



Bilateral Invasive Histiocytoid Lobular Breast Carcinoma with Massive Paget's Disease. Case Report of Rare Tumor with a Controversial Histogenesis and Review of the Literature

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Abstract

Histiocytoid breast carcinoma (HBC) is a rare type of breast cancer with a controversial histogenesis, generally considered to be a variant of invasive lobular carcinoma. It comprises fewer than 0.3% of breast cancer cases. Published reports on this neoplasm are sparse and there exists a significant diagnostic challenge when differentiating these tumors from other tumors with similar presentations. Paget's disease of the breast comprises up to 3% of all breast malignancies. The majority of Paget's disease cases are associated with ductal carcinoma in situ, with bilateral, multifocal, and synchronous pathology rarely reported. While bilateral presentation of invasive lobular carcinoma is well documented, synchronous and metachronous forms are rare. We present a case of a 20-year-old female with bilateral invasive histiocytoid lobular breast carcinoma and concurrent massive bilateral Paget's disease of the breast. The goal of this manuscript is to explore possible pathologic associations and to clarify diagnostic parameters based on current literature.

Keywords: Histiocytoid; Lobular; Ductal; Paget's disease; Bilateral

ABBREVIATIONS

HBC: Histiocytoid breast carcinoma, WHO: World Health Organization, ILC: Invasive lobular carcinoma, IHC: Immunohistochemistry, IDC: Invasive ductal carcinoma, DCIS: Ductal carcinoma in situ, MBI: Molecular breast imaging

INTRODUCTION

Histiocytoid breast carcinoma (HBC) is a rare type of breast cancer with a contested histogenesis that is largely regarded as a variant of invasive lobular carcinoma (ILC). HBC was first introduced in a publication of 13 cases in 1973 by Hood et. al. and there have been few reports of the diagnosis since then, accounting for only 0.3% of all breast cancer cases [1]. HBC exists

as a controversial diagnosis due to its nonspecific symptoms and due to histological similarities with other breast pathologies, including both benign and malignant entities such as lipid-rich carcinoma, apocrine carcinoma, and granular cell tumors [2]. While the World Health Organization (WHO) has yet to acknowledge HBC in their classification of breast cancer, they have expanded their definition of ILC to include extracellular mucus production - one of the nonexclusive characteristics of HBC [3].

Other than previously documented metastasis to the eyelid, little is known about pathologic associations of HBC due to limited documentation of cases [4]. Due to the lack of defined diagnostic parameters to differentiate these various breast pathologies from HBC, there exists a significant diagnostic blind spot to be remedied. This manuscript describes a case of a 20-year-old female with bilateral invasive lobular breast carcinoma and concurrent bilateral Paget's disease of the breast. We believe this case represents the histiocytoid variant of ILC. ILC is the second most common invasive breast cancer, comprising roughly 10-15% of all breast cancer cases, including its variant forms. It originates in the milk-producing glands of the breast and is notable for a decrease in, or loss of, E-cadherin function, defining its characteristic single-file stromal growth pattern [5]. It is generally harder to detect on mammography compared to its counterpart of invasive ductal carcinoma (IDC), which is the most common invasive breast cancer comprising up to 80% of invasive breast cancer cases. The appearance of ILC on imaging is so elusive that its initial clinical presentation can

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be in form of skin metastasis documented previously in a rare case of synchronous ILC [6]. Additionally, about 20% of patients with ILC of the breast have bilateral presentation. Latency in diagnosis is a major contributing factor in prognosis, with greater latency leading to more poorly differentiated and larger lesions [7]. However, strides have been made in recent studies of disease pathology and management of ILC with a focus on prognostic markers, opening the doors to further studies with the goal of improving the time between presentation and diagnosis as well as relapse or recurrence [5].

Paget's disease of the breast comprises up to 3% of all breast malignancies. Although it typically presents unilaterally, with round intraepidermal individual and small clusters of cells in the nipple, there have been some cases documenting bilateral Paget's disease [8]. Paget's typically presents in older patients with a mean diagnostic age of 55 years [9], so this diagnosis in a 20-year-old is significantly rare. The lesions may present multicentrically, synchronously (defined as the second lesion occurring within 3 months of the first lesion), or metachronously (defined as the second lesion occurring greater than 3 months after the first lesion). Metachronous and synchronous breast cancers of all types are exceedingly rare with incidences of 7% and 1%, respectively. Of these cases, bilateral breast cancers are frequently associated with lobular phenotypes. Multiple studies suggest that synchronous lesions are associated with poorer prognoses as well as disease-specific and overall survival [10, 11]. The majority of Paget's disease cases have underlying breast malignancies with the most common being ductal carcinoma *in situ* (DCIS). Rare cases have been documented of synchronous bilateral Paget's disease derived from lobular carcinoma *in situ*, though it is difficult to conclude whether lesions have developed multicentrically without evidence of the presence or absence of continuity, non-invasive components, or distinct histopathological findings [12, 13]. Another significant diagnostic challenge manifests when attempting to differentiate these tumors clinically. Up to 70% of skin metastases are due to primary breast carcinomas, but their non-specific clinical appearance poses a challenge in differentiating these lesions from benign etiologies. As ILC is typically occult on almost all

