Original Article

Correlation of Ultrasound, Cytological, and Histological Features of 110 Benign BI-RADS Categories 4C and 5 Nonpalpable Breast Lesions. The Institut Curie's Experience

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BACKGROUND: The purpose of this study was to determine the pathological and ultrasound (US) features of benign nonpalpable breast lesions (NPBLs) classified as Breast Imaging Reporting and Data System (BI-RADS) category 4C or 5. **METHODS:** Between 2003 and 2007, 849 consecutive NPBLs detected at US and classified as BI-RADS category 4C (505) or 5 (344) initially underwent US-guided fine needle aspiration (FNA) at our institution. Benign diagnoses were established according to surgical excision findings or during a minimal 6-month imaging follow-up (mean, 3.7 years [SD, 2.6 years]). US BI-RADS features were reviewed and compared retrospectively using a chi-square test for the following pathological categories: epithelial and fibrous proliferation (EFP), cystic and papillary lesion (C&P), inflammatory lesion (IL), benign tumor (BT), intramammary lymph node (ILN), intraepithelial proliferative lesion (IPL), and nonspecific morphological alteration (NMA). The performance of FNA in the diagnosis of benignity was assessed. **RESULTS:** Of 849 NPBLs, 110 (12.9%) NPBLs were benign: 88 (17.4%) were BI-RADS category 4C, and 22 (6.4%) were BI-RADS category 5. Forty-four (40%) were EFPs, 21 (19%) were C&Ps, 13 (12%) were NMAs, 11 (10%) were ILs, 11 (10%) were BTs, 8 (7%) were IPLs, and 2 (2%) were ILNs. Lesion shape, US pattern distribution, and posterior features showed statistically significant differences between these categories ($P < .05$): 33 (75%) EFPs exhibited posterior shadowing, 18 (86%) C&Ps were homogenous, 9 (82%) ILs were heterogeneous, 11 (100%) BTs were homogeneous, 9 (82%) BTs were oval, and 6 (75%) IPLs were irregularly shaped. Of the 110 benign NPBLs, FNA diagnosis was falsely positive in 7 (6%), suspicious in 10 (9%), and benign in 90 (82%), and 3 (3%) were inadequate for diagnosis. **CONCLUSION:** A diverse array of benign NPBLs can be classified as BI-RADS category 4C or 5 on US, each showing specific imaging presentations. ***Cancer Cytopathol* 2021;129:479-488.** *© 2021 American Cancer Society.*

KEY WORDS: benign lesions; BI-RADS 4C; BI-RADS 5; breast; fine-needle aspiration; ultrasound guided.

INTRODUCTION

Diagnosis of nonpalpable breast lesions (NPBLs) is currently based on radiological appearance and, when indicated, pathological analysis. The American College of Radiology has proposed the Breast Imaging Reporting and Data System (BI-RADS)[1] lexicon to standardize reporting of breast imaging results and to define clear guidelines for further management. Lesions are classified along 7 main diagnostic categories (0 to 6), with 3 additional subcategories for category 4 (4A, 4B, and 4C). For each BI-RADS category, an increasing positive predictive value (PPV) of malignancy is assigned. According to this classification, there is a risk of overscoring benign lesions classified as BI-RADS category 4C (ie, likely malignant, PPV >50% and <95%) or category 5 (ie, very likely malignant, PPV >95%).

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Received: October 27, 2020; **Revised:** November 24, 2021; **Accepted:** November 25, 2020

Published online March 10, 2021 in Wiley Online Library (wileyonlinelibrary.com)

DOI: 10.1002/cncy.22402, wileyonlinelibrary.com

In patients presenting with such overscored benign lesions, discordant imaging and pathological findings can result in situations that are difficult to manage.[2] Repeat sampling or surgical biopsy is usually performed,[3] increasing patient costs, risks, and anxiety. Currently, correlation of radiological and pathological data is the sole means of resolving such cases to avoid further procedures. However, there are few data in the literature to help the decision making process; imaging features of some specific histological lesions have been described in previous studies,[4-8] but only 1 study has been published on benign histological lesions classified as BI-RADS category 4C or 5 on breast imaging.[9] Better knowledge of their prevalence, imaging, and cytohistological characteristics would improve correlation between imaging and pathological results, and therefore improve patient management.

