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Research Paper

Characteristics of mucinous breast cancer: Epidemiology, prognostic features, and pathological characteristics

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Abstract

Introduction: Although many studies have already investigated breast carcinoma, they have mainly focused on the most common types. Therefore, there is a lack of information about the rarer ones, such as mucinous breast carcinoma (MBC).

Aim: To summarize the knowledge gained so far about the epidemiology, etiology, prognostic factors, pathomorphological changes, and treatment of MBC and to present its characteristics based on original data.

Material and methods: A PubMed literature review was conducted. Tissue samples from 1122 patients with suspected or diagnosed breast carcinoma were analyzed. Tumor types were identified using hematoxylin and eosin staining, and immunohistochemistry was used to assess estrogen (ER), progesterone (PR), and HER2/neu receptor expression.

Results and discussion: The review identified pure MBC (PMC) and mixed MBC (MMC) as two subtypes of the tumor. Our results showed that PMC was the dominant subtype. PMC patients were older at the time of the diagnosis than MMC. None of the females had distant metastases and only two presented with positive lymph node status. ER expression without PR expression was recognized in three cases, HER2 in four, and both ER and PR in fourteen. Patients with PMC showed more frequent expression of ER and PR than those with MMC.

Conclusions: Overall, this study focused on the importance of subtype differentiation and the evaluation of clinical features in determining prognosis and selecting appropriate therapy for MBC. Additionally, we indicated factors that may influence patient prognosis such as hormonal status, lymph node involvement and age.

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1. INTRODUCTION

Breast carcinoma (BC) currently remains the most diagnosed cancer among the female population worldwide[1] and in 2021 caused over 670,000 deaths worldwide[2] with 69,406 in Poland alone.[3] Many authors have already widely described more common types of this carcinoma, especially invasive ductal carcinoma (IDC), responsible for nearly 80% of all BC cases.[4] However, only a few have investigated the topic of other types. It is crucial to investigate rarer subtypes of BC, as it may help to confirm new prognostic factors, enabling more efficient treatment and thus ensuring a more favorable prognosis for affected patients.

1.1. Classification, epidemiology, and etiology of mucinous breast carcinoma (MBC)

Over 20 subtypes of breast carcinomas can be distinguished, mucinous breast cancer (MBC) being one of them; it accounts for 1 to 6% of all BC cases[5] and 2.4% of all infiltrating BCs.[4] The World Health Organization (WHO) has classified MBC as a type of BC characterized with the presence of over 50% mucous components. MBC is also known as colloid or gelatinous carcinoma[6] and these terms perfectly describe the unsolid character of this cancer. The size of the tumor varies between 1 to 20 cm. Microscopically, MBC is characterized by clusters of tumor cells floating in lakes of extracellular mucin.[7] MBC can be divided into two subtypes: pure mucinous breast cancer (PMC) and mixed mucinous breast cancer (MMC). PMC is defined as MBC containing ≥90% mucinous components while MMC contains between 50% to 90%.[8] In some HER2-positive PMC cases, signet-ring cells may be observed, typically showing intracellular mucin accumulation.[9]

Worth noticing is the greater ability of MMC to metastasize to the lymph nodes which could be correlated with a poorer prognosis than in PMC (Table 1).

PMC can be divided into two groups: hypocellular MBC and hypercellular MBC. The main difference between them is the cellular component of the tumor. In hypocellular PMC the cellular structure consists of less than 50% of tumor mass, while in hypercellular it is ≥50%. However, in both subtypes the mucinous component should represent over ≥90%.[5,7,13] Authors have indicated that in hypocellular MC there are larger quantities of extracellular mucin than in the hypercellular type, while in the hypercellular type, neuroendocrine differentiation is more frequent than in the hypocellular type.[14] BCs with mucinous features, but with under 50% of the component are called IDC with mucinous features.[15]

MMC is also divided into two groups: mixed MMC (mMMC) with 50–90% of mucinous components and partial MMC (pMMC) with 30–50% of mucinous components.[15]

As previously mentioned, there are many differences between PMC and MMC but they also share common patterns. Firstly, both are diagnosed mainly in postmenopausal women with a median age of 70–71 years old[16,17] and are rare in populations below 35 years old.[17] What is more, although the prognosis for MMC is worse than for PMC, in both subtypes it is still more favorable in comparison with IDC.[15]

