

Cytological Evaluation of Breast Masses during Pregnancy and Lactation: A Retrospective Analysis

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Abstract

Background: Breast masses are a common problem encountered in pregnancy and lactation. Fine needle aspiration cytology (FNAC) is a rapid and cost-effective procedure in evaluating breast masses in these conditions. However, the cytological interpretation of these masses must be made with caution due to the atypia inherent to secretory changes in glandular epithelium seen in this period (pregnancy and lactation).

Materials and Methods: A retrospective study for a period of 3 years (January 2014 to December 2016) was conducted for evaluating the role of cytology in interpretation of breast masses in pregnancy and lactation during this period. All available clinical and histo-pathological data was also retrieved and analyzed.

Results: Forty five breast masses were identified during pregnancy and lactation. Benign lesions were the most common etiology seen. Among benign lesions, galactocele was the most common etiology identified. Fibroadenoma (FA) was the most common benign tumor seen during this period. Four cases were identified as pregnancy associated breast carcinoma (PABC) constituting 8.8% of all breast masses in this period.

Conclusion: Cytology was an effective tool with minimal surgical intervention in identifying the etiology of breast masses in pregnancy and lactation. However, the cytopathologists must be aware of the characteristic patterns seen in breast FNAC smears during pregnancy and lactation and the associated atypia seen in glandular epithelium during this period. FNAC smears in these conditions must be interpreted with caution considering the associated clinical details and radiological findings. FNAC will provide a very rapid, easy and cost effective tool in identifying the etiology for breast masses. However, the patients must be followed up during pregnancy and postpartum period as majority of benign lesions regress without any intervention. Benign lesions are the most common etiology in breast masses in pregnancy and lactation. But PABC must always be considered in the differential diagnosis for the timely diagnosis and intervention.

Keywords: Fine needle aspiration cytology; Breast masses; Pregnancy; Lactation; Pregnancy associated breast carcinoma

Abbreviations: FNAC: Fine Needle Aspiration Cytology; ABC: Associated Breast Carcinoma; FA: Fibroadenoma; ZN: Zeil - Nelson; CBNAAT: Cartridge Based Nucleic Acid Amplification Test; M.tb: Mycobacterium Tuberculosis; IDC: Infiltrating Ductal Carcinoma; ER/PR: Estrogen and progesterone receptors; PABC: Pregnancy Associated Breast Carcinoma

Introduction

Background

Breast is an organ which is under the influence of steroid hormones from menarche until menopause. During pregnancy and lactation, the levels of various hormones changes. Increased estrogen levels lead to ductal and vascular proliferation. Acinar proliferation is under the influence of progesterone. With the expansion of ductal-lobular units, the fibrolipoma substrate of the breast decreases [1]. Breast masses are a common complaint seen during pregnancy. However, the substantial physiological changes seen in breast during these conditions

make the evaluation of breast masses very challenging. FNAC provides many advantages in the evaluation of breast masses during pregnancy and lactation. These include minimal surgical intervention, rapid procedure, safety and cost effectiveness [2]. Still FNAC of breast masses is not a widely accepted procedure in pregnancy and lactation. This is because the cytological interpretation in these cases is considered problematic due to the atypia inherent to the secretory change in glandular epithelium [3]. We made this retrospective study for a period of three years in order to identify the role of cytology in evaluating the breast masses during pregnancy and lactation.

Procedure

This was a retrospective analysis of breast masses seen during pregnancy and lactation (one year post delivery) for a period of 3 years (January 2014 to December 2016) in the department of Pathology, Dr. RPGMC, Tanda, HP, India. FNAC was performed using 23- or 25- gauge needle by palpation without radiological guidance. The procured material was used to make at least 4-5 smears. Two slides were fixed in 95% ethanol and stained by PAP stain and hematoxylin and eosin stain (H and E stain). Air dried smears were stained with Giemsa stain. Apart from re-evaluation of cytology smears, all available clinical and histo-pathological data was also retrieved and analyzed.

Results

Clinical data

During the particular study period, 45 cases of breast masses in pregnancy and lactation were identified. Patients ranged in age from 20-38 years with a mean age of 26 years. Sixteen FNAC's were taken from pregnant patients and 29 from patients in postpartum period (Table 1). FNAC was performed at 15 weeks of gestation to 12 months post partum.

Table 1: Distribution of breast masses detected during pregnancy and lactation.