For BI-RADS categories 4C and 5, pathological analysis is warranted because of their high PPV for cancer.[1] Ultrasound-guided fine needle aspiration (USFNA) is a first-line diagnostic procedure, before more invasive techniques such as core needle biopsy (CNB), vacuum-assisted biopsy, and surgical biopsy.[10] It is especially suited for fast diagnoses or to assess multiple lesions. We previously published a study on the diagnostic accuracy of USFNA on a consecutive series of 3865 NPBLs.[11] Because all lesions were classified according to the BI-RADS classification before sampling, we used it to study the group of overscored BI-RADS 4C and 5 lesions.

The goal of this study was to describe the pathological characteristics of benign BI-RADS 4C and 5 lesions that underwent USFNA in our institution between 2003 and 2007, as well as to assess the performance of cytological analysis and to describe the main radiological features among these overscored lesions.

MATERIALS AND METHODS

Population

The institutional review board of our institution approved the study, and the need for patient's informed consent was waived. All NPBLs that underwent USFNA by a radiologist/pathologist team between 2003 and 2007 at our institution were considered eligible. In 2891 patients, 3865 NPBLs were consecutively investigated using USFNA during this time frame and corresponded to the cohort we described in our previous study.[11]

Before USFNA, NBPLs were classified according to the BI-RADS lexicon by the radiologist performing the breast ultrasound examination. Classification was established by review of the primary radiological workup available at the time of USFNA and before sampling was performed. Among the 3865 studied lesions, 558 (14.4%) and 361 (9.3%) NBPLs were classified as BI-RADS category 4C and BI-RADS 5 respectively.

Seventy NPBLs (53 [9.5%] BI-RADS category 4C and 17 [4.7%] BI-RADS category 5) in 44 patients were excluded from analysis: 21 (34%) in 18 patients were lost to follow-up; 31 (44%) in 15 patients were treated with radiotherapy, chemotherapy, or hormone therapy during follow-up; and in 18 (29%) in 11 patients, correlation between the sampled lesion at USFNA and the surgical specimen was inconclusive (15 due to neoadjuvant treatment, 2 due to diffuse infiltrating cancer, and 1 due to multiple nodules).

Finally, 505 BI-RADS category 4C (90.5%) and 344 BI-RADS category 5 (95.3%) NPBLs, in 396 and 273 patients, respectively, were analyzed for this study. The mean age was 61.2 years (SD, 11.3 years; range, 30-94 years); 1 (0.1%) lesion was sampled in a man, 54.9% of patients had a history of breast cancer, and the average size of NPBLs was 9.5 mm (SD = 5 mm).

USFNA

The USFNA protocol routinely used at our institution was described in our previous study.[11] All lesions in our study were either sampled by a radiologist/pathologist team comprising 1 of 9 senior radiologists to perform breast US examination and track the target and needle during the procedure and 1 of 4 pathologists to perform aspiration. If the pathologist was unavailable, the radiologist performed both procedures.

Cytological diagnoses were classified into 4 previously described categories[12]: benign, suspicious, malignant, and inadequate. Following our diagnostic criteria, we distributed "atypical" diagnoses between the benign and suspicious categories. Cytological suspicious diagnoses included: 1) occasional cells with cytonuclear atypia amid predominant benign cells; 2) large clusters of irregular boundaries with naked nuclei; 3) paucicellular smears with areas of mucinous or necrotic stroma; and 4) papillary formations comprising irregular cells without cystic

features. Inadequate cytological samples were considered in case of smears showing only debris or hematic smears.

Overall Pathological Classification

The final reports of all available pathological samples were reviewed retrospectively. Correlation between the targeted NPBL at US and the pathological specimen was established according to the respective report's descriptions (location, size, and aspect), US images, and gross pathology cross-section images.

Malignancy was confirmed at CNB or surgical examination. Benignity was established according to benign findings at pathological examination of the surgical specimen or after a minimal 6-month breast imaging follow-up in case of benign findings at USFNA or CNB. In case of coexistence of malignant and benign findings on the surgical excision specimen, both lesions had to be clearly differentiated for the index lesion to be definitively diagnosed as benign; otherwise, it was diagnosed as malignant.

Benign diagnoses were classified into 6 categories (Table 1), which were adapted from the World Health Organization classification of benign breast tumors[13]: epithelial and fibrous proliferation (EFP), cystic and papillary lesion (C&P), inflammatory lesion (IL), benign tumor (BT), intramammary lymph node (ILN), intraepithelial proliferative lesion (IPL), and nonspecific morphological alteration (NMA). "Old" cysts were defined as NPBLs with cystic cytological or histological features and thick, dense aspiration material at FNA. In case of lesions showing multiple histological features, the predominant one was considered for classification. If no main feature was found, NPBLs were considered as complex lesions. When only USFNA was performed, the evoked diagnosis on the cytology report was retained for classification. Analysis and diagnosis of cytological samples were based on routine practice criteria used at our institution and have already been described in previous studies.[12,14] The concordance between the specific diagnosis evoked at cytology and the final histological diagnosis, by CNB or surgical excision when available, were assessed.

