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Upgrade rate of intraductal papilloma without atypia on breast core needle biopsy: A clinical, radiological and pathological correlation study

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ABSTRACT

Background: The aim of the study was to determine the upgrade rate on excision of intraductal papilloma (IDP) without atypia diagnosed on breast core needle biopsy (CNB).
Methods: We searched our pathology department database for breast CNB with a diagnosis of IDP from 2013 to 2018. The exclusion criteria included radiologic-pathologic discordance, atypia on the same CNB, absence of histologic slides to review or absence of excision information. Upgrade was defined as ductal carcinoma in situ (DCIS) or invasive cancer identified on excision.
Results: 126 IDP without atypia cases from 94 patients were identified. The upgrade rate was 1.58% (2/126). Both upgrade cases showed DCIS with low and intermediate nuclear grade. Histologic size of IDP ≥1 cm was the only statistically significant predictor factor for an upgrade on excision.
Conclusion: The results suggest that non-surgical management of patients with radiologic-pathologic concordant IDP without atypia diagnosed on CNB may be appropriate in routine practice.

Introduction

Papillary breast lesions comprise a wide variety of lesions including benign intraductal papilloma (IDP), IDP with atypia, papilloma with ductal carcinoma in situ (DCIS), papillary DCIS and invasive papillary carcinoma. The common features of these lesions are single or multiple intraductal finger-like projections with arborizing fibrovascular cores. Benign IDP differs from other papillary breast lesions by having myoepithelial cells both within papillae and at the periphery of the lesion and benign epithelium covering the fibrovascular core.[1–4] (see Table 1)

IDPs usually affect middle-aged women (30–50 years old) and are generally divided into two groups based on their location. The ones growing in the large central ducts near the nipple are called solitary IDPs. Solitary IDPs usually manifest with nipple discharge, subareolar palpable mass, or pain. They can also involve the peripheral smaller ducts that are farther from the nipple. These peripheral IDPs are less likely to cause symptoms and tend to involve multiple small ducts.[1–4]

Surgical excision is the standard treatment of papillary lesions with any atypia in current practice.[5,6] However, the management of IDPs without atypia diagnosed on core needle biopsy (CNB) is still controversial. The wide range of upgrade rates (0–29%) on surgical excision of IDPs without atypia diagnosed on CNB as well as the absence of any measurements on CNB to predict the upgrade rate on excision are the barriers to establishing standard management protocol for these lesions.[5–23]

Our aim in this study was to analyze the clinical, radiologic, and histologic features of IDPs without atypia diagnosed on CNB and to correlate these features with the final diagnosis on surgical excision.

Material and methods

After receiving the approval from the Institutional Review Board, we electronically searched our pathology department database for the breast CNBs with the diagnosis of “papilloma” from July 1, 2013 to July 30, 2018. Some cases were excluded from the study due to several reasons including (1) presence of any

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Table 1
Clinical characteristics of patients with comparison of upgrade and non-upgrade groups.

	TOTAL	Non-Upgrade	Upgrade	*p value*
Patients	94 (100%)	92 (97.9%)	2 (2.1%)	
Age				
Median (range)	51 (29–84)	51 (29–84)	68 (63–73)	*0,166*
<50 years old	35 (37,2%)	35 (38%)	0 (0%)	*0,498*
≥50 years old	59 (62.8%)	57 (62%)	2 (1005)	
Ethnicity				
Caucasian	64 (68.1%)	62 (67.4%)	2 (100%)	*0.811*
African American	22 (23.4%)	22 (23.9%)	0 (0%)	
Asian/Indian	5 (5.3%)	5 (5.4%)	0 (0%)	
Hispanic	3 (3.1%)	3 (3.3%)	0 (0%)	
Symptoms				
No	74 (78.7%)	73 (79.3%)	1 (50%)	*0,382*
Yes	20 (21.3%)	19 (20.7%)	1 (50%)	
Nipple discharge	13 (13.8%)	12 (13%)	1 (100%)	*0.753*
Pain	5 (5.3%)	5 (5.4%)	0 (0%)	
Palpable mass	2 (2.2%)	2 (2.2%)	0 (0%)	
Personal History of Breast Cancer				
No	80 (85.1%)	79 (85.9%)	1 (50%)	*0,211*
Yes	14 (14.9%)	13 (14.1%)	1 (50%)	
Concurrent				
Yes	7 (7.4%)	6 (6.5%)	1 (50%)	*0,123*
No	87 (92.6%)	86 (93.5%)	1 (50%)	
Concurrent and Ipsilateral				
Yes	3 (3.2%)	2 (2.2%)	1 (50%)	*0,063*
No	91 (96.8%)	90 (97.8%)	1 (50%)	
Prior				
Yes	7 (7.4%)	7 (7.6%)	0 (0%)	-
No	87 (92.6%)	87 (92.4%)	0 (0%)	

