Case Report

Malignant Phyllodes Tumour with Liposarcomatous Differentiation, Invasive Tubular Carcinoma, and Ductal and Lobular Carcinoma In Situ: Case Report and Review of the Literature

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1. Introduction

Phyllodes tumors (PTs) of the breast are uncommon biphasic fibroepithelial neoplasms that account for <1% of all breast tumours. Most PTs are benign and carry a risk of local recurrence whereas malignant PTs have a 13% risk of haematogenous metastasis [1]. The distinction between benign, borderline and malignant PT is based on the assessment of a number of histological features including infiltrative margin, stromal overgrowth, stromal atypia, cellularity, and mitotic activity. However, while histological features are helpful, they are not accurate predictors of tumour behavior, and no single parameter is reliable in all cases [2].

PTs are believed to arise from intralobular or periductal stroma and may arise de novo or from pre-existing fibroadenomas [2]. Up to 30% of PTs show malignant transformation, most often in the form of malignant transformation of the stroma, which usually shows fibrosarcomatous differentiation and rarely heterologous sarcomatous elements. Malignant transformation of epithelial elements is very rare with only 38 cases reported in the literature. Carcinoma is reported in malignant (n = 19), benign (n = 16) and in borderline PTs (n = 3) with invasive carcinoma (n = 18) and pure in situ carcinoma (n = 19) recorded in equal frequency. Carcinoma is more commonly found within the confines of benign PTs; whereas it is more often found surrounding the PT or in the contralateral breast in malignant PTs. Previous radiotherapy treatment is reported in only two cases. The aetiology of co-existing carcinoma is unclear but the rarity of previous radiotherapy treatment suggests that it is incidental. This case highlights the diverse pathology that can occur with PTs, which should be considered when evaluating pathology specimens as they may impact on patient management.
2. Case Report

A 43-year-old woman presented with a palpable lump in the central aspect of the left breast below the nipple. The lump was present for five months. It had increased in size over that time and was tender. Mammography showed a relatively well-circumscribed 3.4 cm mass in the lower central aspect of the breast (Figure 1). An ultrasound-guided biopsy was performed but no axillary lymphadenopathy was identified when the specimen was examined histologically. The tumour showed the characteristic enhanced intracanalicular growth pattern with leaf-like projections into dilated cysts, extensive stromal overgrowth, and marked stromal hypercellularity (Figure 2(a)). Frankly malignant stromal features including nuclear pleomorphism and a high mitotic count (19 per 10 high power fields) were seen (Figure 2(b)). In many areas, liposarcomatous differentiation, characterized by pleomorphic lipoblasts, was present (Figure 2(c)). The margins of the PT were focally infiltrative. The epithelial component within the PT exhibited hyperplasia of usual type as well as foci of DCIS, intermediate grade, with cribriform and solid growth patterns, without necrosis (Figure 2(d)). A small invasive carcinoma, 2 mm in size, was present at the periphery of the PT close to the deep margin of the specimen (Figure 3(a)). This was composed of well-formed tubes that lacked a myoepithelial layer (Smooth Muscle Heavy Chain Myosin and p63 negative) and was regarded as a grade 1 tumour [3] although it was too small to grade accurately based on the absence of sufficient high power fields for scoring of mitotic activity. Oestrogen receptor was strongly expressed and Her-2 was negative. The invasive tumour was adjacent to a small duct with morphological features of low-grade DCIS but there was no morphological transition between invasive carcinoma and the stromal or epithelial components of the adjacent PT. Multiple scattered foci of LCIS were also present peripheral to the PT, confirmed by downregulation of E-Cadherin staining (Figures 3(b) and 3(c)). The scattered nature of the LCIS precludes accurate measurement of its size.

The cavity re-excision specimen (190 g, 98 × 97 × 47 mm) included skeletal muscle and showed no residual PT. A single focus of DCIS, high-nuclear grade with comedonecrosis and microcalcification, 3 mm in size, was present within 1 mm to the medial margin (Figure 3(d)). Multiple foci of LCIS were also noted.