Discordant Lesions Characteristics

US examinations before FNA were reviewed retrospectively by the author, who was blinded to the initial BI-RADS classification and cytological and histological results. The sampled NPBL was described according to the BI-RADS lexicon. The following features were noted: shape (irregular, oval, or round); orientation (greater axis parallel to the skin or perpendicular); margin (circumscribed, macrolobulated, microlobulated, indistinct, angular, spiculated); internal echogenicity (hyperechoic, isoechoic, hypoechoic with regard to fat surrounding tissue and homogeneous or heterogeneous); and US beam transmission (posterior enhancement, absence or presence of posterior attenuation, combined pattern).

TABLE 1. Overall Pathological Classification of Benign Lesions

Epithelial and fibrous proliferations
Fibrocystic changes
Scar/fibrous tissue
Adenosis
Radial scar
Complex epithelial proliferations
Cystic and papillary lesions
Cyst
"Old" cyst
Papilloma
Inflammatory lesions
Fat necrosis
Abscess
Nonspecific inflammatory tissue
Benign tumors
Fibroadenoma
Giant cell tumor
Low-grade phyllodes tumor
Intraepithelial proliferative lesions
Atypical ductal hyperplasia
Lobular neoplasia
Usual ductal hyperplasia
Intramammary lymph node
Nonspecific morphological alterations

Statistical Analysis

The prevalence of each pathological category was calculated. The performance of USFNA and the presentation at breast US between each category were compared using a chi-square test. Because ILNs are described separately in the BI-RADS lexicon, this category was not included in this comparison. The false-positive and false-suspicious results of USFNA, as well as its performance in evoking the definitive histological diagnosis, were also assessed.

RESULTS

Population Characteristics

Among the included 505 NPBLs that were BI-RADS category 4C, 417 (82.5%) were malignant and 88 (17.5%) were benign. Among the 344 NPBLs that were BI-RADS

TABLE 2. Definitive Diagnosis of Benignity for Analyzed Overscored NPBLs

NPBLs	BI-RADS Category 4C	BI-RADS Category 5	Total
Definitive benign diagnosis by surgical excision	44 (50)	12 (55)	56 (51)
Definitive benign diagnosis by follow-up	44 (50)	10 (45)	54 (49)
After sampling both by FNA and CNB	24 (54)	8 (80)	32 (59)
After sampling only by FNA	20 (46)	2 (20)	22 (41)
Total	88 (80)	22(20)	110 (100)

Abbreviations: BI-RADS, Breast Imaging Reporting and Database System; CNB, core-needle biopsy; FNA, fine needle aspiration; NPBLs, nonpalpable breast lesion.
All data are presented as n (%).

category 5, 322 (93.6%) were malignant and 22 (6.4%) were benign. The mean size of the 110 analyzed benign NPBLs was 9.4 mm (SD, 5.6 mm): 8.8 mm (SD, 4.9 mm) for BI-RADS category 4C and 11.7 mm (SD, 7.5 mm) for BI-RADS category 5. Surgical excision establishing a final diagnosis of benignity was performed in 56 (50.9%) NPBLs (Table 2); among these, there was an associated breast cancer that was clearly differentiated from the benign NPBL in only 5 cases (9%), and the other 51 showed benign findings alone. The mean follow-up duration for nonremoved benign NPBLs (54 [49.1%]) was 3.7 years (SD, 2.6 years). No lesion initially diagnosed as benign was found to be malignant during follow-up.

Overall Pathological Classification

Most overscored lesions were represented by EFPs (44 of 110, 40%), followed by C&Ps (21 of 110 [19%]). ILs, BTs, and NMAs showed similar prevalence (11, 11, and 13 of 110 [10%, 10%, and 12%, respectively]). IPLs were less frequent (8 of 110 [7%]): atypical ductal hyperplasia was found in 5 (62.5%) cases, lobular intraepithelial neoplasia in 2 (25%) cases, and usual ductal hyperplasia in 1 (12.5%) case. Two (2%) intramammary lymph nodes were found in our series.

Nonspecific diagnoses such as scar/fibrous tissue, fibrocystic changes, nonspecific inflammatory tissue, and NMA represented most NPBLs (11, 14, 2, and 13 out of 110, respectively [36% total]). Fibroadenomas, adenosis, cysts, and papillomas were found rather frequently as well (10, 8, 12, and 9, respectively [35% total]). Other specific diagnoses (radial scars, fat necrosis, abscess, ILN, granular cell tumor, and IPL) were found less frequently (7, 5, 4, 2, 1, and 7, respectively [24% total]). The surgical excision rates for each diagnostic category are shown in Table 3.