Fischer's exact test and Student's t-test revealed no statistically significant predictive factor.

atypical lesions (IDP with atypia, atypical lobular hyperplasia (ALH), lobular carcinoma in situ (LCIS), atypical ductal hyperplasia (ADH), flat epithelial atypia (FEA), ductal carcinoma in situ (DCIS) or invasive cancer) on the same biopsy, (2) radiologic-pathologic discordance, and (3) absence of the histologic slides to review. IDP with atypia was considered when an IDP was involved by ADH or DCIS. Certain immunohistochemical stains (ER, CK5/6, p63 etc.) were used to confirm the presence or absence of atypia when there was a suspicion on Hematoxylin & Eosion slides.

A total of 175 CNBs with a diagnosis of IDP without atypia from 143 patients were identified after applying the exclusion criteria. Among these, 126 IDPs from 94 patients were surgically excised and included for further analysis. Each IDP in patients with multiple IDPs was diagnosed on different CNB in different location and a separate surgical excision was performed for each IDP. There was no clinical or radiologic follow-up information for the remaining 49 cases.

Table 2
Radiologic characteristics of the targeted lesions with comparison between upgrade and non-upgrade groups.

	TOTAL	Non-Upgrade	Upgrade	*p value*
Lesion on Radiology	126 (100%)	124 (98.42%)	2 (1.58%)	
Mode of biopsy				
US-guided	90 (71.4%)	88 (71%)	2 (100%)	*0.647*
MRI-guided	22 (17.5%)	22 (17.7%)	0 (0%)	
Stereotactic	14 (11.1%)	14 (11.3%)	0 (0%)	
Target Lesion				
Mass	108 (85.7%)	106 (85.5%)	2 (100%)	*0.844*
Calcifications	11 (8.7%)	11 (8.9%)	0 (0%)	
NME	7 (5.6%)	7 (5.6%)	0 (0%)	
Distance from nipple (mm)				
Median (range)	30 (5–110)	30 (5–110)	60 (10–110)	*0,736*
<20 mm	30 (23.8%)	29 (23.4%)	1 (50%)	*0,149*
≥20 mm	96 (76.2%)	95 (76.6%)	1 (50%)	

Fischer's exact test and Student's t-test revealed no statistically significant predictive factor.

Table 3
Histologic characteristics of IDPs and comparison between upgrade and non-upgrade groups.

	TOTAL	Non-Upgrade	Upgrade	*p value*
Intraductal Papilloma	126 (100%)	124 (98.42%)	2 (1.58%)	
Size (mm)				
Median (range)	3 (1–16)	3 (1–16)	6.5 (3–10)	*0,077*
<2 mm	16 (12.7%)	16 (12.9%)	0 (0%)	*1,000*
≥2 mm	110 (87.3%)	108 (87.1%)	2 (100%)	
<5 mm	104 (82.5%)	103 (83.1%)	1 (50%)	*0,320*
≥5 mm	22 (17.5%)	21 (16.9%)	1 (50%)	
<10 mm	123 (97.6%)	122 (93.4%)	1 (50%)	***0,047***[a]
≥10 mm	3 (2.4%)	2 (6.6%)	1 (50%)	
Fragmentation				
Yes	40 (31.7%)	38 (30.6%)	2 (100%)	*0,099*
No	86 (68.3%)	86 (69.4%)	0 (0%)	
Calcifications				
Yes	11 (8.7%)	10 (8.1%)	1 (50%)	*0,168*
No	115 (92.3%)	114 (91.9%)	1 (50%)	
Residual IDP on Excision				
Yes	95 (75.4%)	93 (75%)	2 (100%)	*1,000*
No	31 (24.6%)	31 (25%)	0 (0%)	

Abbreviations: IDP, intraductal papilloma.
[a] Fischer's exact test revealed significantly higher upgrade in IDP ≥ 10 mm compared to IDP < 10 mm.

