

Mucinous Cystadenocarcinoma of the Breast with Axillary Lymph Node Metastasis: An Entity with an Unusual Clinical Course

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ABSTRACT

This is a case of a 54-year-old, perimenopausal, Asian, woman, who presented with an enlarging left breast mass associated with whitish to bloody nipple discharge. A core needle biopsy, done in another institution, showed histologic findings of a mucinous carcinoma with triple negative “basal-like” biomarker status (ER, PR, HER2/neu). Six cycles of neoadjuvant chemotherapy were given after which the subsequent modified radical mastectomy revealed a centrally located, 10.0 cm, well-circumscribed, nodular, ovoid mass on gross examination. Microscopic findings showed tall columnar cells in stratification, tufts and papillary formations, with surrounding abundant extracellular mucin. The individual tumor cells exhibit enlarged, hyperchromatic, basally located nuclei with prominent nucleoli, abundant amphophilic and occasionally oncocyctic cytoplasm which contains intracytoplasmic mucin. Based on the histologic features, “basal-like” biomarker expression, and additional immunohistochemical studies (positive CK7, negative CK20 and CDX2), this case demonstrates a pure mucinous cystadenocarcinoma of the breast. In addition to the rare histologic type, this case is exceptional since, despite multiple cycles of neoadjuvant chemotherapy, presence of extensive lymphovascular invasion and axillary lymph node involvement with extranodal extension remain evident.

Key words: mucinous cystadenocarcinoma, breast cancer, axillary lymph node metastasis

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INTRODUCTION

Mucinous cystadenocarcinoma is a primary mucin-producing carcinoma. Histopathologically, it is described as cystic structures lined by columnar cells with abundant intracellular and extracellular mucin and is most commonly seen in the ovary, pancreas and appendix.¹ Its occurrence on the breast has been included as a new entity in the recent 5th edition of the World Health Organization (WHO) classification of tumors of the breast.¹ More than 30 cases of primary MCA have been reported in the literature. Additionally, several cases of mixed MCA with Invasive ductal carcinoma, not otherwise specified (IDC NOS) have been documented. Furthermore, with similar histomorphological features to its ovarian, pancreatic and gastrointestinal counterparts, demonstration of this tumor on the breast warrants primarily excluding a metastatic lesion as well as the more common primary mucinous carcinoma. In line with this, immunohistochemical studies have been proven to play a crucial role in ruling out the possibility of metastasis. Despite limited information on clinical course and follow-up, case reports on mucinous cystadenocarcinoma of the breast mostly show good prognosis. Most publications report long survivability with no or little occurrence of relapse and lymph node metastasis despite having a triple negative (ER, PR, HER2/neu) biomarker status.²

In the Philippines, no known local studies have been reported with the same features as similar to this case. Since there are only about five (5) cases that have been reported with lymph node metastases, most cases have benign lymph nodes. The purpose of this manuscript is to report a rare case of pure mucinous cystadenocarcinoma of the breast presenting with lymph node metastasis



and lymphovascular invasion. Additional workups such as immunohistochemical and molecular studies are imperative tools to confirm the final diagnosis.

CASE

This is a case of a 54-year-old female who presented with an enlarging left breast mass. Two years prior to admission, she noticed a “ping-pong ball”-sized mass on her left breast with associated whitish to bloody nipple discharge. There was no pain, tenderness or skin dimpling noted hence she did not seek consultation. Six months prior to admission, the patient noticed an increase in the size of the said mass, prompting consultation with her primary attending physician whose assessment was invasive breast cancer, hence initial work-up (ultrasound, mammogram and core needle biopsy) was advised. Performed in another institution, the core needle biopsy result revealed mucinous breast carcinoma and further immunohistochemistry studies for biomarkers (ER, PR, and HER2neu) demonstrated triple negative or “basal-like” expression. The patient had a metastatic work-up (whole abdominal ultrasound, chest X-ray, bone scan and bone densitometry) which revealed unremarkable results. Due to the diagnosis of triple-negative breast cancer, she underwent six (6) cycles of neoadjuvant chemotherapy which included Docetaxel and Carboplatin, followed by modified radical mastectomy of the left breast as the definitive surgical procedure.

