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Role of Cytologic Scoring System in Minimizing "Gray Zone" in Breast Aspiration Cytology

Jung Yeon Kim, M.D., Kyung Ja Cho, M.D.,
Seung Sook Lee, M.D., and Shin Kwang Khang, M.D

Department of Pathology, Korea Cancer Center Hospital

= Abstract =

Fine needle aspiration(FNA) has been quite successful in identifying benign and malignant breast lesions, but a "gray zone" exists. A total of 697 FNAs of breast were performed at Korea Cancer Center Hospital for a period of one year. One hundred and eleven of the 697 FNAs were diagnosed as atypical or suspicious for malignancy. Among them, we reviewed 74 FNAs, in which histologic diagnoses were made, and applied cytologic grading system proposed by Masood et al.(1990) to evaluate the usefulness of this system in minimizing the size of gray zone. Technical problem was responsible for equivocal diagnoses in 19 FNAs. Of the remaining 55 FNAs, 18 were benign and 37 were malignant. Among benign conditions, fibroadenoma(5 cases) and fibrocystic disease with fibroadenomatous feature(3 cases) constituted the largest groups. The majority of malignant conditions were infiltrating ductal carcinoma(29 cases); however, those low grade carcinomas including tubular carcinoma(3 cases), cribriform carcinoma(2 cases), and mucinous carcinoma(2 cases) occupied a relatively large proportion. Cytologic grading system was quite useful in minimizing the size of gray zone. The scores of 27 out of 29 usual infiltrating ductal carcinomas belonged to the group of cytologic malignancy, however, only 2 out of 7 low grade carcinomas got scores of malignancy. FNA from fibroadenoma or fibrocystic disease with fibroadenomatous features showed a tendency toward high scores. Experience of the cytopathologist and familiarity with cytologic alteration in breast disease cannot be overemphasized.

Key words: Breast, Equivocal aspiration, Cytologic grading system, Low grade carcinoma, Fibroadenoma

Introduction

Fine needle aspiration(FNA) cytology of the breast is one of the most valuable diagnostic tools in the evaluation of palpable and nonpalpable breast lesions. The accuracy rate ranges from over 50% to 95%, depending on the experience of the aspirator and interpreter[1]. But a "gray zone" exists in breast cytology. The gray zone is defined as cases in which unequivocal diagnosis of benignancy or malignancy can not be reached based on the FNA cytologic findings due to overlap of the criteria used to distinguish benign and malig-

nant lesions.

Masood et al[2] proposed new numerical grading system in cytologic evaluation of breast to further subclassify benign breast disease and distinguish these forms from neoplastic lesions and a high degree of concordance was found between cytologic findings and histologic diagnosis[2,3]. We applied that grading system to equivocal cases of breast FNAs to evaluate the usefulness of that system in minimizing gray zone.

Materials and Method

A total of 4,394 FNAs were performed at Korea Cancer Center Hospital during the period of one year from January 1994 to December 1994. Six hundred and ninety seven FNAs of the breast were performed by a number of surgeons. The aspirates were smeared directly and fixed immediately in 95% alcohol and then stained by the Papanicolaou method.

One hundred and eleven cases of the 697 FNAs of breast were diagnosed as atypical(69) or suspicious for malignancy(42). Among them, 74 FNAs, in which histologic diagnoses were made by subsequent biopsy or mastectomy, were reviewed and 19 cases(25.7%) out of 74 FNAs of breast were interpretated as unsatisfactory cases for evaluation because of limited cellularity(5), drying artifact(6), limited cellularity combined with drying artifact(5), bloody smear(2), and targeting miss(1): these cases were excluded from the study.

