

Original article:

Multinucleated giant cell on FNAC of breast lesion: A not very uncommon occurrence with varied pathology

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Date of submission: 02 November 2014 ; Date of Publication: 15 December 2014

Abstract:

Introduction: It is well-recognized that cells of the monocyte/macrophage lineage are capable of fusion to form multinucleated giant cells (MGCs). The presence of multinucleated giant cells on FNAC smears of breast lumps have been described only sporadically in the literature. As this is a common specimen in Cytopathology, knowledge of frequency of this variation can be valuable to cytopathologist who identifies the variation and clinician who is involved with the treatment modalities of different breast pathologies.

Material and Methods: The present retrospective as well as prospective study was conducted at the department of Pathology. The smears prepared were both wet and dry fixed and were subsequently stained with May Grunwald Giemsa (MGG) as well as Haematoxylin & Eosin (H& E) stain. The stained smears were observed under microscope by at least two expert cytopathologists. Orell was followed for categorizing different breast lesions and the findings were correlated with histopathology wherever available .

Results: Multinucleated giant cells found were foreign body type, Langhan's type, multinucleated stromal giant cells (MSGC), osteoclast like giant cell and tumour giant cells. Foreign body type giant cells were found in 7 out of 23 cases. Fibroepithelial lesion namely fibroadenoma showed multinucleated stromal giant cells in 5 out of 52 cases while no giant cells were seen in cases of Phyllodes tumour. Langhan's giant cells, tumour giant cells and osteoclastic giant were seen in 2,3 and 1 cases of tubercular mastitis, duct carcinoma, duct carcinoma with osteoclastic giant cells respectively.

Conclusion: Presence of multinucleated giant cells on breast FNA smears, though not so common occurrence, demands recognition as well as correct interpretation to provide an accurate diagnoses to the surgeon. Cytomorphology of various multinucleated giant cells along with ductal epithelial cells help cytopathologists to reach at the correct diagnoses especially in cases of malignancy where various types of giant cells like benign multinucleated giant cells, osteoclast-like giant cells or tumour giant cells are encountered.

Keywords: FNAC, Giant cell

Introduction:

It is well-recognized that cells of the monocyte/macrophage lineage are capable of fusion

to form multinucleated giant cells (MGCs). Multinucleated giant cell phenotypes vary, depending on the local environment and the chemical and

physical (size) nature of the agent to which the MGCs and their monocyte/macrophage precursors are responding [1]. Multinucleated stromal giant cells are described in several breast lesions raising an interesting differential diagnosis, mainly with benign disorders but also on occasion in association with malignant lesions [2].

Due to rarity of presence of multinucleated giant cells in cytological examination of breast lump, recognition and correct interpretation of their presence is difficult, yet crucial to forming an accurate diagnosis. Incorrect interpretation of these unusual cells as malignant cells can lead to misdiagnosis of more sinister conditions, such as malignant phyllodes tumor and metaplastic carcinoma. Consequently treatment of a lesion bearing such giant cells could potentially be misguided [2,3,4].

Hence, the aim and objectives of the present study was to describe various types of multinucleated giant cells on cytomorphological examination of FNA smears of palpable breast lump and their association with different types of breast pathologies. Extensive search of the literature was also done simultaneously to know the pathogenesis involved.

The presence of multinucleated giant cells on FNAC smears of breast lumps have been described only sporadically in the literature. As this is a common specimen in Cytopathology, knowledge of frequency of this variation can be valuable to cytopathologist who identifies the variation and clinician who is involved with the treatment modalities of different breast pathologies.

Material and Methods:

The present retrospective as well as prospective study was conducted at the department of Pathology, ESIPGIMS, ESIC Medical College & ESIC Hospital &

ODC (EZ) in a two year period. All patients who presented in the department for FNAC of the palpable breast lump were included in the study. FNAC was done using 10 cc syringe, 23 G needle and Franzen handle and taking all aseptic precautions.

The smears prepared were both wet and dry fixed and were subsequently stained with May Grunwald Giemsa (MGG) as well as Haematoxylin & Eosin (H& E) stain. The stained smears were observed under microscope by at least two expert cytopathologists. Orell was followed for categorizing different breast lesions and the findings were correlated with histopathology wherever available [5].

