

Pure Mucinous Carcinoma of the Breast: A review of current literature regarding diagnostic performance and genomic testing

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Abstract

Pure mucinous carcinoma, is a rare form of breast cancer with favorable prognosis. Pre-operative diagnosis and correct sub-classification are important first steps for appropriate clinical management of this disease. Knowledge of the cytologic features, diagnostic pitfalls, and potential mimics of PMC, need to be considered when evaluating pathologic material from this variant of breast cancer. Genomic profiling may help to identify a variety of known and emerging therapeutic targets which can potentially improve survival, especially in the metastatic setting.

Introduction

Breast cancer is the most common malignancy among women and its incidence is rising worldwide. Although imaging studies such as mammography, ultrasound, and nuclear medicine technology are important for screening and identifying breast abnormalities, pathological evaluation is pivotal for further characterization and classification of suspicious breast lesions. Fine needle aspiration (FNA) and core needle biopsy (CNB) are the current methods commonly employed to establish the pathologic diagnosis of palpable and non-palpable breast lesions. Each of these methods has its advantages and limitations depending on the skill of the person performing the procedure and interpreting the slides (1, 2).

Mucinous (colloid) carcinoma (MC) is a rare form of breast malignancy representing about 4% (1-7%) of breast carcinomas (2-9). It has a higher incidence in peri- and post-menopausal women (age 55-60 and above) with only 1% of the patients younger than 35 years (4, 10). MC is defined as a tumor where the mucinous component represents 50% or more of the tumor. It is divided into two subtypes, pure and mixed. Mixed mucinous carcinoma (MMC) has a mucinous component comprising up to 90% of the tumor. The remainder of the tumor usually consists of invasive ductal carcinoma, not otherwise specified. From a prognostic standpoint, MMC is associated with a worse prognosis when compared to the pure subtype of MC (2-9, 11, 12).

Pure mucinous carcinoma (PMC) is a rare subtype of MC that is characterized by bland neoplastic cells associated with

a mucinous background comprising more than 90% of the tumor (12, 13). It represents about 2% of all breast cancers, most commonly seen in women aged 55-67 years (4, 10, 14, 15). Clinically, it may present as a non-palpable mass, although tumors as large as 20 cm have also been reported (4). Given the slow growing nature of PMC, they tend to have a favorable prognosis. Pure mucinous tumors can mimic benign lesions radiologically partly due to the abundant mucin which can preclude detection of suspicious mammographic features such as microcalcifications (16, 17).

PMC has two histologic subtypes, a hypocellular variant (PMC-A), showing tubular, cribriform, cord-like, micropapillary, and papillary architectural patterns; and a hypercellular variant (PMC-B) growing in solid nests (18, 19). Cytological features of PMC in FNA specimens include variable cellularity, bland nuclear features, and mucinous background. The background mucin can vary from abundant to scant, making the diagnosis challenging since mucin has been described in 2% of breast malignancies other than MC (20). Also, benign tumors may also have a mucinous background in cytologic samples including mucocoele-like lesions and fibroadenoma. Therefore, given the variety of benign and malignant tumors with associated background mucin, it is imperative to correlate the pathology with the clinical and radiologic findings for appropriate patient management.

The purpose of this study is to review the current literature regarding the cytologic features of pure mucinous carcinoma of the breast, discuss factors

which may affect diagnostic accuracy and clinical impact, and the utility of genomic testing.

