Mucinous Breast Carcinoma: A Single-Center Experience

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OBJECTIVE
To analyze the clinical and histopathological characteristics and treatment outcomes of patients treated and followed up for mucinous breast cancer (MBC).

METHODS
We retrospectively analyzed the clinical and histopathological characteristics and treatment outcomes of 22 patients who were diagnosed with and treated for MBC at our center between 2004 and 2016.

RESULTS
The mean age was 50 (range: 26–68) years. Ten (47.6%) patients were premenopausal. The tumor was in the right side in 11 patients (50%), and 64% of the patients had early-stage disease. There were six patients with the mixed subtype and 16 with the pure subtype. Except for the two patients with metastatic disease, all patients underwent surgery. Axillary lymph node involvement was detected in seven (36%) patients, and the proportion of patients with the pure subtype was 18%. The average duration of follow-up was 59 months, during which, four patients had recurrent disease. At 5 years, 81% of the patients were alive. The 5-year overall survival rate with pure MBC was 93%.

CONCLUSION
MBC is a rare condition and carries a good prognosis. Pure MBC has low axillary lymph node metastasis and a higher survival rate.

Keywords: Mucinous breast cancer; prognosis, treatment.

Introduction
Consistent with the global data, breast cancer represents the leading cancer type among women in our country with a reported incidence of 41.6/100,000.[1] Invasive breast cancer represents a heterogeneous disorder with respect to the pathological classification, presentation, and clinical course. Most tumors arise from the ductal epithelium, particularly the ductal-lobular unit. More than 75% of the cases are diagnosed with infiltrative ductal carcinoma, also known as invasive ductal carcinoma, followed by epithelial invasive lobular carcinoma, occurring in 5%–15% of the patients. Also, many other less frequent sub-types of breast cancer have been described.[2]

Mucinous breast cancer (MBC) is a rare entity, comprising only 1%–6% of all breast carcinomas.[3] Most patients are in the advanced age group, and its prognosis is better than that of IDC.[4] Macroscopically, it has a soft consistency and is well demarcated, which may lead to confusion with benign breast lesions both clinically and radiologically.[5] Histopathological examination shows small cellular islands of uniform cells floating in extensive extracellular mucinous pools...
and glandular structures. Well-differentiated lesions are frequently estrogen receptor (ER) and progesterone receptor (PR) positive and human epidermal growth factor receptor (HER-2) negative.[6]

In this study, we aimed to evaluate the clinical and pathological characteristics and treatment outcomes in patients who were diagnosed with and treated for MBC at our center.

Materials and Methods

Between 2004 and 2016, a file search was performed among 1273 patients treated for breast cancer at our unit. The file searched revealed 22 patients with MBC, and these cases were retrospectively analyzed. Clinical and histopathological findings were retrieved from outpatient follow-up files and hospital records. We received approval from the local ethics committee. As this was a retrospective study, informed consent was obtained not from the patients. Age at diagnosis, menopausal status, family history, clinical stage, tumor location, tumor size, axillary involvement, histological grade, hormone receptor levels, HER-2 expression, and glandular structures. Well-differentiated lesions were identified. Treatments administered, histological Type, type of surgery, menopausal status, family history, clinical stage, tumor location, tumor size, axillary involvement, histological grade, hormone receptor levels, HER-2 expression, and the type of surgery were recorded. ER, PR, and HER2 2 expression are routinely performed in our center. For ER and PR positivity, the cellular staining of 1% and nuclear staining of >1% were considered.[7] HER2 staining intensity was immunohistochemically scored as 0, 1+, 2+, or 3+. A score of 3+ indicated HER2 positivity, whereas a score of 0 or 1+ showed HER2 negativity. In those with a score of 2+, fluorescence in situ hybridization (FISH) was used for gene amplification. FISH was considered positive when HER2 gene copy number exceeded six or when the HER-2/neu signal to chromosome 17 centromere (CEN-17) signal ratio was >2.2.[8] Patients with metastases at the time of diagnosis were identified. Treatments administered, response to treatment, and the duration of follow-up were retrieved from patient files or the automated hospital database. The most recent survival status was ascertained either by the death reporting system or by telephone contact.

Statistical analysis

For statistical analyses, SPSS (Statistical Package for Social Sciences) 20.0 software was used. Survival analyses were based on Kaplan–Meier estimates. For survival analysis, the time of diagnosis was taken as the baseline date, and the time of last follow-up (for surviving patients) or death (for patients who died) was used as the last date of follow-up.

