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Significance and Diagnostic Utility of Micronucleus Scoring on Breast Cytology Smears

Mamta[1], Padam Parmar[2], Laxmi Aheer[3], Anand Raj Kalla[4]

[1,3]Assistant Professor, [4]Senior Professor,
Department of Pathology, Dr S.N. Medical College, Jodhpur, Rajasthan
[2]Consultant Pathologist, Ncure Imaging and Diagnostic, Jodhpur, Rajasthan.

Corresponding Author: Dr. Mamta

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ABSTRACT

Background: Micronucleus (MN) is an indicator of chromosomal damages and genetic instability and scoring helps in diagnosis of difficult cases of malignancy. We scored the micronucleus in breast FNA cytology smears and attempted to classify malignant lesions from borderline grey zone breast cases.
Materials and Methods: Fine needle aspiration cytology (FNAC) smears from breast Lump (n=191) in an interval of 1 year was evaluated with excluding criteria. Giemsa stained smears were evaluated for counting the MN in 1000 breast epithelial cells with using oil immersion lens. The mean score for the benign, atypical hyperplasia and carcinomas cases was compared. One-way analysis of variance (ANOVA) was used for data analysis, and the P value < 0.05 was taken as statistically significant.
Result: The total of 98 cases of breast lump including 59-fibroadenoma, 10-atypical ductal hyperplasia and 29- carcinoma breast was evaluated for MN scoring. Remaining, 93 cases were excluded. Mean score of benign, atypical and malignant cases was 0.10±0.31, 3.10±2.72 and 6.21±3.22 respectively. Difference of scoring and high scoring in malignant cases were statistically significant (ANOVA, p-value=<0.001). Cut-off value ≥ 3.50, then the case is malignant with 86.2% Sensitivity and 70% of Specificity.
Conclusion: Micronucleus scores higher in malignant category and may be used as additional criteria in the diagnosis of difficult breast lesions on FNA smears.

Keywords: Micronucleus, Breast smears, grey zone.

INTRODUCTION

Micronucleus is an indicator of chromosomal damages (lagging of chromosome as a whole or acentric fragments of chromosome) due to genetic instability in malignancy. Micronuclei are small (1/3 to 1/16th the size) and retain the same character and color of the nucleus.[1]
Evans et al first studied on micronucleus.[2] Breast carcinomas are familiar to undergo chromosomal instabilities which have key role in developing and progression of cancer.[3] Theodor Boveri gave hypothesis that chromosomes aberration might contribute towards carcinogenesis.[4] In 1997, a project was conducted by International Human Micronucleus project (HUMN) which proved the score of micronucleus as biomarker of genomic damage.[5,6] Micronucleus scoring has been studied in various malignancies like oral, cervical,

bladder and breast cancer with controversial results.[1,3,6-10]

We conducted this study to find out significance of micronucleus scores on breast fine needle aspiration cytology smears in benign, atypical ductal hyperplasia and malignant cases and to add one more step for a cut off value for scoring for grey zone cases.

MATERIALS & METHODS

Fine needle aspiration cytology smears (FNAC) from breast Lump for an interval of 1 year was evaluated from the Pathology Department. All the relevant clinical details were obtained. All benign tumors, atypical ductal hyperplasias/ suspicious for malignancy, and carcinomas breast cases were included in the study. Benign proliferative breast diseases, cystic disease, inflammatory lesion, poorly stained smears and inadequate smears were excluded from the study.

May Grunwald Giemsa, stained smears were examined for counting the MN in 1000 epithelial cells on breast cytology smears under oil immersion with the support of hemocytometer. The morphologic mimics of micronuclei are apoptotic cells, stain particles and cellular debris like nuclear fragments were carefully eliminated by counting the MN in an intact cell and same texture of chromatin matched with main nucleus. The average score was compared between the benign, atypical hyperplasia and carcinomas cases.

Statistical analysis

All the data (mean, standard deviation of continuous variables, sensitivity, and specificity) obtained were analyzed statistically using IBM SPSS Statistics for Windows, Version 20.0. (IBM Corp., Armonk, NY). One-way analysis of variance (ANOVA) was applied, and P value <0.05 was taken as statistically significant.

RESULT

The total of 191 cases of breast lump in female patients was evaluated for fine needle aspirate smears during the period of one year in the department of pathology. Out of these, 59 cases of fibroadenoma, 10 cases of atypical ductal hyperplasia/ suspicious cases of malignancy and 29 cases of carcinoma breast were evaluated for MN scoring. Remaining, 93 cases were excluded due to low cellularity, inflammatory lesion like mastitis and cystic lesion were exclude from study group.