breast imaging modalities, skin metastases in later stages may be the first presentation of synchronous bilateral ILC resulting in delayed diagnosis [6].

The purpose of our study is multifold: to clarify diagnostic differentiation with a focus on immunohistochemistry (IHC) analysis, explore pathological associations, and discuss the implications of a diagnosis of HBC.

CASE PRESENTATION

A 20-year-old female with an unknown family history of cancer presented with a two-year history of skin scaling lesions of the breasts bilaterally. The lesions first appeared on the left breast nipple and rapidly expanded to include the entirety of the left breast with significant demarcation along the breast perimeter. The lesions then extended along the anterior chest wall, right breast with right nipple involvement, left upper abdomen, and both flanks, with sparing of the majority of the intermammary cleft (**Figure 1 A-B**). On physical examination, the affected area appeared heavily scarred with gray to black scaling and variable thickening. Clinically, the patient presented with frozen, hard-fixed bilateral breasts with wood lymphedema, associated with fixed bilateral axillary lymphadenopathy. No other lymphadenopathy was noted. On CT imaging (3-6mm slice thickness), findings included multiple mildly enlarged lymph nodes at both axillary regions. Chest CT was performed using 3-6mm slice thickness. Imaging was remarkable for bilateral axillary lymphadenopathy with multiple mildly enlarged lymph nodes; with the largest measuring 1.3 cm. Imaging studies could not rule in or rule out presence of tumor masses in either breast. Pulmonary and cardiac findings were unremarkable as well as hilar and mediastinal lymph nodes. No tumor extension into the thoracic skeleton or soft tissues was noted by imaging.

Upon initial presentation, a T-cell lymphoma of the skin was suspected, and a skin biopsy was performed. Microscopic examination revealed scattered single and large tumor nests with pagetoid spread involving the epidermis. In addition, the tumor showed multifocal nodular aggregates of pleomorphic, high grade tumor cells, many with prominent nucleoli

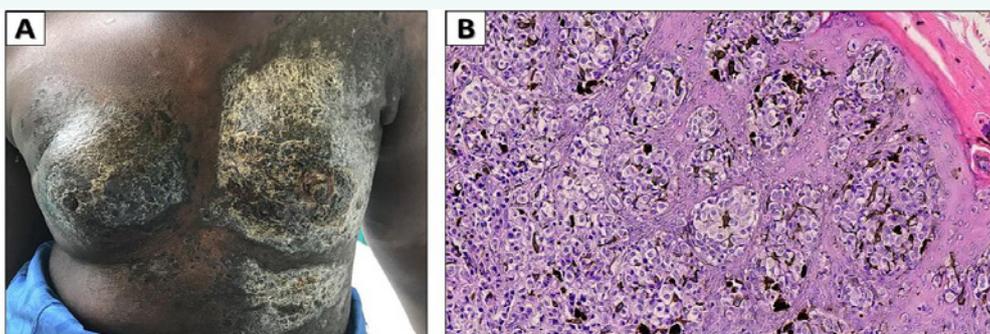


Figure 1 Initial clinical presentation of the patient and skin biopsy

1A: The affected area appeared heavily scarred with gray to black scaling and variable thickening involving both breast and extending to the chest and abdominal wall

1B: Characteristic intraepidermal pagetoid spread of tumor cells (H&E stain X40)



Immunohistochemistry (IHC) studies were utilized for definitive evaluation. The tumor cells were S100 negative, CD45 negative, AE1/AE3 positive, Estrogen 90% strong positive nuclear staining, Progesterone 90% strong positive nuclear staining, and Her2/Neu positive 3+ (Figures 2 A-B-C-D-E).

Despite a lack of evidence of breast tumor on imaging, an infiltrating breast carcinoma with massive Paget's disease was highly suspected and core needle biopsies of both breasts were performed. Microscopic examination of the breast core biopsies showed invasive tumor with similar features to the tumor seen in skin biopsies. The malignant tumor cells were seen in the background of typical single-file pattern and dense fibrotic breast parenchyma (Figure 3 A-B). Many tumor cells showed large granular pink cytoplasm with features reminiscent of apocrine-like features.