On gross examination, a modified radical mastectomy of the left breast was received with the following measurements: left breast - 24.5 x 19.5 x 5.5 cm; axillary tail - 24.5 x 19.0 x 5.5 cm. The overlying skin ellipse is smooth and without any signs of skin dimpling, ulceration, or discoloration. The nipple-areola complex is stretched out to resemble a dark-gray plaque which measures 4.5 x 4.0 cm in greatest dimension. There is no skin dimpling, thickening, or other skin lesions grossly defined. Serial sections show a well-circumscribed ovoid mass located along the central retroareolar aspect (Figure 1) which measures 10.0 x 6.5 cm in greatest dimension with a cream-pink, firm, solid cut surface with scattered cystic spaces (1.0 to 6.0 cm in diameter) filled with yellow to brown thick mucoïd material. The mass is 0.1 cm away from the nearest basal resection margin, and 3.5 to 11.5 cm away from the other peripheral resection margins. The unaffected surrounding tissues show a yellow-tan and glistening, with interspersed tan-white fibrous areas. No other masses or nodules were identified grossly. Multiple pink-tan lymph nodes were isolated from the axillary fat which measure from 0.2 to 0.8 cm in widest diameter. Depicts the representative gross appearance of the left breast mass. A well-circumscribed solid-cystic mass directly underneath the skin and exhibits cream to pink firm cut surfaces and scattered cystic spaces filled with yellow to brown thick mucoïd material (Figure 1).

Microscopic examination of the left breast mass showed a cystic tumor described to have intracystic papillary structures, some forming tufts and stratifications. The individual tumor cells are tall columnar cells with increased nucleus to cytoplasm ratio, enlarged round to oval nuclei with prominent nucleoli, and abundant eosinophilic cytoplasm (Figures 2A to 2F). Some representative sections

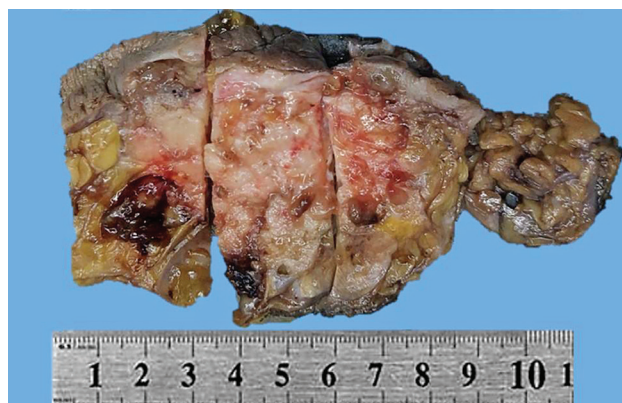


Figure 1. Representative gross appearance of the left breast mass. A well-circumscribed solid-cystic mass directly underneath the skin and exhibits cream to pink firm cut surfaces and scattered cystic spaces filled with yellow to brown thick mucoïd material.

of axillary lymph nodes show macrometastases with positive extracapsular invasion (Figures 3A, 3B, and 3C). Dermal lymphatic and lymphovascular invasion were also noted (Figures 3E and 3F).

Immunohistochemistry studies were done revealing positive membranous and cytoplasmic expression for keratin 7 (CK7), but negative for keratin 20 (CK20), and CDX2 (Figures 4D, 4E, and 4F). Companion diagnostic testing for Estrogen receptor (ER), Progesterone receptor (PR), and HER2/neu (clone 4B5) protein were also done which revealed triple negative or “basal-like” status (Figures 4A, 4B, and 4C). The ki-67 index was not measured for this case.

