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Invasive ductal carcinoma within borderline phyllodes tumor with lymph node metastases: A case report and review of the literature

DI WU[1], HAIPENG ZHANG[2], LIANG GUO[3], XU YAN[3] and ZHIMIN FAN[1]

Departments of [1]Breast Surgery, [2]Obstetrics and [3]Pathology, First Hospital of Jilin University, Changchun, Jilin 130021, P.R. China

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Abstract. Phyllodes tumor (PT) is a rare type of biphasic fibroepithelial neoplasm that may coexist with a breast tumor in rare cases. In the current study, a 52-year-old female presented with a left breast lump. Mammography and sonographic examination results suggested a diagnosis of malignant tumor. Histological analysis revealed a borderline PT with invasive ductal carcinoma (IDC) within the tumor. Due to the presence of a single micrometastasis in three of the sentinel lymph nodes, the patient underwent modified radical mastectomy. The excised tumor contained triple negative breast cancer; therefore, postoperative treatment included six cycles of chemotherapy and 25 cycles of radiotherapy. The patient exhibited no recurrence and no metastatic disease at the 23-month follow-up examination. Thus, the present study discussed the case of a female patient that presented with IDC within borderline PT and reviewed the literature on this rare type of neoplasm. Various types of breast carcinoma have been identified to coexist with PT in different masses; however, no standard therapeutic regimen has been established for the coexistence of PT and breast cancer in the same mass. The present study indicates that determination of an appropriate treatment strategy predominantly depends on the characteristics of the individual breast tumor.

Introduction

Phyllodes tumor (PT) is a rare type of biphasic fibroepithelial neoplasm that accounts for <1% of all breast tumors and represents 2-3% of fibroepithelial neoplasms (1,2) with a peak age of incidence of 45-49 years (3,4). According to the standards set by the World Health Organization (WHO), PTs may be classified as benign, borderline or malignant based on the degree of stromal cell atypia, mitotic status, degree of stromal overgrowth, tumor necrosis and appearance of tumor margins (5). PTs are predominantly benign with only ~10% identified as malignant. The majority of malignant transformation of PTs typically occurs in the stromal compartment and rarely in the epithelial compartment. Breast carcinoma within PT accounts for 1-2% of all PTs (6). Surgery is considered the standard treatment for PT (7). Invasive ductal carcinomas (IDC) of the breast accounts for 80% of all breast cancers, and these tumors demonstrate a worse survival rate than invasive lobular carcinoma (8), with overall 5-year survival rates of 84.1 and 85.6%, respectively (9). An IDC that is incidentally found within a borderline PT has been reported only once before in the literature (10). The current study presents a case of IDC within a borderline PT, and reviews 32 cases of breast carcinoma within a PT that have been reported in the literature.

Case report

In July 2012, a 52-year-old female presented to the Department of Breast Surgery, First Hospital of Jilin University (Changchun, China) with a firm, palpable, irregularly-shaped lump with an ill-defined margin in the outer upper quadrant of the left breast. The lump, which was originally identified by the patient 6 months previously, had increased in size from 1.5x1.0 cm at presentation to 2.5x2.0 cm after 3 months. Physical examination revealed that the tumor did not adhere to or invade the overlying skin or the thoracic wall. Enlarged axillary lymph nodes were not identified upon physical examination. Mammography imaging revealed a high-density mass with a diameter of 2.5 cm and an irregular margin (Fig. 1), and sonographic examination demonstrated a partially ill-defined hypoechoic mass with a diameter of 2.1 cm (Fig. 2). A core needle biopsy revealed borderline or malignant PT with a breast carcinoma component.

