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A single-centre experience

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BACKGROUND: *Breast lesions of uncertain malignant potential, also known as B3 lesions, represent a heterogeneous group of tumors with variable malignancy risk. Surgical excision should be considered depending on clinical, radiological and histological features, family history and following informed consent. The aim of the present paper is to evaluate the positive predictive value (PPV) of diagnosis of malignancy in surgically excised B3 lesions in order to identify possible predictive upgrade criteria. We mainly focused on disclosing the concordance rate between tissue biopsy and final surgical pathology and correlation between radiology and pathology.*
METHODS*: Between January 2018 and December 2021, 83 patients undergoing ultrasound guided tru-cut needle biopsy or VABB with a B3 diagnosis and surgical excision following multidisciplinary discussion were retrospectively reviewed in our Breast Unit.*
RESULTS: *Out of a total of 83 cases with a B3 diagnosis before surgery, atypical ductal hyperplasia accounted for 29/83 cases(34.93%) and the most part of patients presented nodular lesions (n = 34/83, 40.96%). Among the 15 cases of malignancy detected after surgery, micro calcifications were registered in 53.3% of patients on mammography (n = 8/15).*
CONCLUSION: *We assessed the correlation between radiological and pathological criteria in order to guide risk stratification and ensure adequate patient management. Correspondence between histological diagnosis, imaging and type of diagnostic biopsy were evaluated. No statistically significant predictors were identified for the parameters assessed in our study.*

KEY WORDS: B3 Breast Lesions, Lesions of Uncertains Malignant Potential, Mammografic Distortion, Screen Detected Breast Lesion

Introduction

B3 breast lesions account for approximately 3-21% of all breast lesions and carry a low but potential risk of associated malignancy ranging from 21 to 35% [1]. They represent a heterogeneous group of lesions that can be associated with malignancy and are frequently managed by surgical excision, due to such low but potential risk for malignancy. With the increasing use of mammographic screening, the detection rate of B3 lesions in otherwise asymptomatic patients has increased [2,3]. Breast biopsy is commonly performed to evaluate suspicious palpable lesions which often turn out to be benign [4]. These lesions are highly heterogeneous and can be classified according to the presence or absence of associated atypia. For this reason, some authors have suggested

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a further histological classification of B3 lesions in B3a and B3b according to presence or absence of atypia [5]. However, up to 35% of lesions of uncertain character (B3) receive a DCIS or low-grade neoplasia diagnosis on surgical specimen. El Sayed et al reported a 19.1% underestimation rate of malignancy associated with B3 lesions [6] and Brennan's meta-analysis confirmed that approximately one out of four DCIS diagnoses represent underestimated invasive breast cancer [7]. Therefore, correlation between radiological results and histopathological data is essential to assess adequate classification of the risk of malignancy and recommend the best management pathway for individual cases. Radiological imaging features such as well-circumscribed and lobulated irregular masses and associated microcalcifications may be helpful in predicting malignancy [8].

Hence, a careful radiological-pathological correlation is the essence for achieving optimal treatment by identifying parameters that allow to distinguish within the B3 lesion group those to be treated by surgery from the low risk of carcinoma group to be simply followed up. The controversial management of B3 lesions has been discussed in several guidelines, such as those issued by the American Society of Breast Surgeons [9]. General agreement exists in the management of phyllodes tumor only, in which surgical excision is always recommended, whereas different approaches for all remaining B3 lesions consist in surgical excision, vacuum assisted excision (VAE) or follow-up. However, it should be underlined that microcalcifications with suspicious or frankly malignant radiological features as well as histological diagnosis of B3 on core biopsy have the highest PPV (50%) [10].

Even in the case of complete removal of microcalcifications there is a 5% risk of missing malignancy. Pleomorphic lobular carcinoma in situ (LIN3) deserves special discussion, in which microcalcifications or rather comedo-necrosis are frequently more represented and indication for surgery is mandatory [11].

The aim of the present study was to evaluate the positive predictive value (PPV) for malignancy in B3 lesions undergoing surgical excision, identifying possible predictive criteria. Concordance between tissue biopsy and postoperative pathology and correlation between radiology and pathology were recorded. We analysed the correlation between radiological and pathological parameters to measure and classify risk and ensure adequate patient management, assessing the correspondence between pathological diagnosis, diagnostic imaging and biopsy method used for diagnosis.

