Analysis of false positive and false negative cytological diagnosis of breast lesions

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ABSTRACT

Objectives: To study the reasons for interpretive errors in false negative and false positive diagnosis of breast carcinoma on fine needle aspiration cytology material.

Methods: We reviewed only those cases in which cytohistological discrepancies were found, where the cytologic material was abnormal and to some extent misinterpreted or both.

Results: There was only one false negative case (false negative fraction 0.32%) proved histologically as ductal carcinoma and four false positive cases (false positive fraction 1.2%); 2 fibroadenoma; 1 fibrocystic disease; and 1 stromal fibrosis. Smears of the two false positive fibroadenoma cases showed very high cellularity, overcrowded clusters and frequent stripped nuclei. The fibrocystic case showed tight clusters of apocrine cells and sheets of loosely aggregated macrophages that were over interpreted. Smears of the false negative ductal carcinoma was hypocellular overall, and the cells showed minimal nuclear pleomorphism.

Conclusion: Overcrowded clusters and hypercellular smears should be carefully assessed for uniformity of cells and detailed nuclear and cytomorphological features. If the full-blown malignant cytomorphological changes are not visible, a diagnosis of suspicious or inconclusive should be made and frozen section recommended before surgery. Hypocellularity and relatively nuclear monomorphism are the reasons for failure to diagnose malignant breast lesions. Careful attention should be paid to extreme nuclear monomorphism and absence of naked bipolar cells. A cytologically atypical or suspicious diagnosis together with positive radiological and clinical findings should suggest a diagnosis of malignancy

Keywords: Breast neoplasm, fine needle aspiration, false negative diagnosis, false positive diagnosis.

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F ine needle aspiration cytology (FNAC) is a well recognized technique for preoperative diagnosis of breast carcinomas.[1,2] Technical difficulties, particularly sampling errors, are responsible for a significant number of false negative diagnoses.[3] However, interpretive errors are also responsible for both false positive and false negative cytological results.[2] To understand the causes of false positive and false negative breast carcinomas in FNAC, we reviewed all these false positive and negative FNACs of breast lesions that were associated with histological confirmation.

Methods. Between January 1984 and March 2000, 467 fine needle aspirates of the breasts were performed in our hospital. Three hundred and nine breast carcinomas were diagnosed by FNAC. Out of these there were 4 false positive (FPF 1.2%) diagnosis and one false negative (FNF 0.32%) diagnosis encountered in this period. These 4 false positive cases were cytologically diagnosed as positive for malignant cells. We reviewed these false positive cytologic smears and found two as benign, one as malignant and one as suspicious. The false negative case was diagnosed as no malignant seen
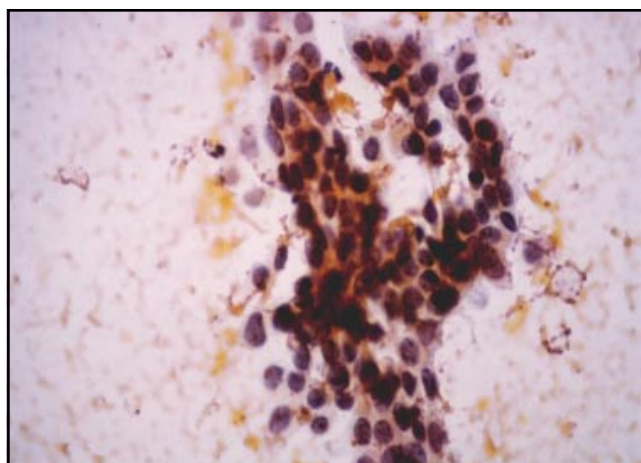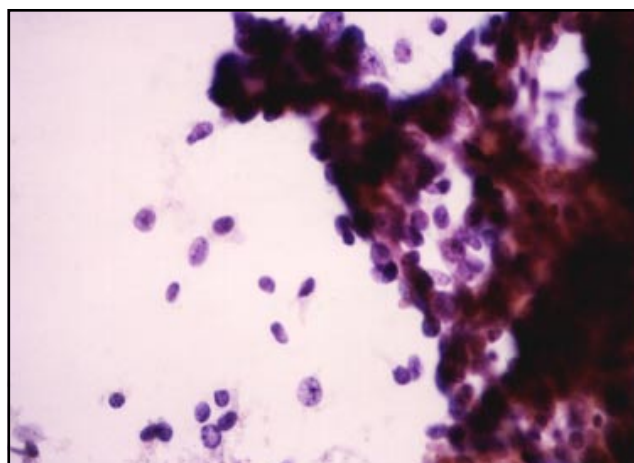
Figure 1 - Hypocellular smear showing one loose cluster of atypical cells with large nuclei, coarse chromatin and prominent nucleoli.

