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Case Report

Invasive ductal carcinoma in background of a fibroadenoma: A rare progression, or an uncommon coincidence? Report of a case with brief review of the literature

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Abstract

We report a case of a 37-year-old woman presenting with a 2.8 cm hypoechoic mass in the upper outer quadrant of the right breast. The original core and fine needle aspiration (FNA) at presentation led to the diagnosis of a fibroadenoma, however the cytopathologist noted few atypical cells insufficient for a malignant diagnosis. The mass was found to be enlarged in size at 3.6 cm at a follow up eleven months later. Repeat FNA and core biopsies demonstrated cytologic features of both fibroadenoma (FA) and invasive ductal carcinoma (IDC). Can a fibroadenoma progress into an invasive carcinoma? Or, is the presence of both of these modalities just a coincidence? We report this case with a brief literature review to investigate this phenomenon.

Keywords: Fibroadenoma; Invasive Ductal Carcinoma; Tumor; Atypical; Malignant

Abbreviations

FA: Fibroadenoma**; DCIS: Ductal carcinoma in situ. IDC:** Invasive Ductal Carcinoma**; FNA:** Fine Needle Aspiration. **FNAC:** Fine Needle Aspiration Cytology. **IHC**: Immunohistochemistry, **H&E**: Hematoxylin and Eosin stain

Introduction

Fibroadenoma (FA) of the breast is a common cause of a benign breast lump in premenopausal women. Overall, there lies a view that women with FA are not at significant increased risk of developing breast cancer. Diagnosis is based on the combination of clinical examination, imaging and non-surgical tissue biopsy (the triple test) [1]. After diagnosis of such a tumor, most patients will choose not to excise the tumor and return for normal breast screenings. A FA is often detected incidentally usually as a discrete solitary breast mass of 1 to 2 cm during a medical or self-examination. Although they can be located anywhere in the breast, the majority originate in the upper outer quadrant. A FA is most often smooth, mobile, nontender, and rubbery in consistency [2]. FA comprise about 50% of all breast biopsies, and this rate rises to 75% for biopsies in women under the age of 20 years [2]. Fibroadenoma is termed as complex fibroadenoma when it contains cysts larger than 3 mm and there is presence of sclerosing adenosis, epithelial calcification or papillary apocrine changes [3].

Although fibroadenomas are benign tumors, there are increasing number of reported cases where they may be associated with increased risk of breast cancer. Most commonly, malignancy has been reported in complex FA, those with proliferative disease accompanying FA, and when there is a relevant family history [4]. In addition to developing within the FA, invasive carcinoma can hold onto the FA itself by originating from the neighboring breast tissue [4]. Azzopardi suggested that carcinoma involving a FA might be due to one of the following: Carcinoma arising in an adjacent breast tissue engulfing or infiltrating a FA, carcinoma in the crevices of a FA as well as in the adjacent breast tissue, carcinoma restricted entirely or at least dominantly, to a FA as well as in the adjacent breast tissue [5]. The literature reports that the epithelial component can develop into a carcinoma in situ and invasive cancer. Invasive Ductal Carcinoma (IDC) development is generally observed in females over 40 years of age [4]. IDC is the most common carcinoma in females.

Granted a malignant transformation in FA is rare, the highest risk has been found in complex FA. Dupont et al. have identified an increased risk (1.89 times) of cancer in complex FA when compared to simple ones. It has been found that the average age for carcinomas developing from FA is during the 5th decade. Clinicians, radiologists, and pathologists must be aware of this possible progression [4]. Gorcon et. al report that a clinical diagnosis of FA alone is unreliable and does not exclude malignancy even in younger women. Since there are no definite clinical or radiological criteria of diagnosing carcinoma

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developing in a FA, histopathological examination of all FA should be performed routinely to rule out malignancy [5]. The choice of imaging is mammography, combined with ultrasound in older women, and ultrasound alone in younger women. Tissue biopsy, by either fine-needle aspiration or core biopsy, is the most practical and accurate means of establishing the diagnosis [1]. In this case report, an invasive ductal carcinoma was diagnosed in background of a previously diagnosed fibroadenoma during follow up. We discuss in this report with a brief review of the literature whether it is a rare progression, or an uncommon coincidence?