Based on histomorphologic and immunohistochemical profiles, this case was signed-out as a Mucinous cystadenocarcinoma of the breast, Nottingham histologic grade II, central (left) breast with accompanying positive for lymphovascular and dermal lymphatic invasion, as well as axillary nodal macrometastases. No evidence of ductal carcinoma in situ (DCIS) was found on the representative sampled sections. Following the College of American Pathologist Protocol, Nottingham over-all histologic grade II was established, assigning Glandular/Tubular differentiation with a score of 2, Nuclear pleomorphism with a score of 2, and Mitotic rate with a score of 2.

In accordance with the American Joint Committee on Cancer (AJCC) 8th edition staging, the pathologic stage is as follows: ypT3 (post treatment with tumor of 10 cm in greatest dimension), ypN2a (macrometastases in 7 harvested axillary lymph nodes), ypM not applicable (no specimen submitted). Assuming that there is no distant metastasis, the Anatomic Stage Group is IIIA while the Prognostic Stage Group is IIIC.

The patient received adjuvant treatment (18 sessions of radiotherapy) which she completed three months after surgery. Four months after her surgery, she had a follow-up consultation and underwent additional metastatic work-up which included whole abdominal ultrasound, chest x-ray, bone scan as well as bone densitometry (non-institutional).

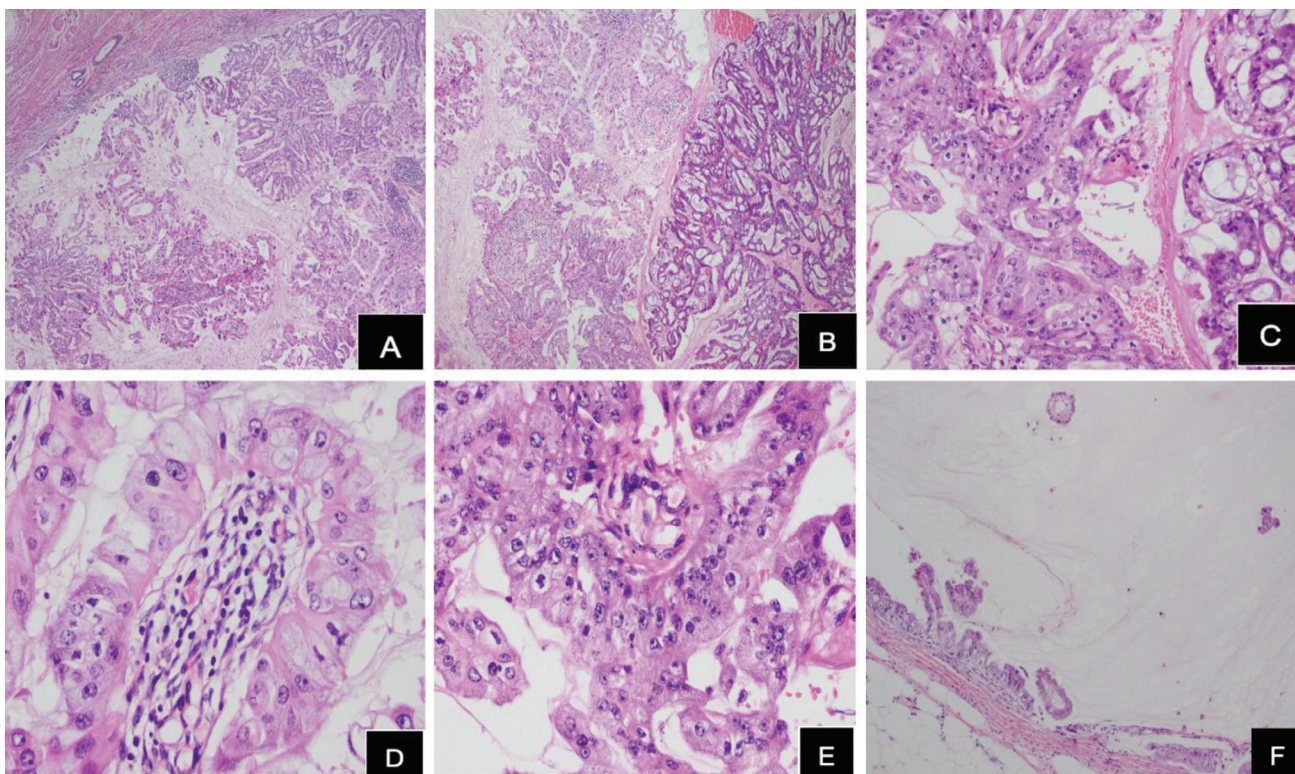


Figure 2. Representative microscopic sections of the mass [Hematoxylin-eosin stain]. (A) Intracystic papillary formation [50x], (B and C) Tufting and stratification [100x], (D) Tall columnar cells with oncocytic cytoplasm and abundant intracytoplasmic mucin [400x], (E) Pseudostratified columnar cells with conspicuous mitotic figures, (F) Hypocellular cystic areas filled with abundant mucin mimicking mucinous carcinoma [100x].