The diagnosis was determined by analysis of the core needle biopsy, as follows. The tumor was well-circumscribed and 3.0x2.5x1.2 cm in size, according to macroscopic examination. The mitotic count in the most active area was 2-4 mitoses per 10 high-powered fields. Based on an increase in the number of mitotic figures and according to the WHO 2003 grading system (11), the tumor was classified as a borderline PT. IDC was also observed in a focal area of spindle cells (Fig. 3). The results of MaxVision™

Correspondence to: Dr Zhimin Fan, Department of Breast Surgery, First Hospital of Jilin University, 71 Xinmin Street, Changchun, Jinlin 130021, P.R. China
E-mail: fanzhimn@163.com

Key words: phyllodes tumor, breast cancer, coexist, diagnosis, treatment

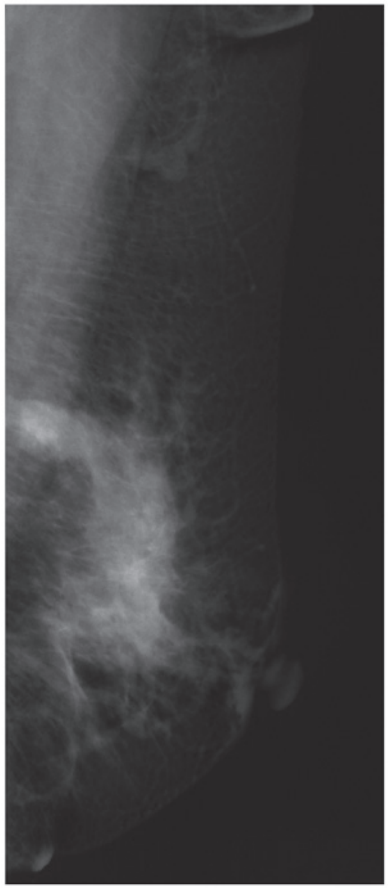

Figure 1. Mammography image revealing a high-density mass with an irregular margin and a diameter of 2.5 cm in the outer upper quadrant of the left breast. The mass was determined as grade 4, according to the Breast Imaging Reporting and Data System classification.

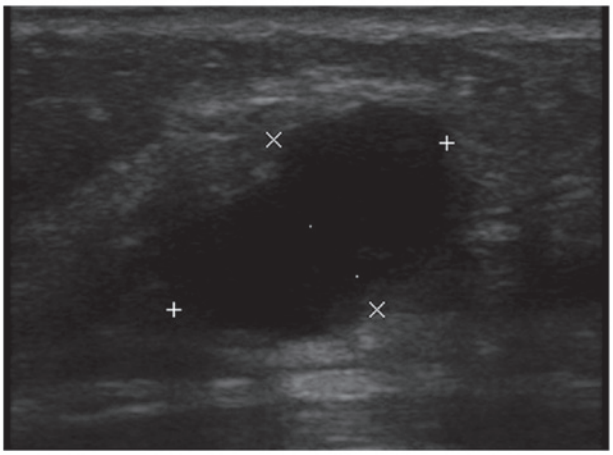

Figure 2. Sonographic examination revealing an irregular, partially ill-defined, hypoechoic mass with a diameter of 2.1 cm. The mass was diagnosed as grade 4B, according to the Breast Imaging Reporting and Data System classification.

immunohistochemical staining (Fuzhou Maixin Biotechnology Development Co., Ltd., Fuzhou, China) of the IDC cells were as follows: Estrogen receptor negative; progesterone receptor negative; HER-2 negative; Ki-67 index, 30%; cytokeratin (CK) 5/6 positive; vimentin positive; and pan-CK positive (Fig. 4).

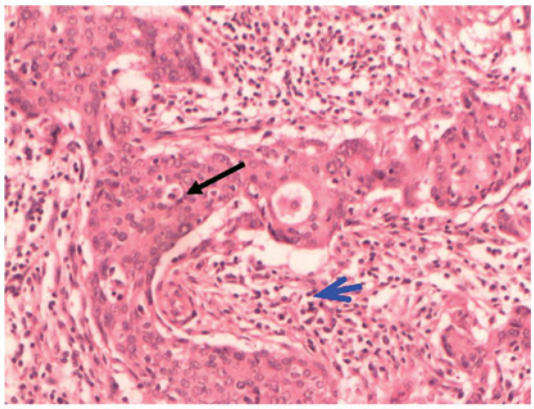

Figure 3. Invasive ductal carcinoma (black arrow) detected within a region of spindle cells (blue arrow) in the phyllodes tumor (hematoxylin and eosin stain; magnification, x100).