4. Discussion and Review

Metaplastic change within PTs is uncommon. In the largest series of PTs reported, stromal metaplasia was present in only 11 of 335 cases, and malignant transformation of epithelium in the form of DCIS and LCIS was seen in only two cases [17]. Stromal changes included adipose and chondromyxoid elements and were seen in benign and borderline PTs whereas malignant heterologous elements were reported in malignant PTs. The latter was most commonly in the form of liposarcomatous differentiation [17, 20, 24, 30, 33, 34], which does not equate with more aggressive clinical behavior [30, 35]. Other forms of heterologous change are reported in PTs including osteosarcoma, rhabdomyosarcoma, leiomyosarcoma, rhadomyosarcoma, and angiosarcoma [17, 36]. Epithelial change in the form of usual-type epithelial hyperplasia is well recognized in PTs [17] but epithelial metaplasia is uncommon. Apocrine and squamous changes can occur but malignant epithelial transformation, as reported in the present case, is exceptionally rare. This case adds to the literature of 38 cases in 31 reports [1, 4–33] of carcinoma arising either within and/or in association with PT (Table 1). It demonstrates the range of changes

Figure 1: Mammogram of the left breast. A relatively well-circumscribed mass was present in lower central aspect of the breast.

Figure 2 Pathology Research International
| Report                          | Age | PT type | Size (mm) | Associated carcinoma | Location of carcinoma relative to PT | Comment                                      | Outcome                        |
|--------------------------------|-----|---------|-----------|----------------------|--------------------------------------|---------------------------------------------|---------------------------------|
| Yamaguchi et al. [4]           | 54  | BPT     | 150       | DCIS                 | Within                               | Complex carcinoma with clear cell, secretory and squamous differentiation | AW at 11 months                |
| Ramdass and Dindyal [5]        | 69  | BPT     | NS        | IDC                  | Within                               | NA                                          | NA                             |
| Parfitt et al. [1]             | 26  | BPT     | 33        | DCIS                 | Within                               | Metastatic adenocarcinoma in 4 of 13 LN     | AW at 36 months                |
| Kodama et al. [6]              | 47  | BPT     | 170       | DCIS                 | Within                               | Lump present for 12 years before treatment | AW at 108 months               |
| De Rosa et al. [7]             | 77  | BPT     | 50        | IDC                  | Ipsilateral                          | Mild atypia in stroma with occasional mitoses | AW at 10 months                |
| Yamasura et al. [8]            | 47  | BPT     | 130       | DCIS, LCIS           | Within                               | History of irradiation to ovaries for climacteric menstrual disorders | AW at 66 months                |
| Knudsen and Ostergaard [9]     | 71  | BPT     | 70        | DCIS, LCIS           | Within                               | NA                                          | NA                             |
| Grove and Deibjerg Kristensen  | 71  | BPT     | 190       | DCIS                 | Within                               | NA                                          | NA                             |
| Christensen et al. [11]        | 42–58 | BPT   | 10–20     | IDC                  | Ipsilateral                          | IDC in close relation to a recurrent PT     | RIP after 3 months from metastatic carcinoma |
| Ishida et al. [12]             |     | BPT     | 56        | Papillotubular       | Within                               | NA                                          | AW at 30 months                |
| Stone-Tolin et al. [13]        | 59  | BPT/NS  | 220       | IDC                  | Contralateral                        | Recurring PT and FA over 36-year period     | AW at 15 months                |
| Leong and Meredith [14]        | 47  | BPT     | 40        | ITC                  | Within                               | Three recurrences of BPT, LCIS in second recurrence and ITC in third recurrence | AW at 21 months                |
| Richards and WAY [15]          | 37  | BPT     | 70        | IDC**                | Ipsilateral                          | Separate tumour nodules. Metastatic carcinoma in LN | RIP after 9 months from metastases¹ |
| Lester and Stout, [16]         | 40  | BPT     | 14        | NS                   | Ipsilateral                          | PT found in mastectomy specimen performed for carcinoma | AW at 144 months               |
| Tan et al. [17]                | NA  | NS      | NA        | DCIS                 | Ipsilateral                          | NA                                          | NA                             |
| Tan et al. [17]                | NA  | NS      | NA        | LCIS                 | Ipsilateral                          | NA                                          | NA                             |
| Deodhar et al. [18]            | 51  | BLPT    | 140       | DCIS                 | Within, Ipsilateral                  | Recurrent PT associated with DCIS in adjacent breast within 12 months of initial diagnosis | RIP after 36 months from unrelated cause |
| Christensen et al. [11]        | 42–58 | BLPT | NS        | DCIS                 | Within, Ipsilateral                  | Metastatic carcinoma in 2 of 12 lymph nodes | RIP after 12 months from metastatic PT |
| Christensen et al. [11]        | 42–58 | BLPT | NS        | DCIS                 | Ipsilateral                          | Metastatic carcinoma in 2 of 12 lymph nodes | AW at 11 months                |
| Korula et al. [19]             | 51  | MPT     | 210       | DCIS                 | Within, Ipsilateral                  | Metastatic carcinoma in 2 of 12 lymph nodes | AW at 11 months                |
| Kefeli et al. [20]             | 26  | MPT     | 45        | IDC                  | Ipsilateral                          | Liposarcomatous and chondrosarcomatous stroma in PT; history of osteosarcoma and radiotherapy | RIP after 12 months³ |
Table 1: Continued.

