

## Synchronous fibroepithelial tumors and carcinoma of the breast

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### Abstract

**Introduction:** Fibroadenoma and phyllodes tumor are fibroepithelial neoplasms of the breast composed of proliferating mammary epithelial and stromal tissues. It is very rare for infiltrating ductal carcinoma to arise within or be associated with a phyllodes tumor or a fibroadenoma.

**Methods and Material:** Over a period of ten years, all the breast carcinoma cases from the departmental archives were reviewed.

**Results:** Nine cases of synchronous fibroepithelial tumors with infiltrating carcinoma of the ipsilateral breast were reported. In four cases, the carcinoma was seen infiltrating the benign tumor- one a phyllodes tumor and the other three fibroadenomas. In rest of the five cases the tumors were independent of each other.

**Conclusion:** The occurrence of a carcinoma in a fibroepithelial neoplasm, however rare, necessitates a thorough histopathological examination of all breast lumps.

**Keywords:** Fibroadenoma, Infiltrating Carcinoma, Phyllodes Tumor.

### Introduction

Fibroepithelial neoplasms (FEN) of breast are biphasic tumors composed of proliferating epithelial and stromal mammary tissues. Fibroadenomas (FA) arise from the stroma and epithelium of the terminal duct lobular unit whereas, phyllodes tumor (PT) are derived primarily from periductal stroma and duct epithelium. The epithelial component of FENs can show features of hyperplasia, adenosis or squamous metaplasia. Rarely in 0.02-0.1% cases malignant transformation of the epithelium can occur within or adjacent to the FEN and may be either an infiltrating ductal or lobular carcinoma. This is extremely uncommon in PT in which malignancy usually involves the stromal rather than the epithelial component. PT with carcinoma showing lymph node metastases is a rarity.

### Materials and Method

A total of 592 cases of breast carcinoma diagnosed over a period of ten years were retrieved. The criteria for selection were adequacy of tissue, axillary lymph node dissection and proper fixation. Tru-cut biopsies and specimens without lymph nodes were excluded from the study. Relevant data such as age, laterality, tumor size, margin status, the type of FEN, associated malignancy and its relation to the FEN and the lymph node status were collected from the records. Hematoxylin and eosin (H and E) stained slides available of all cases were reviewed thoroughly. Immunohistochemical (IHC) staining were performed for estrogen receptor (ER), progesterone receptor (PR) and HER/2 neu status in seven of the nine cases.

### Results

On review of the departmental archives nine cases of infiltrating carcinoma in association with FENs were found (Table 1). The age range was from 35 years to 72 years. A palpable mass was present in the affected breast in all the women. The tumor size ranged from 1.5x1x1 cm to 18x18x8 cm. Of the nine cases, eight cases were diagnosed as infiltrating ductal carcinoma (IDC). Only one case showed infiltrating lobular carcinoma (ILC). In five cases, FA was seen coexisting with infiltrating carcinoma in the same breast. One case of PT and three cases of FA with IDC were found arising from the epithelial component of the lesion and seen extending into the adjacent breast parenchyma. In all the cases modified radical mastectomy with axillary dissection was performed. Lymph node metastasis were seen in six cases, five were FAs and one PT, respectively.

One case was of a 45-year-old woman who presented with eight years history of mass in the right breast with recent rapid enlargement. On examination, a firm to hard, well defined mass of 18 x14 cm was palpable and distorting the entire right breast. The mass was mobile. Examination of the right axillary region revealed a lymph node measuring approximately 1 cm in diameter. Fine needle aspiration cytology of the breast mass and the right axillary node showed an infiltrating ductal carcinoma with axillary metastasis. Based on the cytological diagnosis she received two cycles of chemotherapy, a month apart, consisting of cyclophosphamide, adriamycin and 5-FU followed by modified radical mastectomy with latissimus dorsi flap. Macroscopically, the resected tumor measured 18x18 x8 cm. The cut surface showed a relatively well circumscribed grey white, lobulated and bulging mass occupying almost the entire breast. Grossly twelve enlarged lymph nodes were identified. Microscopy of the

tumor predominantly showed a classical benign PT with an infiltrating ductal carcinoma arising within it and extending into the adjacent breast parenchyma. The PT was composed of bland cellular stroma with epithelial lined ducts in tubular and leaf-like pattern. The infiltrating carcinoma showed cells arranged in nests, sheets and cords separated by desmoplastic stroma with dense lymphocytic infiltrate and areas of necrosis. The cells had hyperchromatic, pleomorphic nuclei with prominent nucleoli. Mitosis (15/10 hpf) were noted and occasional atypical mitotic figures were observed. Large areas of the infiltrating carcinoma showed squamous