TABLE 3. Surgical Excision Rates by Diagnostic Category

Diagnosis	Total	Surgical Excision
Epithelial and fibrous proliferations	44 (40)	22 (50)
Adenosis[a]	8 (7)	5 (62.5)
Radial scar[a]	7 (6)	6 (85.7)
Scar and fibrous tissue	11 (10)	2 (18.2)
Fibrocystic changes	14 (13)	5 (35.7)
Complex proliferations	4 (4)	4 (100)
Cystic and papillary lesions	21 (19)	10 (48)
Cyst	8 (7)	1 (12.5)
"Old" cyst	4 (4)	1 (25)
Papilloma[a]	9 (8)	8 (88.9)
Inflammatory lesions	11 (10)	6 (46.2)
Fat necrosis	5 (5)	0 (0)
Abscess	4 (4)	4 (100)
Nonspecific inflammatory tissue	2 (2)	2 (100)
Benign tumors	11 (10)	8 (72.7)
Fibroadenoma	10 (9)	7 (70)
Giant cell tumor	1 (1)	1 (100)
Lymph node	2 (2)	0 (0)
Intraepithelial proliferative lesions[a]	8 (7)	8 (100)
Nonspecific morphological alterations	13 (12)	2 (15)

All data are presented as n (%).
[a]Known to be associated with a higher risk of breast cancer.[22,23]

Cytological Diagnosis

Figure 1 shows the cytological presentation of benign NPBLs classified as BI-RADS categories 4C and 5. USFNA results were benign in 90 NPBLs (82% true-negative rate), suspicious in 10 NPBLs (9% false-suspicious rate), malignant in 7 NPBLs (6% false-positive rate), and inadequate in 3 NPBLs (3% inadequacy rate). Table 4 shows FNA results among the different pathological categories. The diagnostic performance of USFNA among the main pathological categories (EFP, C&P, IL, BT, ILN, IPL, and NMA) exhibited no statistically significant differences ($P = .09$). The 7 false-positive NPBLs at USFNA included 2 papillomas (28%), 2 IPLs (28%), 1 adenosis (14%), 1 radial scar (14%), and 1 complex EFP (14%), comprising a radial scar, papillomas, and simple epithelial hyperplasia. These 4 categories also represented 70% (7 of 10) of false-positive or false-suspicious lesions at USFNA; the other 30% corresponded to BTs (2 fibroadenomas and 1 granular cell tumor). All other lesions were correctly diagnosed as benign on USFNA.

In 88 (80%) NPBLs, the USFNA results correlated with histological results, either by CNB or surgical excision. Among these, FNA correctly evoked a diagnosis of fat necrosis in 3 NPBLs (of 3 NPBLs with fat necrosis at histological examination [100%]), fibroadenoma in 5 (of 10 [50%]), fibrous lesion in 3 (of 7 [43%]), abscess in 1 (of 4 [25%]), and benign papilloma in 2 (of 9 [22%]). The granular cell tumor was diagnosed as suspicious at USFNA. Among the 12 cystic lesions at FNA, only 3