Results:

A total of 200 cases were studied with a male: female ratio of 1:4.5. Maximum patients were in the age group of 25-45years with youngest patient of 13 years age and oldest 81 years. Neoplastic pathology dominated in the study group with 164 total cases, where benign, premalignant and malignant lesions comprised 63.0%, 2.5% and 16.5% respectively. Only 36 cases of non neoplastic lesions were found where inflammatory pathology (11.5%) dominated followed by unclassified (4.0%), lactational changes (2.0%) and fat necrosis (0.5%). (Table No 1)

Multi-nucleated giant cells were found in both neoplastic as well as non neoplastic lesions. A total of 23 cases were found where such giant cells were noted. Maximum number of cases were associated with benign neoplastic lesions i.e. fibroadenoma and fibrocystic disease of breast, followed by inflammatory lesions, malignancy and fat necrosis. (Table No.1). Mild to moderate degree of dysplasia was also noted along with multinucleated giant cells in 3 cases of fibrocystic disease of breast, 1 case of

fibroadenoma and 4 cases of duct carcinoma. Surprisingly, both multinucleated giant cells as well

as tumour giant cells were seen in one case of duct carcinoma.

S No	Pathology	Total n=200	Giant cells present n=23	Dysplasia +Giant cells
Non Neoplastic (n=36)				
1.	Inflammatory (Mastitis/Abscess/Tuberculosis)	23 (11.5%)	8 (34.8%)	-
2.	Lactational change	4 (2.0%)	-	-
3.	Fat necrosis	1 (0.5%)	1	-
4.	Unclassified/Unsatisfactory	8 (4.0%)	-	-
Neoplastic (n=164)				
Benign				
1.	Fibrocystic disease	59 (29.5%)	5(8.5%)	3
2.	Fibroadenoma	52 (26.0%)	5 (9.6%)	1
3	Gynaecomastia	9 (4.5%)	-	-
4.	Phyllodes tumour	4 (2%)	-	-
5.	Duct Papilloma	2 (1%)	-	-
Premalignant				
1.	Atypical Ductal Hyperplasia	5 (2.5%)	-	-
Malignant				
1.	Duct Carcinoma	31 (15.5%)	4 (13%)	4(13%)
2.	Mucinous Carcinoma	1 (0.5%)	-	NA
3.	Lobular Carcinoma	1 (0.5%)	-	NA

Table no. 1: Spectrum of breast lesions on FNAC with special reference to presence of giant cells in various breast pathologies.

Multinucleated giant cells found were foreign body type, Langan's type, multinucleated stromal giant cells(MSGC), osteoclast like giant cell and tumour giant cells. (Table No 2) Foreign body type giant cells were found in 7 out of 23 cases. (Figure 1) Fibroepithelial lesion namely fibroadenoma showed multinucleated stromal giant cells in 5 out of 52 cases while no giant cells were seen in cases of Phyllodes tumour.(Figure 2)

Langan's giant cells, tumour giant cells and osteoclastic giant were seen in 2,3 and 1 cases of tubercular mastitis, duct carcinoma, duct carcinoma with osteoclastic giant cells respectively. (Figure 3 and Figure 4)

Immunohistochemical study for ER/PR and HER₂ neu was done in cases of carcinomas and it was found that both the neoplastic epithelial cells as well as multinucleated tumour giant cells show similar reaction for these antigens.

Sl No.	Type of giant cells	Breast lesion	No. of lesions containing Giant cells
1.	Foreign body giant cells	Acute mastitis	6 (26 %)
		Fat necrosis	1 (4 %)
2.	Multinucleated stromal giant cells	Fibroadenoma	5 (22 %)
		Fibrocystic disease	5 (22 %)
3.	Langhans giant cell	Tubercular mastitis	2 (9 %)
4.	Tumour giant cells	Duct Carcinoma	3 (13 %)
5.	Osteoclastic giant cell	Duct carcinoma with osteoclastic giant cells	1 (4 %)
Total no. of giant cells			23

Table no. 2: Distribution of different types of giant cells in various breast lesions

Discussion:

Bizzare giant cells in breast lesions were reported in literature way back in 1951 by Treves and Sunderland and subsequently multinucleated stromal giant cells by Rosen, in 1979. They postulated that these cells are not indicative of malignant behavior, rather represents a non-neoplastic and possibly reparative process [6, 7]. On review of literature it has been found out that several cytological differences exists between different types of multinucleated giant cells, and , though not so common, they are seen in varied pathologies of breast.

