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Cytological Findings in Triple Negative Breast Cancer

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I. Introduction

Immunohistochemistry has now become an important tool for prognostic predilection in clinically heterogeneous breast cancer. Present histological classifications do not fully predict the varied clinical course of this disease. Histological type, grade, tumor size, lymph node involvement, in addition to estrogen receptor α (ER), progesterone receptor (PR) and HER-2 receptor status all influence prognosis and the probability of response to systemic therapies.[1]

Although many advanced biological and molecular markers of breast cancer have been identified over the past two decades, traditional markers such as estrogen receptor (ER), progesterone receptor (PR), and HER-2 remain among the most useful and easily available indicators of prognosis and therapeutic response to treatment.[2]

Triple -negative Breast cancer means testing results for all three markers that is estrogen receptors (ER), progesterone receptors (PR), and HER2neu is negative.

These negative results mean that the growth of the cancer is not related to hormonal influence like estrogen and progesterone, nor by the presence of too many HER2 receptors. Therefore, no use in treating these patients with hormonal therapy (such as tamoxifen or aromatase inhibitors) or therapies that target HER2 receptors, such as Herceptin (trastuzumab). However, other medicines can be used to treat triple-negative breast cancer[3] like athracyclins, taxanes and immunotherapy in adjuvant chemotherapy

Clinicopathologic features of triple negative breast cancers

Analyses of gene expression arrays have resulted in the recognition of 5 distinct molecular subtypes of breast cancer with clinical, biologic, and therapeutic implications.[4]The luminal subtypes of breast cancers express ER-responsive genes, and other genes that encode characteristic proteins of luminal epithelial cells. There appear to be at least 2 groups of ER-positive breast cancers, commonly defined as luminal A and luminal B tumors, depending on expression levels of the characteristic genes and of other genes that pertain either to the proliferation cluster and/or to HER-2. The second broad group (ER-negative tumors) is subdivided into 3 groups: HER2-positive tumors, basal-like tumors, and so called normal breast-like tumors.

Among these, basal type breast cancers are associated with worst prognostic and clinical profile especially if not detected at an early age [5,6].Basal-like breast carcinoma (BLBC) is associated with younger patient age, high histological grade, aggressive clinical course, development of distant metastasis, poor prognosis, and relatively high mortality rate.They comprise 15-20% of breast cancers and do not express estrogen receptor, progesterone receptor, or HER2 (triple-negative phenotype). Therefore, these patients with basal-like carcinomas are not likely to benefit from endocrine therapies or trastuzumab, but are likely to benefit from systemic chemotherapy.[7]These patients have a tendency to develop visceral metastases early in the course of their disease.[8]

TNBCs comprise a heterogeneous group of tumors with various histologic features and clinical behaviors. TNBC appears to be more common among young women, and particularly young African American women.[9]

High-grade, invasive ductal carcinomas not otherwise specified are the most frequent. Other carcinomas that usually have a triple-negative phenotype include lowgrade and high-grade metaplastic, medullary, apocrine, adenoid cystic, and juvenile secretory carcinomas.[10 11]

Modified Scarf - Bloom Richardson (SBR) is widely used on histopathology.Attempts are being made to study the morphologic correlates for "triple negative " breast cancers on histology.In the present paper, we present data of cytological features of Triple negative breast carcinoma, and discuss about its morphological spectrum.

There are two known grading methods for breast carcinomain cytology -Robinson's and Mouriquand's grading methods.[12]These methods take into account cellular characters like cell dissociation, cell size, cell

uniformity,nuclear features like nuclear margins and nuclear chromatin, nucleoli and graded into grade I, grade II and grade III, respectively.Robinson grade III includes pleomorphism, single cells, large nuclei, nucleoli.

II. Aims and Objectives

The objective of the current study was to study the cytologic correlates of triple negative breast cancers and comparision of these features with ER ,PR negative and Her2 neu positive cases.