Case Presentation

A 37-year-old woman presents with a right breast mass she discovered in the upper outer quadrant. The patient does not have any significant family history and her medical history includes a prior cholecystectomy with gallstones three years prior, an appendectomy at the age of 22 and a history of type-1 Diabetes Mellitus well-controlled with insulin. An ultrasound revealed a hypoechoic 2.8 cm mass with benign features, but increased central cellularity was noted. FNA and core biopsy led to the diagnosis of a FA. However, the pathologist reported the presence of a few atypical cells insufficient for definitive diagnosis and recommended additional sampling or total excision of the mass and the diagnosis was considered a complex fibroadenoma. The patient refused further sampling or excision due to the benign diagnosis and decided to just follow up.

At follow-up 11 months later, the mass has enlarged in size. Ultrasound showed a 3.6 cm well defined mass with central changes suspicious for malignancy. Tissue sampling of different areas of the mass was suggested and three core biopsies were taken. Out of the three core biopsies taken from different areas of the mass, one showed only FA (**Figure 1A**), one showed IDC in the background of FA (**Figure 1B**), and one from the central area showed only IDC (**Figure 1C**). The mass was excised with sentinel lymph node sampling. The sentinel lymph node was negative, and therefore, there was no further excision of axillary lymph nodes. All surgical margins were negative with adequate safe margins. The excised IDC was positive for ER and PR but HER-2 negative. Ki-67 was low with 9% nuclear staining. The patient underwent postoperative radiation without chemotherapy as well as adjuvant hormonal therapy with tamoxifen. After 7 years of follow up, there was no recurrence or metastasis after which the patient was lost to follow up.

Discussion

A carcinoma arising in a pre-existing FA is a rare occurrence with about 100 cases reported in the world literature. Review of the literature reveals that it is debatable whether this is a rare progression, or an uncommon coincidence?

The diagnosis is usually a histological surprise [5]. The reported cases show that the average age of the patients is about 20 years older than the peak incidence of FA in the general female population. The most common type of neoplastic change is in situ lobular carcinoma. The total number of cases available in the literature is limited and there remains some doubt regarding optimal treatment and prognosis [6].

Kuijper et. al reported a case of a 46-year-old woman, with one first degree family member with breast cancer and another with both breast and ovarian cancer, presenting with multiple palpable masses in both breasts. FNA of one of the lesions in the left breast was inconclusive, a subsequent core biopsy was compatible with FA. Because of clinical and radiological suspicion, excisional biopsy was performed on both breasts. On pathological examination of the hematoxylin and eosin (H&E) stained sections the breast masses were found to be FA. Three FA removed from the left breast showed ductal carcinoma in situ (DCIS) [7]. The patient presented in our case is unique as she presents with no family history and the entire carcinoma was invasive and no evidence of in situ component a single lesion that contains IDC.

In most of the reported cases, the microscopic appearance of carcinoma developing in FA does not differ from that of carcinoma

