Sensitivity and specificity of fine needle aspiration cytology on breast mass as compared to Histology Evaluation

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Abstract:

Introduction: Breast cytology has been used for many years as a diagnostic tool for managing patients with breast lesions. In experienced hands, FNAB was found to be highly sensitive and specific.

Objective: To evaluate the accuracy and diagnostic performance of fine needle aspiration FNA cytology in diagnoses of breast masses.

Methods: FNA diagnoses and biopsy of breast masses of patients who underwent subsequent histopathologic evaluation during June2013-June2014 at Black lion Hospital pathology laboratory were evaluated.

Cytological diagnoses was classified as benign, suspicious for malignancy, malignant, and inadequate or inconclusive and was compared with the histopathologic diagnoses obtained from incisional biopsy or mastectomy specimen to assess the diagnostic performance of FNA.

Result and conclusion: The sensitivity and specificity of FNAc was found to be 86.7% and 90.3% respectively. FNA is still proved to be a good diagnostic modality for immediate diagnosis and patient follow up. The positive and negative predictive values are 86.7% and 90.3% respectively.

1. Introduction

1.1 Background

Breast cancer is a leading cause of death in many countries worldwide and breast lesions remain a common diagnostic dilemma.

Due to simplicity, accuracy, cost effectiveness and less chances of complications, fine needle aspiration is well tolerated by the patients and in many instances; it has replaced open biopsy and frozen sections.

Fine-needle aspiration biopsy (FNAB) has been suggested as the most important, first line, minimally invasive procedure in the management of patients with breast lesions.
With the introduction of stereotactic and ultrasonographically (US) guided methods for no palpable lesions, fine-needle aspiration biopsy (FNAB) have been used more widely in the evaluation of non palpable breast lesions .
Furthermore, the triple-diagnostic method (consisting of clinical evaluation, mammography and FNAB) gives a precise diagnosis and reduces the risk of missed diagnosis of breast cancer to < 1%
FNA cytology is highly dependent on the skill and experience of the aspirator.
The most commonly encountered pitfalls include: Fibroadenoma with atypical features, Mass or thickening associated with lactation, Radial scar with hyperplasia, Papilloma, Radiation changes, Fat necrosis, Atypical apocrine cells, Gynecomastia and Phyllodes tumour.

False negative diagnoses in FNA cytology are more common than false positive diagnoses. Sampling error and interpretation error are the most common reasons for a false negative diagnosis.

Other Situations associated with false negative diagnoses in FNA cytology include:

1. Some lesions may be more difficult to sample.

2. Well-differentiated grade 1 carcinomas may be difficult to diagnose, as the cell yield may be poor or there may be only mild cellular atypia.

3. Infarcted papilloma.

4. Invasive lobular carcinomas may yield few cells, which are often difficult to distinguish from benign cells.

5. Low-grade DCIS, and some tubular carcinoma may yield deceptively ‘benign’ aspirates

6. Necrosis may be present in the centre of a high-grade carcinoma

7. Sclerosis is a potential cause of a low cell yield

The aim of this study is to evaluate the efficacy of FNAB in patients with breast lesions by comparing the diagnostic accuracy of cytology results with that of the gold standard i.e. histologic evaluation.

1.2 Rationale of the study

The fine needle aspiration cytology diagnosis gives the patient an immediate psychological relief and avoids unnecessary aggressive surgery.

To this effect the diagnosis has to be convincingly reliable. However, there are diagnostic challenges in FNA including the techniques of sampling, size of the mass, histological types of the tumor and degree of differentiation.

The study will evaluate the accuracy of FNAc diagnosis in the set up of Tikur Anbassa specialized hospital and compare it with the the outcome in other setups there by assessing the possible limitations and diagnostic pitfalls.