The remaining 55 cases of FNAs of the breast were reviewed by two pathologists, one a senior resident and the other a senior cytopathologist. The histologic slides were reviewed by another pathologist. The FNAs were evaluated for pattern of cellular arrangement, degree of cellular pleomorphism and anisonucleosis, presence of myoepithelial cells or nucleoli and status of the chromatin pattern. Values ranging from 1 to 4 were assigned to each cytologic parameter and a score based on the sum of the individual values was calculated for each case. The minimal score attainable was thus 6 and the maximum was 24. Cytologic diagnoses were made according to criteria proposed by Masood et al.[2,3] Nonproliferative disease was entertained when the total score ranged from 6 to 10. Proliferative disease without atypia was diagnosed with a total score ranging from 11 to 14. Proliferative disease with atypia was reported when the total score ranged from 15 to 18. A cytologic diagnosis of carcinoma was entertained when the total score ranged from 19 to 24(Table 1). Cytologic diagnosis based on this grading system was compared with histologic diagnosis.

Results

Of the 55 cases reviewed, 18 cases were histologically benign and 37 cases were malignant on subsequent biopsy. Initial cytologic diagnosis of 22 cases was "atypical" and the remaining 33 cases were diagnosed as "suspicious for carcinoma". Histologic evaluation of subsequent biopsy revealed that benign lesions(12 cases) outnumbered malignacies(10 cases) in "atypical" group. In contrast, however, the ratio of benign to malignancy was reversed to 6 to 27 in "suspicious for carcinoma" group (Table 2). This discrepancy in ratio of benign to malignant lesions may reflect the different nuance of these two words "atypical" and "suspicious".

Table 1. Cytologic criteria of grading system for interpretation of breast fine needle aspirates

Score	Cellular arrangement	Cellular pleomorphism	Myoepithelial cells	Anisonucleosis	Nucleoli	Chromation clumping
1	Monolayer	Absent	Many	Absent	Absent	Absent
2	Nuclear overriding	Mild	Moderate	Mild	Rare micronucleoli	Rare
3	Nuclear overriding and clustering	Moderate	Few	Moderate	Frequent micronucleoli	Occasional
4	Loss of cohesion	Conspicious	Absent	Conspicuous	Predominantly macronucleoli	Frequent

Total score: nonproliferative breast disease: 6~10
proliferative breast disease without atypia: 11~14
proliferative breast disease with atypia: 15~18
carcinoma: 19~24

Table 2. Histologic diagnoses in the atypical (n=22) and suspicious FNA group (n=33)

Atypical (n=22)				Suspicious (n=33)			
Benign		Malignant		Benign		Malignant	
Fibrocystic disease without proliferation	4	Infiltrating duct carcinoma	9	Fibrocystic disease with proliferation	3	Infiltrating duct carcinoma	20
Fibroaenoma	4	Lobular carcinoma	1	Fibroadenoma	1	Lobular carcinoma	0
Abscess	1	Tubular carcinoma	0	Gynecomastia	1	Tubular carcinoma	3
Phyllodes tumor	1	Cribriform carcinoma	0	Papilloma	1	Cribriform carcinoma	2
Gynecomastia	1	Mucinous carcinoma	0			Mucinous carcinoma	2
Atypical ductal hyperplasia	1						
Total	12		10		6		27

The majority of malignant conditions were infiltrating ductal carcinoma(29 cases)(Fig. 1); however, those low grade carcinoma including tubular carcinomas(3 cases), cribriform carcinomas(2 cases), and mucinous carcinomas(2 cases) occupied a relatively large proportion in the "suspicious" group. One case of lobular carcinoma was included in "atypical" group. Among benign conditions, fibrocystic disease with epithelial proliferation(7 cases) and fibroadenomas(5 cases) were most common lesions, however, 3 out of 7 cases of fibrocystic disease showed fibroadenomatous foci on histologic examination. Thus, on histologic feature, cases showing fibroadenomatous lesions(8 cases) constituted the largest group rendering equivocal diagnosis in interpretation of breast FNAs.

