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Case Report

Histiocytoid breast carcinoma: a case report showing immunohistochemical profiles

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Abstract: Histiocytoid breast carcinoma (HBC) is a rare type of breast cancer with a controversial histogenesis. Here we describe a case report of a 65-year old woman with HBC. The patient presented with two masses in the right breast. Histopathologically, the tumors consisted of a diffuse infiltration of large tumor cells and histological components of carcinoma *in situ* and atypical lobular hyperplasia were also observed. The infiltration pattern was similar to that of invasive lobular carcinoma with targetoid and Indian file arrangements. The invasive histiocytoid cells had finely granular, eosinophilic to vesicular cytoplasm and nuclei with a bland uniform appearance, a single small eosinophilic nucleolus and finely granular chromatin. We compared the immunohistochemical profiles of 17 breast cancer markers between invasive carcinoma, carcinoma *in situ*, atypical lobular hyperplasia and normal breast epithelium. Although they all shared the same reactivity for many of the proteins, they exhibited differences in GCDFP-15, E-cadherin, P120, CEA, HER-2, ER and PR expression, and these are discussed. This is the first case study of two HBC masses occurring in one breast simultaneously. By analyzing and comparing their morphologic characteristics and spectrum of immunohistochemical expression, our study supports the view that HBC is a variant of lobular carcinoma and our findings may assist in future diagnoses of HBC.

Keywords: Histiocytoid, breast cancer, invasive lobular carcinoma, carcinoma *in situ*, atypical lobular hyperplasia

Introduction

Histiocytoid breast carcinoma (HBC) is a rare carcinoma that is generally considered to be a variant of lobular carcinoma. However, it is difficult to recognize and can often be misdiagnosed due to its histological similarities with benign and other forms of malignant breast lesions. Here, we report a case of HBC, in which two masses were presented on one breast. We discuss its histogenesis based on clinicopathological features and immunohistochemical comparisons between invasive carcinoma, carcinoma *in situ*, atypical lobular hyperplasia and normal breast epithelium. The purpose of our study was to clarify the classification and diagnosis of HBC.

Case presentation

Clinical history

A 65-year-old woman presented with right breast masses and was initially admitted for five days. Physical examination revealed two hard masses in the upper inner quadrant of the right breast. There was no tenderness and skin redness, orange peel-like change, nipple retraction and nipple discharge were not observed. The larger mass had a clear border and good activity and there was no lymph node swelling. Ultrasonography displayed two inhomogeneous hypoechoic nodules measuring 1.7 × 1.0 cm and 1.4 × 0.7 cm separated by 1.6 cm (**Figure 1**). A right modified radical mastectomy was performed which showed that the two masses had no clear boundaries or envelopes. Postoperatively, the patient underwent five regimens of chemotherapy with paclitaxel liposome and cisplatin. She remained disease free ten months after surgery.

Macroscopic findings

The surgically resected specimen contained two well-circumscribed firm masses with maximum diameters of 1.7 cm and 1.4 cm, respec-