2. Literature review

Breast cancer is the most common malignant neoplasm affecting women worldwide. Fine needle aspiration (FNA) cytology has become widely accepted as a reliable diagnostic tool for diagnosis of breast masses.
It is a simple and safe method which yields high diagnostic performances.
However, in some cases a definitive diagnosis cannot be made by FNA alone, either due to the inherent limitations of cytology itself or the ability to obtain adequate material for diagnosis.
A study done in *the department of Anatomical Pathology, Bangkok Metropolitan Administration Medical College and Vajira Hospital, Bangkok, Thailand on* 190 breast masses from 190 women who had breast FNA and subsequent histopathology from January 2003-December 2006 showed that the overall sensitivity, specificity, positive predictive value, and negative predictive value were 92.5% , 90.2%, 88.1% and 93.9% respectively.(1)

Similar study done at Northampton General Hospital , Northampton ,revealed that the sensitivity of breast FNA was 91.7% . The study also showed that experience of the pathologist, histologic type of the tumor and size of the tumor affect the sensitivity and specificity of the FNA.(2)

A retrospective study of FNAC of breast done in pathology department of Nepal Medical College Teaching Hospital from January 2003 to December 2005 showed that Sensitivity and specificity of FNAC of breast was found to be 83.3% and 100% respectively.(3)

A systematic review and meta-analysis study on the Diagnostic value of fine-needle aspiration biopsy for breast mass done in the department of Breast Surgery of Guangxi Cancer Hospital & Affiliated Cancer Hospital of Guangxi Medical University, Nanning 530021, Guangxi, P.R.China in January 2012 showed the sensitivity of breast fine needle aspiration cytology was 92.7 (95% confidence interval [CI], 92.1 to 93.3) and specificity, 94.8 (95% CI, 94.3 to 95.2). The pooled sensitivity and specificity for 11 studies, which reported unsatisfactory samples (unsatisfactory samples was considered to be positive in this classification) were 92.0 (95% CI, 90.6 to 93.3) and 76.8 (95% CI, 75.1 to 78.4) respectively. The pooled proportion of unsatisfactory samples that were subsequently upgraded to various grade cancers was 27.5% (95% CI, 22.1 to 29.6).(4)

A study was conducted to assess the efficacy of fine needle aspiration cytology in the diagnosis of breast lumps conducted in Khyber teaching hospital Peshawar, Pakistan from August 2002 to May 2003 on a total of 50 women, who had a clinically palpable breast lump and subjected to concurrent FNAC and excision biopsy. The result showed that out of 12 malignant lesions on excision biopsy, FNAC correctly diagnosed 9, and 2 were diagnosed suspicious, and the remaining one was misdiagnosed as non malignant. So false negative being 1/12 (8.3%). Of 38 benign cases on excision biopsy, FNAC diagnosed correctly duct ectasia 3, tuberculosis 2, and galactocele 1, while out of 22 fibroadenoma, FNAC diagnosed 20, and 2 were diagnosed as unsatisfactory. Ten cases diagnosed as fibrocystic disease on excision biopsy, FNAC picked only 6 cases correctly. The one case diagnosed on FNAC as fibrocystic disease, turned out to be malignant on histology. The remaining 4 cases of fibrocystic disease diagnosed on histopathology were either reported as unsatisfactory (3 cases) or suspicious (1 case) on FNAC. The sensitivity and specificity of FNAC was 91.66% and 96.96% respectively.(5)
A Prospective 2 year study of 334 patients was done to evaluate the diagnostic utility of aspiration biopsy of the breast lesions in *the department of Pathology, Grant Government Medical College. F*ibroadenoma was found to be the most common benign lesion whereas invasive ductal carcinoma was the most common malignant lesion . Cyto-histopathological correlation was found in 181 cases.(6)

A 4 years prospective studyon the use of Fine-Needle Aspiration in the Evaluation of Breast Lumps done in the Department of Pathology, King Edward Medical University, Pakistan revealed that most of the benign lesions were reported in 3rd and 4th decades of life, while maximum numbers of malignant lesions were reported in 5th and 6th decades. It also showed that false positives noted mainly in the interpretation of suspicious smears or with atypical features, were due to uniformly enlarged nuclei with prominent nucleoli, occasional marked nuclear enlargement, and moderate pleomorphism seen in fibrocystic disease or fibroadenoma. Regarding benign proliferative and malignant lesions no false positivity was seen.(7)

A comparative study of the fine-needle aspiration cytology and excisional biopsy of breast lesions done at Ethiopian Health Nutrition Research Institute, Addis Ababa showed that fine-needle aspiration cytology as a routine method in the management of breast diseases was compared to excisional biopsy of the same patients. Sixteen patients (15.7%) had carcinoma of the breast and 86 (84.3%) cases were found to have fibroadenomas of the breast. The sensitivity was 94.3% and the specificity was 78.6%. The positive and negative predictive values were 68.8% and 96.5% respectively. There were three false positive and false negative cases.(8)

A report from the Working Group on the Accuracy of Breast Fine-Needle Aspiration Cytology of the Japanese Society of Clinical Cytology disclosed that inadequate rate, 17.7%; indeterminate rate, 7.8%; positive predictive value of 'malignancy suspected' cells, 92.4%; absolute sensitivity, 76.7%; complete sensitivity, 96.7%; specificity, 84.3%; negative predictive value of 'normal/benign' cells, 98.2%; positive predictive value of 'malignant' cells, 99.5%; false-negative value, 3.31%; and false-positive value, 0.25%. The accuracy rate of breast FNAB was 88.0%.