Material and Methods

A total of 83 patients undergoing biopsy and VABs (vacuum assisted biopsy) and receiving a B3 diagnosis between January 2018 and December 2021 in our Breast Unit were retrospectively assessed. Surgical excision was recommended following multidisciplinary discussion. Lesions were classified according to the degree of radiological suspicion (BIRADS classification). Type of radiological imaging finding (microcalcifications, opacity, and parenchymal distortion), ultrasound visibility, type of biopsy used for diagnosis and type of needle used were all recorded.

All biopsies underwent single pathology lab examination and were discussed by the same multidisciplinary team to ensure standard care. Surgically excised lesions were correlated to final pathology results and were subsequently followed-up. Of the 83 B3 histologically diagnosed cases, 51 cases involved ultrasound detectable findings where a Core Needle Biopsy (CNB) by a 16 Gauge needle was performed for diagnosi, while other 32 cases presented with suspicious mammographic and / or ultrasound modifications and underwent vacuum assisted biopsy (VABB) using a 9 Gauge needle. All patients were treated surgically.

Follow-up included regular clinical breast examination, ultrasound and mammography imaging according international guidelines. We retrospectively analysed the correlation between radiological and pathological findings and the correspondence between pathological diagnosis, diagnostic imaging and type of biopsy in order to draw up any risk criteria and ensure adequate patient management.

Results

Among the total 83 cases we detected 15 cases of malignancy diagnosed on pathology after total surgical excision as B5 lesions (including DCIS, LIN3 and invasive carcinomas) with an overall percentage of upgrade to ductal carcinoma in situ (DCIS) and low-grade invasive tumors of 18% (15/83).

Statistical Analysis

Evaluation of groups was assessed by Fisher's exact test, with a p-value <0.05 considered statistically significant. Statistical analysis was performed using the R software [12].

Concordance between preoperative and postoperative B3 pathology was registered in 81.92% (n = 68/83 patients) whereas discrepancy was documented in 18.07% (n = 15/83 patients).

Out of a total of 83 cases identified as B3 lesions on definitive pathological examination, atypical ductal hyperplasia accounted for 29/83 cases(34.93%), followed by flat epithelial atypia in 19/83 cases (22.89%), lobular intraepithelial neoplasia in 11/83 (13.25%), ductal carcinoma in situ in 8/83 (9.63%), papillary lesions in 6/83 (7.22%), lobular carcinoma in situ in 5/83 (7.22%) and invasive lobular tumor in 2/83 cases(2.40%). Two cases out of 83 received a diagnosis of biphasic phyl-

Table I - *Frequency of B3 lesions in diagnostic biopsy and comparison with surgical specimen histology (ADH: atypical ductal hyperplasia; DCIS: ductal carcinoma in situ; $LIN_{1,2}$: atypical lobular hyperplasia/ classic lobular in situ neoplasia; LIN_3: lobular in situ neoplasia with necrosis or pleomorphic lobular in situ neoplasia).*

Histology before surgery	Histology after surgery
2 Phyllod Tumor	2 Phylloid Tumor
6 Papillar Lesions	6 Papillar Lesions
43 ADH	29 ADH 6 DCIS 5 $LIN_{1,2}$ 3 LIN_3
20 FEA	19 FEA 1 LIN_3
11 $LIN_{1,2}$	6 $LIN_{1,2}$ 2 DCIS 1 LIN_3 2 Invasive Lobular Carcinoma
1 Radial Scar	1 Radial Scar

lodes tumor (2.4%) and one case was related to a radial scar. Summary of frequency of different B3 lesions comparing diagnostic biopsy to post surgery pathology is presented in Table I. No statistical significance ($p > 0.05$) was registered by comparing the frequency of different diagnosis before and after surgery.