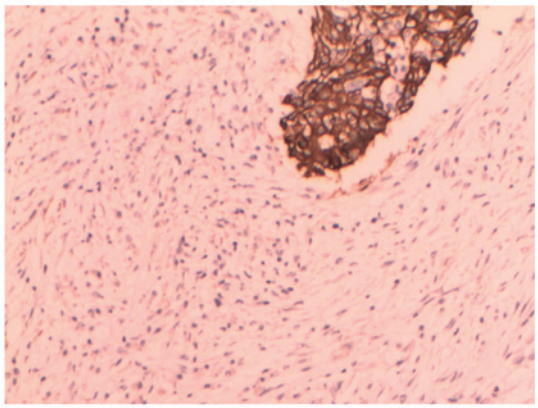

Figure 4. Immunohistochemical staining of the invasive ductal carcinoma, revealing positive pan-cytokeratin expression (stain, hematoxylin and eosin; magnification, x100).

Considering the diagnosis of IDC within a borderline PT, a simple mastectomy and sentinel lymph node biopsy (SLNB) were performed on July 10, 2012. Intraoperative frozen pathological analysis of 3 of the sentinel lymph nodes (SLNs) identified one micrometastasis. An axillary lymph node dissection and subsequent pathological examination did not reveal metastasis in any of the 18 nodes tested. The patient underwent six cycles of chemotherapy cycled every 21 days, consisting of 75 mg/m^2 paclitaxel, 75 mg/m^2 pirarubicin and 500 mg/m^2 cyclophosphamide, all administered on day 1. In addition, the patient underwent seven weeks of radiotherapy (25 cycles at 5,000 cGy; 200 cGy, each treatment). The tumor did not recur and no metastasis was observed during the first 23 months subsequent to treatment.

Discussion

PT may coexist with breast cancer in three situations. It may coexist in the bilateral breast, for example with IDC in one breast and a malignant PT in the other breast (12). PT has also been detected in the ipsilateral breast, such as IDC in the upper outer quadrant of the left breast and malignant PT in the lower outer quadrant of the left breast (13). Finally, PT may coexist with breast cancer in the same mass, as occurred in the current

Table I. Occurrence of breast carcinoma within PT.