The histomorphology and IHC profile were diagnostic of

bilateral ILC with histiocytoid features and extensive Paget's disease involving the entire anterior chest and upper abdominal epidermis. The patient was not a surgical candidate, so the plan of care involved administration of paclitaxel chemotherapy for 6 cycles for a rapid response in clinical symptoms, followed by a prompt shift to Tamoxifen hormonotherapy. On follow-up visits, the patient showed a relatively good response - axillary lymph nodes were no longer palpable, skin lesions gradually improved, and lymphedema severity showed marked improvement. Follow-up imaging showed no evidence of recurrence of metastasis. Patient was lost to follow-up 8 months following initiation of treatment.

DISCUSSION

Histiocytoid breast carcinoma (HBC) is regarded as a subtype of ILC, which is the second most common form of invasive breast cancer, comprising 10-15% of all breast cancer cases.

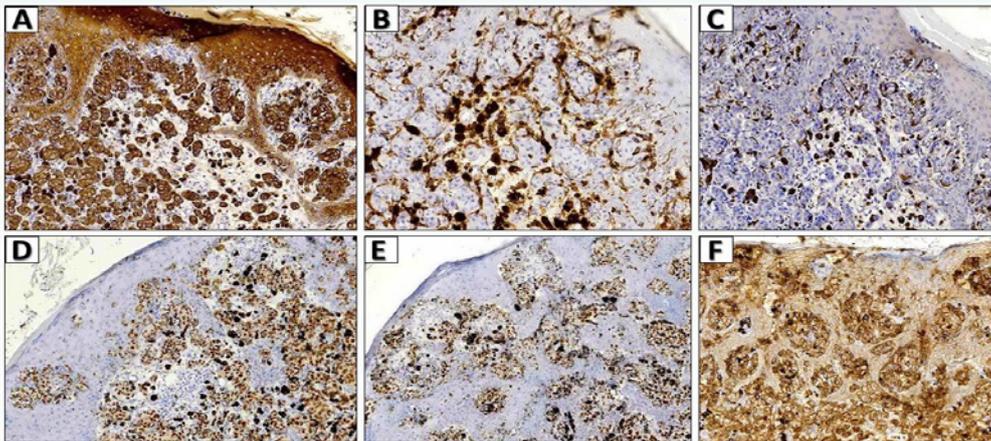


Figure 2 Immunohistochemistry studies of the breast carcinoma
2A: Tumor cells positive for epithelial marker cytokeratin AE1/AE3
2B: Tumor cells negative for lymphoid marker CD45
2C: Tumor cell negative for melanocytic marker S-100
2D: Tumor cells strongly positive for ER
2E: Tumor cells strongly positive for PR
2F: Tumor cells strongly positive for Her-2, 3+

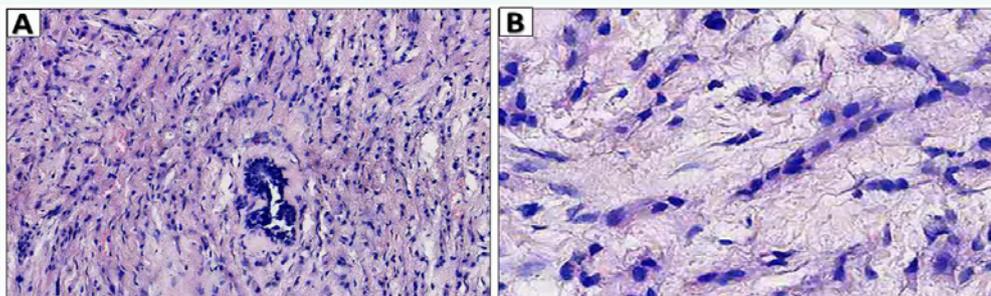


Figure 3 Microscopic examination of bilateral breast core biopsies
3A: Infiltrating tumor without glandular formation, low power view (H&E stain X40)
3B: Tumor cells showing characteristic pattern of invasive lobular carcinoma with typical single-file arrangements and dense fibrotic stroma (H&E stain X60)



The diagnosis of HBC remains controversial, and it has yet to be recognized by the WHO and other major organizations. This is mainly due to its low incidence and morphologic similarities to other forms of breast cancer, malignant and benign, including apocrine ductal carcinoma, lobular carcinoma and its apocrine variant subtype, and lipid rich carcinoma [14]. The diagnosis is largely determined by histology; therefore, it is important to differentiate key histological features of the comparable diagnoses. Of notable interest in our presented case is HBC's coexistence with Paget's disease, particularly one of such extensive and bilateral formation.

