Case Report

Invasive Colloid Carcinoma and the role of Ki-67 and HER2 – Two case reports

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ABSTRACT

Mucinous carcinoma (also termed colloid carcinoma) of the breast accounts for 1%-6% of all breast cancer and is considered to have a good relative prognosis. The most common mammographic appearance of pure mucinous carcinoma is a high-density mass with circumscribed margins and on sonographic examination an isoechoic round mass with circumscribed margins. We report 2 cases of invasive mucinous carcinoma, in which one patient showed an intermediate recurrence risk based on Ki-67 and human epidermal growth factor receptor 2 negativity, while the other showed a low Ki-67 recurrence risk and human epidermal growth factor receptor 2 positive. We also review the literature on Ki-67 and human epidermal growth factor receptor 2 and explore the roles of these molecular markers in mucinous carcinomas.

Introduction

Mucinous carcinoma (colloid carcinoma) is a rare histologic type of mammary neoplasm estimated to be around 1%-6% of all primary breast cancers [1] in which the median age of diagnosis is 55-60 years. There are 2 histologic subtypes: mixed mucinous carcinoma where ductal carcinoma is associated with the colloid component, and the more prognostically favorable pure mucinous carcinoma where the mucin surrounds the tumor tissue and constitutes a mechanical barrier limiting cell invasion and virulence [2]. A precisely de-fined threshold in the percentage of mucinous component for the distinction between pure and mixed mucinous carcinoma is not well-established. However, pure mucinous carcinomas are generally defined as containing more than 90% mucin, and mixed mucinous carcinomas are those containing 50%-90% mucin. Axillary lymph node spread of disease is rarely involved. These features account for the favorable prognosis of this subtype of breast cancer (BC), with a 5-year BC-specific survival rate of 94% compared with 82% of the infiltrating ductal carcinoma (IDC) not otherwise specified counterpart. The overall more favorable outcome is maintained over very prolonged follow-up [3].

On clinical exam, mucinous BC is usually diagnosed in relatively early stages of the disease such as stage IB and IIA [4]. In approximately 50% of patients, physical examination indicates the presence of a well-circumscribed tumor in the breast. For the remaining 50% of patients, in whom clinical symptoms are not present, this form of cancer is diagnosed during screening mammography [5,6].

Tumor biology is the main determinant of BC treatment. Immunohistochemistry (IHC) can be utilized to detect antigens closely associated with cell growth. The basis of IHC divides BC into at least 3 main groups: hormone receptor (HR)-positive, human epidermal growth factor receptor 2 (HER2)-positive, and triple-negative disease (HR- and HER2-negative). IHC helps with targeting endocrine and chemotherapy treatment solutions. Furthermore, in clinical practice IHC classification based on the expression of HER2 and Ki67 is applied as a surrogate of the intrinsic molecular subtypes and proliferation [7,24]. Ki67 has increasingly become part of routine pathology practice and is used to define the creation of luminal A and luminal B subtypes of cancer (both of which are defined as having a negative HER2) where greater Ki-67 (>12%-15%) is defined as luminal B. Ki-67 categories have also been developed stratifying patients with ER-positive tumors, defined as low recurrence risk (0%-10% invasive tumor nuclei stain), intermediate recurrence risk (11%-20% invasive tumor nuclei stain), and high recurrence risk (21%-30% invasive tumor nuclei stain) [24].

We report 2 cases of colloid carcinoma in a 60-year-old patient and a 63-year-old patient, respectively, with low-grade Nottingham score characteristics. One report showed an intermediate recurrence risk based on Ki-67 and HER2 negativity, while the other showed a low Ki-67 recurrence risk and HER2 positive. We review the radiological characteristics and molecular markers of these tumors, and the role Ki-67 and HER2 plays in clinical outcomes and treatment of these tumors.

Case study 1

A 60-year-old woman presented for diagnostic breast imaging. She was 1.5 years overdue for follow-up imaging of a probably benign right breast mass, as well as routine imaging of the left breast. Further history was significant for a sister with hepatic cancer and mother diagnosed with an unknown malignancy. There were no breast complaints. General physical and systemic examination, including lymph nodes were normal with exception of the unchanged right breast mass.

