Pleomorphic Invasive Lobular Carcinoma of the Breast With Extracellular Mucin and *HER2* Amplification

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ABSTRACT: Invasive lobular carcinoma with extracellular mucin is an uncommon pattern of invasive breast carcinoma. The 5th Edition of the World Health Organization Classification of Breast Tumors states that it is unknown whether these tumors are a subtype of mucinous carcinoma or invasive lobular carcinoma. Invasive lobular carcinoma with extracellular mucin frequently presents as a palpable mass and may be more likely to be grade 2 to 3 and HER2-positive than classic invasive lobular carcinoma. This case of pleomorphic invasive lobular carcinoma with extracellular mucin was detected by imaging only and was HER2-amplified, suggesting that a subset of these tumors may be clinically occult with an aggressive phenotype. Invasive lobular carcinoma with extracellular mucin is infrequently encountered and awareness of this entity is helpful in avoiding misdiagnosis.

KEYWORDS: Pleomorphic, lobular, invasive, HER2, breast, diagnosis, pathology, surgery

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Introduction

Invasive lobular breast carcinoma (ILC) is the second most common type of invasive breast cancer, following invasive ductal carcinoma (IDC), accounting for 5% to 15% of invasive breast cancers.[1] Tumors may present as a spiculated mass and/or architectural distortion on mammography or be clinically and mammographically occult with a false-negative rate for mammography approaching 30% in some studies.[2] ILC may be more conspicuous on 3-dimensional digital breast tomosynthesis compared with 2-dimensional digital mammography.[3] Magnetic resonance imaging (MRI) may be more likely to detect ILC, including multifocal ILC.[4] ILC has a higher incidence of synchronous bilateral tumors than IDC.[1]

Histologically, ILC is characterized by small tumor cells that may be arranged in a single-file pattern or dispersed. The tumor cells do not form cohesive groups as is often the case in IDC, and somatic alterations in the gene for the cell adhesion protein E-cadherin are common.[5] ILC tumor cells may contain an intracytoplasmic lumen containing mucoid material.[6] Multiple patterns of ILC have been described, including classic, solid, alveolar, and pleomorphic.[1] Pleomorphic ILC shows the same growth pattern as classic ILC but with higher-grade nuclei, more mitotic activity and, in some cases, apocrine features.[7,8] According to the 5th Edition of the World Health Organization (WHO) Classification of Breast Tumors, it is unknown whether ILC with extracellular mucin is a subtype of ILC or mucinous carcinoma.[9] Approximately 30 cases of ILC with extracellular mucin production have been reported[10-20] with the largest series (n = 10) published in abstract form only.[20] Most of tumors in the published series presented as palpable masses were estrogen receptor (ER)-positive and HER2-negative. However, ILC with extracellular mucin may be more likely to be HER2-positive than classic ILC. Despite being uncommon, ILC with extracellular mucin shows important similarities to conventional patterns of ILC. The tumors show areas of linear or single-file infiltration and the cells may have intracytoplasmic lumens or signet ring cell morphology. A component of lobular carcinoma in situ (LCIS) is often present. Invasive lobular carcinoma with extracellular mucin shows the expected loss of E-cadherin expression and altered localization of beta-catenin and p120 catenin.[18-20] Tumors with this pattern also appear to share some molecular features with classic ILC, including copy number variations in 1q, 16q, and FOXA1 and mutations in PIK3CA.[20] ILC with extracellular mucin also shares some phenotypic features with mucinous carcinomas with many tumors reported as positive for MUC1, MUC2, or MUC6.[18-20]

We report an additional case of HER2-positive pleomorphic ILC with extracellular mucin that was detected on routine follow-up imaging in a patient with a history of ER-positive, progesterone receptor (PR)-positive, HER2-negative ILC.