III. Materials and Methods

A retrospective analysis was done based on immunoprofile of the mastectomy specimens. Cytological features of 29 cases of TNBC and 21 cases of Her2neu positive tumors with cytological diagnosis from the records of the department of Pathology of a tertiary care institute were studied retrospectively using Papanicoloaou and May Grunwald Giemsa (MGG) stained smears. All the tumors were SBR grade III. The duration of study was between January 2010 - march 2014. The analysis was based on the criteria of Bonzanini *et al*. A whole range of morphologic features was scored according to the severity and given scores of 0, 1+, 2+, 3+ for two groups. As it was a retrospective study ethics committee approval is was not taken.

Cytologic Analysis

The following cytologic features were scored: cellularity, the presence of lymphocytes, the presence of syncytial clusters (defined as groups of cells with inconspicuous, intercellular membranes and nuclear overlapping), the presence of tubular/ductal-like clusters (defined as groups of polarized cells forming tubules or gland-like clusters), the presence of large bare nuclei (defined as single, high-grade, malignant nuclei without cytoplasm), the presence of streaming within the clusters, presence of calcifications. Moreover, single-cell features, such as cellular borders, type of cytoplasm, the presence of cytoplasmic vacuoles, nuclear pleomorphism, the presence of prominent nucleoli, and the type of chromatin pattern also were evaluated.

Statistical analysis

Chi square test is used to compare tumor types for each cytologic variable. P values $< .05$ were considered statistically significant.

IV. Results

Total 29 cases were identified as triple-negative after immunohistochemical and /or FISH analysis and 21 cases were identified as ER and PR negative and Her2neu –positive.

Cytological findings

Each individual cytomorphological features were studied for each case from both groups and scored by two pathologists.We found that statistically significant difference was seen in features like vessels, bizzare giant cells, spindle cells which are more frequently seen in TNBC group (fig:1). Whereas calcifications, nucleoli, nuclear pleomorphism are more seen in Her2 neu positive group.

Additional findings observed in TNBC group are intracytoplasmic mucin and tigroid background, 2 cases had small cell morphology with nuclear moulding, 2 cases had neuroendocrine morphology, 1 case had mucin/myxiod stromal fragment (fig:2). One case showed suspicious granuloma. One case of Her2neu positive showed distinct cell borders.

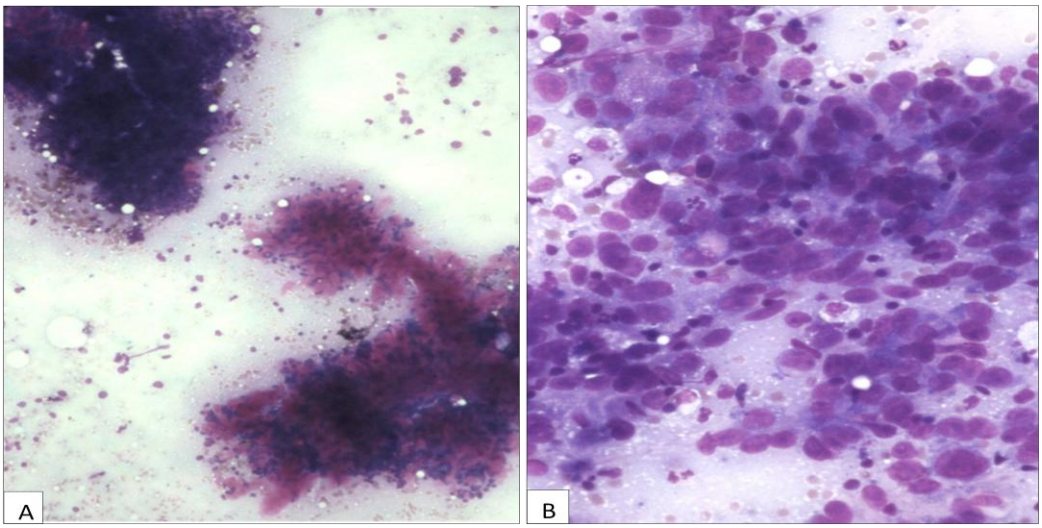

Figure 1:A.MGG 100x spindle cells**.** B.MGG 400x endothelial cells.