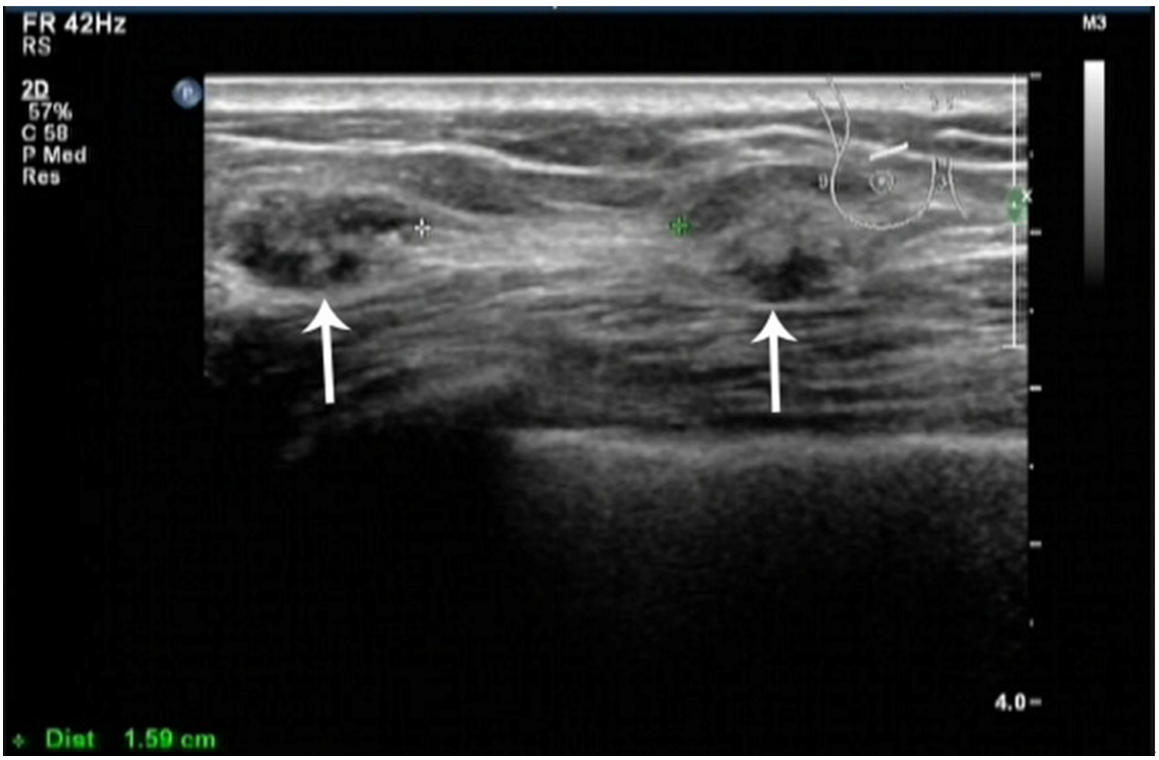

Figure 1. Ultrasonographic appearance of the right breast. The echogram shows two ovoid, hypoechioc masses with irregular internal echo (white arrow).

tively. The cut section was yellow-white with no evidence of hemorrhage or necrosis. The modified radical mastectomy specimen contained 14 lymph nodes in the axillary contents. Further analysis, described below, showed these were all negative.

Histological features

The surgically resected specimen was fixed in 10% neutral-buffered formalin and paraffin-embedded (FFPE) following standard protocols. Sections (3-μm thick) were stained with hematoxylin-eosin (H&E), periodic acid-Schiff (PAS) with or without prior diastase digestion, and alcian blue (AB; pH 2.5).

The two tumors had similar histopathological features exhibiting a diffuse infiltration of histiocytoid cells within fibrous stroma. The cells had an abundant, faintly eosinophilic granular to foamy cytoplasm with a ground glass appearance and occasional vacuolation. The cell borders were polyhedral and indistinct. The nuclei displayed many of the features of classical invasive lobular carcinoma, having smooth round contours, a thin nuclear membrane and finely granular normochromatic chromatin with a single, usually central, small but prominent eosinophilic nucleolus (**Figure 2A**). However, some of the nuclei had a slightly irregular shape with rough edges and inhomogeneous chromatin (**Figure 2B**). The intracytoplasmic vacuoles were often sufficiently large to indent and cause peripheral displacement of the nuclei, resulting in signet ring-like cells (**Figure 2C**). PAS staining, both with and without prior diastase digestion, displayed diffuse granular cytoplasmic positivity in most of the invasive cells. But only a few cells had intracytoplasmic vacuoles that were stained with AB. The invasive carcinoma appeared as diffuse linear or Indian file arrangements, small nests or clusters, individual cells or as loose aggregates, with no obvious glandular differentiation. This pattern, including the targetoid arrangement, was similar to that of invasive lobular carcinoma. There was no evidence of necrosis and mitoses were rare, with a count less than 1/10 HPF. The tumor tissue also exhibited remnants of lobular and duct structures (**Figure 3A**). Some foci of the lobular carcinoma *in situ* showed transition to the histiocytoid cells with-

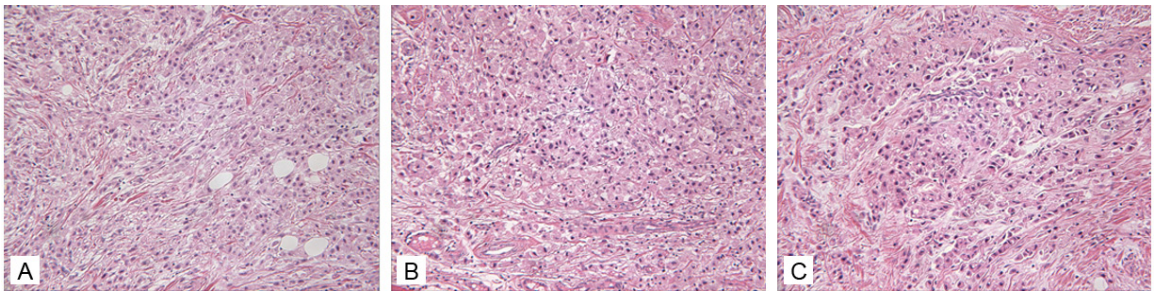

Figure 2. Histopathological features of histiocytoid breast carcinoma. A: Invasive histiocytoid carcinoma consisting of tumor cells with abundant granular eosinophilic cytoplasm; B: Some of the nuclei have a slightly irregular-shape with rough edges and inhomogeneous chromatin; C: Tumor cells with cytoplasmic vacuoles are present. (H&E staining; magnification, ×200).