Bilateral mammography showed the right breast mass unchanged in size, indicating a benign lesion. The left breast mammogram showed a new irregular, hyperdense mass within the inferior medial left breast which persisted on spot compression (Fig. 1). This mass corresponded with a 0.9 × 0.9 × 0.9 cm irregular, hypoechoic mass with posterior acoustic shadowing at 8-o'clock, 3 cm from the nipple (Fig. 2). There was no axillary lymphadenopathy.

Subsequent ultrasound guided core needle biopsy yielded infiltrating well-differentiated duct carcinoma, mucinous type, grade 1 of 3 (Nottingham score = 5) in all 4 cores, with 10 mm longest tumor extent. Coincidentally, ductal carcinoma in-situ, Van Nuys grade 1 of 3 was also found in the left breast at the same site. Serum markers demonstrated an intermediate recurrent risk for Ki-67 (11%-20% invasive tumor nuclei strain), 95% estrogen receptor (ER) positivity, 80% progesterone receptor (PR) positivity, HER2- negativ, and p53-negative for overexpression.

There was extensive discussion regarding the patient's treatment plan and she ultimately opted for a lumpectomy with needle localization and sentinel node biopsy to be followed with radiotherapy. The lumpectomy showed a combination of the original grade 1/3 colloid IDC and grade 1/3 ductal carcinoma in-situ (DCIS) without evidence of metastasis in 4/4 lymph nodes. At the time, adjuvant chemotherapy was not recommended based on the current stage.

The patient completed a course of radiation therapy complicated by grade 1 skin toxicity. She is currently on anastrozole 1 mg daily to complete at least a 5-year course.

Case study 2

A healthy 63-year-old female presented for screening mammogram. She had an extensive family history of BC, diagnosed mostly after age 60. Physical exam findings were significant for a left breast mass measuring 2.5 × 2.5 cm along the edge of areola extending from 1 to 3-o'clock. The mass was mobile, nontender, and without overlying skin changes. No axillary masses were appreciated.

Bilateral mammogram and bilateral breast ultrasound were pursued. Within the left breast several masses were found (Fig. 3). An irregular mass with circumscribed margins at 3-o'clock, 2 cm from the nipple, measured 1.5 × 0.9 × 1.1 cm (Fig. 4). Ultrasound-guided core needle biopsy was recommended. Multiple additional bilateral breast masses demonstrated probably benign characteristics and a 6-month follow-up ultrasound was recommended.

On biopsy of the left breast 3-o'clock mass partial aspiration was performed. The fluid showed a gelatinous consistency and the needle tip was freely moveable within the mass. Laboratory findings were consistent with infiltrating well-differentiated duct carcinoma, colloid type. Serum studies showed levels of Ki-67 less than 10% indicating low recurrence risk, ER positivity 95%, PR positivity 95%, negative-p53 for overexpression, and Her2/neu positive.

At the time, options for breast conservation with further workup of the additional masses vs mastectomy were offered. The patient decided to pursue a left total mastectomy and sentinel node biopsy.

Biopsy showed no metastasis to lymph nodes and an infiltrating well-differentiated duct carcinoma, colloid type, grade 1 of 3 (Nottingham score = 5), measuring 3.6 × 2.6 × 2 cm within the central duct region in the lower outer quadrant.

