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Utility of fine needle aspiration cytology (FNAC) in diagnosis of papillary lesions of the breast

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Abstract
Background: Diagnosis of lesions of the breast using Cytological screening is difficult. Understanding the common cytological features of papillary lesions of the breast can be useful for the diagnosis.
Aims and objectives: To determine the utility of Fine Needle Aspiration Cytology (FNAC) in the diagnosis of papillary lesions of the breast
Materials and methods: A retrospective study was performed from January 2010 to December 2015 in the cytology section, Department of Pathology of a tertiary care and referral hospital including patients diagnosed as papillary lesion on FNAC. Eight four cases were found (includes 44 cases which had histopathology follow-up, 36 cases which didn't had follow-up), 4 cases were removed because of non-availability of slides. Thus, a total of 44 breast aspirates and their corresponding histology were reviewed. All the observations were done on total 44 cases.
Results: Papillary Neoplasms on FNAC (n= 33): 13 cases (29.54%) were histologically confirmed as papillary neoplasms. All 13 cases (100%) showed true papillae with fibrovascular cores. 76% showed presence of columnar cells. 4 were benign and 9 malignant. Dyscohesion and severe atypia was only seen in malignant neoplasms. 20 cases were non papillary lesion on histopathology. Out of the 20 cases, 11 cases (55%) were infiltrating duct carcinoma (IDC), 4 were fibroadenomas (FA), 3 fibrocystic disease and one each was ductal carcinoma in situ (DCIS) and lobular carcinoma. Presence of papillaroid fragments and columnar cells was the most common cause for false positive diagnosis. Papillary Neoplasms Not Suspected Cytologically (n=11): In 5 cases cellularity was scanty and unsatisfactory for opinion. Missing fibrovascular cores in the aspirate was the cause of false negative diagnosis. The overall incidence of false positive was 25% and false negative was 13.75%. Sensitivity of FNAC to diagnose papillary lesions was 54.1%.
Conclusion: Cytodiagnosis of papillary lesions is challenging and identification of true fibrovascular cores is essential for accurate diagnosis.

Keywords: Papillary lesions, fine needle aspiration cytology, histopathology, neoplasms

Introduction
Papillary lesions of the breast encompass a wide spectrum of benign and malignant entities constituting <2% of all breast carcinomas [1].
Papillary lesions of the breast include benign (papilloma) as well as malignant (papillary carcinoma) entities. Both the ends of the spectrum are characterized by the presence of fibrovascular cores (FVC) lined by epithelial proliferation with varying degrees of atypia [2].
Though a definite diagnosis of the nature of tumour is possible on an excision biopsy, the distinction is not easy on aspiration cytology. This is due to the overlapping of cytological features between benign and malignant as well as other entities containing papillary component [3].
Cytological interpretation of papillary lesions of breast continues to be a difficult task. These lesions top the list of conditions in which there is a risk of false-positive diagnosis. Three-dimensional papillary clusters in a breast aspirate may be seen in a broad spectrum of conditions, namely papillary hyperplasia in fibrocystic disease, duct papilloma, papillary or micropapillary ductal carcinoma and pseudopapillary pattern in invasive ductal carcinoma (not otherwise specified) [4]. Hence, in present study we tried to determine the utility of Fine Needle Aspiration Cytology (FNAC) in diagnosis.

Materials and Methods
The present study was undertaken retrospectively from January 2010 to December 2015 in the cytology section, Department of Pathology of a tertiary care and referral hospital.

Inclusion criteria: All the cases which have been diagnosed as papillary lesion on FNAC and also all the lesions which are diagnosed as papillary lesions of breast on histopathology, which have not been diagnosed as papillary lesion on FNAC, so false negative test would not be missed.

Exclusion criteria: Lesions diagnosed as non-papillary lesions on both FNAC and histopathology.

Total 84 cases were found. Which includes 44 cases which had histopathology follow-up, 36 cases which didn't had follow-up. 4 cases were removed because of non-availability of slides. Thus, a total of 44 breast aspirates and their corresponding histology were reviewed.

Age, sex, clinical feature, site, location, size wise distribution done on total 60 cases diagnosed as papillary lesion on cytology but didn't have follow up and cases confirmed as papillary lesion on histopathology, and also the cases which had confirmed papillary lesion on histopathology. All the observations were done on total 44 cases.

Final age, sex, clinical features and cytological feature were compared between total 24 cases which include true positive and false negative cases.

