

Case Report

Mucinous variant of invasive micropapillary carcinoma of breast: report of two cases and literature review

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Abstract: Invasive micropapillary carcinoma (IMPC) is a rare type of malignant tumor of breast with a poor prognosis. There is controversy in the identification of mucinous variant of IMPC with mucinous carcinoma. In the past, it always be diagnosed as micropapillary variant of mucinous carcinoma, but in this study, the author has a different opinion. Here, we report two cases diagnosed as mucinous variant of IMPC. Histological morphologies were similar in the two cases. In difference from mucinous carcinoma, mucinous variant of the IMPC is characterized by micropapillary structure of the tumor cells, higher nuclear atypia, more frequent HER2/Neu overexpression, high proliferation index of Ki-67, increased lymph node metastasis, and poor prognosis. A distinct feature of the 2 cases was that the tumor cells were present as micropapillary or tubular-solid clusters floating in the extracellular mucin pools and most of the floating tumor cells were surrounded by the hyaline lacunae, which can clearly be appreciated even in the background of mucin. Both patients were managed by the standard chemotherapy and radiotherapy combined with simple mastectomy. Up to the time of preparation of this report, both patients have survived for over 4 years. It is important to differentiate a mucinous variants of IMPC from a pure mucinous carcinoma due to their significantly different prognosis and, thereafter, different choices of patient management.

Keywords: Breast, invasive micropapillary carcinoma, mucinous variant

Introduction

Invasive micropapillary carcinoma (IMPC) is a rare breast cancer with a poor prognosis [1]. It is characterized by small micropapillary structures with surrounding clear stromal spaces, high Ki-67 proliferation index, more frequent HER-2/Neu overexpression, high lymph node metastatic rate and poor prognosis [2, 3]. IMPC may occur as a pure form or may be admixed with invasive ductal carcinoma of NST, or rarely, with mucinous carcinoma. It has long been a controversy whether a tumor with both invasive micropapillary and mucinous components should be classified as mucinous variant of micropapillary carcinoma or micropapillary variant of mucinous carcinoma [4]. Since mucinous carcinoma has more favorable prognosis than IMPC [5], a distinction between these two entities will have a significant impact on the managements of the patients. In this report, we present two cases of invasive breast carcinoma with predominant mucinous component diagnosed as mucinous variant of IMPC. The clinical

and histopathological/immunophenotypic features, the diagnostic criteria, differential diagnosis, treatment strategies and prognosis are presented and discussed.

Case presentation

Clinical history

Case 1: A 64-year-old woman presented with a swelling mass in the left axilla for a week before visiting a local doctor. Ultrasound examination in our hospital revealed a 2 cm×1.2 cm mass in the outer upper quadrant of the left breast and multiple hypoechogenic lymph nodes in the left axilla. The laboratory data showed a carcinoembryonic antigen (CEA) level of 12.21 ng/ml. A core needle biopsy was performed and a diagnosis of mucinous variant of invasive micropapillary carcinoma was made based on the morphologic features and immunohistochemical studies. The patient was treated with four courses of TAC (docetaxel, doxorubicin and cyclophosphamide) as neoadjuvant chemotherapy,

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followed by a modified radical mastectomy. The postoperative pathological examination showed a pathologic complete response to neoadjuvant therapy characterized by tumor necrosis and stromal fibrosis with punctate calcification. Seven of sixteen left axillary lymph nodes were positive for metastatic carcinoma (7/16), which also demonstrated partial response to neoadjuvant therapy. The postoperative carcinoembryonic antigen level dropped to 0.5 ng/ml. The patient was given four courses of TAC postoperative adjuvant chemotherapy and has remained recurrence-free for over 4 years.

Case 2: A 54-year-old woman presented with a swelling mass in the left axilla for one year before visiting a local doctor. Ultrasound examination revealed a 3.5 cm×3.2 cm mass in the outer upper quadrant of the left breast and several hypoechogenic lymph nodes in the left axilla. A core needle biopsy was performed and a diagnosis of “invasive breast cancer” was made. A modified radical mastectomy was performed. A 3.5 cm invasive carcinoma with multifocal lymphovascular involvements was identified. A postoperative pathological diagnosis of mucinous variant of invasive micropapillary carcinoma was made based on the morphologic features and immunohistochemical studies. Six of thirty four left axillary lymph nodes were positive for metastatic carcinoma (6/34). The patient was treated with six courses of fluorouracil (5-FU), doxorubicin and cyclophosphamide (FAC) as adjuvant chemotherapy, followed by adjuvant radiotherapy. The patient has remained recurrence-free for over 4 years.