After mastectomy, postoperative complications were reported. It was decided to start adjuvant chemotherapy with trastuzamab with 6 cycles planned. The patient had to be switched to carboplatin/weekly paclitaxel/trastuzumab during cycle 5 due to severe/diffuse painful facial erythema requiring steroids. Chemotherapy was ultimately discontinued after cycle 5. Finally, single agent trastuzumab was initiated
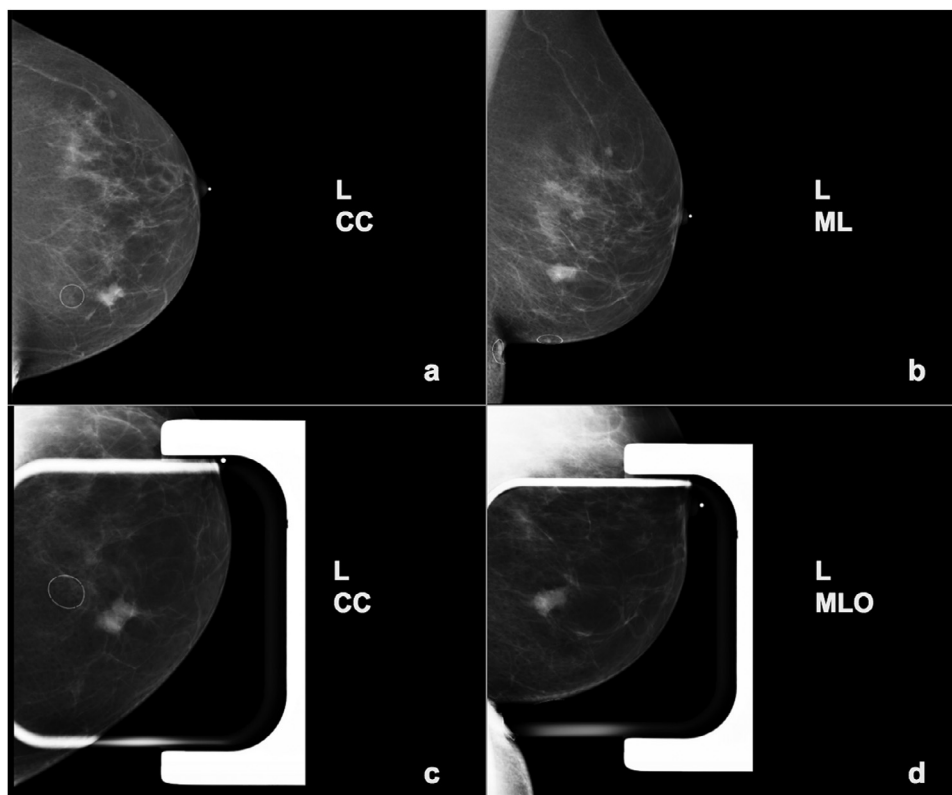
Fig. 1 – Diagnostic mammogram of a 60-year-old female patient. (a) **Left craniocaudal (CC) view and** (b) **left mediolateral (ML) view demonstrate an irregular, hyperdense mass in the inferior medial left breast, which persists on** (c) **left craniocaudal (CC) spot compression and** (d) **left mediolateral-oblique (MLO) spot compression views.**

with adjuvant anastrozole. The patient is currently on anastrozole 1 mg daily to complete a 5-year course.

Discussion

The above cases presented similarly with low-grade invasive colloid carcinomas, however with different immunochemistry profiles. The first case presented with serum markers demonstrating an intermediate recurrent risk for Ki-67 (11%-20% invasive tumor nuclei strain) with HER2 negativity, while the second case demonstrated Ki-67 less than 10% indicating low recurrence risk and HER2/neu positive. Both cases had high levels of ER and PR positivity, defining them as HR-positive. Both malignancies in these cases were pure infiltrating mucinous carcinomas.

There is a particularly good prognosis in patients afflicted with mucinous BC. This is mainly associated with the following independent factors: age, tumor size, status of lymph nodes, and ER positivity [8–10]. However, in the cases presented, there was debate whether a tumor with a histologically favorable prognosis would have a guarded prognosis based upon the immunochemistry.

Evaluation of radiological findings based on HER2 and Ki-67 findings was also of interest. Elias et al found that the presence of microcalcifications on mammography or ultra-

sound, particularly branching or fine linear microcalcification morphology on mammography, high overall suspicion for malignancy on mammography or ultrasound, washout and fast initial kinetics on dynamic contrast enhanced magnetic resonance imaging (DCE-MRI), and increased 18F-fluorodeoxyglucose (^{18}F-FDG) uptake on positron emission tomography (PET) were all associated with increased chance of HER2 overexpression [25]. The current literature regarding the correlation of Ki-67 proliferation index with imaging findings, particularly related to apparent diffusion coefficient (ADC) values, is conflicting. While Molinari et al determined that lower ADC values were associated with elevated Ki-67 proliferation index and more aggressive pathologic features, Surov et al found that ADC cannot be used a surrogate marker for Ki-67 proliferation activity [26,27]. Surov et al concluded that while ADC values between tumors with high expression of Ki-67 ($\geq$25%) differed from those with low levels of Ki-67 (<25%), the calculated specificity and sensitivity were too low, and that this also applied to several alternative thresholds of Ki-67 expression ranging from 10% to 50% [27].