Clinical information of the patients including gender, age at the time of diagnosis, symptoms, and personal history of prior or concurrent breast cancer (P/CBC) were collected from the electronic medical records. Imaging studies of the patients before and after CNB were reviewed to note the following information: mode of biopsy (stereotactic, US-guided or MRI-guided), size of the lesions, and distance of lesions from the nipple. The majority of CNBs were vacuum-assisted biopsy and the needle gauge ranged from 8 to 18.

All histologic slides of CNBs and subsequent surgical excisions were reviewed by two pathologists, one with subspecialty expertise in breast pathology. Slide review revealed no disagreement on the original diagnosis in any case. Benign IDP was defined as lesions with a distinct fibrovascular core lined by inner myoepithelium and outer epithelium without any atypia. The CNBs were evaluated for the size of IDP by measuring the largest fragment, as well as the presence of fragmentation and microcalcification. Surgical excisions were assessed for the presence of residual IDP or any additional atypical findings. The cases were considered to be an "upgrade" if DCIS or invasive cancer was found on the excision specimen. If DCIS or invasive cancer was found, their association with IDP was also noted.

Statistical analyses were performed by using the software SPSS Version 22 for Windows. Fisher's exact test was applied to compare two categorical variables and Student's t-test was used to evaluate the continuous variables. Results were considered as significant at $p < 0.05$.

Results

Clinical, radiological and histopathological characteristics

All patients included in the study were women. Among 94 patients with 126 IDPs, 74 patients had one IDP, 16 patients had two IDPs, two patients had four IDPs, one patient had five IDPs and one patient had seven IDPs.

The median age of the patients at the time of diagnosis was 51 years, ranging from 29 to 84 years. Fourteen patients (14.8%) had a