The etiology of MBC, which is similar to other carcinomas, remains uncertain and is multifactorial. Some authors connect their development with lifestyle and hormonal or reproductive factors.[18] Contrarily, some authors suggest that hormonal changes such as late menarche or early menopause, and childlessness are less important for the carcinogenesis of MBC in comparison with other breast carcinomas.[19]

1.2. The risk factors and prognosis for mucinous breast carcinoma (MBC)

The principal prognostic factors used to establish patient outcomes include lymph node involvement and tumor operability. Other factors associated with a poorer prognosis are higher T classification, higher nuclear grade, HER2 gene amplification, bone marrow metastases, age over 60 at diagnosis, inability to undergo adjuvant therapy, and single marital status.[20,21] Generally, MBC is associated with a favorable prognosis.[8] The five-year disease-free survival rate ranges between 94% and 95%[5,17] while the ten-year disease-free survival rate is estimated at 94%.[22] Recurrence is rare, and metastases, observed in approximately 15% of patients, most often involve the axillary lymph nodes and are correlated with poorer prognosis.[11] Metastases occur in 15–32% of MMC patients and 11.1% of PMC cases, which indicates a greater metastatic potential of MMC.[7]

Table 1. The main differences between PMC and MMC.

Comparable feature	Pure mucinous breast carcinoma (PMC)	Mixed mucinous breast carcinoma (MMC)
Mucinous components	Consists of ≥90% mucinous components[8]	Consists of 50–90% of mucinous components[8]
Molecular subtype	The majority is luminal A molecular subtype (61.8%)[7]	The majority is luminal B molecular subtype (61.8%)[7]
Prognosis	Generally, better prognosis than MMC;[7] more favorable especially in hypocellular subtype[10]	
Cancer progression	Slower growth[11,12]	Greater capacity to metastasize to the lymph nodes (31.6% vs 11,1%)[7]
Treatment		In this type, mastectomy is more frequent (32.9% (MMC) vs 11.1% (PMC);[7] more frequently adjuvant chemotherapy is introduced

1.3. The course of the disease, symptoms, and diagnostic process

MBC grows slowly[6] without causing any alarming symptoms at the beginning, which is associated with their larger size at the moment of the diagnosis.[18] On self-examination in the later stages of MBC development, the patient can feel a firm or solid, palpable mass in the breast.[23] Further diagnostics include ultrasonography (USG), mammography, magnetic resonance imaging (MRI), and as a form of definitive confirmation, biopsy. On mammography and ultrasound, it typically presents as a round mass with well-defined margins and the absence of microcalcification.[7] Suspicious mammographic findings might be precluded by large amounts of mucin.[24] In ultrasonography, echogenicity may serve as a useful parameter for subtype determination.[18] MRI may be useful in distinguishing MBC from benign lesions such as fibroadenomas and low-grade phyllodes tumors.[7] In recent times, there have been endeavors to incorporate biomarkers, including HER2, Ki-67 (tissue markers), CA-15-3, and CA-125 (serum biomarkers), into diagnostic procedures and to utilise them for the estimation of patients' prognoses.[25]

1.4. Treatment possibilities

The most common treatment for both types of MBC is breast-conserving surgery, which is performed in 78.3% of all MBC patients.[7] The newer approach also includes postoperative radiotherapy treatment, which is especially beneficial in populations over 65 years old.[26] Chemotherapy is more frequently introduced for patients with MMC rather than PMC.[7] This treatment is advised amongst patients with negative lymph node status and with T2 status. Contrarily, adjuvant chemotherapy can be omitted in case of positive lymph node status if tumors are smaller than 1 cm.[27] The last treatment option is hormonal therapy which is efficient for both MMC and PMC and is recommended in patients with negative lymph node status and hormone receptor-positive tumors. In cases with positive lymph node status or with one or more metastases in a size larger than 2 mm, hormonal therapy is not advised and chemotherapy should be introduced.[28]

2. AIM

The aim of this study is to assess and analyze the histopathological characteristics of mucinous breast cancer.