Figure 2 - Overcrowded cluster with loose and some naked cells showing prominent nucleoli.
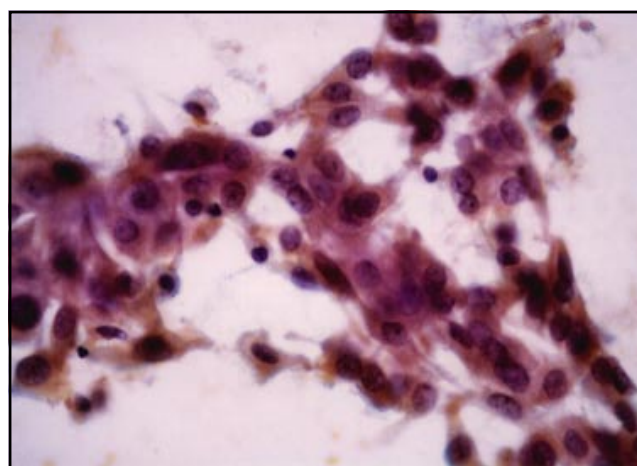
Figure 3 - Apocrine cells interpreted as loose clusters, large nuclei with prominent nucleoli.
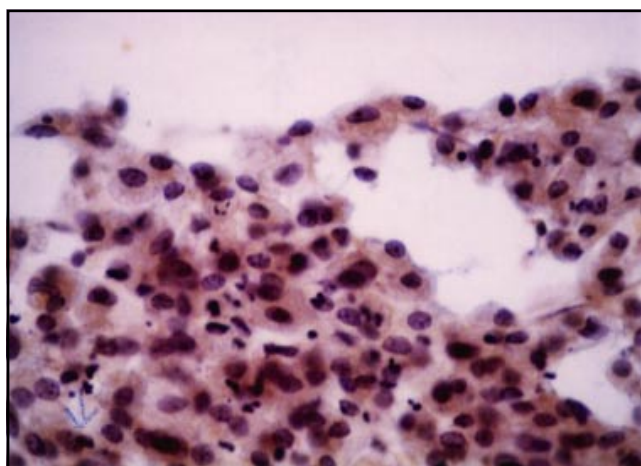
Figure 4 - Sheets of macrophages over-interpreted as epithelial cells.

Figure 5 - Overcrowded cluster of atypical cells and some loose cells showing large hyperchromatic nuclei and necrosis.

Table 1 - Salient clinical features with original cytohistological and reviewed cytological diagnosis of four false positive and one false negative cases.

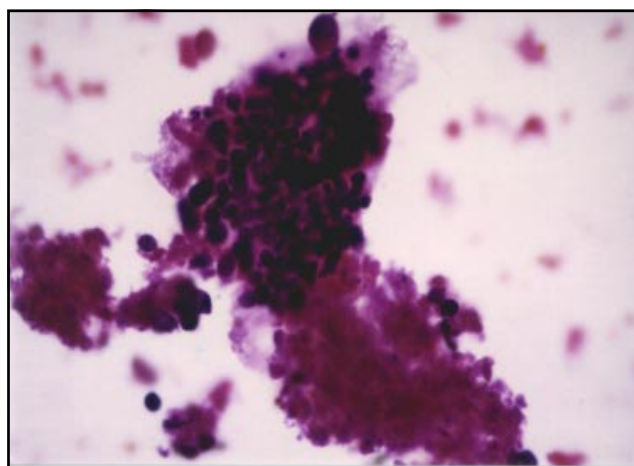| Case No.	Year	Age	Sex	Reviewed	Original cytological Dx.	Histopathologial Dx.
Case 1	1987	42	F	Positive	Positive	Fibroadenoma
Case 2	1989	89	F	Negative	Positive	Fibroadenoma
Case 3	1990	90	F	Negative	Positive	Fibrocytic
Case 4	1992	92	F	Positive	Positive	Stromal fibrosis
Case 5*	1988	88	F	Suspicious	Negative*	Infiltrating Ductal*
Dx. - Diagnosis, *False negative						

and on reviewed examination it was diagnosed as suspicious. The detailed clinical and cy-tologic features of these cases were studied along with the subsequent histologic features.