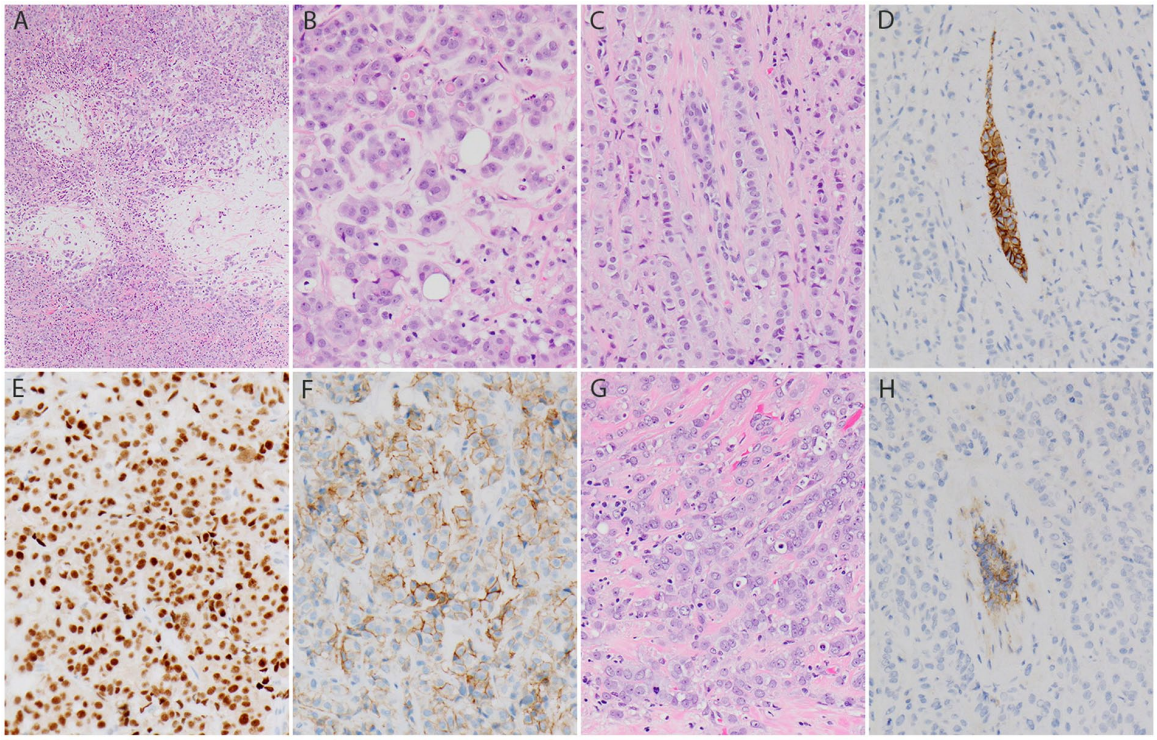

Figure 1. Invasive pleomorphic lobular carcinoma (ILC) with extracellular mucin. (A) The mucinous component comprised approximately 10% of the core needle biopsy (CNB) (hematoxylin-eosin, original magnification ×100). (B) High-grade nuclei and increased mitotic activity consistent with pleomorphic ILC in an area of the CNB with intra- and extracellular mucin (hematoxylin-eosin, original magnification ×400). (C) There were foci with a linear pattern of infiltration in the non-mucinous component in the CNB (hematoxylin-eosin, original magnification ×400). (D) Negative E-cadherin stain with positive internal control in the CNB (E-cadherin, original magnification ×400). (E) Strong, diffuse staining for ER in the CNB (ER, original magnification ×400). (F) Equivocal staining for HER2 in the CNB (FISH was amplified) (HER2, original magnification ×400). (G) The residual tumor in the mastectomy did not show a mucinous component (hematoxylin-eosin, original magnification ×400). (H) Negative E-cadherin stain with positive internal control in the mastectomy (E-cadherin, original magnification ×400).

Materials and Methods

Gross specimens were evaluated and processed according to the Surgical Pathology laboratory's standard sectioning protocols for the generation of hematoxylin and eosin (H&E)-stained slides. Immunohistochemistry (IHC) was performed on 4-μm-thick unstained paraffin sections according to the manufacturers' protocols. Staining for ER (Clone SP1; Ventana Medical Systems, Tucson, AZ), PR (Clone 1E2; Ventana Medical Systems), and HER2 (Clone 4B5; Ventana Medical Systems) was performed on the Ventana BenchMark platform. Staining for E-cadherin (Clone 36B5; Leica Biosystems, Buffalo Grove, IL) was performed on the Leica Bond platform.

Case History

A 70-year-old woman with a personal history of breast cancer presented for routine imaging follow-up. She reported no breast symptoms or palpable masses on breast self-examination. Her medical history was remarkable for ILC in the right breast (grade 2, ER-positive, PR-positive, HER2-negative, pT1c pN1mi) that was diagnosed 14 years prior to presentation. She was previously treated with breast-conserving surgery, adjuvant chemotherapy, radiation therapy, and endocrine therapy. Two years prior to presentation, the patient was diagnosed with ER-positive, PR-positive ductal carcinoma in situ (DCIS) in the left breast and was treated with breast-conserving surgery. She did not have adjuvant radiation due to issues with care coordination, and she discontinued adjuvant endocrine therapy after 1 month due to intolerable side effects. Her family history is remarkable for 2 sisters with Gardner syndrome (familial adenomatous polyposis with extracolonic growths) and a brother with colon cancer. The patient herself was tested for Gardner syndrome and was negative. Genetic testing for inherited predisposition to breast cancer was also negative (Invitae, San Francisco, CA).