3. MATERIAL AND METHODS

The analyzed material consisted of 1122 tissue samples obtained from patients treated for breast cancer, all assessed by one center – the Department of Pathology, Military Medical Institute in Warsaw. No specific inclusion or exclusion criteria were applied. The samples were derived from biopsies, excisional biopsies of primary breast cancer, and modified radical mastectomy. All samples were fixed in 10% phosphate buffered formalin. After 24 hours, the material was dehydrated in alcohol solution of increasing concentrations and paraffin blocks were cut into 4-μm thick slices. The examined samples were stained with haematoxylin and eosin and graded separately by two pathologists according to the WHO classification and grading systems. Histological analysis revealed that MBC was identified in 24 of the 1122 samples. The diagnosis of MBC was established based on characteristic microscopic features, including the presence of monomorphic tumor cells that manifest in substantial clusters, with minimal extracellular mucus, though at times, mucus is present within the cells. Additional diagnostic features of MBC included the presence of polymorphic cells dispersed in small groups, accompanied by abundant extracellular mucin. Immunohistochemical staining with various antibodies was performed to evaluate the expression of ER, PR and HER2 receptors. The expression of ER and PR was considered positive when more than 10% of nuclei were stained; results between 1% and 10% were classified as weakly positive and absence of staining was considered negative. HER2 expression was determined using the HerceptTestTM imaging system (Code: K5204, DAKO, Santa Clara, USA).

4. RESULTS

Twenty-four cases of mucinous breast cancer represented 2.1% of all 1122 analysed breast cancer samples. The age of the patients ranged between 35 and 88 years, with a mean age of 66.5 years. One sample was derived from core needle biopsy, while the remaining samples were obtained from postoperative material. Fourteen tumors were detected in the right breast and ten tumors were detected in the left.

The mucinous component was classified as high grade (G3) in two cases, while 22 were classified as intermediate grade (G2). Tumor size ranged from 0.6 cm to 4.0 cm with a mean size of 2.2 cm. Twenty-two of the 24 tumors showed no nodal involvement (pN0), one was classified as pN1 (metastases in 1 out of 10 lymph nodes) and one as pN2 with 7 out of 10 lymph nodes involved. In five cases assessed as pN0, the number of examined lymph nodes was not specified. None of the cases showed evidence of distant metastases (M1). In ten cases, distant metastases were absent (M0), while in fourteen cases, metastatic status could not be evaluated (MX). Receptor status was also assessed. Fourteen patients showed expression of both ER and PR, three were ER-positive only and seven were negative for both ER- and PR. HER2 expression was detected in four samples.

Among the 24 cases, 6 were classified as the mixed type. Five of these were graded as G2 and one as G3. Tumor size in the mixed-type group varied from 1.8 to 4.0 cm (mean size 2.5 cm). Among 18 cases of pure mucinous carcinoma 17 were assessed as G2 and one as G3. Their size ranged from 0.6 cm to 4.0 cm, with a mean size of 2.1 cm. Regional lymph node status was assessed as pN2 in one mixed-type case (7 of 10 lymph nodes involved) and as pN1 in one pure-type case. In the mixed-type group, five out of six cases were MX and one was M0. In the pure-type group, nine cases were MX

and the other nine were M0. Four mixed-type cases showed ER expression, three showed PR expression and two were HER2-positive. Thirteen of the pure type were ER-positive, 11 were PR-positive and two showed HER2 expression.

5. DISCUSSION

The following study was conducted on a group of 24 patients with MBCs selected from 1122 patients with invasive breast cancer. A thorough analysis of histopathological and clinical features was performed, including the purity of MBC, histological grade, primary tumor size, regional lymph node status, metastatic status and immunohistochemical breast cancer profile.

MBC is a rare subtype of cancer accounting for 1–6% of breast carcinomas. In this study, the incidence rate of MBC was 2.1%. PMC is generally more frequent than MMC (80% vs. 20% of all MBCs, respectively).[5] Our results showed a similar distribution with 75% classified as PMC and 25% as MMC.