Data sheet was completed for each patient. Data sheet contained various identification details of patient, clinical presentation (breast lump, pain, nipple discharge etc.), radiological findings, local examination, microscopic (Cytology) findings, final Impression, histopathology diagnosis and review cytopathology and histopathology diagnosis.

Parameters that will be used to determine utility of FNAC for diagnosing papillary lesions of breast included background (blood, calcification, single scattered columnar cells, hemosiderin laden macrophages), cellular features (cellularity, dissociation, nuclear atypia (focal and diffuse-mild (1+), moderate (2+), severe (3+), cell morphology, e.g., apocrine, columnar), and tissue fragments (long finger-like branching fragment (complex vs. simple branching, presence of fibrovascular cores), complex fragments, other than papillary, cellular balls, single detached papillae)

Sampling was performed by the pathologist using FNAC. Ultrasound guided FNACs was performed for non-palpable and small lump. Cytology slides were prepared and stained. Clinical history and notes were obtained from cytology section in Department of Pathology and Medical record department. All these cytology slides were retrieved and reviewed whenever possible.

All the data analysis was performed using IBM SPSS ver. 20 software. Frequency distribution was performed to prepare the tables. The statistical calculations were based on histolopathological outcome and sensitivity and specificity was calculated.

Results

Majority of the patients had age between 51-60 years (26%) which ranged from 17 to 80 years with female preponderance (97%). Most common presentation was breast lump in 57 cases (93.5%). Nipple discharge seen in only 5 cases. Most of the tumours were located in central region. Second most common location was upper outer quadrant (UOQ). Maximum cases were found in between size 2-5cm (50%). In 3 cases no lump was palpable.

Group A: Papillary Neoplasms (PN) Confirmed Histologically (True positive cases): Of the 33 cases initially called papillary lesion or suspicious for papillary lesion by cytology, 13 cases (29.54%) were histologically confirmed.

Table 1: Cytological features studied: (n=13) (Group A)

Features	No of patients	Percentage
Cellular (3+)	7	54%
Moderately cellular(2+)	5	38.4%
Pauci-cellular (1+)	1	7.65%
True papillae/ Fibrovascular core	13	100%
Papillaroid fragment	13	100%
Complex sheet	6	46.1%
Cell ball	1	7.6%
Dis-cohesion	5	38.4%
Single cell	3	23%
Columnar cell	10	76%
Stromal fragment	0	0%
Cyst macrophages	3	23%
Atypia 3+	2	15.3%
Atypia 2+	2	15.3%
Atypia 1+	1	7.6%
Focal	4	30.7%
Degenerative atypia	1	7.6%
Cell ball	1	7.6%
Dis-cohesion	5	38.4%

Group B: Papillary Neoplasms on cytology with discrepant Histological diagnosis (False negative cases) (n=20)

Cases which turned out to be fibroadenoma (FA) on histopathology (n=4): 2 cases were located in subareolar region. 1 case was presented as nipple discharge. 3 cases showed presence of papillaroid fragment, bare nuclei and stromal fragment (figure 1). Out of these 3, one case showed presence of complex branching papillaroid fragment. Because of papillaroid fragment and columnar cell in these cases impression on FNAC was given as papillary lesion. Out of the 4 cases, one case presented as nipple discharge and located in subareolar region, so impression was given as papillary lesion. In one case complex sheet, bare nuclei, and atypia were there, but no stromal fragment. Lump location was subareolar. Due to the location the impression was given as papillary lesion.