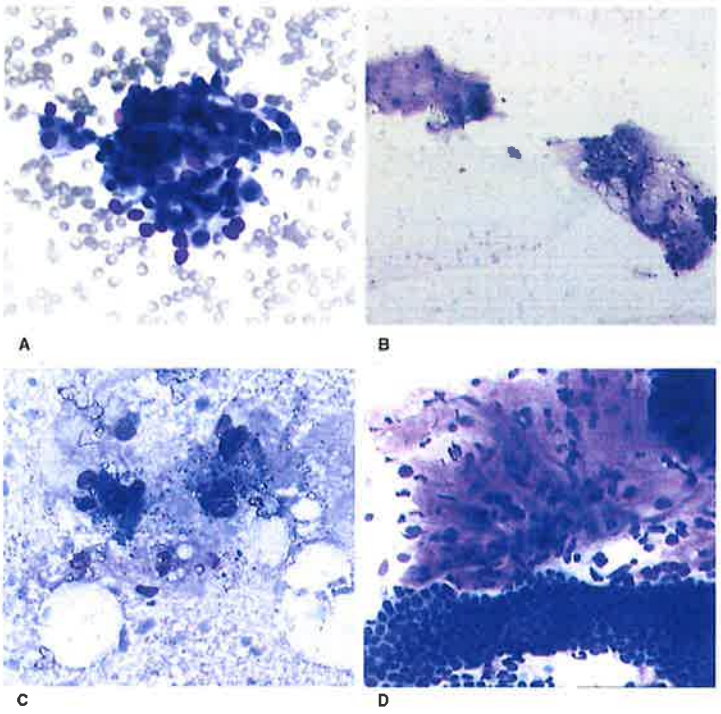

Figure 1. Cytological presentation of benign nonpalpable breast lesions classified as Breast Imaging Reporting and Data System (BI-RADS) category 4C and 5. (A) Clusters of small, cohesive epithelial cells with naked nuclei are found in fibrocystic changes (May-Grünwald-Giemsa staining). (B) Scar tissue exhibits paucicellular smears with sheets of collagen and fibroblasts (May-Grünwald-Giemsa staining). (C) Fat necrosis smears (May-Grünwald-Giemsa staining) show foamy vacuolated macrophages, debris, and fragments of fat. (D) Aspirates from fibroadenoma (May-Grünwald-Giemsa staining) show highly cellular epithelial formations in association with vast areas of fibrous tissue.

underwent biopsy or surgical excision, confirming the diagnosis in all (100%). The remaining 22 NPBLs (20%) were classified by USFNA alone: 3 showed fibrous tissue, 6 cysts, 3 "old" cysts, 2 fat necrosis, 2 lymph nodes, and 6 NMAs. No phyllodes tumors were found in our series.

US Features

Figure 2 shows the US presentation of benign NPBLs classified as BI-RADS categories 4C and 5. Breast US characteristics of overscored lesions are shown in Table 4. Only shape, internal echogenicity distribution, and US beam transmission showed statistically significant differences ($P < .05$) between the primary pathological categories: EFPs exhibited posterior shadowing of the US beam (33 of 44 [75%]), C&Ps were homogenous (18 of 21 [86%]), ILs were heterogeneous (9 of 11 [82%]), and BTs were oval (9 of 11 [82%]) and homogeneous (11 of 11 [100%]). IPLs were irregularly shaped (6 of 8 [75%]).

TABLE 4. Breast US and USFNA Presentation in the 6 Different Pathological Categories

	Pathological Category							
	EFP	C&P	IL	BT	IPL	NMA	Total	P^a
No. of lesions	44 (40)	21 (19)	11 (10)	11 (10)	8 (7)	13 (12)	110 (100)	
Size, mm ± SD	9.5 ± 6.0	8.3 ± 5.2	13.7 ± 4.7	8.5 ± 4.6	11.8 ± 5.7	8.1 ± 3.0	9.4 ± 4.9	.48
USFNA results								.27
Benign	36 (74)	17 (81)	11 (100)	8 (73)	4 (50)	12 (92)	90 (82)	
Suspicious	3 (6)	2 (10)	0 (0)	3 (27)	2 (25)	0 (0)	10 (9)	
Malignant	3 (6)	2 (10)	0 (0)	0 (0)	2 (0)	0 (0)	7 (6)	
Inadequate	2 (4)	0 (0)	0 (0)	0 (0)	0 (0)	1 (8)	3 (3)	
Shape								.0001
Oval	8 (18)	5 (24)	5 (45)	9 (82)	0 (0)	4 (31)	33 (30)	
Round	6 (12)	11 (52)	1 (9)	0 (0)	2 (0)	3 (23)	23 (21)	
Irregular	30 (61)	5 (24)	5 (45)	2 (18)	6 (75)	6 (46)	54 (49)	
Orientation								.53
Parallel	16 (33)	6 (29)	5 (45)	7 (64)	1 (13)	5 (38)	42 (38)	
Perpendicular	9 (18)	4 (19)	2 (18)	1 (9)	2 (25)	4 (31)	22 (20)	
Other	19 (39)	11 (52)	4 (36)	3 (27)	5 (63)	4 (31)	46 (42)	
Margin								.34
Circumscribed	2 (6)	2 (10)	0 (0)	2 (19)	0 (0)	1 (8)	8 (7)	
Microlobulated	4 (8)	2 (10)	2 (18)	1 (9)	1 (13)	1 (8)	11 (10)	
Indistinct	16 (33)	13 (62)	5 (45)	4 (36)	7 (88)	7 (0)	53 (48)	
Angular	16 (33)	4 (19)	3 (27)	4 (36)	0 (0)	2 (15)	29 (26)	
Spiculated	6 (12)	0 (0)	1 (9)	0 (0)	0 (0)	2 (15)	9 (8)	
Ultrasound pattern								
Intensity								.19
Hyperechoic	3 (6)	0 (0)	0 (0)	0 (0)	1 (0)	1 (8)	5 (5)	
Isoechoic	4 (8)	1 (5)	3 (27)	4 (36)	3 (38)	2 (15)	17 (15)	
Hypoechoic	37 (76)	20 (95)	8 (73)	7 (64)	4 (50)	10 (77)	88 (80)	
Distribution								.0002
Homogenous	22 (45)	18 (86)	2 (18)	11 (100)	6 (75)	10 (77)	70 (64)	
Heterogeneous	22 (45)	3 (14)	9 (82)	0 (0)	2 (0)	3 (23)	40 (36)	
US beam transmission								.01
Posterior shadowing	33 (75)	8 (38)	7 (64)	3 (27)	5 (63)	6 (46)	62 (56)	
Normal	11 (25)	9 (43)	3 (27)	7 (64)	3 (38)	6 (46)	40 (36)	
Combined	0 (0)	1 (5)	0 (0)	1 (9)	0 (0)	1 (8)	3 (3)	
Posterior enhancement	0 (0)	0 (0)	1 (9)	0 (0)	0 (0)	0 (0)	2 (2)	

