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Original Research Article

Cell cannibalism: a diagnostic and prognostic marker of breast cancer

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ABSTRACT

Background: Cell cannibalism (cytophagocytosis) is defined as a tumor cell within a tumor cell, such that smaller tumor cells are found in the cytoplasm of larger tumor cells with crescent shaped nuclei. Aims and Objectives were to study the cytomorphological characters of cell cannibalism in primary and metastatic breast cancer, to correlate the histologic type and grade of tumors with positive rate of cannibalism and to study the role of Cannibalism as an independent prognostic factor in breast cancer.
Methods: The study was conducted during the period of July 2003 to June 2005 in the Department of Surgery and Pathology, JNMCH, Aligarh. A total of 42 cases were included in the study. A minimum of 3 FNAC smears per case were assessed for cytophagocytosis. Presence of metastasis was also noted to establish the cytological grade and aggressiveness of the tumor.
Results: Out of 42 cases, significant cannibalistic activity was noted in 30 (71.42%) cases. All grade III (33.4%) breast tumors were found positive for cytophagocytosis (4.28/smear), while the rate was much lower (2.33/smear) in grade II and (1.63/smear) in grade I tumors. LN metastasis was confirmed by histopathological examination in all high grade tumors showing significant cannibalistic activity.
Conclusions: Cannibalism in breast carcinoma is an indicator of both the anaplastic grade and invasiveness. The rate of cytophagocytosis may have a prognostic significance.

Keywords: Breast cancer, Cell cannibalism, Cytophagocytosis, FNAC, Prognostic factor

INTRODUCTION

Cell cannibalism (cytophagocytosis) is defined as the ability of a cell to phagocytose another cell; a tumor cell within a tumor cell.[1] In cytological preparation it is seen as a cell contained within another larger cell that has a crescent-shaped nucleus.[2,3] It was first described by Leydenin in 1904, he called them 'Birds Eye Cells'.[2] This property of tumor cell confers it a survival advantage in low nutrient conditions.[4] Cytologically, it has been found in nipple discharge from breast cancer patients, gall bladder carcinoma, endometrial stromal sarcoma, giant cell cancer of lung, brain tumors, small cell carcinoma lung, melanomas and in urine and effusions.[4-9] Many authors consider cell phagocytosis as an indicator of high grade malignancy and increased cell turnover.[8-11] Cannibalism can be detected in extremely advanced tumors at higher frequencies.[12] Fine needle aspiration cytology (FNAC) may provide a simple, non-invasive, clinically applicable tool for examining cannibalism in breast cancer patients.

The present study was conducted with the following aims and objectives to study the cytomorphological characters of cell cannibalism in primary and metastatic breast cancer, to correlate the histologic type and grade of tumors with positive rate of cannibalism and to study the role of cannibalism as an independent prognostic factor in breast cancer.

METHODS

This is a prospective study conducted from July 2003 to June 2005 in the Departments of Surgery and Pathology, JNMC, Aligarh. Patients attending the Surgical OPD as well as those admitted in the hospital who harboured a cytologically diagnosed breast carcinoma were included after informed consent. After positioning the patient the area was cleaned with spirit swab and FNAC was done using 23 G needle attached to a 10 ml syringe by making multiple passes. Contents of syringe were expelled on glass slides and smears made. These were immediately fixed with 95% alcohol and H and E staining was done. Some of the positive samples were subsequently examined under a transmission electron microscope.

A minimum of 3 FNAC smears per case were assessed for cytophagocytosis. If one or more instance of cell cannibalism was detected the smear was labelled as cannibalistic positive. The total number of tumor cells with evidence of cytophagocytosis were counted and reported per smear.

Exclusion criteria (for inadequate smear)

Hemorrhagic smear with no cellularity, smears with degenerating tumor cells with difficult interpretation of nuclear and cytologic details. Other cytological criteria of malignancy were also studied namely, cellularity and cytoplasmic atypia, degree of pleomorphism, hyperchromasia, prominence of nucleoli, mitotic activity with atypical mitosis and presence of tumor diathesis. Presence of metastasis in lymph nodes and other organs were also noted to establish the cytological grade and aggressiveness of tumor.

The positive rate of cannibalism and the amount of cannibalism per smear was then correlated and analyzed with respect to clinical data of patient, radiological findings and histopathological characteristics of tumor.

RESULTS

A total of 42 cases of breast cancer consented to be a part of this study. All were females with mean age of 47 years. Invasive ductal carcinoma formed the major group with 38 cases (90.48%) of classical (NOS) invasive ductal carcinoma and two cases (4.76%) each of mucinous and medullary carcinoma.

According to Robinson's grading 16 (38%) were grade-1, 12 (28.6%) were grade-2 and 14 (33.4%) grade-3 tumors (Table 1).

Cell cannibalism was demonstrated in 30 cases (71.42%) while it was absent in 12 cases (28.58%). 50% of grade-1 tumors, 66.66% grade-2 and 100% of grade-3 were positive for cytophagocytosis (Figure 1). Comparing mean cell cannibalism with tumor grade it was observed that grade-1 tumor had a mean of 1.63 per smear, grade-2 2.33 per smear and grade-3 recorded the highest mean 4.28 per smear ($p<0.01$).