Cases	Total (n=45)	During Pregnancy (n=16)	During Lactation (n=29)
Galactocele	16	4	12
Lactational Adenoma	5	2	4
Fibroadenoma	8	7	1
Benign cyst	3	1	2
Mastitis	6	0	6
Granulomatous inflammation	3	0	3
Duct cell carcinoma	4	2	1

Pathological data

Galactocele was the most common etiology for breast mass in pregnancy and lactation (16/45; 35.5%). Majority of cases (12/16) were identified in post partum period within 8 months of delivery. Four cases were identified on FNAC in the third trimester. Cytology smears revealed scattered macrophages, acinar cells with lipid droplets as vacuoles in the background (Figure 1a). These patients were followed during pregnancy and post partum period and in majority of patients the swelling subsided, once the lactation was stopped. If the mass persisted or the swelling increased in size, the mass was excised. Corresponding histo-pathological material was identified in four cases. Three cases confirmed the cytological diagnosis. However, one case was reported as lactational adenoma on histopathology.

Fibroadenoma (FA) was identified in 8 cases. In majority of the cases, lump was identified by the gynecologist, during breast examination. In remaining two cases, the lump was identified by the patient before pregnancy. However, during pregnancy the

lump size increased rapidly. FNAC smears were cellular with large, branching sheets of bland epithelial cells and numerous bimodal cells in the background (Figure 1b). Histological correlation was present in 3 cases and these confirmed the cytological findings. Lactational adenoma was seen in 6 cases on cytology. Out of all, 4 cases were identified during lactation. Cytological features consisted of highly cellular smears, monolayered cohesive cell clusters with foamy cytoplasm, bland nuclear features, and minimal bipolar cells in the background and granular proteinaceous material in the background (Figure 2a). Histo-pathological material was available in three cases (Figure 2b). Two cases confirmed the cytological findings. One case turned out to be invasive ductal carcinoma with co-existing lactational adenoma.

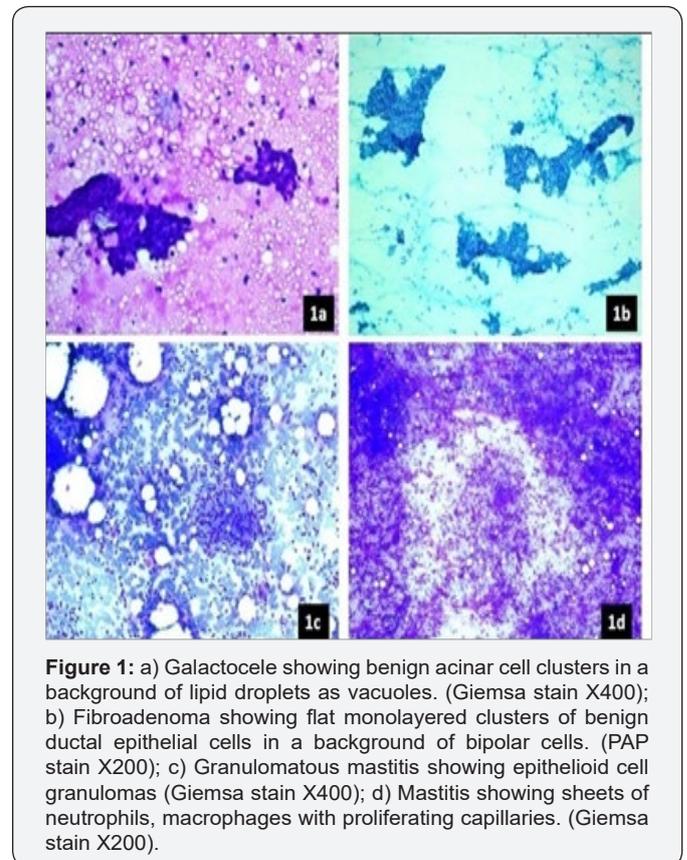


Figure 1: a) Galactocele showing benign acinar cell clusters in a background of lipid droplets as vacuoles. (Giemsa stain X400); b) Fibroadenoma showing flat monolayered clusters of benign ductal epithelial cells in a background of bipolar cells. (PAP stain X200); c) Granulomatous mastitis showing epithelioid cell granulomas (Giemsa stain X400); d) Mastitis showing sheets of neutrophils, macrophages with proliferating capillaries. (Giemsa stain X200).