Diagnostic performance

Few studies have been done to evaluate the performance of pathologists in diagnosing mucinous carcinoma of the breast. Laucirica and colleagues performed a retrospective analysis to evaluate the accuracy of diagnosing mucinous carcinoma of the breast on FNA material. They evaluated the responses of pathologists participating in the College of American Pathologists Interlaboratory comparison program in Nongynecologic Cytopathology (CAP NGC). This consists of a series FNA glass slide challenges that are mailed to participants enrolled in the program. The responses are stratified/classified in the general categories (positive/malignant, negative/benign, and suspicious) and the reference diagnosis of mucinous carcinoma. Of the 8061 responses for mucinous carcinoma, 6353 (78.8%) were positive/malignant, 775 (9.6%) suspicious and 933 (11.6%) negative/benign. Among the positive responses, 2636 (41.5%) of participants correctly made the reference diagnosis of mucinous carcinoma (37.3% of all responses). The other responses in the malignant category were ductal adenocarcinoma (40.2%), lobular carcinoma (7.9%), adenocarcinoma NOS (7.4%), and medullary carcinoma (1.6%). In the benign category, the most frequent incorrect responses were fibroadenoma (51.7%), nonspecified benign lesion (12%), fibrocystic changes (7.8%), and fat necrosis/granulomatosis/foreign body reaction (6.9%). They also evaluated the association between participant performance and the reader type (pathologist versus

cytotechnologist) using the statistical analysis. No significant difference was observed between cytotechnologists and pathologists responses (87.9% versus 88.2%; $P = 0.69$) for the general diagnostic categories (20). Compared to previous reports, this study shows a similar detection rate to the study performed by Kline et al (21). However, compared to the study by Yang et al (16), Laucirica et al documented an improved ability to recognize the mucinous subtype of breast cancer.

Yang and colleagues evaluated the ability of the participants to accurately subclassify breast carcinoma on FNA cytology. Among the 1642 responses, there was a 6.2% false negative and 1.1% false positive rate. Mucinous carcinoma had the highest false-negative general response rate of about 15.2%, in compare with 8.5% for lobular carcinoma, 5.7% for ductal carcinoma, and 0% for medullary carcinoma. Mucinous carcinomas were correctly subclassified as mucinous in 27% of cases and misclassified as ductal carcinoma in 37% of the cases (16). The high false-negative rate in their study may be due to participants' failure to identify cellular groups in the extracellular mucin or the bland cytologic features of MCs. Both factors may contribute to misdiagnosing MC as a benign tumor.

On the other hand, the increase in the detection rate reported by Laucirica et al (20) may be due to the factors including slide preparation type (conventional versus liquid based) and/or stain. Young and colleagues did not segregate their laboratory responses using these criteria (16).

Factors that improve diagnostic accuracy*FNA versus CNB (Cytology versus Histology)*

FNA and CNB are well established methods for diagnosing suspicious breast lesions. FNA is usually performed for palpable lesions, while CNB can be utilized for non-palpable and palpable breast tumors.

Wang and colleagues performed a systematic review and meta-analysis of 12 prospective studies between 1991-2016 including 1802 patients with suspicious breast lesions. All lesions were simultaneously tested by FNA and CNB. The sensitivity with CNB was better than that of FNA cytology (87% versus 74%), while their specificities were similar (98% vs. 96%). Both of these methods showed lower sensitivity for non-palpable versus palpable lesions. This was explained by the use of ultrasound or stereotactic guidance in all studies on non-palpable breast lesions and possibly the skills of the aspirator, cytotechnologists, and cytopathologists. They recommended in patients with non-palpable versus palpable radiologically suspicious lesions, FNA cytology could be considered the initial diagnostic option since it showed a higher degree specificity (22).

Willem and colleagues evaluated FNA versus CNB accuracy for diagnosing breast lesions comparing the results of 29 studies published between 1987-2011. Their review showed that CNB had a higher success rates compared with FNA for palpable (97% vs. 75-90%) and non-palpable breast lesions (94% vs. 34-58%). CNB showed better

sensitivity and specificity compared to FNA especially in those lesions that were equivocally benign or malignant, non-palpable and/or calcified (23).

