Basrah Journal of surgery ***Bas J Surg, September, 10, 2004***

ANALYSIS OF FALSE POSITIVE AND FALSE NEGATIVE FINE-NEEDLE ASPIRATION CYTOLOGY OF BREAST LUMP : A PERSONAL EXPERIENCE

Sawsan S. Al-Haroon.

M.B.,Ch.B., MSc. Path.; FICMS.,Path.Lecturer, Department of Pathology and forensic medicine College of Medicine, University of Basrah, Basrah, Iraq.

Abstract

This study aimed to determine the reasons for sampling and interpretative errors in false negative and false positive diagnoses of breast carcinoma on fine-needle aspiration cytology (FNAC) material. The s*tudy design* is that a totally 912 cases of breast FNAC were performed between 2000 and 2004, and 126 cases of them were diagnosed as breast carcinoma. Only those cases with cytohistological discrepancies were cytologically reviewed, in which the cytological material was abnormal and to some extent misinterpreted or both. There were 8 false negative diagnoses (false negative rate 6.3%) and 3 false positive diagnoses (false positive rate 2.3%). The r*esults* of this study showed that among 8 false negative cases, 5 showed hypocellular smears with minimal nuclear pleomorphism of the cells. Histology revealed 3 infiltrating ductal carcinomas of scirrhous subtype and 2 infiltrating lobular carcinomas. The smears of other 2 false negative cases, which histologically verified as well-differentiated infiltrating ductal and pure intraductal carcinomas, were hypercellular and composed predominantly of groups of cohesive, small, and uniform cells simulating fibroadenoma or fibrocystic changes. Smear of the last false negative case (histologically verified as infiltrating ductal carcinoma with extensive cystic degeneration) revealed large sheets of macrophages and degenerated epithelial cells on inflammatory background. In 3 false positive cases, 2 were histologically proved as fibroadenoma and 1 fibrocystic changes. Smears of the 2 false positive fibroadenomas showed very high cellularity, overlapped clusters, and frequent stripped bipolar nuclei. The fibrocystic case showed tight clusters of apocrine cells and sheets of loosely aggregated macrophages that were over interpreted. The c*onclusion* of this study is that hypocellularity and relatively nuclear monomorphism are the reasons for failure to diagnose breast carcinoma. Careful attention should be paid to extreme nuclear monomorphism and absence of naked bipolar nuclei. So awareness of smear cellularity and subtle cytological features will aid in the correct preoperative diagnosis of lobular; scirrhous; and intraductal carcinomas, and false negative diagnoses can be minimized. A cytologically atypical or suspicious diagnosis together with positive mammographical and clinical findings should suggest a diagnosis of malignancy. Hypercellular smears with overlapped clusters should be carefully assessed for uniformity of the cells and detailed nuclear features. If the full-blown malignant cytomorphological features are not visible, a diagnosis of suspicious or inconclusive should be made and frozen section Created by Wameed Al-Hashimy intraoperative imprint cytology is recommended before surgery.

Correspondence to :
Dr. Sawsan AL- Haroon, Department of Pathalogy and Frensic Medicine, College of Medicine, Basrah, Iraq

Introduction

Fine-needle aspiration cytology (FNAC) is a routine test in the evaluation of breast lesions and play a key role in the preoperative diagnosis of breast carcinoma[1,2].The diagnostic failure of FNAC seemed to be attributed to mainly sampling and/or interpretative errors[3,4].

To understand the causes of diagnostic pitfalls in FNAC, all the false positive and false negative FNACs of breast lumps were reviewed along with their histological confirmation.

Materials and Methods

Between June 2000 and March 2004, 912 fine-needle aspirates of the female breast lumps were performed by the author at the Medical Consultative Center of Basrah University and Basrah Teaching Hospital.