Results of correlation between histologic diagnosis and cytologic scores according to grading system for interpretation of breast FNAs is summarized in table 3 and the grading system was quite useful in minimizing the size of gray

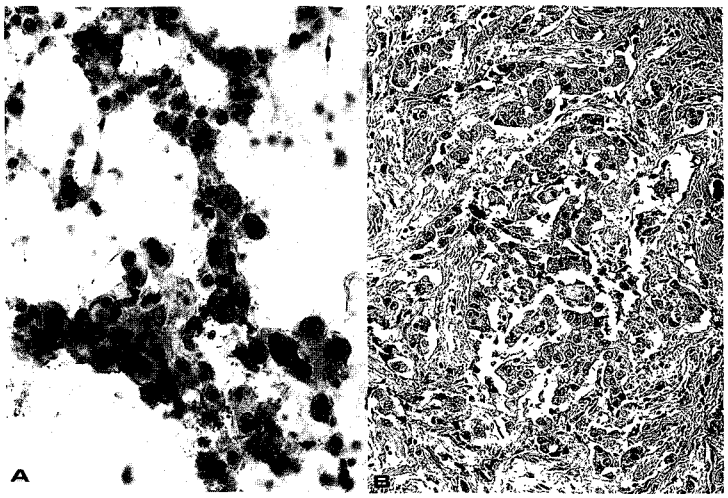

Fig. 1. Infiltrating duct carcinoma. (A) The smear shows loose clusters of tumor cells showing marked cellular pleomorphism, anisonucleosis, macronucleoli, and lack of myoepithelial cells. (B) Histology of same case(A: Papanicolaou, ×200. B: H-E, ×100).

zone. Scores of 30 out of 37 carcinomas belonged to the maliganat group and the remaining 7 cases belonged to the group of proliferative breast disease with atypia. The latter group includes 5 cases of low grade carcinomas and only 2 out of 7 low grade carcinomas were compatible with malignancy(Table 4); they were one case of tubular carcinoma and one case of mucinous carcinoma.

FNAs from fibroadenoma or fibrocystic disease with fibroadenomatous feature showed a tendency toward high scores reaching the scores of malignancy(Table 5). Interpersonal variation between pathologists had a role in interpretating the FNAs of breast and was the source of gray zone. Personal variation between two pathologists is shown in table 6 in interpretating malignant lesions of the breast.

Discussion

The incidence of gray zone in FNAs of the breast varies from 6.9% to 20% by reported cases[4~6]. Among 697 FNAs performed one year in our laboratory we could not make unequivocal cytologic diagnosis in 111 cases, thus the incidence of gray zone reached almost to 16 % and this high incidence of gray zone made us to try this study. The causes of equivocal diagnoses were divided into three categories by Al-Kaisi[1]: (1) technical, in which the smears were either markedly limited in cellularity or obscured by blood and/or drying artifact, (2) inexperience of interpretation and (3) the overlap of cytologic features of benign and malignant lesions due to the nature of the lesion, which is the true gray zone. Peterson et al[4] analyzed a series of 301 cases of atypical FNAs of the breast and the sources of equivocal diagnoses were similar to those of Al-Kaisi[1]. Mulford and Dawson[5] showed similar results[1].

Excluding the first two factors, the size of gray zone has been expected to be minimized by applying more objective and reproducible diagnostic criteria and many investigators have tried to establish criteria distinguishing benign proliferative lesions from malignancy. Significance of various cytologic features including

Table 3. Histocytological correlation of equivocal breast aspirates according to grading system

Histologic diagnosis	Cytologic diagnosis				Table
	Nonproliferative breast disease	Proliferative without atypia	Proliferative with atypia	Carcinoma	
FCD with proliferation		3	3	1	7
ADH				1	1
Fibroadenoma			4	1	5
Gynecomastia		2			2
Phyllodes tumor	1				1
Papilloma		1			1
Abscess				1	1
Carcinoma			7(5)*	30	37
Total	1	6	14	34	55

FCD: fibrocystic disease
ADH: atypical ductal hyperplasia
( ): low grade carcinomas

