Original Research Article

Comparison of Fine Needle Aspiration and Core Needle Biopsy in Diagnosis of Granulomatous Mastitis Presenting with Breast Lump

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Abstract

Granulomatous mastitis is a chronic inflammatory disease of the breast with unknown etiology mostly seen in parous women shortly after their last pregnancy. It is crucial to differentiate granulomatous mastitis from cancer and definite diagnosis is established by histopathological examination. Its treatment is variable and the most appropriate treatment protocol is yet to be identified. Aim of the study was to compare the performances of fine needle aspiration and Core biopsy of breast lump verified by histopathological examination as "Gold standard". 227 women presenting with breast lump were included in this study. After selection, fine needle aspiration and core biopsy were done at same sitting and follow-up resection histopathology with 122 cases (53.74%) were performed in the laboratory. 40(17.62%) cases were diagnosed granulomatous mastitis by either fine needle aspiration or core biopsy, the reports of 23 cases (57.5%) were concordant in both the procedures and discrepancy was observed in reporting of 17 cases (42.5%). 36 cases (90%) were resected for histopathology and 33 (82.5%) breast lumps were diagnosed granulomatous mastitis. Diagnostic accuracy, sensitivity, specificity, negative and positive predictive values of fine needle aspiration cytology and Core biopsy were calculated. The diagnostic accuracy of core biopsy was 97.54% and that of fine needle aspiration cytology was 89.34%. Specificity, sensitivity, positive and negative predictive values of core biopsy were 97.77%, 97.29%, 94.73% and 98.87% respectively. The specificity, sensitivity, positive and negative predictive values of fine needle aspiration were 97.77%, 70.27%, 92.85% and 88.88% respectively. The accuracy of core biopsy was much higher than that of fine needle aspiration and also the performances of the combination of two procedures were superior to the individual test alone.

Keyword: Breast lump, granulomatous mastitis, fine needle aspiration, core needle biopsy, histopathology, accuracy.

INTRODUCTION

Idiopathic granulomatous mastitis, also known as granulomatous lobular mastitis is a chronic inflammatory breast disease recently have been reported to increase in developing countries [1]. This disease is still challenging for specialists and causing cosmetic problems for patients. Deficiency of knowledge in diagnosis and management leads to high rate of recurrence associated with surgery and tissue distortion even recurrence after mastectomy [2]. The most common presenting clinical symptom is painful palpable mass that can be associated with erythema and inflammation, multiple peripheral or rare central abscesses, sinus or fistula to the skin, nipple retraction and axillary adenopathy [3]. Mammographic or sonographic signs are not usually helpful for diagnosis such as hypo-echo tubular lesions, multiple abscesses, hypo-echo lobular

mass, tissue distortion, fistula of skin, axillary adenopathy, focal asymmetry of mammographic findings, diffused hyper-density mass, retraction and tissue heterogeneity which may be similar to cancer [4]. Various diagnostic methods have been developed to evaluate the breast lump with the aim to identify a sensitive, specific, efficient and economical approach to obtain an appropriate diagnosis of breast lump such as physical examination, fine needle aspiration cytology, core needle biopsy, ultrasonography, open excision biopsy and thermography [5]. Fine needle aspiration cytology has been proven to be of great value in the diagnosis of breast lumps. It is simple, quick and effective while it has some limitations such as inability to identify its invasive nature for insufficiency in sampling and false negative results. Recently the diagnosis of breast lump has been dependent on core

biopsy with gradual reduction in the rate of performing fine needle aspiration [6]. Tru-cut biopsy, also known as core needle biopsy is now one of the useful means of obtaining an appropriate diagnosis. It is relatively easy and its use also reduces unnecessary excisional biopsy, lowers inadequacy rate and allows ancillary methods, determines grading and typing of cancer and helps to plan a definitive surgery. However core biopsy has also some limitations and some authors recommended combining the two techniques to improve the diagnostic yield by reducing false positive and false negative rates [7,8]. Mammography, ultrasound and magnetic imaging techniques are useful but the tissue biopsy is necessary to confirm the diagnosis of granulomatous mastitis [9]. It is important to assess the efficiencies of the two procedures for comparison to meet the diagnostic challenge to minimize the controversies in selection of treatment and surgical management of the patients.