Although Wang et al (22) and Willem et al (23) showed improved performance with CNB compared to FNA for diagnosing breast lesions, Moschetta and colleagues showed opposite results (1). They studied 400 suspicious breast lesions between 2011-2013. Seventy nine percent of FNA's and 81% of CNB's yielded diagnostic material. Forty-three percent of the lesions were malignant and the remaining were benign. Their analysis showed similar values for FNA versus CNB for the following metrics: sensitivity (97% vs 97%), specificity (94% vs 96%), and diagnostic accuracy (91% vs 97%) (1). The increase in the sensitivity and specificity of FNA cytology may be in part due to improvement in processing of aspirations.

FNA: Conventional versus Liquid base Cytology

Over the past decade, FNA conventional smears have been replaced by liquid-based cytologic preparations (24). Studies comparing both methods have shown better preservation of cellular morphology including visualization of epithelial and stromal elements with preservation of background material such as mucin and colloid with liquid based preparations. In addition, liquid derived samples can also be used for ancillary tests such as immunohistochemistry and molecular studies, obviating the need for additional biopsies. This led to improvements in

diagnostic sensitivity and specificity with respect to malignant lesions and decreased unsatisfactory rates when compare to conventional FNA-derived specimens (24-29).

Laucirica and colleagues compared different slide preparation methods and its effect on participant performance in diagnosing MC of the breast. The slide preparation was done using Papanicolaou stain (4732, 58.7%), modified Giemsa stain (3177, 39.4%), and Thin Prep (152, 1.9%). In the general category of “positive/malignant”, there was a significant difference between the preparation types ($P < .001$). A better performance was observed using ThinPrep smears (92.1%) and modified Giemsa-stained smears (91.2%) in compare with conventional smears (86.5%). Furthermore, modified Giemsa-stained smears performed best in regard to the reference diagnosis of mucinous carcinoma ($P < .001$) due to the ease of recognizing the mucinous background (20). Some authors did not agreed with these results and believed that MC can be difficult to diagnose on ThinPrep cytology because background mucin can be less apparent (29).

Cytologic features

Increased awareness of the cytologic features of MC may improve accuracy in breast FNA diagnosis. Different diagnostic criteria have been defined for MC by various authors. For some authors, diagnosis of pure mucinous carcinoma can be make when the non-mucinous invasive component accounts for less than 10% of the tumor and no poorly differentiated carcinoma is present. Others recommend that in pure

mucinous tumor all tumor cell clusters should be embedded in extracellular mucin and should not contain any amount of non-mucinous invasive carcinoma (11, 30-33).

Cyrta and colleagues retrospectively reviewed the FNA characteristics of pure mucinous carcinoma by evaluating 22 patients with mucinous carcinoma of breast (5 pure and 17 mixed) and compared the cytological and histopathological findings.

They suggested that PMC should be considered when there is greater than 75% background mucin, small nuclei less than 2x RBC, lack of nucleoli, and/or regular nuclear membranes in all tumor cells. Mixed mucinous carcinoma may be strongly suggested by the presence of at least one of the following features: sparse less than 25% mucin, large greater than 3x RBC nuclei, irregular nuclear outlines in greater than 50% of tumor cells and nucleoli (11). These cytologic features are similar to prior studies with emphasis on presence of abundant mucin and nuclear size (30-33).

Prognostic importance of subclassification

Subclassification of MC (pure versus mixed) is important for treatment choice and determines prognosis and survival. Many authors have shown that PMC has a better prognosis and higher survival rate compared to mixed MC (3-6, 19).

In addition, subclassifying PMC into type A (hypocellular variant) and B (hypercellular variant) also has important clinical impact. Kashiwagi et al showed that PMC-type A has a

favorable prognosis even in the presence of lymph node metastasis. This indicates that subclassifying PMC has clinical validity (19). Another study showed no significant difference in clinicopathologic characteristics between the PMC-A and PMC-B subtypes (9).

Comparing to other types of breast cancer, PMC has favorable biologic characteristics including smaller size, lower rates of lymph node positivity, lower stage, higher expression of hormone receptors, and less HER2 overexpression. (2, 4-6, 19, 34).