in and around the invasive tumor (**Figure 3B**). These cells displayed clear boundaries, ovoid nuclei with homogeneous chromatin and either a single or two small nucleoli. However the large focus of the carcinoma *in situ* may appeare necrotic centrally. Components of atypical lobular hyperplasia were also observed (**Figure 3C**). Although chronic inflammatory cells were not apparent within the invasive tumor, they appeared locally in the surrounding vessels. In addition, all of the 14 sentinel and axillary lymph nodes were negative.

Immunohistochemistry protein expression profiles

Immunohistochemical staining was performed on FFPE tissue sections using a Ventana BenchMark XT system (Ventana, Oro Valley, AZ, USA) [1]. The selected primary antibodies were as follows: GCDFP-15, E-cadherin, HER-2, CEA and CD68 (DAKO, Carpentaria, CA, USA); ER, PR and CAM5.2 (Zhongshan, Beijing, China); EMA, CK34βE12, CK7, AE1/AE3, S-100, CK5/6, CK14, P120 and Vimentin (Maixin, Fujian, China). The analysis of HER-2, ER and PR were performed according the guidelines recommended by the American Society of Clinical Oncology and the College of American Pathologists (ASCO/CAP).

The immunohistochemical staining results for the marker proteins were compared between the invasive carcinoma, carcinoma *in situ*, atypical lobular hyperplasia and normal breast epithelium. They were all positive for EMA, CK34βE12, CK7, AE1/AE3 and CAM5.2, and negative for CD68, S-100, CK5/6, CK14 and Vimentin. However they exhibited differences in expression of GCDFP-15, E-cadherin, P120, CEA, HER-2, ER and PR (**Table 1**; **Figure 3D-O**). Invasive HBC was positive for GCDFP-15 and CEA, and negative for E-cadherin, P120, ER and PR; whereas normal breast epithelium showed the contrary expression patterns. Both carcinoma *in situ* and atypical lobular hyperplasia showed intermediate expression profiles for these proteins, with the exception of HER-2 which was significantly increased. For GCDFP-15, the majority of the invasive tumor cells showed cytoplasmic staining that was variable in intensity.

Discussion

Histiocytoid breast carcinoma is a rare breast carcinoma with morphologic characteristics resembling histiocytes. It was first reported in 1973 by Hood and Zimmerman who described 13 cases of breast cancer with histiocytoid appearance and metastasis to the eyelid [2]. Although there have been occasional subsequent reports in the literature, there is little consensus on how HBC should be classified. Despite being accepted as a variant of breast cancer by many pathologists, the term histiocytoid breast carcinoma is yet to be included in the WHO classification of breast cancer due to its controversial histogenesis. The majority of reports support the origin of HBC as lobular carcinoma, based on its growth pattern, cellular and nuclear characteristics and coexistence of lobular carcinoma *in situ* [2-7]. Eusebi *et al*. defined HBC solely as breast cancer with histiocytoid cells irrespective of origin [8]. Similarly Murali *et al*. defined HBC as breast carcinoma composed predominantly or exclusively of cells with foamy and/or granular cytoplasm [9]. A