MATERIALS AND METHODS

A total of 227 participants having breast lumps were included in this cross-sectional prospective study during the period from July 2020 to June 2022 in Khulna City Medical College Hospital, Khulna and Shahid Sheikh Abu Naser Specialized Hospital, Khulna. It is difficult to differentiate granulomatous mastitis from malignant lesions, other inflammatory lesions and benign tumours on the basis of clinical information. Therefore, the women presenting with breast lump who underwent both fine needle aspiration (FNA) and Core needle biopsy (CNB) at same sitting included in this study to assess the efficiencies of the two procedures. All the aspirates were performed with 2 and 12 passes using a combination of 25, 23, and 21 gauge needle for FNA, and direct smears were made in all cases and alcohol fixed then stained with Papanicolaou or H&E. At the same sitting and after the FNA, a core needle biopsy was performed using an 18 gauge needle for formalin fixation and after laboratory processing, stained with H&E. The nulliparous women, the women of age less than 20 years and more than 70 years, previously diagnosed malignant tumours, clinically abscesses and patients with history of chemotherapy and immunosuppressive drugs were excluded from the study. The indication for core needle biopsy was determined on the basis of selection criteria, cosmetic issue and consent of the patient for acceptable and easy pursuance of follow-up resection biopsy. The cytological reports of study subjects were categorized on the basis of six cytological categories of reporting breast lesions such as I=Malignant, II=Suspicious, III=Atypical/Indeterminate, IV= Benign/Specific, V= Benign/nonspecific, and VI=Unsatisfactory [10].

The cases in which the atypical cells having hyperchromatic nuclei with prominent nucleoli and pleomorphism, were present in the smears but not sufficient for definite diagnosis of malignant tumour and the smears having significantly cellular atypia were considered as atypical cytology. For cytological reporting in some cases with the smears deemed suspicious for a malignant lesion and these were cellular composed of crowded, overlapped dyscohesive epithelial cells with hyperchromatic nuclei showing variation of nuclear outline and size and these were required further evaluation to exclude the malignancy, we preferred to categorize these suspicious cases in atypical category for purpose of the present study.

Benign tumours such as fibroadenoma and phyllodes tumours were grouped in specific benign lesions and also fibrocystic disease, granulomatous mastitis, and other specific chronic mastitis were categorized in specific benign lesions. The FNAC reports with only description of benign breast lesions, only negative for malignant cell, non-specific findings or cytologically unsatisfactory smears were considered as non-diagnostic and for calculation of test performance, these were considered negative. Only adequate cellular smears were examined and the difficult cases were reviewed by senior pathologists.

The diagnostic evidence of granulomatous mastitis are presence of epithelioid cells in the smears either in adequate number or arranged in clusters, histiocytes, occasionally epithelioid histiocytes, plasma cells, giant cells and presence of regular ductal epithelial cells with myoepithelial cells, variable cellular debris and mixed inflammatory cells indicating inflammatory process. For the purposes of this study, accuracy, specificity, sensitivity, positive and negative predictive values were calculated only for cases in which a subsequent resection histopathology were available for use of a "gold standard". An overall accuracy is not reported, instead the accuracy, specificity, sensitivity, positive and negative predictive values of the two techniques were compared and also the combination was evaluated within specific diagnostic categories for only the cases which had follow up histopathological examination as aforementioned. Statistical analysis was done using a 2-tailed Fisher exact test.

OBSERVATIONS AND RESULTS

The series included 227 women with ages ranging from 20 years to 70 years and median of 38 years presented with breast lumps. For 227 patients, the aspirate and the core needle biopsy were performed at the same time and follow up resection were performed later. A total of 122 patients (53.74%) had subsequent resection for histopathological examination. The overall results are summarized in Table-1.