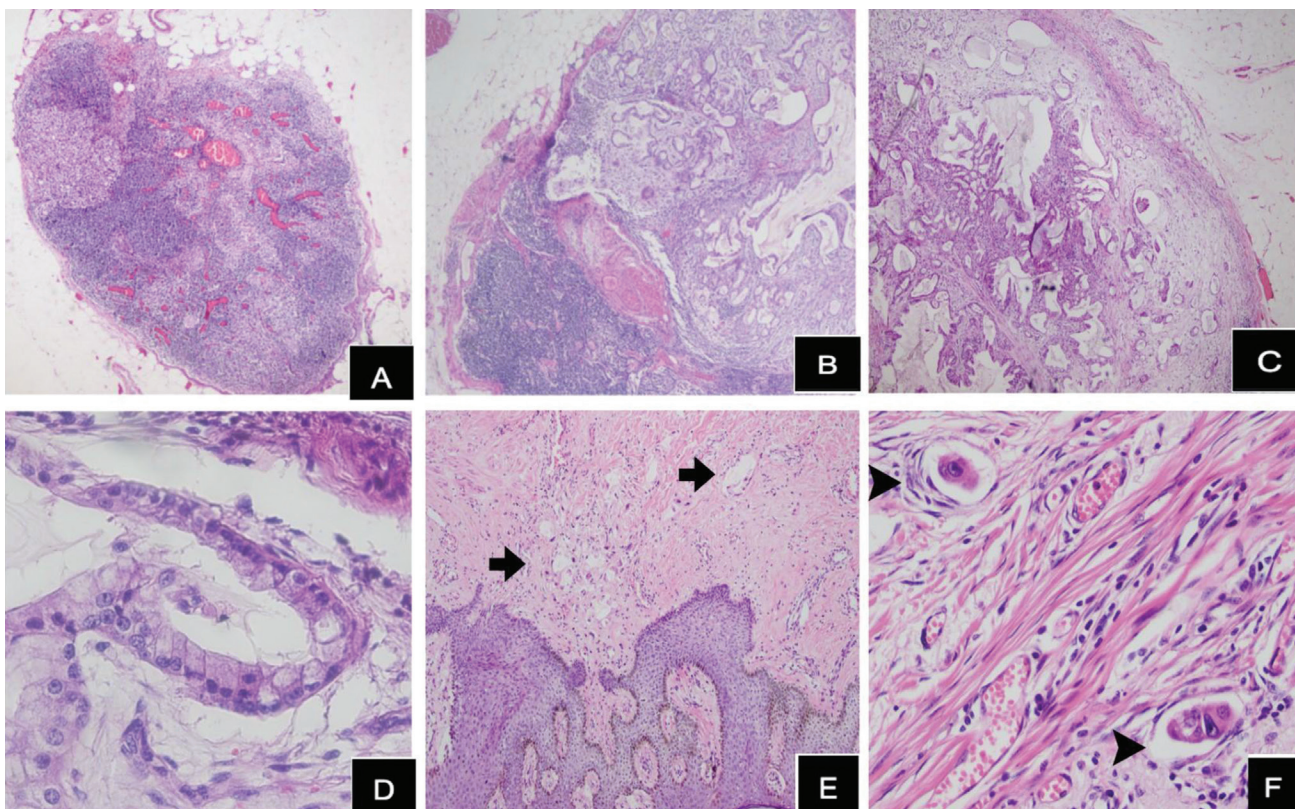


Figure 3. Representative prognostically significant findings [Hematoxylin and eosin stain]. (A and B) Sections of axillary lymph nodes with macrometastasis [40x], (C) Positive lymph node with extracapsular invasion [100x], (D) Higher magnification of metastatic focus show histomorphologic features with