No.	First author (Ref.)	Year	Age, years	Surgery	AxDs	PT		Breast carcinoma		LNI, n	Survival status	Follow-up time, months
						Type	Diameter, cm	Type	Diameter, cm			
1	Leong *et al* (26)	1980	49	LoEx	(-)	Benign	6.0	LCIS	NA	NA	NA	NA
2	Leong *et al* (26)	1980	51	MX	(+)	Benign	4.0	ITC	NA	(-)	Alive	21
3	Cole-Beuglet *et al* (14)	1983	55	LoEx	(-)	Benign	3.5	DCIS + LCIS	NA	NA	NA	NA
4	Cole-Beuglet *et al* (14)	1983	60	LoEx	(-)	Benign	3.0	IDC	NA	NA	NA	NA
5	Grove *et al* (27)	1986	71	MX	(+)	Benign	19.0	DCIS	2.0	(-)	Alive	4
6	Ishida *et al* (10)	1984	41	MX	(-)	Benign	5.6	IDC	Focal	NA	Alive	30
7	Ward *et al* (28)	1986	55	MX	NA	Benign	4.0	LCIS	Focal	NA	NA	NA
8	Knudsen *et al* (15)	1987	71	MX	(+)	Benign	7.0	DCIS + LCIS	Multi-focal	(-)	Alive	6
9	Yasumura *et al* (29)	1988	47	MX	(+)	Benign	13.0	IDC	NA	(-)	Alive	66
10	Kodama *et al* (30)	2003	47	MX	(-)	Benign	17.0	LCIS	Focal	NA	Alive	108
11	Parfitt *et al* (16)	2004	26	LoEx	(+)	Benign	3.3	DCIS + IDC	NA	(+)4/13	Alive	36
12	Ramdass *et al* (31)	2006	69	NA	NA	Benign	NA	SCC	NA	NA	NA	NA
13	Yamaguchi *et al* (1)	2008	54	MX	(-)	Benign	15.0	DCIS	Focal	NA	Alive	12
14	Nio *et al* (23)	2011	53	LoEx	(-)	Benign	3.5	DCIS	0.5	NA	Alive	24
15	Shirah *et al* (17)	2011	49	LoEx		Benign	4.8	LCIS + ILC	0.2	NA	NA	NA
16	Deodhar *et al* (32)	1997	51	LoEx	(-)	Borderline	14.0	DCIS	Focal	NA	NA	NA
17	Kuo *et al* (19)	2010	26	MX	SLNB	Borderline	10.0	IDC	2.5	ITC	Alive	15
18	Quinlan-Davidson *et al* (18)	2011	53	LoEx	SLNB	Borderline	6.5	ITC + LCIS	2.4	(-)	NA	NA
19	Present case	2014	52	MX	(+)	Borderline	3.0	IDC	Focal	(+)1/21	Alive	23
20	Seemayer *et al* (33)	1975	27	MX	(-)	Malignant	6.0	DCIS	Focal	NA	NA	NA
21	Klausner *et al* (34)	1983	60	MX	(+)	Malignant	4.0	IDC	Focal	(-)	NA	NA
22	Hunger *et al* (35)	1984	57	MX	(+)	Malignant	15.5	SCC	NA	(-)	NA	NA
23	Schwickerath *et al* (7)	1992	47	MX	(+)	Malignant	2.0	DCIS	NA	(-)	NA	NA
24	Padmanabhan *et al* (2)	1997	47	MX	(+)	Malignant	7.5	LCIS	Focal	(-)	Alive	6
25	Nishimura *et al* (24)	1998	80	LoEx	(-)	Malignant	10.5	DCIS	NA	NA	Deceased	3
26	Alò *et al* (36)	2001	39	MX	NA	Malignant	9.0	DCIS	NA	NA	NA	NA
27	Lim *et al* (25)	2005	45	MX	(-)	Malignant	12.0	DCIS	0.6	NA	Deceased	108
28	Nomura *et al* (37)	2006	75	MX	(-)	Malignant	3.5	DCIS	NA	NA	Alive	32
29	Sugie *et al* (20)	2007	54	MX	(+)	Malignant	8.0	SCC	NA	(-)	Deceased	40
30	Korula *et al* (21)	2008	51	MX	(+)	Malignant	21.0	DCIS	NA	(+)2/12	Alive	11
31	Macher-Goeppinger *et al* (38)	2010	70	MX	(+)	Malignant	6.0	IDC	2.5	(-)	NA	NA
32	Abdul Aziz *et al* (6)	2010	43	LoEx	(-)	Malignant	3.5	ITC + DCIS	0.2	NA	Alive	12
33	Choi *et al* (22)	2012	62	MX	(+)	Malignant	10.0	ICC	6.0	(-)	Alive	24

AxDs, axillary dissection; DCIS, ductal carcinoma *in situ*; ICC, invasive cribriform carcinoma; IDC, invasive ductal carcinoma; ILC, invasive lobular carcinoma; ITC, invasive tubular carcinoma; LCIS, lobular carcinoma *in situ*; LNI, lymph node involvement; LoEx, local excision; MX, mastectomy; NA, not available; PT, phyllodes tumor; Ref., reference; SCC, squamous cell carcinoma.