To characterize radiological findings in mucinous carcinomas, a brief literature review was performed. There is variation in the literature regarding imaging characteristics of mucinous carcinomas, which commonly present as masses with circumscribed margins and lobular shapes. Pure mucinous BCs are rich in extracellular mucin. This causes the
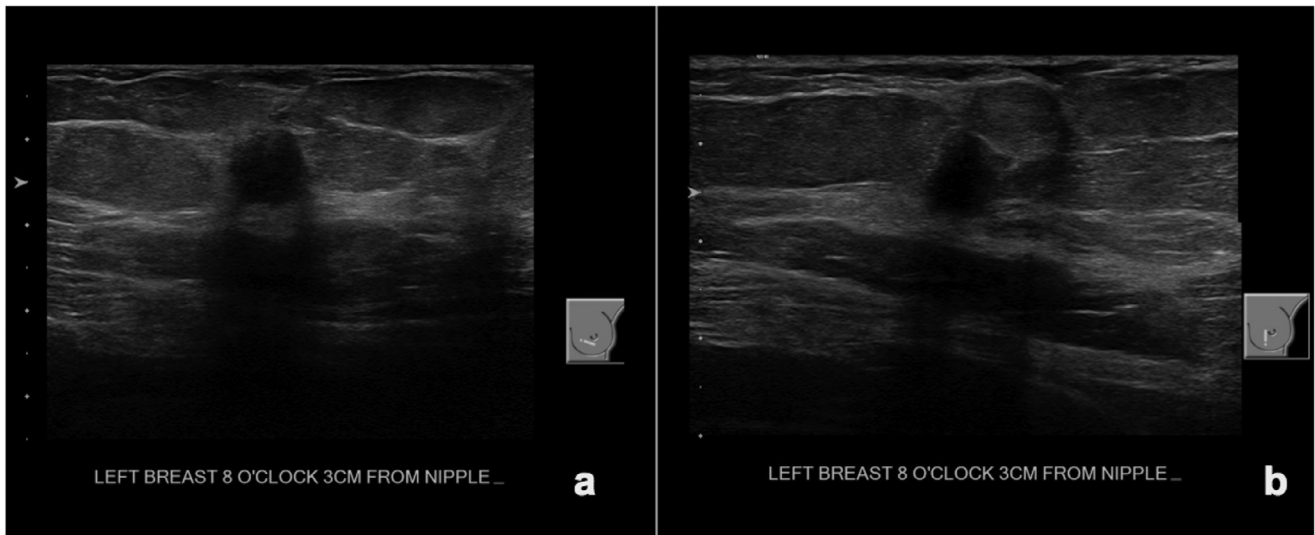
Fig. 2 – (a, b) Sonographic examination of a 60-year-old female patient. (a, b) The left breast demonstrates an irregular, hypoechoic mass with posterior acoustic shadowing at the 8-o'clock position, 3 cm from the nipple.
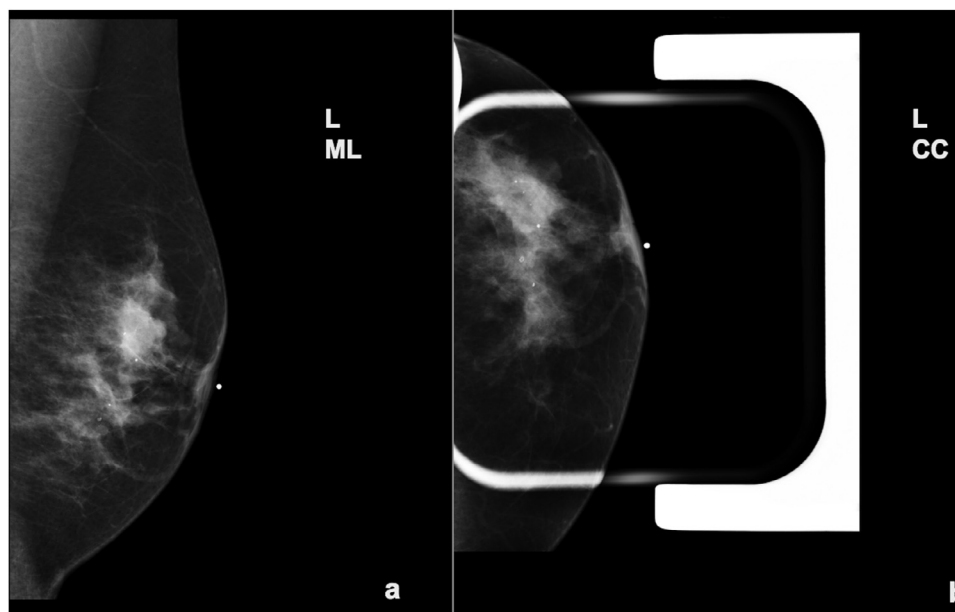