Table-1: Distribution of patients with breast lump in different categories diagnosed by FNA, Core needle biopsy and follow-up resection histopathology (n=227)

No. of cases in different Diagnostic categories	Diagnoses by FNA	Diagnoses by Subsequent CNB	No. of cases with Follow-up resection	Histopathologic Diagnosis
15	Malignant	Malignant	15(100%)	Ca-15
12	Atypical	Malignant	12(100%)	Ca-11, CIS-1
23	Granulomatous Mastitis	Granulomatous Mastitis	22(95.65%)	GLM-21, CIS-1
5	Nondiagnostic	Granulomatous Mastitis	4(80%)	GLM-4
5	Atypical	Granulomatous Mastitis	5(100%)	GLM-4, CIS-1
3	Granulomatous Mastitis	Fibrocystic Disease	2(66.66%)	FCD-1, GLM-1
7	Atypical	CIS	7(100%)	Ca-5, ADH-2
59	Benign Tumour	Benign Tumour	25(42.37%)	FA-21, FCD-2, Phyllodes-2
68	Nondiagnostic	Benign Tumour	24(35.29%)	FA-22, FCD-2
5	nondiagnostic	Nonspecific Chr. Mastitis	1(20%)	LLM-1
21	Fibrocystic disease	Fibrocystic disease	2(9.52%)	FCD-2,
4	Fibrocystic disease	Granulomatous mastitis	3(75%)	GLM-3,
227	227	227	122(53.74%)	122

Ca-Carcinoma, GLM- Granulomatous lobular mastitis, CIS-Carcinoma-in-Situ, FCD-Fibrocystic disease, FA-Fibroadenoma, LLM-Lymphocytic lobular Mastitis, ADH-Atypical ductal hyperplasia.

Among the 227 breast lumps, 26 cases were diagnosed as granulomatous mastitis by FNAC and 37 cases were diagnosed granulomatous mastitis by core needle biopsy and in 40 cases, combinedly either by FNAC or core biopsy, the diagnoses were granulomatous mastitis. A total of 122(53.74%) were resected for histopathology and biopsy revealed 33 cases of granulomatous mastitis. Other diagnoses were 31 breast carcinoma, 3 Carcinoma-in-Situ, 2 Atypical ductal hyperplasia, 43 Fibroadenoma, 7 fibrocystic disease, 2 Phyllodes tumour, and 1 lymphocytic lobular mastitis, (Table-1).

FNAC and Core needle biopsy reports were concordant in 23 cases (57.5%) and in 17 cases (42.5%), reports were dissimilar. In 22 follow up resections, 21 cases were explored granulomatous mastitis and 1 case showed carcinoma-in-situ which was a low grade type. Initially the 2 FNA and 2 core biopsy were reported false positively as granulomatous mastitis and these were diagnosed otherwise in follow up histology. Moreover, the 2 FNA and 3 core needle biopsy were not resected for histopathology because symptoms were non-significant and clinical follow up was advised. Among 201 FNA reports diagnosed other than GLM, 98 cases (48.75%) were resected and histopathology confirmed the diagnoses accordingly, 11 histopathology diagnoses were granulomatous mastitis which had been reported false negatively by cytology. For 190 core biopsy reports diagnosed other than GLM, 88 cases (46.31%) were resected and histopathological examination revealed 87 cases other than granulomatous mastitis and a single case was diagnosed GLM which had been reported false negatively by core biopsy, (Table-1).

Table-2: Diagnostic accuracy, specificity, sensitivity, positive predictive value and negative predictive value of FNA and Core biopsy (n=122)

Procedure	Accuracy	Specificity	Sensitivity	Positive Predictive Value	Negative Predictive Value
FNA	89.34%	97.77%	70.27%	92.85%	88.88%
Core Biopsy	97.54%	97.77%	97.29%	94.73%	98.87%
Combination	97.54%	96.62%	100%	91.66%	100%

Accuracy of core needle biopsy was 97.54% which is similar to the accuracy of combination and higher than that of FNAC (89.34%). The specificity, sensitivity, positive predictive value and negative predictive value of core biopsy were 97.77%, 97.29%, 94.73% and 98.87% respectively which were higher than those of FNAC (97.77%, 70.27%, 92.85% and 88.88% respectively), (Table-2). The sensitivity and negative predictive value of the combination of two procedures

were 100% and the highest among the performances of individual test alone.