The defining characteristic of ILC is its linear single-file infiltrative growth pattern composed of uniform cells resulting from a loss in the E-cadherin (CDH1) protein responsible for cell-cell adhesion [15]. This gene is of particular interest because mutation is associated with the classic ILC phenotype as well as all recognized ILC variants but is rarely ever associated with ductal carcinoma. The most common recognized variants of ILC include pleomorphic (larger pleomorphic cells and prominent nucleoli consistent with its name), solid (grouping of >2 cells thick infiltration between collagen bundles), alveolar (rounded cell grouping), and tubulolobular (infiltration exhibiting both ductal and lobular differentiation, mixed linear and tubular architecture, and typically preserved E-cadherin). Demonstration of myoepithelial cells on IHC using both p63 and calponin for optimal sensitivity and specificity confirms *in situ* nature, whereas absence is supportive of invasion [16]. With classic ILC, we expect to find ER+, PR+, and HER2- staining [5]. ILC has been observed to have a 68.8% rate of metastasis to the peritoneum. Prognosis following a diagnosis of peritoneal metastases is poor and characterized by hormone therapy resistance, with a median survival of 19±9 months [17]. Generally, 1 in 3 breast cancer patients have metastasis to multiple organs simultaneously with the most common ones including bone (41%), lungs (22%), liver (7.3%), and brain (7.3%) [18].

Non-genetic risk factors of ILC include early menarche, late menopause, and increased exposure to female hormones as supported by a steady decline in ILC incidence from 1999-2004 concurrent with decreasing use of menopausal hormone therapy [19]. Genetic risk factors tested in clinical practice include mutations in BRCA1, BRCA2, TP53, and CDH1 with more specificity for ILC in CDH1 and BRCA2. Approximately 50% of individuals with germline mutations in CDH1 are expected to develop ILC during their lifetime and must undergo more intensive breast cancer screening beginning with MRIs and/or mammograms at 30 years old and continuing annually [19]. However, despite this increase in screening frequency, ILC tumor cells possess a low density and lack of desmoplastic stromal reaction on most imaging modalities, which poses a significant barrier in detection by traditional imaging methods [20].

Mammography has demonstrated low sensitivity (below 79%) in detecting ILC with 30% unable to be visualized at all. In fact, detection on imaging is so poor that skin metastases, 70% of which are due to primary breast carcinoma, may be the first presentation of ILC. One such case describes a patient

with a several month history of refractory skin lesions who subsequently presents with a skin nodule of the breast, leading to a diagnosis of bilateral synchronous ILC [6]. Newer imaging technology is in active development to reduce the latency in diagnosis and improve the prognosis of ILC. Latency in diagnosis is a major predictor of prognosis with greater delay associated with more poorly differentiated, larger lesions [7]. The case we are presenting is a clear example of the unfavorable outcome of delayed diagnosis as the patient did not seek early medical attention. Two such technologies, molecular breast imaging (MBI), and tomosynthesis, have demonstrated improved vigilance of tumorigenesis. MBI allows small field-of-view imaging with improved spatial recognition with an overall sensitivity of detecting breast cancer of 89%, and a sensitivity of detecting ILC of 79% - twice that of mammography. Tomosynthesis, on the other hand, is a digital mammogram-based technology utilizing a series of low-dose acquisitions reconstructed into thin slices while an X-ray passes over the region of interest. The function of this method is to minimize obstruction by overlapping structures compared to conventional two-dimensional mammography. Compared to traditional mammography, the ILC detection rate utilizing this novel method increased from 0.27-0.55 per 1,000 cases [21]. Similar advancements in technology are demonstrated in next-generation sequencing. One study utilized exome sequencing in cases of ILC which, in addition to highly recurrent CDH1 and PIK₃CA mutations, demonstrated HER2/ERBB2 mutations in 6 of 22 cases with recurrence or metastasis of ILC post-treatment. Somatic mutations (not amplifications) in ERBB2 are rare in breast cancer but were notably more associated with ILC in this study, occurring in 6 of 155 ILCs [22]. Surgical removal of the primary tumor plus neoadjuvant chemotherapy is the primary treatment strategy in patients with ILC. However, alternative strategies for treatment exist. One alternative is neoadjuvant endocrine therapy, which has demonstrated promising results leading to an increase in breast conservation surgery and less extensive axillary surgery [23]. These improvements in imaging technology, biomarker research and alternative treatment options may aid in arming clinicians with augmented tools to better discern these specific breast pathologies from one another, as well as make specific diagnoses with more confidence. As a result, cancer morbidity may be mitigated by minimizing the delay in diagnosis and more readily anticipating recurrence.