In the benign group, mean age was 26.10± 9.29 years. Mean age of suspicious/atypical hyperplasia and carcinoma breast was 43.9±16.44 years and 53.24±12.58 years respectively. Difference of age in these groups was significant (ANOVA, p-value <0.001). (Table 1)

Mean score of benign cases (n=59) was (0.10±0.31) lower than atypical hyperplasia and malignant cases with range of 0-1. Mean score of atypical cases (n=10) was (3.10±2.72) with range of 0-8. (Table 2) The area under the ROC curve for Benign and Suspicious cases for this category was 0.930 with P-value <0.001. With Cut-off value Greater than or equal to 0.50, Sensitivity and Specificity for suspicious /atypical cases was 90% and 89.8% respectively. (Figure 1)

Mean score of malignant cases (n=29) was 6.21±3.22 with range of 2-16 and was higher than atypical group. Difference of scoring and high scoring in malignant cases were statistically significant (ANOVA, p-value <0.001). Area under ROC curve for Malignant and Suspicious cases was 0.781 with P-value 0.009. Cut-off value Greater than or equal to 3.50, then the case is malignant with 86.2% Sensitivity and 70% of Specificity. (Table 2 and Figure 2)

The cytological findings are shown in Figure 3.

Table 1. Distribution and mean age of different categories of breast lump.

Type of lesion	Total cases (n)	Mean Age (years)	
Suspicious	10	43.9±16.44	ANOVA, F-statistics = 60.13, p-value=<0.001
Malignant	29	53.24±12.58	
Benign	59	26.10± 9.29	
Total	98		

Table: 2. Mean micronucleus score of cases of different categories of breast lump.

Type of lesion	Total cases (n)	Mean Score	Range (Median)	
Suspicious	10	3.10±2.72	0-8 (2.50)	ANOVA, F-statistics = 96.2, p-value = <0.001
Malignant	29	6.21±3.22	2-16 (5.00)	
Benign	59	0.10±0.31	0-1 (0.00)	
Total	98			

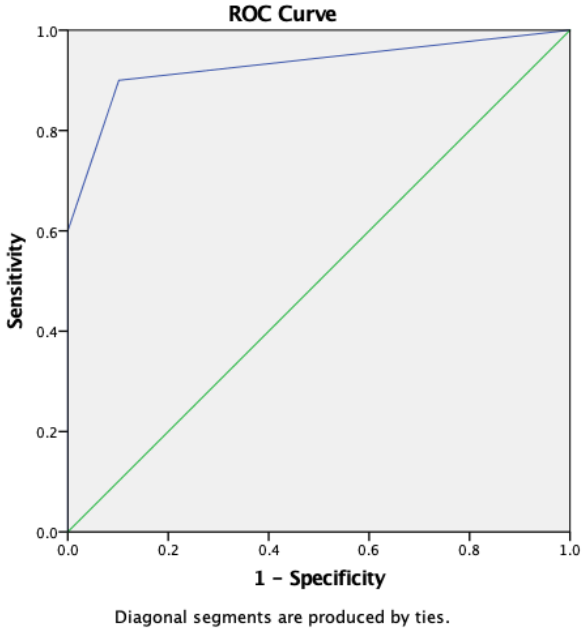

Figure 1: Showing ROC curve between sensitivity and 1-specificity for FNAC of suspicious and atypical cases of breast lesions.

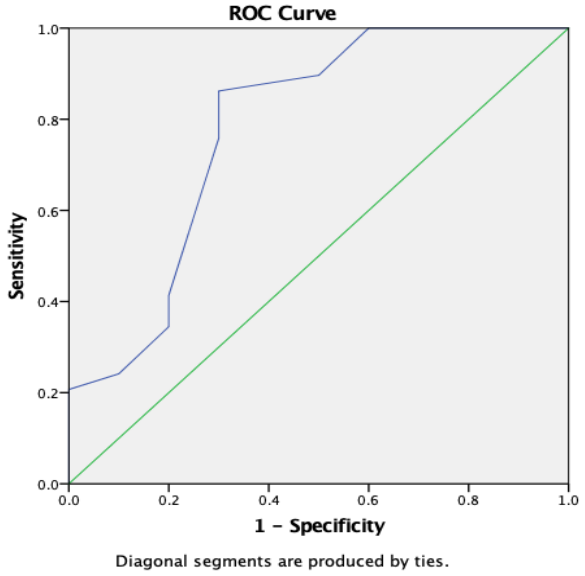

Figure 2: Showing ROC curve between sensitivity and 1-specificity for FNAC of Malignant cases of breast carcinoma