DISCUSSION

Aim of the study was to compare the performances of FNAC and core needle biopsy in diagnosis of breast lumps by assessment of efficiencies of the two procedures using the follow up histopathology as a "gold standard". A breast FNAC or core needle biopsy is indicated in several clinical situations that have mainly diagnostic values and additional usage includes the application of necessary ancilliary techniques such as performing immunohistochemistry for estrogen and progesterone receptors (ER & PR) by True-cut biopsy in the malignant epithelial neoplasms. Both the techniques can be performed for diagnosis of breast lesions with or without the assistance of radiology. Advantages of FNAC are rapidity of diagnosis, high acceptability, coast effectiveness, high sensitivity and specificity, feasibility of multiple sampling in a single sitting, appropriate for preoperative planning, sampling of primary site as well as metastatic lesions, helpful for ancilliary techniques, rapid psychological relief to the patient following a negative diagnosis and it can be used in both palpable and non-palpable lesions and also it can be used as therapeutic purpose with minimal complications [6].

The present study revealed that accuracy, specificity, sensitivity, PPV and NPV of FNAC were 89.34%, 97.77%, 70.27%, 92.85% and 88.88% respectively and accuracy, specificity, sensitivity, PPV and NPV of core biopsy were 97.54%, 97.77%, 97.29%, 94.73% and 98.87% respectively (Table-2), which were comparable with observations in a study carried out by Hossain *et al.,* [7] such as accuracy of 78.3% in FNAC and accuracy of 98.3% in core needle biopsy. A study including 147 patients revealed that 109 (74,1%) had malignant lesions found by core biopsy and 38 patients had benign lesions (32.1%), with sensitivity and specificity of core biopsy and FNAC of 96.55% and 75.10% respectively, also PPV and NPV were 92.4% and 87.5% respectively, [11] which were comparable to the present study. A review article mentioned the findings of a study which revealed that sensitivity of core biopsy was 96% and that of FNAC was 21.1% and inadequacy of sampling, presence of other diseases such as abscess or fat necrosis were mentioned as a cause of low sensitivity of FNAC [12]. A study involving 68 cases presenting with breast lump revealed the sensitivity and specificity of FNAC as 84.6% and 72.4% respectively. Comparatively higher sensitivity and specificity of core needle biopsy were found as 89.7% and 96.5% respectively [13]. Another study carried out by Saha A *et al.,* [14] on 50 cases undergoing three procedures to compare FNAC and core needle biopsy revealed that FNAC showed sensitivity and accuracy of 69% and 74% respectively, whereas core needle biopsy showed sensitivity and accuracy of 88.3% and 86% respectively.

Routine biopsy methods include fine needle aspiration, core needle biopsy, vacuum-assisted biopsy and excisional biopsy and the former two have considerable accuracy but excisional biopsy can be performed if necessary, frozen section evaluation can occasionally be useful in confirming the diagnosis and also to assess the extent of resection. The present study was focused on the diagnostic performances of cytology and core biopsy because it is crucial for clinical management and treatment of a patient having a breast lump caused by granulomatous mastitis and it was also observed that a multidisciplinary approach for the management of the patients of GLM reduces the rate of erroneous initial clinical impression of breast cancer [15] Recently an international multidisciplinary consensus (2021 edition) has formulated 30 recommendations on the basis of The 2010 American College of Physician (ACP) grading system and one of the recommendations on core needle biopsy emphasized on selection of site for core biopsy during inserting the needle as close as possible to the margin of the areola, because if a subsequent operation is planned, the puncture tunnel can be removed at the same time to reduce scar [16].

