Ductal carcinoma in a multiple fibroadenoma: Diagnostic inaccuracies

ABSTRACT
We present the diagnostic inaccuracies encountered in a case of multiple fibroadenoma with malignant transformation. A 30-year-old lady presented with lump in the right breast of one month duration which on clinical examination, X-ray mammogram, sonomammogram were suggestive of multiple fibroadenomas. Fine needle aspiration cytology of the largest lump revealed features of malignancy and a core biopsy showed pleomorphic cells that could not be categorized. Due to the clinical, radiological and pathological diagnostic ambiguity, lumpectomy was performed and frozen section showed features of only conventional fibroadenoma. Representative bits on routine processing showed only features of fibroadenoma. Hence, complete submission of all lumps was done, which revealed fibroadenoma with invasive ductal carcinoma in one. Patient underwent modified radical mastectomy which showed multiple fibroadenomas, focal fibrocystic disease with a focus of residual invasive tumor and metastatic deposit in one axillary lymph node. This case report highlights the diagnostic challenges in detecting malignancy in fibroadenoma and a need for extensive tissue sampling in multiple fibroadenomas to detect the rare occurrence of carcinoma.

KEY WORDS: Cytology, invasive ductal carcinoma, mammogram, multiple fibroadenoma

INTRODUCTION
Benign breast disease has a high prevalence rate with fibroadenoma occurring in one of every five women and one of every two women is affected by fibrocystic disease.[1] Fibroadenomas, a biphasic tumor with stromal and epithelial component, are generally benign tumors of not much concern. Malignant transformation in a fibroadenoma is an uncommon feature. We report a case of a young patient with multiple fibroadenomas harboring invasive ductal carcinoma in one of them.

CASE REPORT
A 30-year-old lady presented with history of lump in the right breast of one month duration. There was no family history of breast or ovarian lesions in the past. Patient had regular menstrual cycles and last child birth eight years back.

On examination, a freely mobile firm mass was felt in right upper quadrant measuring 4 × 2 cm in size. Multiple smaller mobile lumps ranging in size from 0.5 cm to 1 cm were also palpable in upper quadrant near the axillary tail. A clinical diagnosis of multiple fibroadenomas was made.

Mammogram revealed multiple small round nodular lesions with smooth margins and many clusters of macrocalcifications in right breast [Figure 1]. Ultrasound of right breast showed well-defined round to oval shaped hypoechoic lesions with smooth to macrolobulated margins [Figure 1]. Multiple calcifications were seen within the lesions. Findings of ultrasonogram and mammogram suggested benign lesions, possibly multiple fibroadenomas.

Fine needle aspiration cytology (FNAC) of the larger mass in the right breast revealed features of malignancy. An ultrasound guided core biopsy of the same mass revealed fibroadipose tissue with highly pleomorphic atypical cells and a definitive opinion on the type of malignancy could not be given. Patient was planned for frozen section and proceeded further as required. Frozen section of two larger lumps revealed features of fibroadenoma. Routine sections studied also showed histological features of conventional fibroadenoma. Following this, both the lumps were completely sampled and the larger lumps showed features of ductal carcinoma in situ with invasive ductal carcinoma, not otherwise specified [Figure 2]. Patient then underwent radical modified mastectomy of right breast with axillary clearance. An island of tumor cells with features of invasive ductal carcinoma was seen near the area of defect (area of previous surgery). Tumor was negative for estrogen receptor, progesterone receptor and Her2neu. Rest of the breast showed multiple fibroadenomas with focal areas of sclerosis and calcification. Four quadrant...
sampling of breast tissue showed focal areas of fibrocystic disease with sclerosing adenosis and calcification. One of the eight ipsilateral axillary lymph node sampled showed metastasis.

**DISCUSSION**

Epithelial hyperplasia within fibroadenomas is a common finding and infrequently atypical hyperplasia of ductal or lobular type may also be noted.[2] Carter et al. found atypical hyperplasia in 0.81% of fibroadenomas.[2] Review of literature reveals few case studies with in situ/invasive ductal and lobular carcinoma in a fibroadenoma.[3-5] These findings draw our attention to rather rare events that occurs in a fibroadenoma ranging from epithelial hyperplasias to invasive carcinomas. Clinicians, radiologists and pathologists need to be aware of the possible yet uncommon stepwise progression capabilities of fibroadenomas. Progression of epithelial component into in situ and invasive carcinomas is quite rare that occurs usually in women over 40 years.[6] In contrast to this, the patient in the present case was quite young (30 years of age). Since the patient was within the age group of regular fibroadenoma, clinician did not have any suspicion of malignancy considering both the age and clinico-radiological findings.

Triple test done to evaluate breast lesions include FNAC, core biopsy and radio-imaging techniques such as ultrasound and mammogram. Fine needle aspiration cytology is a tool that helps in guiding the surgeon to decide further management. However, not always the diagnosis given on FNAC would reflect the lesion of concern/importance. This occurs due to sampling error which is a known drawback of cytology. During FNAC, the cytologist makes passes with a needle into few areas and quite often only the surrounding area is sampled and the lesional areas remain untouched. Surprisingly, in the present case though the clinical examination and mammogram were suggestive of multiple fibroadenoma, the FNAC revealed features of malignancy which was confirmed on core biopsy. However, frozen and routine sections of two larger lumps sampled showed only features of fibroadenoma. The dilemma was resolved only the entire tissue from both lumps were embedded which revealed ductal in situ and invasive ductal carcinoma. The patient received the required treatment since FNAC detected malignancy in spite of it being missed on mammogram. Had this area not been sampled on cytology considering its drawback of sampling error, the lesion would have been completely missed. This is because fibroadenomas without any suspicion are never completely embedded. The question to be debated further is whether fibroadenomas need to be sampled completely or is it that only multiple fibroadenomas that need entire sampling! Yano et al. encountered a similar situation of ambiguity in cyto-diagnosis and mammogram of a fibroadenoma with a lobular carcinoma and malignancy was proven by image guided core biopsy.[7]