The HBC subtype of ILC was first described by Hood et. al. in a 1973 publication describing 13 peculiar cases of breast carcinoma associated with eyelid metastases, characterized by a histiocytoid histology. It was named for its close resemblance to a benign histiocytic lesion. Of the histological analysis of the 13 case specimens, 3 demonstrated typical ductal pattern, 2 demonstrated pleomorphic properties consistent with malignancy, and 8 had a histiocytoid pattern, with 7 of the 8 cases posing a significant diagnostic challenge due to close histological similarities with other diseases including but not limited to granular cell tumor, apocrine ductal carcinoma, lobular carcinoma and its apocrine variant subtype, and lipid rich carcinoma [4]. HBC typically presents with linear and targetoid infiltration/indian filing



associated with negative E-cadherin. Abundant vacuolated cytoplasm is typically noted with indistinct cell borders and low grade nuclei. The documented age at diagnosis ranges from 41-93 years [16].

Most documented findings support the origin of HBC from lobular carcinoma. However, this theory is not universally accepted as some publications suggest HBC does not belong to an already-established classification. One study reports HBC, invasive or *in situ*, was found to be triple negative for ER, PR, and HER2/neu, inconsistent with classical lobular carcinoma, and negative E-cadherin expression, inconsistent with classical ductal carcinoma - the author argues in favor of a distinct classification [14]. Other investigators link components of HBC to a milk duct or apocrine origin [1].

Li et. al. discusses differences in IHC profiles of 17 breast cancers in a 2013 publication discussing HBC and argues for HBC as a variant of lobular carcinoma, but in the specific IHC patterns discovered, HBC was determined to be triple negative for ER, PR, and HER2/neu. Atypical lobular hyperplasia, on the other hand, stained positive for ER, PR, and HER2/neu. In this regard, HBC is more akin to IDC. However, this paper noted that the invasive HBC cells displayed a uniform histiocytoid appearance with characteristics that resembled lobular carcinoma more than ductal carcinoma [24]. Like ILC, HBC typically demonstrates a lack of membrane staining of E-cadherin. However, in one study, 27.3% of identified cases of HBC stained positive for E-cadherin [25]. Our case depicts a patient with HBC with positive ER, positive PR, and negative HER2/neu. Based on these confounding results, it seems the usual trio of markers alone (ER, PR, HER2) may not be reliable nor sufficient in diagnosing this type of cancer.

HBC possesses a striking histological similarity compared to granular cell tumors. The following markers aid in differentiating granular cell tumor: expression of S100 protein, expression of calretinin, negative hormone receptors. HBC is differentiated from histiocytic lesions with the following markers: negative CD1a, S100, cytokeratin, mucin, oil red O [26]. Another significant histiocytoid carcinoma manifestation is signet ring cell/histiocytoid carcinoma - a rare skin appendage cancer that has, in rare cases, been depicted in the axilla. This neoplasm has histopathological and immunohistochemical features that are very similar to HBC - such that they have been called equivalent [27, 28].

Our reported patient presented with bilateral invasive lobular HBC. Bilateral breast cancer is considered a rare enough phenomenon alone, and reports of bilateral HBC are few and far between. As demonstrated in lobular carcinomas, diagnosis of HBC typically occurs in later stages. Therefore, it is challenging to determine whether multiple lesions are multicentric, synchronous, or metachronous without a clear timeline of lesion formation and change in morphology.

This 20-year-old female patient with bilateral invasive lobular HBC also presented with extensive Paget's disease. Paget's disease appears in three possible forms: associated with an DCIS, associated with an invasive carcinoma, or without any

underlying malignancy. The most common associated form is DCIS with a unilateral Paget's presentation [29]. Skin biopsy is recommended as a definitive screening to rule out or confirm this diagnosis of Paget's disease. On histopathology, the presence of intraepidermal Paget's cells, large cells with abundant clear cytoplasm and hyperchromic, eccentric nuclei, is conclusive. Due to the contested nature of the origin of the Paget's cell, there are two working theories for its pathogenesis. These cells either stem from the ductal epithelium (epidermotropic hypothesis), or the areolar epidermis (intraepidermal transformation hypothesis). IHC analysis of Paget's disease of the breast typically reveals negative ER and PR markers, with variable Her-2 status [8, 29].

A unique study documented Paget's disease of the breast presenting concurrently with lipid-secreting mammary carcinoma, associated with periodic acid-Schiff (PAS)-positive material in the epidermis of the nipple. Lipid-secreting carcinomas account for 1% of breast carcinomas. The recognition of their hallmarks makes them useful in differentiating them from HBC. Lipid-secreting carcinomas resemble scirrhous carcinoma on H&E, with abundant finely vacuolated cytoplasm and honeycomb-appearance. Fat stain (flaming red stain) demonstrates lipid content of the tumor cells. Colostrum-like cells can often be observed in the lumen and epithelial lining of ducts due to their lipid-secreting capabilities [30].