Abbreviations: BT, benign tumor; C&P, cystic and papillary lesion; EFP, epithelial and fibrous proliferation; IL, inflammatory lesion; IPL, atypical hyperplasia; NMA, nonspecific morphological alteration; US, ultrasound; USFNA, ultrasound-guided fine needle aspiration.
All data are presented as n (%) unless noted otherwise.
[a]Boldface values are statistically significant ($P < .05$)

DISCUSSION

Radiopathological correlation is an essential step in diagnosing NPBLs, especially in cases of discordance between radiological presentation and pathological diagnosis.[15] Such a situation arises when pathological analysis of BI-RADS categories 4C and 5 NPBLs yields benign findings, as in 17.5% and 6.4% of NPBLs, respectively, in our series. Because the PPV for cancer is high in these categories, the risk of a missed diagnosis of breast cancer is high as well. Strong confidence in the diagnosis is therefore required before ruling out breast cancer. In some cases, the diagnostic strategy might lead to the surgical excision of a benign lesion: among surgically excised lesions in our series (51% of discordant NPBLs), exclusively benign findings were found on 91%, without any associated breast cancer. These could be considered, post hoc, as unnecessary surgical procedures. On the other hand, benign findings at USFNA (and CNB when performed) avoided surgical excision in the other half of patients.

In our series, EFPs were the most common benign NPBLs presenting as BI-RADS categories 4C and 5 (40%), followed by C&Ps (19%). The prevalence of IPLs (7%) was lower than in other published series, at 10% to 20%.[16,17] Atypical hyperplasia commonly presents as calcifications at breast imaging and is found fortuitously in association with other lesions.[16] Calcifications are seldom seen at US and preferably sampled under stereotactic guidance using vacuum-assisted biopsy.[18] Because our study was based on USFNA as opposed to all lesions detected on mammography, this could explain

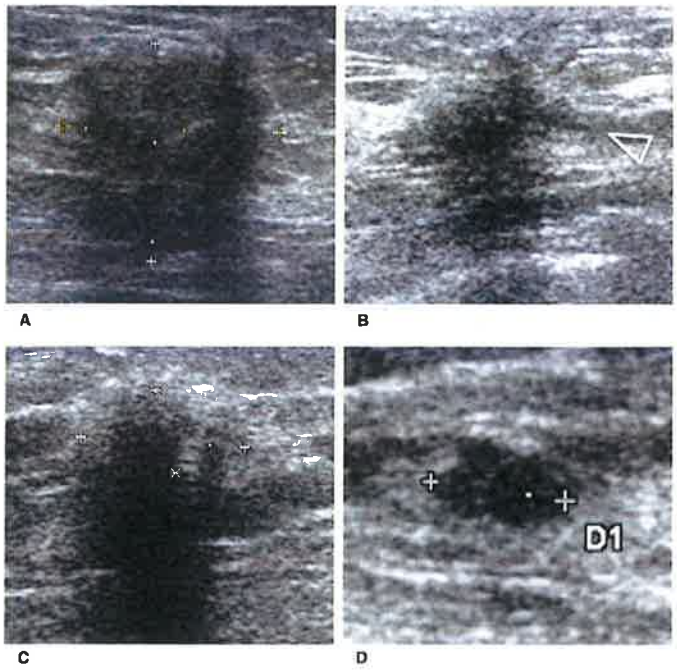

Figure 2. Ultrasound (US) presentation of benign nonpalpable breast lesions classified as Breast Imaging Reporting and Data System (BI-RADS) category 4C and 5. Posterior attenuation of the US beam is present in fibrocystic changes (A) and scar tissue (B), which was a frequent finding in epithelial and fibrous proliferations. (C) Heterogeneous distribution pattern can be seen in fat necrosis, with hyper-, iso-, and hypoechoic areas visible inside the lesion. (D) Fibroadenomas presented with oval shape and homogeneous distribution pattern. Note that all lesions presented indistinct or angulated margins. A spicule can be seen on the periphery of the scar in panel B (arrowhead).