The diagnosis and treatment of a patient having granulomatous mastitis is a great challenge for the clinician and also for the patient who suffers with great impairment of quality of life and most importantly malignancy, usually should be excluded before the diagnosis of GLM can be considered [17]. Clinical manifestations of GLM are diverse which were observed in a study including 3060 cases with granulomatous mastitis frequently had symptoms (80%) with palpable lumps of mean size of 5 cm(3-9cm), and 66% were painful and median age of the patients having granulomatous mastitis was 36 years [18]. Another study reported that 90.7% of the patients had history of pregnancy and 82.7% had history of breastfeeding [19]. The most common signs of the disease are palpable mass, pain, inflammation and erythema, abscess formation, single or multiple fistulas, nipple retraction, breast deformity and occasionally axillary lymphadenopathy [20]. For the clinical management of the patients, GLM is classified into four stages on the basis of its progression and clinical manifestation such as (1) Self-limited stage, (2) Congestive swelling stage, (3) Abscess formation stage, and (4) complete refractory stage [21]. For clinical management and treatment, a multidisciplinary approach is useful and one study suggested that better characterization of specimens make core needle biopsy more efficacious and it provides more dependable preoperative diagnosis which can help to create a rational algorithm for management [22]. Other corroborative diagnostic procedures such as ultrasonography and mammography are conducive to diagnosis of granulomatous mastitis [23,24]. The higher performances of core needle biopsy and the highest sensitivity and negative predictive value of the combination (100%, Table-2)) observed in the present

study lead us to emphasize on use of the combination for diagnosis of granulomatous mastitis and it has a considerable influence on selection of the modalities such as etiologic, medical and surgical treatment.

Cytological diagnosis of GLM requires a perspicacious observation of pathologist to differentiate it from malignancy and other inflammatory clinical conditions and benign lesions especially fibrocystic disease. To differentiate from malignancy, difficulty arises when cellular atypia in the epithelial cells make a confusion for diagnosis, here three dimensional aggregates, arrangement of the cells, absence or presence of myoepithelial cells, interspersed fibro-fatty tissue and pleomorphism may be determining factors. To differentiate it from fibrocystic disease, difficulties arise when histiocytes of various size along with epithelioid histiocytes appear in the smear. In this cases the arrangement of histiocytes, admixture with epithelial cells, absence of foamy histiocyte, presence of inflammatory cells including plasma cells and aggregates of epithelioid cells may be determining factors. Absence of caseation necrosis should be mentioned in cytological reporting of granulomatous mastitis to differentiate from tuberculosis. In core biopsy, there may be adenosis, non-caseating granulomas, multinucleated giant cells and peri-glandular inflammatory infiltrate. In addition to these cytological and biopsy procedures, other laboratory investigations are useful to differentiate it from tuberculosis such as tuberculin test, routine blood test, ESR, C-reactive protein, antinuclear antibody profile and growth of AFB in the tissue [25].

The limitations of the present study were first of all, the prevalence of granulomatous mastitis in the population is not reflected in this study because it was a hospital based research. Secondly, during selection of participants, random sampling technique was not applied and there is sampling bias in this study. Thirdly, inter-observer variation during cytological examination and also for core biopsy were not calculated statistically in this study. Fourthly, immunological study, microbiological examination and molecular diagnostic methods were not performed in the laboratory for study subjects.

CONCLUSION
Fine needle aspiration cytology and core needle biopsy are established laboratory procedures for diagnosis of breast lumps. The diagnostic accuracy of core biopsy was found much higher than FNAC and the combination of these two procedures is preferable to exclude the malignancy. The sensitivity and negative predictive value of combination were observed 100% for diagnosis of granulomatous mastitis and the combination of these two procedures has an important role in follow up management of the patients.

Ethical Clearance
The research protocol for this study and informed consent form were reviewed and approved by the ethical committee of Khulna City Medical College. The written informed consent was then obtained from each participant and a unique identification number was assigned and all records were kept in a secured room to ensure confidentiality.

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