Fig. 3 – Diagnostic mammogram of a 63-year-old female patient. (a) Left mediolateral (ML) view demonstrates a focal asymmetry in the lateral central left breast, anterior depth, which persists on (b) left craniocaudal (CC) spot compression view.

lesions to present as round in shape and limits the infiltration of cancer cells in the area outside of the tumor. Conant et al found a correlation between the quantity of mucin and the mammographic findings [11]; the higher the amount of extracellular mucin, the less aggressive the tumor's appearance on mammography. For that reason a significant number of lesions could be misinterpreted as benign on screening mammograms. Interestingly, a delay in diagnosis may not result in a significant adverse outcome for most women [12].

Judith et al found that pure mucinous BCs can commonly have indistinct or lobulated mammographic and sonographic margins. Mammographic calcifications are absent in the majority (82%). On ultrasound, these neoplasms are commonly isoechoic (51%) with normal posterior acoustic shadowing (80%). However, most (77%) of these lesions have suspicious or definite imaging features of malignancy [13].

Distinguishing between the types of mucinous carcinoma is important as the mixed variant is associated with a worse prognosis. Zhang et al found that there was no significant difference between pure and mixed mucinous BC regarding the shape of the tumor, calcifications, T2 signal intensity, internal mass enhancement, or kinetic curve assessment. No correla-
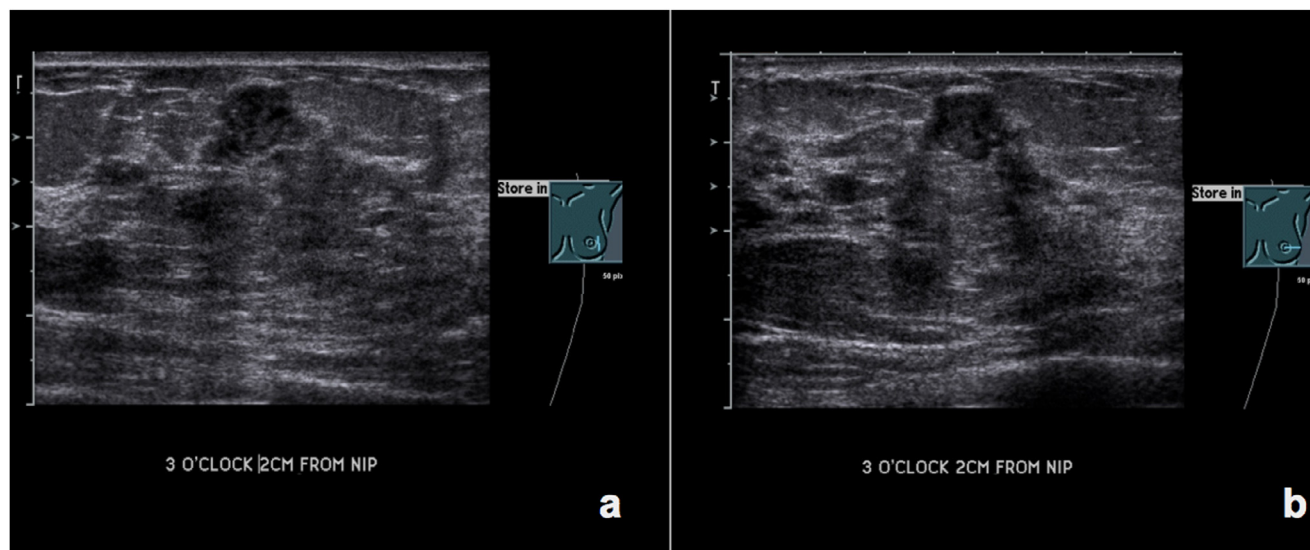
Fig. 4 – (a, b) Sonographic examination of a 63-year-old female patient. (a, b) The left breast demonstrates an irregular, hypoechoic mass with circumscribed margins at the 3-o'clock position, 2 cm from the nipple.

tion between the type of mucinous tumor and positivity for ER, PR, and HER2 was appreciated [14].