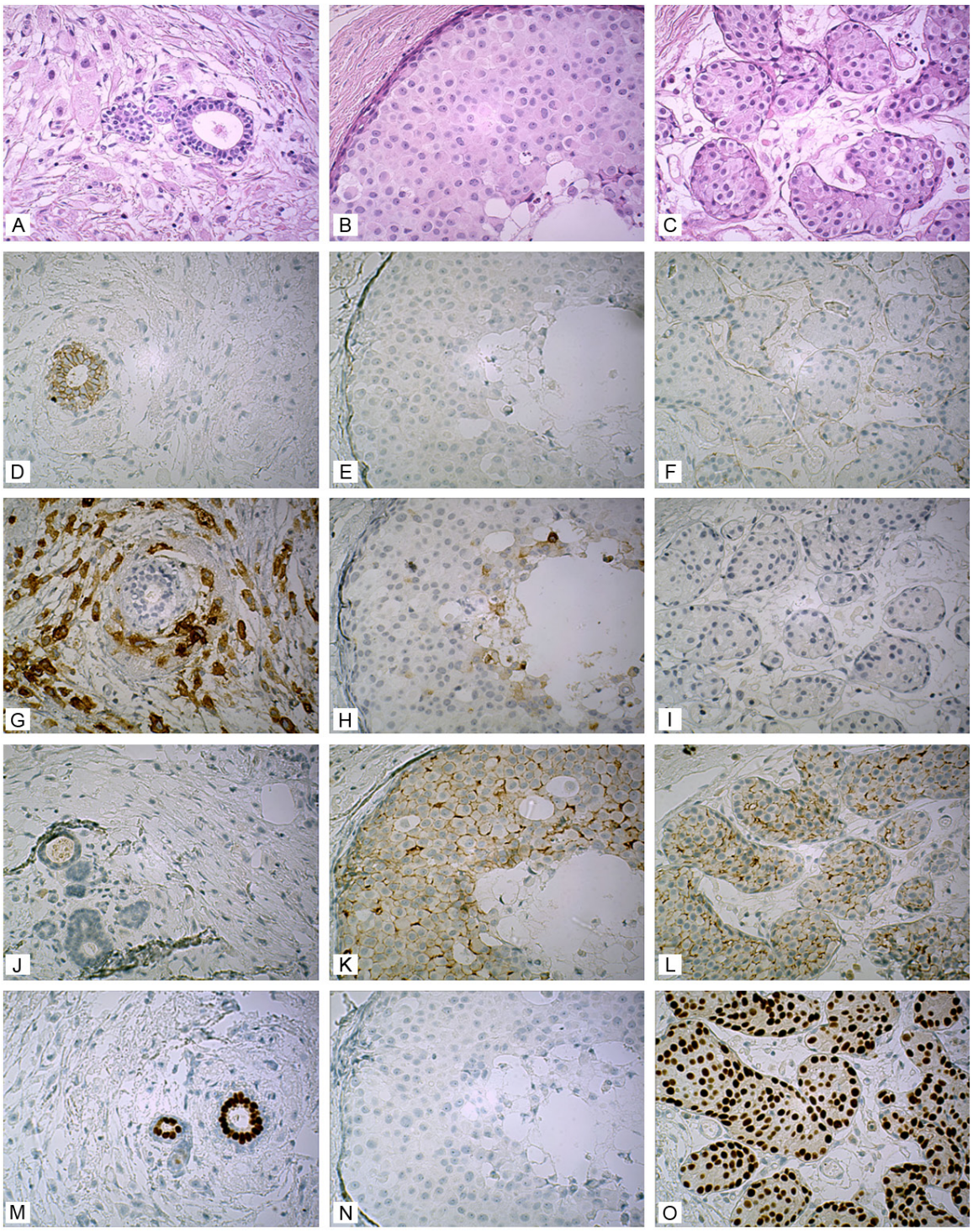

Figure 3. Immunohistochemical findings in histiocytoid breast carcinoma (HBC), normal breast epithelium, carcinoma *in situ* and atypical lobular hyperplasia. A, D, G, J, M: HBC and normal breast epithelium; B, E, H, K, N: Carcinoma *in situ*; C, F, I, L, O: Atypical lobular hyperplasia; A-C: H&E staining; D-F: E-cadherin; G-I: CEA; J-L: HER-2; M-O: ER. (Magnification, ×400).

later report by Yu *et al*. defined its histiocytoid morphological characteristics as having more than 10% tumor cells with small nuclei, inconspicuous nucleoli and granular to foamy cyto-

Table 1. Immunohistochemical patterns of differentially expressed marker proteins observed in histiocytoid breast carcinoma (HBC), carcinoma *in situ*, atypical lobular hyperplasia and normal breast epithelium

antibodies	HBC	carcinoma *in situ*	atypical lobular hyperplasia	normal breast epithelium
GCDFP-15	+	±	±	-
E-cadherin	-	-	- ~ ±	+
P120	-	±	- ~ ±	+
CEA	+	±	-	-
HER-2	-	2+	1+	-
ER	-	-	3+	3+
PR	-	-	2+	3+

-, negative; ±, weak positive; +, positive.

plasm with vacuoles or occasional intracytoplasmic vacuoles [10]. The apocrine nature of HBC has been based on immunohistochemical positivity for GCDFP-15 [3, 8]. Dixon *et al*. proposed the concept of a pleomorphic variant of invasive lobular carcinoma [11]. However, Kasashima *et al*. suggested it was a unique entity due to its poor prognosis and mucin expression compared to classical invasive lobular cancer [4].