The MSGC have 5-25 nuclei with fine chromatin and sporadic small nucleoli and inconspicuous cytoplasm [8]. These cells are identical to the multinucleated giant cells that are occasionally seen in otherwise normal breast stroma. Ng Wk defined these cells containing 5-10 randomly arranged, round to oval nuclei, fine chromatin and sometimes distinct

nucleoli and have found them in two cases of fibroadenoma in a 6 year period. The cytoplasm of these cells was abundant and pale staining, and the cell border was ill defined [2]. Kollur and El Hag found MSGC in 31.8% of the aspirated cases of fibroadenomas [9]. However, in the present study, only 9.6% cases of fibroadenoma of breast showed the presence of MSGC. Cytomorphologically, the cells resemble as described by Ng Wk with round to oval, 5-10 nuclei and abundant pale staining basophilic cytoplasm on MGG stain.

Cytological features of these although bizarre are benign and mitotic figures are absent [10,11]. They may be found in fibroepithelial lesions comprising fibroadenomas, phyllodes as well as other benign breast tumours and are reportedly immunoreactive for p53 and Ki67 [11]. Ultrastructural features of these cells are of fibroblast. Most series reported the presence of these stromal giant cells being present in fibroepithelial lesions of the breast, but were more

common in phyllodes tumor than fibroadenomas [11, 12]. The present study had only 4 cases of phyllodes tumour as compared to 52 cases of fibroadenoma and none of them showed the presence of MNGC. It is a known fact that fibroadenoma is difficult to distinguish from phyllodes tumor using aspiration cytology only [5], therefore a tumour with features of fibroadenoma must not be classified as phyllodes merely on the presence of these giant cells[8].

Sometimes, giant cells may indicate an extra-tumoral reactive process in the surrounding breast tissue which may be due to palpation granuloma or fat necrosis [9]. Early lesion of fat necrosis may show presence of lipid laden histiocytes and foreign body giant cells with foamy cytoplasm [13]. Foreign body type giant cells have multiple nuclei scattered haphazardly throughout the cytoplasm or may be placed centrally [14]. The present study showed only one case of fat necrosis with foreign body type of giant cells. However, no foreign body could be detected on FNA smears.

Chandanwale et al reported 11% of inflammatory lesions of the breast and found cytomorphological features of inflammatory infiltrate of neutrophils in all the cases, suppurative necrosis in 4 cases (80%) and giant cells in 1 case [15]. The present study also had 11% cases of inflammatory breast lesions comprising acute mastitis, breast abscess and tubercular mastitis. Multinucleated giant cells of foreign body type were found in 6 cases of acute mastitis. Scattered foamy macrophages and histiocytes were also seen accompanying these giant cells along with other inflammatory cells

Sometimes, the nuclei are disposed around the periphery of the cell in a horse-shoe or ring, known as Langhans giant cells, believed to evolve from the foreign body type and are conspicuous in lesions of

Tuberculosis. Nevertheless, in granulomatous reactions both type of giant cells are frequently found and the two types should not be regarded as distinct entities [14]. Nayar and Saxena found 3.4% of tuberculosis in breast aspiration specimens consisting of epithelioid histiocytes, polygonal or elongated Langhans giant cells and varying number of neutrophils, lymphocytes and plasma cells. They concluded that neutrophils may obscure the granulomatous character where necrotizing abscesses or sinus tracts, in which case specimen must be subjected for culture and Acid Fast stain [16]. Two cases of tubercular mastitis displaying epithelioid cell granulomas and Langhans giant cells were seen in the present study. Both the cases were positive for acid fast bacilli on ZN stain.

Osteoclast-like giant cells are large cells with abundant cytoplasm and centrally located nuclei ranging in size and number along with prominent nucleoli. Diagnosis of osteoclast-like giant cells can be extremely difficult on cytological exam as these cells can be bland in appearance and have a similar appearance to foreign-body giant cells associated with fat necrosis [17]. However, the mechanism of development of these cells are different from other giant cells. Rosen et al hypothesized that the cancer cells secrete vasoendothelial growth factor, which promotes angiogenesis and macrophage migration to the neoplasm. Eventually, stromal cells of monocyte origin fuse with each other to become osteoclast-like giant cells [18]. However, as compared to the MNGC which are p53 and ki67 positive, these osteoclast type giant cells have no expression of p53 [8,10,11,19]. Osteoclast-like giant cells have an immunohistochemistry profile typical of histiocytic differentiation, staining positive for the typical osteoclast markers, CD68, CD1a, tartrate-resistant

acid phosphatase (TRAP), and negative for cytokeratin, epithelial membrane antigen, lysozyme, and estrogen and progesterone receptors [20].