Lam et al [15] describe that as many as 21.2% (7/33) of mucinous carcinomas cannot be detected mammographically. When detected mammographically, more than 92% of the tumors presented as a mass, either oval or lobular in shape. Microlobulations were present in 38.5% of these lesions. The margin of the lesion, as seen on mammography, could be used to predict the histologic grade. A circumscribed margin was associated with a favorable histologic grade ($P = .01$), whereas an indistinct margin was more commonly associated with the mixed type of lesion ($P = .05$).

Role of immune markers in tumors with favorable prognosis

No referenced literature has described the role of Ki-67 in regard to mucinous carcinoma. The St. Gallen International Expert Consensus currently endorses Ki-67 for treatment decision-making in ER-positive early (1-3 axillary nodes) BC patients [16]. Furthermore, a recent prognostic study demonstrated clinical significance of Ki-67 in ER-positive breast tumors [17].

The majority of mucinous carcinomas are HR-positive. In our cases, both demonstrated greater than 80% receptivity to estrogen and progesterone. Several recent studies have demonstrated the value of increased Ki-67 in disease prognosis. In a study of 191 patients, Perez-Lopez et al found that the biological parameter related to the worst survival in the absence of nodal involvement and ER status was an elevated Ki-67 value. Neither PR nor HER2 status showed prognostic significance in this group in the study [18]. In another study of Luminal B cancers, Soliman et al found that a Ki-67 level higher than 15% was observed in 69% of patients, and recurrence was 39% for these patients [19].

Usually, tumors with poor prognoses demonstrate patterns of both histologic invasion and concerning molecular markers. For example, metastatic IDCs are generally poorly differentiated and ER-, PR-, and HER2-negative with elevated Ki-67 and p53 positivity. Pleomorphic lobular carcinomas show more aggressive characteristics, evidenced by higher-grade cytological features, the presence of lymphovascular invasion, and a more advanced stage at presentation. HER2 is overexpressed in up to 30% of these cases. In invasive micropapillary carcinoma, expression of ER and PR is reported in approximately two-thirds of cases and a positive HER2 status is described in up to 50% of cases. This reconfirms the need to be cognizant of both the immunochemistry and histologic findings in each cancer, but to not rely on them exclusively.

In regard to case 2, there have been few other case studies that demonstrated a mucinous carcinoma with HER2 positivity [20,21]. Trastuzumab is approved for both the treatment of advanced BC and as an adjuvant therapy for early-stage HER2-positive tumors. Interestingly, in the published cases of mucinous tumors with HER2 positivity, the tumors showed resistance to Trastuzumab, which was the therapy of choice for our case 2 patient.

It is assumed by current international guidelines that the same chemotherapy regimens used for common BC histotypes should also be proposed in cases of uncommon histologies, when indicated. However, most of the favorable-prognosis endocrine-sensitive rare histotypes usually belong in the Luminal A subtype, which tends to be chemoresistant [22]. In a retrospective study of more than 500 BC patients treated with conventional neoadjuvant chemotherapy, the clinicopathologic response of BC with rare histotypes was significantly poorer. However, despite a low rate of response, the prognosis of mucinous and apocrine BC was good [23].

In summary, for mucinous carcinoma of the breast molecular markers and their relationship to radiographic findings, histologic grade, and clinical outcomes is not definitively clear. As our first case demonstrates, a relatively favorable subtype of IDC showed intermediate Ki-67 recurrence risk. This case demonstrates the complexity of categorizing malignant tumors as more or less aggressive. Indeed, the next evolution in medicine is the individualization of treatment plans after thorough review of patient demographics, radiographic features, and histopathologic findings. A review of current available data may help physicians in their clinical practice to approach rare BCs; however, the development of clear clinical recommendations is not yet possible. Management of patients with rare BC histologies should be derived from careful case-by-case multidisciplinary evaluations.

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