One hundred and twenty-six breast carcinomas were diagnosed by FNAC; there were 8 false negative diagnoses (false negative rate 6.3%) and 3 false positive diagnoses (false positive rate 2.3%). On reviewed examination of their cytological smears, the 8 false negative cases for malignant cells were diagnosed as; 4 suspicious; 3 benign; and 1 malignant. The 3 false positive cases for malignant cells were re-diagnosed as 2 suspicious and 1 benign. The detailed clinical and cytological features of these cases were correlated with the Subsequent histological features.

Results

A summary of the original and reviewed cytological diagnoses, along with the histological diagnosis, and the age of the patients is shown in Table I. All cytologically positive cases were followed by histological examination of the excised pathological specimens (excisional biopsy or mastectomy); which in these 3 false positive cases revealed as 2 fibroadenomas and 1 fibrocystic changes (disease). The 8 false negative cases were also followed by excisional biopsy because of their clinical and mammographical suspicions. On histological examination, they revealed 2 infiltrating lobular carcinomas of classic subtype; 3 infiltrating ductal carcinomas of scirrhous subtype; 1 infiltrating ductal carcinoma of classic subtype; 1 infiltrating ductal carcinoma with massive cystic degeneration; and 1 intraductal (in-situ) carcinoma.

Table II and III analyses the detailed cytological features of these 11 false positive and false negative cases by tabulating them with the criterion for benign and malignant features.

Discussion

Fine-needle aspiration cytology is a well recognized preoperative diagnostic technique that has been used to diagnose breast cancer for over 50 years[2,5].

Case No.	Year	Age	Original cytodiagnosis	Reviewed cytodiagnosis	Histological diagnosis
Case 1	2000	49	Negative	Suspicious	IDC, scirrhous subtype
Case2	2000	50	Negative	Negative	ILC, classic subtype
Case3	2001	42	Negative	Negative	IDC, with massive cystic degeneration
Case4	2001	55	Negative	Positive	IDC, classic subtype
Case5	2001	30	Negative	Negative	Intraductal (in-situ) carcinoma
Case6	2002	43	Negative	Suspicious	ILC, classic subtype
Case7	2003	40	Negative	Suspicious	IDC, scirrhous subtype
			Negative	Suspicious	IDC, scirrhous subtype
Case8	2003	52	Positive*	Suspicious*	Fibrocystic changes (disease)*
Case9*	2002*	60*	Positive*	Negative*	Fibroadenoma*
Case10*	2002*	42*	Positive*	Suspicious*	Fibroadenoma*
Case11*	2003*	51*			

Table I. The age, original and reviewed cytodiagnosis with histological diagnosis of eight false negative and three false positive cases.
* False positive cases
IDC: Infiltrating Ductal Carcinoma
ILC: Infiltrating Lobular Carcinoma

Criteria	**Case 1**	**Case 2**	**Case 3**	**Case 4**	**Case 5**	**Case 6**	**Case 7**	**Case 8**	**Case 9***	**Case 10***	**Case 11***
Cellularity	+	+	++	+++	+++	+	+	+	+++	+++	+++
Good cell cohesion	-	-	-	++	+++	-	-	-	+++	+++	+
Normal cell size	-	+	-	++	++	+	-	-	+++	+++	+
Honeycomb sheets	-	-	-	+	+	-	-	-	-	+++	+
Frequent stripped bipolar nuclei	-	-	-	+	++	-	-	-	-	+++	++
Uniformity of cells	-	+	-	++	+++	-	-	-	++	+++	-
Apocrine cells	-	-	-	-	-	-	-	-	+++	-	-
Histiocytes	-	-	+++	-	-	-	-	-	+++	-	-
Stromal elements	-	+	-	-	-	-	+	-	+	+	-

Table II. Cytological features of false negative and false positive cases by tabulating them with the criterion for benign features.
* False positive cases
Absent (-), Few (+), Many (++), Abundant (+++)