It is important to consider possible explanations for such aggressive disease presentations at a young age, with our patient's initial pathogenesis beginning at age 18, 2 years prior to late presentation and diagnosis. As discussed, there are many well-recognized non-genetic risk factors of breast carcinogenesis. With regards to pathology in younger women, there is stronger emphasis placed on genetic risk factors including germline mutations in BRCA1 and TP53. These are most associated with ductal carcinoma, which is the more common predisposing factor for Paget's disease compared to lobular carcinoma, the latter of which is more commonly associated with mutations in CDH1 and BRCA 2 [19]. Dense breasts, family history, and radiation exposure are other risk factors associated with younger presentation of breast cancer, none of which were noted in this case. In our case, resources were not adequate to perform molecular analysis of the cancer.

Presentation of Paget's disease may be further classified by the timeline of lesion development. Synchronous bilateral Paget's disease has been documented in extremely rare cases. Of these rare cases, more than 95% are associated with an underlying carcinoma of the breast or nipple, with virtually all of them reported as ductal carcinoma with or without invasive characteristics. However, one case was found with the typical cytomorphology of Paget cells and involvement of lactiferous ducts by lobular carcinoma *in situ*, with absence of DCIS and absence of HER2/neu and E-cadherin staining. These findings support a rare derivation of Paget's disease from a lobular pathogenesis rather than ductal [12]. A second case found synchronous bilateral Paget's disease in a patient presenting with bilateral pruritis of the nipples with no mass noted on imaging modalities and no histological evidence of underlying DCIS or IDC



[8]. Another case depicts a synchronous unilateral triple breast cancer consisting with IDC, ILC, and Paget's disease. Multicentric development was supported by the absence of continuity between the three tumors and distinct histopathologic findings [13]. These findings demonstrate that additional care should be taken when constructing a list of differential diagnoses for a patient with nonspecific bilateral clinical breast pathology. Bilateral and synchronous presentations of Paget's are exceedingly rare and may therefore be initially overlooked but warrant a keen investigative perspective due to their significant disease burden.

One promising novel technique for diagnosis of Paget's disease is described in a study of 26 women with nipple-areola complex changes and suspicion of Paget's disease. The work outlined the use of core needle biopsy with a semiautomated 14-gauge needle referred to as nipple-core needle biopsy - the needle spring position is moved for the withdrawal of 2-4 core samples in a quick, painless, and low-risk process. Of the 26 women with suspected Paget's, 13 were determined by nipple-core needle biopsy to have Paget's disease and were later confirmed by histological examination, whereas the other 13 were labeled benign and remained without malignant lesions/transformation upon follow-up [31].

HBC remains a controversial diagnosis because it shares many histological features with breast cancers of other entities. Few reports of HBC exist; therefore, little is known about the disease, the parameters for diagnosis, and the possible pathologic associations [1]. Superimposed bilateral Paget's disease of the breast further complicates our case with an unclear timeline and localization of tumorigenesis due to its uncommon bilateral presentation. Despite lack of tumor evidence on CT imaging in our case, core needle biopsies were performed on both breasts which revealed ILC. Upon diagnosis, chemotherapy was administered with 6 cycles of paclitaxel, a mitotic inhibitor used as the therapy of choice in many forms of cancer. This demonstrated a relatively good response with improvement in bilateral axillary lymphadenopathy and severity of lymphedema.

Although not recognized by the most recent listing of WHO as a separate entity, we believe our case represents a histiocytoid variant of ILC based on our experience and the analysis of the available literature on this subject. In addition, our case reports the association of massive bilateral Paget's disease not reported before our case. We hope our report will raise awareness of this breast carcinoma subtype and generate additional reporting to continue the debate regarding this entity. Advancement in technology and diagnostic measures is promising for more opportunities to study the pathogenesis, management, and diagnostic parameters of HBC such that it may be more easily differentiated from other breast subtypes and recognized as a separate entity. This will be paramount in improving the efficiency and confidence of diagnosis, management and improving patient outcomes.