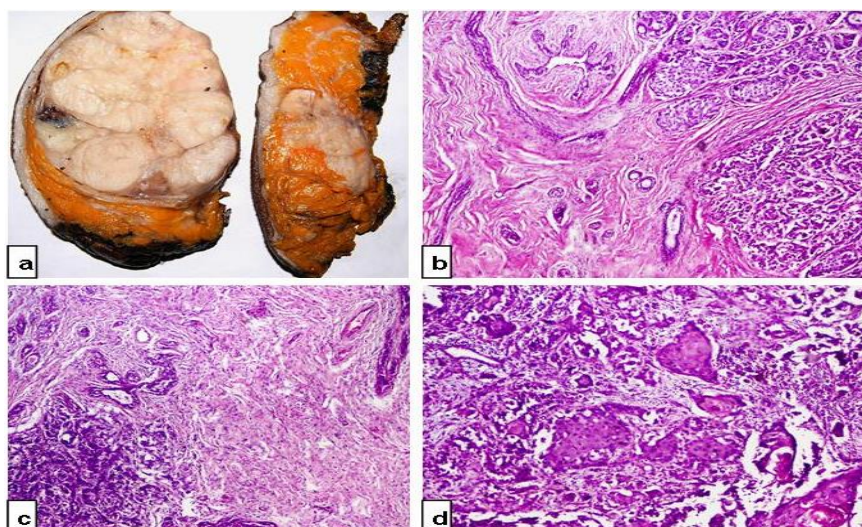
differentiation. Lymphovascular emboli were also seen. All the twelve axillary lymph nodes showed metastatic ductal carcinoma.

In three cases, microscopically the tumor was made up of pleomorphic round to polygonal cells with vesicular nuclei and prominent nucleoli. Adjacent to this tumor a small FA was seen with foci of invasion by the IDC. Ductal carcinoma in situ was seen in one of the cases (Case 3).

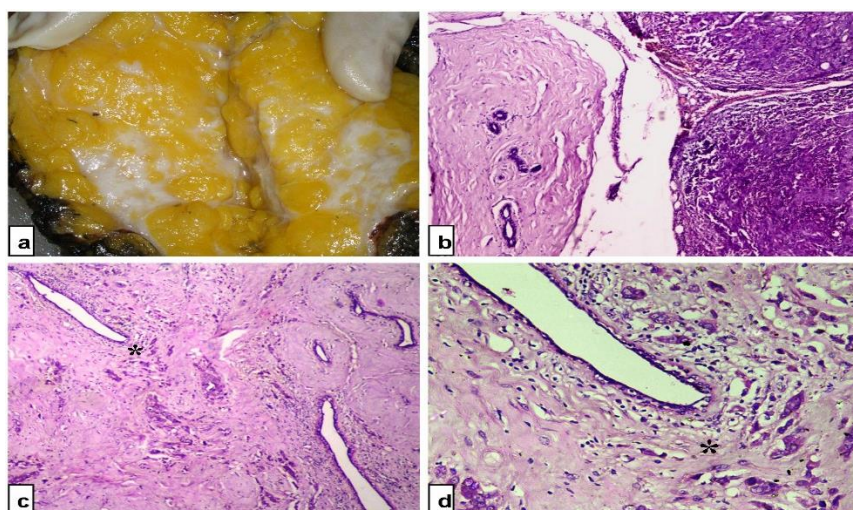
In four cases, the IDC and FA were independent of each other. Only one case revealed ILC separate from the FA.

**Table 1: A summary of clinical features and pathological findings in the nine cases**

Case	Age (yrs)	Laterality	Infiltrating tumor size (cm <sup>3</sup> )	FEN size (cm <sup>3</sup> )	Associated FEN	Lymph Node status	Margin status	Malignancy & it's relation to FEN	IHC stain
Case 1	45	Right	—	18x 18x 8	PT	12/12 showed metastasis	Free	IDC seen arising from epithelial component of PT	ER – PR – HER/2 neu+
Case 2	48	Right	3x3x3	1x1x1	FA	7/7 free	Free	IDC is seen involving foci of FA	NA
Case 3	49	Left	3x3x2	1x 0.5x 0.5	FA	15/15 showed metastasis	Involved by IDC	IDC is seen focally involving FA	ER – PR – HER/2 neu+
Case 4	46	Left	4x3x2	0.1x 0.1x 0.1	FA	2/8 showed metastasis	Free	IDC seen separate from FA	ER – PR –
Case 5	72	Left	1.5x1x1	0.5x 0.5x 0.5	FA	6/6 free	Free	IDC seen separate from FA	ER – PR –
Case 6	56	Right	5x5x5	3x2x2	FA	7/7 free	Free	IDC seen separate from FA	NA
Case 7	75	Left	9x4x3	3x1x1	FA	1/10 showed metastasis	Free	FA showed infiltration by IDC	ER + PR+
Case 8	35	Left	16x13x8	2x1x1	FA	1/11 showed metastasis	Free	IDC seen separate from FA	ER – PR – HER/2 neu–
Case 9	38	Right	5.5x4x2.5	2x1.1 x1	FA	4/6 showed metastasis	Involved by ILC	ILC seen separate from FA	ER – PR – HER/2 neu+



**Fig. 1: Phyllodes tumour (PT) with infiltrating ductal carcinoma (IDC); (a). Gross appearance of Case 1; (b) & (c). Microscopy shows PT with IDC component (H&E x40); (d). Focus of IDC showing squamous differentiation (H&E x100)**