Criteria	**Case 1**	**Case 2**	**Case 3**	**Case 4**	**Case 5**	**Case 6**	**Case 7**	**Case 8**	**Case 9***	**Case 10***	**Case 11***
High cellularity	-	-	++	+++	+++	-	-	-	+++	+++	+++
Loss of cell cohesion	++	++	+++	+	-	+++	++	++	+	+	++
Pleomorphism	+	+	+	+	+	+	+	+	+	+	++
Increase cell size	++	+	++	-	-	+	+	++	++	+	+++
Nuclear hyperchromasia	+	+	-	+	+	+	++	+	-	-	+
Nuclear membrane irregularity	+	+	-	-	-	+	+	++	-	-	-
Prominent nucleoli	+	-	+	-	-	-	++	-	++	+	++
Irregular angulated atypical cells	+	+	-	-	-	+	+	+	+	-	++
Single cell with cytoplasm	+	-	-	++	++	-	++	+	-	+	+
Overlap in clusters	-	-	-	++	+	-	-	-	+	+	+
Necrotic debris	-	-	++	-	-	-	-	-	-	-	-
Lymphocytes response	-	-	++	-	-	-	-	-	+	-	-
Mitotic figures	-	-	-	+	-	-	-	-	-	-	-
Signetring cells	-	-	-	-	-	-	-	-	-	-	-

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

* False positive cases

Absent (-), Few (+), Many (++), Abundant (+++)

Author	No. of cases	Sensitivity %	Specificity %	Positive predictive value%	Negative predictive value%	False positive rate%	False negative rate%
Present study	912	93.9	98.6	97.6	96.6	2.3	6.3
Barrows et al. [5]	1248	92.2	86.0	91.0	87.5	8.9	12.5
Ahmed [8]	465	97.8	96.8	98.9	93.8	3.2	2.3
Bell et al. [10]	1145	77.6	97.1	90.2	93.3	9.8	6.7
Park et al. [14]	669	76.9	91.61	82.2	90.5	1.0	10.6
Al-Azawi et al. [17]	80	96.9	100	100	95.0	0	1.7
Kerin et al. [18]	1500	84.0	99.0	97.0	95.8	0.4	2.2
Horgan et al. [19]	2000	85.3	99.2	95.2	97.4	4.8	2.6
Klijanienko et al. [20]	654	87.8	94.5	94.6	86.9	0	11.4
Palombini et al. [21]	674	96.9	89.8	96.5	90.9	3.5	9.1
Ciatto et al. [22]	534	97.4	99.3	98.6	98.7	1.4	1.3

Table IV. Analytical comparison of FNAC results between the present study and other ten studies in literature

The specificity of FNAC approaches that of frozen section analysis[6]. The reported specificity rates for FNAC vary from 96% to 100%[4-11]. Most recent studies reported false positive rates ranging from 0 to 6%[4,8,9,11-15]. This high degree of diagnostic accuracy allows definitive therapy to proceed on the basis of FNAC diagnosis of malignancy[14,15].

The sensitivity of FNAC for the detection of palpable carcinoma varies widely in reported series (65% to 98%). It is lower than that achieved by frozen section[4-11]. The sensitivity of the diagnostic procedure is determined by technical and interpretative limitations with the reported false negative rates range from 0 to 35%[4,8,9,12-16]. Table 4 shows sensitivity, specificity, positive predictive value, negative predictive value, false positive and false negative rates of the present study in comparison with other ten studies in literature[5,8,10,14,17-22].

In this study, 5 out of 8 false negative cases (case ***1,2,6,7,*** **and** ***8*****)** were diagnosed as negative for malignant cells mainly because of very low cellularity, little nuclear pleomorphism, and low atypism. These 5 cases were histologically diagnosed as 3 infiltrating ductal carcinomas of scirrhous subtype and 2 infiltrating lobular carcinomas of

classic subtype. Poor cellular yield with subtle cytological features of infiltrating lobular and scirrhous (fibrotic) carcinomas have been found to be a source of false negative FNAC; and mammography showed a better discrimination in such cases.[1,14,18,19,23,24]