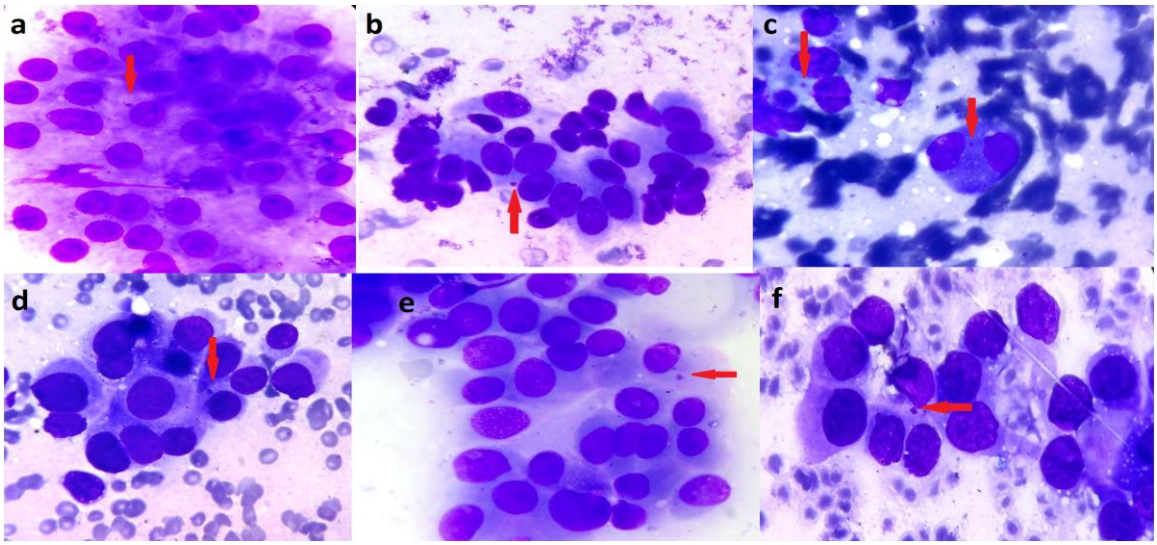

Figure 3. Giemsa-stained cytology smears of breast lump showing micronucleus in a) benign case b) suspicious case and c-f) malignant cases. (100X)

DISCUSSION

Micronucleus represents the genetic instability and involves various oncogenes and tumor suppressor genes like P53 mutations and BRCA mutations in breast cancer.[3] In breast carcinoma patient's occurrence of micro nuclei has been investigated in lymphocytes by Rothfu A et al.[11] and in buccal smears by Dey P et al.[12] have reported with significant increase in numbers.

The diagnosis of suspicious malignant cases of breast (grey zone category) is difficult on FNAC smears due to overlie cytological features, inconclusive imaging studies, interobserver variability and lack of firm criteria. For this category we have analyzed micronucleus scoring as additional criteria to differentiate these categories. Few studies of micronucleus on breast cytology conducted and compared the benign and malignant groups.[1,3]

In our study, mean score of benign cases (n=59) was 0.10±0.31 which was lower than atypical hyperplasia and malignant cases with range of 0-1 and comparable to normal individuals of 1.08–1.23. Previous studies on breast cytology by Samanta et al[9] and Sylvia et al.[1] also found Similar lower scores of 0.6 ± 1 and 0.5 respectively. However, in the study of Hemalatha et al.[3] score was high (1.8 ± 1.9) in the benign group.

Mean score of atypical cases (n=10) was (3.10±2.72) with range of 0-8 which is higher than benign group. Mean score of atypical cases was lower as compared to study of Sylvia et al[1] (6.6 with range of 3-10). The area under the ROC curve for Benign and Suspicious cases for this category was 0.930 with significant p-value. With Cut-off value Greater than or equal to 0.50, Sensitivity and Specificity for suspicious /atypical cases was 90% and 89.8% respectively. In the atypical cases, careful examination of cytomorphological features, with supportive micronucleus scoring may help to differentiate this category clearly from benign cases and guide for further work up to rule out malignancy.

In our study group, mean score of malignant cases (n=29) was 6.21±3.22 with range of 2-16 and was higher than atypical and benign group. Difference of scoring and high scoring in malignant cases were statistically significant (ANOVA, p-value=<0.001). Area under ROC curve for Malignant and Suspicious cases was 0.781 with Cut-off value ≥ 3.50 with 86.2% Sensitivity and 70% of Specificity. Therefore, micronucleus scoring may be used as additional criteria for diagnosis of malignancy in breast lesion. This scoring is comparable with study of Goel et al. (9.3)[10] and lower than study of Samanta et al.[9] (13.6), Sylvia et al.[1] (19.2)

and Hemalatha et al.[3] (46.76). Due to these variables mean score, further extensive studies are needed to decide cut off value of scoring which can differentiate malignant cases from grey zone cases.

CONCLUSION

Micronucleus scores increase from the benign to the malignant category which is indicator of genomic damage and may be used as additional criteria in making the diagnosis of difficult breast lesions on FNA smears chiefly the borderline gray zone categories.

Declaration by Authors

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