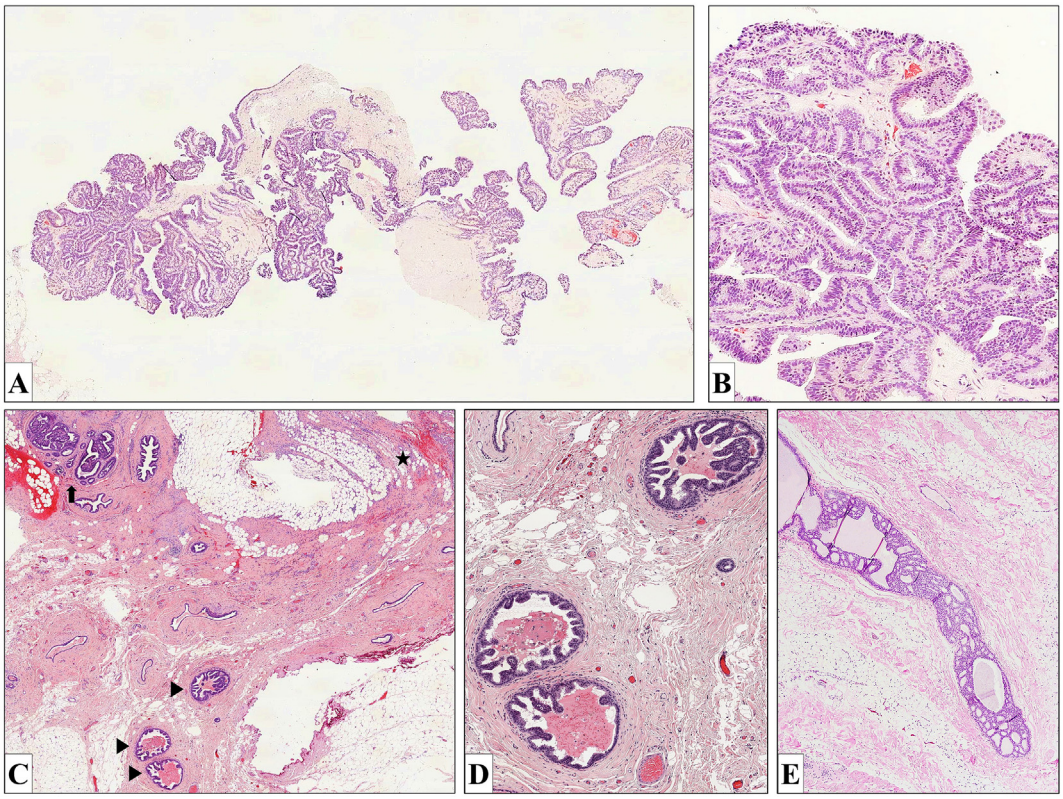

Fig. 1. IDP with Upgrade on Excision (Case 1).
Benign intraductal papilloma (IDP) on breast core needle biopsy (CNB) with upgrade on excision. A–B: Low-power (H&E, x20) and high-power view (H&E, x60) of IDP on CNB. C: Low power view (H&E, x10) of excision specimen. Arrow points the residual IDP, star designates the previous biopsy site and arrow heads point to ductal carcinoma in situ (DCIS). The distance between IDP and DCIS is 3 mm. D: High-power (H&E, x40) view of DCIS with low nuclear grade and micropapillary pattern. E: DCIS with low nuclear grade and cribriform pattern identified in a different section of the excision specimen (H&E, x20).

personal history of P/CBC. In this population of patients with a history of breast cancer, seven patients had a prior history of breast cancer (7.4%) and the remaining seven had concurrent breast cancer (7.4%); each of these groups had five patients with contralateral and two with ipsilateral breast cancer. Patients with P/CBC in the ipsilateral breast was not associated with IDPs and was located in a different quadrant.(Table 1)

Ninety out of 126 (71.4%) CNBs were obtained using ultrasound guidance. One hundred and eight of 126 (85.7%) targeted lesions on radiology were mass, 11 (8.9%) were calcifications, and seven (5.6%) were non-mass enhancements (NME). The median size of the targeted lesions on radiology was 6 mm (range 2–45 mm). One hundred and five of 126 (83.3%) lesions were radiologically <1 cm and 21 (16.9%) of them were ≥1 cm. The distance between the targeted radiologic lesion and the nipple ranged from 0.5 cm to 11 cm with a median distance of 3 cm.(Table 2)

Microscopically, the IDPs measured from 1 mm to 16 mm with a median size of 3 mm. Using 2 mm and 5 mm size cut-offs revealed 16 (12.7%) IDPs to be < 2 mm, 89 (62.7) IDPs to be 2–5 mm and 21 (24.6%) IDPs to be ≥ 5 mm. Additionally, only three (2.4%) IDPs measured ≥ 10 mm. Excision specimens showed residual IDPs in 95 (75.4%) cases. Two of 126 IDPs diagnosed on CNB were upgraded to DCIS on surgical excision; therefore, the upgrade rate on excision specimens was 1.58%. Additionally, 14 (11.1%) cases showed other atypical lesions (3 ALH, 3 LCIS, 4 ADH, 3 LCIS + ADH, 1 ADH + FEA) on the excision specimen.(Table 3)

Comparison of characteristics of the upgrade and non-upgrade cases

The median age of the patients was 68 years (range 63–73 years) for the upgrade and 51 years (range 29–84 years) for the non-upgrade cases. Of the two patients that were upgraded, one (50%) presented with nipple discharge and had concurrent breast cancer. In patients with no upgrade, six (4.8%) were found to have concurrent cancer and seven (5.6%) had prior breast cancer. Both upgrades occurred in patients with a single papilloma.

The CNBs were done by US guidance in two of two (100%) upgrade cases and 88 of 124 (71%) non-upgrade cases. One upgrade IDP was central (1 cm from the nipple) and the other one was peripheral IDP (11 cm from the nipple). Twenty-nine (23.8%) cases with no upgrade were central and 95 (76.2%) of them were peripheral.