It also states that after re-evaluating the false-negative cases ,re-categorization into a new category upon re-evaluation were as follows: 'inadequate' (the small number and/or poor quality of cells made re-evaluation difficult in this category), there were only small clusters in 70% and the other 30% were composed of small clusters with drying or degeneration; 'normal/benign', 175 of 212 cases (82.5%) were benign and/or normal epithelial cells (not atypical, benign small clusters with myoepithelial cells), and the other 37 cases (17.5%) showed other benign findings (i.e., apocrine metaplasia, foamy cells, fat cells, fibroadenoma-like findings); 'indeterminate' 38.8% had clusters of unclear myoepithelial cells, 18.7% with a small number of atypical cells presented in the specimens, 5 cases (10.2%) showed abundant papillary clusters, 3 cases (6.1%) showed mild atypia and 14 cases (26.6%) were for other reasons.(9)

A study conducted in Bedfordshire and Hertfordshire Breast Screening Unit , Dunstable Hospital, UK on the Role of fine-needle aspiration cytology and core biopsy in the preoperative diagnosis of screen-detected breast carcinoma showed that the absolute sensitivity, which considers only the definitely malignant (C5 or B5) results, was 80% for CB and 65% for FNAC. Complete sensitivity, which considers all abnormal results (B3 and above and C3 and above), was 93 and 82%, respectively. When both tests are combined, the absolute sensitivity was 87% and complete sensitivity was 98%. Complete sensitivity of FNAC varied with the final histology: it was 89% for IDC, 73% for ILC, 81% for mixed ductal and lobular carcinoma, 72% for TC and 73% for DCIS. Corresponding figures for CB were 92, 98, 94, 86 and 94%, respectively. Overall, the complete sensitivity of CB was higher than that of FNAC regardless of whether the tumour was DCIS or invasive, mammographic presentation (microcalcification or soft tissue lesion) or the mode (clinical, US or stereotaxis) of biopsy . Core biopsy suggested (B3 or above) 86% of the cancers missed by FNAC and FNAC was abnormal (C3 or above) in 65% of those missed by CB. When only the 555 patients who had both tests performed under the same modality (clinical, US or stereotaxis) were considered, the absolute and complete sensitivities were 62 and 78% for FNAC and 80 and 93% for CB, respectively. The corresponding figures for the combination were 82 and 97%.(10)

3. Objective

3.1 General objective:

To assess the sensitivity and specificity of fine needle aspiration cytology diagnosis of breast tumors as compared to biopsy evaluation of the same case.

3.2 Specific objectives:

- To determine the accuracy of FNAc diagnosis.

- To compare the diagnostic precision of the hospital laboratory with other setups.

- To identify the possible causes of false positive and false negative results in FNAc.

4. Subjects and methods

4.1 Study area: TASH, Addis Ababa, Ethiopia

4.2 Study design: Prospective study of all patients coming to TASH pathology department laboratory with a complaint of breast mass on whom FNA is performed and with subsequent biopsy sent to the department from June 2013 to June 2014 .

4.3 Study population: All patients with breast tumor subjected to FNAc and subsequent biopsy at TASH from June 2013 to June 2014.

4.4 Sample size determination: The sample size n required to estimate a population proportion with a given level of precision d is

$$n = \frac{Z^2_{1-\alpha/2}}{d^2} p(1-p)$$

- d (Precision) with 95% confidence interval=0.05
- Z=1.96 reflects the confidence level

n= $\frac{(1.96)(1.96)(0.91)(0.11)}{(0.05)(0.05)}$

n=138

4.5 Sampling procedures:

The fine needle aspirations was done according to the standard methods by using a 21 gauge needle and 10 ml disposable syringe.
Two to four slides were made from the aspirates and were air dried.
The smears were stained by Wright stain following the standard procedure.
In adequate or in conclusive aspirates done by the attending resident were repeated by the responsible senior staff pathologist.
After thorough examination of the smears the cases were grouped into four major diagnostic categories.
1. Positive for malignant cells.
2. Suspicious of malignancy.
3. Benign
4. In adequate or inconclusive

4.6 Data collection: The signed out slides of breast aspiration were kept separately and retrieved when the corresponding biopsy slides came. Broken and lost biopsy slides were replaced by sectioning from the paraffin block.
The gross and microscopic description and diagnosis of both cytology and histology slides were compared and analyzed.