| Report                  | Age | PT type | Size (mm) | Associated carcinoma | Location of carcinoma relative to PT | Comment                                                                 | Outcome                                      |
|-------------------------|-----|---------|-----------|----------------------|--------------------------------------|-------------------------------------------------------------------------|----------------------------------------------|
| Sugie et al. [21]       | 54  | MPT     | 60        | IDC, DCIS            | Within                               | Carcinoma showed squamous differentiation                              | RIP after 40 months from metastatic PT       |
| Merck et al. [22]       | NS  | MPT     | NS        | IDC                  | Contralateral                        |                                                                         | AW at 32 months                              |
| Nomura et al. [23]      | 75  | MPT     | 35        | DCIS                 | Within                               |                                                                         | AW at 32 months                              |
| Lim and Tan [24]        | 45  | MPT     | 120       | DCIS                 | Within                               | Liposarcomatous differentiation in PT; two FAs in contralateral breast | RIP after 108 months from unrelated cause    |
| Tan et al. [17]         | NS  | MPT     | NS        | DCIS                 | Within                               | PT recurred after 40 months with metastases                            | RIP after 51 months from metastases         |
| Auerbach [25]           | 69  | MPT     | NS        | IDC                  | Ipsilateral                          |                                                                         |                                              |
| Gebrim et al. [26]      | 58  | MPT     | 300       | ILC                  | Contralateral                        | ILC within FA in contralateral breast                                  | AW at 84 months                              |
| Nishimura et al. [27]   | 80  | MPT     | 105       | DCIS                 | Within                               | Osteosarcomatous, rhabdomyosarcomatous, fibrosarcomatous stroma in PT  | RIP after 3 months from metastases          |
| Padmanabhan et al. [28] | 47  | MPT     | 75        | LCIS                 | Within                               | Liposarcomatous and fibrosarcomatous stroma in PT                      | AW at 6 months                               |
| Kasami et al. [29]      | 47  | MPT     | NS        | ILC                  | Contralateral                        | 46XX/46XY mosaic karyotype; three sisters with breast carcinoma. Recurrent PT at autopsy | NA                                           |
| Powell and Rosen [30]   | 17–71 | MPT  | 8–100     | DCIS                 | Ipsilateral                          | Liposarcomatous stroma in PT                                           | NA                                           |
| Powell and Rosen [30]   | 17–71 | MPT  | 8–100     | LCIS                 | Contralateral                        | Liposarcomatous stroma in PT                                           | NA                                           |
| Powell and Rosen [30]   | 17–71 | MPT  | 8–100     | IDC                  | Ipsilateral, Contralateral           | Initially BPT, recurred as MPT with liposarcomatous differentiation in PT; Ipsilateral DCIS; Contralateral IDC | NA                                           |
| Morimoto et al. [31]    | 49  | MPT     | 110       | LCIS                 | Contralateral                        | LCIS within contralateral FA                                            | AW at 132 months                             |
| Christensen et al. [11] | 42–58 | MPT  | LCIS      | Ipsilateral          |                                      |                                                                         | RIP after 12 months from metastatic PT        |
| Huntrakoon [32]         | 31  | MPT     | 90        | IDC                  | Ipsilateral                          | Liposarcomatous differentiation in PT. Contralateral MPT after initial mastectomy | AW at 24 months                             |
| Seemayer et al. [33]    | 27  | Stromal sarcoma*** | 60 | DCIS | Within | Liposarcomatous differentiation in PT. DCIS within PT. IDC and LCIS in ipsilateral breast. Previous radiotherapy for lymphoma. | AW at 12 months                             |
| Current case            | 43  | MPT     | 35        | IDC, LCIS            | Within, Ipsilateral                  |                                                                         |                                              |