Results

A total of 22 patients (21 female, one male) were diagnosed with mucinous carcinoma, comprising 1.7% of all patients diagnosed at our center during the study period. The mean age was 50 (range, 26–68) years, with 10 (47.6%) patients having a premenopausal and 11 (52.4%) patients having a postmenopausal status. Family history for breast cancer was positive in two (9%) patients. The tumor was on the right or left side in 11 patients each. The mean diameter of tumor was 3.8 (range, 1.3–12) cm. Of all patients, 64% had early-stage disease, whereas 36% had advanced disease at the time of diagnosis (Table 1).

Except for two patients who had metastatic disease at the time of diagnosis, all patients underwent surgery. Breast-conserving surgery was performed in two patients and modified radical mastectomy+axillary dissection (MRM+AD) was performed in the remaining. Of the patients undergoing surgery, two were operated after neoadjuvant chemotherapy. Histopathological examination revealed mucinous carcinoma with neuroendocrine differentiation in two patients, inflammatory carcinoma+mucinous carcinoma in one, papillary carcinoma+mucinous carcinoma in two, and invasive ductal carcinoma+mucinous carcinoma in one. Also, one patient had the clinical appearance of inflammatory breast carcinoma. ER, PR, and HER2 positivity was present in 19, 16, and 10 patients, respectively, whereas two patients were triple negative. Among the operated patients, seven (36%) had axillary involvement. Of the patients with lymph node involvement, four had mixed-type and three had pure mucinous type carcinoma. Patients with axillary lymph node involvement also had histopathological signs indicative of poor prognosis (triple negative, neuroendocrine differentiation, inflammatory disease characteristics, and receptor-negative/HER2-positive). No associations between axillary lymph node involvement and tumor size were observed (3.8 cm with nod− vs. 4 cm with nod+). Of the patients with histological grading in pathology reports, 84.6% had grade 2 and 15.4% had grade 1 disease.

Neoadjuvant chemotherapy, adjuvant chemotherapy, and adjuvant radiotherapy were given to two, 15, and 18 patients, respectively. Adjuvant hormone therapy was initiated in 16 patients. In a male patient diagnosed with luminal (ER+, PR+, HER2−)–early stage breast carcinoma, chemotherapy was not given following surgery; he received adjuvant RT. Currently, he is in remission with continued hormonal therapy. After adjuvant treatment, four cases of recurrence were detected during the follow-up. Recurrences were found in the bone in two patients, lungs in one, and brain in another. Recurrences occurred in the two patients with neuroendocrine differentiation and in those with receptor-negative/HER2-positive disease.

The mean duration of follow-up was 59 months, during which, four patients died. Of these patients, two had metastatic disease at the time of diagnosis and the remaining two had recurrence during the follow-up. Of the patients who died, three had mixed subtype and one had pure mucinous subtype. Overall, 81.5% of the patients were still alive. The overall 5-year survival rate for patients with pure mucinous subtype was 93%. DFS analysis could not be performed due to the small sample size.

Discussion

In clinical practice, mucinous carcinoma comprises 1%–6% of all breast cancers.[9] Accordingly, 1.7% of our patients had MBC, consistent with the published data. This disease generally affects the elderly individuals, with <1% of the patients being ≥35 years of age.[6] The mean age of our group was 50 years, in line with previous reports from our country.[10] Conversely, in a large patient series published by Savario et al.[6], the mean patient age was 71 years.

In mucinous carcinomas, mucin is responsible for adjuvant treatment, four cases of recurrence were detected during the follow-up. Recurrences were found in the bone in two patients, lungs in one, and brain in another. Recurrences occurred in the two patients with neuroendocrine differentiation and in those with receptor-negative/HER2-positive disease. The mean duration of follow-up was 59 months, during which, four patients died. Of these patients, two had metastatic disease at the time of diagnosis and the remaining two had recurrence during the follow-up. Of the patients who died, three had mixed subtype and one had pure mucinous subtype. Overall, 81.5% of the patients were still alive. The overall 5-year survival rate for patients with pure mucinous subtype was 93%. DFS analysis could not be performed due to the small sample size.