Results. Table 1 shows the original cytologic diagnosis, reviewed cytological diagnosis, along with the histologic diagnosis. In our institute all the positive cases are followed by frozen section histological examination, which in these 4 false positive cases revealed as; 2 fibroadenoma; 1 fibrocystic disease; and 1 stromal fibrosis. The false negative case was also followed by frozen because clinically and radiographically it was suspicious and it revealed infiltrating ductal carcinoma. Table 2 and 3 analyses the detailed cytologic features of these 5 cases by tabulating them with the criterion for benign features and malignant features. Various cytologic features were studied, such as cell adhesion, cellularity, single cells, pleomorphism, nucleolar prominence, chromatin pattern, presence of bipolar cells, apocrine cells, foam cells, inflammatory cells,

Table 2 - Cytological features of false positive and false negative cases by tabulating them with the criterion for benign features.

Features	Case 1	Case 2	Case 3	Case 4	Case 5*
Good cell adhesion	-	+++	+++	-	-
Cellularlty	-	-	+++	-	-
Histeocytes	-	-	+++	-	-
Frequent stripped nucile	-	+++	-	-	-
Normal cell size	-	+++	+++	-	-
Uniformity of cells	-	+++	+++	-	-
Coars but regular nuclie	-	++	-	-	-
Absent -, Occasional +, Abundant +++, *False negative					

stromal fragments and overcrowded clusters.

Discussion. FNAC is a helpful preoperative diagnostic procedure in cases of breast lumps. However, the sensitivity of FNAC is very variable and ranges from 66% to 98%[4-23] with a specificity of 82-100%. Table 4 shows specificity, sensitivity, positive predictive value, negative predictive value, FPF and FNF calculated from ten studies in literature.[8,9,11-23]

In our study the false negative case (case 5) was diagnosed as negative for malignant cells mainly because of very low cellularity, little nuclear pleomorphism (Figure 1). However in hypocellular smears all the criterions for the benign and malignancy should be carefully taken under consideration; for example lack of bipolar cells, loss of normal cell adhesion and presence of some atypical nuclei should raise the suspicious of malignancy especially if clinically or radiographically suspected so.

In false positive cases there were 2 out of four (50%) cases that histologically turned out as fibroadenoma, pointing to the difficulty of diagnosing this lesion sometimes. As in case number one (Figure 2) fibroadenoma was diagnosed positive even on reviewed examination. It showed highly cellular smear with large cells having obvious nucleoli, as well as naked nuclei and nuclei with some cytoplasm. There were few overcrowded clusters with little pleomorphism too. These features mislead towards positive diagnosis. The second case (case 2) of fibroadenoma was misinterpreted on the original cytological diagnosis because it showed high cellularity and frequent large naked nuclei. Our experience is supported by literature since fibroadenoma is considered one of the major pitfalls in diagnosing breast malignancies. The third false positive case was histologically proved as fibrocystic disease. There were tight clusters of apocrine cells and sheets of loosely aggregated macrophages (Figure 3 and 4). These clusters of apocrine cells as

Table 3 - Cytological features of false positive and false negative cases by tabulating them with the criterion for malignant features.