Materials and methods

The surgical specimen was fixed in 10% formaldehyde and embedded in paraffin. Sections (4 μm) were obtained for conventional histopathological examination and fluorescence in situ hybridization (FISH). A panel of primary antibodies was used by immunohistochemistry analysis (source and solutions): Estrogen Receptor (ER, MAB-0062, 1D5), Ready-to-use, Maixin Bio, Fujian, China; Progesterone Receptor (PR, MAB-0675, MX009), Ready-to-use, Maixin Bio, Fujian, China; C-erbB-2 (Her-2, RMA-0555, SP3), Ready-to-use, Maixin Bio, Fujian, China; EGFR (RMA-0554, SP9), Maixin Bio, Fujian, China; Epithelial Membrane Antigen (EMA, ZM-0095, E29), ZSGB-Bio, Beijing, China; Ki-67

(ZM-0166, K2), Ready-to-use, ZSGB-Bio, Beijing, China. Sections were lightly counterstained with hematoxylin. Appropriate positive and negative controls were performed concurrently for all the applied antisera. FISH was performed with probes for HER2 genes (Abbott PathVysion). Abbott PathVysion HER2 DNA Probe Kit was used for FISH assay to determine HER2 amplification.

Pathological findings

Histological morphologies were similar in the two cases. **Figure 1A** and **1B** show the histological features of the core biopsy specimen of case number 1 and those of mastectomy specimen of case number 2. The tumor cells were present as micropapillary or tubular-solid clusters floating in the extracellular mucin pools. No fibrovascular cores were seen in the tumor clusters. The tumor cells were columnar or cuboidal with round or oval nuclei, with the apical surfaces polarized to the surrounding mucin. The nuclear atypia varied from intermediate to high grades. No tumor necrosis was observed. A distinct feature was that most of the floating tumor cells were surrounded by the hyaline lacunae, which can clearly be appreciated even in the background of mucin (**Figure 1B**, red arrows). In the non-mucinous area, fine fibrous septa were observed in mesenchyme, but there were no desmoplastic changes. Interestingly enough, in the lymph node with metastatic carcinoma of case number 2, the features of a classic invasive micropapillary carcinoma were largely retained with almost no extracellular mucin present (**Figure 1C**). Sections of the mastectomy specimen of case number 1 demonstrated diffuse tumor necrosis with calcification, consistent with pathologic complete response to neoadjuvant therapy (data not shown).

Diagnosis

Both cases were diagnosed as mucinous variants of invasive micropapillary carcinoma.

Immunohistochemistry

The two cases had the same immunological phenotypes. The tumor cells were stained positive for HER2-Neu (**Figure 1D**) and EMA (**Figure 1E**), negative for ER, PR and EGFR. The proliferation index of Ki-67 was approximately 30%.

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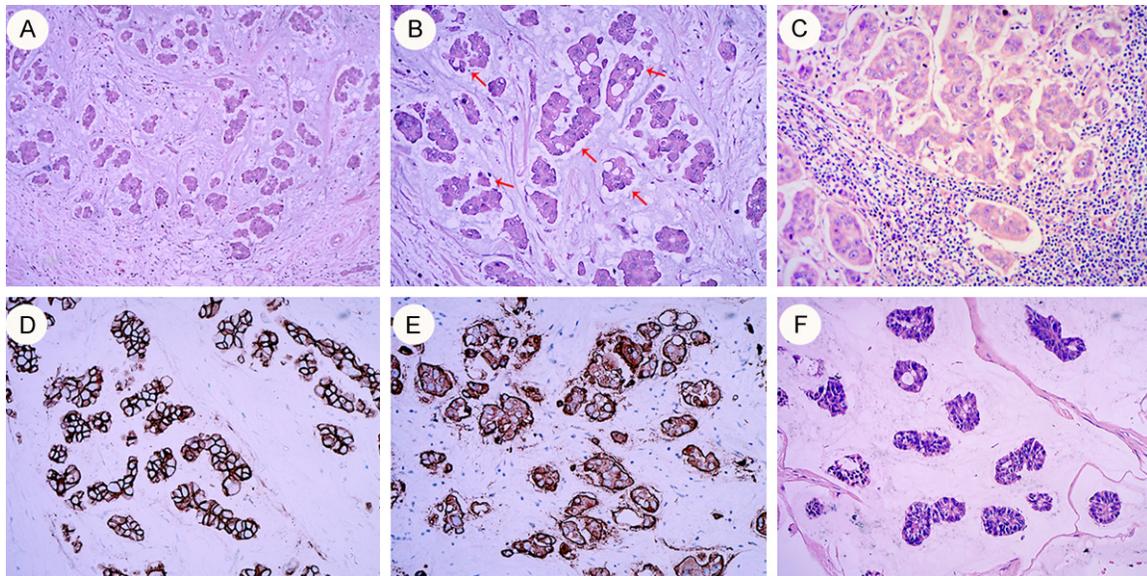