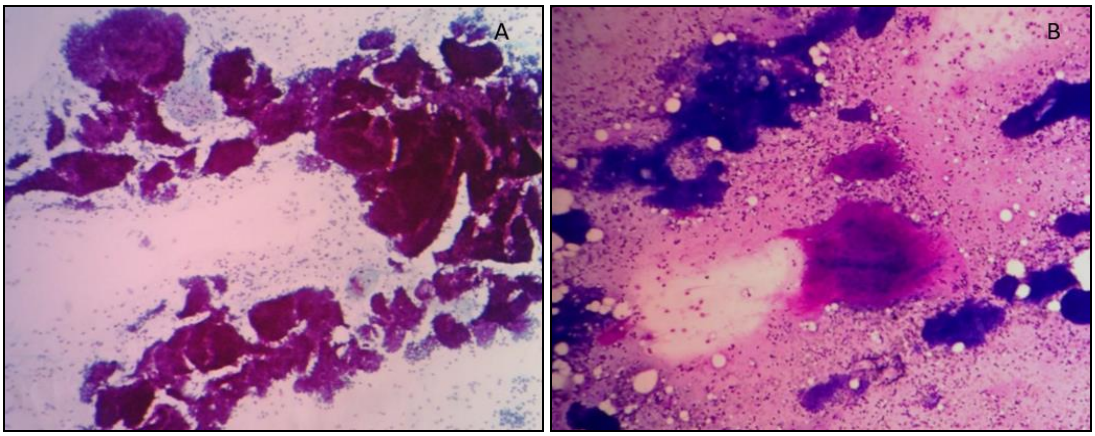


Fig 1: Papillaroid fragment, bare nuclei and stromal fragment (A-Pap & B-Giemsa 10X)

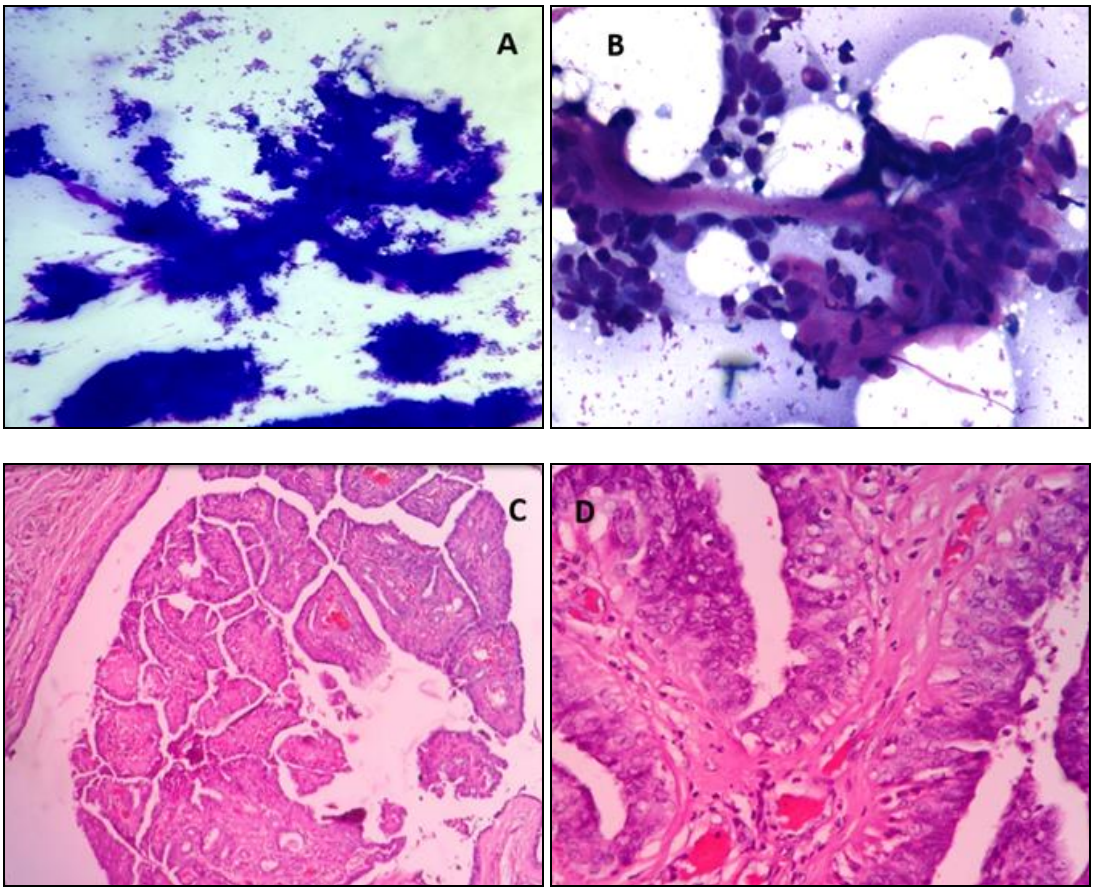


Fig 2: Showing Papilloma (A-Giemsa-40x, B-Giemsa-400x, C& D-H&E-100X)