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case. Breast carcinoma arising within PT is extremely rare. A literature search of the PubMed database (www.pubmed.com) was performed using the following search terms: 'breast cancer with phyllodes tumor' and 'coexistence of breast cancer and phyllodes tumor'. A total of 1,593 studies were retrieved. Using the following criteria, it was determined that <40 cases of breast carcinoma arising within PT have previously been reported in the literature (Table I) (1,2,7,8,10,11,14-38). Inclusion criteria: i) published between 1974 and 2013; ii) English language; and iii) PT coexisting with breast cancer in the same tumor. Exclusion criteria: i) PT and breast cancer coexisting in the bilateral breast; ii) PT and breast cancer coexisting in the ipsilateral breast in different tumors; iii) no detailed pathological results; and iv) only the abstract available in English, full-text in a different language. The age of the patients with a coexistent breast carcinoma and PT ranged between 26 and 80 years, with a median age of 52 years. The reported breast carcinoma subtypes included *in situ* and invasive lobular and ductal (no specific type) carcinoma, invasive tubular carcinoma, squamous cell carcinoma and invasive cribriform carcinoma. Malignant epithelial elements were reported in all types of PT. Breast carcinoma was most commonly reported in malignant (n=14) and benign (n=15) PTs, but rarely in borderline PTs (n=4, including the present case). Of the three cases of borderline PTs reported (excluding the present case), Kuo *et al* presented the case of a patient with a painless mass in the left breast, which had been present for 4 years. Following rapid growth of the tumor, the patient was diagnosed with invasive ductal carcinoma arising within a phyllodes tumor with isolated tumor cells identified in the sentinel lymph node (19). Mastectomy and sentinel lymph node biopsy were performed followed by hormonal therapy (goserelin acetate and tamoxifen), adjuvant chemotherapy (5-fluorouracil, epirubicin and cyclophosphamide) and reconstructive surgery. No tumor recurrence was reported during the 15 month follow-up period. Quinlan-Davidson *et al* (18) reported the case of a patient with a painless mass in the right breast that had been present for several years. Following two years of rapid growth of the mass the patient was diagnosed with borderline phyllodes tumor with an incidental invasive tubular carcinoma and lobular carcinoma *in situ* component. An excisional biopsy was performed and subsequently the patient underwent a re-excision for margin safety and a sentinel lymph node biopsy, which revealed that all three sentinel lymph nodes were negative for malignancy. In addition, Deodhar *et al* (32) reported a case of borderline phyllodes tumor with a ductal carcinoma *in situ* (DCIS) component. However, the outcome of the patient was not reported. Coexisting breast carcinoma within PTs more commonly demonstrated a ductal phenotype (IDC, n=7; DCIS, n=15) compared with a lobular phenotype (ILC, n=1; lobular carcinoma *in situ*, n=7). A pure carcinoma *in situ* element was identified in 17 cases and was determined to be invasive in the other 16 cases. In addition, 6 cases were found to possess two types of malignant epithelial elements (6,14-18). The PT size was not described in one case and the mean diameter of the tumor was 7.9±5.3 cm. Yamaguchi *et al* (1) reported 7 cases of DCIS in PTs with a mean tumor size of 11.9 cm (15). Nio *et al* (23) reported that the mean diameter of breast carcinoma within PTs was 8.0 cm (14). The carcinoma size of the present case could not be measured.

In the previously reported literature, 10 cases were treated with local excision and 23 cases were treated with mastectomy. Of the 16 cases that received axillary surgery, three cases exhibited axillary lymph node metastasis and one possessed an isolated tumor cell in the SLN. As there is no standard adjuvant treatment strategy for this type of disease, a variety of systemic therapies were applied to the various cases. In total, 6 cases received chemotherapy with various regimens (16,19-23), 5 cases received radiotherapy (13,16,18,20), and 4 cases received endocrine therapy, 3 of which received tamoxifen (1,16,21) and 1 received tamoxifen and goserelin (19). Patient outcomes were described in 19 cases. The follow-up time was between 3 and 108 months. In total, 16 patients were alive at the end of last follow-up. Distance metastasis occurred in the lung in 2 cases at 3 and 32 months subsequent to surgery, respectively (20,24). Similar to the current case, Kuo *et al* (19) and Parfitt *et al* (16) reported the combination of surgery, chemotherapy and radiotherapy for patients with lymph node metastasis who present breast carcinoma within PT. In addition, 3 cases succumbed to the disease, 3, 40 and 108 months subsequent to surgery, respectively (20,24,25) (Table I).

In summary, the present study reports a rare case of IDC within a borderline PT. The imaging experiments performed lacked specificity. Instead, histology and immunohistochemistry are the golden standard for diagnosing this type of disease. The combination treatment of surgery, chemotherapy and radiotherapy was effective in the current case. Various types of breast carcinoma have been identified to coexist with PT in different masses; however, no standard therapeutic regimen has been established for the coexistence of PT and breast cancer in the same mass. The determination of an appropriate treatment strategy predominantly depends on the characteristics of the individual breast tumor, such as the hormone receptor status, HER-2 status and axillary lymph node metastasis status. Thus, future cases should undergo detailed analysis of tumor characteristics with reference to the molecular subtype and clinical pathological characteristics in order to select the optimal treatment strategy for breast cancer within phyllodes tumors.

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