the breast mass [400x], (E and F) Dermal lymphatic invasion (arrow) [100x] and lymphovascular space invasion (arrowhead) [400x].

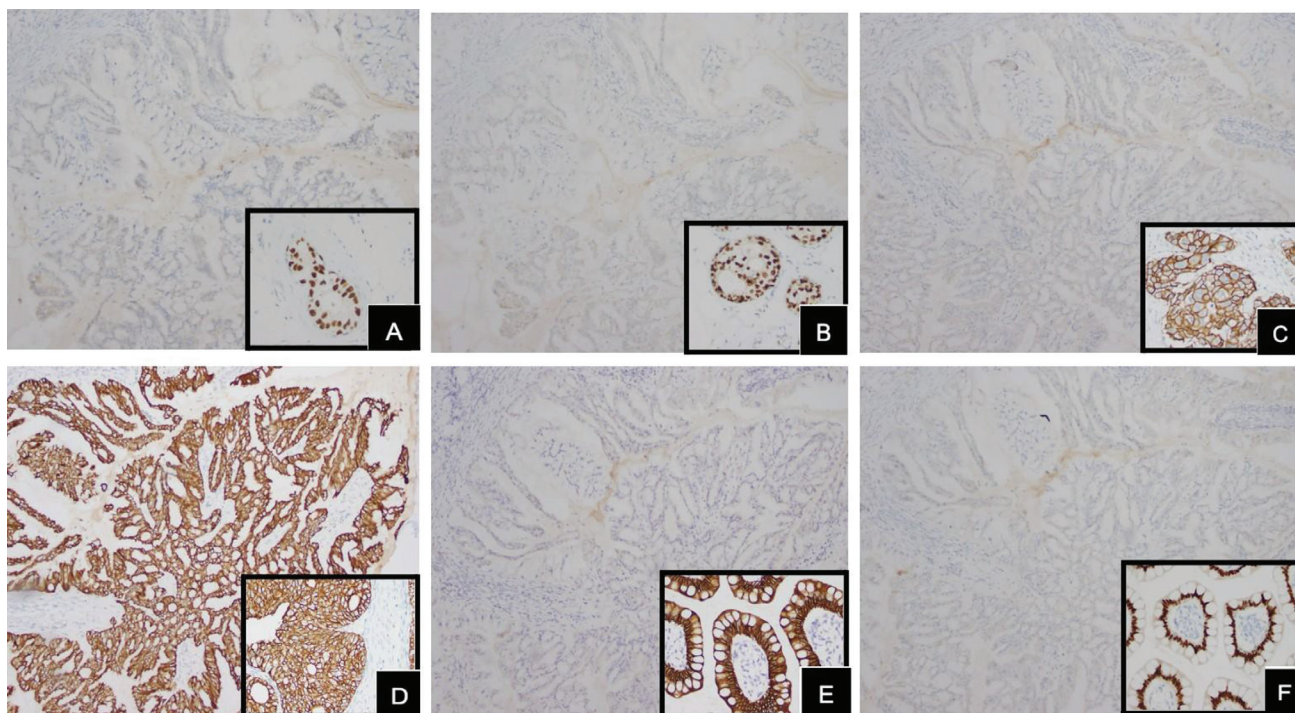


Figure 4. Immunohistochemistry stains [Horseradish peroxidase method, 100x] with respective positive controls (inset): (A) ER, (B) PR, (C) HER2, (D) CK7, (E) CK20, (F) CDX2.