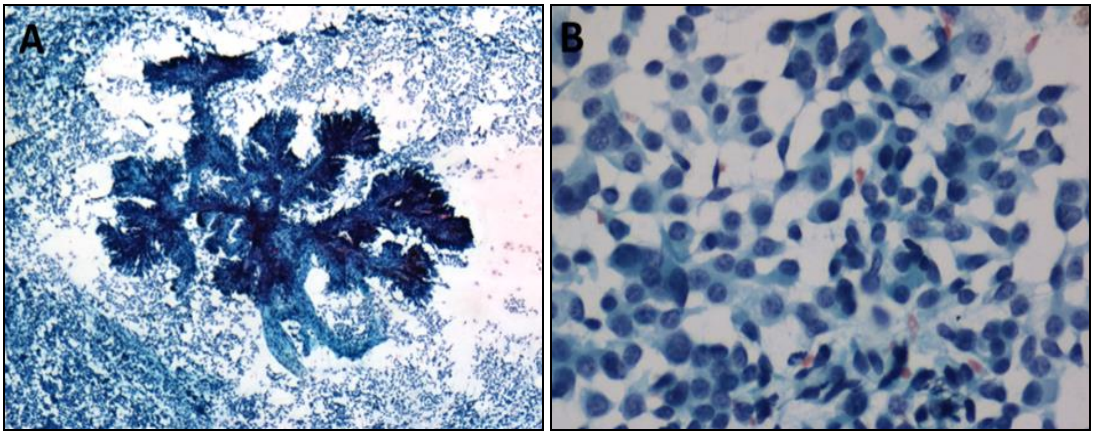


Fig 3: Papillary carcinoma (A-Pap-100X, B-Pap-400X)