Figure 1. Pathological analysis. A. Micropapillary and small tubular clusters of tumor cells floating in extracellular mucin pools. B. Characteristic hyaline lacunae surrounding the tumor cell cluster (red arrows). C. Micropapillary component in lymph node metastases. D. Result of immunohistochemical staining for HER2/Neu. E. Result of immunohistochemical staining for EMA. F. Absence of hyaline lacunae between tumor clusters and mucus around in pure mucinous carcinoma and less fibrous septa is observed in mesenchyme. Tissue section was from a surgical specimen of mucinous carcinoma of breast.

Fluorescence in situ hybridization (FISH)

Both cases were positive for HER2-Neu amplification.

Clinical follow-up

The patients have been followed up for 4 years with no recurrence or distant metastasis.

Discussion

WHO Classification of Tumors of the Breast (2003, 2012) identified IMPC as a rare special type of breast cancer, accounting for about 1.2% to 2.7% of total invasive breast cancer [6, 7]. IMPC has a high degree of lymphovascular involvement, lymph node metastasis and poor prognosis. Since pure IMPC is rare, the WHO classification did not explicitly specify the proportion of IMPC components for the diagnosis of IMPC. It is generally accepted that a greater than 50% of the invasive micropapillary component of the total tumor mass is the quantitative requirement for the diagnosis. However, there were also results to confirm that the frequency of lymph node metastasis was similar in tumors with an invasive micropapillary component constituting only < 25% or even < 10% [8]. Accordingly, it is important that an invasive

micropapillary component is recognized in an invasive breast cancer even if represent as a minor proportion. In our study, the tumor was nearly entirely of the mucinous variant of IMPC in the core needle biopsy specimen of case number 1 and approximately 90% of the mucinous variant and 10% the classic type of IMPC in the surgical specimen of case number 2.

Diagnosis

IMPC is similar with non specific invasive ductal carcinoma (IDC-NOS) in clinical features, both with painless masses as the main manifestation [9]. Since metastases to axillary lymph nodes were seen in more than 70% of IMPC cases, axillary lymph node enlargements were general findings in the initial imaging examinations [10]. In our study, seven of sixteen axillary lymph nodes (7/16) in case number 1 and six of thirty four (6/34) axillary lymph nodes were positive for metastases, consistent with the clinical and pathological features of IMPC.

IMPC has well been described histologically in previous reports. First, the tumor cells form micropapillary, tubular-alveolar cluster with diffuse infiltrating growth pattern. Second, tumor cell clusters are surrounded by a characteristic zona pellucida without fibrovascular cores; fine

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fibrous septa are observed in mesenchyme, but there are no desmoplastic changes. Third, the tumor cell cytoplasm is eosinophilic and the nuclei have different degrees of atypia; tumor necrosis is rare. Fourth, the metastatic tumor cells in lymph nodes and pleura generally retain the growth pattern of micropapillary. The majority of IMPC are ER positive and almost half are PR positive. Her-2/Neu overexpression by IMPC was reported with different frequency by different authors with an overall overexpression rate up to one-third of reported cases [11]. Tumor cells of IMPC have a unique inverted “inside-out” papillary arrangement, with the apical surface polarized to the outside, toward the surrounding clear spaces. This feature can be highlighted using immunostains for EMA and MUC1, which normally stain the luminal surfaces of the benign ducts and those of well-differentiated adenocarcinoma [4, 12]. In contrast, HER-2/Neu and intercellular adhesion molecule (such as E-cadherin, N-cadherin and CD44) are positive in the intercellular junctions of micropapillary clusters but negative in the apical surface [4, 12]. In our study, both cases were negative for ER/PR and positive for HER-2/Neu amplifications by FISH. EMA was positive on apical surface of the micropapillary clusters while HER-2 was positive in the intercellular junctions of the clusters, consistent with immunophenotypic features of IMPC.