Table 4. Results of cytologic scoring of low grade carcinomas

Histologic diagnosis	Cytologic diagnosis				Table
	Nonproliferative breast disease (6~10)	Proliferative without atypia (11~14)	Proliferative with atypia (15~18)	Carcinoma (19~24)	
Tubular carcinoma			2	1	3
Cribriform carcinoma			2		2
Mucinous carcinoma			1	1	2
Total			5	2	7

( ): cytologic score

Table 5. Results of cytologic scoring of fibroadenomas and fibrocystic diseases with fibroadenomatous feature

Histologic diagnosis	Cytologic diagnosis				Table
	Nonproliferative breast disease (6~10)	Proliferative without atypia (11~14)	Proliferative with atypia (15~18)	Carcinoma (19~24)	
Fibroadenoma			4	1	5
Fibrocystic disease with fibroadenomatous feature		1	1	1	3
Total		1	5	2	8

( ): cytologic score

Table 6. Interpersonal variations between two pathologists in cytologic scoring

	R1	R2
Unable to interpret	0	6
Nonproliferative breast disease	0	1
Proliferative without atypia	0	8
Proliferative with atypia	7	10
Carcinoma	30	12
Total	37	37

R1: reader 1, R2: reader 2

epithelial cellularity, architectural arrangement, nuclear overriding, cellular pleomorphism, anisonucleosis, and presence or absence of myoepithelial cells have been investigated. However, none of single cytologic parameter has been proved to be statistically significant in distinguishing proliferative and nonproliferative breast disease or in differentiating benign proliferative disease from malignant lesions[7]. Bibbo et al[8] devised a histological numerical grading system to subclassify atypical hyperplasia based on 6 histologic features. A value ranging from 1 to 3 was assigned to each histologic criterion and a score based on the sum of the individual value was calculated for each case. Then hyperplasia was graded according to the total score of each case. Masood's grading system can be considered as a cytologic modification of Bibbo's system. Masood's grading system was initially intended to differentiate benign nonproliferative change from proliferative breast change, because of the 5 times increased risk of development of breast carcinoma in patients with atypical hyperplasia. And the distinction between proliferative and nonproliferative fibrocystic changes was made on the basis of total cytologic score but individual cytologic parameters were not compared. It was also proved to be useful in distinguishing benign proliferative lesions from malignancies showing high concordance rate between cytologic and histologic diagnosis[2]. In present study, Masood's grading system proved to be useful in minimizing the size of gray zone.

Of the 37 cases of histologically proven carcinomas, 30 cases got score of malignancy and only 7 carcinomas belonged to proliferative with atypia group. Five out of those 7 carcinomas were low grade carcinoma: 2 tubular carcinomas, 2 cribriform carcinomas and 1 mucinous carcinoma in contrast to the fact that only 2 out of 29 usual ductal carcinomas got score of atypical hyperplasia. It is evident that Masood's grading system has pitfall in diagnosis of low grade carcinomas.

Sneige and Staerkel[9] emphasized the application of both cytological and architectural criteria to the interpretation of FNA smears and that it was more reliable than cytology alone in the identification of proliferative breast lesions and low grade carcinoma. They also insisted that diagnosis of low grade carcinoma could be made with confidence if the aspirates are cellular with many single atypical epithelial cells and lack an admixture of benign cellular element. But there is an overlap of features between ductal hyperplasia and atypical ductal hyperplasia as well as between atypical ductal hyperplasia and low grade carcinoma. In fact, one of atypical ductal hyperplasia in our study was placed in the malignant group by this grading system.

The scores of two cases of tubular carcinomas, whose scores correspond to that of atypical hyperplasia, showed relative uniformity in size and shape and minimal anisonucleosis. Nucleoli are small or absent, but shows angular epithelial clusters with branching tubular structures which raise the possibility of tubular carcinoma(Fig. 2). One of two cases of mucinous carcinomas got scores of malignancy while score of the other one is that of proliferative breast disease with atypia. Both cases show mucin in background and mucin would be more important characteristic finding than cytologic feature in cytodiagnosis of mucinous carcinoma(Fig. 3). The cytologic features of two cases of cribriform carcinoma(Fig. 4) were very similar to those of tubular carcinoma but showed irregular spacing between cell groups in a single cluster of epithelial cells. In low grade carcinomas, architectural criteria including smear background would be more important in diagnosis.