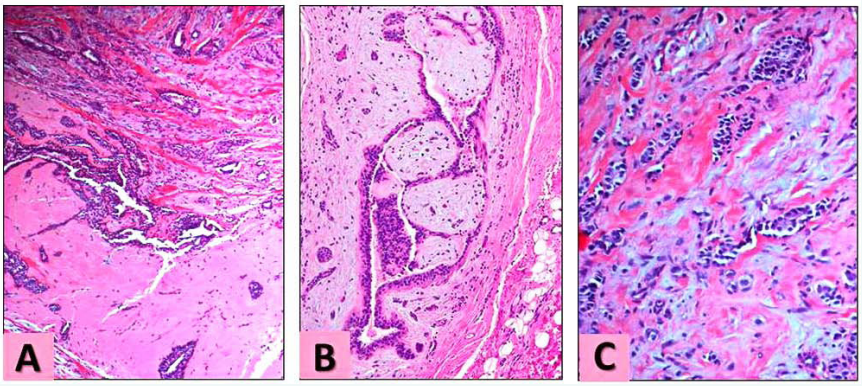

Figure 1 Microscopic examination of different components of the tumor mass

Figure 1A: Low power view showing invasive ductal carcinoma in the superior part of the Image, and fibroadenoma in the lower part of the image (H&E X20)

Figure 1B: Intermediate power view showing Fibroadenoma (H&E X40)

Figure 1C: High power view showing invasive ductal carcinoma (H&E X60)

unassociated with FA. Fondo et. al described twelve patients who had noninvasive carcinoma either in the in FA alone, or in the fibroadenoma and adjacent breast tissue. Lobular carcinoma in situ was confined to the FA in six patients including one patient with bilateral FA. Two other patients had in situ lobular carcinoma in the FA and adjacent breast tissue. There were four instances in which noninvasive duct carcinoma involved the adjacent breast tissue and FA. Two of these patients also had in situ lobular carcinoma in the adjacent breast tissue and FA [8]. There is no data available to indicate that carcinoma in a FA is clinically different from carcinoma in non-fibroadenomatous breast tissue [6].

Cysts and carcinomas are better distinguished from FA by ultrasound imaging; however, overlapping findings in nonhomogeneous FA that can also include occasional calcification and non-circumscribed margins can often mimic the findings in other types of breast masses [9]. As other benign lesions are seen in the breast, FA are usually seen as a round mass with hypoechoic or isoechoic appearance. Although FA is not an encapsulated lesion, a thin layer of echogenicity surrounds it due to the compressed normal breast tissue. Any areas of thickened echogenicity questions the diagnosis of FA and could be suggestive of a potential malignant pathology [9]. Smith and Burrows declared in their study that there were no discrepancies of diagnosis between ultrasound and biopsy samples for FA; and therefore concluded that it is not indicated to investigate all cases through biopsy unless there are added abnormalities in the physical examination or patient's history [10]. In addition to ultrasound, diagnosis can also include the use of MRI. With dynamic MRI, benign FA and IDC can be differentiated according to differences in vascularity. Parameter color maps can also demonstrate the extent of DCIS within a FA [11]. However, in the case described here, sonography revealed a well-defined, sharply circumscribed hypoechoic lesion with increased central cellularity. Preoperative imaging to differentiate benign from malignant FA was not conclusive, and therefore tissue sampling was performed to obtain a tissue diagnosis [11]. However, multiple sampling was necessary to map the entire mass and identify various components.

Fine needle aspiration cytology (FNAC) has become a popular and valuable tool in assessing breast masses, and it shows high accuracy, sensitivity, and specificity. FNAC has an easy approach, is inexpensive and rarely has few complications [12]. In the evaluation of breast masses, the triple assessment combines clinical, radiological, and pathological information, and FNAC, together with core needle biopsy creates the method of choice in pathological study [12]. FNAC has significantly contributed to the reduction of excisional biopsies in the assessment of breast lesions. Nevertheless, there still exists a significant false negative rate for FNAC of breast masses, in the range of 1.2–10.6%. [12]. Perhaps this significant false negative rate is due to sampling error where significant areas of the mass are not sampled.

