous breast carcinoma is strongly and diffusely positive both for ER and PR (5). Previous observations, however, indicate the possible occurrence of other breast cancer molecular subtypes among MCA. For this reason, it seems to be necessary to include lineage markers as CDX2, GATA3, GCDFP and PAX8 in the diagnostic panel of mucinous adenocarcinoma.

Although MCA usually occurs as a pure type, it is rarely described as a mixed form, in which MCA co-exists with other breast cancer subtypes foci, especially ductal carcinoma in situ (DCIS) or invasive ductal breast carcinoma (IDC) components. In some of these cases cystic dilatation catheters covered by a monolayer or stratified high columnar mucous cells in diverse degrees of cell dysplasia have been observed. The co-existence of DCIS and MCA in some cases indicates that cancer cells of MCA may transform through metaplasia of epithelial cells of DCIS, accompanied by estrogen and progesterone receptors expression loss (7). According to the theory presented by Chen *et al.* [2004] it is believed that these DCIS components originates from the mucinous metaplasia of epithelial cells of widespread DCIS (5), and it was named as the *in situ* carcinoma form of MCA.

Lee and Chaung [2008] suggested that the concentration of extracellular mucus in the intraductal papillary carcinoma with mucous epithelial metaplasia brings to cystic growth of the lumen, loss of myoepithelium and adjacent interstitial infiltration, leading to the development of MCA (8). Nevertheless, this hypothesis doesn't elucidate the biologic behaviour of MCA, which prevalently presents a basal-like immunophenotype while a favourable prognosis.

The observations made so far indicate that primary breast MCA has a good prognosis with low incidence of local recurrence and lymph node metastasis. Although axillary lymph node involvement is infrequent, it has been reported in the literature. The prognosis despite regional lymph node involvement is favourable with no distant metastasis or recurrence described after complete resection, yet (9).

The pathogenesis of primary MCA of the breast has not been clarified because of its rarity and deficiency of molecular analyses. It is only proved that the vast majority of these tumours are triple negative. Lin *et al.* [2021] as first analysed the extensive genetic MCA profile using next-generation sequencing (NGS) of 580 genes, widely approved to be associated with carcinogenesis. The authors identified mutations in TP53, BAP1, and RB1 genes, thus suggested that primary breast MCA is driven mostly by alternations in suppressor genes, mostly those controlling cell cycle and chromatin remodelling (10). In spite of morphologic similarities between primary breast MCA and their ovarian and pancreatic counterparts, this tumour seems to behave definitely contrasting. Ovarian MCAs are usually associated with mutations in TP53, P16/CDKN2A and KRAS genes along with marked HER2 amplification (11) while pancreatic mucinous cancers most commonly harbours TP53, and P16/CDKN2A, RNF43 and KRAS mutations (12).

The limited number of primary breast MCA cases causes lack of established standards of its treatment strategies. In the majority of the previously described case reports, patients underwent partial or radical mastectomy, and received adjuvant chemotherapy and/or complementary radiotherapy (13). However, because of the favourable overall prognosis, the significance of chemotherapy and radiotherapy remains doubtful. What is more, the triple-negative molecular phenotype and high proliferative index of primary breast MCA can lead to false perceptions or overtreatment with redundant radiotherapy and/or chemotherapy in some patients (14).

Ultimately, MCA is an exceptionally infrequent subtype of the primary breast cancer. Differential diagnosis includes other mucin-producing breast tumours and metastatic MCA, in particular, from pancreatic and ovarian origin. Despite its high proliferative index and triple-negative molecular profile, MCA is characterized by favourable prognosis. Because of limited prevalence, MCA etiopathogenesis remains unknown and clinical management is uncertain. Studies on more cases are needed to develop standards for diagnosis and treatment.

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