Recently cytologic criteria for distinguishing carcinoma in situ from atypical ductal hyperplasia have been described[8,10~12]. Adendroth et al[12] demonstrated that the distinction between some cases of ductal carcinoma in situ and atypical ductal hyperplasia may be possible on FNA. The features favoring for ductal carcinoma in situ were loose dyshesive clusters, irregular nuclear spacing with more overlap and absence of myoepithelial cells. Above feature also reflects importance of architectural pattern in distinguishing benign proliferative lesions from malignancies. But FNAs cannot reliably diagnose carcinoma in situ from invasive carcinoma and the separation of ductal carcinoma in situ from invasive carcinoma may not be critical, because many authors recommended the same treatment options for ductal carcinoma in situ as for invasive ductal carcinoma. In our study one case of ductal carcinoma in situ was included, whose score belonged to group of carcinoma.

Fibroadenoma and fibrocystic disease with fibroadenomatous feature constituted the large single cause of falsely atypical and suspicious FNA interpretation which is similar to other

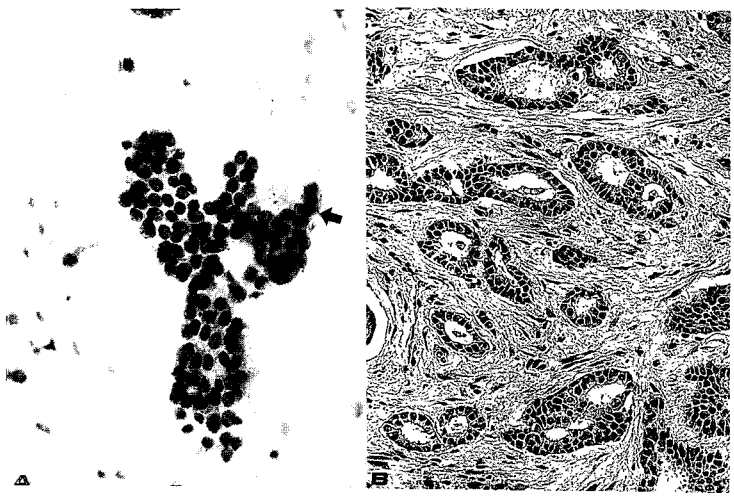

Fig. 2. Tubular carcinoma. (A) An epithelial cell cluster shows minimal pleomorphism, anisonucleosis, and rare micronucleoli, but branching tubular structure with angular appearance(arrow) raises suspicion for tubular carcinoma. (B) Infiltrating tubular carcinoma in resected specimen(A: Papanicolaou, ×200. B: H-E, ×100).

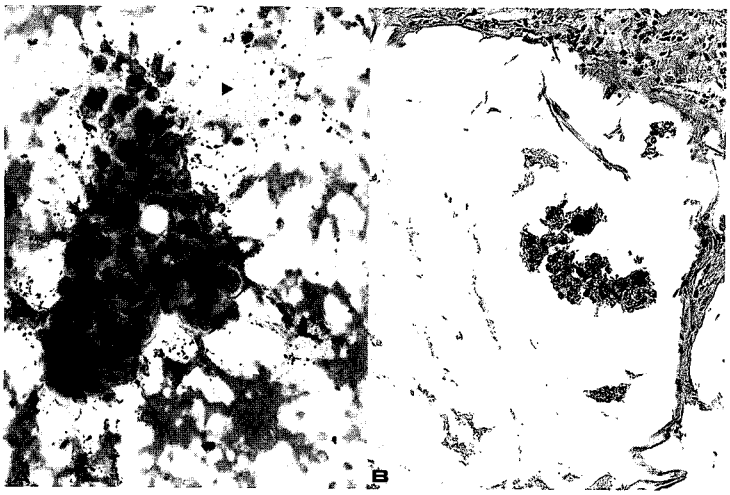

Fig. 3. *Mucinous carcinoma.* (A) A tight cluster of epithelial cells in mucinous background. (B) Histology of same case(A: Papanicolaou, x200. B: H-E, × 100).