In our case study, both masses displayed similar morphologic features and the morphological spectrum, from atypical hyperplasia and carcinoma *in situ* to invasive carcinoma, suggested a process of tumorigenesis. The invasive HBC cells displayed a uniform histiocytoid appearance with characteristics more similar to lobular carcinoma than to ductal carcinoma. These included an Indian filing and targetoid infiltration pattern, intracytoplasmic vacuoles, nuclei with finely dispersed chromatin, a single eosinophilic nucleolus, smooth finely contoured nuclear membranes and minimal mitotic activity. Furthermore, the HBC in this case study displayed characteristics that were common with several other forms of breast cancer, such as pleomorphic lobular carcinoma, carcinoma with signet ring-cell differentiation and carcinoma with apocrine differentiation. In agreement with Eusebi *et al*. [8], these observations indicated that HBC could reasonably be defined as unique variant of breast cancer with histiocytoid cells.

Immunohistochemistry comparisons showed that the invasive histiocyte-like cells, carcinoma *in situ*, atypical lobular hyperplasia and normal ductal epithelium displayed the same expression patterns for many of the selected epithelial markers, with positive reactivity for EMA, CK34βE12, CK7, AE1/AE3 and CAM5.2, and negative reactivity for CD68, S-100 and Vimentin. However, differences were observed for the following proteins, including gross cystic disease fluid protein-15, GCDFP-15, which is a putative marker for apocrine differentiation. Whereas GCDFP-15 was positive for the majority of invasive HBC cells with varying staining intensity, both carcinoma *in situ* and atypical lobular hyperplasia were weakly positive for GCDFP-15, and normal ductal epithelium was negative. This indicated that apocrine differentiation gradually increased during the process of tumorigenesis. The expressions of E-cadherin and P120, which are involved in mediating cell-cell adhesion, decreased from atypical lobular hyperplasia to carcinoma *in situ* and invasive carcinoma relative to normal ductal epithelium. This suggested loss of adhesion during tumorigenesis and loose tumor cellular cohesiveness, which is characteristic of lobular carcinoma. The expression pattern of the carcinoembryonic antigen, CEA, reflected an increase of CEA during the process of tumorigenesis, whereas the reactivity of the estrogen and progesterone receptors, ER and PR, exhibited decreased expression. Human epidermal growth factor receptor 2, HER-2, was weakly positive in carcinoma *in situ* and atypical lobular hyperplasia, but was negative in both invasive carcinoma and normal ductal epithelium. This is similar to the process of tumorigenesis observed in invasive ductal carcinoma. In summary, these changes in protein expression reflected a spectrum of tumorigenesis from normal epithelium to invasive carcinoma, which supports the proposition that HBC is a unique variant of invasive lobular carcinoma originating in the terminal duct.

Accurate diagnosis of HBC presents considerable difficulties due to its low incidence, histogenesis and cytodifferentiation of pleomorphic cells, and an immunophenotypic profile consistent with both lobular and ductal differentiation [12]. As such, it has been misdiagnosed as sclerosing inflammatory lesions, xanthomatous lesions, histiocytic lesions, granular cell tumor

and other forms of breast cancer including pleomorphic lobular carcinoma, lipid-rich carcinoma, carcinoma with signet ring cell differentiation and carcinoma with apocrine differentiation [2, 5, 10, 12-14]. Characteristics that may help pathologists reach the correct diagnosis include discovering tumor cells with increased cytological atypia, the presence of cytoplasmic vacuoles and secretions, and patterns of traditional invasive lobular carcinoma and/or lobular neoplasias. In addition, immunohistochemistry can be a valuable tool for confirming the epithelial nature of the cells [5].

Conclusion

In this study we have reported the first case of two HBC masses occurring simultaneously in one breast. Both tumors exhibited similar morphologic characteristics, including carcinoma *in situ* and atypical lobular hyperplasia, suggesting that they developed concurrently rather than as intramammary metastasis. Our findings have provided a unique insight into the morphology and tumorigenesis of HBC which may assist in future diagnoses and help classify of HBC.

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Written informed consent was obtained from the patient for publication of this case report and accompanying images.

Disclosure of conflict of interest

The authors declare no conflicts of interest.

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