4.7 Data quality control:

Quality aspiration slides were obtained under the supervision of the senior pathologists.
Representative sections from the lumpectomy or mastectomy specimens were taken and new blocs were added when not conclusive or representative .

4.8 Exclusion criteria:

1. Patients with recurrent malignancy.
2. Patients who underwent FNAC but did not undergo subsequent histopathological diagnosis.

4.9 Operational definitions

- **Breast mass:** Any abnormal growth on the breast tissue detected by the patient and the referring physician
- **Positive for malignant cells:** FNA shows conclusive cytological evidence of malignancy.
- **Suspicious of malignancy:** Cells that are significantly atypical but inconclusive for malignancy are seen in the smear.
- **Benign:** An adequate number of well- preserved benign epithelial cells occur in the sample.
- **In adequate or inconclusive:** The cellular findings in the material are not diagnostic.

4.10 Data processing and analysis.

The demographic, clinical and pathologic parameters of the collected data is analyzed using frequency tables as follows:

Table 1: Patients demographic data

Sex		**Age**			**Parity**	
Female	**Male**	**<30yr**	**30-50yr**	**>50yr**	**Nulliparous**	**Parous**
138	**0**	**28**	**78**	**32**	**47**	**91**
Total=138		**=138**			**=138**	

Table 2: Diagnostic categories of fine needle aspiration specimens.

Diagnostic category	**No**	**%**
Positive for malignant cells	45	32.6%
Suspicious for malignancy	18	13.0%
Benign	62	44.9%
Inadequate or Inconclusive	13	9.5%
Total	138	100%

Table 3: FNA Specific diagnosis of breast mass(Exclude the suspicious and inconclusive reports)

Diagnosis	**No**	**Percent**
1. Ductal carcinoma	43	40.2%
2. Fibroadenoma	31	29%
3. phyllodes tumor	14	13.13%
4. Papillary neoplasm	7	6.5%
5. . Tuberculosis	6	5.6%
6 Duct ectasia	4	3.7%
7. Lobular carcinoma	2	1.87%
Total	107	100%

Table 4. Comparison of FNA and Histopathology Findings

	Histopathology		
FNA	Benign (No& %)	Malignant (No& %)	Total
Benign(T=62)	56(90.3%) (TN)	6(9.7) (FN)	62
Suspicious (T=18)	5(27.7%)	13(72.3%)	18
Malignant(T=45)	6(13.3%) (FP)	39(86.7%) (TP)	45
Inconclusive or In adequate (T=13)	11(84.6%)	2(15.4%)	11
Total	78	60	

Table5. Diagnostic Performance of Fine Needle Aspiration Cytology for Breast Masses

Parameter	**Value (%)**
Accuracy (TP+TN/P+N)	88.8%
Sensitivity(TP/TP+FN)	86.7%
Specificity (TN/FP+TN)	90.3%
Positive predictive value (TP/TP+FP)	86.7%
Negative predictive value(TN/TN+FN)	90.3%

4.11 Ethical considerations: All patients undergoing the fine needle aspiration procedure were informed about the procedure and done on voluntary basis as being practiced routinely. The remaining steps are done from the tissues and slides.

4.12 Dissemination of results:

The research out comes will be submitted to the department of pathology . It will also be submitted to the medical journals in the country for possible publication.

5. Strengths and limitations:

The availability of resources and consulting senior pathologists is the strength of the research.
The possible limitations include:
1. Technical competency in sampling, smearing, staining and interpretation.
2. Some biopsy specimens were not handled appropriately before being submitted to the lab.
3. It was difficult to retrieve filed histology slides
4. Patients with benign cytology results might not have undergone subsequent surgery and hence the specificity of benign diagnosis lacks adequate comparison.

