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Abstract

Objectives. Flat epithelial atypia (FEA) is recognized as a precursor of breast cancer and its management (surgical excision or intensive follow-up) remains unclear after diagnosis on core needle biopsy (CNB). The aim of this study was to determine the underestimation rate of pure FEA on CNB and clinical, radiological and pathological factors of underestimation.

Materials and Methods. 4,062 CNBs from 5 breast cancer centers, performed over a 5-year period, were evaluated. A CNB diagnosis of pure FEA was made in 60 cases (1.5%), (the presence of atypical ductal hyperplasia, lobular neoplasia, radial scars, phyllodes tumor, papillary lesions, ductal carcinoma *in situ* or invasive carcinoma at CNB were exclusion criteria), and subsequent surgical excision was systematically performed. The histological diagnosis was retrospectively reviewed using standardized criteria and the precise terminology of the World Health Organization by two pathologist physicians.

Results. At surgical excision, 6 (10%) ductal carcinoma *in situ* and 2 (3%) invasive carcinoma were diagnosed. The total underestimation rate was 13%. FEA was associated with atypical ductal hyperplasia in 10 (17%) cases and with lobular neoplasia in 2 (3%) at final pathology. Residual FEA was found in 14 (23%) cases. No clinical, radiological or pathological factors were significantly associated with underestimation.

Conclusion. Our data highlight the importance of recognizing and diagnosing FEA in core needle biopsies. Thus, the presence of FEA on CNB, even in isolation, warrants follow-up excision.

Keywords

Breast cancer, core needle biopsy, flat epithelial atypia, surgical excision.

Introduction

The frequency of mammary epithelial atypia diagnosis has increased with mammographic screening programs and with the development of percutaneous large core needle biopsy (CNB) methods using stereotactic mammography or ultrasound guidance. In 1985, the diagnosis of epithelial atypia was 3.6% of excisional breast biopsies *versus* 23% in 2007[1, 2]. As defined by the World Health Organization (WHO) Working Group on Pathology and Genetics of Tumors of the Breast [3], epithelial atypia is divided into atypical ductal hyperplasia (ADH) (or DIN 1b), flat epithelial atypia (FEA) (or DIN 1a) and lobular neoplasia (LN). Due to a lack of standardized terminology, FEA and ADH are sometimes poorly differentiated on pathological examination [4]. As defined by the WHO[3], FEA is an "intraductal alteration characterized by replacement of the native epithelial cells by a single or 3 to 5 layers of mildly atypical cells. The ducts involved are variably distended and often contain intraluminal microcalcifications or secretory material". In the past, a wide variety of names were used to describe it, including "small ectatic ducts lined by atypical duct cells with apocrine snouts" [5], "columnar alteration with prominent apical snouts and secretions" (CAPSS),[6] "atypical cystic lobules" [7] , and "ductal intraepithelial neoplasia-flat type" [8]. FEA frequently coexists with several types of low-grade carcinoma [5, 9], and emerging genetic evidence shows the same molecular alterations[10, 11].These points suggest that FEA may be the earliest precursor of low-grade ductal carcinomas—both invasive and *in situ* [12]. However, surgical cohort studies have shown that FEA does not necessarily evolve to invasive cancer [1]. Thus, the clinical significance of FEA remains unclear.

In several retrospective studies, core needle biopsy with diagnosis of atypical ductal hyperplasia or lobular neoplasia shows a false-negative rate of around 20% when seeking associated invasive carcinoma (IC) or ductal carcinoma *in situ* (DCIS) with follow-up surgical excision[13, 14]. An important clinical parameter of FEA raises an immediate clinical

concern: whether follow-up excision is necessary for patients with FEA diagnosed on CNB. Data is scarce on FEA diagnosed on CNB. A few small studies (less than 40 cases) (almost all published in abstract form) were confused and showed a more advanced lesion, either DCIS or IC, in between 0 and 30% of cases of subsequent surgical excision after FEA diagnosed with CNB [4, 15-21]. Thus, published studies are rare, lack standardized terminology and sometimes confuse FEA and ADH on pathology [4, 16]. Uniform management guidelines for surgical excision or clinical follow-up are lacking.