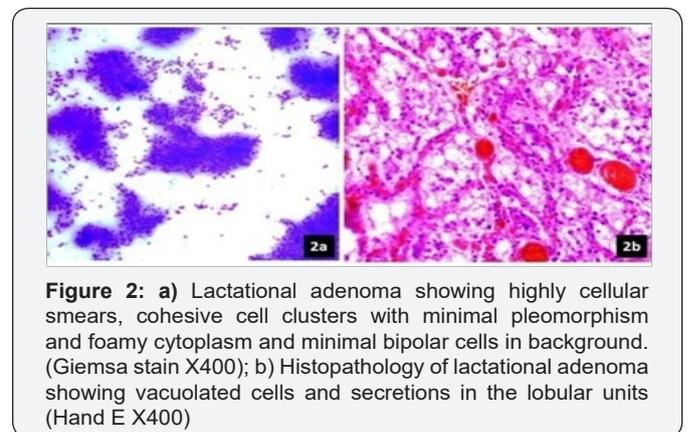


Figure 2: a) Lactational adenoma showing highly cellular smears, cohesive cell clusters with minimal pleomorphism and foamy cytoplasm and minimal bipolar cells in background. (Giemsa stain X400); b) Histopathology of lactational adenoma showing vacuolated cells and secretions in the lobular units (Hand E X400)

Granulomatous inflammation was seen in three cases, all during lactational period (Figure 1c). Zeil- Nelson (ZN) staining was non- contributory in all cases. Aspirate samples were sent for cartridge based nucleic acid amplification test (CBNAAT) testing and was negative for mycobacterium tuberculosis (M.tb). One case was confirmed on histopathology. Three cases were reported as benign cyst on cytology. The cyst fluid was completely aspirated and the swelling nearly regressed in size. Reaspiration was done from the residual lump to rule out any hidden pathology. Cytological smears examined revealed cyst macrophages, bland ductal epithelial cells in a proteinaceous background. Six cases were reported as mastitis on FNAC. These cases were seen during the lactation period. FNAC smears examined revealed benign bimodal population of non-neoplastic breast tissue in a background of acute and chronic inflammatory cells (Figure1d). Patient was put on antibiotic therapy and the patient recovered in all cases.

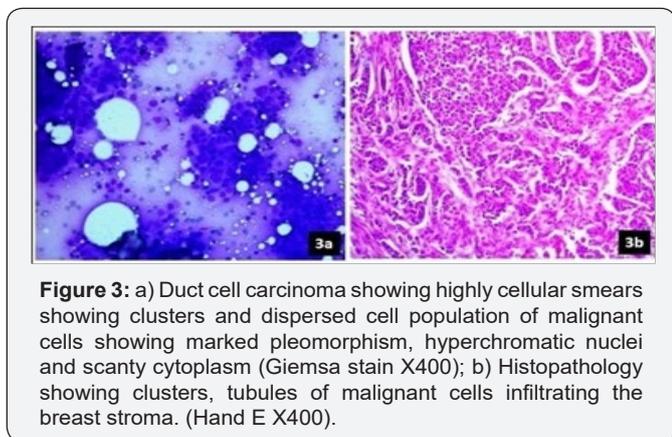


Figure 3: a) Duct cell carcinoma showing highly cellular smears showing clusters and dispersed cell population of malignant cells showing marked pleomorphism, hyperchromatic nuclei and scanty cytoplasm (Giemsa stain X400); b) Histopathology showing clusters, tubules of malignant cells infiltrating the breast stroma. (Hand E X400).

Three cases were reported as duct cell carcinoma on cytology. Two cases were identified in second trimester of pregnancy and one case was identified in the postpartum period at fourth month. One case was identified as duct cell carcinoma on histopathology which was initially reported as lactational adenoma on cytology. The age range of all carcinoma cases was between 28-35 years. None of the patients had any family history of carcinoma breast. Median clinical tumor size was 4.2cm. Cytology smears revealed highly cellular smears with dispersed cell population, highly pleomorphic cells, high nuclear-cytoplasmic ratio, hyperchromasia and prominent nucleoli. Atypical mitosis was also seen occasionally (Figure 3a). On histo-pathological examination of mastectomy specimens, three cases were reporting as infiltrating ductal carcinoma (IDC) grade 2, based on Modified Bloom Richardson Scoring system (Figure 3b). One case was reported as IDC grade 3 along with a component of lactational adenoma.