Sampling number, known as number of cells, clusters, plays a role in false negative cases. Layfield et. al studied a subgroup of 183 cases with known outcome to determine the minimum number of cell clusters (defined as five or more cells) necessary to ensure that adequate cellular material was present for accurate diagnosis in cytology FNA sampling. Correlation was made between these values and the false-negative rate at various cellularity cutpoints. Based on the data gathered in this study, the authors believe that the sampling false-negative and unsatisfactory rates can be minimized by selecting a cut point for satisfactory smears at a level of 6 or more cell clusters (cumulative total) or the presence ≥ 10 intact bipolar cells per 10 medium-power fields (×200). They concluded that the use of these criteria will decrease the false-negative rate of sampling in epithelial lesions of the breast [13].

Even though in current case it was not done, immunohistochemical (IHC) studies have been used in other studies to differentiate malignant and benign tumors that cannot be distinguished on imaging and Hematoxylin and eosin (H&E) regularly stained sections. Koutselini et al. studied p53 expression in cytologic specimens from benign and malignant breast lesions. They did not find p53 overexpression in any case of benign cystic disease of the breast. They found only one case of p53 positive FA out of 12 cases. Out of total 40 cases of carcinoma, they found 21 cases positive for p53 overexpression. In addition, invasiveness was studied using immunohistochemical staining with a monoclonal antibody against 34 βE12. They found that all the controls and benign breast lesions have continuous basal or myoepithelial cell layer, whereas all the cases of invasive carcinoma showed discontinuous pattern of staining They concluded that morphometry and IHC help in the proper diagnosis of different breast lesions that lie in the grey zone on routine histopathology [14].

After ruling out malignancy in a complex fibroadenoma, patient follow-up is important. The patient in this case returned after 11 months to find that her fibroadenoma had grown from 2.8 cm to 3.6 cm. Gordon et. al report that solid breast masses diagnosed as FA at FNA may be safely followed up if volume growth rate is less than 16% per month in those younger than 50 years and less than 13% per month in those 50 years or older. Acceptable mean change in dimension for a 6-month interval is 20% for all ages [15]. Traditionally, symptomatic FA were treated by surgical excision, and this option should always be offered. There is increasing evidence that a conservative approach is safe and acceptable, provided the result of an adequate triple test is both negative for cancer and consistent with a FA. Patients who choose conservative management need to be informed of the limitation of this approach and must be assessed promptly if there is symptomatic or clinical change [1].

Although malignant transformation in a FA is rare, high suspicion index in middle aged women with FA, especially complex ones, and associated risk factors like strong family history and/or BRCA-1, BRCA-2 mutation is recommended [5]. It is specifically necessary to be careful with patients over 35 years of age with FA that is larger than 2 cm. The behavior of invasive carcinoma developing from FA or not is not different. Therefore, treatment modalities do not differ as well. In our presented case, the diagnosis was complex fibroadenoma, the pathologist

expressed concern and additional tissue sampling should have been obtained and examined. The patient's refusal of further surgery contributed to the progression of the tumor.

Conclusion

Sampling of different areas of large fibroadenomas, especially complex ones, is essential to guarantee adequate sampling of the entire mass. Although most cases of FA with carcinoma have been reported in females with a family history of breast cancer, this patient did not have such a history. Therefore, it is important that masses that appear non-homogeneous on ultrasound are thoroughly investigated regardless of family history.

FNA assessment of atypia in cases of FA is difficult. Even conventional nuclear morphometry, though supporting the initial impression of atypia, does not help with this assessment. Also, based on morphometry alone, there may be difficulty separating FA with atypia and low-grade carcinomas. Larger studies, employing other morphometric parameters, such as chromatin texture and fractal dimension, may shed further light on the subject [16]. However, patients should be advised that the presence of atypia in breast FNA and core biopsy samples can be serious and that they must follow up with additional sampling or excision.

This case begs the question, is this a coincidence? Or, can FA progress to IDC? Intensive review of literature failed to provide a definitive answer to this question. It is our hope that this report raises awareness of what remains an unmet need in understanding the phenomenon of coincidence of fibroadenoma and breast carcinoma. We hope that continued investigation drives further development of efficacious and safe diagnosis and treatments of this condition for improving patient outcomes.

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