Criteria used to diagnose a malignant condition in FNAC of the breast are well established and; in satisfactory specimens, allow a definitive diagnosis in most cases of breast cancer[25]. However, despite these criteria, there remain cases of breast carcinoma in which the malignant nuclei are small and uniform and most cells are in cohesive clusters mimicking fibroadenoma or fibrocystic changes[26]. Such a diagnostic difficulty was encountered in the present study and was responsible for 2 false negative cases (case ***4*** and ***5***). It has been observed Created by Wameed Al-HashimysCreated by Wameed Al-Hashimyuch malignant lesions are usually well-differentiated infiltrating ductal or intraductal carcinomas[25-27]. This study supports this observation, in which case ***4*** was histologically diagnosed as well- differentiated infiltrating ductal carcinoma with intraductal (in- situ) component and case ***5*** as pure intraductal carcinoma arising on the background of proliferative fibrocystic changes. The last false negative case (case ***3***) was histologically proved as infiltrating ductal carcinoma with massive cystic degeneration. In this case, the aspirated cloudy fluid was cytologically misinterpreted as fibrocystic changes even in reviewed examination; because it showed large sheets of macrophages with degenerated epithelial cells, as well as inflammatory cells and necrotic debris. Most recent studies reported that FNAC tended to be less reliable and inadequate with a high false negative rate in the diagnosis of lobular, scirrhous, and intraductal carcinomas[1,14,18,19,23,24]. However, in both hypocellular and hypercellular cytological smears all the criterions for the benignancy and malignancy should be carefully taken under consideration; for example lack of single bipolar nuclei, loss of normal cell adhesion and presence of some atypical nuclei should raise the suspicion of malignancy especially if clinically and radiographically suspected so, or when abnormal tissue texture is felt at the time of aspiration.

Fibroadenoma and fibrocystic changes are the most common benign breast lesions to be distinguished from adenocarcinoma by FNAC[26].

In the present study, 2 out of 3 false positive cases were histologically verified as fibroadenoma, pointing to the difficulty of diagnosing this lesion sometimes. The smears of these 2 false positive cases (case ***10*** and ***11***) were misinterpreted on the original cytological diagnosis because they showed highly cellular smears with large cells having prominent nucleoli, as well as frequent naked bipolar nuclei and few nuclei with cytoplasm. There were few overlapped clusters with some pleomorphism too. These features mislead towards positive diagnosis or suspicious interpretation. The third false positive case (case ***9***) was histologically turned out as fibrocystic changes. There were many tight clusters of apocrine cells with obvious nucleoli and large sheets of loosely aggregated macrophages; that were over interpreted as malignant cells and loss of cell cohesion. These observations are supported by literature since fibroadenoma and fibrocystic changes are considered the major pitfalls in diagnosing breast carcinoma[26,28]. Rogers and Lee[26] reported that no combination of cytological features accurately separated all benign and malignant cases in their study. In conclusion, FNAC represents a most valuable preoperative procedure for the diagnosis of breast cancer as the false positive and false

negative rates were acceptable i.e 2.3% and 6.3% respectively, but still lesions such as fibroadenoma and fibrocystic changes can create some difficulties. FNAC of the breast has some unavoidable limitations mainly due to poor sampling; poor yield of cells caused by tumour fibrosis, small size tumour, poor preservation, and difficulty in identifying small well-differentiated malignant cells; or atypical benign cells with inadequate interpretation. Because the sensitivity and specificity rates of FNAC are not always 100%, the technique should be used with this limitation in mind[29].

The combination of clinical examination, aspiration cytological findings, and mammography allows one to accurately assess the benign or malignant nature of the breast disease preoperatively in nearly all patients[15]. Frozen section or intraoperative imprint cytology can serve as an additional confirmation to avoid unnecessary mastectomy following a false positive FNAC diagnosis.

So FNAC still can achieve significant monetary savings, a reduction in patient morbidity, an increased speed of diagnosis, and increased opportunity for preoperative patient counseling without reduction in diagnostic accuracy or compromise of patient prognosis[29].

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