This multi-institutional study reports on follow-up surgical excision and frequency of subsequent invasive breast carcinoma or ductal carcinoma *in situ* among 60 patients with pure FEA (WHO definition) identified in a retrospective review of 4,062 CNBs over a 5-year period. The aim of this study was to determine the underestimation rate of FEA on CNB and clinical, radiological and pathological factors of underestimation.

Materials and Methods

Study population. Using the medical center pathology database, we identified all lesions described as FEA from the pathology reports of stereotactic- or ultrasound-guided breast CNBs performed in 5 breast cancer centers (Rennes, Nantes, Angers, Tours and Belfort) for patients enrolled in the study between January 1, 2004 and December 31, 2008. The total number of CNBs taken in the 5 centers was 4,062 for the period. Inclusion criteria were the presence of FEA on breast specimens obtained by CNB followed by surgical excision, which was systematically performed after CNB diagnosis of FEA. Five patients with FEA on CNB were excluded because they refused subsequent surgery for personal reasons. The presence of atypical ductal hyperplasia (ADH), lobular neoplasia (LN), radial scars, phyllodes tumor, papillary lesions, ductal carcinoma *in situ* (DCIS) or invasive carcinoma (IC) at CNB all constituted exclusion criteria. Forty-four patients were excluded due to FEA being associated

with ADH (32 cases) or with LN (8 cases) or both (2 cases) or with a papillary lesion (2 cases) on CNB. Finally, 60 patients who underwent follow-up surgical excision on diagnosis of pure FEA as the most advanced lesion on CNB were eligible. We received institutional review board approval. The slides were retrieved from the surgical pathology files and all The needle biopsy slides were retrospectively evaluated by two pathologists (C. Sagan and P. Tas) who were blinded to the follow-up information. The clinical records of the cases included were reviewed: the relevant clinical data (age, parity, menopausal status and treatment, personal or family history of breast cancer) and the clinical and radiological signs that led to the CNB were also noted. The radiology records of the cases included were reviewed: (1) mammographic and/or ultrasound findings (calcifications *versus* mass), (2) breast imaging reporting and data system classification of the lesion,[22] and (3) entity of lesion removed on mammograms performed after needle biopsy: lesion entirely or almost entirely removed (>90%) *versus* lesion only partially removed (<90%). The CNB protocol was also reviewed (stereotactic or echo-guided biopsy, size of needle, number of biopsy specimens). Finally, the pathology files were searched for subsequent surgical procedures: for all cases, the slides were reviewed and final diagnosis on excision biopsy was recorded and compared with the needle biopsy findings.

Morphology review. Needle breast biopsy specimens were fixed in 10% formaldehyde and embedded in paraffin. Each block was cut to create 3 slides, which were stained with hematoxylin-eosin-safran and examined. In the presence of FEA, 3 additional levels were cut and some unstained sections were saved for potential immunohistochemistry. According to established criteria (WHO),[3] in our analysis we included cases of pure FEA as the most advanced lesion (variably distended acini lined by 1 to several layers of monotonous, mildly atypical, cuboidal to columnar cells growing in an exclusively, real ‘‘flat’’ pattern, with complete absence of intraluminal proliferation with architectural atypia). Cases with the

presence of a single atypical intraluminal structure such as arcade, bar, Roman bridge, tuft, or cribriform-micropapillary formations were considered sufficient for a diagnosis of concomitant ADH and were excluded.

Statistical analysis. Statistical analysis was based on Student's t-tests for parametric continuous variables and the Chi square test or Fisher's exact test, as appropriate, for categorical variables. We tested clinical and radiological characteristics in univariate analysis for association with the IC or DCIS diagnosis in the findings of the surgical excision. P values less than 0.05 were considered to denote significant differences. Statistical analyses were performed using SAS Version 9.2 software.