Fibroadenomas in a patient with strong family history are of concern as they may undergo malignant transformation, the signs of which may not be evident clinically or radiologically.[6] A benign tumor, still a relative risk of malignancy, exists in cases with histological evidence of hyperplasia in adjacent breast tissue and positive family history. Kujper et al. reported a case of synchronous in situ lesions within multiple fibroadenomas and on complete sequencing of BRCA1 and BRCA2 genes, an evidence of a BRCA 1 mutation was also noticed.[6] Their case also gave positive family history of breast carcinomas. This further implies that patients with fibroadenoma having a positive family history need to be thoroughly investigated to rule out a malignant transformation.

However, in our documented case, there was no past family...
history of breast/ovarian carcinoma and patient was not evaluated for BRCA gene mutation.

Malignant transformation in a pre-existing fibroadenoma is a rare event with limited documented cases in literature.[10] There are several theories suggested for a carcinoma arising in a fibroadenoma. Fibroadenoma can get involved by an adjacent carcinoma. It may be a simultaneous cancer involving the crevices of fibroadenoma as well as adjacent breast tissue or carcinoma could entirely be limited to fibroadenoma.[10] It is the complex fibroadenoma which needs greater attention, as the risk of malignant transformation is higher in this subset of fibroadenomas. [10] Complex fibroadenomas occur in older women and feature calcification, apocrine metaplasia, sclerosing adenosis and cyst formation. Though our patient was younger, the excised breast lumps did exhibit features of complex fibroadenoma. Dupont et al. have found the risk of malignancy in complex fibroadenoma to be 1.89 times higher than a conventional/simple fibroadenoma.[11] Malignant transformation in fibroadenoma on histology features either an in situ or invasive carcinoma of ductal/lobular type.[12] Four quadrant sampling of the mastectomy specimen in our case showed features similar to Kuiper et al. with evidence of fibrocystic disease, sclerosing adenosis and calcification.[10]

Ultrasound is a reliable non-invasive technique to diagnose fibroadenomas. Generally, clinical and ultrasound features consistent with diagnosis of conventional fibroadenoma are not biopsied and managed either conservatively or excised completely. Ultrasonography of fibroadenoma exhibits an elliptical, lobulated, isoechoclastic or minimally hypoechoic, solid nodule with homogenous echo texture. Changes such as increase in color flow signals in Doppler study suggest morphological changes like epithelial hyperplasia, atypia or carcinoma in a fibroadenoma. Detection of malignancy in a fibroadenoma is difficult on imaging techniques since or carcinoma could entirely be limited to fibroadenoma.[10] It is the complex fibroadenoma which needs greater attention, as the risk of malignant transformation is higher in this subset of fibroadenomas.[10] Complex fibroadenomas occur in older women and feature calcification, apocrine metaplasia, sclerosing adenosis and cyst formation. Though our patient was younger, the excised breast lumps did exhibit features of complex fibroadenoma. Dupont et al. have found the risk of malignancy in complex fibroadenoma to be 1.89 times higher than a conventional/simple fibroadenoma.[11] Malignant transformation in fibroadenoma on histology features either an in situ or invasive carcinoma of ductal/lobular type.[12] Four quadrant sampling of the mastectomy specimen in our case showed features similar to Kuiper et al. with evidence of fibrocystic disease, sclerosing adenosis and calcification.[10]

Ultrasound is a reliable non-invasive technique to diagnose fibroadenomas. Generally, clinical and ultrasound features consistent with diagnosis of conventional fibroadenoma are not biopsied and managed either conservatively or excised completely. Ultrasonography of fibroadenoma exhibits an elliptical, lobulated, isoechoclastic or minimally hypoechoic, solid nodule with homogenous echo texture. Changes such as increase in color flow signals in Doppler study suggest morphological changes like epithelial hyperplasia, atypia or carcinoma in a fibroadenoma. Detection of malignancy in a fibroadenoma is difficult on imaging techniques since characteristic radiological signs are usually not evident until a breach occurs in the false capsule.[13] Unequivocal mammographic features of carcinoma originating within fibroadenoma include indistinct margins and clustered microcalcifications. These features were not evident in our case imaging. Color Doppler sonography demonstrates increased color flow signals in carcinomas due to prominent angiogenesis. However, this pattern may also be seen in benign cellular tumors. A cautious search for these features in a fibroadenoma would further help in identifying this uncommon event in a fibroadenoma. Any morphological changes in a known benign tumor should alert the radiologists to suggest the clinician for further evaluation by FNAC or biopsy to rule out the rare occurrence of carcinoma within a fibroadenoma.

Carcinomas arising within fibroadenoma behave in a similar fashion as a regular breast carcinoma. Hence, there is no difference in the treatment modality.[14] Our patient underwent modified radical mastectomy with axillary clearance of the right breast. Patient was not given any targeted therapy as the carcinoma was negative for ER, PR and Her2/neu immunomarkers. Chemotherapy regimen followed for this patient included combination of taxol, adriamycin and cyclophosphamide every 21 days in six cycles. She also received radiation to local chest wall and drainage area by 3 D conformal radiotherapy with 50Gy @ 2Gy/25 fraction over five weeks. Patient has been disease free for seven months.

To conclude, this case report highlights the need for extensive tissue sampling in multiple fibroadenomas as the clinicoradiological features of malignant transformation may be quite subtle to be easily missed on routine examination.

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