6. Results and Discussion

A one year study was done to evaluate the diagnostic utility of fine needle aspiration cytology of breast lesions. Age of patient varied from 11-65 yrs. Most of the benign cases were in patients below 30yrs of age and malignant cases were in 40-50 yrs age group. 138 cases were categorized as inadequate 11(84.6%), benign 56(90.3%) , suspicious 5(27.7%)and malignant 6(13.3%) .

Fibroadenoma 31(29%) was the commonest benign lesion followed by phyllodes tumor 14(13.3%) and papillary neoplasm 7(6.5%)

Amongst malignancies, commonest lesion was ductal carcinoma,43(40.2%) followed by lobular carcinoma,2(1.87%). Majority of the cases reported as suspicious(72.3%) turned out to be malignant on histological examination

Positive cytohistopathological correlation was seen in 86.7%of the cases. Cytological nuclear grading was comparable with histopathological grading in all cases ofinvasive ductal carcinoma. Invasive ductal carcinoma grade II was the most common grade on cytology as well as on histopathology.

The classical fibroadenoma revealed biphasic pattern consisting of epithelial and fibromyxoid stromal fragments. The monolayered sheet of cells showed typical antler horn pattern and presence of myoepithelial cells within these sheets. The background comprised of numerous bare nuclei which were typically bipolar or spindle in shape. The inconclusive smears which turned out to be fibroadenoma histologically lack many of these features. Some with fibrosed stroma were reported as inconclusive(See fig.1)

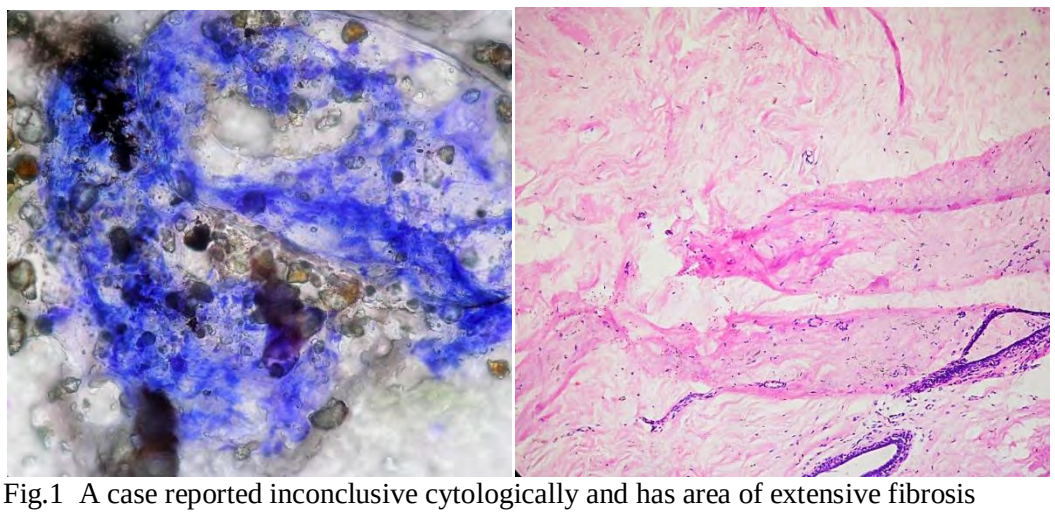

Fig.1 A case reported inconclusive cytologically and has area of extensive fibrosis

Only two cases of lobular carcinoma were diagnosed correctly. A case reported as suspicious for malignancy because of few atypical cells in the field turned out to be lobular carcinoma(See fig.2)