There were no reports of recurrence or any metastasis. At present, the patient is doing well and remains disease-free.

DISCUSSION

Mucinous cystadenocarcinoma (MCA) is a rare primary malignancy of the breast. It was first described in 1998 by Koenig and Tavassoli,³ reported to be a variant of invasive ductal carcinoma of low-grade usually seen in postmenopausal women. With the recent 5th edition publication of the WHO Classification Breast Tumors, it now belongs as a separate entity under the epithelial tumors of the breast.

Based on literature, most cases of MCA may belong in the peri- and postmenopausal women. According to the World Health Organization, it has an average age of 61 years old which may range from 41 to 96 years.⁴ The described patient is in the perimenopausal age of 54 years old.

MCA, like what was described in this case, is grossly a well-circumscribed solid and cystic mass with gelatinous material found along the cystic spaces. The size of the breast masses reported ranges from 3 to 10 cm in length^{1,5,6} with a well-circumscribed soft cut surface. Consistently, this case shows a similar gross description with the greatest dimension of 10.0 cm.

Histologically, MCA is a carcinoma composed of generally tall, columnar cells with architectural features showing stratification, tufting and papillae. It is accompanied by nuclei that are located basally with the accumulation of intracytoplasmic mucin and extracellular mucin found in the surrounding cystic spaces.⁴ With consideration of being a low-grade variant, it was reported to have a

favorable prognosis. Microscopically can be described as tall columnar mucinous cells with either papillary, cribriform and fused glandular features. Nuclei atypia may be evident, together with the presence of mitosis with a Nottingham score of 1, accompanied by mucinous lakes in the surrounding stroma.²

The differential diagnoses for MCA of the breast would usually include the following: mucinous carcinoma of the breast and encapsulated papillary carcinoma of the breast. The similarity between mucinous cystadenoma carcinoma and mucinous carcinoma of the breast is evidence of large pools of mucin production. However, the main difference between the two entities is that the latter entity does not show any evidence of intracytoplasmic mucin accumulation, rather, it shows clusters of epithelial tumor cells floating in pools of extracellular mucin.⁴ Furthermore, biomarker status plays a major role in differentiating MCA from mucinous carcinoma. The latter can be described as ER and/or PR positive under the luminal group, while the biomarker status of MCA is triple-negative (ER, PR, and HER2/neu negative) or “basal-like” as similarly described in most literature.^{2,5,7-12} Although ER, PR and/or HER2/neu positivity in MCA has been reported, it is considered exceptionally rare.^{1,6,7,13} On the other hand, similarities between MCA and encapsulated papillary carcinoma of the breast can be seen based on its architecture, exhibiting papillary-like fronds within cystic spaces as well as columnar epithelial cell lining that are arranged in single or multiple cell layers, able to form micropapillary or cribriform structures that fill in the gaps and separating adjacent papillae.¹⁴ But unlike mucinous cystadenocarcinoma, encapsulated papillary carcinoma lacks intracytoplasmic mucin, and is described to mostly show ER and/or PR positivity.