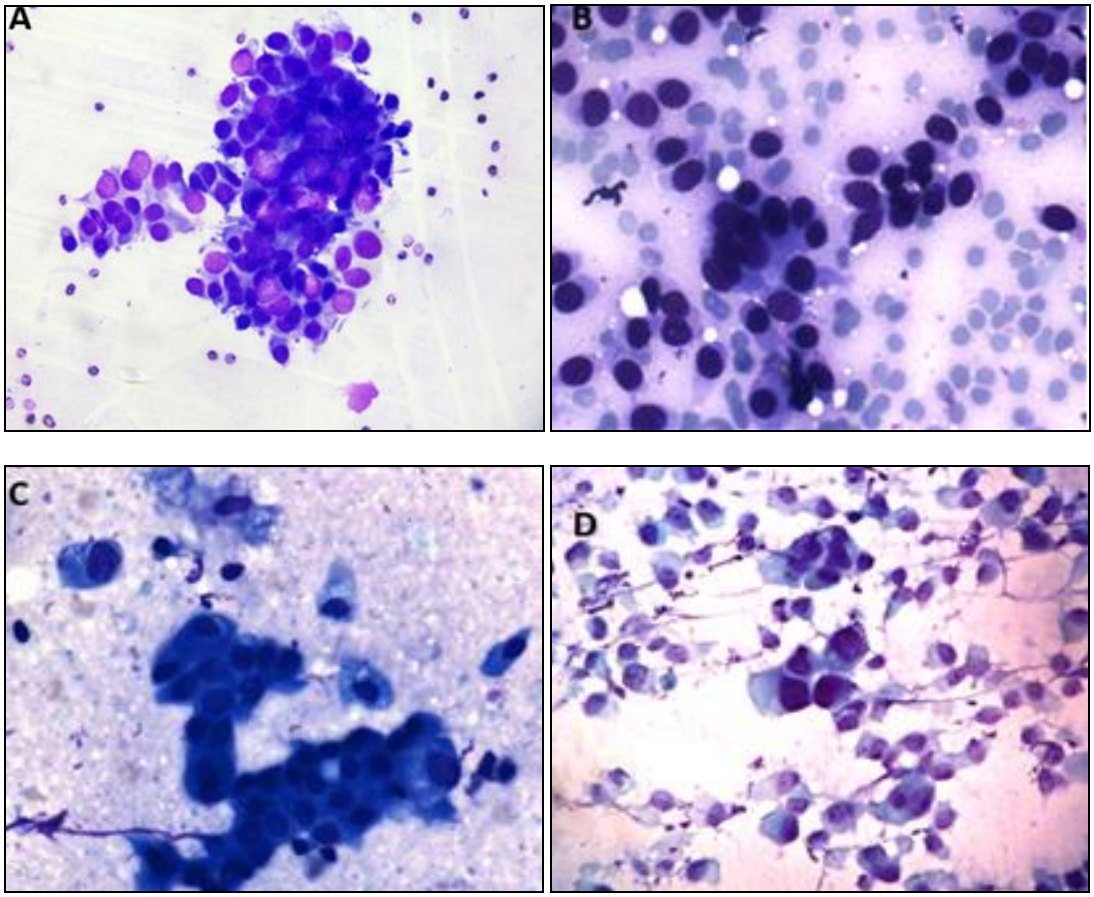


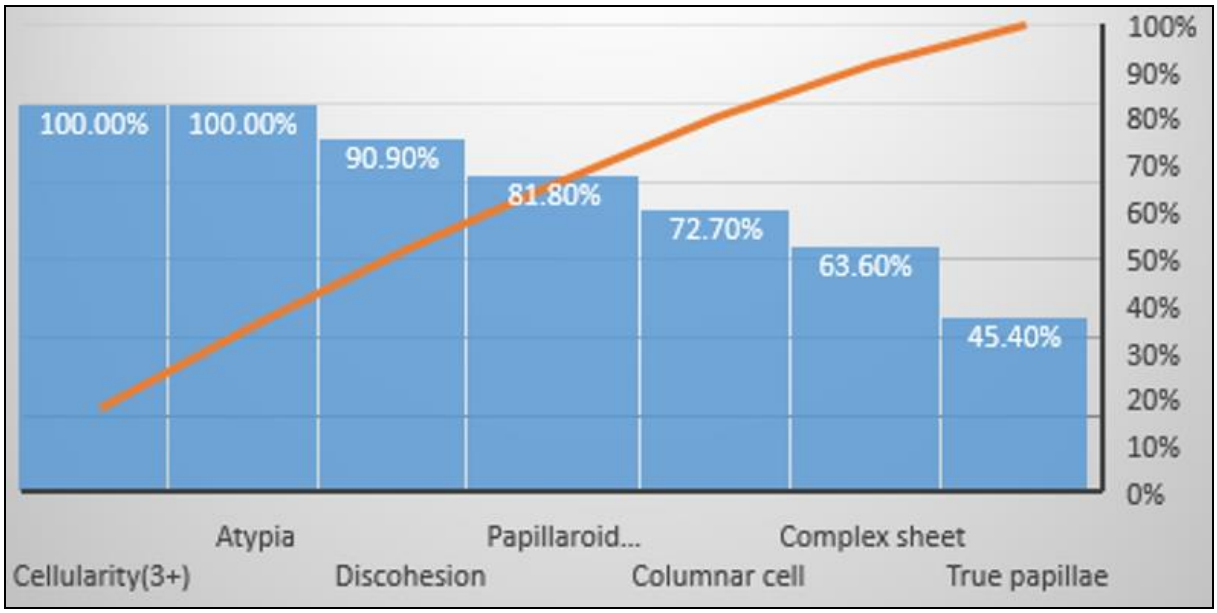
Fig 4: Papillary carcinoma (A-Giemsa-100X, B-Giemsa400X, C & D-Pap-400X)

Cases which turned out to be fibrocystic disease (FCD) on histopathology (n=2)

- **A 45 year female presented with nipple discharge**: On examination ill-defined diffuse lump was palpable which was located in subareolar region. On FNAC sero-sanguinous fluid was aspirated. Cytology features: Moderately cellular smear shows presence of papillaroid fragments and complex sheets of benign ductal epithelial cells. Background shows presence of cyst macrophages and fluid. Due to complain of nipple discharge, lump was located in subareolar region and smears show presence of papillaroid fragment, it was misinterpreted as papillary lesion. But no obvious true papillae were seen.
- **A 47 year old female presented as breast lump:** On USG impression was given as cystic lesion. O/E lump was located in subareolar region. Cytology finding: Moderately cellular smear show presence of complex sheets of benign ductal epithelial cells and few apocrine cells were also there. Focal atypia was there. Background shows presence of macrophages and columnar cells. Because of presence of columnar cells it was misinterpreted as Intracystic papillary carcinoma (IPC).
- **Benign proliferative breast lesion with features of adenosis:** Didn't show presence of true papillae only columnar cell and papillaroid fragment was there.