Diagnostic mammography revealed an irregular 15 mm mass with indistinct margins in the lower inner quadrant, middle depth of the right breast, and a separate oval 5 mm mass in the lower inner quadrant, anterior depth. The 2 masses were approximately 30 mm apart. Ultrasound showed an ill-defined 15 mm × 14 mm × 14 mm hypoechoic mass that appeared to correspond to the mammographic abnormality. On ultrasound, the smaller oval hypoechoic mass measured 6 mm × 4 mm × 4 mm with irregular margins. The findings were assessed as BI-RADS Category 4C, high suspicion for malignancy. The larger mass was best seen on mammography, and core needle biopsies of both masses were performed under stereotactic guidance.

Histologic examination of the core needle biopsy of the 15-mm mass demonstrated pleomorphic ILC with extracellular mucin (Figure 1). The mucinous component accounted for

Table 1. Published series and case reports of invasive lobular carcinoma with extracellular mucin.

	N	AGE	PRESENTATION	SIZE (MM)	GRADE	ER	PR	HER2	LN
Rosa et al[10]	1	60	Palpable mass	90	NR	pos	pos	neg	NR
Yu et al[11]	1	65	Radiologic mass	30	NR	pos	neg	pos	pos
Haltas et al[12]	1	43	Palpable mass	25	NR	pos	pos	neg	pos
Bari et al[13]	1	38	Palpable mass	35	NR	pos	pos	neg	pos
Gómez Macías et al[14]	1	60	Palpable mass	9	1	pos	pos	neg	neg
Boukhechba et al[15]	1	75	Palpable mass	15	NR	pos	pos	neg	NR
Koufopoulos et al[16]	1	65	Palpable mass	13	2	pos	neg	neg	neg
Baig et al[17]	1	67	Palpable mass	60	3	pos	neg	neg	ITC
Current case	1	70	Radiologic mass	23	3	pos	pos	pos	neg
Cserni et al[18]	8	63 (45-75)	Palpable mass (n=8)	22-90	2 (n=7) 3 (n=1)	pos (n=8)	pos (n=7)	pos (n=1)	pos (n=5) neg (n=3)
Soong et al[20]	10	69 (31-77)	Palpable mass (n=1) Radiologic mass (n=8)	>20 (n=5)	2 (n=7) 3 (n=3)	pos (n=9)	pos (n=6)	pos (n=3)	pos (n=4)
Singh et al[19]	4	77 (70-87)	Palpable mass (n=3) Radiologic mass (n=1)	8-100	1 (n=1) 2 (n=2) 3 (n=2)	pos	NR	neg	pos (n=1) neg (n=3)

Abbreviations: ER, estrogen receptor; PR, progesterone receptor; LN, lymph node; NR, not reported; ITC, isolated tumor cells (<0.2 mm).

approximately 10% of the tumor in the biopsy specimen. Some areas showed both extracellular and intracellular mucin with signet ring cell morphology. An immunohistochemistry study for E-cadherin was negative, confirming lobular histology. The tumor had a high combined histologic grade with a tubule score of 3, nuclear grade of 3, and a mitotic score of 2 for a total of 8/9. Microcalcifications were associated with invasive carcinoma. A minor component of LCIS, classic type, was present. Hormone receptor studies were positive for ER (90%, strong intensity) and PR (80%, strong intensity). HER2 immunohistochemistry was equivocal (2+) and *HER2* FISH was amplified with a *HER2*:CEP17 ratio of 4.6 and a mean HER2 copy number of 5.5. The smaller mass was IDC (E-cadherin-positive) with a high combined histologic grade (8/9). The IDC was positive for ER and PR (95%, strong intensity for both) and negative for HER2 (1+).