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* Category of PT not specified in original report, interpreted as benign PT.

** Classified as scirrhous adenocarcinoma.

*** Sarcomatous stroma with liposarcomatous differentiation, tumour lacked circumscription and features of PT, for example, leaf-like structures were not present.

† Metastatic component (sarcoma versus carcinoma) not specified.

‡ Cause not specified.

∞ Category of PT not specified.

AW: alive and well; BPT, benign PT; BLPT, borderline PT; DCIS, ductal carcinoma in situ; FA, fibroadenoma; IDC, invasive ductal carcinoma; ILC, invasive lobular carcinoma; ITC, invasive tubular carcinoma; LCIS, lobular carcinoma in situ; LN, lymph node; MPT, malignant PT; NA, not available; NS, not specified.
that can be seen in association with a PT, including both liposarcomatous stroma and DCIS within the tumour and DCIS, LCIS, and invasive carcinoma in the peritumoural ipsilateral breast.

Malignant epithelial elements are reported in all categories of PT. In situ and invasive carcinoma may involve the tumour itself and/or coexist with a PT elsewhere in the same or contralateral breast. Carcinoma is most commonly reported \((n = 19)\) in malignant PTs. In the malignant PT category, carcinoma occurred more frequently in the ipsilateral \([11, 20, 25, 30, 32]\) or contralateral \([22, 26, 29–31]\) breast rather than within the confines of the PT \((n = 7)\) \([17, 21, 23, 24, 27, 28, 33]\). Coexisting carcinoma in malignant PTs is more commonly ductal (invasive ductal carcinoma, \(n = 6\); DCIS, \(n = 10\)) than lobular phenotype (invasive lobular carcinoma, \(n = 2\); LCIS, \(n = 4\)) \([11, 17, 19–33]\). Heterologous stroma, most often liposarcomatous differentiation, was common in malignant PTs where carcinoma was also found \((n = 8, 47\%)\) \([20, 21, 24, 27, 30, 33]\). From the available data, five patients with malignant PTs with coexisting carcinoma died from metastatic PT, between three months to 51 months after diagnosis \([11, 20, 21, 25, 27]\), and one patient had metastatic carcinoma in two lymph nodes \([19]\).