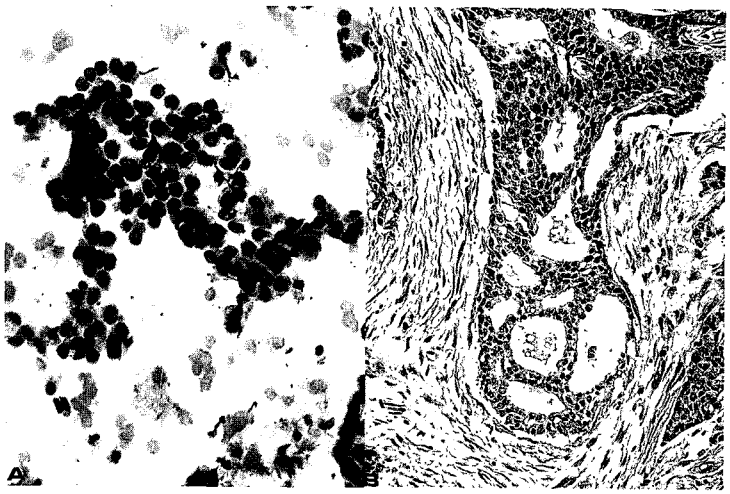

Fig. 4. Cribriform carcinoma. (A) A loose cluster of uniform epithelial cells. Irregular spacing between groups of nuclei and mild anisonucleosis are features distinguishing from benign proliferative lesion. (B) Invasive cribriform nests in resected specimen(A: Papanicolaou, ×200. B: H-E, ×100).

reports[1,4,6,13,14]. Cytologically, dyshesiveness of large clusters, nuclear enlargement with prominent nucleoli, paucity of myoepithelial cells prompted the diagnosis of atypia(Fig. 5). The diagnosis of fibroadenoma, however, should be considered in cases showing naked stromal cells in the background, myxoid connective stroma and large branching, tight clusters of epithelial cells that have monolayer sheet-like arrangement with multiple holes[7]. Sometimes, confusion between fibroadenoma or ductal papilloma and proliferating mammary dysplasia exists and in these cases cellular atypia does not permit the exclusion of malignancy[15]. The one case of intraductal papilloma received a score of 13. Intraductal papilloma sometimes cannot be distinguished from papillary carcinoma but the monomorphic cell population, mild to moderate pleomorphism, increased mitotic activity, and increased dyshesiveness in forms of isol-