Both upgrade cases showed residual IDPs in the excision specimen and the distance between the residual IDP and DCIS was 3 mm and 8 mm. The nuclear grade of DCIS was low and intermediate with micropapillary and cribriform patterns (Figs. 1 and 2). The median microscopic size of IDPs in the upgrade cases was 6.5 mm while it was 3.0 mm in the non-upgrade cases. The upgrade rate was 33% (1/3) for IDPs ≥1 cm and 0.8% (1/123) for IDPs < 1 cm.

Statistical analyses of the clinical, radiologic and histopathologic characteristics revealed the microscopic size of IDP ≥1 cm on CNB to be the only statistically significant predictor factor for an upgrade on excision ($p = 0.047$).

Discussion

Management of IDP without atypia diagnosed on CNB is still controversial due to a wide range of upgrade rates reported in the literature.[5,23] However, some studies with a high upgrade rate did not give any details about the radiologic-pathologic correlation of

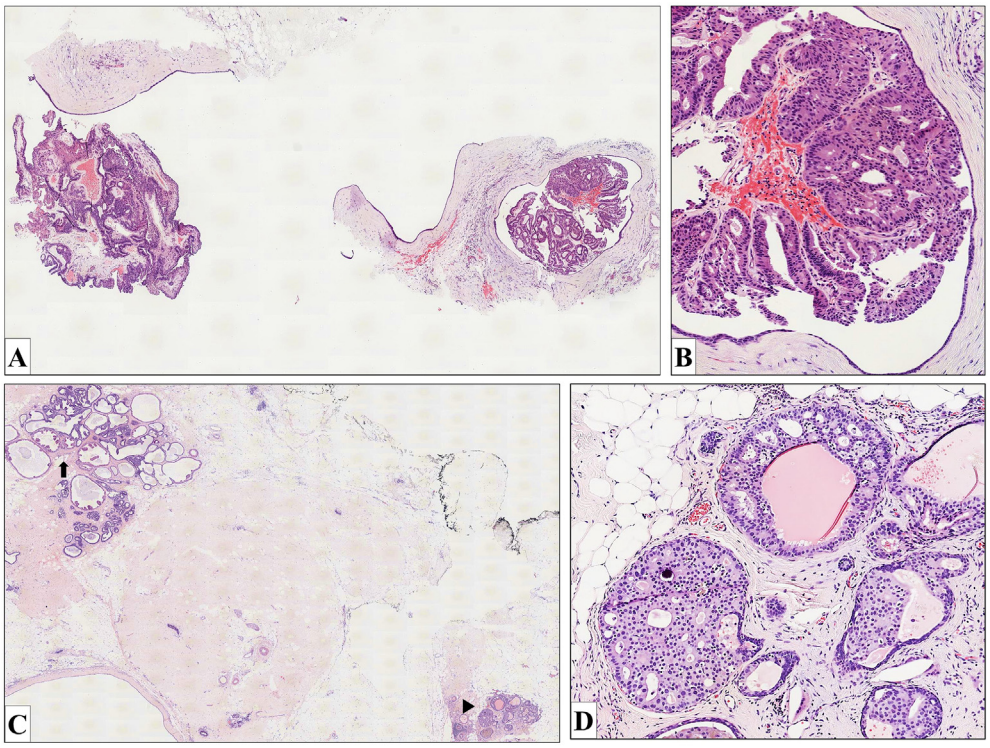

Fig. 2. IDP with Upgrade on Excision (Case 2).
Benign intraductal papilloma (IDP) on breast core needle biopsy (CNB) with upgrade on excision. A–B: Low-power (H&E, x10) and high-power (H&E, x60) view of IDP on CNB. C: Low power view (H&E, x5) of excision specimen. Arrow points the residual IDP and arrow head points ductal carcinoma in situ (DCIS). The distance between IDP and DCIS is 8 mm. D: High-power (H&E, x60) view of DCIS with intermediate nuclear grade and cribriform pattern.