Correlation between radiologic imaging and B5 lesion diagnosis after surgical excision

Out of our 83 cases, 36.14% (n = 30/83) presented with microcalcifications, 40.96% of cases with nodular lesions (n = 34/83), 16.86% of cases with parenchymal distortion (n = 14/83), in 3.61% of cases (n = 3/83) nodules were associated with microcalcifications and in 2.40% of cases (n = 2/83) microcalcifications were associated with parenchymal distortion (Table II).
Among the 15 cases of malignancy diagnosed on final pathology, in 33.33% (n = 5/15) of patients diagnostic imaging included mammography only, the remaining 66.66% (n = 10/15) both ultrasound and mammography. 13.33% of the patients (n= 2/15) underwent MRI to complete diagnosis.
Microcalcifications were registered in 53.3% of patients on mammography (n = 8/15) and 20% of them showed architectural distortion (n = 4/15) while, 25% of lesions presented as a nodular mass (n = 3/15) on ultrasound. The most frequent radiological risk classification was BIRADS4a. The (Table III) shows the correlation between the radiological imaging and the presence of B5 lesions at hystology after surgery. Overall, no statistical significance ($p>0,05$) emerged in our series when correlating radiological imaging findings and diagnosis of B5 lesions on final pathological examination.

Table II - *Diagnostic imaging presentation of all 83 cases examined.*

Radiological presentation	Number of cases
Microcalcifications	30
Distortion	14
Nodule	34
Nodule + microcalcifications	2
Micocalcification + distortion	2
TOTAL	83

Table III - *Correlation between imaging features on presentation and postoperative histopatologic results. (DCIS: ductal carcinoma in situ; LIN_3: lobular in situ neoplasia with necrosis or pleomorphic lobular in situ neoplasia; ILC: invasive lobular carcinoma).*

Imaging features on presentation	Number of cases	Histology after surgical excision
Microcalcifications	8	4 DCSI + 1ILC + 3 LIN_3
Distortion	4	2 DCSI + 1 LIN_3+ 1ILC
Nodule	3	2 DCSI+ 1 LIN_3

Correlation between diagnostic upgrade and biopsy procedures

In order to identify cancer probability indicators related to B3 lesions at microhistology, we also examined the correlation between histology after surgery and type of biopsy used for diagnosis. The biopsies were performed by experienced breast surgery physicians. Procedures using stereotactic guidance were performed through variable positioning, according to the site of the lesion, by combination of a digital technique to an analogic mammography unit equipped with an indirect digitalization system, using 9 Gauge needles.
Ultrasound-guided biopsy procedures were performed using a high frequency linear probe and 16 Gauge needles for sampling. The lesions were classified by two expert radiologists, according to various criteria (radio-

Table IV - *Correlation between histology after VABB and pathological diagnosis after surgical excision (ADH: atypical DUCTAL hyperplasia; DCIS: ductal carcinoma in situ; $LIN_{1,2}$: atypical lobular hyperplasia/ classic lobular in situ neoplasia; LIN_3: lobular in situ neoplasia with necrosis or pleomorphic lobular in situ neoplasia; ILC: invasive lobular carcinoma)*

Histology after VABB (n =32)	Histology after surgical excision	
	B3	B5
14 FEA	13 FEA	1 LIN_3
8 $LIN_{1,2}$	5 $LIN_{1,2}$	2 ILC 1 LIN_3
9 ADH	3 ADH	5 DCIS 1 LIN_3
1 Radial Scar	1 Radial Scar	0

Table V - *Correlation between histology after CNB and final histological findings (ADH: atypical ductal hyperplasia; DCIS: ductal carcinoma in situ; LIN $_{1,2}$: atypical lobular hyperplasia/ classic lobular in situ neoplasia; LIN$_3$: lobular in situ neoplasia with necrosis or pleomorphic lobular in situ neoplasia; ILC: invasive lobular carcinoma).*

Histology after CNB (n=51)	Histology after surgical excision	
	B3	B5
6 FEA	6 FEA	0
3 LIN$_{1,2}$	1 LIN$_{1,2}$	2 DCIS
6 Papillary Lesions	6 Papillary Lesions	0
34 ADH	26 ADH 5 LIN$_{1,2}$	1 DCIS 2 LIN$_3$
2 Phyllod Tumor	2 Phyllod Tumor	0

logical characteristics, dimension, radiological judgment of suspicion). In our case series, however, there was no statistical significance in the correlation between biopsy type of procedure used and detection of malignancy upon surgical excision (Table IV, Table V).