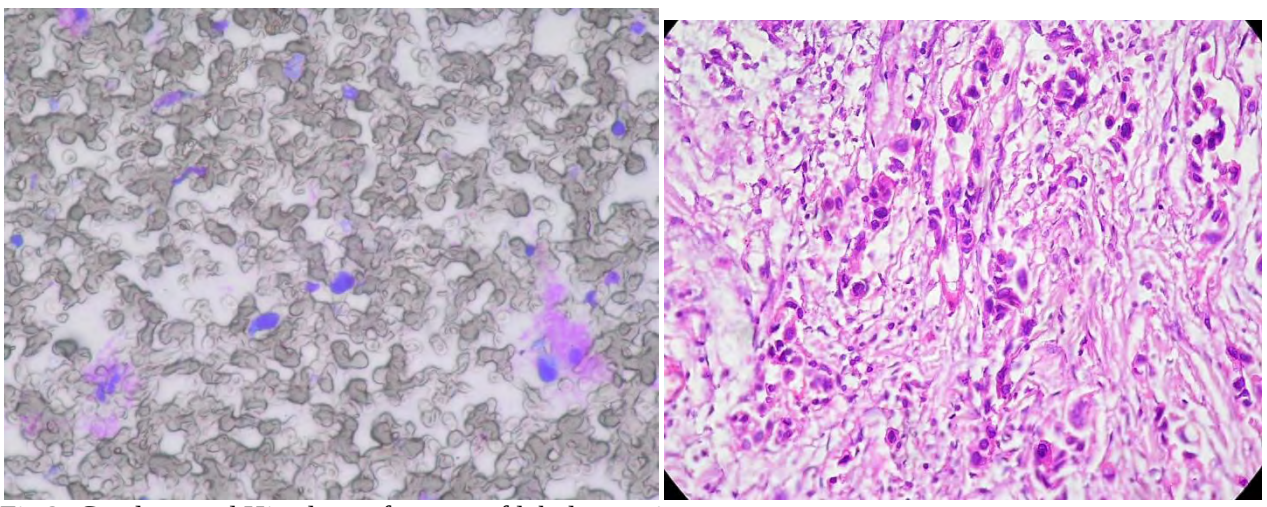

Fig.2- Cytology and Histology of a case of lobular carcinoma

A 37 years old patient presented right breast ill defined mass diagnosed to have benign breast lesion by cytology turned out to have invasive ductal carcinoma histological. Cytology showed only fat globules with spindle cells and few bland epithelial cells. Biopsy revealed that there were atypical epithelial cells with forming ducts and embedded within the fat (See fig.3).

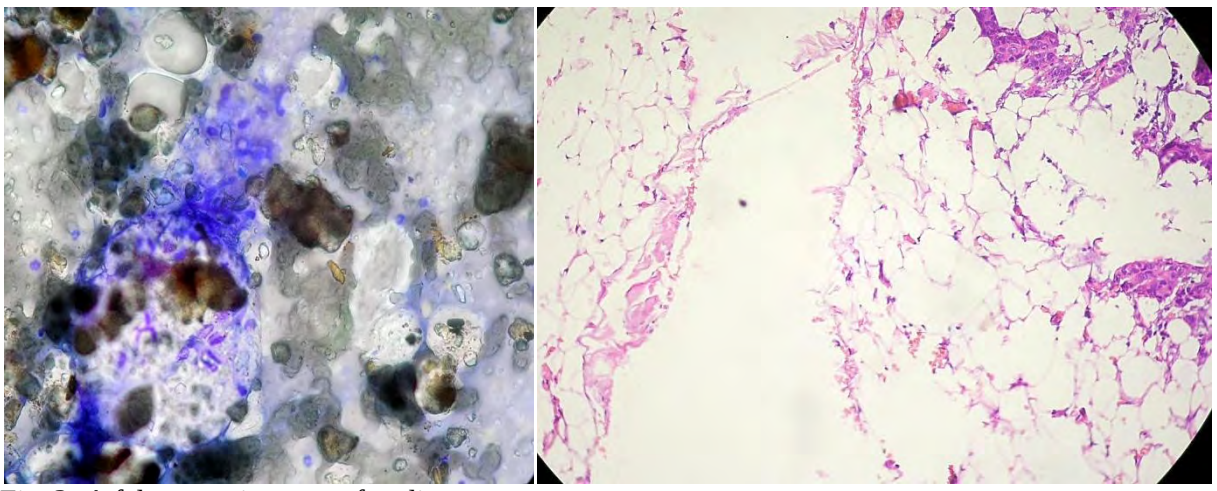
Fig. 3- A false negative case of malignancy

Many of the phyllodes tumor cases were cellular composed mainly of spindle cells in a myxoid background. Cases with low yield were reported as inconclusive but showed benign phyllodes in histology(see fig.4)