**Fig. 2: Fibroadenoma (FA) with infiltrating ductal carcinoma (IDC); (a). Gross appearance of Case 2; (b). IDC abutting the FA (H&E x40); (c). Foci of FA infiltrated by IDC (H&E x40); (d). Infiltrating tumor cells are pleomorphic round to polygonal with vesicular nuclei (H&E x100)**

## Discussion

FA is a common benign breast tumor prevalent among young women, with peak incidence between 20 and 30 years. The risk of malignancy developing in FA is rare. The reported incidence of carcinoma arising in FA varies from 0.02-0.125%.<sup>(1)</sup> Most frequently carcinoma arises in the adjacent breast tissue and secondarily infiltrate a preexisting FA; and uncommonly a carcinoma can arise within the epithelial component of FA.<sup>(2)</sup> It is observed that FA with cysts greater than 3mm, sclerosing adenosis, epithelial calcification or papillary change increased the relative risk for breast cancer.<sup>(3,4)</sup> However, Carter et al found that atypical hyperplasia within a FA cannot predict for the presence of atypia within the adjacent parenchyma and also that epithelial atypia confined within FA does not have a clinically

significant risk of development of breast carcinoma in the long term.<sup>(4)</sup> Kuijper et al reported that invasive carcinoma were seen 3 times more in the surrounding parenchyma of FA, without involvement of the FA itself.<sup>(5)</sup> Carcinoma in situ is the most frequently encountered epithelial malignancy than invasive carcinoma. Lobular carcinoma is the most common type of invasive neoplasm arising in FA.<sup>(6,7)</sup> Wu et al in their study found predominantly small carcinomatous focus in relatively large FAs.<sup>(1)</sup> The mean age of patients developing carcinoma in FA is 20 years older than the age at which isolated FA occurs.<sup>(3,6,7,8)</sup>

PT, originally called cystosarcoma phyllodes, is an uncommon breast tumor. It is seen more in middle aged women (median age 45 years). PT are classified as benign, borderline and malignant based on histologic

features of the stromal component including hypercellularity, atypia, high mitotic rate, infiltrative tumor border and necrosis.<sup>(9)</sup> The epithelial component of PT may also show hyperplasia, adenosis or squamous metaplasia. While malignant change of the stroma in PT can hardly be termed exceptional, malignant epithelial change is an unusual occurrence. About nineteen cases have been reported with invasive carcinoma arising in PT.<sup>(10)</sup> Carcinomas can occur in any type of PT.<sup>(11)</sup> The most common association has been seen with benign and malignant PTs, and least with borderline PTs.<sup>(12)</sup> The histological subtypes reported are ductal and lobular carcinoma in situ,<sup>(13)</sup> invasive ductal carcinoma,<sup>(14,15)</sup> infiltrating lobular carcinoma,<sup>(16)</sup> squamous carcinoma,<sup>(17)</sup> tubular and schirrous carcinoma.<sup>(18)</sup> Carcinomas developing in PT are more commonly lobular than ductal.<sup>(15)</sup> Ductal carcinoma with squamous differentiation arising in PT have also been documented.<sup>(19)</sup> Our case was not only unusual in that the carcinoma arose within a large benign PT, but also in that it showed extensive squamous metaplasia.

The incidence of lymph node metastasis developing in invasive carcinoma associated with FA is low.<sup>(8,20)</sup> Although sarcomatous PTs do not develop axillary metastases, the carcinomatous component can show lymphatic invasion and axillary lymph node deposits.<sup>(10,14,21)</sup> This highlights the importance of axillary lymph node biopsy in histopathologically proven cases of invasive carcinoma arising in FEN. Lymph node status is the most important determinant for use of chemotherapy.<sup>(22)</sup>

Genetic abnormalities are thought to be responsible for the development of carcinoma in FEN. The epithelium exhibit distinct molecular changes as part of the neoplastic process. Transformation of the hyperplastic epithelium to carcinoma is probably due to genetic alteration.<sup>(23)</sup> Oncogene activation and tumor suppressor gene inactivation are important mechanism.<sup>(24)</sup> However, further studies are required to elucidate the genetic basis for the development of breast carcinoma in FEN.

FEN should be treated carefully due to the possible coexistence of a carcinoma within or outside a long standing lesion. The management of benign FEN consists of surgical excision removal. The prognosis of carcinoma developing in FEN is favorable.<sup>(12)</sup> Breast conserving surgery with adequate marginal clearance is the preferred treatment to prevent local recurrence. Mastectomy is performed in cases of malignant PT as well as in very large benign lesions. Adjuvant radiotherapy is indicated in patients with incomplete resected margins. In cases, with invasive carcinomatous components axillary lymph nodes dissection is mandatory. These patients are treated as for the usual invasive breast carcinomas.<sup>(6)</sup>

The radiological and clinical findings lack specificity to differentiate between benign FEN and those with coexisting epithelial malignancies.

Microscopy and immunohistochemistry are considered gold standard for detection and correct diagnosis of breast cancer.<sup>(12)</sup>

## Summary

While malignant change of the stroma in PT can hardly be termed exceptional, malignant transformation of the epithelial component is unusual. Despite the rarity of development of carcinoma in FEN, all FENs should undergo thorough and detailed histopathologic examination.

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