Several studies have shown that lymph node metastasis is associated with higher chances of recurrence and poor prognosis (3, 5, 6, 35). The incidence of axillary metastases ranged from 2% to 14% in PMC (3, 6, 13, 36-38) and 45% to 64% in mixed MC (6, 38, 39). Di Saverio and colleagues reviewed 11422 cases of PMC, correlating nodal status with survival. There was a low rate regional lymph node metastasis (12 % versus 36%) and excellent survival (81 % versus 62%) after 20 years of follow-up for PMC versus patients with invasive ductal carcinoma of no special type (4). PMC has also been shown to be associated with a better short-term survival compared to IDC of no special type. However, other studies reported contrasting results with identical long-term survival for both types of breast cancers (3, 6, 7, 40).

Genomic testing

During the past two decades, molecular testing including target specific mutations has improved treatment

regimens in breast cancer (41, 42). Traditional DNA sequencing is targeted and quick. However, due to the high rate of false negatives and limitations in the type of alterations, new methods such as comprehensive genomic profiling (CGP) has replaced DNA sequencing for identifying mutations in breast cancer. Several studies have been done demonstrating the unique genomic profiling of MC.

Fuji and colleagues conducted the first study of molecular aberrations in mucinous breast carcinoma using the CGP by next generation sequencing and loss of heterogeneity (LOH). Their results show that PMC have less genetic instability, LOH and extensive genomic alterations when compared to the more traditional variants of breast cancer. This was confirmed by Lacroix-Triki using array-comparative genomic hybridization. They suggested that the molecular signature of PMC is most likely different from that of usual ductal breast carcinoma. This difference may imply a distinct histogenesis and molecular pathogenesis between PMC and invasive ductal carcinoma-not otherwise specified (43, 44).

Other authors performed CGP looking for clinically relevant genomic alterations with potential treatment options in metastatic PMC. They showed a significantly higher amplification of FGFR1 (a major regulator of angiogenesis and the cell cycle) and ERB2 in PMC versus non-mucinous carcinoma. This finding translates to increase sensitivity to anti-FGFR and anti-HER2 therapy or dual FGFR/HER2 kinase inhibitors (42). May and colleagues evaluated the expression of transcription factors with cytoplasmic

and nuclear immunoreactivity including FGFR-2, STAT-5, and RUNX-2 in MC. Their investigation showed higher expression of FGFR-2 and RUNX-2 in MC versus non-MC cancers (45).

Among the breast cancer related mutations, activating point mutations in Phosphatidylinositol-3-kinase (PIK3CA) is the most common molecular defect in invasive breast cancers. PIK3CA is a key cell membrane protein in epithelial cell signal transduction, which activates or inhibits elements of downstream signaling, resulting in cell growth, cell proliferation, inhibition of apoptosis. Kehr and colleagues evaluated the presence of this point mutation in PMC. Their results showed no PIK3CA mutation in PMC (46). On the other hand, Ross and Gay showed PIK3CA mutation in metastatic PMC (42).

MicroRNA (miRNA) is a new class of small noncoding RNA, which is always dysregulated in malignancies and has a key role in cancer progression. Zhou and colleagues studied the miRNA

expression profile in PMC using miRNA microarray and real-time PCR. MiR-143 and miR-224-5p were found to be significantly down regulated in PMC. Based on this finding, the authors suggested that the down regulation of miR-143 may be a common event in the formation of the mucinous cancer phenotype (51).

Conclusion

Pure mucinous carcinoma, is a rare form of breast cancer with favorable prognosis. Pre-operative diagnosis and correct sub-classification are important first steps for appropriate clinical management of this disease. Knowledge of the cytologic features, diagnostic pitfalls, and potential mimics of PMC need to be considered when evaluating pathologic material from this variant of breast cancer. Finally, genomic profiling may help to identify a variety of known and emerging therapeutic targets which can potentially improve survival, especially in the metastatic setting (42).

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