the lower prevalence of IPLs. In addition, ILs, BTs, and NMAs showed similar prevalence rates (~10% each). Interestingly, for radiopathological correlation, 3 US features (shape, internal echogenicity distribution, and US beam transmission) displayed significant differences in their distributions among these groups, and each category had 1 or 2 characteristic features: EFPs demonstrated posterior shadowing, C&Ps demonstrated homogenous echogenicity, ILs demonstrated hererogeneous echogenicity, BTs demonstrated oval shape and homogeneous echogenicity, and IPLs demonstrated irregular shape. Knowledge of these typical presentations should help avoid the need for further investigation in concordant cases or, in cases of discordance, help confirm the need for additional sampling.

Because all NPBLs in our series underwent USFNA, we also assessed its performance in diagnosing such lesions. No significant differences were found among the primary pathological categories, but EFPs, C&Ps, and IPLs represented all false-positive results and most suspicious NPBLs on USFNA. This finding is supported by previous FNA studies.[19-22] If we integrate these results

TABLE 5. Comparison of BI-RADS Category 4C and 5 Lesions Between the Present Study and Kim et al[9]

Pathological Category	Kim et al		Present Study (n = 110)
	Original Results (n = 71)	Adjusted Results (n = 56)[a]	
EFP	4 (6)	10 (18)	44 (40)
C&P	18 (25)	18 (32)	21 (19)
IL	15 (21)	15 (27)	11 (10)
BT	14 (20)	9 (16)	11 (10)
NMA	10 (14)	4 (7)	13 (12)
CMC	10 (14)	NA	NA
ILN	NA	NA	2 (2)
IPL	NA	NA	8 (7)

Abbreviations: BT, benign tumor; C&P, papillary and cystic lesion; CMC, clustered calcification; EFP, epithelial and fibrous proliferation; IL, inflammatory lesion; ILN, intramammary lymph node; IPL, intraepithelial proliferative lesion; NA, not available; NMA, nonspecific morphological modifications.
All data are presented as n (%).
[a]Results adjusted for differences in classification: exclusion of 5 (7%) phyllodes tumors, 10 (14%) CMCs, and 6 (8%) NMAs reclassified as EFPs.

with the radiological presentation of EFPs and IPLs, we can conclude that BI-RADS categories 4C and 5 featuring irregular shape or posterior shadowing should not be sampled by USFNA alone. We hypothesize that selection of BI-RADS categories 4C and 5 for USFNA sampling using these criteria might improve the overall performance of USFNA. Indeed, in our previous study assessing the diagnostic performance of USFNA,[11] specificity was lowest in these categories, at 87.7% (range, 78.5%-93.9%) and 66.7% (range, 43%-85.4%), respectively (vs a range of 96.3%-99.7% in other categories), whereas sensitivity was highest at 94.5% (range, 91.8%-96.5%) and 94.1% (range, 90.9%-96.4%) (vs a range of 80%-92.1% in other categories). The results of both studies suggest that better selection of the lesions to be sampled could lower the number of false-positive results and therefore improve USFNA's specificity in these categories where diagnosis is the most challenging.