Differential diagnosis

How to classify an invasive breast cancer with both micropapillary and mucinous components has long been controversial. Is it a mixed tumor, a mucinous variant of invasive micropapillary carcinoma, or a micropapillary variant of mucinous carcinoma? It is important to differentiate a mucinous variants of IMPC from a pure mucinous carcinoma due to their significantly different prognosis and, thereafter, different choices of patient management. In 2002, Ng et al [4] reported 5 cases of mucinous carcinoma with micropapillary growth pattern and first proposed a new subtype of mucinous carcinoma. Since the arrangement of tumor cells in the mucin pools were the same as those of invasive micropapillary carcinoma with pseudopapillary or pseudoglandular/tubular structures and “inside-out” surface of the cell clusters, other scholars proposed that this type of tumor should be classified as IMPC (mucinous variant) [1]. Barbashina et al [13] reported 15

cases with micropapillary structure in the background of the mucinous carcinoma. Compared with classic mucinous carcinoma, the cases they reported showed distinct pathological features: higher nuclear atypia, higher lymph node metastasis rate with more prominent calcifications, higher positive rate of p53 and more frequent HER-2/Neu overexpression. Among the cases, 1 case had been diagnosed as IMPC when recrudesced. The authors proposed that this type of tumor should be separated from the classic mucinous carcinoma [13]. We classified the two cases in study as mucinous variants of IMPC rather than micropapillary variants of mucinous carcinoma based on the following observations: varied but general high nuclear atypia of the tumor cells, increased lymph node metastasis, overexpression of HER2/Neu and high proliferation index of Ki-67. EMA is also positive on the surfaces of the tumor clusters in a classic mucinous carcinoma of breast, and it is, therefore, not a reliable immuno marker for differential diagnosis between IMPC and mucinous carcinoma. By a careful histological observation, we found that there were no hyaline lacunae between the tumor clusters and the mucin around in classic mucinous carcinoma, and there was less fibrous septa in mesenchyme (**Figure 1F**). In contrast, the tumor cell clusters were surrounded by characteristic hyaline lacunae in the cases of our study, which can be clearly appreciated even in the background of mucin pools (**Figure 1B**). The hyaline lacunae remain exist in the metastatic tumor in the lymph node (**Figure 1C**). There were also more fine fibrous septa in the mesenchyma as compared to mucinous carcinoma (**Figure 1B**). We believe that these are important histologic features when combined with others for the classification of an invasive breast cancer with both micropapillary and mucinous components.

Treatment and prognosis

IMPC is a breast cancer with frequent lymph node metastasis and recrudescence with a 5 years survival rate significantly lower than that of IDC-NOS of the same grade [14]. A more aggressive treatment including the standard radical mastectomy and postoperative radiotherapy and chemotherapy is generally the choice of management. Patient number 1 was treated with neoadjuvant chemotherapy with a good response as signified by a reduced mass

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size and a decreased level of CEA. The patient underwent a standardized chemotherapy after radical surgery. The follow-up has been for 4 years with no recurrence or distant metastasis. Patient number 2 has been followed up for 4 years after the standard chemotherapy and radiotherapy after modified mastectomy, with no recurrence or metastasis identified up to present.

Conclusions

Both of the mucinous variant of the IMPC and the mucinous carcinoma show clusters of tumor cells floating in extracellular mucin pools. However, different classification of the tumor has significant impacts on the choice of management, leading to either excessive treatment or inadequate treatment. Compared to the managements of patients with mucinous carcinoma, who generally have a favorable prognosis, more aggressive treatments including the standard radical mastectomy and postoperative radiotherapy and chemotherapy are generally required for patients with IMPC.

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Disclosure of conflict of interest

None.

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