Typically osteoclast-like giant cells have been associated with invasive ductal adenocarcinoma of the breast. However, they have also been associated with cribriform, tubular, squamous, papillary, and mucinous breast carcinomas [17,21]. The present study had 33 cases of malignancy, out of which 31 cases were ductal carcinoma, one was lobular and one was mucinous adenocarcinoma. Four cases (13.0%) had presence of multinucleated giant cells. Only one case of ductal carcinoma had osteoclast type of giant cells, the other three showed the presence of tumour giant cells. The tumour giant cells had nuclear features similar to the neoplastic ductal epithelial cells. These tumour giant cells were also positive for ER/PR antigens similar to the ductal neoplastic cells as opposed to the osteoclast like giant cells which are negative for the same. A distinction must be made between these two cell types as it has diagnostic and prognostic implications. In fact osteoclast-like giant cells in association with malignant breast epithelial cells is indicative of a mammary carcinoma with postulated poor prognosis. Several reports have noted a less favourable outcome for patients with mammary carcinomas containing osteoclast-like giant cells when compared with conventional ductal adenocarcinoma [22].

In the present study, out of 10 cases of benign neoplastic breast lesions where MSGC were noted, four cases exhibited mild atypia in the ductal epithelial cells. In review of literature, it was found that MSGC may also be seen in association with malignant lesions of the breast [2,8,12,23]. Benign multinucleated cells in breast carcinoma, however, are a very unusual phenomenon and have been said to

arise from the fusion of mononuclear cells, in response to increased vascularity [24]. Long follow up of these patients is required to know whether these cases develop breast carcinoma and still show the presence of multinucleated stromal giant cells.

In the present case 5 cases (21%) showed presence of Multinucleated stromal giant cells in fibrocystic disease having similar incidence like that of fibroadenoma. On cytology, Fibrocystic disease of breast is classified as Non proliferative and proliferative fibrocystic disease. Presence of apocrine cells, macrophages, and ductal cells are the characteristic features of a nonproliferative type of fibrocystic changes, which yields only scanty materials. However, when there is a significant epithelial proliferative component, sheets and tight clusters of cells are usually prominent [25]. In the present study, 29.5% cases were classified on FNAC as Fibrocystic disease but were not subclassified. Maygarden SJ et al found 37.5% of FCD on FNAC and have concluded that the distinction between proliferative and nonproliferative fibrocystic change is less reliable, and cytologic differences observed is not statistically significant [26].

All the giant cells found in the fibrocystic disease were multinucleated stromal giant cells and cystic changes were seen in all the cases. However, even after extensive research of literature, data regarding presence of multinucleated giant cells in fibrocystic disease could not be found. MNSGC in these cases may have formed by the fusion of cells of the monocyte/macrophage lineage.

In the present study 4% of the cases were unsatisfactory compared to 4.2 % in study conducted by Sudarat et al [27]. Unsatisfactory sample can be due to inexperience of the pathologist or due to nature of lesion itself and further repeat aspiration or

incisional biopsy may be done for analysis [28]. Low cellularity, non image guided FNA in vague breast lesions and nature of vague lesions in few cases was the major reasons of inadequate smears in our study.

Conclusion:

Presence of multinucleated giant cells on breast FNA smears, though not so common occurrence, demands recognition as well as correct interpretation to provide an accurate diagnoses to the surgeon. Cytomorphology of various multinucleated giant cells along with ductal epithelial cells help cytopathologists to reach at the correct diagnoses especially in cases of malignancy where various types of giant cells like benign multinucleated giant cells, osteoclast-like giant cells or tumour giant cells are encountered.

Also, long term follow up studies on large scale is needed to know the exact behavioral nature of these different types of giant cells in both benign and malignant lesions of the breast.

Figure 1: Microphotograph showing presence of lipid laden histiocytes and foreign body giant cell with foamy cytoplasm in cytology smear and tissue biopsy(a-MGG, 400X and b-H&E, 400X)

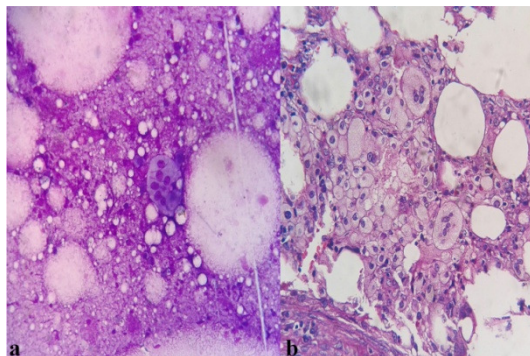


Figure 2: Multinucleated stromal giant cells containing 5-10 randomly arranged, round to oval nuclei, fine chromatin and moderate to abundant pale cytoplasm in a case of fibroadenoma.(a& b-FNAC smear, MGG, 400X and c-Histopathology, H&E,400X)