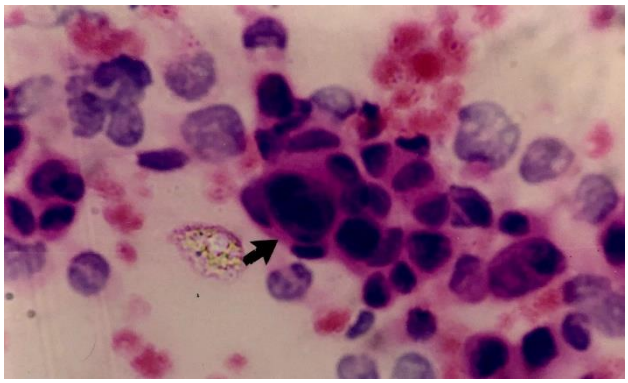

Figure 1: Grade II ductal carcinoma breast showing cytophagocytosis, H&E, 20X [x2.5].

Table 1: Cell cannibalism in relation to Robinson's grade in breast tumors.

Grade	Cannibalism positivity (%)	Mean cannibalism/ smear	Range
I (n=16)	50	1.63	0-5
II (n=12)	66.60	2.33	0-5
III (n=14)	100	4.28	3-7

Table 2: Cannibalism in relation to tumor diathesis and lymphnode metastasis.

Canni-balism	Tumor diathesis		Lymphnode metastasis	
	Present	**Absent**	**Present**	**Absent**
	N (%)	**N (%)**	**N (%)**	**N (%)**
Present	26 (62)	4 (9.5)	22 (55.2)	8 (19)
Absent	8 (19)	4 (9.5)	4 (9.5)	8 (19)

Cannibalism rate was significantly higher in grade- 3 (4.28 per smear) than in grade-1 and 2 breast carcinoma ($p<0.01$) and also higher in metastatic than early breast cancer ($p<0.01$). Tumor diathesis and evidence of metastasis were also studied in relation to cell cannibalism. Twenty six (62%) of 42 cases were positive for both cell cannibalism as well as tumor diathesis and in 4 cases (9.5%) both diathesis and cannibalism was negative. Metastasis and cannibalism were positive in 22 cases (52.5%) and in 8 cases (19%) both were negative.

It was observed that both tumor diathesis and metastasis were commonly encountered in cannibalism positive cases (Table 2).

DISCUSSION

Cell cannibalism is defined as a large cell enclosing a small cell and is considered to be an independent feature to distinguish benign lesions from malignant ones and is

associated with aggressiveness of the tumor.[10] Cannibalism should be looked for in that part of the slide where the smear is well dispersed so as to avoid false positive impression due to cell overlapping.[13]

A total of 42 cases of breast carcinoma were studied, all females with a mean age of 47 years. Abodief et al studied cell cannibalism in 50 cases of ductal breast cancer, while Mohan et al assessed 62 cases of breast carcinoma for the presence of cell cannibalism on FNAC.[11,14]

It was encountered 38% (16) grade 1, 28.6% (12) grade 2 and 33.4% (14) grade 3 tumors according to the Robinson's grading. Cell cannibalism was demonstrated in 30 cases (71.42%) while it was absent in 12 cases (28.5%). Fifty percent of grade 1 tumors, 66.6% grade 2 and 100% of grade 3 tumors were positive for cytophagocytosis. grade 1 tumors had a mean cell cannibalism of 1.63/smear, grade 2 2.33/smear and grade 3 recorded the highest mean of 4.28/smear ($p<0.01$). Mohan et al in their study reported cell cannibalism in 67.74% cases of breast carcinoma, almost similar to study observation.[11] They reported cell cannibalism in 50% of grade 1, 65% grade 2 and 100% grade 3 tumors and a mean cannibalism rate of 1.66/smear in grade 1, 2.23/smear in grade 2 and 3.40/smear in grade 3 tumors, which are in concordance to our observations.

Abodief et al in their study of 50 cases of breast cancer had 14 grade 1 and 18 cases each of grade 2 and grade 3 breast carcinoma.[14] They reported an average cell cannibalism index of 1.07±0.83, 2.67±1.03 and 4.89±1.94 respectively in grade 1, 2 and 3 breast carcinomas. It was observed that cell cannibalism rates were higher in grade 3 (4.28/smear) compared to grade 1 and 2 ($p<0.01$) and also higher in metastatic breast carcinoma than in early breast cancer ($p<0.01$). Since cell cannibalism was seen more frequently in high grade tumors, it can be regarded as a marker of anaplasia and aggressive tumor behavior as reported by other studies too.[11] Cell cannibalism is probably related to the aggressiveness of the tumor cells and increased number of cannibalistic cells and may also be used for grading of breast cancer.[11,14] It was noticed 26 (62%) out of 42 cases were positive for both cell cannibalism as well as tumor diathesis and in 4 cases (9.5%) both were absent. Lymph node metastasis and cell cannibalism were positive in 22 cases (52.5%) and in 8 cases (19%) both were negative. Both tumor diathesis and metastasis were commonly encountered in cell cannibalism positive cases. Mohan et al also reported that tumor diathesis and metastasis were found more in cell cannibalism positive cases.[11] Jose et al reported that increased number of Cell cannibalism was significantly associated with lymphnode metastasis.[15]

CONCLUSION

Cell cannibalism in breast cancer is an indicator of both the anaplastic grade and invasiveness of the tumor. The rate of cytophagocytosis correlates with the proliferative potential of the tumor and may have an independent prognostic significance. This is a preliminary study with limited sample size. Besides author know little about the mode of action of triggers and inhibitors of Cell cannibalism. Further assessment with large sample size and molecular studies are warranted to elucidate the true potential of its use as a prognostic indicator.

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