Results

A CNB diagnosis of pure FEA was made in 60/4062 cases (1.5%). All the patients were women. The mean age of patients was 53 ±12 years (40-74). The mean parity was 2.4 ±1.35 (0-6). Family history of breast cancer was found in 18% of patients. Two patients (3%) had personal history of breast cancer: both were contralateral ductal carcinoma *in situ*. Fifty percent of patients were menopausal at the time of CNB and 40% were receiving hormone replacement therapy (Table 1). Mammographic abnormalities were found for 60 patients: 56 (92%) cases with microcalcifications, 4 cases with masses (1 stellar opacity and 3 round opacities). The mean size of microcalcifications was 18±21 mm (3-110). Ultrasound examination was performed on 38 patients. Ultrasound abnormalities were found in 10 patients. Radiological abnormalities were classified as BI-RADS 3 in 3 cases (3%), BI-RADS 4 in 54 cases (94%) and BI-RADS 5 in 3 cases (3%) (Table 1). CNB was performed on 6 patients using an ultrasound-guided procedure with a 14-gauge needle for 5 patients and an 11-gauge needle for one. CNB was performed on 54 patients using a stereotactic-guided procedure (guided vacuum biopsy, Mammotome® or Vacora®). The biopsy needles used for

stereotactic biopsies were 11-gauge in 28 cases (54%), 10-gauge in 13 cases (23%) and 8-gauge in 13 cases (23%). The number of samples was recorded in 100% of 60 procedures with a mean of 11±6.5 (3-48). The lesion was entirely or almost entirely removed (>90%) in 18 cases (30%) (Table 1). Subsequent surgical excisions were available in 100% of cases (inclusion criteria) and revealed the following: no residual disease in 26 cases, residual pure FEA in 14 cases, and other lesions with atypia in 12 cases (10 with ADH and 2 with LN1), 6 cases of DCIS and 2 cases of invasive carcinoma. Thus, 8/60 patients (13%) with a diagnosis of pure FEA at CNB were underestimated and the diagnosis was upgraded to DCIS or IC with follow-up surgical excision. The 6 DCIS cases were grade 1 (DIN 1c) in 4 cases and grade 2 (DIN 2) in 2 cases (according to the WHO classification).[3] The mean size of DCIS was 19±27 mm and the range from 4 to 80 mm. The 2 IC cases were invasive ductal carcinoma, sized 3 and 16 mm, SBR 2 and 1, respectively. Both were positive for hormone receptors and without over-expression of HER2. Table 3 provides details of the clinical and radiological data of 8 patients with underestimation, *i.e.* with DCIS or IC in the findings of the subsequent surgical excision. Table 1 summarizes the underestimation rates in all patients according to clinical, radiological and pathological variables. No underestimation factors were reported within the clinical history and radiological findings.

Discussion

To our knowledge, this study reports the highest number of patients with FEA diagnosed on CNB and undergoing immediate follow-up surgical excision. Our data highlight the importance of recognizing and diagnosing FEA in core needle biopsies. The underestimation rate of CNB diagnosis of pure FEA was 13% (8/60) and no clinical and/or radiological and/or pathological criteria alone or in combination identified a subset of patients at low risk of DCIS or IC in a secondary surgical excision. Although limited by its retrospective nature, the