Axillary lymph node metastasis was seen in 75% of cases of IDC (2/12 involved lymph nodes in 1 case, 6/10 involved lymph nodes in case 2 and 1/7 involved lymph nodes in case 3). One case did not have any lymph node metastasis (0/13). Estrogen and progesterone receptors (ER/PR) were evaluated

in all four cases. All four cases of PABC were negative for ER/PR expression. Her2 Neu expression was seen in two cases. Two cases were negative for all three (ER/PR/Her2 Neu) receptors. Post surgery, all carcinoma patients were further managed with chemo-radiation. On follow up, one patient had died (two years after treatment). She had metastasis to bones and liver. Another patient had tumor metastasis to opposite breast and is on second line chemotherapy. Remaining two patients are on regular follow up and do not report any complications.

Discussion

In our study, benign lesions constituted the main etiology for breast masses in pregnancy (41/45; 91%), as reported in other studies [2,3]. Among benign lesions, galactocele was the commonest etiology seen; fibroadenoma was the commonest benign tumor in pregnancy and lactation in our study. Four cases were reported as PABC constituting 8.8% of all breast masses in pregnancy.

Role of cytology in breast masses during pregnancy and lactation

FNAC is a very useful procedure to identify the underlying etiology of breast masses during pregnancy. It provides an easy and rapid diagnosis in majority of cases and reduces the surgical intervention to a minimum during pregnancy. It is important to evaluate the aspirate smears from breast lumps in pregnancy and lactation with caution. This is because of the physiological changes seen in breast during pregnancy and lactation. Due to altered hormonal levels in these conditions, there is marked ductal, acinar and vascular proliferation. Cytological smears in pregnancy and lactation show increased cellularity, dispersed acinar cell population, lack of bipolar nuclei and prominent nucleoli seen in acinar cells. These features may be misinterpreted as carcinoma in the absence of clinical information [3].

In order to avoid false positive diagnosis, it is important to pay attention to the nuclear features as the nuclear chromatin is bland, granular and evenly distributed. The nuclei are uniformly round with smooth outline. The background of abundant milky secretion with lipid droplets seen as vacuoles are a characteristic finding of actively secreting breast tissue seen in pregnancy and lactation. On the other hand, a malignant lesion could be under called due to fears of over diagnosis of lactation changes as malignancy [4]. It is important that the cytologists must be aware of the changes which are expected in breast FNAC smears during pregnancy and lactation. Secondly, FNAC smears of breast lump in pregnancy and lactation should be evaluated considering the clinical data and ultrasonography.

Benign causes

Benign diseases were a major etiology seen in pregnancy and lactation. Cytology was effective in diagnosing majority of these cases. Galactocele was a major etiology for benign lesions during pregnancy and lactation. Galactocele is a retention cyst containing milk/milky substance usually located in mammary

gland. It results in a painless discrete mass as seen in majority of our cases. A milky fluid was usually aspirated in these cases and the swelling resolves more or less completely after aspiration. These findings along with the cytological smears showing macrophages, acinar cells in a lipid background helped to clinch the diagnosis. These findings were noted in majority of our cases. Majority of these swellings regressed on its own post lactation. Fibroadenoma was the most common benign breast tumor in pregnancy and lactation as reported in few studies [5,6]. It is believed that fibroadenoma may be present before pregnancy; however it may be extremely small to be palpable on self breast examination. As the hormone levels increases during pregnancy, its size increases due to its high sensitivity to hormones. We found two cases of fibroadenoma where the mass was present before pregnancy and the size increased during the course of pregnancy. Cytology was an effective tool in our study in making diagnosis in all the cases. Histological correlation was present in three cases which confirmed the diagnosis.

Lactational adenoma was another common benign tumor identified during pregnancy and lactation in our study. It consists of proliferation of epithelial component only compared to fibroadenoma where there is proliferation of both epithelial and stromal elements. Cytology plays a very important role in identifying lactational adenoma cases, as in our study. The characteristic cytological findings which helped to clinch the diagnosis included- highly cellular smears, mono-layered cohesive cell clusters with foamy cytology, minimal bipolar cells in the background and granular proteinaceous background. Bland nuclear features, minimal pleomorphism and secretions in the background are the key features which help to clinch the diagnosis [7,8].