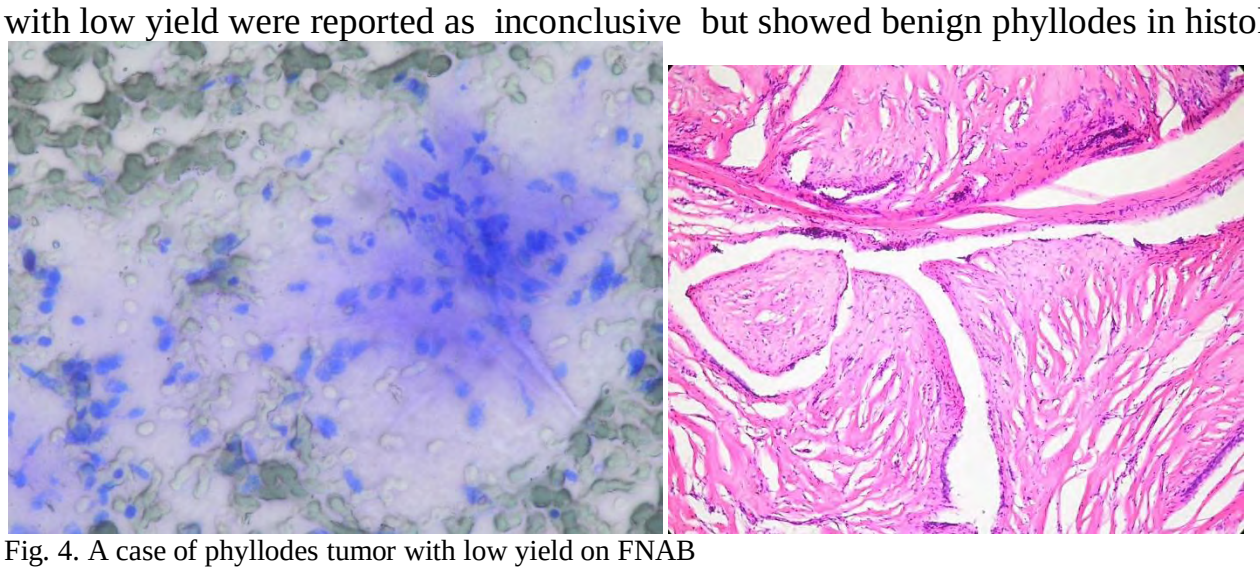
Fig. 4. A case of phyllodes tumor with low yield on FNAB

Many studies have reported the efficacy of FNAworldwide. In a study by Choi et al 1297 cases of FNA were evaluated and compared to histological diagnoses. About 29.7% of the cases were benign, 73.7% were suspicious, 68.1% were malignant and 14.6% were unsatisfactory. Sensitivity, specificity, positive and negative predictive values were 77.7%, 99.2%, 98.4%, and 88% respectively. Two cases were false positives and 35 were reported false negatives. Accuracy was 91.1%. They concluded that FNA should be used together with other diagnostic modalities such as physical examination and imaging in evaluating breast lesions(7)

Mansoor et al have studied the diagnostic efficacy of FNA in breast lesions of 72 patients. Sensitivity, specificity, PPV, and NPV were 98.4%, 60%, 93.9%, and 93%, respectively. False positive and false negative fractions were 6% and 14.2%. They concluded that FNA is an efficient diagnostic method in breast lesions(8)

7. Conclusion

On the whole, the current evidence shows that fine-needle aspiration biopsy (FNAB) is an accurate biopsy for evaluating breast malignancy if rigorous criteria are used. With high sensitivity and specificity, most benign and malignant breast lesions can be reliably diagnosed by FNAB. FNAB may provide a favorable screening method and permit an improvement of treatment planning. With the introduction of imaging guided methods for percutaneous sampling of nonpalpable lesions, FNAB can be used more widely in the evaluation of breast lesions However, as inconclusive and suspicious reports rate is not low such cytological reports warrant further invasive procedures including core biopsies or open surgical biopsy in order to minimize the chance of missed diagnosis of breast cancer. Fine needle aspiration continues to be an acceptable and reliable procedure for the preoperative diagnosis of breast lesions, particularly in developing countries

8.Recommendation

1. Biopsy specimen handling should be given due attention for some autolyzed specimen were seen during processing.
3.It would be best if both cytology and biopsy diagnosis are made in the same center for patient care .
2. For dry aspiration which usually is due to fibrosis, core needle biopsy has to be practiced before surgical management
3. Some patients refereed by the attending physician as having breast lump do not have a distinct palpable mass(jut lumpiness). These patients should first have imaging of the breast to localize the tumor appropriately.
4.It would be a good practice to trace the cytology report of patients on which histology is being reported . That would serve as an internal quality control and also essential for academic purpose.

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