findings of our study may assist in the management of patients with CNB diagnosis of FEA. Thus, the presence of FEA on CNB, even in isolation, cannot be considered "probably benign" and warrants follow-up excision. Indeed, a lesion may be considered "probably benign" if there is a <2% possibility of carcinoma, as indicated by the definition of category 3 in the Breast Imaging Reporting and Data System (BI-RADS) lexicon of the American College of Radiology.[22] Pure FEA was recognized in 1.5% (60/4062) of our CNB: a higher frequency (3.6% and 3.7%) was reported by other authors [15, 23]. This low rate of pure FEA at CNB was probably correlated with the strict criteria for diagnosis of pure FEA, with no confusing ADH. As in previous reports, we confirm that almost all patients (92%) with pure FEA underwent needle biopsy for calcifications [15, 16, 23]. Like other studies, FEA is detected in association with ADH (30% in this study) and/or lobular neoplasia (10%) on CNB and with DCIS (10%) and IC (3%) on excisional biopsy [4, 6, 12, 15, 16, 24, 25]. The diagnosis and identification of FEA, especially on CNB, represents a challenge to surgical pathologists with inter- and intra-observer variability [26, 27]. Furthermore, standardization of the morphologic criteria and terminology are crucial for establishing guidelines. Indeed, the morphologic criteria used to define FEA differ between studies: Guerra-Wallace *et al* described CAPSS with atypical features as having architectural atypia (including micropapillary tufts, epithelial bridges, and early cribriform formations) [4]. FEA as defined by the WHO Working Group on the Pathology and Genetics of Tumors of the Breast (criteria used to define FEA in our series) lacks the architectural features of ADH or low-grade DCIS. Hence, some of their cases of CAPSS with atypia may also contain concomitant ADH and interfere with the possibility of comparing published studies. These changes in terminology, coupled with inter-and intra-individual variation in histological diagnosis, reflect changes in underestimates of IC or DCIS on surgical excision after secondary diagnosis of FEA at CNB (Table 2). Thus managing these patients diagnosed with FEA with percutaneous biopsy is

difficult. Piubello *et al* proposed that the management decision for a given patient with a CNB diagnosis of pure FEA be taken in a multidisciplinary team meeting and be based on factors of the following types: pathologic (standardized criteria and common terminology for the diagnosis), clinical and radiological (entity of target removal, presence or absence of other lesions, concordance or non-concordance between histology findings and radiological data), and technical (caliber of the needles and method—vacuum-assisted vs. automated gun—of the needle biopsy adopted)" [15]. But clinically occult, more advanced DIN and low-grade carcinomas may be missed. Underestimation rates for the percutaneous biopsy diagnosis of pure FEA vary from 0% to 30% with an average of 16%, similar to our study (Table 2). This high rate led us to offer a routine surgical audit before discovering FEA using percutaneous breast biopsy. To cut the costs of this surgical audit, a subset of patients with a low risk of underestimation when the diagnosis of FEA on CNB was made, is required. As discussed by Kunju and Keer, "the discovery of biomarkers that can predict which FEA or ADH lesions are associated with carcinoma" [16], especially when FEA was diagnosed on CNB, is one solution. Similarly, the discovery of clinical and/or radiological criteria alone or in combination in the form of nomograms (as proposed for HCA)[11] used to define a subset of patients at low risk of detection of DCIS or IC in secondary surgical excision would offer an alternative to systematic secondary surgery while ensuring patient safety. In our series, it was not possible to determine such criteria (Table 1) when attempting to identify a population at low risk of underestimation. But, because of small number of FEA, there is lack of power to detect a difference between groups. Thus, further studies with a large number of patients and prospective registration would establish criteria and provide recommendations to avoid secondary surgery in these patients.

Conclusion

This study reports the highest number of patients with FEA diagnosed at CNB and immediate follow-up surgical excision. Our data highlight the importance of recognizing and diagnosing FEA in core needle biopsies. The underestimation rate of CNB diagnosis of pure FEA was 13%: 8/60 patients had DCIS or IC in subsequent surgical excision. Thus, the presence of FEA on CNB, even in isolation, warrants follow-up excision. Larger prospective studies are required to establish guidelines with clinical and radiological criteria that define a group of patients with a low risk of underestimation and could spare subsequent surgery.

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Conflicts of interest

None declared

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TABLE 1. Underestimation rates for 60 cases of Flat Epithelial Atypia at Core Needle Biopsy according to clinical, radiological and histological variables.