CNB which plays an important role in the decision-making process.[14,22] Additionally, recent studies that included only radiologic-pathologic concordant cases reported very low upgrade rates.[5,6,9,17] Moreover, Youk et al. divided the cases into two groups based on radiologic-pathologic correlation and reported the upgrade rate as 3.1% for radiologic-pathologic concordant cases and 14% for discordant cases.[15] In another study, radiologic-pathologic discordance was found to be a significant predictor for an upgrade on excision.[7] Therefore, we may clearly state that radiologic-pathologic correlation should be taken into consideration during the management process of the patients as well as in future studies.

Our results showed a very low upgrade rate (1.58%) on the excision of IDP without atypia diagnosed on breast CNB with a radiologic-pathologic concordance. Detailed analysis of the characteristics of the patients or IDPs showed some differences between the upgrade and non-upgrade groups, however, the microscopic size of IDP $\geq$10 mm on CNB was the only statistically significant predictor factor for an upgrade on excision. This may be due to a low number of upgrade cases in our cohort.

Both patients with an upgrade in our study were older than 50 years old and the median age of patients with upgrade was higher than those with no upgrade (68 years vs. 55 years); however, this difference was not statistically significant. Similarly, some of the previous studies reported the mean age of patients with upgrade higher than those with no upgrade; furthermore, the majority of patients in these studies were older than 50 years of age.[8,14,15] However, two separate studies reported patients with upgrade who were younger than 50 years old.[9,10]

Two patients, one with upgrade, had concurrent ipsilateral cancer in different quadrant, however, this was not a statistically significant predictor for the upgrade, most likely due to the low number of patients with an upgrade in our study. However, in two studies, the history of concurrent ipsilateral breast cancer and concurrent contralateral breast cancer were found to be significant predictor factors for having an upgrade on excision.[5,9] Therefore, a special attention should be given to patients with concurrent breast cancer.

Most of the CNBs including both cases with an upgrade was performed by ultrasound guidance and the target was confirmed to be a mass in the majority. We were unable to identify a radiologic characteristic to predict upgrade on excision. Regarding the mass size on radiology, the upgrade rate was found to be significantly higher in lesions $\geq$10 mm and >20 mm in two different studies.[10,15] Additionally, a mass lesion on radiology as well as a palpable mass as a symptom were reported as predictive factors for an upgrade on excision in one of the studies.[24]

Analyses of histologic characteristics of CNB and excision specimens showed IDP with a size of $\geq$10 mm as the only predictive factor for an upgrade on excision. Additionally, fragmentation and microcalcifications on CNB were also identified more commonly in cases with upgrade than those with no upgrade, however, the differences did not reach to a statistically significant level. Similar results were also reported in two different studies. In an analysis of 370 IDP cases, Xin Li et al. reported the presence of microcalcifications simultaneously on both CNB and imaging as a predictive factor for an upgrade on excision.[8] Pareja et al. analyzed 174 cases of IDP and described the fragmentation of IDP on CNB as a predictive factor for an upgrade on excision.[5]

All of the histologic slides of CNB and excision specimens were reviewed by a breast pathologist in our study. Jakate et al. analyzed the correlation between CNB and excision diagnoses for papillary breast lesions according to pathologists' expertise in breast pathology. The correlation was found significantly greater for breast pathologists than for non-breast pathologists.[25] Therefore, an

accurate classification of papillary breast lesions plays an essential role in the management plan of patients.

Our study has some limitations. It was difficult to reach to a statistically significant result on comparison of upgrade and non-upgrade cases because the upgrade group consisted of only two cases. We did not have any follow-up information for patients who did not have a surgery in our health system or who never had a surgical excision, which creates a possibility of selection bias that might have occurred in our study as well as prevents us to get an idea about long term behavior of these lesions if they do not get excised.

In conclusion, we found a very low upgrade rate on the excision of IDP without atypia diagnosed on CNB with a radiologic-pathologic concordance similar to recent studies. Our findings suggest that close clinical and radiologic follow-up may be a reasonable option for the majority of these patients in routine practice.

Declaration of competing interest

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