Features	Case 1	Case 2	Case 3	Case 4	Case 5*
Loss of cell adhesion	+++	-	-	++	++
High cellularity	+++	+++	-	++	+
Lack of striped bipolar nuclie	-	-	-	-	++
Increase cell size	+++	-	-	++	+
Pleomorphism	+	-	-	++	+
Variable nuclear chromatin and prominent nucleoll	+	-	-	+	-
Lymphocyte response	-	-	-	-	-
Single cells with intact cytoplasm	+	-	-	++	+
Irregular angulated atypical cells	++	-	-	++	-
Necrosis	-	-	-	++	-
Signet ring cells	-	-	-	-	-
Single cells without cytoplasm	+++	-	-	++	-
Overcrowded 3D clusters	+++	-	-	+	-
Apocrine cells	-	-	+++	-	-
Stromal element	-	-	-	-	+
Absent -, Occasional +, Many ++, Abundant +++, *False negative					

well as the sheets of macrophages were over interpreted as malignant cells and loss of cell adhesion. The last false positive case was histologically diagnosed as stromal fibrosis on cytology it showed large hyperchromatic nuclei, loss of cell adhesion, few overcrowded clusters and necrosis. Some of the cells were really atypical (Figure 5). We have no explanation on why stromal fibrosis could have large atypical epithelial cells; one explanation for these atypical cells could be that these cells were immature young fibroblasts that were over interpreted as malignant cells.

In conclusion our experience expressed in this study showed FNAC as an excellent pre-operative tool to screen for breast malignancies as our false positive and false negative fractions were very small i.e. 1% and 0.32%, but still lesions such as fibroadenoma, fibrocystic disease and stromal fibrosis can create difficulties. FNA of the breast has some unavoidable limitations mainly due to poor sampling; poor cellular yield of mammary tumors with fibrotic stroma, poor preservation and difficulty in cytologic differentiation of atypical benign lesions. Because the sensitivity and specificity rates of FNA are not always 100%, the technique should be used with this limitation in mind.[6-16] The clinical utility of a diagnostic procedure depends on the context in which it is used. Screening tests should have as high a sensitivity rate as possible, and the lower specificity rate is acceptable in this setting. The test used definitive diagnosis requires both high sensitivity and specificity rates. If FNA always yields a definitive diagnosis, it will no longer be a screening test but rather a diagnostic test and must diagnose breast

Table 4 - Analytical comparison of sensitivity, specificity, positive predictive value, negative predictive value, FPF and FNF from 10 studies in literature.

Author	No of cases	Sensitivity	Specificity	Positive predictive value	Negative predictive value	False positive fraction	False negative fraction
Barrows et al[8]	1283	92.2	86.0	91.0	87.5	8.9	12.5
Bell et al[9]	1145	77.6	97.1	90.2	93.3	9.8	6.7
Ciatto et al[14]	534	97.4	99.3	98.6	98.7	1.4	1.3
Kine et al[17]	3545	90.3	98.1	84.5	98.8	15.5	1.2
Scheikh et al[18]	2623	100	98.2	87.9	100	12.1	0
Horrgan et al[19]	2000	85.3	99.2	95.2	97.4	4.8	2.6
Palombini et al[20]	674	96.9	89.8	96.5	90.9	3.5	9.1
Martelli et al[21]	1708	83	96.1	95.5	84.8	4.5	15.2
Guimaraes et al[22]	496	87.6	99.3	98.8	92.5	1.2	7.5
Zajdela et al[23]	2772	96.1	95.3	97.2	93.5	2.8	6.5

lesion to the high degree of both sensitivity and specificity. Frozen section can serve as an additional and confirmatory check to avoid unnecessary mastectomies following a false positive FNA diagnosis. So FNA still can achieve significant monetary savings, reduction in patient morbidity, increased speed in diagnosis and increased opportunity for pre operative patient counseling without a reduction in diagnostic accuracy or compromise of prognosis.[1,6-16]