Aside from primary carcinomas of the breast, another factor that must be considered is an MCA originating from either the ovary, pancreas or gastrointestinal tract that eventually metastasized to the breast. In this scenario, immunohistochemical markers play a major role in ruling out this possibility. The typical immunohistochemical studies profile of primary breast MCA is the following: positive CK7 expression, but negative for CK20 and CDX2 expression, as reported in most literature,^{2,5,8,9,13} and cited in the 5th edition of WHO³ which is like our case. As opposed to immunohistochemistry profile of MCA originating from the ovary which would show positive expression of CK7 and variable expression for both CK20 and CDX2^{15,16} and MCA originating from the pancreas and gastrointestinal tract which may show positive expression for CK7, but more consistently show positive expression for both CK20 and CDX2.^{15,17-19}

For this type of carcinoma, the presence of metastasis to the axillary lymph node, with only four (4) reported cases at present⁴ while lymphovascular invasion also had minimal reporting in the literature. Despite few reported cases globally, in the Philippines, MCA with axillary lymph nodes and lymphovascular invasion with extranodal extension is the first known case up to this date. The rarity of the said case can explore the possibility of such metastasis despite it being considered a low-grade variant. In our case, seven out of twenty harvested lymph nodes showed evidence of metastasis and presence of lymphovascular space invasion.

Due to the rarity of the case, standard treatments have yet to be established. According to the National Comprehensive Cancer Network (NCCN) guidelines for invasive breast carcinoma, the recommended treatment for breast cancer, in general, is either breast-conserving therapy (lumpectomy) or mastectomy.²⁰ The documented surgical plan these patients usually received was either lumpectomy or mastectomy with axillary lymph node dissections.^{2,6,8,11,12} In our case since the tumor was measured to be 10 cm in widest diameter, a lumpectomy procedure was contraindicated, hence the surgical procedure of choice was mastectomy. Also stated in the NCCN guidelines, adjuvant radiation therapy is highly advised especially for those individuals who had findings of positive results for axillary lymph node metastasis after mastectomy. Meta-analysis has also proven the reduction of both recurrence and breast cancer mortality in women even if systemic therapy was administered, hence, adjuvant radiation therapy was offered to the patient.²⁰ Studies regarding the benefits of chemotherapy in this case are still quite unclear and limited. Our patient received six cycles of neoadjuvant chemotherapy followed by a modified radical mastectomy and despite this, the tumor on resection was still quite large and histopathologic findings still showed extensive lymphovascular invasion and axillary lymph node involvement with extranodal extension. Despite the extensive findings mentioned up to this day, the patient is well and still for metastatic work-up. The possibility of local recurrence is unusual for MCA, although it has been mentioned in a few publications.⁴

The majority of published reports showed negative HER2/neu receptor status, which is like this case. To date, there were only two reported cases that have shown

strong membranous HER2/neu immunohistochemistry expression.²¹ The use of Her2/neu gene amplification using fluorescence in situ hybridization studies has been reported and achieved concordant results with its HER2/neu staining.²¹ Genomic alterations testing and other gene amplification studies (such as using c-MYC and ZNF217 genes) for breast cancer progression for MCA of the breast are quite limited in the literature review, thus, no known pathognomonic molecular alterations are currently noted.²²

CONCLUSION

Diagnosing MCA of the breast involves a combination of clinicopathologic and immunohistochemical modalities. Awareness of its existence and ruling out the possibility of metastasis are necessary for proper documentation, prognostication, and management. Due to the rarity of the case, standard treatments have yet to be established but it is reported to have a favorable overall prognosis with rare reports of local recurrence and distant metastasis. In addition, months after her surgery, the patient continued her usual follow-ups and underwent metastatic work-up (bone scan and bone densitometry) with her attending physician. There were no reports of recurrence or any metastasis. At present, the patient is doing well and remains disease-free. This case is exceptional since, despite the MCA histologic type and multiple cycles of neoadjuvant chemotherapy, the presence of extensive lymphovascular invasion and axillary lymph node involvement with extranodal extension remains evident, resulting in an advanced stage at presentation despite favoring good prognostic outcomes.

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ETHICAL CONSIDERATIONS

Patient consent was obtained prior to submission.

STATEMENT OF AUTHORSHIP

The authors certified fulfillment of ICMJE authorship criteria.

AUTHOR DISCLOSURE

The authors declared no conflict of interest.

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