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REFERENCES

1. Terakawa H, Gabata R, Ishikawa S, et al. *Gan To Kagaku Ryoho*. 2019;46(6):1049-1051.
2. Kempson, Richard L. "Surgpathcriteria.stanford.edu/Breast/Histiocabr/Printable.html." *Surgical Pathology Criteria*, Stanford University Medical Center, 1 May 2006, <http://surgpathcriteria.stanford.edu/breast/histiocabr/printable.html>.
3. Tan, P H, Ellis, I, Allison, K, Brogi, E, Fox, S B, Lakhani, S, Lazar, A J, Morris, E A, Sahin, A, Salgado, R, Sapino, A, Sasano, H, Schnitt, S, Sotiriou, C, van Diest, P, White, V A, Lokuhetty, D, Cree, I A & for the WHO Classification of Tumours Editorial Board. (2020) *Histopathology* 77, 181– 185. <https://doi.org/10.1111/his.14091> The 2019 World Health Organization classification of tumours of the breast
4. Hood, C.I., Font, R.L. and Zimmerman, L.E. (1973), Metastatic mammary carcinoma in the eyelid with histiocytoid appearance. *Cancer*, 31: 793-800.
5. Reed, A.E.M., Kalinowski, L., Simpson, P.T. et al. Invasive lobular carcinoma of the breast: the increasing importance of this special subtype. *Breast Cancer Res* 23, 6 (2021). <https://doi.org/10.1186/s13058-020-01384-6>
6. Khodair S, Ewais I, Abolmagd H, El Sheikh R, Raza S, Portnow LH, Gewefel H. Skin Nodules as a First Presentation of Synchronous Bilateral Invasive Lobular Breast Carcinoma: A Case Report. *Journal of Global Radiology* 2021;7(1):1147. <https://doi.org/10.7191/jgr.2021.1147>
7. Yang C, Lei C, Zhang Y, Zhang J, Ji F, Pan W, Zhang L, Gao H, Yang M, Li J, Wang K. Comparison of Overall Survival Between Invasive Lobular Breast Carcinoma and Invasive Ductal Breast Carcinoma: A Propensity Score Matching Study Based on SEER Database. *Front Oncol*. 2020 Dec 22;10:590643. doi: 10.3389/fonc.2020.590643. PMID: 33415073; PMCID: PMC7783385.
8. Xie B, Zheng H, Lan H, Cui B, Jin K, Cao F. Synchronous bilateral Paget's disease of the breast: A case report. *Oncol Lett*. 2012;4(1):83-85. doi:10.3892/ol.2012.676
9. Liu J, Zhao Z, Zhou J, Zhang J. An unusual presentation of Paget's disease of the nipple in a young woman: a case report. *Int J Clin Exp Med*. 2015;8(3):4694-4696.
10. Jobsen, J.J., van der Palen, J., Ong, F. et al. Bilateral breast cancer, synchronous and metachronous; differences and outcome. *Breast Cancer Res Treat* 153, 277–283 (2015). <https://doi.org/10.1007/s10549-015-3538-5>
11. Fanshawe, A., Hadjiminias, D., Leff, D., Invasive lobular carcinoma and bilateral breast cancer: Results from a cohort of patients with metachronous and synchronous disease, *European Journal of Surgical Oncology*, Volume 44, Issue 6, 2018, Page 892, ISSN 0748-7983, <https://doi.org/10.1016/j.ejso.2018.02.134>.
12. Sahoo S, Green I, Rosen PP. Bilateral paget disease of the nipple associated with lobular carcinoma in situ. *Arch Pathol Lab Med*. 2002;126(1):90-92. doi:10.5858/2002-126-0090-BPDOTN
13. Onoe, S., Tsuda, H., Akashi-Tanaka, S. et al. Synchronous unilateral triple breast cancers composed of invasive ductal carcinoma, invasive lobular carcinoma, and Paget's disease. *Breast Cancer* 21, 241–245 (2014). <https://doi.org/10.1007/s12282-010-0245-2>
14. Ma XL, Du Q, Liu Y, Zhao RM, Zhang SY, Zhao HF. Histiocytoid breast carcinoma, neither lobular nor ductal? A case report and literature review. *Transl Cancer Res* 2020;9(11):7372-7378. doi: 10.21037/tcr-19-756