Carcinoma is less common in benign PTs compared with malignant PTs, given the higher prevalence of the former. Coexistent carcinoma is reported in 16 benign PTs (including four of unspecified malignant potential) \([7, 13, 17]\) and in three of these cases it was only seen in a recurrence of a benign PT \([11, 13, 14]\). Carcinoma was found more commonly within the benign PT \((n = 10)\) \([1, 4–6, 8–10, 12, 14, 17]\) rather than peripheral to it in the ipsilateral \((n = 5)\) \([7, 11, 15–17]\) or contralateral breast \((n = 1)\) \([13]\). The majority of these carcinomas \((n = 10)\) were invasive, with or without an in situ component and most were ductal NST type \((n = 6)\) \([1, 7, 8, 11, 13, 15]\) with individual reports of invasive lobular \([6]\), papillotubular \([12]\), and tubular carcinoma \([14]\). One case had both invasive squamous carcinoma and invasive ductal carcinoma showing clear cell, secretory, and squamous differentiation \([5]\). Two patients died from breast disease \([11, 15]\), one of which had metastatic carcinoma in lymph nodes \([15]\). Another patient had metastatic carcinoma in four lymph nodes but remained alive and well at follow-up \([1]\).

There are only three reports of carcinoma (DCIS) arising in association with borderline PT. Two patients had DCIS both within the PT and in the ipsilateral breast \([11, 18]\), one
of whom died within three years from unrelated causes. In the other case, DCIS occurred in the ipsilateral breast at the time of diagnosis of a recurrent PT and death occurred from metastatic PT one year after the recurrence [18].

The molecular events involved in transformation and progression of PTs are largely unknown, and the rarity of coexisting epithelial malignancy makes it difficult to draw conclusions about the aetiopathological association between the carcinoma and PT in these cases. Genetic aberrations have been consistently demonstrated in PTs with increasing frequency from benign to borderline to malignant PTs. Most studies to date focused on stromal alterations and showed recurrent copy number gains and losses at +1q, −13q, −6q, +5, and −10p [37–39]. Where epithelium was evaluated separately, distinct molecular alterations were demonstrated in the Wnt2-APC-B-catenin pathway, and a role was postulated for both stroma and epithelium in the neoplastic process [40, 41]. It is unclear, however, if the malignant transformation of epithelium results from stromal-epithelial interactions within the PT or if it represents cancerisation of a PT by carcinoma arising in the duct system peripheral to the PT. The latter may play a role in cases where carcinoma is present within the PT as well as peripheral to it in the ipsilateral breast. The finding of carcinoma in benign, borderline, and malignant PT and within fibroadenomas suggests that it is unlikely to be directly related to the number of genetic aberrations in the different categories of PT. A role of exogenous carcinogen exposure in malignant transformation merits consideration as an etiological agent because two patients [10, 20] in addition to the present case had a history of previous radiation. In all cases the radiotherapy field was remote from the breast which suggest that it is likely to be incidental.

The present case taken together with those in the literature demonstrates the diverse pathology that can be found with PTs, both within the tumour and in the surrounding and/or contralateral breast. The distinction between a malignant PT with coexisting carcinoma and a metaplastic carcinoma or carcinosarcoma should be considered in the diagnosis as these entities are managed differently and the distinction affects patient outcome. Carcinosarcomas have mixed malignant epithelial and stromal components with the latter showing no reactivity for epithelial immunohistochemical markers. While the present case fulfils these criteria, the characteristic leaf-like structure with malignant heterologous differentiation favours a diagnosis of malignant PT.
with coexisting carcinoma rather than a true carcinosarcoma. Carcinomas coexisting with PTs are generally diagnosed incidentally on the wide local excision, and the prognosis is dictated by the category of PT. In the present case, the malignant PT and not the carcinomatous elements will have the greatest impact on prognosis. However, the presence of coexistent carcinoma must be taken into account in management decisions, especially for benign and borderline PTs. Wider adequacy of excision of carcinoma, as in this case, and lymph node sampling should be considered.

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