Majority of cases of lactational adenoma regressed spontaneously. In our study, one case where the swelling persisted turned out to be invasive ductal carcinoma along with lactational adenoma. Coexistence of IDC and lactational adenoma has been rarely reported in literature [9,10]. The underlying pathogenesis behind this co-existence is still unclear. One theory states that lactational adenoma is a benign tumor without any risk factor for the development of carcinoma. The coexistence of IDC and LA may be the result of collision tumor. Other theory supports malignant transformation of LA.

Granulomatous mastitis is an unusual breast condition reported during pregnancy. This lesion can mimic carcinoma both clinically and radiologically. FNA smears will show granulomas, scattered epithelioid cells, histiocytes along with acinar cell clusters. It is important to exclude tubercular mastitis in such cases, especially in developing countries like India. ZN stain was non-contributory in our cases of granulomatous inflammation. Aspirate material was sent for CBNAAT, which was negative for M.tb. The mass was surgically excised in both cases and histopathology confirmed the cytological findings. An autoimmune etiology is believed to be responsible for

granulomatous mastitis. Three cases were reported as benign cyst in our study. The clinical findings included the complete disappearance of lump on aspiration and the smears examined revealed macrophages, few groups of apocrine acinar cells in a proteinaceous background. Re-aspiration must be attempted from any residual lump (post aspiration) to rule out any hidden pathology.

Mastitis and abscess formation seen in our study are the common benign diseases reported in pregnancy. This is believed to be due to the entry of common pathogens (*Staphylococcus aureus*, *Streptococcus*) from the nose and throat of new born babies into the breast via damaged epithelial cells of nipple-areola complex during breast feeding. Mastitis patients were treated with antibiotics and showed good response.

Pregnancy associated breast carcinoma (PABC)

PABC are defined as the breast carcinomas which occur during the course of pregnancy or within one year post delivery [11]. We reported 4 cases of PABC among 45 breast masses during pregnancy and lactation, constituting nearly 8.8% of all breast masses during this period. This high number of PABC in our study may be attributed to increase in the child bearing age, as the incidence of breast carcinoma increases with age [12]. Cytology was effective in identifying 3 cases as IDC and biopsy was done later for confirmation of the disease and ER/PR/Her2 evaluation. The cytological features which helped to clinch the diagnosis were dispersed cell population, highly pleomorphic cells with high nuclear-cytoplasmic ratio, hyperchromasia and prominent nucleoli. Atypical mitosis was seen in some tumor cells in some cases. Lack of milky background in such cases is an important feature to clinch the diagnosis. One case was diagnosed as LA on cytology; however lumpectomy specimen revealed coexistence of LA and IDC.

PABC are believed to be high grade, aggressive malignancies with lymph node and distant metastasis. These malignancies are associated with poor prognosis [13]. The findings in our cases support this view as 3/4 cases of PABC show axillary lymph node metastasis. On follow up, one case reported with bone and liver metastasis and succumbed to disease within two years of diagnosis. Previous studies report bone as the commonest site of metastasis in PABC. Another case on follow up developed opposite breast metastasis within three years of diagnosis and is on second line chemotherapy. Other two cases are on regular follow up without any evidence of metastasis. PABC reveal less frequent expression of ER and PR. We support this finding as all 4 cases of PABC in our study were ER/PR negative. The aggressive nature of PABC may be attributed to the late diagnosis of the tumors as these may be misinterpreted as physiological changes in breast and result in delayed diagnosis. Secondly, during this period there are marked changes in the breast micro environment in the form of vascular and ducto-lobular units' proliferation. This may be responsible for the rapid tumor growth and metastasis. Many times the surgery is deferred till

delivery which may also be responsible for inferior survival [14].

Conclusion

FNAC proves itself as an effective tool with minimal surgical intervention in identifying the etiology in majority of breast masses in pregnancy and lactation. FNA smears from breast lumps in pregnancy and lactation can be a difficult problem for interpretation due to the physiological changes seen in breast under these conditions. The cyto-pathologists must be aware of the characteristic findings which are expected in cytology smears from breast masses in pregnancy and lactation. Secondly, the aspirate smears in pregnancy and lactation must be evaluated with caution in order to avoid over/under diagnosis. Majority of breast masses in pregnancy and lactation are benign. However, the physicians must be aware of PABC which are on rise due to increase in the child bearing age group. It must be kept in the differential diagnosis while evaluating breast lumps in these conditions for timely diagnosis and intervention.

Conflict of interest

There is no conflict of interest with any individual or organization.

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