Discussion and Comment

B3 lesions are considered precursors of malignant lesions, most frequently in the form of ductal carcinoma in situ (DCIS) and less frequently invasive low-grade tumor. Columnar cell lesions with flat epithelial atypia (DIN1a), also known as FEA (flat epithelial atypia), display a biological behaviour that is not yet fully understood. Atypical intraductal proliferation (DIN1b) is a non-obligatory indicator / precursor of homolateral and contralateral infiltrating ductal carcinoma in situ, usually low grade (cribriform ductal carcinoma in situ, infiltrating tubular and lobular carcinoma), as evidenced by numerous molecular studies [13-15]. Proliferative breast disease with atypia diagnosed women have a four to ten times greater risk of developing breast cancer than those without atypia in any part of the breast or contralateral breast.

A very recent European Consensus publication [9] limits indications for surgery to appropriately selected B3 lesions through multidisciplinary discussion. In fact, indications for surgical excision should be based on clinical-radiological and histological data, with special consideration of the patient's family history and following adequate informed consent. This is even more important in case of VAAB sampling where microcalcifications appear completely removed on post-biopsy mammography [16-17]. According to recent guidelines, high-risk lesions can be managed by follow-up imaging, vacuum assisted excision (VAE), or surgery [18]. The risk of developing an invasive neoplasia following B3 diagnosis increases over time (10 years 3.8% and 3.7%; 15 years 8.9% and 8.6%; 25 years 30.5% and 26.2% both in the same breast as well as the contralateral one respectively) [19].

Nevertheless, in our series the choice between surgical excision and follow-up was based on radiological and histological criteria (BIRADS IV imaging lesions, high-risk histological characteristics such as cellular necrosis and atypia, residual microcalcifications after VABB).

Such indications received multidisciplinary evaluation. Similar criteria have also been reported in other papers [20,21] as supported by Rageth et al in the first and second international consensus conferences about lesions of uncertain malignant potential in the breast [22]. Most ductal carcinoma in situ lesions present as microcalcifications on mammography with an approximate 57.69% rate, while 38.46% of cases present as nodular mass lesion. Up to 26.92% of DCIS can present as asymmetry and approximately 12% may be associated with a palpable finding [23].

In our study the malignancy underestimation rate was 18.07% compared to 19.1% reported by El-Sayed et al [6]. The biopsy needle size was documented for all B3 lesions undergoing surgery in our Breast Unit, registering the underestimation rate for each type of needle used. Different size needles were used, 9 Gauge for VABs and 16 Gauge needles were used for CNBs (core needle biopsies).

By the way, there was no significant difference in terms of either correlation between initial imaging or needle gauge used and type of biopsy used for sampling in underestimating the rate of malignancy. However, we are aware of the limitations of the retrospective nature of our study.

Conclusions

B3 lesions incorporate a range of heterogeneous presentations. A large amount of research aimed to identify different subtypes of B3 lesions, improve risk stratification through careful radiological-pathological correlation and provide optimal treatment. Management of B3 lesions also includes discussion in a multidisciplinary setting to avoid overtreatment. According to international guidelines, surgical excision should be recommended in the presence of atypia. Our data confirm the heterogeneity of B3 diagnosed lesions and their risk of associated malignancy.

There was no statistical significance among the predictive criteria compared in assessing risk of malignancy in our B3 lesion subgroups. Improved sequencing technologies may allow for careful selection of a larger cohort of uncertain histological findings, provide early diagnosis and recommend prevention therapeutic pathways to avoid overtreatment. However, more research is needed to explore molecular differences between lesion subtypes. The focus on early management of these lesions with uncertain behaviour is in fact shifting towards personalization of therapy, implementing the morphological, biological and molecular variables of the disease.

Riassunto

Le lesioni mammarie B3 rappresentano circa il 3-21% di tutte le lesioni mammarie e comportano un potenziale rischio di tumori maligni associati che varia fino al 35%. Il nostro lavoro mira a dimostrare che è necessaria un'attenta selezione delle caratteristiche radiologiche e patologiche per il trattamento ottimale di diverse lesioni mammarie B3. Si è cercato di individuare i fattori predittivi correlando parametri radiologici e patologici al fine di avere una guida per la stratificazione del rischio e garantire un'adeguata gestione personalizzata del paziente, verificando la corrispondenza tra la diagnosi istologica con l'imaging iniziale e il metodo bioptico utilizzato per la diagnosi. Secondo la nostra esperienza, non sono stati identificati fattori predittivi statisticamente significativi tra i parametri analizzati nel nostro studio.

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