Approximately 2 months later, the patient underwent right mastectomy with sentinel lymph node biopsy. Both biopsy sites and clips were identified in the mastectomy specimen. On gross examination, one mass was present in the area corresponding to the lower inner quadrant, middle depth biopsy site. This mass measured 23 mm in greatest dimension and was yellow-white, firm, with biopsy site changes. Histologic examination confirmed pleomorphic ILC with a high combined histologic grade, similar to the prior core needle biopsy (Figure 1). However, a mucinous component was not identified in the residual tumor in the mastectomy specimen. No residual tumor was identified at the site of the IDC in the lower inner quadrant, anterior depth. Three ipsilateral axillary lymph nodes, including 2 sentinel lymph nodes, were negative for carcinoma on H&E slides and immunohistochemistry studies for cytokeratin.

The patient was treated with 6 cycles of adjuvant docetaxel, carboplatin, and trastuzumab (TCH). She remains on adjuvant trastuzumab with plans to complete 1 year of HER2-directed therapy and will also receive adjuvant endocrine therapy. At the time of last follow-up 8 months after the initial diagnosis, the patient was alive with no evidence of disease.

Discussion

Most reported cases of ILC with extracellular mucin presented as palpable masses with grade 2 to 3, hormone-receptor positive, HER2-negative tumors (Table 1). However, it must be noted that a combined histologic grade was not reported for all cases and ILC with extracellular mucin may be more likely to be HER2-positive than classic ILC. Published data on patient outcomes are very limited but suggest that some ILC with extracellular mucin may have a poor prognosis. In 2 studies with 8 and 10 cases each and median follow-up periods of ⩽3 years, the breast cancer-specific mortality was 20% to 40%.[18,20] Alternatively, the outcomes data may reflect a tendency for ILC with extracellular mucin to present at a higher stage.[20]

In this case, the patient had a history of an ipsilateral ILC (grade 2, ER-positive, PR-positive, HER2-negative) that was diagnosed 14 years prior to presentation. Her recurrence, a grade 3, ER-positive, PR-positive, HER2-positive pleomorphic ILC with extracellular mucin, was detected on routine follow-up imaging. There are pre-clinical data suggesting that

chemotherapy[21] or radiation therapy[22] may induce HER2 expression, but there is no evidence to demonstrate this phenomenon in the clinical setting. Furthermore, the clinically recurrent tumor could represent a new primary rather than a locoregional recurrence of the prior tumor given the differing clinical phenotype and long disease-free interval.

Approximately 10% of the tumor in the core needle biopsy was mucinous and the range reported in the literature is 5% to 95%. The residual tumor in the mastectomy did not show mucinous features. There is no well-established threshold for the amount of mucinous component required to make a diagnosis of ILC with extracellular mucin. In fact, many of the reported cases have had a substantial to dominant non-mucinous component.[18] The relationship of the mucinous component to the mode of tumor detection remains unclear. However, one could hypothesize that tumors with a minor mucinous component may be more likely to present as imaging abnormalities as opposed to palpable masses.

Only a few cases of pleomorphic ILC with extracellular mucin have been reported.[17,18] However, other case series and case reports have included grade 3 tumors that may have represented pleomorphic ILC. Even if the grade 3 and pleomorphic tumors were combined, they still would only account for a little more than 25% of all reported cases (Table 1). Although a minority of ILC with extracellular mucin have been HER2-positive,[11] the rate of HER2 amplification or overexpression in ILC with extracellular mucin appears to be higher than what has been reported for classic ILC. HER2-positive pleomorphic ILC with extracellular mucin seems to be one of the least common patterns and phenotypes among ILC variants.

The differential diagnosis of breast carcinomas with mucinous features includes mucinous carcinoma, solid papillary carcinoma, mucinous variant of invasive micropapillary carcinoma, polymorphous adenocarcinoma of the breast, matrix-producing metaplastic carcinoma, and ILC with extracellular mucin. DCIS is also known to produce extracellular mucin, as well as some benign mucocele-like lesions. Invasive lobular carcinoma with extracellular mucin production has been reportedly misdiagnosed as mucinous carcinomas or as invasive carcinomas of no special type with extracellular mucin production.[17,18] Yu et al[11] noted that 10% of pure mucinous carcinomas may show reduced E-cadherin expression. Awareness of this unusual pattern of ILC should help reduce misdiagnosis in the future. The case presented here also provides further evidence that a subset of ILC with extracellular mucin may be detected solely by imaging and have an aggressive (ie, grade 3, HER2-positive) phenotype.

Author Contributions

BCC and MJB designed the study, collected and analyzed the data, reviewed the literature and drafted and revised the manuscript. EMR, DWO, SMO and JDH contributed to data analysis, literature review and revision of the manuscript.

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