15. Ciriello G, Gatz ML, Beck AH, et al. Comprehensive Molecular Portraits of Invasive Lobular Breast Cancer. *Cell*. 2015;163(2):506-519. doi:10.1016/j.cell.2015.09.033
16. Kempson, R. (2006). Infiltrating Lobular Carcinoma of the Breast. Stanford School of Medicine. Retrieved November 8, 2021, from <http://surgpathcriteria.stanford.edu/breast/inflobcabr/printable.html>.
17. Inoue M, Nakagomi H, Nakada H, et al. Specific sites of metastases in invasive lobular carcinoma: a retrospective cohort study of metastatic breast cancer. *Breast Cancer*. 2017;24(5):667-672. doi:10.1007/s12282-017-0753-4
18. Berman AT, Thukral AD, Hwang WT, Solin LJ, Vapiwala N. Incidence and patterns of distant metastases for patients with early-stage breast cancer after breast conservation treatment. *Clin Breast Cancer*. 2013;13(2):88-94. doi:10.1016/j.clbc.2012.11.001
19. Dossus, L., Benusiglio, P.R. Lobular breast cancer: incidence and genetic and non-genetic risk factors. *Breast Cancer Res* 17, 37 (2015). <https://doi.org/10.1186/s13058-015-0546-7>
20. Oluyemi, E., Peshtani, A., White, M.J. et al. Radiologic and Pathologic Correlation of Invasive Lobular Carcinoma of the Breast. *Curr Breast Cancer Rep* (2021). <https://doi.org/10.1007/s12609-021-00434-y>
21. Johnson, K., Sarma, D. & Hwang, E.S. Lobular breast cancer series: imaging. *Breast Cancer Res* 17, 94 (2015). <https://doi.org/10.1186/s13058-015-0605-0>
22. Reed, A.E.M., Kutasovic, J.R., Lakhani, S.R. et al. Invasive lobular carcinoma of the breast: morphology, biomarkers and 'omics. *Breast Cancer Res* 17, 12 (2015). <https://doi.org/10.1186/s13058-015-0519-x>
23. Mukhtar, R.A., Hoskin, T.L., Habermann, E.B. et al. Changes in Management Strategy and Impact of Neoadjuvant Therapy on Extent of Surgery in Invasive Lobular Carcinoma of the Breast: Analysis of the National Cancer Database (NCDB). *Ann Surg Oncol* 28, 5867-5877 (2021). <https://doi.org/10.1245/s10434-021-09715-3>
24. Li P, Zheng J, Zhang T, Cao R, Chen X, Geng M. Histiocytoid breast carcinoma: a case report showing immunohistochemical profiles. *Int J Clin Exp Pathol*. 2013;6(11):2609-2614. Published 2013 Oct 15.
25. Gupta D, Croitoru CM, Ayala AG, Sahin AA, Middleton LP. E-cadherin immunohistochemical analysis of histiocytoid carcinoma of the breast. *Ann Diagn Pathol*. 2002;6(3):141-147. doi:10.1053/adpa.2002.33880 [https://doi.org/10.1002/1097-0142\(197304\)31:4<793::AID-CNCR2820310406>3.0.CO;2](https://doi.org/10.1002/1097-0142(197304)31:4<793::AID-CNCR2820310406>3.0.CO;2)
26. Mufti, Shagufta & Al-Zahrani, Ibrahim. (2010). Histiocytoid breast carcinoma: A diagnostic delimita, Case report and literature review. *New Egyptian journal of medicine*. 42. 487-492.
27. Misago, N., Shinoda, Y., Okawa, T., Aoki, S., Toda, S., Koike, K. and Narisawa, Y. (2011), Histiocytoid and signet-ring cell carcinoma of the axilla: a type of cutaneous apocrine carcinoma equivalent to histiocytoid lobular carcinoma of the breast?. *Clinical and Experimental Dermatology*, 36: 874-877 doi.org/10.1111/j.1365-2230.2011.04106.x
28. Ito, Y, Ishida, M, Ohe, C, Miyasaka, C, Tsuta, K. Signet-ring cell/histiocytoid carcinoma in the axilla: A case report with genetic analysis using next-generation sequencing. *J Cutan Pathol*. 2021; 48(1): 102- 105. <https://doi.org/10.1111/cup.13838>
29. Barth D. Bilateral Paget's Disease of the Breast-Case Report of Long-Time Misdiagnosed Tumors with Underlying Ductal Carcinomas and Review of the Literature. *Case Rep Dermatol Med*. 2014;2014:152836. doi:10.1155/2014/152836
30. Aboumrad, M.H., Horn, R.C., Jr and Fine, G. (1963), Lipid-secreting mammary carcinoma. Report of a case associated with paget's disease of the nipple. *Cancer*, 16: 521-525. [https://doi.org/10.1002/1097-0142\(196304\)16:4<521::AID-CNCR2820160414>3.0.CO;2](https://doi.org/10.1002/1097-0142(196304)16:4<521::AID-CNCR2820160414>3.0.CO;2)
31. Nori J, Bicchierai G, Amato F, et al. A new technique for the histological diagnosis of Paget's disease of the breast using a semiautomated core needle biopsy with a 14-gauge needle. *Radiol Med*. 2021;126(7):936-945. doi:10.1007/s11547-021-01358-4