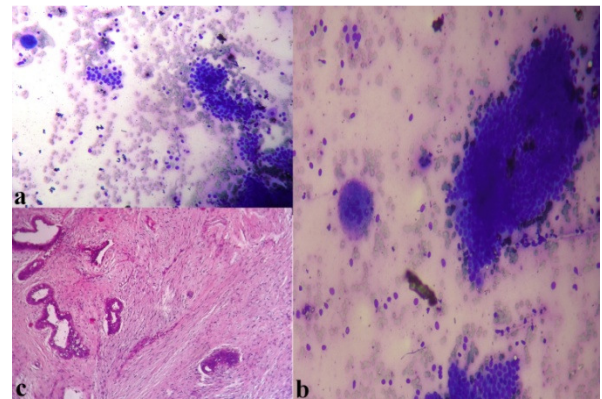


Figure 3: Microphotograph showing tumour giant cells with nuclear features similar to the neoplastic ductal epithelial cells. Note that the tumour giant cell is positive for ER antigen similar to the ductal neoplastic cell.

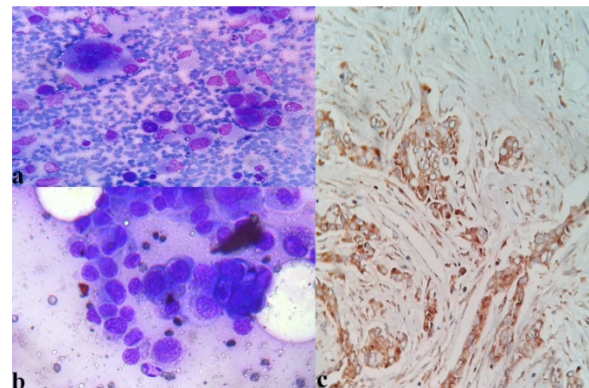
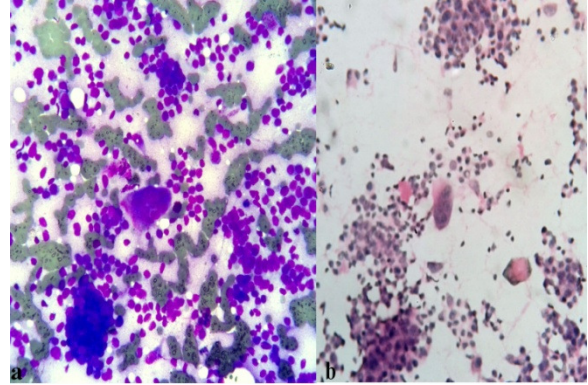


Figure 4: FNAC smears with Osteoclast like giant cells showing abundant cytoplasm and centrally located nuclei ranging in size and number along with prominent nucleoli. (a-MGG, b- PAP Stain)



References:

1. Brodbeck W G, Anderson J M. Giant cell formation and function. *Curr Opin Hematol* 2009; 16(1): 53–57.
2. Ng WK: Fine needle aspiration cytology of fibroadenoma with multinucleated stromal giant cells. A review of cases in a six-year period. *Acta cytologica* 2002; 46(3):535-539.
3. Cai N, Koizumi J, Vazquez M. Mammary Carcinoma with Osteoclast-Like Giant Cells: A study of four cases and a review of the literature. *Diagnostic Cytopathology* 2005; 33(4):246-251.
4. Kobayashi TK, Sugihara H, Kato M, Watanabe S. Cytologic features of granulomatous mastitis: report of a case with fine needle aspiration cytology and immunochemical findings. *Acta cytologica* 1998; 42:716-720.
5. Orell SR, Grogory FS, Walters MNI, Whitaker D: *Manual and Atlas of Fine Needle Aspiration Cytology*. 3rd edition. Churchill Livingstone. 2001
6. Treves N, Sunderland DA. Cystosarcoma Phyllodes of the breast; a malignant and a benign tumour. A clinicopathological study of seventy seven cases. *Cancer* 1951; 4:1286-1332.
7. Rosen P. Multinucleated mammary stromal giant cells – A benign lesion that simulates invasive carcinoma. *Cancer* 1979; 44(4):1305-1308.
8. Ryska A, Reynolds C, Keeney GL. Benign tumors of the breast with multinucleated stromal giant cells. Immunohistochemical analysis of six cases and review of the literature. *Virchows Arch* 2001; 439:768-775.
9. Kollur S M, Hag IAE. FNA of breast fibroadenoma: observer variability and review of cytomorphology with cytohistological correlation. *Cytopathology* 2006; 17(5): 239–244,.
10. Huo L, Gilcrease MZ. Fibroepithelial lesions of breastwith pleomorphic giant cells: a clinicopathologic study of four cases and review of literature. *Ann Diagn Pathol* 2009; 13(4):226-232.
11. Powell C M, Cranor M L, and. Rosen P P. Multinucleated stromal giant cells in mammary fibroepithelial neoplasms: a study of 11 patients. *Archives of Pathology and Laboratory Medicine* 1994; 118(9):912–916.
12. Tse G, Law BK, Chan KF, Mas TK: Multinucleated stromal giant cells in mammary phyllodes tumours. *Pathology* 2001; 33(2):153-156.
13. Coyne JD, Parkinson D, Baildam AD. Membranous fat necrosis of the breast. *Histopathology* 1996; 28(1):24-27.
14. Walter J B, Talbot I C, Gardner H A, Halloran P F, Zuckerman M, Bird A G. Forbes A. Walter and Israel *General Pathology*. Churchill Livingstone publishing 2011.7th ed; ch 11: p 198.

15. Chandanwale S, Rajpal M, Pradeep J, Sood S, Gupta K, Gupta N. Pattern of Benign Lesions on FNAC in consecutive 100 cases: A study at tertiary care hospital in India. *IJPBS* 2013; 3(4):129-138.
16. Nayar M, Saxena HMK. Tuberculosis of the breast. A cytomorphological study of needle aspirates and nipple discharges. *Acta Cytol* 1984;28:325-328.
17. Cai N, Koizumi J, Vazquez M. Mammary Carcinoma With Osteoclast-Like Giant Cells: A Study of Four Cases and a Review of Literature. *Diagnostic Cytopathology* 2005; 33:246–251.
18. Rosen PP, Hoda S, Dershaw D, Liberman Leditors. *Breast Pathology: Diagnosis by Needle Core Biopsy*. 2nd ed. Lippincott: Williams & Wilkins; 2005.
19. Takahashi T, Moriki T, Hiroi M, Nakayama H. Invasive lobular carcinoma of the breast with osteoclast-like giant cells: a case report. *Acta Cytol* 1998;42:734–741.
20. Gjerdrum L, Lauridsen MC, Sørensen FB: Breast carcinoma with osteoclast-like giant cells: morphological and ultrastructural studies of a case with review of the literature. *The Breast* 2001; 10(3):231-236.
21. Kurokawa K, Mouri Y, Asano A, Kamei K, Iwata Y, Isogai M et al. Pleomorphic carcinoma with osteoclastic giant cells of the breast: Immunohistochemical differentiation between coexisting neoplastic and reactive giant cells. *Pathology International*. 2009;59: 91–97.
22. Agnantis NT, Rosen PP: Mammary carcinoma with osteoclast-like giant cells: a study of eight cases with follow-up data. *American Journal of Clinical Pathology* 1979; 72:383-389.
23. Berean K, Tron VA, Churg A, Clement PB: Mammary fibroadenoma with multinucleated stromal giant cells. *American Journal of Surgical Pathology* 1986;10(11):823-827.
24. McMahon RF, Ahmed A, Connolly CE. Breast carcinoma with stromal multinucleated giant cells--a light microscopic, histochemical and ultrastructural study. *J Pathol*.1986;150(3):175-179.
25. Mendoza P, Lacambra M, Tan P H, Tse G M. T. Fine Needle Aspiration Cytology of the Breast: The Nonmalignant Categories. *Pathology Research International* 2011;2011: 547580.
26. Maygarden SJ, Novotny DB, Johnson DE, Frable WJ. Subclassification of benign breast disease by fine needle aspiration cytology. Comparison of cytologic and histologic findings in 265 palpable breast masses. *Acta Cytol*. 1994; 38(2):115-29.
27. Sudarat N, Somneuk J, Siriwan T. Accuracy of FNAC from breast masses in Thailand. *AJCP* 2009;10: 623-626.
28. Shrestha A, Chalise S, Karki S, Shakya G. Fine needle aspiration cytology in a palpable breast lesion. *Journal of Pathology of Nepal* 2011; 1:131-135.