References

1. Costa MJ, Tadros T, Hilton C, Birdsong G: Breast fine needle aspiration cytology: Utility as a screening tool for clinically palpable lesions. Acta Cytol 1993; 7:461-471
2. Eisenberg AJ, Hajdu SI, Wilhemus I, Melamed MR. Kinne D: Preoperative aspiration cytology of breast tumors. Ada Cvtol 1986; 10: 135-146.
3. Zarbo RJ, Howanitz PJ, Bachner P. Interinstitutional compar-ison of performance in breast fine-needle aspiration cytology. Q-Probe quality indicator study. Arch Pathol Lab Med 1991; 115:743-750.
4. Frable WJ. Thin-needle aspiration biopsy. In: Major Problems in Pathology. Edited by JL Benington. Fourteenth volume. Philadelphia; WB Saunders: 1983. p. 9-15.
5. Grant CS, Goellner JR, Welche JS. Martin JK. Fine needle aspiration of the breast. Mayo Clin Proc 1986; 61: 377-381.
6. Al-Kaisi N. The spectrum of the "gray zone" in breast cytology. A review of 186 cases of atypical and suspicious cytology. Acta Cytol 1994; 38: 898-908.
7. Alvarez PLF, Velasco JRR, Heros CA, Zapatero H. La puncion-aspiracion con aguja fina de la mama como tecnica diagnostica preoperatoria: Evaluacion del metodo y revison de la literatura. Rev Clin Esp 1987; 181: 480-485.
8. Atamdede FI, Isaacs JH. The role of fine needle aspiration in the diagnosis of breast lesions. Gynecol Oncol 1993; 50: 159-163.
9. Barrows GH, Anderson TJ, Lamb JL, Dixon JM. Fine-needle aspiration of breast cancer: Relationship of clinical factors to cytology results in 689 primary malignancies. Cancer 1986; 58: 1493-1498.
10. Bell DA, Hajdu SI, Urban JA, Gaston JP. Role of aspiration cytology in the diagnosis and management of mammary lesions in office practice. Cancer 1983; 51: 182-1189.
11. Beltrani B, Tacchino RM, Gui D: Validita diagnostica della citologia per agoaspirazione nei noduli della mammella. Minerva Chir 1985; 40: 617-620.
12. Bottles K, Taylor RN. Diagnosis of breast masses in pregnant and lactating women by aspiration cytology: Obstet Gynecol (suppl 3) 1985; 66: 76-78.
13. Butler JA, Vargas HI, Worthen N, Wilson SE. Accuracy of combined clinical-mammographic-cytologic diagnosis of dominant breast masses: A prospective study. Arch Surg 1990; 125: 893-896.
14. Ciatto S, Catania S, Bravetti P, Bonardi R, Cariaggi P, Pacifico E: Fine-needle cytology of the breast: A controlled study of aspiration versus nonaspiration. Diagn Cytopathol 1990; 7: 125-127.
15. Frable WJ. Needle aspiration biopsy: Past, present, and future. Hum Pathol 1989; 20: 504-517.
16. Koss LG. The palpable breast nodule: A cost-effectiveness analysis of alternate diagnostic approaches: The role of the needle aspiration biopsy. Cancer 1993; 1: 1499-1502.
17. Kline TS, Lalita P, Neal HS. Fine needle aspiration of the breast: Diagnosis and pitfalls. A review of 3545 cases. Cancer 1979; 44: 1458-1464.
18. Sheik FA, Tinkoff GH, Kline TS, Neal HS. Final diagnosis by fine-needle aspiration biopsy for definitive operation in breast cancer. Am J Surg 1987; 154: 470-475.
19. Horgan PG, Waldron D, Mooney E, O'Brein D, McGuire M, Given HF. The role of aspiration cytologic examination in the diagnosis of carcinoma of the breast. Surg Gynecol Obstet 1991; 172: 290-292.
20. Palombini L; Fulciniti F, Vetrani A, Rosa G, Benedetto G, Zeppa P, Troncone G: Fine needleaspiration biopsy of breast masses: A critical analysis of 1956 cases in 8 years (1976-1984). Cancer 1988; 61: 2273-2277.
21. Martelli G, Pilotti S, Yoldi GC, Viganotti G, Fariselli G, Lepra P, Moglia D. Diagnostic efficacy of physical examination, mammography, fine needle aspiration cytology (triple test) in solid breast lumps: An analysis of 1708 consective cases. Tumori 1990; 76: 476-479.
22. Guimaraes EM, Fernades PC, Cervilha N, Oliveira DF, Alcantara TM, Menezes FC. Puncao com agulha fina da mama: Resultados e dificuldades. J Bras Patol 1996; 32: 153-160.
23. Zajdela A, Ghossein NA, Pilleron JP, Ennuyer A. The value of aspiration cytology in the diagnosis of breast cancer; Experience at the foundation Curie. Cancer 1975; 35: 499-506.