Variables	No.	No. of underestimates	Underestimated rate (%)	p
Age at biopsy (years)				
<50	23	2	9%	
≥50	37	6	16%	0.66
Menopausal				
Yes	30	6	20%	

No	30	2	7%	0.25
HRT (in 30 menopausal women)				
Yes	11	4	36%	
No	19	2	11%	0.22
Personal or family history of breast cancer				
Yes	11	2	18%	
No	49	6	12%	0.97
Clinical breast abnormality				
Yes	3	2	67%	
No	57	6	11%	0.06
Mammographic findings: microcalcifications				
Yes	55	6	11%	
No	5	2	40%	0.25
Mammographic findings: mass				
Yes	4	1	25%	
No	56	7	13%	0.95
Ultrasound abnormalities				
Yes	10	1	10%	
No	28	7	25%	0.58
BI-RADS:				
3	3	0	0%	
4	54	8	15%	
5	3	0	0%	0.60

Percentage of lesion removed by CNB:				
>90%	18	1	6%	
<90%	42	7	17%	0.46
Biopsy guidance				
ultrasound	6	1	17%	
stereotactic	54	6	11%	0.79
Needle size if vacuum CNB				
8-gauge	13	3	23%	
10-gauge	13	1	8%	
11-gauge	29	4	14%	
14-gauge	5	0	0%	0.53
No. of cores taken at biopsy				
≤11	31	4	13%	
≥12	29	4	14%	0.78

HRT: Hormone Replacement Therapy; CNB: Core Needle Biopsy; NS: Not Significant

TABLE 2. Results of studies where Flat Epithelial Atypia on Core Needle Biopsy was followed by immediate surgical investigation.

Authors	**Number of cases with FEA at CNB**	**Number of DCIS or IC at surgical biopsy**	**DCIS or IC at surgical biopsy (%)**

Brogi *et al* (2002) [Abstract]	23	7	30%
Nasser *et al* (2003) [Abstract]	27	6	22%
Bonnett *et al* (2003) [Abstract]	9	2	22%
Guerra-Wallace *et al* (2004) [Abstract]	31	4	13%
Kunju *et al* (2006)	14	3	21%
Piubello *et al* (2009)	20	0	0%
Present study	60	8	13%
Total	**185**	**30**	**16%**

FEA: Flat Epithelial Atypia; CNB: Core Needle Biopsy; DCIS: Ductal Carcinoma *In situ*; IC: Invasive Carcinoma.

Table 3. Summary of clinicoradiologic Data of patients with diagnosis of Ductal Carcinoma *In situ* or Invasive Carcinoma on subsequent surgery after initial Core Needle Biopsy of pure Flat Epithelial Atypia.

Cases	Age at Biopsy	Menopausal	HRT	Personal or familial history of breast cancer	Breast Clinical abnormality	Mammographic findings	Ultrasound abnormalities	BI-RADS	Percentage of lesion removed by CNB	Biopsy guidance	Size of needle	Number of sample	Histology of the surgical specimen
1	59	yes	no	no	no	mca 54mm		4	<90%	stereotactic	8 G	6	DCIS 5mm grade 1
2	58	yes	yes	no	Yes : induration	no	yes	NC	<90%	ultrasound	11G	12	DCIS 80mm grade 2
3	46	no		no	no	mca 7mm		4	<90%	stereotactic	10G	10	DCIS 5mm
4	68	yes	no	no	no	mca	no	4	<90%	stereotactic	11G	14	DCIS 4mm grade 2
5	57	yes	yes	Familial 1 case	no	Round opacit	no	4	<90%	stereotactic	11G	10	DCIS 15mm grade 2

						y							
6	50	yes	yes	no	nipple discharge	Mca 4mm	no	4	>90%	stereotactic	11G	12	DCI 3mm SBR 2 ER+ PR+ HER2-
7	44	no		Familial 1 case	no	Mca 15mm	no	4	<90%	stereotactic	8G	13	DCIS 6mm grade1
8	57	yes	yes	no	no	Mca 35mm	no	4	<90%	stereotactic	8G	9	DCI 16mm SBR1 ER+ PR+ HER2-

HRT: Hormonal Replacement Therapy; mca : microcalcification ; DCIS: ductal carcinoma *in situ* ; IDC: Invasive Ductal Carcinoma. NC: Not Communicated