Case which turned out to be Lobular ca on histology

- 35 year old female presented with breast lump. O/E lump was located in UOQ. Cytology findings: Cellular smear shows presence of loosely cohesive clusters of ductal epithelial cell. Diffuse 2+ atypia was there. Background shows presence of single cells and macrophages. Impression: Suggestive of neoplastic breast lesion 1. Low grade duct carcinoma 2.papillary lesion. We are ascertained about reason for diagnosis of papillary lesion.



Pareto Chart plot: Cytology features notes for cases which out to be ductal carcinoma on histology (n=11)

Group C: Papillary Neoplasms Not Suspected Cytologically (n=11)

In 5 cases cellularity was scanty, so these cases were unsatisfactory for opinion. In that one case shows only hemorrhage. In 4 cases impression was given as duct ca, one case high grade malignancy and in one case suspicious of ductal carcinoma in situ (DCIS).

Table 3: Features seen in cytology (Group C)

Features	Cases (n=11)	Percentage
Cellular (3+)	3	27.2%
Moderately cellular(2+)	2	18.2%
Pauci-cellular (1+)	1	9.1%
True papillae/ Fibrovascular core	3/5	27.2/ 45.4%
Papillaroid fragment	3	27.2%
Complex sheet	2	18.2%
Cell ball	2	18.2%
Dis-cohesion	6	54.5%
Single cell	4	36.3%
Columnar cell	2	18.2%
Atypia- 3+	5	45.4%

After reviewing these cases in 3 cases true papillae were found and in two cases fibrovascular core was present which was missed out in original diagnosis. In one case which was given as high grade malignancy, it turned out to be micropapillary carcinoma. In one case which was given as Suspicious of DCIS, many fibrovascular cores were there in the background, on histopathology this case was diagnosed as papillomatosis.

Table 4: Diagnosis (Group A+C) (n=24)

Benign (n=11)		Malignant (n=13)	
Intraductal papilloma	8	Invasive Papillary ca	10
Papillomatosis	2	Micropapillary ca	2
Infarcted papillary lesion	1	Intracystic papillary ca	1

Incidence of papillary lesion was 2.4%. Sensitivity of FNAC to diagnose papillary lesion was 54.1%.

Discussion

The present study was undertaken in Cytology section, Department of Pathology, at a tertiary care hospital from January 2010 to December 2015. Eighty cases of papillary lesions of breast were studied. Forty four cases had histology follow up. In these 44 cases cytology slides were retrieved and reviewed. The incidence of papillary lesions of breast in our study was 2.4% and this incidence was similar to the incidence reported by Nassar *et al.* (<2%) [1]. In our study papillary lesions were found in the age group of 17-80 years (average 48 years) peak was in the 5th decade which is in line with the previous study done by Nassar *et al.* [1] and Gomez *et al.* [5].

In our study, breast lump was the most common presentation for both benign and malignant papillary lesions. In some cases nipple discharge (9 cases) was also seen. The presence of FVCs and their appearance are significantly different in papillary carcinoma (PCA) and intraductal papilloma (IDP). Because the FVCs are thicker in IDP, they tended to be incompletely aspirated and appeared either as a small thick fibrous portion at the periphery of the branching fragments. In our study we found presence of thick fibrovascular core. Gomez *et al.* in their study found abundant cellular material in papillary carcinoma and relatively less material in papilloma, which was not in concordance with our study [5]. Dowson *et al.* in their analysis of papillary lesions, found increased cellularity and presence of single cells in the background helpful in distinguishing papillary carcinoma from benign papilloma [6].

As noted from our study for 44 cases follow up was available, only 30% of papillary neoplasms were accurately classified as such on cytology (group A), and (group B, 45%) were incorrectly suspected to be papillary neoplasms on cytology. A smaller numbers of papillary neoplasms (group C, 25%) were not recognized as such on cytology. In our study, we found that of the 33 cases we classified as a papillary lesion, more than one-half were not true papillary neoplasms on follow-up. Among benign and malignant