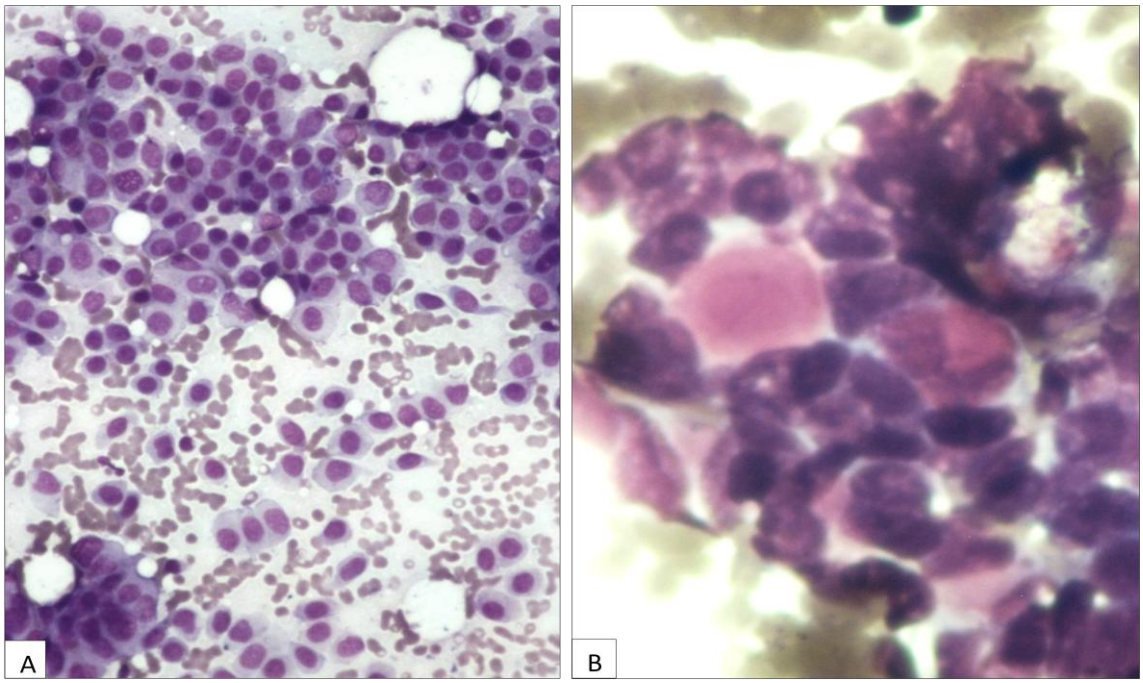

Figure 2:A.MGG 100x neuroendocrine morphology B.MGG 400x matrix production

V. Discussion

There is a need to predict TNBC on morphology and grading in cytology gives morphological prediction on histopathology. The present study was compared with Bonzanini et al. Where TNBCs were more likely to have an abundant necrotic background, many lymphocytes, many syncytial clusters, and ill defined cell borders than non-TNBCs.

A tubular/ductal pattern was observed only rarely in TNBCs. Other features like cytoplasmic vacuoles, and cellular pleomorphism are also helpful. They concluded that Although TNBCs embrace a heterogeneous group of tumors, they exhibited some common cytologic features that can help to distinguish them from other high-grade breast carcinomas in daily practice.

The current study demonstrates that there are significant cytologic differences between TNBC and non-TNBC. Our statistical study demonstrated that there is a probability of identifying TNBC by cytomorphological features like vessels, bizzare giant cells, spindle cells.

In a study done by Duflothet.all[16] the cytological criteria for all cases were reviewed blindly by two pathologists according to five cytological criteria: cellularity, cell pattern, presence of necrosis, nucleoli, and nuclear atypia. They found that Necrosis, as well as prominent nucleoli and abundant cellularity are criteria more frequently associated to the basal phenotype of breast carcinoma.

[17]Akashi et al studied the cytological characteristics of Basal like Breast Carcinoma and compared with those of other types. He found that lymphocyte infiltration, squamous metaplasia, and nuclear findings such as a high mitotic index, naked or large nuclei, an irregular nuclear margin and the presence of nucleoli, may be clues indicating TNBC.

VI. Conclusion

Triple negative breast cancers have recognisable cytomorphologic features. vessels, bizzare giant cells, spindle cells are useful morphological features to suspect triple negative breast carcinomas.

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