Our results should help avoid surgery in some cases of benign lesions that are classified as BI-RADS categories 4C and 5. Unfortunately, there are scant data in the literature regarding this subject. Only 1 study, by Kim et al,[9] examined the radiopathological presentation of 71 benign lesions classified as BI-RADS categories 4C and 5; a comparison of their results with ours is shown in Table 5. Although the results reported by Kim et al are substantially different from ours, they can be explained in part by differences in the study population and the classification of lesions. First, we found no phyllodes tumors, whereas Kim et al found 5 (7%), probably because they included palpable lesions in their series: phyllodes tumors commonly present as large lesions (>1-2 cm) and are therefore palpable.[23] Clustered calcifications accounted for 14% of lesions in their series and could not be correlated with any of our diagnostic categories. Scar and fibrous tissue were classified as NMA (6 [8%]) in their series, whereas we classified these as EFPs. Finally, lesions with atypical hyperplasia were excluded in the Kim et al study. Yet even after accounting for these differences, we still found a higher prevalence of EFPs and NMAs and a lower prevalence in other categories—namely C&Ps, ILs, and BTs. This could be due to different study designs: our study was based on a review of all cases undergoing USFNA, whereas Kim et al based their study on surgically proven diagnoses. We assert that relying on surgical excision specimen's diagnoses is more reliable than relying on percutaneous samples. Nevertheless, it would not be ethical to excise every lesion classified as BI-RADS category 4C or 5 to simply obtain a definitive histological diagnosis. Limiting analyzed lesions to surgical excision diagnoses reduces the number and, potentially, the spectrum of studied lesions. Indeed, there could be a selection bias whereby patients with higher-risk lesions on breast imaging and/or sampling are more likely to undergo surgery. In our series, excision rates were higher in lesions known to be at high risk for associated cancer,[24,25] and lesions at low risk for associated cancer were more frequent than in the study by Kim et al. Regarding radiological presentation, Kim et al reported that only margin features showed statistically significant differences between the different pathological categories, whereas we found no significant differences for this BI-RADS descriptor. In our study, most NPBLs presented indistinct or angulated margins regardless of diagnosis, which could be expected since these two margin features are highly suspicious findings of malignancy and a major component in upgrading

NPBLs to higher US BI-RADS categories.[26] Interestingly, very few NPBLs presented spiculated margins (8%), a sign found in 37% to 50% of cancers,[27,28] suggesting that this finding is very specific of malignancy.

In addition to the absence of surgical excision of all NPBLs, our study has other limitations. We limited our study to a series of USFNA-sampled NPBLs, which has 2 potential drawbacks: first, there could be a selection bias, because not all BI-RADS category 4C and 5 NPBLs are routinely sampled by USFNA at our institution. For example, lesions presenting with cystic features at imaging might be preferably sampled with FNA rather than undergoing CNB first, whereas NPBLs without cystic features at imaging might undergo CNB only. Additionally, only 22 NPBLs (20% of analyzed NPBLs) underwent USFNA without further sampling by CNB or surgical excision, and the overall pathological classification was based on USFNA's results alone. Yet, in most NPBLs (13 [59%]), USFNA yielded findings consistent with cysts, fat necrosis, and lymph nodes, which can be reliably diagnosed at FNA,[29,30] therefore limiting classification errors due to the lack of histological analysis. We also set a minimal-follow-up of 6 months, since benignity of the lesion was confirmed at USFNA and, in most cases (58%) with CNB as well, so the risk of missed false-negative results among studied NPBLs was low. Moreover, because our institution is a referral center for breast cancer, follow-up examinations are outsourced, and patients only return in case of new, suspicious findings. Setting a longer follow-up threshold would have unnecessarily excluded several benign lesions, so we prioritized an accurate representation of the prevalence of the different categories.

Finally, we only studied breast US features and did not assess mammographic or breast magnetic resonance imaging (MRI) presentations, which were not available for all NPBLs. Nevertheless, US is the preferred breast imaging modality for sampling NPBLs, excluding calcifications.[41] Analysis of NPBL presentation at breast US examination will always be available in cases of US sampling, whereas these might not be seen at mammography examinations, and breast MRI is performed in limited numbers of cases.

In conclusion, we found that a diverse panel of benign lesions might be classified as BI-RADS category 4C or 5 at US examination. The most common lesions were EFPs, followed by C&Ps. Regarding imaging presentation, shape, internal echogenicity distribution, and posterior attenuation of the US beam showed statistically significant differences between each category and should be considered in cases of difficult radiopathological correlation. USFNA showed good performance overall in the detection of benignity and yielded most false-positive diagnoses in adenosis, radial scars, papillomas and atypical hyperplasia: such cases, usually presenting with irregular shape or posterior shadowing of the US beam, should be sampled with CNB in addition to USFNA.

FUNDING SUPPORT

No specific funding was disclosed.

CONFLICT OF INTEREST DISCLOSURES

The authors made no disclosures.

AUTHOR CONTRIBUTIONS

Josep A. Farras Roca: Data curation, formal analysis, methodology, visualization, writing–original draft, writing–review and editing. **Anne Tardivon:** Conceptualization, investigation, methodology, validation. **Fabienne Thibault:** Conceptualization, investigation, methodology, validation. **Roman Rouzier:** Conceptualization, investigation, methodology, validation. **Jerzy Klijanienko:** Conceptualization, investigation, methodology, project administration, supervision.

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