MBC occurs more frequently in older postmenopausal women,[20] and is typically associated with presenting with a higher mean age at diagnosis compared with no special type (NST) breast carcinomas.[29] Only about 1% of patients are diagnosed with MBC before the age of 35 years.[17] In the present study, the mean age at diagnosis was 66.5 years, slightly lower than the median age of 70–71 reported in most previous studies,[16,17] although some authors have described a considerably younger age at MBC diagnosis.[13] PMC tends to occur at a younger age than MMC.[7] However, other studies have not found a significant difference in the age of diagnosis between the two subtypes.[11,16] This is worth mentioning, as the age at diagnosis is considered the second most important prognostic factor after nodal status.[7]

The tumor size of MBC ranged from 0.6 cm to 4.0 cm with a mean size of 2.2 cm, whereas the mean tumor size of all 1122 studied samples was 1.9 cm. In this study, the pure and mixed subtypes of MBC demonstrated relatively similar sizes, with mean maximal diameters of 2.1 cm and 2.5 cm, respectively. The small sample size limits conclusions regarding size differences between the two subtypes. In general, the pure subtype is considered to grow more slowly and therefore tends to have a smaller diameter.[16] The impact of tumor size on survival remains a matter of debate. It may not be significant in the American Joint Committee of Cancer (AJCC) staging system as a large portion of the tumor volume consists of mucin.[23] Nevertheless, some authors regard tumor size as an independent prognostic factor.[17]

Almost all cases of MBC were graded as G2, with the exception of two cases classified as G3. These findings are consistent with the previous reports indicating that MBC is usually moderately differentiated and rarely poorly differentiated.[4]

The incidence of lymph node metastases in MBC is relatively low. Zhang et al. reported nodal involvement in approximately 12% of cases,[16] whereas in the present study the rate was lower (8.3%). It is important to note that nodal involvement is associated with a less favorable 5-year disease-free survival (DFS) and overall survival (OS), and in some studies it is considered the most important prognostic factor.[7,17] Lymph node metastases are considerably more common in MMC than in PMC with rates ranging from 45–64% for MMC and 2–14% for PMC.[5] Among other factors, this difference contributes to the better prognosis in PMC cases. The existing literature does not provide consistent evidence for whether lymph node metastases are directly related to tumor size.[7,17,29] None of the investigated cases in this study showed evidence of distant metastasis (M1), which is consistent with findings from other reviews.[23,24] A retrospective analysis of 11,400 PMC cases revealed distant metastases in only 2% of patients.[17]

Previous studies have demonstrated a strong association between MBC and hormone receptor expression,[7] which is consistent with our findings; PR positivity was observed in 58.3% of cases and ER positivity in 70.8%. According to the latest NCCN guidelines, the recommended management of hormone receptor-positive tumors without nodal metastases includes adjuvant endocrine therapy. However, such therapy may be avoided when the tumor measures less than 1 cm, should be considered if the tumor size is between 1–2.9 cm and is strongly recommended for tumors larger than 3 cm. In cases with nodal involvement, chemotherapy may be added to the treatment regimen. HER2/neu overexpression was relatively low, detected in 16.7% of MBCs, which is consistent with published data.[5,16] In rare cases of HER-2 overexpressing MBC, neoadjuvant therapy with trastuzumab, pertuzumab has been shown to be effective.[7]

6. CONCLUSIONS

(1) Mucinous breast cancer (MBC) is a rare type of breast cancer, more commonly found in older females.
(2) It is typically diagnosed early, grows slowly, and rarely involves lymph nodes or distant metastases.
(3) While the role of tumor size in disease prognosis remains controversial, nodal involvement possibly could be recognized as a key prognostic factor.
(4) The relationship between tumor size and nodal involvement is still unclear.
(5) MBC commonly shows hormone receptor expression, supporting the use of adjuvant endocrine therapy.
(6) HER2/neu overexpression is relatively rare but can be effectively treated with targeted therapies.
(7) The most significant limitation of this study is the small sample size.

Ethical approval

This article does not contain any studies with human participants performed by any of the authors. Our study was retrospective and did not require ethical approval as only archival samples were used. Nevertheless, the ethical commission was informed about our research.

Conflicts of interest
The authors have no relevant financial or non-financial interests to disclose.

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Data availability statement
The authors confirm that the data supporting the findings of this study are available within the article.

Author Contributions
Study design: AD, JP, AMB-K
Data collection: JP
Statistical analysis: MB
Data interpretation: AF
Manuscript preparation: AF, KB, AP, AL-T, AMB-K

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