Table 1

<table>
<thead>
<tr>
<th>Stage</th>
<th>Number</th>
<th>%</th>
</tr>
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<tbody>
<tr>
<td>I</td>
<td>12</td>
<td>54.5</td>
</tr>
<tr>
<td>II</td>
<td>6</td>
<td>27.2</td>
</tr>
<tr>
<td>III</td>
<td>2</td>
<td>9.1</td>
</tr>
<tr>
<td>IV</td>
<td>16</td>
<td>72.7</td>
</tr>
<tr>
<td>Negative</td>
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</tr>
<tr>
<td>Positive</td>
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<td>72.7</td>
</tr>
<tr>
<td>HER2 status</td>
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<td>68.1</td>
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<tr>
<td>Positive</td>
<td>10</td>
<td>45.5</td>
</tr>
<tr>
<td>Negative</td>
<td>12</td>
<td>54.5</td>
</tr>
</tbody>
</table>

IDC: Invasive ductal carcinoma, HER: Human epidermal growth factor receptor.

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MBC is a slow-growing neoplasia, with a growth rate of only one third of the general invasive breast cancers. Also, this malignancy has a lower predilection for axillary involvement. In the study by Komenaka et al.[14], 14% of the patients with pure mucinous carcinoma had axillary involvement. Previously published figures for axillary involvement range between 2% and 14% for pure mucinous carcinomas [15,16], whereas the corresponding figures for mixed-type mucinous carcinoma varies between 46% and 64%.[16] In our study, 18% and 66% of the patients with pure or mixed mucinous breast carcinoma had axillary involvement, respectively.

Mucinous tumors are histopathologically divided into two groups. The pure type generally produces mucin around the tumor tissue, whereas in the mixed type, other components in addition to mucin exist. Pure mucinous carcinomas are often well-differentiated with positive hormone receptors and negative HER-2 [3]. Among our patients, 86% and 72% had ER and PR positivity, respectively, consistent with most of the previously reported figures.[6,12] Conversely, at odds with published data, the HER-2 positivity was exceedingly high. In previous reports [12], HER-2 positivity was present in 5% of the cases, whereas in our series, approximately 45% cases were HER-2 positive, perhaps indicating a requirement for the revision of our pathologic data.

Rarely, mucinous breast carcinomas may be identified through neuroendocrine differentiation defined with the presence of cytoplasmic argyrophilia or synaptophisin, chromogranin, or immunoreactivity against neuron-specific markers such as enolase.[17] Although neuroendocrine differentiation was associated with a good histology and outcome in one previous study [18], others failed to observe such an association.[19] In our study, patients with neuroendocrine differentiation had poor survival and histopathological characteristics.

In early-stage breast cancer, breast-conserving surgery is recommended. In locally advanced mucinous breast carcinomas, MRM following neoadjuvant chemotherapy may be appropriate.[6] Postoperative adjuvant therapy may include chemotherapy, radiotherapy, and/or hormonal therapy depending on histopathology and lymph node involvement. ERs and/or PRs are positive in almost all cases of mucinous carcinomas, suggesting that hormonal therapy may be an effective option.[20] All patients with hormone receptor positivity received adjuvant hormonal therapy in our study. The prognosis, overall survival, and disease-specific survival of patients with pure mucinous breast carcinoma was good, and the reported 5-, 10-, 15-, and 20-year survival rates were 94%, 89%, 85%, and 81%, respectively.[6] In our study, the 5-year survival rate (93%) was comparable with that in the literature data.

Limitations
Our study has some limitations. The histopathologic subtype of mucinous breast carcinoma could not be optimally diagnosed because the pathologic specimens were evaluated by different pathologists. Furthermore, because of the low number of patients, no comparison was made regarding the clinicopathologic features between those with pure and mixed-type carcinomas. Another limitation was that we could not analyze BRCA1-2, p53 mutation. We could have discussed the results of clinical differences between BRCA1 and non-BRCA1 in relation to tumors in patients with mucinous breast carcinoma had the analysis been performed.

Conclusion
MBC is a rare malignancy with good prognosis. The incidence of pure MBC is even lower; however, this condition is associated with low predisposition for axillary lymph node metastasis, low or moderate histological grade, low rate of recurrence, and higher survival. Studies with larger sample size and longer follow-up are warranted to better delineate optimal adjuvant treatment and characteristics of this tumor.

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Conflict of Interest: The authors declare that there is no conflict of interest.


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