categories, fibroadenoma and fibrocystic changes with ductal hyperplasia and low-grade DCIS with cribriform, micropapillary, and papillary patterns were the most common cytological look-alikes. Of the 33 cases with papillary cytological diagnosis, only 6 were papillomas (21%), 5 were PCA (15%), and 1 was intracystic papillary carcinoma (3%). Similar study conducted by Nayar *et al*., only 45% of papillary neoplasms were accurately classified as such on cytology (group A), and a similar number of cases (group B, 40%) were incorrectly suspected to be papillary neoplasms on cytology. A smaller number of papillary neoplasms (group C, 15%) were not recognized as such on cytology.[7] In another similar study by Simisir *et al*., author reported that of the 70 cases they classified as a papillary lesion, more than one-half were not true papillary neoplasms on follow-up. Of the 70 cases with papillary cytologic diagnosis, only 29 were papillomas (41%), 2 were IPC (3%), and 1 was a micropapillary carcinoma (1.4%). Only 44% of papillary neoplasms were accurately classified on cytology [3]. Michael and buschmann after reviewing 32 cases diagnosed as PN noted that PCA should be distinguished from DP which is possible with attention to cellularity, prominent cell discohesion and cellular atypia [8]. Gita Jayaram found in her study of 65 cases that cellularity was not a useful features in a distinguishing benign from malignant, but prominent cell discohesion and cellular atypia were characteristic features in distinguishing benign from malignant [9].

Fibroadenoma, fibrocystic changes, and papilloma display overlapping cytologic features. Sometimes it is difficult to differentiate papilloma from these. This is an important issue because surgical excision is the treatment of choice for papilloma, whereas FA and FCD are managed conservatively. Our study, 21% (7 of 33) of the lesions classified as papillary on FNAB was fibroadenomas and fibrocystic changes. Fibroadenomas are often as cellular as papillomas. Smears from fibroadenomas contain numerous oval bare nuclei, easily identifiable fragments of stroma (not associated with epithelial fragments) no FVC and columnar epithelial cells [10].

Out of the 4 cases of fibroadenoma, in our study 3 cases showed presence of papillaroid fragments and one case had subareolar location and nipple discharge leading to mistaken diagnosis of papillary lesion. However 3 cases did showed presence of stromal fragment and bare nuclei which were missed out at the time of original report. Two cases showed presence of columnar cell.

Smears from fibrocystic diseases show mild to moderately cellularity in comparison with high cellular papillomas. Three-dimension complex branched sheets may be seen in ductal hyperplasia but FVCs are generally not present. FCD can also present with nipple discharge if epithelial hyperplasia is present.

In our study two cases were misinterpreted as intracystic papillary ca because of columnar cell present in the smear. However the cellularity for columnar cells were very scanty compared to papillary lesion. One of these cases also had nipple discharge adding to the diagnosis. In the study conducted by Simsir *et al.*, 25% (17 of 69) of the lesions classified as papillary on FNAB were fibroadenomas and fibrocystic changes. Three fibroadenomas were impossible to distinguish from papilloma, even after retrospective review, due to the abundance of 3-D branched epithelial sheets, vascular stromal fragments intimately associated with the epithelial cell groups, and the background containing apocrine metaplastic and foamy cells similar to papilloma. In all other cases, adherence to strict criteria would have made this distinction possible [3].

Smears of fibrocystic changes are mild or moderately cellular compared with papillomas. Three-dimensional complex branched sheets may be seen in ductal hyperplasia but FVCs are generally not present. Examples of fibrocystic changes with ductal epithelial hyperplasia may yield single benign columnar cells. However, the cellularity is much less compared with papilloma and the smears lack the other diagnostic characteristics of papillomas. In our study DCIS, invasive ductal carcinoma and lobular carcinoma were mistaken as papillary on cytology. This is in concordance with Michael and Buschmann in which mucinous carcinoma and cribriform DCIS were among malignant lesions misdiagnosed as a papillary neoplasm [8]. Simsir *et al*. also found in their study that DCIS, IDC and tubular carcinoma were mistaken as papillary neoplasm [3].

Our study also showed presence of micropapillary carcinoma, which generally does not show presence of true papillae/fibrovascular core, these are characterized by an "inside-out" growth pattern, in which cells are aligned in rounded clusters with basally located nuclei at the centre and apical cytoplasm at the periphery. Sensitivity of FNAC to diagnose papillary lesions in present study was 54.1%. This is in concordance with the study done by Aggarwal *et al.* (42%) [2] and Tse *et al.* (59%) [11].

Being a cross sectional nature of the study, present study findings cannot be applied to large population, there is a need of a large randomized clinical trial to provide strength to present study findings.

Conclusion

Based on the present study findings it can be concluded that due to low sensitivity and specificity cytological diagnosis of papillary lesions is difficult. We found a significant overlap in terms of architecture and cytological atypia, which is usually mild. If a papillary lesion is suspected in the FNAC, prompt histological evaluation is warranted for accurate diagnosis.

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