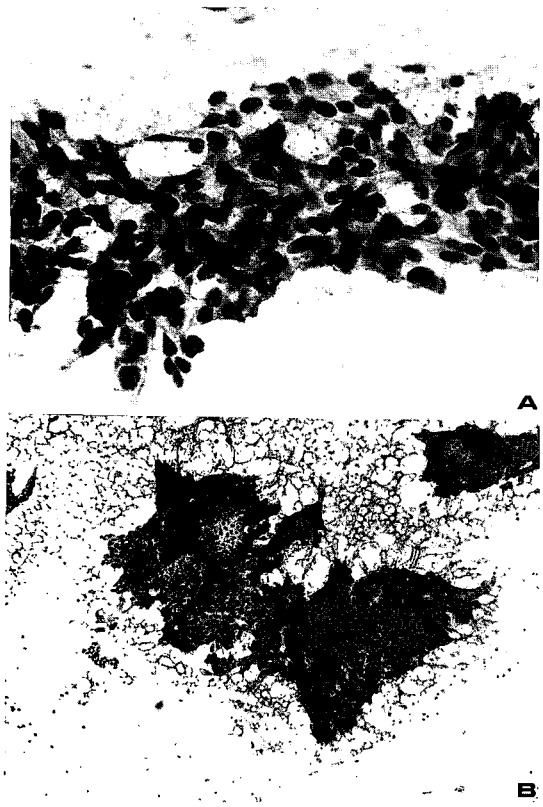

Fig. 5. FNA of fibroadenoma. (A) Nuclear overriding, moderate pleomorphism, anisonucleosis and paucity of myoepithelial cells lead to high cytologic score. (B) Numerous cells on low power view characterize fibroadenoma (A, B: Papanicolaou, ×200, ×40).

ated cells with intact cytoplasm favor the diagnosis of papillary carcinoma. In papilloma, three dimensional, branched architecture of the epithelium is characteristic[7].

Interpersonal variation between two pathologists existed in this study. It was due to less prominent cytologic atypia of breast carcinoma than carcinoma of other organs. Stanley et al[16] insisted that the generally accepted criteria for designation of breast FNA as atypical is nonspecific, and some carcinomas show relatively little cytologic aberration while strikingly atypical cells may be encountered in benign conditions such as fibroadenoma. Experience of the cytopathologist interpretating the FNAs of the breast cannot be overemphasized in making the diagnosis of cancer, especially in the light of irreversible therapeutic implications. Obtaining a well aspirated specimen is also important.

In summary, cytologic grading system is useful in evaluation of equivocal breast aspirations. But in cases of low grade carcinoma and fibroadenoma or fibrocystic disease with fibroadenomatous feature, a caution should be taken in applying scoring system. Experience of the cytopathologist and familiarity with cytologic alteration in breast disease are very important in reducing interpersonal variations and gray zone.

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= 국문 요약 =

진단이 애매했던 유방 세침흡인 세포검사에서 등급 점수표의 역할

원자력병원 해부병리과

김 정 연 · 조 경 자 · 이 승 숙 · 강 신 광

세침흡인 검사는 촉지되거나 혹은 촉지되지 않는 양성과 악성 유방 질환을 인지하는 매우 유용한 방법이나 진단이 애매한 회색 지역이 존재한다. 1년동안 시행한 697예의 유방 세침흡인 검사 중 111예가 비정형적 혹은 악성이 의심된다고 보고되었으며 이 중 조직학적으로 확진된 74예를 재검색하여 Masood 등(1990)이 제안한 등급 점수표가 회색 지역을 줄이는데 유용한지 살펴보았다. 기술적 문제가 19예에서 나타났으며 나머지 55예 중 18예는 양성으로, 37예는 악성으로 조직학적으로 진단되었다. 양성 질환 중 섬유선종(5예) 및 섬유선종의 성상을 지닌 섬유낭성 질환(3예)이 가장 많았고 악성은 대부분 침윤성 관암종이였으며(29예), 관상암종(3예), 사상암종(2예) 및 점액암종(2예) 등 분화가 좋은 암종들이 상대적으로 많았다. 등급 점수표는 회색 지역을 줄이는데 상당히 유용하여 29예의 관암종중 27예가 세포학적 악성 범주에 속했다. 그러나 분화가 좋은 암종은 7예중 2예만이 세포학적 악성 범주에 속했고 섬유선종 및 섬유선종의 성상을 지닌 섬유낭성 질환은 비교적 높은 점수를 보였다. 따라서 등급 점수표의 응용은 유방 세침흡인 검사에서 양성과 악성 병변의 감별에 매우 유용하게 이용될 수 있으나 분화가 좋은 암종들과 섬유선종의 진단에는 주의가 필요할 것으로 사료되며 유방 세침흡인 세포학적 검사에는 세포 병리 의사의 경험 및 유방질환의 세포학적 변조에 대한 친숙성이 강조되어야 할 것이다.